

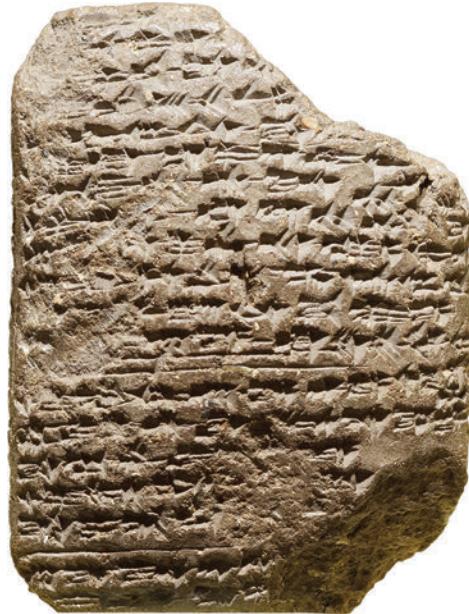
WHAT'S AHEAD

- 28.1 ► Aldehydes, Ketones, and the Carbonyl Group
- 28.2 ► Preparation of Aldehydes and Ketones
- 28.3 ► Reactions of Aldehydes and Ketones
- 28.4 ► Carbohydrates

28

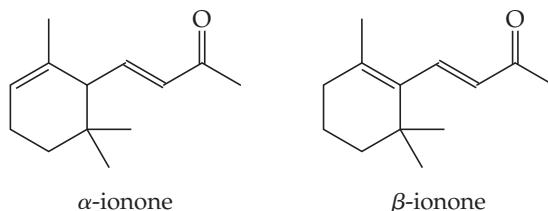
ALDEHYDES, KETONES, AND CARBOHYDRATES

28.1 | Aldehydes, Ketones, and the Carbonyl Group



The first written reference to a chemist occurred about 4000 years ago. The perfume maker Tapputi is mentioned on a cuneiform tablet from Mesopotamia. She is said to have distilled flowers and essential oils in order to extract their fragrant essence. Over the centuries, there have been many reports in documents right across the ancient world of similar activities. There are, of course, very many different substances that are used in the perfume industry however, the aldehyde and ketone functional groups are frequently encountered.

For example, a class of compounds called the ionones are central to the fragrance of roses and violets. They may be formed from α -carotene by an enzyme-mediated reaction. For example, a class of compounds called the ionones are central to the fragrance. A mixture of α -ionone and β -ionone results in the scent of violets, while β -ionone is a significant contributor to the scent of roses.



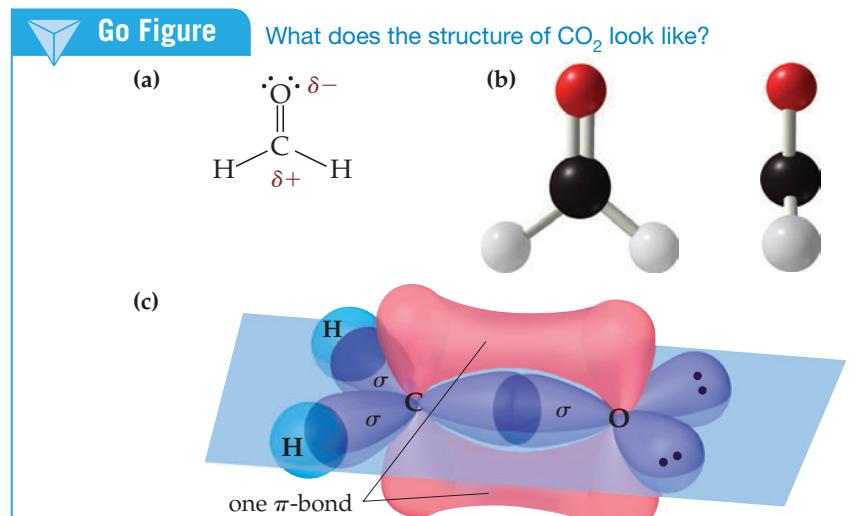
By the end of this section, you should be able to:

- Recognize and systematically name simple aldehydes and ketones.

Many important functional groups contain a double bond between carbon and oxygen—a combination of atoms called the **carbonyl group**. In Table 24.8, the carbonyl group appears in the aldehyde, ketone, carboxylic acid, ester and amide functional groups. The chemistry of the latter three functional groups differs from that of aldehydes and ketones and so will be dealt with in the next chapter. The geometry of the carbonyl group is similar to that of an alkene. The presence of the carbon–oxygen double bond (Figure 28.1) signifies that both the carbon and oxygen atoms are sp^2 hybridized. That is, a set of hybridized orbitals forms the σ -bond and a set of unhybridized p orbitals forms the π -bond of the carbon–oxygen double bond by direct overlap. Figure 28.1(c) illustrates the bonding in methanal (formaldehyde), the simplest of all the carbonyl-containing compounds. Because the oxygen in the carbonyl group is sp^2 hybridized, its lone pairs have a trigonal planar arrangement. Notice the polarity of the C—O group, which is due to the difference in electronegativity between the carbon atom and the more electron-rich oxygen atom. This polarity, and the nature of the π -bond, is very important for the reactivity of carbonyl compounds.

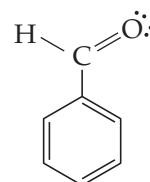
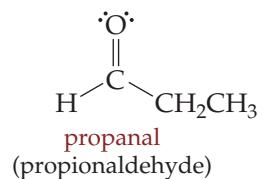
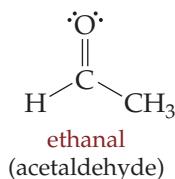
The carbonyl double bond is shorter, stronger and more polarized than a carbon–carbon double bond.

	Length	Bond enthalpy
$C=O$	123 pm	745 kJ/mol
$C=C$	134 pm	611 kJ/mol

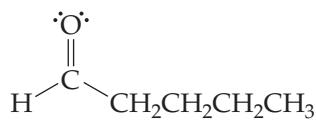
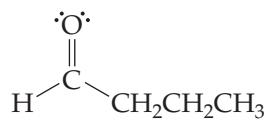


▲ **Figure 28.1** The carbonyl group of methanal. (a) The structural formula; (b) a molecular model representation, in front-on and side-on views; (c) a molecular orbital view of the bonding, indicating σ - and π -bonds.

An **aldehyde** is characterized by the functional group CHO. The structures and systematic names of five simple aldehydes (with common names in blue) are:



benzaldehyde

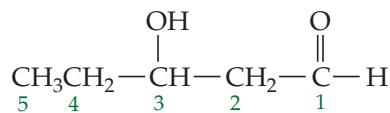


butanal
(butyraldehyde)

pentanal

Aldehyde nomenclature requires the selection of the parent alkane (longest alkyl chain) containing the carbonyl group. The carbon of the carbonyl group constitutes part of that parent alkane's name. The suffix *-ane* is partly retained, replacing the *e* with *al*. (Note the difference with benzaldehyde. Here the aldehyde group lies outside the ring system. Aromatic compounds such as this have their own unique nomenclature.) As you can see from these examples, an aldehyde group, by definition, must also occur at the beginning (or end) of a hydrocarbon chain. As a result, there is no need to number the position of the aldehyde—it is always assigned position 1.

In terms of hierarchy, the aldehyde group takes precedence over alkene and alkyne functionality. Two aliphatic aldehyde examples illustrate this:

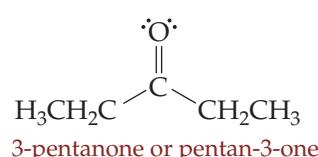
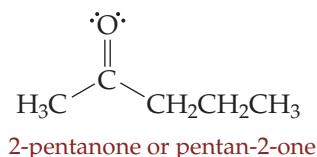
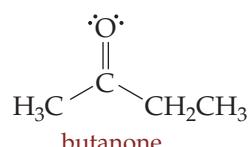
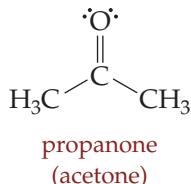


3-hydroxypentanal



pent-2-enal

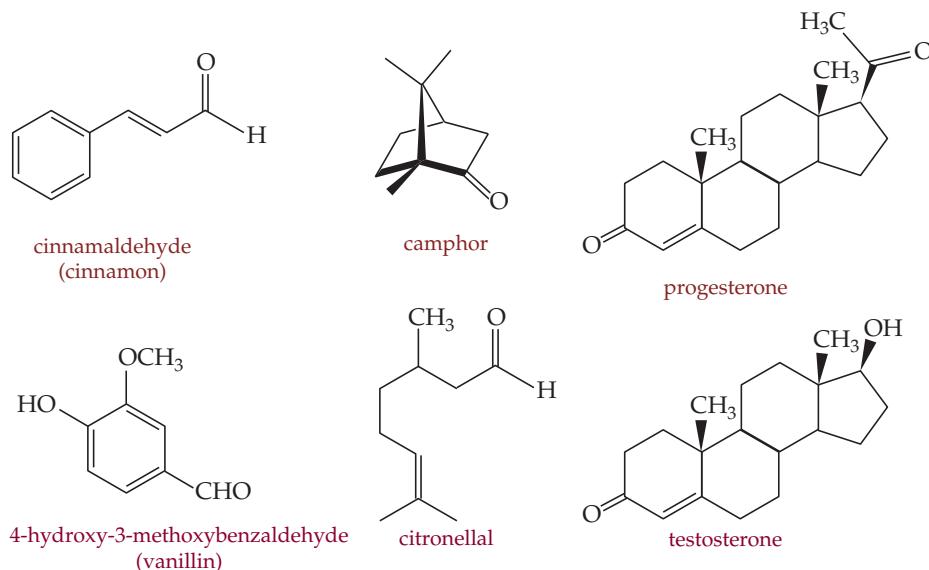
In **ketones** the carbonyl group occurs within the interior of a hydrocarbon chain and is therefore flanked on either side by carbon atoms:



In naming ketones, the parent alkane is derived from the longest chain containing the carbonyl group. The suffix *-ane* is partly retained, replacing the *e* with *one*. Ketones containing parent alkanes greater than C4 can exist as constitutional isomers, so require numbering to define unambiguously the position of the carbonyl group. Two representations of the names to describe the compound are shown and are commonly interconverted.

Many compounds found in nature possess an aldehyde or ketone functional group. Vanilla and cinnamon flavorings are derived from the naturally occurring aldehydes, vanillin, and cinnamaldehyde. Citronellal is a naturally occurring insect repellent. Carvone

(see figure 27.7) and camphor are ketones that impart characteristic flavors and scents. Steroids, such as testosterone and progesterone, are also ketones. Testosterone is predominantly a male hormone; progesterone is predominantly a female hormone used by the body to stop further ovulation after an ovum has been fertilized.



Ketones are less reactive than aldehydes and are used extensively as solvents. Acetone, which boils at 56 °C, is the most widely used ketone. Acetone is completely miscible with water, yet it dissolves a wide range of organic substances. These features made it ideal for use as an early nail polish remover, among other domestic uses. Butanone ($\text{CH}_3\text{COCH}_2\text{CH}_3$), which boils at 80 °C, is used as an industrial solvent.



Sample Exercise 28.1

Naming Aldehydes and Ketones

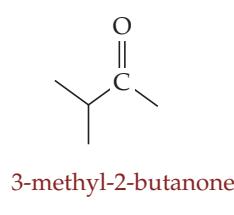
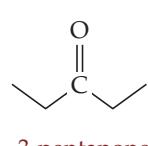
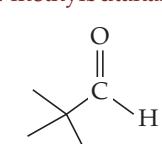
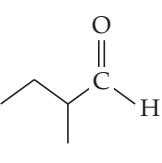
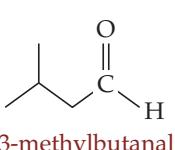
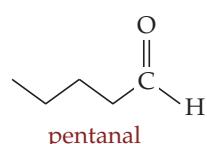
Write the structural formulas for all aldehydes and ketones of molecular formula $\text{C}_5\text{H}_{10}\text{O}$ and name each structure systematically.

SOLUTION

Analyze We are given a molecular formula and asked to generate as many different aldehydes and ketones as possible. We are given one oxygen atom in the molecular formula.

Plan Draw out the carbon skeleton, add the carbonyl group starting at one end (this will give an aldehyde) then progress this along the chain.

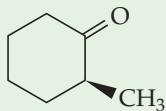
Solve



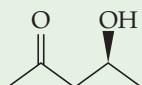
► Practice Exercise

Name these compounds including stereochemistry:

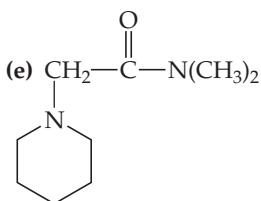
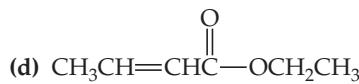
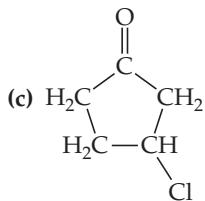
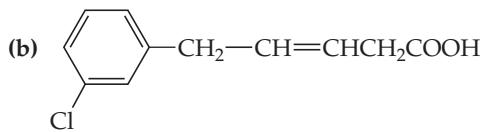
(a)



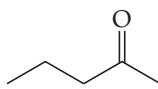
(b)

**Self-Assessment Exercise****28.1** What is the systematic name of citranellal?

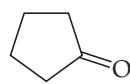
- (a) 3,7-dimethyloct-6-enal
 (b) 3,7,7-trimethylhept-6-enal
 (c) 2,6-dimethyloct-2-enal

Exercises**28.2** Why do propanone and butanone not require position numbers for the carbonyl group?**28.3** Identify the functional groups in each of the following compounds:**28.4** Give the structural formula for (a) an aldehyde that is an isomer of acetone, (b) an ether that is an isomer of propanone.**28.5** Name the following compounds:

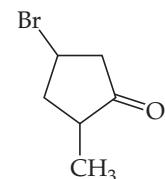
(a)



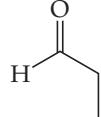
(b)



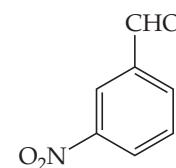
(c)



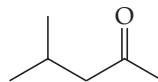
(d)



(e)



(f)



28.1 (a)

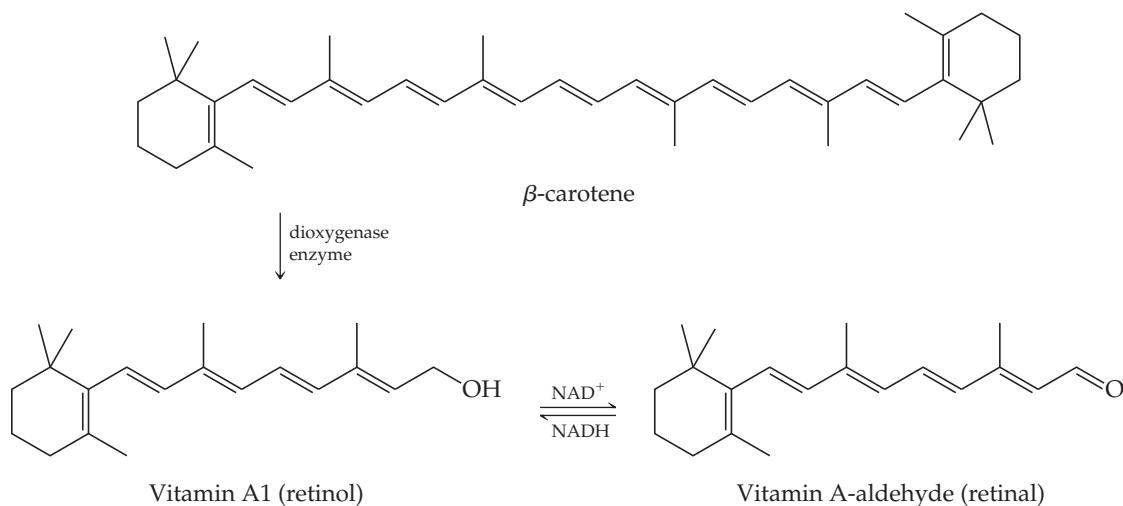
Answers to Self-Assessment Exercises



28.2 | Preparation of Aldehydes and Ketones



Vitamin A is essential for the function of vision as well as many other processes involving our immune system, gene transcription, and skin health. This group of vitamins may be obtained directly from animal sources, for example cod liver oil, or derived from the carotenes, which are present in many fruits and vegetables. The orange color of carrots is due to β -carotene, which is the principle vegetable source of retinol—Vitamin A1. Retinol is the form in which the vitamin is stored in the body and may be easily converted to retinal, which enters the visual cycle.

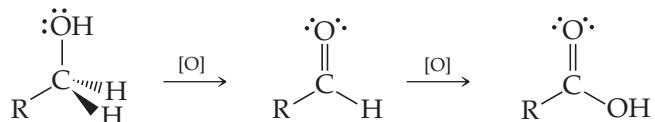


In this section, we look at the synthesis of aldehydes and ketones by two methods, the principal of which is the oxidation of an alcohol to the carbonyl compound. By the end of the section, you should be able to:

- Understand the preparation of aldehydes and ketones by an oxidation reaction.

Go Figure

What is the major organic product formed by the oxidation of 1-propanol, 2-propanol?



Number of

a 1° alcohol

1

an aldehyde

2

a carboxylic acid

3

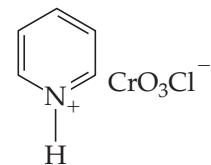
▲ Figure 28.2 Oxidation of primary alcohols. Primary alcohols are converted to carboxylic acids under standard experimental conditions. The symbol [O] represents an oxidation. To demonstrate the oxidation (that is, addition of oxygen) imagine C=O as being $2 \times C-O$.

Aldehydes and ketones are generally prepared by using similar reactions. Here, we concentrate on two sample types. The first involves the oxidation of alcohols, which is the standard technique for their preparation. The second involves the ozonolysis of alkenes.

Oxidation of 1° and 2° Alcohols

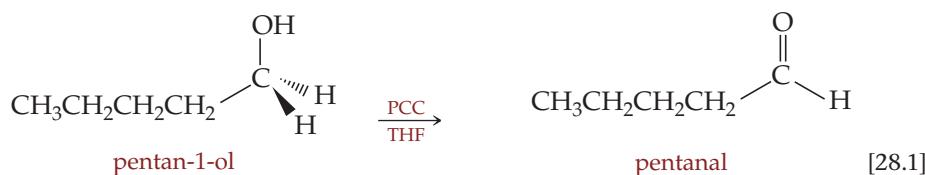
When primary alcohols are oxidized using strong oxidising agents such as potassium dichromate ($K_2Cr_2O_7$) in H_2SO_4 or chromic acid ($CrO_3/H_2O/H_2SO_4$), they are usually converted to the corresponding carboxylic acid, via the intermediary aldehyde (Figure 28.2).

Pyridinium chlorochromate (PCC), on the other hand, is a mild oxidizing agent capable of converting primary alcohols to aldehydes.

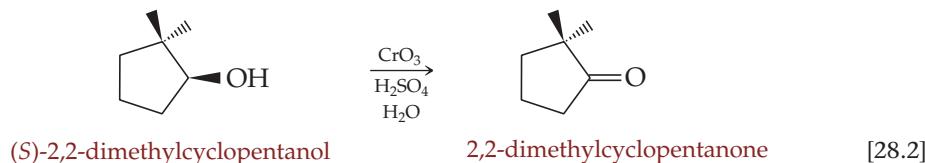


pyridinium chlorochromate

Unlike other oxidising agents, PCC is soluble in organic solvents such as tetrahydrofuran (THF) and dichloromethane. The oxidation of pentan-1-ol using this reagent yields the aldehyde as the major oxidation product.



Secondary alcohols are oxidized by PCC, chromic acid or potassium dichromate to yield the corresponding ketone. Further reaction is restricted because it would require the breaking of a C—C bond.

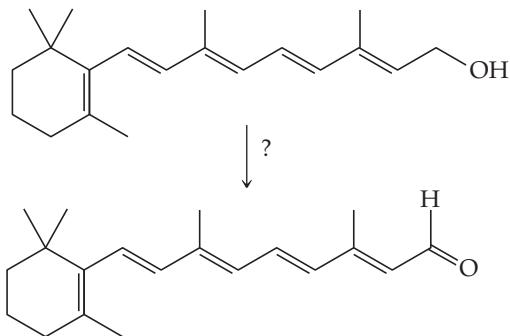


Tertiary alcohols resist oxidation altogether, as a C—C bond would have to be broken for any oxidation to occur.

Sample Exercise 28.2

Oxidation of Alcohols

What reagent would you use to convert retinol (vitamin A) into retinal in the laboratory?



SOLUTION

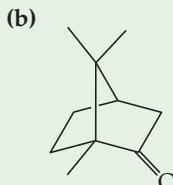
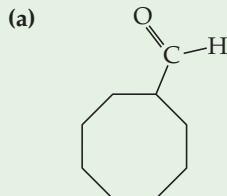
Analyze We are asked how to convert an alcohol to an aldehyde.

Plan Determine the type of alcohol, where the conversion takes place and what is retained from starting material to product.

Solve This conversion is the oxidation of a primary alcohol to an aldehyde. To achieve this, pyridinium chlorochromate in acetone is the best reagent. The mild reactivity of this reagent does not affect the alkene groups and produces the aldehyde in excellent yield. Note that the reaction is conducted in acetone solvent. This solvent is useful for oxidations because it cannot be further oxidized under the experimental conditions employed.

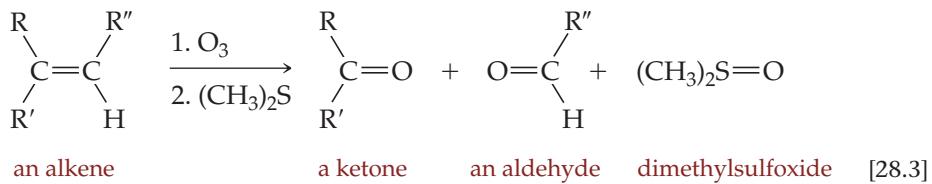
► Practice Exercise

What starting alcohol would you use to prepare the following compounds?

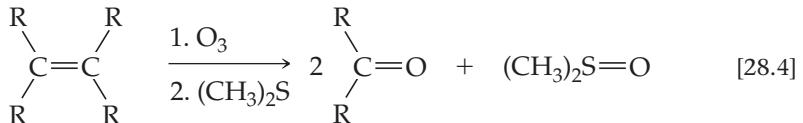


Ozonolysis

Aldehydes and ketones can be prepared in good yield by the reaction of alkenes with ozone, followed by a mild reduction using dimethylsulfide. This process, called **ozonolysis**, is a synthetically useful way of generating aldehydes and ketones.



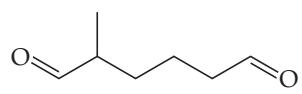
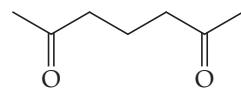
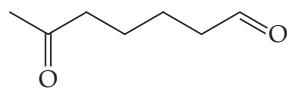
Whether an aldehyde, ketone or a mixture of the two are formed depends solely on the substitution of the alkene. For symmetrical alkenes, only one product is formed.



In some instances, ozonolysis leads to the formation of one high molecular weight and one low molecular weight product, which can easily be separated by distillation.

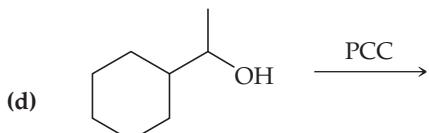
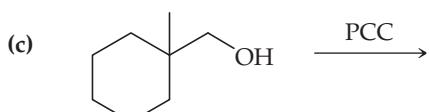
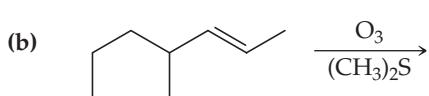
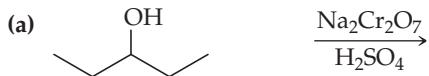
Self-Assessment Exercise

28.6 Which carbonyl compound is formed on treatment of 1-methylcyclohexene with ozone followed by dimethyl sulfide?

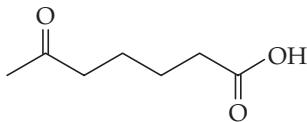


Exercises

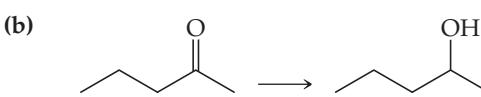
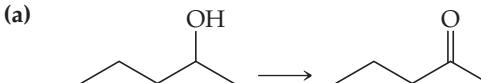
28.7 Provide the structure of the major organic products in the following reactions:



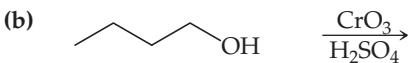
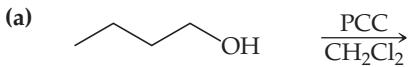
28.8 An unknown alkene was treated with ozone/dimethylsulfide and then with $\text{K}_2\text{Cr}_2\text{O}_7$, forming the following product. What was the alkene?



28.9 Suggest ways of conducting the following transformations.



28.10 Suggest a possible stable reaction product for each of the following reactions:



28.6 (a)

Answers to Self-Assessment Exercises

28.3 | Reactions of Aldehydes and Ketones

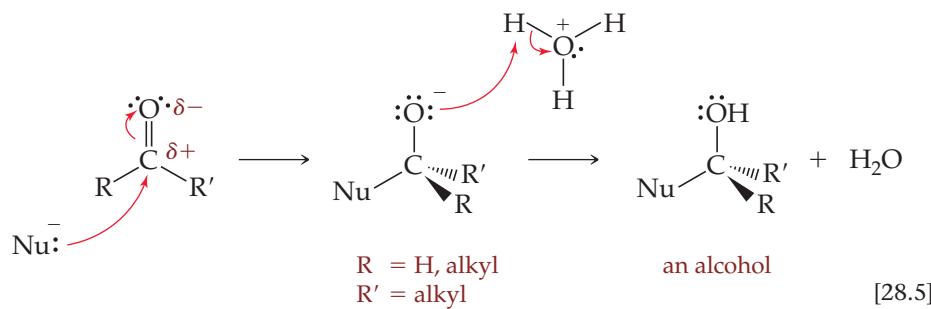


Throughout history, dyes have been used to color fabrics, as paints, and for skin coloring. The Picts of ancient Scotland were literally “The Painted People,” who used the leaves of the woad plant (*Isatis tinctoria*) to produce a deep blue color. A more abundant source was provided by the plant *Indigofera tinctoria*, which grows in the tropics. As early as two thousand years ago, there was trade in the dye from India to the Mediterranean, where the highly prized dye became known as indigo. It was one of the few dyes that could color cotton in a process that involved soaking the cloth in a vat containing the water-soluble, reduced form of the dye and hanging the cloth to dry where aerial oxidation would produce the insoluble blue pigment familiar to us in denim jeans. The dye was very expensive, and, when Adolf von Baeyer discovered a synthetic route to indigo from 2-nitrobenzaldehyde and acetone, a new industry was born. He was awarded the Nobel Prize in chemistry in 1905 “in recognition of his services in the advancement of organic chemistry and the chemical industry, through his work on organic dyes and hydroaromatic compounds”.

Carbonyl compounds form the basis of many important synthetic transformations, and, by the end of this section, you should be able to:

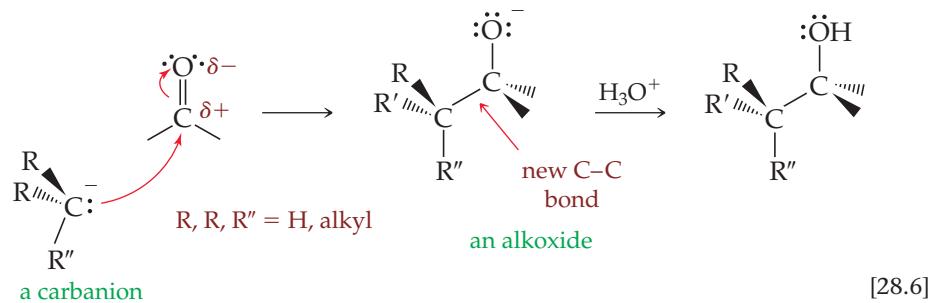
- Recognize a variety of nucleophilic addition reactions to carbonyl compounds
- Identify the structural factors that allow tautomerism
- Understand the mechanism of substitution α to a carbonyl group

The carbon in a carbonyl group has a partial positive charge. Consequently it is susceptible to nucleophilic attack. Many important synthetic reactions depend on this fact. In this section we concentrate on reactions where the tetrahedral intermediate formed from the initial attack on an aldehyde or ketone by a nucleophile is reacted with acid to produce an alcohol. Generally, the reaction can be described as:

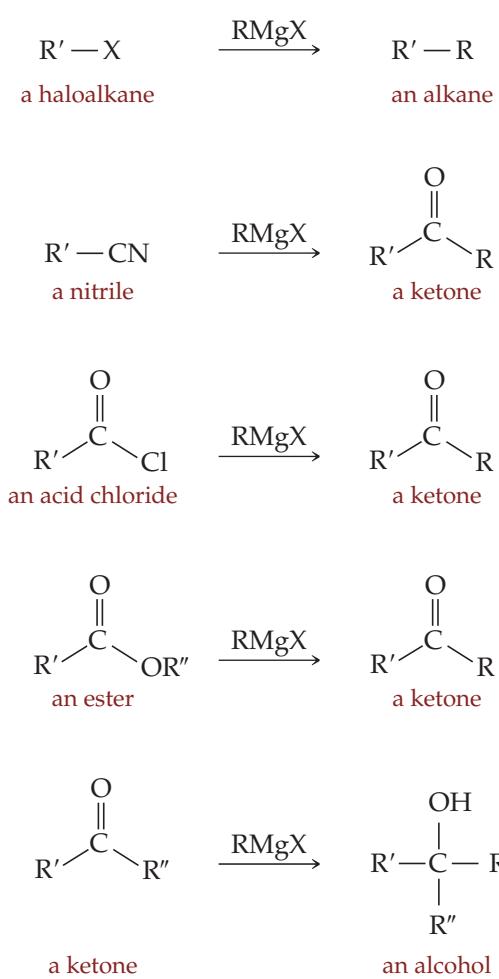
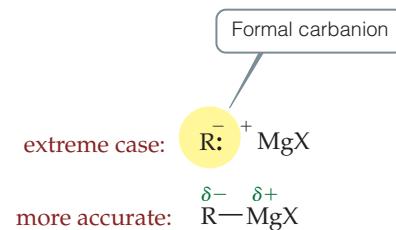


Addition of Carbon Nucleophiles—Grignard Reactions

Of the reaction types available to organic chemists, those that form new C—C bonds are especially useful. One example of C—C bond formation is the reaction of carbon nucleophiles, or **carbanions**, with carbonyl compounds:



Organometallic compounds such as Grignard reagents are a useful source of carbanions. An organometallic compound contains a bond between a carbon atom and a metal (designated C—M, where M = metal). The nature of the C—M bond can be ionic or covalent, depending on the choice of the metal. A **Grignard reagent** is one that uses magnesium as the metal, forming organomagnesium compounds of the general

**▲ Figure 28.3** The versatility of Grignard reagents.**▲ Figure 28.4** Grignard reagents as carbanion equivalents. The bonding between carbon and magnesium is best described as polar covalent. It is still useful to think of Grignard reagents as a form of carbanion.

type $RMgX$, where $R =$ alkyl or aryl, and $X =$ halide. For this discovery in 1902 and the general usefulness of these reagents in organic synthesis (**Figure 28.3**), Victor Grignard (1871–1935) shared the 1912 Nobel Prize for Chemistry with Paul Sabatier (1854–1941).

Many C—M bonds are covalent, but in bonds between carbon and more electropositive metals, the electrons that make up the bond reside closer to the carbon atom. Most C—M bonds, such as those formed between carbon and magnesium, are classed as polar covalent (**Figure 28.4**). Although an alkyl group bonded to a metal is not formally a carbanion, we can approximate it as such. Grignard reagents are formed by the addition of magnesium metal to a haloalkane in an ether solvent (for example, THF or diethyl ether). This exothermic reaction is sometimes called an oxidative metallation because the magnesium metal is oxidized to Mg^{2+} . The Grignard reagents are named as the alkyl magnesium halide.

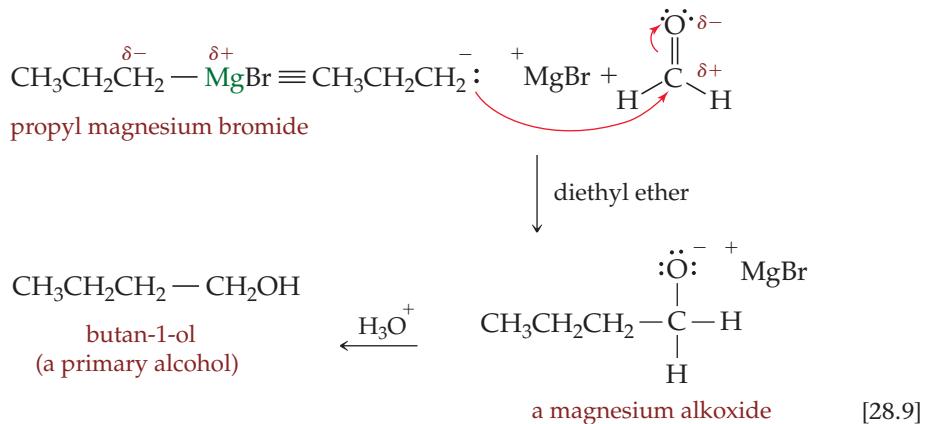


The effect of magnesium insertion changes the polarity of the carbon that used to bear the halogen from positively polarized to negatively polarized. This change has a dramatic effect on reactivity.

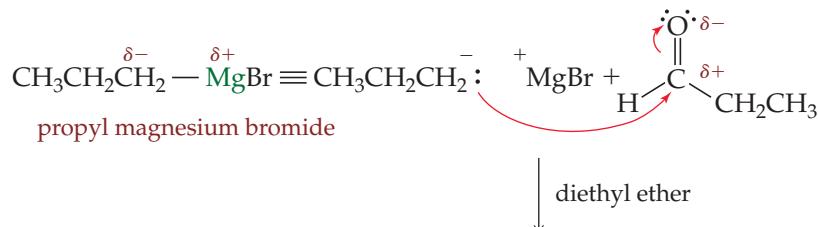
Grignard reagents are strong bases (as well as nucleophiles), so they are moisture-sensitive and tend to be prepared when needed rather than stored in a bottle. The presence of water will immediately protonate the Grignard reagent and generate the corresponding hydrocarbon.

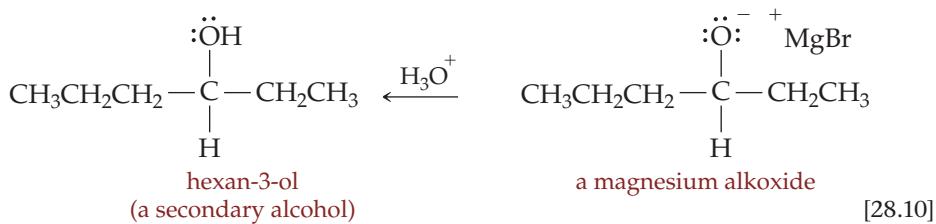


The type of alcohol formed (1° , 2° or 3°) in a Grignard reaction is dictated by the nature of the carbonyl compound used. For example, addition of the Grignard reagent propyl magnesium bromide to formaldehyde yields butan-1-ol, a 1° alcohol, upon aqueous workup.

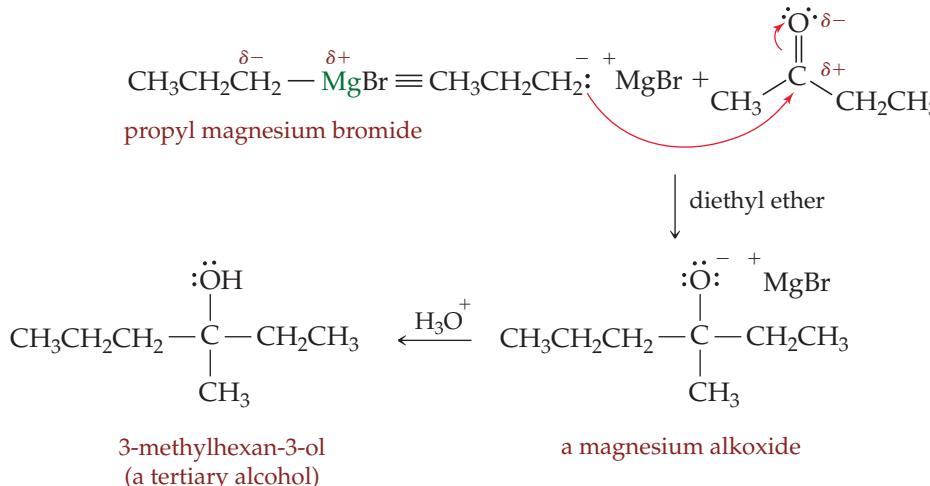


The addition of propyl magnesium bromide to any other aldehyde—for example, propanal—yields a 2° alcohol upon aqueous workup.





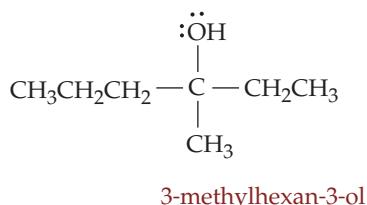
The addition of propyl magnesium bromide to any ketone, such as 2-butanone, yields a 3° alcohol upon aqueous workup.



Sample Exercise 28.3

Addition of Grignard Reagents

The compound 3-methylhexan-3-ol can be prepared from three different combinations of ketones and Grignard reagents. Show each combination.

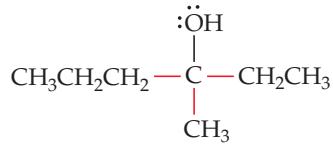


SOLUTION

Analyze How can 3-methylhexan-3-ol be formed from three different ketones?

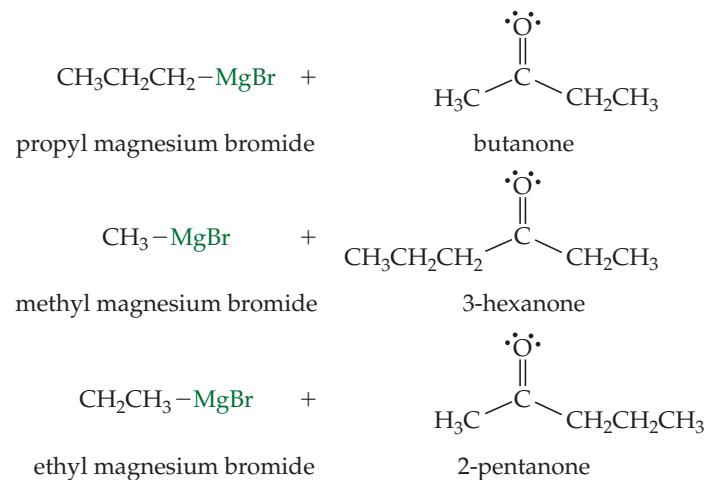
Plan Tertiary alcohols can be formed from ketones by reaction with carbanions and their equivalents. Since reaction about the C=O group leads to the formation of a C—C bond, we need to investigate the groups tethered off the C—OH group.

Solve First, let us identify in red the three C—C bonds that could be formed about the carbonyl carbon. This gives us a clue to the identification of ketones and Grignard reagents:



The C—OH grouping is derived from the carbonyl of the starting ketone. The substituents attached to this group could each be

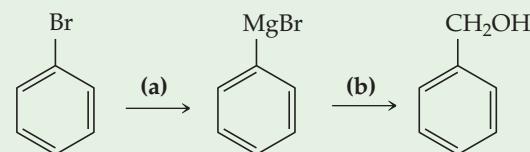
used to form the Grignard reagent. Hence, the three combinations are:



Continued

► Practice Exercise

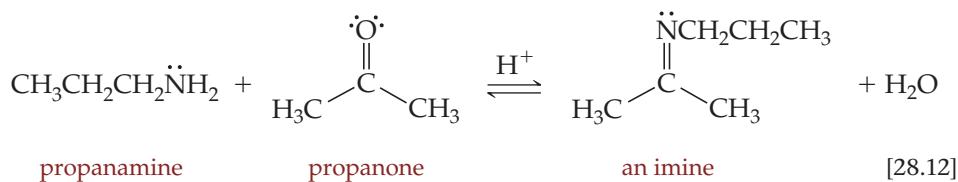
What reagents would you use to bring about the following transformations?



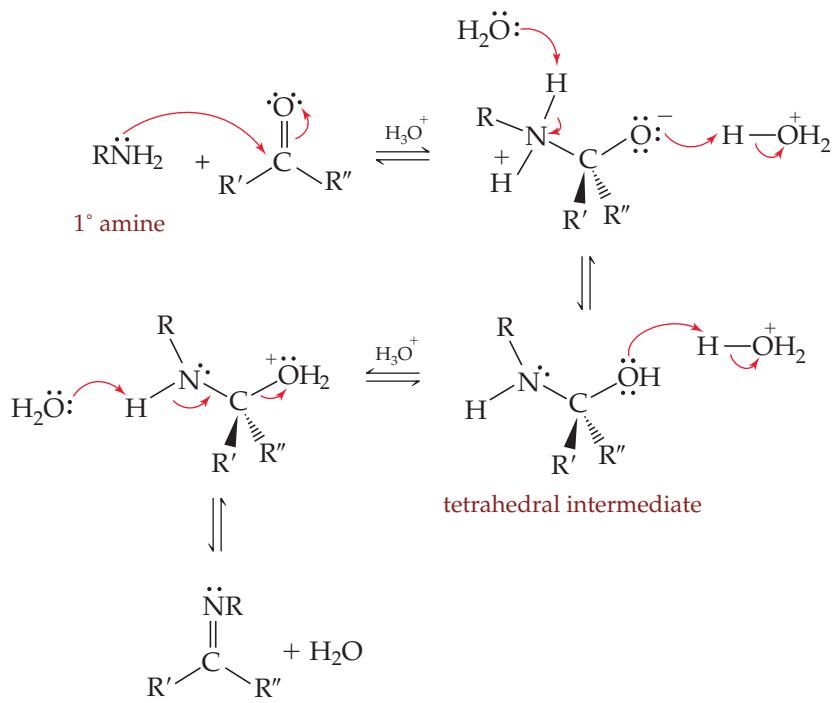
Addition of Nitrogen and Oxygen Nucleophiles: Formation of Imines and Acetals

The formation of new C—C bonds through the reaction of a carbonyl compound with a Grignard reagent is not only high yielding, but also occurs only in the forward direction. This means that the reaction is not under the same level of equilibrium control we have discussed for the hydration of an alkene or the dehydration of an alcohol. However, other nucleophiles are able to react with carbonyl compounds, under equilibrium conditions, to form stable compounds. The two most important reactions are those of carbonyl compounds with amines (nitrogen-containing weak organic bases) to form *imines*, and those of carbonyl compounds with alcohols to form *acetals* and *hemiacetals*. Both reactions have biological significance.

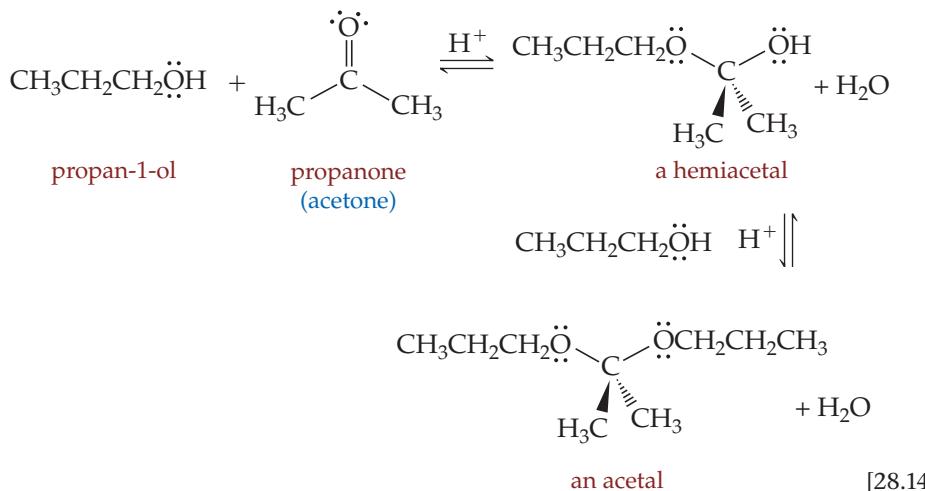
Imines, also known as Schiff bases, are formed by the acid-catalyzed condensation of a *primary amine* (RNH_2 , R = alkyl, aryl) an aldehyde or ketone. For example, the reaction of propanamine, an aliphatic 1° amine, with propanone is shown here. Imines are characterized by a C—N double bond. They have geometries similar to those of alkenes, with the lone pair occupying one of the trigonal planar positions.



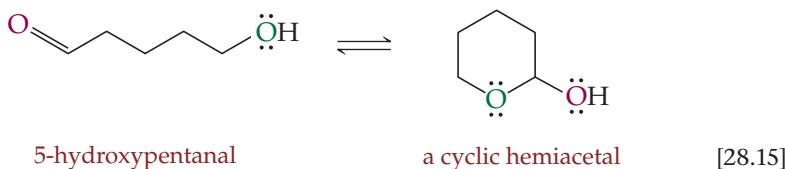
The mechanism of imine formation is shown in Equation 28.13. Attack of the nucleophilic amine on the electrophilic carbonyl carbon atom leads to a tetrahedral intermediate amino alcohol. The acid-catalyzed dehydration of this intermediate yields the imine. The reaction usually occurs at room temperature and in high yield. Removal of water as the reaction proceeds ensures near quantitative yields.



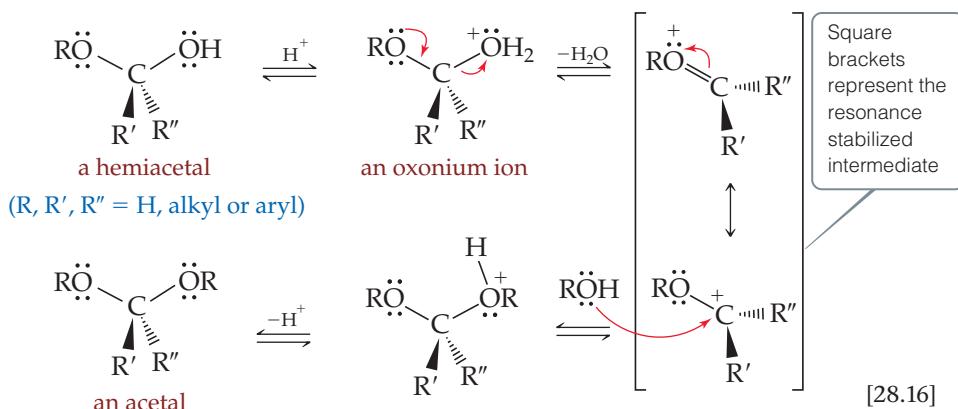
Acetals and **hemiacetals** are formed by the reaction of alcohols with aldehydes and ketones in the presence of an acid catalyst. In such reactions, the hemiacetal is formed in minor yield because it is relatively unstable. Further reaction with alcohol usually yields the acetal and water. Acetals are stable under basic and nucleophilic conditions, so provide a common way to protect aldehydes and ketones during complex reaction sequences in organic synthesis. Because the reaction is in equilibrium, acetal formation can be reversed by the addition of H_3O^+ .



Hemiacetals are important in the function of *carbohydrates*, a class of biologically active molecules, of which sugars and cellulose are members. Carbohydrates gain their stability by undergoing *intramolecular* hemiacetal formation. To do this, carbohydrates must have aldehyde and alcohol functionality within the same molecule and at a distance apart that allows for cyclization. Typically, cyclic hemiacetals are five-membered (furanose) or six-membered (pyranose) systems. The equilibrium between cyclic and acyclic compounds is heavily favored towards the cyclic hemiacetal. The cyclization of 5-hydroxypentanal demonstrates the principle.



The mechanism of acetal formation can be divided into two steps. The first, formation of the hemiacetal, follows a mechanism similar to that described for the reaction of amines with carbonyl compounds (without loss of water, Equation 28.13). Formation of the acetal from the hemiacetal is an acid-catalyzed process involving the generation of an oxonium ion. Loss of water leads to a resonance-stabilized carbocation. This carbocation reacts with another molecule of alcohol, which, after proton transfer, yields the acetal.



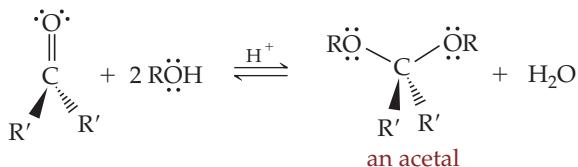
**Sample Exercise 28.4****Acetals**

Diols such as ethene glycol (1,2-ethanediol) are useful reagents with which to protect aldehydes and ketones in chemical syntheses. Give the product of the acid-catalyzed reaction of ethene glycol and cyclohexanone.

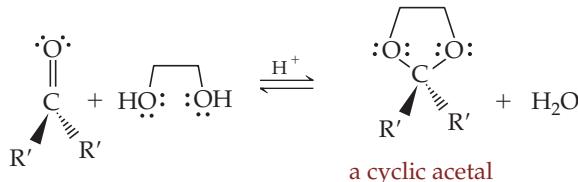
SOLUTION

Analyze We are asked for the outcome of a reaction between an alcohol functional group and a ketone.

Plan Acetals require the acid-catalyzed addition of two alcohols to a ketone:



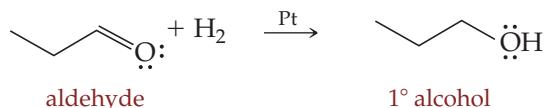
Solve Ethene glycol acts to satisfy this need because it is a diol. Hence the product of this reaction is

**► Practice Exercise**

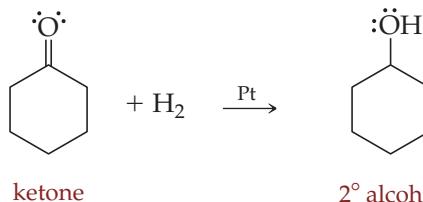
What product would you expect from the acid-catalyzed reaction of benzaldehyde and ethanol?

Reduction Reactions

Aldehydes and ketones are easily reduced to the corresponding primary and secondary alcohols, respectively. Catalytic hydrogenation, using Pd, Pt, Ni or Rh metal catalysts, is typically a high-yielding reaction and the product is easily isolated and purified.

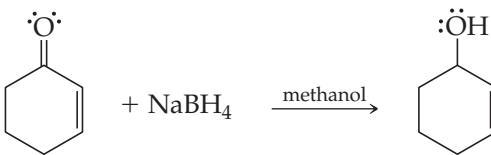
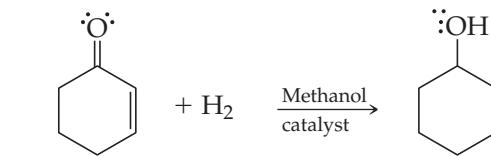


[28.17]



[28.18]

In a laboratory situation, the reduction of aldehydes and ketones using **metal hydrides** is preferred over catalytic hydrogenation because it selectively reduces the carbonyl group rather than any alkene double bonds present and no gas-handling equipment is required.

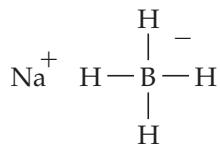


[28.19]

The two most common metal hydride reagents are sodium borohydride (NaBH_4) and lithium aluminum hydride (LiAlH_4). These compounds behave as a source of **hydride ion** (H^-),


Go Figure

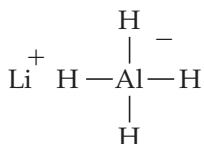
How soluble would sodium borohydride be in typical organic solvents? Why?



sodium borohydride

Non-reactive in water or methanol

Mild reductant

Selective for aldehydes
and ketones

lithium aluminum hydride

Highly reactive in water or methanol

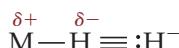
Powerful reductant

Reduces aldehydes, ketones,
carboxylic acids and esters

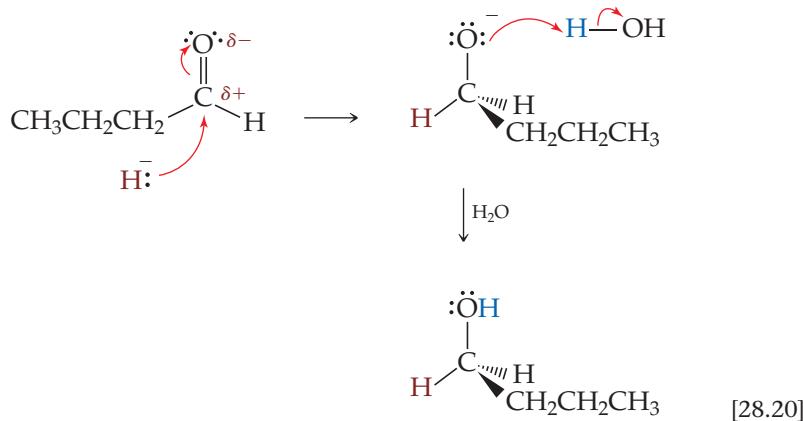
▲ **Figure 28.5 Metal hydrides.** The two most common metal hydrides for reduction are sodium borohydride and lithium aluminum hydride.

which is a powerful nucleophile. **Figure 28.5** shows the structural formula of both metal hydrides and compares their chemical reductive properties.

Metal hydrides act as a source of hydride ion (H^-) because they contain polar metal–hydrogen bonds, which place a partial negative charge on hydrogen in the same way as a negative charge is placed on carbon within a Grignard reagent:

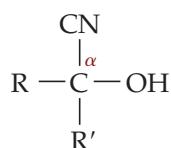


In fact, the mechanism for the reduction of an aldehyde or ketone by a metal hydride, which involves nucleophilic attack on the carbonyl group by hydride, followed by protonation, follows a similar pathway to that demonstrated for the Grignard reaction in Equation 28.10. A typical mechanism, showing the reduction of butanal using hydride, is



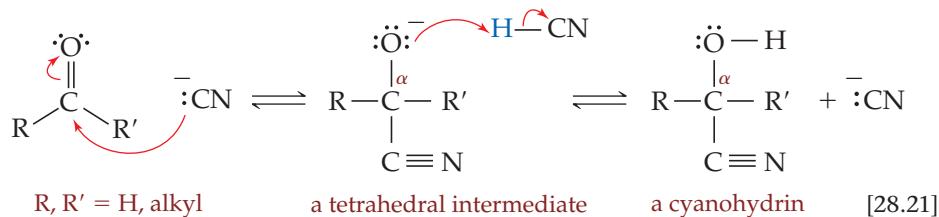
Cyanohydrins

Cyanohydrins are a class of compounds containing a hydroxy ($-\text{OH}$) and nitrile ($-\text{CN}$) group, both directly bonded to an α -carbon. Organic compounds containing the CN group are called **nitriles**. A cyanohydrin is therefore an *α -hydroxynitrile*.



a cyanohydrin

Cyanohydrins are formed by the addition of the cyanide ion ($\text{^-\text{CN}}$) to an aldehyde or ketone. Cyanide ion is the conjugate base of hydrogen cyanide (HCN), which is itself a weak acid ($\text{pK}_\text{a} \sim 9.2$). The cyanide ion is small, and because it is both a base and a strong nucleophile, it can add to the carbonyl group by a **nucleophilic addition** mechanism.



In the first step, the strong $\text{^-\text{CN}}$ nucleophile adds to the electropositive carbonyl carbon to give a tetrahedral alkoxide intermediate. Protonation of the alkoxide yields the cyanohydrin. Note that in the example here, the protonation step regenerates cyanide ion. Thus the process is truly catalytic in the addition of cyanide ion and this reaction is classed as a *base-catalyzed reaction*.

As shown by the mechanism in Equation 28.21, cyanohydrin formation is reversible. The formation of cyanohydrins is best with aldehydes, with formaldehyde being quantitative. Ketones are slower to react, though for simple ketones the yields are still greater than 90%. Bulky ketones do not react well, being slow and poor yielding. Note that the reversibility of cyanohydrin formation is put to use by the millipede *Apheloria corrugata*, which releases the cyanohydrin mandelonitrile from a storage gland to an outer chamber (**Figure 28.6**). There it is enzymatically degraded to benzaldehyde and hydrogen cyanide before being sprayed at an enemy as a defense mechanism. Cyanohydrins can be formed by using HCN with a catalytic amount of sodium or potassium cyanide to initiate reaction. Hydrogen cyanide, however, is highly toxic and volatile. A more practical method is to use sodium or potassium cyanide in a stoichiometric quantity dissolved in a protic solvent such as ethanol.

Nitriles such as those found in cyanohydrins are readily hydrolyzed to carboxylic acids under acidic conditions. In this case, cyanohydrins hydrolyze to give *α -hydroxy acids*.

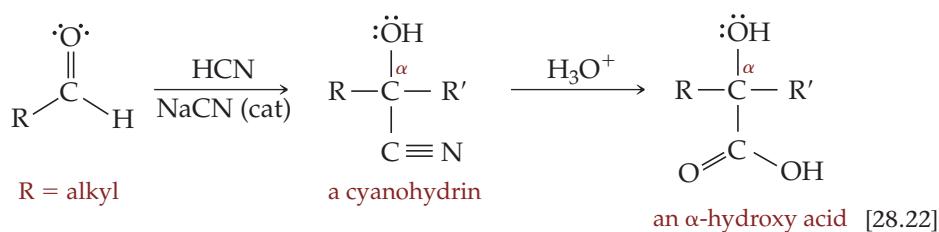


Go Figure

Suggest the structure of the organic compound produced by the generation of HCN from mandelonitrile.

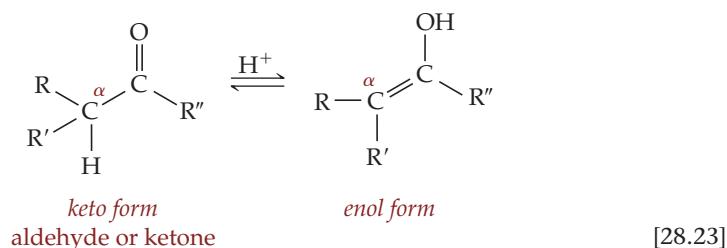


▲ **Figure 28.6** Millipede defense. *Apheloria corrugata* releases mandelonitrile as part of its defense strategy. The nitrile is degraded to hydrogen cyanide which is deadly to predators.

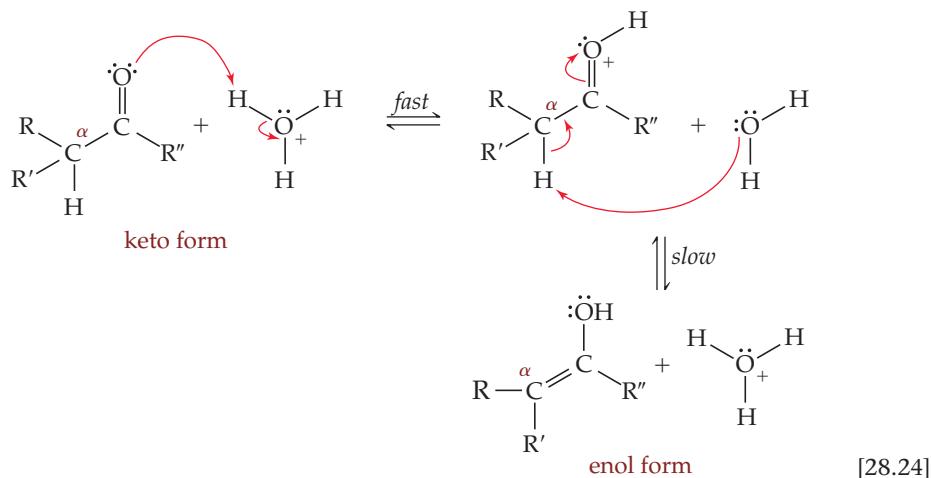


Tautomerism in Aldehydes and Ketones

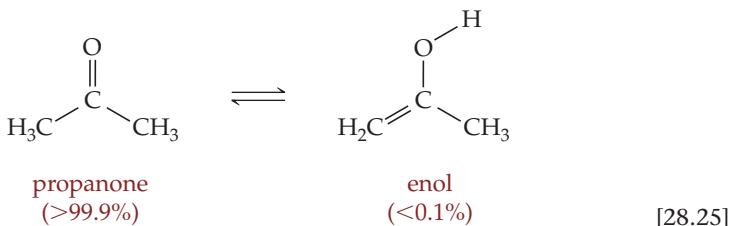
Aldehydes and ketones bearing an α -hydrogen (that is, a hydrogen on a carbon atom next to the carbonyl carbon) are able to undergo tautomerism to form enols ("ene ols", or a compound bearing a double bond (alkene) and a hydroxyl group (alcohol)). Enols are constitutional isomers of their respective *keto* form (that is, an aldehyde or ketone). **Tautomerism** is the process by which two isomers, in this case the aldehyde or ketone and the enol, are interconverted by a formal movement of an atom or group, following normal valency rules. Hence an enol and its keto form are *tautomers* of the same structure.

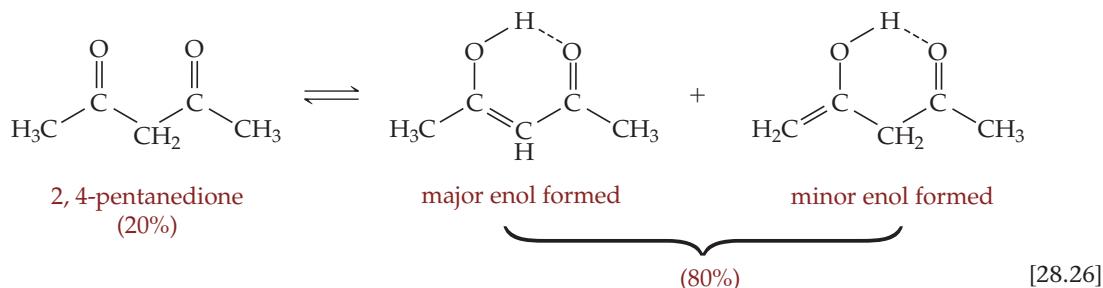


Aldehydes and ketones are in equilibrium with their enol forms and this equilibrium is acid catalyzed. The process involves two separate proton transfers rather than a single proton jump, as might be expected just by looking at Equation 28.23. What tautomerism exploits is essentially the relative acidity of the α -hydrogen ($\text{pK}_a \sim 9-13$).



The extent of tautomerization depends very much on the aldehyde or ketone. For example, propanone (acetone) exists $>99.9\%$ in the ketone form, whereas 2,4-pentanedione exists preferentially as the enol ($\sim 80\%$) by virtue of stabilising hydrogen bonding.



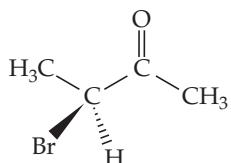


Though many aldehydes and ketones do not exist in the enol form to a large extent, enols do play a significant part in the reactivity of aldehydes and ketones. One example, that of halogenation, is the next topic of discussion.

Sample Exercise 28.5

Keto–enol Tautomerism

Some ketones, such as the one shown here, are chiral. In solution, such compounds are quite stable and retain their optical activity. However, the addition of a small amount of acid causes the optical rotation to tend to 0° over time. Comment on why this is so.



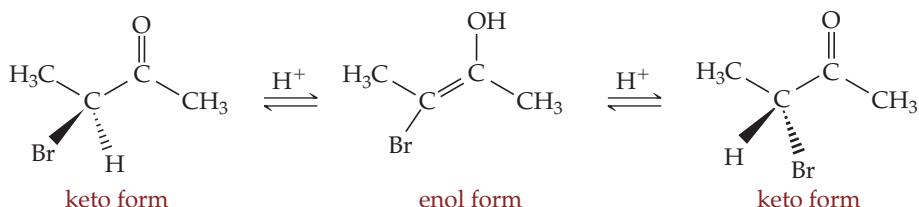
SOLUTION

Analyze We are asked about the acid-catalyzed stereoisomerization of ketones bearing a stereocenter on the α -carbon.

Plan Ketones undergo tautomerism to the enol form if they possess a hydrogen atom alpha to the carbonyl group. We need to explain the loss of optical activity.

Solve There are two possible causes. Since this ketone has an α -hydrogen, and optical activity is lost under acidic conditions,

there is a high chance that tautomerism is occurring, leading to the achiral enol. However, we know that tautomerism is an equilibrium, so the enol is able to reconver to the keto form. In this case, the proton could add from behind the page (leading to the original structure) or it could add from in front of the page, leading to the enantiomer. Since there is nothing to favour the addition from one face or the other, both are equally likely, leading to a racemic mix. This can be summarized as the following:

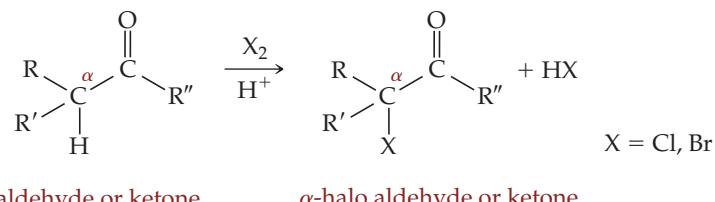


► Practice Exercise

Draw the enol forms of (a) cyclohexanone, (b) 3-pentanone and (c) propanal.

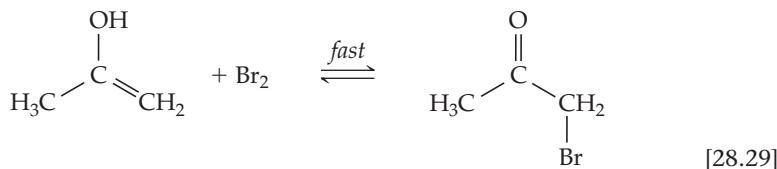
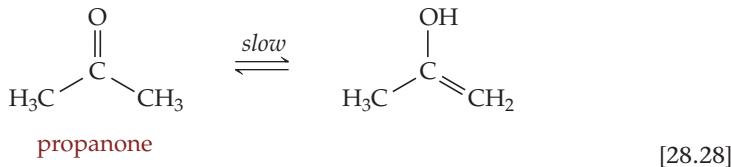
Halogenation of Aldehydes and Ketones

Aldehydes and ketones undergo a substitution reaction at the α -carbon in the presence of molecular chlorine or bromine in good yield.

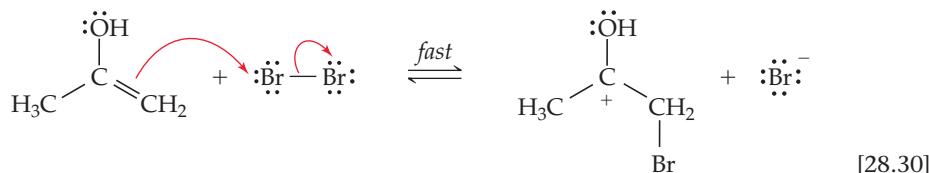


[28.27]

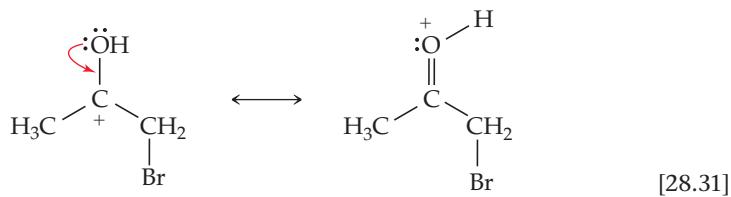
This reaction is *regiospecific* in that *only* the α -hydrogen is substituted under these conditions. Interestingly, when the reaction was first studied mechanistically by Arthur Lapworth (1872–1941) in 1904, he discovered that the rates of chlorination, bromination and iodination were all the same. This meant that halogenation occurred after the rate-determining step. We now know that the rate-determining step is the conversion of the ketone to its enol isomer. Let us look at this reaction in more detail, using the bromination of propanone (acetone) as the example.



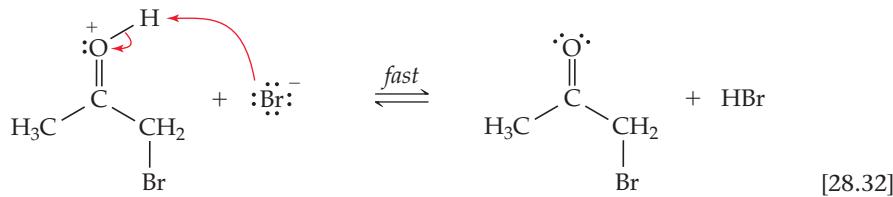
We can understand the enol halogenation by comparing it to the halogenation of an alkene. The first step involves attack of the double bond of the enol on bromine.



If the reaction followed the bromination of an alkene, then the next phase of the mechanism would be the formation of the second C—Br bond by attack of the bromide ion on the carbocation intermediate in an *intermolecular* reaction. However, in this case, the lone pair on the oxygen can stabilize the carbocation by resonance with the major resonance contributor being the oxonium ion.

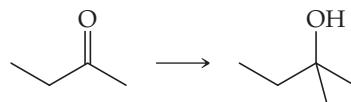


The final stage is loss of a proton to yield the desired α -haloketone.



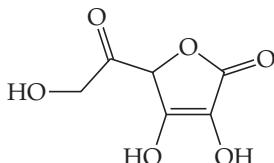
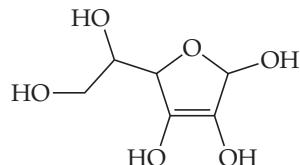
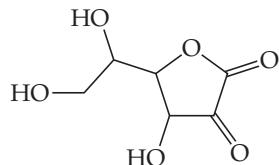
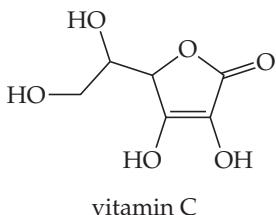
Self-Assessment Exercises

28.11 What reagent is used in the following transformation?

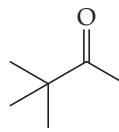
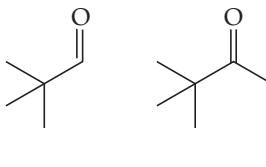
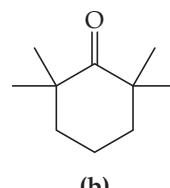
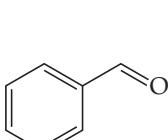


- (a) NaBH_4 followed by H_3O^+
- (b) CH_3MgI followed by H_3O^+
- (c) HCN

28.12 Which of the following structures is a tautomer of vitamin C?



28.13 Which of the following molecules will react with iodine?

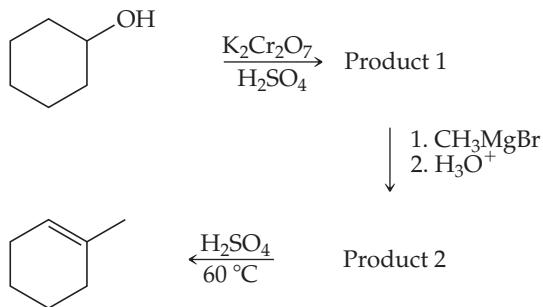


Exercises

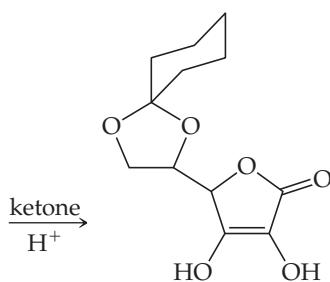
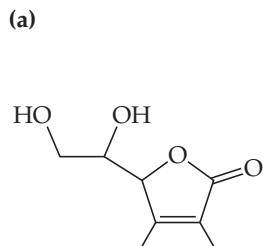
28.14 Which reducing agent is best used in this reaction?



28.15 Draw the likely product for each transformation.

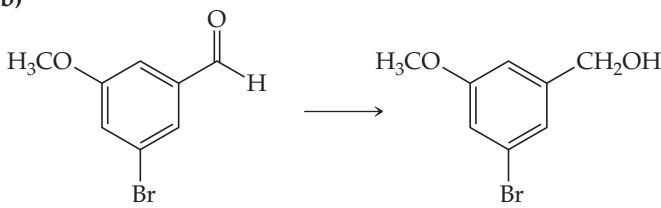


28.16 Write down the reagents necessary to make the following conversions:

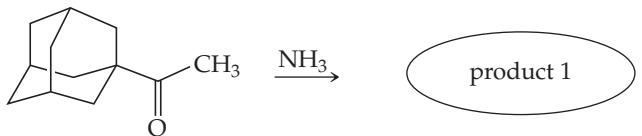


ascorbic acid

(b)

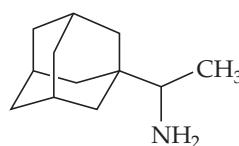


28.17 Rimantadine is effective in preventing infections caused by the influenza A virus. The final steps in the synthesis of this compound are shown. Complete the reaction sequence by placing in the missing structure.



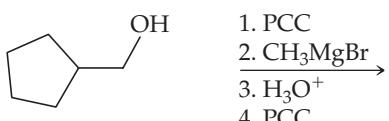
product 1

$\downarrow \text{H}_2 / \text{Pd} / \text{C}$

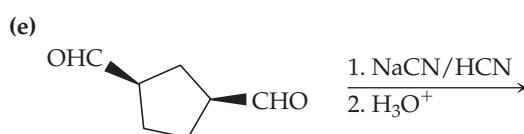
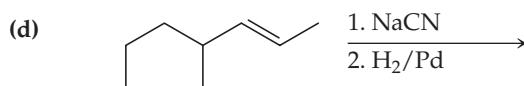
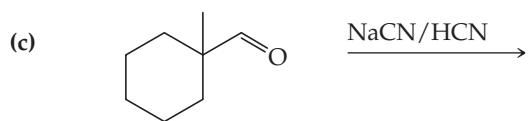
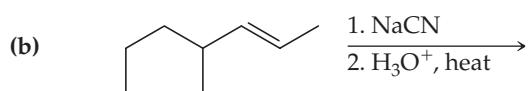


rimantadine

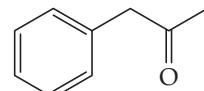
28.18 Provide the major organic product for the following set of reactions.



28.19 Provide the major organic product for the following set of reactions.



28.20 Draw the most stable enol tautomer of the ketone shown here. Explain your choice.



28.21 What is the carbon nucleophile that attacks molecular bromine in the acid-catalyzed α -bromination of a ketone?

28.11 (b) 28.12 (a) 28.13 (d)

Answers to Self-Assessment Exercises

28.4 | Carbohydrates



Sugar is one of the oldest and best documented of all commodities. The crystallinity of the popular sugars—mainly sucrose, lactose, and fructose—as well as their sweet flavor has made them popular for over two millennia.

Sugar is classified as a member of the carbohydrate food group, and its main natural sources are sugar cane (*Saccharum spp.*) and sugar beets (*Beta vulgaris*), in which sugar can account for 12% to 20% of the plant's dry weight. During the times of Alexander the Great,

sugar cane arose as a popular alternative to honey, with people chewing on the raw cane to extract its sweetness.

Today, most sugar cane comes from countries with warm climates, such as Brazil, India, China, Thailand, Mexico, and Australia, the top sugar-producing countries in the world. From a regional perspective, Asia produces more sugar cane than any other region.

Refined sugar can be made by dissolving raw sugar and purifying it using phosphoric acid. Alternative methods of purification include a carbonation process involving calcium hydroxide and carbon dioxide, or various filtration strategies. The sugar is then further purified by filtration through a bed of activated carbon or bone char, depending on where the processing takes place. White refined sugar is typically sold as granulated sugar, which has been dried to prevent clumping.

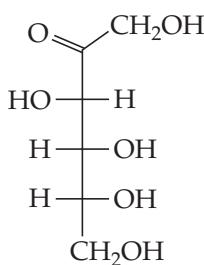
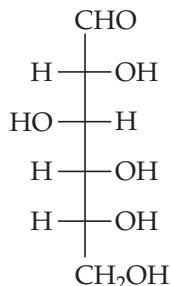
Understanding the chemistry of sugars and appreciating their structure requires a grounding in the chemistry of the carbonyl ($C=O$) group from which aldehydes and ketones are formed. By the end of this section, you should be able to:

- Understand the components that make up a carbohydrate
- Be able to identify an anomeric carbon atom
- Recognize the meaning of the different parts that make up a name of a carbohydrate molecule

Carbohydrates are an important class of naturally occurring substances, found in both plant and animal matter. They perform a variety of vital functions, such as energy storage; they act as structural components in plants; and they are an essential component of the nucleic acids, DNA and RNA, which store genetic information. The name **carbohydrate** (hydrate of carbon) comes from the empirical formulas for most substances in this class, which can be written as $C_x(H_2O)_y$, (x, y integers). For example, **glucose**, the most abundant carbohydrate, has the molecular formula $C_6H_{12}O_6$, which could also be written as $C_6(H_2O)_6$. Carbohydrates are not really hydrates of carbon; rather, they are polyhydroxyaldehydes and ketones. Glucose, for example, is a six-carbon aldehyde sugar; *fructose*, the sugar that occurs widely in fruit, is a six-carbon ketone sugar (Figure 28.7).

Go Figure

How many chiral centers are there in the open-chain form of glucose?



▲ Figure 28.7 Linear structure of glucose and fructose.

Together with galactose, glucose and fructose are the most common carbohydrates found in nature.

TABLE 28.1 Classifying monosaccharides

Name	Formula
Triose	$C_3H_6O_3$
Tetrose	$C_4H_8O_4$
Pentose	$C_5H_{10}O_5$
Hexose	$C_6H_{12}O_6$
Heptose	$C_7H_{14}O_7$
Octose	$C_8H_{16}O_8$

Monosaccharides

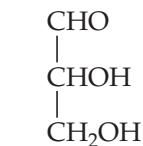
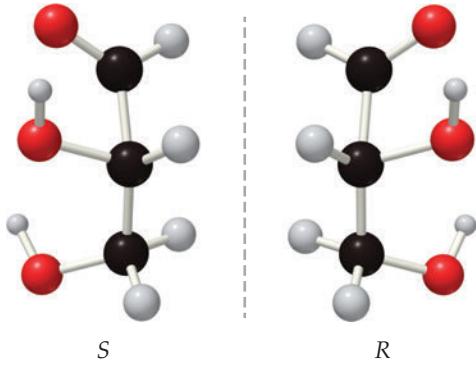
Both glucose and fructose are examples of **monosaccharides**—simple sugars that can't be broken into smaller molecules by hydrolysis with aqueous acids. Monosaccharides have the general formula $C_nH_{2n}O_n$ (where the integer $n = 3$ to 8). They are classified by their functionality as well as by the number of carbon atoms they contain.

Polyhydroxyaldehydes are known as **aldoses** to signify the aldehyde functional group, while polyhydroxyketones are classified as **ketoses** to signify the ketone group within the molecule. For example, *glucose* is an *aldose* and *fructose* is a *ketose* (see Figure 28.7). Table 28.1 lists the names of different monosaccharide classes based on the number of carbon atoms within that molecule. Based on this table, glucose can be further classified as an *alohexose*, and fructose as a *ketohexose*. The simplest monosaccharides are the trioses: glyceraldehyde and 1,3-dihydroxyacetone (Figure 28.8). These two molecules are constitutional isomers. Glyceraldehyde, an aldriose, is chiral because the central carbon atom is a stereocenter. The achiral dihydroxyacetone is classified as a ketotriose.

Let's return to Figure 28.7. Notice that the structures have been named D-glucose and D-fructose, yet there is no indication of stereochemistry using the now customary bold and dashed wedges. In fact, these two molecules do infer stereochemistry and are being shown as **Fischer projections**. This representation, which is most common among carbohydrates, is a two-dimensional representation of chiral centers. The carbon stereocenters are not shown, which is an indication that Fischer projections are being used. Figure 28.9 illustrates how the Fischer projections for glyceraldehyde relate to the types of structures you have become familiar with. Fischer projections are drawn so that the most oxidized carbon (usually the aldehyde or ketone) is positioned at the top of the drawing. The vertical lines

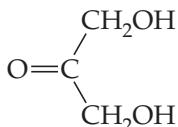
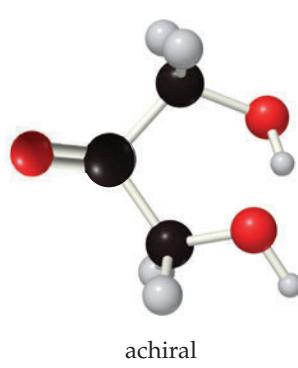
Go Figure

Why is dihydroxyacetone achiral?

Glyceraldehyde
(an aldotriose)

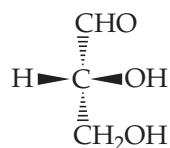
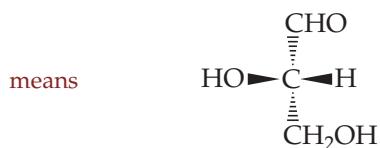
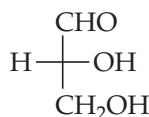
S

R

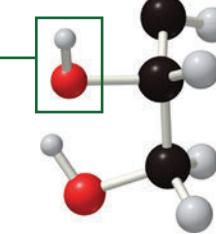
Dihydroxyacetone
(a ketotriose)

achiral

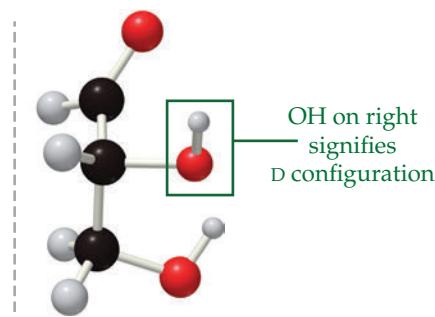
▲ Figure 28.8 Glyceraldehyde and dihydroxyacetone. A structural formula and ball-and-stick representations of the two trioses are shown. Glyceraldehyde, which contains a stereocenter, is chiral and can exist as an S- or R-enantiomer.



OH on left
signifies
L configuration

L-glyceraldehyde
 $[\alpha]_D^{25} = -13.5^\circ$

OH on right
signifies
D configuration

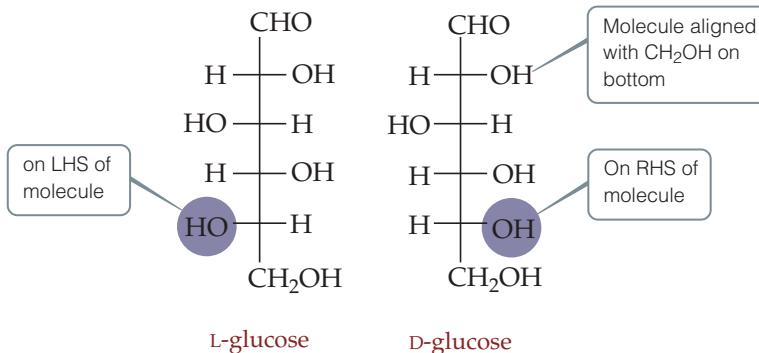
D-glyceraldehyde
 $[\alpha]_D^{25} = +13.5^\circ$

◀ Figure 28.9 Fischer projections. The D and L nomenclature for monosaccharides is referenced from D- and L-glyceraldehyde. The reference point is the position of the carbon stereocenter furthest away from the carbonyl group (aldehyde or ketone).

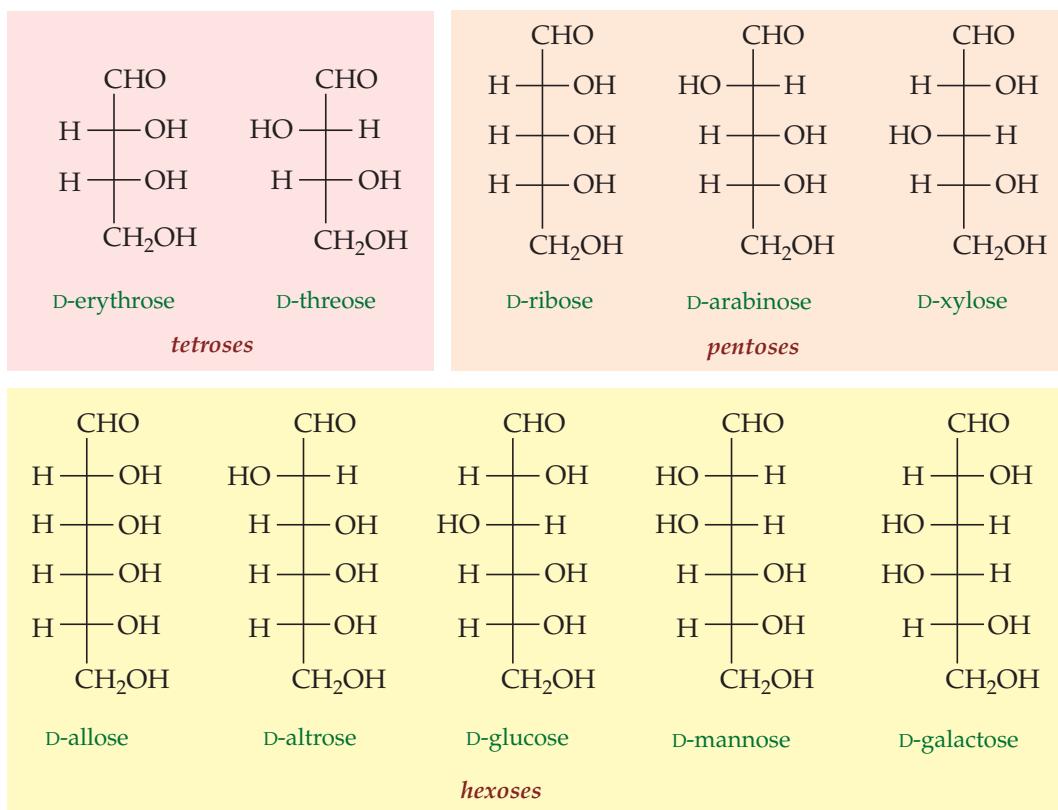
represent bonds oriented back into the page, while the horizontal lines represent bonds coming out of the page. The point at which they cross indicates a stereocenter.

The trioses D- and L-glyceraldehyde serve as the reference for determining whether a carbohydrate has the D or L configuration. According to the conventions proposed by Fischer, the D form of a carbohydrate implies that the OH group on the carbon stereocenter furthest away from the aldehyde (or ketone) is positioned on the right-hand side of the molecule, as is the case for D-glyceraldehyde (Figure 28.10). Conversely, a carbohydrate is in

► **Figure 28.10** Fischer projections of D- and L-glucose.



► **Figure 28.11**
Configurational relationships between selected naturally occurring aldoses.

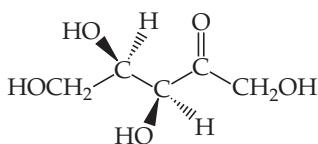


the L form when the OH group on the furthest stereocenter from the aldehyde (or ketone) is positioned on the left-hand side of the molecule. Almost all biological carbohydrates are of the D form. Several of the more common naturally occurring carbohydrates are shown in **Figure 28.11**.

Sample Exercise 28.6

Fischer Projections

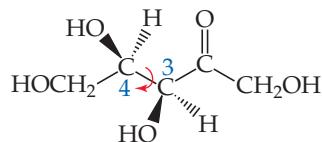
Draw the Fischer projection of the following carbohydrate. By what name would you classify this molecule? Is this molecule in the D or L configuration?



SOLUTION

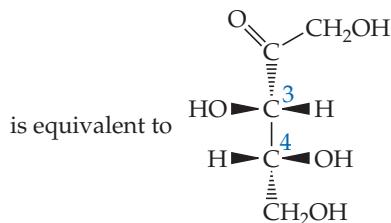
Analyze We are asked to convert the open-chain form of a carbohydrate into its Fischer projection, class it as aldose or ketose, and determine its configuration using the D, L nomenclature.

Plan To begin, we need to arrange the molecule in such a way that the OH groups and H atoms point out of the page and convert this to a Fischer projection. The Fischer projection will also help

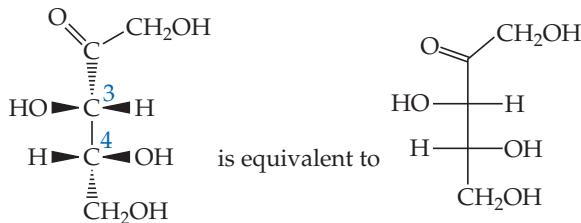


determine D, L configuration based on glyceraldehyde. We can classify this carbohydrate based on the number of carbon atoms present and the carbonyl functional group contained—whether aldehyde or ketone.

Solve Arranging the structure in such a way that the OH groups and H atoms point out of the page is achieved by rotating about the C3–C4 bond:



Position the structure in such a way that the ketone group is at the top of the molecule. From this point, the conversion from a stereoview to the Fischer projection is:

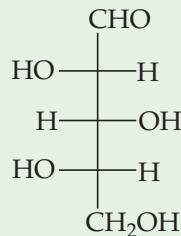


This molecule is classified as a *ketopentose*. It has the D configuration because the OH group on the stereocenter furthest from the ketone is positioned on the RHS, comparable with D-glyceraldehyde.

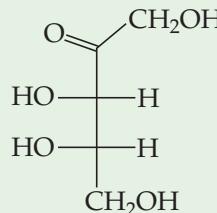
► Practice Exercise

Which molecules are D-monosaccharides and which are L-monosaccharides? What are their classifications?

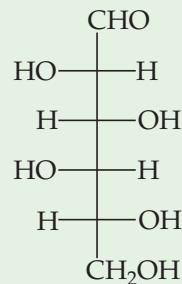
(a)



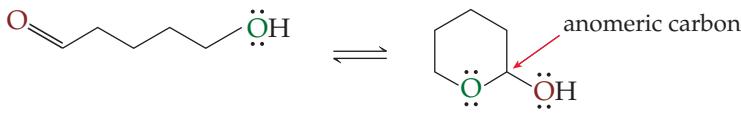
(b)



(c)

**Cyclic versus Open-Chain Structures**

In Section 28.3 we discussed the reaction of aldehydes and ketones with alcohols to form hemiacetals and acetals. We also discussed the formation of cyclic hemiacetals by an intramolecular reaction between a hydroxyl group and an aldehyde or ketone. For example, 5-hydroxypentanal forms a cyclic six-membered hemiacetal. Notice that this reaction converts an acyclic, achiral molecule into a cyclic, chiral molecule. The new stereocenter created in forming the cyclic structure is called the **anomeric carbon**.



5-hydroxypentanal

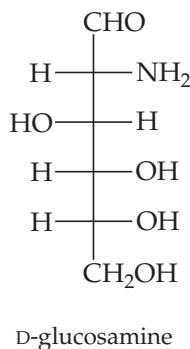
a cyclic hemiacetal

[28.33]

CHEMISTRY AND LIFE

Glucosamine

Amino sugars such as glucosamine contain an NH_2 group in place of one of the OH groups (Figure 28.12). Only three amino sugars are commonly found in nature: D-glucosamine, D-mannosamine and



▲ Figure 28.12 Glucosamine is sold as a dietary supplement.

D-galactosamine. D-Glucosamine is an amino derivative of glucose that is found especially in the polysaccharides contained within chitin, shellfish and cell membranes. Its use in the formation and repair of cartilage has more recently seen its popularity increase as a *nutraceutical*—a natural product with the capacity to prevent or heal disease.

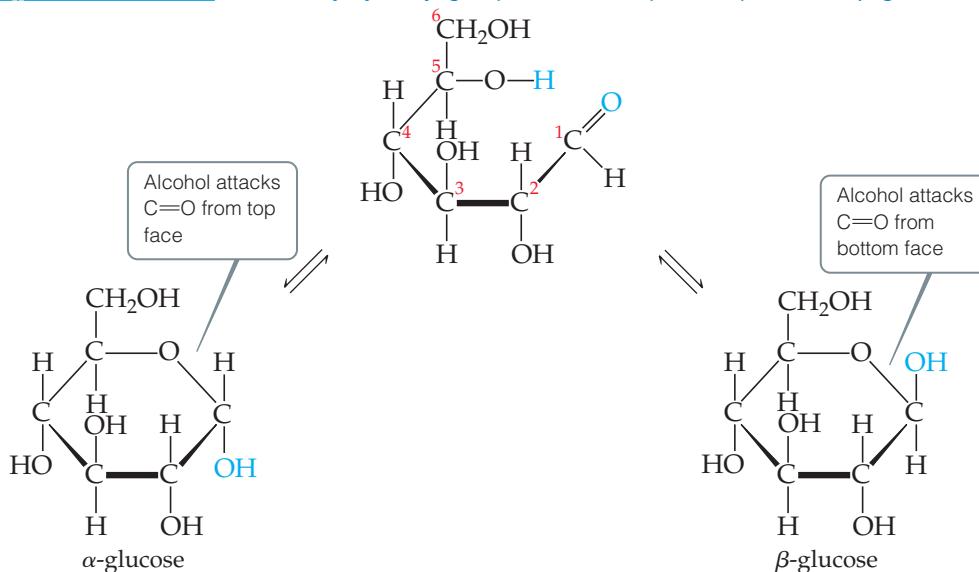
Glucosamine and its salts, most commonly the hydrochloride or sulfate salts, have been included in recent guidelines as therapy options for people with symptomatic osteoarthritis, especially in the knees. Osteoarthritis is a condition that involves damage to the cartilage in the joints of humans and animals, causing pain and stiffness. Glucosamine can be isolated in quantity from shellfish or shark cartilage or prepared synthetically.

Glucosamine and its salts are widely available as licensed products or health supplements, and may also be combined with chondroitin, vitamins and various herbs. In Australia, glucosamine is classified as a complementary medicine and is available as over-the-counter supplements. It is thought that supplementing glucosamine levels in the body will replace the deficit and restore the proper glucosamine balance.

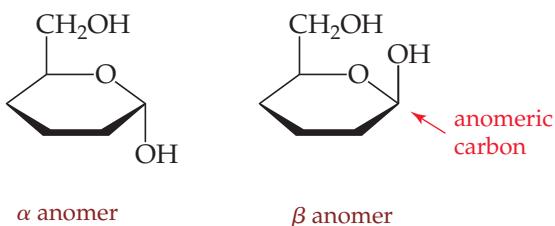
Glucose, having both hydroxyl and carbonyl groups, and a reasonably long and flexible backbone so as to form an unstrained ring structure, can also react intramolecularly to form a six-membered ring structure, as shown in Figure 28.13. In fact, only a small percentage of glucose molecules are in the open-chain form in aqueous solution. Of the two cyclic forms for D-glucose, the β form is present in greater proportion in glucose solutions. Although the ring is often drawn as if it were planar, the molecules are actually non-planar because of the tetrahedral bond angles around the C and O atoms of the ring. This planar way of representing the cyclic structures of monosaccharides is known as a **Haworth projection**. Named after W. Norman Haworth (1883–1950), recipient of the 1937 Nobel Prize for Chemistry for research in carbohydrate chemistry, this representation is a simplified way to visualize the complexities of cyclic saccharides. Convention is to write the structure with the anomeric carbon on the right side and the hemiacetal ring oxygen in the back right position.

Go Figure

How many hydroxyl groups are in an equatorial position in β -glucose?



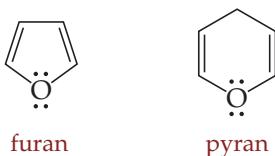
▲ Figure 28.13 Cyclic glucose. The carbonyl group of a glucose molecule can react with one of the hydroxyl groups to form either of two six-membered ring structures, designated α and β .



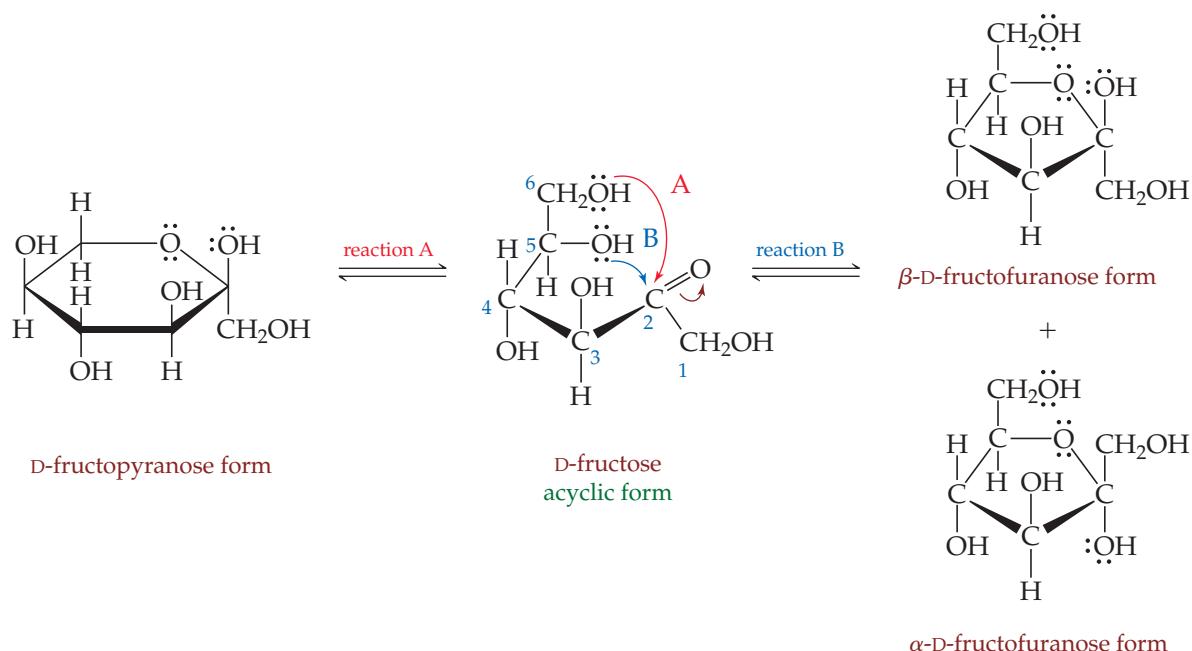
◀ Figure 28.14 Anomers. The α and β anomers differ by their orientation to the CH_2OH group outside the ring.

Figure 28.13 indicates that the ring structure of glucose can have two relative orientations at the anomeric carbon. In the α form, the OH group on the anomeric carbon (C1) and the CH_2OH group on C5 point in opposite directions. In the more stable β form, the OH group on the anomeric carbon and the CH_2OH group on C5 point in the same direction. The α and β forms are called **anomers** (Figure 28.14). Although the difference between the α and β forms might seem small, it has enormous biological consequences. As we will soon see, this one small change in structure accounts for the vast difference in properties between the biopolymers starch and cellulose.

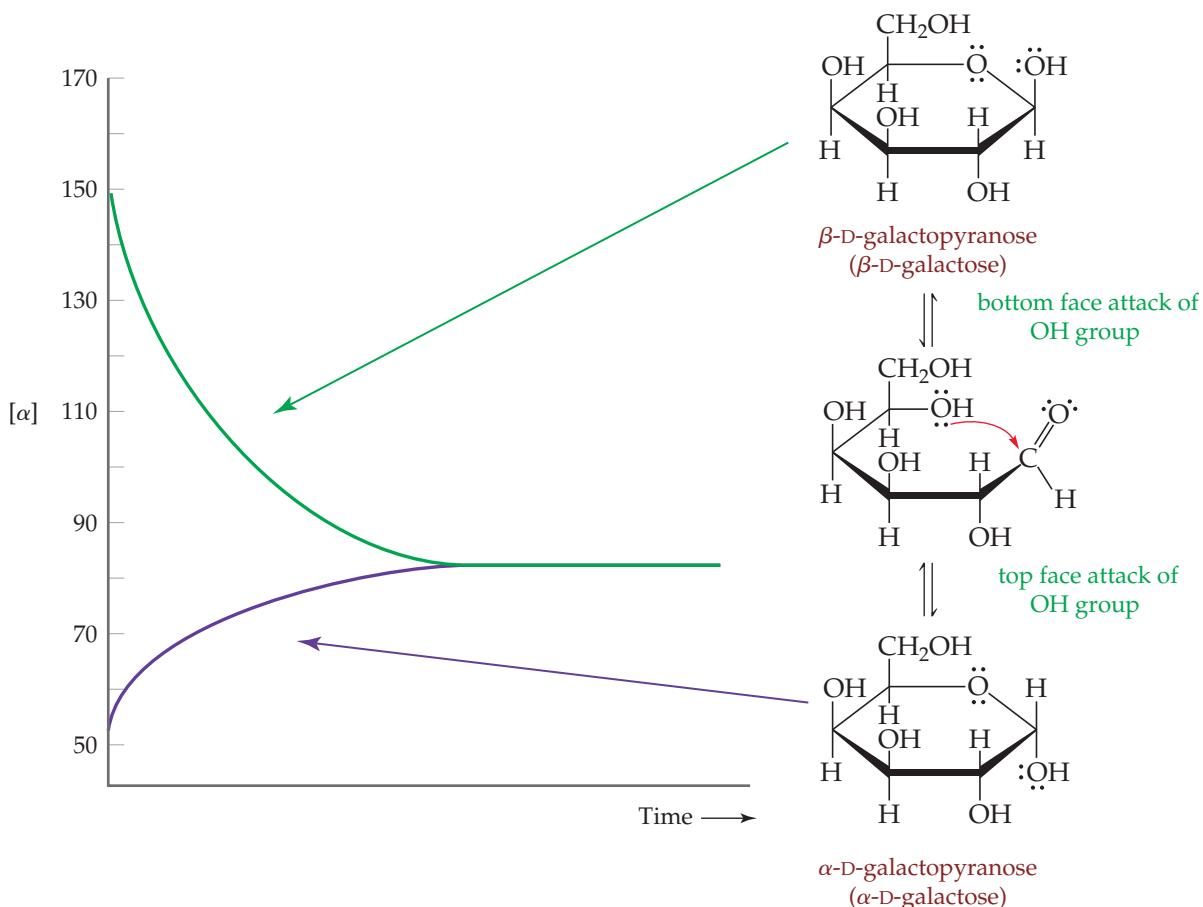
Fructose can cyclize to form either five- or six-membered rings (Figure 28.15). The five-membered ring forms when the OH group on C5 reacts with the carbonyl group on C2 (reaction B in Figure 28.15). The six-membered ring results from the reaction between the OH group on C6 and the carbonyl group on C2 (reaction A in Figure 28.15). Monosaccharides that exist as six-membered rings are named as derivatives of the oxygen-containing heterocycle, pyran. Hence, a cyclic monosaccharide that forms a six-membered ring is named a *pyranose*. Five-membered ringed monosaccharides are named as derivatives of the oxygen-containing heterocycle, furan. Hence, a cyclic monosaccharide that forms a five-membered ring is named a *furanose*.



We are now armed with enough information to name a cyclic monosaccharide unambiguously. For example, the top right-hand structure shown in Figure 28.15 has the name



▲ Figure 28.15 Fructofuranose and fructopyranose. Fructose is just one of many monosaccharides that are able to exist in furanose and pyranose forms.



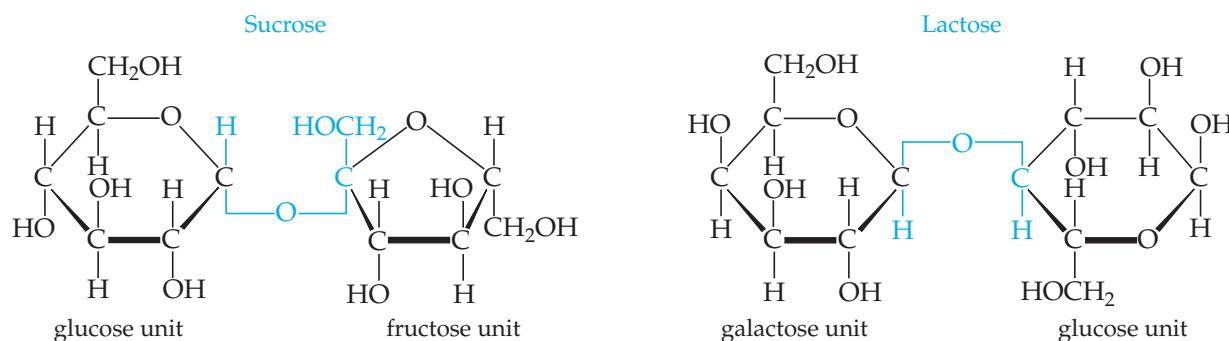
▲ Figure 28.16 Mutarotation of D-galactose. At equilibrium, D-galactose exists as a 72 : 28 mixture of α : β anomers. The mutarotation process is easily followed by changes in the specific rotation of pure samples of both anomers.

β -D-fructofuranose. This name indicates that the five-membered cyclic monosaccharide is derived from D-fructose. The β anomer has the OH and CH₂OH group found on C5 of the furanose form on the same side, which allows us to put in place the only unanswered variable from the open-chain form. As a point of completion, the two structures in Figure 28.13 are fully named α -D-glucopyranose and β -D-glucopyranose, although α -D-glucose and β -D-glucose are also acceptable.

The inference that the α and β anomers are interconvertible through an acyclic intermediate, as shown in Figure 28.15, is entirely true. This process, called **mutarotation**, is common to all carbohydrates that exist in a cyclic hemiacetal form. Mutarotation is easily observable by monitoring the specific rotation of an aqueous solution of either anomer over time. For example, a solution prepared by dissolving crystalline β -D-galactose in water shows an initial rotation of +151°. Over time, this value decreases until, at equilibrium, a rotation value of +80° is observed (Figure 28.16). The value of the rotation corresponds to a 72 : 28 ratio of α : β anomers in solution. A similar experiment can be performed using crystalline α -D-galactose. Initially, the rotation of a solution of α -D-galactose in water is +53°. Over time, this value rises as a result of the mutarotation, forming larger quantities of β -D-galactose. At equilibrium, a rotation value of +80° is also achieved (Figure 28.16). The value of the rotation still corresponds to a 72 : 28 ratio of α : β anomers in solution at equilibrium.

Oligosaccharides and Polysaccharides

Two monosaccharide units can be linked together by a condensation reaction to form a *disaccharide*. The structures of two common disaccharides, *sucrose* (table sugar) and *lactose* (milk sugar), are shown in Figure 28.17. The word *sugar* makes us think of sweetness. All



▲ Figure 28.17 Two disaccharides. The structures of sucrose (left) and lactose (right). Note that the glycosidic bond (blue) is often shown with a 90°-kink in it. This is for ease of representation and does *not* indicate an extra carbon atom.

sugars are sweet, but they differ in the degree of sweetness we perceive when we taste them. Sucrose is about six times sweeter than lactose, slightly sweeter than glucose, but only about half as sweet as fructose. Disaccharides can react with water (hydrolysis) in the presence of an acid catalyst to form two monosaccharides. When sucrose is hydrolyzed, the

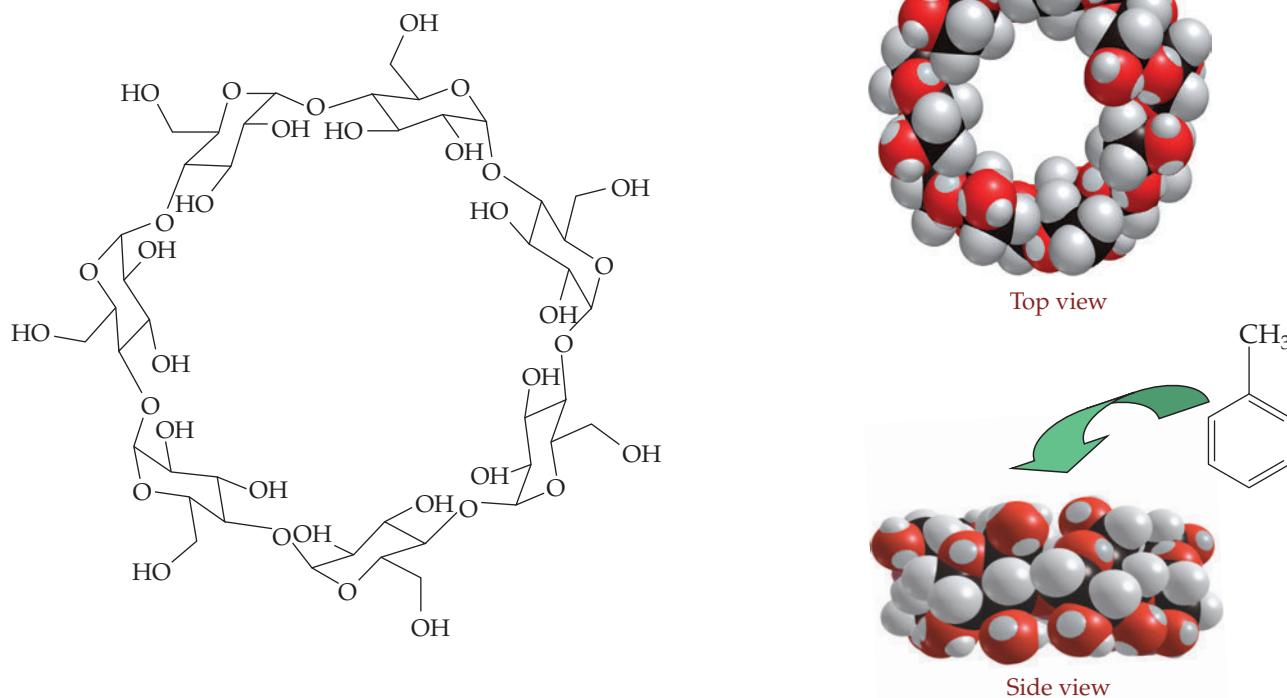
CHEMISTRY AND LIFE | Cyclodextrins

Cyclodextrins, such as the one shown in Figure 28.18, are *macrocyclic* compounds with the ability to include small organic molecules within their cavity. These cyclic molecules, which are composed of glucose units, have a *hydrophobic* (water-hating) interior and a *hydrophilic* (water-loving) exterior, due to the fact that the OH groups radiate out from the macrocycle rather than in towards the center. This feature causes cyclodextrins to be water soluble. Molecules that are hydrophobic (that is, do not mix with water) are easily included within the cyclodextrin cavity, provided they are not too large.

Cyclodextrins have found uses recently as solubilising agents. For example, toluene is immiscible with water, forming a

separate layer when added to water. The addition of cyclodextrin to the aqueous layer causes the two layers to mix by providing a way of optimising the interactions between cyclodextrin, water and toluene. The use of cyclodextrins in the pharmaceutical industry is ever-increasing as scientists realize their benefits as both a non-toxic solubilising agent at physiological pH and as a chiral "reaction vessel" with which to carry out enantioselective reactions.

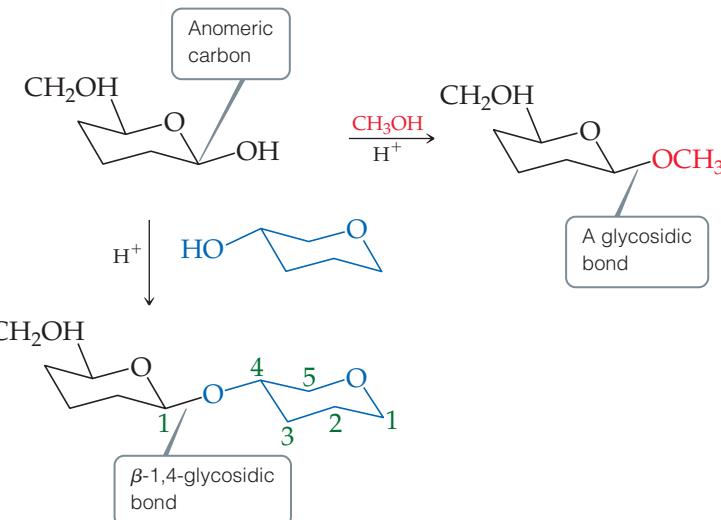
Cyclodextrins are formed by the enzymatic action of cyclodextrin glucanotransferase (CGTase) on glucose. Using this green process, tonnes of cyclodextrin can be prepared industrially.



▲ Figure 28.18 Cyclodextrins as solubilising agents.

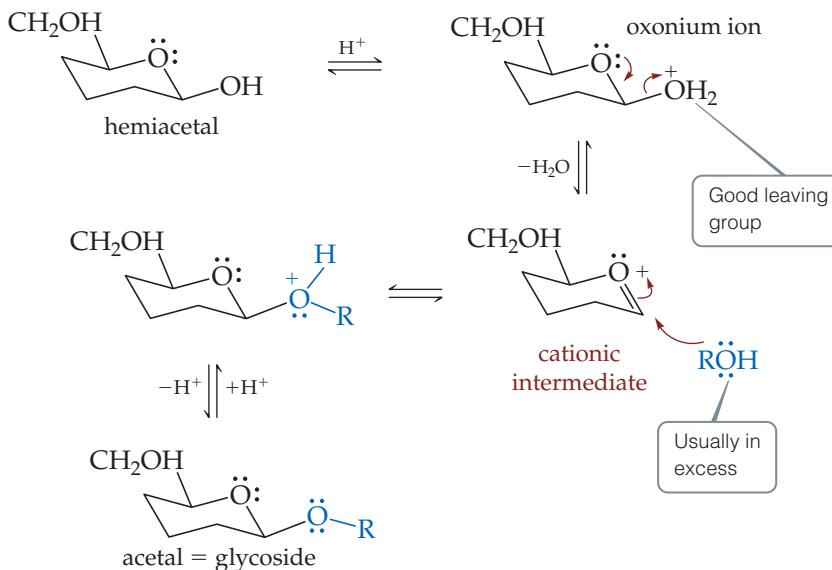
mixture of glucose and fructose that forms, called *invert sugar*, is sweeter to the taste than the original sucrose. The sweet syrup present in canned fruits and lollies is largely invert sugar formed from the hydrolysis of added sucrose.

You might recall from our discussion on the formation of acetals in Section 28.3 that, provided there is an excess of alcohol present, the major product of the acid-catalyzed reaction of an aldehyde or ketone with an alcohol is the acetal and not the intermediate hemiacetal. The same can be stated for cyclic monosaccharides, which in the presence of excess alcohol form acetals, as illustrated by the following reactions:

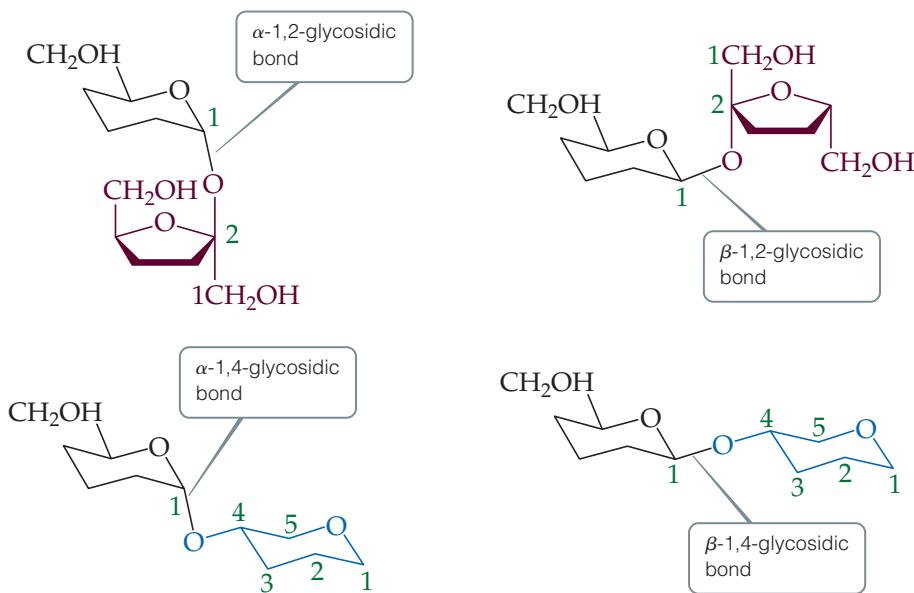


A cyclic acetal formed from a monosaccharide is called a **glycoside**. Both sucrose and lactose are *glycosides*. The bond between the anomeric carbon and the exocyclic alkoxy group of the acetal is called a **glycosidic bond**. Glycosides are stable in water, unlike simple acetals, and *do not* undergo mutarotation since, unlike the hemiacetal, the glycoside is not in equilibrium with its open-chain form in neutral solution. Hydrolysis of the glycoside is possible in aqueous acid, as is shown by the example of invert sugar.

The mechanism for the formation of the glycoside from the cyclic hemiacetal is illustrated in the set of equilibria given in Equation 28.35 for a simplified β -monosaccharide and the general alcohol, ROH. The acid-catalysed reaction occurs mainly by an elimination pathway. Elimination of H_2O by use of one of the lone pairs on the endocyclic oxygen yields the cationic intermediate (Equation 28.35). Attack at what used to be the anomeric carbon by ROH leads to an intermediate oxonium ion, which on proton loss yields the glycoside. This reaction pathway is unique to carbohydrate chemistry.



The position of the glycosidic bond in a carbohydrate is important for the properties it exhibits. Glycosidic bonds are classified by their orientation—that is, whether they are α or β bonds (equating to axial and equatorial bonds in the chair conformation, respectively), as well as on which carbons link the two monosaccharide subunits. Some examples of naming glycosidic bonds are:

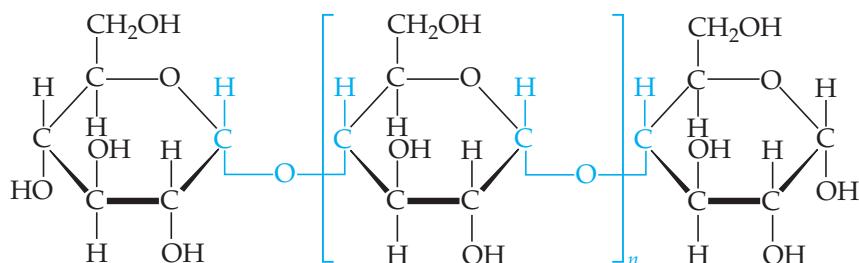


Polysaccharides are made up of many monosaccharide units, joined together by a bonding arrangement similar to those shown for the disaccharides in Figure 28.17. The most important polysaccharides are starch, glycogen and cellulose, which are formed from repeating glucose units.

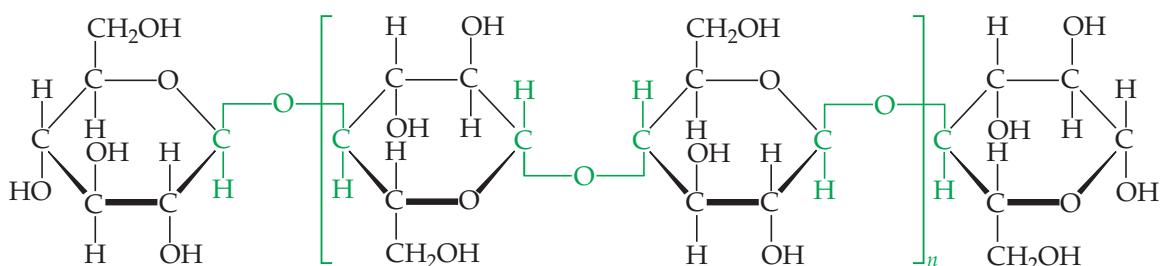
Starch is not a pure substance. The term refers to a group of polysaccharides found in plants, composed of glucose units bound by α -1,4-glycosidic bonds. Starches serve as a major method of food storage in plant seeds and tubers. Corn, potatoes, wheat and rice all contain substantial amounts of starch. These plant products serve as major sources of food energy for humans. Enzymes within the digestive system called *amylases* catalyze the hydrolysis of starch to glucose. Starch molecules that form unbranched chains are called **amyloses**, whereas those that are branched are called **amylopectins**. Figure 28.19 illustrates an unbranched structure of starch. In this structure, the glucose units are in the α form.

Glycogen is a starch-like substance synthesized in animals, consisting of glucose units connected by α -1,4- and α -1,6-glycosidic bonds. Glycogen molecules vary in molecular weight from about 5000 u to more than 5 million u. Glycogen acts as a kind of energy bank in the body and is concentrated in the muscles and liver. In muscles it serves as an immediate source of energy; in the liver it serves as a storage place for glucose and helps to maintain a constant glucose level in the blood.

Cellulose forms the major structural unit of land plants. Wood is about 50% cellulose; cotton fibres are almost entirely cellulose. Cellulose consists of unbranched chains of glucose units linked by β -1,4-glycosidic bonds, with molecular weights averaging more than 500 000 u. The structure of cellulose is shown in Figure 28.20. At first glance



◀ **Figure 28.19 Structure of a starch molecule.** The molecule consists of many glucose units of the kind enclosed in brackets, joined by linkages of the α form. Note the glycosidic bond (blue) is often shown with a 90° -kink in it. This is for ease of representation and does *not* indicate an extra carbon atom.



▲ **Figure 28.20** Structure of cellulose. Like starch, cellulose is a polymer. The repeating unit is shown between brackets. The linkage in cellulose is of the β form, different from that in starch (see Figure 28.19).

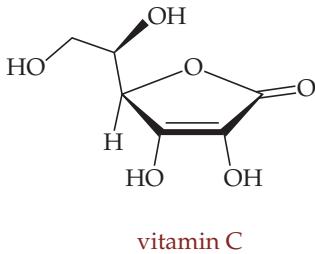
this structure looks very similar to that of starch. In cellulose, however, the glucose units are in the β form.

The distinction between starch and cellulose is made clearer when we examine their structures in a more realistic three-dimensional representation, as shown in Figure 28.21. The individual glucose units have different relationships to one another in the two structures. Because of this fundamental difference, enzymes that readily hydrolyze starches do not hydrolyze cellulose.

CHEMISTRY AND LIFE Vitamin C

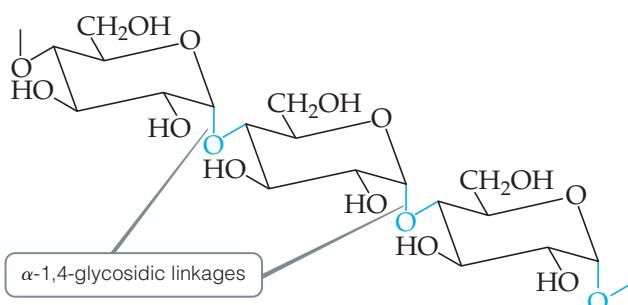
L-Ascorbic acid, more commonly known as vitamin C, is derived from D-glucose via the uronic acid pathway. Although many animals synthesize vitamin C, primates (and guinea pigs) cannot. The structural formula of L-ascorbic acid resembles the furanose form of a cyclic monosaccharide.

The most important reaction requiring ascorbate as a cofactor is the hydroxylation of proline residues in collagen. This reaction is required for the maintenance of normal connective tissue, as well as for healing wounds. The best-known functions of vitamin C are its use as a reducing agent and antioxidant. Deficiency in vitamin C leads to the disease *scurvy*. Scurvy is characterized by easily bruised skin, muscle fatigue, soft swollen gums, decreased wound healing, haemorrhaging, osteoporosis and anaemia.

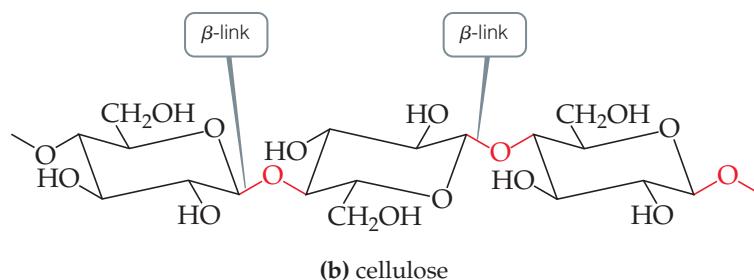


vitamin C

► **Figure 28.21** Structural differences in starch and cellulose. These representations show the geometrical arrangements of bonds about each carbon atom. The glucose rings are orientated differently with respect to one another in the two structures.



(a) starch

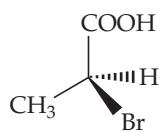


(b) cellulose

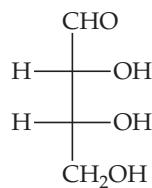
You might eat a kilogram of cellulose and receive no caloric value from it whatsoever, even though the heat of combustion per unit weight is essentially the same for both cellulose and starch. A kilogram of starch, in contrast, would represent a substantial caloric intake. The difference is that the starch is hydrolyzed to glucose, which is eventually oxidized with release of energy. Cellulose, however, is not readily hydrolyzed by enzymes present in the body, so it passes through the digestive system relatively unchanged. Many bacteria contain enzymes, called *cellulases*, that hydrolyze cellulose. These bacteria are present in the digestive systems of grazing animals, such as cattle, which use cellulose for food.

Self-Assessment Exercises

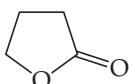
- 28.22** Which of the following structures represent a carbohydrate molecule?



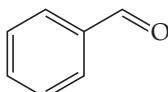
(a)



(b)

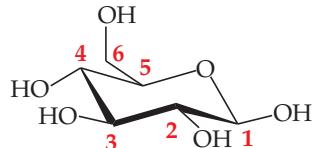


(c)



(d)

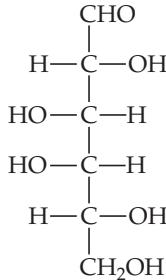
- 28.23** One representation of D-glucose looks like this:



- ## Exercises

- 28.25** **(a)** What is the difference between α -glucose and β -glucose? **(b)** Show the condensation of two glucose molecules to form a disaccharide with a 1,4- α -linkage; **(c)** with a 1,4- β -linkage.

- 28.26** The structural formula for the linear form of galactose is:

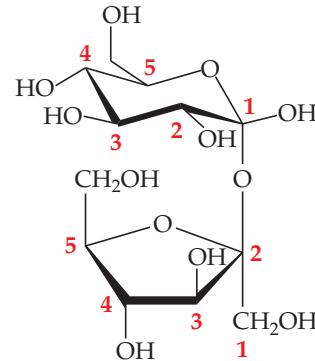


- (a)** How many chiral carbons are present in the molecule?
(b) Draw the structure of the pyranose ring form of this sugar.

The carbon atoms are numbered as shown in red. Which atom is the anomeric carbon?

- (a)** 1 **(b)** 2 **(c)** 3
(d) 4 **(e)** 5 **(f)** 6

- 28.24** Sucrose is a disaccharide composed of glucose and fructose, shown here with some of the carbon atoms numbered:



How is the linkage between the two sugars described?

- (a)** α -1,1-glycosidic bond
 - (b)** β -1,1-glycosidic bond
 - (c)** α -1,2-glycosidic bond
 - (d)** β -1,2-glycosidic bond

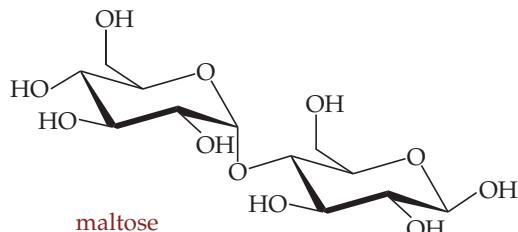
- 28.27** (a) What is the empirical formula of cellulose? (b) What is the unit that forms the basis of the cellulose polymer? (c) What form of linkage joins these monomeric units?

- 28.28** Monosaccharides can be categorized in terms of the number of carbon atoms (pentoses have five carbons and hexoses have six carbons) and according to whether they contain an aldehyde (prefix *aldo-*, as in aldopentose) or ketone group (prefix *keto-*, as in ketopentose). Classify galactose and ribose in this way.

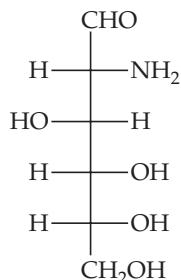
- 28.29** Aqueous solutions of pure α -D-galactose and β -D-galactose have specific rotations of $+52.8^\circ$ and $+150.7^\circ$, respectively. After standing for several hours, a solution of α -D-galactose is found to have a new specific rotation of $+80^\circ$. **(a)** Name the process observed. **(b)** Calculate the percentage of the α -anomer in the solution.

- 28.30** The structure of maltose is drawn here. **(a)** Is this a monosaccharide, disaccharide and/or a glycoside? **(b)** Identify the anomeric carbon/s. **(c)** Highlight the glycosidic bond and determine its connectivity—for example, 1,2-, 1,3-, 1,4-. **(d)** The identity of the anomer of maltose drawn below can

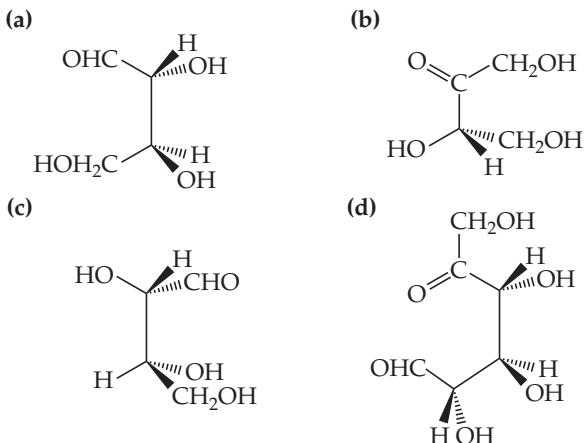
be determined by the orientation of the OH group on the non-glycosidic anomeric carbon. Which anomer is it?



- 28.31** The open-chain structure of glucosamine is drawn here. (a) Determine whether the structure drawn is D- or L-glucosamine. (b) Draw glucosamine in its β -pyranose form.



- 28.32** Convert each compound to a Fischer projection and hence class it as having D or L configuration.



28.22 (b) 28.23 (a) 28.24 (c)

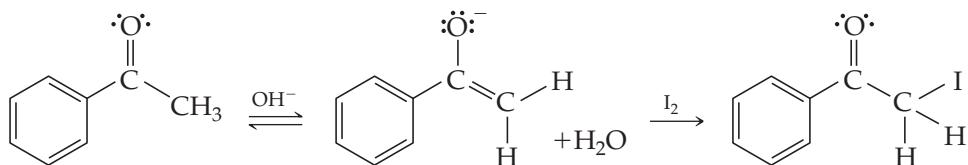
Answers to Self-Assessment Exercises



Sample Integrative Exercise

Putting Concepts Together

The halogenation of an aldehyde or ketone is promoted by the presence of a base, for example:



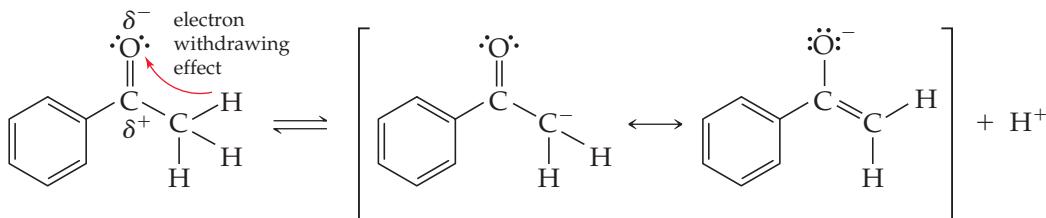
A hydrogen attached to a carbon atom is not normally acidic. (a) Suggest a reason why the hydrogen atom α to the carbonyl group may be lost as H^+ . The equilibrium between the ketone and the enolate ion lies heavily on the left-hand side. (b) Explain what happens to the equilibrium when iodination takes place. (c) Predict whether the remaining α hydrogen atoms of the iodoform ketone are more or less acidic than those of the starting material. If excess hydroxide solution and iodine are used in this reaction, formation of iodoform, CHI_3 , occurs rapidly. (d) Predict the structure of the other product formed.

SOLUTION

Analyze This question focuses on factors that affect an acid-base equilibrium.

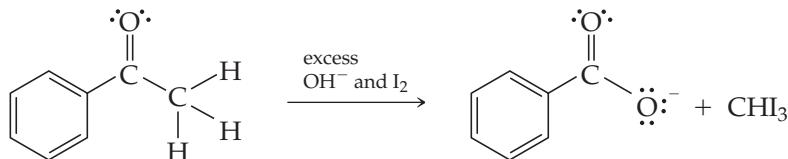
Solve

- (a) There are two factors at work here. The carbonyl group has an electron withdrawing influence on the adjacent atoms which increases the ease with which H^+ is lost from the α carbon atom and the resulting anion is resonance stabilized.



Plan Examine the structure or equilibrium involved and determine the relative stability of the species involved.

- (b) Reaction of iodine with the enolate ion lowers the concentration of the enolate ion, which shifts the equilibrium to the right-hand side. Even though there is a very small amount of enolate present at any time, the reaction can go almost to completion as more enolate ion is generated as the iodination reaction proceeds.
- (c) Substitution of a hydrogen atom with a more electronegative halogen atom increases the electron withdrawing effect on the remaining hydrogen atoms and consequently makes them more acidic.
- (d) A carboxylic acid is the other product from this reaction which, under the basic conditions present, will exist as the carboxylate ion.



Chapter Summary and Key Terms

SECTIONS 28.1 AND 28.2 Aldehydes and ketones are compounds containing a **carbonyl group** ($\text{C}=\text{O}$). Aldehydes contain the functional group CHO , whereas ketones contain a carbonyl group within a hydrocarbon chain. The polarity of the carbonyl group makes it susceptible to nucleophilic attack on carbon. Aldehydes and ketones can be prepared by the oxidation of 1° or 2° alcohols, respectively. Another approach to their preparation is through the **ozonolysis** of alkenes.

SECTION 28.3 The conversion of ketones and aldehydes to alcohols can occur by attack of an **organometallic compound** such as a **Grignard reagent** (RMgX) that acts as the nucleophile. Grignard reagents are equivalent to **carbanions** in reactivity. Reaction of aldehydes and ketones with amines yield **imines** and with alcohols yield **hemiacetals** and **acetals**. Imines can be catalytically hydrogenated to yield amines. **Metal hydrides** such as sodium borohydride act as a source of **hydride ion**, which can reduce ketones and aldehydes to alcohols. The **nucleophilic addition** reaction of aldehydes and ketones with cyanide ion (CN^-) leads to the formation of **cyanohydrins**, which can be converted to α -hydroxy acids by hydrolysis of the nitrile group. Compounds containing the CN functional group are often called **nitriles**. **Tautomerism** occurs in carbonyl compounds bearing an α -hydrogen.

SECTION 28.4 Carbohydrates, which are polyhydroxyaldehydes and ketones, are the major structural constituents of plants and are a source of energy in both plants and animals.

Glucose is the most common **monosaccharide**, or simple sugar. Monosaccharides are classed as **aldoses** or **ketoses** depending on what functional group is present in its open-chain form. The open-chain form of a monosaccharide is often drawn as a **Fischer projection**, which is an easy way to determine whether the monosaccharide is of the D- or L-form.

Monosaccharides are usually drawn as a **Haworth projection** in their cyclic form. Two cyclic forms are common: the pyranose (six-membered ring) and furanose (five-membered ring) forms. Monosaccharides are classed as one of two **anomers** according to the stereochemistry of the groups on the **anomeric carbon**. **Mutarotation** occurs when the two anomeric forms come to equilibrium in solution. A **glycoside** is formed when some group other than OH is bonded to the anomeric carbon. Glycosides do not interconvert between anomeric forms and do not exist in open chain and cyclic forms. The link between two monosaccharide units via the anomeric carbon is termed the **glycosidic bond**.

Two monosaccharides can be linked together by means of a condensation reaction to form a disaccharide. **Polysaccharides** are complex carbohydrates made up of many monosaccharide units joined together. The three most important polysaccharides are **starch**, which is found in plants; **glycogen**, which is found in animals; and **cellulose**, which is also found in plants. Starch molecules that form largely unbranched chains are called **amylose**, whereas those that are highly branched are called **amylopectins**.

Key Skills

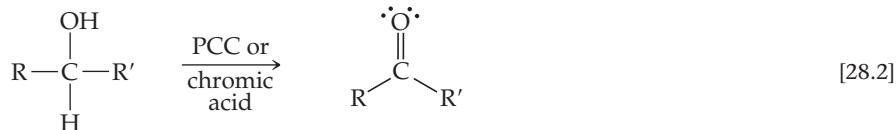
- Understand how to identify aldehyde and ketone functional groups and use systematic approaches to naming. (Section 28.1)
- Be able to predict that the oxidation of primary alcohols gives aldehydes and oxidation of secondary alcohols give ketones and be able to quote the reagents necessary to undertake these interconversions. (Section 28.2)
- Understand the generality of nucleophilic addition to carbonyl compounds in the context of acetals, hemiacetals, imines and cyanohydrins. (Section 28.3)
- Be able to form and use Grignard reagents for nucleophilic addition. (Section 28.3)
- Be able to identify the major carbohydrates and identify whether a sugar is a mono-, di- or polysaccharide. (Section 28.4)
- Understand the stereochemistry of carbohydrates, the difference between α - and β -anomers, D and L and how it relates to carbohydrates. (Section 28.4)
- Be able to draw and interpret Fischer projections. (Section 28.4)

Key Equations

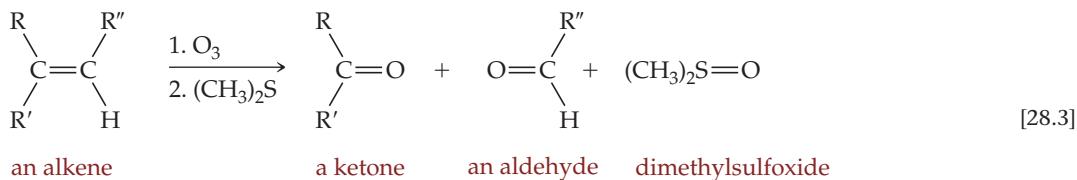
- Oxidation of 1° alcohols



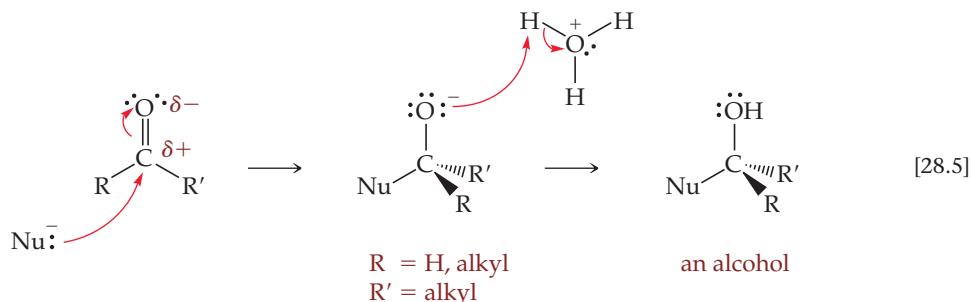
- Oxidation of 2° alcohols



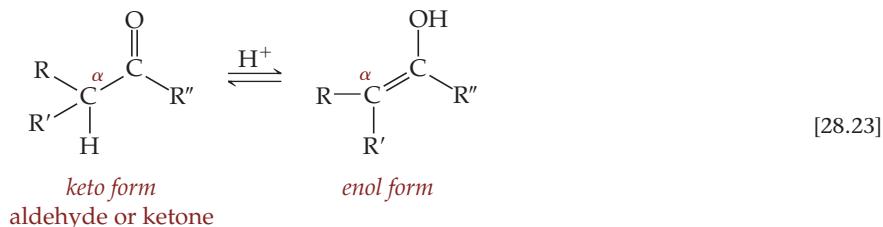
- Ozonolysis



- Nucleophilic addition reaction



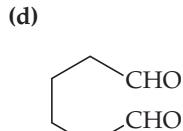
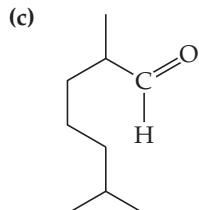
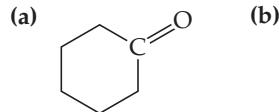
- Tautomerization



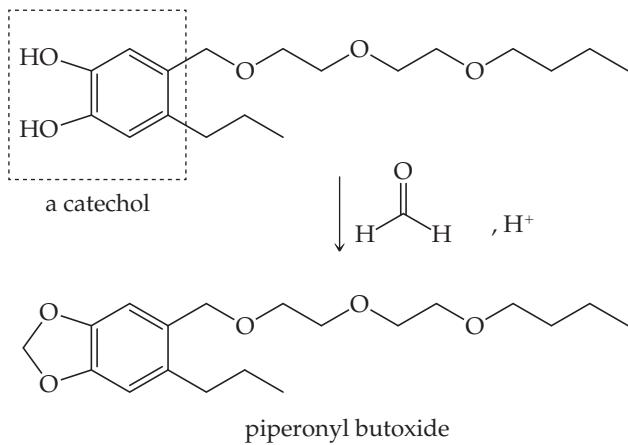
Exercises

Visualizing concepts

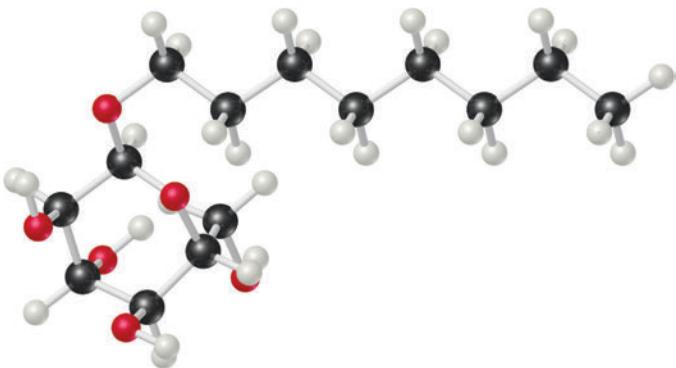
- 28.33** Draw the structure of the alcohol precursor, its systematic name and the reaction conditions you might use to obtain the following compounds by oxidation. [Section 28.2]



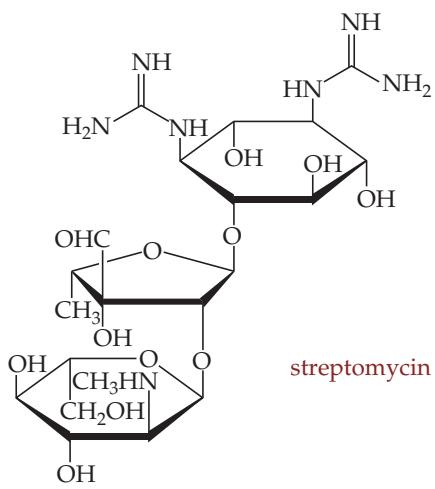
- 28.34** Piperonyl butoxide is used commercially as an additive to pyrethrum-based insecticides to enhance their effect. In this case, the cyclic ether is prepared by the action of formaldehyde on a catechol derivative. By what other functional group might this cyclic ether be named? [Section 28.3]



- 28.35** The molecule *n*-octylglucoside is widely used in biochemical research as a non-ionic detergent for “solubilizing” large hydrophobic protein molecules. What characteristics of this molecule are important for its use in this way? [Section 28.4]

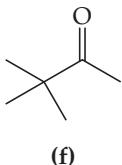
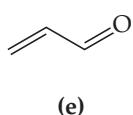
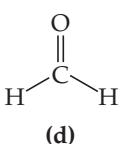
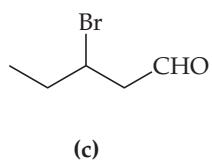
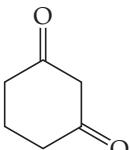
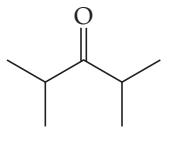


- 28.36** Streptomycin is a potent antibiotic produced by certain soil types. Its structure is shown here. Highlight the furanose and pyranose rings in streptomycin. [Section 28.4]



Aldehydes, Ketones and the Carbonyl Group (Section 28.1)

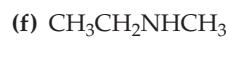
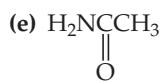
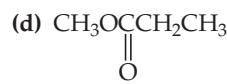
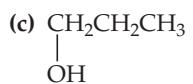
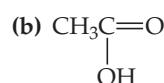
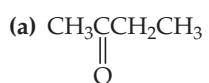
- 28.37** Name the following compounds:



- 28.38** Draw the structural formula for the following aldehydes or ketones: (a) propanal, (b) 2-pentanone, (c) 3-methylbutanone, (d) 2-methylbutanal.

- 28.39** Draw the condensed structural formulas for two molecules containing a carbonyl group with the formula C_3H_4O .

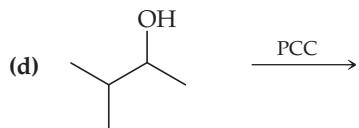
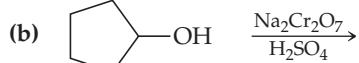
- 28.40** Identify the functional groups in each of the following compounds:



Preparation of Aldehydes and Ketones (Section 28.2)

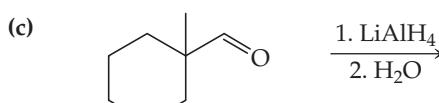
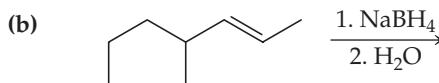
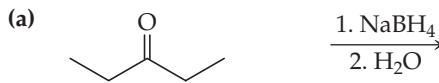
- 28.41** A chemical oxidation requires the species being oxidized to lose electrons. Write the half-equation for the oxidation of 2-propanol to propanone

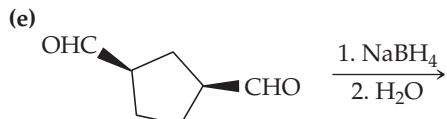
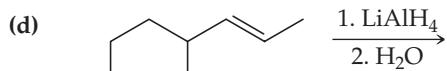
- 28.42** Provide the structure for the major organic product in the following reactions:



Reactions of Aldehydes and Ketones (Section 28.3)

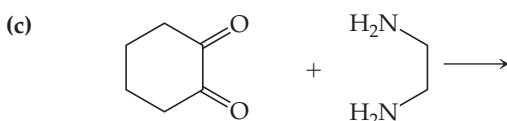
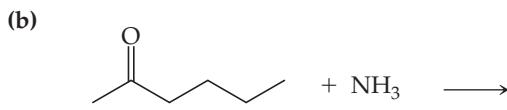
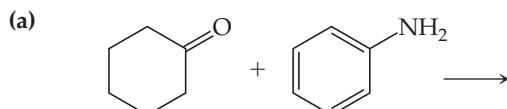
- 28.43** Provide the major organic product(s) of the following reactions:





28.44 Why is it only possible to form imines with primary amines?

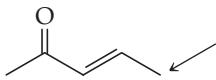
28.45 Draw the major product expected under the following conditions:



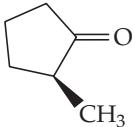
28.46 Write a mechanism for the acid-catalyzed reaction of methanol with propanal to form an acetal. What solvent would you choose to maximize the conversion of propanal to its acetal?

28.47 (a) Draw the product formed when acid is added to a solution of 5-hydroxypentanal. (b) What general class of compound is this?

28.48 (a) Draw the resonance contributors for the structure you would form by deprotonating at the methyl group indicated with the arrow. (b) Identify the keto and enolate forms. (c) What might you say about the acidity of these methyl protons compared to pentane? (d) What other tautomer is possible?



28.49 How many Hs in this compound are replaced by Ds when it is shaken in D₂O containing trace acid?

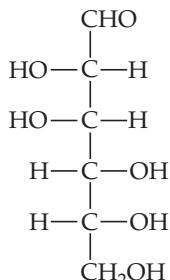


28.50 How would you prepare 2-cyanocyclohexanone from cyclohexanone?

Carbohydrates (Section 28.4)

28.51 In your own words, define the following terms: (a) carbohydrate, (b) monosaccharide, (c) disaccharide, (d) anomer, (e) glycoside.

28.52 The structural formula for the linear form of D-mannose is as follows:



(a) How many chiral carbons are present in the molecule?

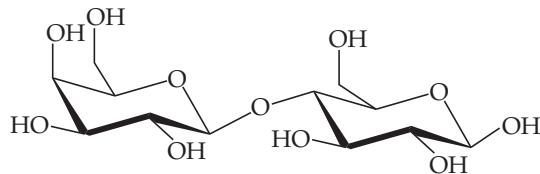
(b) Draw the structure of the pyranose ring form of this sugar.

28.53 Starch, glycogen, and cellulose are all polymers of glucose.

(a) What are the structural differences between them?

(b) Explain the structural differences that cause the difference in water solubility between these polymers.

28.54 The structure of lactose is shown. (a) Is this a monosaccharide, disaccharide and/or a glycoside? (b) Identify the anomeric carbon/s. (c) Highlight the glycosidic bond and determine whether it is a 1,2-, 1,3- or 1,4-glycosidic bond.

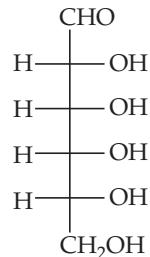


lactose

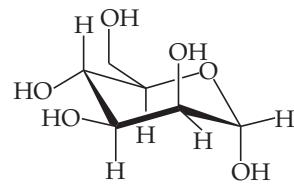
28.55 Arbutin is the principal antibacterial agent of the traditional herbal medicine called *uva-ursi*. Its systematic name is 4-hydroxyphenyl-β-D-glucopyranoside. Draw the structure of arbutin.

28.56 Convert each into a Haworth projection.

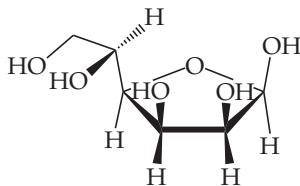
(a) Convert into an α-pyranose form



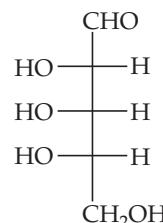
(b) Convert into an α-pyranose form



(c) Convert into an α-pyranose form



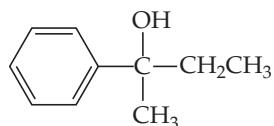
(d) Convert into a β-furanose form



28.57 Give the structure of the alkene that would yield propanone and propanal upon ozonolysis.

Integrative Exercises

- 28.58** 2-Phenyl-2-butanol can be synthesized by three different combinations of a Grignard reagent and a ketone. Show each combination.



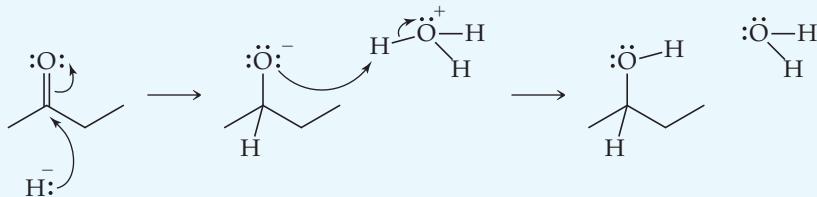
- 28.59** Acetone, $(\text{CH}_3)_2\text{CO}$, is widely used as an industrial solvent. **(a)** Draw the Lewis structure for the acetone molecule, and predict the geometry around each carbon atom. **(b)** Is the acetone molecule polar or non-polar? **(c)** What kinds of intermolecular attractive forces exist between acetone molecules? **(d)** 1-Propanol, $\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}$, has a molecular weight that is very similar to that of acetone, yet acetone boils at 56.5°C and 1-propanol boils at 97.2°C . Explain the difference.
- 28.60** **(a)** How many stereocenters are present in 3-methylpentan-2-ol? List the configuration of the

stereocenters for each possible isomer and indicate the relationship (enantiomers or diastereoisomers) that exists between the isomers. **(b)** Write the equation for the reaction of 3-methylpentan-2-ol with acidified dichromate solution. **(c)** How many stereoisomers are there in the product of this reaction? **(d)** Draw two structures representing the enol forms of this product. **(e)** Describe the change in optical rotation that you might expect if you performed this reaction on a single stereoisomer of starting material.

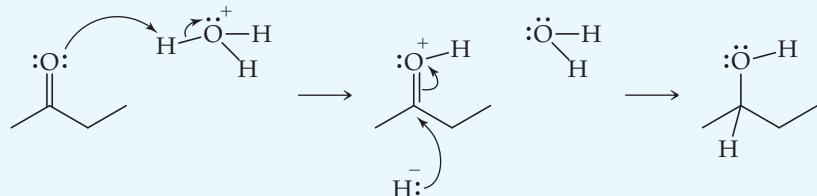
- 28.61** Use Figure 8.8 on page 283 to determine the difference in electronegativity of the following pairs of atoms and classify the bond between them as ionic, polar covalent or non-polar covalent: $\text{Na} - \text{Cl}$; $\text{Mg} - \text{Cl}$; $\text{H} - \text{Cl}$; $\text{C} - \text{Cl}$; $\text{C} - \text{Mg}$; $\text{C} - \text{C}$.
- 28.62** Use the following data to determine whether glucose ($\text{C}_6\text{H}_{12}\text{O}_6$) or sucrose ($\text{C}_{12}\text{H}_{22}\text{O}_{11}$) provides the greatest energy per gram. $\Delta_{\text{combustion}}H^\circ$ (glucose) = -2803 kJ mol^{-1} ; $\Delta_{\text{combustion}}H^\circ$ (sucrose) = -5640 kJ mol^{-1} .

Design an Experiment

A nucleophilic addition reaction, the reduction of a ketone for example, is a two-step process in which the nucleophile adds to the carbon of the carbonyl followed by protonation of the oxygen. The mechanism may be written as follows:



But what if protonation of oxygen was the first step? This is shown in this mechanism:



How are you going to distinguish the two possibilities? Assuming that the first step in each case is the slow step of the reaction, describe the kinetic experiments you might conduct to determine which mechanism is the likely one. What precautions do you need to take if you were to add a water-sensitive compound such as lithium aluminum hydride to a substrate that had been treated with aqueous acid? The intermediate drawn in the second mechanism is resonance stabilized. Draw the other resonance contributor. From your knowledge of Lewis structures, is the contributor you have just drawn or the intermediate in the first mechanism likely to be more stable? Why?