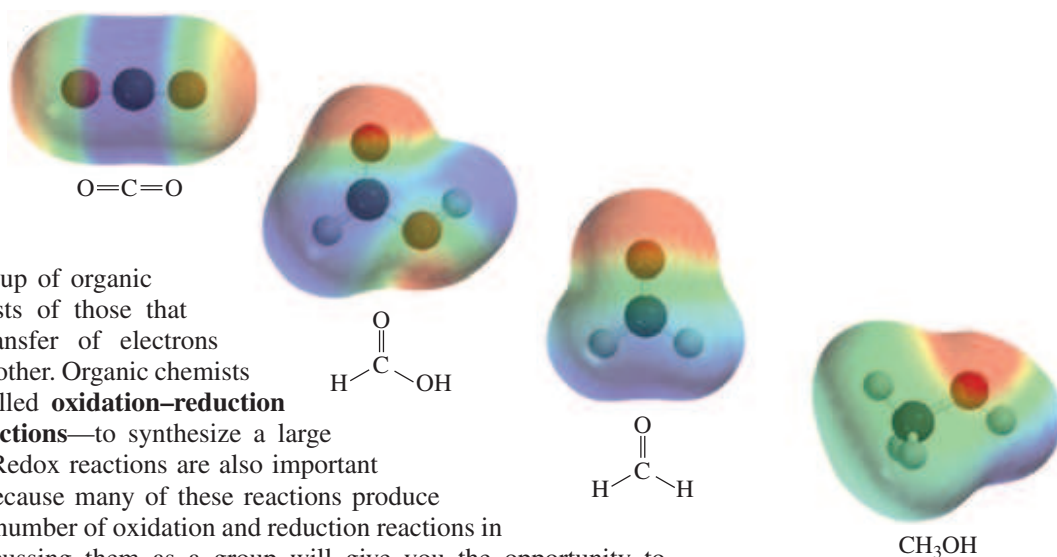


## 20

# More About Oxidation–Reduction Reactions



An important group of organic reactions consists of those that involve the transfer of electrons from one molecule to another. Organic chemists use these reactions—called **oxidation–reduction reactions** or **redox reactions**—to synthesize a large variety of compounds. Redox reactions are also important in biological systems because many of these reactions produce energy. You have seen a number of oxidation and reduction reactions in other chapters, but discussing them as a group will give you the opportunity to compare them.

In an oxidation–reduction reaction, one compound loses electrons and one compound gains electrons. The compound that loses electrons is oxidized, and the one that gains electrons is reduced. One way to remember the difference between oxidation and reduction is with the phrase “LEO the lion says GER”: *Loss of Electrons is Oxidation; Gain of Electrons is Reduction*.

The following is an example of an oxidation–reduction reaction involving inorganic reagents:



In this reaction,  $\text{Cu}^+$  loses an electron, so  $\text{Cu}^+$  is oxidized.  $\text{Fe}^{3+}$  gains an electron, so  $\text{Fe}^{3+}$  is reduced. The reaction demonstrates two important points about oxidation–reduction reactions. First, *oxidation is always coupled with reduction*. In other words, a compound cannot gain electrons (be reduced) unless another compound in the reaction simultaneously loses electrons (is oxidized). Second, the compound that is oxidized ( $\text{Cu}^+$ ) is called the **reducing agent** because it loses the electrons that are used to reduce the other compound ( $\text{Fe}^{3+}$ ). Similarly, the compound that is reduced ( $\text{Fe}^{3+}$ ) is called the **oxidizing agent** because it gains the electrons given up by the other compound ( $\text{Cu}^+$ ) when it is oxidized.

It is easy to tell whether an organic compound has been oxidized or reduced simply by looking at the change in the structure of the compound. We will be looking primarily

at reactions where **oxidation** or **reduction** has taken place on carbon: If the reaction increases the number of C—H bonds or decreases the number of C—O, C—N, or C—X bonds (where X denotes a halogen), the compound has been reduced. If the reaction decreases the number of C—H bonds or increases the number of C—O, C—N, or C—X bonds, the compound has been oxidized. Notice that the **oxidation state** of a carbon atom equals the total number of its C—O, C—N, and C—X bonds.



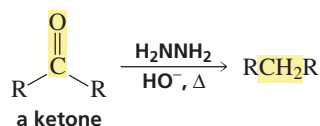
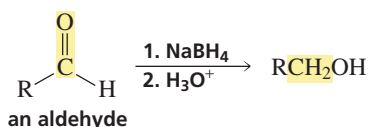
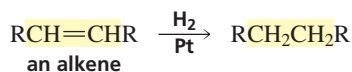
Tutorial:  
Changes in oxidation state

OXIDATION STATE number of C—Z bonds (Z = O, N, or halogen)	0	1	2	3	4
	CH <sub>4</sub>	CH <sub>3</sub> OH	$\begin{array}{c} \text{O} \\ \parallel \\ \text{HCH} \end{array}$	$\begin{array}{c} \text{O} \\ \parallel \\ \text{HCOH} \end{array}$	O=C=O
		CH <sub>3</sub> OCH <sub>3</sub>	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3\text{CCH}_3 \end{array}$	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3\text{COCH}_3 \end{array}$	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3\text{OCOCH}_3 \end{array}$
			$\begin{array}{c} \text{NCH}_3 \\ \parallel \\ \text{CH}_3\text{CCH}_3 \end{array}$	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3\text{CNH}_2 \end{array}$	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3\text{OCNHCH}_3 \end{array}$
			$\begin{array}{c} \text{OCH}_3 \\   \\ \text{CH}_3\text{CCH}_3(\text{H}) \\   \\ \text{OCH}_3 \end{array}$	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3\text{CCl} \end{array}$	$\begin{array}{c} \text{O} \\ \parallel \\ \text{ClCCl} \end{array}$

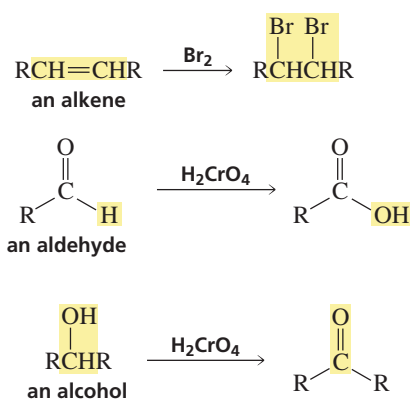
Let's now take a look at some examples of oxidation–reduction reactions that take place on carbon. You have seen these reactions in previous chapters. Notice that in each of the following reactions, the product has more C—H bonds than the reactant has: The alkene, aldehyde, and ketone, therefore, are being reduced (Sections 4.11, 18.5, and 15.15). Hydrogen, sodium borohydride, and hydrazine are the reducing agents.

Reduction at carbon increases the number of C—H bonds or decreases the number of C—O, C—N, or C—X bonds.

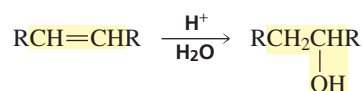
Oxidation at carbon decreases the number of C—H bonds or increases the number of C—O, C—N, or C—X bonds.



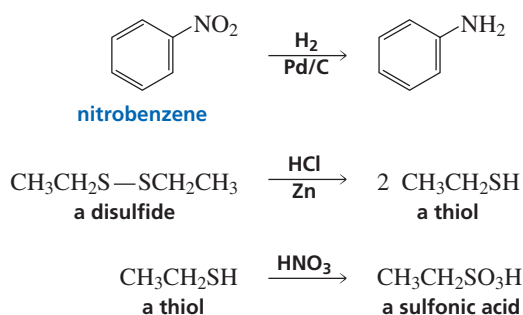
In the next group of reactions, the number of C—Br bonds increases in the first reaction. In the second and third reactions, the number of C—H bonds decreases and the number of C—O bonds increases. This means that the alkene, the aldehyde, and the alcohol are being oxidized. Bromine and chromic acid (H<sub>2</sub>CrO<sub>4</sub>) are the oxidizing agents. Notice that the increase in the number of C—O bonds in the third reaction results from a carbon–oxygen single bond becoming a carbon–oxygen double bond.



If water is added to an alkene, the product has one more C—H bond than the reactant, but it also has one more C—O bond. In this reaction, one carbon is reduced and another is oxidized. The two processes cancel each other as far as the overall molecule is concerned, so the overall reaction is neither an oxidation nor a reduction.



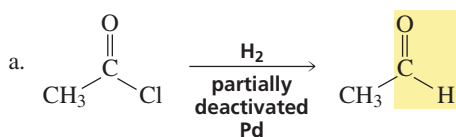
Oxidation–reduction reactions that take place on nitrogen or sulfur show similar structural changes. The number of N—H or S—H bonds increases in reduction reactions, and the number of N—O or S—O bonds increases in oxidation reactions. In the following reactions, nitrobenzene and the disulfide are being reduced (Sections 16.2 and 23.7), and the thiol is being oxidized to a sulfonic acid:

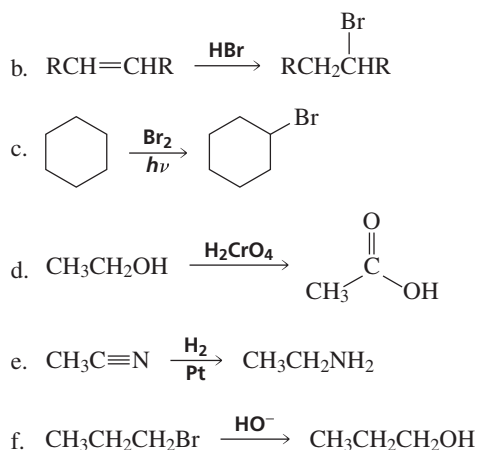


Many oxidizing reagents and many reducing reagents are available to organic chemists. This chapter highlights only a small fraction of the available reagents. The ones selected are some of the more common reagents that illustrate the types of transformations caused by oxidation and reduction.

### PROBLEM 1

Indicate whether each of the following reactions is an oxidation reaction, a reduction reaction, or neither:

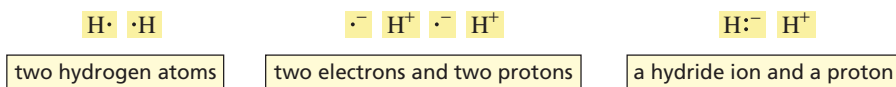




## 20.1 Reduction Reactions

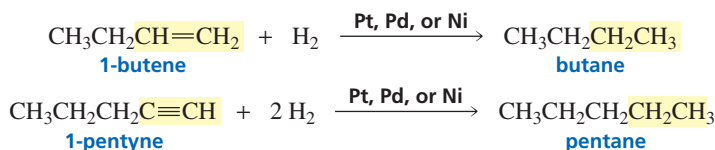
An organic compound is reduced when hydrogen ( $\text{H}_2$ ) is added to it. A molecule of  $\text{H}_2$  can be thought of as being composed of (1) two hydrogen atoms, (2) two electrons and two protons, or (3) a hydride ion and a proton. In the sections that follow, you will see that these three ways to describe  $\text{H}_2$  correspond to the three mechanisms by which  $\text{H}_2$  is added to an organic compound.

### components of $\text{H}_2$



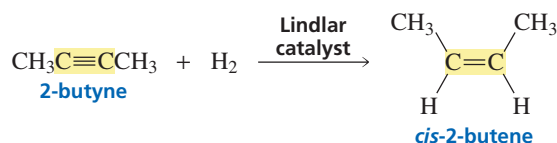
### Reduction by Addition of Two Hydrogen Atoms

You have already seen that hydrogen can be added to carbon–carbon double and triple bonds in the presence of a metal catalyst (Sections 4.11 and 6.8). These reactions, called **catalytic hydrogenations**, are reduction reactions because there are more C—H bonds in the products than in the reactants. Alkenes and alkynes are both reduced to alkanes.



In a catalytic hydrogenation, the H—H bond breaks homolytically (Section 4.11). This means that the reduction reaction involves the addition of two hydrogen atoms to the organic molecule.

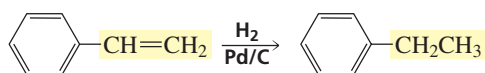
We have seen that the catalytic hydrogenation of an alkyne can be stopped at a cis alkene if a partially deactivated catalyst is used (Section 6.8).



Only the alkene substituent is reduced in the following reaction. The very stable benzene ring can be reduced only under special conditions.

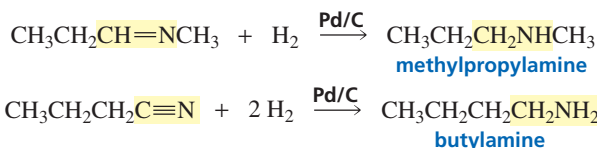


Movie:  
Catalytic hydrogenations

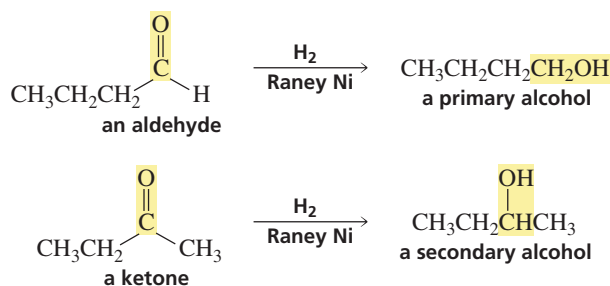


3-D Molecules:  
Styrene;  
Ethyl benzene

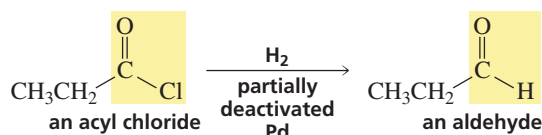
Catalytic hydrogenation can also be used to reduce carbon–nitrogen double and triple bonds. The reaction products are amines.



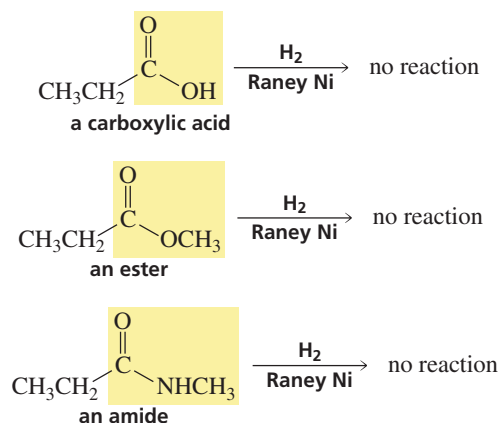
The carbonyl group of ketones and aldehydes can be reduced by catalytic hydrogenation, with Raney nickel as the metal catalyst. (Raney nickel is finely dispersed nickel with adsorbed hydrogen, so an external source of  $\text{H}_2$  is not needed.) Aldehydes are reduced to primary alcohols, and ketones are reduced to secondary alcohols.



The reduction of an acyl chloride can be stopped at an aldehyde if a partially deactivated catalyst is used. This reaction is known as the **Rosenmund reduction**. The catalyst for the Rosenmund reduction is similar to the partially deactivated palladium catalyst used to stop the reduction of an alkyne at a cis alkene (Section 6.8).



The carbonyl groups of carboxylic acids, esters, and amides are less reactive, so they are harder to reduce than the carbonyl groups of aldehydes and ketones (Section 18.5). They cannot be reduced by catalytic hydrogenation (except under extreme conditions). They can, however, be reduced by a method we will discuss later in this section.

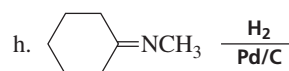
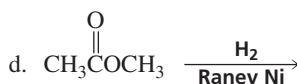
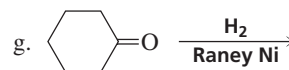
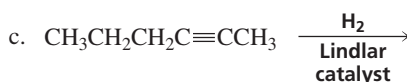
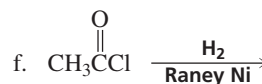
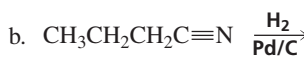
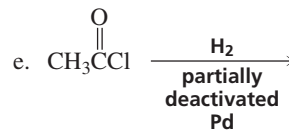
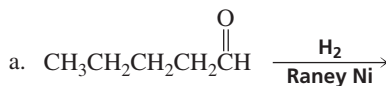


**Murray Raney (1885–1966)** was born in Kentucky. He received a B.A. from the University of Kentucky in 1909, and in 1951 the university awarded him an honorary Doctor of Science. He worked at the Gilman Paint and Varnish Co. in Chattanooga, Tennessee, where he patented several chemical and metallurgical processes. In 1963, the company was sold and renamed W. R. Grace & Co., Raney Catalyst Division.

**Karl W. Rosenmund (1884–1964)** was born in Berlin. He was a professor of chemistry at the University of Kiel.

**PROBLEM 2**

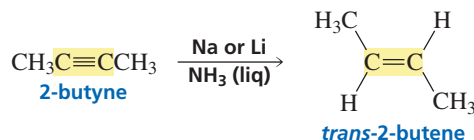
Give the products of the following reactions:



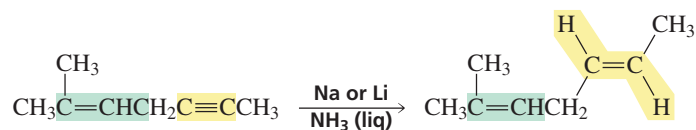
### Reduction by Addition of an Electron, a Proton, an Electron, and a Proton

When a compound is reduced using sodium in liquid ammonia, sodium donates an electron to the compound and ammonia donates a proton. This sequence is then repeated, so the overall reaction adds two electrons and two protons to the compound. Such a reaction is known as a **dissolving-metal reduction**.

In Section 6.8, you saw the mechanism for the dissolving-metal reduction that converts an alkyne to a trans alkene.

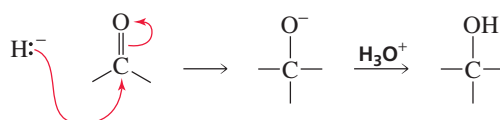


Sodium (or lithium) in liquid ammonia cannot reduce a carbon–carbon double bond. This makes it a useful reagent for reducing a triple bond in a compound that also contains a double bond.

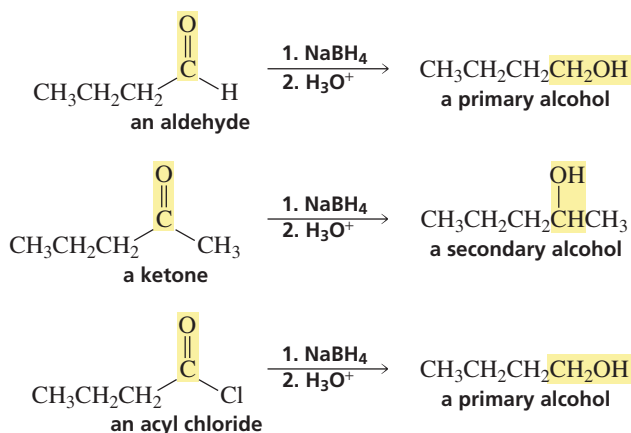


### Reduction by Addition of a Hydride Ion and a Proton

Carbonyl groups are easily reduced by metal hydrides such as sodium borohydride ( $\text{NaBH}_4$ ) or lithium aluminum hydride. The actual reducing agent in **metal-hydride reductions** is hydride ion ( $\text{H}^-$ ). Hydride ion adds to the carbonyl carbon, and the alkoxide ion that is formed is subsequently protonated. In other words, the carbonyl group is reduced by adding an  $\text{H}^-$  followed by an  $\text{H}^+$ . The mechanisms for reduction by these reagents are discussed in Section 18.5.

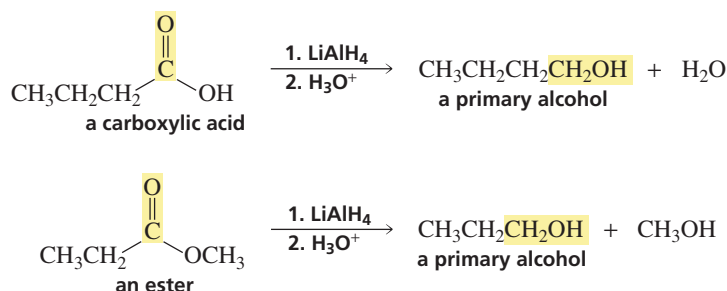


Aldehydes, ketones, and acyl halides can be reduced by sodium borohydride.

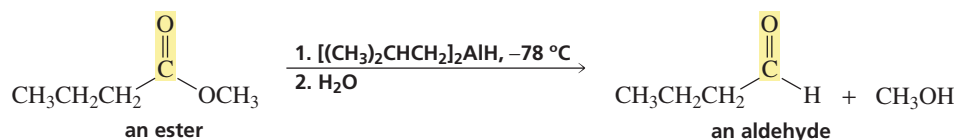


Remember, the numbers in front of the reagents above or below a reaction arrow indicate that the second reagent is not added until reaction with the first reagent is completed.

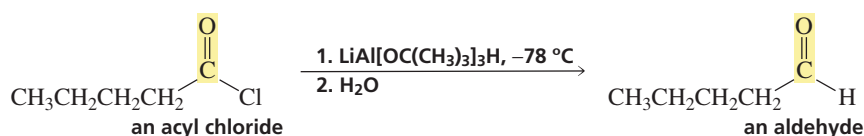
The metal–hydrogen bonds in lithium aluminum hydride are more polar than the metal–hydrogen bonds in sodium borohydride. As a result,  $\text{LiAlH}_4$  is a stronger reducing agent than  $\text{NaBH}_4$ . Consequently, both  $\text{LiAlH}_4$  and  $\text{NaBH}_4$  reduce aldehydes, ketones, and acyl halides, but  $\text{LiAlH}_4$  is not generally used for this purpose since  $\text{NaBH}_4$  is safer and easier to use.  $\text{LiAlH}_4$  is generally used to reduce only compounds—such as carboxylic acids, esters, and amides—that cannot be reduced by the milder reagent.

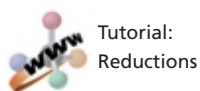


If diisobutylaluminum hydride (DIBALH) is used as the hydride donor at a low temperature instead of  $\text{LiAlH}_4$ , the reduction of the ester can be stopped after the addition of one equivalent of hydride ion. Therefore, the final products of the reaction are an aldehyde and an alcohol (Section 18.5).

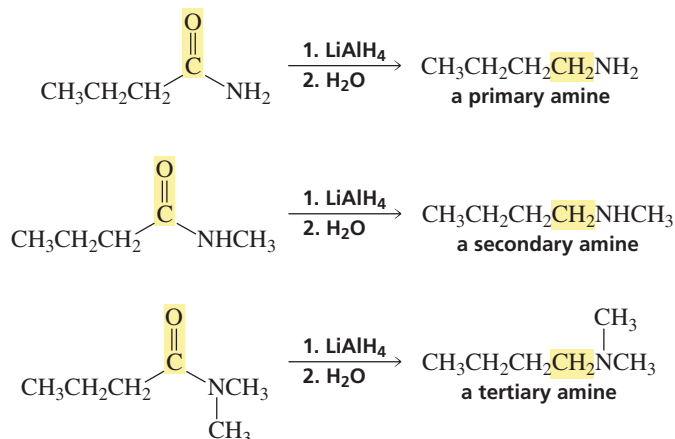


Replacing some of the hydrogens of  $\text{LiAlH}_4$  with OR groups decreases the reactivity of the metal hydride. For example, lithium tri-*tert*-butoxyaluminum hydride reduces an acyl chloride to an aldehyde, whereas  $\text{LiAlH}_4$  reduces the acyl chloride all the way to an alcohol.

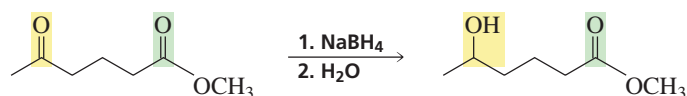




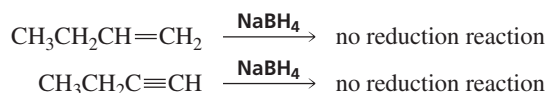
The carbonyl group of an amide is reduced to a methylene group ( $\text{CH}_2$ ) by lithium aluminum hydride (Section 18.5). Primary, secondary, and tertiary amines are formed, depending on the number of substituents bonded to the nitrogen of the amide. To obtain the amine in its neutral basic form, acid is not used in the second step of the reaction.



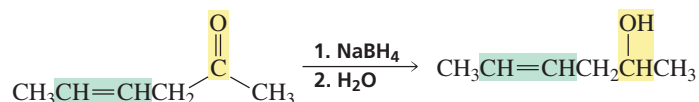
Because sodium borohydride cannot reduce an ester, an amide, or a carboxylic acid, it can be used to selectively reduce an aldehyde or a ketone group in a compound that also contains a less reactive group. Acid is not used in the second step of the following reaction, in order to avoid hydrolyzing the ester:



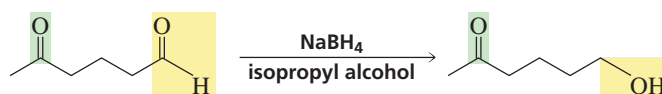
The multiply bonded carbon atoms of alkenes and alkynes do not possess a partial positive charge and therefore will not react with reagents that reduce compounds by donating a hydride ion.



Because sodium borohydride cannot reduce carbon–carbon double bonds, a carbonyl group in a compound that also has an alkene functional group can be selectively reduced, as long as the double bonds are not conjugated (Section 18.13). Acid is not used in the second step of the reaction, in order to avoid addition to the double bond.

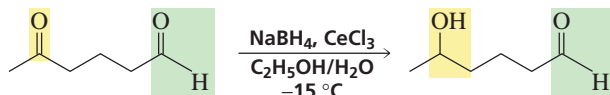


A **chemoselective reaction** is a reaction in which a reagent reacts with one functional group in preference to another. For example,  $\text{NaBH}_4$  in isopropyl alcohol reduces aldehydes faster than it reduces ketones.





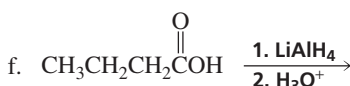
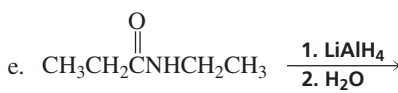
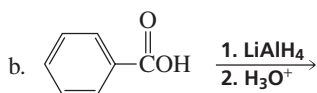
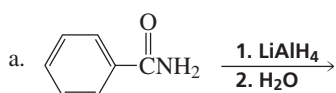
In contrast,  $\text{NaBH}_4$  in aqueous ethanol at  $-15^\circ\text{C}$  in the presence of cerium trichloride reduces ketones faster than it reduces aldehydes. There are many reducing reagents—and conditions under which those reagents should be used—available to the synthetic chemist. We can cover only a fraction of these in this chapter.

**PROBLEM 3**

Explain why terminal alkynes cannot be reduced by Na in liquid  $\text{NH}_3$ .

**PROBLEM 4** ♦

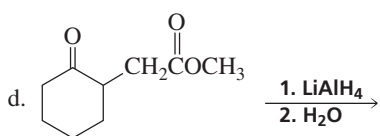
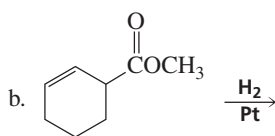
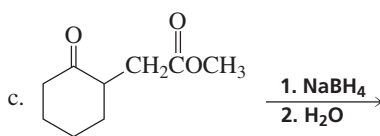
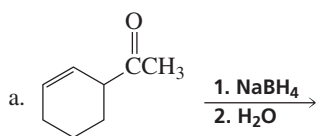
Give the products of the following reactions:

**PROBLEM 5**

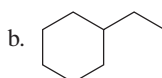
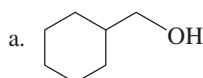
Can carbon–nitrogen double and triple bonds be reduced by lithium aluminum hydride? Explain your answer.

**PROBLEM 6**

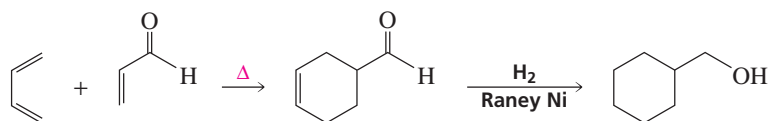
Give the products of the following reactions (assume that excess reducing agent is used in d):

**PROBLEM 7 SOLVED**

How could you synthesize the following compounds from starting materials containing no more than four carbons?

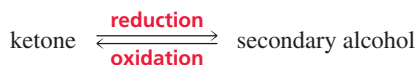


**SOLUTION TO 7a** The six-membered ring indicates that the compound can be synthesized by means of a Diels–Alder reaction.

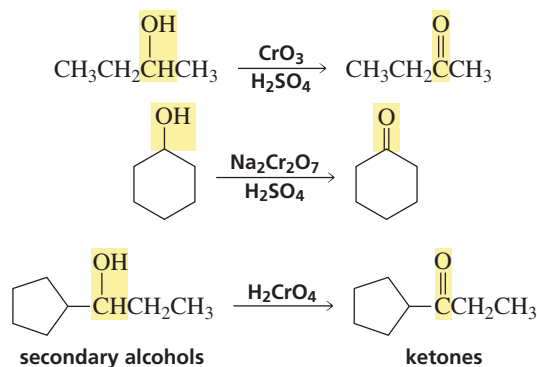


## 20.2 Oxidation of Alcohols

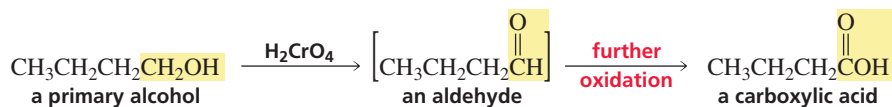
Oxidation is the reverse of reduction. For example, a ketone is *reduced* to a secondary alcohol, and the reverse reaction is the *oxidation* of a secondary alcohol to a ketone.



A reagent that is often used to oxidize alcohols is chromic acid (H<sub>2</sub>CrO<sub>4</sub>), which is formed when chromium trioxide (CrO<sub>3</sub>) or sodium dichromate (Na<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub>) is dissolved in aqueous acid. These reactions are easily recognized as oxidations because the number of C—H bonds in the reactant decreases and the number of C—O bonds increases.



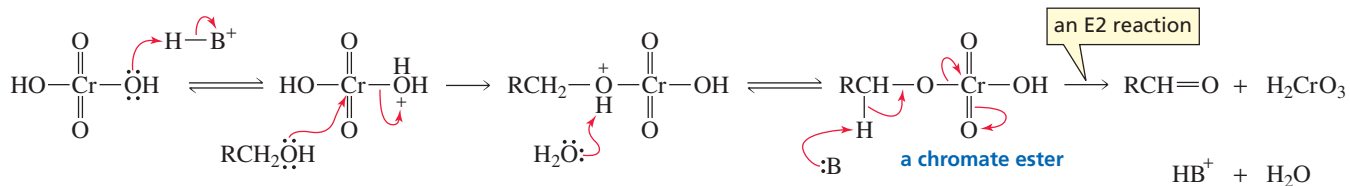
Primary alcohols are initially oxidized to aldehydes by these reagents. The reaction, however, does not stop at the aldehyde. Instead, the aldehyde is further oxidized to a carboxylic acid.



Notice that the oxidation of either a primary or a secondary alcohol involves removal of a hydrogen from the carbon to which the OH is attached. The carbon bearing the OH group in a tertiary alcohol is not bonded to a hydrogen, so the OH group cannot be oxidized to a carbonyl group.

Chromic acid and the other chromium-containing oxidizing reagents oxidize an alcohol by first forming a chromate ester. The carbonyl compound is formed when the chromate ester undergoes an E2 elimination (Section 11.1).

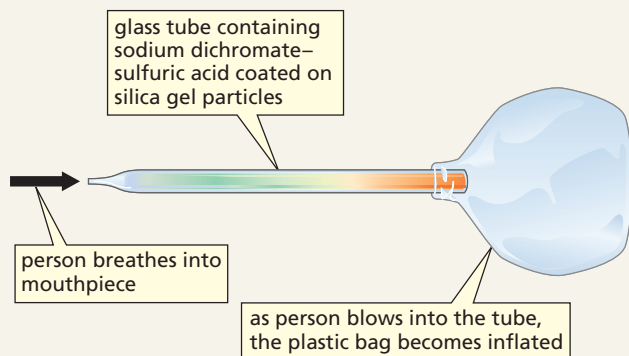
### mechanism for alcohol oxidation by chromic acid



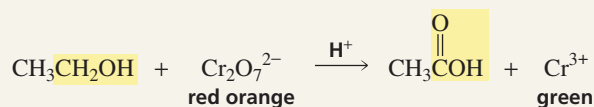


### BLOOD ALCOHOL CONTENT

As blood passes through the arteries in the lungs, an equilibrium is established between the alcohol in one's blood and the alcohol in one's breath. So if the concentration of one is known, the concentration of the other can be estimated. The test that law enforcement agencies use to approximate a person's blood alcohol level is based on the oxidation of breath ethanol by sodium dichromate. The test employs a sealed glass tube that contains the oxidizing agent impregnated onto an inert material. The ends of the tube are broken off, and one end of the tube is attached to a mouthpiece and the other to a balloon-type bag. The person undergoing the test blows into the mouthpiece until the bag is filled with air.

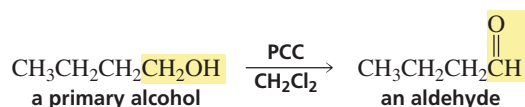


Any ethanol in the breath is oxidized as it passes through the column. When ethanol is oxidized, the red-orange oxidizing agent ( $\text{Cr}_2\text{O}_7^{2-}$ ) is reduced to green chromic ion. The greater the concentration of alcohol in the breath, the farther the green color spreads through the tube.



If the person fails this test—determined by the extent to which the green color spreads through the tube—a more accurate Breathalyzer<sup>®</sup> test is administered. The Breathalyzer<sup>®</sup> test also depends on the oxidation of breath ethanol by sodium dichromate, but it provides more accurate results because it is quantitative. In the test, a known volume of breath is bubbled through an acidic solution of sodium dichromate, and the concentration of chromic ion is measured precisely with a spectrophotometer.

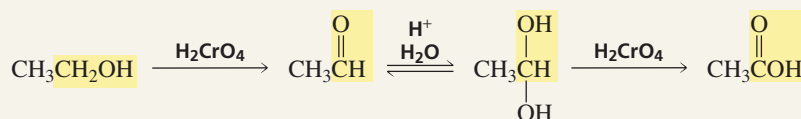
The oxidation of a primary alcohol can be easily stopped at the aldehyde if pyridinium chlorochromate (PCC) is used as the oxidizing agent and the reaction is carried out in an anhydrous solvent such as dichloromethane, as explained in the following box:



### THE ROLE OF HYDRATES IN THE OXIDATION OF PRIMARY ALCOHOLS

When a primary alcohol is oxidized to a carboxylic acid, the alcohol is initially oxidized to an aldehyde, which is in equilibrium with its hydrate (Section 18.7). It is the hydrate that is subsequently oxidized to a carboxylic acid.

The oxidation reaction can be stopped at the aldehyde if the reaction is carried out with pyridinium chlorochromate (PCC), because PCC is used in an anhydrous solvent. If water is not present, the hydrate cannot be formed.

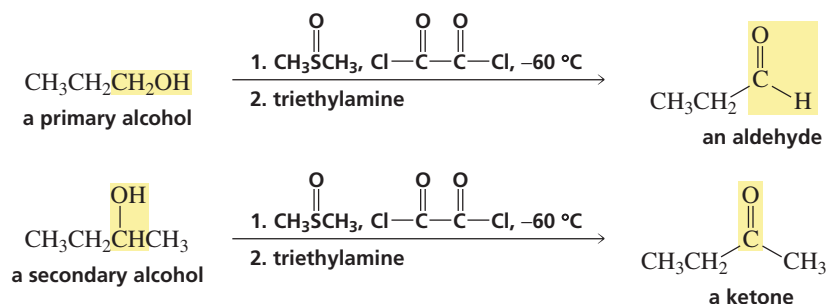


Because of the toxicity of chromium-based reagents, other methods for the oxidation of alcohols have been developed. One of the most widely employed methods, called the **Swern oxidation**, uses dimethyl sulfoxide  $[(\text{CH}_3)_2\text{SO}]$ , oxalyl chloride  $[(\text{COCl})_2]$ , and triethylamine. Since the reaction is *not* carried out in an



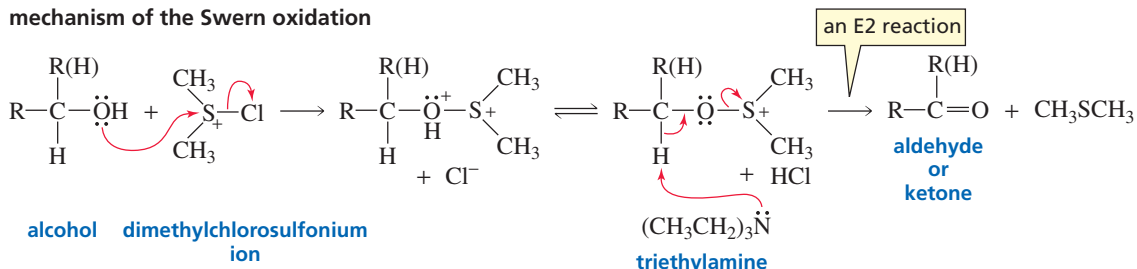
3-D Molecules:  
Pyridinium chlorochromate (PCC); Dimethyl sulfoxide; Oxalyl chloride

aqueous solution, the oxidation of a primary alcohol (like PCC oxidation) stops at the aldehyde. Secondary alcohols are oxidized to ketones.



The actual oxidizing agent in the Swern oxidation is dimethylchlorosulfonium ion, which is formed from the reaction of dimethyl sulfoxide and oxalyl chloride. Like chromic acid oxidation, the Swern oxidation uses an E2 reaction to form the aldehyde or ketone.

#### mechanism of the Swern oxidation



To understand how dimethyl sulfoxide and oxalyl chloride react to form the dimethylchlorosulfonium ion, see Problem 64.

#### PROBLEM 8

Give the product formed from the reaction of each of the following alcohols with

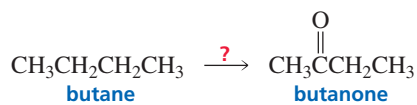
- a. an acidic solution of sodium dichromate:
- b. the reagents required for a Swern oxidation:
  1. 3-pentanol
  3. 2-methyl-2-pentanol
  5. cyclohexanol
  2. 1-pentanol
  4. 2,4-hexanediol
  6. 1,4-butanediol

#### PROBLEM 9

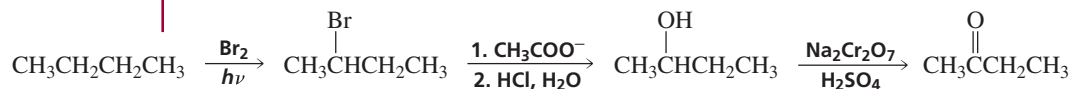
Propose a mechanism for the chromic acid oxidation of 1-propanol to propanal.

#### PROBLEM 10 SOLVED

How could butanone be prepared from butane?

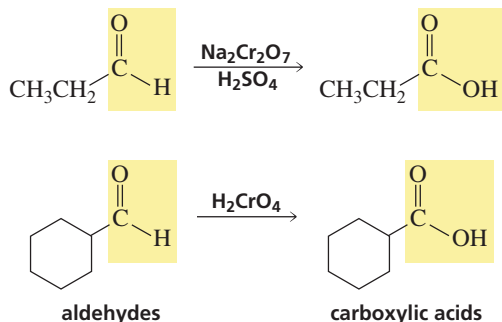


**SOLUTION** We know that the first reaction has to be a radical halogenation because that is the only reaction that an alkane undergoes. Bromination will lead to a greater yield of the desired 2-halo-substituted compound than will chlorination because the bromine radical is more selective than a chlorine radical. To maximize the yield of substitution product (Section 11.8), the alkyl bromide is treated with acetate ion and the ester is then hydrolyzed to the alcohol, which forms the target compound when it is oxidized.

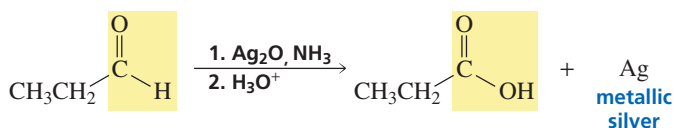


## 20.3 Oxidation of Aldehydes and Ketones

Aldehydes are oxidized to carboxylic acids. Because aldehydes are generally easier to oxidize than primary alcohols, any of the reagents described in the preceding section for oxidizing primary alcohols to carboxylic acids can be used to oxidize aldehydes to carboxylic acids.



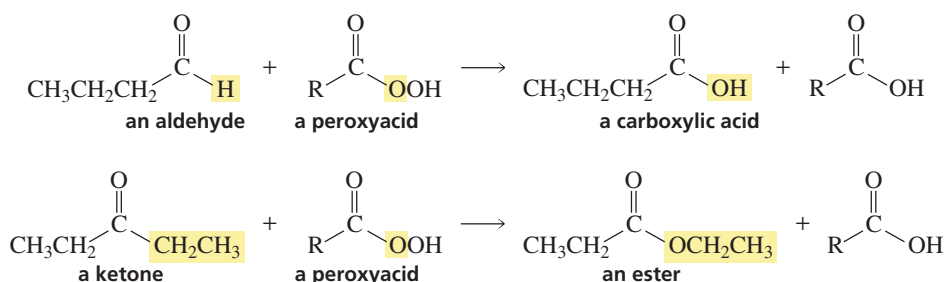
Silver oxide is a mild oxidizing agent. A dilute solution of silver oxide in aqueous ammonia (*Tollens reagent*) will oxidize an aldehyde, but it is too weak to oxidize an alcohol or any other functional group. An advantage to using Tollens reagent to oxidize an aldehyde is that the reaction occurs under basic conditions. Therefore, you do not have to worry about harming other functional groups in the molecule that may undergo a reaction in an acidic solution.



The oxidizing agent in Tollens reagent is  $\text{Ag}^+$ , which is reduced to metallic silver. The **Tollens test** is based on this reaction: If Tollens reagent is added to a small amount of an aldehyde in a test tube, the inside of the test tube becomes coated with a shiny mirror of metallic silver. Consequently, if a mirror is not formed when Tollens reagent is added to a compound, it can be concluded that the compound does not have an aldehyde functional group.

Ketones do not react with most of the reagents used to oxidize aldehydes. However, both aldehydes *and* ketones can be oxidized by a peroxyacid. Aldehydes are oxidized to carboxylic acids and ketones are oxidized to esters. A **peroxyacid** (also called a percarboxylic acid or an acyl hydroperoxide) contains one more oxygen than a carboxylic acid, and it is this oxygen that is inserted between the carbonyl carbon and the H of an aldehyde or the R of a ketone. The reaction is called a **Baeyer–Villiger oxidation**.

### Baeyer–Villiger oxidations



If the two alkyl substituents attached to the carbonyl group of the ketone are not the same, on which side of the carbonyl carbon is the oxygen inserted? For example, does

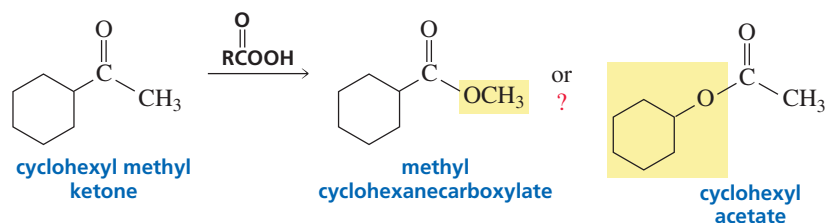
**Bernhard Tollens (1841–1918)** was born in Germany. He was a professor of chemistry at the University of Göttingen, the same university from which he received a Ph.D.



**Johann Friedrich Wilhelm Adolf von Baeyer (1835–1917)** started his study of chemistry under Bunsen and Kekulé at the University of Heidelberg and received a Ph.D. from the University of Berlin, studying under Hofmann. (See also Section 2.11.)

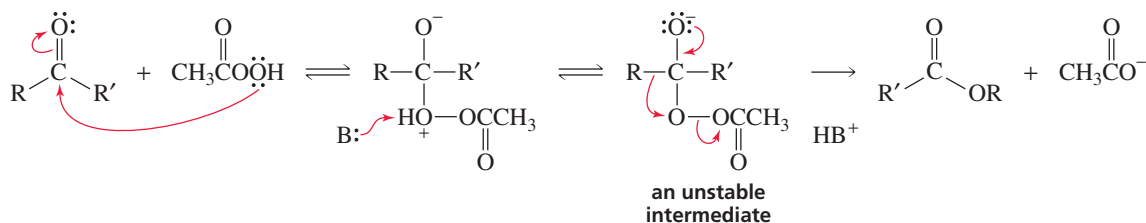
**Victor Villiger (1868–1934)** was Baeyer's student. The two published the first paper on the Baeyer–Villiger oxidation in *Chemische Berichte* in 1899.

the oxidation of cyclohexyl methyl ketone form methyl cyclohexanecarboxylate or cyclohexyl acetate?



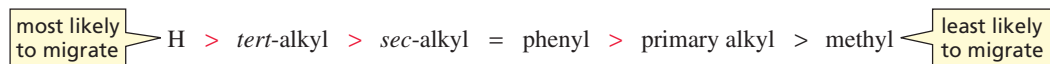
To answer this question, we must look at the mechanism of the reaction. The ketone and the peroxyacid react to form an unstable tetrahedral intermediate with a very weak O—O bond. As the O—O bond breaks heterolytically, one of the alkyl groups migrates to an oxygen. This rearrangement is similar to the 1,2-shifts that occur when carbocations rearrange (Section 4.6).

#### mechanism of the Baeyer–Villiger oxidation



Several studies have established the following order of group migration tendencies:

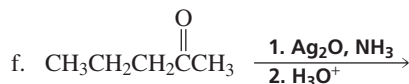
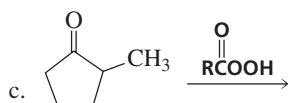
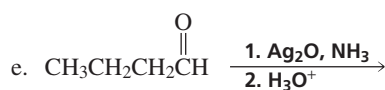
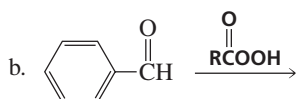
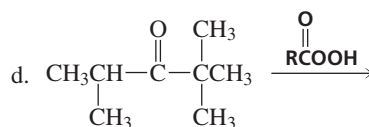
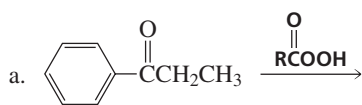
#### relative migration tendencies



Therefore, the product of the Baeyer–Villiger oxidation of cyclohexyl methyl ketone will be cyclohexyl acetate because a secondary alkyl group (the cyclohexyl group) is more likely to migrate than a methyl group. Aldehydes are always oxidized to carboxylic acids, since H has the greatest tendency to migrate.

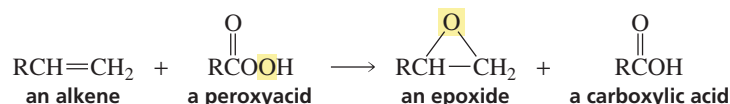
### PROBLEM 11

Give the products of the following reactions:

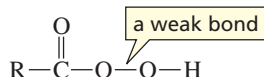


## 20.4 Oxidation of Alkenes with Peroxyacids

An alkene can be oxidized to an epoxide by a peroxyacid. The overall reaction amounts to the transfer of an oxygen atom from the peroxyacid to the alkene.

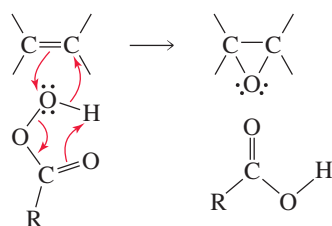


Recall that an O—O bond is weak and easily broken (Section 20.3).

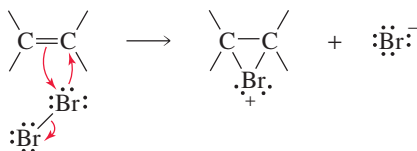


The oxygen atom of the OH group of the peroxyacid accepts a pair of electrons from the  $\pi$  bond of the alkene, causing the weak O—O bond to break heterolytically. The electrons from the O—O bond are delocalized onto the carbonyl group. The electrons left behind as the O—H bond breaks add to the carbon of the alkene that becomes electron deficient when the  $\pi$  bond breaks. Notice that **epoxidation** of an alkene is a concerted reaction: All the bond-forming and bond-breaking processes take place in a single step.

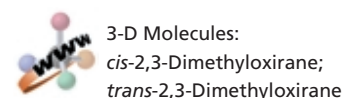
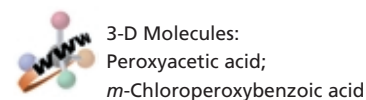
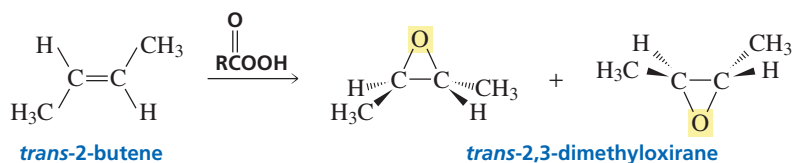
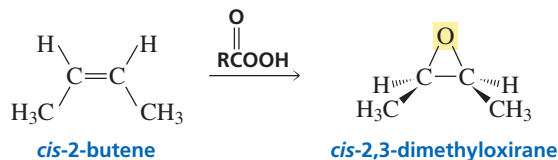
### mechanism for epoxidation of an alkene



The mechanism for the addition of oxygen to a double bond to form an epoxide is analogous to the mechanism described in Section 4.7 for the addition of bromine to a double bond to form a cyclic bromonium ion. In one case the electrophile is oxygen, and in the other it is bromine. So the reaction of an alkene with a peroxyacid, like the reaction of an alkene with  $\text{Br}_2$ , is an electrophilic addition reaction.

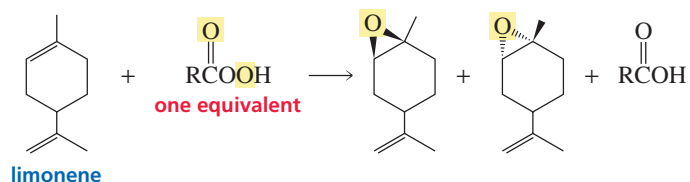


The addition of oxygen to an alkene is a stereospecific reaction. Because the reaction is concerted, the C—C bond cannot rotate, so there is no opportunity for the relative positions of the groups bonded to the  $sp^2$  carbons of the alkene to change. Therefore, a cis alkene forms a cis epoxide. Similarly, a trans alkene forms a trans epoxide.

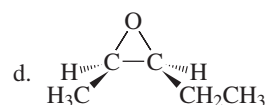
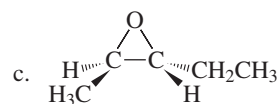
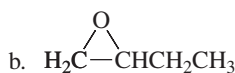
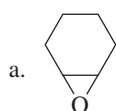


Because the oxygen can add from the top or the bottom of the plane containing the double bond, *trans*-2-butene forms a pair of enantiomers; *cis*-2-butene forms a meso compound—it and its mirror image are identical (Section 5.10).

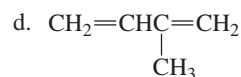
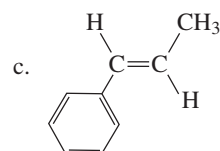
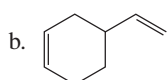
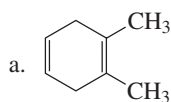
Increasing the electron density of the double bond increases the rate of epoxidation because it makes the double bond more nucleophilic. Alkyl substituents increase the electron density of the double bond. Therefore, if a diene is treated with only enough peroxyacid to react with one of the double bonds, it will be the most substituted double bond that is epoxidized.

**PROBLEM 12**

What alkene would you treat with a peroxyacid in order to obtain each of the following epoxides?

**PROBLEM 13**

Give the major product of the reaction of each of the following compounds with one equivalent of a peroxyacid. Indicate the configuration of the product.

**PROBLEM 14**

Show how the following target molecules could be synthesized from propene:

a. 1-methoxy-2-propanol

b. 2-butanol

c. 2-butanone

**PROBLEM 15**

Explain why an epoxide is a relatively stable product, whereas a bromonium ion is a reactive intermediate.

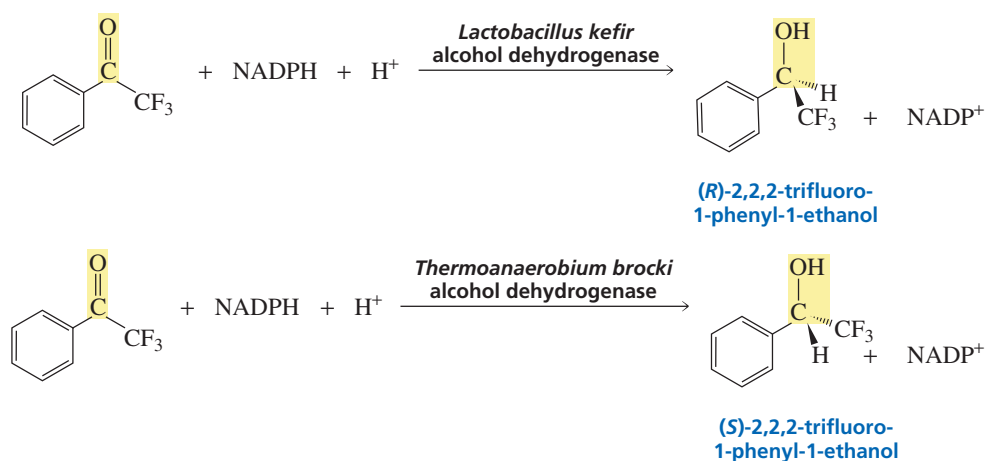


## 20.5 Designing a Synthesis VII: Controlling Stereochemistry



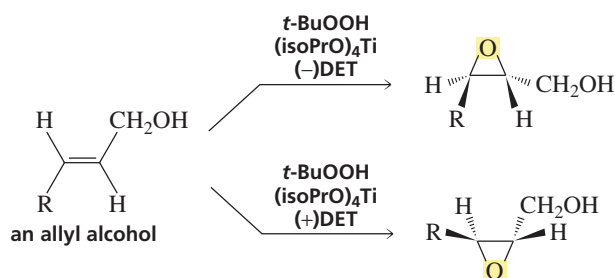
The target molecule of a synthesis may be one of several stereoisomers. The actual number of stereoisomers depends on the number of double bonds and asymmetric carbons in the molecule because each double bond can exist in an *E* or *Z* configuration (Section 3.5) and each asymmetric carbon can have an *R* or *S* configuration (Section 5.6). In addition, if the target molecule has rings with a common bond, the rings can be either trans fused or cis fused (Section 2.15). In designing a synthesis, care must be taken to make sure that each double bond, each asymmetric carbon, and each ring fusion in the target molecule has the appropriate configuration. If the stereochemistry of the reactions is not controlled, the resulting mixture of stereoisomers may be difficult or even impossible to separate. Therefore, in planning a synthesis, an organic chemist must consider the stereochemical outcomes of all reactions and must use highly stereoselective reactions to achieve the desired configurations. Some stereoselective reactions are also *enantioselective*; an **enantioselective reaction** forms more of one enantiomer than of another.

We have seen that an enantiomerically pure target molecule can be obtained if an enzyme is used to catalyze the reaction that forms the target molecule. Enzyme-catalyzed reactions result in the exclusive formation of one enantiomer since enzymes are chiral (Section 5.20). For example, ketones are enzymatically reduced to alcohols by enzymes called alcohol dehydrogenases. Whether the *R* or the *S* enantiomer is formed depends on the particular alcohol dehydrogenase used: Alcohol dehydrogenase from the bacterium *Lactobacillus kefir* forms *R* alcohols, whereas alcohol dehydrogenases from yeast, horse liver, and the bacterium *Thermoanaerobium brocki* form *S* alcohols. The alcohol dehydrogenases use NADPH to carry out the reduction (Section 25.2). Using an enzyme-catalyzed reaction to control the configuration of a target molecule is not a universally useful method because enzymes require substrates of very specific size and shape (Section 24.8).

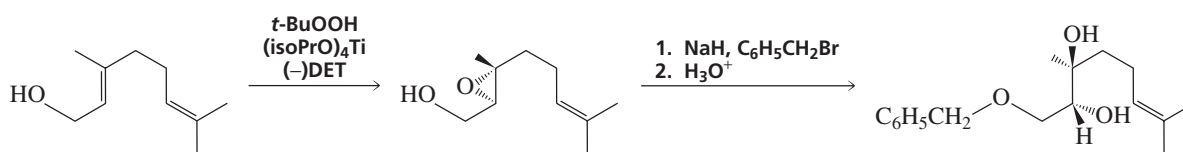


Alternatively, an enantiomerically pure catalyst that is not an enzyme can be used to obtain an enantiomerically pure target molecule. For example, an enantiomerically pure epoxide of an allylic alcohol can be prepared by treating the alcohol with *tert*-butyl hydroperoxide, titanium isopropoxide, and enantiomerically pure diethyl tartrate (DET). The structure of the epoxide depends on the enantiomer of diethyl tartrate used.

**K. Barry Sharpless** was born in Philadelphia in 1941. He received a B.A. from Dartmouth in 1963 and a Ph.D. in chemistry from Stanford in 1968. He served as a professor at MIT and Stanford. Currently, he is at the Scripps Research Institute in La Jolla, California. He received the 2001 Nobel Prize in chemistry for his work on chirally catalyzed oxidation reactions. (See also Section 24.3.)



This method, developed in 1980 by Barry Sharpless, has proven to be useful for the synthesis of a wide variety of enantiomerically pure compounds, because an epoxide can easily be converted into a compound with two adjacent asymmetric carbons, since epoxides are very susceptible to attack by nucleophiles. In the following example, an allylic alcohol is converted into an enantiomerically pure epoxide, which is used to form an enantiomerically pure diol.



#### PROBLEM 16

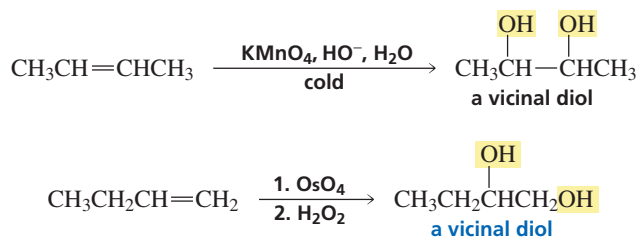
What is the product of the reaction of methylmagnesium bromide with either of the enantiomerically pure epoxides that can be prepared from (*E*)-3-methyl-2-pentene by the preceding method? Assign *R* or *S* configurations to the asymmetric carbons of each product.

#### PROBLEM 17♦

Is the addition of  $\text{Br}_2$  to an alkene such as *trans*-2-pentene a stereoselective reaction? Is it a stereospecific reaction? Is it an enantioselective reaction?

## 20.6 Hydroxylation of Alkenes

An alkene can be oxidized to a 1,2-diol either by potassium permanganate ( $\text{KMnO}_4$ ) in a cold basic solution or by osmium tetroxide ( $\text{OsO}_4$ ). The solution of potassium permanganate must be basic, and the oxidation must be carried out at room temperature or below. If the solution is heated or if it is acidic, the diol will be oxidized further (Section 20.8). A diol is also called a **glycol**. The OH groups are on adjacent carbons in 1,2-diols, so 1,2-diols are also known as **vicinal diols** or **vicinal glycols**.



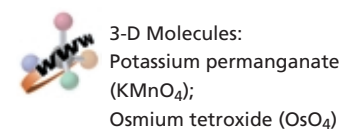
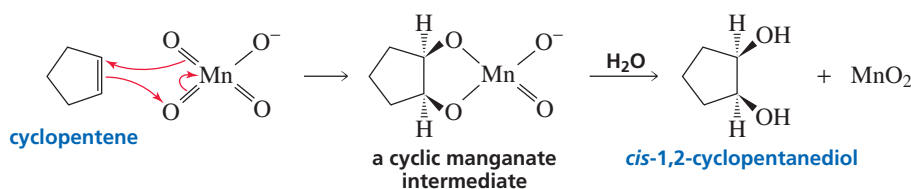
Both  $\text{KMnO}_4$  and  $\text{OsO}_4$  form a cyclic intermediate when they react with an alkene. The reactions occur because manganese and osmium are in a highly positive oxidation state and, therefore, attract electrons. (Since the oxidation state is given by the number



Tutorial:  
Hydroxylation reactions—  
synthesis

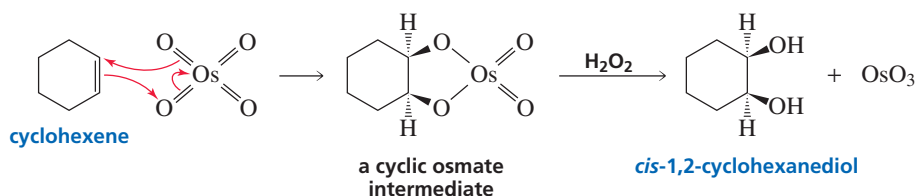
of bonds to oxygen, magnesium and osmium have oxidation states of +7 and +8, respectively.) Formation of the cyclic intermediate is a syn addition because both oxygens are delivered to the same side of the double bond. Therefore, the oxidation reaction is stereospecific—a cis cycloalkene forms only a cis diol.

#### mechanism for cis glycol formation



The cyclic osmate intermediate is hydrolyzed with hydrogen peroxide that reoxidizes osmium to osmium tetroxide.

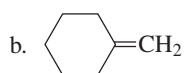
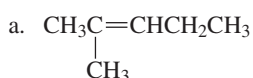
#### mechanism for cis glycol formation



Higher yields of the diol are obtained with osmium tetroxide because the cyclic osmate intermediate is less likely to undergo side reactions.

#### PROBLEM 18

Give the products that would be formed from the reaction of each of the following alkenes with OsO<sub>4</sub>, followed by aqueous H<sub>2</sub>O<sub>2</sub>:



#### PROBLEM 19

What stereoisomers would be formed from the reaction of each of the following alkenes with OsO<sub>4</sub> followed by H<sub>2</sub>O<sub>2</sub>?

a. *trans*-2-butene

c. *cis*-2-pentene

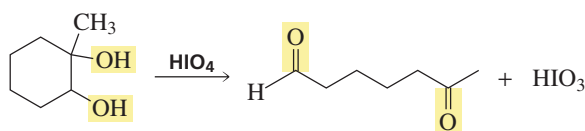
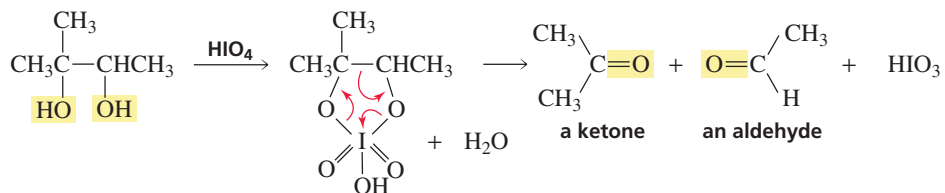
b. *cis*-2-butene

d. *trans*-2-pentene

## 20.7 Oxidative Cleavage of 1,2-Diols

1,2-Diols are oxidized to ketones and/or aldehydes by periodic acid (HIO<sub>4</sub>). Periodic acid reacts with the diol to form a cyclic intermediate. The reaction takes place because iodine is in a highly positive oxidation state (+7), so it readily accepts electrons. When the intermediate breaks down, the bond between the two carbons bonded to the OH groups breaks. If the carbon that is bonded to an OH group is also bonded to two

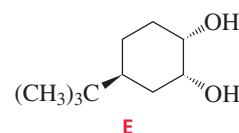
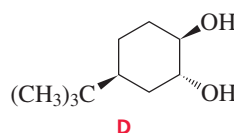
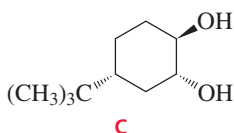
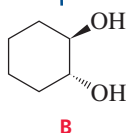
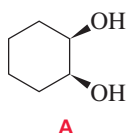
R groups, the product will be a ketone. If the carbon is bonded to an R and an H, the product will be an aldehyde. Because this oxidation reaction cuts the reactant into two pieces, it is called an **oxidative cleavage**.

**PROBLEM 20♦**

An alkene is treated with  $\text{OsO}_4$  followed by  $\text{H}_2\text{O}_2$ . When the resulting diol is treated with  $\text{HIO}_4$ , the only product obtained is an unsubstituted cyclic ketone with molecular formula  $\text{C}_6\text{H}_{10}\text{O}$ . What is the structure of the alkene?

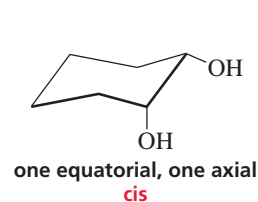
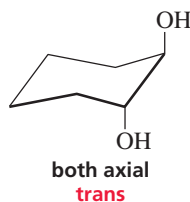
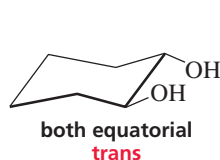
**PROBLEM-SOLVING STRATEGY**

Of the following five compounds, explain why only **D** cannot be cleaved by periodic acid.



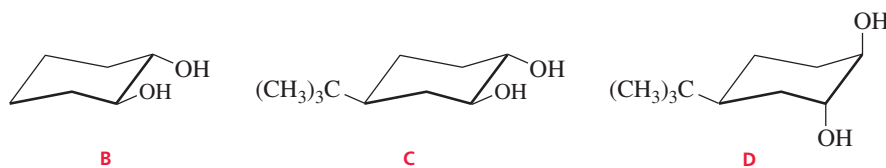
To figure out why one of a series of similar compounds is unreactive, we first need to consider what kinds of compounds undergo the reaction and any stereochemical requirements of the reaction. We know that periodic acid cleaves 1,2-diols. Because the reaction forms a cyclic intermediate, the two OH groups of the diol must be positioned so that they can form the intermediate.

The two OH groups of a 1,2-cyclohexanediol can both be equatorial, they can both be axial, or one can be equatorial and the other axial.



In a cis 1,2-cyclohexanediol, one OH is equatorial and the other is axial. Because both cis 1,2-diols (**A** and **E**) are cleaved, we know that the cyclic intermediate can be formed when the OH groups are in these positions. In a trans 1,2-diol, both OH groups are equatorial *or* both are axial (Section 2.14). Two of the trans 1,2-diols can be cleaved (**B** and **C**), and one cannot (**D**). We can conclude that the one that cannot be cleaved must have both OH groups in axial positions because they would be too far from each other to form a

cyclic intermediate. Now we need to draw the most stable conformers of B, C, and D to see why only D has both OH groups in axial positions.

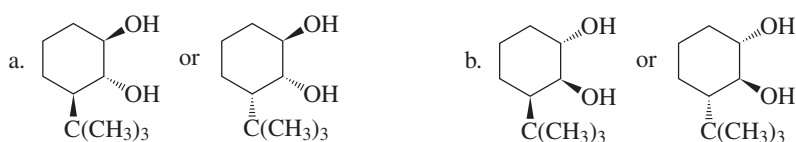


The most stable conformer of B is the one with both OH groups in equatorial positions. The steric requirements of the bulky *tert*-butyl group force it into an equatorial position, where there is more room for such a large substituent. This causes both OH groups in compound C to be in equatorial positions and both OH groups in compound D to be in axial positions. Therefore, C can be cleaved by periodic acid, but D cannot.

Now continue on to Problem 21.

### PROBLEM 21

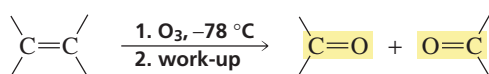
Which of each pair of diols is cleaved more rapidly by periodic acid?



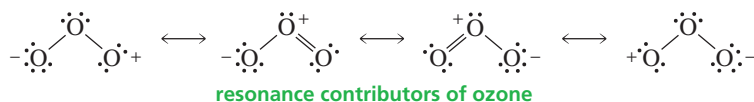
## 20.8 Oxidative Cleavage of Alkenes

### Ozonolysis

We have seen that alkenes can be oxidized to 1,2-diols and that 1,2-diols can be further oxidized to aldehydes and ketones (Sections 20.6 and 20.7, respectively). Alternatively, alkenes can be directly oxidized to aldehydes and ketones by ozone ( $O_3$ ). When an alkene is treated with ozone at low temperatures, the double bond breaks and the carbons that were doubly bonded to each other find themselves doubly bonded to oxygens instead. This oxidation reaction is known as **ozonolysis**.



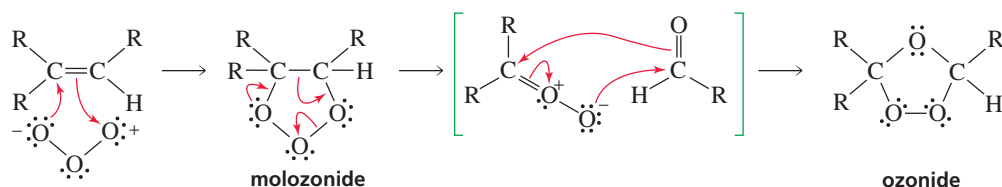
Ozone is produced by passing oxygen gas through an electric discharge. The structure of ozone can be represented by the following resonance contributors:



Ozone and the alkene undergo a concerted cycloaddition reaction—the oxygen atoms add to the two  $sp^2$  carbons in a single step. The addition of ozone to the alkene should remind you of the electrophilic addition reactions of alkenes discussed in Chapter 4. An electrophile adds to one of the  $sp^2$  carbons, and a nucleophile adds to the other. The electrophile is the oxygen at one end of the ozone molecule, and the nucleophile is the oxygen at the other end. The product of ozone addition to an alkene is a

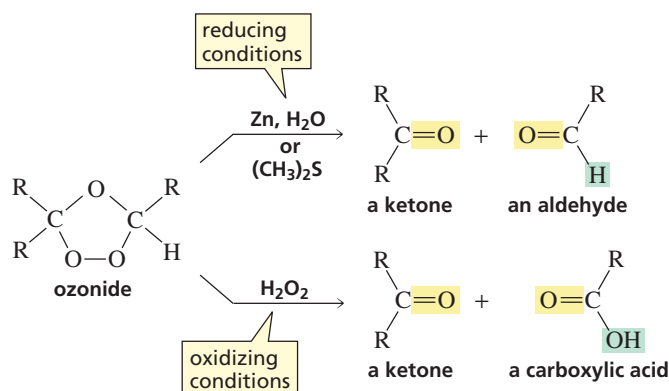
**molozonide.** (The name “molozonide” indicates that one mole of ozone has added to the alkene.) The molozonide is unstable because it has two O—O bonds; it immediately rearranges to a more stable **ozonide**.

**mechanism for ozonide formation**



3-D Molecules:  
Ozone;  
Molozonide;  
Ozonide

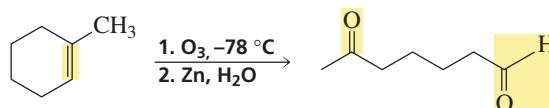
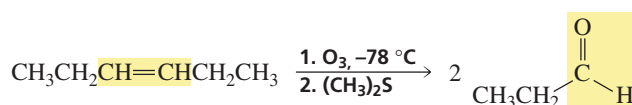
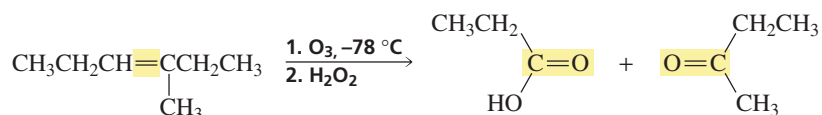
Ozonides are explosive, so they are seldom isolated. In solution, they are easily cleaved to carbonyl compounds. If the ozonide is cleaved in the presence of a reducing agent such as zinc or dimethyl sulfide, the products will be ketones and/or aldehydes. (The product will be a ketone if the  $sp^2$  carbon of the alkene is bonded to two carbon-containing substituents; the product will be an aldehyde if at least one of the substituents bonded to the  $sp^2$  carbon is a hydrogen.) The reducing agent prevents aldehydes from being oxidized to carboxylic acids. Cleaving the ozonide in the presence of zinc or dimethyl sulfide is referred to as “working up the ozonide under reducing conditions.”



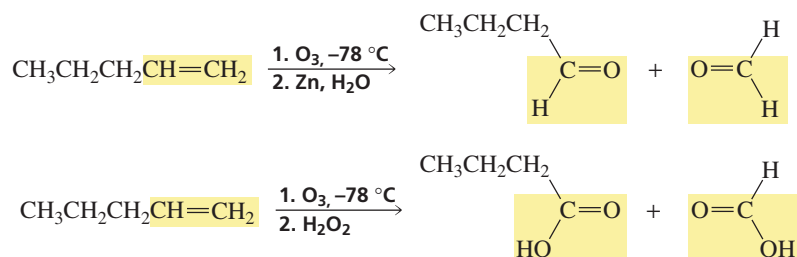
If the ozonide is cleaved in the presence of an oxidizing agent such as hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), the products will be ketones and/or carboxylic acids. Carboxylic acids are formed instead of aldehydes because any aldehyde that is initially formed will be immediately oxidized to a carboxylic acid by hydrogen peroxide. Cleavage in the presence of H<sub>2</sub>O<sub>2</sub> is referred to as “working up the ozonide under oxidizing conditions.”

The following reactions are examples of the oxidative cleavage of alkenes by ozonolysis:

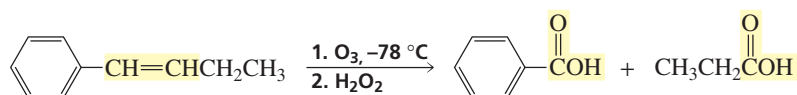
To determine the product of ozonolysis, replace C=C with C=O O=C. If work-up is done under oxidizing conditions, convert any aldehyde products to carboxylic acids.



The one-carbon fragment obtained from the reaction of a terminal alkene with ozone will be oxidized to formaldehyde if the ozonide is worked up under reducing conditions and to formic acid if it is worked up under oxidizing conditions.



Only the side-chain double bond will be oxidized in the following reaction because the stable benzene ring is oxidized only under prolonged exposure to ozone.

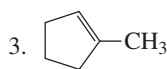
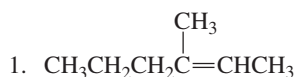
**PROBLEM 22**

Give an example of an alkene that will form the same ozonolysis products, regardless of whether the ozonide is worked up under reducing conditions (Zn, H<sub>2</sub>O) or oxidizing conditions (H<sub>2</sub>O<sub>2</sub>).

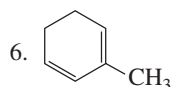
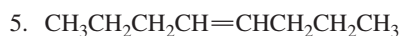
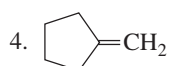
**PROBLEM 23**

Give the products that you would expect to obtain when the following compounds are treated with ozone, followed by work-up with

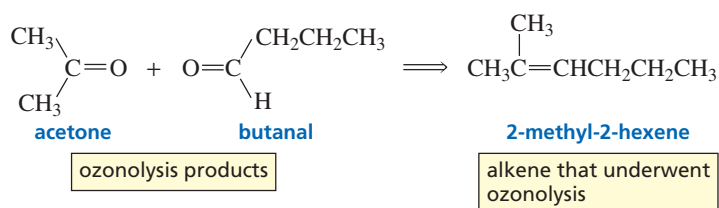
a. Zn, H<sub>2</sub>O:



b. H<sub>2</sub>O<sub>2</sub>:



Ozonolysis can be used to determine the structure of an unknown alkene. If you know what carbonyl compounds are formed by ozonolysis, you can mentally work backward to deduce the structure of the alkene. For example, if ozonolysis of an alkene followed by a work-up under reducing conditions forms acetone and butanal as products, you can conclude that the alkene was 2-methyl-2-hexene.



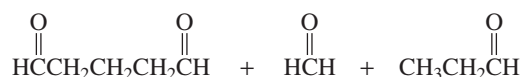
Tutorial:  
Ozonolysis reactions—  
synthesis

**PROBLEM 24**

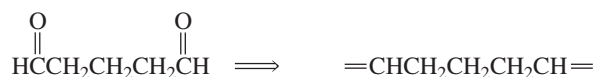
- What alkene would give only acetone as a product of ozonolysis?
- What alkenes would give only butanal as a product of ozonolysis?

**PROBLEM 25 SOLVED**

The following products were obtained from ozonolysis of a diene followed by work-up under reducing conditions. Give the structure of the diene.



**SOLUTION** The five-carbon dicarbonyl compound indicates that the diene must contain five carbons flanked by two double bonds.



One of the carbonyl compounds obtained from ozonolysis has one carbon atom, and the other has three carbon atoms. Therefore, one carbon has to be added to one end of the diene, and three carbons have to be added to the other end.

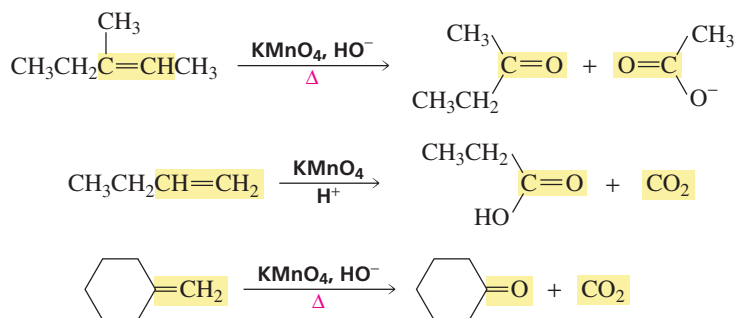
**PROBLEM 26**

What aspect of the structure of the alkene does ozonolysis not tell you?

**Permanganate Cleavage**

We have seen that alkenes are oxidized to 1,2-diols by a basic solution of potassium permanganate at room temperature or below, and the 1,2-diols can subsequently be cleaved by periodic acid to form aldehydes and/or ketones (Sections 20.6 and 20.7). If, however, the basic solution of potassium permanganate is heated or if the solution is acidic, the reaction will not stop at the diol. Instead, the alkene will be cleaved, and the reaction products will be ketones and carboxylic acids. If the reaction is carried out under basic conditions, any carboxylic acid product will be in its basic form ( $\text{RCOO}^-$ ); if the reaction is carried out under acidic conditions, any carboxylic acid product will be in its acidic form ( $\text{RCOOH}$ ) (Section 1.20). Terminal alkenes form  $\text{CO}_2$  as a product.

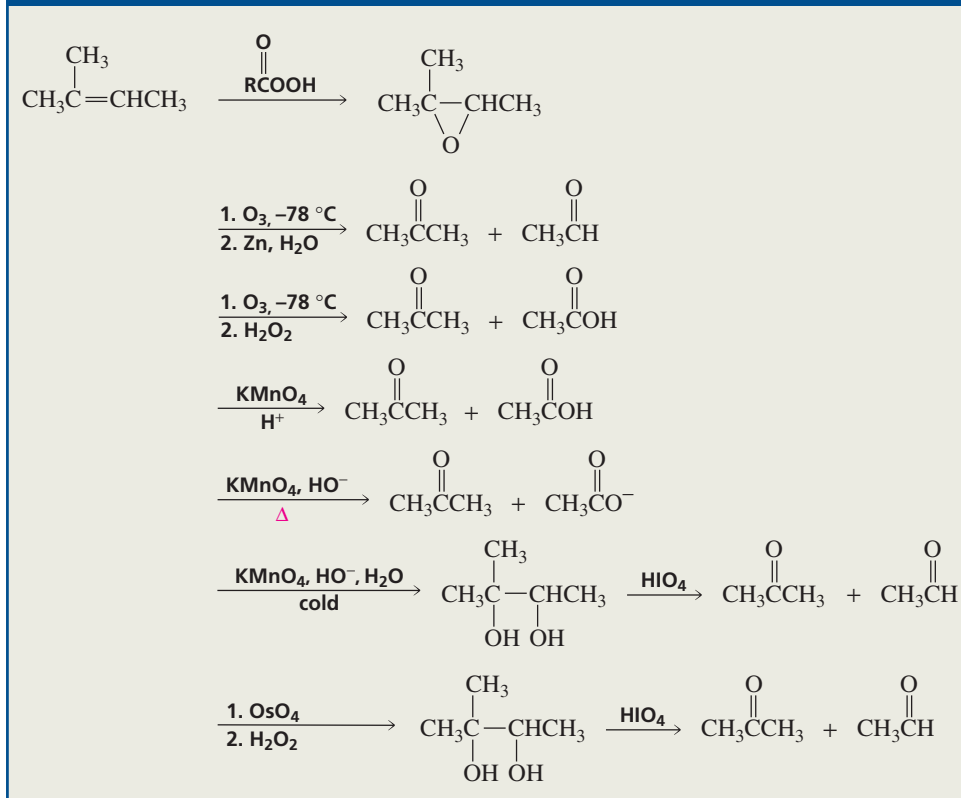
A peroxyacid,  $\text{OsO}_4$ , and (cold basic)  $\text{KMnO}_4$  break only the  $\pi$  bond of the alkene. Ozone and acidic (or hot basic)  $\text{KMnO}_4$  break both the  $\pi$  bond and the  $\sigma$  bond.



The various methods used to oxidize an alkene are summarized in Table 20.1.

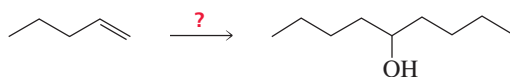


Table 20.1 Summary of the Methods Used to Oxidize an Alkene

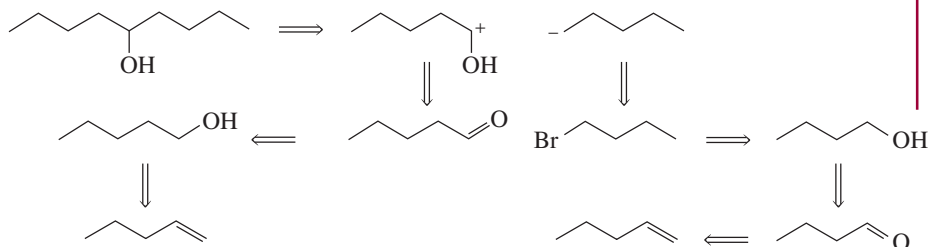


## PROBLEM 27 SOLVED

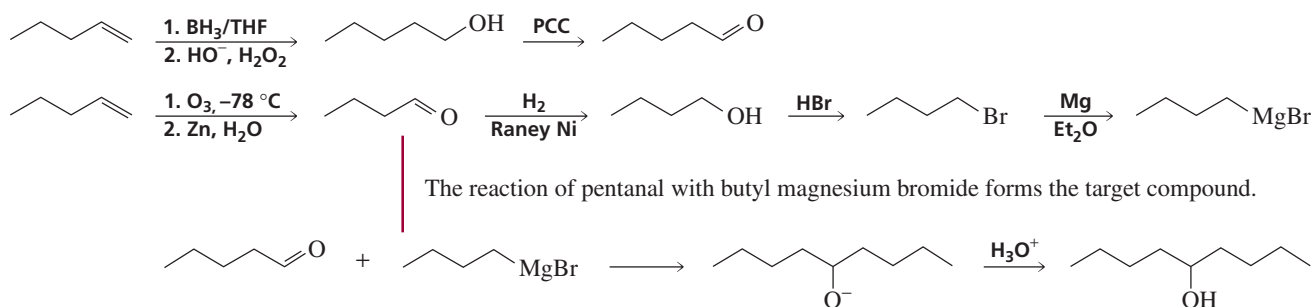
Describe how the following compound could be prepared, using the given starting materials (perform a retrosynthetic analysis to help you arrive at your answer):



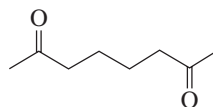
**SOLUTION** Retrosynthetic analysis shows that the target molecule can be disconnected to give a five-carbon positively charged fragment and a four-carbon negatively charged fragment (Section 18.12). Pentanal and a butyl magnesium bromide are the synthetic equivalents for the two fragments. The five-carbon starting material can be converted to the required four-carbon compound by ozonolysis.



Now the synthesis of pentanal and butyl magnesium bromide from the given starting material can be written in the forward direction, including the reagents necessary for the transformations.

**PROBLEM 28**

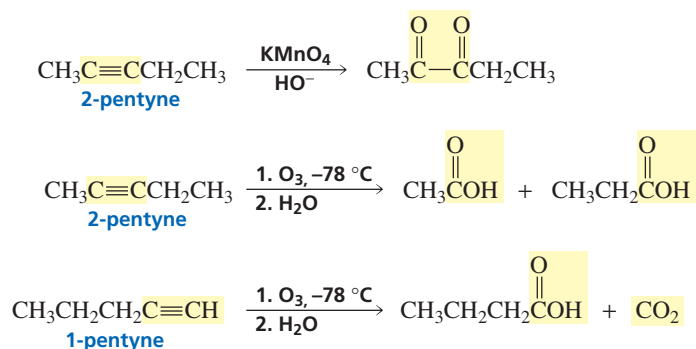
- a. How could you synthesize the following compound from starting materials containing no more than four carbons? (*Hint:* A 1,6-diketone can be synthesized by oxidative cleavage of a 1,2-disubstituted cyclohexene.)



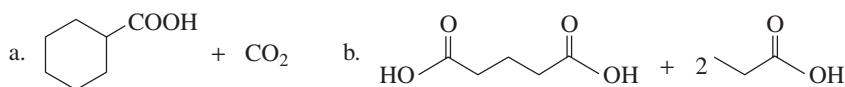
- b. How could you synthesize the same compound in two steps from starting materials containing no more than six carbons?

**20.9 Oxidative Cleavage of Alkynes**

The same reagents that oxidize alkenes also oxidize alkynes. Alkynes are oxidized to diketones by a basic solution of  $\text{KMnO}_4$  at room temperature and are cleaved by ozonolysis to carboxylic acids. Ozonolysis requires neither oxidative nor reductive work-up—it is followed only by hydrolysis. Carbon dioxide is obtained from the  $\text{CH}$  group of a terminal alkyne.

**PROBLEM 29**

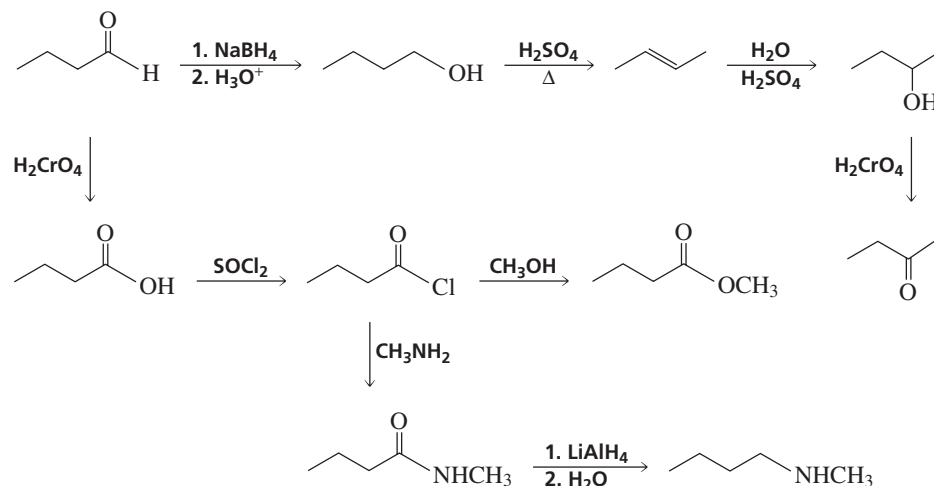
What is the structure of the alkyne that gives each of the following sets of products upon ozonolysis followed by hydrolysis?



## 20.10 Designing a Synthesis VIII: Functional Group Interconversion

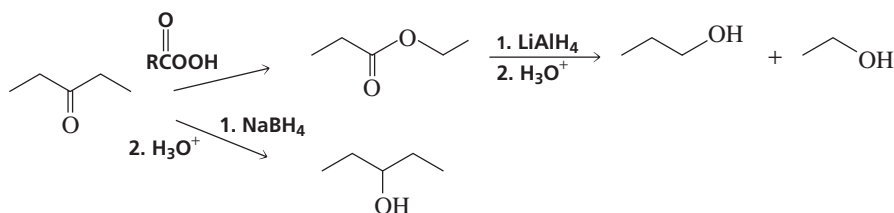


Converting one functional group into another is called **functional group interconversion**. Our knowledge of oxidation–reduction reactions has greatly expanded our ability to carry out functional group interconversions. For example, an aldehyde can be converted into a primary alcohol, an alkene, a secondary alcohol, a ketone, a carboxylic acid, an acyl chloride, an ester, an amide, or an amine.



Tutorial:  
Multistep synthesis

A ketone can be converted into an ester or an alcohol.

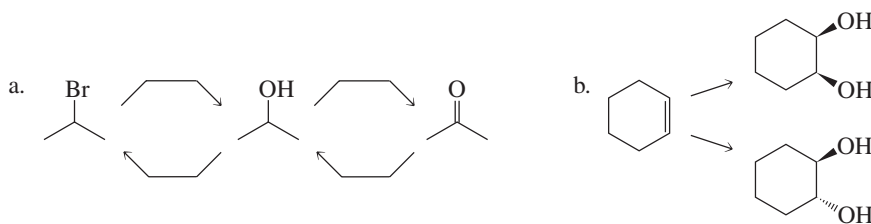


As the number of reactions you learn grows, so will the number of functional group interconversions you can perform. You will also find that you have more than one route available when you design a synthesis. The route you actually decide to use will depend on the availability and cost of the starting materials and on the ease with which the reactions in the synthetic pathway can be carried out.

Tutorial:  
Common terms:  
oxidation–reduction reactions

### PROBLEM 30

Add the necessary reagents over the reaction arrows.

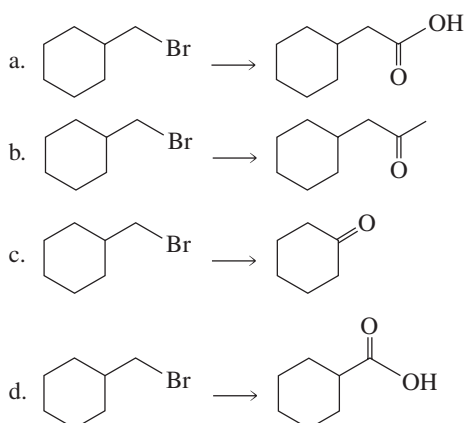


**PROBLEM 31**

- Show two ways to convert an alkyl halide into an alcohol that contains one additional carbon atom.
- Show how a primary alkyl halide can be converted into an amine that contains one additional carbon atom.
- Show how a primary alkyl halide can be converted into an amine that contains one less carbon atom.

**PROBLEM 32**

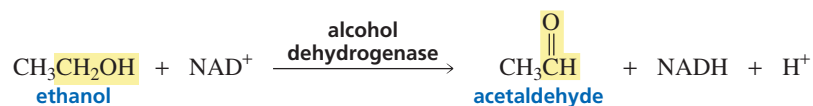
Show how each of the following compounds could be synthesized from the given starting material:

**PROBLEM 33**

How many different functional groups can you use to synthesize a primary alcohol?

**20.11 Biological Oxidation–Reduction Reactions**

Both oxidation reactions and reduction reactions are important in living systems. An example of an oxidation reaction that takes place in animal cells is the oxidation of ethanol to acetaldehyde, a reaction catalyzed by the enzyme alcohol dehydrogenase. Ingestion of a moderate amount of ethanol lowers inhibitions and causes a light-headed feeling, but the physiological effects of acetaldehyde are not as pleasant. Acetaldehyde is responsible for the feeling known as a hangover. (In Section 25.4, we will see how vitamin B<sub>1</sub> can help cure a hangover.)



The enzyme cannot oxidize ethanol to acetaldehyde unless an oxidizing agent is present. Oxidizing agents used by organic chemists, such as chromate and permanganate salts, are not present in living systems. NAD<sup>+</sup> (nicotinamide adenine dinucleotide), the most common oxidizing agent available in living systems, is used by cells to oxidize alcohols to aldehydes (Section 25.2). Notice that NAD<sup>+</sup> is written with a positive charge to reflect the positive charge on the nitrogen atom of the pyridine ring.

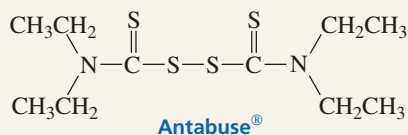
NAD<sup>+</sup> is reduced to NADH when it oxidizes a compound. NADH is used by the cell as a reducing agent. When NADH reduces a compound, it is oxidized back to NAD<sup>+</sup>, which can then be used for another oxidation. Although NAD<sup>+</sup> and NADH are complicated-looking molecules, the structural changes that occur when they act as oxidizing and reducing agents take place on a relatively small part of the molecule. The



## TREATING ALCOHOLICS WITH ANTABUSE

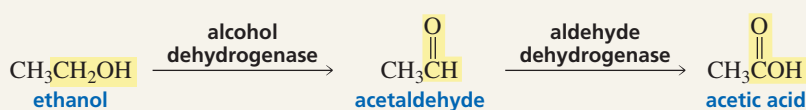
Disulfiram, most commonly known by one of its trade names, Antabuse<sup>®</sup>, is used to treat alcoholics. The drug

causes violently unpleasant effects when ethanol is consumed, even when it is consumed a day or two after Antabuse<sup>®</sup> is taken.

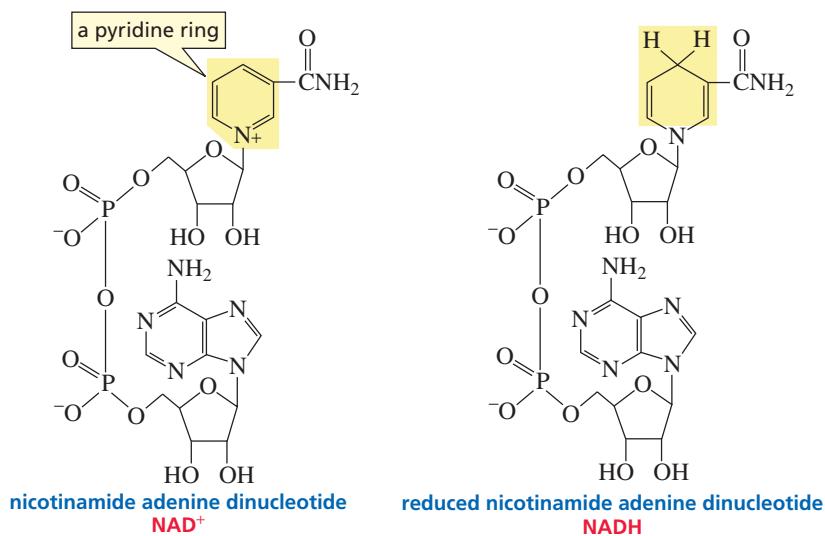


Antabuse<sup>®</sup> inhibits aldehyde dehydrogenase, the enzyme responsible for oxidizing acetaldehyde to acetic acid, resulting in a buildup of acetaldehyde. Acetaldehyde causes the unpleasant physiological effects of intoxication: intense flushing, nausea, dizziness, sweating, throbbing headaches, decreased blood pres-

sure, and, ultimately, shock. Consequently, Antabuse<sup>®</sup> should be taken only under strict medical supervision. In some people, aldehyde dehydrogenase does not function properly. Their symptoms in response to ingesting alcohol are nearly the same as those of individuals who are medicated with Antabuse<sup>®</sup>.

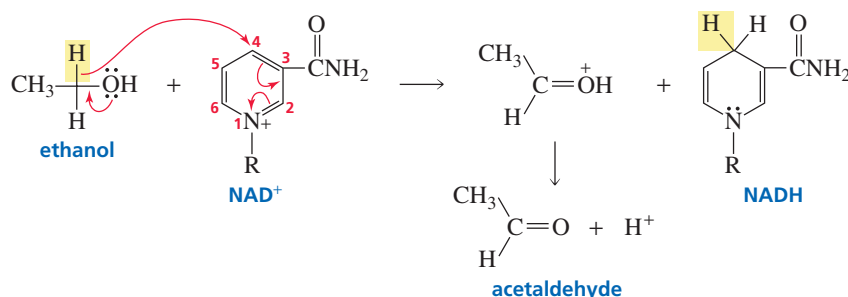


rest of the molecule is used to bind  $\text{NAD}^+$  or  $\text{NADH}$  to the proper site on the enzyme that catalyzes the reaction.

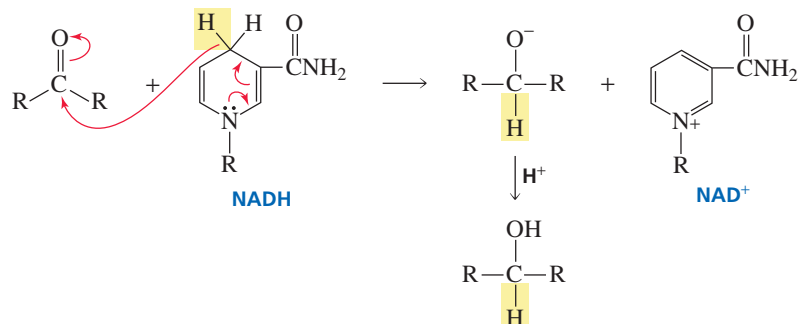


3-D Molecules:  
 $\text{NAD}^+$ ;  $\text{NADH}$

$\text{NAD}^+$  oxidizes a compound by accepting a hydride ion from it. In this way, the number of carbon–hydrogen bonds in the compound decreases (the compound is oxidized) and the number of carbon–hydrogen bonds in  $\text{NAD}^+$  increases ( $\text{NAD}^+$  is reduced).  $\text{NAD}^+$  can accept a hydride ion at the 4-position of the pyridine ring because the electrons can be delocalized onto the positively charged nitrogen atom. Although  $\text{NAD}^+$  could also accept a hydride ion at the 2-position, the hydride ion is always delivered to the 4-position in enzyme-catalyzed reactions.



NADH reduces a compound by donating a hydride ion from the 4-position of the six-membered ring. Thus, NADH,  $\text{NaBH}_4$ , and  $\text{LiAlH}_4$  all act as reducing agents in the same way—they donate a hydride ion.

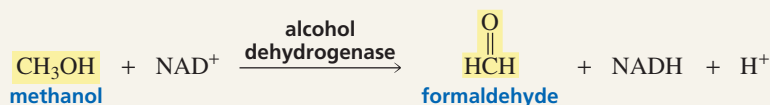


### AN UNUSUAL ANTIDOTE

Alcohol dehydrogenase, the enzyme that catalyzes the oxidation of ethanol to acetaldehyde, catalyzes the oxidation of other alcohols as well. For example, it catalyzes the oxidation of methanol to formaldehyde.

Methanol itself is not harmful, but ingestion of methanol can be fatal because formaldehyde is extremely toxic. The treat-

ment for methanol ingestion consists of giving the patient intravenous injections of ethanol. Alcohol dehydrogenase has 25 times the affinity for ethanol that it has for methanol. Thus, if the enzyme can be kept loaded with ethanol, methanol will be excreted before it has the opportunity to be oxidized.



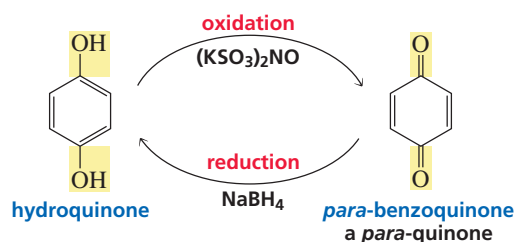
### FETAL ALCOHOL SYNDROME

The damage done to a human fetus when the mother drinks alcohol during her pregnancy is known as *fetal alcohol syndrome*. It has been shown that the harmful effects—growth retardation, decreased mental func-

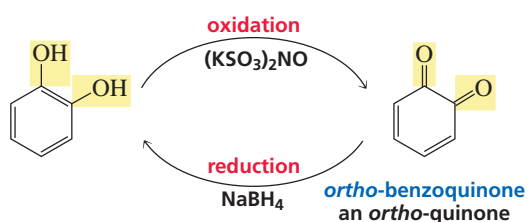
tioning, and facial and limb abnormalities—are attributable to the acetaldehyde that is formed from the oxidation of ethanol, which crosses the placenta and accumulates in the liver of the fetus.

## 20.12 Oxidation of Hydroquinones and Reduction of Quinones

Hydroquinone, a *para*-benzenediol, is easily oxidized to *para*-benzoquinone. Although a wide variety of oxidizing agents can be used, Fremy's salt (dipotassium nitrosodisulfonate) is the preferred oxidizing agent. The quinone can easily be reduced back to hydroquinone.

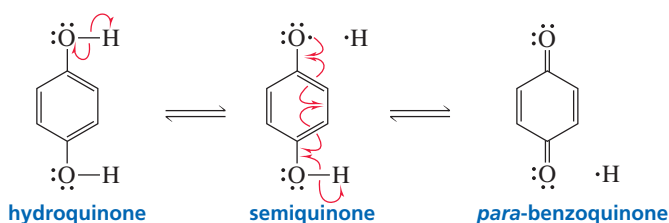


Similarly, *ortho*-benzenediols are oxidized to *ortho*-quinones.



Overall, the oxidation reaction involves the loss of two hydrogen atoms and the reduction reaction involves the gain of two hydrogen atoms. In Section 9.8, we saw that phenols are used as radical inhibitors because of their ability to lose a hydrogen atom.

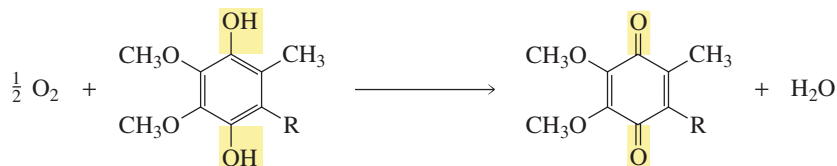
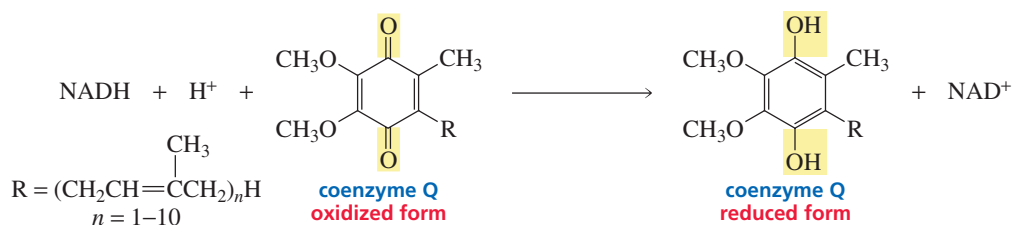
#### mechanism for hydroquinone oxidation–quinone reduction



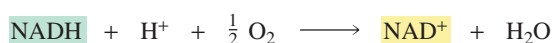
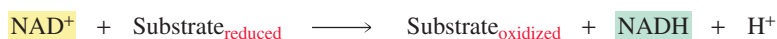
Coenzyme Q (CoQ) is a quinone found in the cells of all aerobic organisms. It is also called ubiquinone because it is ubiquitous (found everywhere) in nature. Its function is to carry electrons in the electron-transport chain. The oxidized form of CoQ accepts a pair of electrons from a biological reducing agent such as NADH and ultimately transfers them to  $O_2$ .



3-D Molecules:  
Coenzyme Q (oxidized form);  
Coenzyme Q (reduced form)



In this way, biological oxidizing agents are recycled:  $\text{NAD}^+$  oxidizes a compound, thereby forming NADH, which is oxidized back to  $\text{NAD}^+$  by oxygen, via coenzyme Q, which is unchanged in the overall reaction. Biological redox reagents and their recycling are discussed further in Sections 25.2 and 25.3.





### THE CHEMISTRY OF PHOTOGRAPHY

Black-and-white photography depends on the fact that hydroquinone is easily oxidized. Photographic film is covered by an emulsion of silver bromide. When light hits the film, the silver bromide is sensitized. Sensitized silver bromide is a better oxidizing agent than silver bromide that has not been exposed to light. When the exposed film is put into a solution of hydroquinone (a common photographic developer), hydro-

quinone is oxidized to quinone by sensitized silver ion and the silver ion is reduced to silver metal, which remains in the emulsion. The exposed film is “fixed” by washing away unsensitized silver bromide with  $\text{Na}_2\text{S}_2\text{O}_3/\text{H}_2\text{O}$ . Black silver deposits are left in regions where light has struck the film. This is the black, opaque part of a photographic negative.

## Summary

Oxidation is coupled with reduction: A **reducing agent** is oxidized and an **oxidizing agent** is reduced. For reactions in which oxidation or reduction has taken place on carbon, if the reaction increases the number of C—H bonds or decreases the number of C—O, C—N, or C—X bonds (where X denotes a halogen), the compound has been reduced; if the reaction decreases the number of C—H bonds or increases the number of C—O, C—N, or C—X bonds, the compound has been oxidized. Similarly, the number of N—H or S—H bonds increases in reduction reactions, and the number of N—O or S—O bonds increases in oxidation reactions. The **oxidation state** of a carbon atom equals the total number of its C—O, C—N, and C—X bonds.

An organic compound is reduced by the addition of  $\text{H}_2$  by one of three mechanisms: **Catalytic hydrogenations** add two hydrogen atoms, **dissolving metal reductions** add two electrons and two protons, and **metal hydride reductions** involve the addition of a hydride ion followed by a proton. Carbon–carbon, carbon–nitrogen, and some carbon–oxygen multiple bonds can be reduced by catalytic hydrogenation. An alkyne is reduced by sodium and liquid ammonia to a trans alkene.  $\text{LiAlH}_4$  is a stronger reducing agent than  $\text{NaBH}_4$ .  $\text{NaBH}_4$  is used to reduce aldehydes, ketones, and acyl halides;  $\text{LiAlH}_4$  is used to reduce carboxylic acids, esters, and amides. Replacing some of the hydrogens of  $\text{LiAlH}_4$  with OR groups decreases the reactivity of the metal hydride. Multiply bonded carbon atoms cannot be reduced by metal hydrides.

Primary alcohols are oxidized to carboxylic acids by chromium-containing reagents and to aldehydes by PCC or a **Swern oxidation**. Secondary alcohols are oxidized to ketones. Tollens reagent can oxidize only aldehydes. A **peroxyacid** oxidizes an aldehyde to a carboxylic acid, a ketone to an ester (in a **Baeyer–Villiger oxidation**), and an alkene to an epoxide. Alkenes are oxidized to 1,2-diols by potassium permanganate ( $\text{KMnO}_4$ ) in a cold basic solution or by osmium tetroxide ( $\text{OsO}_4$ ).

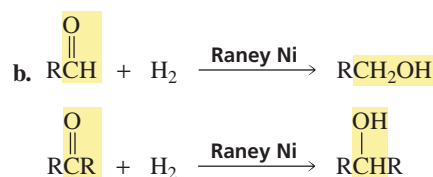
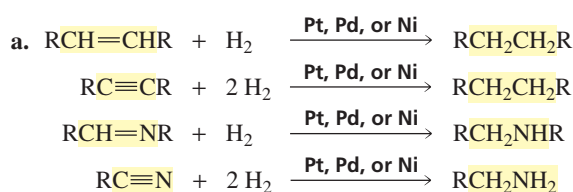
1,2-Diols are **oxidatively cleaved** to ketones and/or aldehydes by periodic acid ( $\text{HIO}_4$ ). Ozonolysis oxidatively cleaves alkenes to ketones and/or aldehydes when worked up under reducing conditions and to ketones and/or carboxylic acids when worked up under oxidizing conditions. Acidic solutions and hot basic solutions of potassium permanganate also oxidatively cleave alkenes to ketones and/or carboxylic acids.

A **chemoselective reaction** is a reaction in which a reagent reacts with one functional group in preference to another. An **enantioselective reaction** forms more of one enantiomer than of another. Converting one functional group into another is called **functional group interconversion**.

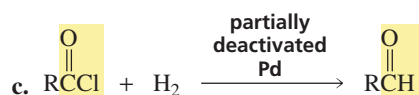
$\text{NAD}^+$  and  $\text{NADH}$  are the most common redox reagents in living systems.  $\text{NAD}^+$  oxidizes a compound by accepting a hydride ion from it;  $\text{NADH}$  reduces a compound by donating a hydride ion to it.

## Summary of Reactions

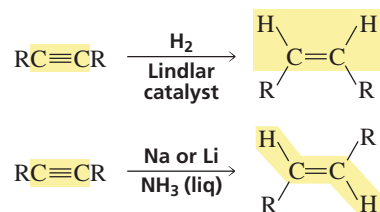
1. Catalytic hydrogenation of double and triple bonds (Section 20.1).



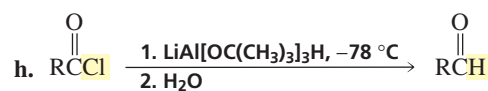
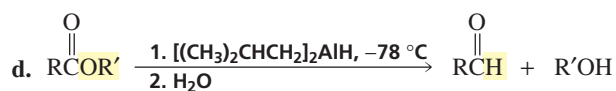
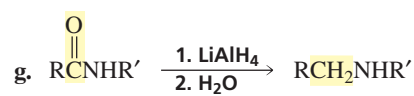
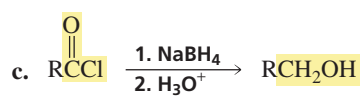
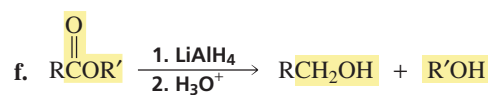
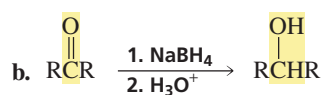
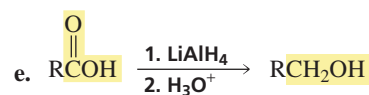
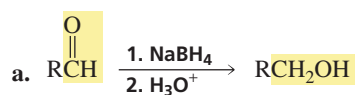




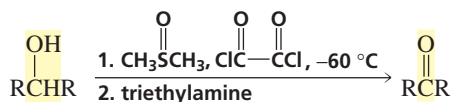
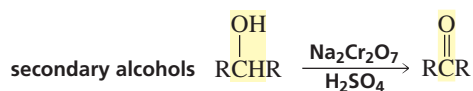
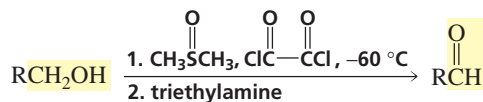
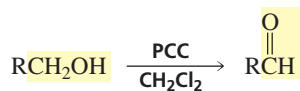
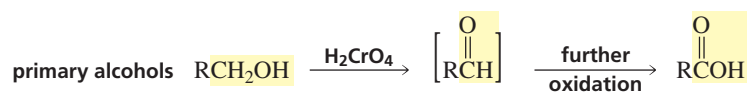
2. Reduction of alkynes to alkenes (Section 20.1).



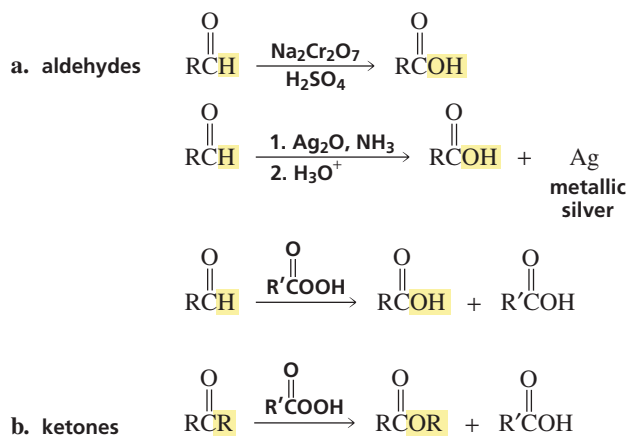
3. Reduction of carbonyl compounds with reagents that donate hydride ion (Section 20.1).



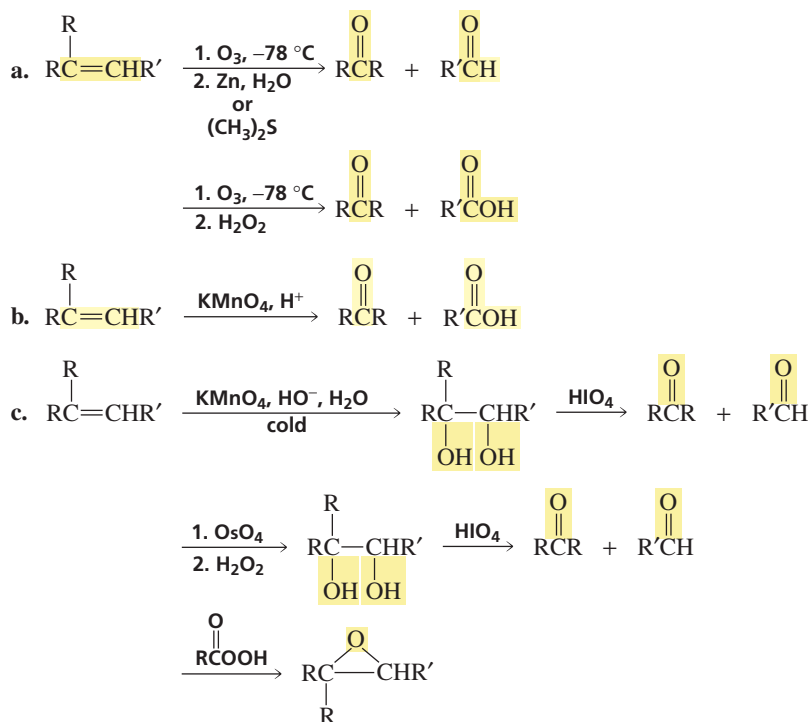
4. Oxidation of alcohols (Section 20.2).



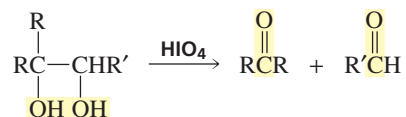
## 5. Oxidation of aldehydes and ketones (Section 20.3).



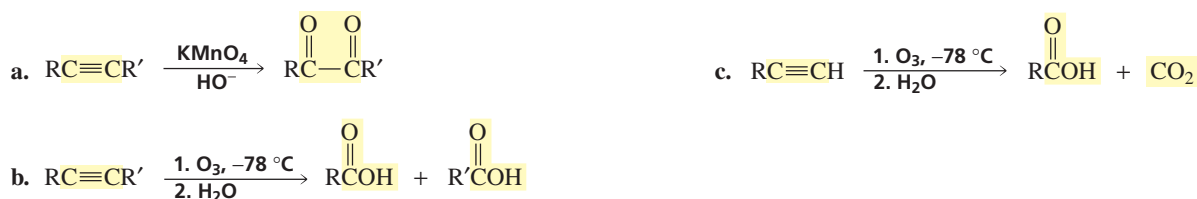
## 6. Oxidation of alkenes (Sections 20.4, 20.6, 20.8).



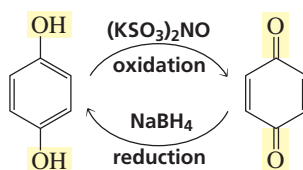
## 7. Oxidation of 1,2-diols (Section 20.7).



## 8. Oxidation of alkynes (Section 20.9).



## 9. Oxidation of hydroquinones and reduction of quinones (Section 20.12).



## Key Terms

Baeyer–Villiger oxidation (p. 853)  
 catalytic hydrogenation (p. 844)  
 chemoselective reaction (p. 848)  
 dissolving-metal reduction (p. 846)  
 enantioselective reaction (p. 857)  
 epoxidation (p. 855)  
 functional group interconversion (p. 867)  
 glycol (p. 858)  
 metal-hydride reduction (p. 846)

molozonide (p. 862)  
 oxidation (p. 842)  
 oxidation–reduction reaction (p. 841)  
 oxidation state (p. 842)  
 oxidative cleavage (p. 860)  
 oxidizing agent (p. 841)  
 ozonide (p. 862)  
 ozonolysis (p. 861)  
 peroxyacid (p. 853)

redox reaction (p. 841)  
 reducing agent (p. 841)  
 reduction (p. 842)  
 Rosenmund reduction (p. 845)  
 Swern oxidation (p. 851)  
 Tollens test (p. 853)  
 vicinal diol (p. 858)  
 vicinal glycol (p. 858)

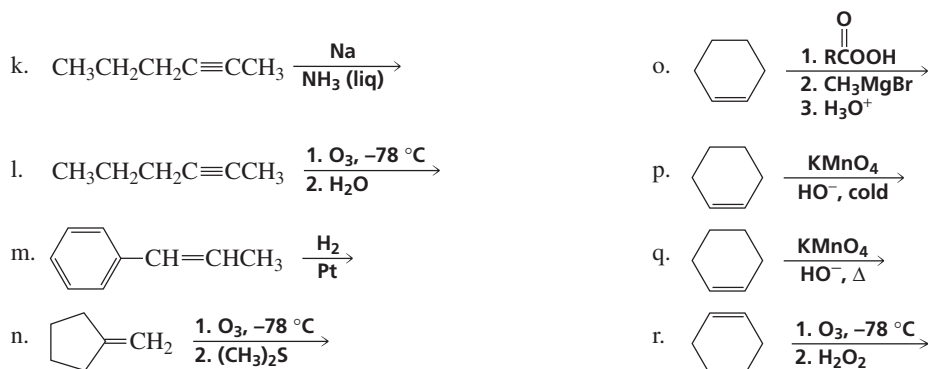
## Problems

34. Fill in the blank with “oxidized” or “reduced.”

- Secondary alcohols are \_\_\_\_\_ to ketones.
- Acyl halides are \_\_\_\_\_ to aldehydes.
- Aldehydes are \_\_\_\_\_ to primary alcohols.
- Alkenes are \_\_\_\_\_ to aldehydes and/or ketones.
- Aldehydes are \_\_\_\_\_ to carboxylic acids.
- Alkenes are \_\_\_\_\_ to 1,2-diols.
- Alkenes are \_\_\_\_\_ to alkanes.

35. Give the products of the following reactions. Indicate whether each reaction is an oxidation or a reduction:

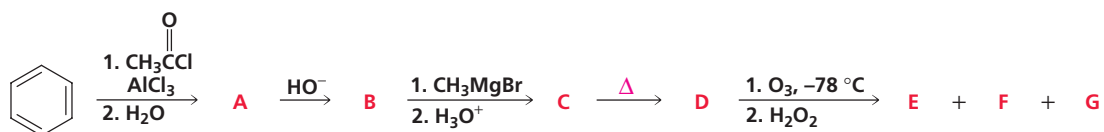
- $$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH} \xrightarrow[\text{H}_2\text{SO}_4]{\text{Na}_2\text{Cr}_2\text{O}_7}$$
- $$\text{C}_6\text{H}_5\text{CH}=\text{CH}_2 \xrightarrow[\text{HO}^-, \Delta]{\text{KMnO}_4}$$
- $$\text{CH}_3\text{CH}_2\text{CH}_2\text{COCl} \xrightarrow[\text{partially deactivated Pd}]{\text{H}_2}$$
- $$\text{CH}_3\text{CH}_2\text{C}\equiv\text{CH} \xrightarrow[4. \text{H}_3\text{O}^+]{1. \text{disiamylborane}, 2. \text{H}_2\text{O}_2, \text{HO}^-, \text{H}_2\text{O}, 3. \text{LiAlH}_4}$$
- $$\text{CH}_3\text{CH}_2\text{CH}=\text{CHCH}_2\text{CH}_3 \xrightarrow[2. \text{Zn}, \text{H}_2\text{O}]{1. \text{O}_3, -78^\circ\text{C}}$$
- $$\text{CH}_3\text{CH}_2\text{CH}_2\text{CONHCH}_3 \xrightarrow[2. \text{H}_2\text{O}]{1. \text{LiAlH}_4}$$
- $$\text{C}_6\text{H}_5\text{CHO} \xrightarrow{\text{RCOOH}}$$
- $$\text{C}_6\text{H}_5\text{COCH}_2\text{CH}_3 \xrightarrow[2. \text{H}_3\text{O}^+]{1. \text{LiAlH}_4}$$
- $$\text{H}_3\text{C}-\text{C}(\text{H})=\text{C}(\text{H})-\text{CH}_3 \xrightarrow{\text{RCOOH}}$$
- $$\text{C}_6\text{H}_5\text{CHO} \xrightarrow[\text{Raney Ni}]{\text{H}_2}$$



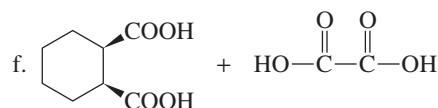
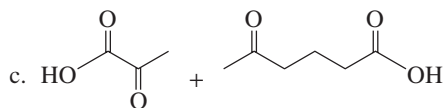
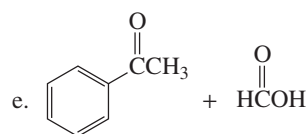
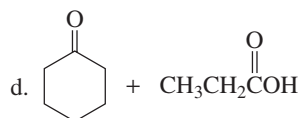
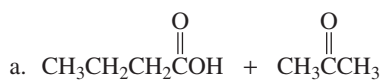
36. How could each of the following compounds be converted to  $\text{CH}_3\text{CH}_2\text{CH}_2\text{COOH}$ ?



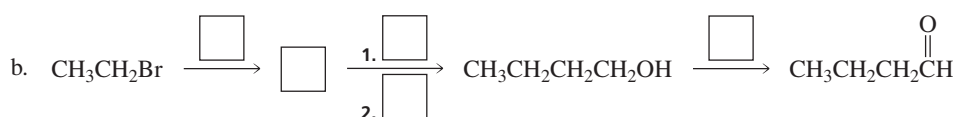
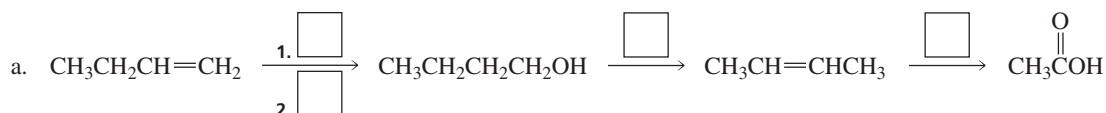
37. Identify A–G:

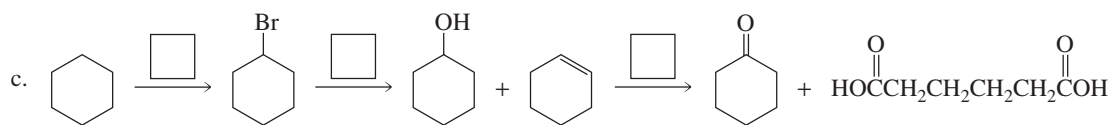


38. Identify the alkene that would give each of the following products upon ozonolysis followed by treatment with hydrogen peroxide:

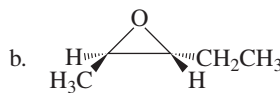
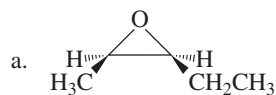


39. Fill in each box with the appropriate reagent:

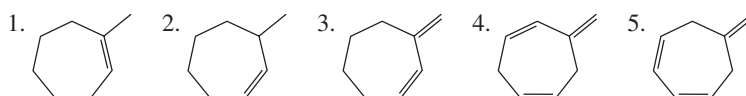




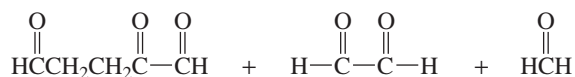
40. Describe how 1-butyne can be converted into each of the following compounds:



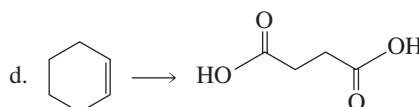
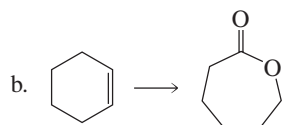
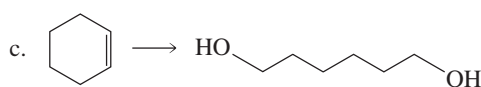
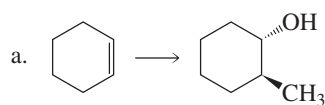
41. a. Give the products obtained from ozonolysis of each of the following compounds, followed by work-up under oxidizing conditions:



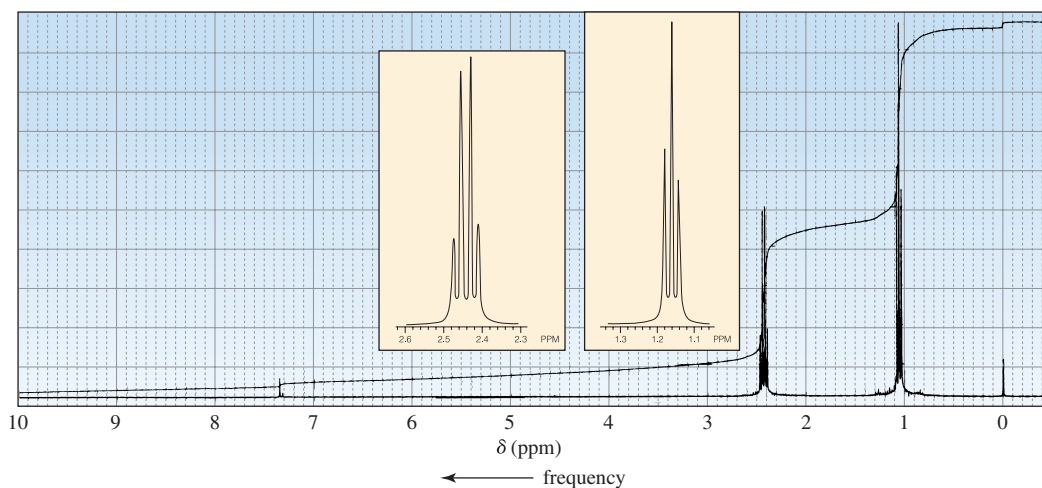
b. What compound would form the following products upon reaction with ozone, followed by work-up under reducing conditions?



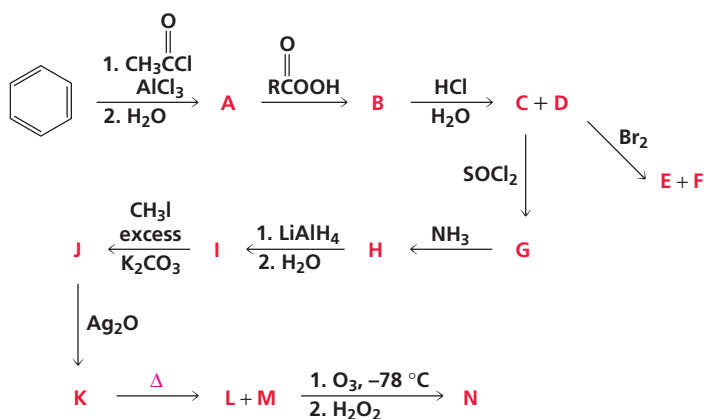
42. Show how each of the following compounds can be prepared from cyclohexene:



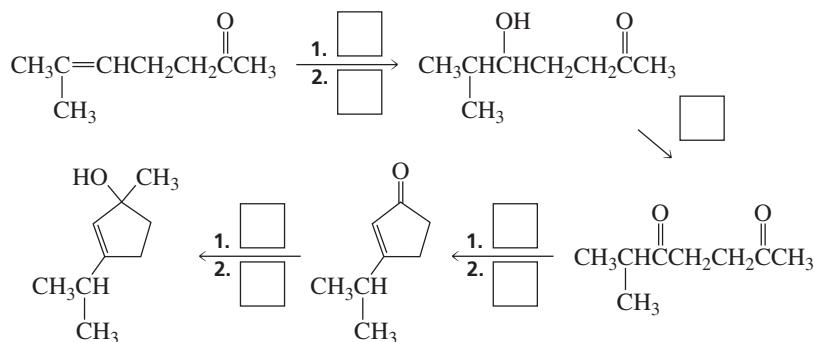
43. The  $^1\text{H}$  NMR spectrum of the product obtained when an unknown alkene reacts with ozone and the ozonolysis product is worked up under oxidizing conditions is shown. Identify the alkene.



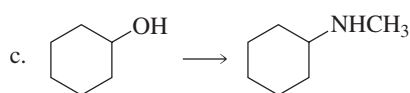
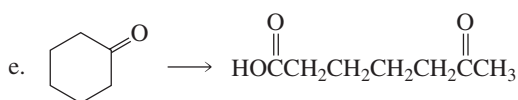
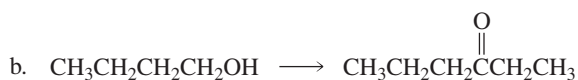
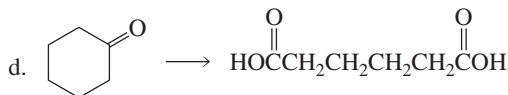
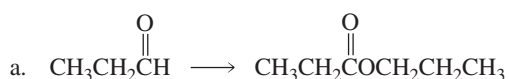
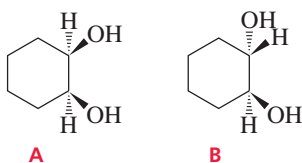
44. Identify A–N:

45. Chromic acid oxidizes 2-propanol six times faster than it oxidizes 2-deuterio-2-propanol. Explain. (*Hint*: See Section 11.7.)

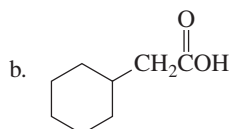
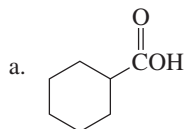
46. Fill in each box with the appropriate reagent:



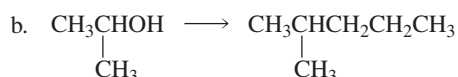
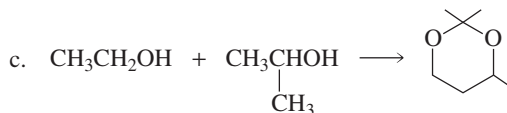
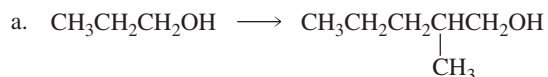
47. Show how each of the following compounds could be prepared, using the given starting material:

48. Upon treatment with ozone followed by work-up with hydrogen peroxide, an alkene forms formic acid and a compound that shows three signals (a singlet, a triplet, and a quartet) in its  $^1\text{H}$  NMR spectrum. Identify the alkene.49. Which of the following compounds would be more rapidly cleaved by  $\text{HIO}_4$ ?

50. Show how cyclohexylacetylene can be converted into each of the following compounds:



51. Show how the following compounds could be synthesized. The only carbon-containing reagents that are available for each synthesis are shown.



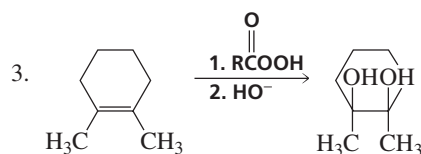
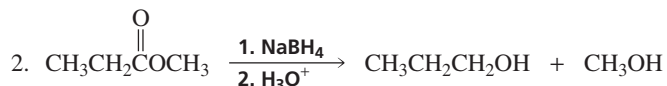
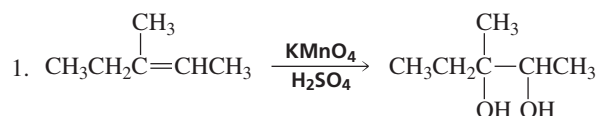
52. The catalytic hydrogenation of 0.5 g of a hydrocarbon at 25 °C consumed about 200 mL of H<sub>2</sub> under 1 atm of pressure. Reaction of the hydrocarbon with ozone, followed by treatment with hydrogen peroxide gave one product, which was found to be a four-carbon carboxylic acid. Identify the hydrocarbon.

53. Tom Thumbs was asked to prepare the following compounds from the given starting materials. The reagents he chose to use for each synthesis are shown.

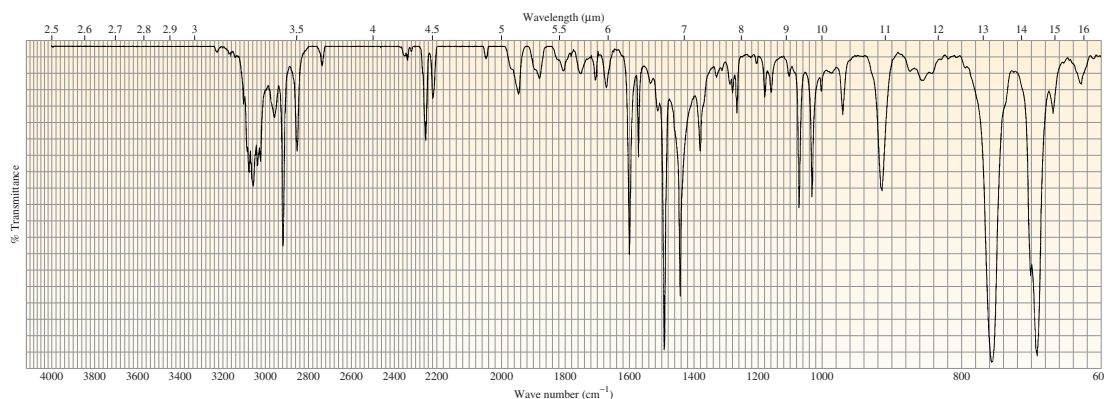
a. Which of his syntheses were successful?

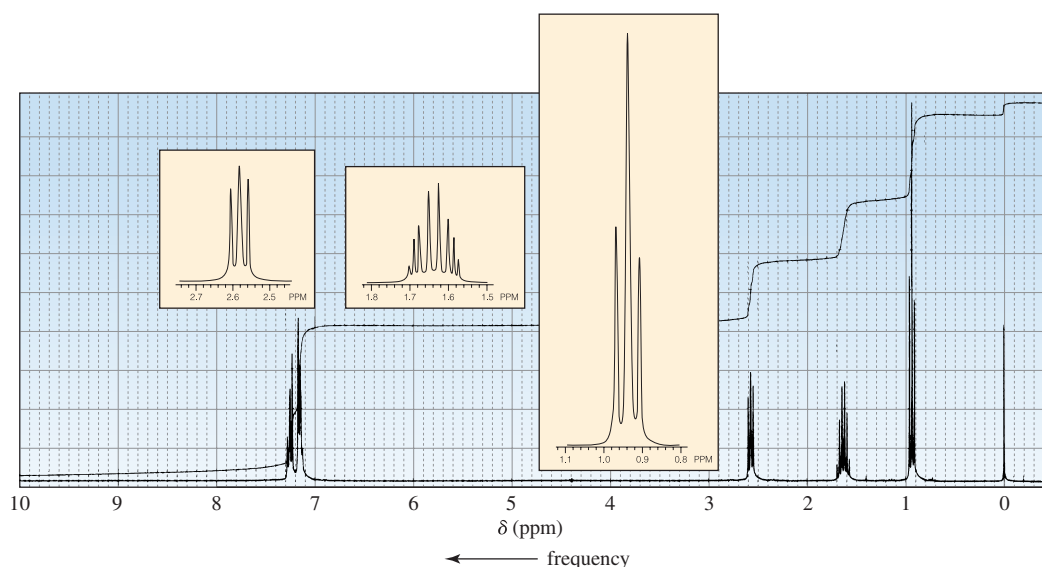
b. What products did he obtain from the other syntheses?

c. In his unsuccessful syntheses, what reagents should he have used to obtain the desired product?

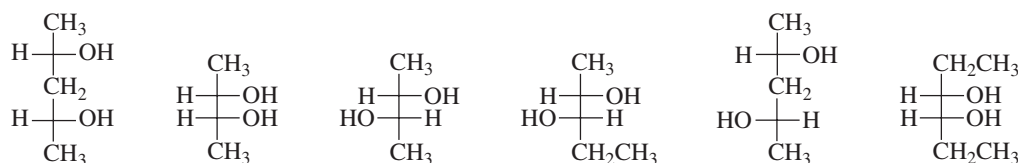


54. The catalytic hydrogenation of compound A formed compound B. The IR spectrum of compound A and the <sup>1</sup>H NMR spectrum of compound B are shown. Identify the compounds.





55. Diane Diol worked for several days to prepare the following compounds:



She labeled them carefully and went to lunch. To her horror, when she returned, she found that the labels had fallen off the bottles and onto the floor. Gladys Glycol, the student at the next bench, told her that the diols could be easily distinguished by two experiments. All Diane had to do was determine which ones were optically active and how many products were obtained when each was treated with periodic acid. Diane did what Gladys suggested and found the following to be true:

1. Compounds A, E, and F are optically active, and B, C, and D are optically inactive.
2. One product is obtained from the reaction of A, B, and D with periodic acid.
3. Two products are obtained from the reaction of F with periodic acid.
4. C and E do not react with periodic acid.

Will Diane be able to distinguish among the six diols and label them from A to F with only the preceding information? Label the structures.

56. Show how propyl propionate could be prepared, using allyl alcohol as the only source of carbon.

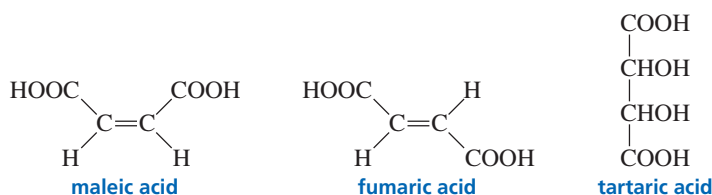
57. Compound A has a molecular formula of  $\text{C}_5\text{H}_{12}\text{O}$  and is oxidized by an acidic solution of sodium dichromate to give compound B, whose molecular formula is  $\text{C}_5\text{H}_{10}\text{O}$ . When compound A is heated with  $\text{H}_2\text{SO}_4$ , C and D are obtained. Considerably more D is obtained than C. Compound C reacts with  $\text{O}_3$ , followed by treatment with  $\text{H}_2\text{O}_2$ , to give two products: formic acid and compound E, whose molecular formula is  $\text{C}_4\text{H}_8\text{O}$ . Compound D reacts with  $\text{O}_3$ , followed by treatment with  $\text{H}_2\text{O}_2$ , to give compound F, whose molecular formula is  $\text{C}_3\text{H}_6\text{O}$ , and compound G, whose molecular formula is  $\text{C}_2\text{H}_4\text{O}_2$ . What are the structures of compounds A through G?

58. A compound forms *cis*-1,2-dimethylcyclopropane when it is reduced with  $\text{H}_2$  and Pd/C. The  $^1\text{H}$  NMR spectrum of the compound shows only two singlets. What is the structure of the compound?

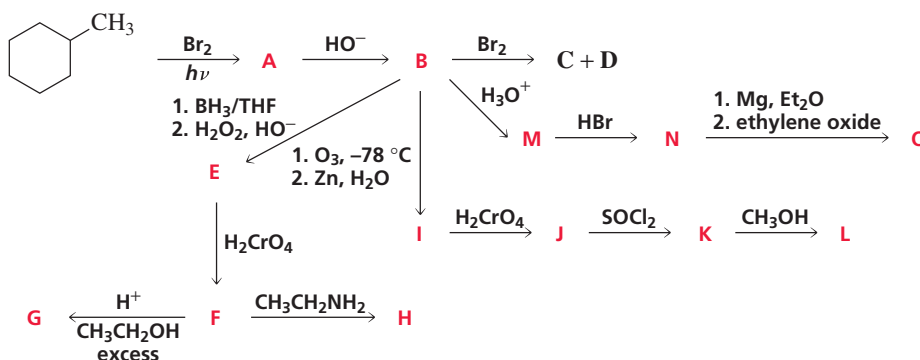
59. Show how you could convert

- |   |   |
|---|---|
| <ol style="list-style-type: none"> <li>a. maleic acid to (2<i>R</i>,3<i>S</i>)-tartaric acid</li> <li>b. fumaric acid to (2<i>R</i>,3<i>S</i>)-tartaric acid</li> </ol> | <ol style="list-style-type: none"> <li>c. maleic acid to (2<i>R</i>,3<i>R</i>)- and (2<i>S</i>,3<i>S</i>)-tartaric acid</li> <li>d. fumaric acid to (2<i>R</i>,3<i>R</i>)- and (2<i>S</i>,3<i>S</i>)-tartaric acid</li> </ol> |
|---|---|

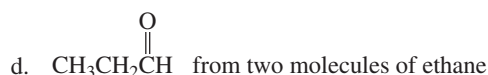
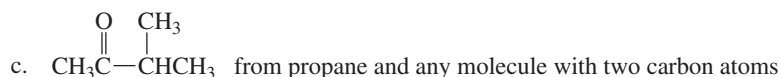
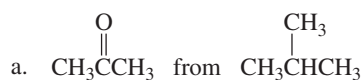




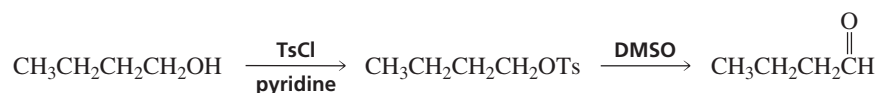
60. Identify A through O:



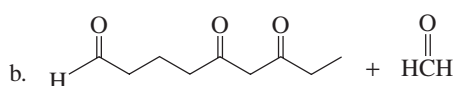
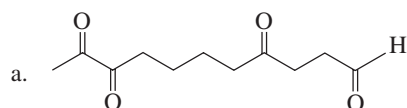
61. Show how the following compounds could be prepared, using only the indicated starting material as the source of carbon:



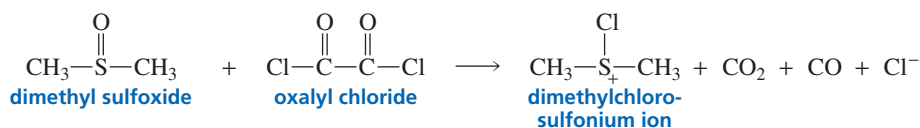
62. A primary alcohol can be oxidized only as far as the aldehyde stage if the alcohol is first treated with tosyl chloride (TsCl) and the resulting tosylate is allowed to react with dimethyl sulfoxide (DMSO). Propose a mechanism for this reaction. (*Hint*: See Section 20.2.)



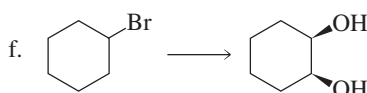
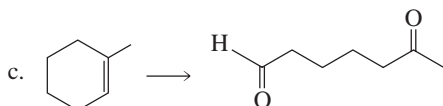
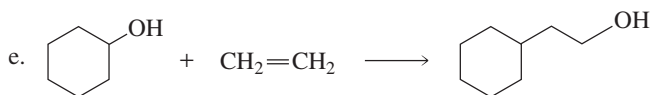
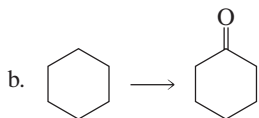
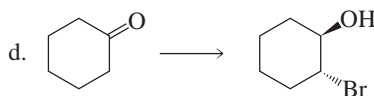
63. Identify the alkene that gives each of the following products upon ozonolysis, followed by treatment with dimethyl sulfide:



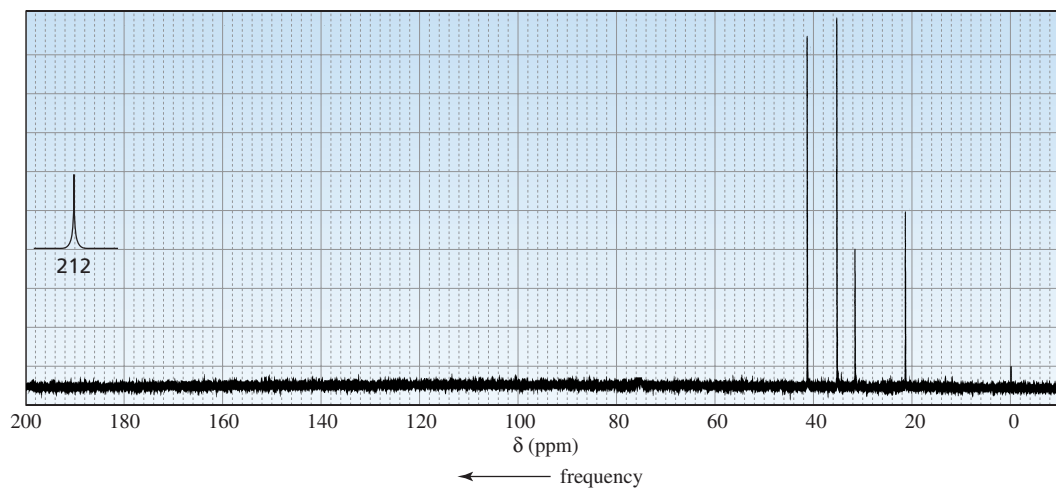
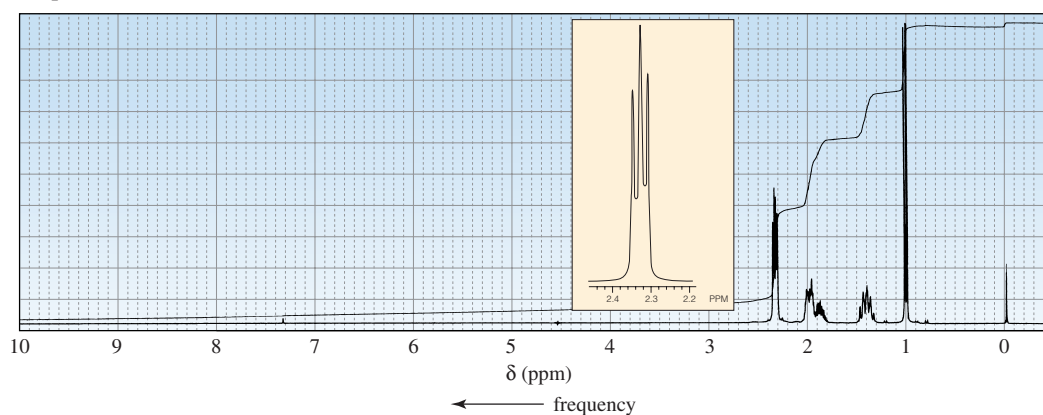
64. Propose a mechanism to explain how dimethyl sulfoxide and oxalyl chloride react to form the dimethylchlorosulfonium ion used as the oxidizing agent in the Swern oxidation.



65. Show how the following compounds could be prepared, using only the indicated starting material as the source of carbon:



66. Terpineol ( $C_{10}H_{18}O$ ) is an optically active compound with one asymmetric carbon. It is used as an antiseptic. Reaction of terpineol with  $H_2/Pt$  forms an optically inactive compound ( $C_{10}H_{20}O$ ). Heating the reduced compound in acid followed by ozonolysis and work-up under reducing conditions produces acetone and a compound whose  $^1H$  NMR and  $^{13}C$  NMR are shown. What is the structure of terpineol?



67. Propose a mechanism for the following enzyme-catalyzed reaction. (*Hint*: Notice that Br is attached to the more substituted carbon.)

