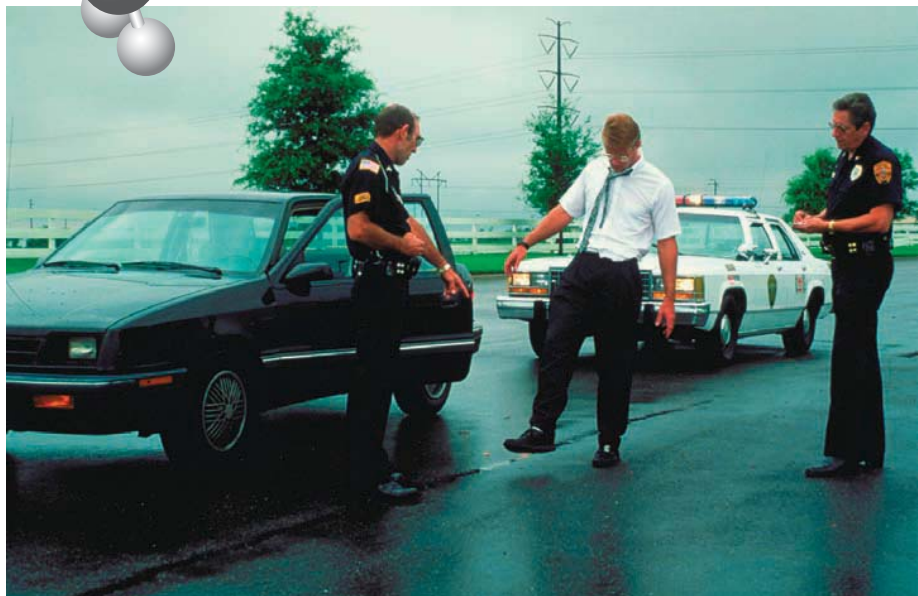
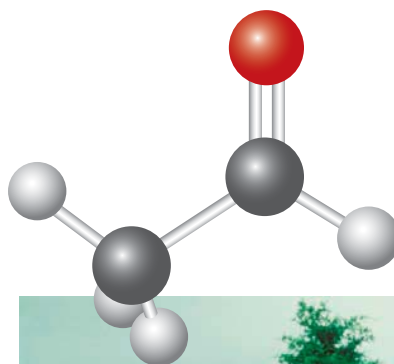


12

Aldehydes and Ketones

Ethanol from alcoholic beverages is first metabolized to acetaldehyde before being broken down further in the body. The reactivity of the carbonyl group of acetaldehyde allows it to bind to proteins in the body, the products of which lead to tissue damage and organ disease. Inset: A model of acetaldehyde. (Novastock/Stock Connection/Glow Images)



KEY QUESTIONS

- 12.1 What Are Aldehydes and Ketones?
- 12.2 How Are Aldehydes and Ketones Named?
- 12.3 What Are the Physical Properties of Aldehydes and Ketones?
- 12.4 What Is the Most Common Reaction Theme of Aldehydes and Ketones?
- 12.5 What Are Grignard Reagents, and How Do They React with Aldehydes and Ketones?
- 12.6 What Are Hemiacetals and Acetals?
- 12.7 How Do Aldehydes and Ketones React with Ammonia and Amines?

- 12.8 What Is Keto–Enol Tautomerism?
- 12.9 How Are Aldehydes and Ketones Oxidized?
- 12.10 How Are Aldehydes and Ketones Reduced?

HOW TO

- 12.1 How to Predict the Product of a Grignard Reaction
- 12.2 How to Determine the Reactants Used to Synthesize a Hemiacetal or Acetal

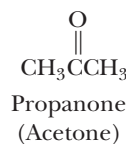
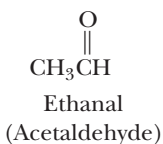
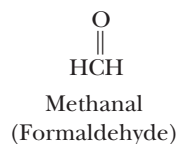
CHEMICAL CONNECTIONS

- 12A A Green Synthesis of Adipic Acid

IN THIS AND several of the following chapters, we study the physical and chemical properties of compounds containing the carbonyl group, $C=O$. Because this group is the functional group of aldehydes, ketones, and carboxylic acids and their derivatives, it is one of the most important functional groups in organic chemistry and in the chemistry of biological systems. The chemical properties of the carbonyl group are straightforward, and an understanding of its characteristic reaction themes leads very quickly to an understanding of a wide variety of organic reactions.

12.1 What Are Aldehydes and Ketones?

The functional group of an **aldehyde** is a carbonyl group bonded to a hydrogen atom (Section 1.7C). In methanal (common name: formaldehyde), the simplest aldehyde, the carbonyl group is bonded to two hydrogen atoms. In other aldehydes, it is bonded to one hydrogen atom and one carbon atom. The functional group of a **ketone** is a carbonyl group bonded to two carbon atoms (Section 1.7C). Following are Lewis structures for the aldehydes methanal and ethanal, and a Lewis structure for propanone, the simplest ketone. Under each in parentheses is its common name:



Aldehyde A compound containing a carbonyl group bonded to hydrogen (a CHO group).

Ketone A compound containing a carbonyl group bonded to two carbons.

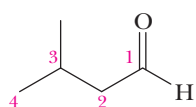
A carbon–oxygen double bond consists of one sigma bond formed by the overlap of sp^2 hybrid orbitals of carbon and oxygen and one pi bond formed by the overlap of parallel $2p$ orbitals. The two nonbonding pairs of electrons on oxygen lie in the two remaining sp^2 hybrid orbitals (Figure 1.20).

12.2 How Are Aldehydes and Ketones Named?

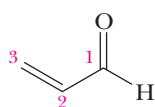
A. IUPAC Nomenclature

The IUPAC system of nomenclature for aldehydes and ketones follows the familiar pattern of selecting the longest chain of carbon atoms that contains the functional group as the parent alkane. We show the aldehyde group by changing the suffix *-e* of the parent alkane to *-al*, as in methanal (Section 3.5). Because the carbonyl group of an aldehyde can appear only at the end of a parent chain and numbering must start with that group as carbon-1, its position is unambiguous; there is no need to use a number to locate it.

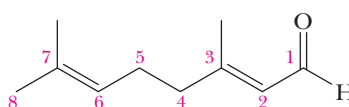
For **unsaturated aldehydes**, the presence of a carbon–carbon double bond is indicated by the infix *-en-*. As with other molecules with both an infix and a suffix, the location of the suffix determines the numbering pattern.



3-Methylbutanal

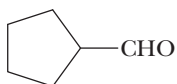


2-Propenal
(Acrolein)

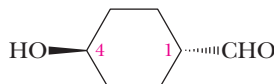


(2*E*)-3,7-Dimethyl-2,6-octadienal
(Geranial)

For cyclic molecules in which —CHO is bonded directly to the ring, we name the molecule by adding the suffix *-carbaldehyde* to the name of the ring. We number the atom of the ring bearing the aldehyde group as number 1:



Cyclopentanecarbaldehyde



trans-4-Hydroxycyclohexanecarbaldehyde



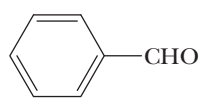
Among the aldehydes for which the IUPAC system retains common names are benzaldehyde and cinnamaldehyde. Note here the alternative ways of writing the phenyl group.

Ken Karp for John Wiley & Sons

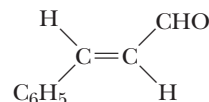
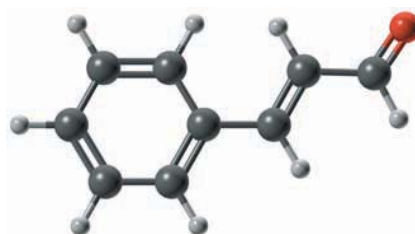


Dihydroxyacetone is the active ingredient in several artificial tanning preparations.

In benzaldehyde it is written as a line-angle formula, and in cinnamaldehyde it is abbreviated C_6H_5- .

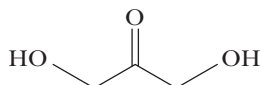


Benzaldehyde

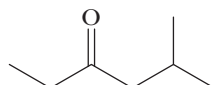
*trans*-3-Phenyl-2-propenal
(Cinnamaldehyde)

Two other aldehydes whose common names are retained in the IUPAC system are formaldehyde and acetaldehyde.

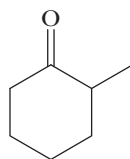
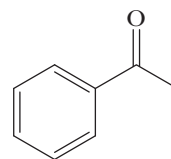
In the IUPAC system, we name ketones by selecting the longest chain that contains the carbonyl group and making that chain the parent alkane. We indicate the presence of the ketone by changing the suffix from *-e* to *-one* (Section 3.5). We number the parent chain from the direction that gives the carbonyl carbon the smaller number. The IUPAC system retains the common names acetophenone and benzophenone:



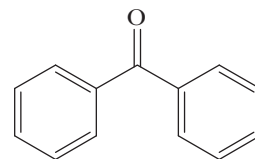
Dihydroxyacetone



5-Methyl-3-hexanone

2-Methyl-
cyclohexanone

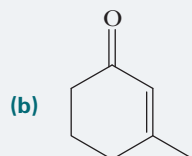
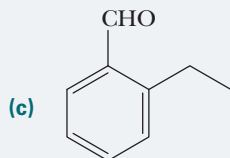
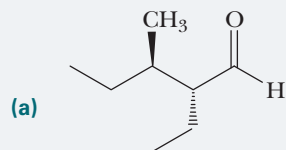
Acetophenone



Benzophenone

EXAMPLE 12.1

Write the IUPAC name for each compound:



STRATEGY

First determine the root name from the longest chain of carbons that contains the carbonyl group. If the carbonyl is an aldehyde, the suffix will be *-al*. If the carbonyl is a ketone, the suffix will be *-one*. Then identify the atoms or groups of

atoms that are not part of that chain of carbons. These are your substituents. If the root name indicates a ring and an aldehyde is bonded to the ring, the suffix *-carbaldehyde* is used. Finally, remember that certain aldehydes and ketones retain their common names in the IUPAC system.

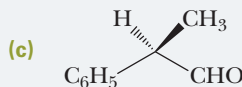
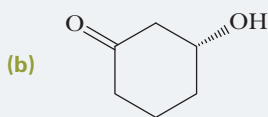
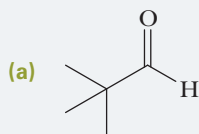
SOLUTION

- The longest chain has six carbons, but the longest chain that contains the carbonyl group has five carbons. The IUPAC name of this compound is (2*R*,3*R*)-2-ethyl-3-methylpentanal.
- Number the six-membered ring beginning with the carbonyl carbon. The IUPAC name of this compound is 3-methyl-2-cyclohexenone.
- This molecule is derived from benzaldehyde. Its IUPAC name is 2-ethylbenzaldehyde.

See problems 12.17, 12.18

PROBLEM 12.1

Write the IUPAC name for each compound:

**EXAMPLE 12.2**

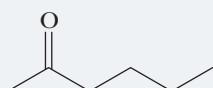
Write structural formulas for all ketones with the molecular formula $C_6H_{12}O$, and give each its IUPAC name. Which of these ketones are chiral?

STRATEGY

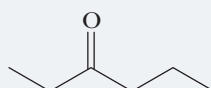
Start with an unbranched carbon skeleton. Place the carbonyl group, one at a time, at each position (except carbon-1). Next, consider branching possibilities, and repeat the process of placing the carbonyl at different positions. A ketone will be chiral if it has one stereocenter or if it has two or more stereocenters and is not superposable on its mirror image.

SOLUTION

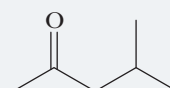
Following are line-angle formulas and IUPAC names for the six ketones with the given molecular formula:



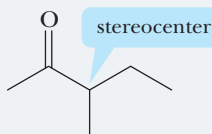
2-Hexanone



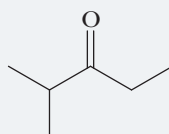
3-Hexanone



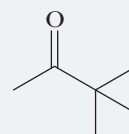
4-Methyl-2-pentanone



3-Methyl-2-pentanone



2-Methyl-3-pentanone



3,3-Dimethyl-2-butanone

Only 3-methyl-2-pentanone has a stereocenter and is chiral.

See problems 12.15, 12.16

PROBLEM 12.2

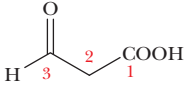
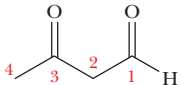
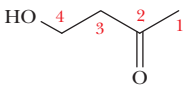
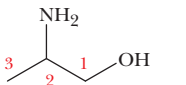
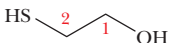
Write structural formulas for all aldehydes with molecular formula $C_6H_{12}O$, and give each its IUPAC name. Which of these aldehydes are chiral?

B. IUPAC Names for More Complex Aldehydes and Ketones

In naming compounds that contain more than one functional group, the IUPAC has established an **order of precedence of functional groups**. Table 12.1 gives the order of precedence for the functional groups we have studied so far.

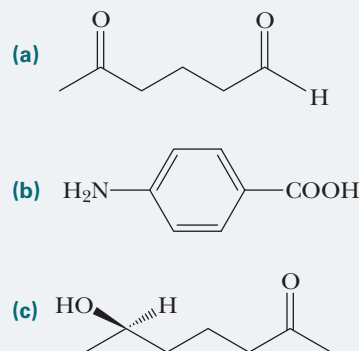
Order of precedence of functional groups A system for ranking functional groups in order of priority for the purposes of IUPAC nomenclature.

TABLE 12.1 Increasing Order of Precedence of Six Functional Groups

Functional Group	Suffix	Prefix	Example of When the Functional Group Has Lower Priority	
Carboxyl	-oic acid	—		
Aldehyde	-al	oxo-	3-Oxopropanoic acid	
Ketone	-one	oxo-	3-Oxobutanal	
Alcohol	-ol	hydroxy-	4-Hydroxy-2-butanone	
Amino	-amine	amino-	2-Amino-1-propanol	
Sulfhydryl	-thiol	mercapto-	2-Mercaptoethanol	

EXAMPLE 12.3

Write the IUPAC name for each compound:

**STRATEGY**

First determine the root name from the longest chain of carbons that contains the carbonyl group. Use the priority rules in Table 12.1 to determine the suffix and prefix. For benzene ring compounds, remember to use any common names that have been retained in the IUPAC system.

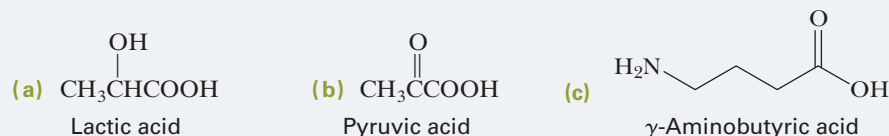
SOLUTION

- (a) An aldehyde has higher precedence than a ketone, so we indicate the presence of the carbonyl group of the ketone by the prefix *oxo*-. The IUPAC name of this compound is 5-oxohexanal.
- (b) The carboxyl group has higher precedence, so we indicate the presence of the amino group by the prefix *amino*-. The IUPAC name is 4-aminobenzoic acid. Alternatively, the compound may be named *p*-aminobenzoic acid, abbreviated PABA. PABA, a growth factor of microorganisms, is required for the synthesis of folic acid.
- (c) The C=O group has higher precedence than the —OH group, so we indicate the —OH group by the prefix *hydroxy*-. The IUPAC name of this compound is (*R*)-6-hydroxy-2-heptanone.

See problems 12.17, 12.18

PROBLEM 12.3

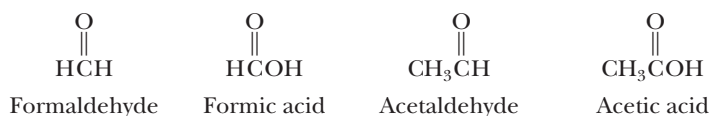
Write IUPAC names for these compounds, each of which is important in intermediary metabolism:



The name shown is the one by which the compound is more commonly known in the biological sciences.

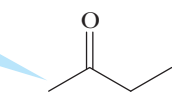
C. Common Names

The common name for an aldehyde is derived from the common name of the corresponding carboxylic acid by dropping the word *acid* and changing the suffix *-ic* or *-oic* to *-aldehyde*. Because we have not yet studied common names for carboxylic acids, we are not in a position to discuss common names for aldehydes. We can, however, illustrate how they are derived by reference to two common names of carboxylic acids with which you are familiar. The name formaldehyde is derived from formic acid, and the name acetaldehyde from acetic acid:

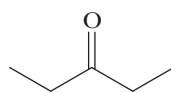


Common names for ketones are derived by naming each alkyl or aryl group bonded to the carbonyl group as a separate word, followed by the word *ketone*. Groups are generally listed in order of increasing atomic weight. (Methyl ethyl ketone, abbreviated MEK, is a common solvent for varnishes and lacquers):

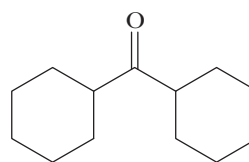
the lower-molecular-weight group bonded to the carbonyl comes first in the common name for a ketone



Methyl ethyl ketone
(MEK)



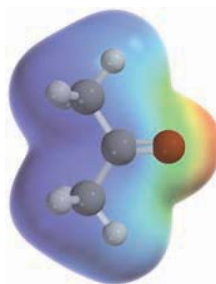
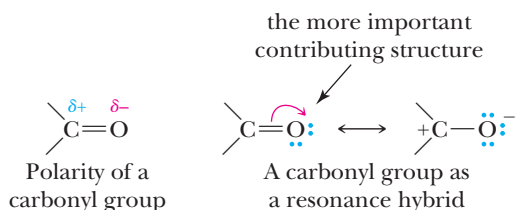
Diethyl ketone



Dicyclohexyl ketone

12.3 What Are the Physical Properties of Aldehydes and Ketones?

Oxygen is more electronegative than carbon (3.5 compared with 2.5; Table 1.4); therefore, a carbon–oxygen double bond is polar, with oxygen bearing a partial negative charge and carbon bearing a partial positive charge:



The electron density model shows that the partial positive charge on an acetone molecule is distributed both on the carbonyl carbon and on the two attached methyl groups as well.

In addition, the resonance structure on the right emphasizes that, in reactions of a carbonyl group, carbon acts as an electrophile and a Lewis acid. The carbonyl oxygen, by contrast, acts as a nucleophile and a Lewis base.

Because of the polarity of the carbonyl group, aldehydes and ketones are polar compounds and interact in the liquid state by dipole–dipole interactions. As a result, aldehydes and ketones have higher boiling points than those of nonpolar compounds with comparable molecular weight.

Table 12.2 lists the boiling points of six compounds of comparable molecular weight. Pentane and diethyl ether have the lowest boiling points of these six compounds. Both butanal and 2-butanone are polar compounds, and because of the intermolecular attraction between carbonyl groups, their boiling points are higher than those of pentane and diethyl ether. Alcohols (Section 8.1C) and carboxylic acids (Section 13.3) are polar compounds, and their molecules associate by hydrogen bonding; their boiling points are higher than those of butanal and 2-butanone, compounds whose molecules cannot associate in that manner.

TABLE 12.2 Boiling Points of Six Compounds of Comparable Molecular Weight

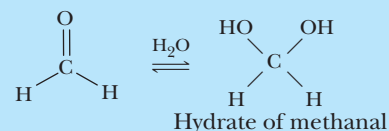
Name	Structural Formula	Molecular Weight	Boiling Point (°C)
Diethyl ether	$\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_3$	74	34
Pentane	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	72	36
Butanal	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CHO}$	72	76
2-Butanone	$\text{CH}_3\text{CH}_2\text{COCH}_3$	72	80
1-Butanol	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$	74	117
Propanoic acid	$\text{CH}_3\text{CH}_2\text{COOH}$	72	141

Because the carbonyl groups of aldehydes and ketones interact with water molecules by hydrogen bonding, low-molecular-weight aldehydes and ketones are more soluble in water than are nonpolar compounds of comparable molecular weight. Table 12.3 lists the boiling points and solubilities in water of several low-molecular-weight aldehydes and ketones.

TABLE 12.3 Physical Properties of Selected Aldehydes and Ketones

IUPAC Name	Common Name	Structural Formula	Boiling Point (°C)	Solubility (g/100 g water)
Methanal	Formaldehyde	HCHO	-21	infinite
Ethanal	Acetaldehyde	CH_3CHO	20	infinite
Propanal	Propionaldehyde	$\text{CH}_3\text{CH}_2\text{CHO}$	49	16
Butanal	Butyraldehyde	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CHO}$	76	7
Hexanal	Caproaldehyde	$\text{CH}_3(\text{CH}_2)_4\text{CHO}$	129	slight
Propanone	Acetone	CH_3COCH_3	56	infinite
2-Butanone	Methyl ethyl ketone	$\text{CH}_3\text{COCH}_2\text{CH}_3$	80	26
3-Pentanone	Diethyl ketone	$\text{CH}_3\text{CH}_2\text{COCH}_2\text{CH}_3$	101	5

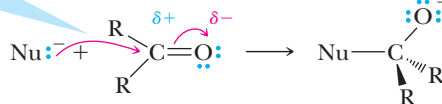
although the “solubilities” of methanal and ethanal are reported as “infinite,” it should be noted that 99% of initial methanal and 57% of initial ethanal are converted to compounds known as hydrates upon addition of water



12.4 What Is the Most Common Reaction Theme of Aldehydes and Ketones?

The partially positive charge on the carbonyl carbon (Section 12.3) is the cause of the most common reaction theme of the carbonyl group, the addition of a nucleophile to form a **tetrahedral carbonyl addition intermediate**. In the following general reaction, the nucleophilic reagent is written as Nu^- to emphasize the presence of its unshared pair of electrons:

this is the common mechanism pattern: **Reaction of a nucleophile and an electrophile to form a covalent bond**



Tetrahedral carbonyl addition intermediate

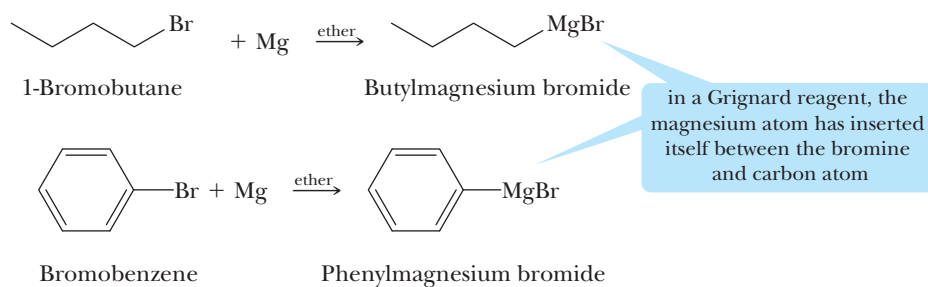
12.5 What Are Grignard Reagents, and How Do They React with Aldehydes and Ketones?

From the perspective of the organic chemist, the addition of carbon nucleophiles is the most important type of nucleophilic addition to a carbonyl group because these reactions form new carbon–carbon bonds. In this section, we describe the preparation and reactions of Grignard reagents and their reaction with aldehydes and ketones.

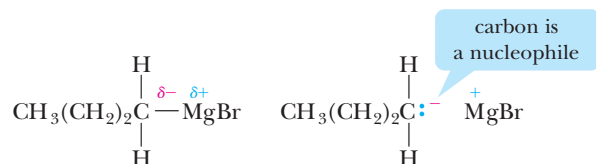
A. Formation and Structure of Organomagnesium Compounds

Alkyl, aryl, and vinylic halides react with Group I, Group II, and certain other metals to form **organometallic compounds**. Within the range of organometallic compounds, organomagnesium compounds are among the most readily available, easily prepared, and easily handled. They are commonly named **Grignard reagents**, after Victor Grignard, who was awarded the 1912 Nobel Prize in Chemistry for their discovery and their application to organic synthesis.

Grignard reagents are typically prepared by the slow addition of a halide to a stirred suspension of magnesium metal in an ether solvent, most commonly diethyl ether or tetrahydrofuran (THF). Organoiodides and bromides generally react rapidly under these conditions, whereas chlorides react more slowly. Butylmagnesium bromide, for example, is prepared by adding 1-bromobutane to an ether suspension of magnesium metal. Aryl Grignards, such as phenylmagnesium bromide, are prepared in a similar manner:



Given that the difference in electronegativity between carbon and magnesium is 1.3 units (2.5 – 1.2), the carbon–magnesium bond is best described as polar covalent, with carbon bearing a partial negative charge and magnesium bearing a partial positive charge. In the structural formula on the right, the carbon–magnesium bond is shown as ionic to emphasize its nucleophilic character. Note that although we can write a Grignard reagent as a **carbanion**, a more accurate representation shows it as a polar covalent compound:



Organometallic compound
A compound containing a carbon–metal bond.

Grignard reagent An organomagnesium compound of the type RMgX or ArMgX.

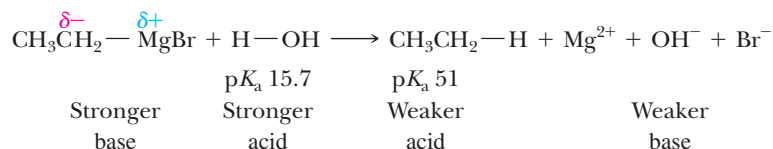
Carbanion An anion in which carbon has an unshared pair of electrons and bears a negative charge.

The feature that makes Grignard reagents so valuable in organic synthesis is that the carbon bearing the halogen is now transformed into a nucleophile.

B. Reaction with Protic Acids

Grignard reagents are very strong bases and react readily with a wide variety of acids (proton donors) to form alkanes. Ethylmagnesium bromide, for example, reacts instantly with

water to give ethane and magnesium salts. This reaction is an example of a stronger acid and a stronger base reacting to give a weaker acid and a weaker base (Section 2.4):



Any compound containing an O—H, N—H, and S—H group or a relatively acidic hydrogen will react with a Grignard reagent by proton transfer. Following are examples of compounds containing those functional groups:

HOH	ROH	ArOH	RCOOH	RNH ₂	RSH	R—C≡C—H
Water	Alcohols	Phenols	Carboxylic acids	Amines	Thiols	Terminal alkynes

Because Grignard reagents react so rapidly with these proton acids, Grignard reagents cannot be made from any halogen-containing compounds that also contain them.

EXAMPLE 12.4

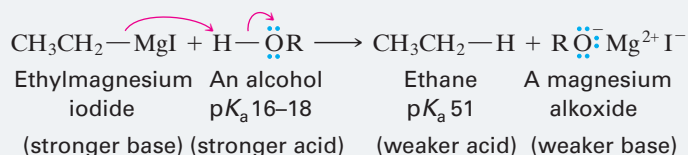
Write an equation for the acid–base reaction between ethylmagnesium iodide and an alcohol. Use curved arrows to show the flow of electrons in this reaction. In addition, show that the reaction is an example of a stronger acid and stronger base reacting to form a weaker acid and weaker base.

STRATEGY

Show the reaction of the Grignard reagent with a generic alcohol (ROH) to form an alkane and a magnesium alkoxide. In drawing the mechanism, remember that the Grignard reagent reacts as a base by donating the electrons in its C—Mg bond to form a new bond to the electrophile (in this case, H⁺).

SOLUTION

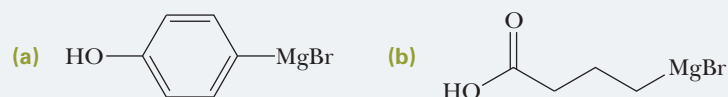
The alcohol is the stronger acid, and ethyl carbanion is the stronger base:

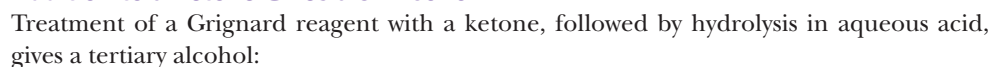


See problems 12.19, 12.21, 12.22

PROBLEM 12.4

Explain how these Grignard reagents react with molecules of their own kind to “self-destruct”:

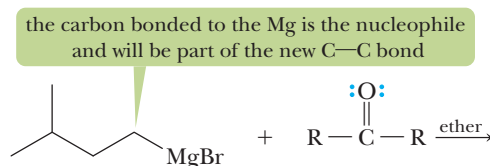




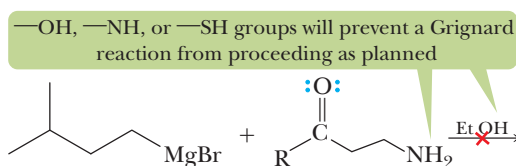
HOW TO 12.1

Predict the Product of a Grignard Reaction

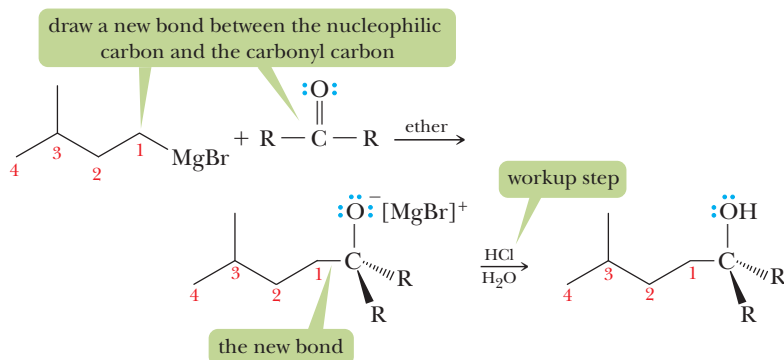
- (a) Using the fact that a Grignard reaction involves the formation of a carbon-carbon bond, identify the nucleophilic carbon (i.e., the carbon bonded to the magnesium atom).



- (b) Check to see that there are no O—H, N—H, or S—H groups in the reagents or solvent. These will undergo proton transfer with the Grignard reagent and prevent the reaction with the carbonyl from occurring.



- (c) Create a new bond between the carbon identified in (a) and the carbonyl carbon. The nucleophilic carbon from the Grignard reagent will no longer be bonded to MgBr. Instead, the MgBr should be shown to be ionically coordinated with the negatively charged oxygen that was part of the carbonyl. If there is a workup step, the magnesium salt is converted to an alcohol.



EXAMPLE 12.5

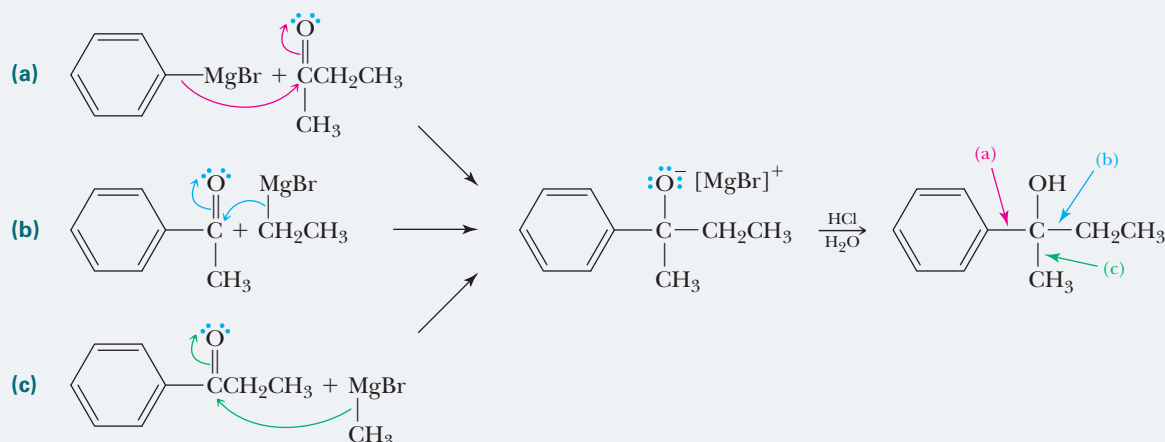
2-Phenyl-2-butanol can be synthesized by three different combinations of a Grignard reagent and a ketone. Show each combination.

STRATEGY

The Grignard reagent used to synthesize any alcohol can be determined by identifying a C—C bond connecting the alcohol carbon to the continuing carbon chain. Remove this bond, convert the C—OH to C=O, and convert the other piece to a Grignard reagent.

SOLUTION

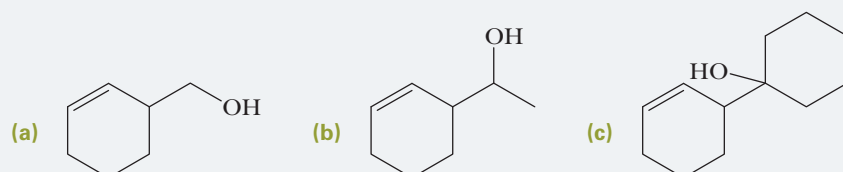
Curved arrows in each solution show the formation of the new carbon–carbon bond and the alkoxide ion, and labels on the final product show which set of reagents forms each bond:



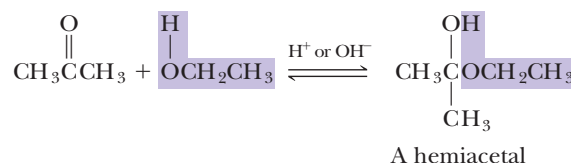
See problems 12.21, 12.22

PROBLEM 12.5

Show how these three compounds can be synthesized from the same Grignard reagent:

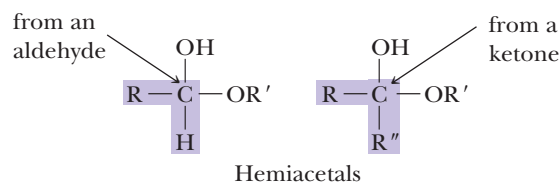
**12.6 What Are Hemiacetals and Acetals?****A. Formation of Acetals**

The addition of a molecule of alcohol to the carbonyl group of an aldehyde or a ketone forms a **hemiacetal** (a half-acetal). This reaction is catalyzed by both acid and base: Oxygen adds to the carbonyl carbon and hydrogen adds to the carbonyl oxygen:



Hemiacetal A molecule containing an —OH and an —OR or —OAr group bonded to the same carbon.

The functional group of a hemiacetal is a carbon bonded to an —OH group and an —OR or —OAr group:

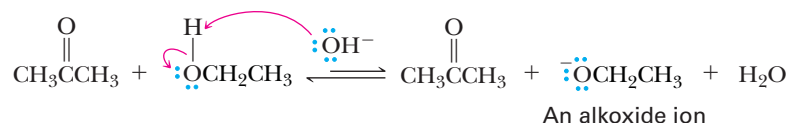


The mechanism for the base-catalyzed conversion of an aldehyde or a ketone to a hemiacetal can be divided into three steps. Note that the base OH^- is a true catalyst in this reaction; it is used in Step 1, but a replacement OH^- is generated in Step 3.

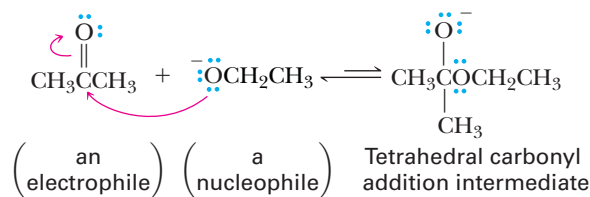
Mechanism

Base-Catalyzed Formation of a Hemiacetal

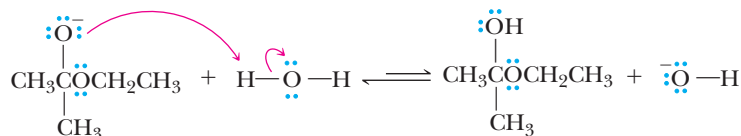
STEP 1: Take a proton away. Proton transfer from the alcohol to the base gives an alkoxide ion:



STEP 2: Reaction of an electrophile and a nucleophile to form a new covalent bond. Addition of the alkoxide ion to the carbonyl gives a tetrahedral carbonyl addition intermediate:



STEP 3: Add a proton. Proton transfer from water to the tetrahedral carbonyl addition intermediate gives the hemiacetal and regenerates the hydroxide ion catalyst:

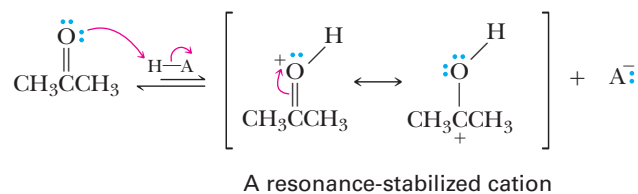


The mechanism for the acid-catalyzed conversion of an aldehyde or ketone to a hemiacetal can be divided into three steps. Note that the acid $\text{H}-\text{A}$ is a true catalyst in this reaction; it is used in Step 1, but a replacement $\text{H}-\text{A}$ is generated in Step 3.

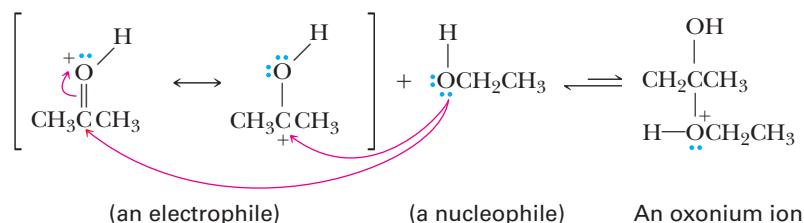
Mechanism

Acid-Catalyzed Formation of a Hemiacetal

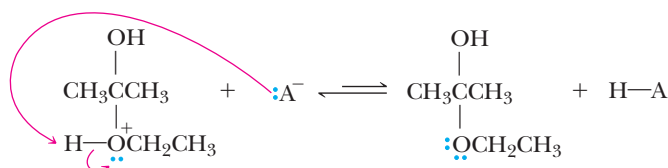
STEP 1: Add a proton. Proton transfer from $\text{H}-\text{A}$ to the carbonyl gives a resonance-stabilized cation. The more significant resonance structure places the positive charge on the carbon:



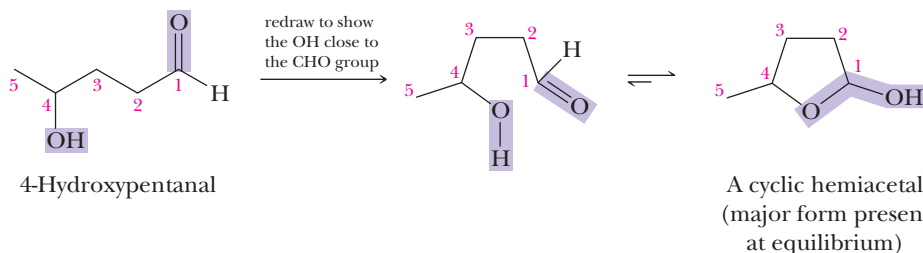
STEP 2: Reaction of an electrophile and a nucleophile to form a new covalent bond. Addition of the alcohol to the resonance-stabilized cation gives an oxonium ion. *Note:* The attack of the alcohol can be to either contributing structure:



STEP 3: Take a proton away. Proton transfer from the oxonium ion to A^- gives the hemiacetal and regenerates the acid catalyst:

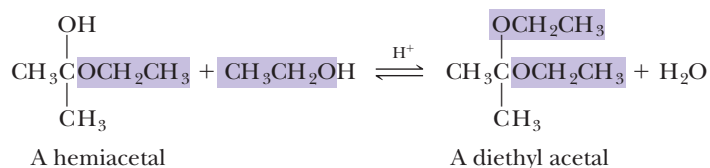


Hemiacetals are generally unstable and are only minor components of an equilibrium mixture, except in one very important type of molecule. When a hydroxyl group is part of the same molecule that contains the carbonyl group, and a five- or six-membered ring can form, the compound exists almost entirely in a cyclic hemiacetal form:



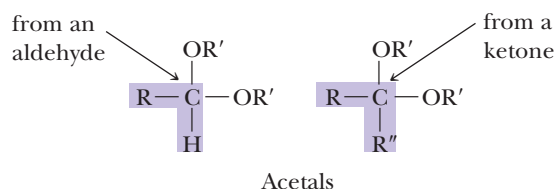
We shall have much more to say about cyclic hemiacetals when we consider the chemistry of carbohydrates in Chapter 17.

Hemiacetals can react further with alcohols to form **acetals** plus a molecule of water. This reaction is acid catalyzed:



Acetal A molecule containing two $—OR$ or $—OAr$ groups bonded to the same carbon.

The functional group of an acetal is a carbon bonded to two $—OR$ or $—OAr$ groups:

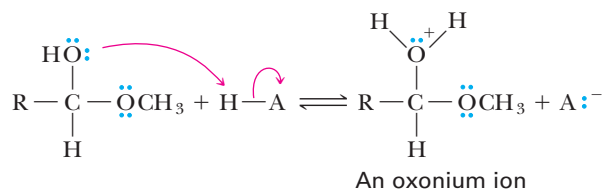


The mechanism for the acid-catalyzed conversion of a hemiacetal to an acetal can be divided into four steps. Note that acid $H-A$ is a true catalyst in this reaction; it is used in Step 1, but a replacement $H-A$ is generated in Step 4.

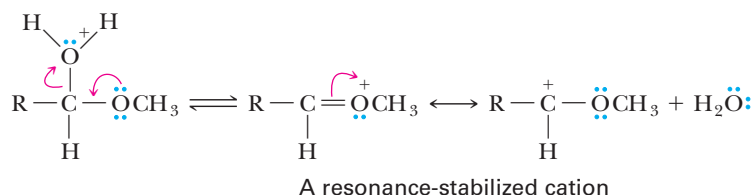
Mechanism

Acid-Catalyzed Formation of an Acetal

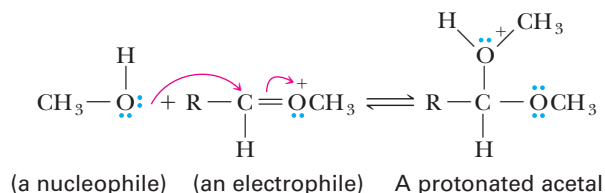
STEP 1: Add a proton. Proton transfer from the acid, $\text{H}-\text{A}$, to the hemiacetal OH group gives an oxonium ion:



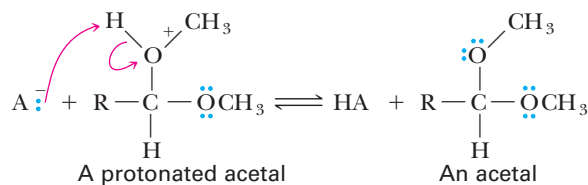
STEP 2: Break a bond to form a stable ion or molecule. Loss of water from the oxonium ion gives a resonance-stabilized cation:



STEP 3: Reaction of an electrophile and a nucleophile to form a new covalent bond. Reaction of the resonance-stabilized cation (an electrophile) with methanol (a nucleophile) gives the conjugate acid of the acetal:



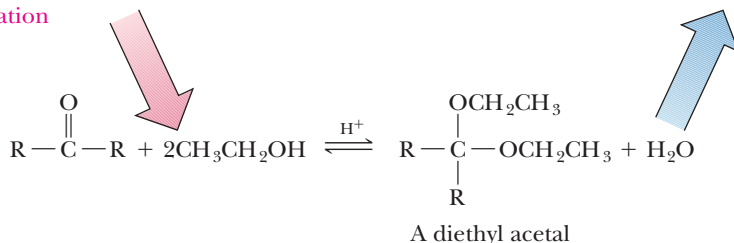
STEP 4: Take a proton away. Proton transfer from the protonated acetal to A^- gives the acetal and generates a new molecule of $\text{H}-\text{A}$, the acid catalyst:



Formation of acetals is often carried out using the alcohol as a solvent and dissolving either dry HCl (hydrogen chloride) or arenesulfonic acid (Section 9.6B), ArSO_3H , in the alcohol. Because the alcohol is both a reactant and the solvent, it is present in large molar excess, which drives the reaction to the right and favors acetal formation. Alternatively, the reaction may be driven to the right by the removal of water as it is formed:

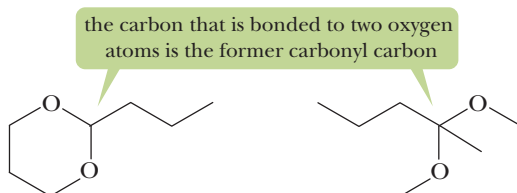
An excess of alcohol pushes the equilibrium toward acetal formation

Removal of water favors acetal formation

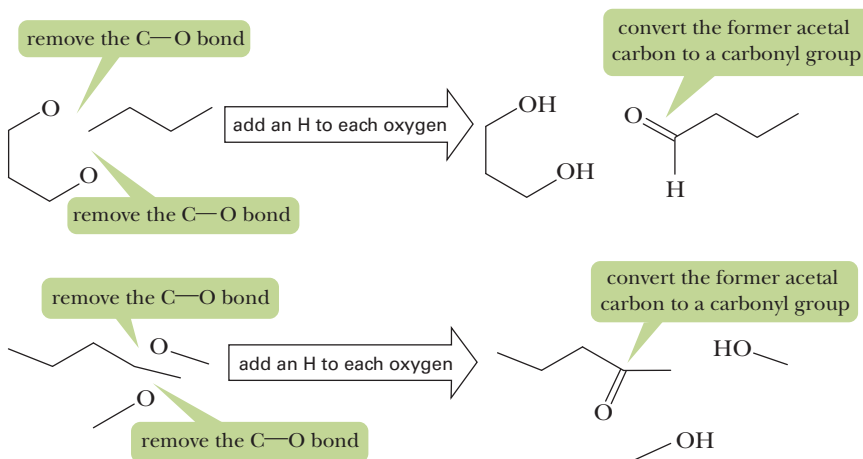


Determine the Reactants Used to Synthesize a Hemiacetal or Acetal

- (a) Identify the carbon atom that is bonded to two oxygen atoms. This carbon atom is the carbonyl carbon that was converted to the carbon of the acetal or hemiacetal group.

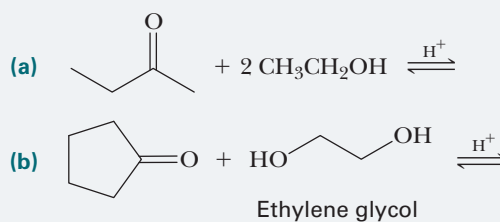


- (b) Remove both C—O bonds and add back a hydrogen to each oxygen to obtain the alcohol reagent(s) used. Then convert the carbon identified in (a) to a carbonyl group.



EXAMPLE 12.6

Show the reaction of the carbonyl group of each ketone with one molecule of alcohol to form a hemiacetal and then with a second molecule of alcohol to form an acetal (note that, in part (b), ethylene glycol is a diol, and one molecule of it provides both —OH groups):



STRATEGY

In forming the hemiacetal, one molecule of the alcohol is added to the carbonyl carbon, resulting in an OR group and an OH group bonded to the carbon that was previously part of the carbonyl. In forming an acetal, two molecules of the alcohol are added to the carbonyl carbon, resulting in two OR groups bonded to the carbon that was previously part of the carbonyl.

See problems 12.23–12.26

PROBLEM 12.6

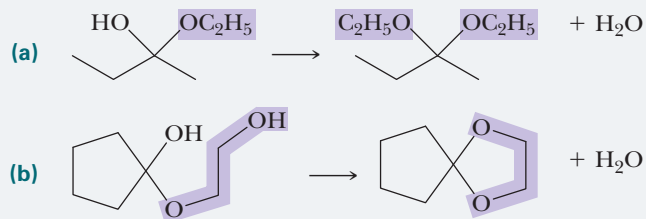
The hydrolysis of an acetal forms an aldehyde or a ketone and two molecules of alcohol. Following are structural formulas for three acetals:



Draw the structural formulas for the products of the hydrolysis of each in aqueous acid (i.e., provide the carbonyl compound and alcohol(s) from which each acetal was derived).

SOLUTION

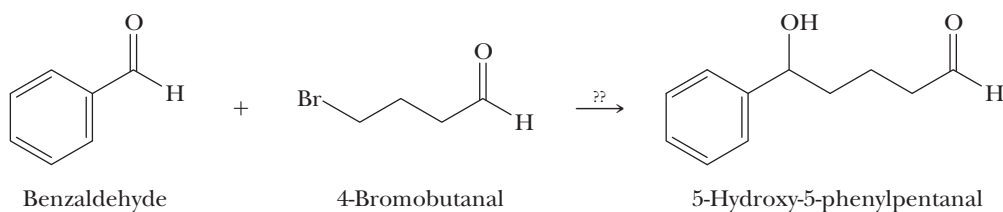
Here are structural formulas of the hemiacetal and then the acetal:



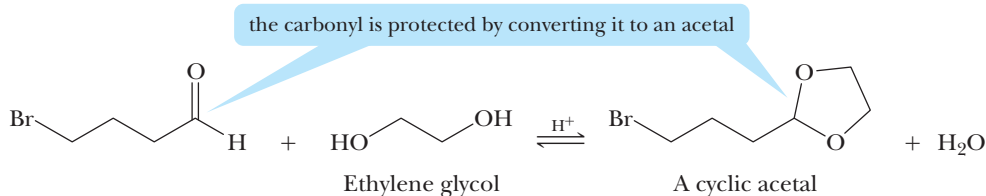
Like ethers, acetals are unreactive to bases, to reducing agents such as H_2/M , to Grignard reagents, and to oxidizing agents (except, of course, those which involve aqueous acid). Because of their lack of reactivity toward these reagents, acetals are often used to protect the carbonyl groups of aldehydes and ketones while reactions are carried out on functional groups in other parts of the molecule.

B. Acetals as Carbonyl-Protecting Groups

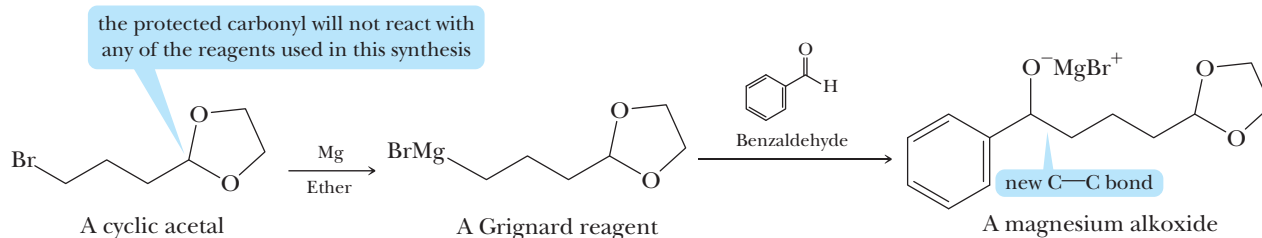
The use of acetals as carbonyl-protecting groups is illustrated by the synthesis of 5-hydroxy-5-phenylpentanal from benzaldehyde and 4-bromobutanal:



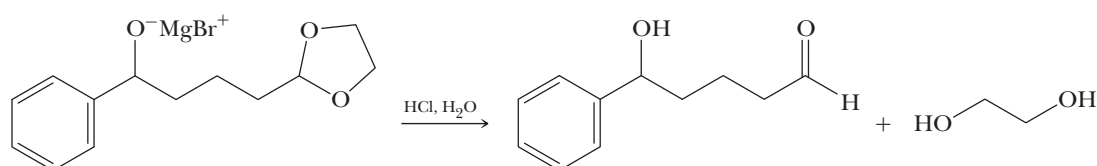
One obvious way to form a new carbon–carbon bond between these two molecules is to treat benzaldehyde with the Grignard reagent formed from 4-bromobutanal. This Grignard reagent, however, would react immediately with the carbonyl group of another molecule of 4-bromobutanal, causing it to self-destruct during preparation (Section 12.5B). A way to avoid this problem is to protect the carbonyl group of 4-bromobutanal by converting it to an acetal. Cyclic acetals are often used because they are particularly easy to prepare.



Treatment of the protected bromoaldehyde with magnesium in diethyl ether, followed by the addition of benzaldehyde, gives a magnesium alkoxide:



Treatment of the magnesium alkoxide with aqueous acid accomplishes two things. First, protonation of the alkoxide anion gives the desired hydroxyl group, and then, **hydrolysis** of the cyclic acetal regenerates the aldehyde group:



EXAMPLE 12.7

Propose a method for the following transformation. *Note:* Catalytic hydrogenation adds H₂ across C=O double bonds as well as across C=C double bonds.

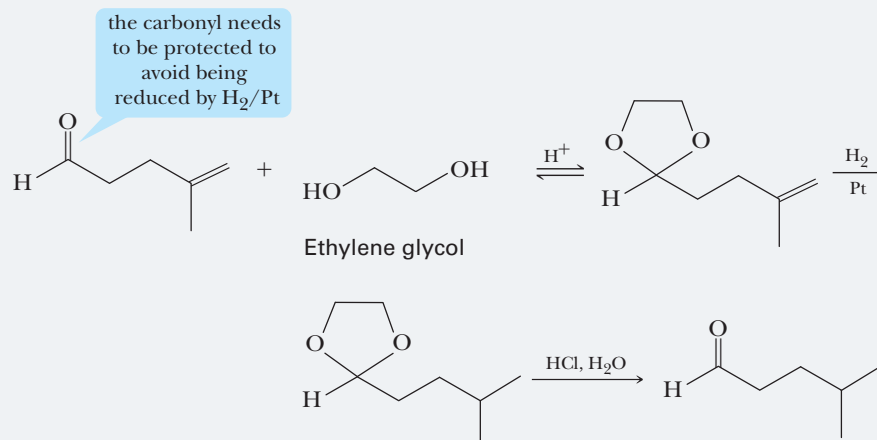


STRATEGY

Decide which reaction(s) are needed to achieve the interconversion of functional groups. Before applying any reaction to the targeted functional group, determine whether any other functional groups in the compound will react with the reagents proposed. If these other reactions are undesirable, determine whether the functional groups can be protected.

SOLUTION

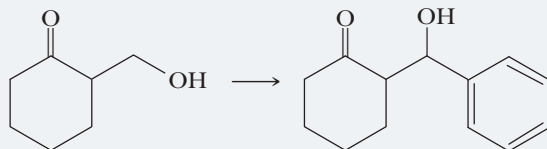
It is important to protect the carbonyl group. Otherwise, it will be reduced to an alcohol by H₂/Pt:



See problems 12.38–12.45

PROBLEM 12.7

Propose a method for the following transformation:



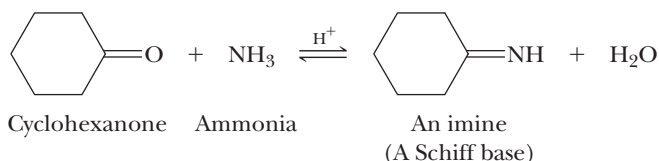
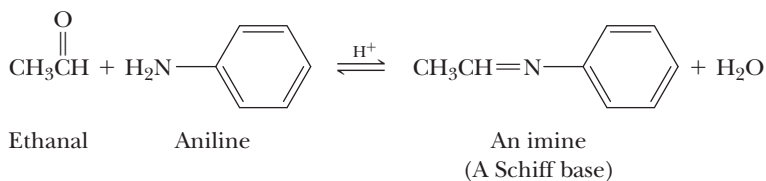
12.7 How Do Aldehydes and Ketones React with Ammonia and Amines?

A. Formation of Imines

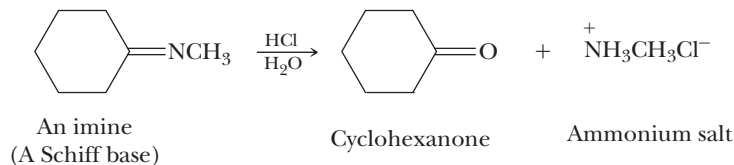
Ammonia, primary aliphatic amines (RNH_2), and primary aromatic amines (ArNH_2) react with the carbonyl group of aldehydes and ketones in the presence of an acid catalyst to give a product that contains a carbon–nitrogen double bond. A molecule containing a carbon–nitrogen double bond is called an **imine** or, alternatively, a **Schiff base**:

Imine A compound containing a carbon–nitrogen double bond; also called a Schiff base.

Schiff base An alternative name for an imine.



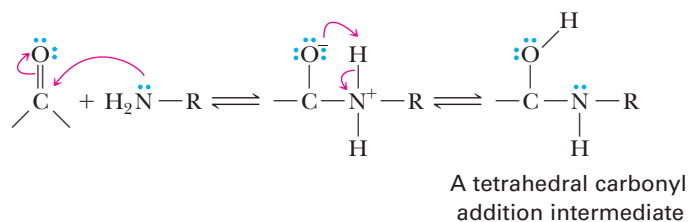
As with hemiacetal- and acetal-forming reactions, imine formation is reversible; acid-catalyzed hydrolysis of an imine gives a 1° amine and an aldehyde or a ketone. When one equivalent of acid is used, the 1° amine, a weak base, is converted to an ammonium salt.



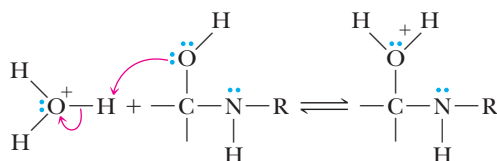
Mechanism

Formation of an Imine from an Aldehyde or a Ketone

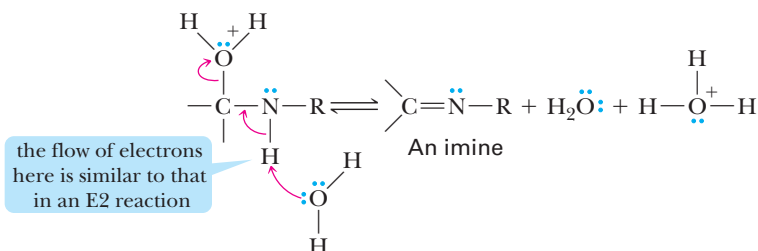
STEP 1: Reaction of an electrophile with a nucleophile to form a new bond. Addition of the nitrogen atom of ammonia or a primary amine, both good nucleophiles, to the carbonyl carbon, followed by a proton transfer, gives a tetrahedral carbonyl addition intermediate:



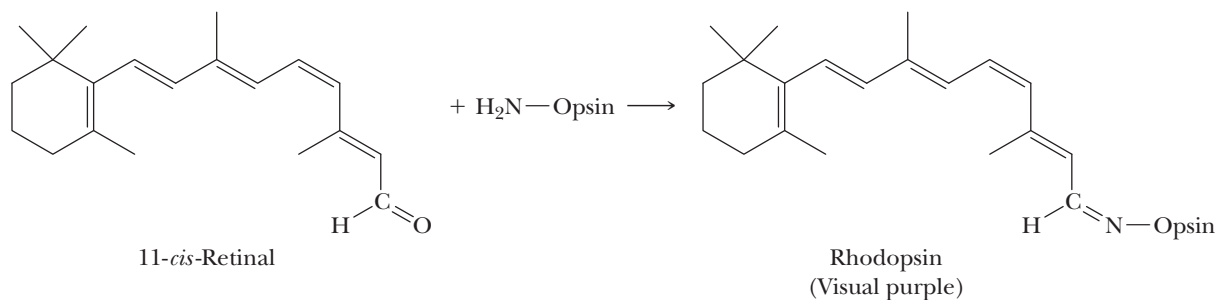
STEP 2: Add a proton. Protonation of the OH group to form —OH_2^+ , a good leaving group.



STEP 3: Take a proton away and break a bond to form a stable molecule. Loss of water and proton transfer to solvent gives the imine. Notice that the loss of water and the proton transfer have the characteristics of an E2 reaction. Three things happen simultaneously in this dehydration: a base (in this case a water molecule) removes a proton from N, the carbon–nitrogen double bond forms, and the leaving group (in this case, a water molecule) departs:

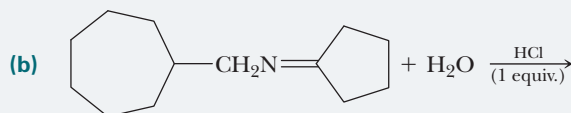
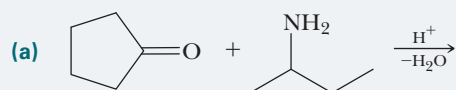


To give but one example of the importance of imines in biological systems, the active form of vitamin A aldehyde (retinal) is bound to the protein opsin in the human retina in the form of an imine called *rhodopsin* or *visual purple* (see Chemical Connections 4B). The amino acid lysine (see Table 18.1) provides the primary amino group for this reaction:



EXAMPLE 12.8

Predict the products formed in each reaction:

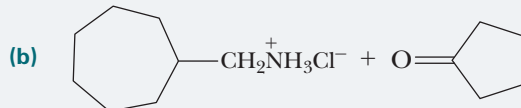
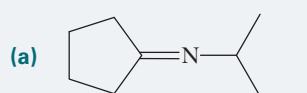


STRATEGY

In an imine-forming reaction, the $\text{C}=\text{O}$ group is converted to a $\text{C}=\text{N}$ group and the nitrogen of the former 1° amine loses both of its hydrogens. In the reverse process, the $\text{C}=\text{N}$ group is converted back to a $\text{C}=\text{O}$ group and two hydrogens are added back to the nitrogen to form a 1° amine.

SOLUTION

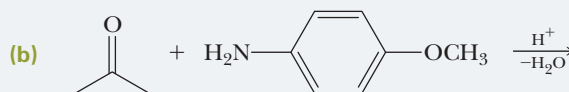
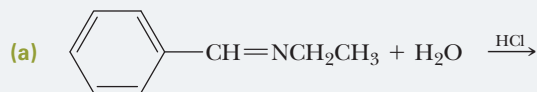
Reaction (a) is an imine-forming reaction, while reaction (b) is the acid-catalyzed hydrolysis of an imine to an ammonium salt and a ketone:



See problems 12.29–12.32

PROBLEM 12.8

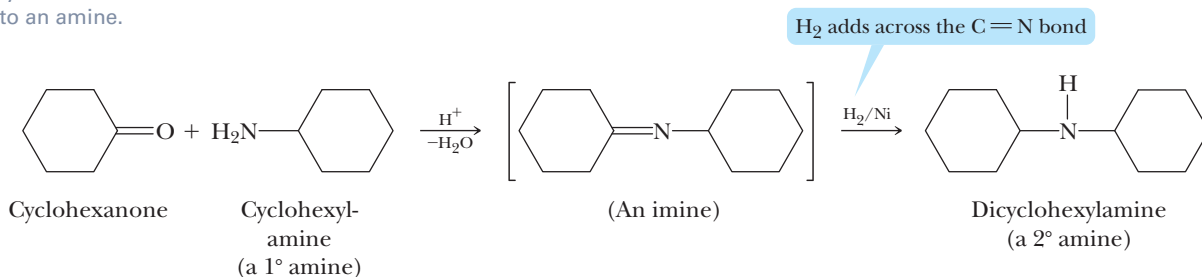
Predict the products formed in each reaction. *Note:* Acid-catalyzed hydrolysis of an imine gives an amine and an aldehyde or a ketone. When one equivalent of acid is used, the amine is converted to its ammonium salt.



B. Reductive Amination of Aldehydes and Ketones

Reductive amination The formation of an imine from an aldehyde or a ketone, followed by the reduction of the imine to an amine.

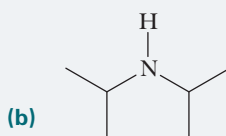
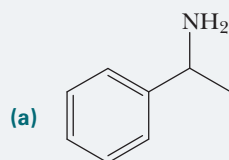
One of the chief values of imines is that the carbon–nitrogen double bond can be reduced to a carbon–nitrogen single bond by hydrogen in the presence of a nickel or other transition metal catalyst. By this two-step reaction, called **reductive amination**, a primary amine is converted to a secondary amine by way of an imine, as illustrated by the conversion of cyclohexylamine to dicyclohexylamine:



Conversion of an aldehyde or a ketone to an amine is generally carried out in one laboratory operation by mixing together the carbonyl-containing compound, the amine or ammonia, hydrogen, and the transition metal catalyst. The imine intermediate is not isolated.

EXAMPLE 12.9

Show how to synthesize each amine by a reductive amination:

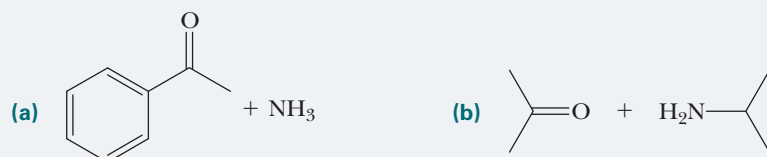


STRATEGY

Identify the C–N bond formed in the reductive amination. The carbon of the C–N bond is part of the carbonyl starting material, and the nitrogen is part of the 1° amine.

SOLUTION

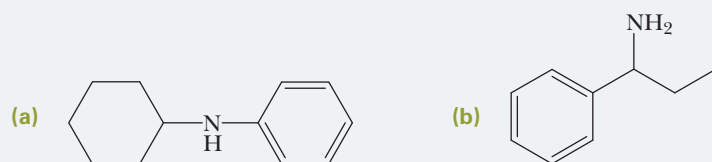
Treat the appropriate compound, in each case a ketone, with ammonia or an amine in the presence of H_2/Ni :



See problems 12.29–12.32

PROBLEM 12.9

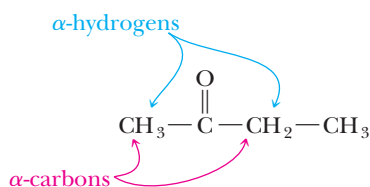
Show how to prepare each amine by the reductive amination of an appropriate aldehyde or ketone:



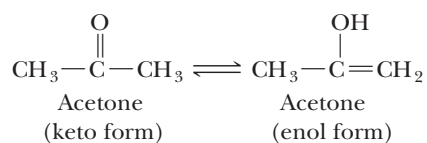
12.8 What Is Keto–Enol Tautomerism?

A. Keto and Enol Forms

A carbon atom adjacent to a carbonyl group is called an **α -carbon**, and any hydrogen atoms bonded to it are called **α -hydrogens**:



An aldehyde or ketone that has at least one α -hydrogen is in equilibrium with a constitutional isomer called an **enol**. The name *enol* is derived from the IUPAC designation of it as both an alkene (*-en-*) and an alcohol (*-ol*):



Keto and enol forms are examples of **tautomers**—constitutional isomers that are in equilibrium with each other and that differ in the location of a hydrogen atom and a double


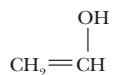

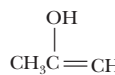
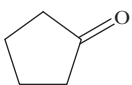
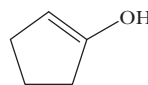
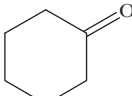
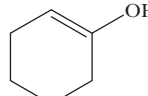
α -Carbon A carbon atom adjacent to a carbonyl group.

α -Hydrogen A hydrogen on an α -carbon.

Enol A molecule containing an —OH group bonded to a carbon of a carbon–carbon double bond.

Tautomers Constitutional isomers that differ in the location of hydrogen and a double bond relative to O, N, or S.

TABLE 12.4 The Position of Keto–Enol Equilibrium for Four Aldehydes and Ketones*

Keto Form	Enol Form	% Enol at Equilibrium
CH_3CHO 	$\text{CH}_2=\text{CHOH}$ 	6×10^{-5}
CH_3COCH_3 	$\text{CH}_3\text{C}(\text{OH})=\text{CH}_2$ 	6×10^{-7}
		1×10^{-6}
		4×10^{-5}

*Data from J. March, *Advanced Organic Chemistry*, 4th ed. (New York, Wiley Interscience, 1992) p. 70.

bond relative to a heteroatom, most commonly O, S, or N. This type of isomerism is called **tautomerism**.

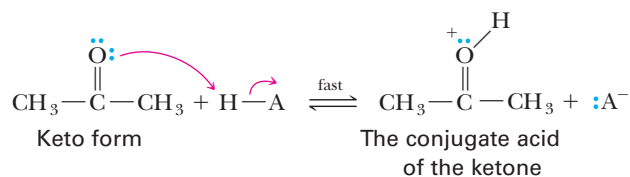
For most simple aldehydes and ketones, the position of the equilibrium in keto–enol tautomerism lies far on the side of the keto form (Table 12.4), because a carbon–oxygen double bond is stronger than a carbon–carbon double bond.

The equilibration of keto and enol forms is catalyzed by acid, as shown in the following two-step mechanism (note that a molecule of $\text{H}-\text{A}$ is consumed in Step 1, but another is generated in Step 2):

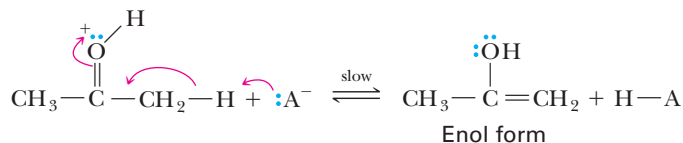
Mechanism

Acid-Catalyzed Equilibration of Keto and Enol Tautomers

STEP 1: Add a proton. Proton transfer from the acid catalyst, $\text{H}-\text{A}$, to the carbonyl oxygen forms the conjugate acid of the aldehyde or ketone:

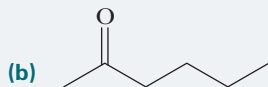
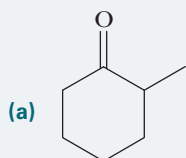


STEP 2: Take a proton away. Proton transfer from the α -carbon to the base, A^- , gives the enol and generates a new molecule of the acid catalyst, $\text{H}-\text{A}$:



EXAMPLE 12.10

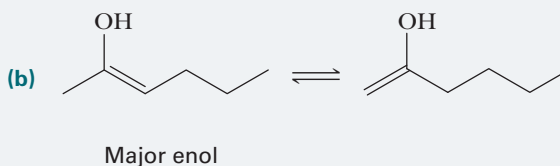
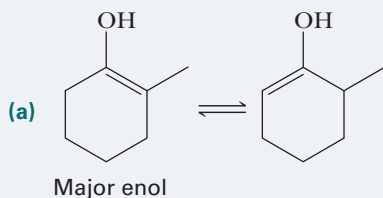
Write two enol forms for each compound, and state which enol of each predominates at equilibrium:

**STRATEGY**

An enol can form on either side of the carbonyl as long as there is an α -hydrogen to be abstracted in Step 2 of the mechanism. To decide which enol predominates, recall that the more substituted an alkene is, the more stable it is (see Section 5.7B).

SOLUTION

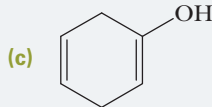
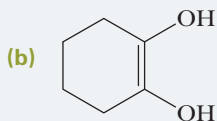
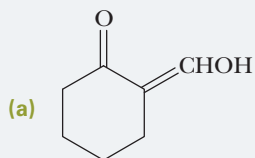
In each case, the major enol form has the more substituted (the more stable) carbon–carbon double bond:



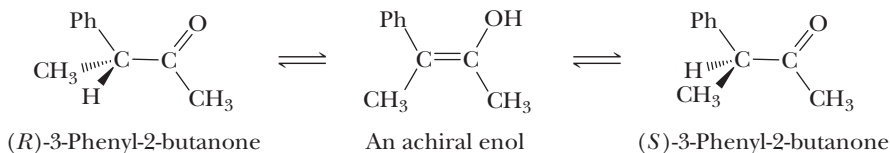
See problem 12.34

PROBLEM 12.10

Draw the structural formula for the keto form of each enol:

**B. Racemization at an α -Carbon**

When enantiomerically pure (either *R* or *S*) 3-phenyl-2-butanone is dissolved in ethanol, no change occurs in the optical activity of the solution over time. If, however, a trace of acid (for example, HCl) is added, the optical activity of the solution begins to decrease and gradually drops to zero. When 3-phenyl-2-butanone is isolated from this solution, it is found to be a racemic mixture (Section 6.8C). This observation can be explained by the acid-catalyzed formation of an achiral enol intermediate. Tautomerism of the achiral enol to the chiral keto form generates the *R* and *S* enantiomers with equal probability:

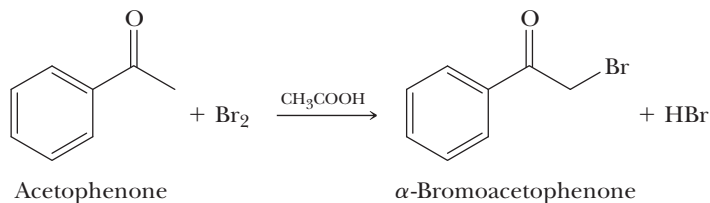


Racemization by this mechanism occurs only at α -carbon stereocenters with at least one α -hydrogen. This process is usually an undesired side effect of acid impurities in a sample, because it is often, in medicine for example, important to have an enantiomerically pure form of a compound rather than a racemic mixture.

Racemization The conversion of a pure enantiomer into a racemic mixture.

C. α -Halogenation

Aldehydes and ketones with at least one α -hydrogen react with bromine and chlorine at the α -carbon to give an α -haloaldehyde or α -haloketone. Acetophenone, for example, reacts with bromine in acetic acid to give an α -bromoketone:

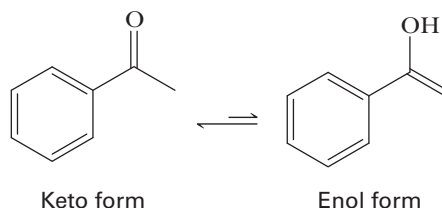


α -Halogenation is catalyzed by both acid and base. For acid-catalyzed halogenation, the HBr or HCl generated by the reaction catalyzes further reaction.

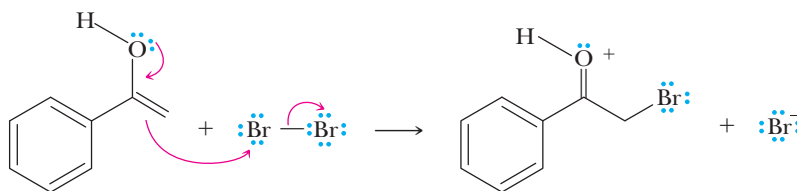
Mechanism

Acid-Catalyzed α -Halogenation of a Ketone

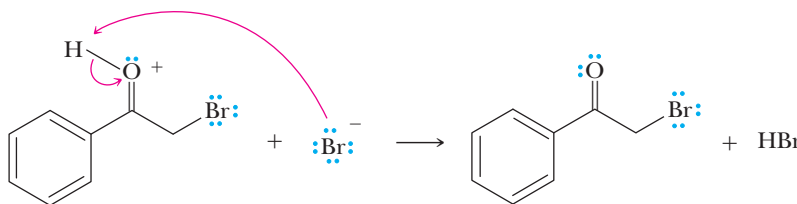
STEP 1: Keto–enol tautomerism (Section 12.8A). A small amount of enol is formed under acid-catalyzed conditions:



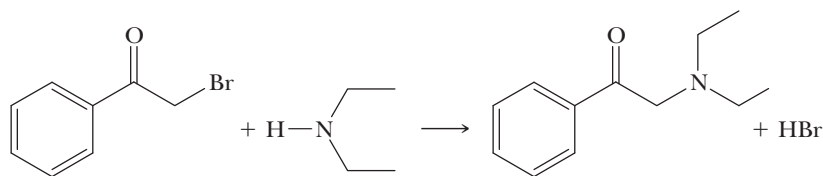
STEP 2: Reaction of an electrophile with a nucleophile to form a new covalent bond.
Nucleophilic attack of the enol on the halogen molecule:



STEP 3: Take a proton away. Proton transfer generates HBr and gives the α -haloketone:



The value of α -halogenation is that it converts an α -carbon into a center that now has a good leaving group bonded to it and that is therefore susceptible to attack by a variety of good nucleophiles. In the following illustration, diethylamine (a nucleophile) reacts with the α -bromoketone to give an α -diethylaminoketone:

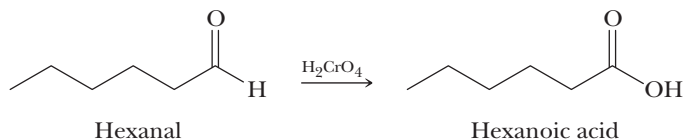
An α -bromoketoneAn α -diethylaminoketone

In practice, this type of nucleophilic substitution is generally carried out in the presence of a weak base such as potassium carbonate to neutralize the HX as it is formed.

12.9 How Are Aldehydes and Ketones Oxidized?

A. Oxidation of Aldehydes to Carboxylic Acids

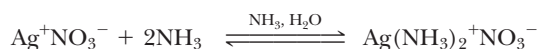
Aldehydes are oxidized to carboxylic acids by a variety of common oxidizing agents, including chromic acid and molecular oxygen. In fact, aldehydes are one of the most easily oxidized of all functional groups. Oxidation by chromic acid (Section 8.2F) is illustrated by the conversion of hexanal to hexanoic acid:



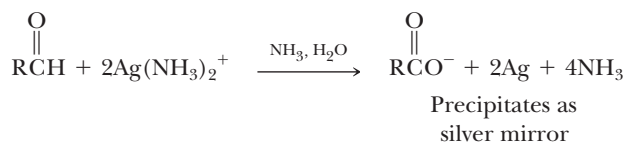
Hexanal

Hexanoic acid

Aldehydes are also oxidized to carboxylic acids by silver ion. One common laboratory procedure uses **Tollens' reagent**, prepared by dissolving AgNO_3 in water, adding sodium hydroxide to precipitate silver ion as Ag_2O , and then adding aqueous ammonia to redissolve silver ion as the silver–ammonia complex ion:

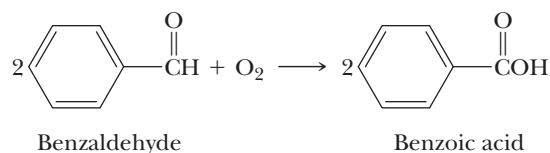


When Tollens' reagent is added to an aldehyde, the aldehyde is oxidized to a carboxylic anion, and Ag^+ is reduced to metallic silver. If this reaction is carried out properly, silver precipitates as a smooth, mirrorlike deposit—hence the name **silver-mirror test**:



Nowadays, Ag^+ is rarely used for the oxidation of aldehydes, because of the cost of silver and because other, more convenient methods exist for this oxidation. The reaction, however, is still used for silvering mirrors. In the process, formaldehyde or glucose is used as the aldehyde to reduce Ag^+ .

Aldehydes are also oxidized to carboxylic acids by molecular oxygen and by hydrogen peroxide.



Benzaldehyde

Benzoic acid

Molecular oxygen is the least expensive and most readily available of all oxidizing agents, and, on an industrial scale, air oxidation of organic molecules, including aldehydes, is common. Air oxidation of aldehydes can also be a problem: Aldehydes that are liquid at room temperature are so sensitive to oxidation by molecular oxygen that they must be protected from contact with air during storage. Often, this is done by sealing the aldehyde in a container under an atmosphere of nitrogen.



Charles D. Winters

A silver mirror has been deposited in the inside of this flask by the reaction of an aldehyde with Tollens' reagent.

EXAMPLE 12.11

Draw a structural formula for the product formed by treating each compound with Tollens' reagent, followed by acidification with aqueous HCl:

- (a) Pentanal (b) Cyclopentanecarbaldehyde

STRATEGY

Aldehydes are oxidized to carboxylic acids by Tollens' reagent.

See problems 12.36, 12.37

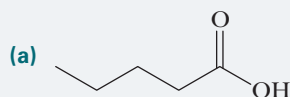
PROBLEM 12.11

Complete these oxidations:

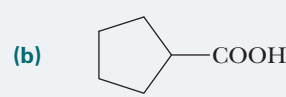
- (a) 3-Oxobutanal + O₂ → (b) 3-Phenylpropanal + Tollens' reagent →

SOLUTION

The aldehyde group in each compound is oxidized to a carboxyl group:



Pentanoic acid



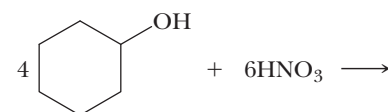
Cyclopentanecarboxylic acid

Chemical

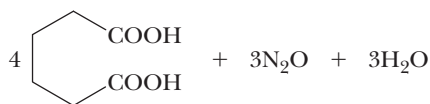
Connections 12A

A GREEN SYNTHESIS OF ADIPIC ACID

The current industrial production of adipic acid relies on the oxidation of a mixture of cyclohexanol and cyclohexanone by nitric acid:



Cyclohexanol

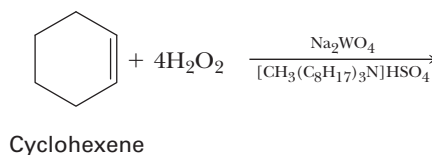


Hexanedioic acid
(Adipic acid)

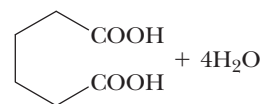
Nitrous
oxide

A by-product of this oxidation is nitrous oxide, a gas considered to play a role in global warming and the depletion of the ozone layer in the atmosphere, as well as contributing to acid rain and acid smog. Given the fact that worldwide production of adipic acid is approximately 2.2 billion metric tons per year, the production of nitrous oxide is enormous. In spite of technological advances that allow for the recovery and recycling of nitrous oxide, it is estimated that approximately 400,000 metric tons escapes recovery and is released into the atmosphere each year.

Recently, Ryoji Noyori (2001 Nobel Prize in Chemistry) and coworkers at Nagoya University in Japan developed a "green" route to adipic acid, one that involves the oxidation of cyclohexene by 30% hydrogen peroxide catalyzed by sodium tungstate, Na₂WO₄:



Cyclohexene



Hexanedioic acid
(Adipic acid)

In this process, cyclohexene is mixed with aqueous 30% hydrogen peroxide, and sodium tungstate and methyltrioctylammonium hydrogen sulfate are added to the resulting two-phase system. (Cyclohexene is insoluble in water.) Under these conditions, cyclohexene is oxidized to adipic acid in approximately 90% yield.

While this route to adipic acid is environmentally friendly, it is not yet competitive with the nitric acid oxidation route because of the high cost of 30% hydrogen peroxide. What will make it competitive is either a considerable reduction in the cost of hydrogen peroxide or the institution of more stringent limitations on the emission of nitrous oxide into the atmosphere (or a combination of these).

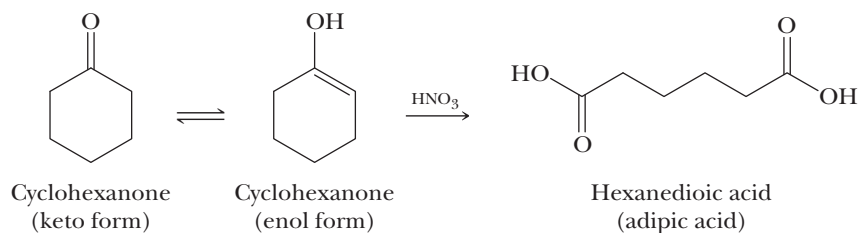
Question

Using chemistry presented in this and previous chapters, propose a synthesis for adipic acid from cyclohexene.

B. Oxidation of Ketones to Carboxylic Acids

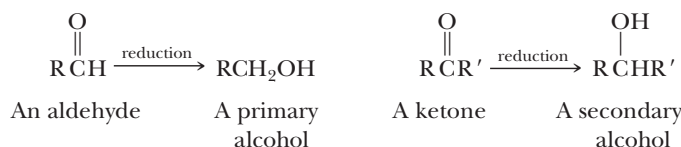
Ketones are much more resistant to oxidation than are aldehydes. For example, ketones are not normally oxidized by chromic acid or potassium permanganate. In fact, these reagents are used routinely to oxidize secondary alcohols to ketones in good yield (Section 8.2F).

Ketones undergo oxidative cleavage, via their enol form, by potassium dichromate and potassium permanganate at higher temperatures and by higher concentrations of nitric acid, HNO_3 . The carbon–carbon double bond of the enol is cleaved to form two carboxyl or ketone groups, depending on the substitution pattern of the original ketone. An important industrial application of this reaction is the oxidation of cyclohexanone to hexanedioic acid (adipic acid), one of the two monomers required for the synthesis of the polymer nylon 66 (Section 16.4A):



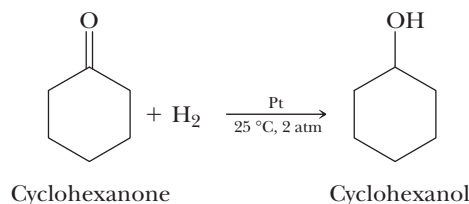
12.10 How Are Aldehydes and Ketones Reduced?

Aldehydes are reduced to primary alcohols and ketones to secondary alcohols:

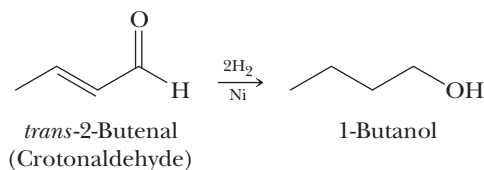


A. Catalytic Reduction

The carbonyl group of an aldehyde or a ketone is reduced to a hydroxyl group by hydrogen in the presence of a transition metal catalyst, most commonly finely divided palladium, platinum, nickel, or rhodium. Reductions are generally carried out at temperatures from 25 to 100 °C and at pressures of hydrogen from 1 to 5 atm. Under such conditions, cyclohexanone is reduced to cyclohexanol:



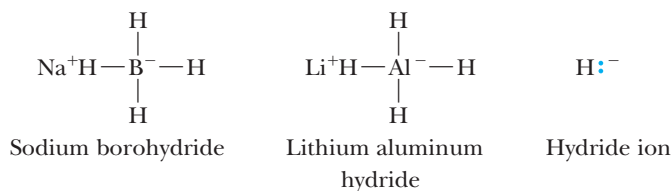
The catalytic reduction of aldehydes and ketones is simple to carry out, yields are generally very high, and isolation of the final product is very easy. A disadvantage is that some other functional groups (for example, carbon–carbon double bonds) are also reduced under these conditions.



Hydride ion A hydrogen atom with two electrons in its valence shell; H^- .

B. Metal Hydride Reductions

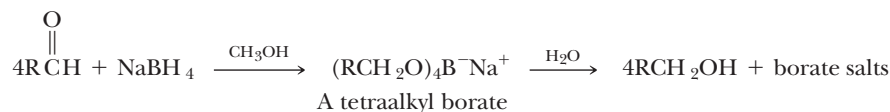
By far the most common laboratory reagents used to reduce the carbonyl group of an aldehyde or a ketone to a hydroxyl group are sodium borohydride and lithium aluminum hydride. Each of these compounds behaves as a source of **hydride ion**, a very strong nucleophile. The structural formulas drawn here for these reducing agents show formal negative charges on boron and aluminum:



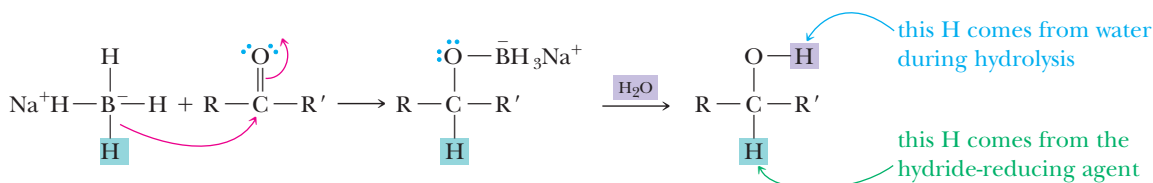
In fact, hydrogen is more electronegative than either boron or aluminum ($\text{H} = 2.1$, $\text{Al} = 1.5$, and $\text{B} = 2.0$), and the formal negative charge in the two reagents resides more on hydrogen than on the metal.

Lithium aluminum hydride is a very powerful reducing agent; it rapidly reduces not only the carbonyl groups of aldehydes and ketones, but also those of carboxylic acids (Section 13.5) and their functional derivatives (Section 14.8). Sodium borohydride is a much more selective reagent, reducing only aldehydes and ketones rapidly.

Reductions using sodium borohydride are most commonly carried out in aqueous methanol, in pure methanol, or in ethanol. The initial product of reduction is a tetraalkyl borate, which is converted to an alcohol and sodium borate salts upon treatment with water. One mole of sodium borohydride reduces 4 moles of aldehyde or ketone:

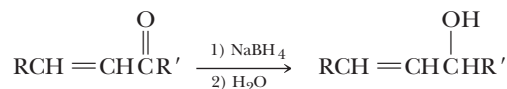


The key step in the metal hydride reduction of an aldehyde or a ketone is the transfer of a hydride ion from the reducing agent to the carbonyl carbon to form a tetrahedral carbonyl addition intermediate. In the reduction of an aldehyde or a ketone to an alcohol, only the hydrogen atom attached to carbon comes from the hydride-reducing agent; the hydrogen atom bonded to oxygen comes from the water added to hydrolyze the metal alkoxide salt.



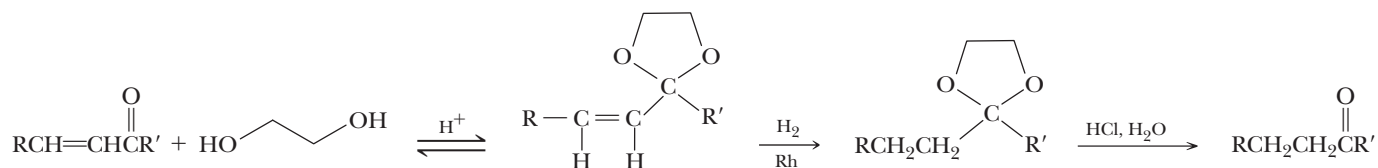
The next two equations illustrate the selective reduction of a carbonyl group in the presence of a carbon-carbon double bond and, alternatively, the selective reduction of a carbon-carbon double bond in the presence of a carbonyl group.

Selective reduction of a carbonyl group:



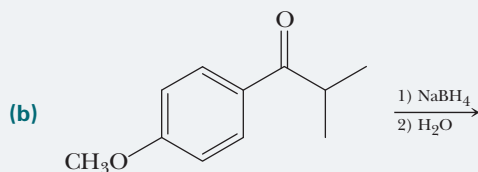
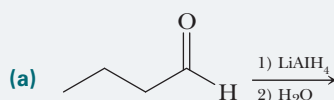
A carbon-carbon double bond can be reduced selectively in the presence of a carbonyl group by first protecting the carbonyl group using an acetal.

Selective reduction of a carbon–carbon double bond using a protecting group:



EXAMPLE 12.12

Complete these reductions:

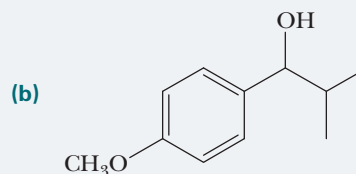
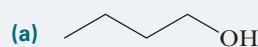


STRATEGY

Consider all the functional groups that can react with each reducing reagent. Alkenes, ketones, aldehydes, and imines are just some examples of functional groups that can be reduced.

SOLUTION

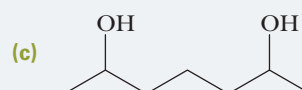
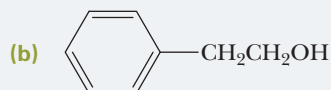
The carbonyl group of the aldehyde in (a) is reduced to a primary alcohol, and that of the ketone in (b) is reduced to a secondary alcohol:



See problems 12.36, 12.37

PROBLEM 12.12

What aldehyde or ketone gives each alcohol upon reduction by NaBH_4 ?



SUMMARY OF KEY QUESTIONS

12.1 What Are Aldehydes and Ketones?

- An **aldehyde** contains a carbonyl group bonded to a hydrogen atom and a carbon atom.
- A **ketone** contains a carbonyl group bonded to two carbons.

12.2 How Are Aldehydes and Ketones Named?

- An aldehyde is named by changing *-e* of the parent alkane to *-al*.
- A CHO group bonded to a ring is indicated by the suffix *-carbaldehyde*.
- A ketone is named by changing *-e* of the parent alkane to *-one* and using a number to locate the carbonyl group.
- In naming compounds that contain more than one functional group, the IUPAC system has established an **order of precedence of functional groups**. If the carbonyl group of an aldehyde or a ketone is lower in precedence than other functional groups in the molecule, it is indicated by the infix **-oxo-**.

12.3 What Are the Physical Properties of Aldehydes and Ketones?

- Aldehydes and ketones are polar compounds and interact in the pure state by dipole–dipole interactions.
- Aldehydes and ketones have higher boiling points and are more soluble in water than are nonpolar compounds of comparable molecular weight.

12.4 What Is the Most Common Reaction Theme of Aldehydes and Ketones?

- The common reaction theme of the carbonyl group of aldehydes and ketones is the addition of a nucleophile to form a **tetrahedral carbonyl addition intermediate**.

12.5 What Are Grignard Reagents, and How Do They React with Aldehydes and Ketones?

- Grignard reagents** are organomagnesium compounds with the generic formula RMgX .
- The carbon–metal bond in Grignard reagents has a high degree of partial ionic character.
- Grignard reagents behave as **carbanions** and are both strong bases and good nucleophiles. They react with aldehydes and ketones by adding to the carbonyl carbon.

12.6 What Are Hemiacetals and Acetals?

- The addition of a molecule of alcohol to the carbonyl group of an aldehyde or a ketone forms a **hemiacetal**.
- Hemiacetals can react further with alcohols to form **acetals** plus a molecule of water.
- Because of their lack of reactivity toward nucleophilic and basic reagents, acetals are often used to protect the carbonyl groups of aldehydes and ketones while reactions are carried out on functional groups in other parts of the molecule.

12.7 How Do Aldehydes and Ketones React with Ammonia and Amines?

- Ammonia, 1° aliphatic amines (RNH_2), and 1° aromatic amines (ArNH_2) react with the carbonyl group of aldehydes and ketones in the presence of an acid catalyst to give **imines**, compounds that contain a carbon–nitrogen double bond.

12.8 What Is Keto–Enol Tautomerism?

- A carbon atom adjacent to a carbonyl group is called an **α -carbon**, and any hydrogen atoms bonded to it are called **α -hydrogens**.
- An aldehyde or a ketone, which is said to be in its **keto** form, that has at least one α -hydrogen is in equilibrium with a constitutional isomer called an **enol**. This type of isomerism is called **tautomerism**.
- Tautomerism, catalyzed by trace amounts of acid or base, is the cause of **racemization** of chiral aldehydes and ketones when a stereocenter exists at an α -carbon.
- The enol form allows aldehydes and ketones to be halogenated at the α -position.

12.9 How Are Aldehydes and Ketones Oxidized?

- Aldehydes are oxidized to carboxylic acids by a variety of common oxidizing agents, including chromic acid, the Tollens' reagent, and molecular oxygen.
- Ketones are much more resistant to oxidation than are aldehydes. However, they undergo **oxidative cleavage**, via their enol form, by potassium dichromate and potassium permanganate at higher temperatures and by higher concentrations of HNO_3 .

12.10 How Are Aldehydes and Ketones Reduced?

- Aldehydes are reduced to primary alcohols and ketones to secondary alcohols by catalytic hydrogenation or through the use of the metal hydrides NaBH_4 or LiAlH_4 .

QUICK QUIZ

Answer true or false to the following questions to assess your general knowledge of the concepts in this chapter. If you have difficulty with any of them, you should review the appropriate section in the chapter (shown in parentheses) before attempting the more challenging end-of-chapter problems.

1. In a compound that contains both an aldehyde and a C—C double bond, each functional group can be reduced exclusive of the other. (12.10)
2. Nucleophiles react with aldehydes and ketones to form tetrahedral carbonyl addition intermediates. (12.4)
3. The carboxyl group (COOH) has a higher priority in naming than all other functional groups. (12.2)
4. A stereocenter at the α -carbon of an aldehyde or a ketone will undergo racemization over time in the presence of an acid or a base. (12.8)
5. Acetone is the lowest-molecular-weight ketone. (12.3)
6. Aldehydes can be oxidized to ketones and carboxylic acids. (12.9)
7. Ketones are less water soluble than alcohols with comparable molecular weight. (12.3)
8. A Grignard reagent cannot be formed in the presence of an NH, OH, or SH group. (12.5)
9. Ketones have higher boiling points than alkanes with comparable molecular weight. (12.3)
10. An aldehyde has a higher priority in naming than a ketone. (12.2)
11. A Grignard reagent is a good electrophile. (12.5)
12. Any reaction that oxidizes an aldehyde to a carboxylic acid will also oxidize a ketone to a carboxylic acid. (12.9)
13. Aldehydes are more water soluble than ethers with comparable molecular weight. (12.3)
14. Aldehydes react with Grignard reagents (followed by acid workup) to form 1° alcohols. (12.5)
15. An imine can be reduced to an amine through catalytic hydrogenation. (12.7)
16. Sodium borohydride, NaBH₄, is more reactive and less selective than lithium aluminum hydride, LiAlH₄. (12.10)
17. An acetal can only result from the base-catalyzed addition of an alcohol to a hemiacetal. (12.6)
18. A Grignard reagent is a strong base. (12.5)
19. Acetal formation is reversible. (12.6)
20. An imine is the result of the reaction of a 2° amine with an aldehyde or a ketone. (12.7)
21. Ketones react with Grignard reagents (followed by acid workup) to form 2° alcohols. (12.5)
22. Aldehydes and ketones can undergo tautomerism. (12.8)
23. Acetaldehyde is the lowest-molecular-weight aldehyde. (12.3)
24. A ketone that possesses an α -hydrogen can undergo α -halogenation. (12.8)
25. A carbonyl group is polarized such that the oxygen atom is partially positive and the carbon atom is partially negative. (12.3)
26. Acetals are stable to bases, nucleophiles, and reducing agents. (12.6)
27. A “carbaldehyde” is an aldehyde in which the carbonyl group is adjacent to a C—C double bond. (12.1)
28. A hemiacetal can result from the acid-catalyzed or base-catalyzed addition of an alcohol to an aldehyde or a ketone. (12.6)

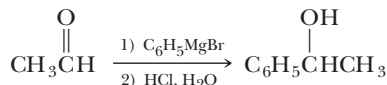
Answers: (1) T (2) T (3) T (4) T (5) T (6) T (7) T (8) T (9) T (10) T (11) F (12) F (13) T (14) F (15) T (16) F (17) F (18) T (19) T (20) F (21) F (22) T (23) F (24) T (25) F (26) T (27) F (28) T

Detailed explanations for many of these answers can be found in the accompanying Solutions Manual.

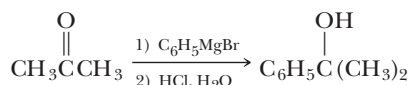
KEY REACTIONS

1. Reaction with Grignard Reagents (Section 12.5C)

Treatment of formaldehyde with a Grignard reagent, followed by hydrolysis in aqueous acid, gives a primary alcohol. Similar treatment of any other aldehyde gives a secondary alcohol:



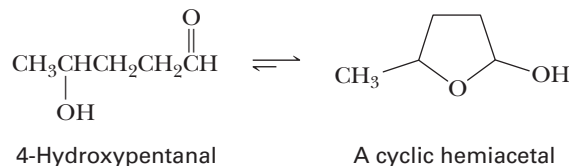
Treatment of a ketone with a Grignard reagent gives a tertiary alcohol:



2. Addition of Alcohols to Form Hemiacetals (Section 12.6)

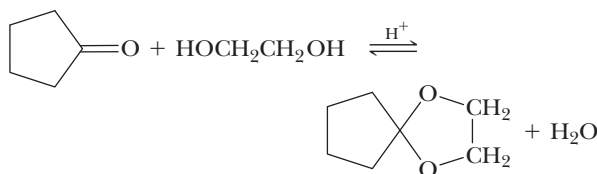
Hemiacetals are only minor components of an equilibrium mixture of aldehyde or ketone and alcohol, except

where the —OH and C=O groups are parts of the same molecule and a five- or six-membered ring can form:



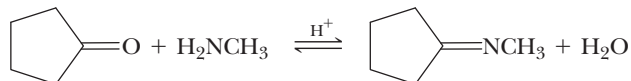
3. Addition of Alcohols to Form Acetals (Section 12.6)

The formation of acetals is catalyzed by acid:

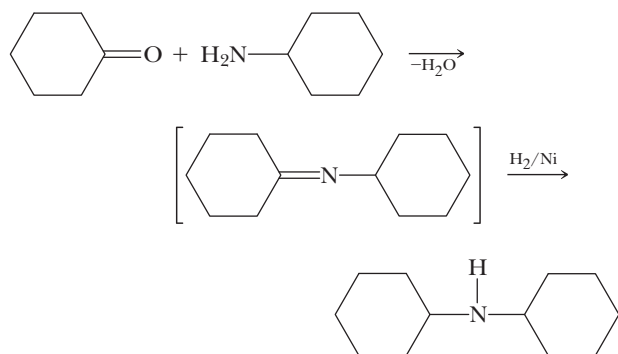


4. Addition of Ammonia and Amines (Section 12.7)

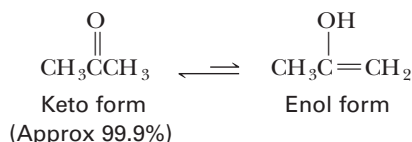
The addition of ammonia or a primary amine to the carbonyl group of an aldehyde or a ketone forms a tetrahedral carbonyl addition intermediate. Loss of water from this intermediate gives an imine (a Schiff base):

**5. Reductive Amination to Amines (Section 12.7B)**

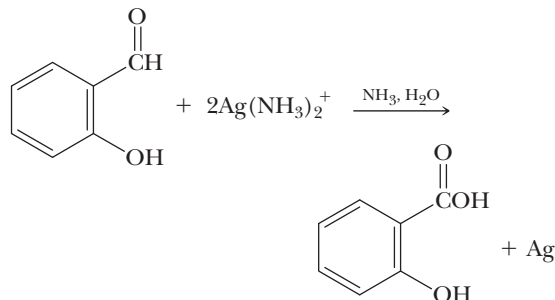
The carbon–nitrogen double bond of an imine can be reduced by hydrogen in the presence of a transition metal catalyst to a carbon–nitrogen single bond:

**6. Keto–Enol Tautomerism (Section 12.8A)**

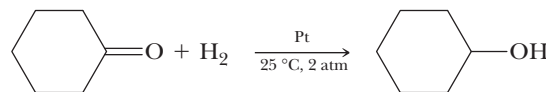
The keto form generally predominates at equilibrium:

**7. Oxidation of an Aldehyde to a Carboxylic Acid (Section 12.9)**

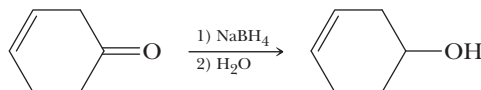
The aldehyde group is among the most easily oxidized functional groups. Oxidizing agents include H_2CrO_4 , Tollens' reagent, and O_2 :

**8. Catalytic Reduction (Section 12.10A)**

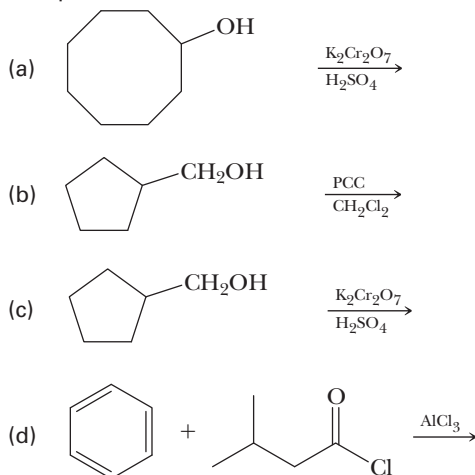
Catalytic reduction of the carbonyl group of an aldehyde or a ketone to a hydroxyl group is simple to carry out, and yields of alcohols are high:

**9. Metal Hydride Reduction (Section 12.10B)**

Both LiAlH_4 and NaBH_4 reduce the carbonyl group of an aldehyde or a ketone to an hydroxyl group. They are selective in that neither reduces isolated carbon–carbon double bonds:

**PROBLEMS**

A problem marked with an asterisk indicates an applied “real-world” problem. Answers to problems whose numbers are printed in blue are given in Appendix D.

Preparation of Aldehydes and Ketones (see also Chapters 8 and 9)**12.13** Complete these reactions:**12.14** Show how you would bring about these conversions:

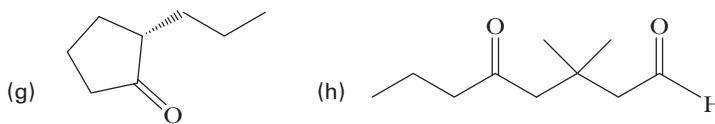
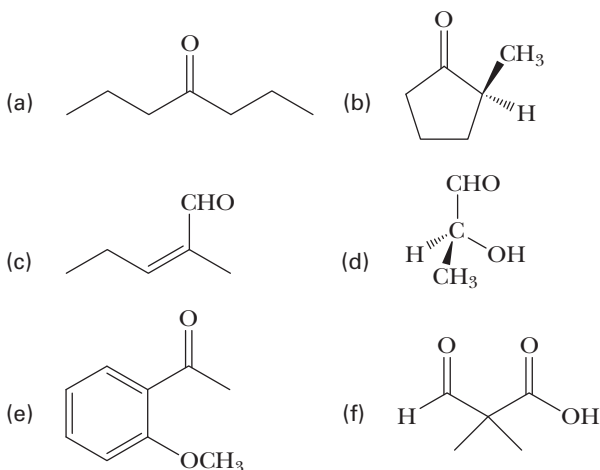
- 1-Pentanol to pentanal
- 1-Pentanol to pentanoic acid
- 2-Pentanol to 2-pentanone
- 1-Pentene to 2-pentanone
- Benzene to acetophenone
- Styrene to acetophenone
- Cyclohexanol to cyclohexanone
- Cyclohexene to cyclohexanone
- Benzene to 2-phenylethanal
- 1-Methylcyclohexene to (\pm)-2-methylcyclohexanone
- 1-Hexene to hexanal

Sections 12.1 and 12.2 Structure and Nomenclature

12.15 Draw a structural formula for the one ketone with molecular formula C_4H_8O and for the two aldehydes with molecular formula C_4H_8O . (See Example 12.2)

12.16 Draw structural formulas for the four aldehydes with molecular formula $C_5H_{10}O$. Which of these aldehydes are chiral? (See Example 12.2)

12.17 Name these compounds: (See Examples 12.1, 12.3)



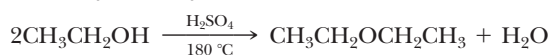
12.18 Draw structural formulas for these compounds: (See Examples 12.1, 12.3)

- 1-Chloro-2-propanone
- 3-Hydroxybutanal
- 4-Hydroxy-4-methyl-2-pentanone
- 3-Methyl-3-phenylbutanal
- (*S*)-3-bromocyclohexanone
- 3-Methyl-3-buten-2-one
- 5-Oxohexanal
- 2,2-Dimethylcyclohexanecarbaldehyde
- 3-Oxobutanoic acid
- 3-Phenylethanal
- (*R*)-2-Methylcyclohexanone
- 2,4-Pentanedione

Section 12.5 Addition of Carbon Nucleophiles

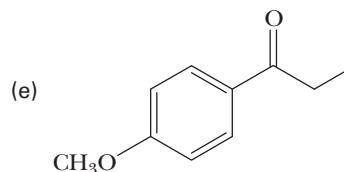
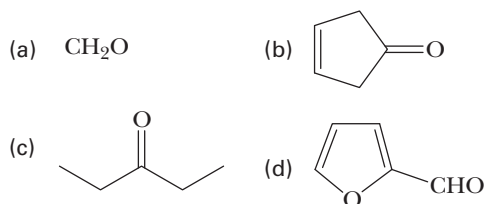
12.19 Write an equation for the acid–base reaction between phenylmagnesium iodide and a carboxylic acid. Use curved arrows to show the flow of electrons in this reaction. In addition, show that the reaction is an example of a stronger acid and stronger base reacting to form a weaker acid and weaker base. (See Example 12.4)

12.20 Diethyl ether is prepared on an industrial scale by the acid-catalyzed dehydration of ethanol:

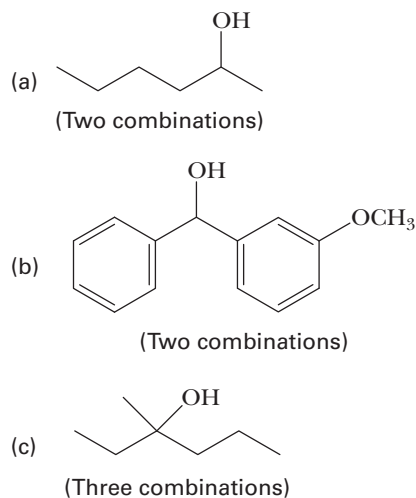


Explain why diethyl ether used in the preparation of Grignard reagents must be carefully purified to remove all traces of ethanol and water.

12.21 Draw structural formulas for the product formed by treating each compound with propylmagnesium bromide, followed by hydrolysis in aqueous acid: (See Examples 12.4, 12.5)

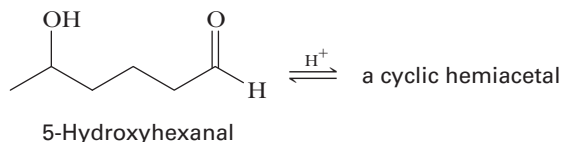


12.22 Suggest a synthesis for each alcohol, starting from an aldehyde or a ketone and an appropriate Grignard reagent (the number of combinations of Grignard reagent and aldehyde or ketone that might be used is shown in parentheses below each target molecule): (See Examples 12.4, 12.5)

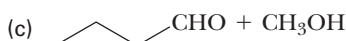
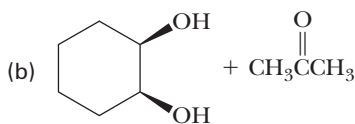
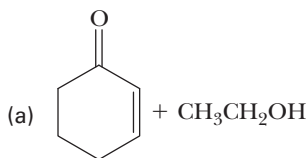


Section 12.6 Addition of Oxygen Nucleophiles

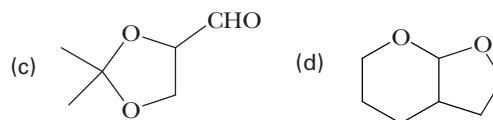
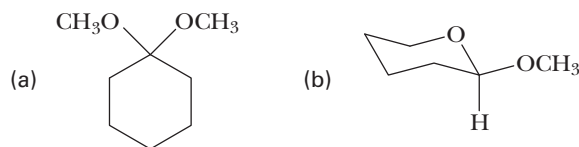
12.23 5-Hydroxyhexanal forms a six-membered cyclic hemiacetal that predominates at equilibrium in aqueous solution: (See Example 12.6)



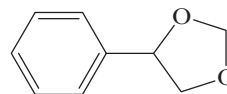
- Draw a structural formula for this cyclic hemiacetal.
 - How many stereoisomers are possible for 5-hydroxyhexanal?
 - How many stereoisomers are possible for the cyclic hemiacetal?
 - Draw alternative chair conformations for each stereoisomer.
 - For each stereoisomer, which alternative chair conformation is the more stable?
- 12.24** Draw structural formulas for the hemiacetal and then the acetal formed from each pair of reactants in the presence of an acid catalyst: (See Example 12.6)



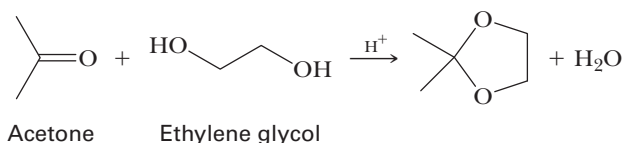
12.25 Draw structural formulas for the products of hydrolysis of each acetal in aqueous acid: (See Example 12.6)



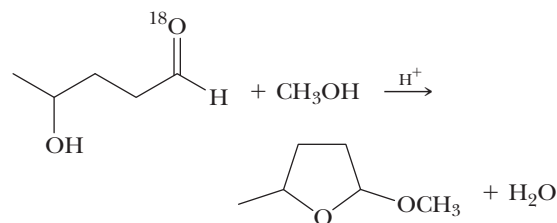
12.26 The following compound is a component of the fragrance of jasmine: From what carbonyl-containing compound and alcohol is the compound derived? (See Example 12.6)



12.27 Propose a mechanism for the formation of the cyclic acetal by treating acetone with ethylene glycol in the presence of an acid catalyst. Make sure that your mechanism is consistent with the fact that the oxygen atom of the water molecule is derived from the carbonyl oxygen of acetone.

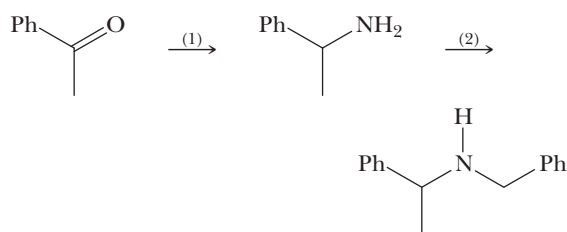


12.28 Propose a mechanism for the formation of a cyclic acetal from 4-hydroxypentanal and one equivalent of methanol: If the carbonyl oxygen of 4-hydroxypentanal is enriched with oxygen-18, does your mechanism predict that the oxygen label appears in the cyclic acetal or in the water? Explain.

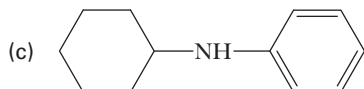
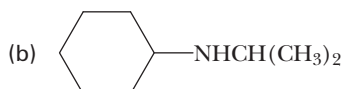
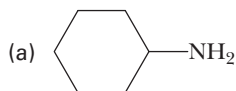


Section 12.7 Addition of Nitrogen Nucleophiles

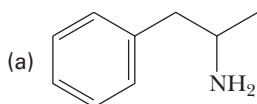
12.29 Show how this secondary amine can be prepared by two successive reductive aminations: (See Examples 12.8, 12.9)



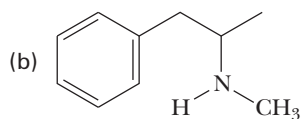
12.30 Show how to convert cyclohexanone to each of the following amines: (See Examples 12.8, 12.9)



***12.31** Following are structural formulas for amphetamine and methamphetamine: (See Examples 12.8, 12.9)



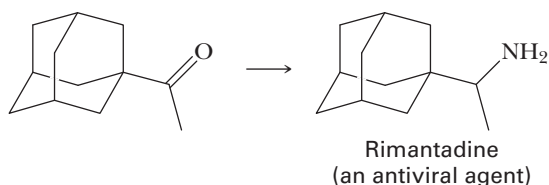
Amphetamine



Methamphetamine

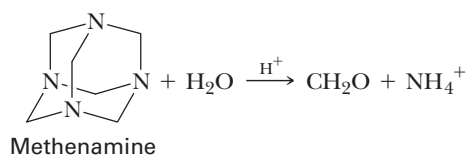
The major central nervous system effects of amphetamine and amphetaminelike drugs are locomotor stimulation, euphoria and excitement, stereotyped behavior, and anorexia. Show how each drug can be synthesized by the reductive amination of an appropriate aldehyde or ketone.

***12.32** Rimantadine is effective in preventing infections caused by the influenza A virus and in treating established illness. The drug is thought to exert its antiviral effect by blocking a late stage in the assembly of the virus. Following is the final step in the synthesis of rimantadine: (See Examples 12.8, 12.9)



- (a) Describe experimental conditions to bring about this final step.
(b) Is rimantadine chiral?

***12.33** Methenamine, a product of the reaction of formaldehyde and ammonia, is a *prodrug*—a compound that is inactive by itself, but is converted to an active drug in the body by a biochemical transformation. The strategy behind the use of methenamine as a prodrug is that nearly all bacteria are sensitive to formaldehyde at concentrations of 20 mg/mL or higher. Formaldehyde cannot be used directly in medicine, however, because an effective concentration in plasma cannot be achieved with safe doses. Methenamine is stable at pH 7.4 (the pH of blood plasma), but undergoes acid-catalyzed hydrolysis to formaldehyde and ammonium ion under the acidic conditions of the kidneys and the urinary tract:

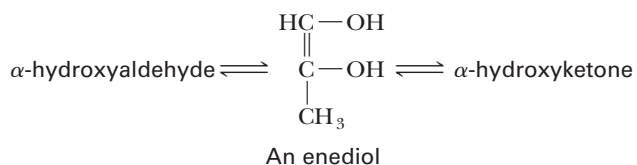


Thus, methenamine can be used as a site-specific drug to treat urinary infections.

- (a) Balance the equation for the hydrolysis of methenamine to formaldehyde and ammonium ion.
(b) Does the pH of an aqueous solution of methenamine increase, remain the same, or decrease as a result of the hydrolysis of the compound? Explain.
(c) Explain the meaning of the following statement: The functional group in methenamine is the nitrogen analog of an acetal.
(d) Account for the observation that methenamine is stable in blood plasma, but undergoes hydrolysis in the urinary tract.

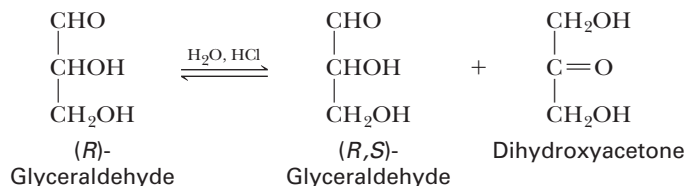
Section 12.8 Keto–Enol Tautomerism

12.34 The following molecule belongs to a class of compounds called enediols: Each carbon of the double bond carries an —OH group:



Draw structural formulas for the α -hydroxyketone and the α -hydroxyaldehyde with which this enediol is in equilibrium. (See Example 12.10)

12.35 In dilute aqueous acid, (*R*)-glyceraldehyde is converted into an equilibrium mixture of (*R,S*)-glyceraldehyde and dihydroxyacetone:



Propose a mechanism for this isomerization.

Section 12.9 Oxidation/Reduction of Aldehydes and Ketones

12.36 Draw a structural formula for the product formed by treating butanal with each of the following sets of reagents: (See Examples 12.11, 12.12)

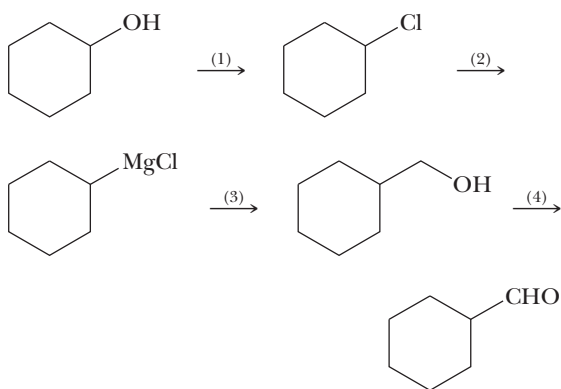
- LiAlH_4 followed by H_2O
- NaBH_4 in $\text{CH}_3\text{OH}/\text{H}_2\text{O}$
- H_2/Pt

- $\text{Ag}(\text{NH}_3)_2^+$ in $\text{NH}_3/\text{H}_2\text{O}$ and then $\text{HCl}/\text{H}_2\text{O}$
- H_2CrO_4
- $\text{C}_6\text{H}_5\text{NH}_2$ in the presence of H_2/Ni

12.37 Draw a structural formula for the product of the reaction of *p*-bromoacetophenone with each set of reagents in Problem 12.36. (See Examples 12.11, 12.12)

Synthesis

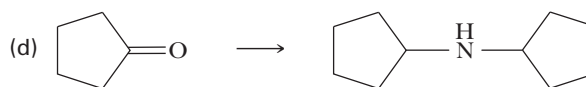
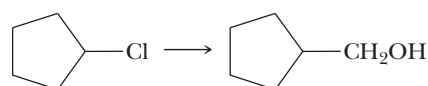
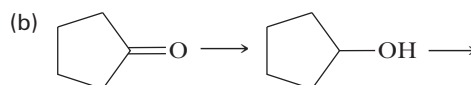
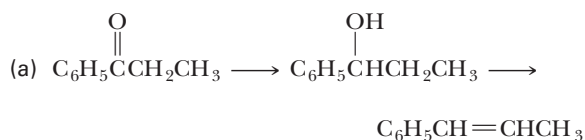
12.38 Show the reagents and conditions that will bring about the conversion of cyclohexanol to cyclohexanecarbaldehyde: (See Example 12.7)



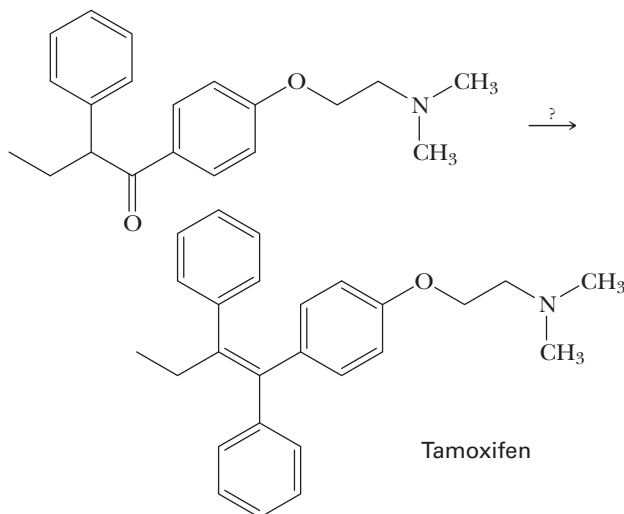
12.39 Starting with cyclohexanone, show how to prepare these compounds (in addition to the given starting material, use any other organic or inorganic reagents, as necessary): (See Example 12.7)

- Cyclohexanol
- Cyclohexene
- Bromocyclohexane
- 1-Methylcyclohexanol
- 1-Methylcyclohexene
- 1-Phenylcyclohexanol
- 1-Phenylcyclohexene
- Cyclohexene oxide
- trans*-1,2-Cyclohexanediol

12.40 Show how to bring about these conversions (in addition to the given starting material, use any other organic or inorganic reagents, as necessary): (See Example 12.7)

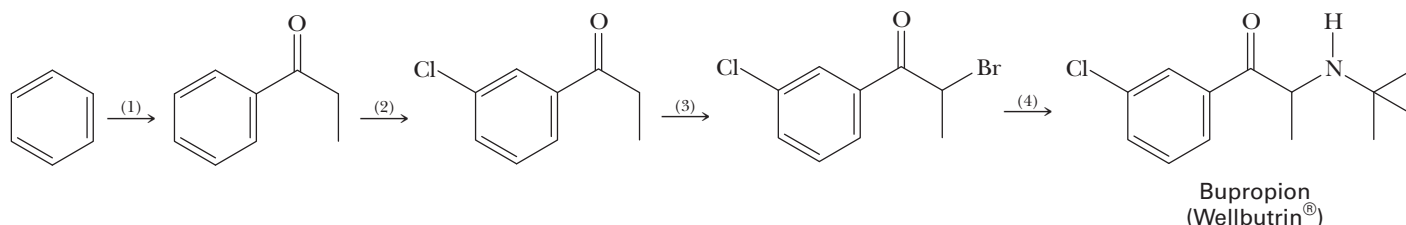


***12.41** Many tumors of the breast are estrogen dependent. Drugs that interfere with estrogen binding have anti-tumor activity and may even help prevent the occurrence of tumors. A widely used antiestrogen drug is tamoxifen: (See Example 12.7)



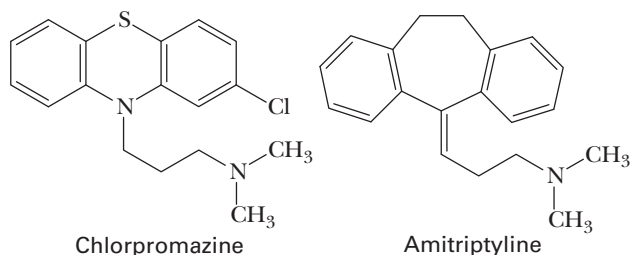
- How many stereoisomers are possible for tamoxifen?
- Specify the configuration of the stereoisomer shown here.
- Show how tamoxifen can be synthesized from the given ketone using a Grignard reaction, followed by dehydration.

***12.42** Following is a possible synthesis of the antidepressant bupropion (Wellbutrin®): (See Example 12.7)



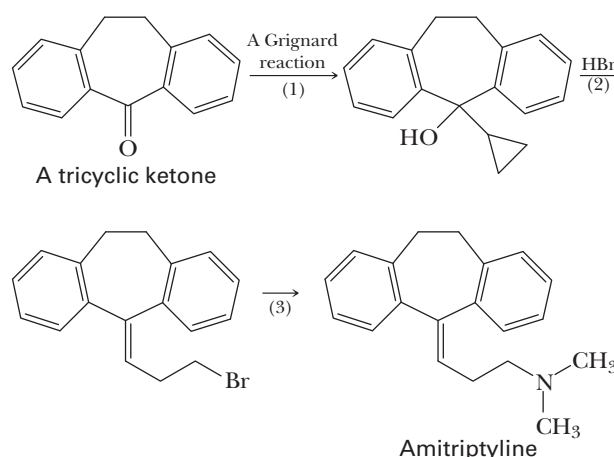
Show the reagents that will bring about each step in this synthesis.

***12.43** The synthesis of chlorpromazine in the 1950s and the discovery soon thereafter of the drug's antipsychotic activity opened the modern era of biochemical investigations into the pharmacology of the central nervous system. One of the compounds prepared in the search for more effective antipsychotics was amitriptyline. (See Example 12.7)



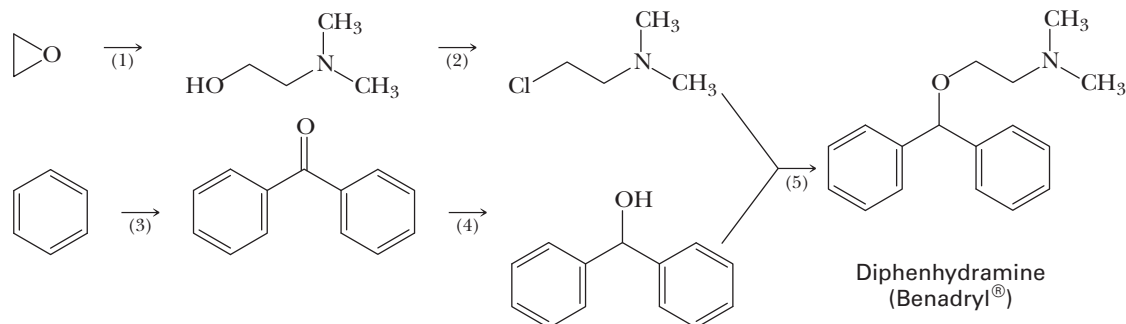
Surprisingly, amitriptyline shows antidepressant activity rather than antipsychotic activity. It is now known that amitriptyline inhibits the reuptake of norepinephrine and serotonin from the synaptic cleft. Because the reuptake of these neurotransmitters is inhibited, their effects are potentiated. That is, the two neurotransmitters remain available to interact with serotonin and norepinephrine receptor sites

longer and continue to cause excitation of serotonin and norepinephrine-mediated neural pathways. The following is a synthesis for amitriptyline:



- Propose a reagent for Step 1.
- Propose a mechanism for Step 2. (Note: It is not acceptable to propose a primary carbocation as an intermediate.)
- Propose a reagent for Step 3.

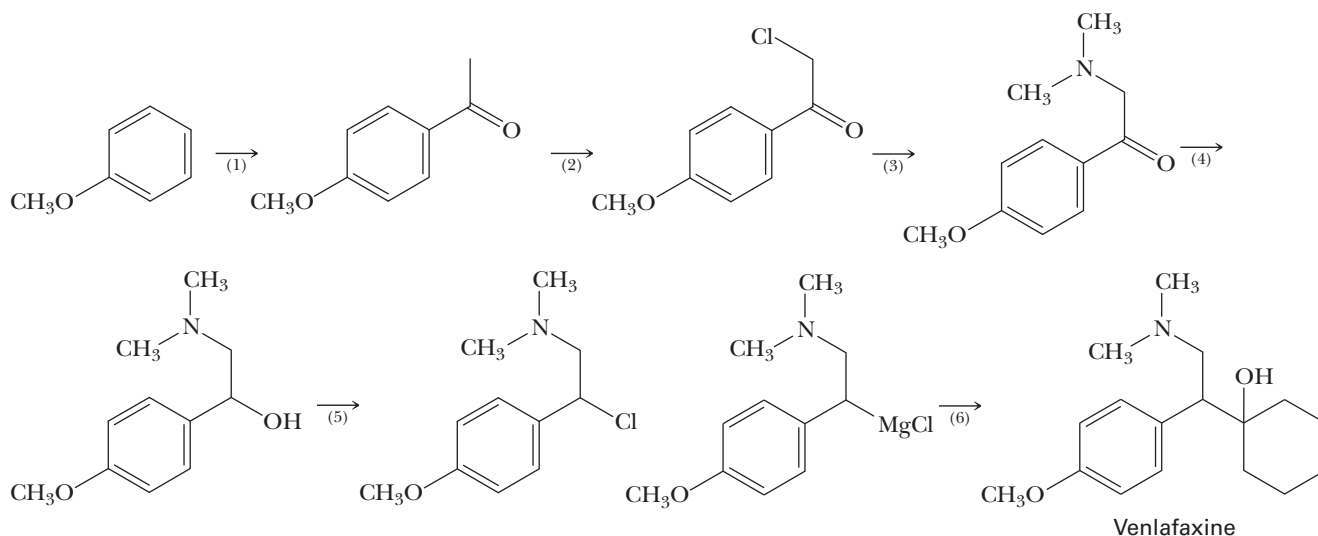
***12.44** Following is a synthesis for diphenhydramine: (See Example 12.7)



The hydrochloride salt of this compound, best known by its trade name, Benadryl®, is an antihistamine.

- Propose reagents for Steps 1 and 2.
- Propose reagents for Steps 3 and 4.
- Show that Step 5 is an example of nucleophilic aliphatic substitution. What type of mechanism— S_N1 or S_N2 —is more likely for this reaction? Explain.

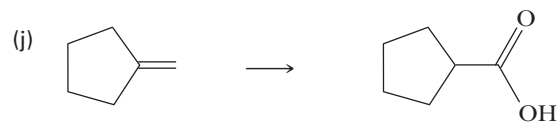
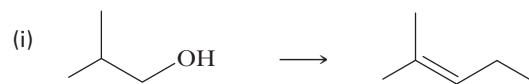
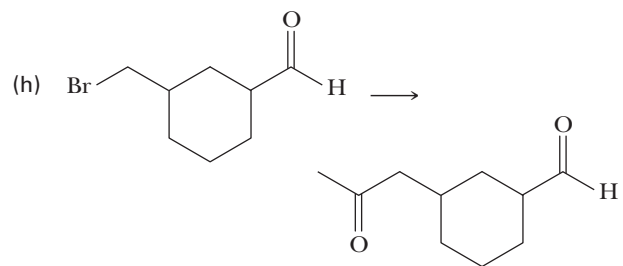
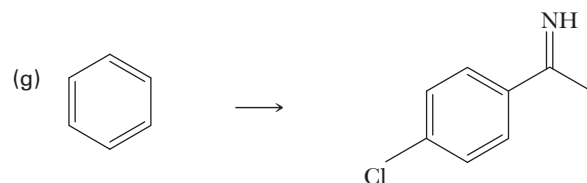
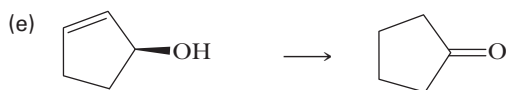
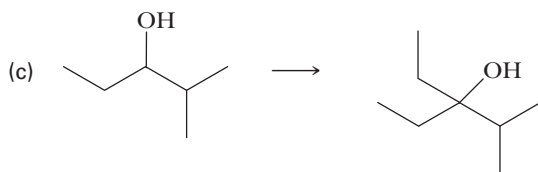
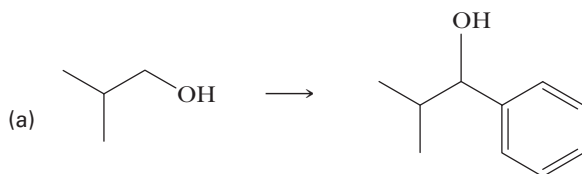
***12.45** Following is a synthesis for the antidepressant venlafaxine: (See Example 12.7)

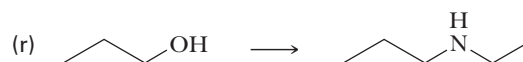
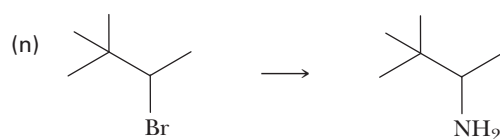
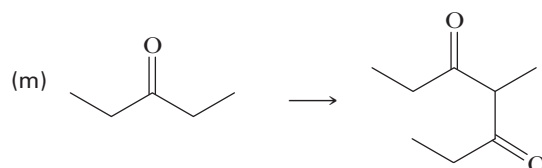
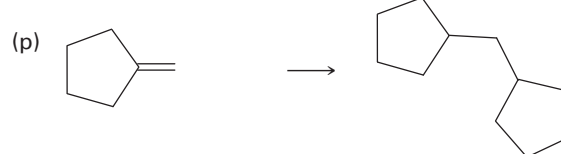
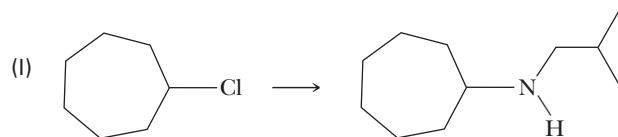
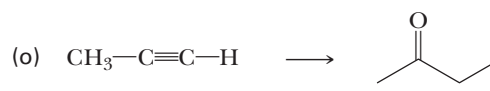


- Propose a reagent for Step 1, and name the type of reaction that takes place.
- Propose reagents for Steps 2 and 3.
- Propose reagents for Steps 4 and 5.
- Propose a reagent for Step 6, and name the type of reaction that takes place.

CHEMICAL TRANSFORMATIONS

12.46 Test your cumulative knowledge of the reactions learned thus far by completing the following chemical transformations. *Note:* Some will require more than one step.



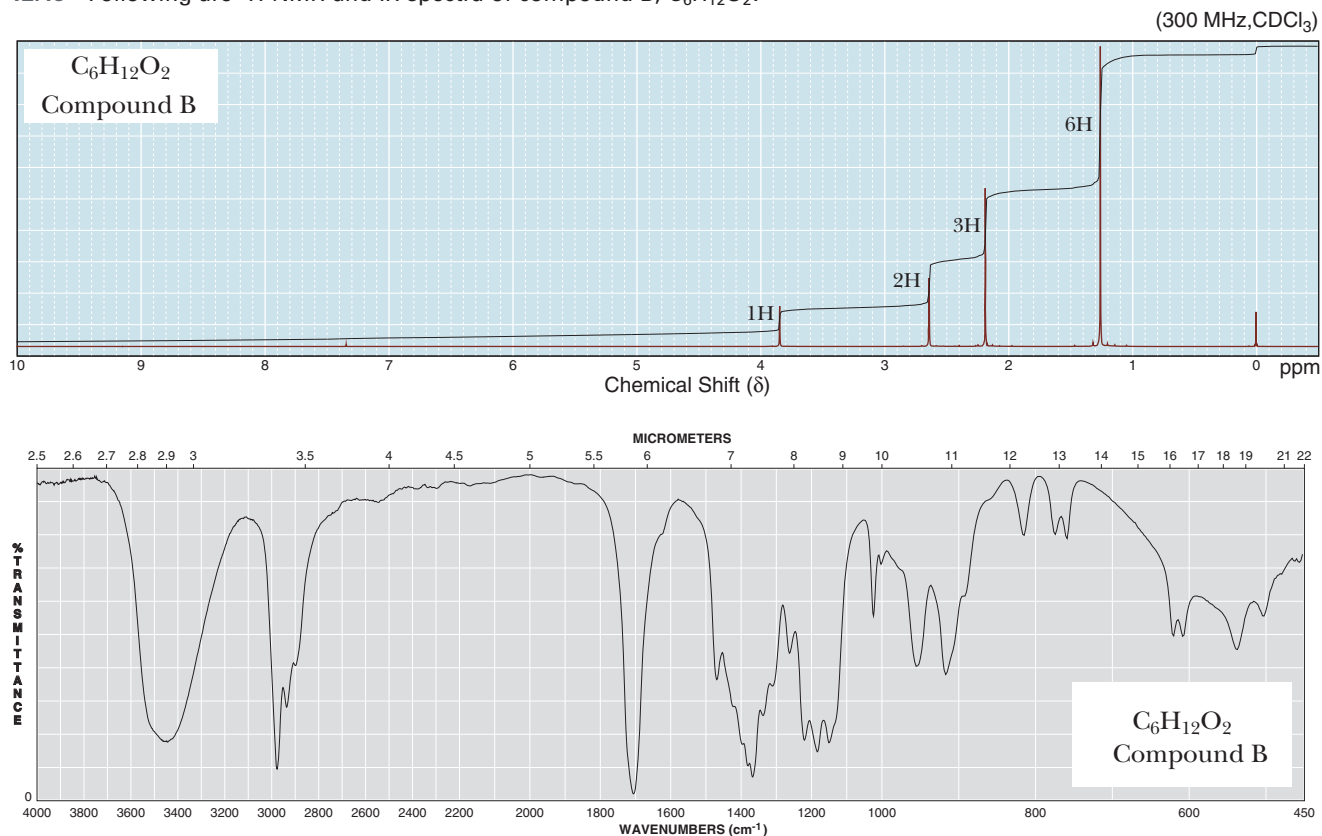


SPECTROSCOPY

12.47 Compound A, $\text{C}_5\text{H}_{10}\text{O}$, is used as a flavoring agent for many foods that possess a chocolate or peach flavor. Its common name is isovaleraldehyde, and it

gives ^{13}C -NMR peaks at δ 202.7, 52.7, 23.6, and 22.6. Provide a structural formula for isovaleraldehyde and give its IUPAC name.

12.48 Following are ^1H -NMR and IR spectra of compound B, $\text{C}_6\text{H}_{12}\text{O}_2$:



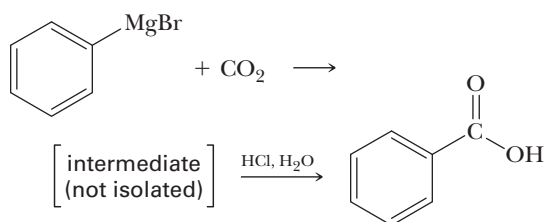
Propose a structural formula for compound B.

- 12.49** Compound C, $C_9H_{18}O$, is used in the automotive industry to retard the flow of solvent and thus improve the application of paints and coatings. It

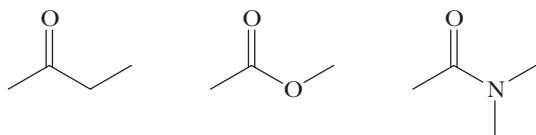
yields ^{13}C -NMR peaks at δ 210.5, 52.4, 24.5, and 22.6. Provide a structure and an IUPAC name for compound C.

LOOKING AHEAD

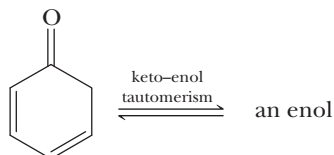
- 12.50** Reaction of a Grignard reagent with carbon dioxide, followed by treatment with aqueous HCl, gives a carboxylic acid. Propose a structural formula for the bracketed intermediate formed by the reaction of phenylmagnesium bromide with CO_2 , and propose a mechanism for the formation of this intermediate:



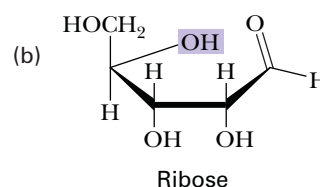
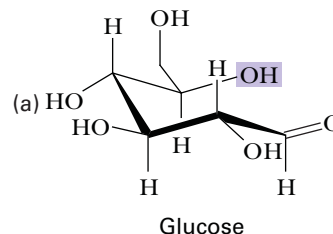
- 12.51** Rank the following carbonyls in order of increasing reactivity to nucleophilic attack, and explain your reasoning.



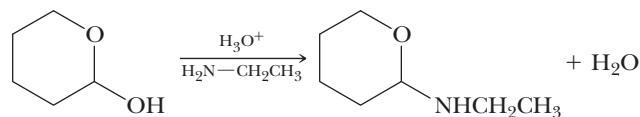
- 12.52** Provide the enol form of this ketone and predict the direction of equilibrium:



- 12.53** Draw the cyclic hemiacetal formed by reaction of the highlighted $-OH$ group with the aldehyde group:

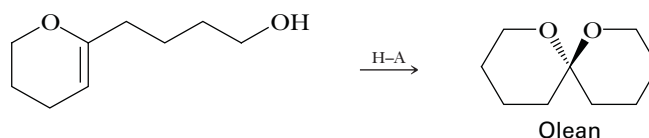


- 12.54** Propose a mechanism for the acid-catalyzed reaction of the following hemiacetal, with an amine acting as a nucleophile:



GROUP LEARNING ACTIVITIES

- 12.55** Pheromones are important organic compounds in agriculture because they represent one means of baiting and trapping insects that may be harmful to crops. Olean, the sex pheromone for the olive fruit fly, *Dacus oleae*, can be synthesized from the hydroxyenol ether shown by treating it with a Brønsted acid (H-A).



As a group, answer the following questions related to this agriculturally important product:

- Name the functional group in Olean.
- Propose a mechanism for the reaction. *Hint:* The mechanism consists of the following patterns: (1) add a proton, (2) reaction of an electrophile and a nucleophile to form a new covalent bond, and (3) take a proton away.
- Is Olean chiral? If so, how many stereoisomers are possible? *Hint:* Build a model of olean. Then build a second model in which the two central C—O bonds are swapped.
- Predict the product formed by acid-catalyzed hydrolysis of Olean.