21

The lives of rock climbers depend on their ropes, typically made of a nylon polymer prepared by a nucleophilic acyl substitution reaction.

Carboxylic Acid Derivatives: Nucleophilic Acyl Substitution Reactions

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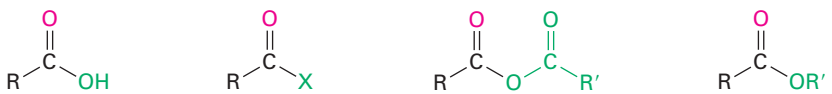
Closely related to the carboxylic acids and nitriles discussed in the previous chapter are the **carboxylic acid derivatives**, compounds in which an acyl group is bonded to an electronegative atom or substituent that can act as a leaving group in the nucleophilic acyl substitution reaction that we saw briefly in the *Preview of Carbonyl Chemistry:*

Many kinds of acid derivatives are known, but we'll be concerned primarily with four of the more common ones: **acid halides**, **acid anhydrides**, **esters**, and **amides**. Acid halides and acid anhydrides are used only in the laboratory, while esters and amides are common in both laboratory and biological chemistry. In addition, carboxylic acid derivatives called **thioesters** and **acyl phosphates** are encountered primarily in biological chemistry. Note the structural similarity between acid anhydrides and acyl phosphates.

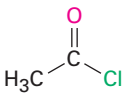


Why This Chapter? Carboxylic acid derivatives are among the most widely occurring of all molecules, both in laboratory chemistry and in biological pathways. Thus, a study of them and their primary reaction—nucleophilic acyl substitution—is fundamental to understanding organic chemistry. We'll begin this chapter by first learning about carboxylic acid derivatives, and we'll then explore the chemistry of acyl substitution reactions.

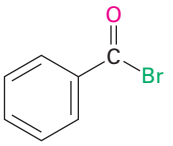
21.1 Naming Carboxylic Acid Derivatives

Acid Halides, RCOX

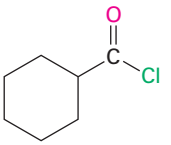
Acid halides are named by identifying first the acyl group and then the halide. As described in **Section 20.1** and shown in Table 20.1 on page 780, the acyl group name is derived from the carboxylic acid name by replacing the *-ic acid* or *-oic acid* ending with *-oyl,* or the *-carboxylic acid* ending with *-carbonyl*. To keep things interesting, however, IUPAC recognizes eight exceptions for which a *-yl* rather than an *-oyl* ending is used: formic (formyl), acetic (acetyl), propionic (propionyl), butyric (butyryl), oxalic (oxalyl), malonic (malonyl), succinic (succinyl), and glutaric (glutaryl).



Acetyl chloride



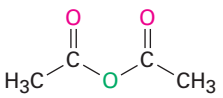
Benzoyl bromide



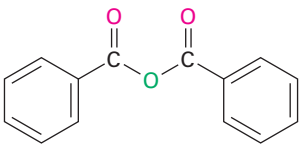
Cyclohexanecarbonyl chloride

Acid Anhydrides, RCO_2COR'

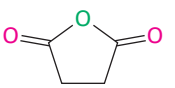
Symmetrical anhydrides of unsubstituted monocarboxylic acids and cyclic anhydrides of dicarboxylic acids are named by replacing the word *acid* with *anhydride*.



Acetic anhydride

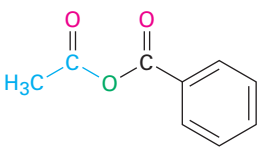


Benzoic anhydride



Succinic anhydride

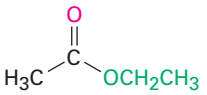
Unsymmetrical anhydrides—those prepared from two different carboxylic acids—are named by citing the two acids alphabetically and then adding *anhydride*.



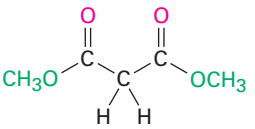
Acetic benzoic anhydride

Esters, RCO_2R'

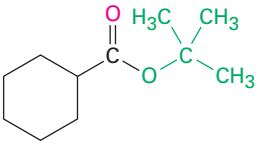
Esters are named by first identifying the alkyl group attached to oxygen and then the carboxylic acid, with the *-ic acid* ending replaced by *-ate*.



Ethyl acetate



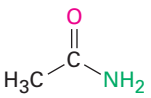
Dimethyl malonate



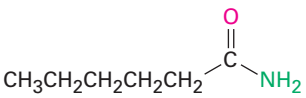
***tert*-Butyl cyclohexane-carboxylate**

Amides, $RCONH_2$

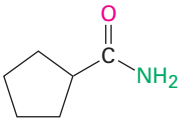
Amides with an unsubstituted $-NH_2$ group are named by replacing the *-oic acid* or *-ic acid* ending with *-amide*, or by replacing the *-carboxylic acid* ending with *-carboxamide*.



Acetamide

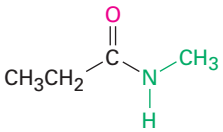


Hexanamide

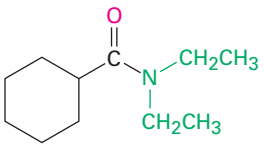


Cyclopentane-carboxamide

If the nitrogen atom is further substituted, the compound is named by first identifying the substituent groups and then the parent amide. The substituents are preceded by the letter *N* to identify them as being directly attached to nitrogen.



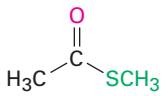
***N*-Methylpropanamide**



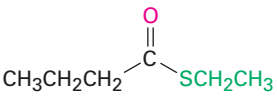
***N,N*-Diethylcyclohexanecarboxamide**

Thioesters, $RCOSR'$

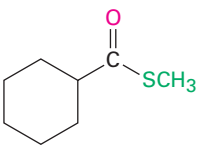
Thioesters are named like the corresponding esters. If the related ester has a common name, the prefix *thio-* is added to the name of the carboxylate: acetate becomes thioacetate, for instance. If the related ester has a systematic name, the *-oate* or *-carboxylate* ending is replaced by *-thioate* or *-carbothioate:* butanoate becomes butanethioate and cyclohexanecarboxylate becomes cyclohexane-carbothioate, for instance.



Methyl thioacetate



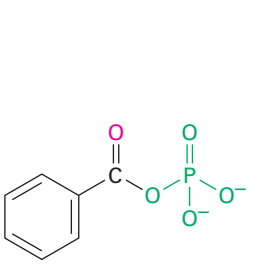
Ethyl butanethioate



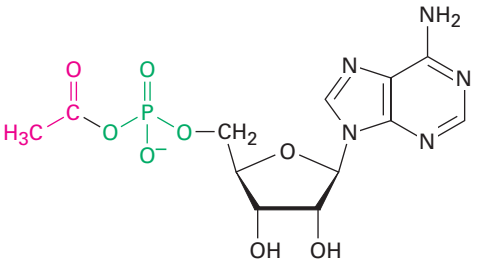
Methyl cyclohexane-carbothioate

Acyl Phosphates, $RCO_2PO_3^{2-}$ and $RCO_2PO_3R'^{-}$

Acyl phosphates are named by citing the acyl group and adding the word *phosphate*. If an alkyl group is attached to one of the phosphate oxygens, it is identified after the name of the acyl group. In biological chemistry, acyl adenosyl phosphates are particularly common.



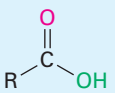
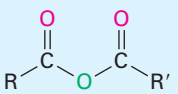
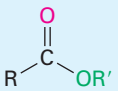
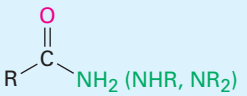
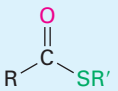
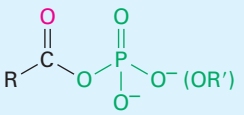
Benzoyl phosphate



Acetyl adenosyl phosphate

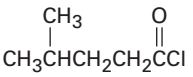
A summary of nomenclature rules for carboxylic acid derivatives is given in Table 21.1.

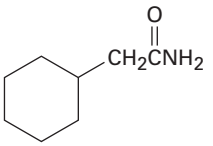
Table 21.1 Nomenclature of Carboxylic Acid Derivatives

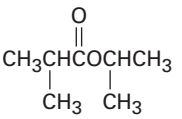
Functional group	Structure	Name ending
Carboxylic acid		*-ic acid (-carboxylic acid)*
Acid halide		*-oyl halide (-carbonyl halide)*
Acid anhydride		*anhydride*
Amide		*-amide (-carboxamide)*
Ester		*-oate (-carboxylate)*
Thioester		*-thioate (-carbothioate)*
Acyl phosphate		*-oyl phosphate*

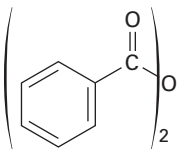
Problem 21.1

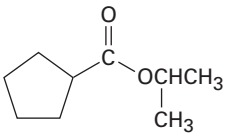
Give IUPAC names for the following substances:

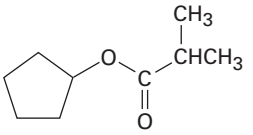
(a) 

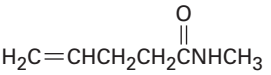
(b) 

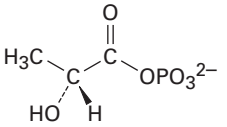
(c) 

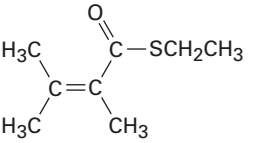
(d) 

(e) 

(f) 

(g) 

(h) 

(i) 

Problem 21.2

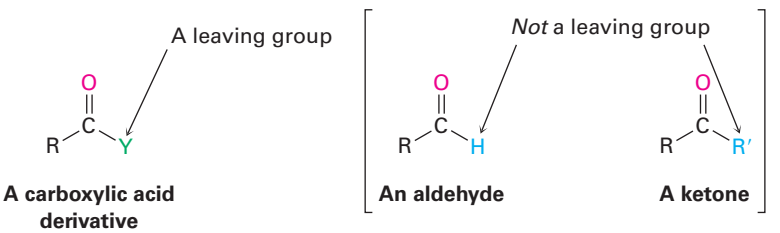
Draw structures corresponding to the following names:

(a) Phenyl benzoate
(b) *N*-Ethyl-*N*-methylbutanamide
(c) 2,4-Dimethylpentanoyl chloride
(d) Methyl 1-methylcyclohexanecarboxylate
(e) Ethyl 3-oxopentanoate
(f) Methyl *p*-bromobenzenethioate
(g) Formic propanoic anhydride
(h) *cis*-2-Methylcyclopentanecarbonyl bromide

21.2 Nucleophilic Acyl Substitution Reactions

The addition of a nucleophile to a polar C=O bond is the key step in three of the four major carbonyl-group reactions. We saw in Chapter 19 that when a nucleophile adds to an aldehyde or ketone, the initially formed tetrahedral intermediate can be protonated to yield an alcohol. When a nucleophile adds to a carboxylic acid derivative, however, a different reaction course is followed. The initially formed tetrahedral intermediate eliminates one of the two substituents originally bonded to the carbonyl carbon, leading to a net **nucleophilic acyl substitution reaction** **(Figure 21.1)**.

The difference in behavior between aldehydes/ketones and carboxylic acid derivatives is a consequence of structure. Carboxylic acid derivatives have an acyl carbon bonded to a group –Y that can act as a leaving group, often as a stable anion. As soon as the tetrahedral intermediate is formed, the leaving group is expelled to generate a new carbonyl compound. Aldehydes and ketones have no such leaving group, however, and therefore don't undergo substitution.



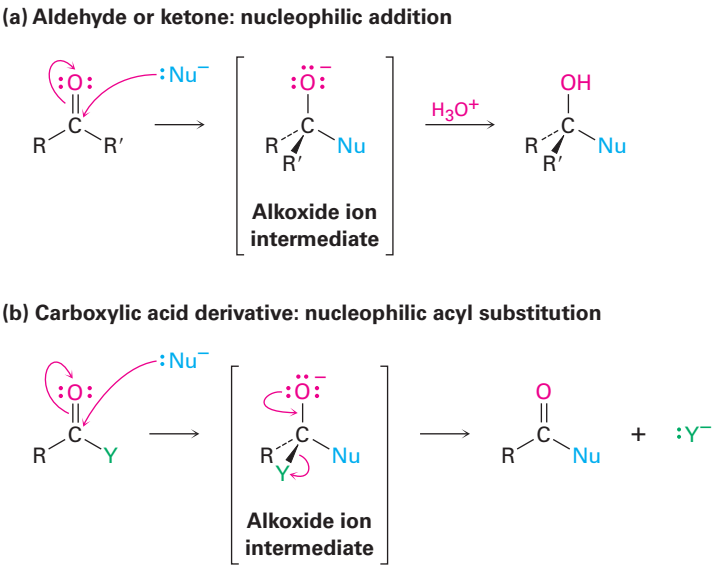
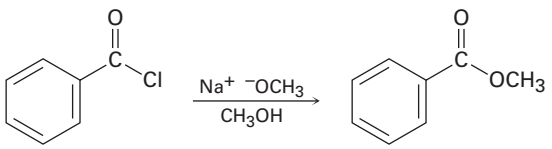


Figure 21.1 The general mechanisms of nucleophilic addition and nucleophilic acyl substitution reactions. Both reactions begin with addition of a nucleophile to a polar C=O bond to give a tetrahedral, alkoxide ion intermediate. **(a)** The intermediate formed from an aldehyde or ketone is protonated to give an alcohol, but **(b)** the intermediate formed from a carboxylic acid derivative expels a leaving group to give a new carbonyl compound.

The net effect of the addition/elimination sequence is a substitution of the nucleophile for the −Y group originally bonded to the acyl carbon. Thus, the overall reaction is superficially similar to the kind of nucleophilic substitution that occurs during an S_N2 reaction **(Section 11.3)**, but the mechanisms of the two reactions are completely different. An S_N2 reaction occurs in a single step by backside displacement of the leaving group, while a nucleophilic acyl substitution takes place in two steps and involves a tetrahedral intermediate.

Problem 21.3

Show the mechanism of the following nucleophilic acyl substitution reaction, using curved arrows to indicate the electron flow in each step:

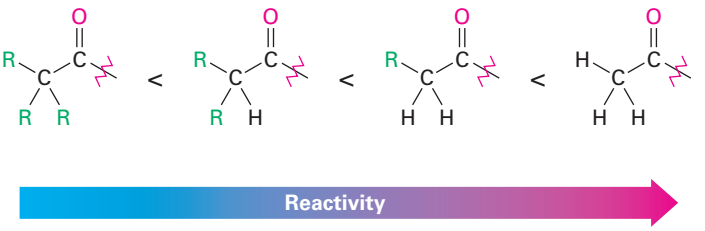


Relative Reactivity of Carboxylic Acid Derivatives

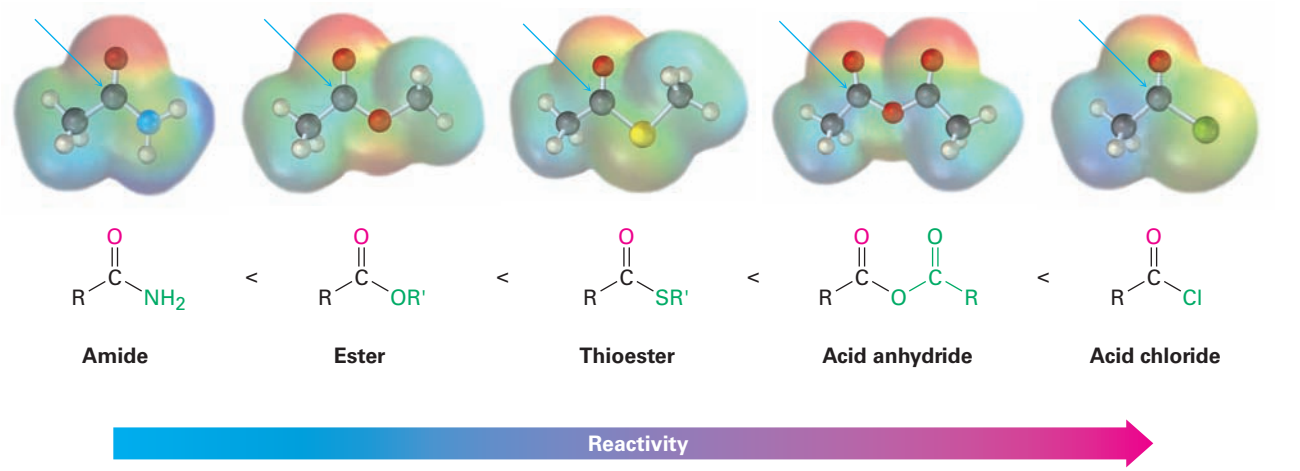
Both the initial addition step and the subsequent elimination step can affect the overall rate of a nucleophilic acyl substitution reaction, but the addition step is generally the rate-limiting one. Thus, any factor that makes the carbonyl group more reactive toward nucleophiles favors the substitution process.

Steric and electronic factors are both important in determining reactivity. Sterically, we find within a series of similar acid derivatives that unhindered,

accessible carbonyl groups react with nucleophiles more readily than do sterically hindered groups. The reactivity order is



Electronically, we find that strongly polarized acyl compounds react more readily than less polar ones. Thus, acid chlorides are the most reactive because the electronegative chlorine atom withdraws electrons from the carbonyl carbon, whereas amides are the least reactive. Although subtle, electrostatic potential maps of various carboxylic acid derivatives indicate the differences by the relative blueness on the C=O carbons. Acyl phosphates are hard to place on this scale because they are not often used in the laboratory, but in biological systems they appear to be somewhat more reactive than thioesters.



The way in which various substituents affect the polarization of a carbonyl group is similar to the way they affect the reactivity of an aromatic ring toward electrophilic substitution **(Section 16.5)**. A chlorine substituent, for example, inductively withdraws electrons from an acyl group in the same way that it withdraws electrons from and thus deactivates an aromatic ring. Similarly, amino, methoxyl, and methylthio substituents donate electrons to acyl groups by resonance in the same way that they donate electrons to, and thus activate, aromatic rings.

As a consequence of these reactivity differences, it's usually possible to convert a more reactive acid derivative into a less reactive one. Acid chlorides, for instance, can be directly converted into anhydrides, thioesters, esters, and amides, but amides can't be directly converted into esters, thioesters, anhydrides, or acid chlorides. Remembering the reactivity order is therefore a way to keep track of a large number of reactions **(Figure 21.2)**. Another consequence, as noted previously, is that only acyl phosphates, thioesters, esters, and amides are commonly

found in nature. Acid halides and acid anhydrides react with water so rapidly that they can't exist for long in living organisms.

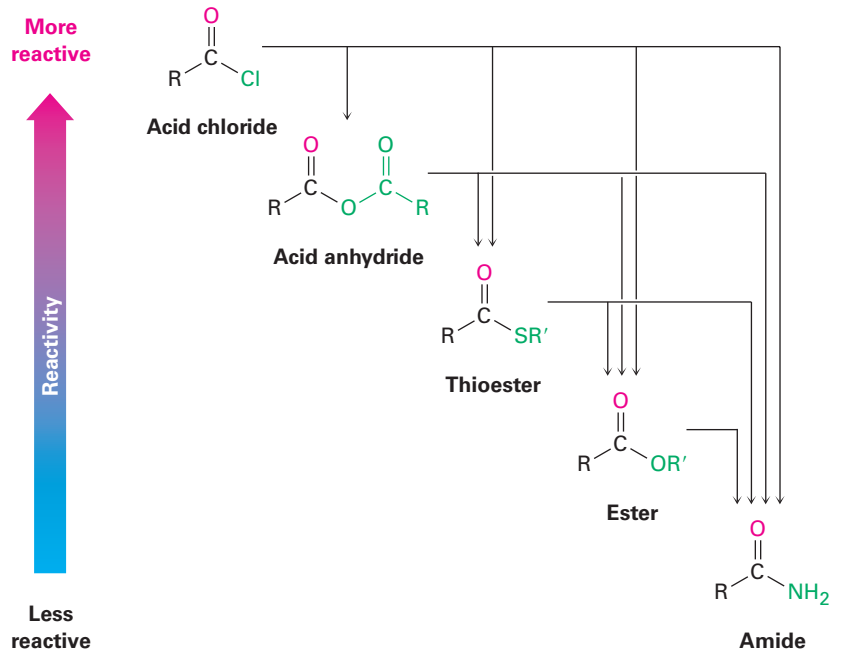


Figure 21.2 Interconversions of carboxylic acid derivatives. A more reactive acid derivative can be converted into a less reactive one, but not vice versa.

In studying the chemistry of carboxylic acid derivatives in the next few sections, we'll be concerned largely with the reactions of just a few nucleophiles and will see that the same kinds of reactions keep occurring **(Figure 21.3)**.

- **Hydrolysis** Reaction with water to yield a carboxylic acid
- **Alcoholysis** Reaction with an alcohol to yield an ester
- **Aminolysis** Reaction with ammonia or an amine to yield an amide
- **Reduction** Reaction with a hydride reducing agent to yield an aldehyde or an alcohol
- **Grignard reaction** Reaction with an organometallic reagent to yield a ketone or an alcohol

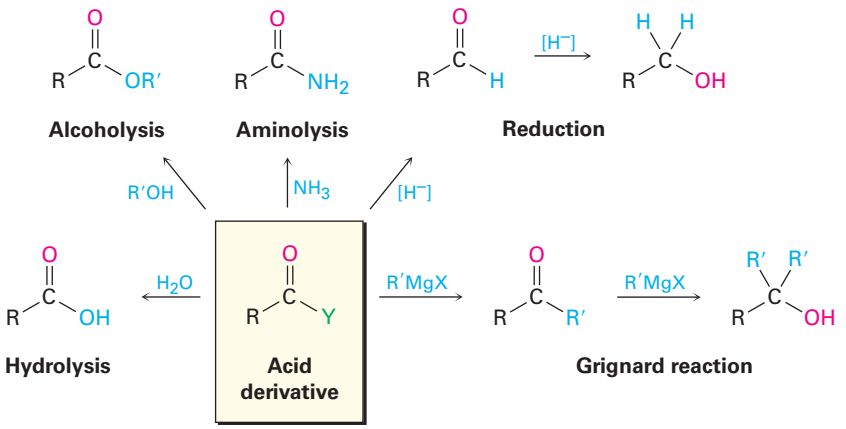
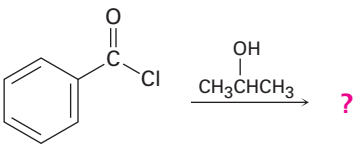


Figure 21.3 Some general reactions of carboxylic acid derivatives.

Worked Example 21.1 Predicting the Product of a Nucleophilic Acyl Substitution Reaction

Predict the product of the following nucleophilic acyl substitution reaction of benzoyl chloride with 2-propanol:

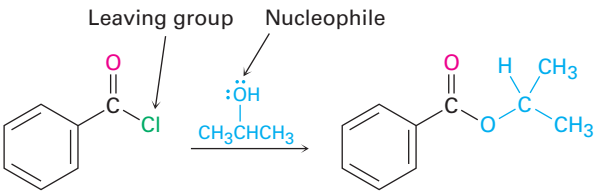


Benzoyl chloride

Strategy

A nucleophilic acyl substitution reaction involves the substitution of a nucleophile for a leaving group in a carboxylic acid derivative. Identify the leaving group (Cl^- in the case of an acid chloride) and the nucleophile (an alcohol in this case), and replace one by the other. The product is isopropyl benzoate.

Solution



Benzoyl chloride **Isopropyl benzoate**

Problem 21.4

Rank the compounds in each of the following sets in order of their expected reactivity toward nucleophilic acyl substitution:

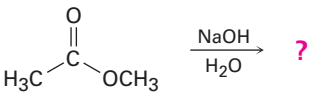
(a) CH_3CCl, CH_3COCH_3, CH_3CNH_2

(b) $CH_3COCH_2CH_3$, $CH_3COCH_2CCl_3$, $CH_3COCH(CF_3)_2$

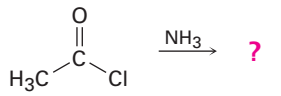
Problem 21.5

Predict the products of the following nucleophilic acyl substitution reactions:

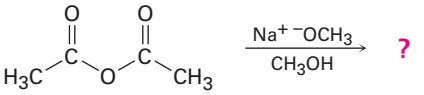
(a)



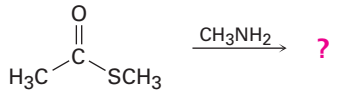
(b)



(c)

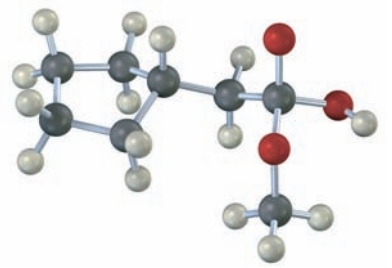


(d)



Problem 21.6

The following structure represents a tetrahedral alkoxide ion intermediate formed by addition of a nucleophile to a carboxylic acid derivative. Identify the nucleophile, the leaving group, the starting acid derivative, and the ultimate product.

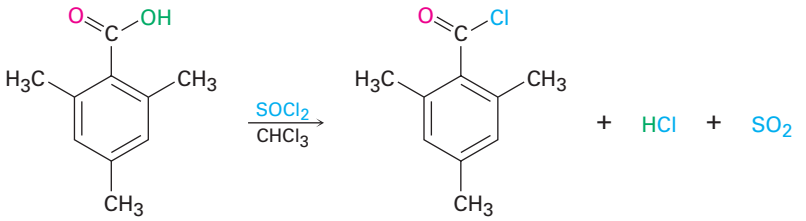


21.3 Nucleophilic Acyl Substitution Reactions of Carboxylic Acids

The direct nucleophilic acyl substitution of a carboxylic acid is difficult because −OH is a poor leaving group **(Section 11.3)**. Thus, it's usually necessary to enhance the reactivity of the acid, either by using a strong acid catalyst to protonate the carboxyl and make it a better acceptor or by converting the −OH into a better leaving group. Under the right circumstances, however, acid chlorides, anhydrides, esters, and amides can all be prepared from carboxylic acids by nucleophilic acyl substitution reactions.

Conversion of Carboxylic Acids into Acid Chlorides

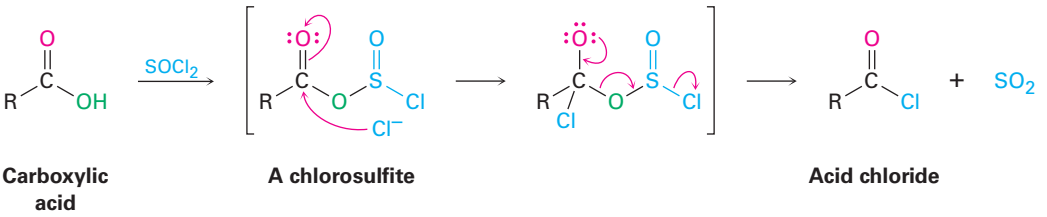
In the laboratory, carboxylic acids are converted into acid chlorides by treatment with thionyl chloride, $SOCl_2$.



2,4,6-Trimethylbenzoic acid **2,4,6-Trimethylbenzoyl chloride (90%)**

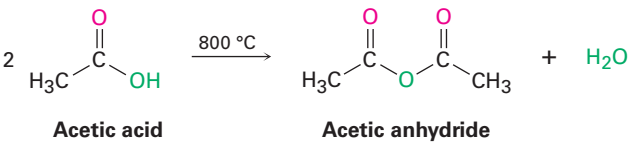
The reaction occurs by a nucleophilic acyl substitution pathway in which the carboxylic acid is first converted into an acyl chlorosulfite intermediate, thereby replacing the −OH of the acid with a much better leaving group. The chlorosulfite then reacts with a nucleophilic chloride ion. You might recall

from **Section 17.6** that an analogous chlorosulfite is involved in reaction of an alcohol with $SOCl_2$ to yield an alkyl chloride.



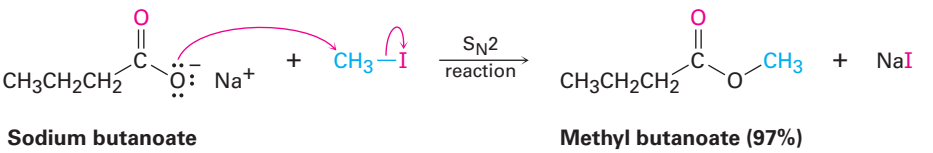
Conversion of Carboxylic Acids into Acid Anhydrides

Acid anhydrides can be derived from two molecules of carboxylic acid by heating to remove 1 equivalent of water. Because of the high temperatures needed, however, only acetic anhydride is commonly prepared this way.

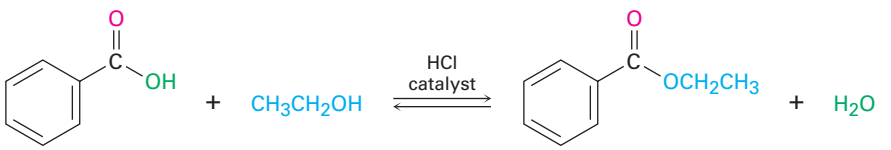


Conversion of Carboxylic Acids into Esters

Perhaps the most useful reaction of carboxylic acids is their conversion into esters. There are many methods for accomplishing the transformation, including the S_N2 reaction of a carboxylate anion with a primary alkyl halide that we saw in **Section 11.3**.



Esters can also be synthesized by an acid-catalyzed nucleophilic acyl substitution reaction of a carboxylic acid with an alcohol, a process called the **Fischer esterification reaction**. Unfortunately, the need to use an excess of a liquid alcohol as solvent effectively limits the method to the synthesis of methyl, ethyl, propyl, and butyl esters.

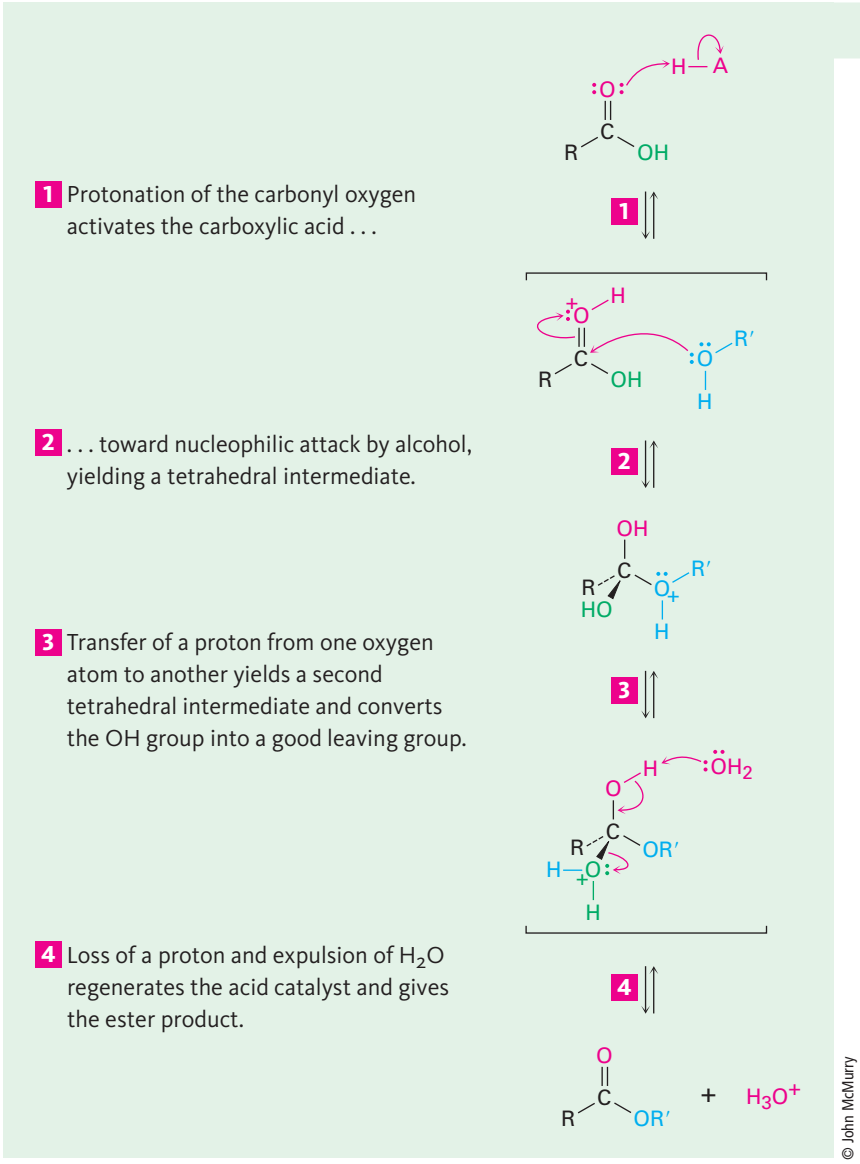


The mechanism of the Fischer esterification reaction is shown in **Figure 21.4**. Carboxylic acids are not reactive enough to undergo nucleophilic addition directly, but their reactivity is greatly enhanced in the presence of a strong acid such as HCl or H_2SO_4. The mineral acid protonates the carbonyl-group oxygen atom, thereby giving the carboxylic acid a positive charge and

rendering it much more reactive. Subsequent loss of water from the tetrahedral intermediate yields the ester product.

Figure 21.4 | MECHANISM

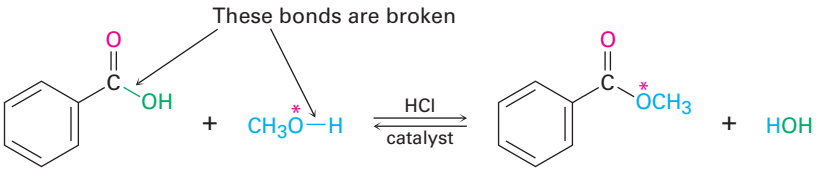
Mechanism of Fischer esterification. The reaction is an acid-catalyzed, nucleophilic acyl substitution of a carboxylic acid.



The net effect of Fischer esterification is substitution of an −OH group by −OR′. All steps are reversible, and the reaction typically has an equilibrium constant close to 1. Thus, the reaction can be driven in either direction by choice of reaction conditions. Ester formation is favored when a large excess of alcohol is used as solvent, but carboxylic acid formation is favored when a large excess of water is present.

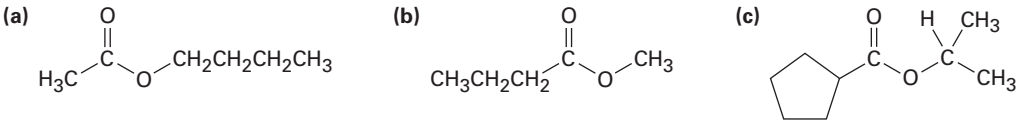
Evidence in support of the mechanism shown in Figure 21.4 comes from isotope-labeling experiments. When ^{18}O-labeled methanol reacts with benzoic acid, the methyl benzoate produced is found to be ^{18}O-labeled but the water produced is unlabeled. Thus, it is the C–OH bond of the carboxylic acid that is

broken during the reaction rather than the CO–H bond and the RO–H bond of the alcohol that is broken rather than the R–OH bond.



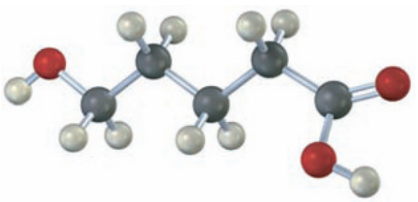
Problem 21.7

How might you prepare the following esters from the corresponding acids?



Problem 21.8

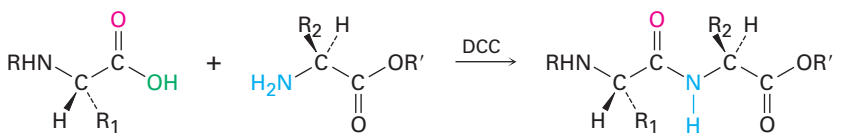
If the following molecule is treated with acid catalyst, an intramolecular esterification reaction occurs. What is the structure of the product? (*Intramolecular* means within the same molecule.)



Conversion of Carboxylic Acids into Amides

Amides are difficult to prepare by direct reaction of carboxylic acids with amines because amines are bases that convert acidic carboxyl groups into their unreactive carboxylate anions. Thus, the –OH must be replaced by a better, nonacidic leaving group. In practice, amides are usually prepared by treating the carboxylic acid with dicyclohexylcarbodiimide (DCC) to activate it, followed by addition of the amine. As shown in **Figure 21.5**, the acid first adds to a C=N double bond of DCC, and nucleophilic acyl substitution by amine then ensues. Alternatively, and depending on the reaction solvent, the reactive acyl intermediate might also react with a second equivalent of carboxylate ion to generate an acid anhydride that then reacts with the amine. The product from either pathway is the same.

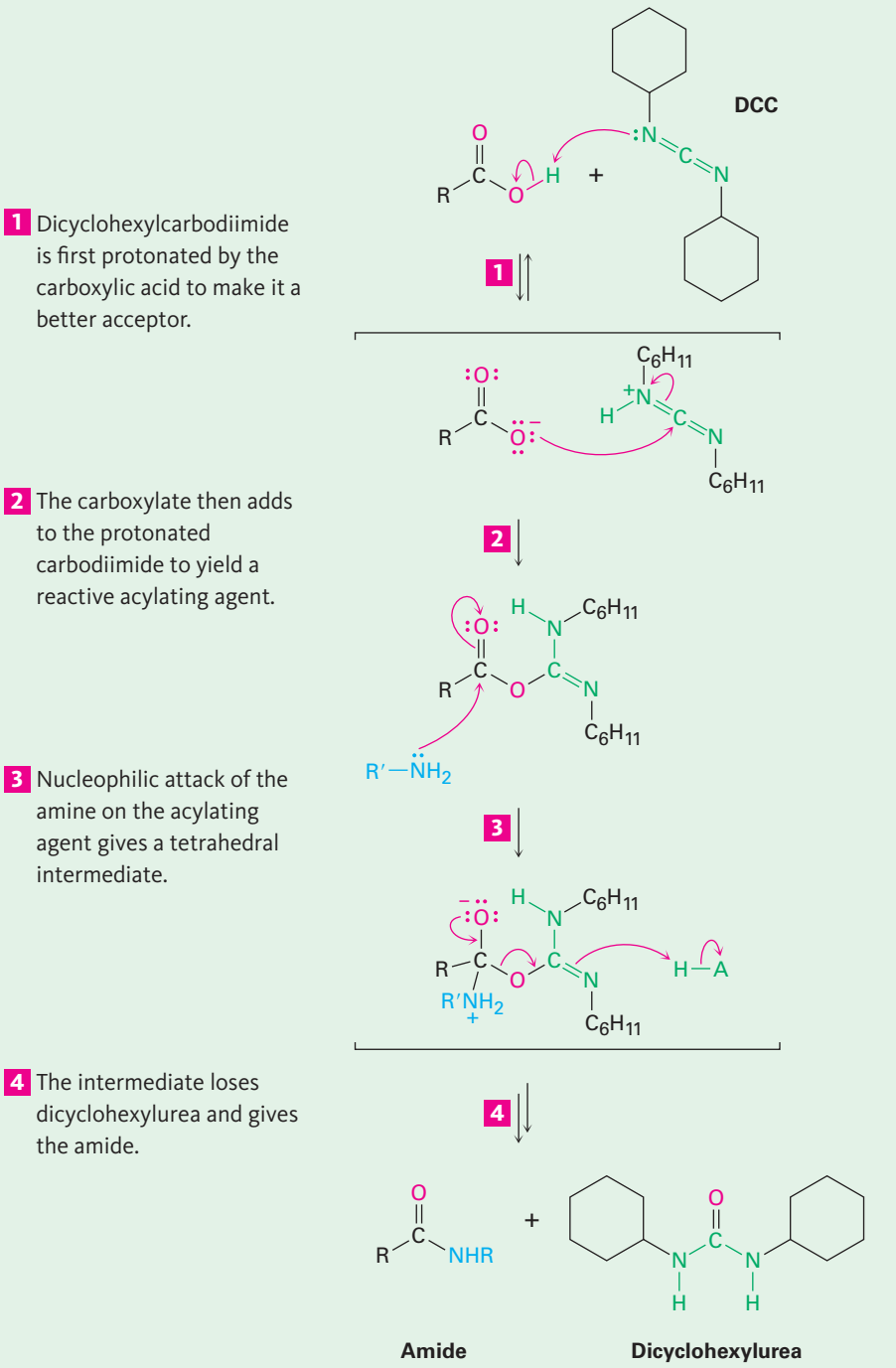
We'll see in **Section 26.7** that this DCC-induced method of amide formation is the key step in the laboratory synthesis of small proteins, or *peptides*. For instance, when one amino acid with its NH_2 rendered unreactive and a second amino acid with its $-CO_2H$ rendered unreactive are treated with DCC, a dipeptide is formed.



Amino acid 1 **Amino acid 2** **A dipeptide**

Figure 21.5 | MECHANISM

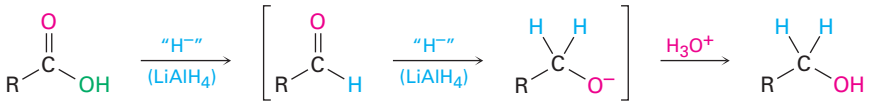
Mechanism of amide formation by reaction of a carboxylic acid and an amine with dicyclohexylcarbodiimide (DCC).



Conversion of Carboxylic Acids into Alcohols

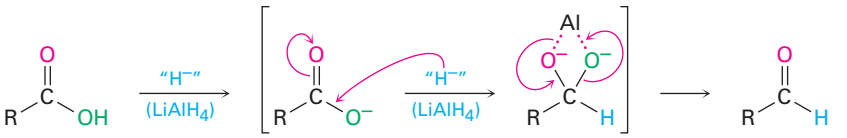
We said in **Section 17.4** that carboxylic acids are reduced by $LiAlH_4$ to give primary alcohols, but we deferred a discussion of the reaction mechanism at that time. In fact, the reduction is a nucleophilic acyl substitution reaction in

which −H replaces −OH to give an aldehyde, which is further reduced to a primary alcohol by nucleophilic addition. The aldehyde intermediate is much more reactive than the starting acid, so it reacts immediately and is not isolated.



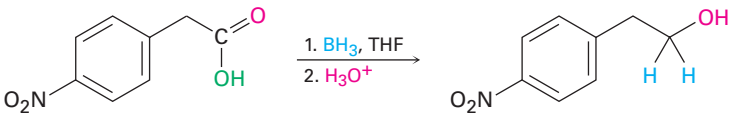
A carboxylic acid — **An aldehyde (not isolated)** — **An alkoxide ion** — **A 1° alcohol**

Because hydride ion is a base as well as a nucleophile, the actual nucleophilic acyl substitution step takes place on the carboxylate ion rather than on the free carboxylic acid and gives a high-energy *dianion* intermediate. In this intermediate, the two oxygens are undoubtedly complexed to a Lewis acidic aluminum species. Thus, the reaction is relatively difficult, and acid reductions require higher temperatures and extended reaction times.



A carboxylic acid — **A carboxylate** — **A dianion** — **An aldehyde**

Alternatively, borane in tetrahydrofuran (BH_3/THF) is a useful reagent for reducing carboxylic acids to primary alcohols. Reaction of an acid with BH_3/THF occurs rapidly at room temperature, and the procedure is often preferred to reduction with $LiAlH_4$ because of its relative ease and safety. Borane reacts with carboxylic acids faster than with any other functional group, thereby allowing selective transformations such as that on *p*-nitrophenylacetic acid. If the reduction of *p*-nitrophenylacetic acid were done with $LiAlH_4$, both nitro and carboxyl groups would be reduced.



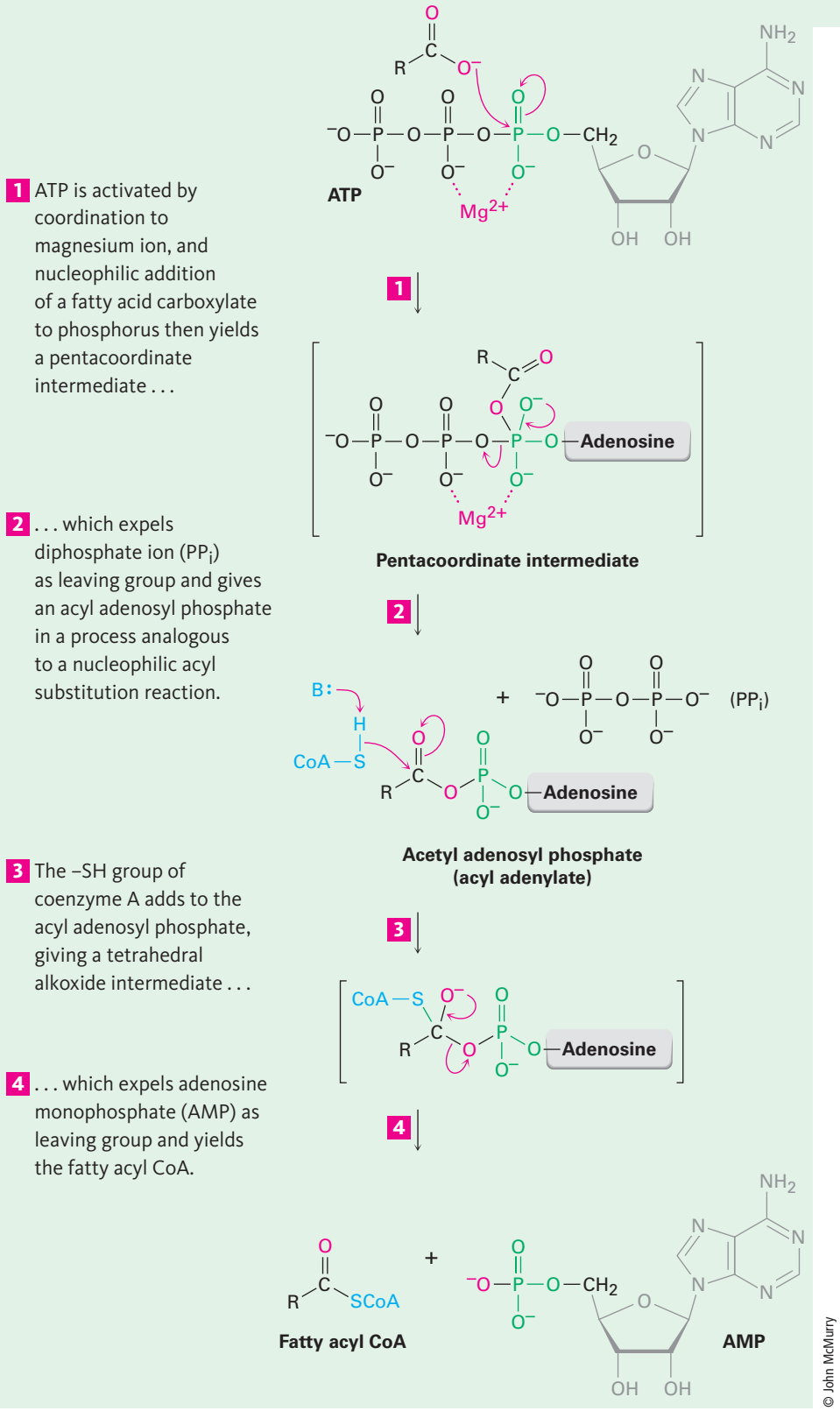
***p*-Nitrophenylacetic acid** — **2-(*p*-Nitrophenyl)ethanol (94%)**

Biological Conversions of Carboxylic Acids

The direct conversion of a carboxylic acid to an acyl derivative by nucleophilic acyl substitution does not occur in biological chemistry. As in the laboratory, the acid must first be activated by converting the −OH into a better leaving group. This activation is often accomplished in living organisms by reaction of the acid with adenosine triphosphate (ATP) to give an acyl adenosyl phosphate, or *acyl adenylate*, a mixed anhydride between a carboxylic acid and adenosine monophosphate (AMP, also known as adenylic acid). In the biosynthesis of fats, for example, a long-chain carboxylic acid reacts with ATP to give an acyl adenylate, followed by subsequent nucleophilic acyl substitution of a thiol group in coenzyme A to give the corresponding acyl CoA **(Figure 21.6)**.

Figure 21.6 | MECHANISM

In fatty-acid biosynthesis, a carboxylic acid is activated by reaction with ATP to give an acyl adenylate, which undergoes nucleophilic acyl substitution with the —SH group on coenzyme A. (ATP = adenosine triphosphate; AMP = adenosine monophosphate.)



Note that the first step in Figure 21.6—reaction of the carboxylate with ATP to give an acyl adenylate—is itself a nucleophilic acyl substitution on *phosphorus*. The carboxylate first adds to a P=O double bond, giving a five-coordinate phosphorus intermediate that expels diphosphate ion as leaving group.

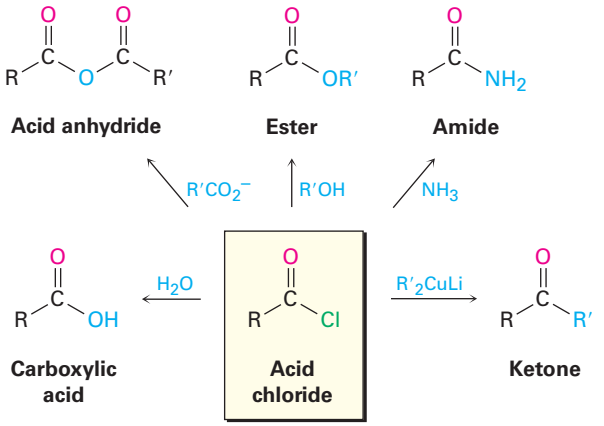
21.4 Chemistry of Acid Halides

Preparation of Acid Halides

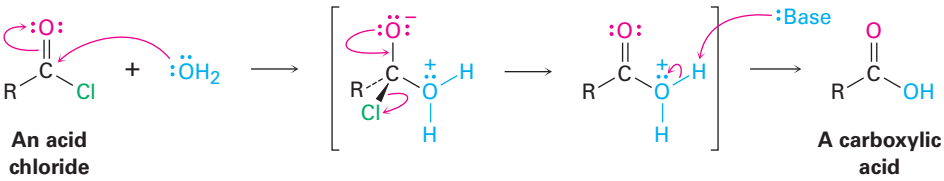
Acid chlorides are prepared from carboxylic acids by reaction with thionyl chloride ($SOCl_2$), as we saw in the previous section. Similar reaction of a carboxylic acid with phosphorus tribromide (PBr_3) yields the acid bromide.

Reactions of Acid Halides

Acid halides are among the most reactive of carboxylic acid derivatives and can be converted into many other kinds of compounds by nucleophilic acyl substitution mechanisms. The halogen can be replaced by −OH to yield an acid, by −OCOR to yield an anhydride, by −OR to yield an ester, by $-NH_2$ to yield an amide, or by R′ to yield a ketone. In addition, the reduction of an acid halide yields a primary alcohol, and reaction with a Grignard reagent yields a tertiary alcohol. Although the reactions we'll be discussing in this section are illustrated only for acid chlorides, similar processes take place with other acid halides.

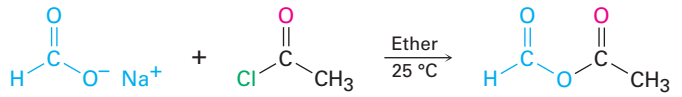


Conversion of Acid Halides into Acids: Hydrolysis Acid chlorides react with water to yield carboxylic acids. This hydrolysis reaction is a typical nucleophilic acyl substitution process and is initiated by attack of water on the acid chloride carbonyl group. The tetrahedral intermediate undergoes elimination of Cl^- and loss of H^+ to give the product carboxylic acid plus HCl.



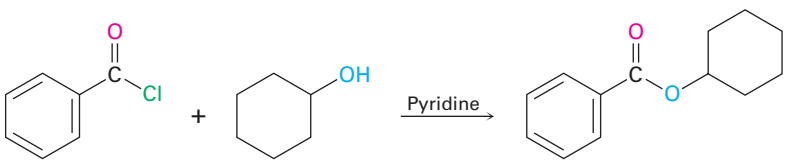
Because HCl is formed during the hydrolysis, the reaction is often carried out in the presence of a base such as pyridine or NaOH to remove the HCl and prevent it from causing side reactions.

Conversion of Acid Halides into Anhydrides Nucleophilic acyl substitution reaction of an acid chloride with a carboxylate anion gives an acid anhydride. Both symmetrical and unsymmetrical acid anhydrides can be prepared.



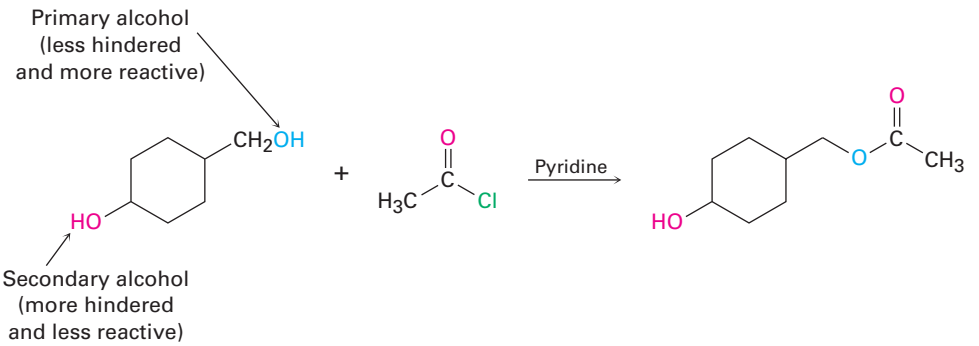
Sodium formate + **Acetyl chloride** → **Acetic formic anhydride (64%)**

Conversion of Acid Halides into Esters: Alcoholysis Acid chlorides react with alcohols to yield esters in a process analogous to their reaction with water to yield acids. In fact, this reaction is probably the most common method for preparing esters in the laboratory. As with hydrolysis, alcoholysis reactions are usually carried out in the presence of pyridine or NaOH to react with the HCl formed.



Benzoyl chloride + **Cyclohexanol** → **Cyclohexyl benzoate (97%)**

The reaction of an alcohol with an acid chloride is strongly affected by steric hindrance. Bulky groups on either partner slow down the reaction considerably, resulting in a reactivity order among alcohols of primary > secondary > tertiary. As a result, it's often possible to esterify an unhindered alcohol selectively in the presence of a more hindered one. This can be important in complex syntheses in which it's sometimes necessary to distinguish between similar functional groups. For example,



Problem 21.9

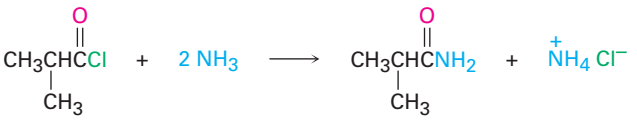
How might you prepare the following esters using a nucleophilic acyl substitution reaction of an acid chloride?

(a) $CH_3CH_2CO_2CH_3$ **(b)** $CH_3CO_2CH_2CH_3$ **(c)** Ethyl benzoate

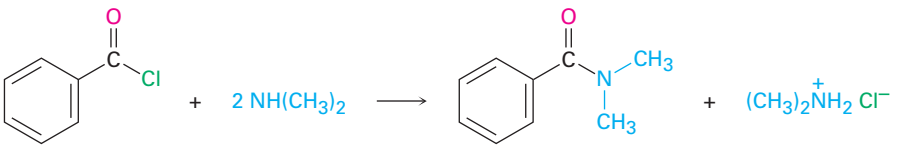
Problem 21.10

Which method would you choose if you wanted to prepare cyclohexyl benzoate—Fischer esterification or reaction of an acid chloride with an alcohol? Explain.

Conversion of Acid Halides into Amides: Aminolysis Acid chlorides react rapidly with ammonia and amines to give amides. As with the acid chloride-plus-alcohol method for preparing esters, this reaction of acid chlorides with amines is the most commonly used laboratory method for preparing amides. Both monosubstituted and disubstituted amines can be used, but not trisubstituted amines (R_3N).

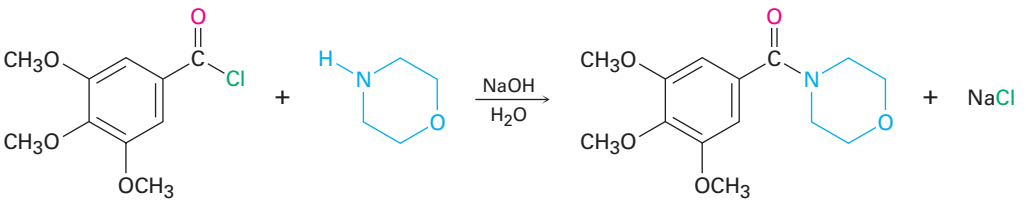


2-Methylpropanoyl chloride **2-Methylpropanamide (83%)**



Benzoyl chloride ***N,N*-Dimethylbenzamide (92%)**

Because HCl is formed during the reaction, 2 equivalents of the amine must be used. One equivalent reacts with the acid chloride, and one equivalent reacts with the HCl by-product to form an ammonium chloride salt. If, however, the amine component is valuable, amide synthesis is often carried out using 1 equivalent of the amine plus 1 equivalent of an inexpensive base such as NaOH. For example, the sedative trimetozine is prepared commercially by reaction of 3,4,5-trimethoxybenzoyl chloride with the amine morpholine in the presence of 1 equivalent of NaOH.



3,4,5-Trimethoxybenzoyl chloride **Morpholine** **Trimetozine (an amide)**

Problem 21.11

Write the mechanism of the reaction just shown between 3,4,5-trimethoxybenzoyl chloride and morpholine to form trimetozine. Use curved arrows to show the electron flow in each step.

Problem 21.12

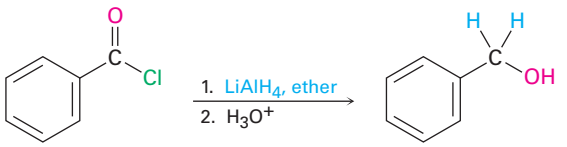
How could you prepare the following amides using an acid chloride and an amine or ammonia?

(a) $CH_3CH_2CONHCH_3$ **(b)** *N*,*N*-Diethylbenzamide **(c)** Propanamide

Conversion of Acid Chlorides into Alcohols: Reduction and Grignard Reaction

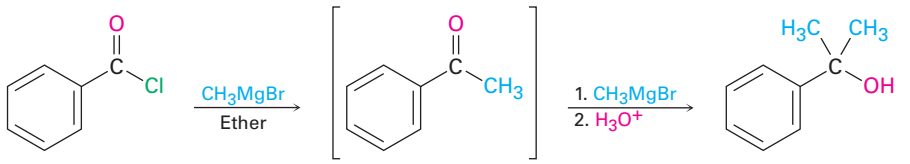
Acid chlorides are reduced by $LiAlH_4$ to yield primary alcohols. The reaction is of little practical value, however, because the parent carboxylic acids are generally more readily available and can themselves be reduced by $LiAlH_4$ to yield alcohols.

Reduction occurs via a typical nucleophilic acyl substitution mechanism in which a hydride ion ($H:^-$) adds to the carbonyl group, yielding a tetrahedral intermediate that expels Cl^-. The net effect is a substitution of $-Cl$ by $-H$ to yield an aldehyde, which is then further reduced by $LiAlH_4$ in a second step to yield the primary alcohol.



Benzoyl chloride **Benzyl alcohol (96%)**

Grignard reagents react with acid chlorides to yield tertiary alcohols in which two of the substituents are the same. The mechanism of the reaction is similar to that of $LiAlH_4$ reduction. The first equivalent of Grignard reagent adds to the acid chloride, loss of Cl^- from the tetrahedral intermediate yields a ketone, and a second equivalent of Grignard reagent immediately adds to the ketone to produce an alcohol.

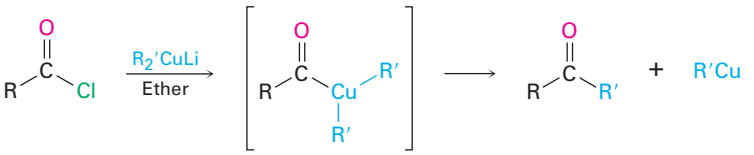


Benzoyl chloride **Acetophenone** ***(Not isolated)*** **2-Phenyl-2-propanol (92%)**

Conversion of Acid Chlorides into Ketones: Diorganocopper Reaction

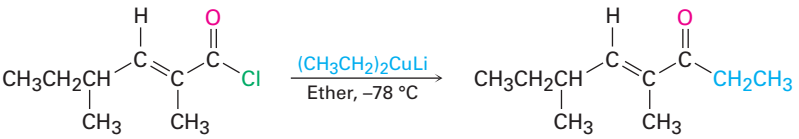
The ketone intermediate formed in during the reaction of an acid chloride with a Grignard reagent can't usually be isolated because addition of the second equivalent of organomagnesium reagent occurs too rapidly. A ketone *can,*

however, be isolated from the reaction of an acid chloride with a lithium diorganocopper (Gilman) reagent, $Li^+ R_2Cu^-$. The reaction occurs by initial nucleophilic acyl substitution on the acid chloride by the diorganocopper anion to yield an acyl diorganocopper intermediate, followed by loss of R′Cu and formation of the ketone.



An acid chloride **An acyl diorganocopper** **A ketone**

The reaction is generally carried out at −78 °C in ether solution, and yields are often excellent. For example, manicone, a substance secreted by male ants to coordinate ant pairing and mating, has been synthesized by reaction of lithium diethylcopper with (*E*)-2,4-dimethyl-2-hexenoyl chloride.



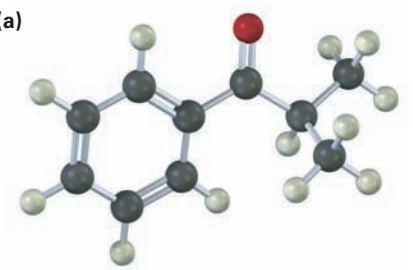
2,4-Dimethyl-2-hexenoyl chloride **4,6-Dimethyl-4-octen-3-one (manicone, 92%)**

Note that the diorganocopper reaction occurs only with acid chlorides. Carboxylic acids, esters, acid anhydrides, and amides do not react with lithium diorganocopper reagents.

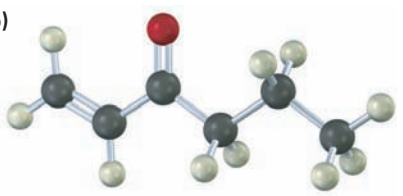
Problem 21.13

How could you prepare the following ketones by reaction of an acid chloride with a lithium diorganocopper reagent?

(a)



(b)

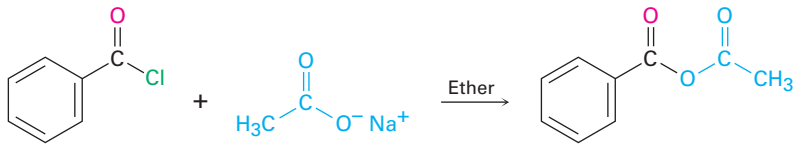


21.5 Chemistry of Acid Anhydrides

Preparation of Acid Anhydrides

Acid anhydrides are typically prepared by nucleophilic acyl substitution reaction of an acid chloride with a carboxylate anion, as we saw in **Section 21.4**.

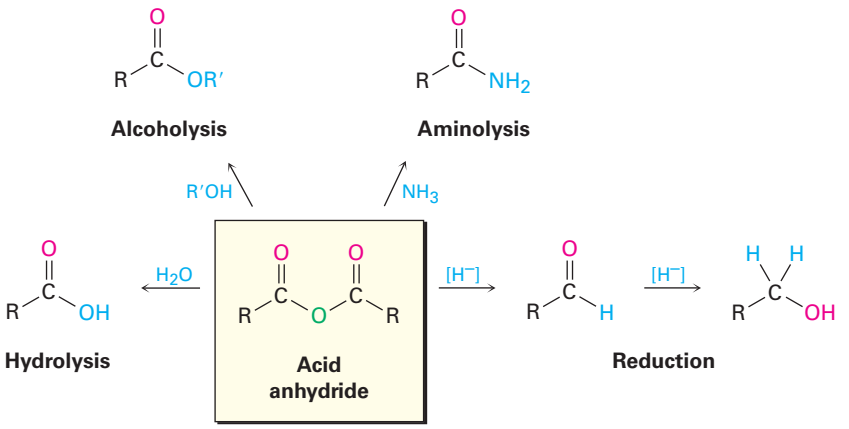
Both symmetrical and unsymmetrical acid anhydrides can be prepared in this way.



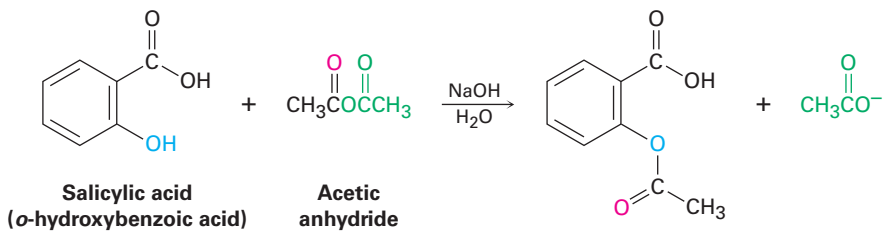
Benzoyl chloride **Sodium acetate** **Acetic benzoic anhydride**

Reactions of Acid Anhydrides

The chemistry of acid anhydrides is similar to that of acid chlorides, although anhydrides react more slowly. Thus, acid anhydrides react with water to form acids, with alcohols to form esters, with amines to form amides, and with $LiAlH_4$ to form primary alcohols. Only the ester and amide forming reactions are commonly used, however.



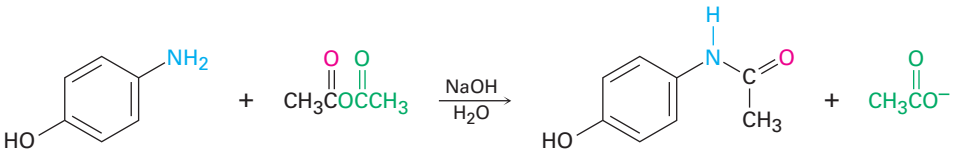
Conversion of Acid Anhydrides into Esters Acetic anhydride is often used to prepare acetate esters from alcohols. For example, aspirin (acetylsalicylic acid) is prepared commercially by the acetylation of *o*-hydroxybenzoic acid (salicylic acid) with acetic anhydride.



Salicylic acid (*o*-hydroxybenzoic acid) **Acetic anhydride** **Aspirin (an ester)**

Conversion of Acid Anhydrides into Amides Acetic anhydride is also commonly used to prepare *N*-substituted acetamides from amines. For example, acetaminophen, a drug used in over-the-counter analgesics such as Tylenol, is

prepared by reaction of *p*-hydroxyaniline with acetic anhydride. Only the more nucleophilic $-NH_2$ group reacts rather than the less nucleophilic $-OH$ group.



***p*-Hydroxyaniline** **Acetic anhydride** **Acetaminophen**

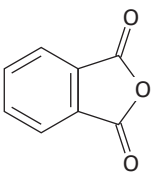
Notice in both of the previous reactions that only "half" of the anhydride molecule is used, while the other half acts as the leaving group during the nucleophilic acyl substitution step and produces acetate ion as a by-product. Thus, anhydrides are inefficient to use, and acid chlorides are normally preferred for introducing acyl substituents other than acetyl groups.

Problem 21.14

Write the mechanism of the reaction between *p*-hydroxyaniline and acetic anhydride to prepare acetaminophen.

Problem 21.15

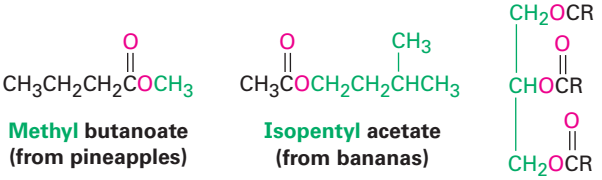
What product would you expect from reaction of 1 equivalent of methanol with a cyclic anhydride, such as phthalic anhydride (1,2-benzenedicarboxylic anhydride)? What is the fate of the second "half" of the anhydride?



Phthalic anhydride

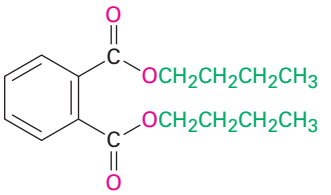
21.6 Chemistry of Esters

Esters are among the most widespread of all naturally occurring compounds. Many simple esters are pleasant-smelling liquids that are responsible for the fragrant odors of fruits and flowers. For example, methyl butanoate is found in pineapple oil, and isopentyl acetate is a constituent of banana oil. The ester linkage is also present in animal fats and in many biologically important molecules.



Methyl butanoate (from pineapples) **Isopentyl acetate (from bananas)** **A fat ($R = C_{11-17}$ chains)**

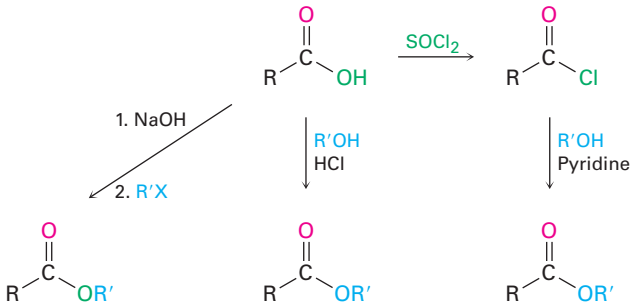
The chemical industry uses esters for a variety of purposes. Ethyl acetate, for instance, is a commonly used solvent, and dialkyl phthalates are used as plasticizers to keep polymers from becoming brittle. You may be aware that there is current concern about possible toxicity of phthalates at high concentrations, although a recent assessment by the U.S. Food and Drug Administration found the risk to be minimal for most people, with the possible exception of male infants.



Dibutyl phthalate (a plasticizer)

Preparation of Esters

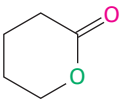
Esters are usually prepared from carboxylic acids by the methods already discussed. Thus, carboxylic acids are converted directly into esters by S_N2 reaction of a carboxylate ion with a primary alkyl halide or by Fischer esterification of a carboxylic acid with an alcohol in the presence of a mineral acid catalyst. In addition, acid chlorides are converted into esters by treatment with an alcohol in the presence of base **(Section 21.4)**.



Method limited to primary alkyl halides | **Method limited to simple alcohols** | **Method is very general**

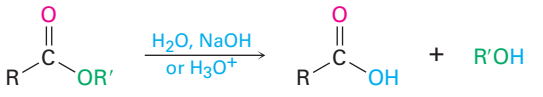
Reactions of Esters

Esters undergo the same kinds of reactions that we've seen for other carboxylic acid derivatives, but they are less reactive toward nucleophiles than either acid chlorides or anhydrides. All their reactions are applicable to both acyclic and cyclic esters, called **lactones**.



A lactone (cyclic ester)

Conversion of Esters into Carboxylic Acids: Hydrolysis An ester is hydrolyzed, either by aqueous base or by aqueous acid, to yield a carboxylic acid plus an alcohol.



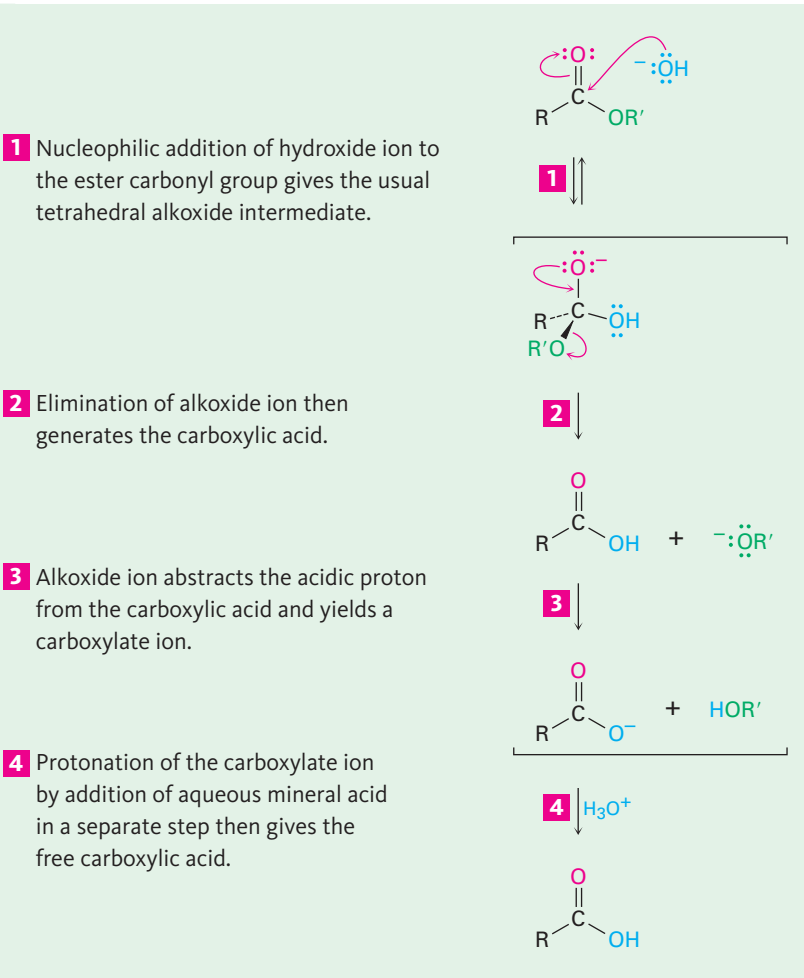
Ester | **Acid** | **Alcohol**

Ester hydrolysis in basic solution is called **saponification**, after the Latin word *sapo*, meaning "soap." We'll see in **Section 27.2** that soap is in fact made by boiling animal fat with aqueous base to hydrolyze the ester linkages.

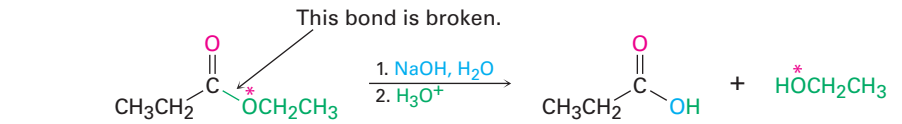
As shown in **Figure 21.7**, ester hydrolysis occurs through a typical nucleophilic acyl substitution pathway in which hydroxide ion is the nucleophile that adds to the ester carbonyl group to give a tetrahedral intermediate. Loss of alkoxide ion then gives a carboxylic acid, which is deprotonated to give the carboxylate ion. Addition of aqueous HCl in a separate step after the saponification is complete protonates the carboxylate ion and gives the carboxylic acid.

Figure 21.7 | MECHANISM

Mechanism of base-induced ester hydrolysis (saponification)



The mechanism shown in Figure 21.7 is supported by isotope-labeling studies. When ethyl propanoate labeled with ^{18}O in the ether-like oxygen is hydrolyzed in aqueous NaOH, the ^{18}O label shows up exclusively in the ethanol product. None of the label remains with the propanoic acid, indicating that saponification occurs by cleavage of the C–OR′ bond rather than the CO–R′ bond.



Acid-catalyzed ester hydrolysis can occur by more than one mechanism, depending on the structure of the ester. The usual pathway, however, is just the reverse of a Fischer esterification reaction **(Section 21.3)**. As shown in **Figure 21.8**, the ester is first activated toward nucleophilic attack by protonation of the carboxyl oxygen atom, and nucleophilic addition of water then occurs. Transfer of a proton and elimination of alcohol yields the carboxylic acid. Because this hydrolysis reaction is the reverse of a Fischer esterification reaction, Figure 21.8 is the reverse of Figure 21.4.

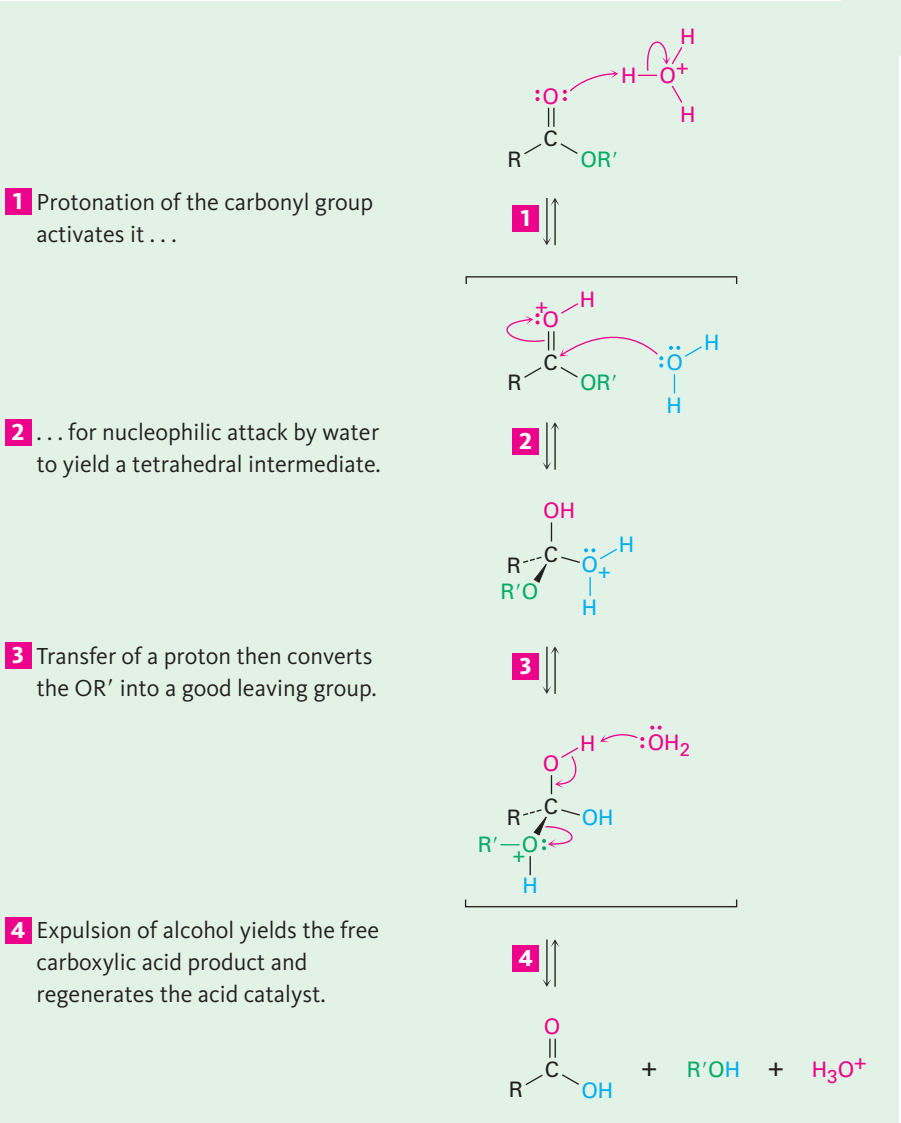
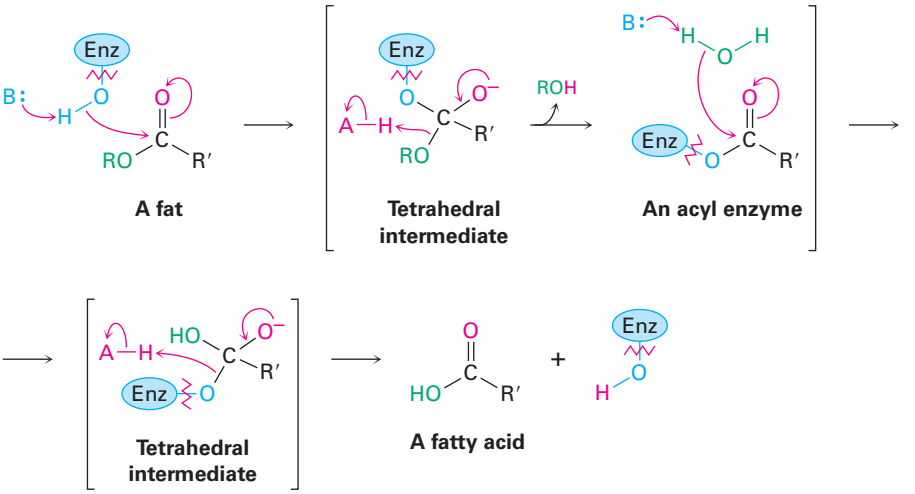


Figure 21.8 | MECHANISM

Mechanism of acid-catalyzed ester hydrolysis. The forward reaction is a hydrolysis; the back-reaction is a Fischer esterification and is thus the reverse of Figure 21.4.

Ester hydrolysis is common in biological chemistry, particularly in the digestion of dietary fats and oils. We'll save a complete discussion of the mechanistic details of fat hydrolysis until **Section 29.2** but will note for now that the reaction is catalyzed by various lipase enzymes and involves two sequential nucleophilic acyl substitution reactions. The first is a *transesterification* reaction in which an alcohol group on the lipase adds to an ester linkage in the fat molecule to give

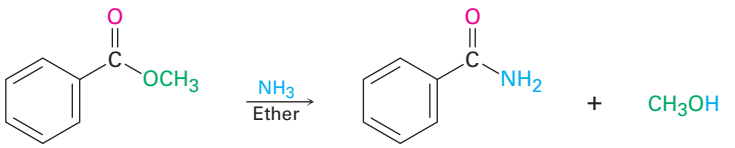
a tetrahedral intermediate that expels alcohol and forms an acyl enzyme intermediate. The second is an addition of water to the acyl enzyme, followed by expulsion of the enzyme to give a hydrolyzed acid plus regenerated enzyme.



Problem 21.16

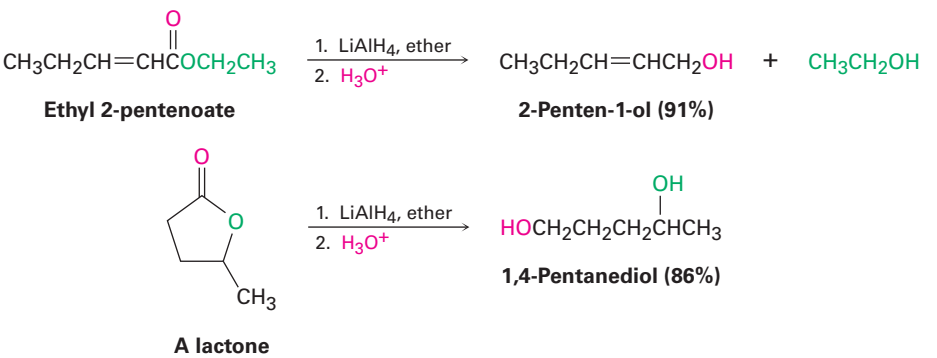
Why is the saponification of an ester irreversible? In other words, why doesn't treatment of a carboxylic acid with an alkoxide ion yield an ester?

Conversion of Esters into Amides: Aminolysis Esters react with ammonia and amines to yield amides. The reaction is not often used, however, because it's usually easier to prepare an amide by starting with an acid chloride **(Section 21.4)**.

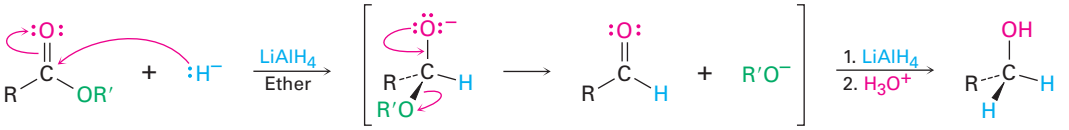


Methyl benzoate **Benzamide**

Conversion of Esters into Alcohols: Reduction Esters are easily reduced by treatment with $LiAlH_4$ to yield primary alcohols **(Section 17.4)**.

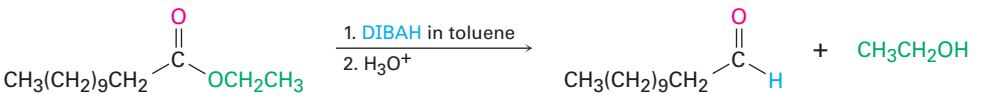


The mechanism of ester reduction is similar to that of acid chloride reduction in that a hydride ion first adds to the carbonyl group, followed by elimination of alkoxide ion to yield an aldehyde. Further reduction of the aldehyde gives the primary alcohol.



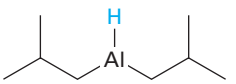
Aldehyde **A primary alcohol**

The aldehyde intermediate can be isolated if 1 equivalent of diisobutylaluminum hydride (DIBAH, or DIBAL-H) is used as the reducing agent instead of $LiAlH_4$. The reaction has to be carried out at −78 °C to avoid further reduction to the alcohol. Such partial reductions of carboxylic acid derivatives to aldehydes also occur in numerous biological pathways, although the substrate is either a thioester or acyl phosphate rather than an ester.



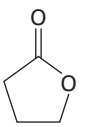
Ethyl dodecanoate **Dodecanal (88%)**

where DIBAH =



Problem 21.17

What product would you expect from the reaction of butyrolactone with $LiAlH_4$? With DIBAH?

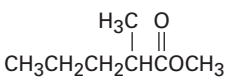


Butyrolactone

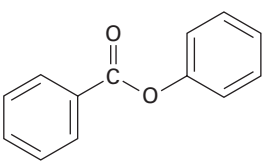
Problem 21.18

Show the products you would obtain by reduction of the following esters with $LiAlH_4$:

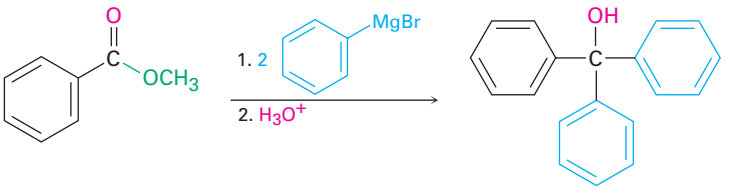
(a)



(b)



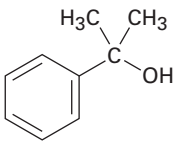
Conversion of Esters into Alcohols: Grignard Reaction Esters react with 2 equivalents of a Grignard reagent to yield a tertiary alcohol in which two of the substituents are identical **(Section 17.5)**. The reaction occurs by the usual nucleophilic substitution mechanism to give an intermediate ketone, which reacts further with the Grignard reagent to yield a tertiary alcohol.

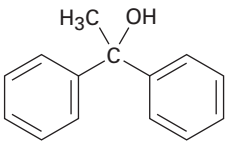


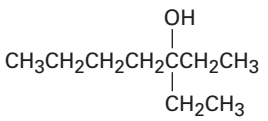
Methyl benzoate **Triphenylmethanol (96%)**

Problem 21.19

What ester and what Grignard reagent might you start with to prepare the following alcohols?

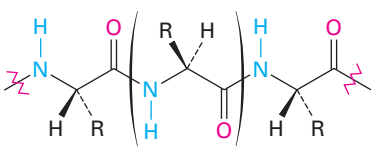
(a) 

(b) 

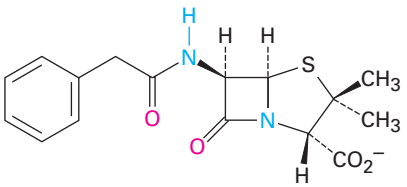
(c) 

21.7 Chemistry of Amides

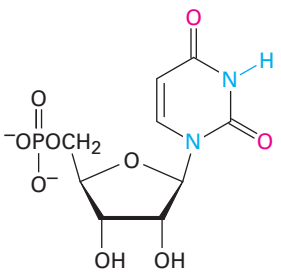
Amides, like esters, are abundant in all living organisms. Proteins, nucleic acids, and many pharmaceutical agents have amide functional groups. The reason for this abundance of amides is that they are stable to the aqueous conditions found in living organisms. Amides are the least reactive of the common acid derivatives and undergo relatively few nucleophilic acyl substitution reactions.



A protein segment



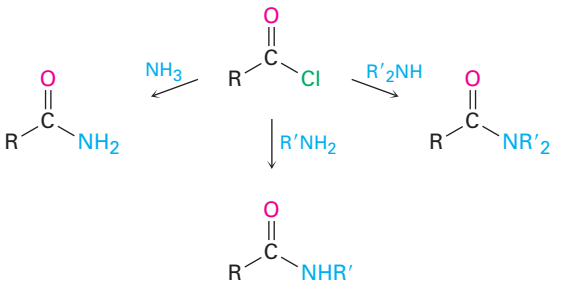
Benzylpenicillin (penicillin G)



Uridine 5′-phosphate (a ribonucleotide)

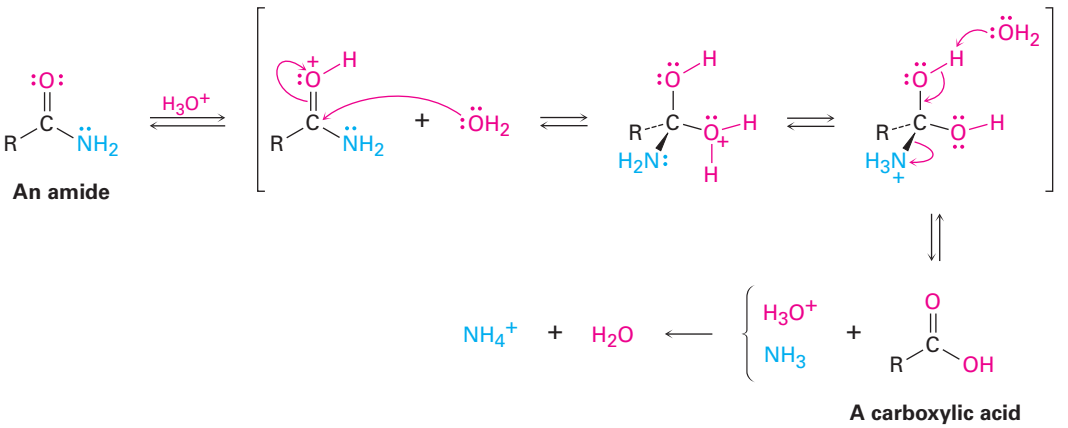
Preparation of Amides

Amides are usually prepared by reaction of an acid chloride with an amine **(Section 21.4)**. Ammonia, monosubstituted amines, and disubstituted amines all undergo the reaction.



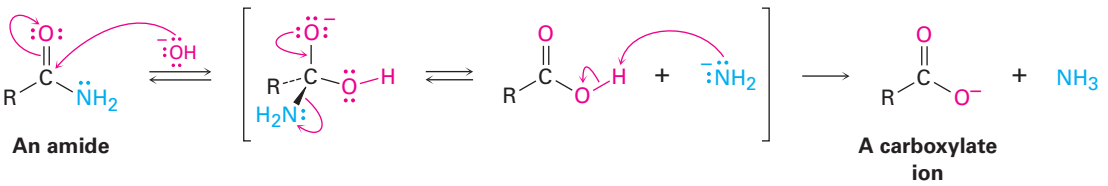
Reactions of Amides

Conversion of Amides into Carboxylic Acids: Hydrolysis Amides undergo hydrolysis to yield carboxylic acids plus ammonia or an amine on heating in either aqueous acid or aqueous base. The conditions required for amide hydrolysis are more severe than those required for the hydrolysis of acid chlorides or esters, but the mechanisms are similar. Acidic hydrolysis reaction occurs by nucleophilic addition of water to the protonated amide, followed by transfer of a proton from oxygen to nitrogen to make the nitrogen a better leaving group and subsequent elimination. The steps are reversible, with the equilibrium shifted toward product by protonation of NH_3 in the final step.

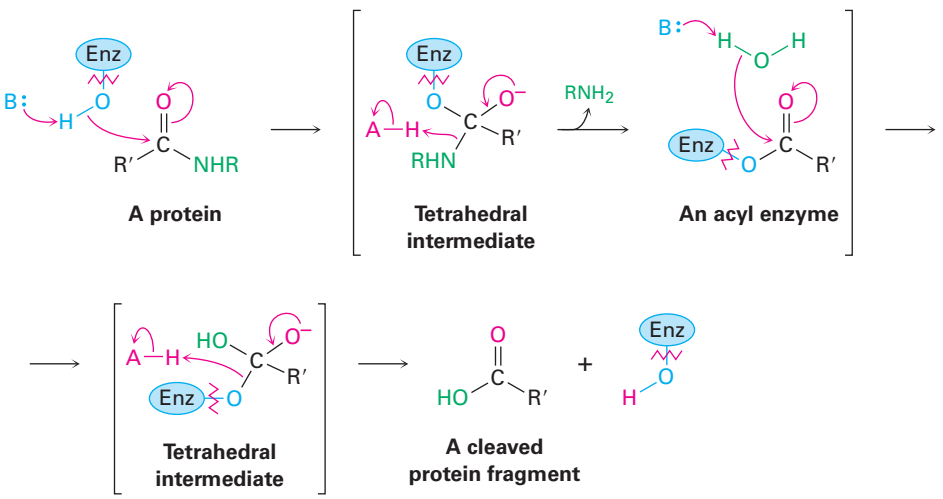


Basic hydrolysis occurs by nucleophilic addition of OH^- to the amide carbonyl group, followed by elimination of amide ion ($^-NH_2$) and subsequent deprotonation of the initially formed carboxylic acid by ammonia. The steps are reversible, with the equilibrium shifted toward product by the final deprotonation of the carboxylic acid. Basic hydrolysis is substantially more difficult than

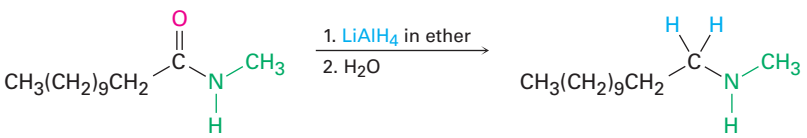
the analogous acid-catalyzed reaction because amide ion is a very poor leaving group, making the elimination step difficult.



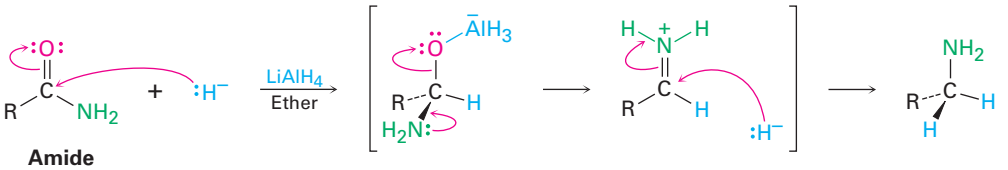
Amide hydrolysis is common in biological chemistry. Just as the hydrolysis of esters is the initial step in the digestion of dietary fats, the hydrolysis of amides is the initial step in the digestion of dietary proteins. The reaction is catalyzed by protease enzymes and occurs by a mechanism almost identical to that we just saw for fat hydrolysis. That is, an initial nucleophilic acyl substitution of an alcohol group in the enzyme on an amide linkage in the protein gives an acyl enzyme intermediate that then undergoes hydrolysis.



Conversion of Amides into Amines: Reduction Like other carboxylic acid derivatives, amides can be reduced by $LiAlH_4$. The product of the reduction, however, is an amine rather than an alcohol. The net effect of an amide reduction reaction is thus the conversion of the amide carbonyl group into a methylene group (C=O → CH_2). This kind of reaction is specific for amides and does not occur with other carboxylic acid derivatives.

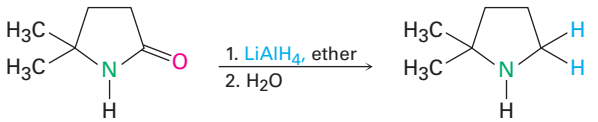


Amide reduction occurs by nucleophilic addition of hydride ion to the amide carbonyl group, followed by expulsion of the *oxygen* atom as an aluminate anion leaving group to give an iminium ion intermediate. The intermediate iminium ion is then further reduced by $LiAlH_4$ to yield the amine.



Amide **Iminium ion** **Amine**

The reaction is effective with both acyclic and cyclic amides, or **lactams**, and is a good method for preparing cyclic amines.



A lactam **A cyclic amine (80%)**

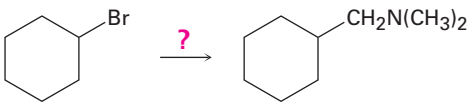
Problem 21.20

How would you convert *N*-ethylbenzamide to each of the following products?

(a) Benzoic acid **(b)** Benzyl alcohol **(c)** $C_6H_5CH_2NHCH_2CH_3$

Problem 21.21

How would you use the reaction of an amide with $LiAlH_4$ as the key step in going from bromocyclohexane to (*N*,*N*-dimethylaminomethyl)cyclohexane? Write all the steps in the reaction sequence.



(*N*,*N*-Dimethylaminomethyl)cyclohexane

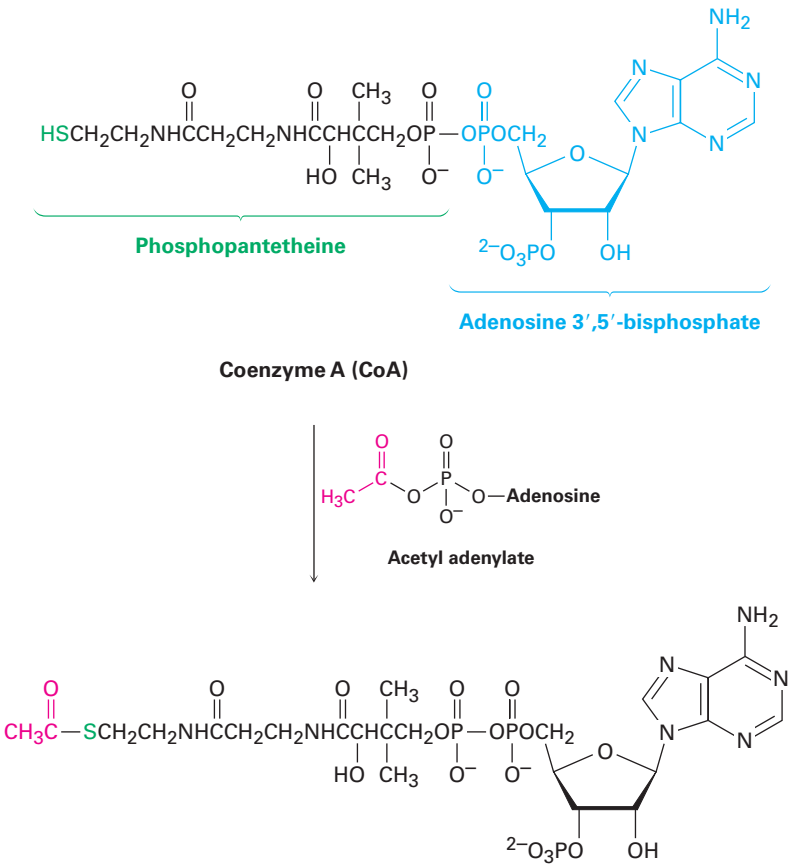
21.8 Chemistry of Thioesters and Acyl Phosphates: Biological Carboxylic Acid Derivatives

As mentioned in the chapter introduction, the substrate for a nucleophilic acyl substitution reaction in living organisms is generally either a thioester (RCOSR′) or an acyl phosphate ($RCO_2PO_3^{2-}$ or $RCO_2PO_3R'^{-}$). Neither is as reactive as an acid chloride or acid anhydride, yet both are stable enough to exist in living organisms while still reactive enough to undergo acyl substitution.

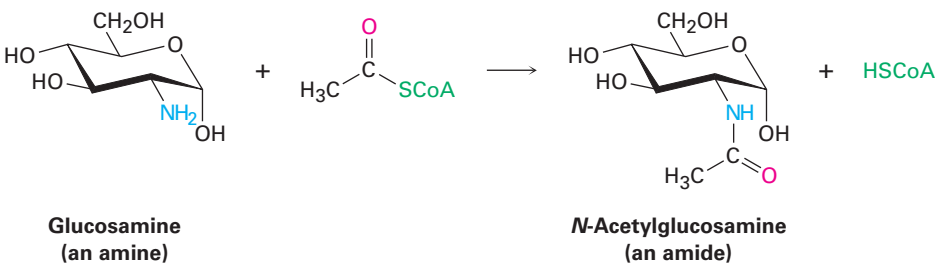
Acyl CoA's, such as acetyl CoA, are the most common thioesters in nature. Coenzyme A, abbreviated CoA, is a thiol formed by a phosphoric anhydride linkage (O=P–O–P=O) between phosphopantetheine and adenosine

3′,5′-bisphosphate. (The prefix *bis-* means "two" and indicates that adenosine 3′,5′-bisphosphate has two phosphate groups, one on C3′ and one on C5′.) Reaction of coenzyme A with an acyl phosphate or acyl adenylate gives the acyl CoA **(Figure 21.9)**. As we saw in **Section 21.3** (Figure 21.6), formation of the acyl adenylate occurs by reaction of a carboxylic acid with ATP and is itself a nucleophilic acyl substitution reaction that takes place on phosphorus.

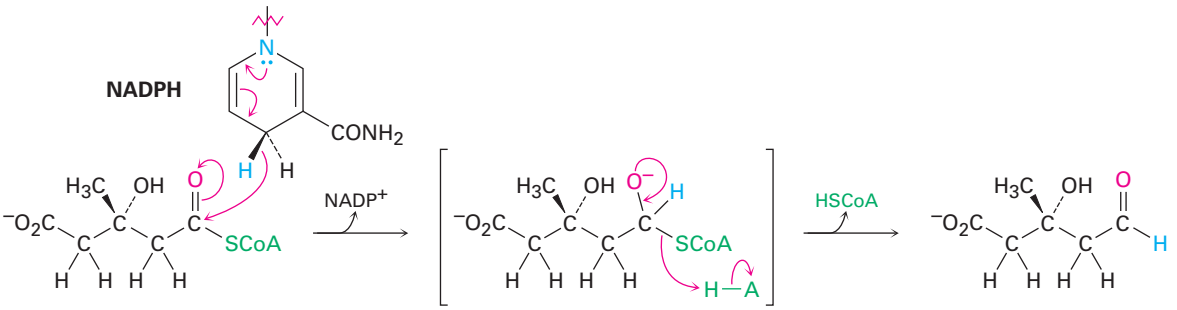
Figure 21.9 Formation of the thioester acetyl CoA by nucleophilic acyl substitution reaction of coenzyme A (CoA) with acetyl adenylate.



Once formed, an acyl CoA is a substrate for further nucleophilic acyl substitution reactions. For example, *N*-acetylglucosamine, a component of cartilage and other connective tissues, is synthesized by an aminolysis reaction between glucosamine and acetyl CoA.



Another example of a nucleophilic acyl substitution reaction on a thioester, this one a substitution by hydride ion to effect partial reduction of a thioester to an aldehyde, occurs in the biosynthesis of mevaldehyde, an intermediate in terpenoid synthesis, which we'll discuss in some detail in **Section 27.5**. In this reaction, (3*S*)-3-hydroxy-3-methylglutaryl CoA is reduced by hydride donation from NADPH.



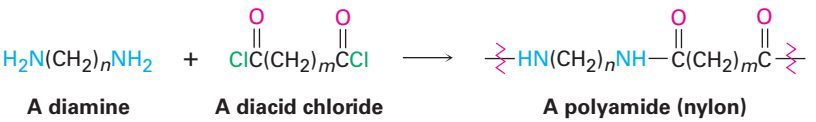
(3*S*)-3-Hydroxy-3-methylglutaryl CoA **(*R*)-Mevaldehyde**

Problem 21.22

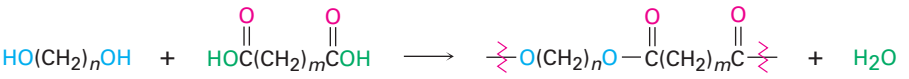
Write the mechanism of the reaction shown in Figure 21.9 between coenzyme A and acetyl adenylate to give acetyl CoA

21.9 Polyamides and Polyesters: Step-Growth Polymers

When an amine reacts with an acid chloride, an amide is formed. What would happen, though, if a *diamine* and a *diacid chloride* were allowed to react? Each partner could form two amide bonds, linking more and more molecules together until a giant polyamide resulted. In the same way, reaction of a diol with a diacid would lead to a polyester.



A diamine **A diacid chloride** **A polyamide (nylon)**

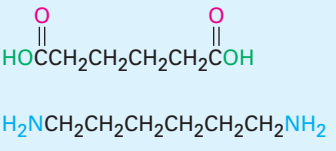
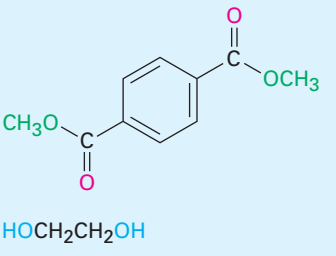
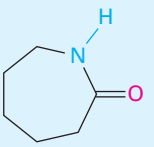
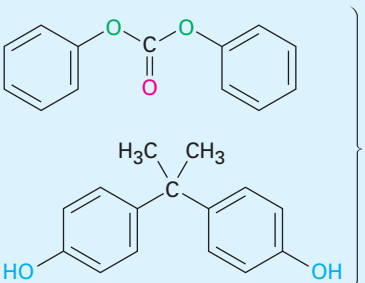
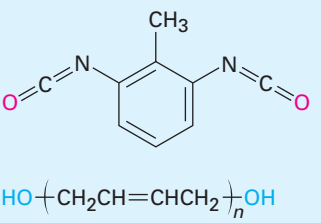


A diol **A diacid** **A polyester**

There are two main classes of synthetic polymers: *chain-growth polymers* and *step-growth polymers*. Polyethylene and other alkene and diene polymers like those we saw in **Sections 8.10 and 14.6** are chain-growth polymers because

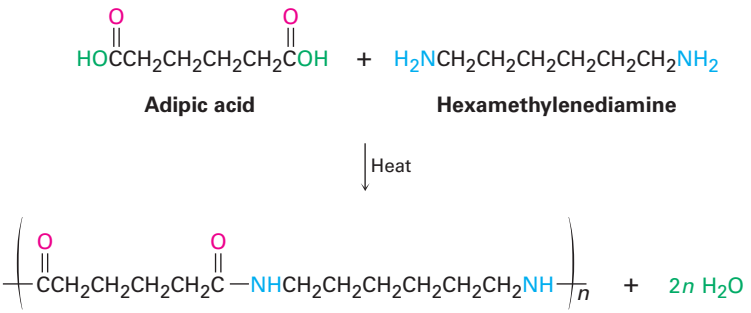
they are produced in chain-reaction processes. An initiator adds to a C=C bond to give a reactive intermediate, which adds to a second alkene molecule to produce a new intermediate, which adds to a third molecule, and so on. By contrast, polyamides and polyesters are **step-growth polymers** because each bond in the polymer is formed in a discrete step, independent of the others. The key bond-forming step is often a nucleophilic acyl substitution of a carboxylic acid derivative. Some commercially important step-growth polymers are shown in Table 21.2.

Table 21.2 Some Common Step-Growth Polymers and Their Uses

Monomers	Structure	Polymer	Uses
Adipic acid + Hexamethylenediamine		Nylon 66	Fibers, clothing, tire cord
Dimethyl terephthalate + Ethylene glycol		Dacron, Mylar, Terylene	Fibers, clothing, films, tire cord
Caprolactam		Nylon 6, Perlon	Fibers, castings
Diphenyl carbonate + Bisphenol A		Lexan, polycarbonate	Equipment housing, molded articles
Toluene-2,6-diisocyanate + Poly(2-butene-1,4-diol)		Polyurethane, Spandex	Fibers, coatings, foams

Polyamides (Nylons)

The best known step-growth polymers are the polyamides, or *nylons,* first prepared by Wallace Carothers at the DuPont Company by heating a diamine with a diacid. For example, nylon 66 is prepared by reaction of adipic acid (hexanedioic acid) with hexamethylenediamine (1,6-hexanediamine) at 280 °C. The designation "66" tells the number of carbon atoms in the diamine (the first 6) and the diacid (the second 6).



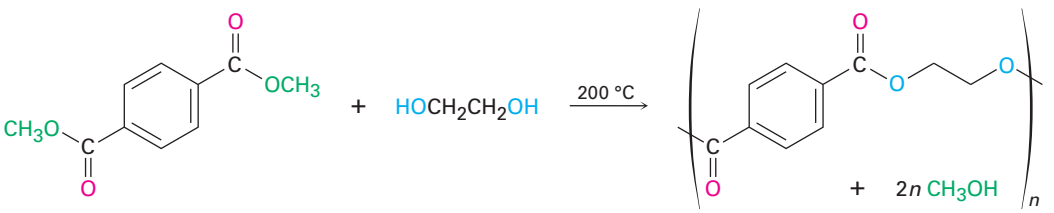
Adipic acid **Hexamethylenediamine**

Nylon 66

Nylons are used both in engineering applications and in making fibers. A combination of high impact strength and abrasion resistance makes nylon an excellent metal substitute for bearings and gears. As fiber, nylon is used in a variety of applications, from clothing to tire cord to ropes.

Polyesters

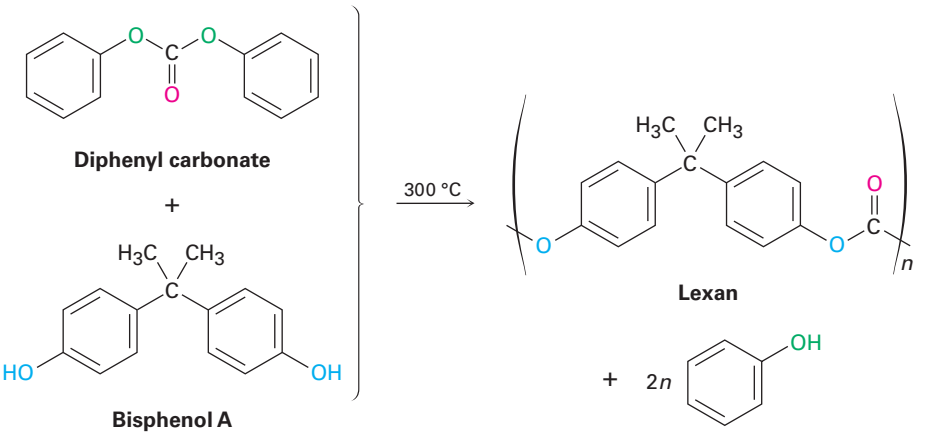
The most generally useful polyester is that made by reaction between dimethyl terephthalate (dimethyl 1,4-benzenedicarboxylate) and ethylene glycol (1,2-ethanediol). The product is used under the trade name Dacron to make clothing fiber and tire cord and under the name Mylar to make recording tape. The tensile strength of poly(ethylene terephthalate) film is nearly equal to that of steel.



Dimethyl terephthalate **Ethylene glycol** **A polyester (Dacron, Mylar)**

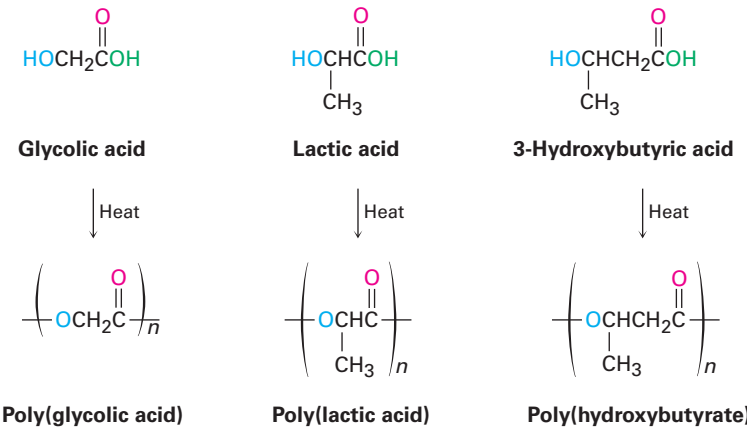
Lexan, a polycarbonate prepared from diphenyl carbonate and bisphenol A, is another commercially valuable polyester. Lexan has an unusually high impact

strength, making it valuable for use in telephones, bicycle safety helmets, and laptop computer cases.



Sutures and Biodegradable Polymers

Because plastics are too often thrown away rather than recycled, much work has been carried out on developing biodegradable polymers, which can be broken down rapidly in landfills by soil microorganisms. Among the most common biodegradable polymers are poly(glycolic acid) (PGA), poly(lactic acid) (PLA), and poly(hydroxybutyrate) (PHB). All are polyesters and are therefore susceptible to hydrolysis of their ester links. Copolymers of PGA with PLA have found a particularly wide range of uses. A 90/10 copolymer of poly(glycolic acid) with poly(lactic acid) is used to make absorbable sutures, for instance. The sutures are entirely hydrolyzed and absorbed by the body within 90 days after surgery.



In Europe, interest has centered particularly on poly(hydroxybutyrate), which can be made into films for packaging as well as into molded items. The polymer degrades within 4 weeks in landfills, both by ester hydrolysis and by an E1cB elimination reaction of the oxygen atom β to the carbonyl group. The use of poly(hydroxybutyrate) is limited at present by its cost—about four times that of polypropylene.

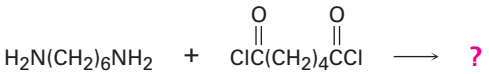
Problem 21.23

Draw structures of the step-growth polymers you would expect to obtain from the following reactions:

(a) $BrCH_2CH_2CH_2Br + HOCH_2CH_2CH_2OH \xrightarrow{\text{Base}} ?$

(b) $HOCH_2CH_2OH + HO_2C(CH_2)_6CO_2H \xrightarrow{H_2SO_4\ \text{catalyst}} ?$

(c)



Problem 21.24

Kevlar, a nylon polymer prepared by reaction of 1,4-benzenedicarboxylic acid (terephthalic acid) with 1,4-benzenediamine (*p*-phenylenediamine), is so strong that it's used to make bulletproof vests. Draw the structure of a segment of Kevlar.

21.10 Spectroscopy of Carboxylic Acid Derivatives

Infrared Spectroscopy

All carbonyl-containing compounds have intense IR absorptions in the range 1650 to 1850 cm^{-1}. As shown in Table 21.3, the exact position of the absorption provides information about the specific kind of carbonyl group. For comparison, the IR absorptions of aldehydes, ketones, and carboxylic acids are included in the table, along with values for carboxylic acid derivatives.

Acid chlorides are easily detected by their characteristic absorption near 1800 cm^{-1}. Acid anhydrides can be identified because they show two absorptions in the carbonyl region, one at 1820 cm^{-1} and another at 1760 cm^{-1}. Esters are detected by their absorption at 1735 cm^{-1}, a position somewhat higher than

Table 21.3 Infrared Absorptions of Some Carbonyl Compounds

Carbonyl type	Example	Absorption (cm^{-1})
Saturated acid chloride	Acetyl chloride	1810
Aromatic acid chloride	Benzoyl chloride	1770
Saturated acid anhydride	Acetic anhydride	1820, 1760
Saturated ester	Ethyl acetate	1735
Aromatic ester	Ethyl benzoate	1720
Saturated amide	Acetamide	1690
Aromatic amide	Benzamide	1675
N-Substituted amide	*N*-Methylacetamide	1680
N,*N*-Disubstituted amide	*N*,*N*-Dimethylacetamide	1650
(Saturated aldehyde	Acetaldehyde	1730)
(Saturated ketone	Acetone	1715)
(Saturated carboxylic acid	Acetic acid	1710)

that for either aldehydes or ketones. Amides, by contrast, absorb near the low wavenumber end of the carbonyl region, with the degree of substitution on nitrogen affecting the exact position of the IR band.

Problem 21.25

What kinds of functional groups might compounds have if they show the following IR absorptions?

(a) Absorption at 1735 cm^{-1}
(b) Absorption at 1810 cm^{-1}
(c) Absorptions at 2500–3300 cm^{-1} and 1710 cm^{-1}
(d) Absorption at 1715 cm^{-1}

Problem 21.26

Propose structures for compounds that have the following formulas and IR absorptions:

(a) $C_6H_{12}O_2$, 1735 cm^{-1} **(b)** C_4H_9NO, 1650 cm^{-1} **(c)** C_4H_5ClO, 1780 cm^{-1}

Nuclear Magnetic Resonance Spectroscopy

Hydrogens on the carbon next to a carbonyl group are slightly deshielded and absorb near 2 δ in the ^1H NMR spectrum. The identity of the carbonyl group can't be determined by ^1H NMR, however, because the α hydrogens of all acid derivatives absorb in the same range. **Figure 21.10** shows the ^1H NMR spectrum of ethyl acetate.

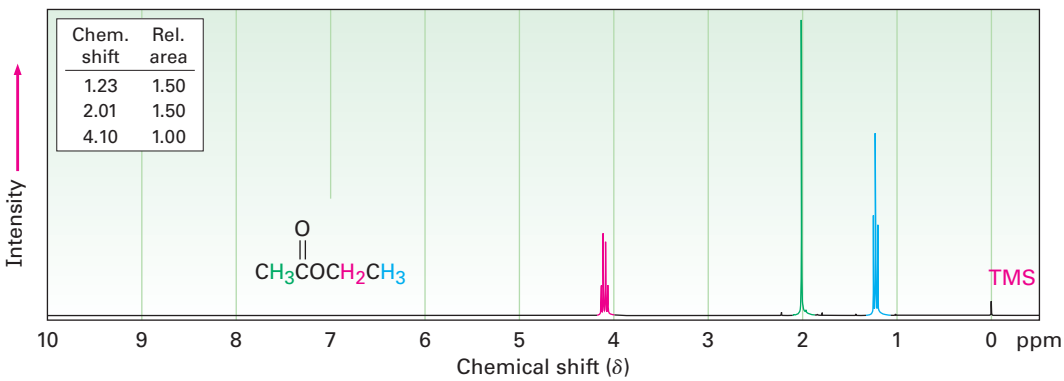


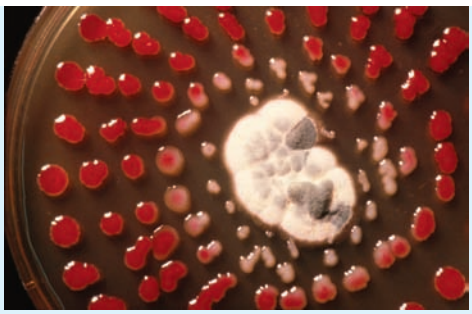
Figure 21.10 Proton NMR spectrum of ethyl acetate.

Although ^{13}C NMR is useful for determining the presence or absence of a carbonyl group in a molecule, the identity of the carbonyl group is difficult to determine. Aldehydes and ketones absorb near 200 δ, while the carbonyl carbon atoms of various acid derivatives absorb in the range 160 to 180 δ (Table 21.4).

Table 21.4 ^{13}C NMR Absorptions in Some Carbonyl Compounds

Compound	Absorption (δ)	Compound	Absorption (δ)
Acetic acid	177.3	Acetic anhydride	166.9
Ethyl acetate	170.7	Acetone	205.6
Acetyl chloride	170.3	Acetaldehyde	201.0
Acetamide	172.6		

A DEEPER LOOK β-Lactam Antibiotics



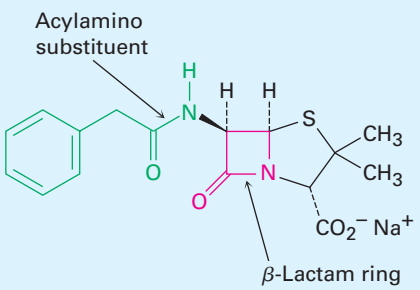
Penicillium **mold growing in a petri dish.**

You should never underestimate the value of hard work and logical thinking, but it's also true that blind luck plays a role in most real scientific breakthroughs. What has been called "the supreme example of luck in all scientific history" occurred in the late summer of 1928, when the Scottish bacteriologist Alexander Fleming went on vacation, leaving in his lab a culture plate recently inoculated with the bacterium *Staphylococcus aureus*.

While Fleming was away, an extraordinary chain of events occurred. First, a 9-day cold spell lowered the laboratory temperature to a point where the *Staphylococcus* on the plate could not grow. During this time, spores from a colony of the mold *Penicillium notatum* being grown on the floor below wafted up into Fleming's lab and landed in the culture plate. The temperature then rose, and both *Staphylococcus* and *Penicillium* began to grow. On returning from vacation, Fleming discarded the plate into a tray of antiseptic, intending to sterilize it. Evidently, though, the plate did not sink deeply enough into the antiseptic, because when Fleming happened to glance at it a few days later, what he saw changed the course of human history. He noticed that the growing *Penicillium* mold appeared to dissolve the colonies of staphylococci.

Fleming realized that the *Penicillium* mold must be producing a chemical that killed the *Staphylococcus* bacteria, and he spent several years trying to isolate the substance. Finally, in 1939, the Australian pathologist Howard Florey and the German refugee Ernst Chain managed to isolate the active substance, called *penicillin*. The dramatic ability of penicillin to cure infections in mice was soon demonstrated, and successful tests in humans followed shortly thereafter. By 1943, penicillin was being produced on a large scale for military use in World War II, and by 1944 it was being used on civilians. Fleming, Florey, and Chain shared the 1945 Nobel Prize in Medicine.

Now called benzylpenicillin, or penicillin G, the substance first discovered by Fleming is but one member of a large class of so-called β-lactam antibiotics,compounds with a four-membered lactam (cyclic amide) ring. The four-membered lactam ring is fused to a five-membered, sulfur-containing ring, and the carbon atom next to the lactam carbonyl group is bonded to an acylamino substituent, RCONH—. This acylamino side chain can be varied in the laboratory to provide many hundreds of penicillin analogs with different biological activity profiles. Ampicillin, for instance, has an α-aminophenylacetamido substituent [$PhCH(NH_2)CONH—$].



Benzylpenicillin (penicillin G)

Closely related to the penicillins are the *cephalosporins*, a group of β-lactam antibiotics that contain an unsaturated six-membered, sulfur-containing ring. Cephalexin, marketed

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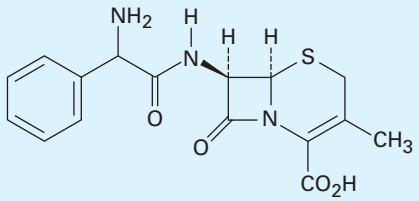
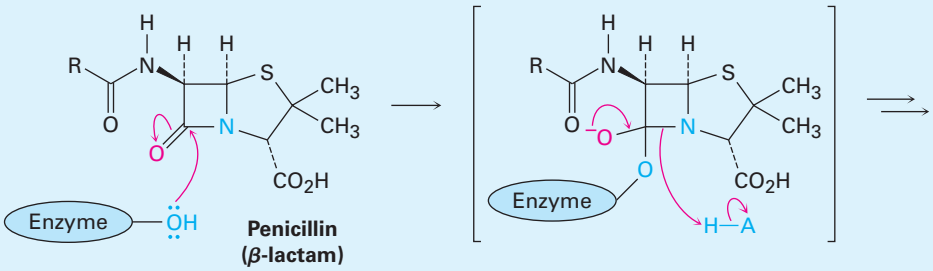
under the trade name Keflex, is an example. Cephalosporins generally have much greater antibacterial activity than penicillins, particularly against resistant strains of bacteria.



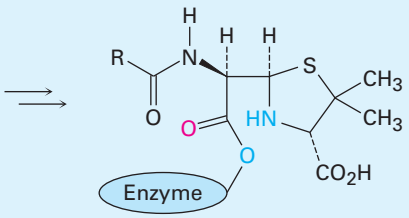
Cephalexin (a cephalosporin)

The biological activity of penicillins and cephalosporins is due to the presence of the strained β-lactam ring, which reacts with and deactivates the transpeptidase enzyme needed to synthesize and repair bacterial cell walls. With the wall either incomplete or weakened, the bacterial cell ruptures and dies.



Transpeptidase (active enzyme)

Penicillin (β-lactam)



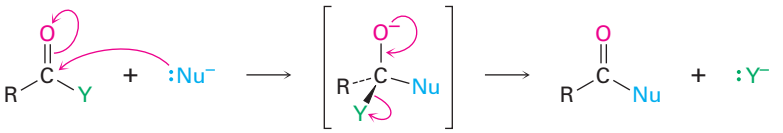
(inactive enzyme)

Summary

Key words

Carboxylic acid derivatives—compounds in which the −OH group of a carboxylic acid has been replaced by another substituent—are among the most widely occurring of all molecules and are involved in almost all biological pathways. In this chapter, we covered the chemistry necessary for understanding them and thus also necessary for understanding the chemistry of living organisms. **Acid halides**, **acid anhydrides**, **esters**, and **amides** are the most common such derivatives in the laboratory; **thioesters** and **acyl phosphates** are common in biological molecules.

The chemistry of carboxylic acid derivatives is dominated by the **nucleophilic acyl substitution reaction**. Mechanistically, these substitutions take place by addition of a nucleophile to the polar carbonyl group of the acid derivative to give a tetrahedral intermediate, followed by expulsion of a leaving group.



The reactivity of an acid derivative toward substitution depends both on the steric environment near the carbonyl group and on the electronic nature of the substituent, Y. The reactivity order is acid halide > acid anhydride > thioester > ester > amide.

The most common reactions of carboxylic acid derivatives are substitution by water to yield an acid (hydrolysis), by an alcohol to yield an ester (alcoholysis), by an amine to yield an amide (aminolysis), by hydride ion to yield an alcohol (reduction), and by an organomagnesium halide to yield an alcohol (Grignard reaction).

Step-growth polymers, such as polyamides and polyesters, are prepared by reactions between difunctional molecules. Polyamides (nylons) are formed by reaction between a diacid and a diamine; polyesters are formed from a diacid and a diol.

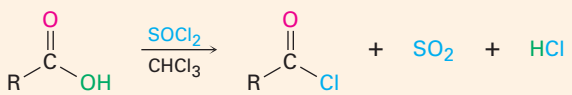
IR spectroscopy is a valuable tool for the structural analysis of acid derivatives. Acid chlorides, anhydrides, esters, and amides all show characteristic IR absorptions that can be used to identify these functional groups.

Key words—cont'd

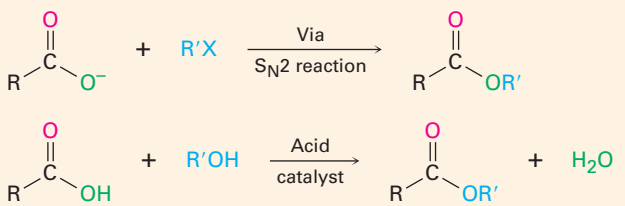
carboxylic acid derivative, 814
ester (RCO_2R'), 814
Fischer esterification reaction, 824
lactam, 845
lactone, 837
nucleophilic acyl substitution reaction, 818
saponification, 838
step-growth polymer, 848
thioester (RCOSR'), 814

Summary of Reactions

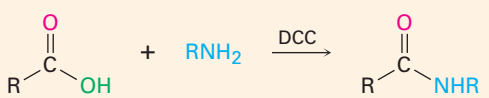
1. Reactions of carboxylic acids (Section 21.3)
   (a) Conversion into acid chlorides



   (b) Conversion into esters

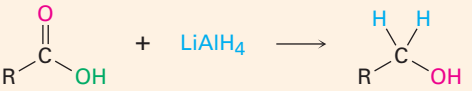


   (c) Conversion into amides



(continued)

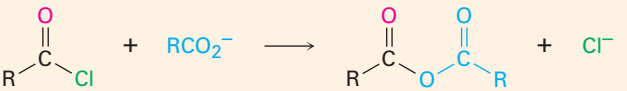
(d) Reduction to yield primary alcohols



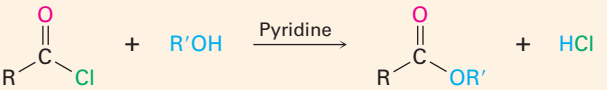
2. Reactions of acid chlorides (Section 21.4)

(a) Hydrolysis to yield acids

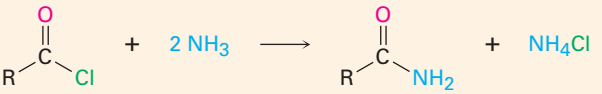
(b) Reaction with carboxylates to yield anhydrides



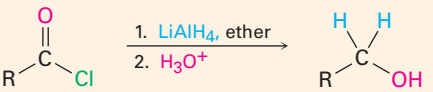
(c) Alcoholysis to yield esters



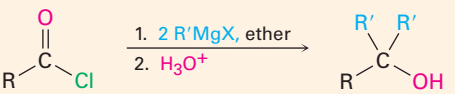
(d) Aminolysis to yield amides



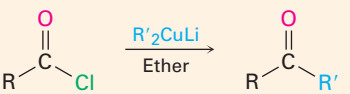
(e) Reduction to yield primary alcohols



(f) Grignard reaction to yield tertiary alcohols

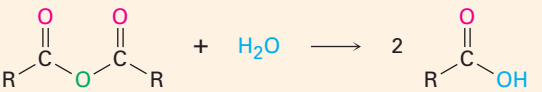


(g) Diorganocopper reaction to yield ketones



3. Reactions of acid anhydrides (Section 21.5)

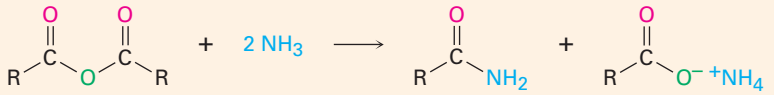
(a) Hydrolysis to yield acids



(continued)

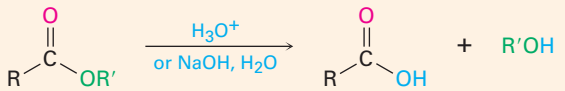
(b) Alcoholysis to yield esters

(c) Aminolysis to yield amides

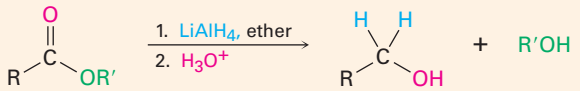


4. Reactions of esters (Section 21.6)

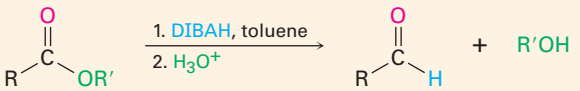
(a) Hydrolysis to yield acids



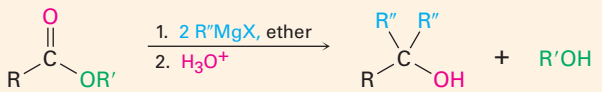
(b) Reduction to yield primary alcohols



(c) Partial reduction to yield aldehydes

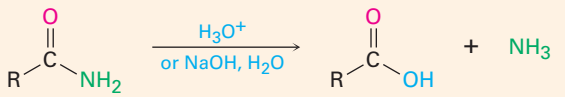


(d) Grignard reaction to yield tertiary alcohols

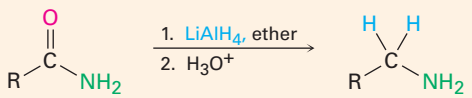


5. Reactions of amides (Section 21.7)

(a) Hydrolysis to yield acids



(b) Reduction to yield amines



Exercises

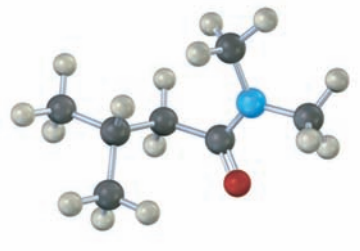
OWL Interactive versions of these problems are assignable in OWL for Organic Chemistry.

Visualizing Chemistry

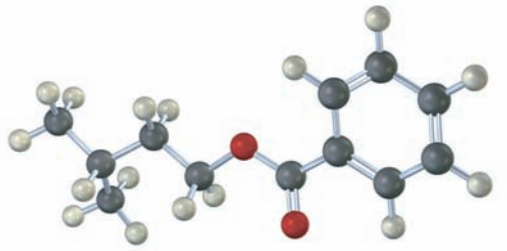
(Problems 21.1–21.26 appear within the chapter.)

21.27 Name the following compounds:

(a)

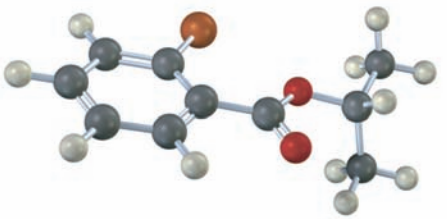


(b)

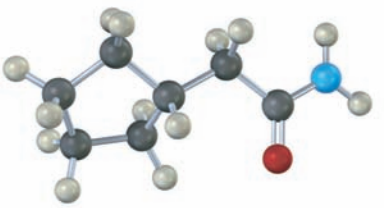


21.28 How would you prepare the following compounds starting with an appropriate carboxylic acid and any other reagents needed? (Reddish brown = Br.)

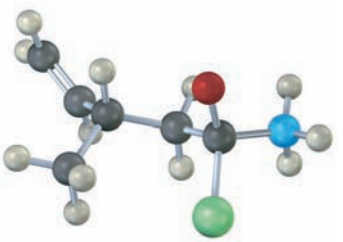
(a)



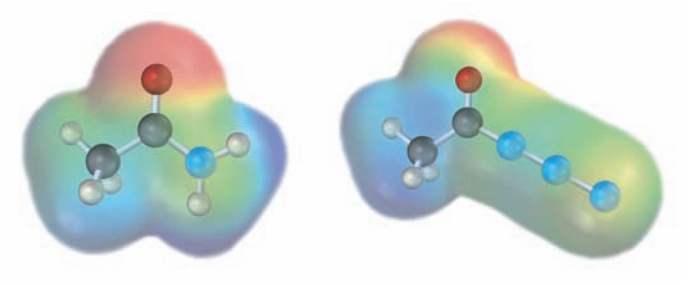
(b)

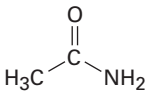
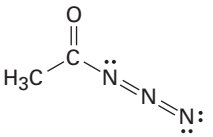


21.29 The following structure represents a tetrahedral alkoxide-ion intermediate formed by addition of a nucleophile to a carboxylic acid derivative. Identify the nucleophile, the leaving group, the starting acid derivative, and the ultimate product (green = Cl).



21.30 Electrostatic potential maps of a typical amide (acetamide) and an acyl azide (acetyl azide) are shown. Which of the two do you think is more reactive in nucleophilic acyl substitution reactions? Explain.

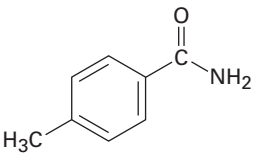


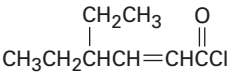
Acetamide   **Acetyl azide**

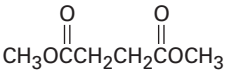
Additional Problems

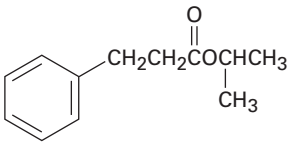
Naming Carboxylic Acid Derivatives

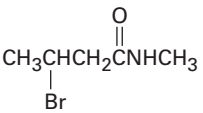
21.31 Give IUPAC names for the following compounds:

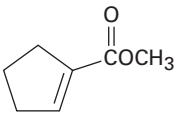
(a) 

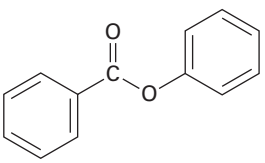
(b) 

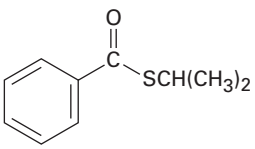
(c) 

(d) 

(e) 

(f) 

(g) 

(h) 

21.32 Draw structures corresponding to the following names:

(a) *p*-Bromophenylacetamide
(b) *m*-Benzoylbenzamide
(c) 2,2-Dimethylhexanamide
(d) Cyclohexyl cyclohexanecarboxylate
(e) Ethyl 2-cyclobutenecarboxylate
(f) Succinic anhydride

21.33 Draw and name compounds that meet the following descriptions:

(a) Three acid chlorides having the formula C_6H_9ClO
(b) Three amides having the formula $C_7H_{11}NO$

Nucleophilic Acyl Substitution Reactions

21.34 Predict the product, if any, of reaction between propanoyl chloride and the following reagents:

(a) $Li(Ph)_2Cu$ in ether
(b) $LiAlH_4$, then H_3O^+
(c) CH_3MgBr, then H_3O^+
(d) H_3O^+
(e) Cyclohexanol
(f) Aniline
(g) $CH_3CO_2^-\ ^+Na$

21.35 Answer Problem 21.34 for reaction of the listed reagents with methyl propanoate.

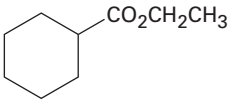
21.36 Answer Problem 21.34 for reaction of the listed reagents with propanamide.

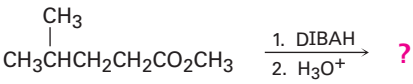
21.37 What product would you expect to obtain from Grignard reaction of an excess of phenylmagnesium bromide with dimethyl carbonate, $CH_3OCO_2CH_3$?

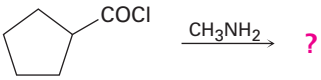
21.38 How might you prepare the following compounds from butanoic acid?

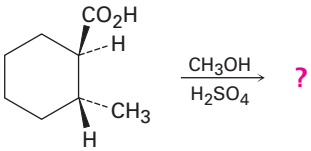
(a) 1-Butanol
(b) Butanal
(c) 1-Bromobutane
(d) Pentanenitrile
(e) 1-Butene
(f) *N*-Methylpentanamide
(g) 2-Hexanone
(h) Butylbenzene
(i) Butanenitrile

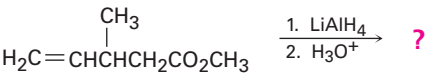
21.39 Predict the product(s) of the following reactions:

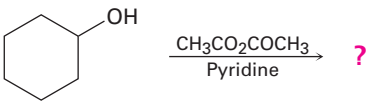
(a) 

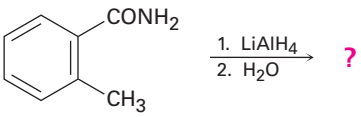
(b) 

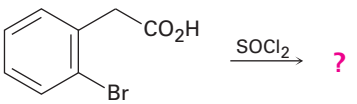
(c) 

(d) 

(e) 

(f) 

(g) 

(h) 

21.40 The following reactivity order has been found for the saponification of alkyl acetates by aqueous NaOH. Explain.

$$CH_3CO_2CH_3 > CH_3CO_2CH_2CH_3 > CH_3CO_2CH(CH_3)_2 > CH_3CO_2C(CH_3)_3$$

21.41 Explain the observation that attempted Fischer esterification of 2,4,6-trimethylbenzoic acid with methanol and HCl is unsuccessful. No ester is obtained, and the acid is recovered unchanged. What alternative method of esterification might be successful?

21.42 Outline methods for the preparation of acetophenone (phenyl methyl ketone) starting from the following:

(a) Benzene **(b)** Bromobenzene **(c)** Methyl benzoate
(d) Benzonitrile **(e)** Styrene

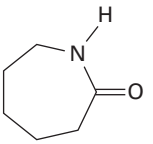
21.43 Treatment of 5-aminopentanoic acid with DCC (dicyclohexylcarbodiimide) yields a lactam. Show the structure of the product and the mechanism of the reaction.

21.44 When *ethyl* benzoate is heated in methanol containing a small amount of HCl, *methyl* benzoate is formed. Propose a mechanism for the reaction.

21.45 *tert*-Butoxycarbonyl azide, a reagent used in protein synthesis, is prepared by treating *tert*-butoxycarbonyl chloride with sodium azide. Propose a mechanism for this reaction.

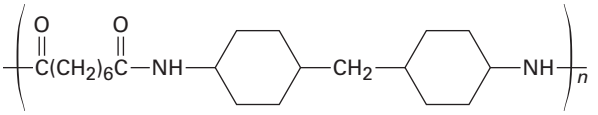
Step-Growth Polymers

21.46 The step-growth polymer nylon 6 is prepared from caprolactam. The reaction involves initial reaction of caprolactam with water to give an intermediate open-chain amino acid, followed by heating to form the polymer. Propose mechanisms for both steps, and show the structure of nylon 6.



Caprolactam

21.47 *Qiana,* a polyamide fiber with a silky texture, has the following structure. What are the monomer units used in the synthesis of Qiana?

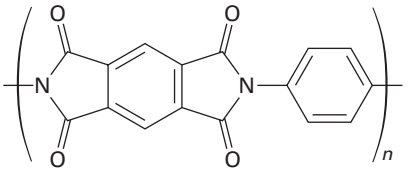


Qiana

21.48 What is the structure of the polymer produced by treatment of β-propiolactone with a small amount of hydroxide ion?

β-Propiolactone

21.49 Polyimides having the structure shown are used as coatings on glass and plastics to improve scratch resistance. How would you synthesize a polyimide? (See Problem 21.59.)



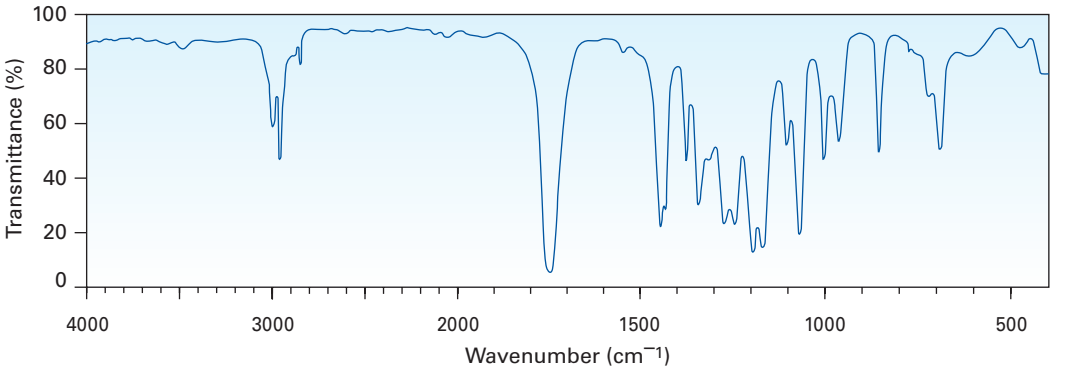
A polyimide

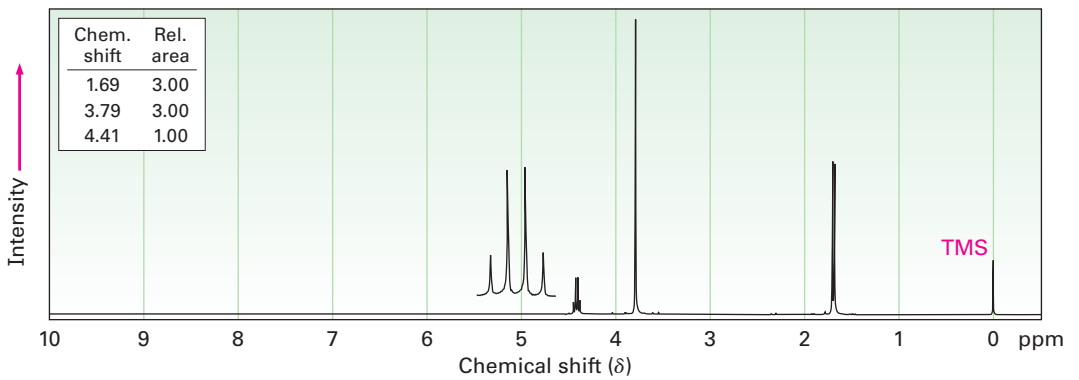
Spectroscopy

21.50 How would you distinguish spectroscopically between the following isomer pairs? Tell what differences you would expect to see.

(a) *N*-Methylpropanamide and *N*,*N*-dimethylacetamide
(b) 5-Hydroxypentanenitrile and cyclobutanecarboxamide
(c) 4-Chlorobutanoic acid and 3-methoxypropanoyl chloride
(d) Ethyl propanoate and propyl acetate

21.51 Propose a structure for a compound, $C_4H_7ClO_2$, that has the following IR and ^1H NMR spectra:

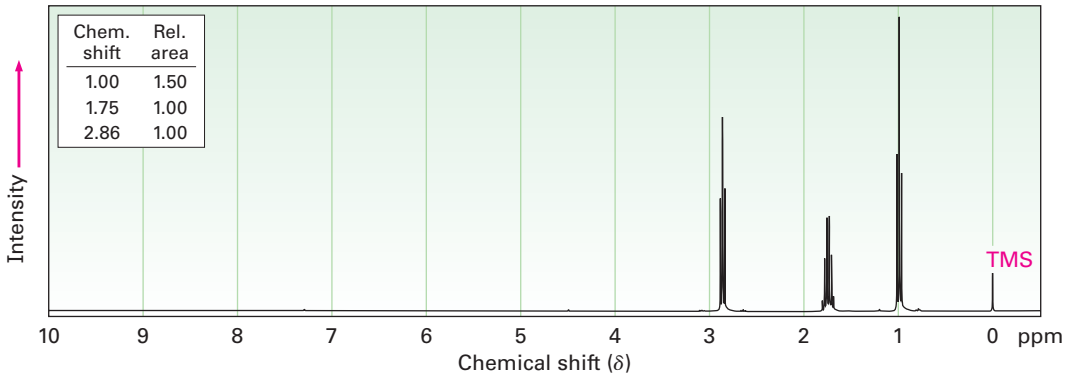




21.52 Assign structures to compounds with the following ^{1}H NMR spectra:

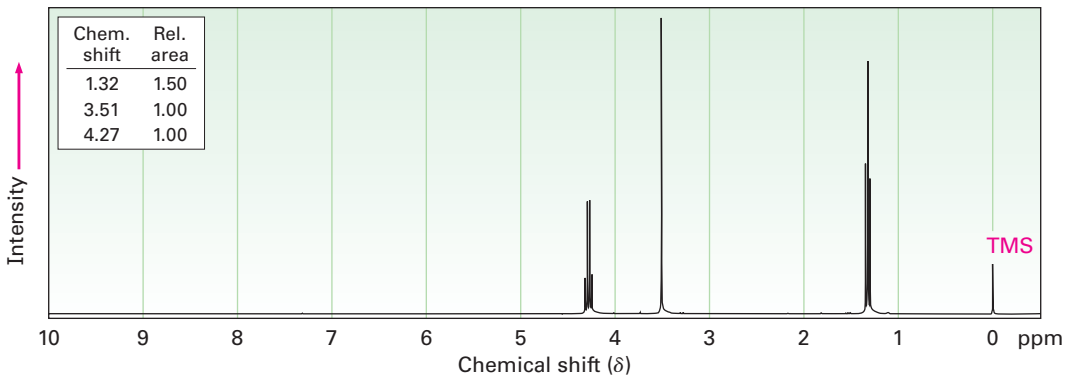
(a) C_4H_7ClO

IR: 1810 cm^{-1}



(b) $C_5H_7NO_2$

IR: 2250, 1735 cm^{-1}

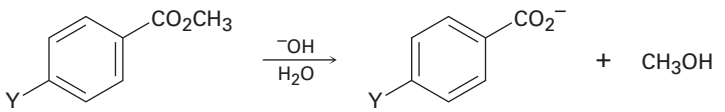


General Problems

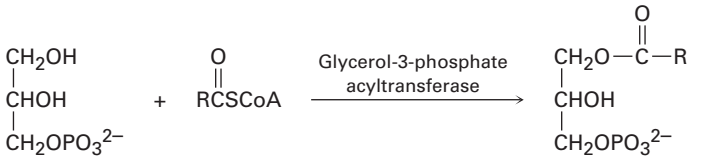
21.53 The following reactivity order has been found for the basic hydrolysis of *p*-substituted methyl benzoates:

$$Y = NO_2 > Br > H > CH_3 > OCH_3$$

How can you explain this reactivity order? Where would you expect Y = C≡N, Y = CHO, and Y = NH_2 to be in the reactivity list?

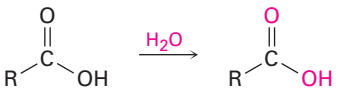


21.54 Fats are biosynthesized from glycerol 3-phosphate and fatty-acyl CoA's by a reaction sequence that begins with the following step. Show the mechanism of the reaction.



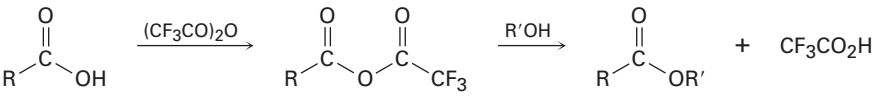
Glycerol 3-phosphate **Fatty-acyl CoA** **1-Acylglycerol 3-phosphate**

21.55 When a carboxylic acid is dissolved in isotopically labeled water, the label rapidly becomes incorporated into *both* oxygen atoms of the carboxylic acid. Explain.



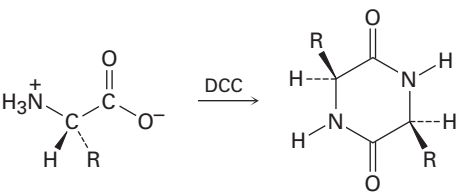
21.56 We said in Section 21.6 that mechanistic studies on ester hydrolysis have been carried out using ethyl propanoate labeled with ^{18}O in the ether-like oxygen. Assume that ^{18}O-labeled acetic acid is your only source of isotopic oxygen, and then propose a synthesis of the labeled ethyl propanoate.

21.57 Treatment of a carboxylic acid with trifluoroacetic anhydride leads to an unsymmetrical anhydride that rapidly reacts with alcohol to give an ester.



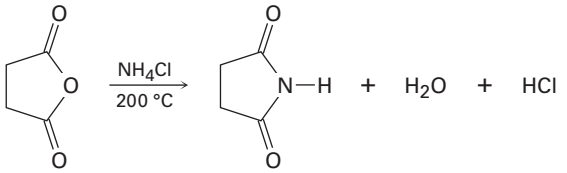
(a) Propose a mechanism for formation of the unsymmetrical anhydride.
(b) Why is the unsymmetrical anhydride unusually reactive?
(c) Why does the unsymmetrical anhydride react as indicated rather than giving a trifluoroacetate ester plus carboxylic acid?

21.58 Treatment of an α-amino acid with DCC yields a 2,5-diketopiperazine. Propose a mechanism.

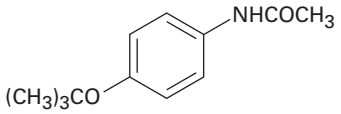


An α-amino acid **A 2,5-diketopiperazine**

21.59 Succinic anhydride yields the cyclic imide succinimide when heated with ammonium chloride at 200 °C. Propose a mechanism for this reaction. Why do you suppose such a high reaction temperature is required?

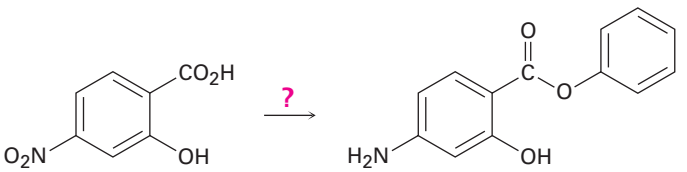


21.60 Butacetin is an analgesic (pain-killing) agent that is synthesized commercially from *p*-fluoronitrobenzene. Propose a synthesis.



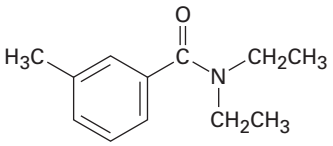
Butacetin

21.61 Phenyl 4-aminosalicylate is a drug used in the treatment of tuberculosis. Propose a synthesis of this compound starting from 4-nitrosalicylic acid.



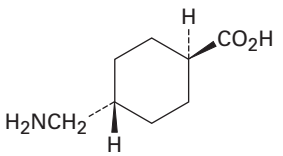
4-Nitrosalicylic acid **Phenyl 4-aminosalicylate**

21.62 *N,N*-Diethyl-*m*-toluamide (DEET) is the active ingredient in many insect-repellent preparations. How might you synthesize this substance from *m*-bromotoluene?



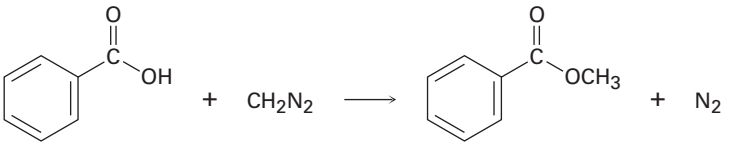
***N,N*-Diethyl-*m*-toluamide**

21.63 Tranexamic acid, a drug useful against blood clotting, is prepared commercially from *p*-methylbenzonitrile. Formulate the steps likely to be used in the synthesis. (Don't worry about cis–trans isomers; heating to 300 °C interconverts the isomers.)



Tranexamic acid

21.64 One frequently used method for preparing methyl esters is by reaction of carboxylic acids with diazomethane, CH_2N_2.



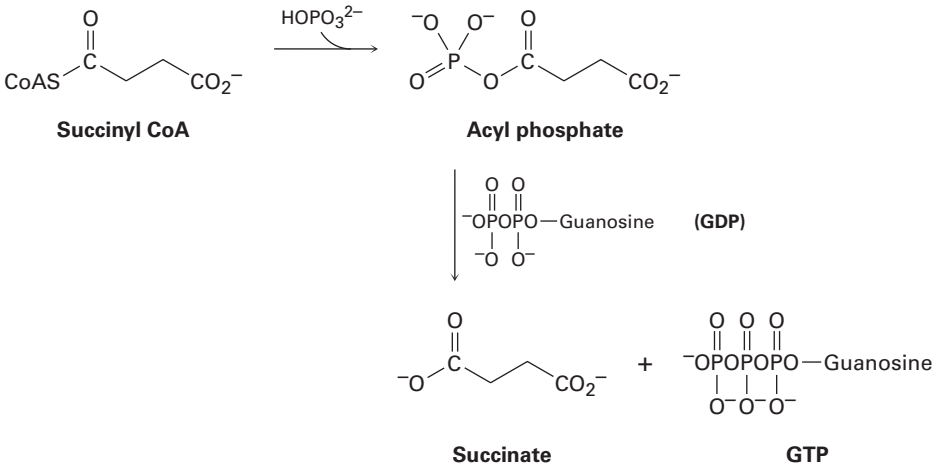
Benzoic acid **Diazomethane** **Methyl benzoate (100%)**

The reaction occurs in two steps: (1) protonation of diazomethane by the carboxylic acid to yield methyldiazonium ion, $CH_3N_2^+$, plus a carboxylate ion; and (2) reaction of the carboxylate ion with $CH_3N_2^+$.

(a) Draw two resonance structures of diazomethane, and account for step 1.

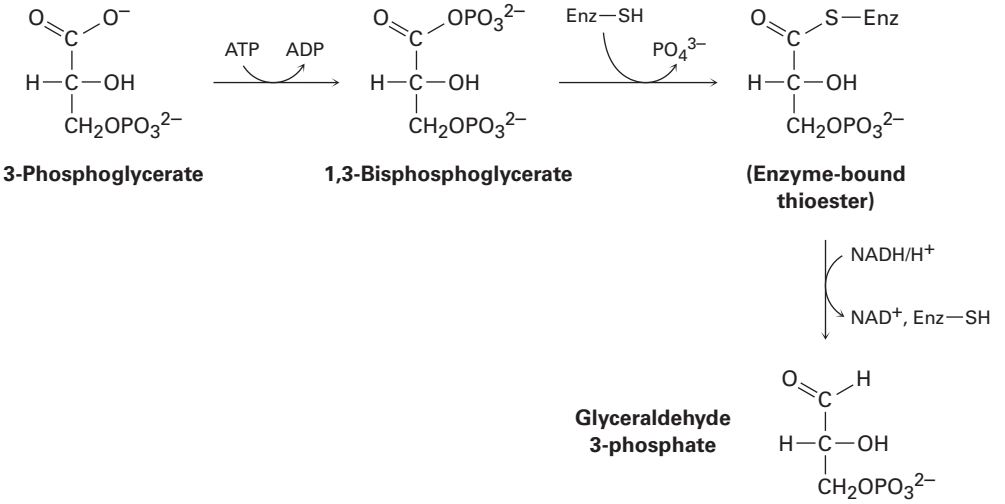
(b) What kind of reaction occurs in step 2?

21.65 The hydrolysis of a biological thioester to the corresponding carboxylate is often more complex than the overall result might suggest. The conversion of succinyl CoA to succinate in the citric acid cycle, for instance, occurs by initial formation of an acyl phosphate, followed by reaction with guanosine diphosphate (GDP, a relative of adenosine diphosphate [ADP]) to give succinate and guanosine triphosphate (GTP, a relative of ATP). Suggest mechanisms for both steps.



Succinyl CoA **Acyl phosphate** **Succinate** **GTP**

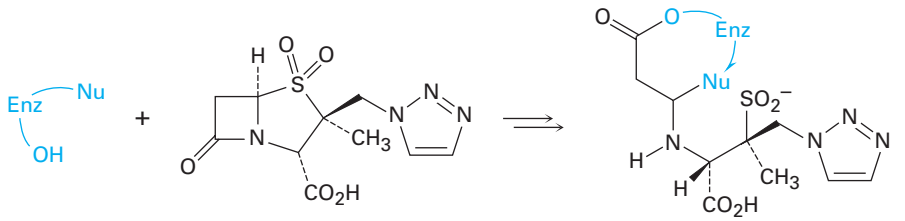
21.66 One step in the *gluconeogenesis* pathway for the biosynthesis of glucose is the partial reduction of 3-phosphoglycerate to give glyceraldehyde 3-phosphate. The process occurs by phosphorylation with ATP to give 1,3-bisphosphoglycerate, reaction with a thiol group on the enzyme to give an enzyme-bound thioester, and reduction with NADH. Suggest mechanisms for all three reactions.



3-Phosphoglycerate **1,3-Bisphosphoglycerate** **(Enzyme-bound thioester)**

Glyceraldehyde 3-phosphate

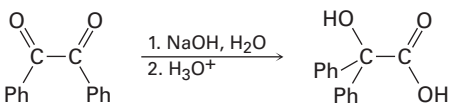
21.67 Penicillins and other β-lactam antibiotics (see *A Deeper Look* in this chapter) typically develop a resistance to bacteria due to bacterial synthesis of β-lactamase enzymes. Tazobactam, however, is able to inhibit the activity of the β-lactamase by trapping it, thereby preventing resistance from developing.



β-Lactamase **Tazobactam** **Trapped β-lactamase**

(a) The first step in trapping is reaction of a hydroxyl group on the β-lactamase to open the β-lactam ring of tazobactam. Show the mechanism.
(b) The second step is opening of the sulfur-containing ring in tazobactam to give an acyclic imine intermediate. Show the mechanism.
(c) Cyclization of the imine intermediate gives the trapped β-lactamase product. Show the mechanism.

21.68 The following reaction, called the *benzylic acid rearrangement,* takes place by typical carbonyl-group reactions. Propose a mechanism (Ph = phenyl).

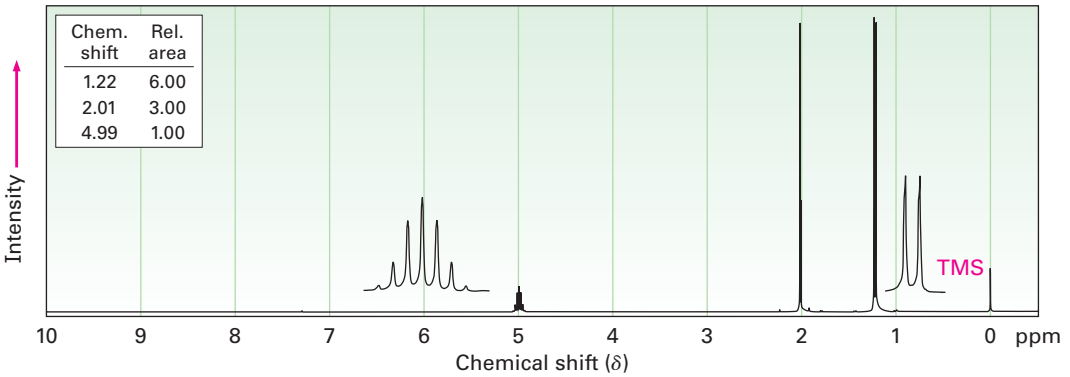


Benzil **Benzylic acid**

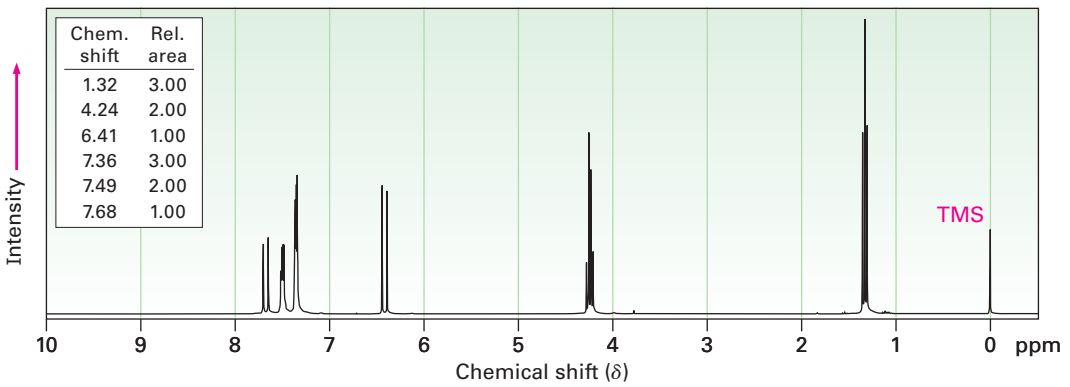
21.69 Draw the structure of the polymer you would expect to obtain from reaction of dimethyl terephthalate with a triol such as glycerol. What structural feature would this new polymer have that was not present in Dacron (Table 21.2)? How do you think this new feature might affect the properties of the polymer?

21.70 Assign structures to compounds with the following ^{1}H NMR spectra:

(a) $C_5H_{10}O_2$
IR: 1735 cm^{-1}

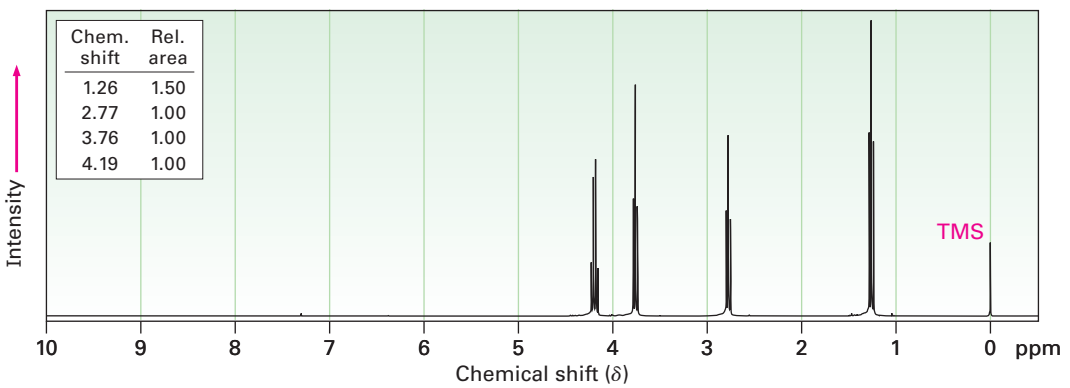


(b) $C_{11}H_{12}O_2$
IR: 1710 cm^{-1}

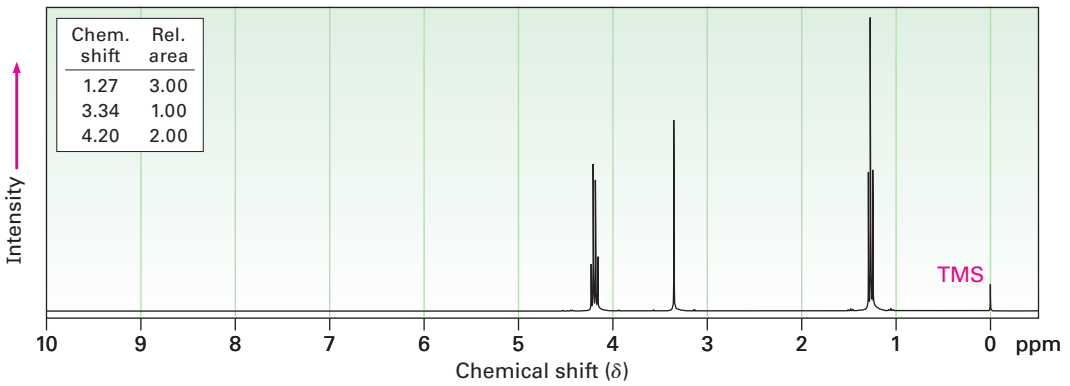


21.71 Propose structures for compounds with the following ^{1}H NMR spectra:

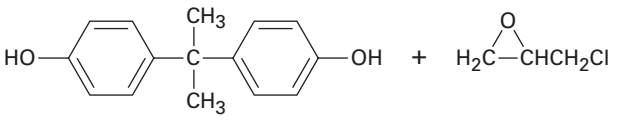
(a) $C_5H_9ClO_2$
IR: 1735 cm^{-1}



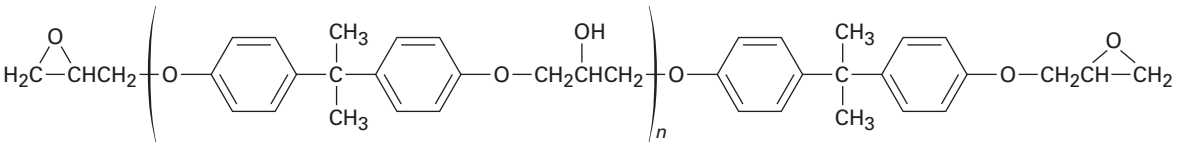
(b) $C_7H_{12}O_4$
IR: 1735 cm^{-1}



21.72 Epoxy adhesives are prepared in two steps. S_N2 reaction of the disodium salt of bisphenol A with epichlorohydrin forms a "prepolymer," which is then "cured" by treatment with a triamine such as $H_2NCH_2CH_2NHCH_2CH_2NH_2$.



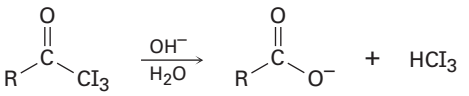
Bisphenol A **Epichlorohydrin**



"Prepolymer"

Draw structures to show how addition of the triamine results in strengthening the polymer.

21.73 In the *iodoform reaction,* a triiodomethyl ketone reacts with aqueous NaOH to yield a carboxylate ion and iodoform (triiodomethane). Propose a mechanism for this reaction.



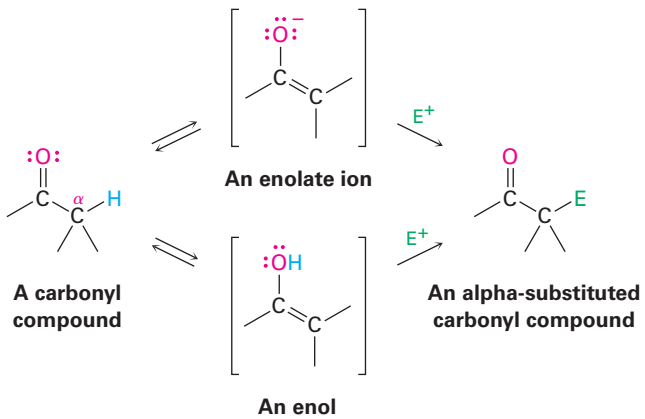
22

The tear gas used by police and military for riot control is a simple chloro ketone made by a carbonyl α-substitution reaction.

Carbonyl Alpha-Substitution Reactions

We said in the *Preview of Carbonyl Chemistry* that much of the chemistry of carbonyl compounds can be explained by just four fundamental reaction types: nucleophilic additions, nucleophilic acyl substitutions, α substitutions, and carbonyl condensations. Having studied the first two of these reactions in the past three chapters, let's now look in more detail at the third major carbonyl-group process—the **α-substitution reaction**.

Alpha-substitution reactions occur at the position next to the carbonyl group—the *α position*—and involve the substitution of an α hydrogen atom by an electrophile, E, through either an enol or enolate ion intermediate. Let's begin by learning more about these two species.



Why This Chapter? As with nucleophilic additions and nucleophilic acyl substitutions, many laboratory schemes, pharmaceutical syntheses, and biochemical pathways make frequent use of carbonyl α-substitution reactions. Their great value is that they constitute one of the few general methods for forming carbon–carbon bonds, thereby making it possible to build larger molecules from smaller precursors. We'll see how and why these reactions occur in this chapter.

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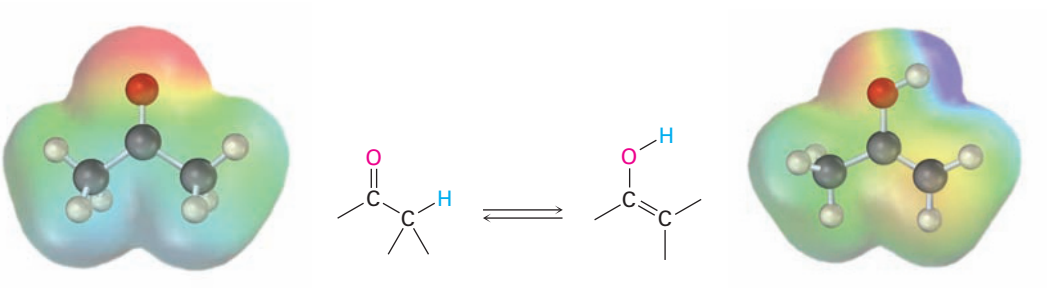
22.1 Keto–Enol Tautomerism

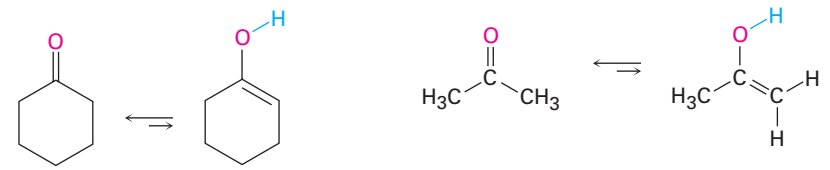
A carbonyl compound with a hydrogen atom on its α carbon is in an equilibrium with its corresponding **enol** isomer **(Section 9.4)**. This spontaneous interconversion between two isomers, usually with the change in position of a hydrogen, is called *tautomerism,* from the Greek *tauto,* meaning "the same," and *meros,* meaning "part." The individual keto and enol isomers are called **tautomers**.



Keto tautomer **Enol tautomer**

Note the difference between tautomers and resonance forms. Tautomers are constitutional isomers—different compounds with different structures—while resonance forms are different representations of a single compound. Tautomers have their *atoms* arranged differently, while resonance forms differ only in the position of their π and nonbonding *electrons*.

Most monocarbonyl compounds exist almost entirely in their keto form at equilibrium, and it's usually difficult to isolate the pure enol. Cyclohexanone, for example, contains only about 0.0001% of its enol tautomer at room temperature. The percentage of enol tautomer is even less for carboxylic acids, esters, and amides. Only when the enol can be stabilized by conjugation or by intramolecular hydrogen bond formation does the enol sometimes predominate. Thus, 2,4-pentanedione is about 76% enol tautomer. Although enols are present only to a small extent at equilibrium, they are nevertheless responsible for much of the chemistry of carbonyl compounds because they are so reactive.



99.999 9% 0.000 1% 99.999 999 9% 0.000 000 1%

Cyclohexanone **Acetone**

Keto–enol tautomerism of carbonyl compounds is catalyzed by both acids and bases. Acid catalysis occurs by protonation of the carbonyl oxygen atom to give an intermediate cation that loses H^+ from its α carbon to yield a neutral enol **(Figure 22.1a)**. This proton loss from the cation intermediate is similar to what occurs during an E1 reaction when a carbocation loses H^+ to form an alkene **(Section 11.10)**.

Base-catalyzed enol formation occurs because the presence of a carbonyl group makes the hydrogens on the α carbon weakly acidic. Thus, a carbonyl

compound can act as an acid and donate one of its α hydrogens to a sufficiently strong base. The resultant resonance-stabilized anion, an **enolate ion**, is then protonated to yield a neutral compound. If protonation of the enolate ion takes place on the α carbon, the keto tautomer is regenerated and no net change occurs. If, however, protonation takes place on the oxygen atom, then an enol tautomer is formed **(Figure 22.1b)**.

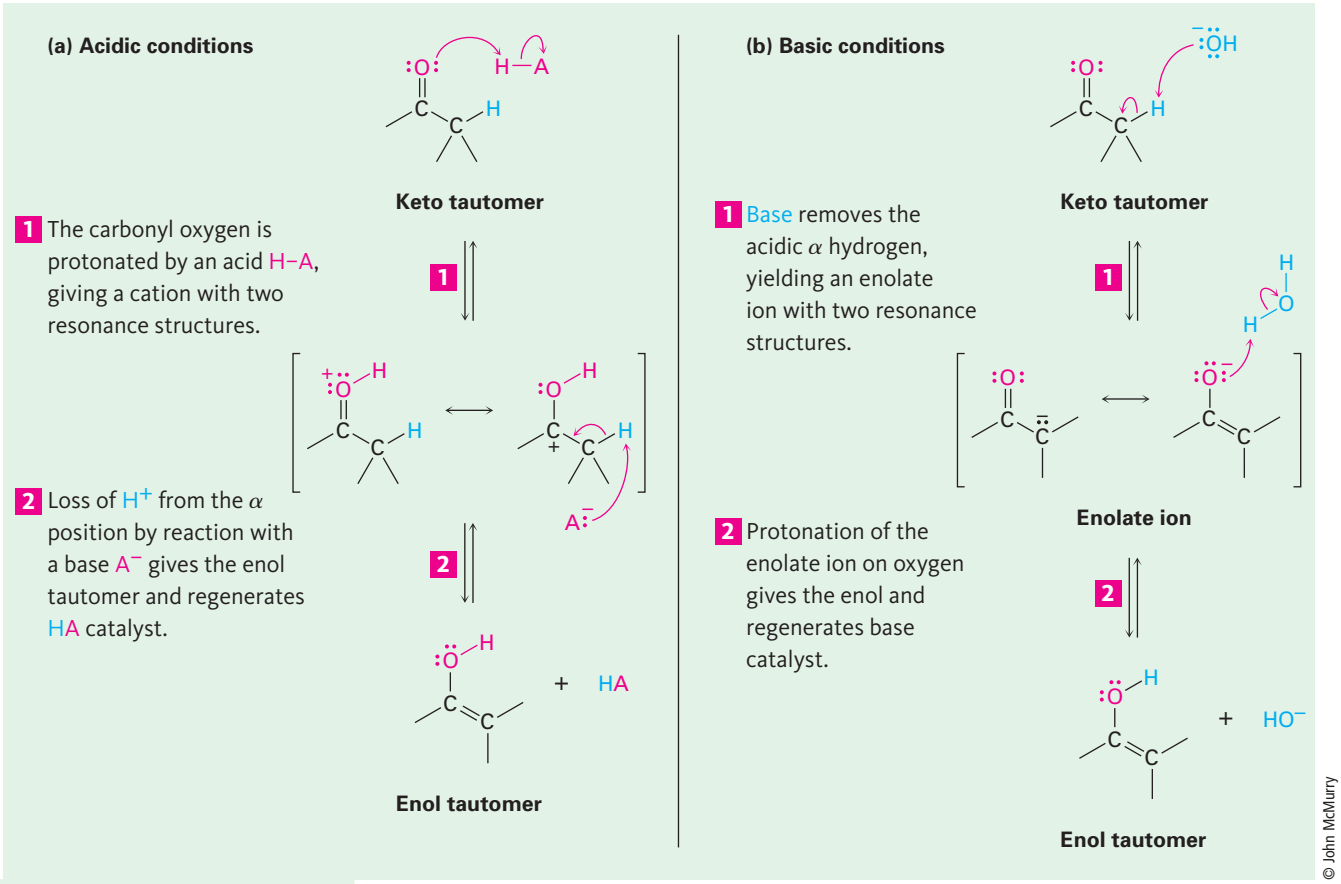
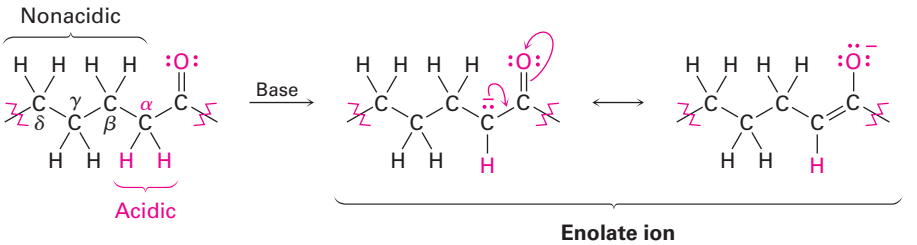


Figure 22.1 | MECHANISM

Mechanism of enol formation under both acid-catalyzed and base-catalyzed conditions. **(a)** Acid catalysis involves (1) initial protonation of the carbonyl oxygen followed by (2) removal of H^+ from the α position. **(b)** Base catalysis involves (1) initial deprotonation of the α position to give an enolate ion, followed by (2) reprotonation on oxygen.

Note that only the hydrogens on the α position of carbonyl compounds are acidic. Hydrogens at β, γ, δ, and so on, aren't acidic and can't be removed by base because the resulting anions can't be resonance-stabilized by the carbonyl group.



Problem 22.1

Draw structures for the enol tautomers of the following compounds:

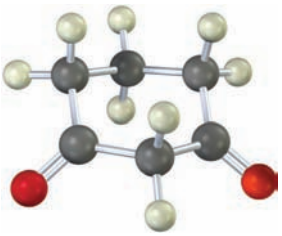
(a) Cyclopentanone **(b)** Methyl thioacetate **(c)** Ethyl acetate
(d) Propanal **(e)** Acetic acid **(f)** Phenylacetone

Problem 22.2

How many acidic hydrogens does each of the molecules listed in Problem 22.1 have? Identify them.

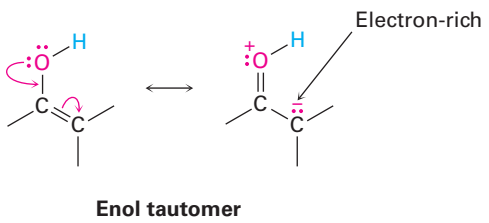
Problem 22.3

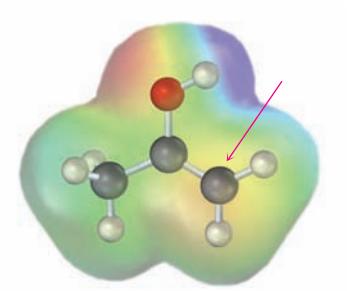
Draw structures for all monoenol forms of the following molecule. Which would you expect to be most stable? Explain.



22.2 Reactivity of Enols: The Mechanism of Alpha-Substitution Reactions

What kind of chemistry do enols have? Because their double bonds are electron-rich, enols behave as nucleophiles and react with electrophiles in much the same way that alkenes do. But because of resonance electron donation of a lone-pair of electrons on the neighboring oxygen, enols are more electron-rich and correspondingly more reactive than alkenes. Notice in the following electrostatic potential map of ethenol ($H_2C{=}CHOH$) how there is a substantial amount of electron density (yellow-red) on the α carbon.

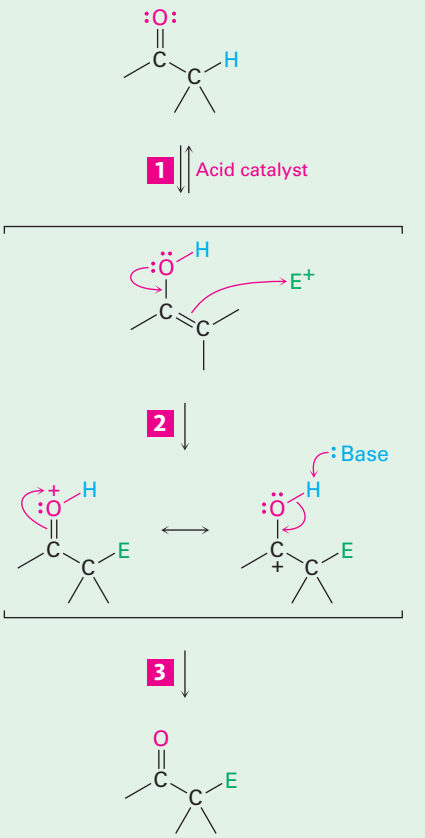




When an *alkene* reacts with an electrophile, E^+, initial addition gives an intermediate cation and subsequent reaction with a nucleophile such as a halide ion yields an addition product **(Section 7.7)**. When an *enol* reacts with an electrophile, however, only the initial addition step is the same **(Figure 22.2)**. Instead of reacting with a nucleophile to give an addition product, the intermediate cation loses the −OH proton to give an α-substituted carbonyl compound.

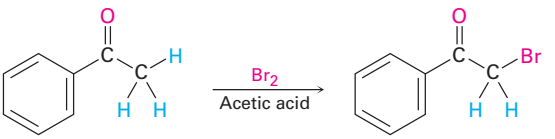
Figure 22.2 | MECHANISM

General mechanism of a carbonyl α-substitution reaction. In step 3, the initially formed cation loses H^+ to regenerate a carbonyl compound.



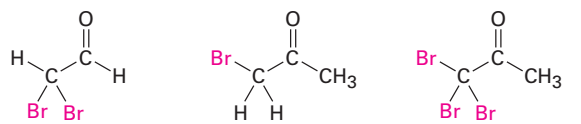
22.3 Alpha Halogenation of Aldehydes and Ketones

A particularly common α-substitution reaction in the laboratory is the halogenation of aldehydes and ketones at their α positions by reaction with Cl_2, Br_2, or I_2 in acidic solution. Bromine in acetic acid solvent is often used.



Acetophenone **α-Bromoacetophenone (72%)**

Remarkably, ketone halogenation also occurs in biological systems, particularly in marine alga, where dibromoacetaldehyde, bromoacetone, 1,1,1-tribromoacetone, and other related compounds have been found.

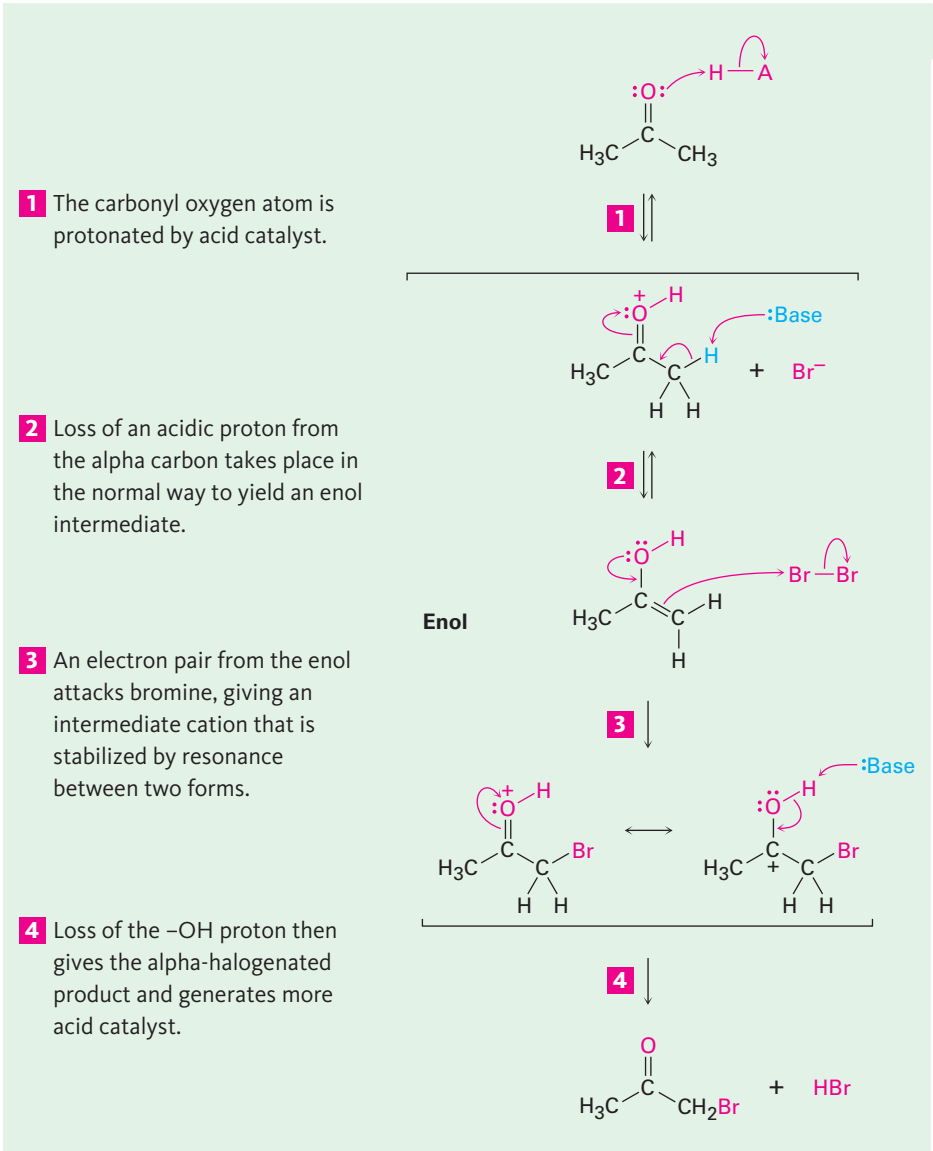


From the Hawaiian alga *Asparagopsis taxiformis*

The halogenation is a typical α-substitution reaction that proceeds by acid-catalyzed formation of an enol intermediate, as shown in **Figure 22.3**.

Figure 22.3 | MECHANISM

Mechanism of the acid-catalyzed bromination of acetone.

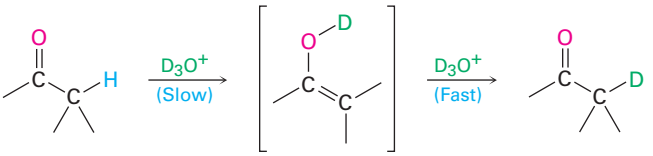


Evidence for the mechanism shown in Figure 22.3 includes the observation that acid-catalyzed halogenations show second-order kinetics and follow the rate law

$$\text{Reaction rate} = k\,[\text{Ketone}]\,[\text{H}^+]$$

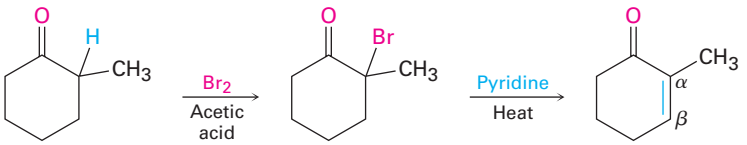
In other words, the rate of halogenation depends only on the concentrations of ketone and acid and is independent of halogen concentration. Halogen is not involved in the rate-limiting step, so chlorination, bromination, and iodination of a given substrate all occur at the same rate.

Furthermore, if an aldehyde or ketone is treated with D_3O^+, the acidic α hydrogens are replaced by deuterium. For a given ketone, the rate of deuterium exchange is identical to the rate of halogenation, implying that a common intermediate—presumably the enol—is involved in both processes.



Enol

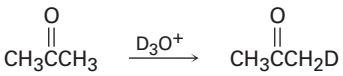
α-Bromo ketones are useful in the laboratory because they can be dehydrobrominated by base treatment to yield α,β-unsaturated ketones. For example, 2-methylcyclohexanone gives 2-bromo-2-methylcyclohexanone on halogenation, and the α-bromo ketone gives 2-methyl-2-cyclohexenone when heated in pyridine. The reaction takes place by an E2 elimination pathway **(Section 11.8)** and is a good method for introducing a C=C bond into a molecule. Note that bromination of 2-methylcyclohexanone occurs primarily on the more highly substituted α position because the more highly substituted enol is favored over the less highly substituted one **(Section 7.6)**.



2-Methylcyclohexanone | **2-Bromo-2-methylcyclohexanone** | **2-Methyl-2-cyclohexenone (63%)**

Problem 22.4

Write the complete mechanism of the deuteration of acetone on treatment with D_3O^+.

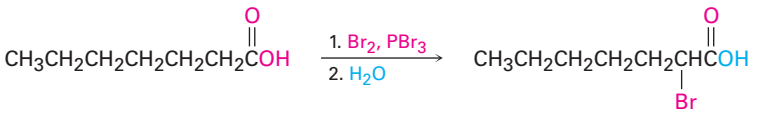


Problem 22.5

Show how you might prepare 1-penten-3-one from 3-pentanone.

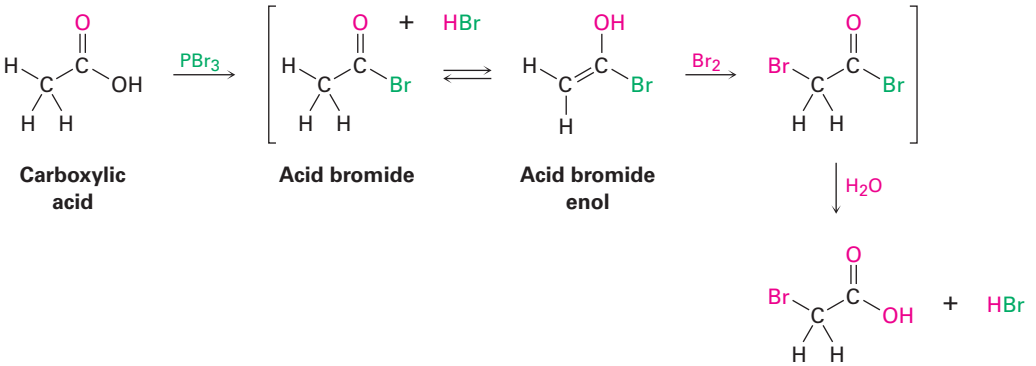
22.4 Alpha Bromination of Carboxylic Acids

The α bromination of carbonyl compounds by Br_2 in acetic acid is limited to aldehydes and ketones because acids, esters, and amides don't enolize to a sufficient extent. Carboxylic acids, however, can be α brominated by a mixture of Br_2 and PBr_3 in the *Hell–Volhard–Zelinskii (HVZ) reaction.*



Heptanoic acid | **2-Bromoheptanoic acid (90%)**

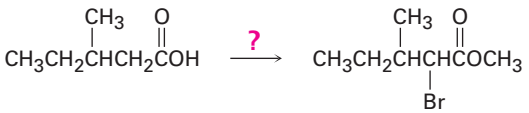
The Hell–Volhard–Zelinskii reaction is a bit more complex than it looks and actually involves α substitution of an acid bromide enol rather than a carboxylic acid enol. The process begins with reaction of the carboxylic acid with PBr_3 to form an acid bromide plus HBr **(Section 21.4)**. The HBr then catalyzes enolization of the acid bromide, and the resultant enol reacts with Br_2 in an α-substitution reaction to give an α-bromo acid bromide. Addition of water hydrolyzes the acid bromide in a nucleophilic acyl substitution reaction and yields the α-bromo carboxylic acid product.



Carboxylic acid — **Acid bromide** — **Acid bromide enol** — **α-Bromo carboxylic acid**

Problem 22.6

If methanol rather than water is added at the end of a Hell–Volhard–Zelinskii reaction, an ester rather than an acid is produced. Show how you could carry out the following transformation, and propose a mechanism for the ester-forming step.



22.5 Acidity of Alpha Hydrogen Atoms: Enolate Ion Formation

As noted in **Section 22.1**, a hydrogen on the α position of a carbonyl compound is weakly acidic and can be removed by a strong base to yield an enolate ion. In comparing acetone ($pK_a = 19.3$) with ethane ($pK_a \approx 60$), for instance, the presence of a neighboring carbonyl group increases the acidity of the ketone over the alkane by a factor of 10^{40}.

Acetone ($pK_a = 19.3$)

Ethane ($pK_a \approx 60$)

Proton abstraction from a carbonyl compound occurs when the α C–H bond is oriented roughly parallel to the p orbitals of the carbonyl group. The α carbon atom of the enolate ion is sp^2-hybridized and has a p orbital that overlaps the neighboring carbonyl p orbitals. Thus, the negative charge is shared by the electronegative oxygen atom, and the enolate ion is stabilized by resonance **(Figure 22.4)**.

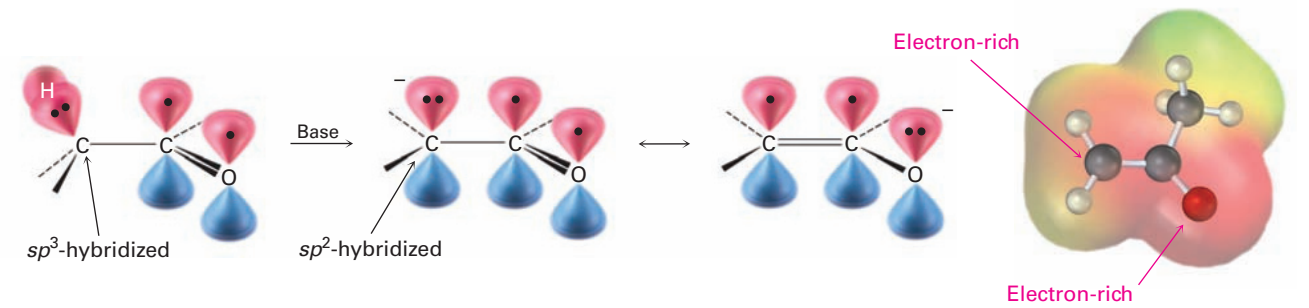
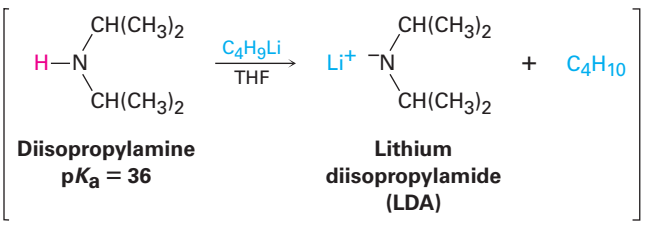
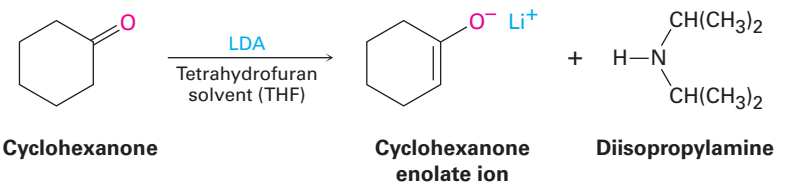


Figure 22.4 Mechanism of enolate ion formation by abstraction of an α proton from a carbonyl compound. The enolate ion is stabilized by resonance, and the negative charge (red) is shared by the oxygen and the α carbon atom, as indicated by the electrostatic potential map.

Because carbonyl compounds are only weakly acidic, a strong base is needed for enolate ion formation. If an alkoxide ion, such as sodium ethoxide, is used as base, deprotonation takes place only to the extent of about 0.1% because acetone is a weaker acid than ethanol ($pK_a = 16$). If, however, a more powerful base is used, then a carbonyl compound is completely converted into its enolate ion.

In practice, the strong base lithium diisopropylamide [$LiN(i\text{-}C_3H_7)_2$; abbreviated LDA] is commonly used for making enolate ions. As the lithium salt of the weak acid diisopropylamine, $pK_a = 36$, LDA can readily deprotonate most carbonyl compounds. It is easily prepared by reaction of butyllithium with diisopropylamine and is soluble in organic solvents because of its two alkyl groups.





Many types of carbonyl compounds, including aldehydes, ketones, esters, thioesters, acids, and amides, can be converted into enolate ions by reaction

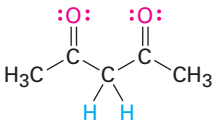
with LDA. Table 22.1 lists the approximate pK_a values of different types of carbonyl compounds and shows how these values compare to other acidic substances we've seen. Note that nitriles, too, are acidic and can be converted into enolate-like anions.

Table 22.1 Acidity Constants for Some Organic Compounds

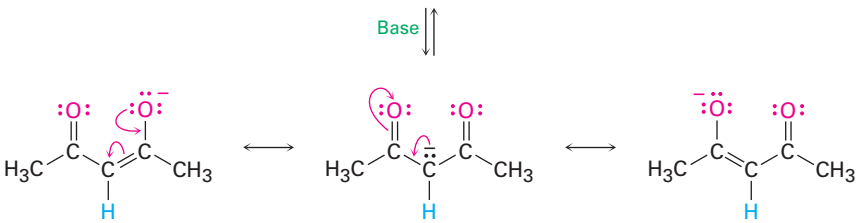
Functional group	Example	pK_a
Carboxylic acid	CH_3COH	5
1,3-Diketone	$CH_3CCH_2CCH_3$	9
3-Keto ester	$CH_3CCH_2COCH_3$	11
1,3-Diester	$CH_3OCCH_2COCH_3$	13
Alcohol	CH_3OH	16
Acid chloride	CH_3CCl	16
Aldehyde	CH_3CH	17
Ketone	CH_3CCH_3	19
Thioester	CH_3CSCH_3	21
Ester	CH_3COCH_3	25
Nitrile	$CH_3C{\equiv}N$	25
N,*N*-Dialkylamide	$CH_3CN(CH_3)_2$	30
Dialkylamine	$HN(i\text{-}C_3H_7)_2$	36

When a hydrogen atom is flanked by two carbonyl groups, its acidity is enhanced even more. Table 22.1 thus shows that 1,3-diketones (β-diketones), 3-oxo esters (β-keto esters), and 1,3-diesters (malonic esters) are even more acidic than water. The enolate ions derived from these β-dicarbonyl compounds are stabilized by sharing of the negative charge by both neighboring carbonyl oxygens. The enolate ion of 2,4-pentanedione, for instance, has three

resonance forms. Similar resonance forms can be drawn for other doubly stabilized enolate ions.

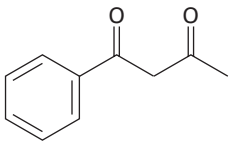


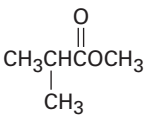
2,4-Pentanedione ($pK_a = 9$)

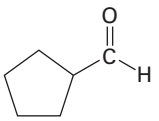


Worked Example 22.1 Identifying the Acidic Hydrogens in a Compound

Identify the most acidic hydrogens in each of the following compounds, and rank the compounds in order of increasing acidity:

(a) 

(b) 

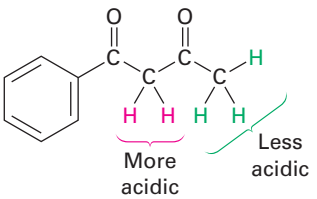
(c) 

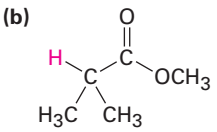
Strategy

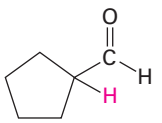
Hydrogens on carbon next to a carbonyl group are acidic. In general, a β-dicarbonyl compound is most acidic, a ketone or aldehyde is next most acidic, and a carboxylic acid derivative is least acidic. Remember that alcohols, phenols, and carboxylic acids are also acidic because of their —OH hydrogens.

Solution

The acidity order is (a) > (c) > (b). Acidic hydrogens are shown in red.

(a) 

(b) 

(c) 

Problem 22.7

Identify the most acidic hydrogens in each of the following molecules:

(a) CH_3CH_2CHO **(b)** $(CH_3)_3CCOCH_3$ **(c)** CH_3CO_2H
(d) Benzamide **(e)** $CH_3CH_2CH_2CN$ **(f)** $CH_3CON(CH_3)_2$

Problem 22.8

Draw a resonance structure of the acetonitrile anion, $^-$**:**$CH_2C{\equiv}N$, and account for the acidity of nitriles.

22.6 Reactivity of Enolate Ions

Enolate ions are more useful than enols for two reasons. First, pure enols can't normally be isolated but are instead generated only as short-lived intermediates in low concentration. By contrast, stable solutions of pure enolate ions are easily prepared from most carbonyl compounds by reaction with a strong base. Second, enolate ions are more reactive than enols and undergo many reactions that enols don't. Whereas enols are neutral, enolate ions are negatively charged, making them much better nucleophiles.

Because they are resonance hybrids of two, nonequivalent forms, enolate ions can be looked at either as vinylic alkoxides (C=C–O$^-$) or as α-keto carbanions ($^-$C–C=O). Thus, enolate ions can react with electrophiles either on oxygen or on carbon. Reaction on oxygen yields an enol derivative, while reaction on carbon yields an α-substituted carbonyl compound **(Figure 22.5)**. Both kinds of reactivity are known, but reaction on carbon is more common.

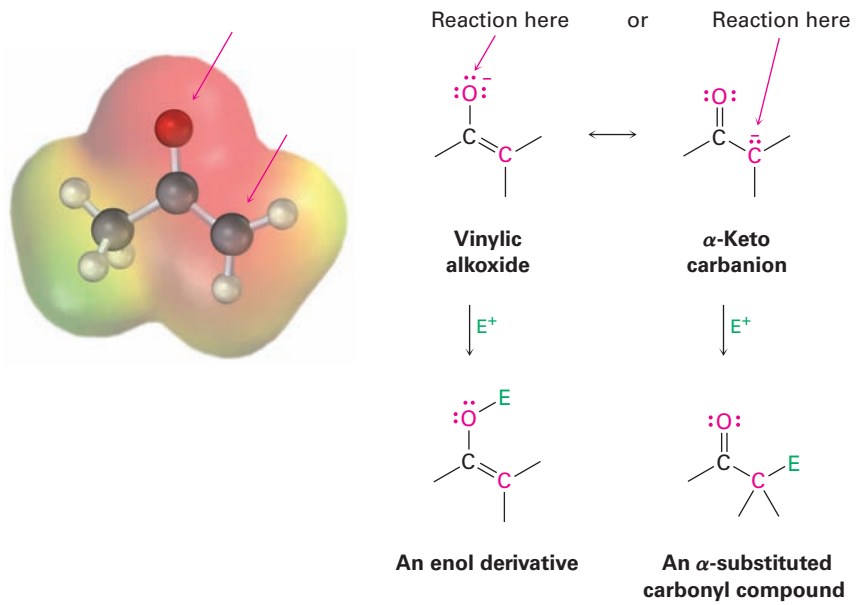
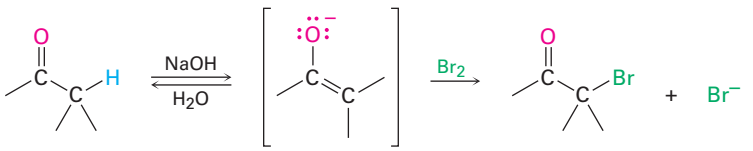


Figure 22.5 The electrostatic potential map of acetone enolate ion shows how the negative charge is delocalized over both the oxygen and the α carbon. As a result, two modes of reaction of an enolate ion with an electrophile E^+ are possible. Reaction on carbon to yield an α-substituted carbonyl product is more common.

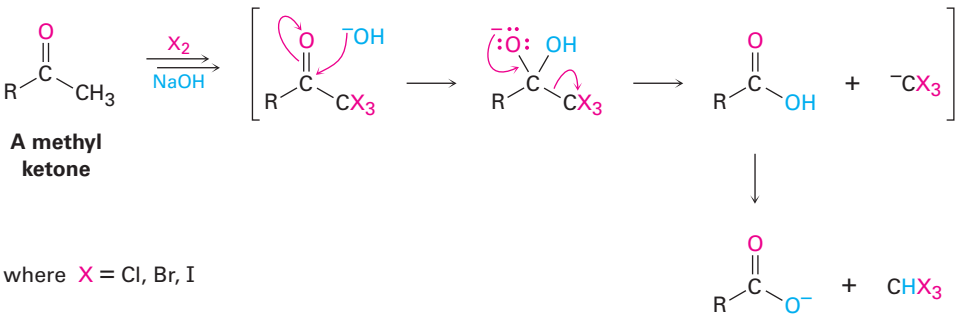
As an example of enolate-ion reactivity, aldehydes and ketones undergo base-promoted α halogenation. Even relatively weak bases such as hydroxide ion are effective for halogenation because it's not necessary to convert the ketone completely into its enolate ion. As soon as a small amount of enolate is generated, halogen reacts with it immediately, removing it from the reaction and driving the equilibrium toward further enolate ion formation.



Base-promoted halogenation of aldehydes and ketones is little used in practice because it's difficult to stop the reaction at the monosubstituted product. An α-halogenated ketone is generally more acidic than the starting, unsubstituted ketone because of the electron-withdrawing inductive effect of the

halogen atom. Thus, the monohalogenated products are themselves rapidly turned into enolate ions and further halogenated.

If excess base and halogen are used, a methyl ketone is triply halogenated and then cleaved by base in the *haloform reaction*. The products are a carboxylic acid plus a so-called haloform (chloroform, $CHCl_3$; bromoform, $CHBr_3$; or iodoform, CHI_3). Note that the second step of the reaction is a nucleophilic acyl substitution of $^-CX_3$ by ^-OH. That is, a halogen-stabilized carbanion acts as a leaving group.

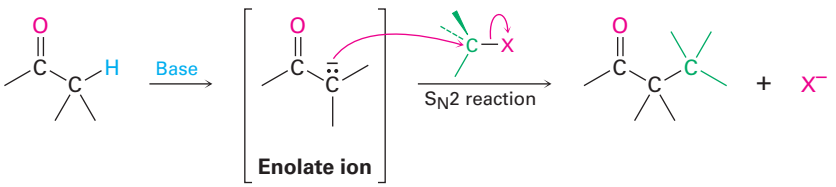


Problem 22.9

Why do you suppose ketone halogenations in acidic media are referred to as being acid-*catalyzed*, whereas halogenations in basic media are base-*promoted*? In other words, why is a full equivalent of base required for halogenation?

22.7 Alkylation of Enolate Ions

Perhaps the most useful reaction of enolate ions is their alkylation by treatment with an alkyl halide or tosylate, thereby forming a new C–C bond and joining two smaller pieces into one larger molecule. Alkylation occurs when the nucleophilic enolate ion reacts with the electrophilic alkyl halide in an S_N2 reaction and displaces the leaving group by backside attack.

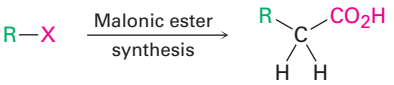


Alkylation reactions are subject to the same constraints that affect all S_N2 reactions **(Section 11.3)**. Thus, the leaving group X in the alkylating agent R–X can be chloride, bromide, iodide, or tosylate. The alkyl group R should be primary or methyl, and preferably should be allylic or benzylic. Secondary halides react poorly, and tertiary halides don't react at all because a competing E2 elimination of HX occurs instead. Vinylic and aryl halides are also unreactive because backside approach is sterically prevented.

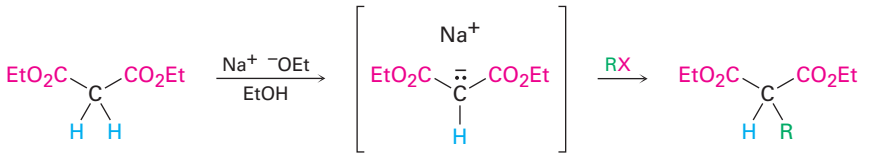
$$R{-}X \begin{cases} -X\text{: Tosylate} > -I > -Br > -Cl \\ R{-}\text{: Allylic} \approx \text{Benzylic} > H_3C{-} > RCH_2{-} \end{cases}$$

The Malonic Ester Synthesis

One of the oldest and best known carbonyl alkylation reactions is the **malonic ester synthesis**, a method for preparing a carboxylic acid from an alkyl halide while lengthening the carbon chain by two atoms.

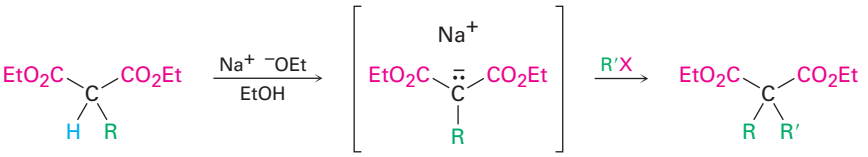


Diethyl propanedioate, commonly called diethyl malonate, or *malonic ester,* is relatively acidic (pK_a = 13) because its α hydrogens are flanked by two carbonyl groups. Thus, malonic ester is easily converted into its enolate ion by reaction with sodium ethoxide in ethanol. The enolate ion, in turn, is a good nucleophile that reacts rapidly with an alkyl halide to give an α-substituted malonic ester. Note in the following examples that the abbreviation "Et" is used for an ethyl group, $-CH_2CH_3$.



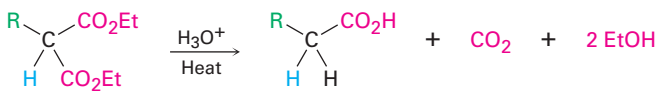
Diethyl propanedioate (malonic ester) — **Sodio malonic ester** — **An alkylated malonic ester**

The product of a malonic ester alkylation has one acidic α hydrogen remaining, so the alkylation process can be repeated to yield a dialkylated malonic ester.



An alkylated malonic ester — **A dialkylated malonic ester**

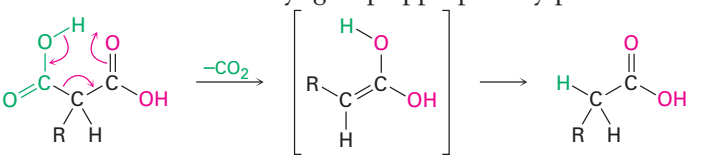
On heating with aqueous hydrochloric acid, the alkylated (or dialkylated) malonic ester undergoes hydrolysis of its two ester groups followed by *decarboxylation* (loss of CO_2) to yield a substituted monocarboxylic acid.

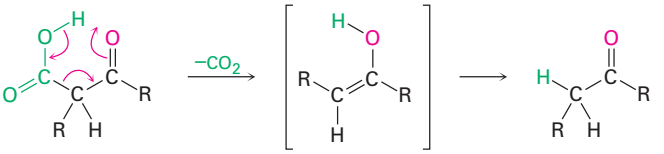


An alkylated malonic ester — **A carboxylic acid**

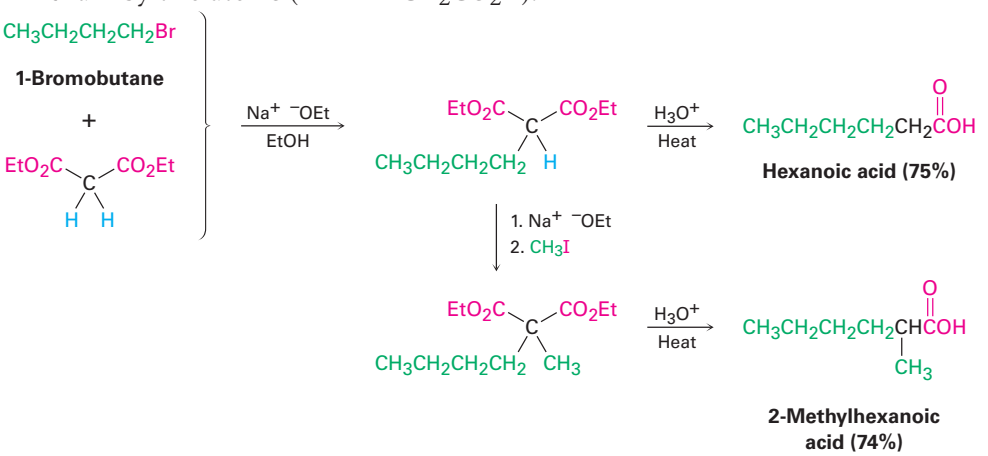
Decarboxylation is not a general reaction of carboxylic acids. Rather, it is unique to compounds that have a second carbonyl group two atoms away from the $-CO_2H$. That is, only substituted malonic acids and β-keto acids undergo loss of CO_2 on heating. The decarboxylation reaction occurs by a cyclic

mechanism and involves initial formation of an enol, thereby accounting for the need to have a second carbonyl group appropriately positioned.

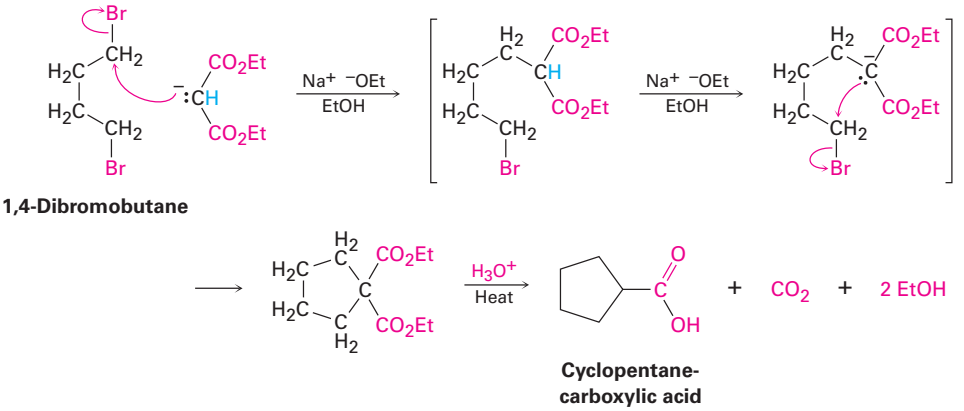




As noted previously, the overall effect of the malonic ester synthesis is to convert an alkyl halide into a carboxylic acid while lengthening the carbon chain by two atoms ($RX \rightarrow RCH_2CO_2H$).



The malonic ester synthesis can also be used to prepare *cyclo*alkanecarboxylic acids. For example, when 1,4-dibromobutane is treated with diethyl malonate in the presence of 2 equivalents of sodium ethoxide base, the second alkylation step occurs intramolecularly to yield a cyclic product. Hydrolysis and decarboxylation then give cyclopentanecarboxylic acid. Three-, four-, five-, and six-membered rings can be prepared in this way, but yields decrease for larger ring sizes.



Using the Malonic Ester Synthesis to Prepare a Carboxylic Acid

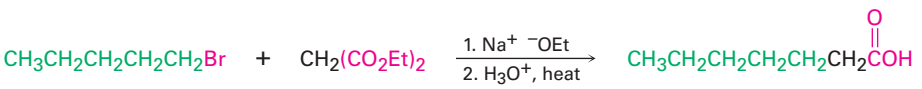
Worked Example 22.2

How would you prepare heptanoic acid using a malonic ester synthesis?

Strategy

The malonic ester synthesis converts an alkyl halide into a carboxylic acid having two more carbons. Thus, a seven-carbon acid chain must be derived from the five-carbon alkyl halide 1-bromopentane.

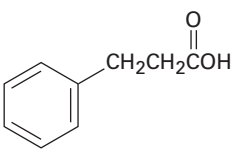
Solution



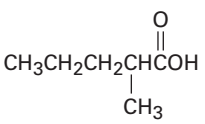
Problem 22.10

How could you use a malonic ester synthesis to prepare the following compounds? Show all steps.

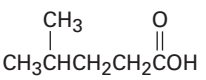
(a)



(b)



(c)

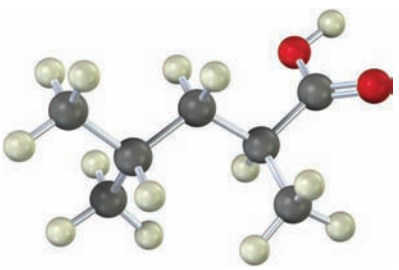


Problem 22.11

Monoalkylated and dialkylated acetic acids can be prepared by the malonic ester synthesis, but trialkylated acetic acids (R_3CCO_2H) can't be prepared. Explain.

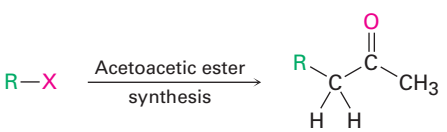
Problem 22.12

How could you use a malonic ester synthesis to prepare the following compound?

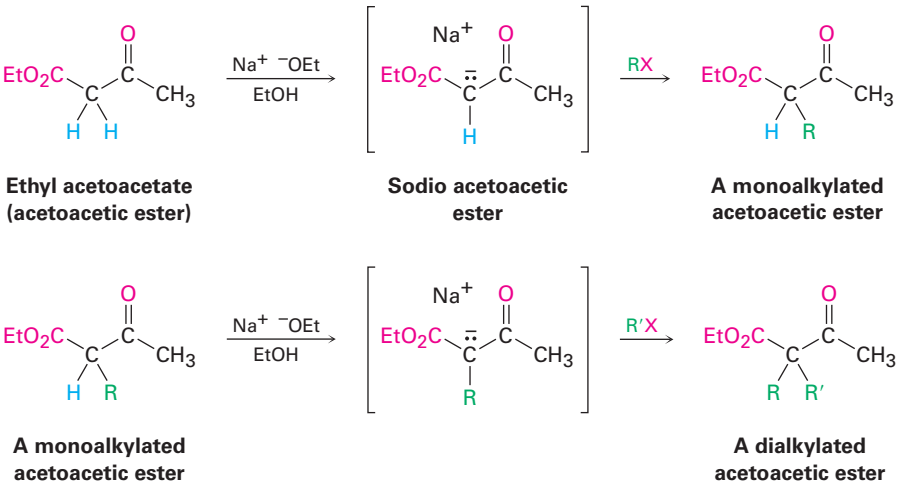


The Acetoacetic Ester Synthesis

Just as the malonic ester synthesis converts an alkyl halide into a carboxylic acid, the **acetoacetic ester synthesis** converts an alkyl halide into a methyl ketone having three more carbons.



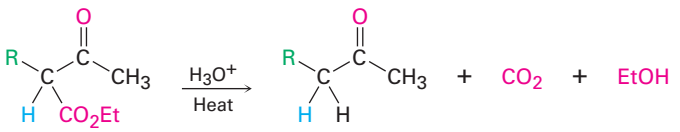
Ethyl 3-oxobutanoate, commonly called ethyl acetoacetate, or *acetoacetic ester,* is much like malonic ester in that its α hydrogens are flanked by two carbonyl groups. It is therefore readily converted into its enolate ion, which can be alkylated by reaction with an alkyl halide. A second alkylation can also be carried out if desired, since acetoacetic ester has two acidic α hydrogens.



Ethyl acetoacetate (acetoacetic ester) — **Sodio acetoacetic ester** — **A monoalkylated acetoacetic ester**

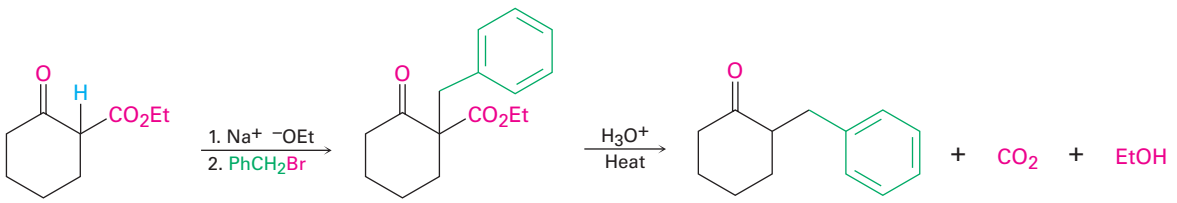
A monoalkylated acetoacetic ester — **A dialkylated acetoacetic ester**

On heating with aqueous HCl, the alkylated (or dialkylated) acetoacetic ester is hydrolyzed to a β-keto acid, which then undergoes decarboxylation to yield a ketone product. The decarboxylation occurs in the same way as in the malonic ester synthesis and involves a ketone enol as the initial product.



An alkylated acetoacetic ester — **A methyl ketone**

The three-step sequence of (1) enolate ion formation, (2) alkylation, and (3) hydrolysis/decarboxylation is applicable to all β-keto esters with acidic α hydrogens, not just to acetoacetic ester itself. For example, cyclic β-keto esters, such as ethyl 2-oxocyclohexanecarboxylate, can be alkylated and decarboxylated to give 2-substituted cyclohexanones.



Ethyl 2-oxocyclohexane-carboxylate (a cyclic β-keto ester) — **2-Benzylcyclohexanone (77%)**

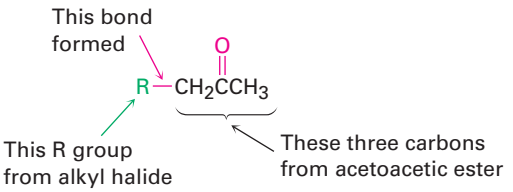
Using the Acetoacetic Ester Synthesis to Prepare a Ketone

Worked Example 22.3

How would you prepare 2-pentanone by an acetoacetic ester synthesis?

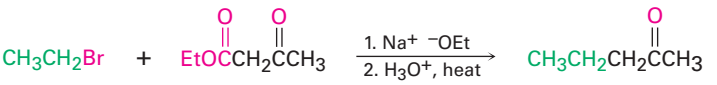
Strategy

The acetoacetic ester synthesis yields a methyl ketone by adding three carbons to an alkyl halide.



Thus, the acetoacetic ester synthesis of 2-pentanone must involve reaction of bromoethane.

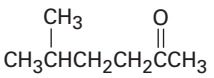
Solution

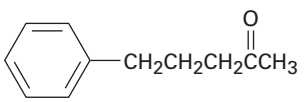


2-Pentanone

Problem 22.13

What alkyl halides would you use to prepare the following ketones by an acetoacetic ester synthesis?

(a) 

(b) 

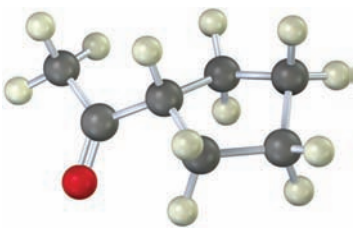
Problem 22.14

Which of the following compounds *cannot* be prepared by an acetoacetic ester synthesis? Explain.

(a) Phenylacetone **(b)** Acetophenone **(c)** 3,3-Dimethyl-2-butanone

Problem 22.15

How would you prepare the following compound using an acetoacetic ester synthesis?



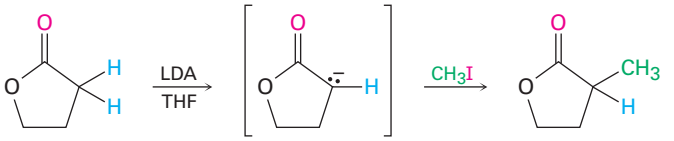
Direct Alkylation of Ketones, Esters, and Nitriles

Both the malonic ester synthesis and the acetoacetic ester synthesis are easy to carry out because they involve relatively acidic dicarbonyl compounds. As a result, sodium ethoxide in ethanol as solvent can be used to prepare the necessary enolate ions. Alternatively, however, it's also possible in many cases to directly alkylate the α position of *mono*carbonyl compounds. A strong, sterically

hindered base such as LDA is needed so that complete conversion to the enolate ion takes place rather than a nucleophilic addition, and a nonprotic solvent must be used.

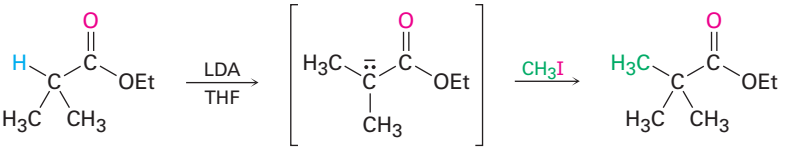
Ketones, esters, and nitriles can all be alkylated using LDA or related dialkylamide bases in THF. Aldehydes, however, rarely give high yields of pure products because their enolate ions undergo carbonyl condensation reactions instead of alkylation. (We'll study this condensation reaction in the next chapter.) Some specific examples of alkylation reactions are shown.

Lactone



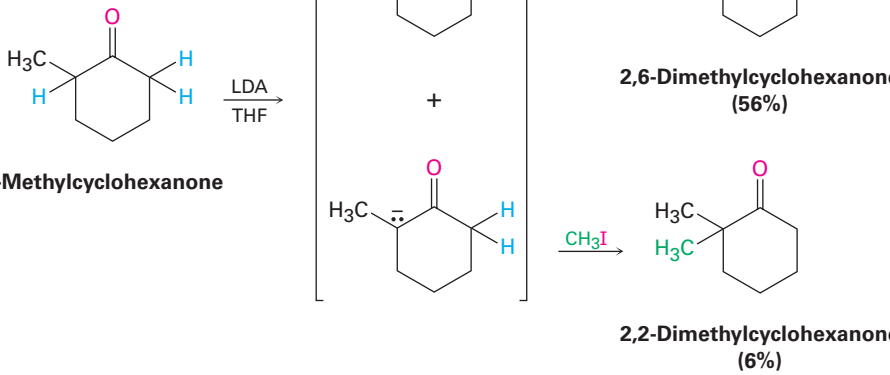
Butyrolactone **2-Methylbutyrolactone (88%)**

Ester



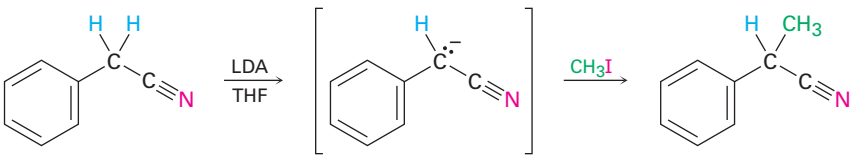
Ethyl 2-methylpropanoate **Ethyl 2,2-dimethylpropanoate (87%)**

Ketone



2-Methylcyclohexanone **2,6-Dimethylcyclohexanone (56%)** **2,2-Dimethylcyclohexanone (6%)**

Nitrile



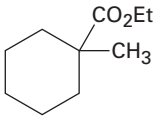
Phenylacetonitrile **2-Phenylpropanenitrile (71%)**

Note in the ketone example that alkylation of 2-methylcyclohexanone leads to a mixture of products because both possible enolate ions are formed. In general, the major product in such cases occurs by alkylation at the less hindered, more accessible position. Thus, alkylation of 2-methylcyclohexanone occurs primarily at C6 (secondary) rather than C2 (tertiary).

Using an Alkylation Reaction to Prepare a Substituted Ester

Worked Example 22.4

How might you use an alkylation reaction to prepare ethyl 1-methylcyclohexanecarboxylate?

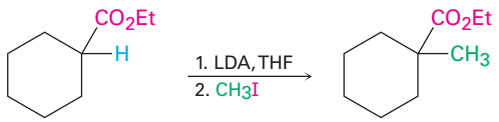


Ethyl 1-methylcyclohexanecarboxylate

Strategy

An alkylation reaction is used to introduce a methyl or primary alkyl group onto the α position of a ketone, ester, or nitrile by S_N2 reaction of an enolate ion with an alkyl halide. Thus, we need to look at the target molecule and identify any methyl or primary alkyl groups attached to an α carbon. In the present instance, the target has an α methyl group, which might be introduced by alkylation of an ester enolate ion with iodomethane.

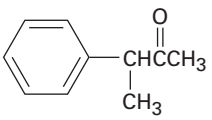
Solution



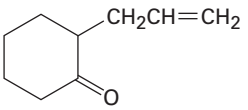
Ethyl cyclohexane-carboxylate → **Ethyl 1-methylcyclo-hexanecarboxylate**

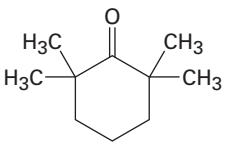
Problem 22.16

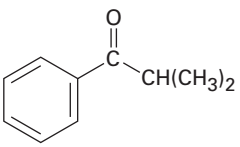
Show how you might prepare the following compounds using an alkylation reaction as the key step:

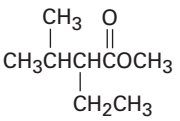
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

Biological Alkylations

Alkylations are rare but not unknown in biological chemistry. One example occurs during biosynthesis of the antibiotic indolmycin from indolylpyruvate when a base abstracts an acidic hydrogen from an α position and the resultant

enolate ion carries out an S_N2 alkylation reaction on the methyl group of *S*-adenosylmethionine (SAM; **Section 11.6**). Although it's convenient to speak of "enolate ion" intermediates in biological pathways, it's unlikely that they exist for long in an aqueous cellular environment. Rather, proton removal and alkylation probably occur at essentially the same time **(Figure 22.6)**.

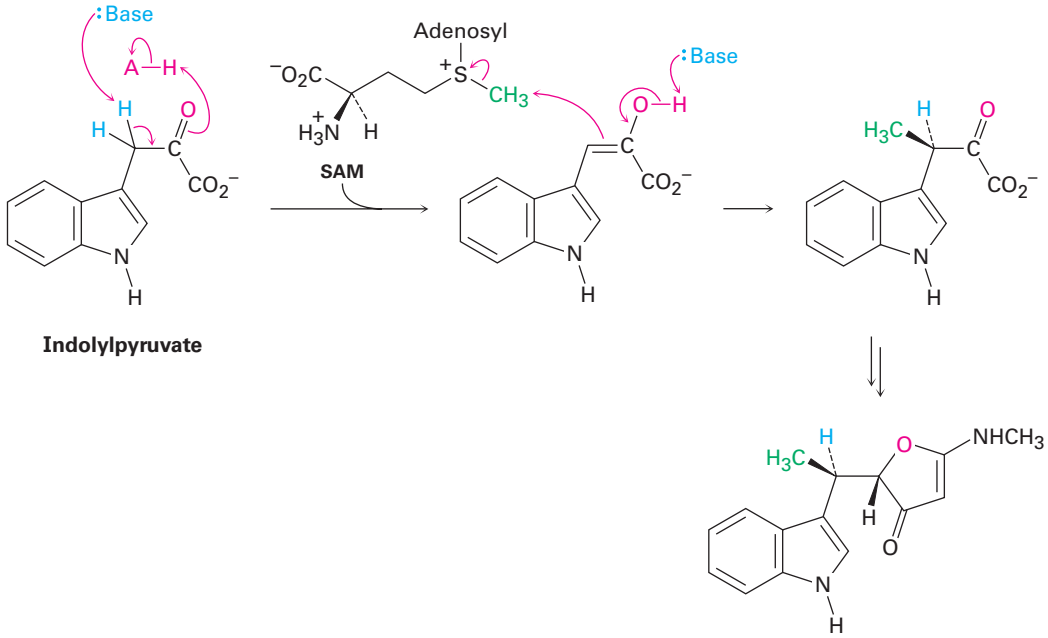
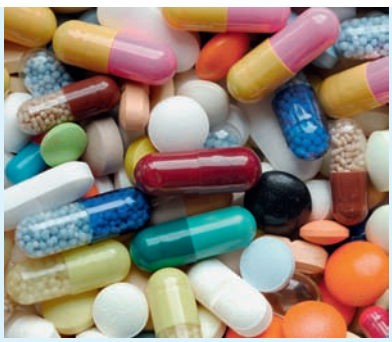


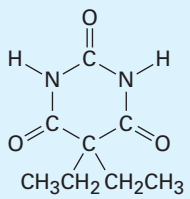
Figure 22.6 The biosynthesis of indolmycin from indolylpyruvate occurs through a pathway that includes an alkylation reaction of a short-lived enolate ion intermediate.



Different barbiturates come in a multitude of colors, giving rise to similarly colorful street names when the drugs are abused.

Barbiturates | A DEEPER LOOK

Using herbal remedies to treat illness and disease goes back thousands of years, but the medical use of chemicals prepared in the laboratory has a much shorter history. The barbiturates, a large class of drugs with a wide variety of uses, constitute one of the earliest successes of medicinal chemistry. The synthesis and medical use of barbiturates goes back to 1904 when Bayer, a German chemical company, first marketed a compound called barbital, trade named Veronal, as a treatment for insomnia. Since that time, more than 2500 different barbiturate analogs have been synthesized by drug companies, more than 50 have been used medicinally, and about a dozen are still in use as anesthetics, anticonvulsants, sedatives, and anxiolytics.



Barbital (Veronal), the first barbiturate

(continued)

(continued)

The synthesis of barbiturates is relatively simple and relies on reactions that are now familiar: enolate alkylations and nucleophilic acyl substitutions. Starting with diethyl malonate, or malonic ester, alkylation of the corresponding enolate ion with simple alkyl halides provides a wealth of different disubstituted malonic esters. Reaction with urea, $(H_2N)_2C{=}O$, then gives the product barbiturates by a twofold nucleophilic acyl substitution reaction of the ester groups with the $-NH_2$ groups of urea **(Figure 22.7)**. Amobarbital (Amytal), pentobarbital (Nembutal), and secobarbital (Seconal) are typical examples.

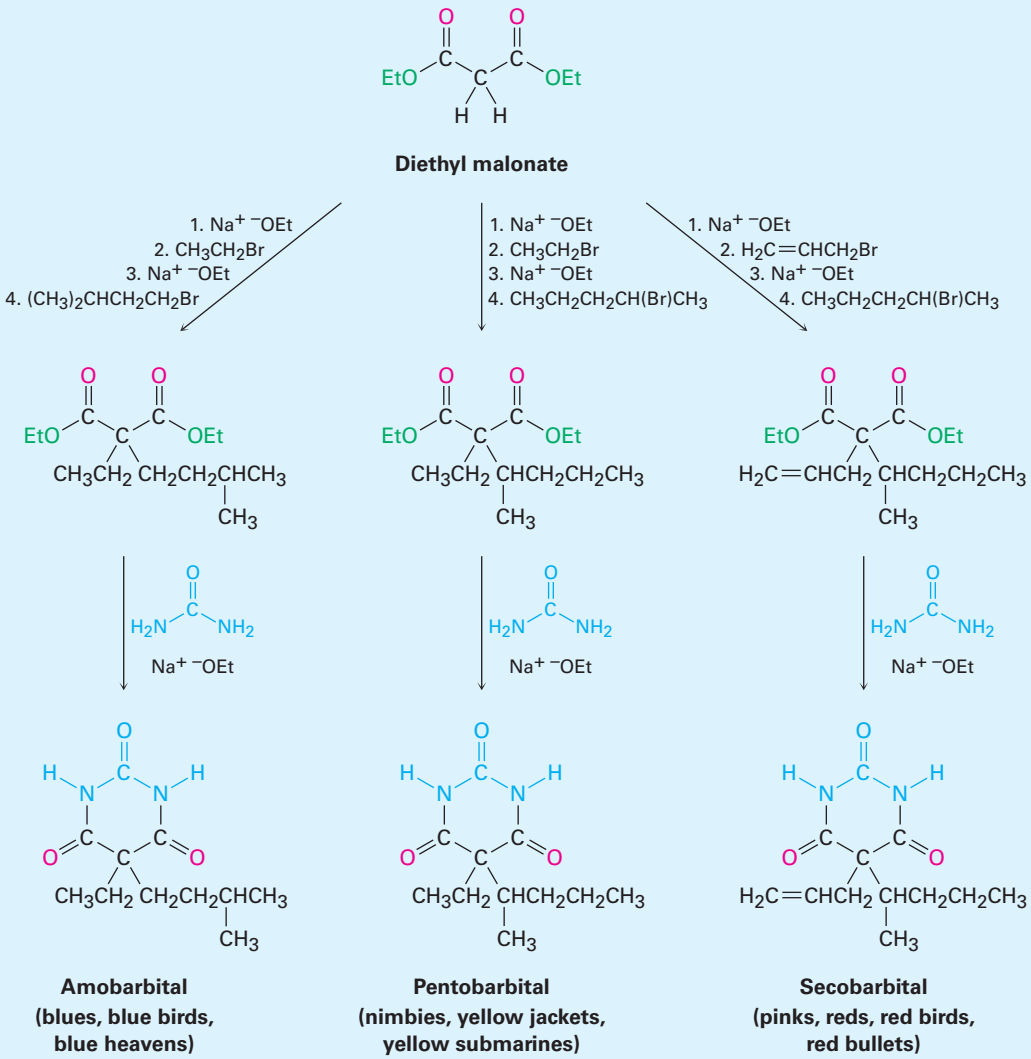


Figure 22.7 The synthesis of barbiturates relies on malonic ester alkylations and nucleophilic acyl substitution reactions. More than 2500 different barbiturates have been synthesized over the past 100 years. In addition to their legal medical uses, some barbiturates are also used illegally as street drugs under many colorful names.

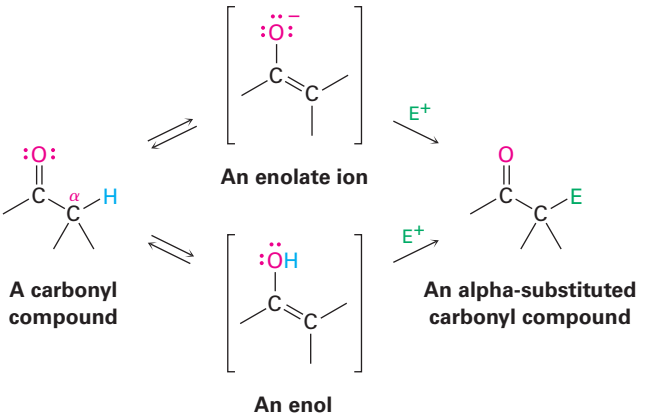
In addition to their prescribed medical uses, many barbiturates have also found widespread illegal use as street drugs. Each barbiturate comes as a tablet of regulated size, shape, and color, and their street names often mimic those colors. Although still used today, most barbiturates have been replaced by safer, more potent alternatives with markedly different structures.

Summary

Key words

acetoacetic ester synthesis, 885
α-substitution reaction, 870
enol, 871
enolate ion, 872
malonic ester synthesis, 883
tautomer, 871

The α-substitution reaction of a carbonyl compound through either an **enol** or **enolate ion** intermediate is one of the four fundamental reaction types in carbonyl-group chemistry.

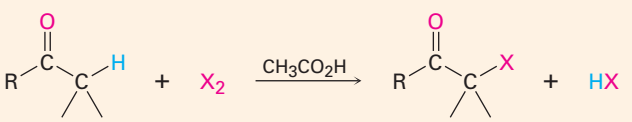


Carbonyl compounds are in an equilibrium with their enols, a process called keto–enol tautomerism. Although enol **tautomers** are normally present to only a small extent at equilibrium and can't usually be isolated pure, they nevertheless contain a highly nucleophilic double bond and react with electrophiles in an ***α*-substitution reaction**. An example is the α halogenation of ketones on treatment with Cl_2, Br_2, or I_2 in acid solution. Alpha bromination of carboxylic acids can be similarly accomplished by the Hell–Volhard–Zelinskii (HVZ) reaction, in which an acid is treated with Br_2 and PBr_3. The α-halogenated products can then undergo base-induced E2 elimination to yield α,β-unsaturated carbonyl compounds.

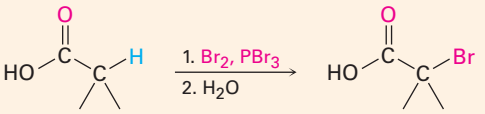
Alpha hydrogen atoms of carbonyl compounds are weakly acidic and can be removed by strong bases, such as lithium diisopropylamide (LDA), to yield nucleophilic enolate ions. The most useful reaction of enolate ions is their S_N2 alkylation with alkyl halides. The **malonic ester synthesis** converts an alkyl halide into a carboxylic acid with the addition of two carbon atoms ($RX \rightarrow RCH_2CO_2H$). Similarly, the **acetoacetic ester synthesis** converts an alkyl halide into a methyl ketone with the addition of three carbon atoms ($RX \rightarrow RCH_2COCH_3$). In addition, many carbonyl compounds, including ketones, esters, and nitriles, can be directly alkylated by treatment with LDA and an alkyl halide.

Summary of Reactions

1. Aldehyde/ketone halogenation (Section 22.3)

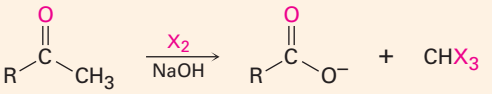


2. Hell–Volhard–Zelinskii bromination of acids (Section 22.4)



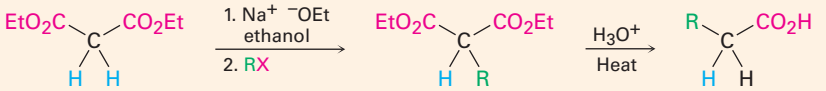
3. Dehydrobromination of α-bromo ketones (Section 22.3)

4. Haloform reaction (Section 22.6)



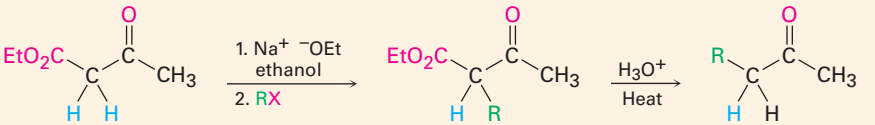
5. Alkylation of enolate ions (Section 22.7)

(a) Malonic ester synthesis



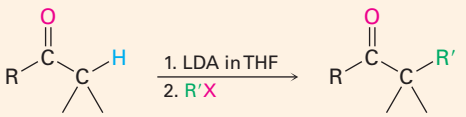
+ CO_2 + 2 EtOH

(b) Acetoacetic ester synthesis

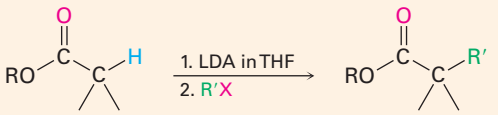


+ CO_2 + EtOH

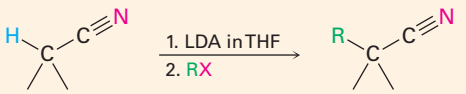
(c) Direct alkylation of ketones



(d) Direct alkylation of esters



(e) Direct alkylation of nitriles



Exercises

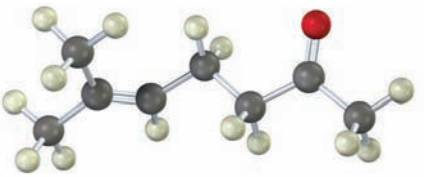
OWL Interactive versions of these problems are assignable in OWL for Organic Chemistry.

Visualizing Chemistry

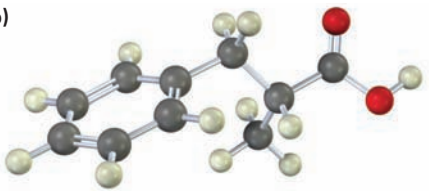
(Problems 22.1–22.16 appear within the chapter.)

22.17 Show the steps in preparing each of the following substances using either a malonic ester synthesis or an acetoacetic ester synthesis:

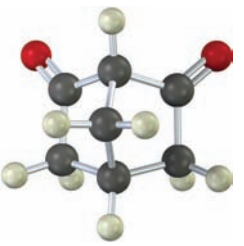
(a)



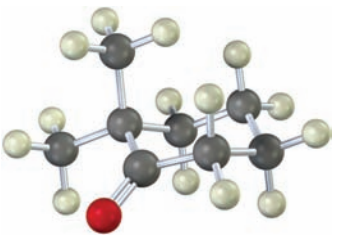
(b)



22.18 Unlike most β-diketones, the following β-diketone has no detectable enol content and is about as acidic as acetone. Explain.



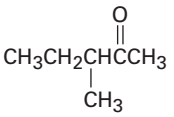
22.19 For a given α hydrogen atom to be acidic, the C–H bond must be parallel to the p orbitals of the C=O double bond (that is, perpendicular to the plane of the adjacent carbonyl group). Identify the most acidic hydrogen atom in the conformation shown for the following structure. Is it axial or equatorial?

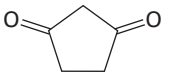


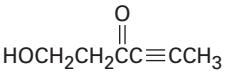
Additional Problems

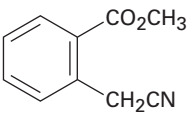
Acidity of Carbonyl Compounds

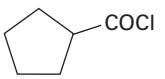
22.20 Identify all the acidic hydrogens ($pK_a < 25$) in the following molecules:

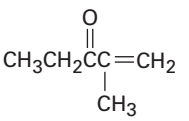
(a) 

(b) 

(c) 

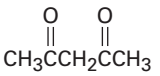
(d) 

(e) 

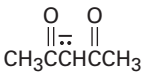
(f) 

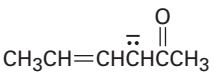
22.21 Rank the following compounds in order of increasing acidity:

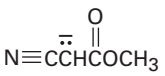
(a) $CH_3CH_2CO_2H$ **(b)** CH_3CH_2OH **(c)** $(CH_3CH_2)_2NH$

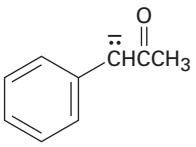
(d) CH_3COCH_3 **(e)**  **(f)** CCl_3CO_2H

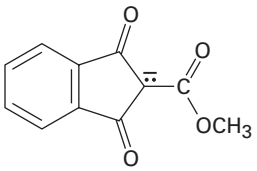
22.22 Write resonance structures for the following anions:

(a) 

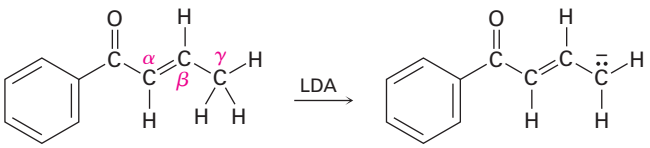
(b) 

(c) 

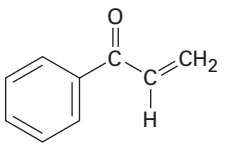
(d) 

(e) 

22.23 Base treatment of the following α,β-unsaturated carbonyl compound yields an anion by removal of H^+ from the γ carbon. Why are hydrogens on the γ carbon atom acidic?



22.24 Treatment of 1-phenyl-2-propenone with a strong base such as LDA does not yield an anion, even though it contains a hydrogen on the carbon atom next to the carbonyl group. Explain.

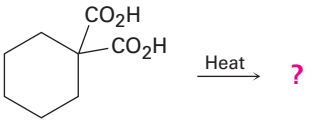


1-Phenyl-2-propenone

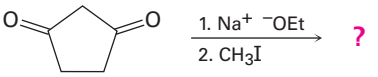
α-Substitution Reactions

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

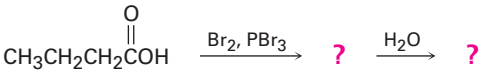
(a)



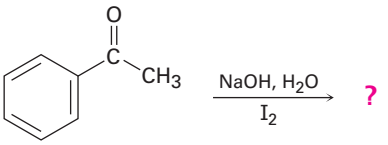
(b)



(c)



(d)

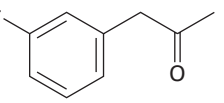


22.26 Which, if any, of the following compounds can be prepared by a malonic ester synthesis? Show the alkyl halide you would use in each case.

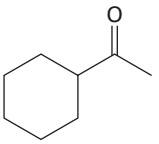
(a) Ethyl pentanoate **(b)** Ethyl 3-methylbutanoate
(c) Ethyl 2-methylbutanoate **(d)** Ethyl 2,2-dimethylpropanoate

22.27 Which, if any, of the following compounds can be prepared by an acetoacetic ester synthesis? Explain.

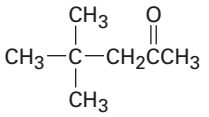
(a)



(b)

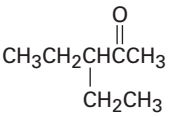


(c)

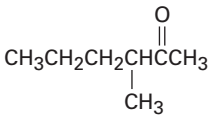


22.28 How would you prepare the following ketones using an acetoacetic ester synthesis?

(a)

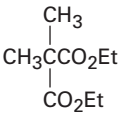


(b)

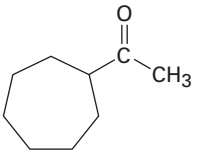


22.29 How would you prepare the following compounds using either an acetoacetic ester synthesis or a malonic ester synthesis?

(a)



(b)



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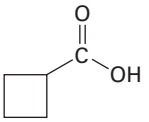
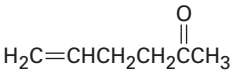


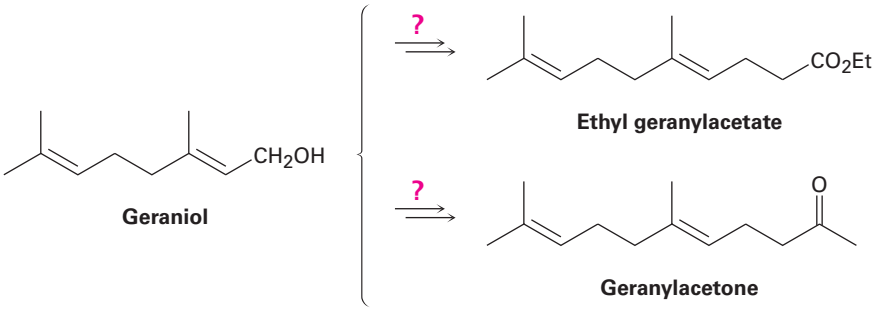
(d)



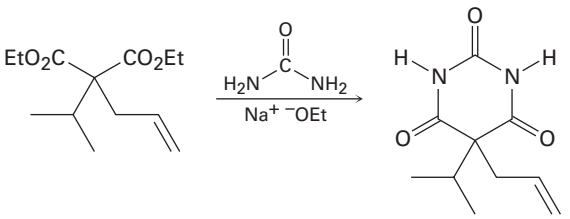
22.30 Which of the following substances would undergo the haloform reaction?

(a) CH_3COCH_3 **(b)** Acetophenone **(c)** CH_3CH_2CHO
(d) CH_3CO_2H **(e)** $CH_3C{\equiv}N$

22.31 How might you convert geraniol into either ethyl geranylacetate or geranylacetone?



22.32 Aprobarbital, a barbiturate once used in treating insomnia, is synthesized in three steps from diethyl malonate. Show how you would synthesize the necessary dialkylated intermediate, and then propose a mechanism for the reaction of that intermediate with urea to give aprobarbital.



Aprobarbital

General Problems

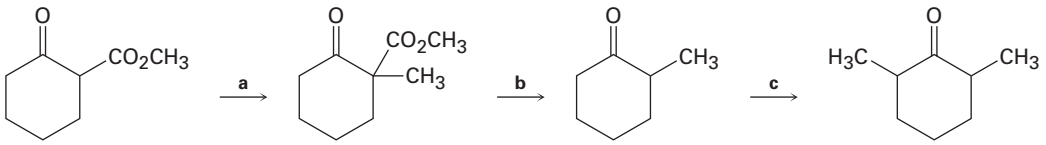
22.33 One way to determine the number of acidic hydrogens in a molecule is to treat the compound with NaOD in D_2O, isolate the product, and determine its molecular weight by mass spectrometry. For example, if cyclohexanone is treated with NaOD in D_2O, the product has MW = 102. Explain how this method works.

22.34 When optically active (*R*)-2-methylcyclohexanone is treated with either aqueous base or acid, racemization occurs. Explain.

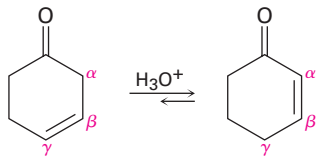
22.35 Would you expect optically active (*S*)-3-methylcyclohexanone to be racemized on acid or base treatment in the same way as 2-methylcyclohexanone (Problem 22.34)? Explain.

22.36 When an optically active carboxylic acid such as (*R*)-2-phenylpropanoic acid is brominated under Hell–Volhard–Zelinskii conditions, is the product optically active or racemic? Explain.

22.37 Fill in the reagents **a–c** that are missing from the following scheme:

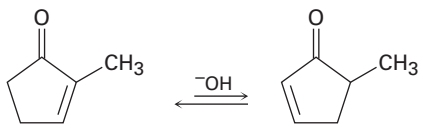


22.38 Nonconjugated β,γ-unsaturated ketones, such as 3-cyclohexenone, are in an acid-catalyzed equilibrium with their conjugated α,β-unsaturated isomers. Propose a mechanism for this isomerization.

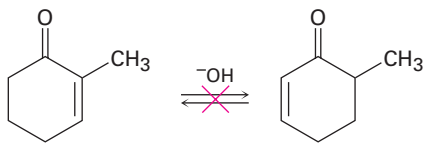


22.39 The interconversion of unsaturated ketones described in Problem 22.38 is also catalyzed by base. Explain.

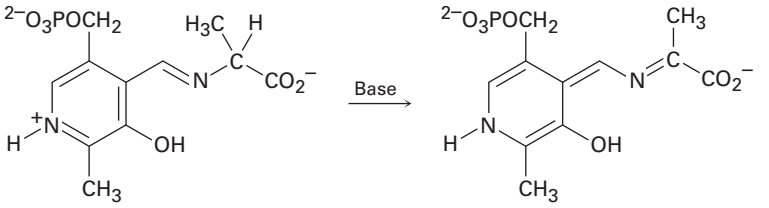
22.40 One consequence of the base-catalyzed isomerization of unsaturated ketones described in Problem 22.39 is that 2-substituted 2-cyclopentenones can be interconverted with 5-substituted 2-cyclopentenones. Propose a mechanism for this isomerization.



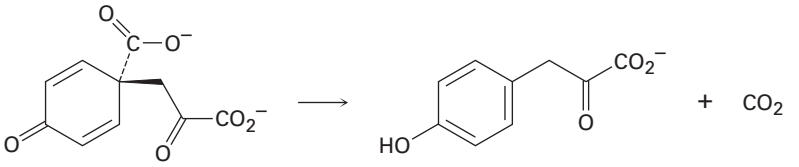
22.41 Although 2-substituted 2-cyclopentenones are in a base-catalyzed equilibrium with their 5-substituted 2-cyclopentenone isomers (Problem 22.40), the analogous isomerization is not observed for 2-substituted 2-cyclohexenones. Explain.



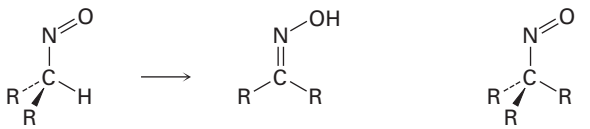
22.42 Using curved arrows, propose a mechanism for the following reaction, one of the steps in the metabolism of the amino acid alanine.



22.43 Using curved arrows, propose a mechanism for the following reaction, one of the steps in the biosynthesis of the amino acid tyrosine.

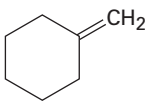


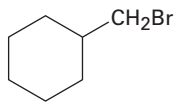
22.44 All attempts to isolate primary and secondary nitroso compounds result only in the formation of oximes. Tertiary nitroso compounds, however, are stable. Explain.

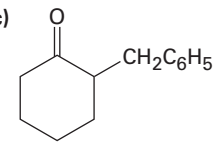


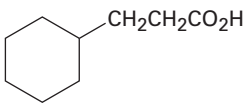
A 1° or 2° nitroso compound (unstable) **An oxime** **A 3° nitroso compound (stable)**

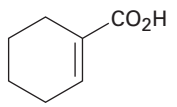
22.45 How would you synthesize the following compounds from cyclohexanone? More than one step may be required.

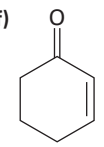
(a) 

(b) 

(c) 

(d) 

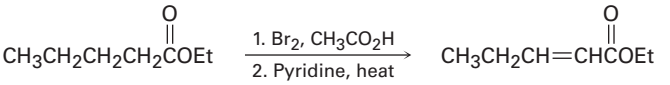
(e) 

(f) 

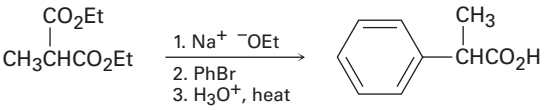
22.46 The two isomers *cis*- and *trans*-4-*tert*-butyl-2-methylcyclohexanone are interconverted by base treatment. Which isomer do you think is more stable, and why?

22.47 The following synthetic routes are incorrect. What is wrong with each?

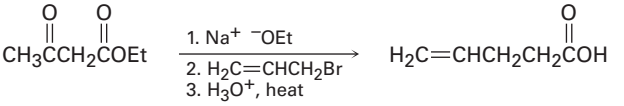
(a)



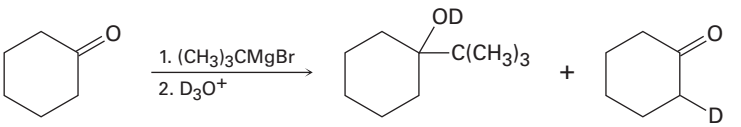
(b)



(c)

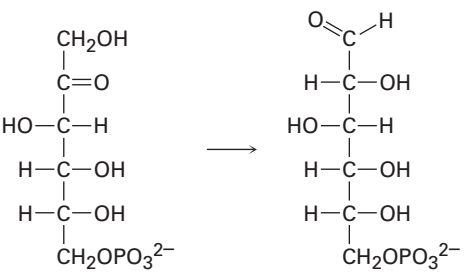


22.48 Attempted Grignard reaction of cyclohexanone with *tert*-butylmagnesium bromide gives only about 1% yield of the expected addition product along with 99% unreacted cyclohexanone. If D_3O^+ is added to the reaction mixture after a suitable period, however, the "unreacted" cyclohexanone is found to have one deuterium atom incorporated into it. Explain.



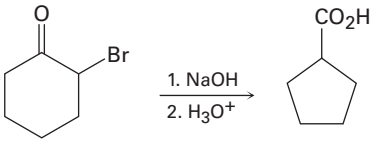
1% **99%**

22.49 One of the later steps in glucose biosynthesis is the isomerization of fructose 6-phosphate to glucose 6-phosphate. Propose a mechanism, using acid or base catalysis as needed.

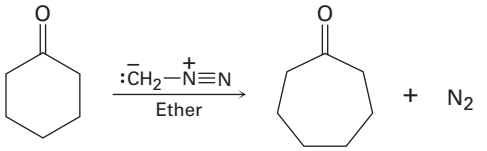


Fructose 6-phosphate **Glucose 6-phosphate**

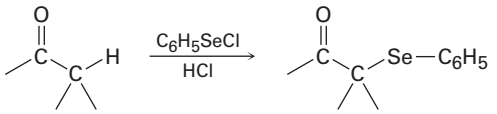
22.50 The *Favorskii reaction* involves treatment of an α-bromo ketone with base to yield a ring-contracted product. For example, reaction of 2-bromocyclohexanone with aqueous NaOH yields cyclopentanecarboxylic acid. Propose a mechanism.



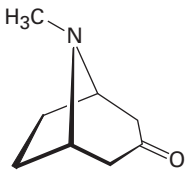
22.51 Treatment of a cyclic ketone with diazomethane is a method for accomplishing a *ring-expansion reaction*. For example, treatment of cyclohexanone with diazomethane yields cycloheptanone. Propose a mechanism.



22.52 Ketones react slowly with benzeneselenenyl chloride in the presence of HCl to yield α-phenylseleno ketones. Propose a mechanism for this acid-catalyzed α-substitution reaction.



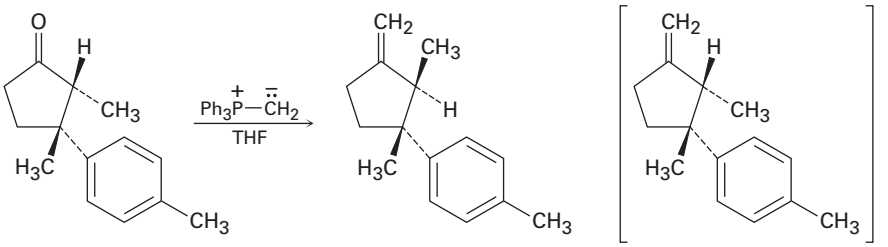
22.53 As far back as the 16th century, South American Incas chewed the leaves of the coca bush, *Erythroxylon coca,* to combat fatigue. Chemical studies of *Erythroxylon coca* by Friedrich Wöhler in 1862 resulted in the discovery of *cocaine,* $C_{17}H_{21}NO_4$, as the active component. Basic hydrolysis of cocaine leads to methanol, benzoic acid, and another compound called *ecgonine,* $C_9H_{15}NO_3$. Oxidation of ecgonine with CrO_3 yields a keto acid that readily loses CO_2 on heating, giving tropinone.



Tropinone

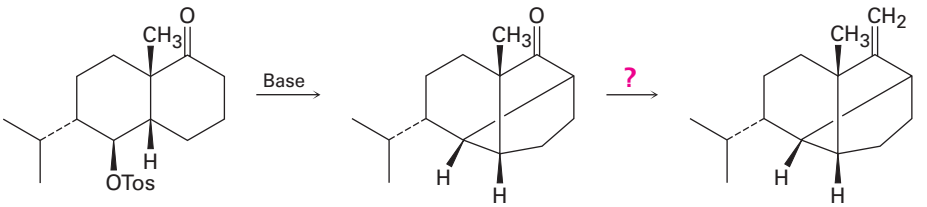
(a) What is a likely structure for the keto acid?
(b) What is a likely structure for ecgonine, neglecting stereochemistry?
(c) What is a likely structure for cocaine, neglecting stereochemistry?

22.54 The final step in an attempted synthesis of laurene, a hydrocarbon isolated from the marine alga *Laurencia glandulifera,* involved the Wittig reaction shown. The product obtained, however, was not laurene but an isomer. Propose a mechanism to account for these unexpected results.



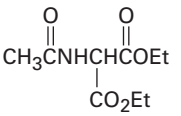
Laurene
(Not formed)

22.55 The key step in a reported laboratory synthesis of sativene, a hydrocarbon isolated from the mold *Helminthosporium sativum,* involves the following base treatment of a keto tosylate. What kind of reaction is occurring? How would you complete the synthesis?



A keto tosylate **Sativene**

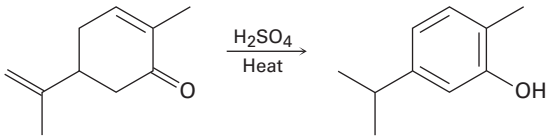
22.56 Amino acids can be prepared by reaction of alkyl halides with diethyl acetamidomalonate, followed by heating the initial alkylation product with aqueous HCl. Show how you would prepare alanine, $CH_3CH(NH_2)CO_2H$, one of the twenty amino acids found in proteins, and propose a mechanism for acid-catalyzed conversion of the initial alkylation product to the amino acid.



Diethyl acetamidomalonate

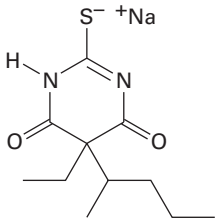
22.57 Amino acids can also be prepared by a two-step sequence that involves Hell–Volhard–Zelinskii reaction of a carboxylic acid followed by treatment with ammonia. Show how you would prepare leucine, $(CH_3)_2CHCH_2CH(NH_2)CO_2H$, and identify the mechanism of the second step.

22.58 Heating carvone with aqueous sulfuric acid converts it into carvacrol. Propose a mechanism for the isomerization.



Carvone **Carvacrol**

22.59 Sodium Pentothal is a short-acting barbiturate derivative used as a general anesthetic and known in popular culture as a truth serum. It is synthesized like other barbiturates (see the *A Deeper Look* at the end of this chapter), using thiourea, $(H_2N)_2C{=}S$, in place of urea. How would you synthesize Sodium Pentothal?



Sodium Pentothal

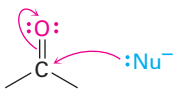
23

Many of life's molecules needed by all growing organisms are biosynthesized using carbonyl condensation reactions. © Picturebank/Alamy

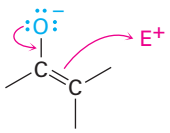
Carbonyl Condensation Reactions

OWL Sign in to OWL for Organic Chemistry at **www.cengage.com/owl** to view tutorials and simulations, develop problem-solving skills, and complete online homework assigned by your professor.

We've now studied three of the four general kinds of carbonyl-group reactions and have seen two general kinds of behavior. In nucleophilic addition and nucleophilic acyl substitution reactions, a carbonyl compound behaves as an electrophile when an electron-rich reagent adds to it. In α-substitution reactions, however, a carbonyl compound behaves as a nucleophile when it is converted into its enol or enolate ion. In the carbonyl condensation reaction that we'll study in this chapter, the carbonyl compound behaves *both* as an electrophile and as a nucleophile.



Electrophilic carbonyl group reacts with nucleophiles.



Nucleophilic enolate ion reacts with electrophiles.

Why This Chapter? We'll see later in this chapter and again in Chapter 29 that carbonyl condensation reactions occur in a large number of metabolic pathways. In fact, almost all classes of biomolecules—carbohydrates, lipids, proteins, nucleic acids, and many others—are biosynthesized through pathways that involve carbonyl condensation reactions. As with the α-substitution reaction discussed in the previous chapter, the great value of carbonyl condensations is that they are one of the few general methods for forming carbon–carbon bonds, thereby making it possible to build larger molecules from smaller precursors. We'll see how and why these reactions occur in this chapter.

23.1 Carbonyl Condensations: The Aldol Reaction

Carbonyl condensation reactions take place between two carbonyl partners and involve a combination of nucleophilic addition and α-substitution steps. One partner is converted into an enolate-ion nucleophile and adds to the electrophilic

carbonyl group of the second partner. In so doing, the nucleophilic partner undergoes an α-substitution reaction and the electrophilic partner undergoes a nucleophilic addition. The general mechanism of the process is shown in **Figure 23.1**.

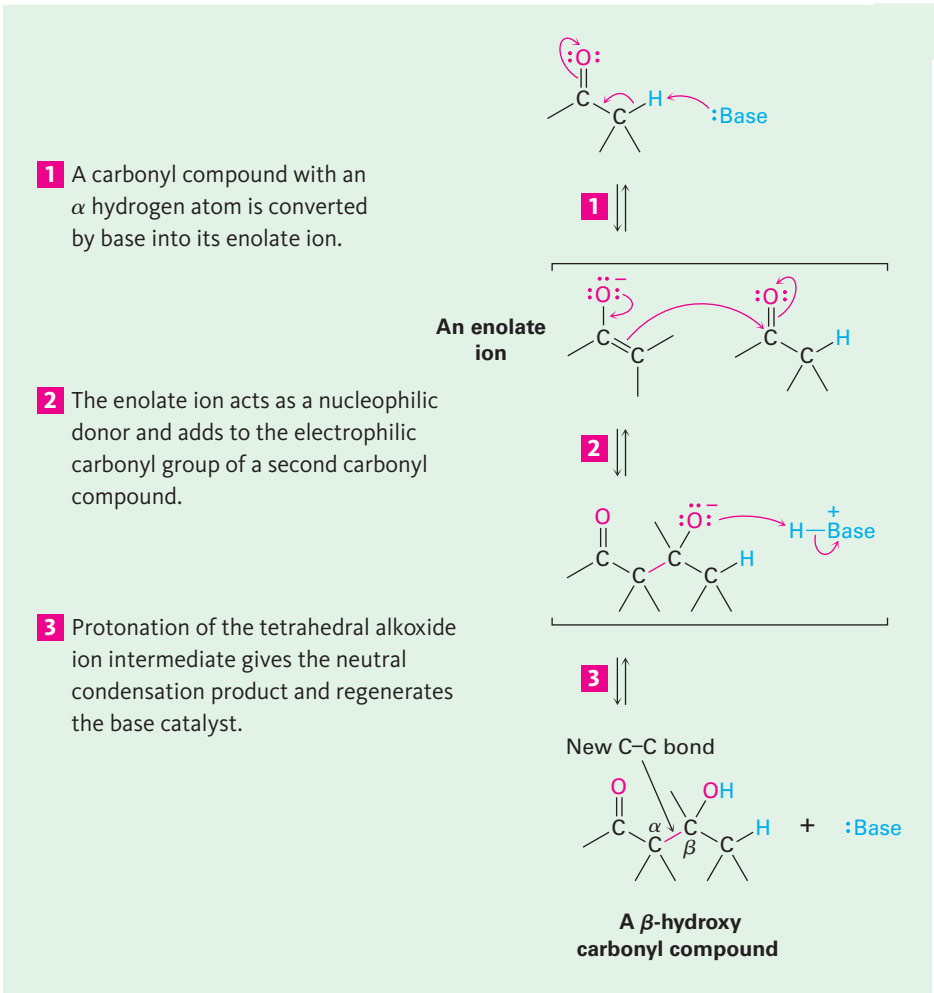
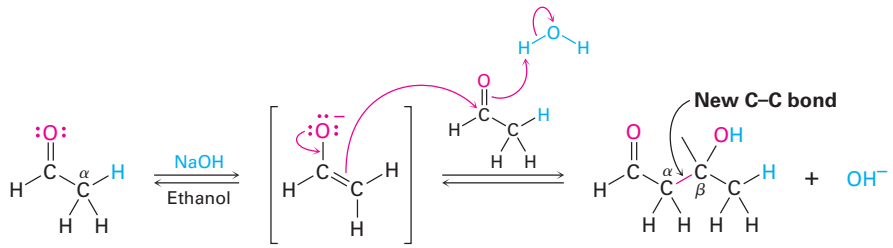


Figure 23.1 | MECHANISM

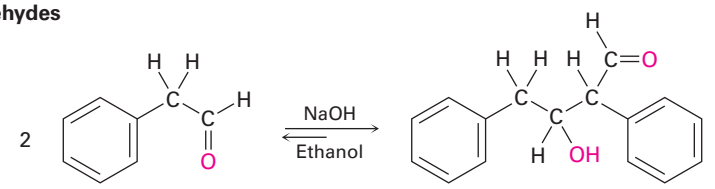
The general mechanism of a carbonyl condensation reaction. One partner becomes a nucleophilic donor and adds to the second partner as an electrophilic acceptor. After protonation, the final product is a β-hydroxy carbonyl compound.

Aldehydes and ketones with an α hydrogen atom undergo a base-catalyzed carbonyl condensation reaction called the **aldol reaction**. For example, treatment of acetaldehyde with a base such as sodium ethoxide or sodium hydroxide in a protic solvent leads to rapid and reversible formation of 3-hydroxybutanal, known commonly as *aldol* (*ald*ehyde + alcoho*l*), hence the general name of the reaction.



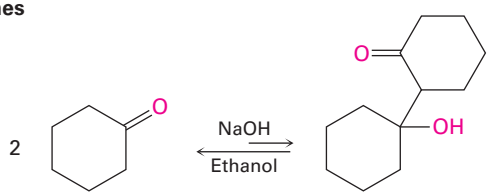
The exact position of the aldol equilibrium depends both on reaction conditions and on substrate structure. The equilibrium generally favors condensation product in the case of aldehydes with no α substituent (RCH_2CHO) but favors reactant for disubstituted aldehydes (R_2CHCHO) and for most ketones. Steric factors are probably responsible for these trends, since increased substitution near the reaction site increases steric congestion in the aldol product.

Aldehydes



Phenylacetaldehyde (10%) **(90%)**

Ketones



Cyclohexanone (78%) **(22%)**

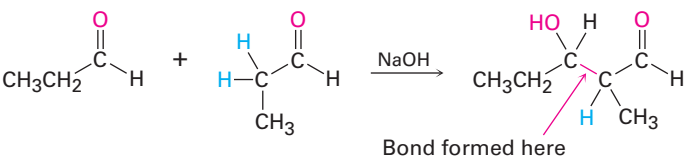
Worked Example 23.1 Predicting the Product of an Aldol Reaction

What is the structure of the aldol product from propanal?

Strategy

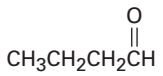
An aldol reaction combines two molecules of reactant by forming a bond between the α carbon of one partner and the carbonyl carbon of the second partner. The product is a β-hydroxy aldehyde or ketone, meaning that the two oxygen atoms in the product have a 1,3 relationship.

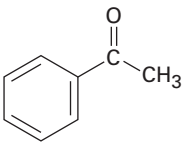
Solution

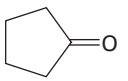


Problem 23.1

Predict the aldol reaction product of the following compounds:

(a) 

(b) 

(c) 

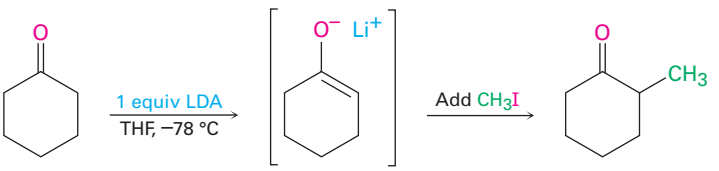
Problem 23.2

Using curved arrows to indicate the electron flow in each step, show how the base-catalyzed retro-aldol reaction of 4-hydroxy-4-methyl-2-pentanone takes place to yield 2 equivalents of acetone.

23.2 Carbonyl Condensations versus Alpha Substitutions

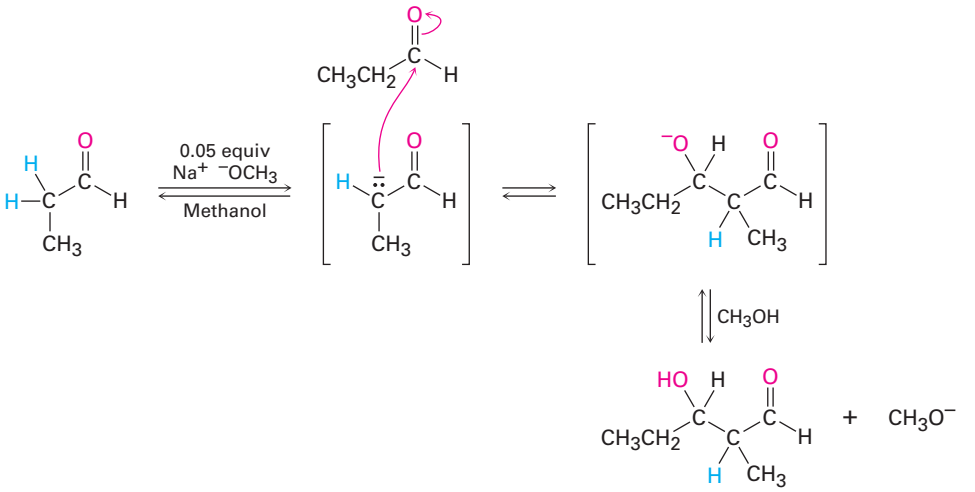
Two of the four general carbonyl-group reactions—carbonyl condensations and α substitutions—take place under basic conditions and involve enolate-ion intermediates. Because the experimental conditions for the two reactions are similar, how can we predict which will occur in a given case? When we generate an enolate ion with the intention of carrying out an α alkylation, how can we be sure that a carbonyl condensation reaction won't occur instead?

There is no simple answer to this question, but the exact experimental conditions usually have much to do with the result. Alpha-substitution reactions require a full equivalent of strong base and are normally carried out so that the carbonyl compound is rapidly and completely converted into its enolate ion at a low temperature. An electrophile is then added rapidly to ensure that the reactive enolate ion is quenched quickly. In a ketone alkylation reaction, for instance, we might use 1 equivalent of lithium diisopropylamide (LDA) in tetrahydrofuran solution at −78 °C. Rapid and complete generation of the ketone enolate ion would occur, and no unreacted ketone would be left so that no condensation reaction could take place. We would then immediately add an alkyl halide to complete the alkylation reaction.



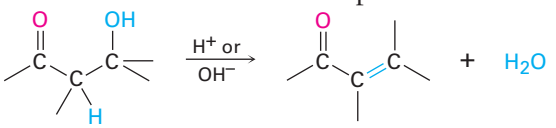
On the other hand, carbonyl condensation reactions require only a catalytic amount of a relatively weak base rather than a full equivalent so that a small amount of enolate ion is generated in the presence of unreacted carbonyl compound. Once a condensation has occurred, the basic catalyst is regenerated. To carry out an aldol reaction on propanal, for instance, we might dissolve the

aldehyde in methanol, add 0.05 equivalent of sodium methoxide, and then warm the mixture to give the aldol product.



23.3 Dehydration of Aldol Products: Synthesis of Enones

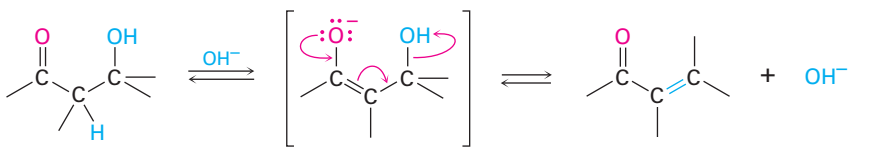
The β-hydroxy aldehydes or ketones formed in aldol reactions can be easily dehydrated to yield α,β-unsaturated products, or conjugated enones. In fact, it's this loss of water that gives the *condensation* reaction its name, because water condenses out of the reaction when the enone product forms.



A β-hydroxy ketone or aldehyde **A conjugated enone**

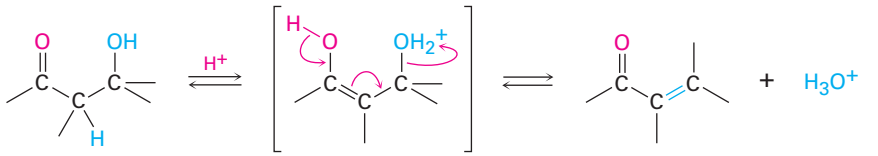
Most alcohols are resistant to dehydration by base **(Section 17.6)** because hydroxide ion is a poor leaving group, but aldol products dehydrate easily because of the carbonyl group. Under basic conditions, an acidic α hydrogen is removed, yielding an enolate ion that expels the $^{-}$OH leaving group in an E1cB reaction **(Section 11.10)**. Under acidic conditions, an enol is formed, the −OH group is protonated, and water is expelled in an E1 or E2 reaction.

Base-catalyzed



Enolate ion

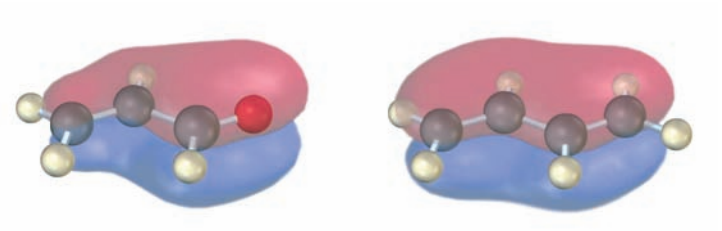
Acid-catalyzed



Enol

The reaction conditions needed for aldol dehydration are often only a bit more vigorous (slightly higher temperature, for instance) than the conditions needed for the aldol formation itself. As a result, conjugated enones are usually obtained directly from aldol reactions without isolating the intermediate β-hydroxy carbonyl compounds.

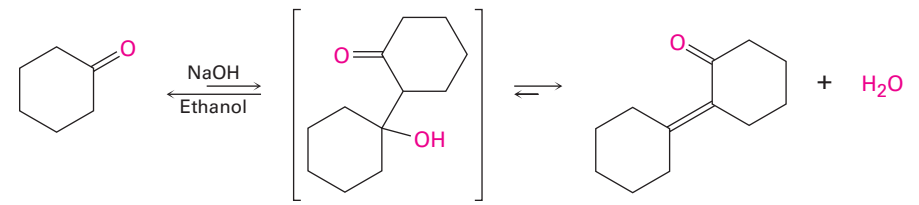
Conjugated enones are more stable than nonconjugated enones for the same reason that conjugated dienes are more stable than nonconjugated dienes **(Section 14.1)**. Interaction between the π electrons of the C=C bond and the π electrons of the C=O group leads to a molecular orbital description for a conjugated enone that shows an interaction of the π electrons over all four atomic centers **(Figure 23.2)**.



Propenal **1,3-Butadiene**

Figure 23.2 The π bonding molecular orbitals of a conjugated enone (propenal) and a conjugated diene (1,3-butadiene) are similar in shape and are spread over the entire π system.

The real value of aldol dehydration is that removal of water from the reaction mixture can be used to drive the aldol equilibrium toward product. Even though the initial aldol step itself may be unfavorable, as it usually is for ketones, the subsequent dehydration step nevertheless allows many aldol condensations to be carried out in good yield. Cyclohexanone, for example, gives cyclohexylidenecyclohexanone in 92% yield even though the initial equilibrium is unfavorable.



Cyclohexanone **Cyclohexylidenecyclohexanone (92%)**

Predicting the Product of an Aldol Reaction

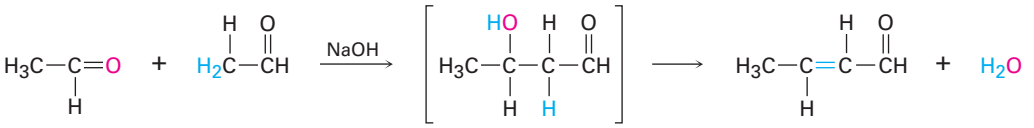
Worked Example 23.2

What is the structure of the enone obtained from aldol condensation of acetaldehyde?

Strategy

In the aldol reaction, H_2O is eliminated and a double bond is formed by removing two hydrogens from the acidic α position of one partner and the carbonyl oxygen from the second partner. The product is thus an α,β-unsaturated aldehyde or ketone.

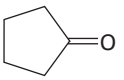
Solution

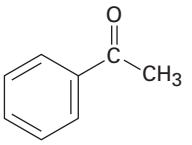


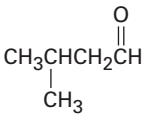
2-Butenal

Problem 23.3

What enone product would you expect from aldol condensation of each of the following compounds?

(a) 

(b) 

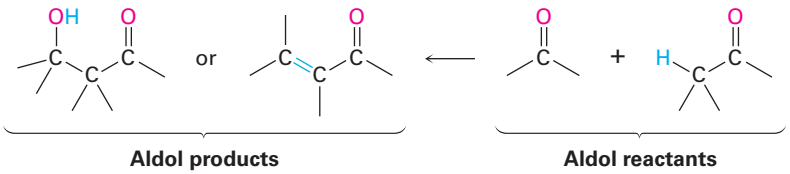
(c) 

Problem 23.4

Aldol condensation of 3-methylcyclohexanone leads to a mixture of two enone products, not counting double-bond isomers. Draw them.

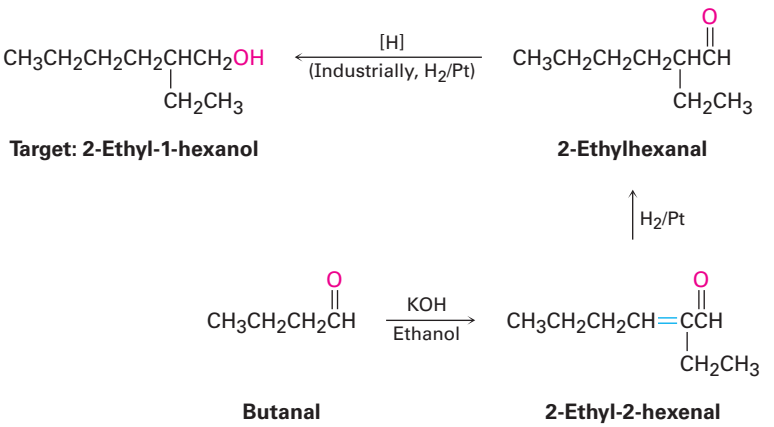
23.4 Using Aldol Reactions in Synthesis

The aldol reaction yields either a β-hydroxy aldehyde/ketone or an α,β-unsaturated aldehyde/ketone, depending on the experimental conditions. By learning how to think backward, it's possible to predict when the aldol reaction might be useful in synthesis. Whenever the target molecule contains either a β-hydroxy aldehyde/ketone or a conjugated enone functional group, it might come from an aldol reaction.



We can extend this kind of reasoning even further by imagining that subsequent transformations might be carried out on the aldol products. For example, a saturated ketone might be prepared by catalytic hydrogenation of the enone product. A good example can be found in the industrial

preparation of 2-ethyl-1-hexanol, an alcohol used in the synthesis of plasticizers for polymers. Although 2-ethyl-1-hexanol bears little resemblance to an aldol product at first glance, it is in fact prepared commercially from butanal by an aldol reaction. Working backward, we can reason that 2-ethyl-1-hexanol might come from 2-ethylhexanal by a reduction. 2-Ethylhexanal, in turn, might be prepared by catalytic reduction of 2-ethyl-2-hexenal, which is the aldol condensation product of butanal. The reactions that follow show the sequence in reverse order.



Problem 23.5

Which of the following compounds are aldol condensation products? What is the aldehyde or ketone precursor of each?

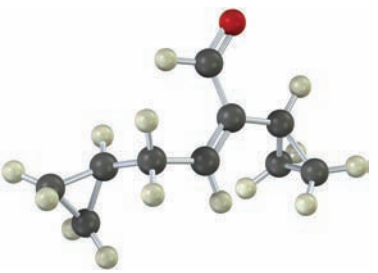
(a) 2-Hydroxy-2-methylpentanal **(b)** 5-Ethyl-4-methyl-4-hepten-3-one

Problem 23.6

1-Butanol is prepared commercially by a route that begins with an aldol reaction. Show the steps that are likely to be involved.

Problem 23.7

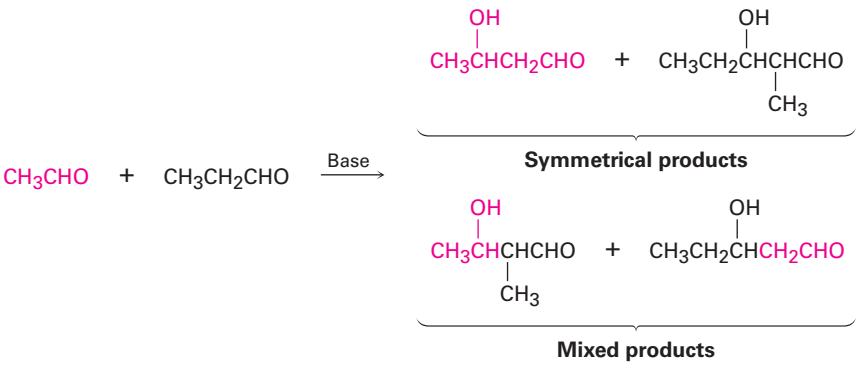
Show how you would synthesize the following compound using an aldol reaction:



23.5 Mixed Aldol Reactions

Until now, we've considered only symmetrical aldol reactions, in which the two carbonyl components have been the same. What would happen, though, if an aldol reaction were carried out between two different carbonyl partners?

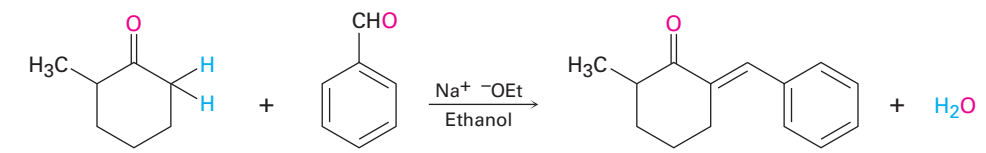
In general, a mixed aldol reaction between two similar aldehyde or ketone partners leads to a mixture of four possible products. For example, base treatment of a mixture of acetaldehyde and propanal gives a complex product mixture containing two "symmetrical" aldol products and two "mixed" aldol products. Clearly, such a reaction is of no practical value.



On the other hand, mixed aldol reactions can lead cleanly to a single product if either of two conditions is met:

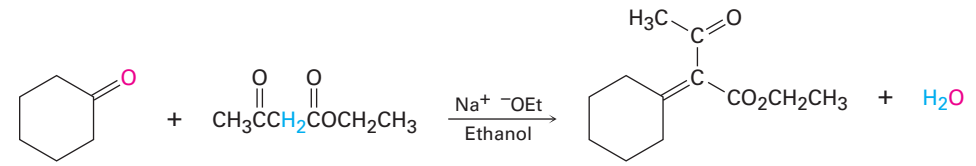
- If one of the carbonyl partners contains no α hydrogens, and thus can't form an enolate ion to become a donor, but does contain an unhindered carbonyl group and so is a good acceptor of nucleophiles, then a mixed aldol reaction is likely to be successful. This is the case, for instance, when either benzaldehyde or formaldehyde is used as one of the carbonyl partners.

  Neither benzaldehyde nor formaldehyde can form an enolate ion to add to another partner, yet both compounds have an unhindered carbonyl group. The ketone 2-methylcyclohexanone, for instance, gives the mixed aldol product on reaction with benzaldehyde.



2-Methylcyclohexanone (donor) **Benzaldehyde (acceptor)** **78%**

- If one of the carbonyl partners is much more acidic than the other and so is transformed into its enolate ion in preference to the other, then a mixed aldol reaction is likely to be successful. Ethyl acetoacetate, for instance, is completely converted into its enolate ion in preference to enolate ion formation from monocarbonyl partners. Thus, aldol condensations of monoketones with ethyl acetoacetate occur preferentially to give the mixed product.



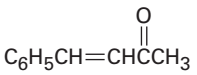
Cyclohexanone (acceptor) **Ethyl acetoacetate (donor)** **80%**

The situation can be summarized by saying that a mixed aldol reaction leads to a mixture of products unless one of the partners either has no α hydrogens but is a good electrophilic acceptor (such as benzaldehyde) or is an unusually acidic nucleophilic donor (such as ethyl acetoacetate).

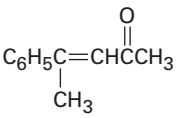
Problem 23.8

Which of the following compounds can probably be prepared by a mixed aldol reaction? Show the reactants you would use in each case.

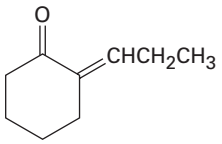
(a)



(b)



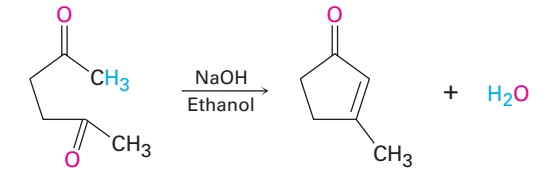
(c)



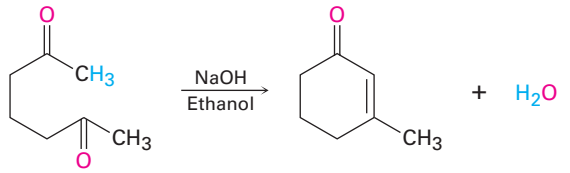
23.6 Intramolecular Aldol Reactions

The aldol reactions we've seen thus far have all been intermolecular, meaning that they have taken place between two different molecules. When certain *di*carbonyl compounds are treated with base, however, an intramolecular aldol reaction can occur, leading to the formation of a cyclic product. For example, base treatment of a 1,4-diketone such as 2,5-hexanedione yields a

cyclopentenone product, and base treatment of a 1,5-diketone such as 2,6-heptanedione yields a cyclohexenone.



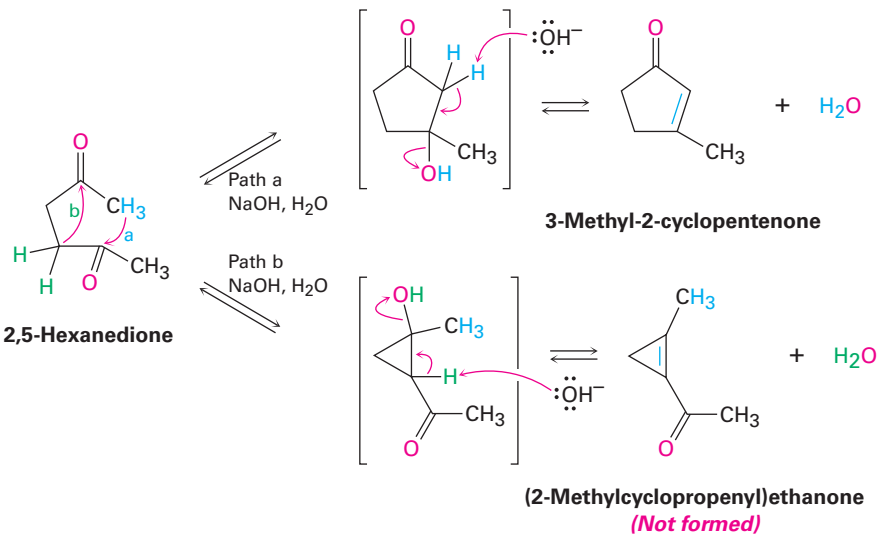
2,5-Hexanedione (a 1,4-diketone) **3-Methyl-2-cyclopentenone**



2,6-Heptanedione (a 1,5-diketone) **3-Methyl-2-cyclohexenone**

The mechanism of intramolecular aldol reactions is similar to that of intermolecular reactions. The only difference is that both the nucleophilic carbonyl anion donor and the electrophilic carbonyl acceptor are now in the same molecule. One complication, however, is that intramolecular aldol reactions might lead to a mixture of products, depending on which enolate ion is formed. For example, 2,5-hexanedione might yield either the five-membered-ring product 3-methyl-2-cyclopentenone or the three-membered-ring product (2-methylcyclopropenyl)ethanone **(Figure 23.3)**. In practice, though, only the cyclopentenone is formed.

Figure 23.3 Intramolecular aldol reaction of 2,5-hexanedione yields 3-methyl-2-cyclopentenone rather than the alternative cyclopropene.



2,5-Hexanedione

3-Methyl-2-cyclopentenone

(2-Methylcyclopropenyl)ethanone
(Not formed)

The selectivity observed in the intramolecular aldol reaction of 2,5-hexanedione is due to the fact that all steps in the mechanism are reversible, so an

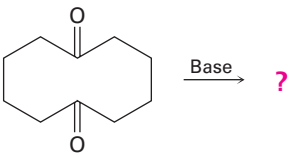
equilibrium is reached. Thus, the relatively strain-free cyclopentenone product is considerably more stable than the highly strained cyclopropene alternative. For similar reasons, intramolecular aldol reactions of 1,5-diketones lead only to cyclohexenone products rather than to acylcyclobutenes.

Problem 23.9

Treatment of a 1,3-diketone such as 2,4-pentanedione with base does not give an aldol condensation product. Explain.

Problem 23.10

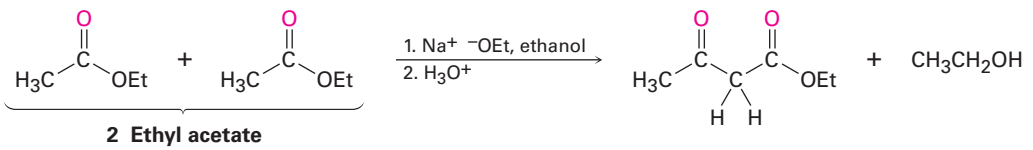
What product would you expect to obtain from base treatment of 1,6-cyclodecanedione?



1,6-Cyclodecanedione

23.7 The Claisen Condensation Reaction

Esters, like aldehydes and ketones, are weakly acidic. When an ester with an α hydrogen is treated with 1 equivalent of a base such as sodium ethoxide, a reversible carbonyl condensation reaction occurs to yield a β-keto ester. For instance, ethyl acetate yields ethyl acetoacetate on base treatment. This reaction between two ester molecules is known as the **Claisen condensation reaction**. (We'll use ethyl esters, abbreviated "Et," for consistency, but other esters will also work.)



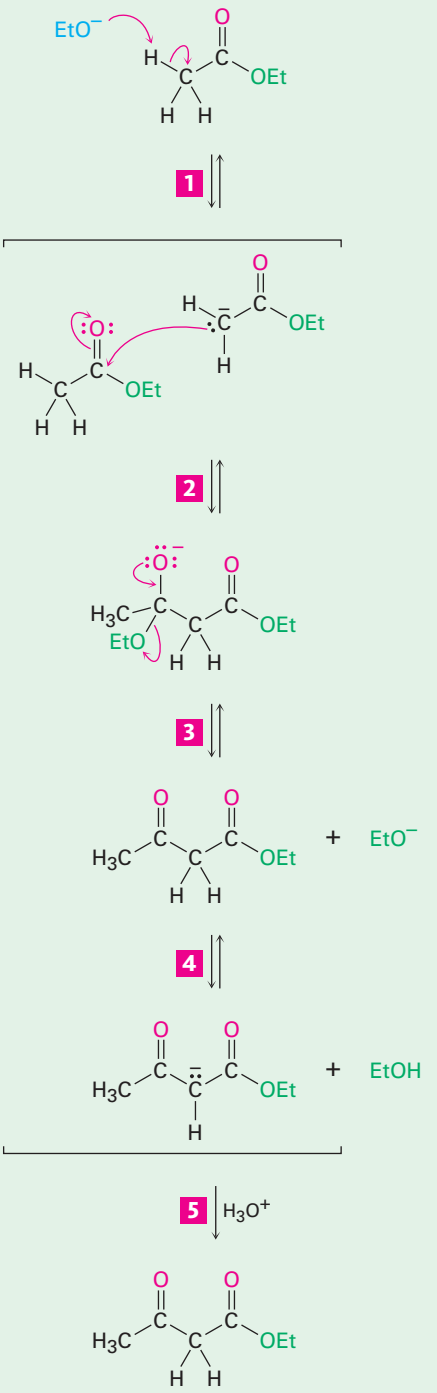
2 Ethyl acetate

Ethyl acetoacetate, a β-keto ester (75%)

The mechanism of the Claisen condensation is similar to that of the aldol condensation and involves the nucleophilic addition of an ester enolate ion to the carbonyl group of a second ester molecule **(Figure 23.4)**. The only difference between the aldol condensation of an aldehyde or ketone and the Claisen condensation of an ester involves the fate of the initially formed tetrahedral intermediate. The tetrahedral intermediate in the aldol reaction is protonated to give an alcohol product—exactly the behavior previously seen for aldehydes and ketones **(Section 19.4)**. The tetrahedral intermediate in the Claisen reaction, however, expels an alkoxide leaving group to yield an acyl substitution product—exactly the behavior previously seen for esters **(Section 21.6)**.

Figure 23.4 | MECHANISM

Mechanism of the Claisen condensation reaction.



1 Base abstracts an acidic alpha hydrogen atom from an ester molecule, yielding an ester enolate ion.

2 The enolate ion adds in a nucleophilic addition reaction to a second ester molecule, giving a tetrahedral alkoxide intermediate.

3 The tetrahedral intermediate expels ethoxide ion to yield a new carbonyl compound, ethyl acetoacetate.

4 But ethoxide ion is a strong enough base to deprotonate ethyl acetoacetate, shifting the equilibrium and driving the overall reaction to completion.

5 Protonation of the enolate ion by addition of aqueous acid in a separate step yields the final β-keto ester product.

If the starting ester has more than one acidic α hydrogen, the product β-keto ester has a highly acidic, doubly activated hydrogen atom that can be abstracted by base. This deprotonation of the product requires that a full equivalent of base rather than a catalytic amount be used in the reaction. Furthermore, the deprotonation serves to drive the equilibrium completely to the product side so that high yields are usually obtained in Claisen condensations.

Predicting the Product of a Claisen Condensation Reaction

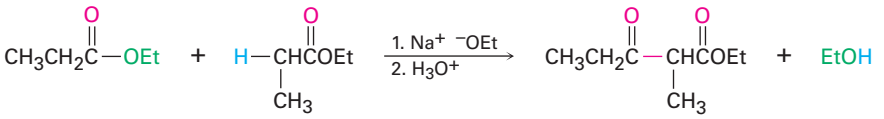
Worked Example 23.3

What product would you obtain from Claisen condensation of ethyl propanoate?

Strategy

The Claisen condensation of an ester results in loss of one molecule of alcohol and formation of a product in which an acyl group of one reactant bonds to the α carbon of the second reactant. The product is a β-keto ester.

Solution



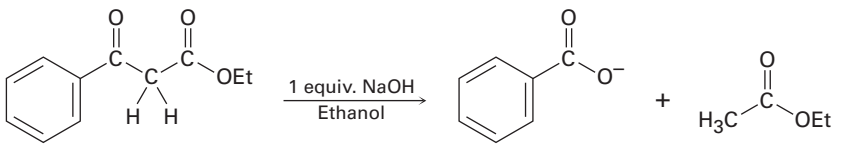
2 Ethyl propanoate **Ethyl 2-methyl-3-oxopentanoate**

Problem 23.11

Show the products you would expect to obtain by Claisen condensation of the following esters:
(a) $(CH_3)_2CHCH_2CO_2Et$ **(b)** Ethyl phenylacetate **(c)** Ethyl cyclohexylacetate

Problem 23.12

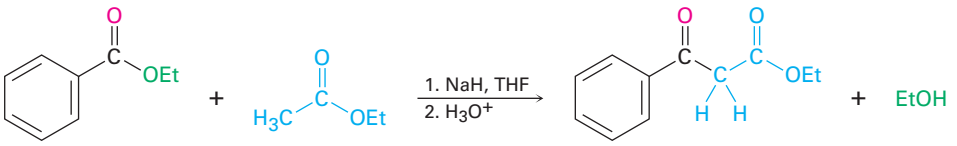
As shown in Figure 23.4, the Claisen reaction is reversible. That is, a β-keto ester can be cleaved by base into two fragments. Using curved arrows to indicate electron flow, show the mechanism by which this cleavage occurs.



23.8 Mixed Claisen Condensations

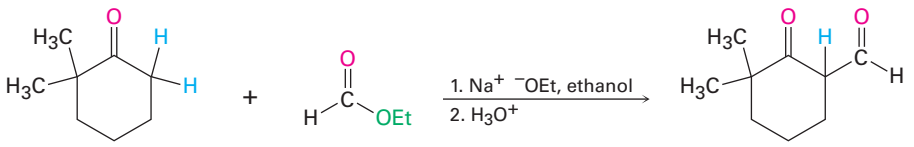
The mixed Claisen condensation of two different esters is similar to the mixed aldol condensation of two different aldehydes or ketones **(Section 23.5)**. Mixed Claisen reactions are successful only when one of the two ester components has no α hydrogens and thus can't form an enolate ion. For example, ethyl benzoate and ethyl formate can't form enolate ions and thus can't serve

as donors. They can, however, act as the electrophilic acceptor components in reactions with other ester anions to give mixed β-keto ester products.



Ethyl benzoate (acceptor) **Ethyl acetate (donor)** **Ethyl benzoylacetate**

Mixed Claisen-like reactions can also be carried out between an ester and a ketone, resulting in the synthesis of a β-diketone. The reaction works best when the ester component has no α hydrogens and thus can't act as the nucleophilic donor. For example, ethyl formate gives high yields in mixed Claisen condensations with ketones.



2,2-Dimethylcyclohexanone (donor) **Ethyl formate (acceptor)** **A β-keto aldehyde (91%)**

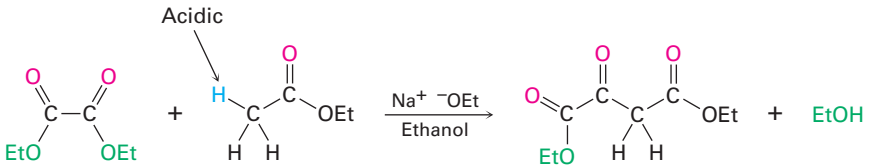
Worked Example 23.4 Predicting the Product of a Mixed Claisen Condensation Reaction

Diethyl oxalate, $(CO_2Et)_2$, often gives high yields in mixed Claisen reactions. What product would you expect to obtain from a mixed Claisen reaction of ethyl acetate with diethyl oxalate?

Strategy

A mixed Claisen reaction is effective when only one of the two partners has an acidic α hydrogen atom. In the present case, ethyl acetate can be converted into its enolate ion, but diethyl oxalate cannot. Thus, ethyl acetate acts as the donor and diethyl oxalate as the acceptor.

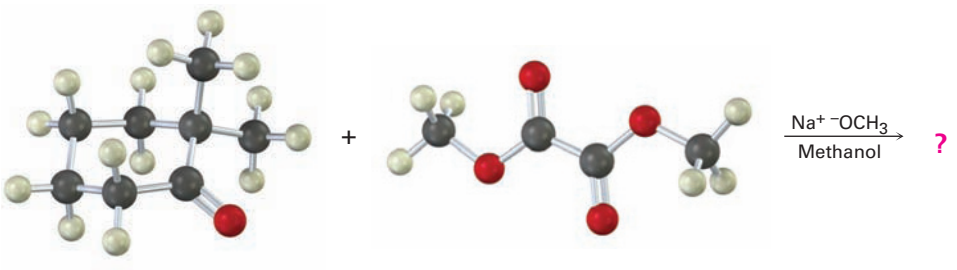
Solution



Diethyl oxalate **Ethyl acetate**

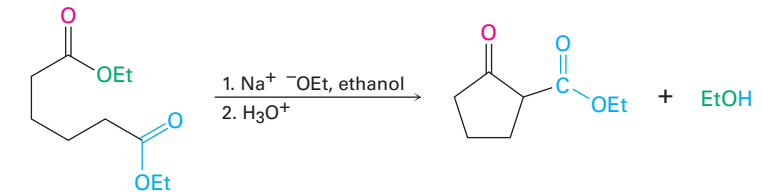
Problem 23.13

What product would you expect from the following mixed Claisen-like reaction?



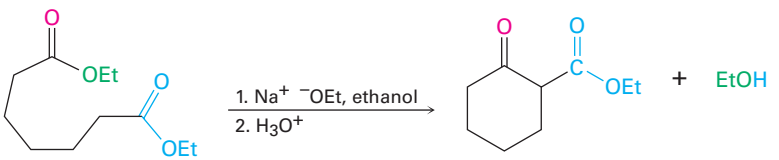
23.9 Intramolecular Claisen Condensations: The Dieckmann Cyclization

Intramolecular Claisen condensations can be carried out with diesters, just as intramolecular aldol condensations can be carried out with diketones **(Section 23.6)**. Called the **Dieckmann cyclization**, the reaction works best on 1,6-diesters and 1,7-diesters. Intramolecular Claisen cyclization of a 1,6-diester gives a five-membered cyclic β-keto ester, and cyclization of a 1,7-diester gives a six-membered cyclic β-keto ester.



Diethyl hexanedioate (a 1,6-diester)

Ethyl 2-oxocyclopentanecarboxylate (82%)



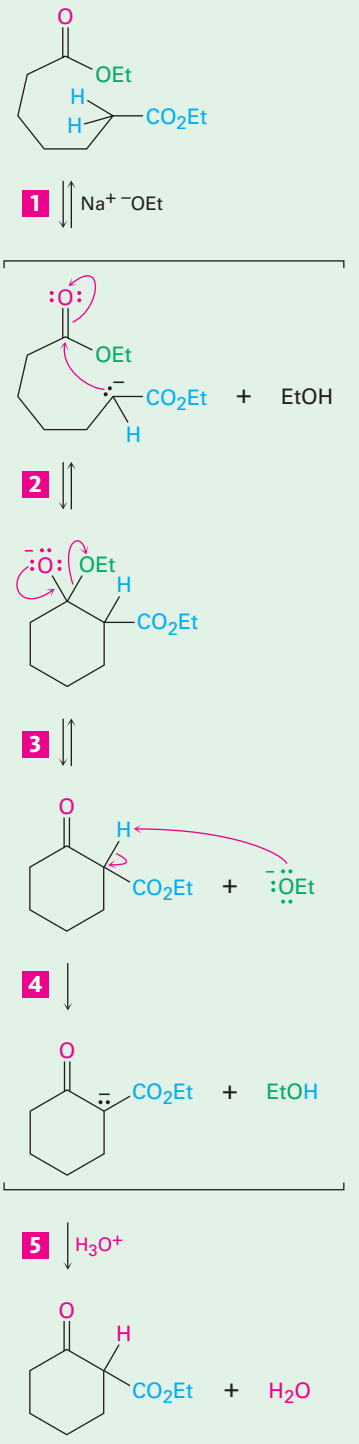
Diethyl heptanedioate (a 1,7-diester)

Ethyl 2-oxocyclohexanecarboxylate

The mechanism of the Dieckmann cyclization, shown in **Figure 23.5**, is the same as that of the Claisen condensation. One of the two ester groups is converted into an enolate ion, which then carries out a nucleophilic acyl substitution on the second ester group at the other end of the molecule. A cyclic β-keto ester product results.

Figure 23.5 | MECHANISM

Mechanism of the Dieckmann cyclization of a 1,7-diester to yield a cyclic β-keto ester product.



1 Base abstracts an acidic α proton from the carbon atom next to one of the ester groups, yielding an enolate ion.

2 Intramolecular nucleophilic addition of the ester enolate ion to the carbonyl group of the second ester at the other end of the chain then gives a cyclic tetrahedral intermediate.

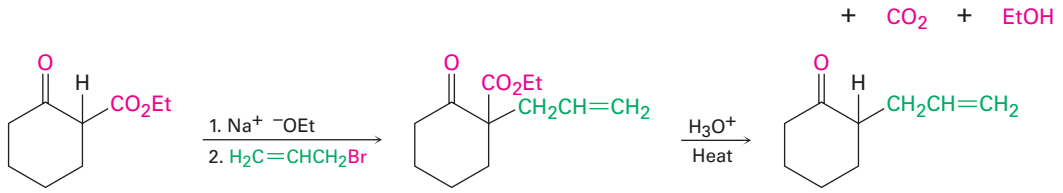
3 Loss of alkoxide ion from the tetrahedral intermediate forms a cyclic β-keto ester.

4 Deprotonation of the acidic β-keto ester gives an enolate ion . . .

5 . . . which is protonated by addition of aqueous acid at the end of the reaction to generate the neutral β-keto ester product.

The cyclic β-keto ester produced in a Dieckmann cyclization can be further alkylated and decarboxylated by a series of reactions analogous to those used in the acetoacetic ester synthesis **(Section 22.7)**. Alkylation and subsequent

decarboxylation of ethyl 2-oxocyclohexanecarboxylate, for instance, yields a 2-alkylcyclohexanone. The overall sequence of (1) Dieckmann cyclization, (2) β-keto ester alkylation, and (3) decarboxylation is a powerful method for preparing 2-substituted cyclopentanones and cyclohexanones.

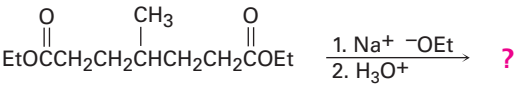


Ethyl 2-oxocyclohexanecarboxylate

2-Allylcyclohexanone (83%)

Problem 23.14

What product would you expect from the following reaction?

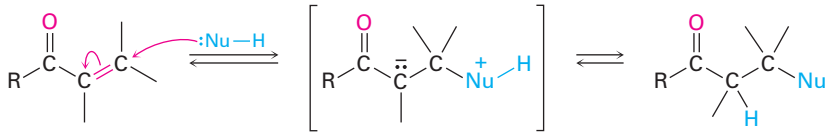


Problem 23.15

Dieckmann cyclization of diethyl 3-methylheptanedioate gives a mixture of two β-keto ester products. What are their structures, and why is a mixture formed?

23.10 Conjugate Carbonyl Additions: The Michael Reaction

We saw in **Section 19.13** that certain nucleophiles, such as amines, react with α,β-unsaturated aldehydes and ketones to give the conjugate addition product, rather than the direct addition product.

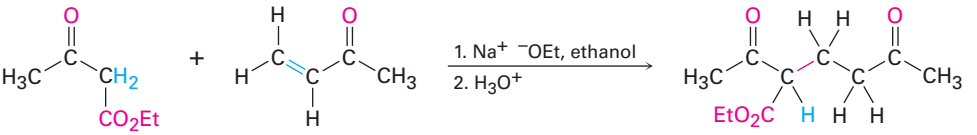


Conjugate addition product

Exactly the same kind of conjugate addition can occur when a nucleophilic enolate ion reacts with an α,β-unsaturated carbonyl compound—a process known as the **Michael reaction**.

The best Michael reactions are those that take place when a particularly stable enolate ion such as that derived from a β-keto ester or other 1,3-dicarbonyl

compound adds to an unhindered α,β-unsaturated ketone. For example, ethyl acetoacetate reacts with 3-buten-2-one in the presence of sodium ethoxide to yield the conjugate addition product.



Ethyl acetoacetate **3-Buten-2-one**

Michael reactions take place by addition of a nucleophilic enolate ion donor to the β carbon of an α,β-unsaturated carbonyl acceptor, according to the mechanism shown in **Figure 23.6**.

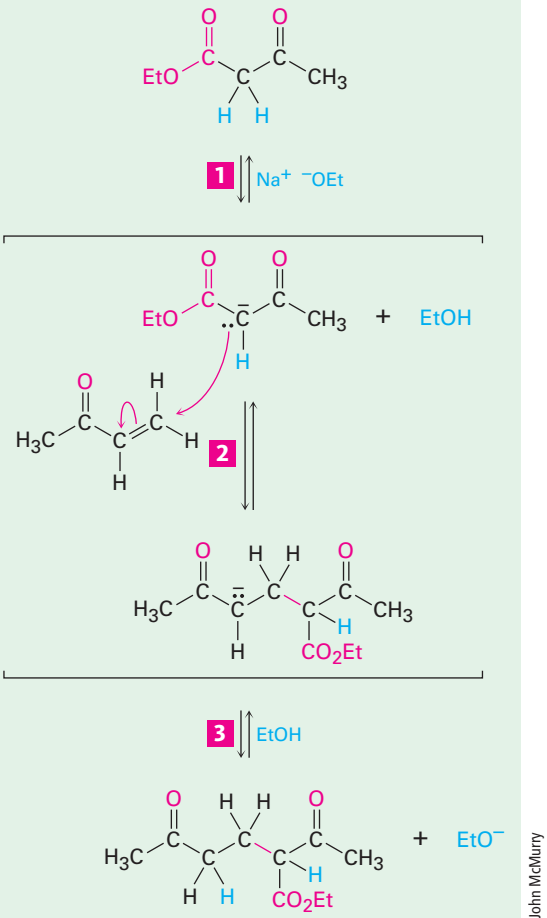
Figure 23.6 | MECHANISM

Mechanism of the Michael reaction between a β-keto ester and an α,β-unsaturated ketone. The reaction is a conjugate addition of an enolate ion to the unsaturated carbonyl compound.

1 The base catalyst removes an acidic alpha proton from the starting β-keto ester to generate a stabilized enolate ion nucleophile.

2 The nucleophile adds to the α,β-unsaturated ketone electrophile in a Michael reaction to generate a new enolate as product.

3 The enolate product abstracts an acidic proton, either from solvent or from starting keto ester, to yield the final addition product.



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The Michael reaction occurs with a variety of α,β-unsaturated carbonyl compounds, not just conjugated ketones. Unsaturated aldehydes, esters, thioesters, nitriles, amides, and nitro compounds can all act as the electrophilic acceptor

component in Michael reactions (Table 23.1). Similarly, a variety of different donors can be used, including β-diketones, β-keto esters, malonic esters, β-keto nitriles, and nitro compounds.

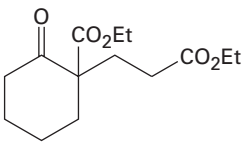
Table 23.1 Some Michael Acceptors and Michael Donors

Michael acceptors		Michael donors	
$H_2C{=}CHCH{=}O$	Propenal	$RCCH_2CR'$ (O, O)	β-Diketone
$H_2C{=}CHCCH_3$ (O)	3-Buten-2-one	$RCCH_2COEt$ (O, O)	β-Keto ester
$H_2C{=}CHCOEt$ (O)	Ethyl propenoate	$EtOCCH_2COEt$ (O, O)	Diethyl malonate
$H_2C{=}CHCNH_2$ (O)	Propenamide	$RCCH_2C{\equiv}N$ (O)	β-Keto nitrile
$H_2C{=}CHC{\equiv}N$	Propenenitrile	RCH_2NO_2	Nitro compound
$H_2C{=}CH(NO_2)$	Nitroethylene		

Using the Michael Reaction

Worked Example 23.5

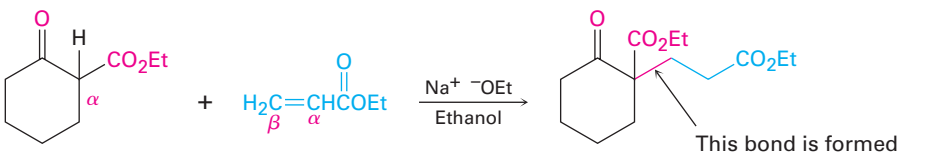
How might you obtain the following compound using a Michael reaction?



Strategy

A Michael reaction involves the conjugate addition of a stable enolate ion donor to an α,β-unsaturated carbonyl acceptor, yielding a 1,5-dicarbonyl product. Usually, the stable enolate ion is derived from a β-diketone, β-keto ester, malonic ester, or similar compound. The C–C bond made in the conjugate addition step is the one between the α carbon of the acidic donor and the β carbon of the unsaturated acceptor.

Solution



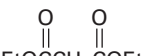
Problem 23.16

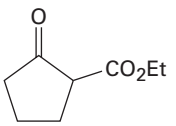
What product would you obtain from a base-catalyzed Michael reaction of 2,4-pentanedione with each of the following α,β-unsaturated acceptors?

(a) 2-Cyclohexenone **(b)** Propenenitrile **(c)** Ethyl 2-butenoate

Problem 23.17

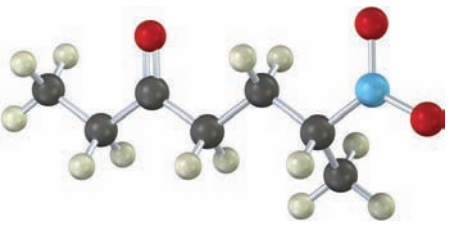
What product would you obtain from a base-catalyzed Michael reaction of 3-buten-2-one with each of the following nucleophilic donors?

(a) 

(b) 

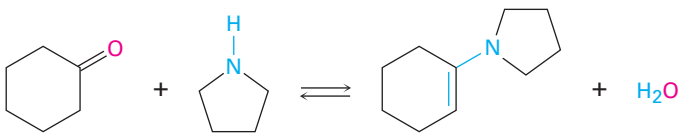
Problem 23.18

How would you prepare the following compound using a Michael reaction?



23.11 Carbonyl Condensations with Enamines: The Stork Reaction

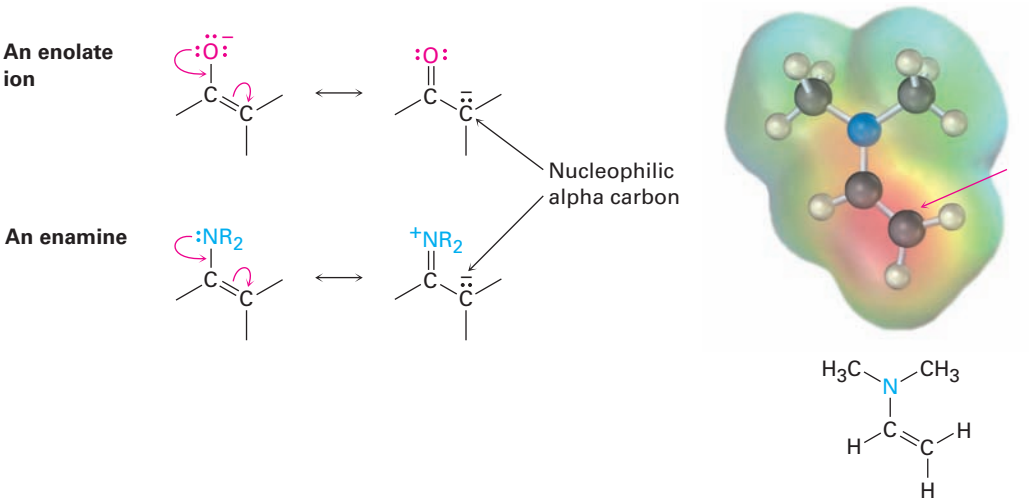
In addition to enolate ions, other kinds of carbon nucleophiles also add to α,β-unsaturated acceptors in Michael-like reactions. Among the most important and useful of such nucleophiles, particularly in biological chemistry, are *enamines*, which are readily prepared by reaction between a ketone and a secondary amine **(Section 19.8)**. For example:



Cyclohexanone **Pyrrolidine** **1-Pyrrolidino-cyclohexene (87%)**

As the following resonance structures indicate, enamines are electronically similar to enolate ions. Overlap of the nitrogen lone-pair orbital with the double-bond *p* orbitals leads to an increase in electron density on the α carbon atom, making that carbon nucleophilic. An electrostatic potential

map of *N,N*-dimethylaminoethylene shows this shift of electron density (red) toward the α position.



Enamines behave in much the same way as enolate ions and enter into many of the same kinds of reactions. In the **Stork reaction**, for example, an enamine adds to an α,β-unsaturated carbonyl acceptor in a Michael-like process. The initial product is then hydrolyzed by aqueous acid to yield a 1,5-dicarbonyl compound. The overall reaction is thus a three-step sequence of (1) enamine formation from a ketone, (2) Michael addition to an α,β-unsaturated carbonyl compound, and (3) enamine hydrolysis back to a ketone.

The net effect of the Stork reaction is the Michael addition of a ketone to an α,β-unsaturated carbonyl compound. For example, cyclohexanone reacts with the cyclic amine pyrrolidine to yield an enamine; further reaction with an enone such as 3-buten-2-one yields a Michael adduct; and aqueous hydrolysis completes the sequence to give a 1,5-diketone **(Figure 23.7)**.

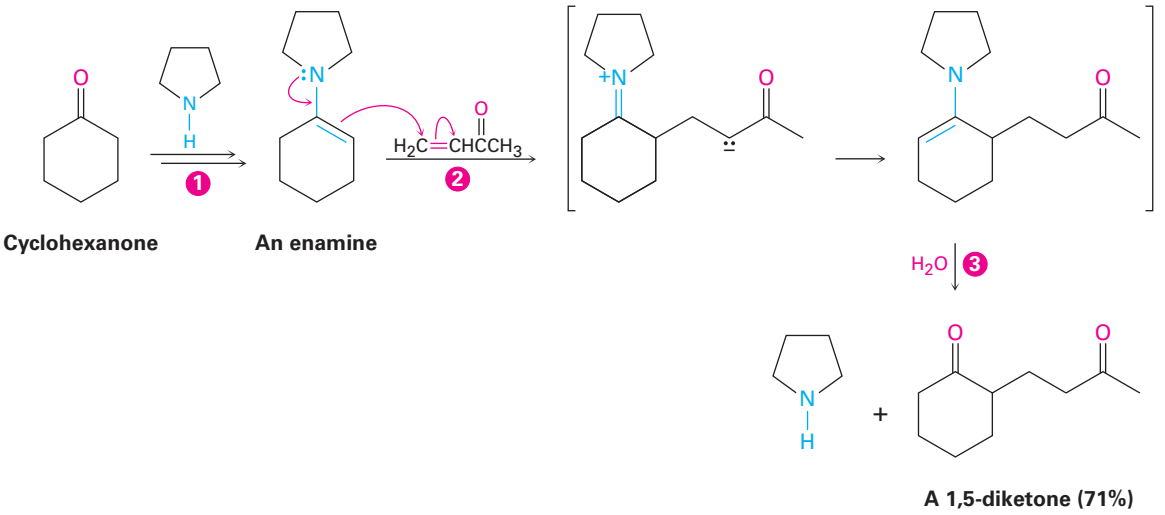
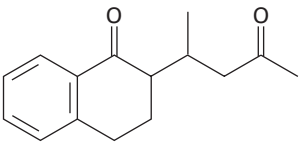


Figure 23.7 The Stork reaction between cyclohexanone and 3-buten-2-one. (1) Cyclohexanone is first converted into an enamine, (2) the enamine adds to the α,β-unsaturated ketone in a Michael reaction, and (3) the conjugate addition product is hydrolyzed to yield a 1,5-diketone.

The enamine–Michael reaction has two advantages over the enolate-ion–Michael reaction that makes it particularly useful in biological pathways. First, an enamine is neutral, easily prepared, and easily handled, while an enolate ion is charged, sometimes difficult to prepare, and must be handled with care. Second, an enamine from a *mono*ketone can be used in the Michael addition, whereas enolate ions only from β-dicarbonyl compounds can be used.

Worked Example 23.6 Using the Stork Enamine Reaction

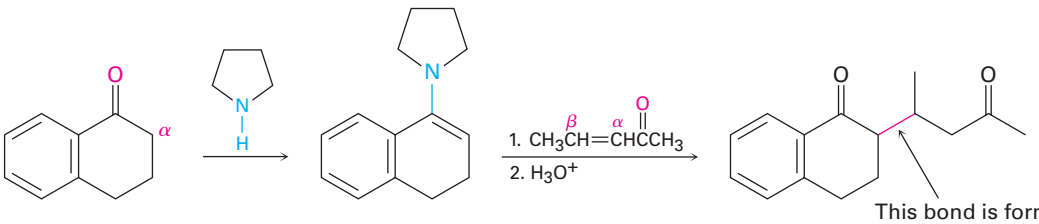
How might you use an enamine reaction to prepare the following compound?



Strategy

The overall result of an enamine reaction is the Michael addition of a ketone as donor to an α,β-unsaturated carbonyl compound as acceptor, yielding a 1,5-dicarbonyl product. The C–C bond made in the Michael addition step is the one between the α carbon of the ketone donor and the β carbon of the unsaturated acceptor.

Solution



Problem 23.19

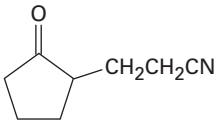
What products would result after hydrolysis from reaction of the enamine prepared from cyclopentanone and pyrrolidine with the following α,β-unsaturated acceptors?

(a) $H_2C{=}CHCO_2Et$ **(b)** $H_2C{=}CHCHO$ **(c)** $CH_3CH{=}CHCOCH_3$

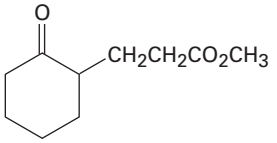
Problem 23.20

Show how you might use an enamine reaction to prepare each of the following compounds:

(a)



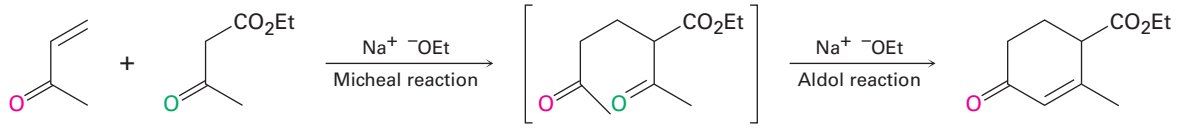
(b)



23.12 The Robinson Annulation Reaction

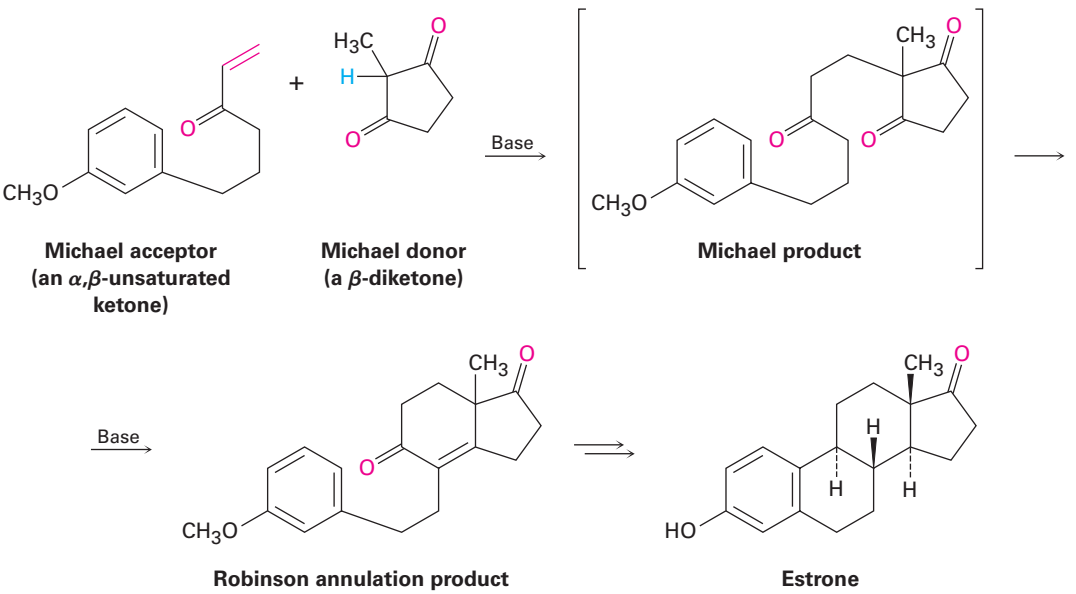
Carbonyl condensation reactions are perhaps the most versatile methods available for synthesizing complex molecules. By putting a few fundamental reactions together in the proper sequence, some remarkably useful transformations can be carried out. One such example is the **Robinson annulation reaction** for the synthesis of polycyclic molecules. The word *annulation* comes from the Latin *annulus,* meaning "ring," so an annulation reaction builds a new ring onto a molecule.

The Robinson annulation is a two-step process that combines a Michael reaction with an intramolecular aldol reaction. It takes place between a nucleophilic donor, such as a β-keto ester, an enamine, or a β-diketone, and an α,β-unsaturated ketone acceptor, such as 3-buten-2-one. The product is a substituted 2-cyclohexenone.



3-Buten-2-one + **Ethyl acetoacetate** → **Michael product** → **Annulation product**

The first step of the Robinson annulation is simply a Michael reaction. An enamine or an enolate ion from a β-keto ester or β-diketone effects a conjugate addition to an α,β-unsaturated ketone, yielding a 1,5-diketone. But as we saw in **Section 23.6**, 1,5-diketones undergo intramolecular aldol condensation to yield cyclohexenones when treated with base. Thus, the final product contains a six-membered ring, and an annulation has been accomplished. An example occurs during a synthesis of the steroid hormone estrone **(Figure 23.8)**.



Michael acceptor (an α,β-unsaturated ketone) + **Michael donor (a β-diketone)** → **Michael product**

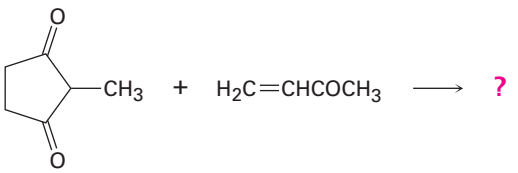
Robinson annulation product ⇌ **Estrone**

Figure 23.8 Synthesis of the steroid hormone estrone using a Robinson annulation reaction. The nucleophilic donor is a β-diketone.

In this example, the β-diketone 2-methyl-1,3-cyclopentanedione is used to generate the enolate ion required for Michael reaction and an aryl-substituted α,β-unsaturated ketone is used as the acceptor. Base-catalyzed Michael reaction between the two partners yields an intermediate triketone, which then cyclizes in an intramolecular aldol condensation to give a Robinson annulation product. Several further transformations are required to complete the synthesis of estrone.

Problem 23.21

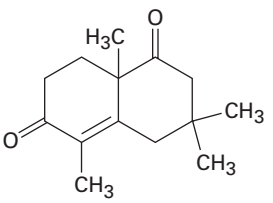
What product would you expect from a Robinson annulation reaction of 2-methyl-1,3-cyclopentanedione with 3-buten-2-one?



2-Methyl-1,3-cyclopentanedione **3-Buten-2-one**

Problem 23.22

How would you prepare the following compound using a Robinson annulation reaction between a β-diketone and an α,β-unsaturated ketone? Draw the structures of both reactants and the intermediate Michael addition product.



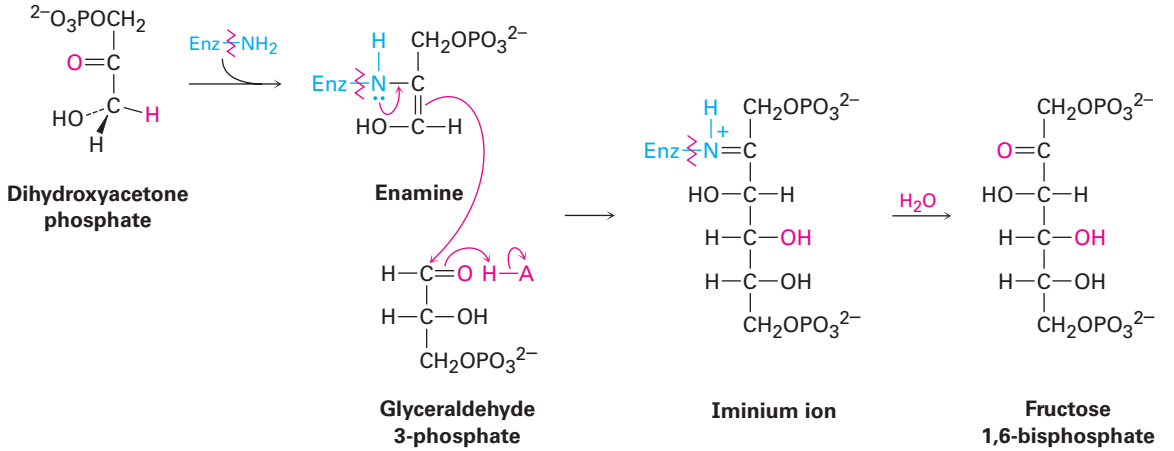
23.13 Some Biological Carbonyl Condensation Reactions

Biological Aldol Reactions

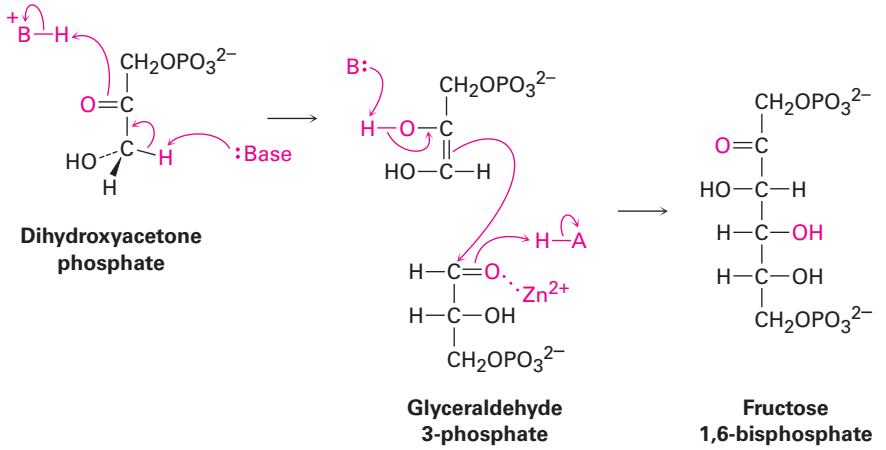
Aldol reactions occur in many biological pathways but are particularly common in carbohydrate metabolism where enzymes called *aldolases* catalyze the addition of a ketone enolate ion to an aldehyde. Aldolases occur in all organisms and are of two types. Type I aldolases occur primarily in animals and higher plants; type II aldolases occur primarily in fungi and bacteria. Both types catalyze the same kind of reaction, but type I aldolases operate through an enamine while type II aldolases require a metal ion (usually Zn^{2+}) as Lewis acid and operate through an enolate ion.

An example of an aldolase-catalyzed reaction occurs in glucose biosynthesis when dihydroxyacetone phosphate reacts with glyceraldehyde 3-phosphate to give fructose 1,6-bisphosphate. In animals and higher plants, dihydroxyacetone phosphate is first converted into an enamine by reaction with the $-NH_2$ group on a lysine amino acid in the enzyme. The enamine then adds to glyceraldehyde 3-phosphate, and the iminium ion that results is hydrolyzed. In bacteria and fungi, the aldol reaction occurs directly, with the ketone carbonyl group of glyceraldehyde 3-phosphate complexed to a Zn^{2+} ion to make it a better acceptor.

Type I aldolase



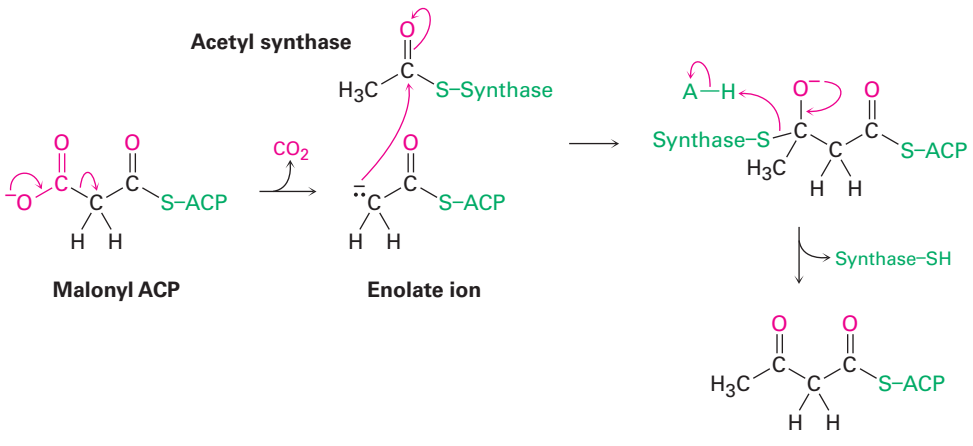
Type II aldolase



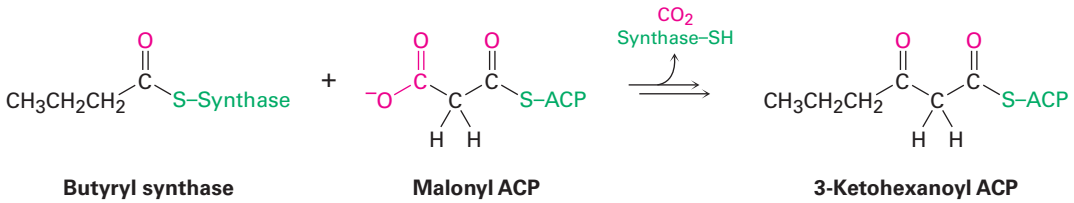
Note that the aldolase-catalyzed reactions are mixed aldol reactions, which take place between two different partners, as opposed to the symmetrical aldol reactions between identical partners usually carried out in the laboratory. Mixed aldol reactions between different partners often give mixtures of products in the laboratory but are successful in living systems because of the selectivity of the enzyme catalysts.

Biological Claisen Condensations

Claisen condensations, like aldol reactions, also occur in a large number of biological pathways. In fatty-acid biosynthesis, for instance, an enolate ion generated by decarboxylation **(Section 22.7)** of malonyl ACP adds to the carbonyl group of another acyl group bonded through a thioester linkage to a synthase enzyme. The tetrahedral intermediate that results then expels the synthase, giving acetoacetyl ACP. (The abbreviation ACP stands for acyl carrier protein, which forms thioester bonds to acyl groups.)



Mixed Claisen condensations also occur frequently in living organisms, particularly in the pathway for fatty-acid biosynthesis that we'll discuss in **Section 29.4**. Butyryl synthase, for instance, reacts with malonyl ACP in a mixed Claisen condensation to give 3-ketohexanoyl ACP.



A Prologue to Metabolism | A DEEPER LOOK

Biochemistry *is* carbonyl chemistry. Almost all metabolic pathways used by living organisms involve one or more of the four fundamental carbonyl-group reactions we've seen in Chapters 19 through 23. The digestion and metabolic breakdown of all the major classes of food molecules—fats, carbohydrates, and proteins—take place by nucleophilic addition reactions, nucleophilic acyl substitutions, α substitutions, and carbonyl condensations. Similarly, hormones and other crucial biological molecules are built up from smaller precursors by these same carbonyl-group reactions.

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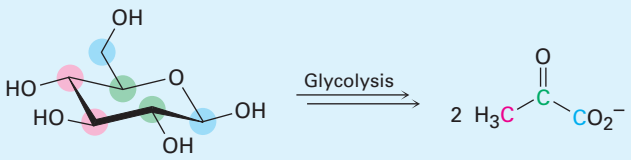
Take *glycolysis*, for example, the metabolic pathway by which organisms convert glucose to pyruvate as the first step in extracting energy from carbohydrates.

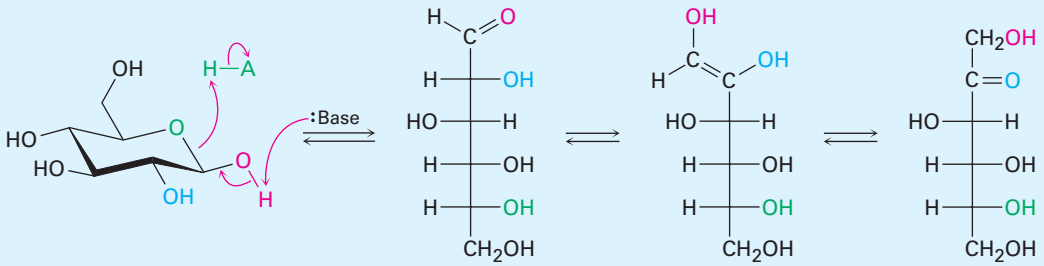


Glucose **Pyruvate**

Erich Lessing/Art Resource, NY

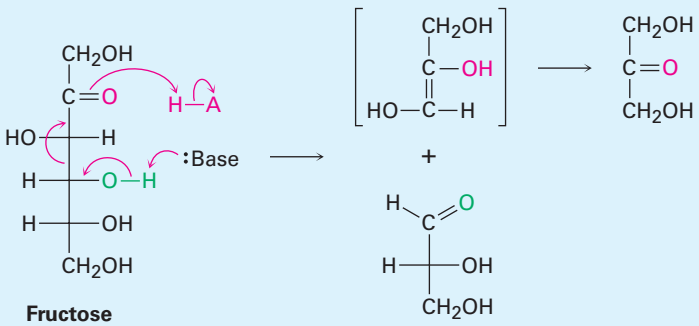
You are what you eat. Food molecules are metabolized by pathways that involve the four major carbonyl-group reactions.

Glycolysis is a ten-step process that begins with isomerization of glucose from its cyclic hemiacetal form to its open-chain aldehyde form—the reverse of a nucleophilic addition reaction. The aldehyde then undergoes tautomerization to yield an enol, which undergoes yet another tautomerization to give the ketone fructose.



Glucose (hemiacetal) **Glucose (aldehyde)** **Glucose (enol)** **Fructose**

Fructose, a β-hydroxy ketone, is then cleaved by a retro-aldol reaction into two three-carbon molecules—one ketone and one aldehyde. Still further carbonyl-group reactions then occur until pyruvate results.



Fructose

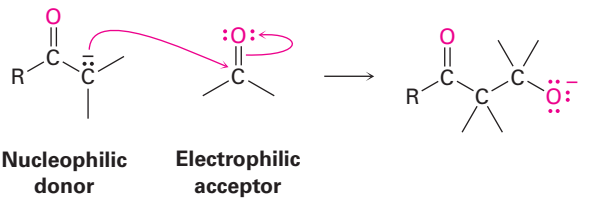
These few examples are only an introduction; we'll look at several of the major metabolic pathways in more detail in Chapter 29. The bottom line is that you haven't seen the end of carbonyl-group chemistry. A solid grasp of carbonyl-group reactions is crucial to an understanding of biochemistry.

Summary

Key words

aldol reaction, 905
carbonyl condensation reaction, 904
Claisen condensation reaction, 915
Dieckmann cyclization, 919
Michael reaction, 921
Robinson annulation reaction, 927
Stork reaction, 925

In this chapter, we've discussed the fourth and last of the common carbonyl-group reactions—the carbonyl condensation. A **carbonyl condensation reaction** takes place between two carbonyl partners and involves both nucleophilic addition and α-substitution processes. One carbonyl partner is converted by base into a nucleophilic enolate ion, which then adds to the electrophilic carbonyl group of the second partner. The first partner thus undergoes an α substitution, while the second undergoes a nucleophilic addition.



The **aldol reaction** is a carbonyl condensation that occurs between two aldehyde or ketone molecules. Aldol reactions are reversible, leading first to β-hydroxy aldehydes/ketones and then to α,β-unsaturated products after dehydration. Mixed aldol condensations between two different aldehydes or ketones generally give a mixture of all four possible products. A mixed reaction can be successful, however, if one of the two partners is an unusually good donor (ethyl acetoacetate, for instance) or if it can act only as an acceptor (formaldehyde and benzaldehyde, for instance). Intramolecular aldol condensations of 1,4- and 1,5-diketones are also successful and provide a good way to make five- and six-membered rings.

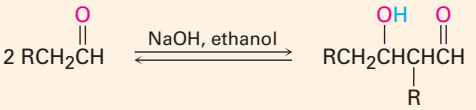
The **Claisen condensation reaction** is a carbonyl condensation that occurs between two ester components and gives a β-keto ester product. Mixed Claisen condensations between two different esters are successful only when one of the two partners has no acidic α hydrogens (ethyl benzoate and ethyl formate, for instance) and thus can function only as the acceptor partner. Intramolecular Claisen condensations, called **Dieckmann cyclization reactions**, yield five- and six-membered cyclic β-keto esters starting from 1,6- and 1,7-diesters.

The conjugate addition of a carbon nucleophile to an α,β-unsaturated acceptor is known as the **Michael reaction**. The best Michael reactions take place between relatively acidic donors (β-keto esters or β-diketones) and unhindered α,β-unsaturated acceptors. Enamines, prepared by reaction of a ketone with a disubstituted amine, are also good Michael donors.

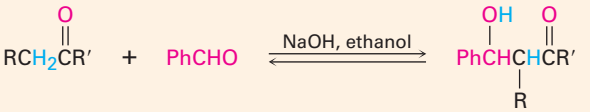
Carbonyl condensation reactions are widely used in synthesis. One example of their versatility is the **Robinson annulation reaction**, which leads to the formation of an substituted cyclohexenone. Treatment of a β-diketone or β-keto ester with an α,β-unsaturated ketone leads first to a Michael addition, which is followed by intramolecular aldol cyclization. Condensation reactions are also used widely in nature for the biosynthesis of such molecules as fats and steroids.

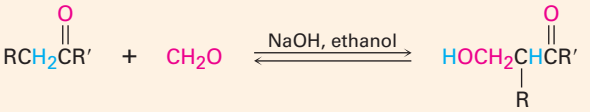
Summary of Reactions

1. Aldol reaction (Section 23.1)

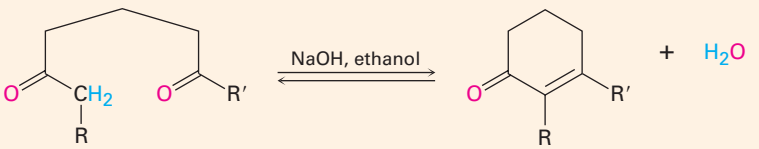


2. Mixed aldol reaction (Section 23.5)

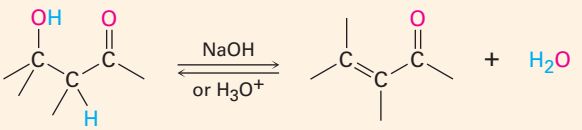




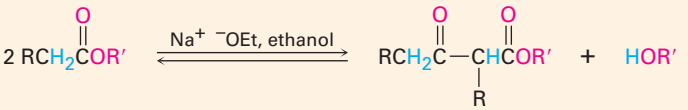
3. Intramolecular aldol reaction (Section 23.6)



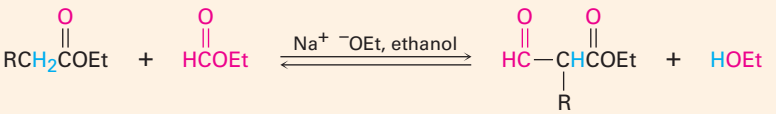
4. Dehydration of aldol products (Section 23.3)



5. Claisen condensation reaction (Section 23.7)



6. Mixed Claisen condensation reaction (Section 23.8)



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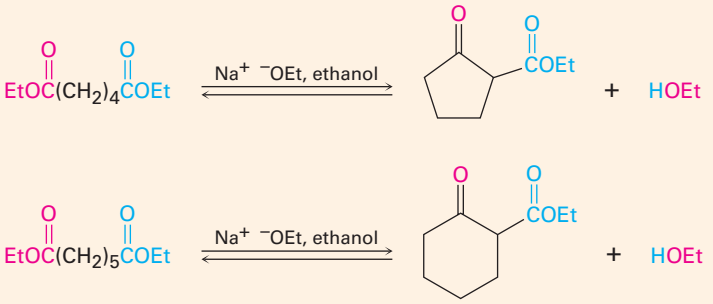
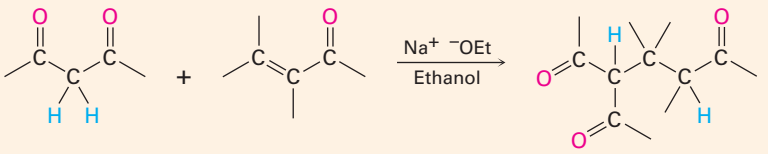
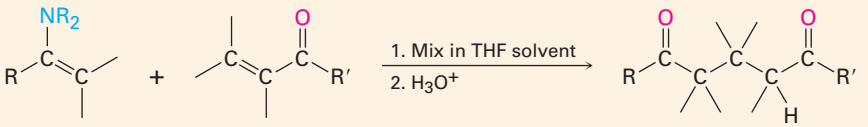
7. Intramolecular Claisen condensation (Dieckmann cyclization; Section 23.9)



8. Michael reaction (Section 23.10)



9. Carbonyl condensations with enamines (Stork reaction; Section 23.11)



Exercises

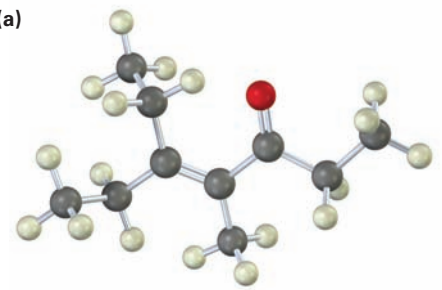
OWL Interactive versions of these problems are assignable in OWL for Organic Chemistry.

Visualizing Chemistry

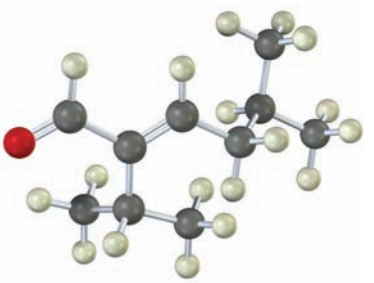
(Problems 23.1–23.22 appear within the chapter.)

23.23 What ketones or aldehydes might the following enones have been prepared from by aldol reaction?

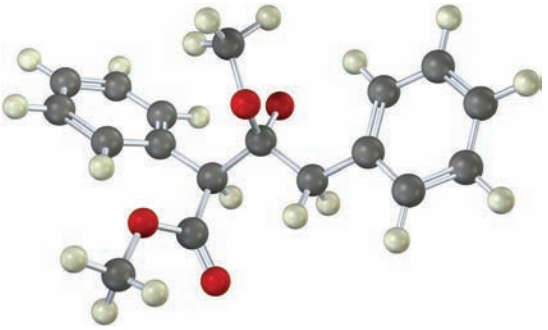
(a)



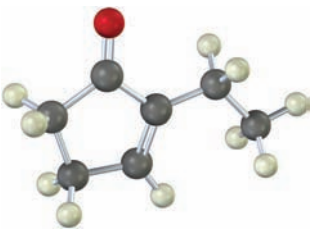
(b)



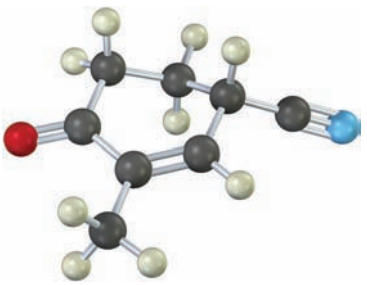
23.24 The following structure represents an intermediate formed by addition of an ester enolate ion to a second ester molecule. Identify the reactant, the leaving group, and the product.



23.25 The following molecule was formed by an intramolecular aldol reaction. What dicarbonyl precursor was used for its preparation?



23.26 The following molecule was formed by a Robinson annulation reaction. What reactants were used?



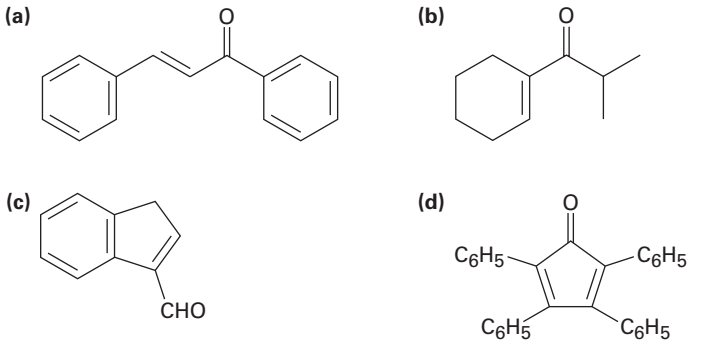
Additional Problems

Aldol Reactions

23.27 Which of the following compounds would you expect to undergo aldol self-condensation? Show the product of each successful reaction.

(a) Trimethylacetaldehyde
(b) Cyclobutanone
(c) Benzophenone (diphenyl ketone)
(d) 3-Pentanone
(e) Decanal
(f) 3-Phenyl-2-propenal

23.28 How might you synthesize each of the following compounds using an aldol reaction? Show the structure of the starting aldehyde(s) or ketone(s) you would use in each case.



23.29 What product would you expect to obtain from aldol cyclization of hexanedial, $OHCCH_2CH_2CH_2CH_2CHO$?

23.30 Intramolecular aldol cyclization of 2,5-heptanedione with aqueous NaOH yields a mixture of two enone products in the approximate ratio 9:1. Write their structures, and show how each is formed.

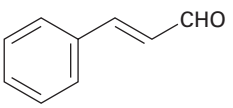
23.31 The major product formed by intramolecular aldol cyclization of 2,5-heptanedione (Problem 23.30) has two singlet absorptions in the ^1H NMR spectrum, at 1.65 δ and 1.90 δ, and has no absorptions in the range 3 to 10 δ. What is its structure?

23.32 Treatment of the minor product formed in the intramolecular aldol cyclization of 2,5-heptanedione (Problems 23.30 and 23.31) with aqueous NaOH converts it into the major product. Propose a mechanism to account for this base-catalyzed isomerization.

23.33 How can you account for the fact that 2,2,6-trimethylcyclohexanone yields no detectable aldol product even though it has an acidic α hydrogen?

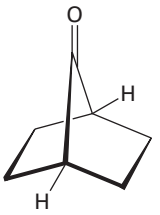
23.34 The aldol reaction is catalyzed by acid as well as by base. What is the reactive nucleophile in the acid-catalyzed aldol reaction? Propose a mechanism.

23.35 Cinnamaldehyde, the aromatic constituent of cinnamon oil, can be synthesized by a mixed aldol condensation. Show the starting materials you would use, and write the reaction.



Cinnamaldehyde

23.36 The bicyclic ketone shown below does not undergo aldol self-condensation even though it has two α hydrogen atoms. Explain.



Claisen Condensations

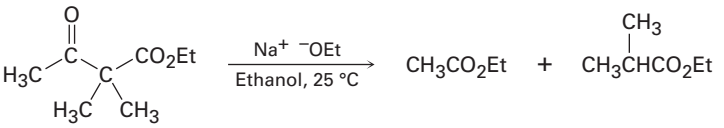
23.37 Give the structures of the possible Claisen condensation products from the following reactions. Tell which, if any, you would expect to predominate in each case.

(a) $CH_3CO_2Et + CH_3CH_2CO_2Et$ **(b)** $C_6H_5CO_2Et + C_6H_5CH_2CO_2Et$

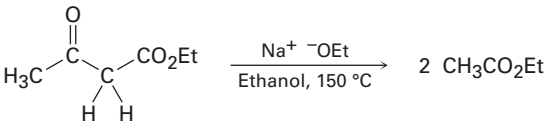
(c) $EtOCO_2Et$ + cyclohexanone **(d)** $C_6H_5CHO + CH_3CO_2Et$

23.38 In the mixed Claisen reaction of cyclopentanone with ethyl formate, a much higher yield of the desired product is obtained by first mixing the two carbonyl components and then adding base rather than by first mixing base with cyclopentanone and then adding ethyl formate. Explain.

23.39 Ethyl dimethylacetoacetate reacts instantly at room temperature when treated with ethoxide ion to yield two products, ethyl acetate and ethyl 2-methylpropanoate. Propose a mechanism for this cleavage reaction.



23.40 In contrast to the rapid reaction shown in Problem 23.39, ethyl acetoacetate requires a temperature over 150 °C to undergo the same kind of cleavage reaction. How can you explain the difference in reactivity?



Michael and Enamine Reactions

23.41 How might the following compounds be prepared using Michael reactions? Show the nucleophilic donor and the electrophilic acceptor in each case.

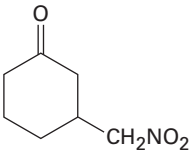
(a) $CH_3CCHCH_2CH_2CC_6H_5$ (with CO_2Et)

(b) $CH_3CCH_2CH_2CH_2CCH_3$

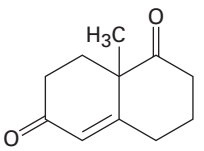
(c) $EtOCCHCH_2CH_2C{\equiv}N$ (with CO_2Et)

(d) $CH_3CHCH_2CH_2COEt$ (NO_2)

(e) $EtOCCHCH_2CH_2NO_2$ (with CO_2Et)

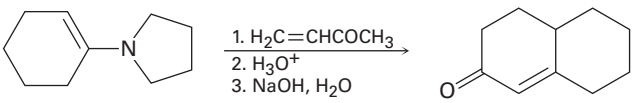
(f) 

23.42 The so-called Wieland–Miescher ketone is a valuable starting material used in the synthesis of steroid hormones. How might you prepare it from 1,3-cyclohexanedione?

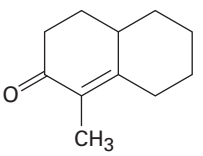


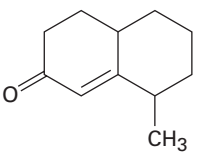
Wieland–Miescher ketone

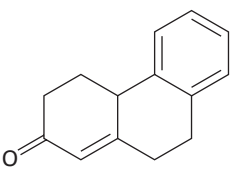
23.43 The Stork enamine reaction and the intramolecular aldol reaction can be carried out in sequence to allow the synthesis of cyclohexenones. For example, reaction of the pyrrolidine enamine of cyclohexanone with 3-buten-2-one, followed by enamine hydrolysis and base treatment, yields the product indicated. Write each step, and show the mechanism of each.



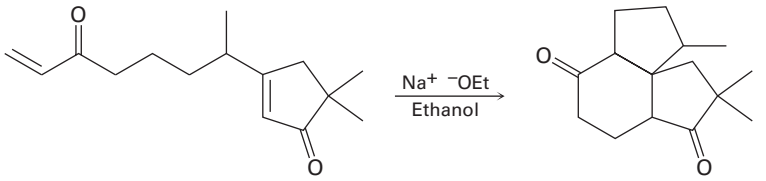
23.44 How could you prepare the following cyclohexenones by combining a Stork enamine reaction with an intramolecular aldol condensation? (See Problem 23.43.)

(a) 

(b) 

(c) 

23.45 The following reaction involves two successive intramolecular Michael reactions. Write both steps, and show their mechanisms.



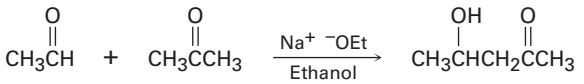
General Problems

23.46 What condensation products would you expect to obtain by treatment of the following substances with sodium ethoxide in ethanol?

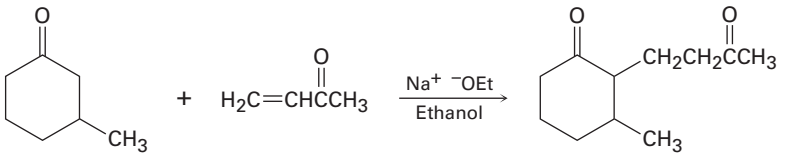
(a) Ethyl butanoate **(b)** Cycloheptanone
(c) 3,7-Nonanedione **(d)** 3-Phenylpropanal

23.47 The following reactions are unlikely to provide the indicated product in high yield. What is wrong with each?

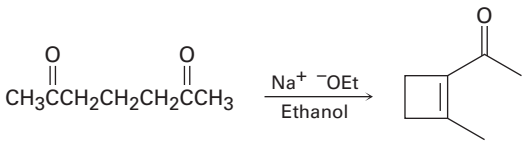
(a)



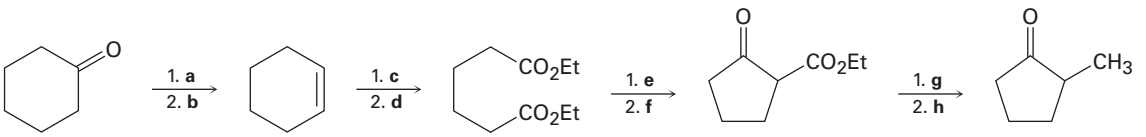
(b)



(c)

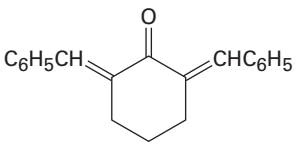


23.48 Fill in the missing reagents **a–h** in the following scheme:

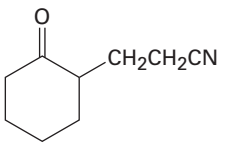


23.49 How would you prepare the following compounds from cyclohexanone?

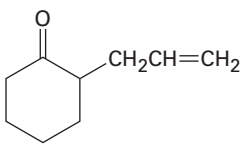
(a)



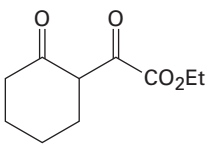
(b)



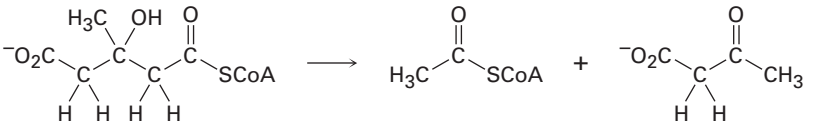
(c)



(d)

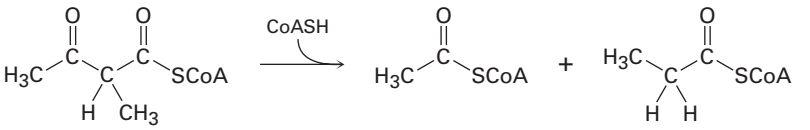


23.50 Leucine, one of the twenty amino acids found in proteins, is metabolized by a pathway that includes the following step. Propose a mechanism.



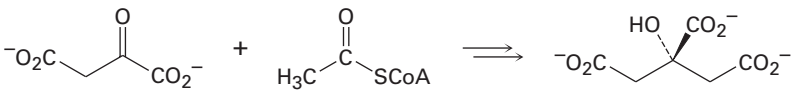
3-Hydroxy-3-methyl-glutaryl CoA **Acetyl CoA** **Acetoacetate**

23.51 Isoleucine, another of the twenty amino acids found in proteins, is metabolized by a pathway that includes the following step. Propose a mechanism.



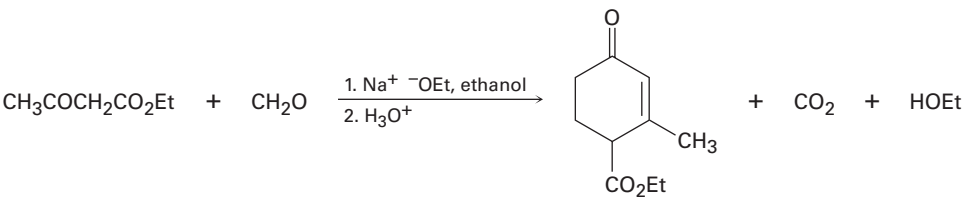
2-Methyl-3-keto-butyryl CoA **Acetyl CoA** **Propionyl CoA (propanoyl CoA)**

23.52 The first step in the citric acid cycle of food metabolism is reaction of oxaloacetate with acetyl CoA to give citrate. Propose a mechanism, using acid or base catalysis as needed.



Oxaloacetate **Acetyl CoA** **Citrate**

23.53 The compound known as Hagemann's ester is prepared by treatment of a mixture of formaldehyde and ethyl acetoacetate with base, followed by acid-catalyzed decarboxylation.



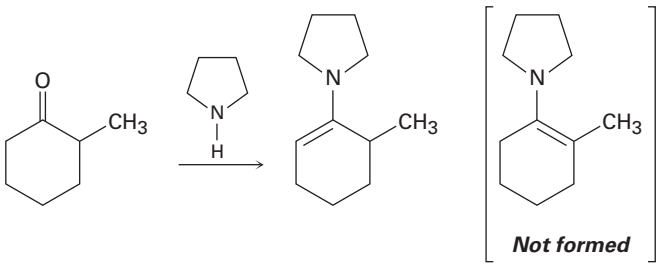
Hagemann's ester

(a) The first step is an aldol-like condensation between ethyl acetoacetate and formaldehyde to yield an α,β-unsaturated product. Write the reaction, and show the structure of the product.

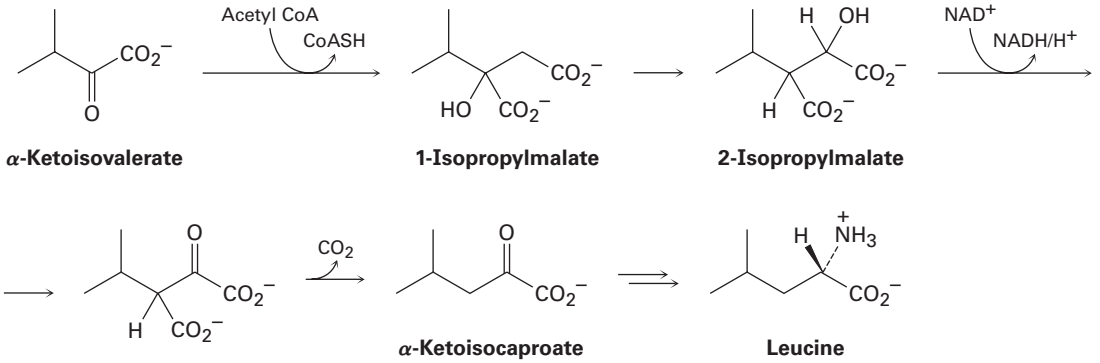
(b) The second step is a Michael reaction between ethyl acetoacetate and the unsaturated product of the first step. Show the structure of the product.

23.54 The third and fourth steps in the synthesis of Hagemann's ester from ethyl acetoacetate and formaldehyde (Problem 23.53) are an intramolecular aldol cyclization to yield a substituted cyclohexenone, and a decarboxylation reaction. Write both reactions, and show the products of each step.

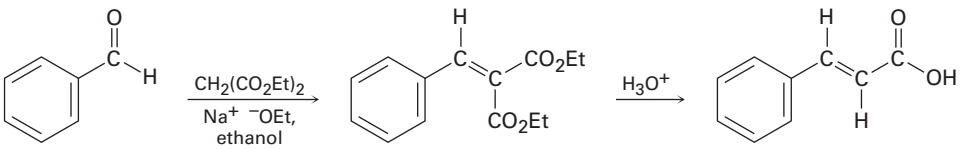
23.55 When 2-methylcyclohexanone is converted into an enamine, only one product is formed despite the fact that the starting ketone is unsymmetrical. Build molecular models of the two possible products and explain the fact that the sole product is the one with the double bond away from the methyl-substituted carbon.



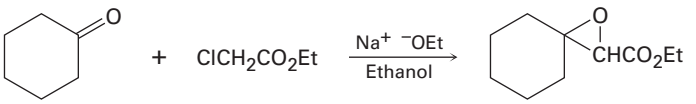
23.56 The amino acid leucine is biosynthesized from α-ketoisovalerate by the following sequence of steps. Show the mechanism of each.



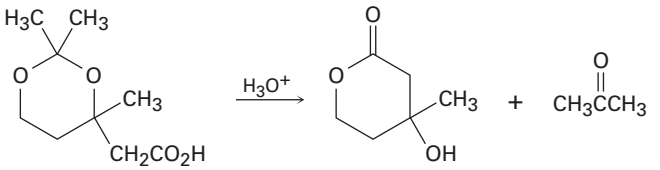
23.57 The Knoevenagel reaction is a carbonyl condensation reaction of an ester with an aldehyde or ketone to yield an α,β-unsaturated product. Show the mechanism of the Knoevenagel reaction of diethyl malonate with benzaldehyde.



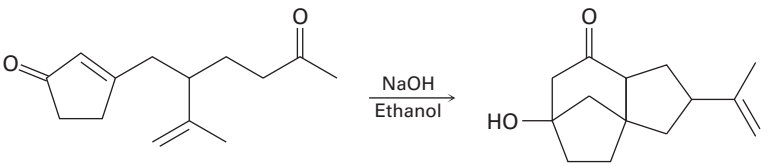
23.58 The Darzens reaction involves a two-step, base-catalyzed condensation of ethyl chloroacetate with a ketone to yield an epoxy ester. The first step is a carbonyl condensation reaction, and the second step is an S_N2 reaction. Write both steps, and show their mechanisms.



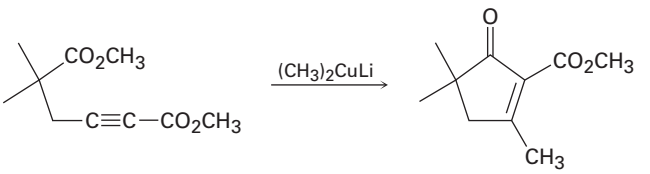
23.59 The following reaction involves a hydrolysis followed by an intramolecular nucleophilic acyl substitution reaction. Write both steps, and show their mechanisms.



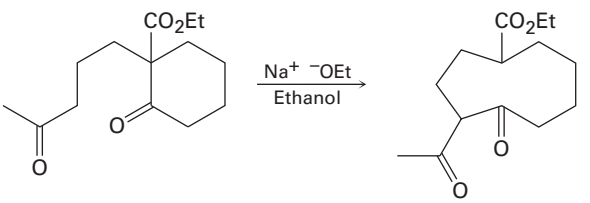
23.60 The following reaction involves an intramolecular Michael reaction followed by an intramolecular aldol reaction. Write both steps, and show their mechanisms.



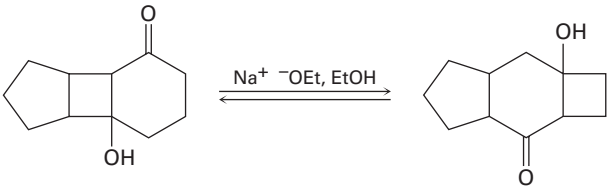
23.61 The following reaction involves a conjugate addition reaction followed by an intramolecular Claisen condensation. Write both steps, and show their mechanisms.



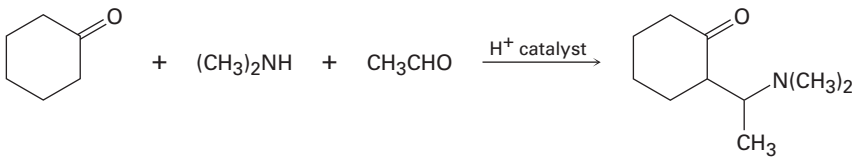
23.62 The following reaction involves an intramolecular aldol reaction followed by a *retro* aldol-like reaction. Write both steps, and show their mechanisms.



23.63 Propose a mechanism for the following base-catalyzed isomerization:



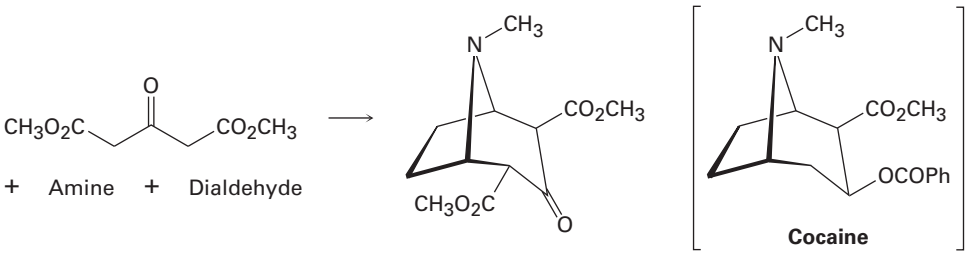
23.64 The Mannich reaction of a ketone, an amine, and an aldehyde is one of the few three-component reactions in organic chemistry. Cyclohexanone, for example, reacts with dimethylamine and acetaldehyde to yield an amino ketone. The reaction takes place in two steps, both of which are typical carbonyl-group reactions.



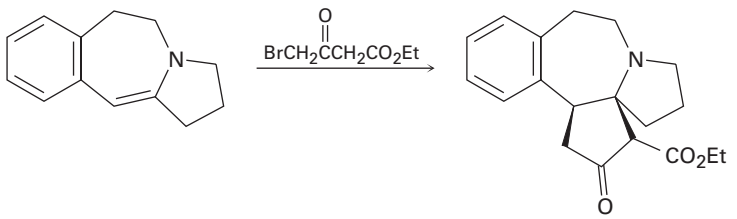
(a) The first step is reaction between the aldehyde and the amine to yield an intermediate iminium ion ($R_2C{=}NR_2^+$) plus water. Propose a mechanism, and show the structure of the intermediate iminium ion.

(b) The second step is reaction between the iminium ion intermediate and the ketone to yield the final product. Propose a mechanism.

23.65 Cocaine has been prepared by a sequence beginning with a Mannich reaction (Problem 23.64) between dimethyl acetonedicarboxylate, an amine, and a dialdehyde. Show the structures of the amine and dialdehyde.



23.66 Propose a mechanism to account for the following reaction of an enamine with an alkyl halide:



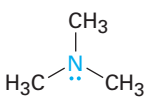
24

The characteristic and unmistakable odor of fish is due to a mixture of simple alkylamines.

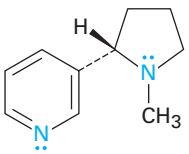
Amines and Heterocycles

Amines are organic derivatives of ammonia in the same way that alcohols and ethers are organic derivatives of water. Like ammonia, amines contain a nitrogen atom with a lone pair of electrons, making amines both basic and nucleophilic. We'll soon see, in fact, that most of the chemistry of amines depends on the presence of this lone pair of electrons.

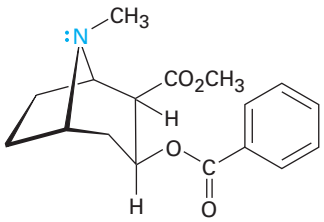
Amines occur widely in all living organisms. Trimethylamine, for instance, occurs in animal tissues and is partially responsible for the distinctive odor of fish; nicotine is found in tobacco; and cocaine is a stimulant found in the leaves of the South American coca bush. In addition, amino acids are the building blocks from which all proteins are made, and cyclic amine bases are constituents of nucleic acids.



Trimethylamine



Nicotine



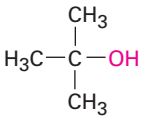
Cocaine

Why This Chapter? By the end of this chapter, we will have seen all the common functional groups. Of those groups, amines and carbonyl compounds are the most abundant and have the richest chemistry. In addition to the proteins and nucleic acids already mentioned, the majority of pharmaceutical agents contain amine functional groups, and many of the common coenzymes necessary for biological catalysis are amines.

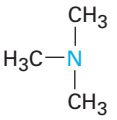
24.1 Naming Amines

Amines can be either alkyl-substituted (**alkylamines**) or aryl-substituted (**arylamines**). Although much of the chemistry of the two classes is similar, there are also substantial differences. Amines are classified as **primary (RNH_2)**, **secondary (R_2NH)**, or **tertiary (R_3N)**, depending on the number of organic substituents attached to nitrogen. Thus, methylamine (CH_3NH_2) is a primary

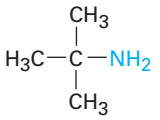
amine, dimethylamine [$(CH_3)_2NH$] is a secondary amine, and trimethylamine [$(CH_3)_3N$] is a tertiary amine. Note that this usage of the terms *primary, secondary,* and *tertiary* is different from our previous usage. When we speak of a tertiary alcohol or alkyl halide, we refer to the degree of substitution at the alkyl carbon atom, but when we speak of a tertiary amine, we refer to the degree of substitution at the nitrogen atom.



***tert*-Butyl alcohol**
(a tertiary alcohol)

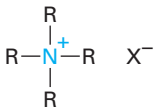


Trimethylamine
(a tertiary amine)



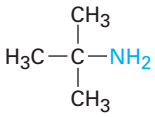
***tert*-Butylamine**
(a primary amine)

Compounds containing a nitrogen atom with four attached groups also exist, but the nitrogen atom must carry a formal positive charge. Such compounds are called **quaternary ammonium salts**.

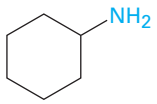


A quaternary ammonium salt

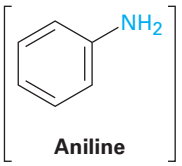
Primary amines are named in the IUPAC system in several ways. For simple amines, the suffix *-amine* is added to the name of the alkyl substituent. You might also recall from Chapter 15 that phenylamine, $C_6H_5NH_2$, has the common name *aniline*.



***tert*-Butylamine**

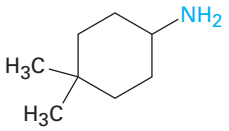


Cyclohexylamine

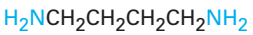


Aniline

Alternatively, the suffix *-amine* can be used in place of the final *-e* in the name of the parent compound.

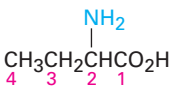


4,4-Dimethylcyclohexanamine

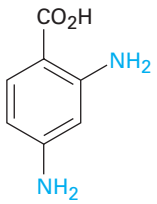


1,4-Butanediamine

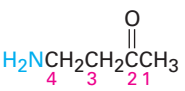
Amines with more than one functional group are named by considering the $-NH_2$ as an *amino* substituent on the parent molecule.



2-Aminobutanoic acid

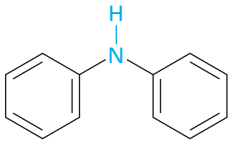


2,4-Diaminobenzoic acid

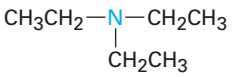


4-Amino-2-butanone

Symmetrical secondary and tertiary amines are named by adding the prefix *di-* or *tri-* to the alkyl group.

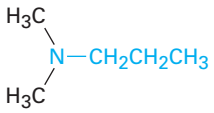


Diphenylamine

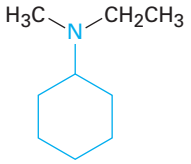


Triethylamine

Unsymmetrically substituted secondary and tertiary amines are named as *N*-substituted primary amines. The largest alkyl group is chosen as the parent name, and the other alkyl groups are considered *N*-substituents on the parent (*N* because they're attached to nitrogen).

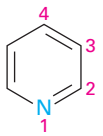


***N,N*-Dimethylpropylamine**

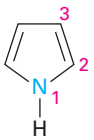


***N*-Ethyl-*N*-methylcyclohexylamine**

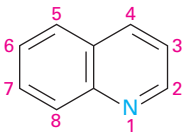
Heterocyclic amines—compounds in which the nitrogen atom occurs as part of a ring—are also common, and each different heterocyclic ring system has its own parent name. The heterocyclic nitrogen atom is always numbered as position 1.



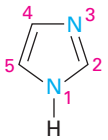
Pyridine



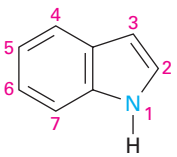
Pyrrole



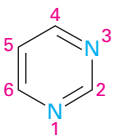
Quinoline



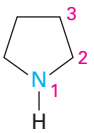
Imidazole



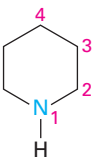
Indole



Pyrimidine



Pyrrolidine



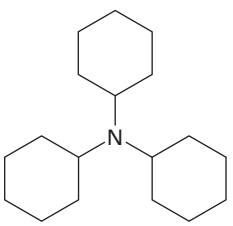
Piperidine

Problem 24.1

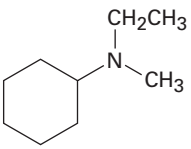
Name the following compounds:

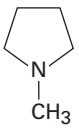
(a) $CH_3NHCH_2CH_3$

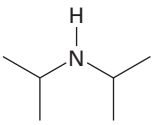
(b)

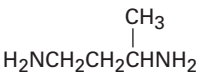


(c)



(d) 

(e) 

(f) 

Problem 24.2

Draw structures corresponding to the following IUPAC names:

(a) Triisopropylamine **(b)** Triallylamine
(c) *N*-Methylaniline **(d)** *N*-Ethyl-*N*-methylcyclopentylamine
(e) *N*-Isopropylcyclohexylamine **(f)** *N*-Ethylpyrrole

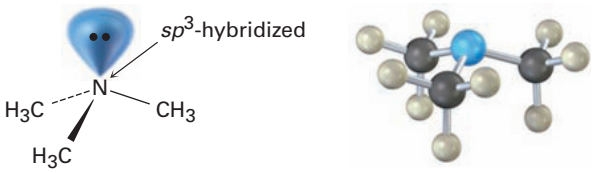
Problem 24.3

Draw structures for the following heterocyclic amines:

(a) 5-Methoxyindole **(b)** 1,3-Dimethylpyrrole
(c) 4-(*N*,*N*-Dimethylamino)pyridine **(d)** 5-Aminopyrimidine

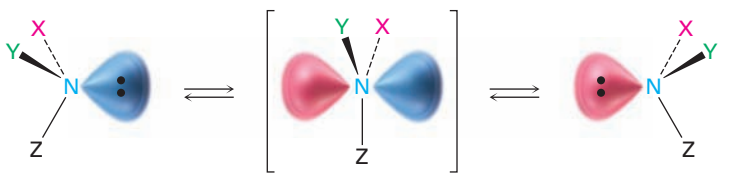
24.2 Structure and Properties of Amines

The bonding in alkylamines is similar to the bonding in ammonia. The nitrogen atom is sp^3-hybridized, with the three substituents occupying three corners of a regular tetrahedron and the lone pair of electrons occupying the fourth corner. As you might expect, the C–N–C bond angles are close to the 109° tetrahedral value. For trimethylamine, the C–N–C bond angle is 108° and the C–N bond length is 147 pm.



Trimethylamine

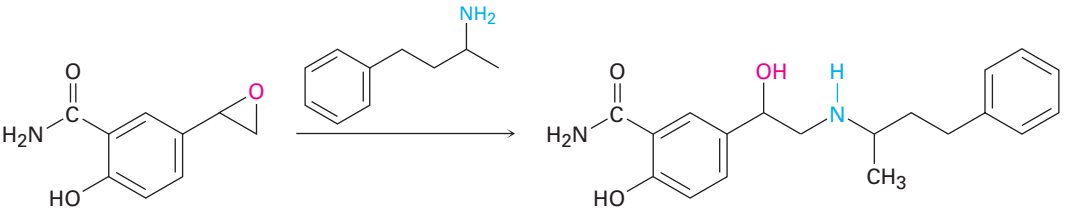
One consequence of tetrahedral geometry is that an amine with three different substituents on nitrogen is chiral, as we saw in **Section 5.10**. Unlike chiral carbon compounds, however, chiral amines can't usually be resolved because the two enantiomeric forms rapidly interconvert by a pyramidal inversion, much as an alkyl halide inverts in an S_N2 reaction. Pyramidal inversion occurs by a momentary rehybridization of the nitrogen atom to planar, sp^2 geometry, followed by rehybridization of the planar intermediate to tetrahedral, sp^3 geometry **(Figure 24.1)**. The barrier to inversion is about 25 kJ/mol (6 kcal/mol), an amount only twice as large as the barrier to rotation about a C–C single bond.



***sp*³-hybridized (tetrahedral)** ***sp*²-hybridized (planar)** ***sp*³-hybridized (tetrahedral)**

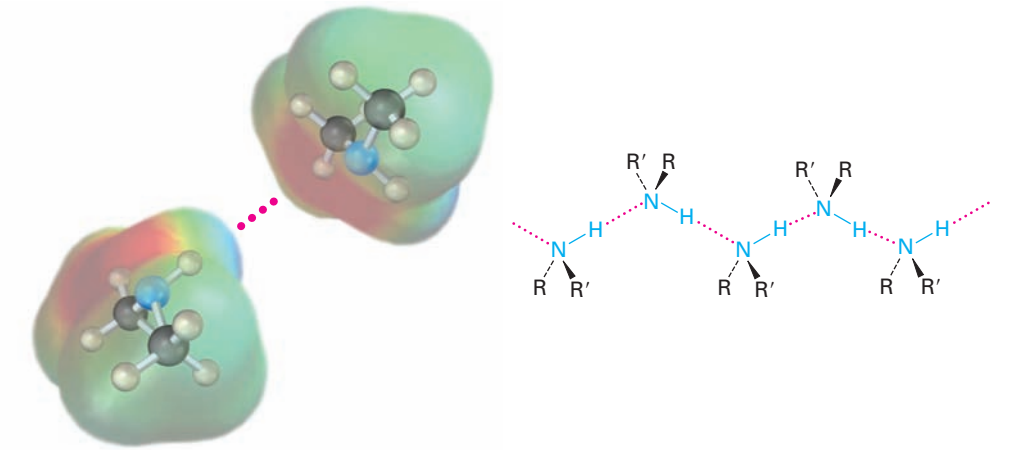
Figure 24.1 Pyramidal inversion rapidly interconverts the two mirror-image (enantiomeric) forms of an amine.

Alkylamines have a variety of applications in the chemical industry as starting materials for the preparation of insecticides and pharmaceuticals. Labetalol, for instance, a so-called β-blocker used for the treatment of high blood pressure, is prepared by S_N2 reaction of an epoxide with a primary amine. The substance marketed for drug use is a mixture of all four possible stereoisomers, but the biological activity derives primarily from the (*R*,*R*) isomer.



Labetalol

Like alcohols, amines with fewer than five carbon atoms are generally water-soluble. Also like alcohols, primary and secondary amines form hydrogen bonds and are highly associated. As a result, amines have higher boiling points than alkanes of similar molecular weight. Diethylamine (MW = 73 amu) boils at 56.3 °C, for instance, while pentane (MW = 72 amu) boils at 36.1 °C.

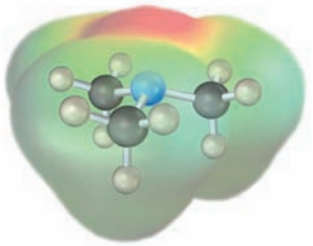


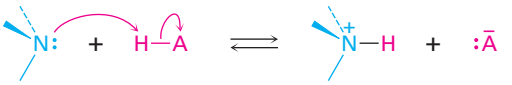
One other characteristic of amines is their odor. Low-molecular-weight amines such as trimethylamine have a distinctive fishlike aroma, while diamines such as cadaverine (1,5-pentanediamine) and putrescine (1,4-butanediamine) have the appalling odors you might expect from their common names. Both these diamines arise from the decomposition of proteins.

24.3 Basicity of Amines

The chemistry of amines is dominated by the lone pair of electrons on nitrogen, which makes amines both basic and nucleophilic. They react with acids to form acid–base salts, and they react with electrophiles in many of the polar reactions seen in past chapters. Note in the following electrostatic potential

map of trimethylamine how the negative (red) region corresponds to the lone-pair of electrons on nitrogen.





An amine (a Lewis base) **An acid** **A salt**

Amines are much stronger bases than alcohols and ethers, their oxygen-containing analogs. When an amine is dissolved in water, an equilibrium is established in which water acts as an acid and transfers a proton to the amine. Just as the acid strength of a carboxylic acid can be measured by defining an acidity constant K_a **(Section 2.8)**, the base strength of an amine can be measured by defining an analogous *basicity constant* K_b. The larger the value of K_b and the smaller the value of pK_b, the more favorable the proton-transfer equilibrium and the stronger the base.

For the reaction

$$RNH_2 + H_2O \rightleftharpoons RNH_3^+ + OH^-$$

$$K_b = \frac{[RNH_3^+]\,[OH^-]}{[RNH_2]}$$

$$pK_b = -\log K_b$$

In practice, K_b values are not often used. Instead, the most convenient way to measure the basicity of an amine (RNH_2) is to look at the acidity of the corresponding ammonium ion (RNH_3^+).

For the reaction

$$RNH_3^+ + H_2O \rightleftharpoons RNH_2 + H_3O^+$$

$$K_a = \frac{[RNH_2]\,[H_3O^+]}{[RNH_3^+]}$$

so

$$K_a \cdot K_b = \left[\frac{[RNH_2]\,[H_3O^+]}{[RNH_3^+]}\right]\left[\frac{[RNH_3^+]\,[OH^-]}{[RNH_2]}\right]$$

$$= [H_3O^+]\,[OH^-] = K_w = 1.00 \times 10^{-14}$$

Thus

$$K_a = \frac{K_w}{K_b} \quad \text{and} \quad K_b = \frac{K_w}{K_a}$$

and

$$pK_a + pK_b = 14$$

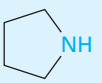
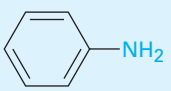
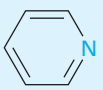
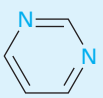
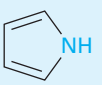
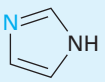
These equations say that the K_b of an amine multiplied by the K_a of the corresponding ammonium ion is equal to K_w, the ion-product constant for water (1.00×10^{-14}). Thus, if we know K_a for an ammonium ion, we also know K_b for the corresponding amine base because $K_b = K_w/K_a$. The more acidic the

ammonium ion, the less tightly the proton is held and the weaker the corresponding base. That is, a weaker base has an ammonium ion with a smaller pK_a and a stronger base has an ammonium ion with a larger pK_a.

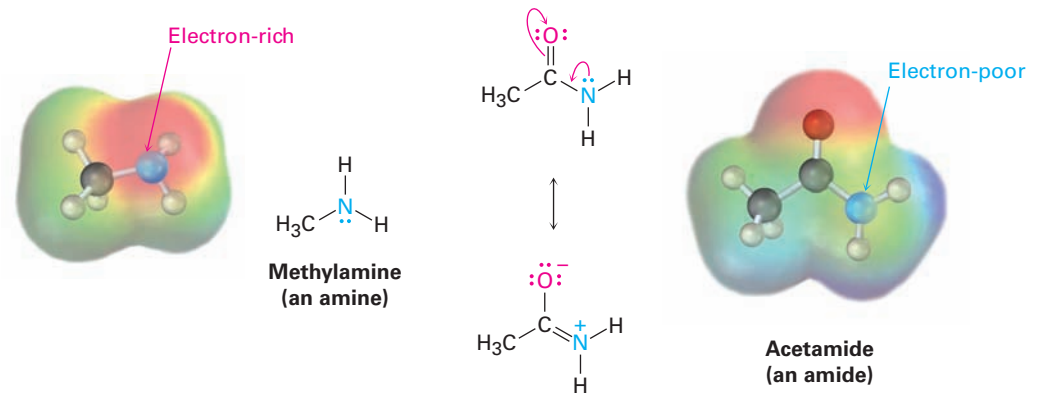
Weaker base	Smaller pK_a for ammonium ion
Stronger base	Larger pK_a for ammonium ion

Table 24.1 lists pK_a values of the ammonium ions from a variety of amines and indicates that there is a substantial range of amine basicities. Most simple alkylamines are similar in their base strength, with pK_a's for their ammonium ions in the narrow range 10 to 11. Arylamines, however, are considerably less basic than alkylamines, as are the heterocyclic amines pyridine and pyrrole.

Table 24.1 Basicity of Some Common Amines

Name	Structure	pK_a of ammonium ion
Ammonia	NH_3	9.26
Primary alkylamine		
Methylamine	CH_3NH_2	10.64
Ethylamine	$CH_3CH_2NH_2$	10.75
Secondary alkylamine		
Diethylamine	$(CH_3CH_2)_2NH$	10.98
Pyrrolidine		11.27
Tertiary alkylamine		
Triethylamine	$(CH_3CH_2)_3N$	10.76
Arylamine		
Aniline		4.63
Heterocyclic amine		
Pyridine		5.25
Pyrimidine		1.3
Pyrrole		0.4
Imidazole		6.95

In contrast with amines, amides ($RCONH_2$) are nonbasic. Amides aren't protonated by aqueous acids, and they are poor nucleophiles. The main reason for this difference in basicity between amines and amides is that an amide is stabilized by delocalization of the nitrogen lone-pair electrons through orbital overlap with the carbonyl group. In resonance terms, amides are more stable and less reactive than amines because they are hybrids of two resonance forms. This amide resonance stabilization is lost when the nitrogen atom is protonated, so protonation is disfavored. Electrostatic potential maps show clearly the decreased electron density on the amide nitrogen.



It's often possible to take advantage of their basicity to purify amines. For example, if a mixture of a basic amine and a neutral compound such as a ketone or alcohol is dissolved in an organic solvent and aqueous acid is added, the basic amine dissolves in the water layer as its protonated salt, while the neutral compound remains in the organic solvent layer. Separation of the water layer and neutralization of the ammonium ion by addition of NaOH then provides the pure amine **(Figure 24.2)**.

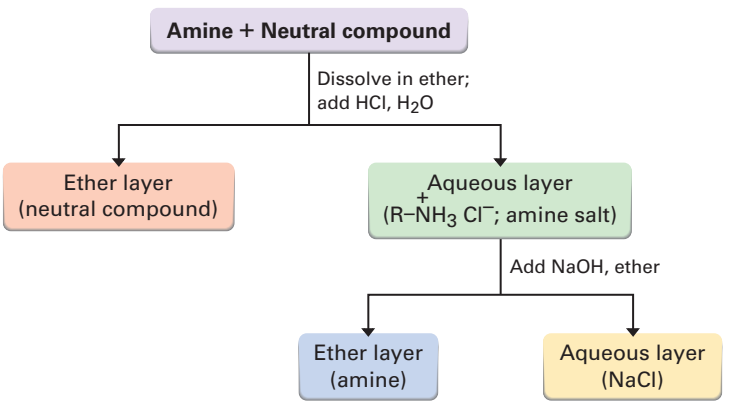
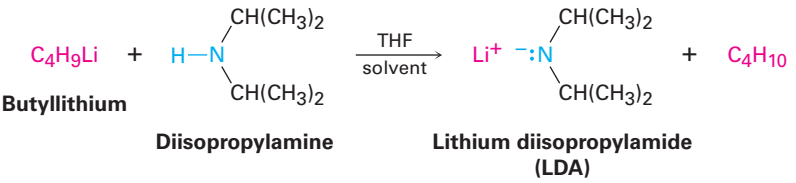


Figure 24.2 Separation and purification of an amine component from a mixture by extraction of its ammonium salt into water.

In addition to their behavior as bases, primary and secondary amines can also act as very weak acids because an N–H proton can be removed by a sufficiently

strong base. We've seen, for example, how diisopropylamine ($pK_a \approx 36$) reacts with butyllithium to yield lithium diisopropylamide (LDA; **Section 22.5**). Dialkylamine anions like LDA are very strong bases that are often used in laboratory organic chemistry for the generation of enolate ions from carbonyl compounds **(Section 22.7)**. They are not, however, encountered in biological chemistry.



Problem 24.4

Which compound in each of the following pairs is more basic?

(a) $CH_3CH_2NH_2$ or $CH_3CH_2CONH_2$ **(b)** NaOH or CH_3NH_2

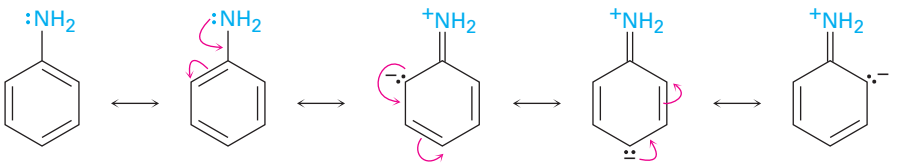
(c) CH_3NHCH_3 or pyridine

Problem 24.5

The benzylammonium ion ($C_6H_5CH_2NH_3^+$) has $pK_a = 9.33$, and the propylammonium ion has $pK_a = 10.71$. Which is the stronger base, benzylamine or propylamine? What are the pK_b's of benzylamine and propylamine?

24.4 Basicity of Arylamines

As noted previously, arylamines are generally less basic than alkylamines. Anilinium ion has $pK_a = 4.63$, for instance, whereas methylammonium ion has $pK_a = 10.64$. Arylamines are less basic than alkylamines because the nitrogen lone-pair electrons are delocalized by interaction with the aromatic ring π electron system and are less available for bonding to H^+. In resonance terms, arylamines are stabilized relative to alkylamines because of their five resonance forms.



Much of the resonance stabilization is lost on protonation, however, so the energy difference between protonated and nonprotonated forms is higher for arylamines than it is for alkylamines. As a result, arylamines are less basic. **Figure 24.3** illustrates the difference.

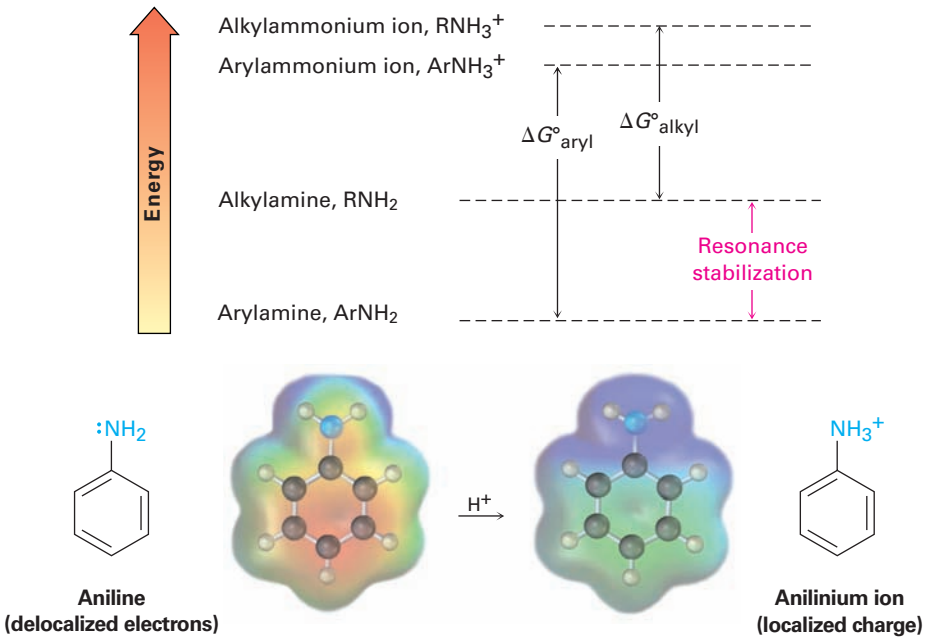


Figure 24.3 Arylamines have a larger positive $\Delta G°$ for protonation and are therefore less basic than alkylamines, primarily because of resonance stabilization of the ground state. Electrostatic potential maps show that lone-pair electron density is delocalized in the amine but the charge is localized in the corresponding ammonium ion.

Substituted arylamines can be either more basic or less basic than aniline, depending on the substituent. Electron-donating substituents, such as $-CH_3$, $-NH_2$, and $-OCH_3$, which increase the reactivity of an aromatic ring toward electrophilic substitution **(Section 16.5)**, also increase the basicity of the corresponding arylamine. Electron-withdrawing substituents, such as $-Cl$, $-NO_2$, and $-CN$, which decrease ring reactivity toward electrophilic substitution, also decrease arylamine basicity. Table 24.2 considers only *p*-substituted anilines, but similar trends are observed for ortho and meta derivatives.

Table 24.2 Base Strength of Some *p*-Substituted Anilines

	Substituent, Y	pK_a	
Stronger base	$-NH_2$	6.15	Activating groups
	$-OCH_3$	5.34	
	$-CH_3$	5.08	
	$-H$	4.63	
	$-Cl$	3.98	Deactivating groups
	$-Br$	3.86	
	$-CN$	1.74	
Weaker base	$-NO_2$	1.00	

Problem 24.6

Without looking at Table 24.2, rank the following compounds in order of ascending basicity.

(a) *p*-Nitroaniline, *p*-aminobenzaldehyde, *p*-bromoaniline

(b) *p*-Chloroaniline, *p*-aminoacetophenone, *p*-methylaniline

(c) *p*-(Trifluoromethyl)aniline, *p*-methylaniline, *p*-(fluoromethyl)aniline

24.5 Biological Amines and the Henderson–Hasselbalch Equation

We saw in **Section 20.3** that the extent of dissociation of a carboxylic acid HA in an aqueous solution buffered to a given pH can be calculated with the Henderson–Hasselbalch equation. Furthermore, we concluded that at the physiological pH of 7.3 inside living cells, carboxylic acids are almost entirely dissociated into their carboxylate anions, RCO_2^-.

Henderson–Hasselbalch equation: $$\text{pH} = \text{p}K_a + \log\frac{[\text{A}^-]}{[\text{HA}]} \qquad \text{so} \qquad \log\frac{[\text{A}^-]}{[\text{HA}]} = \text{pH} - \text{p}K_a$$

What about amine bases? In what form do they exist at the physiological pH inside cells? As the amine ($A^- = RNH_2$), or as the ammonium ion ($HA = RNH_3^+$)? Let's take a 0.0010 M solution of methylamine at pH = 7.3, for example. According to Table 24.1, the pK_a of methylammonium ion is 10.64, so from the Henderson–Hasselbalch equation, we have

$$\log\frac{[\text{RNH}_2]}{[\text{RNH}_3^+]} = \text{pH} - \text{p}K_a = 7.3 - 10.64 = -3.34$$

$$\frac{[\text{RNH}_2]}{[\text{RNH}_3^+]} = \text{antilog}(-3.34) = 4.6 \times 10^{-4} \qquad \text{so} \qquad [\text{RNH}_2] = \left(4.6 \times 10^{-4}\right)[\text{RNH}_3^+]$$

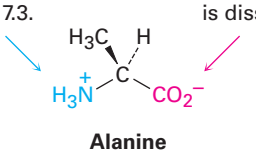
In addition, we know that

$$[\text{RNH}_2] + [\text{RNH}_3^+] = 0.0010\ \text{M}$$

Solving the two simultaneous equations gives $[RNH_3^+] = 0.0010$ M and $[RNH_2] = 5 \times 10^{-7}$ M. In other words, at a physiological pH of 7.3, essentially 100% of the methylamine in a 0.0010 M solution exists in its protonated form as methylammonium ion. The same is true of other amine bases, so we always write cellular amines in their protonated form and amino acids in their ammonium carboxylate form to reflect their structures at physiological pH.

The amino group is protonated at pH = 7.3.

The carboxylic acid group is dissociated at pH = 7.3.



Alanine (an amino acid)

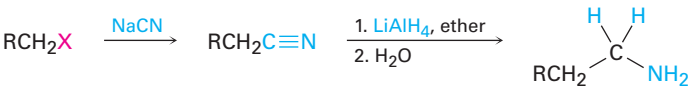
Problem 24.7

Calculate the percentages of neutral and protonated forms present in a solution of 0.0010 M pyrimidine at pH = 7.3. The pK_a of pyrimidinium ion is 1.3.

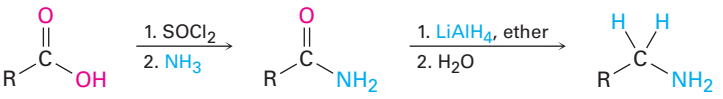
24.6 Synthesis of Amines

Reduction of Nitriles, Amides, and Nitro Compounds

We've already seen in **Sections 20.7 and 21.7** how amines can be prepared by reduction of nitriles and amides with $LiAlH_4$. The two-step sequence of S_N2 displacement with CN^- followed by reduction thus converts an alkyl halide into a primary alkylamine having one more carbon atom. Amide reduction converts carboxylic acids and their derivatives into amines with the same number of carbon atoms.

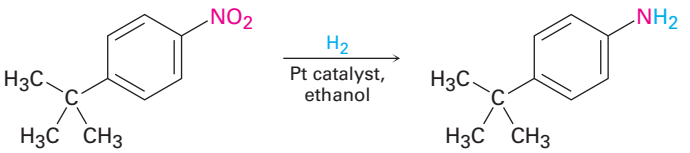


Alkyl halide **1° amine**

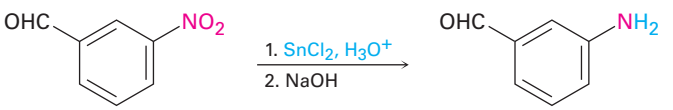


Carboxylic acid **1° amine**

Arylamines are usually prepared by nitration of an aromatic starting material, followed by reduction of the nitro group **(Section 16.2)**. The reduction step can be carried out in many different ways, depending on the circumstances. Catalytic hydrogenation over platinum works well but is often incompatible with the presence elsewhere in the molecule of other reducible groups, such as C=C bonds or carbonyl groups. Iron, zinc, tin, and tin(II) chloride ($SnCl_2$) are also effective when used in acidic aqueous solution. Tin(II) chloride is particularly mild and is often used when other reducible functional groups are present.



***p*-*tert*-Butylnitrobenzene** ***p*-*tert*-Butylaniline (100%)**



***m*-Nitrobenzaldehyde** ***m*-Aminobenzaldehyde (90%)**

Problem 24.8

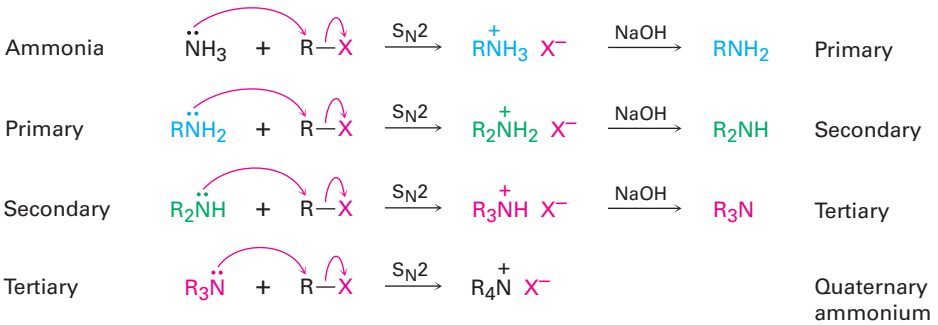
Propose structures for either a nitrile or an amide that might be a precursor of each of the following amines:

(a) $CH_3CH_2CH_2NH_2$ **(b)** $(CH_3CH_2CH_2)_2NH$

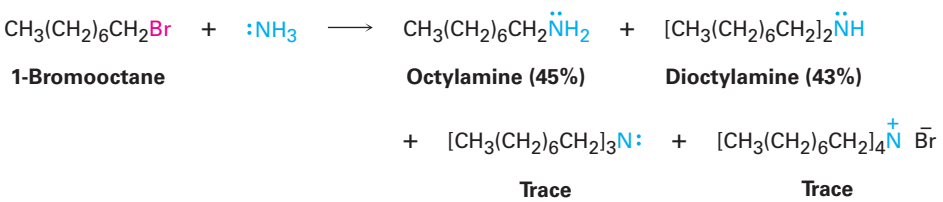
(c) Benzylamine, $C_6H_5CH_2NH_2$ **(d)** *N*-Ethylaniline

S_N2 Reactions of Alkyl Halides

Ammonia and other amines are good nucleophiles in S_N2 reactions. As a result, the simplest method of alkylamine synthesis is by S_N2 alkylation of ammonia or an alkylamine with an alkyl halide. If ammonia is used, a primary amine results; if a primary amine is used, a secondary amine results; and so on. Even tertiary amines react rapidly with alkyl halides to yield quaternary ammonium salts, $R_4N^+ X^-$.

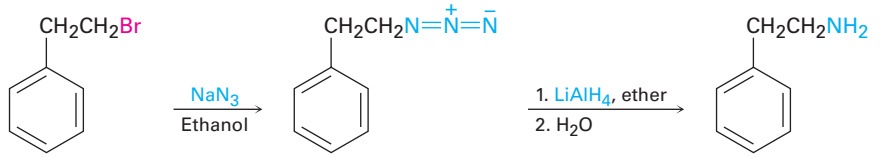


Unfortunately, these reactions don't stop cleanly after a single alkylation has occurred. Because ammonia and primary amines have similar reactivity, the initially formed monoalkylated substance often undergoes further reaction to yield a mixture of products. Even secondary and tertiary amines undergo further alkylation, although to a lesser extent. For example, treatment of 1-bromooctane with a twofold excess of ammonia leads to a mixture containing only 45% of octylamine. A nearly equal amount of dioctylamine is produced by double alkylation, along with smaller amounts of trioctylamine and tetraoctylammonium bromide.



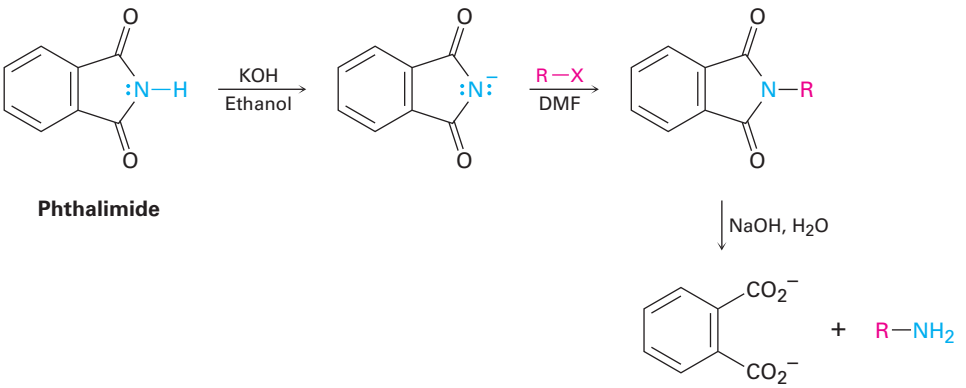
A better method for preparing primary amines is to use azide ion, N_3^-, as the nucleophile rather than ammonia for S_N2 reaction with a primary or secondary alkyl halide. The product is an alkyl azide, which is not nucleophilic, so overalkylation can't occur. Subsequent reduction of the alkyl azide with $LiAlH_4$

then leads to the desired primary amine. Although the method works well, low-molecular-weight alkyl azides are explosive and must be handled carefully.



1-Bromo-2-phenylethane **2-Phenylethyl azide** **2-Phenylethylamine (89%)**

Another alternative for preparing a primary amine from an alkyl halide is the **Gabriel amine synthesis**, which uses a *phthalimide* alkylation. An **imide** (**−CONHCO−**) is similar to a β-keto ester in that the acidic N−H hydrogen is flanked by two carbonyl groups. Thus, imides are deprotonated by such bases as KOH, and the resultant anions are readily alkylated in a reaction similar to the acetoacetic ester synthesis **(Section 22.7)**. Basic hydrolysis of the *N*-alkylated imide then yields a primary amine product. The imide hydrolysis step is analogous to the hydrolysis of an amide **(Section 21.7)**.



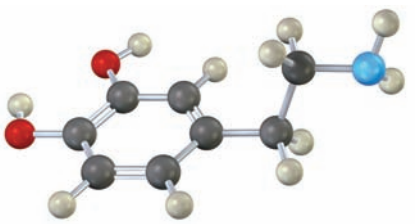
Phthalimide

Problem 24.9

Write the mechanism of the last step in the Gabriel amine synthesis, the base-promoted hydrolysis of a phthalimide to yield an amine plus phthalate ion.

Problem 24.10

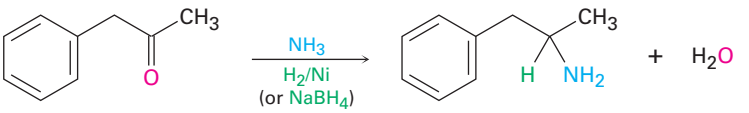
Show two methods for the synthesis of dopamine, a neurotransmitter involved in regulation of the central nervous system. Use any alkyl halide needed.



Dopamine

Reductive Amination of Aldehydes and Ketones

Amines can be synthesized in a single step by treatment of an aldehyde or ketone with ammonia or an amine in the presence of a reducing agent, a process called **reductive amination**. For example, amphetamine, a central nervous system stimulant, is prepared commercially by reductive amination of phenyl-2-propanone with ammonia using hydrogen gas over a nickel catalyst as the reducing agent. In the laboratory, either $NaBH_4$ or the related $NaBH(OAc)_3$ is commonly used (OAc = acetate).

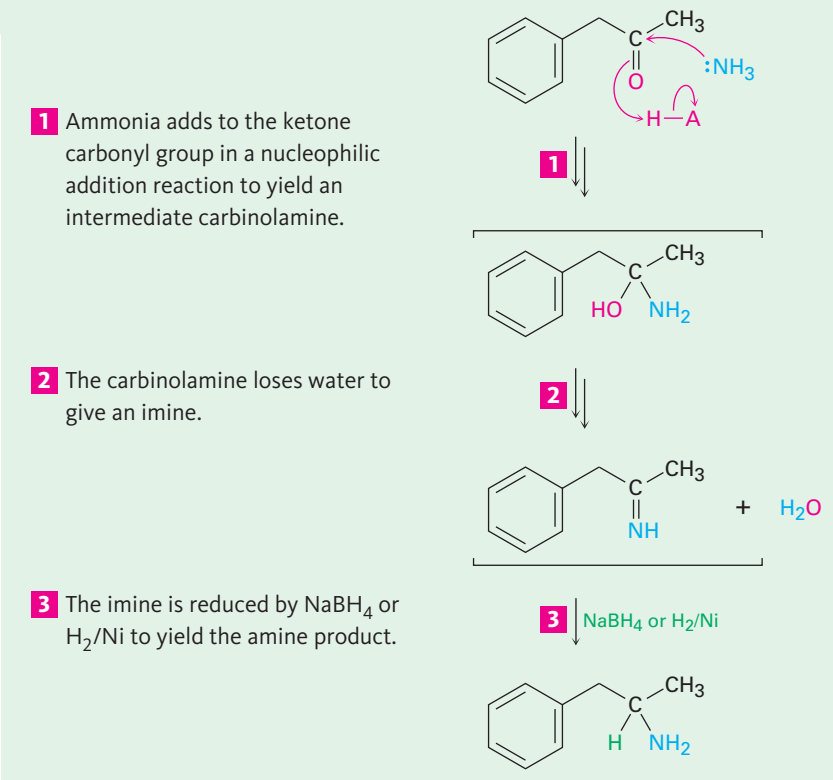


Phenyl-2-propanone **Amphetamine**

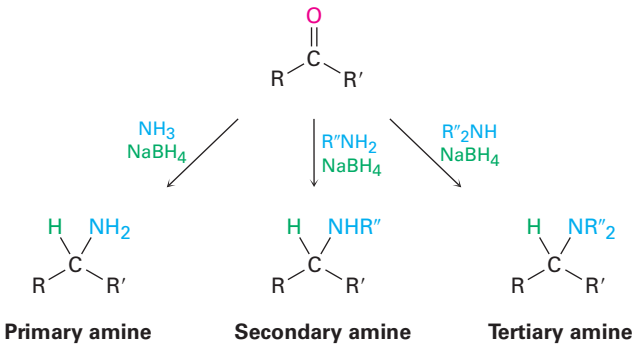
Reductive amination takes place by the pathway shown in **Figure 24.4**. An imine intermediate is first formed by a nucleophilic addition reaction **(Section 19.8)**, and the C=N bond of the imine is then reduced to the amine, much as the C=O bond of a ketone can be reduced to an alcohol.

Figure 24.4 | MECHANISM

Mechanism of reductive amination of a ketone to yield an amine. Details of the imine-forming step were shown in Figure 19.6 on page 737.

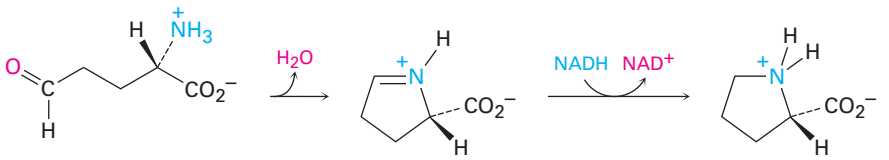


Ammonia, primary amines, and secondary amines can all be used in the reductive amination reaction, yielding primary, secondary, and tertiary amines, respectively.



Primary amine **Secondary amine** **Tertiary amine**

Reductive aminations also occur in various biological pathways. In the biosynthesis of the amino acid proline, for instance, glutamate 5-semialdehyde undergoes internal imine formation to give 1-pyrrolinium 5-carboxylate, which is then reduced by nucleophilic addition of hydride ion to the C=N bond. Reduced nicotinamide adenine dinucleotide, NADH, acts as the biological reducing agent.

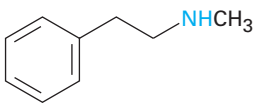


Glutamate 5-semialdehyde **1-Pyrrolinium 5-carboxylate** **Proline**

Using a Reductive Amination Reaction

Worked Example 24.1

How might you prepare *N*-methyl-2-phenylethylamine using a reductive amination reaction?

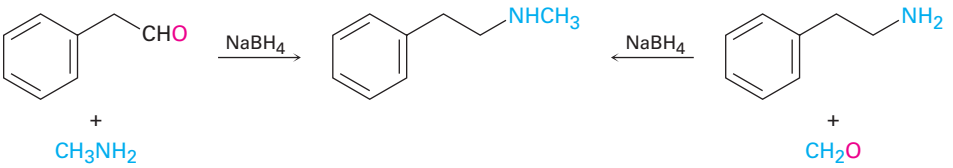


***N*-Methyl-2-phenylethylamine**

Strategy

Look at the target molecule, and identify the groups attached to nitrogen. One of the groups must be derived from the aldehyde or ketone component, and the other must be derived from the amine component. In the case of *N*-methyl-2-phenylethylamine, two combinations can lead to the product: phenylacetaldehyde plus methylamine or formaldehyde plus 2-phenylethylamine. It's usually better to choose the combination with the simpler amine component—methylamine in this case—and to use an excess of that amine as reactant.

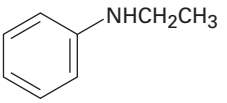
Solution

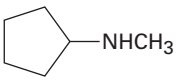


Problem 24.11

How might the following amines be prepared using reductive amination reactions? Show all precursors if more than one is possible.

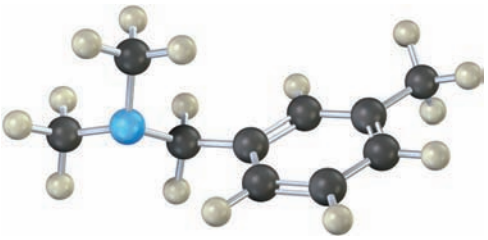
(a) $CH_3CH_2NHCHCH_3$ (CH_3 branch)

(b) 

(c) 

Problem 24.12

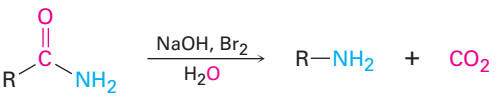
How could you prepare the following amine using a reductive amination reaction?



Hofmann and Curtius Rearrangements

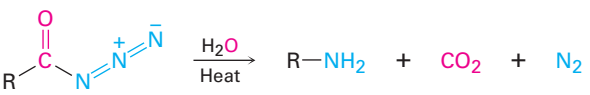
Carboxylic acid derivatives can be converted into primary amines with loss of one carbon atom by both the **Hofmann rearrangement** and the **Curtius rearrangement**. Although the Hofmann rearrangement involves a primary amide and the Curtius rearrangement involves an acyl azide, both proceed through similar mechanisms.

Hofmann rearrangement



An amide

Curtius rearrangement

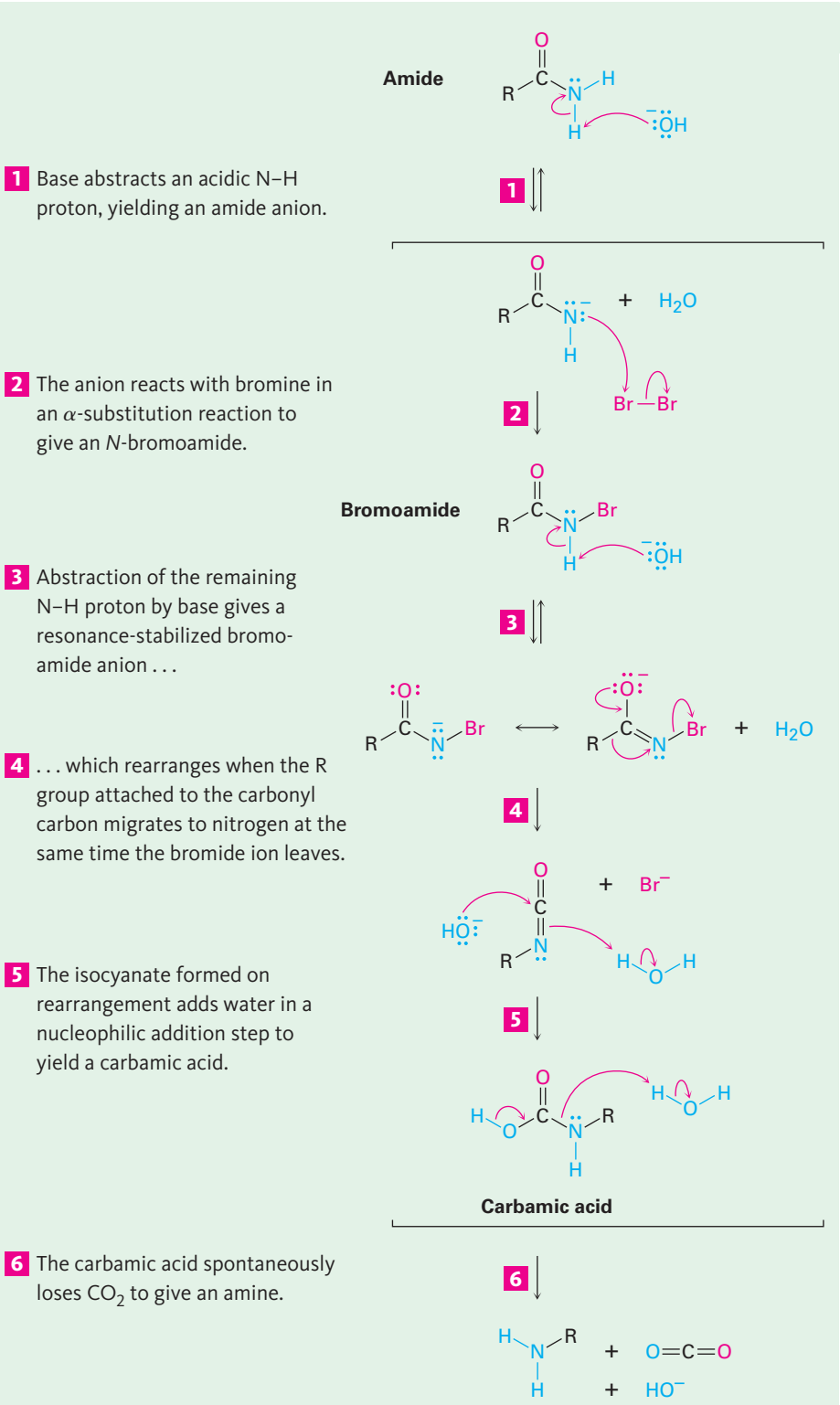


An acyl azide

Hofmann rearrangement occurs when a primary amide, $RCONH_2$, is treated with Br_2 and base **(Figure 24.5)**. The overall mechanism is lengthy, but most of the individual steps have been encountered before. Thus, the bromination of

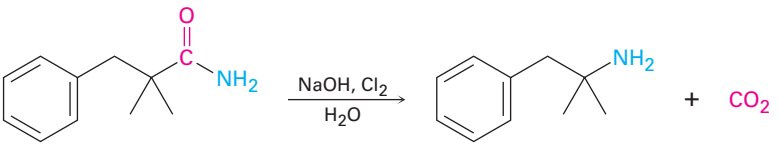
Figure 24.5 | MECHANISM

Mechanism of the Hofmann rearrangement of an amide to an amine. Each step is analogous to a reaction studied previously.



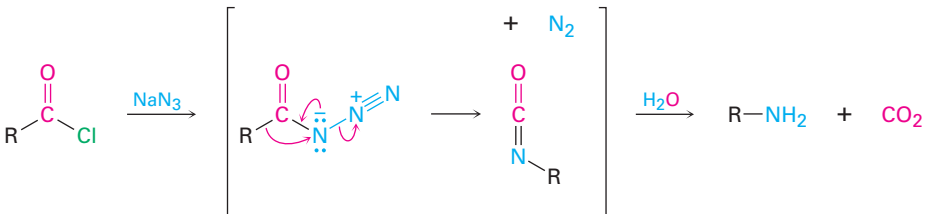
an amide in steps 1 and 2 is analogous to the base-promoted bromination of a ketone enolate ion **(Section 22.6)**, and the rearrangement of the bromoamide anion in step 4 is analogous to a carbocation rearrangement **(Section 7.11).** Nucleophilic addition of water to the isocyanate carbonyl group in step 5 is a typical carbonyl-group process **(Section 19.4)**, as is the final decarboxylation step 6 **(Section 22.7)**.

Despite its mechanistic complexity, the Hofmann rearrangement often gives high yields of both arylamines and alkylamines. For example, the appetite-suppressant drug phentermine is prepared commercially by Hofmann rearrangement of a primary amide. Commonly known by the name Fen-Phen, the combination of phentermine with another appetite-suppressant, fenfluramine, is suspected of causing heart damage.



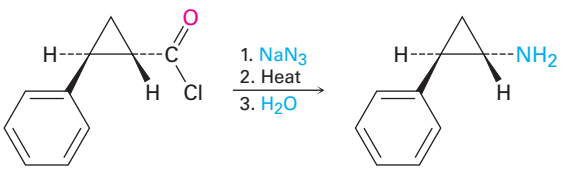
2,2-Dimethyl-3-phenyl-propanamide **Phetermine**

The Curtius rearrangement, like the Hofmann rearrangement, involves migration of an −R group from the C=O carbon atom to the neighboring nitrogen with simultaneous loss of a leaving group. The reaction takes place on heating an acyl azide that is itself prepared by nucleophilic acyl substitution of an acid chloride.



Acid chloride **Acyl azide** **Isocyanate** **Amine**

Also like the Hofmann rearrangement, the Curtius rearrangement is often used commercially. The antidepressant drug tranylcypromine, for instance, is made by Curtius rearrangement of 2-phenylcyclopropanecarbonyl chloride.



***trans*-2-Phenylcyclo-propanecarbonyl chloride** **Tranylcypromine**

Using the Hofmann and Curtius Reactions

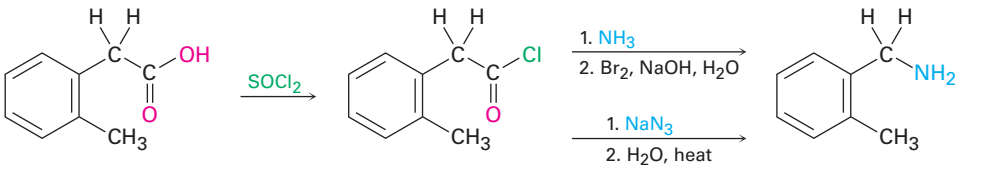
Worked Example 24.2

How would you prepare *o*-methylbenzylamine from a carboxylic acid, using both Hofmann and Curtius rearrangements?

Strategy

Both Hofmann and Curtius rearrangements convert a carboxylic acid derivative—either an amide (Hofmann) or an acid chloride (Curtius)—into a primary amine with loss of one carbon, RCOY → RNH_2. Both reactions begin with the same carboxylic acid, which can be identified by replacing the $-NH_2$ group of the amine product by a $-CO_2H$ group. In the present instance, *o*-methylphenylacetic acid is needed.

Solution

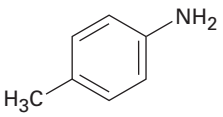


***o*-Methylphenylacetic acid** ***o*-Methylbenzylamine**

Problem 24.13

How would you prepare the following amines, using both Hofmann and Curtius rearrangements on a carboxylic acid derivative?

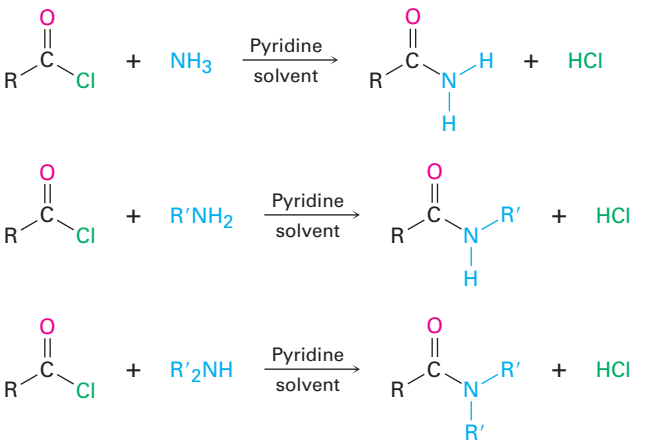
(a) $CH_3CH_3CCH_2CH_2NH_2$ (CH_3 above and below the central C)

(b) 

24.7 Reactions of Amines

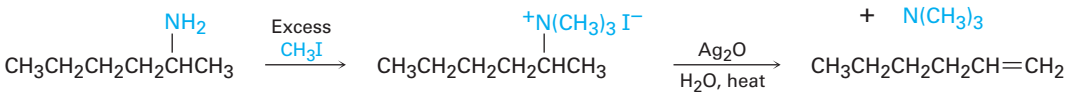
Alkylation and Acylation

We've already studied the two most general reactions of amines—alkylation and acylation. As we saw earlier in this chapter, primary, secondary, and tertiary amines can be alkylated by reaction with a primary alkyl halide. Alkylations of primary and secondary amines are difficult to control and often give mixtures of products, but tertiary amines are cleanly alkylated to give quaternary ammonium salts. Primary and secondary (but not tertiary) amines can also be acylated by nucleophilic acyl substitution reaction with an acid chloride or an acid anhydride to yield an amide **(Sections 21.4 and 21.5)**. Note that overacylation of the nitrogen does not occur because the amide product is much less nucleophilic and less reactive than the starting amine.



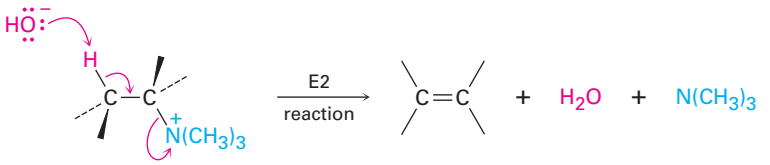
Hofmann Elimination

Like alcohols, amines can be converted into alkenes by an elimination reaction. But because an amide ion, NH_2^-, is such a poor leaving group, it must first be converted into a better leaving group. In the **Hofmann elimination reaction**, an amine is completely methylated by reaction with an excess amount of iodomethane to produce the corresponding quaternary ammonium salt. This salt then undergoes elimination to give an alkene on heating with a base, typically silver oxide, Ag_2O. For example, 1-methylpentylamine is converted into 1-hexene.



1-Methylpentylamine → **(1-Methylpentyl)trimethylammonium iodide** → **1-Hexene (60%)**

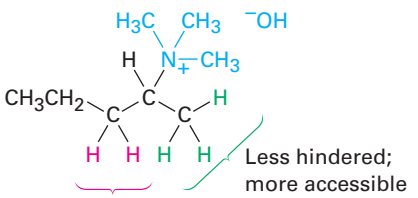
Silver oxide acts by exchanging iodide ion for hydroxide ion in the quaternary salt, thus providing the base necessary for elimination. The actual elimination step is an E2 reaction **(Section 11.8)** in which hydroxide ion removes a proton at the same time that the positively charged nitrogen atom leaves.



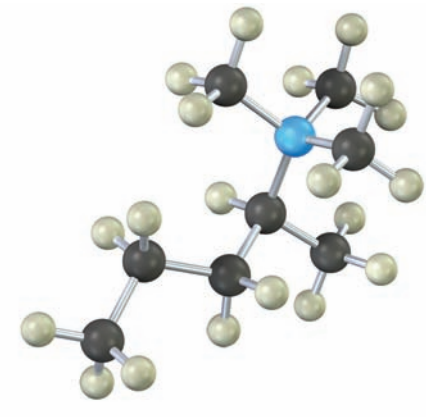
Quaternary ammonium salt → **Alkene**

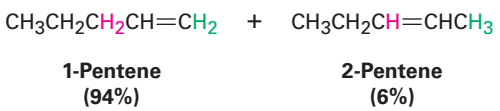
Unlike what happens in other E2 reactions, the major product of the Hofmann elimination is the less highly substituted alkene rather than the more highly substituted one, as shown by the reaction of (1-methylbutyl)trimethylammonium hydroxide to give 1-pentene rather than the alternative 2-pentene. The reason for this non-Zaitsev result is probably steric. Because of the large size

of the trialkylamine leaving group, the base must abstract a hydrogen from the more accessible, least hindered position.



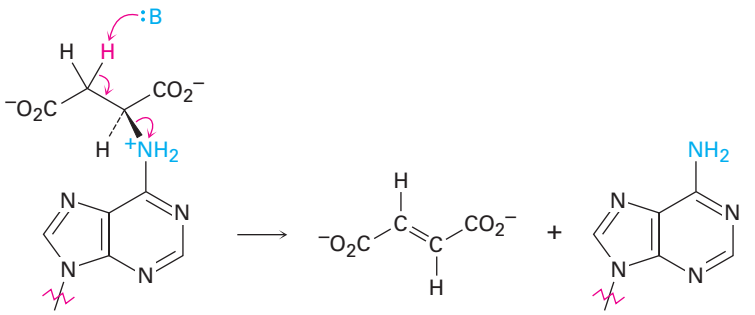
(1-Methylbutyl)trimethylammonium hydroxide





1-Pentene (94%) **2-Pentene (6%)**

The Hofmann elimination reaction is not often used today in the laboratory, but analogous biological eliminations occur frequently, although usually with protonated ammonium ions rather than quaternary ammonium salts. In the biosynthesis of nucleic acids, for instance, a substance called adenylosuccinate undergoes an elimination of a positively charged nitrogen to give fumarate plus adenosine monophosphate.

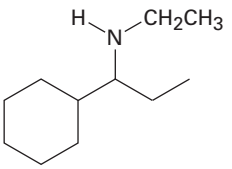


Adenylosuccinate **Fumarate** **Adenosine monophosphate**

Predicting the Product of a Hofmann Elimination

Worked Example 24.3

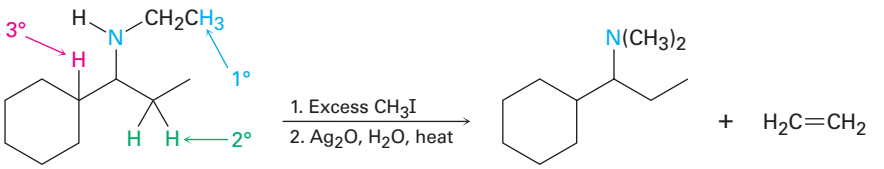
What product would you expect from Hofmann elimination of the following amine?



Strategy

The Hofmann elimination is an E2 reaction that converts an amine into an alkene and occurs with non-Zaitsev regiochemistry to form the less highly substituted double bond. To predict the product, look at the reactant and identify the positions from which elimination might occur (the positions two carbons removed from nitrogen). Then carry out an elimination using the most accessible hydrogen. In the present instance, there are three possible positions from which elimination might occur—one primary, one secondary, and one tertiary. The primary position is the most accessible and leads to the least highly substituted alkene, ethylene.

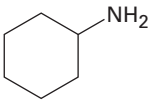
Solution



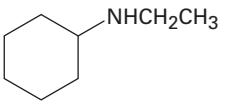
Problem 24.14

What products would you expect from Hofmann elimination of the following amines? If more than one product is formed, indicate which is major.

(a) $CH_3CH_2CH_2\underset{\displaystyle NH_2}{\underset{|}{C}}HCH_2CH_2CH_2CH_3$

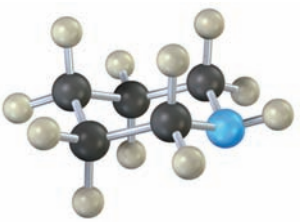
(b) 

(c) $CH_3CH_2CH_2\underset{\displaystyle NH_2}{\underset{|}{C}}HCH_2CH_2CH_3$

(d) 

Problem 24.15

What product would you expect from Hofmann elimination of a heterocyclic amine such as piperidine? Write all the steps.



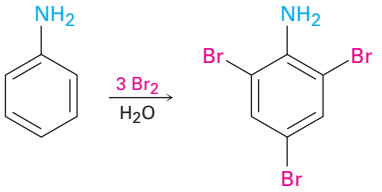
Piperidine

24.8 Reactions of Arylamines

Electrophilic Aromatic Substitution

An amino group is strongly activating and ortho- and para-directing in electrophilic aromatic substitution reactions **(Section 16.5)**. This high reactivity of amino-substituted benzenes can be a drawback at times because it's often difficult to prevent polysubstitution. Reaction of aniline with Br_2, for instance, takes

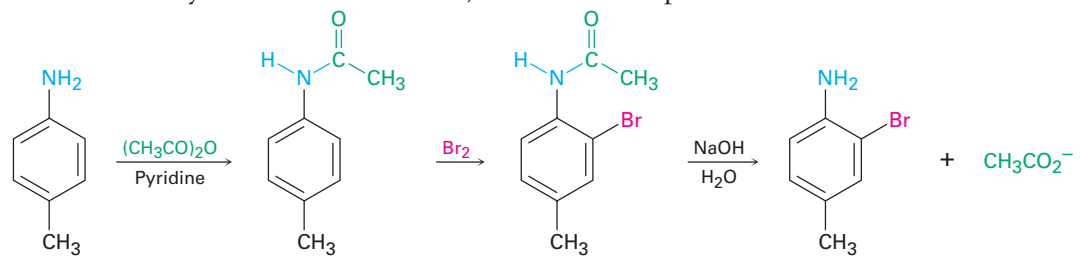
place rapidly and yields the 2,4,6-tribrominated product. The amino group is so strongly activating that it's not possible to stop at the monobromo stage.



Aniline **2,4,6-Tribromoaniline (100%)**

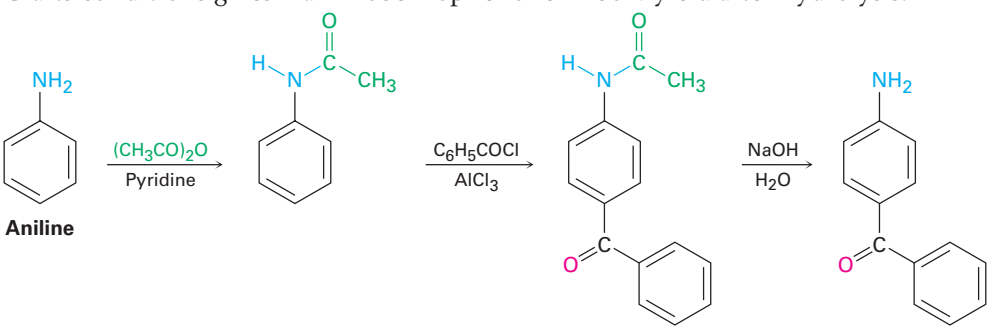
Another drawback to the use of amino-substituted benzenes in electrophilic aromatic substitution reactions is that Friedel–Crafts reactions are not successful **(Section 16.3)**. The amino group forms an acid–base complex with the $AlCl_3$ catalyst, which prevents further reaction from occurring. Both drawbacks can be overcome, however, by carrying out electrophilic aromatic substitution reactions on the corresponding amide rather than on the free amine.

As we saw in **Section 21.5**, treatment of an amine with acetic anhydride yields the corresponding acetyl amide, or acetamide. Although still activating and ortho-, para-directing, amido substituents (−NHCOR) are less strongly activating and less basic than amino groups because their nitrogen lone-pair electrons are delocalized by the neighboring carbonyl group. As a result, bromination of an *N*-arylamide occurs cleanly to give a monobromo product, and hydrolysis of the amide with aqueous base then gives the free amine. For example, *p*-toluidine (4-methylaniline) can be acetylated, brominated, and hydrolyzed to yield 2-bromo-4-methylaniline. None of the 2,6-dibrominated product is obtained.



***p*-Toluidine** **2-Bromo-4-methylaniline (79%)**

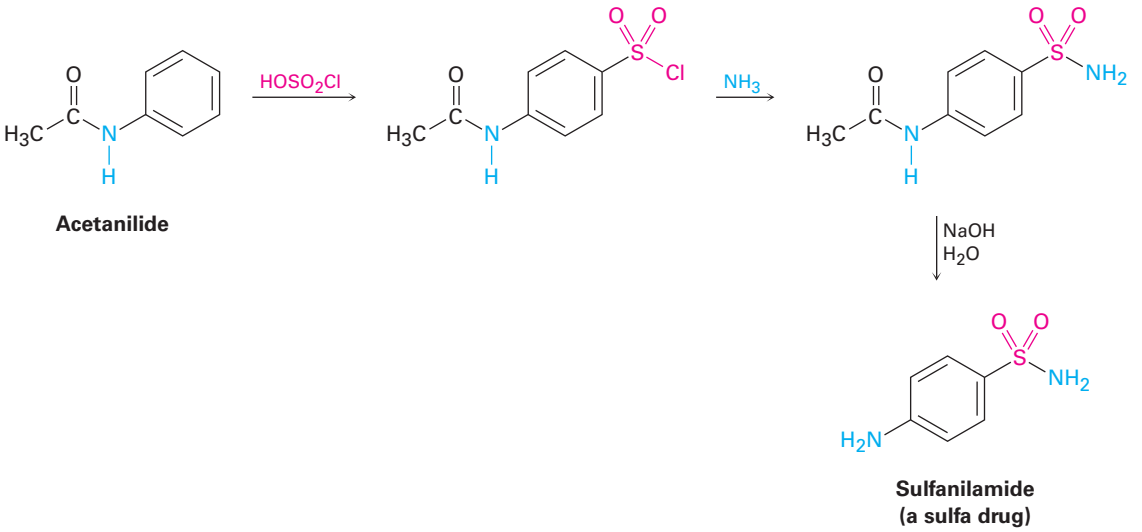
Friedel–Crafts alkylations and acylations of *N*-arylamides also proceed normally. For example, benzoylation of acetanilide (*N*-acetylaniline) under Friedel–Crafts conditions gives 4-aminobenzophenone in 80% yield after hydrolysis.



Aniline **4-Aminobenzophenone (80%)**

Modulating the reactivity of an amino-substituted benzene by forming an amide is a useful trick that allows many kinds of electrophilic aromatic substitutions to be carried out that would otherwise be impossible. An example is the preparation of the sulfa drugs, such as sulfanilamide.

Sulfa drugs were among the first pharmaceutical agents to be used clinically against bacterial infection. Although they have largely been replaced today by safer and more powerful antibiotics, sulfa drugs are credited with saving the lives of thousands of wounded during World War II and are still prescribed for urinary tract infections. They are prepared by chlorosulfonation of acetanilide, followed by reaction of *p*-(*N*-acetylamino)benzenesulfonyl chloride with ammonia or some other amine to give a sulfonamide. Hydrolysis of the amide then yields the sulfa drug. Note that hydrolysis of the amide can be carried out in the presence of the sulfonamide group because sulfonamides hydrolyze very slowly.

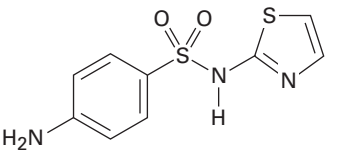


Acetanilide

Sulfanilamide (a sulfa drug)

Problem 24.16

Propose a synthesis of the drug sulfathiazole from benzene and any necessary amine.



Sulfathiazole

Problem 24.17

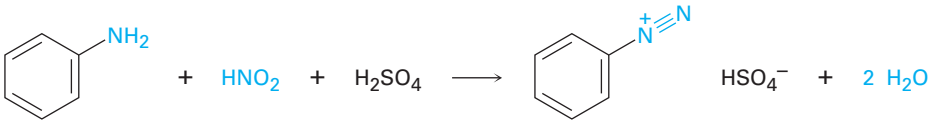
Propose syntheses of the following compounds from benzene:

(a) *N*,*N*-Dimethylaniline **(b)** *p*-Chloroaniline
(c) *m*-Chloroaniline **(d)** 2,4-Dimethylaniline

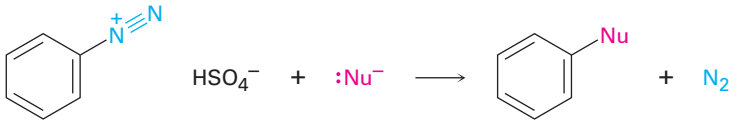
Diazonium Salts: The Sandmeyer Reaction

Primary arylamines react with nitrous acid, HNO_2, to yield stable *arenediazonium* salts, $Ar—\overset{+}{N}{\equiv}N\ X^-$, a process called a *diazotization* reaction. Alkylamines also react with nitrous acid, but the corresponding alkanediazonium products

are so reactive they can't be isolated. Instead, they lose nitrogen instantly to yield carbocations. The analogous loss of N_2 from an arenediazonium ion to yield an aryl cation is disfavored by the instability of the cation.

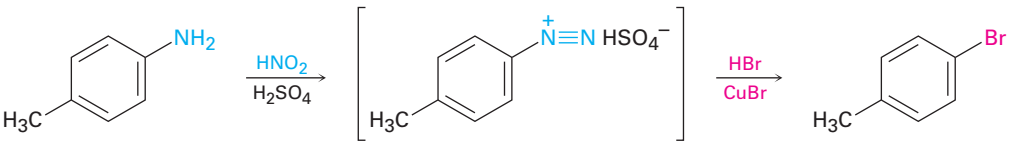


Arenediazonium salts are useful because the diazonio group (N_2) can be replaced by a nucleophile in a substitution reaction.

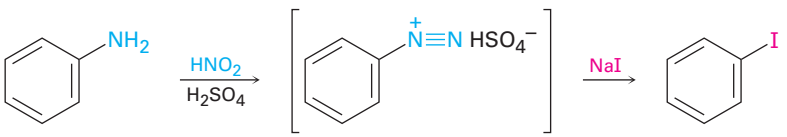


Many different nucleophiles—halide, hydride, cyanide, and hydroxide among others—react with arenediazonium salts, yielding many different kinds of substituted benzenes. The overall sequence of (1) nitration, (2) reduction, (3) diazotization, and (4) nucleophilic substitution is perhaps the single most versatile method of aromatic substitution.

Aryl chlorides and bromides are prepared by reaction of an arenediazonium salt with the corresponding copper(I) halide, CuX, a process called the **Sandmeyer reaction**. Aryl iodides can be prepared by direct reaction with NaI without using a copper(I) salt. Yields generally fall between 60% and 80%.

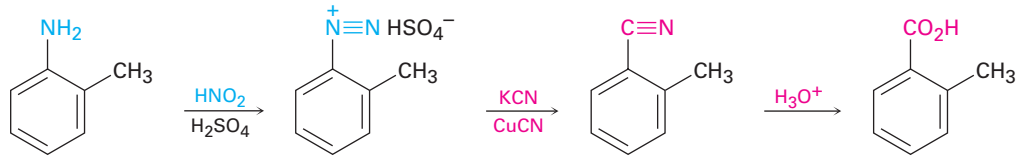


***p*-Methylaniline** ***p*-Bromotoluene (73%)**



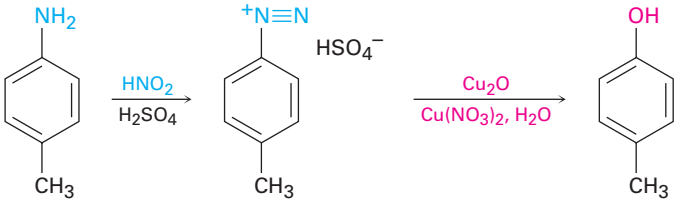
Aniline **Iodobenzene (67%)**

Similar treatment of an arenediazonium salt with CuCN yields the nitrile, ArCN, which can then be further converted into other functional groups such as carboxyl. For example, Sandmeyer reaction of *o*-methylbenzenediazonium bisulfate with CuCN yields *o*-methylbenzonitrile, which can be hydrolyzed to give *o*-methylbenzoic acid. This product can't be prepared from *o*-xylene by the usual side-chain oxidation route because both methyl groups would be oxidized.



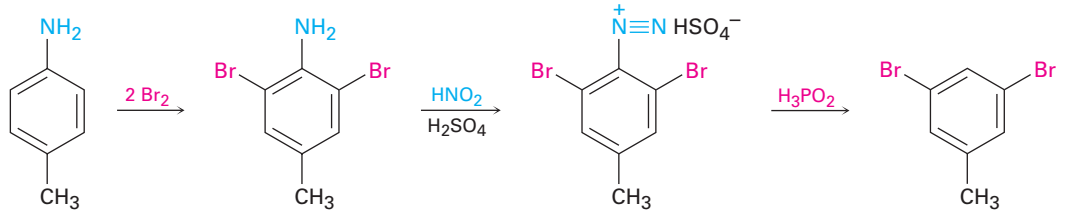
***o*-Methylaniline** ***o*-Methylbenzene-diazonium bisulfate** ***o*-Methylbenzonitrile** ***o*-Methylbenzoic acid**

The diazonio group can also be replaced by −OH to yield a phenol and by −H to yield an arene. A phenol is prepared by reaction of the arenediazonium salt with copper(I) oxide in an aqueous solution of copper(II) nitrate, a reaction that is especially useful because few other general methods exist for introducing an −OH group onto an aromatic ring.

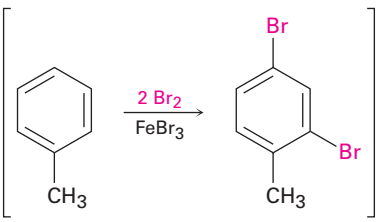


***p*-Methylaniline (*p*-Toluidine)** ***p*-Cresol (93%)**

Reduction of a diazonium salt to give an arene occurs on treatment with hypophosphorous acid, H_3PO_2. This reaction is used primarily when there is a need for temporarily introducing an amino substituent onto a ring to take advantage of its directing effect. Suppose, for instance, that you needed to make 3,5-dibromotoluene. The product can't be made by direct bromination of toluene because reaction would occur at positions 2 and 4. Starting with *p*-methylaniline (*p*-toluidine), however, dibromination occurs ortho to the strongly directing amino substituent, and diazotization followed by treatment with H_3PO_2 to remove the amino group yields the desired product.

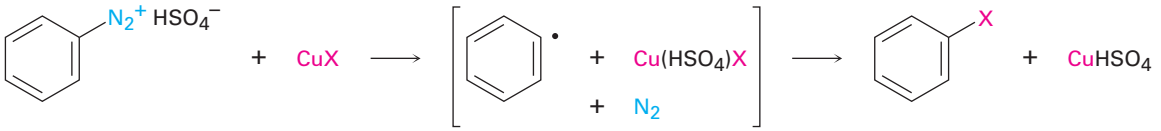


***p*-Methylaniline** **3,5-Dibromotoluene**



Toluene **2,4-Dibromotoluene**

Mechanistically, these diazonio replacement reactions occur through radical rather than polar pathways. In the presence of a copper(I) compound, for instance, it's thought that the arenediazonium ion is first converted to an aryl radical plus copper(II), followed by subsequent reaction to give product plus regenerated copper(I) catalyst.

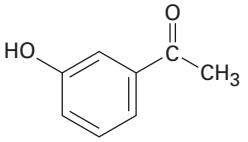


Diazonium compound **Aryl radical**

Using Diazonium Replacement Reactions

Worked Example 24.4

How would you prepare *m*-hydroxyacetophenone from benzene, using a diazonium replacement reaction in your scheme?



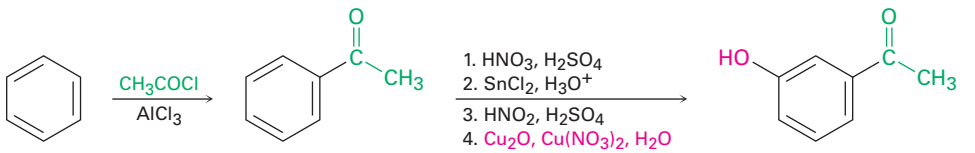
***m*-Hydroxyacetophenone**

Strategy

As always, organic syntheses are planned by working retrosynthetically from the final product, one step at a time. First, identify the functional groups in the product and recall how those groups can be synthesized. *m*-Hydroxyacetophenone has an —OH group and a $-COCH_3$ group in a meta relationship on a benzene ring. A hydroxyl group is generally introduced onto an aromatic ring by a four-step sequence of nitration, reduction, diazotization, and diazonio replacement. An acetyl group is introduced by a Friedel–Crafts acylation reaction.

Next, ask yourself what an immediate precursor of the target might be. Since an acetyl group is a meta director while a hydroxyl group is an ortho and para director, acetophenone might be a precursor of *m*-hydroxyacetophenone. Benzene, in turn, is a precursor of acetophenone.

Solution



Benzene **Acetophenone** ***m*-Hydroxyacetophenone**

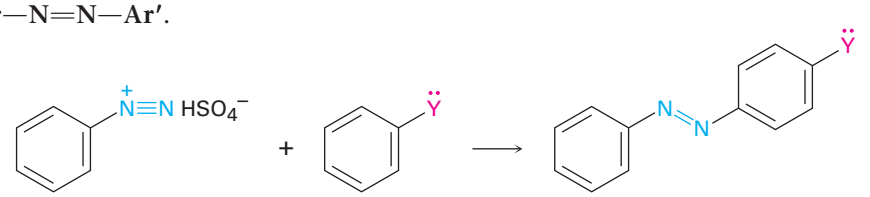
Problem 24.18

How would you prepare the following compounds from benzene, using a diazonium replacement reaction in your scheme?

(a) *p*-Bromobenzoic acid **(b)** *m*-Bromobenzoic acid **(c)** *m*-Bromochlorobenzene
(d) *p*-Methylbenzoic acid **(e)** 1,2,4-Tribromobenzene

Diazonium Coupling Reactions

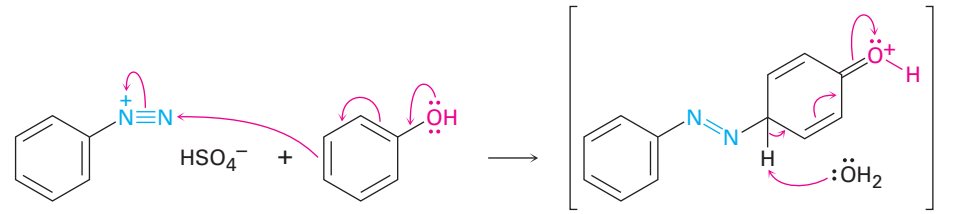
Arenediazonium salts undergo a coupling reaction with activated aromatic rings such as phenols and arylamines to yield brightly colored **azo compounds**, **Ar—N=N—Ar′**.



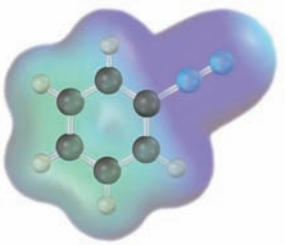
An azo compound

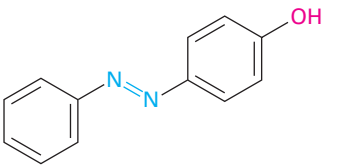
where Y = —OH or $-NR_2$

Diazonium coupling reactions are typical electrophilic aromatic substitutions in which the positively charged diazonium ion is the electrophile that reacts with the electron-rich ring of a phenol or arylamine. Reaction usually occurs at the para position.



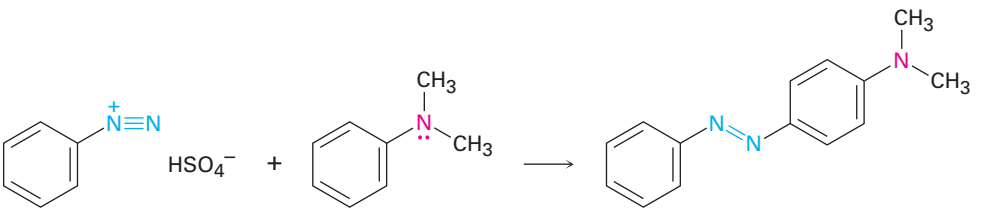
Benzenediazonium bisulfate **Phenol**





***p*-Hydroxyazobenzene (orange crystals, mp 152 °C)**

Azo-coupled products are widely used as dyes for textiles because their extended conjugated π electron system causes them to absorb in the visible region of the electromagnetic spectrum **(Section 14.9)**. *p*-(Dimethylamino)-azobenzene, for instance, is a bright yellow compound that was at one time used as a coloring agent in margarine.



Benzenediazonium bisulfate ***N,N*-Dimethylaniline** ***p*-(Dimethylamino)azobenzene (yellow crystals, mp 127 °C)**

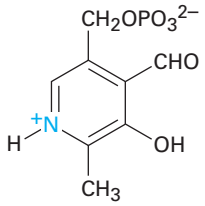
Problem 24.19

Propose a synthesis of *p*-(dimethylamino)azobenzene from benzene as your only organic starting material.

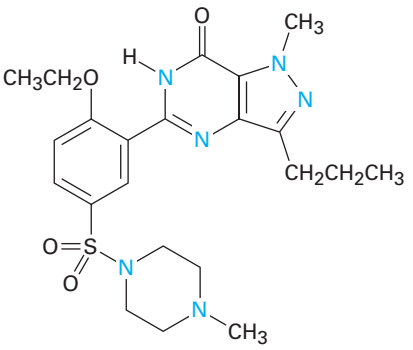
24.9 Heterocyclic Amines

As noted in **Section 15.5** in connection with a discussion of aromaticity, a cyclic organic compound that contains atoms of two or more elements in its ring is a called a *heterocycle*. Heterocyclic amines are particularly common, and

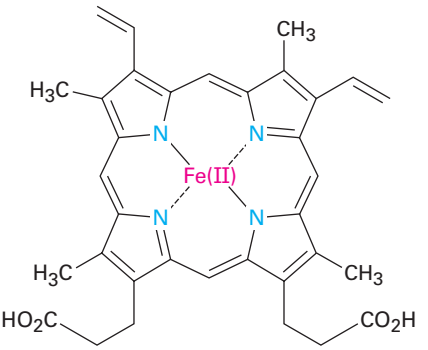
many have important biological properties. Pyridoxal phosphate, a coenzyme; sildenafil (Viagra), a well-known pharmaceutical; and heme, the oxygen carrier in blood, are examples.



Pyridoxal phosphate (a coenzyme)



Sildenafil (Viagra)

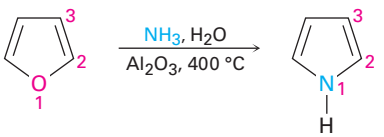


Heme

Most heterocycles have the same chemistry as their open-chain counterparts. Lactones and acyclic esters behave similarly, lactams and acyclic amides behave similarly, and cyclic and acyclic ethers behave similarly. In certain cases, however, particularly when the ring is unsaturated, heterocycles have unique and interesting properties.

Pyrrole and Imidazole

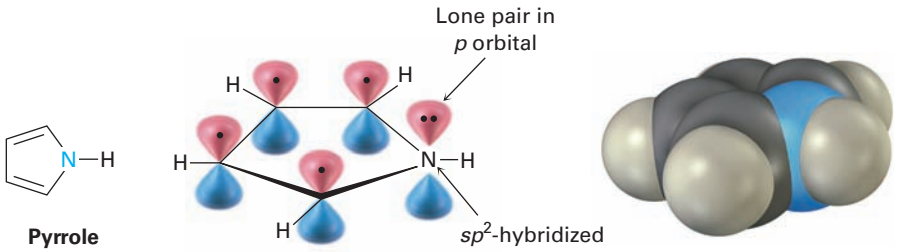
Pyrrole, the simplest five-membered unsaturated heterocyclic amine, is obtained commercially by treatment of furan with ammonia over an alumina catalyst at 400 °C. Furan, the oxygen-containing analog of pyrrole, is obtained by acid-catalyzed dehydration of the five-carbon sugars found in oat hulls and corncobs.



Furan **Pyrrole**

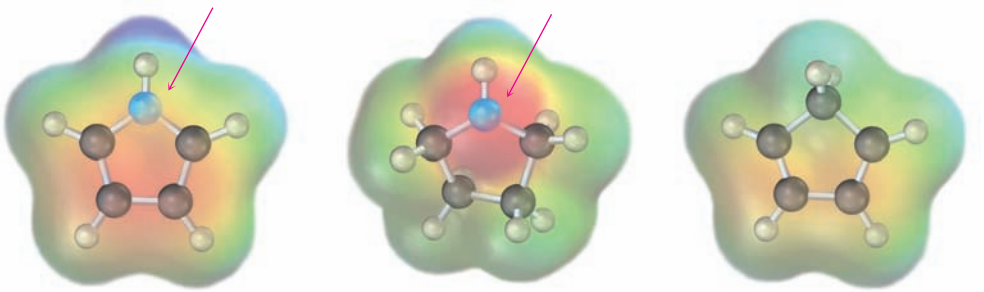
Although pyrrole appears to be both an amine and a conjugated diene, its chemical properties are not consistent with either of these structural features. Unlike most other amines, pyrrole is not basic—the pK_a of the pyrrolinium ion is 0.4; unlike most other conjugated dienes, pyrrole undergoes electrophilic substitution reactions rather than additions. The reason for both these properties, as noted in **Section 15.5** is that pyrrole has six π electrons and is aromatic.

Each of the four carbons contributes one π electron, and the sp^2-hybridized nitrogen contributes two more from its lone pair.



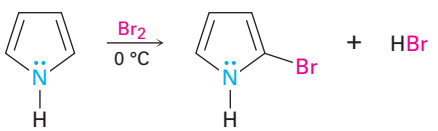
Six π electrons

Because the nitrogen lone pair is a part of the aromatic sextet, protonation on nitrogen would destroy the aromaticity of the ring. The nitrogen atom in pyrrole is therefore less electron-rich, less basic, and less nucleophilic than the nitrogen in an aliphatic amine. By the same token, the carbon atoms of pyrrole are more electron-rich and more nucleophilic than typical double-bond carbons. The pyrrole ring is therefore reactive toward electrophiles in the same way that enamines are **(Section 23.11)**. Electrostatic potential maps show how the pyrrole nitrogen is electron-poor (less red) compared with the nitrogen in its saturated counterpart pyrrolidine, while the pyrrole carbon atoms are electron-rich (more red) compared with the carbons in 1,3-cyclopentadiene.



Pyrrole **Pyrrolidine** **1,3-Cyclopentadiene**

The chemistry of pyrrole is similar to that of activated benzene rings. In general, however, the heterocycles are more reactive toward electrophiles than benzene rings are, and low temperatures are often necessary to control the reactions. Halogenation, nitration, sulfonation, and Friedel–Crafts acylation can all be accomplished. For example:



Pyrrole **2-Bromopyrrole (92%)**

Electrophilic substitutions normally occur at C2, the position next to the nitrogen, because reaction at this position leads to a more stable intermediate cation having three resonance forms, whereas reaction at C3 gives a less stable cation with only two resonance forms **(Figure 24.6)**.

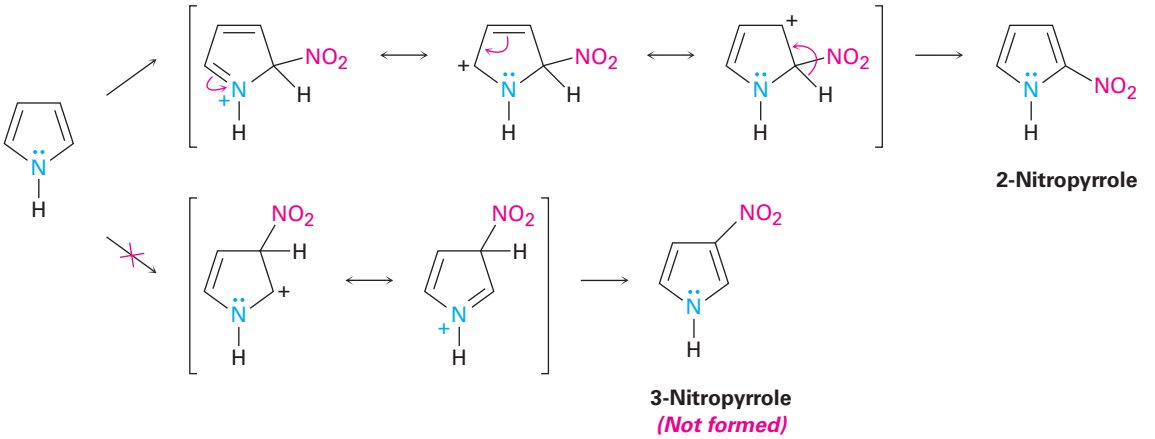
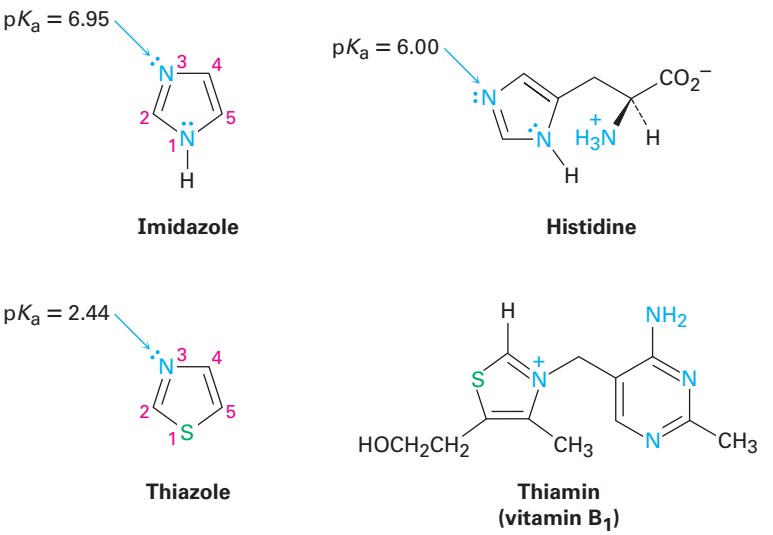


Figure 24.6 Electrophilic nitration of pyrrole. The intermediate produced by reaction at C2 is more stable than that produced by reaction at C3.

Other common five-membered heterocyclic amines include imidazole and thiazole. Imidazole, a constituent of the amino acid histidine, has two nitrogens, only one of which is basic. Thiazole, the five-membered ring system on which the structure of thiamin (vitamin B_1) is based, also contains a basic nitrogen that is alkylated in thiamin to form a quaternary ammonium ion.



Problem 24.20

Draw an orbital picture of thiazole. Assume that both the nitrogen and sulfur atoms are sp^2-hybridized, and show the orbitals that the lone pairs occupy.

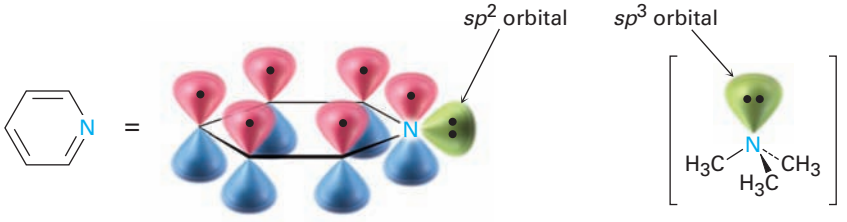
Problem 24.21

What is the percent protonation of the imidazole nitrogen atom in histidine at a physiological pH of 7.3 **(Section 24.5)**?

Pyridine and Pyrimidine

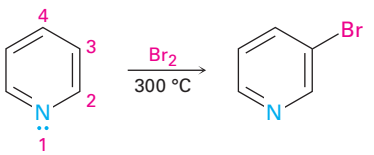
Pyridine is the nitrogen-containing heterocyclic analog of benzene. Like benzene, pyridine is a flat, aromatic molecule, with bond angles of 120° and C–C bond lengths of 139 pm, intermediate between typical single and double bonds. The five carbon atoms and the sp^2-hybridized nitrogen atom each contribute one π electron to the aromatic sextet, and the lone-pair electrons occupy an sp^2 orbital in the plane of the ring **(Section 15.5)**.

As shown previously in Table 24.1, pyridine (pK_a = 5.25) is a stronger base than pyrrole but a weaker base than alkylamines. The diminished basicity of pyridine compared with that of alkylamines is due to the fact that the lone-pair electrons on the pyridine nitrogen are in an sp^2 orbital, while those on an alkylamine nitrogen are in an sp^3 orbital. Because *s* orbitals have their maximum electron density at the nucleus but *p* orbitals have a node at the nucleus, electrons in an orbital with more *s* character are held more closely to the positively charged nucleus and are less available for bonding. As a result, the sp^2-hybridized nitrogen atom (33% *s* character) in pyridine is less basic than the sp^3-hybridized nitrogen in an alkylamine (25% *s* character).



Pyridine

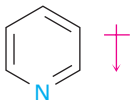
Unlike benzene, pyridine undergoes electrophilic aromatic substitution reactions with difficulty. Halogenation can be carried out under drastic conditions, but nitration occurs in very low yield, and Friedel–Crafts reactions are not successful. Reactions usually give the 3-substituted product.



Pyridine **3-Bromopyridine (30%)**

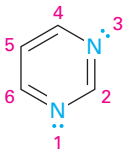
The low reactivity of pyridine toward electrophilic aromatic substitution is caused by a combination of factors. One is that acid–base complexation between the basic ring nitrogen atom and the incoming electrophile places a positive charge on the ring, thereby deactivating it. Equally important is that the electron density of the ring is decreased by the electron-withdrawing inductive effect of the electronegative nitrogen atom. Thus, pyridine has a substantial dipole moment (μ = 2.26 D), with the ring carbons acting as the positive end

of the dipole. Reaction of an electrophile with the positively polarized carbon atoms is therefore difficult.



$\mu = 2.26$ D

In addition to pyridine, the six-membered diamine pyrimidine is also found commonly in biological molecules, particularly as a constituent of nucleic acids. With a pK_a of 1.3, pyrimidine is substantially less basic than pyridine because of the inductive effect of the second nitrogen.



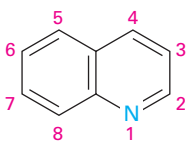
Pyrimidine
pK_a = 1.3

Problem 24.22

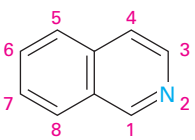
Electrophilic aromatic substitution reactions of pyridine normally occur at C3. Draw the carbocation intermediates resulting from reaction of an electrophile at C2, C3, and C4, and explain the observed result.

Polycyclic Heterocycles

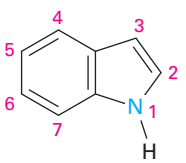
As we saw in **Section 15.6**, quinoline, isoquinoline, indole, and purine are common polycyclic heterocycles. The first three contain both a benzene ring and a heterocyclic aromatic ring, while purine contains two heterocyclic rings joined together. All four ring systems occur commonly in nature, and many compounds with these rings have pronounced physiological activity. The quinoline alkaloid quinine, for instance, is widely used as an antimalarial drug; tryptophan is a common amino acid; and the purine adenine is a constituent of nucleic acids.



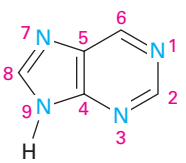
Quinoline



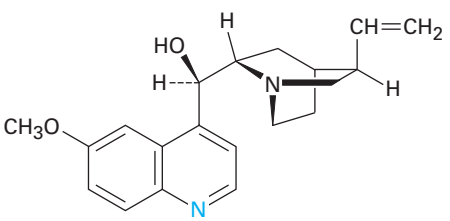
Isoquinoline



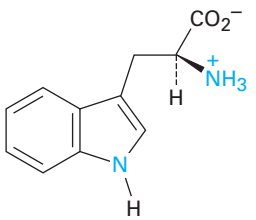
Indole



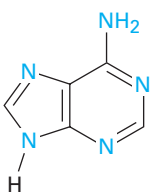
Purine



Quinine
(antimalarial)

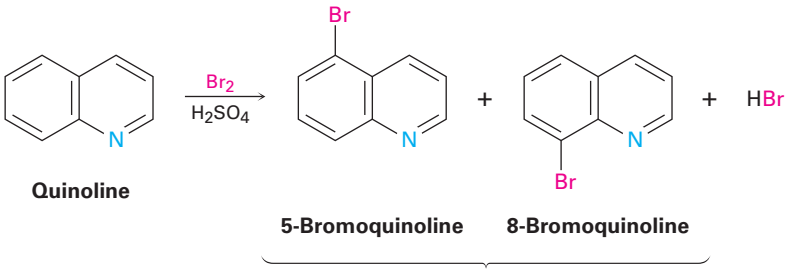


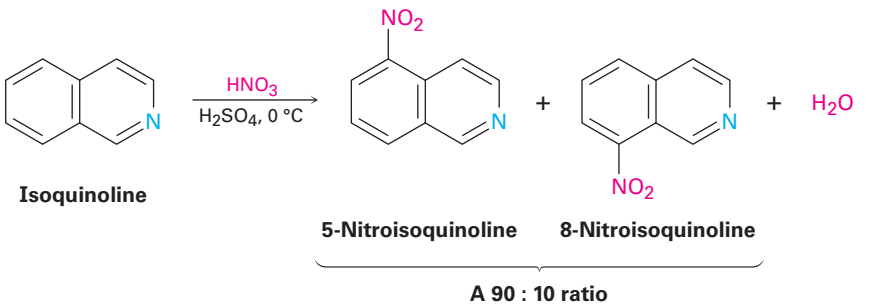
Tryptophan
(amino acid)



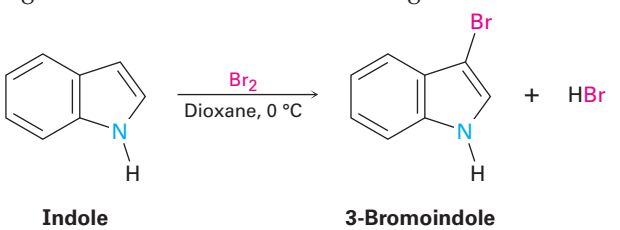
Adenine
(DNA constituent)

The chemistry of these polycyclic heterocycles is just what you might expect from a knowledge of the simpler heterocycles pyridine and pyrrole. Quinoline and isoquinoline both have basic, pyridine-like nitrogen atoms, and both undergo electrophilic substitutions. As with pyridine, both quinoline and isoquinoline are less reactive toward electrophilic substitution than benzene because of the electronegative nitrogen atom that withdraws electrons from the ring. Reaction occurs on the benzene ring rather than on the nitrogen-containing pyridine ring, and a mixture of substitution products is obtained.

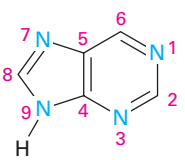


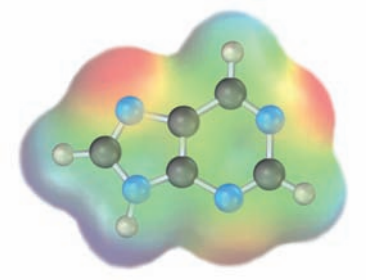


Indole has a nonbasic, pyrrole-like nitrogen and undergoes electrophilic substitution more easily than benzene. Substitution occurs at C3 of the electron-rich pyrrole ring rather than on the benzene ring.



Purine has three basic, pyridine-like nitrogens with lone-pair electrons in sp^2 orbitals in the plane of the ring. The remaining purine nitrogen is nonbasic and pyrrole-like, with its lone-pair electrons as part of the aromatic π electron system.

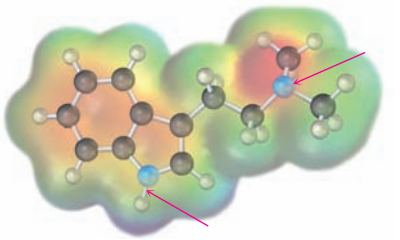




Purine

Problem 24.23

Which nitrogen atom in the hallucinogenic indole alkaloid *N*,*N*-dimethyltryptamine is more basic? Explain.



***N*,*N*-Dimethyltryptamine**

Problem 24.24

Indole reacts with electrophiles at C3 rather than at C2. Draw resonance forms of the intermediate cations resulting from reaction at C2 and C3, and explain the observed results.

24.10 Spectroscopy of Amines

Infrared Spectroscopy

Primary and secondary amines can be identified by a characteristic N–H stretching absorption in the 3300 to 3500 cm^{-1} range of the IR spectrum. Alcohols also absorb in this range **(Section 17.11)**, but amine absorption bands are generally sharper and less intense than hydroxyl bands. Primary amines show a pair of bands at about 3350 and 3450 cm^{-1}, and secondary amines show a single band at 3350 cm^{-1}. Tertiary amines have no absorption in this region because they have no N–H bonds. An IR spectrum of cyclohexylamine is shown in **Figure 24.7**.

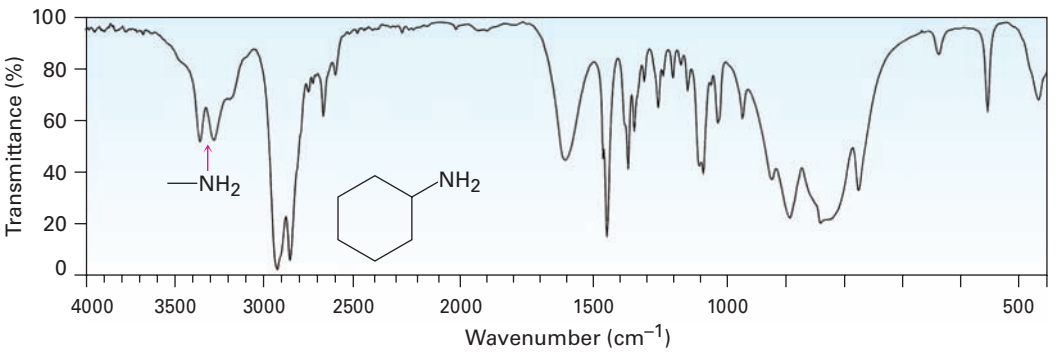
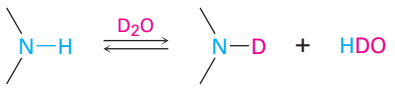


Figure 24.7 IR spectrum of cyclohexylamine.

Nuclear Magnetic Resonance Spectroscopy

Amines are difficult to identify solely by ^1H NMR spectroscopy because N–H hydrogens tend to appear as broad signals without clear-cut coupling to neighboring C–H hydrogens. As with O–H absorptions **(Section 17.11)**,

amine N–H absorptions can appear over a wide range and are best identified by adding a small amount of D_2O to the sample tube. Exchange of N–D for N–H occurs, and the N–H signal disappears from the NMR spectrum.



Hydrogens on the carbon next to nitrogen are deshielded because of the electron-withdrawing effect of the nitrogen, and they therefore absorb at lower field than alkane hydrogens. *N*-Methyl groups are particularly distinctive because they absorb as a sharp three-proton singlet at 2.2 to 2.6 δ. This *N*-methyl resonance at 2.42 δ is easily seen in the ^{1}H NMR spectrum of *N*-methylcyclohexylamine **(Figure 24.8)**.

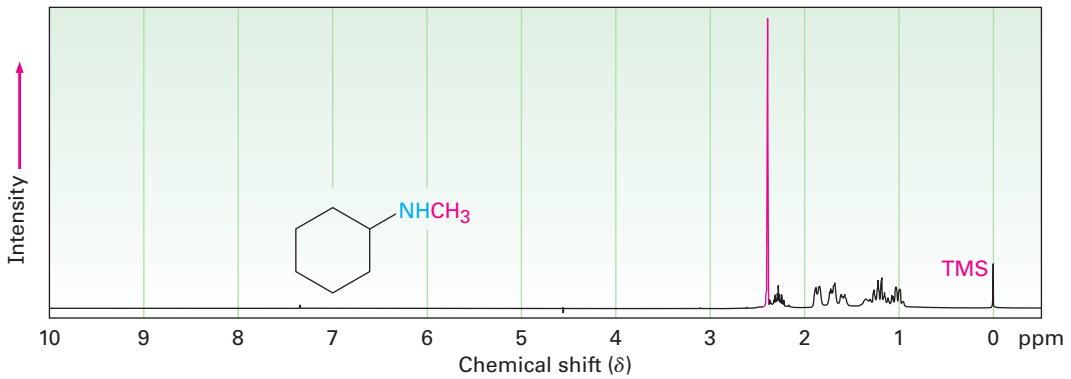
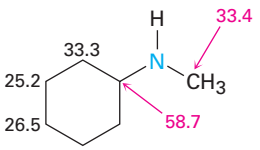


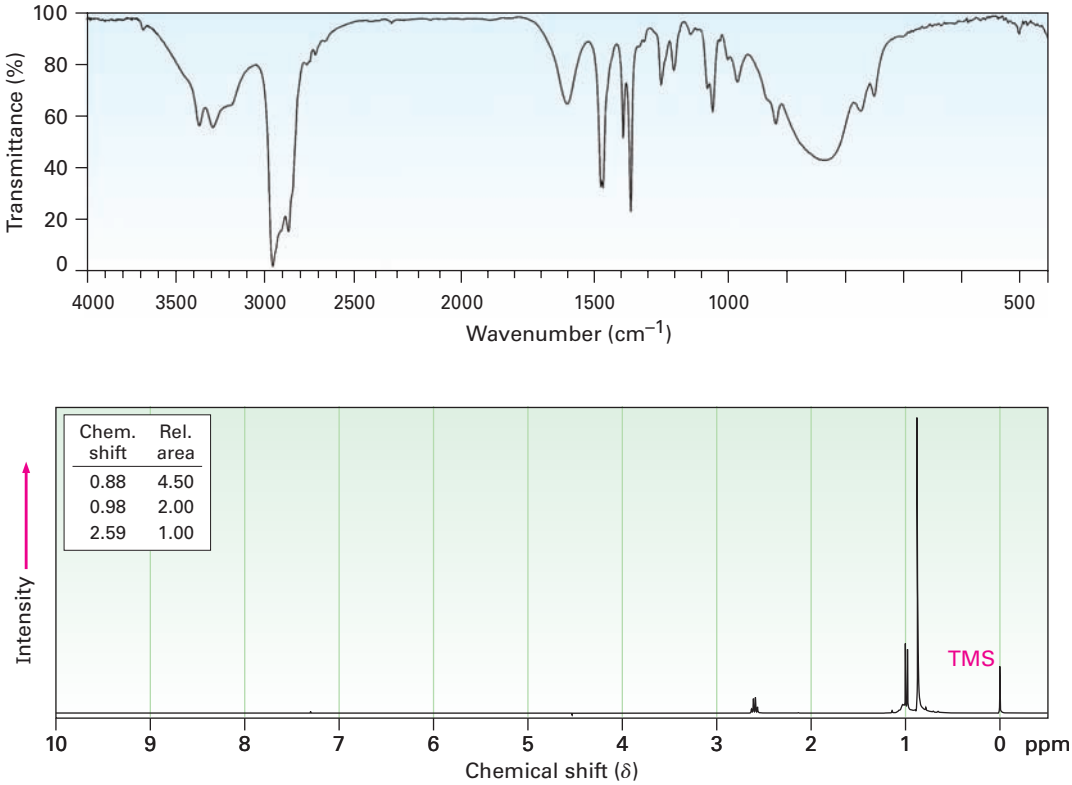
Figure 24.8 Proton NMR spectrum of *N*-methylcyclohexylamine.

Carbons next to amine nitrogens are slightly deshielded in the ^{13}C NMR spectrum and absorb about 20 ppm downfield from where they would absorb in an alkane of similar structure. In *N*-methylcyclohexylamine, for example, the ring carbon to which nitrogen is attached absorbs at a position 24 ppm lower than that of any other ring carbon.



Problem 24.25

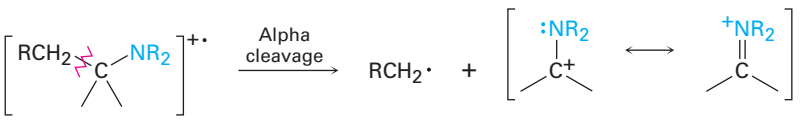
Compound **A**, $C_6H_{12}O$, has an IR absorption at 1715 cm^{-1} and gives compound **B**, $C_6H_{15}N$, when treated with ammonia and $NaBH_4$. The IR and ^{1}H NMR spectra of **B** are shown. What are the structures of **A** and **B**?



Mass Spectrometry

The *nitrogen rule* of mass spectrometry says that a compound with an odd number of nitrogen atoms has an odd-numbered molecular weight. Thus, the presence of nitrogen in a molecule is detected simply by observing its mass spectrum. An odd-numbered molecular ion usually means that the unknown compound has one or three nitrogen atoms, and an even-numbered molecular ion usually means that a compound has either zero or two nitrogen atoms. The logic behind the rule derives from the fact that nitrogen is trivalent, thus requiring an odd number of hydrogen atoms. For example, morphine has the formula $C_{17}H_{19}NO_3$ and a molecular weight of 285 amu.

Alkylamines undergo a characteristic α cleavage in the mass spectrometer, similar to the cleavage observed for alcohols **(Section 17.11)**. A C–C bond nearest the nitrogen atom is broken, yielding an alkyl radical and a resonance-stabilized, nitrogen-containing cation.



As an example, the mass spectrum of *N*-ethylpropylamine shown in **Figure 24.9** has peaks at $m/z = 58$ and $m/z = 72$, corresponding to the two possible modes of α cleavage.

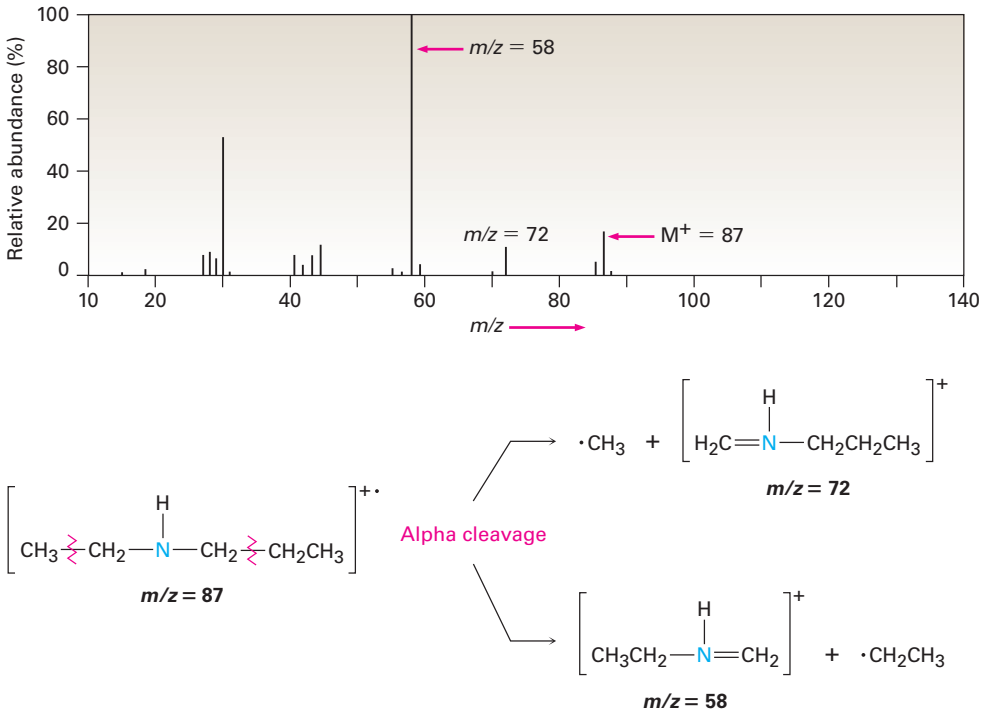


Figure 24.9 Mass spectrum of *N*-ethylpropylamine. The two possible modes of α cleavage lead to the observed fragment ions at $m/z = 58$ and $m/z = 72$.

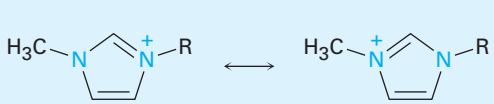
Courtesy of Dr. Robin Rogers

Yes, this liquid really does consist of an ionic rather than a molecular substance.

Green Chemistry II: Ionic Liquids | A DEEPER LOOK

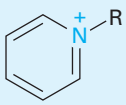
Liquids made of ions? Usually when we think of ionic compounds, we think of high-melting solids: sodium chloride, magnesium sulfate, lithium carbonate, and so forth. But yes, there also ionic compounds that are liquid at room temperature, and they are gaining importance as reaction solvents, particularly for use in green chemistry processes (see the Chapter 11 *A Deeper Look*). More than 1500 ionic liquids are known, and about 500 are available commercially.

Ionic liquids have been known for nearly a century; the first to be discovered was ethylammonium nitrate, $CH_3CH_2NH_3^+\ NO_3^-$, with a melting point of 12 °C. More generally, however, the ionic liquids in use today are salts in which the cation is unsymmetrical and in which one or both of the ions are bulky so that the charges are dispersed over a large volume. Both factors minimize the crystal lattice energy and disfavor formation of the solid. Typical cations are quaternary ammonium ions from heterocyclic amines, either 1,3-dialkylimidazolium ions, *N*-alkylpyridinium ions, or ring-substituted *N*-alkylpyridinium ions.



[R = $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3$]

1,3-Dialkylimidazolium ions



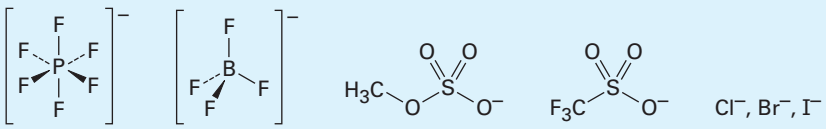
[R = $-CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_2CH_2CH_3$]

***N*-Alkylpyridinium ions**

(continued)

(continued)

Anions are just as varied as the cations. Hexafluorophosphate, tetrafluoroborate, alkyl sulfates, trifluoromethanesulfonates (triflates), and halides are some anion possibilities.

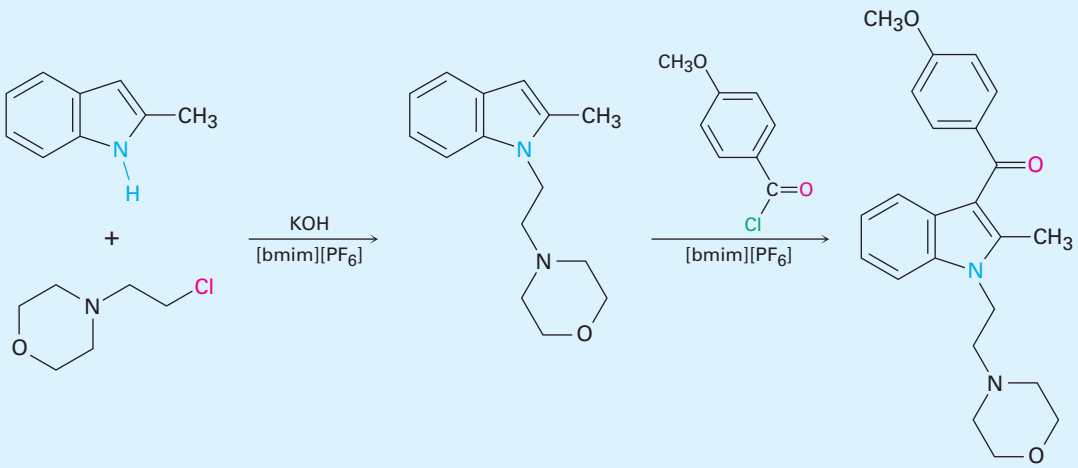


Hexafluoro-phosphate **Tetrafluoro-borate** **Methyl sulfate** **Trifluoromethane-sulfonate** **Halide**

Ionic liquids have several important features that make them attractive for use, both as solvents in green chemistry and as specialty chemicals in such applications as paint additives and refrigerants:

- They dissolve both polar and nonpolar organic compounds, giving high solute concentrations and thereby minimizing the amount of solvent needed.
- They can be optimized for specific reactions by varying cation and anion structures.
- They are nonflammable.
- They are thermally stable.
- They have negligible vapor pressures and do not evaporate.
- They are generally recoverable and can be reused many times.

As an example of their use in organic chemistry, the analgesic drug pravadoline has been synthesized in two steps using 1-butyl-3-methylimidazolium hexafluorophosphate, abbreviated [bmim][PF_6], as the solvent for both steps. The first step is a base-induced S_N2 reaction of 2-methylindole with a primary alkyl halide, and the second is a Friedel–Crafts acylation. Both steps take place in 95% yield, and the ionic solvent is recovered simply by washing the reaction mixture, first with toluene and then with water.



Pravadoline

(continued)

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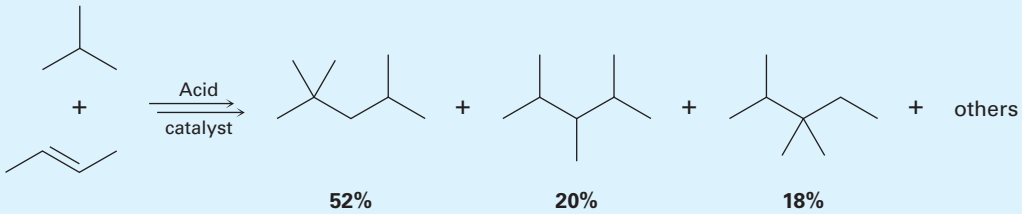
The first commercial process using an ionic liquid catalyst was introduced by PetroChina in 2008, when they opened a plant producing 65,000 tons per year of alkylate gasoline from isobutane. The aluminum-based ionic liquid catalyst replaced the sulfuric acid and hydrofluoric acid catalysts that had previously been used.



Key words

Summary

We've now seen all the common functional groups that occur in organic and biological chemistry. Of those groups, amines are among the most abundant and have among the richest chemistry. In addition to proteins and nucleic acids, the majority of pharmaceutical agents contain amine functional groups and many of the common coenzymes necessary for biological reactions are amines.

Amines are organic derivatives of ammonia. They are named in the IUPAC system either by adding the suffix *-amine* to the name of the alkyl substituent or by considering the amino group as a substituent on a more complex parent molecule.

The chemistry of amines is dominated by the lone-pair electrons on nitrogen, which makes amines both basic and nucleophilic. The basicity of **arylamines** is generally lower than that of **alkylamines** because the nitrogen lone-pair electrons are delocalized by interaction with the aromatic π system. Electron-withdrawing substituents on the aromatic ring further weaken the basicity of a substituted aniline, while electron-donating substituents increase basicity. Alkylamines are sufficiently basic that they exist almost entirely in their protonated form at the physiological pH of 7.3 inside cells.

Heterocyclic amines are compounds that contain one or more nitrogen atoms as part of a ring. Saturated heterocyclic amines usually have the same chemistry as their open-chain analogs, but unsaturated heterocycles such as pyrrole, imidazole, pyridine, and pyrimidine are aromatic. All four are unusually stable, and all undergo aromatic substitution on reaction with electrophiles. Pyrrole is nonbasic because its nitrogen lone-pair electrons are part of the aromatic π system. Fused-ring heterocycles such as quinoline, isoquinoline, indole, and purine are also commonly found in biological molecules.

Arylamines are prepared by nitration of an aromatic ring followed by reduction. Alkylamines are prepared by S_N2 reaction of ammonia or an amine with an alkyl halide or by the **Gabriel amine synthesis**. Amines can also be prepared by a number of reductive methods, including $LiAlH_4$ reduction of amides, nitriles, and azides. Also important is the **reductive amination** reaction in which a ketone or an aldehyde is treated with an amine in the presence of a reducing agent such as $NaBH_4$. In addition, amines result from the **Hofmann**

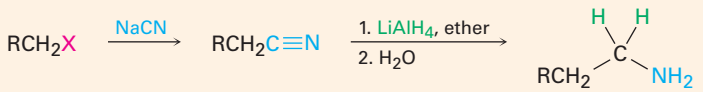
and **Curtius rearrangements** of carboxylic acid derivatives. Both methods involve migration of the −R group bonded to the carbonyl carbon and yield a product that has one less carbon atom than the starting material.

Many of the reactions of amines are familiar from past chapters. Thus, amines react with alkyl halides in S_N2 reactions and with acid chlorides in nucleophilic acyl substitution reactions. Amines also undergo E2 elimination to yield alkenes if they are first quaternized by treatment with iodomethane and then heated with silver oxide, a process called the **Hofmann elimination**.

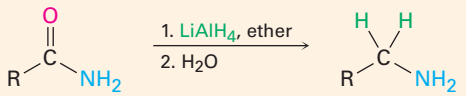
Arylamines are converted by diazotization with nitrous acid into arenediazonium salts, $ArN_2^+ X^-$. The diazonio group can then be replaced by many other substituents in the **Sandmeyer reaction** to give a wide variety of substituted aromatic compounds. Aryl chlorides, bromides, iodides, and nitriles can be prepared from arenediazonium salts, as can arenes and phenols. In addition to their reactivity toward substitution reactions, diazonium salts undergo coupling with phenols and arylamines to give brightly colored **azo compounds**.

Summary of Reactions

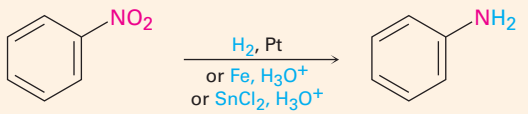
1. Synthesis of amines (Section 24.6)
   (a) Reduction of nitriles



   (b) Reduction of amides



   (c) Reduction of nitrobenzenes

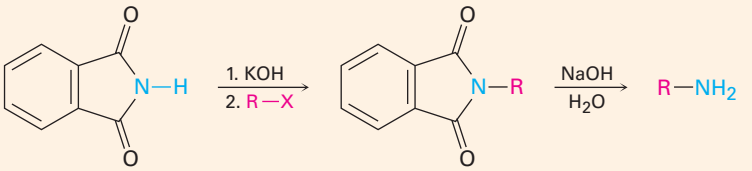


   (d) S_N2 Alkylation of alkyl halides

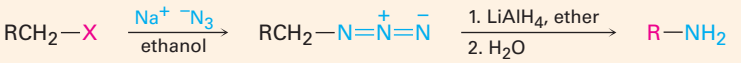
Ammonia	$\ddot{N}H_3$	+ R—X	⟶	$R\overset{+}{N}H_3\ X^-$	NaOH ⟶	RNH_2	Primary
Primary	$R\ddot{N}H_2$	+ R—X	⟶	$R_2\overset{+}{N}H_2\ X^-$	NaOH ⟶	R_2NH	Secondary
Secondary	$R_2\ddot{N}H$	+ R—X	⟶	$R_3\overset{+}{N}H\ X^-$	NaOH ⟶	R_3N	Tertiary
Tertiary	$R_3\ddot{N}$	+ R—X	⟶	$R_4\overset{+}{N}\ X^-$			Quaternary ammonium

(continued)

(e) Gabriel amine synthesis

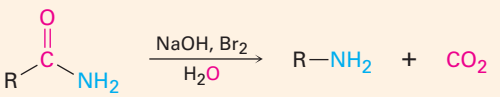


(f) Reduction of azides

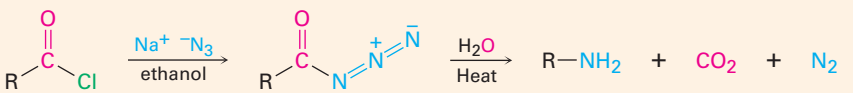


(g) Reductive amination of aldehydes/ketones

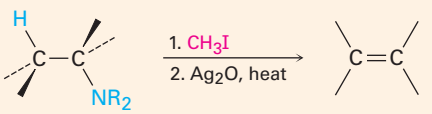
(h) Hofmann rearrangement of amides



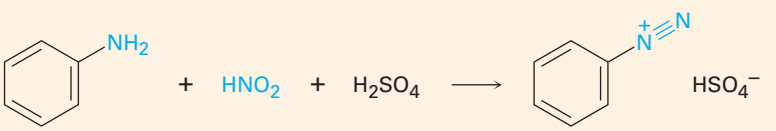
(i) Curtius rearrangement of acyl azides



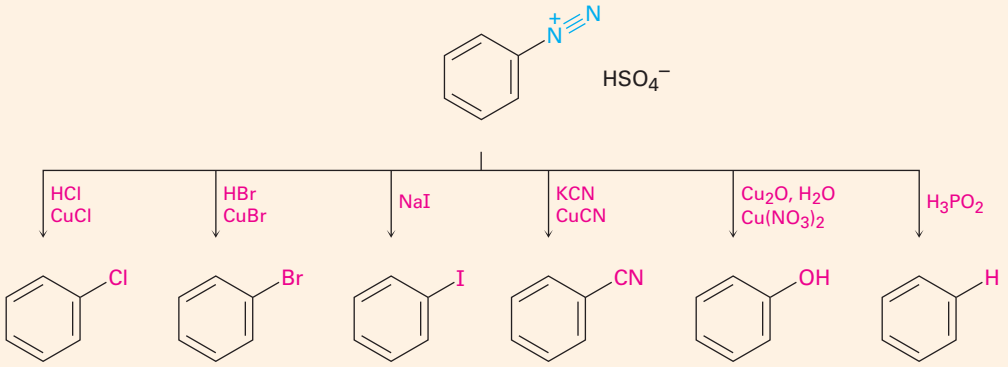
2. Reactions of amines
   (a) Alkylation with alkyl halides; see reaction 1(d)
   (b) Hofmann elimination (Section 24.7)



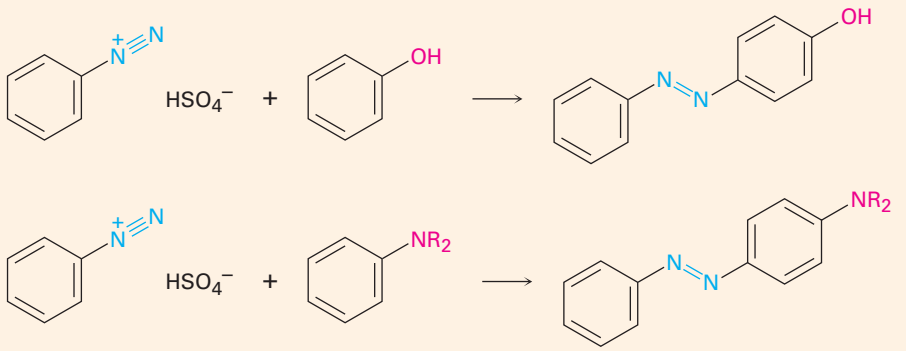
(c) Diazotization (Section 24.8)



3. Reactions of arenediazonium salts (Section 24.8)
   (a) Nucleophilic substitutions



(b) Diazonium coupling



Exercises

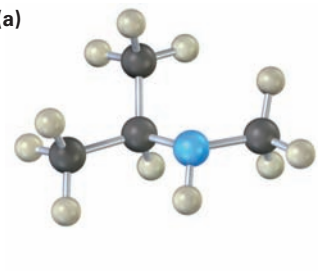
Visualizing Chemistry

OWL Interactive versions of these problems are assignable in OWL for Organic Chemistry.

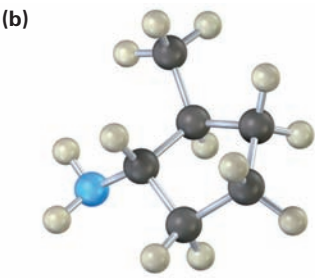
(Problems 24.1–24.25 appear within the chapter.)

24.26 Name the following amines, and identify each as primary, secondary, or tertiary:

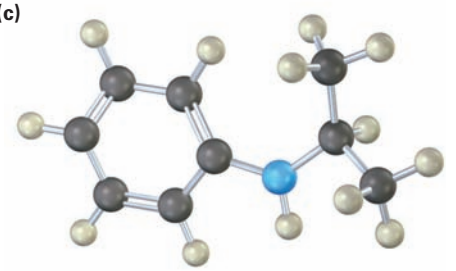
(a)



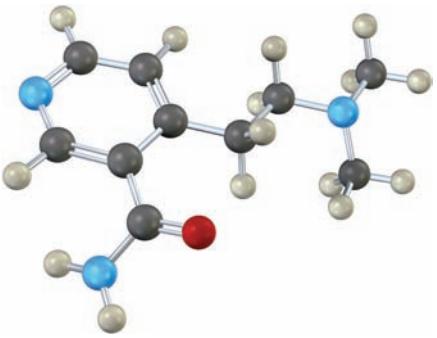
(b)



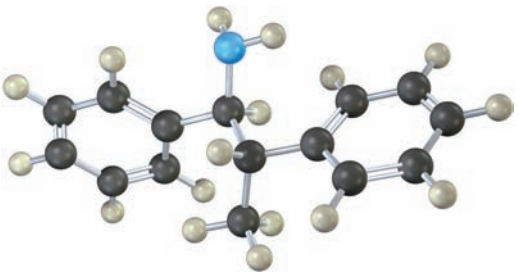
(c)



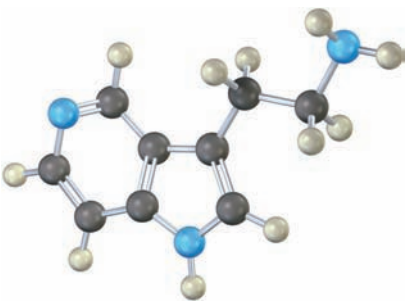
24.27 The following compound contains three nitrogen atoms. Rank them in order of increasing basicity.



24.28 Name the following amine, including *R*,*S* stereochemistry, and draw the product of its reaction with excess iodomethane followed by heating with Ag_2O (Hofmann elimination). Is the stereochemistry of the alkene product *Z* or *E*? Explain.



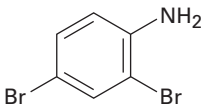
24.29 Which nitrogen atom in the following compound is most basic? Explain.

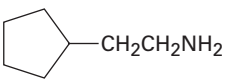


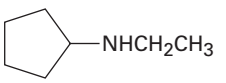
Additional Problems

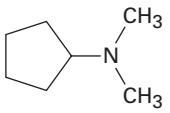
Naming Amines

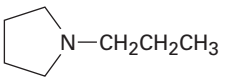
24.30 Name the following compounds:

(a) 

(b) 

(c) 

(d) 

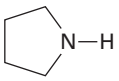
(e) 

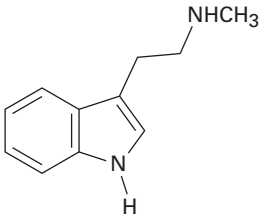
(f) $H_2NCH_2CH_2CH_2CN$

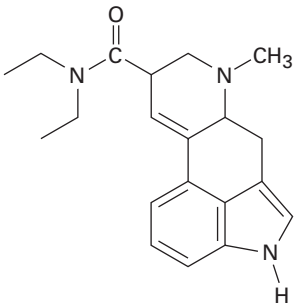
24.31 Draw structures corresponding to the following IUPAC names:

(a) *N*,*N*-Dimethylaniline
(b) (Cyclohexylmethyl)amine
(c) *N*-Methylcyclohexylamine
(d) (2-Methylcyclohexyl)amine
(e) 3-(*N*,*N*-Dimethylamino)propanoic acid

24.32 Classify each of the amine nitrogen atoms in the following substances as primary, secondary, or tertiary:

(a) 

(b) 

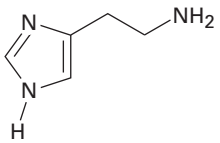
(c) 

Lysergic acid diethylamide

Amine Basicity

24.33 Although pyrrole is a much weaker base than most other amines, it is a much stronger acid ($pK_a \approx 15$ for the pyrrole versus 35 for diethylamine). The N–H proton is readily abstracted by base to yield the pyrrole anion, $C_4H_4N^-$. Explain.

24.34 Histamine, whose release in the body triggers nasal secretions and constricted airways, has three nitrogen atoms. List them in order of increasing basicity, and explain your ordering.



Histamine

24.35 Account for the fact that *p*-nitroaniline (pK_a = 1.0) is less basic than *m*-nitroaniline (pK_a = 2.5) by a factor of 30. Draw resonance structures to support your argument. (The pK_a values refer to the corresponding ammonium ions.)

Synthesis of Amines

24.36 How would you prepare the following substances from 1-butanol?
(a) Butylamine **(b)** Dibutylamine **(c)** Propylamine
(d) Pentylamine **(e)** *N*,*N*-Dimethylbutylamine **(f)** Propene

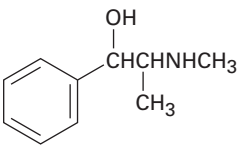
24.37 How would you prepare the following substances from pentanoic acid?
(a) Pentanamide **(b)** Butylamine **(c)** Pentylamine
(d) 2-Bromopentanoic acid **(e)** Hexanenitrile **(f)** Hexylamine

24.38 How would you prepare aniline from the following starting materials?
(a) Benzene **(b)** Benzamide **(c)** Toluene

24.39 How would you prepare benzylamine, $C_6H_5CH_2NH_2$, from benzene? More than one step is needed.

24.40 How might you prepare pentylamine from the following starting materials?
(a) Pentanamide **(b)** Pentanenitrile **(c)** 1-Butene
(d) Hexanamide **(e)** 1-Butanol **(f)** 5-Decene
(g) Pentanoic acid

24.41 How might a reductive amination be used to synthesize ephedrine, an amino alcohol that is widely used for the treatment of bronchial asthma?



Ephedrine

Reactions of Amines

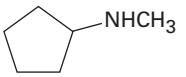
24.42 How would you convert aniline into each of the following products?
(a) Benzene **(b)** Benzamide **(c)** Toluene

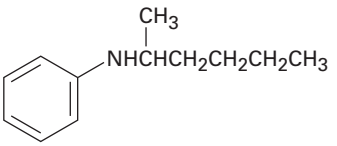
24.43 Give the structures of the major organic products you would expect from reaction of *m*-toluidine (*m*-methylaniline) with the following reagents:
(a) Br_2 (1 equivalent) **(b)** CH_3I (excess)
(c) CH_3COCl in pyridine **(d)** The product of (c), then HSO_3Cl

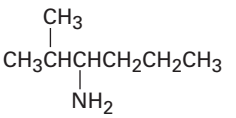
24.44 Show the products from reaction of *p*-bromoaniline with the following reagents:

(a) CH_3I (excess) **(b)** HCl **(c)** HNO_2, H_2SO_4
(d) CH_3COCl **(e)** CH_3MgBr **(f)** CH_3CH_2Cl, $AlCl_3$
(g) Product of (c) with CuCl, HCl
(h) Product of (d) with CH_3CH_2Cl, $AlCl_3$

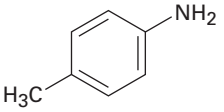
24.45 What are the major products you would expect from Hofmann elimination of the following amines?

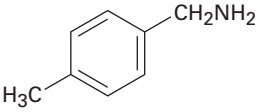
(a) 

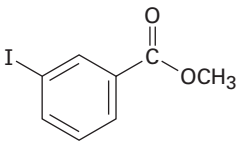
(b) 

(c) 

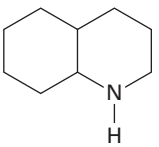
24.46 How would you prepare the following compounds from toluene? A diazonio replacement reaction is needed in some instances.

(a) 

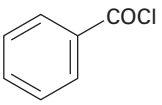
(b) 

(c) 

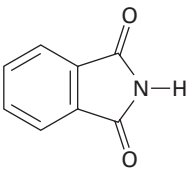
24.47 Predict the product(s) of the following reactions. If more than one product is formed, tell which is major.

(a) 

$\xrightarrow{CH_3I\ (excess)}$ **A?** $\xrightarrow{Ag_2O,\ H_2O}$ **B?** $\xrightarrow{Heat}$ **C?**

(b) 

$\xrightarrow{NaN_3}$ **A?** $\xrightarrow{Heat}$ **B?** $\xrightarrow{H_2O}$ **C?**

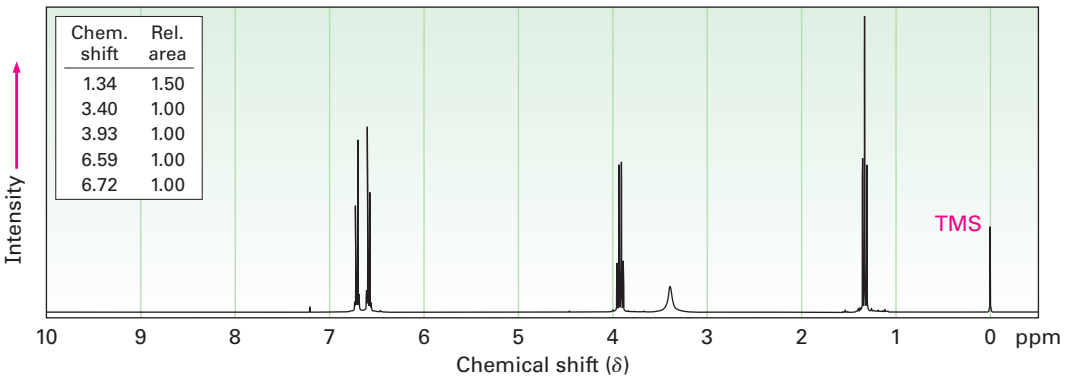
(c) 

$\xrightarrow{KOH}$ **A?** $\xrightarrow{C_6H_5CH_2Br}$ **B?** $\xrightarrow[H_2O]{KOH}$ **C?**

(d) $BrCH_2CH_2CH_2CH_2Br$ + 1 equiv CH_3NH_2 $\xrightarrow[H_2O]{NaOH}$ **?**

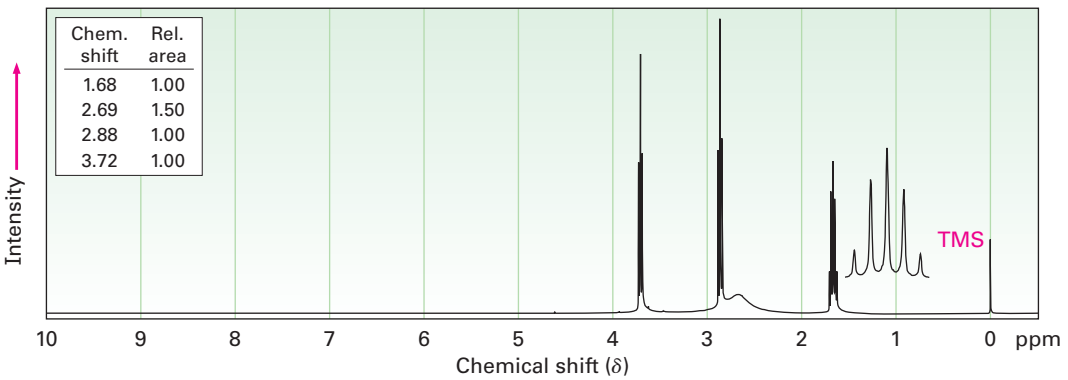
Spectroscopy

24.48 Phenacetin, a substance formerly used in over-the-counter headache remedies, has the formula $C_{10}H_{13}NO_2$. Phenacetin is neutral and does not dissolve in either acid or base. When warmed with aqueous NaOH, phenacetin yields an amine, $C_8H_{11}NO$, whose ^1H NMR spectrum is shown. When heated with HI, the amine is cleaved to an aminophenol, C_6H_7NO. What is the structure of phenacetin, and what are the structures of the amine and the aminophenol?

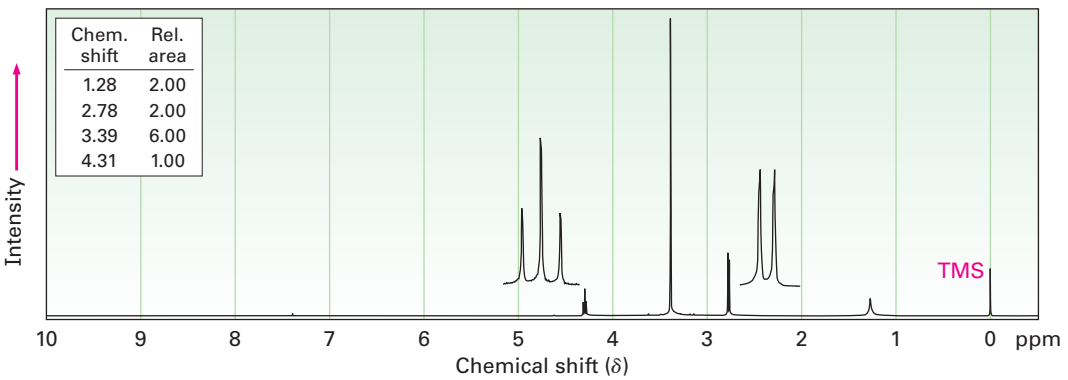


24.49 Propose structures for amines with the following ^1H NMR spectra:

(a) C_3H_9NO

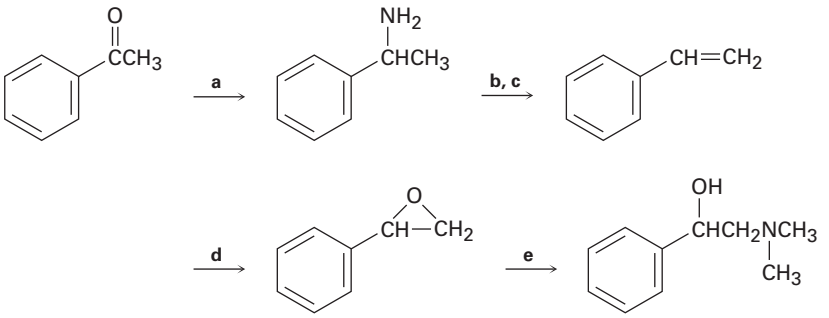


(b) $C_4H_{11}NO_2$



General Problems

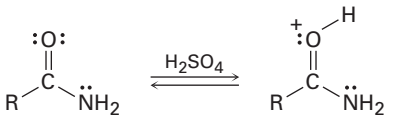
24.50 Fill in the missing reagents **a–e** in the following scheme:



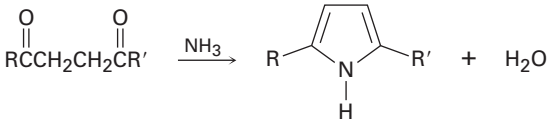
24.51 Oxazole is a five-membered aromatic heterocycle. Would you expect oxazole to be more basic or less basic than pyrrole? Explain.

Oxazole

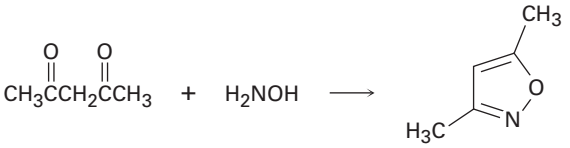
24.52 Protonation of an amide using strong acid occurs on oxygen rather than on nitrogen. Suggest a reason for this behavior, taking resonance into account.



24.53 Substituted pyrroles are often prepared by treatment of a 1,4-diketone with ammonia. Propose a mechanism.

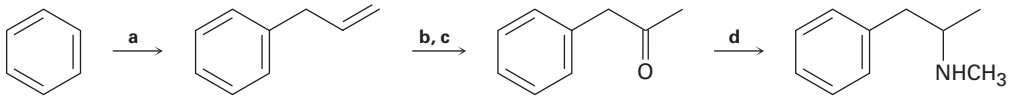


24.54 3,5-Dimethylisoxazole is prepared by reaction of 2,4-pentanedione with hydroxylamine. Propose a mechanism.



3,5-Dimethylisoxazole

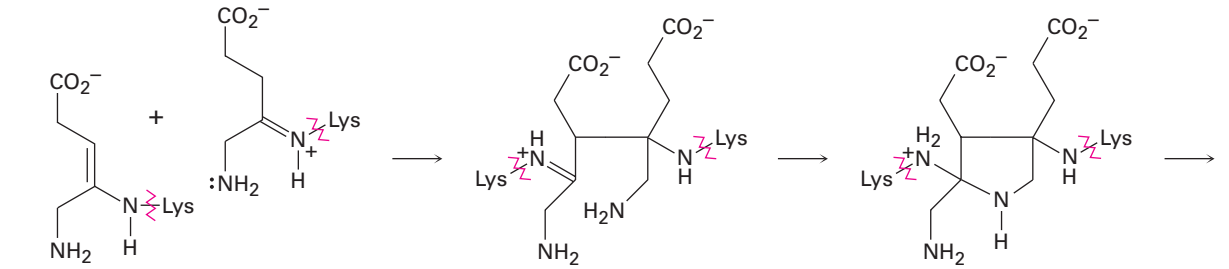
24.55 Fill in the missing reagents **a–d** in the following synthesis of racemic methamphetamine from benzene.



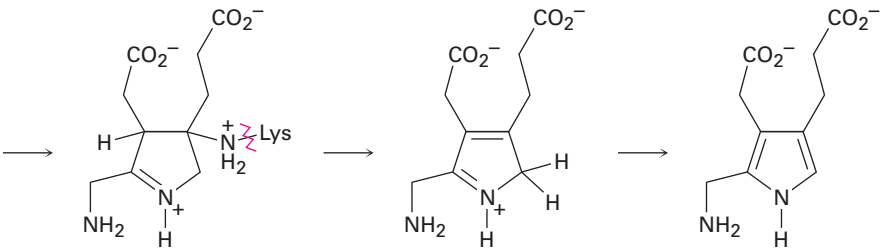
(*R,S*)-Methamphetamine

24.56 One problem with reductive amination as a method of amine synthesis is that by-products are sometimes obtained. For example, reductive amination of benzaldehyde with methylamine leads to a mixture of *N*-methylbenzylamine and *N*-methyldibenzylamine. How do you suppose the tertiary amine by-product is formed? Propose a mechanism.

24.57 Chlorophyll, heme, vitamin B_{12}, and a host of other substances are biosynthesized from porphobilinogen (PBG), which is itself formed from condensation of two molecules of 5-aminolevulinate. The two 5-aminolevulinates are bound to lysine (Lys) amino acids in the enzyme, one in the enamine form and one in the imine form, and their condensation is thought to occur by the following steps. Using curved arrows, show the mechanism of each step.

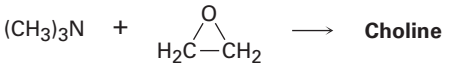


Enzyme-bound 5-aminolevulinate

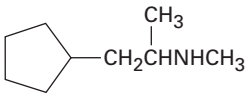


Porphobilinogen (PBG)

24.58 Choline, a component of the phospholipids in cell membranes, can be prepared by S_N2 reaction of trimethylamine with ethylene oxide. Show the structure of choline, and propose a mechanism for the reaction.

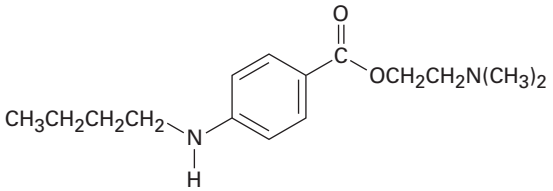


24.59 Cyclopentamine is an amphetamine-like central nervous system stimulant. Propose a synthesis of cyclopentamine from materials of five carbons or less.



Cyclopentamine

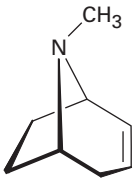
24.60 Tetracaine is a substance used as a spinal anesthetic.



Tetracaine

(a) How would you prepare tetracaine from the corresponding aniline derivative, $ArNH_2$?
(b) How would you prepare tetracaine from *p*-nitrobenzoic acid?
(c) How would you prepare tetracaine from benzene?

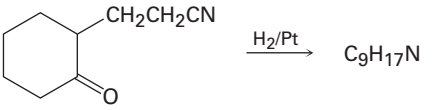
24.61 Atropine, $C_{17}H_{23}NO_3$, is a poisonous alkaloid isolated from the leaves and roots of *Atropa belladonna,* the deadly nightshade. In small doses, atropine acts as a muscle relaxant; 0.5 ng (nanogram, 10^{-9} g) is sufficient to cause pupil dilation. On basic hydrolysis, atropine yields tropic acid, $C_6H_5CH(CH_2OH)CO_2H$, and tropine, $C_8H_{15}NO$. Tropine is an optically inactive alcohol that yields tropidene on dehydration with H_2SO_4. Propose a structure for atropine.



Tropidene

24.62 Tropidene (Problem 24.61) can be converted by a series of steps into tropilidene (1,3,5-cycloheptatriene). How would you accomplish this conversion?

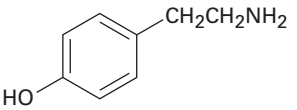
24.63 Propose a structure for the product with formula $C_9H_{17}N$ that results when 2-(2-cyanoethyl)cyclohexanone is reduced catalytically.



24.64 Coniine, $C_8H_{17}N$, is the toxic principle of the poison hemlock drunk by Socrates. When subjected to Hofmann elimination, coniine yields 5-(*N*,*N*-dimethylamino)-1-octene. If coniine is a secondary amine, what is its structure?

24.65 How would you synthesize coniine (Problem 24.64) from acrylonitrile ($H_2C{=}CHCN$) and ethyl 3-oxohexanoate ($CH_3CH_2CH_2COCH_2CO_2Et$)? (*Hint:* See Problem 24.63.)

24.66 Tyramine is an alkaloid found, among other places, in mistletoe and ripe cheese. How would you synthesize tyramine from benzene? From toluene?

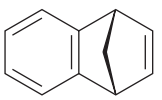


Tyramine

24.67 Reaction of anthranilic acid (*o*-aminobenzoic acid) with HNO_2 and H_2SO_4 yields a diazonium salt that can be treated with base to yield a neutral diazonium carboxylate.

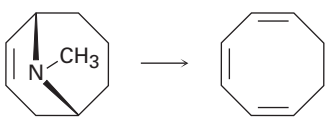
(a) What is the structure of the neutral diazonium carboxylate?

(b) Heating the diazonium carboxylate results in the formation of CO_2, N_2, and an intermediate that reacts with 1,3-cyclopentadiene to yield the following product:



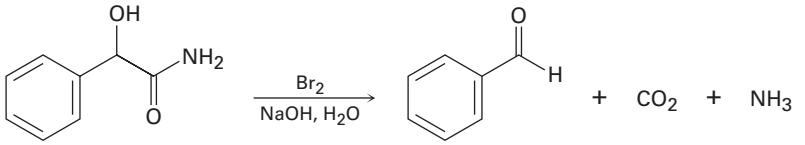
What is the structure of the intermediate, and what kind of reaction does it undergo with cyclopentadiene?

24.68 Cyclooctatetraene was first synthesized in 1911 by a route that involved the following transformation:

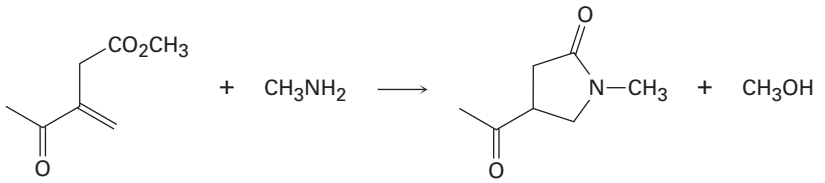


How might you use the Hofmann elimination to accomplish this reaction? How would you finish the synthesis by converting cyclooctatriene into cyclooctatetraene?

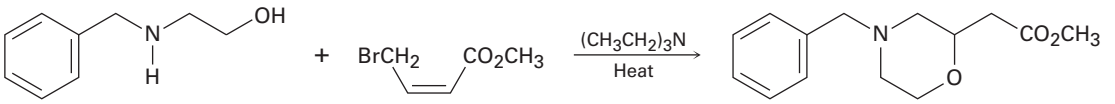
24.69 When an α-hydroxy amide is treated with Br_2 in aqueous NaOH under Hofmann rearrangement conditions, loss of CO_2 occurs and a chain-shortened aldehyde is formed. Propose a mechanism.



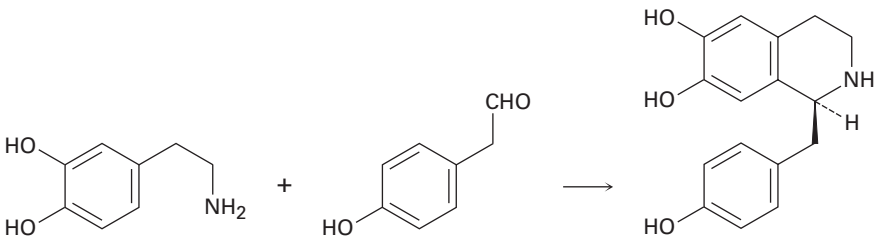
24.70 The following transformation involves a conjugate nucleophilic addition reaction (Section 19.13) followed by an intramolecular nucleophilic acyl substitution reaction (Section 21.2). Show the mechanism.



24.71 Propose a mechanism for the following reaction:

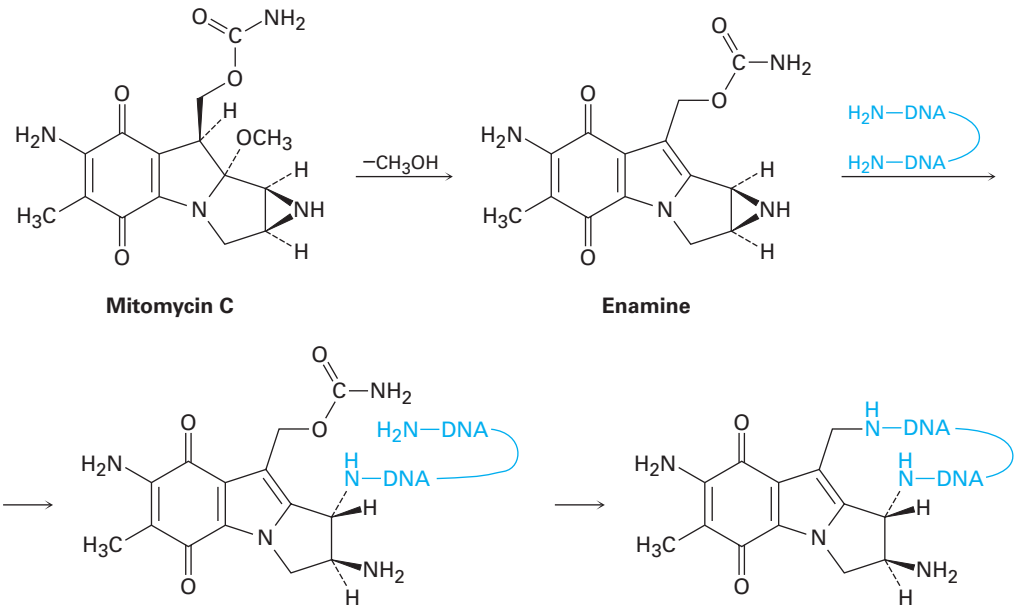


24.72 One step in the biosynthesis of morphine is the reaction of dopamine with *p*-hydroxyphenylacetaldehyde to give (*S*)-norcoclaurine. Assuming that the reaction is acid-catalyzed, propose a mechanism.



Dopamine | ***p*-Hydroxyphenylacetaldehyde** | **(*S*)-Norcoclaurine**

24.73 The antitumor antibiotic mitomycin C functions by forming cross-links in DNA chains.



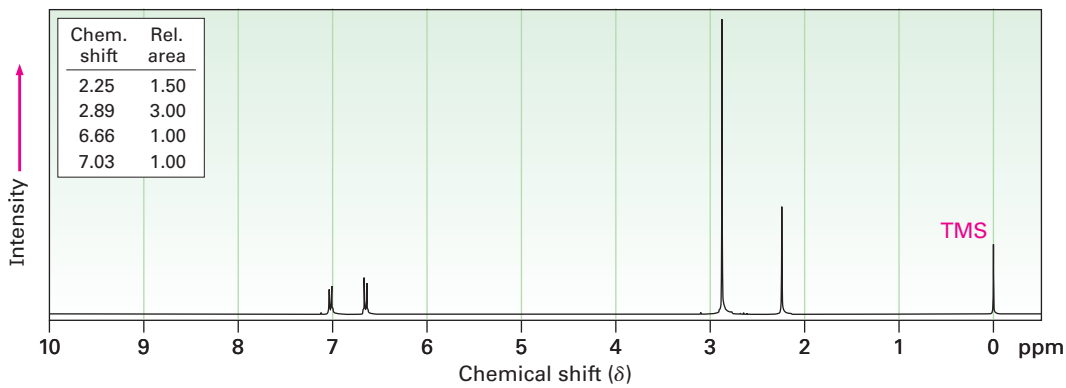
(a) The first step is loss of methoxide and formation of an iminium ion intermediate that is deprotonated to give an enamine. Show the mechanism.

(b) The second step is reaction of the enamine with DNA to open the three-membered, nitrogen-containing (aziridine) ring. Show the mechanism.

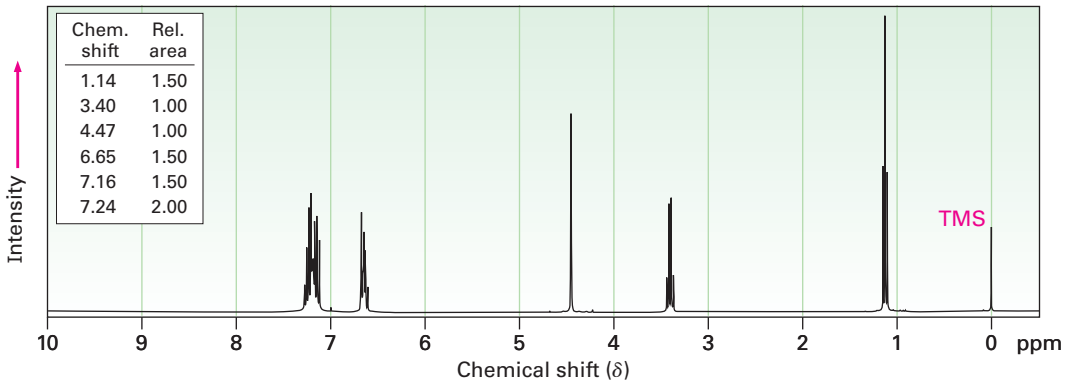
(c) The third step is loss of carbamate ($NH_2CO_2^-$) and formation of an unsaturated iminium ion, followed by a conjugate addition of another part of the DNA chain. Show the mechanism.

24.74 Propose structures for compounds that show the following ^1H NMR spectra.

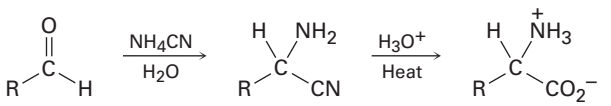
(a) $C_9H_{13}N$



(b) $C_{15}H_{17}N$

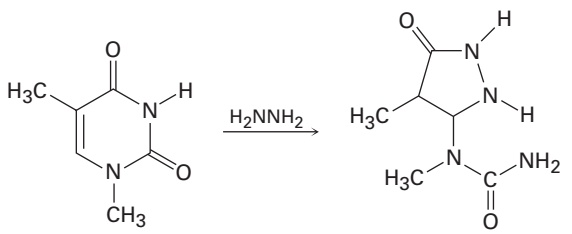


24.75 α-Amino acids can be prepared by the Strecker synthesis, a two-step process in which an aldehyde is treated with ammonium cyanide followed by hydrolysis of the amino nitrile intermediate with aqueous acid. Propose a mechanism for the reaction.



An α-amino acid

24.76 One of the reactions used in determining the sequence of nucleotides in a strand of DNA is reaction with hydrazine. Propose a mechanism for the following reaction, which occurs by an initial conjugate addition followed by internal amide formation.



25

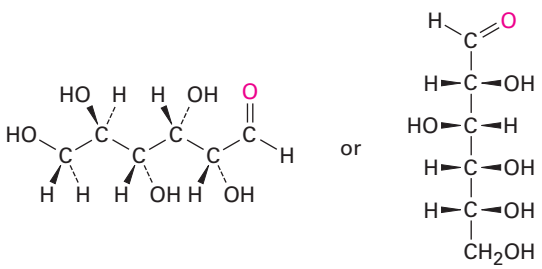
Produced by honeybees from the nectar of flowers, honey is primarily a mixture of the two simple sugars fructose and glucose. Image copyright Olga Langerova, 2010. Used under license from Shutterstock.com

Biomolecules: Carbohydrates

OWL Sign in to OWL for Organic Chemistry at **www.cengage.com/owl** to view tutorials and simulations, develop problem-solving skills, and complete online homework assigned by your professor.

Carbohydrates occur in every living organism. The sugar and starch in food, and the cellulose in wood, paper, and cotton are nearly pure carbohydrates. Modified carbohydrates form part of the coating around living cells, other carbohydrates are part of the nucleic acids that carry our genetic information, and still others are used as medicines.

The word **carbohydrate** derives historically from the fact that glucose, the first simple carbohydrate to be obtained pure, has the molecular formula $C_6H_{12}O_6$ and was originally thought to be a "hydrate of carbon, $C_6(H_2O)_6$." This view was soon abandoned, but the name persisted. Today, the term *carbohydrate* is used to refer loosely to the broad class of polyhydroxylated aldehydes and ketones commonly called sugars. Glucose, also known as dextrose in medical work, is the most familiar example.



Glucose (dextrose), a pentahydroxyhexanal

Carbohydrates are synthesized by green plants during photosynthesis, a complex process in which sunlight provides the energy to convert CO_2 and H_2O into glucose plus oxygen. Many molecules of glucose are then chemically linked for storage by the plant in the form of either cellulose or starch. It has been estimated that more than 50% of the dry weight of the earth's biomass—all plants and animals—consists of glucose polymers. When eaten and metabolized, carbohydrates then provide animals with a source of readily available

energy. Thus, carbohydrates act as the chemical intermediaries by which solar energy is stored and used to support life.

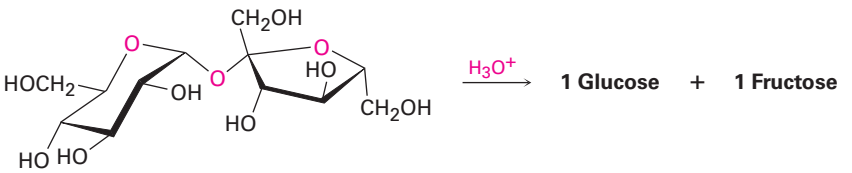
$$6\,CO_2 + 6\,H_2O \xrightarrow{\text{Sunlight}} 6\,O_2 + \underset{\text{Glucose}}{C_6H_{12}O_6} \longrightarrow \text{Cellulose, starch}$$

Because humans and most other mammals lack the enzymes needed for digestion of cellulose, they require starch as their dietary source of carbohydrates. Grazing animals such as cows, however, have microorganisms in their first stomach that are able to digest cellulose. The energy stored in cellulose is thus moved up the biological food chain when these ruminant animals eat grass and are themselves used for food.

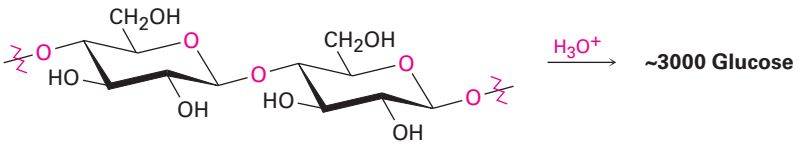
Why This Chapter? We've now seen all the common functional groups and reaction types that occur in organic and biological chemistry. In this and the next four chapters, we'll focus on the major classes of biological molecules, beginning with a look at the structures and primary biological functions of carbohydrates. Then in Chapter 29, we'll return to the subject to see how carbohydrates are both synthesized and degraded in organisms.

25.1 Classification of Carbohydrates

Carbohydrates are generally classed as either simple or complex. **Simple sugars**, or **monosaccharides**, are carbohydrates like glucose and fructose that can't be converted into smaller sugars by hydrolysis. **Complex carbohydrates** are made of two or more simple sugars linked together by acetal bonds **(Section 19.10)**. Sucrose (table sugar), for example, is made up of one glucose linked to one fructose. Similarly, cellulose is made up of several thousand glucose units linked together. Enzyme-catalyzed hydrolysis of a complex carbohydrate breaks it down into its constituent monosaccharides.

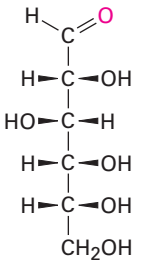


Sucrose
(a disaccharide)

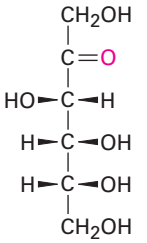


Cellulose
(a polysaccharide)

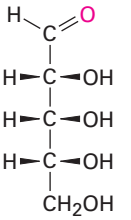
Monosaccharides are further classified as either **aldoses** or **ketoses**. The *-ose* suffix designates a carbohydrate, and the *aldo-* and *keto-* prefixes identify the kind of carbonyl group in the molecule, whether aldehyde or ketone. The number of carbon atoms in the monosaccharide is indicated by the appropriate numerical prefix *tri-*, *tetr-*, *pent-*, *hex-*, and so forth, in the name. Putting it all together, glucose is an aldohexose, a six-carbon aldehydo sugar; fructose is a ketohexose, a six-carbon keto sugar; ribose is an aldopentose, a five-carbon aldehydo sugar; and sedoheptulose is a ketoheptose, a seven-carbon keto sugar. Most of the common simple sugars are either pentoses or hexoses.



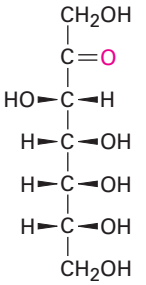
Glucose
(an aldohexose)



Fructose
(a ketohexose)



Ribose
(an aldopentose)

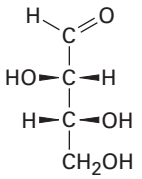


Sedoheptulose
(a ketoheptose)

Problem 25.1

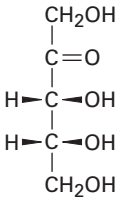
Classify each of the following monosaccharides:

(a)



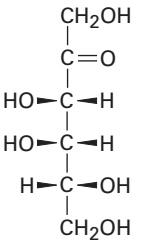
Threose

(b)



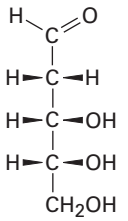
Ribulose

(c)



Tagatose

(d)

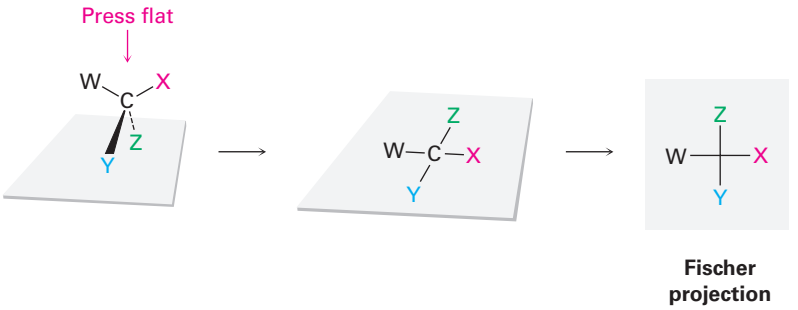


2-Deoxyribose

25.2 Depicting Carbohydrate Stereochemistry: Fischer Projections

Because carbohydrates usually have numerous chirality centers, it was recognized long ago that a quick method for representing their stereochemistry is needed. In 1891, the German chemist Emil Fischer suggested a method based on the projection of a tetrahedral carbon atom onto a flat surface. These **Fischer projections** were soon adopted and are now a common means of representing stereochemistry at chirality centers, particularly in carbohydrate chemistry.

A tetrahedral carbon atom is represented in a Fischer projection by two crossed lines. The horizontal lines represent bonds coming out of the page, and the vertical lines represent bonds going into the page.



For example, (*R*)-glyceraldehyde, the simplest monosaccharide, can be drawn as in **Figure 25.1**.

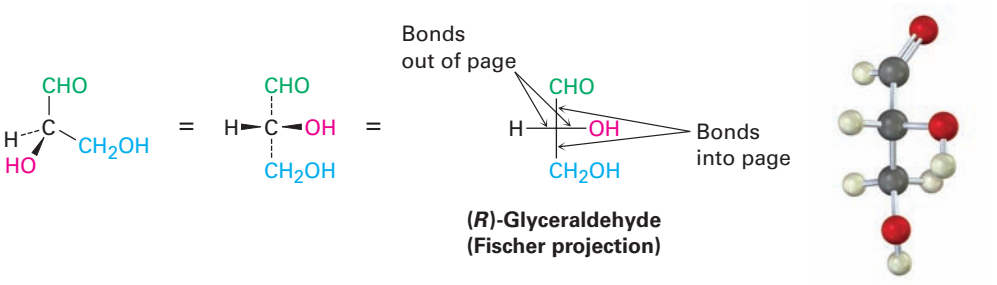
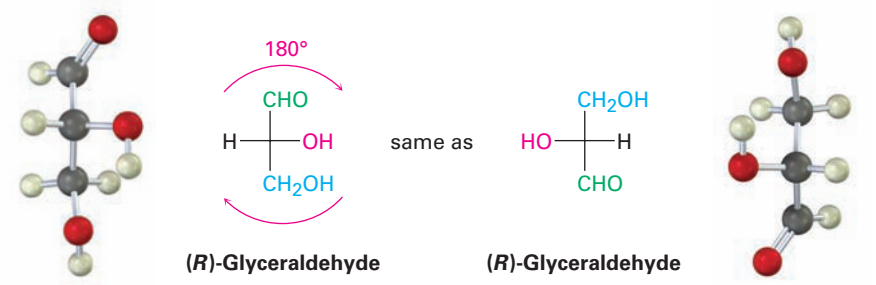


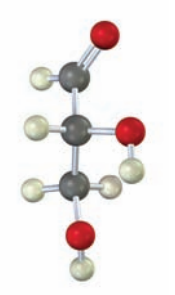
Figure 25.1 A Fischer projection of (*R*)-glyceraldehyde.

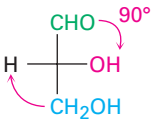
Because a given chiral molecule can be drawn in many ways, it's sometimes necessary to compare two projections to see if they represent the same or different enantiomers. To test for identity, Fischer projections can be moved around on the paper, but only two kinds of motions are allowed; moving a Fischer projection in any other way inverts its meaning.

- A Fischer projection can be rotated on the page by 180°, but not by 90° or 270°. Only a 180° rotation maintains the Fischer convention by keeping the same substituent groups going into and coming out of the plane. In the following Fischer projection of (*R*)-glyceraldehyde, for example, the −H and −OH groups come out of the plane both before and after a 180° rotation.



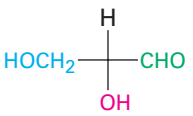
A 90° rotation breaks the Fischer convention by exchanging the groups that go into the plane and those that come out. In the following Fischer projections of (*R*)-glyceraldehyde, the −H and −OH groups come out of the plane before rotation but go into the plane after a 90° rotation. As a result, the rotated projection represents (S)-glyceraldehyde.



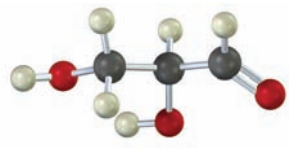


(*R*)-Glyceraldehyde

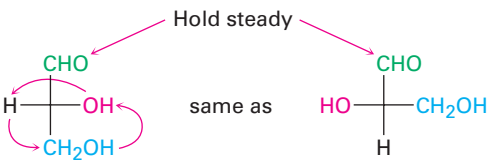
Not same as



(*S*)-Glyceraldehyde

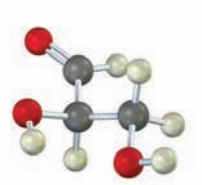


- A Fischer projection can have one group held steady while the other three rotate in either a clockwise or a counterclockwise direction. The effect is simply to rotate around a single bond, which does not change the stereochemistry.



(*R*)-Glyceraldehyde

(*R*)-Glyceraldehyde



R,*S* stereochemical designations **(Section 5.5)** can be assigned to the chirality center in a Fischer projection by following three steps, as shown in Worked Example 25.1.

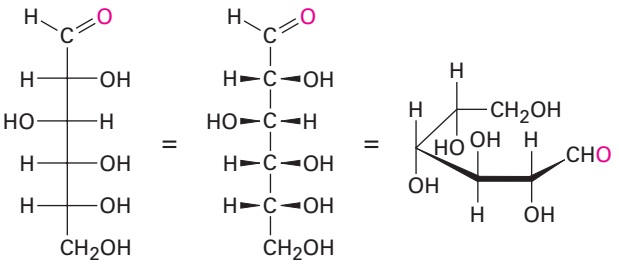
STEP 1
Rank the four substituents in the usual way **(Section 5.5)**.

STEP 2
Place the group of lowest ranking, usually H, at the top of the Fischer projection by using one of the allowed motions. This means that the lowest-ranked group is oriented back, away from the viewer, as required for assigning configuration.

STEP 3
Determine the direction of rotation 1 → 2 → 3 of the remaining three groups, and assign *R* or *S* configuration.

Carbohydrates with more than one chirality center are shown in Fischer projections by stacking the centers on top of one another, with the carbonyl carbon at or near the top. Glucose, for example, has four chirality centers

stacked on top of one another in a Fischer projection. Such representations don't, however, give an accurate picture of a molecule's true three-dimensional conformation, which is curled around on itself like a bracelet.

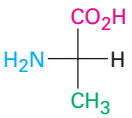


Glucose
(carbonyl group at top)

Assigning *R* or *S* Configuration to a Fischer Projection

Worked Example 25.1

Assign *R* or *S* configuration to the following Fischer projection of alanine:



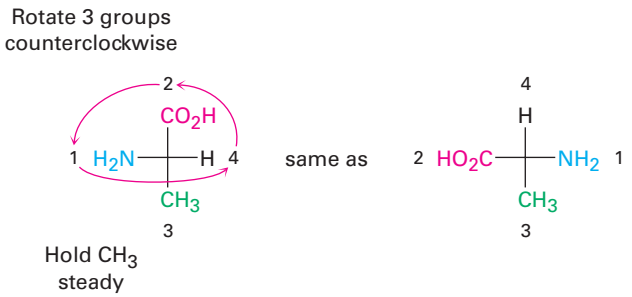
Alanine

Strategy

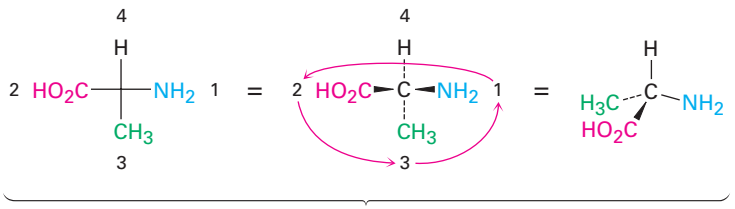
Follow the steps in the text. (1) Rank the four substituents on the chiral carbon. (2) Manipulate the Fischer projection to place the group of lowest ranking at the top by carrying out one of the allowed motions. (3) Determine the direction 1 → 2 → 3 of the remaining three groups.

Solution

The rankings of the groups are (1) $-NH_2$, (2) $-CO_2H$, (3) $-CH_3$, and (4) $-H$. To bring the group of lowest ranking ($-H$) to the top, we might want to hold the $-CH_3$ group steady while rotating the other three groups counterclockwise.



Going from first- to second- to third-highest ranking requires a counterclockwise turn, corresponding to *S* stereochemistry.



***S* configuration**

Problem 25.2

Convert each of the following Fischer projections into a tetrahedral representation, and assign *R* or *S* stereochemistry:

(a) CO_2H, H_2N, H, CH_3 **(b)** CHO, H, OH, CH_3 **(c)** CH_3, H, CHO, CH_2CH_3

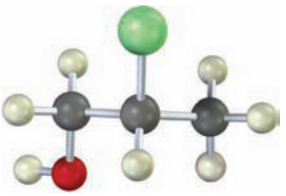
Problem 25.3

Which of the following Fischer projections of glyceraldehyde represent the same enantiomer?

A CHO, HO, H, CH_2OH **B** OH, $HOCH_2$, H, CHO **C** H, HO, CH_2OH, CHO **D** CH_2OH, H, CHO, OH

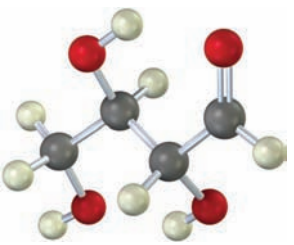
Problem 25.4

Redraw the following molecule as a Fischer projection, and assign *R* or *S* configuration to the chirality center (green = Cl):



Problem 25.5

Redraw the following aldotetrose as a Fischer projection, and assign *R* or *S* configuration to each chirality center:



25.3 D,L Sugars

Glyceraldehyde, the simplest aldose, has only one chirality center and thus has two enantiomeric (nonidentical mirror-image) forms. Only the dextrorotatory enantiomer occurs naturally, however. That is, a sample of naturally occurring glyceraldehyde placed in a polarimeter rotates plane-polarized light in a clockwise direction, denoted (+). Since (+)-glyceraldehyde has been found to have an *R* configuration at C2, it can be represented in a Fischer projection as shown

in Figure 25.1. For historical reasons dating back long before the adoption of the *R,S* system, (*R*)-(+)-glyceraldehyde is also referred to as D-glyceraldehyde (D for dextrorotatory). The other enantiomer, (*S*)-(−)-glyceraldehyde, is known as L-glyceraldehyde (L for levorotatory).

Because of the way that monosaccharides are biosynthesized in nature, glucose, fructose, and most other naturally occurring monosaccharides have the same *R* stereochemical configuration as D-glyceraldehyde at the chirality center farthest from the carbonyl group. In Fischer projections, therefore, most naturally occurring sugars have the hydroxyl group at the bottom chirality center pointing to the right **(Figure 25.2)**. All such compounds are referred to as **D sugars**.

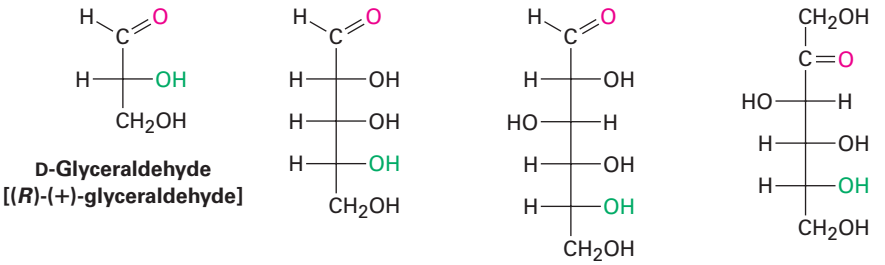
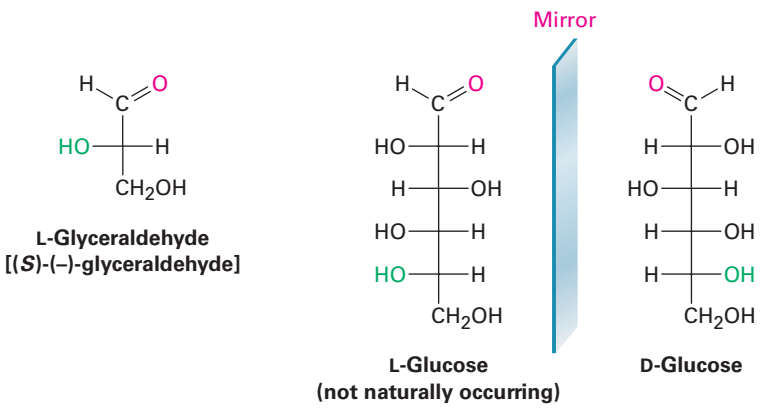


Figure 25.2 Some naturally occurring D sugars. The —OH group at the chirality center farthest from the carbonyl group has the same configuration as (*R*)-(+)-glyceraldehyde and points toward the right in Fischer projections.

In contrast with D sugars, **L sugars** have an *S* configuration at the lowest chirality center, with the bottom —OH group pointing to the left in Fischer projections. Thus, an L sugar is the mirror image (enantiomer) of the corresponding D sugar and has the opposite configuration from the D sugar at all chirality centers.



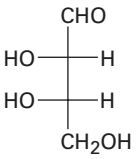
Note that the D and L notations have no relation to the direction in which a given sugar rotates plane-polarized light. A D sugar can be either dextrorotatory

or levorotatory. The prefix D indicates only that the −OH group at the lowest chirality center has *R* stereochemistry and points to the right when the molecule is drawn in the standard way in a Fischer projection. Note also that the D,L system of carbohydrate nomenclature describes the configuration at only one chirality center and says nothing about the configuration of other chirality centers that may be present.

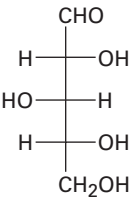
Problem 25.6

Assign *R* or *S* configuration to each chirality center in the following monosaccharides, and tell whether each is a D sugar or an L sugar:

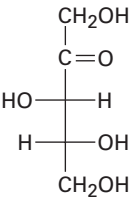
(a)



(b)



(c)



Problem 25.7

(+)-Arabinose, an aldopentose that is widely distributed in plants, is systematically named (2*R*,3*S*,4*S*)-2,3,4,5-tetrahydroxypentanal. Draw a Fischer projection of (+)-arabinose, and identify it as a D sugar or an L sugar.

25.4 Configurations of Aldoses

Aldotetroses are four-carbon sugars with two chirality centers. Thus, there are $2^2 = 4$ possible stereoisomeric aldotetroses, or two D,L pairs of enantiomers named erythrose and threose.

Aldopentoses have three chirality centers and a total of $2^3 = 8$ possible stereoisomers, or four D,L pairs of enantiomers. These four pairs are called ribose, arabinose, xylose, and lyxose. All except lyxose occur widely. D-Ribose is an important constituent of RNA (ribonucleic acid), L-arabinose is found in many plants, and D-xylose is found in wood.

Aldohexoses have four chirality centers and a total of $2^4 = 16$ possible stereoisomers, or eight D,L pairs of enantiomers. The names of the eight are allose, altrose, glucose, mannose, gulose, idose, galactose, and talose. Only D-glucose, from starch and cellulose, and D-galactose, from gums and fruit pectins, are widely distributed in nature. D-Mannose and D-talose also occur naturally but in lesser abundance.

Fischer projections of the four-, five-, and six-carbon D aldoses are shown in **Figure 25.3**. Starting with D-glyceraldehyde, we can imagine constructing the two D aldotetroses by inserting a new chirality center just below the aldehyde carbon. Each of the two D aldotetroses then leads to two D aldopentoses (four total), and each of the four D aldopentoses leads to two D aldohexoses (eight total). In addition, each of the D aldoses in Figure 25.3 has an L enantiomer, which is not shown.

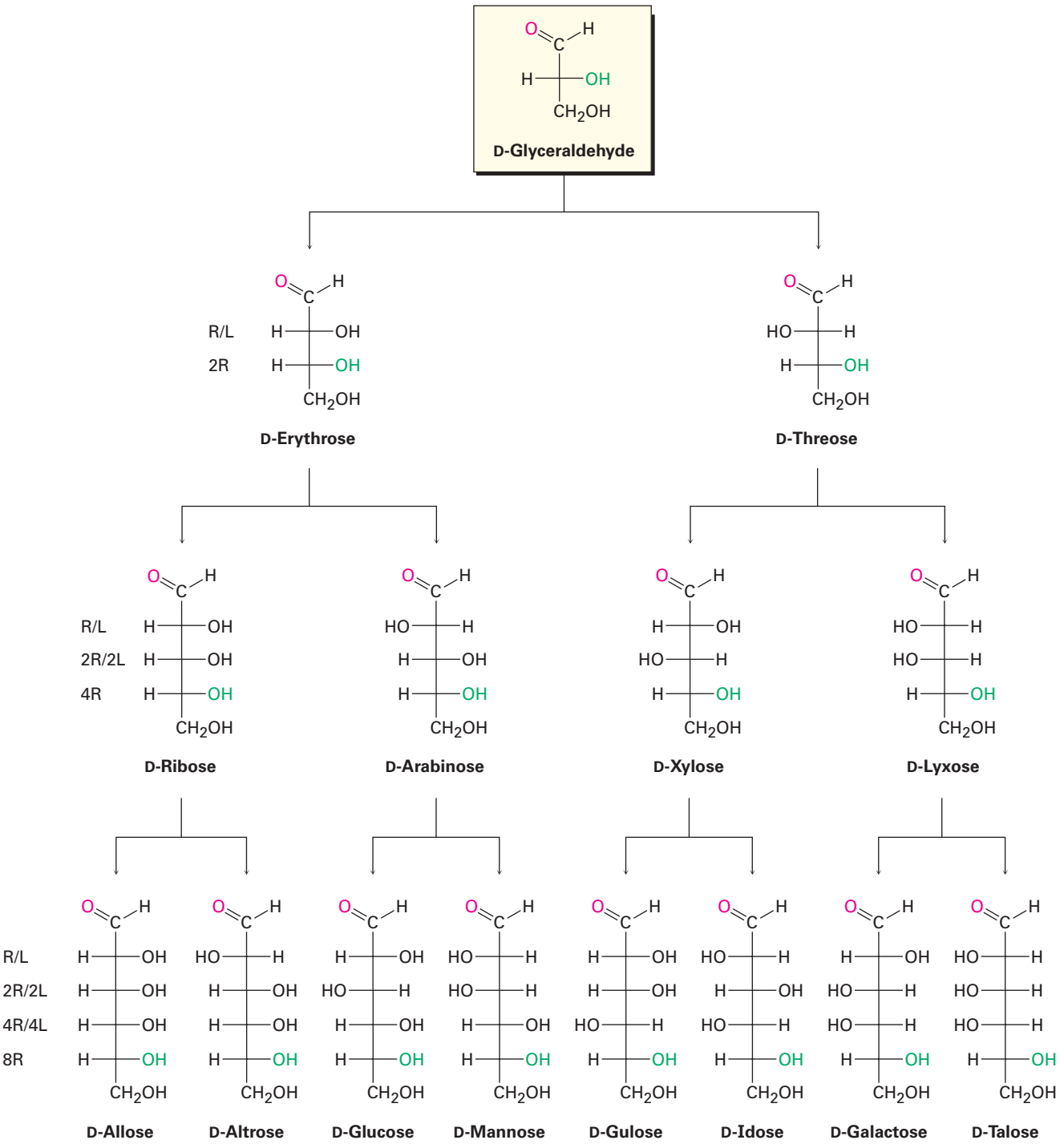


Figure 25.3 Configurations of D aldoses. The structures are arranged from left to right so that the —OH groups on C2 alternate right/left (R/L) in going across a series. Similarly, the —OH groups at C3 alternate two right/two left (2R/2L), the —OH groups at C4 alternate 4R/4L, and the —OH groups at C5 are to the right in all eight (8R). Each D aldose has a corresponding L enantiomer, which is not shown.

Louis Fieser of Harvard University suggested the following procedure for remembering the names and structures of the eight D aldohexoses:

STEP 1
Set up eight Fischer projections with the −CHO group on top and the $-CH_2OH$ group at the bottom.

STEP 2
At C5, place all eight −OH groups to the right (D series).

STEP 3
At C4, alternate four −OH groups to the right and four to the left.

STEP 4
At C3, alternate two −OH groups to the right, two to the left.

STEP 5
At C2, alternate −OH groups right, left, right, left.

STEP 6
Name the eight isomers using the mnemonic "**All alt**ruists **gl**adly **ma**ke **gu**m **in gal**lon **ta**nks."

The structures of the four D aldopentoses can be generated in a similar way and named by the mnemonic suggested by a Cornell University undergraduate: "**Rib**s **ar**e extra **l**ean."

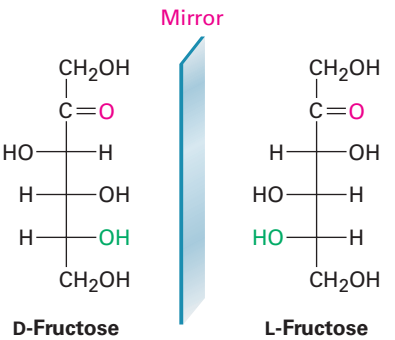
Worked Example 25.2 Drawing a Fischer Projection

Draw a Fischer projection of L-fructose.

Strategy

Because L-fructose is the enantiomer of D-fructose, simply look at the structure of D-fructose and reverse the configuration at each chirality center.

Solution



Problem 25.8

Only the D sugars are shown in Figure 25.3. Draw Fischer projections for the following L sugars:

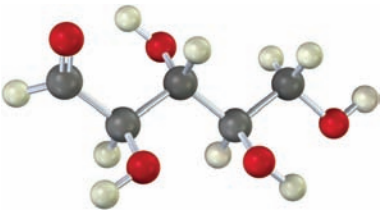
(a) L-Xylose **(b)** L-Galactose **(c)** L-Allose

Problem 25.9

How many aldoheptoses are there? How many are D sugars, and how many are L sugars?

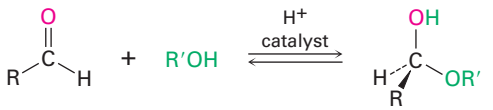
Problem 25.10

The following model is that of an aldopentose. Draw a Fischer projection of the sugar, name it, and identify it as a D sugar or an L sugar.



25.5 Cyclic Structures of Monosaccharides: Anomers

We said in **Section 19.10** that aldehydes and ketones undergo a rapid and reversible nucleophilic addition reaction with alcohols to form hemiacetals.



An aldehyde **A hemiacetal**

If the carbonyl and the hydroxyl group are in the same molecule, an intramolecular nucleophilic addition can take place, leading to the formation of a cyclic hemiacetal. Five- and six-membered cyclic hemiacetals are relatively strain-free and particularly stable, and many carbohydrates therefore exist in an equilibrium between open-chain and cyclic forms. Glucose, for instance, exists in aqueous solution primarily in the six-membered, **pyranose** form resulting from intramolecular nucleophilic addition of the –OH group at C5 to the C1 carbonyl group **(Figure 25.4)**. The word *pyranose* is derived from *pyran*, the name of the unsaturated six-membered cyclic ether.

Like cyclohexane rings **(Section 4.6)**, pyranose rings have a chairlike geometry with axial and equatorial substituents. By convention, the rings are usually drawn by placing the hemiacetal oxygen atom at the right rear, as shown in Figure 25.4. Note that an –OH group on the right in a Fischer projection is on the bottom face of the pyranose ring, and an –OH group on the left in a Fischer projection is on the top face of the ring. For D sugars, the terminal $-CH_2OH$ group is on the top of the ring, whereas for L sugars, the $-CH_2OH$ group is on the bottom.

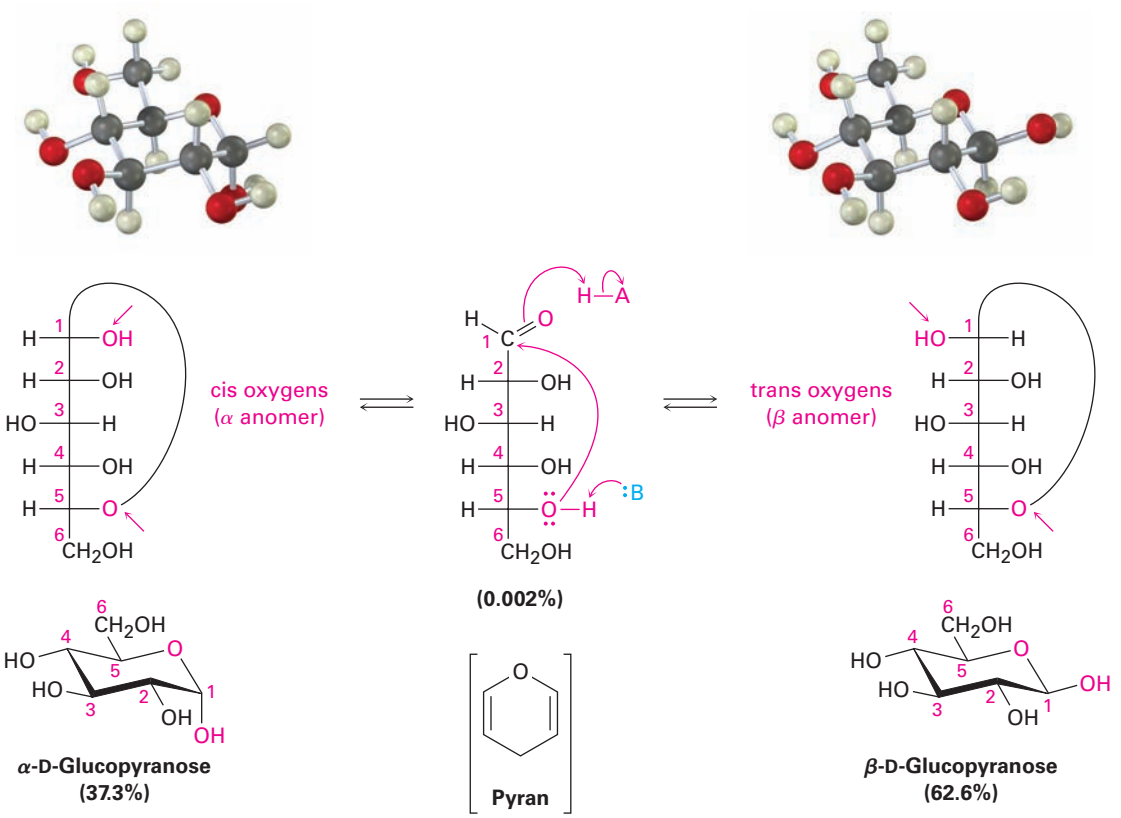


Figure 25.4 Glucose in its cyclic pyranose forms. As explained in the text, two anomers are formed by cyclization of glucose. The molecule whose newly formed —OH group at C1 is cis to the oxygen atom on the lowest chirality center (C5) in a Fischer projection is the α anomer. The molecule whose newly formed —OH group is trans to the oxygen atom on the lowest chirality center in a Fischer projection is the β anomer.

When an open-chain monosaccharide cyclizes to a pyranose form, a new chirality center is generated at the former carbonyl carbon and two diastereomers, called **anomers**, are produced. The hemiacetal carbon atom is referred to as the **anomeric center**. For example, glucose cyclizes reversibly in aqueous solution to a 37:63 mixture of two anomers (Figure 25.4). The compound with its newly generated —OH group at C1 cis to the —OH at the lowest chirality center in a Fischer projection is called the ***α* anomer**; its full name is α-D-glucopyranose. The compound with its newly generated —OH group trans to the —OH at the lowest chirality center in a Fischer projection is called the ***β* anomer**; its full name is β-D-glucopyranose. Note that in β-D-glucopyranose, all the substituents on the ring are equatorial. Thus, β-D-glucopyranose is the least sterically crowded and most stable of the eight D aldohexoses.

Some monosaccharides also exist in a five-membered cyclic hemiacetal form called a **furanose**. D-Fructose, for instance, exists in water solution as 70% β-pyranose, 2% α-pyranose, 0.7% open-chain, 23% β-furanose, and 5% α-furanose. The pyranose form results from addition of the —OH at C6 to the carbonyl group, while the furanose form results from addition of the —OH at C5 to the carbonyl group **(Figure 25.5)**.

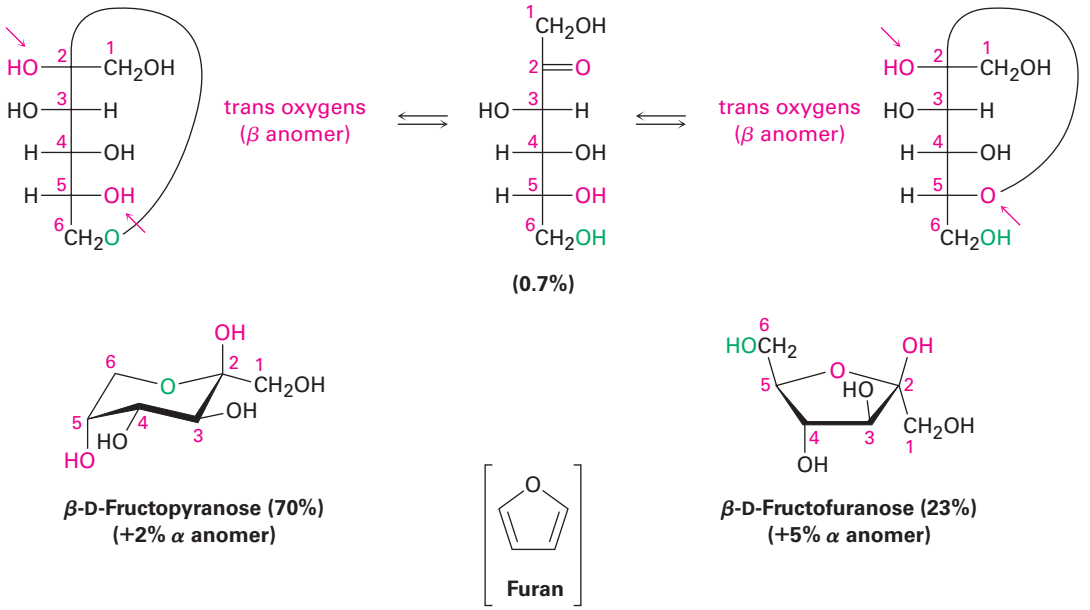
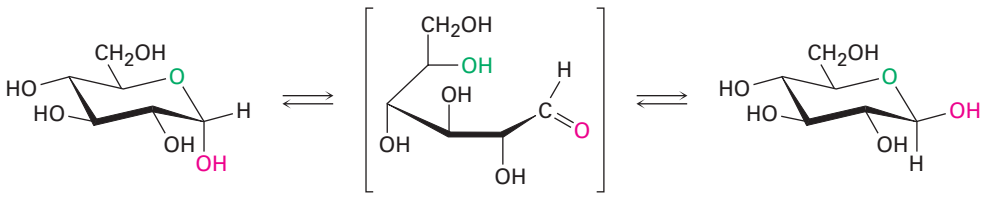


Figure 25.5 Pyranose and furanose forms of fructose in aqueous solution. The two pyranose anomers result from addition of the C6 —OH group to the C2 carbonyl; the two furanose anomers result from addition of the C5 —OH group to the C2 carbonyl.

Both anomers of D-glucopyranose can be crystallized and purified. Pure α-D-glucopyranose has a melting point of 146 °C and a specific rotation $[\alpha]_D = +112.2$; pure β-D-glucopyranose has a melting point of 148 to 155 °C and a specific rotation $[\alpha]_D = +18.7$. When a sample of either pure anomer is dissolved in water, however, its optical rotation slowly changes until it reaches a constant value of +52.6. That is, the specific rotation of the α-anomer solution decreases from +112.2 to +52.6, and the specific rotation of the β-anomer solution increases from +18.7 to +52.6. Called **mutarotation**, this change in optical rotation is due to the slow interconversion of the pure anomers to give a 37 : 63 equilibrium mixture.

Mutarotation occurs by a reversible ring-opening of each anomer to the open-chain aldehyde, followed by reclosure. Although the equilibration is slow at neutral pH, it is catalyzed by both acid and base.



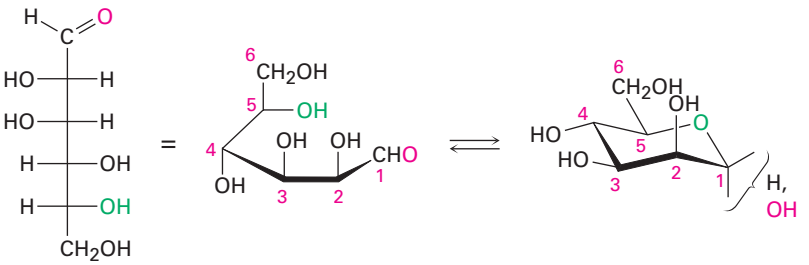
Worked Example 25.3 Drawing the Chair Conformation of an Aldohexose

D-Mannose differs from D-glucose in its stereochemistry at C2. Draw D-mannose in its chairlike pyranose form.

Strategy

First draw a Fischer projection of D-mannose. Then lay it on its side, and curl it around so that the —CHO group (C1) is on the right front and the —CH_2OH group (C6) is toward the left rear. Now, connect the —OH at C5 to the C1 carbonyl group to form the pyranose ring. In drawing the chair form, raise the leftmost carbon (C4) up and drop the rightmost carbon (C1) down.

Solution



D-Mannose **(Pyranose form)**

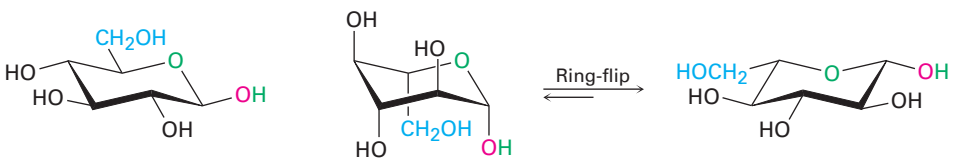
Worked Example 25.4 Drawing the Chair Conformation of a Pyranose

Draw β-L-glucopyranose in its more stable chair conformation.

Strategy

It's probably easiest to begin by drawing the chair conformation of β-D-glucopyranose. Then draw its mirror-image L enantiomer by changing the stereochemistry at every position on the ring, and carry out a ring-flip to give the more stable chair conformation. Note that the —CH_2OH group is on the bottom face of the ring in the L enantiomer as is the anomeric —OH.

Solution



β-D-Glucopyranose **β-L-Glucopyranose**

Problem 25.11

Ribose exists largely in a furanose form, produced by addition of the C4 —OH group to the C1 aldehyde. Draw D-ribose in its furanose form.

Problem 25.12

Figure 25.5 shows only the β-pyranose and β-furanose anomers of D-fructose. Draw the α-pyranose and α-furanose anomers.

Problem 25.13

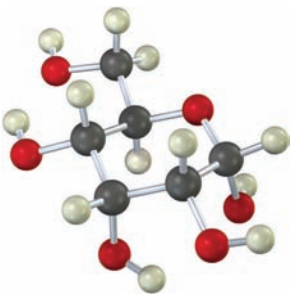
Draw β-D-galactopyranose and β-D-mannopyranose in their more stable chair conformations. Label each ring substituent as either axial or equatorial. Which would you expect to be more stable, galactose or mannose?

Problem 25.14

Draw β-L-galactopyranose in its more stable chair conformation, and label the substituents as either axial or equatorial.

Problem 25.15

Identify the following monosaccharide, write its full name, and draw its open-chain form in Fischer projection.



25.6 Reactions of Monosaccharides

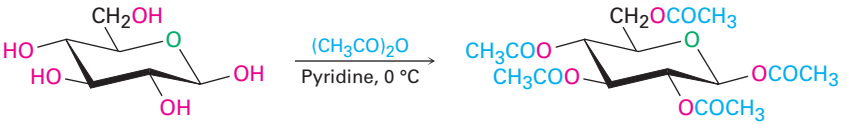
Because monosaccharides contain only two kinds of functional groups, hydroxyls and carbonyls, most of the chemistry of monosaccharides is the familiar chemistry of these two groups. As we've seen, alcohols can be converted to esters and ethers and can be oxidized; carbonyl compounds can react with nucleophiles and can be reduced.

Ester and Ether Formation

Monosaccharides behave as simple alcohols in much of their chemistry. For example, carbohydrate −OH groups can be converted into esters and ethers, which are often easier to work with than the free sugars. Because of their many hydroxyl groups, monosaccharides are usually soluble in water but insoluble in organic solvents such as ether. They are also difficult to purify and have a tendency to form syrups rather than crystals when water is removed. Ester and ether derivatives, however, are soluble in organic solvents and are easily purified and crystallized.

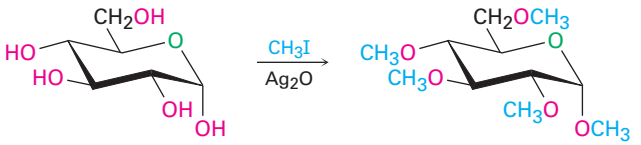
Esterification is normally carried out by treating the carbohydrate with an acid chloride or acid anhydride in the presence of a base **(Sections 21.4 and 21.5)**. All the −OH groups react, including the anomeric one. For example,

β-D-glucopyranose is converted into its pentaacetate by treatment with acetic anhydride in pyridine solution.



β-D-Glucopyranose **Penta-*O*-acetyl-β-D-glucopyranose (91%)**

Carbohydrates are converted into ethers by treatment with an alkyl halide in the presence of base—the Williamson ether synthesis **(Section 18.2)**. Standard Williamson conditions using a strong base tend to degrade sensitive sugar molecules, but silver oxide works well as a mild base and gives high yields of ethers. For example, α-D-glucopyranose is converted into its pentamethyl ether in 85% yield on reaction with iodomethane and Ag_2O.

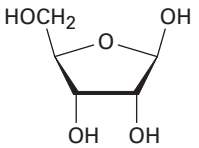


α-D-Glucopyranose **α-D-Glucopyranose pentamethyl ether (85%)**

Problem 25.16

Draw the products you would obtain by reaction of β-D-ribofuranose with:

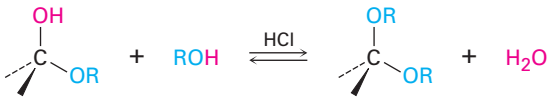
(a) CH_3I, Ag_2O **(b)** $(CH_3CO)_2O$, pyridine



β-D-Ribofuranose

Glycoside Formation

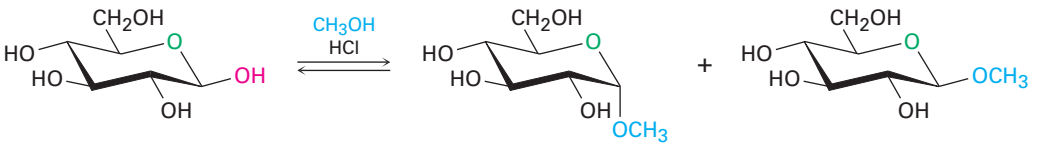
We saw in **Section 19.10** that treatment of a hemiacetal with an alcohol and an acid catalyst yields an acetal.



A hemiacetal **An acetal**

In the same way, treatment of a monosaccharide hemiacetal with an alcohol and an acid catalyst yields an acetal called a **glycoside**, in which the

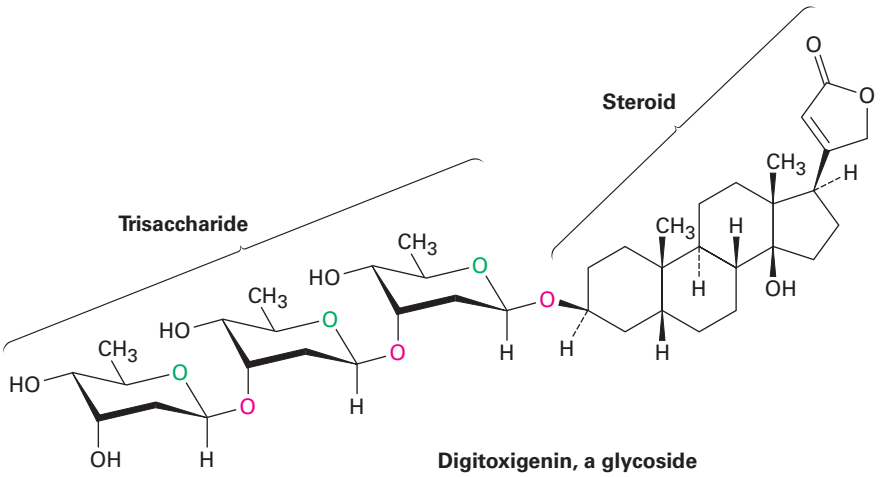
anomeric −OH has been replaced by an −OR group. For example, reaction of β-D-glucopyranose with methanol gives a mixture of α and β methyl D-glucopyranosides. (Note that a *gly*coside is the functional group name for any sugar, whereas a *glu*coside is formed specifically from glucose.)



β-D-Glucopyranose (a cyclic hemiacetal) | **Methyl α-D-glucopyranoside (66%)** | **Methyl β-D-glucopyranoside (33%)**

Glycosides are named by first citing the alkyl group and then replacing the *-ose* ending of the sugar with *-oside*. Like all acetals, glycosides are stable to neutral water. They aren't in equilibrium with an open-chain form, and they don't show mutarotation. They can, however, be hydrolyzed to give back the free monosaccharide plus alcohol on treatment with aqueous acid **(Section 19.10)**.

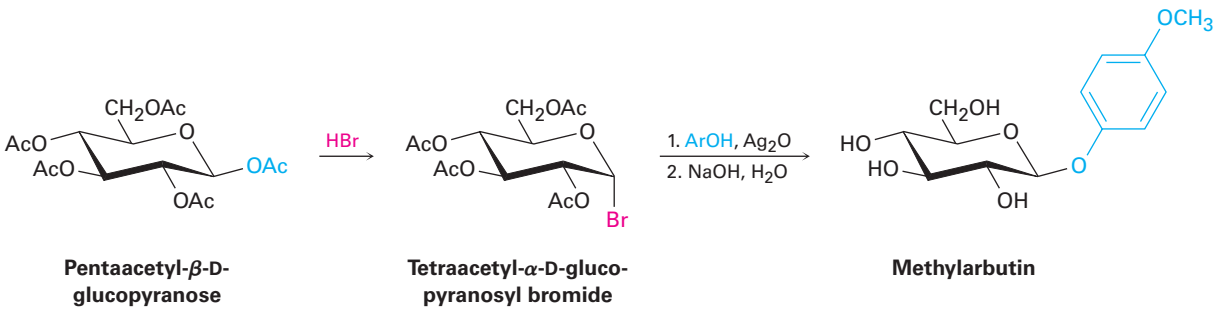
Glycosides are abundant in nature, and many biologically important molecules contain glycosidic linkages. For example, digitoxin, the active component of the digitalis preparations used for treatment of heart disease, is a glycoside consisting of a steroid alcohol linked to a trisaccharide. Note also that the three sugars are linked to one another by glycoside bonds.



Digitoxigenin, a glycoside

The laboratory synthesis of glycosides can be difficult because of the numerous −OH groups on the sugar molecule. One method that is particularly suitable for preparing glucose β-glycosides involves treatment of glucose pentaacetate with HBr, followed by addition of the appropriate alcohol in the presence of silver oxide. Called the *Koenigs–Knorr reaction*, the sequence involves formation of a pyranosyl bromide, followed by nucleophilic substitution. For example, methylarbutin, a glycoside found in

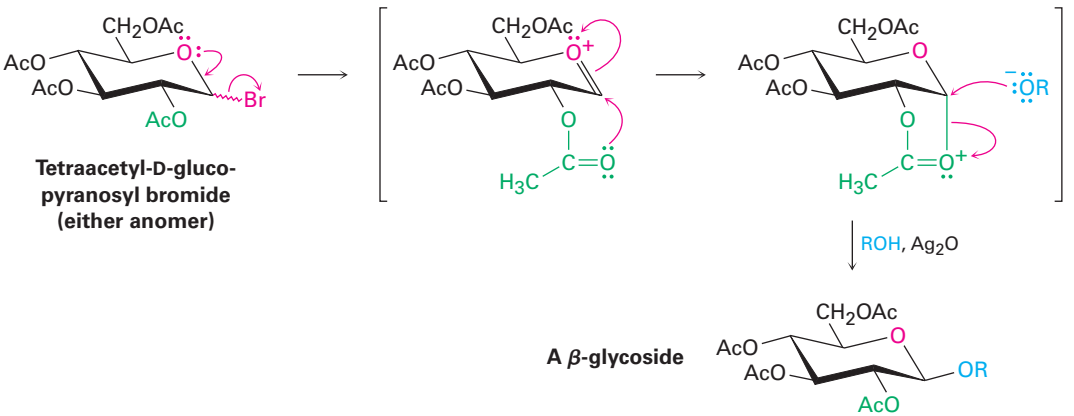
pears, has been prepared by reaction of tetraacetyl-α-D-glucopyranosyl bromide with *p*-methoxyphenol.



Pentaacetyl-β-D-glucopyranose | **Tetraacetyl-α-D-glucopyranosyl bromide** | **Methylarbutin**

Although the Koenigs–Knorr reaction appears to involve a simple backside S_N2 displacement of bromide ion by alkoxide ion, the situation is actually more complex. Both α and β anomers of tetraacetyl-D-glucopyranosyl bromide give the same β-glycoside product, implying that they react by a common pathway.

The results can be understood by assuming that tetraacetyl-D-glucopyranosyl bromide (either α or β anomer) undergoes a spontaneous S_N1-like loss of Br^-, followed by internal reaction with the ester group at C2 to form an oxonium ion. Since the acetate at C2 is on the bottom of the glucose ring, the C–O bond also forms from the bottom. Backside S_N2 displacement of the oxonium ion then occurs with the usual inversion of configuration, yielding a β-glycoside and regenerating the acetate at C2 **(Figure 25.6)**.



Tetraacetyl-D-glucopyranosyl bromide (either anomer)

Figure 25.6 Mechanism of the Koenigs–Knorr reaction, showing the neighboring-group effect of a nearby acetate.

The participation shown by the nearby acetate group in the Koenigs–Knorr reaction is referred to as a *neighboring-group effect* and is a common occurrence in organic chemistry. Neighboring-group effects are usually noticeable only because they affect the rate or stereochemistry of a reaction; the nearby group itself does not undergo any evident change during the reaction.

Biological Ester Formation: Phosphorylation

In living organisms, carbohydrates occur not only in the free form but also linked through their anomeric center to other molecules such as lipids (glycolipids) or proteins (glycoproteins). Collectively called *glycoconjugates*, these sugar-linked molecules are components of cell walls and are crucial to the mechanism by which different cell types recognize one another.

Glycoconjugate formation occurs by reaction of the lipid or protein with a glycosyl nucleoside diphosphate. This diphosphate is itself formed by initial reaction of a monosaccharide with adenosine triphosphate (ATP) to give a glycosyl monophosphate, followed by reaction with uridine triphosphate (UTP), to give a glycosyl uridine diphosphate. (We'll see the structures of nucleoside phosphates in **Section 28.1**.) The purpose of the phosphorylation is to activate the anomeric —OH group of the sugar and make it a better leaving group in a nucleophilic substitution reaction by a protein or lipid **(Figure 25.7)**.

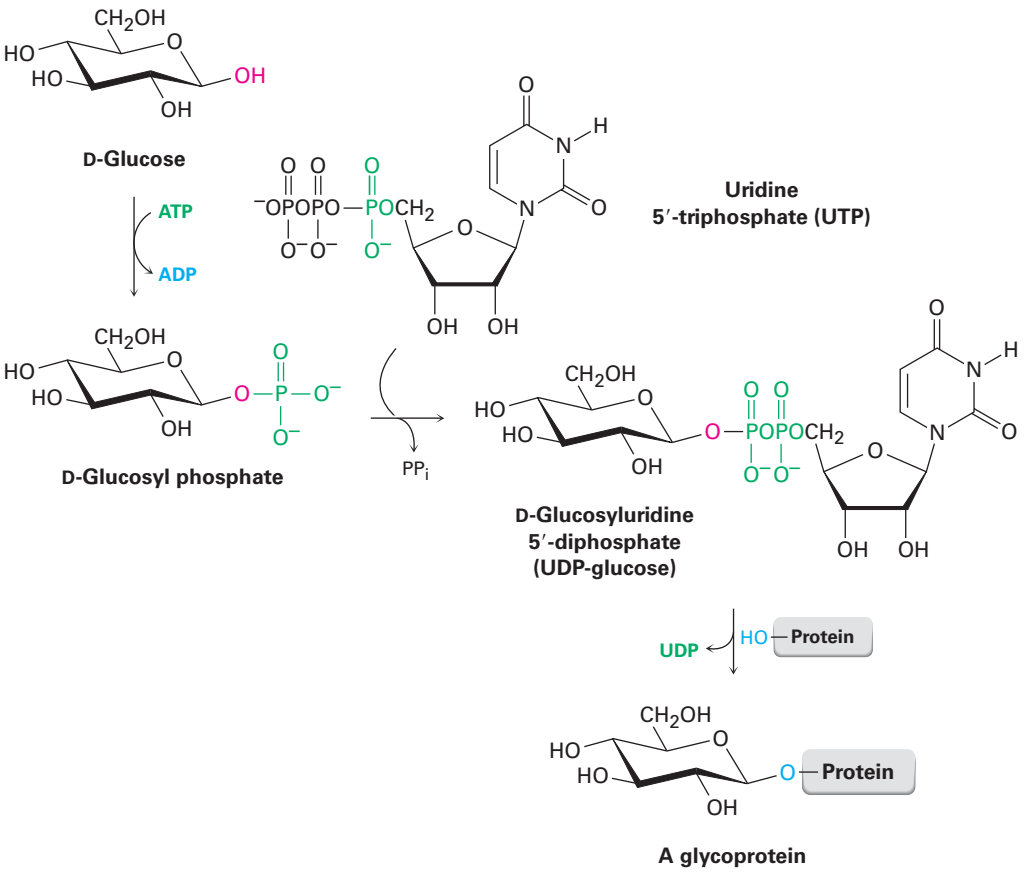
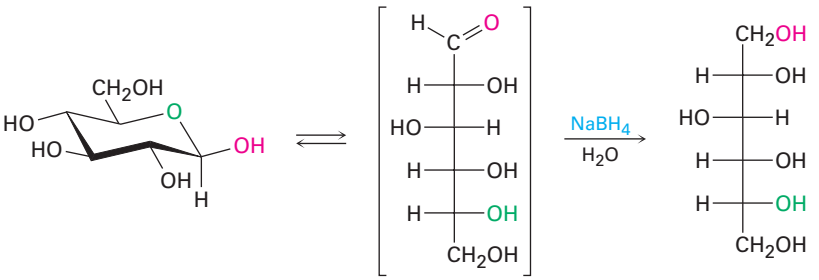


Figure 25.7 Glycoprotein formation occurs by initial phosphorylation of the starting carbohydrate with ATP to a glycosyl monophosphate, followed by reaction with UTP to form a glycosyl uridine 5′-diphosphate. Nucleophilic substitution by an —OH (or $-NH_2$) group on a protein then gives the glycoprotein.

Reduction of Monosaccharides

Treatment of an aldose or ketose with $NaBH_4$ reduces it to a polyalcohol called an **alditol**. The reduction occurs by reaction of the open-chain form present in the aldehyde/ketone ⇄ hemiacetal equilibrium. Although only a small amount of the open-chain form is present at any given time, that small amount is reduced, more is produced by opening of the pyranose form, that additional amount is reduced, and so on, until the entire sample has undergone reaction.



β-D-Glucopyranose **D-Glucose** **D-Glucitol (D-sorbitol), an alditol**

D-Glucitol, the alditol produced by reduction of D-glucose, is itself a naturally occurring substance found in many fruits and berries. It is used under the name D-sorbitol as a sweetener and sugar substitute in many foods.

Problem 25.17

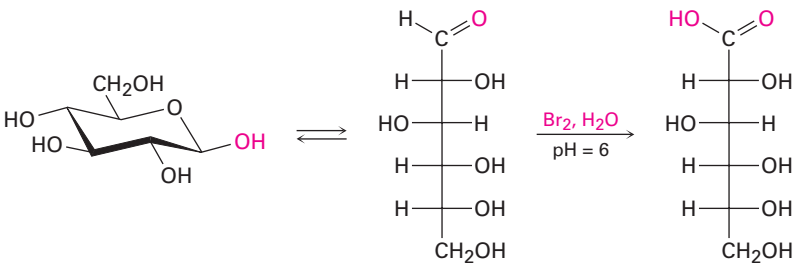
Reduction of D-glucose leads to an optically active alditol (D-glucitol), whereas reduction of D-galactose leads to an optically inactive alditol. Explain.

Problem 25.18

Reduction of L-gulose with $NaBH_4$ leads to the same alditol (D-glucitol) as reduction of D-glucose. Explain.

Oxidation of Monosaccharides

Like other aldehydes, aldoses are easily oxidized to yield the corresponding carboxylic acids, called **aldonic acids**. A buffered solution of aqueous Br_2 is often used for the purpose.



D-Glucose **D-Gluconic acid (an aldonic acid)**

Historically, the oxidation of an aldose with either Ag^+ in aqueous ammonia (called Tollens' reagent) or Cu^{2+} with aqueous sodium citrate (Benedict's reagent) formed the basis of simple tests for what are called **reducing sugars**. (*Reducing*

because the aldose reduces the metal oxidizing agent.) Some simple diabetes self-test kits sold in drugstores still use Benedict's reagent to detect glucose in urine, but more modern methods have largely replaced the chemical test.

All aldoses are reducing sugars because they contain an aldehyde group, but some ketoses are reducing sugars as well. Fructose reduces Tollens' reagent, for example, even though it contains no aldehyde group. Reduction occurs because fructose is readily isomerized to a mixture of aldoses (glucose and mannose) in basic solution by a series of keto–enol tautomeric shifts **(Figure 25.8)**. Glycosides, however, are nonreducing because the acetal group is not hydrolyzed to an aldehyde under basic conditions.

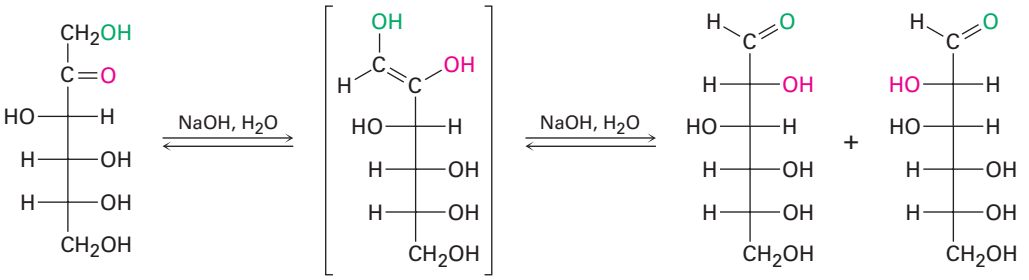
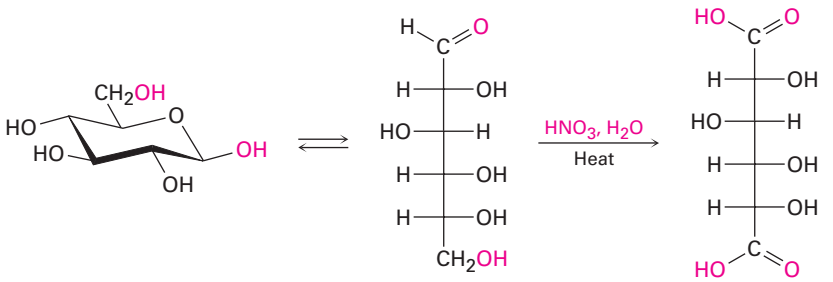
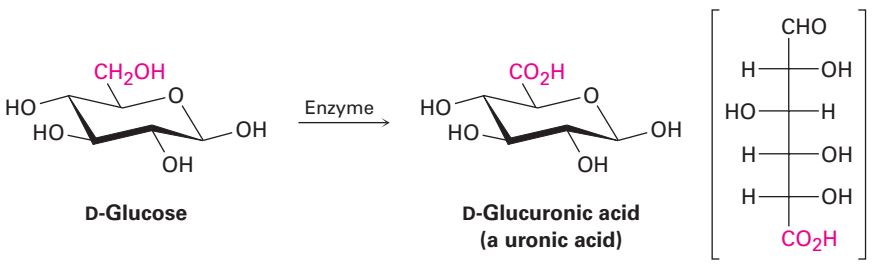


Figure 25.8 Fructose, a ketose, is a reducing sugar because it undergoes two base-catalyzed keto–enol tautomerizations that result in conversion to a mixture of aldoses.

If warm dilute HNO_3 (nitric acid) is used as the oxidizing agent, an aldose is oxidized to a dicarboxylic acid called an **aldaric acid**. Both the aldehyde carbonyl and the terminal $-CH_2OH$ group are oxidized in this reaction.



Finally, if only the $-CH_2OH$ end of the aldose is oxidized without affecting the $-CHO$ group, the product is a monocarboxylic acid called a **uronic acid**. The reaction can only be done enzymatically; no chemical reagent is known that can accomplish this selective oxidation in the laboratory.



Problem 25.19

D-Glucose yields an optically active aldaric acid on treatment with HNO_3, but D-allose yields an optically inactive aldaric acid. Explain.

Problem 25.20

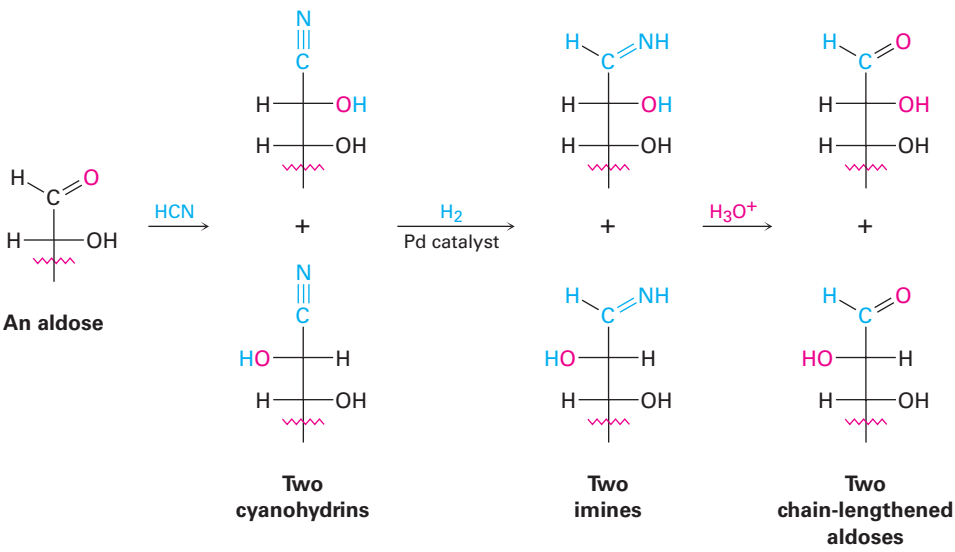
Which of the other six D aldohexoses yield optically active aldaric acids on oxidation, and which yield optically inactive (meso) aldaric acids? (See Problem 25.19.)

Chain Lengthening: The Kiliani–Fischer Synthesis

Much early activity in carbohydrate chemistry was devoted to unraveling the stereochemical relationships among monosaccharides. One of the most important methods used was the *Kiliani–Fischer synthesis,* which results in the lengthening of an aldose chain by one carbon atom. The C1 aldehyde group of the starting sugar becomes C2 of the chain-lengthened sugar, and a new C1 carbon is added. For example, an aldopentose is converted by the Kiliani–Fischer synthesis into two aldohexoses.

Discovery of the chain-lengthening sequence was initiated by the observation of Heinrich Kiliani in 1886 that aldoses react with HCN to form cyanohydrins **(Section 19.6)**. Emil Fischer immediately realized the importance of Kiliani's discovery and devised a method for converting the cyanohydrin nitrile group into an aldehyde.

Fischer's original method for conversion of the nitrile into an aldehyde involved hydrolysis to a carboxylic acid, ring closure to a cyclic ester (lactone), and subsequent reduction. A modern improvement is to reduce the nitrile over a palladium catalyst, yielding an imine intermediate that is hydrolyzed to an aldehyde. Note that the cyanohydrin is formed as a mixture of stereoisomers at the new chirality center, so two new aldoses, differing only in their stereochemistry at C2, result from Kiliani–Fischer synthesis. Chain extension of D-arabinose, for example, yields a mixture of D-glucose and D-mannose.



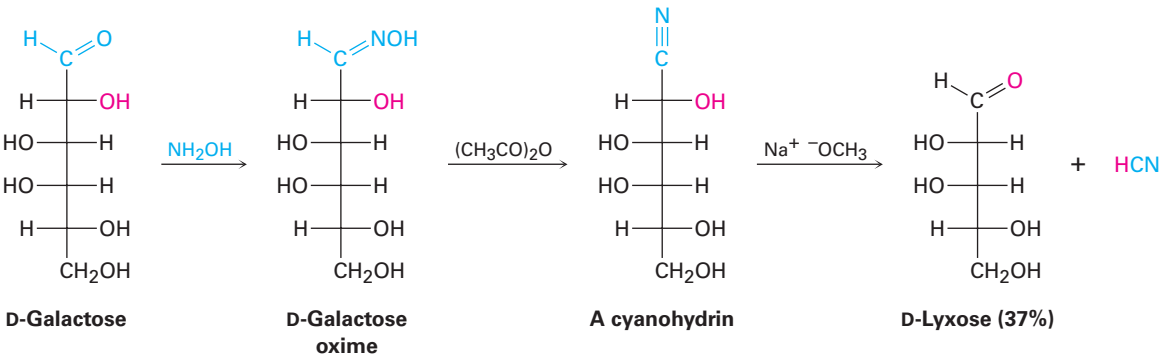
Problem 25.21
What product(s) would you expect from Kiliani–Fischer reaction of D-ribose?

Problem 25.22
What aldopentose would give a mixture of L-gulose and L-idose on Kiliani–Fischer chain extension?

Chain Shortening: The Wohl Degradation

Just as the Kiliani–Fischer synthesis lengthens an aldose chain by one carbon, the *Wohl degradation* shortens an aldose chain by one carbon. The Wohl degradation is almost the exact opposite of the Kiliani–Fischer sequence. That is, the aldose aldehyde carbonyl group is first converted into a nitrile, and the resulting cyanohydrin loses HCN under basic conditions—the reverse of a nucleophilic addition reaction.

Conversion of the aldehyde into a nitrile is accomplished by treatment of an aldose with hydroxylamine to give an imine called an *oxime* **(Section 19.8)**, followed by dehydration of the oxime with acetic anhydride. The Wohl degradation does not give particularly high yields of chain-shortened aldoses, but the reaction is general for all aldopentoses and aldohexoses. For example, D-galactose is converted by Wohl degradation into D-lyxose.



Problem 25.23
Two of the four D aldopentoses yield D-threose on Wohl degradation. What are their structures?

25.7 The Eight Essential Monosaccharides

Humans need to obtain eight monosaccharides for proper functioning. Although all eight can be biosynthesized from simpler precursors if necessary, it's more energetically efficient to obtain them from the diet. The eight are L-fucose (6-deoxy-L-galactose), D-galactose, D-glucose, D-mannose, *N*-acetyl-D-glucosamine, *N*-acetyl-D-galactosamine, D-xylose, and *N*-acetyl-D-neuraminic acid **(Figure 25.9)**.

All are used for the synthesis of the glycoconjugate components of cell walls, and glucose is also the body's primary source of energy.

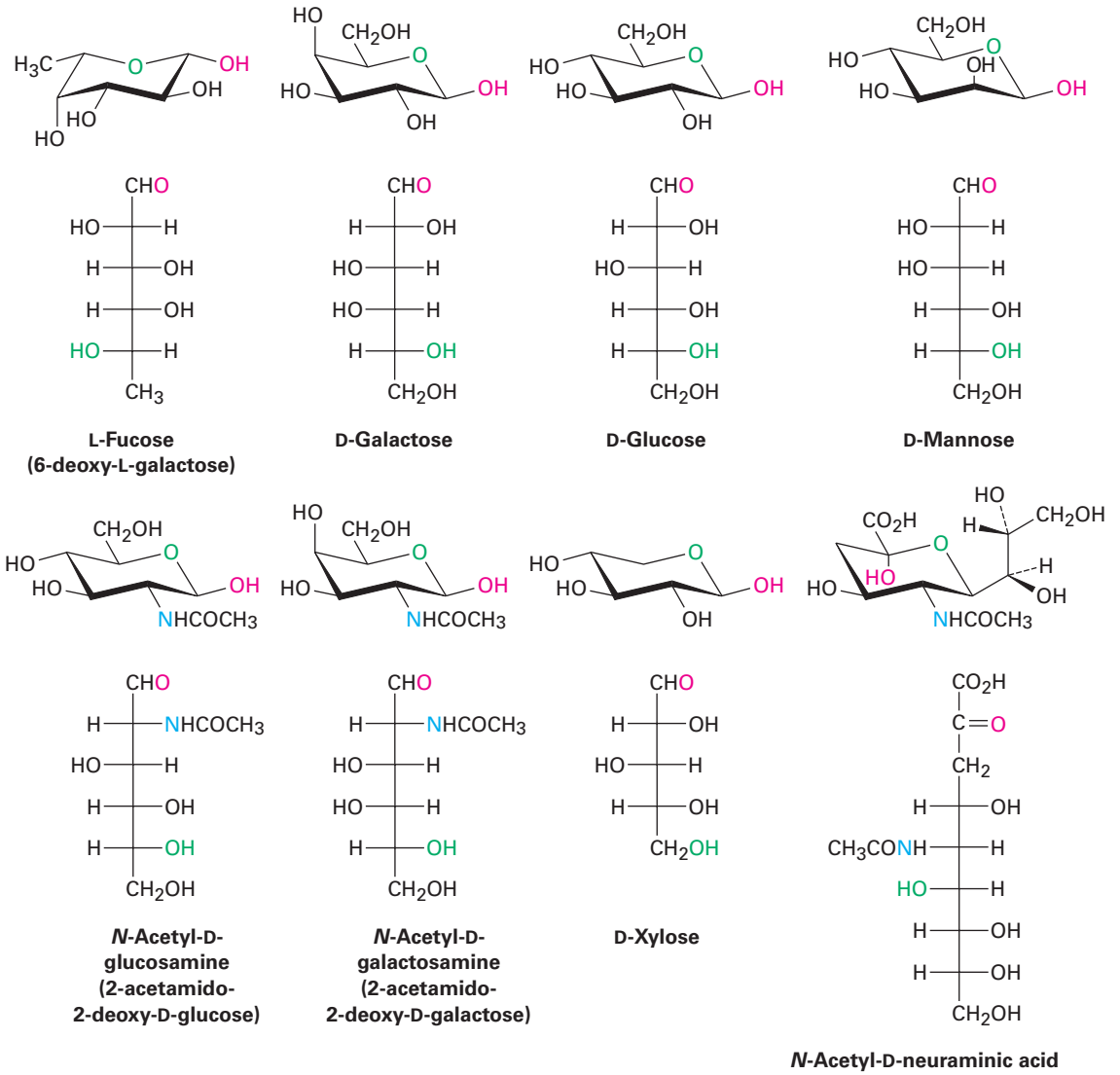


Figure 25.9 Structures of the eight monosaccharides essential to humans.

Of the eight essential monosaccharides, galactose, glucose, and mannose are simple aldohexoses, while xylose is an aldopentose. Fucose is a **deoxy sugar**, meaning that it has an oxygen atom "missing." That is, an −OH group (the one at C6) is replaced by an −H. *N*-Acetylglucosamine and *N*-acetylgalactosamine are amide derivatives of **amino sugars** in which an −OH (the one at C2) is replaced by an $-NH_2$ group. *N*-Acetylneuraminic acid is the parent compound of the sialic acids, a group of more than 30 compounds with different modifications, including various oxidations, acetylations, sulfations, and methylations. Note that neuraminic acid has nine carbons and is an aldol reaction product of *N*-acetylmannosamine with pyruvate ($CH_3COCO_2^-$). We'll see in **Section 25.11**

that neuraminic acid is crucially important to the mechanism by which an influenza virus spreads.

All the essential monosaccharides arise from glucose, by the conversions summarized in **Figure 25.10**. We'll not look specifically at these conversions, but might note that Problems 25.54 through 25.56 and 25.71 at the end of the chapter lead you through several of the biosynthetic pathways.

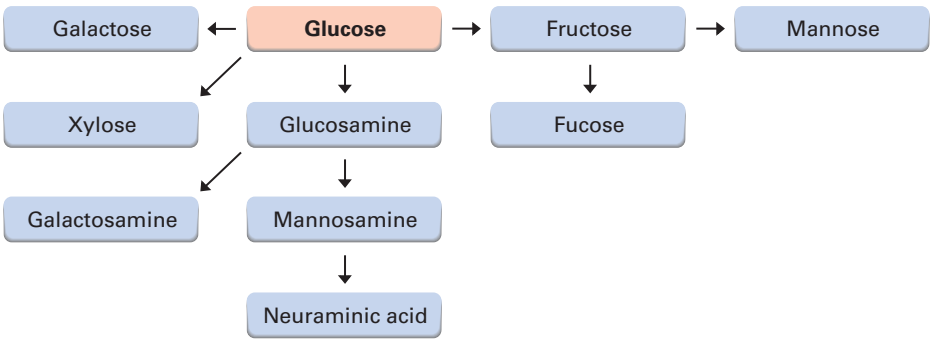
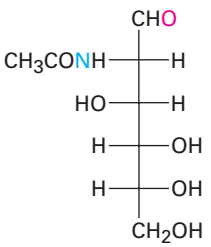


Figure 25.10 An overview of biosynthetic pathways for the eight essential monosaccharides.

Problem 25.24

Show how neuraminic acid can arise by an aldol reaction of *N*-acetylmannosamine with pyruvate ($CH_3COCO_2^-$).



***N*-Acetylmannosamine**

25.8 Disaccharides

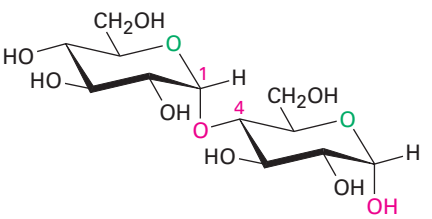
We saw in **Section 25.6** that reaction of a monosaccharide with an alcohol yields a glycoside in which the anomeric −OH group is replaced by an −OR substituent. If the alcohol is itself a sugar, the glycosidic product is a **disaccharide**.

Maltose and Cellobiose

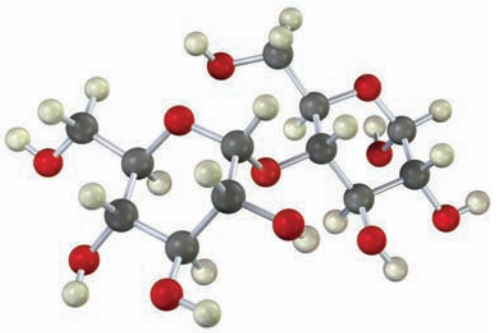
Disaccharides contain a glycosidic acetal bond between the anomeric carbon of one sugar and an −OH group at any position on the other sugar. A glycosidic bond between C1 of the first sugar and the −OH at C4 of the second sugar is particularly common. Such a bond is called a *1→4 link*.

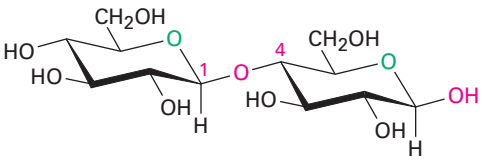
The glycosidic bond to an anomeric carbon can be either α or β. Maltose, the disaccharide obtained by enzyme-catalyzed hydrolysis of starch, consists of two α-D-glucopyranose units joined by a 1→4-α-glycoside bond. Cellobiose, the

disaccharide obtained by partial hydrolysis of cellulose, consists of two β-D-glucopyranose units joined by a 1→4-β-glycoside bond.

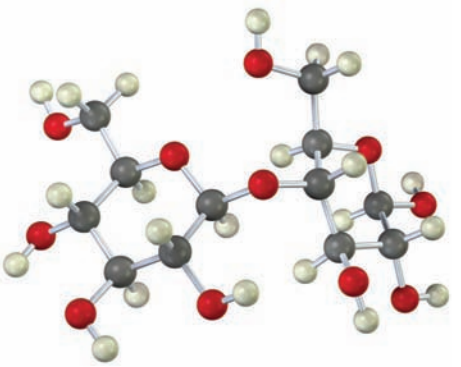


Maltose, a 1→4-α-glycoside
[4-*O*-(α-D-glucopyranosyl)-α-D-glucopyranose]

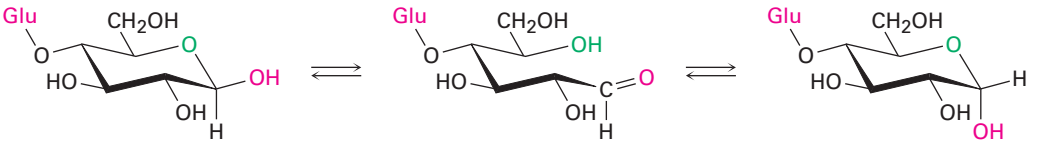




Cellobiose, a 1→4-β-glycoside
[4-*O*-(β-D-glucopyranosyl)-β-D-glucopyranose]



Maltose and cellobiose are both reducing sugars because the anomeric carbons on the right-hand glucopyranose units have hemiacetal groups and are in equilibrium with aldehyde forms. For a similar reason, both maltose and cellobiose exhibit mutarotation of α and β anomers of the glucopyranose unit on the right.



Maltose or cellobiose (β anomers) ⇌ **Maltose or cellobiose (aldehydes)** ⇌ **Maltose or cellobiose (α anomers)**

Despite the similarities of their structures, cellobiose and maltose have dramatically different biological properties. Cellobiose can't be digested by humans and can't be fermented by yeast. Maltose, however, is digested without difficulty and is fermented readily.

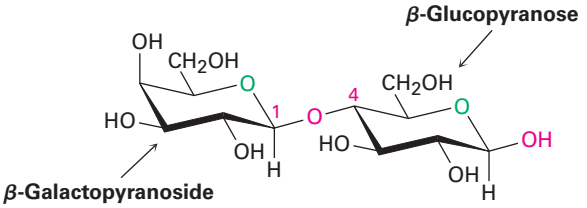
Problem 25.25

Show the product you would obtain from the reaction of cellobiose with the following reagents:

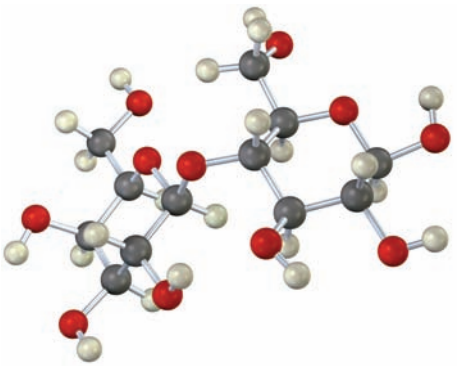
(a) $NaBH_4$ **(b)** Br_2, H_2O **(c)** CH_3COCl, pyridine

Lactose

Lactose is a disaccharide that occurs naturally in both human and cow's milk. It is widely used in baking and in commercial milk formulas for infants. Like maltose and cellobiose, lactose is a reducing sugar. It exhibits mutarotation and is a 1→4-β-linked glycoside. Unlike maltose and cellobiose, however, lactose contains two different monosaccharides—D-glucose and D-galactose—joined by a β-glycosidic bond between C1 of galactose and C4 of glucose.



Lactose, a 1→4-β-glycoside
[4-*O*-(β-D-galactopyranosyl)-β-D-glucopyranose]

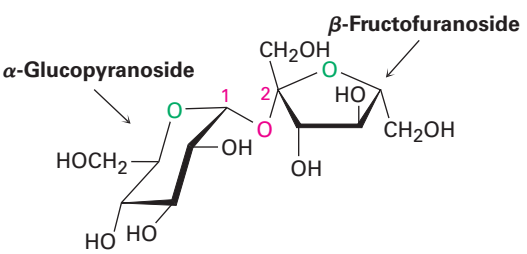


Sucrose

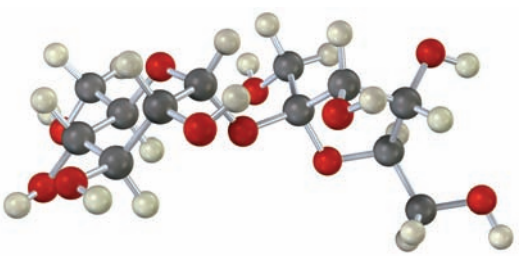
Sucrose, or ordinary table sugar, is probably the most abundant pure organic chemical in the world. Whether from sugar cane (20% sucrose by weight) or sugar beets (15% by weight), and whether raw or refined, all table sugar is sucrose.

Sucrose is a disaccharide that yields 1 equivalent of glucose and 1 equivalent of fructose on hydrolysis. This 1:1 mixture of glucose and fructose is often referred to as *invert sugar* because the sign of optical rotation changes, or inverts, during the hydrolysis of sucrose ($[\alpha]_D = +66.5$) to a glucose/fructose mixture ($[\alpha]_D = -22.0$). Some insects, such as honeybees, have enzymes called invertases that catalyze the sucrose hydrolysis. Honey, in fact, is primarily a mixture of glucose, fructose, and sucrose.

Unlike most other disaccharides, sucrose is not a reducing sugar and does not undergo mutarotation. These observations imply that sucrose is not a hemiacetal and suggest that glucose and fructose must both be glycosides. This can happen only if the two sugars are joined by a glycoside link between the anomeric carbons of both sugars—C1 of glucose and C2 of fructose.



Sucrose, a 1→2-glycoside
[2-*O*-(α-D-glucopyranosyl)-β-D-fructofuranoside]

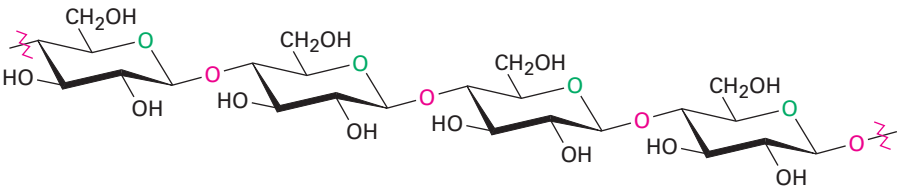


25.9 Polysaccharides and Their Synthesis

Polysaccharides are complex carbohydrates in which tens, hundreds, or even thousands of simple sugars are linked together through glycoside bonds. Because they have only the one free anomeric –OH group at the end of a very long chain, polysaccharides aren't reducing sugars and don't show noticeable mutarotation. Cellulose and starch are the two most widely occurring polysaccharides.

Cellulose

Cellulose consists of several thousand D-glucose units linked by 1→4-β-glycoside bonds like those in cellobiose. Different cellulose molecules then interact to form a large aggregate structure held together by hydrogen bonds.

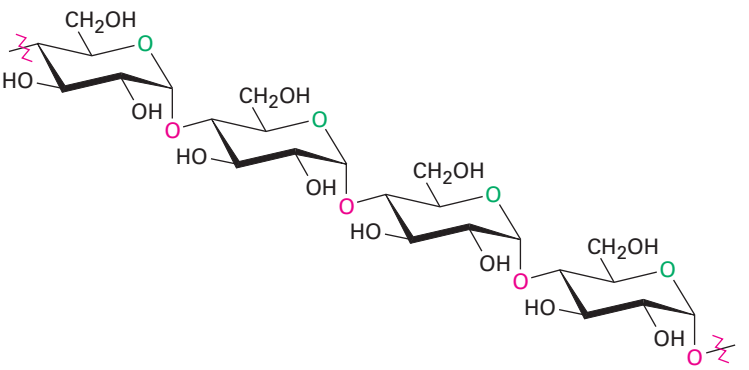


Cellulose, a 1→4-*O*-(β-D-glucopyranoside) polymer

Nature uses cellulose primarily as a structural material to impart strength and rigidity to plants. Leaves, grasses, and cotton, for instance, are primarily cellulose. Cellulose also serves as raw material for the manufacture of cellulose acetate, known commercially as acetate rayon, and cellulose nitrate, known as guncotton. Guncotton is the major ingredient in smokeless powder, the explosive propellant used in artillery shells and in ammunition for firearms.

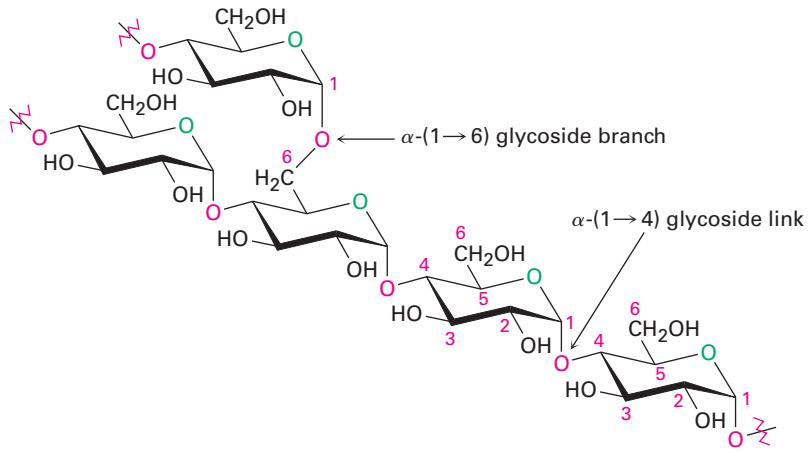
Starch and Glycogen

Potatoes, corn, and cereal grains contain large amounts of *starch,* a polymer of glucose in which the monosaccharide units are linked by 1→4-α-glycoside bonds like those in maltose. Starch can be separated into two fractions: amylose and amylopectin. Amylose accounts for about 20% by weight of starch and consists of several hundred glucose molecules linked together by 1→4-α-glycoside bonds.



Amylose, a 1→4-*O*-(α-D-glucopyranoside) polymer

Amylopectin accounts for the remaining 80% of starch and is more complex in structure than amylose. Unlike cellulose and amylose, which are linear polymers, amylopectin contains 1→6-α-glycoside branches approximately every 25 glucose units.



Amylopectin: α-(1→4) links with α-(1→6) branches

Starch is digested in the mouth and stomach by α-glycosidases, which catalyze the hydrolysis of glycoside bonds and release individual molecules of glucose. Like most enzymes, α-glycosidases are highly selective in their action. They hydrolyze only the α-glycoside links in starch and leave the β-glycoside links in cellulose untouched. Thus, humans can digest potatoes and grains but not grass and leaves.

Glycogen is a polysaccharide that serves the same energy storage function in animals that starch serves in plants. Dietary carbohydrates not needed for immediate energy are converted by the body to glycogen for long-term storage. Like the amylopectin found in starch, glycogen contains a complex branching structure with both 1→4 and 1→6 links **(Figure 25.11)**. Glycogen molecules are larger than those of amylopectin—up to 100,000 glucose units—and contain even more branches.

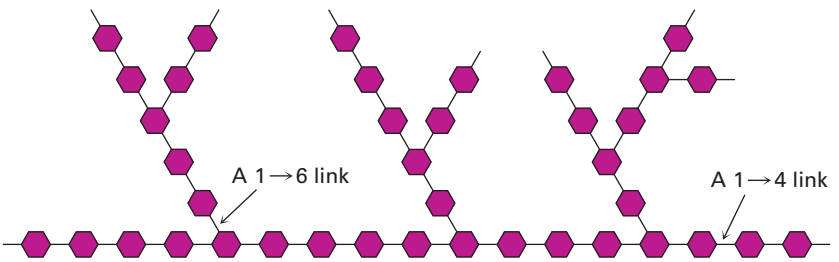


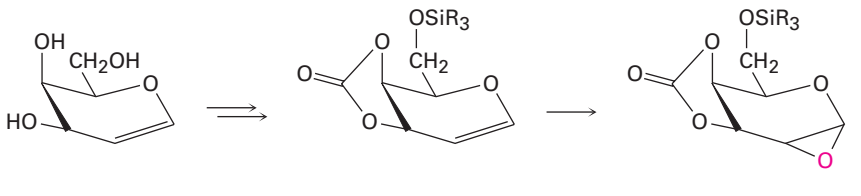
Figure 25.11 A representation of the structure of glycogen. The hexagons represent glucose units linked by 1→4 and 1→6 glycoside bonds.

Polysaccharide Synthesis

With numerous −OH groups of similar reactivity, polysaccharides are so structurally complex that their laboratory synthesis has been a particularly difficult problem. Several methods have recently been devised, however, that have

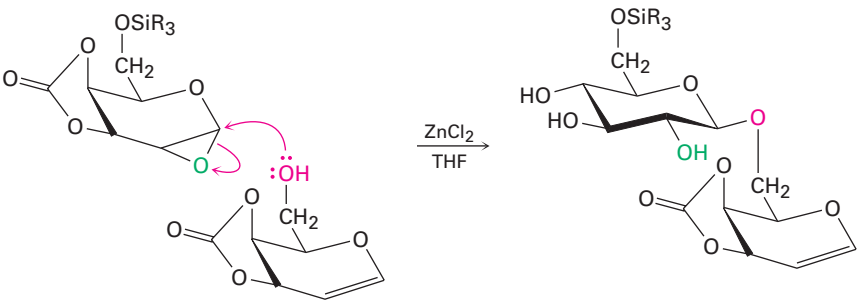
greatly simplified the problem. Among these approaches is the *glycal assembly method*.

Easily prepared from the appropriate monosaccharide, a glycal is an unsaturated sugar with a C1–C2 double bond. To ready it for use in polysaccharide synthesis, the glycal is first protected at its primary −OH group by formation of a silyl ether **(Section 17.8)** and at its two adjacent secondary −OH groups by formation of a cyclic carbonate ester. Then, the protected glycal is epoxidized.



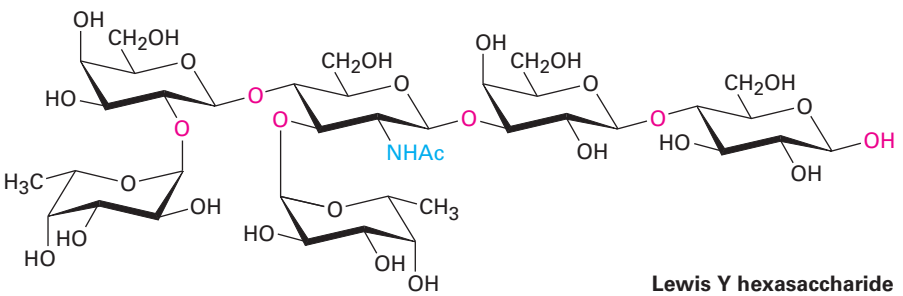
A glycal **A protected glycal** **An epoxide**

Treatment of the protected glycal epoxide in the presence of $ZnCl_2$ as a Lewis acid with a second glycal having a free −OH group causes acid-catalyzed opening of the epoxide ring by S_N2 backside attack **(Section 18.6)** and yields a disaccharide. The disaccharide is itself a glycal, so it can be epoxidized and coupled again to yield a trisaccharide, and so on. Using the appropriate sugars at each step, a great variety of polysaccharides can be prepared. After the appropriate sugars are linked, the silyl ethers and cyclic carbonate protecting groups are removed by hydrolysis.



A disaccharide glycal

Among the numerous complex polysaccharides that have been synthesized in the laboratory is the Lewis Y hexasaccharide, a tumor marker that is currently being explored as a potential cancer vaccine.

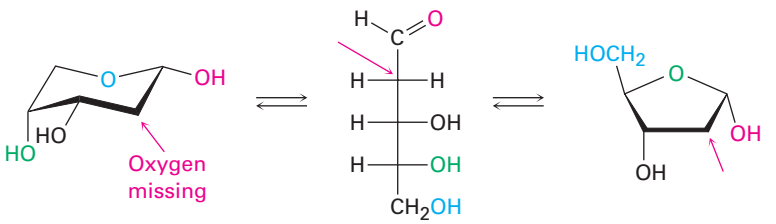


Lewis Y hexasaccharide

25.10 Other Important Carbohydrates

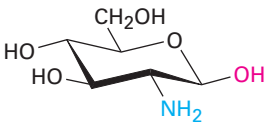
In addition to the common carbohydrates mentioned in previous sections, there are a variety of important carbohydrate-derived materials. Their structural resemblance to sugars is clear, but they aren't simple aldoses or ketoses.

Deoxy sugars, as we saw in **Section 25.7**, have an oxygen atom "missing." That is, an −OH group is replaced by an −H. The most common deoxy sugar is 2-deoxyribose, a monosaccharide found in DNA (deoxyribonucleic acid). Note that 2-deoxyribose exists in water solution as a complex equilibrium mixture of both furanose and pyranose forms.

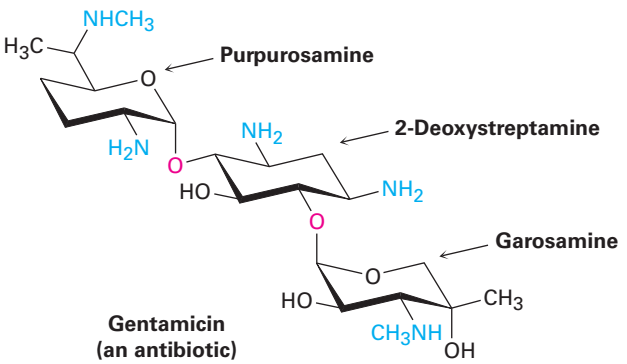


α-D-2-Deoxyribopyranose (40%) (+ 35% β anomer) **(0.7%)** **α-D-2-Deoxyribofuranose (13%) (+ 12% β anomer)**

Amino sugars, such as D-glucosamine, have an −OH group replaced by an $-NH_2$. The *N*-acetyl amide derived from D-glucosamine is the monosaccharide unit from which chitin, the hard crust that protects insects and shellfish, is made. Still other amino sugars are found in antibiotics such as streptomycin and gentamicin.



β-D-Glucosamine



Gentamicin (an antibiotic)

25.11 Cell-Surface Carbohydrates and Influenza Viruses

It was once thought that carbohydrates were useful in nature only as structural materials and energy sources. Although carbohydrates do indeed serve these purposes, they have many other important biochemical functions as well. As noted in **Section 25.6**, for instance, glycoconjugates are centrally involved in cell–cell recognition, the critical process by which one type of cell distinguishes another. Small polysaccharide chains, covalently bound by glycosidic links to −OH or $-NH_2$ groups on proteins, act as biochemical markers on cell surfaces, as illustrated by influenza viruses.

Each year, seasonal outbreaks of influenza occur throughout the world, usually without particular notice. These outbreaks are caused by subtypes of known flu viruses that are already present in the population, and they can usually be controlled or prevented by vaccination. Every 10 to 40 years, however, a new and virulent subtype never before seen in humans appears. The result can be a worldwide pandemic, capable of causing great disruption and killing millions.

Three such pandemics struck in the 20th century, the most serious of which was the 1918–1919 "Spanish flu" that killed an estimated 50 million people worldwide, including many healthy young adults. It has now been more than 40 years since the last pandemic, an outbreak of "Hong Kong flu" in 1968–1969, and many public heath officials fear that another may occur soon.

Two potentially serious influenza outbreaks have occurred in recent years. The first, discovered in 1997, is commonly called "bird flu"; the second, found in early 2009, is "swine flu." Bird flu is caused by the transfer to humans of an avian H5N1 virus that has killed tens of millions of birds, primarily in Southeast Asia. Human infection by this virus was first noted in Hong Kong in 1997, and by mid-2010, 503 cases with 299 deaths had been confirmed in 15 countries. Swine flu is caused by an H1N1 virus that is very closely related to the 1918 virus and is now found in pigs. The virus appears to spread rapidly in humans—more than 3000 cases were found in the first 2 months after it was identified. By mid-2010, 18,449 deaths in 214 countries had been reported.

The classifications H5N1 and H1N1 for the two viral strains are based on the behavior of two kinds of glycoproteins that coat the viral surface—hemagglutinin (H, type 5 or type 1) and neuraminidase (N, type 1), an enzyme. Infection occurs when a viral particle, or *virion,* binds to the sialic acid part **(Section 25.7)** of a receptor glycoprotein on the target cell and is then engulfed by the cell. New viral particles are produced inside the infected cell, pass back out, and are again held by sialic acid bonded to glycoproteins in cell-surface receptors. Finally, the neuraminidase enzyme present on the viral surface cleaves the bond between receptor glycoprotein and sialic acid, thereby releasing the virion and allowing it to invade a new cell **(Figure 25.12)**.

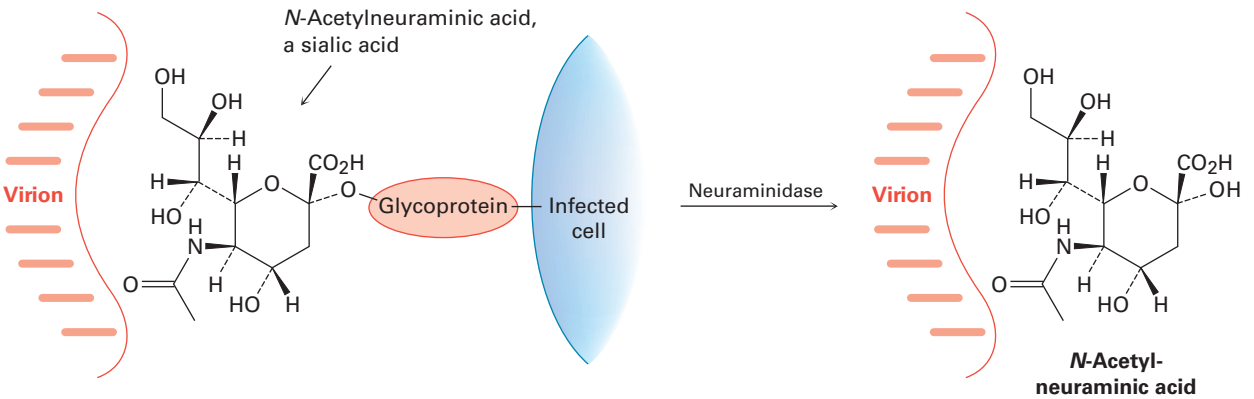
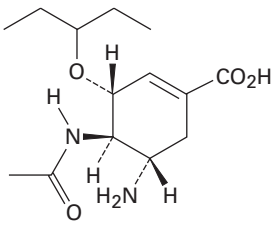


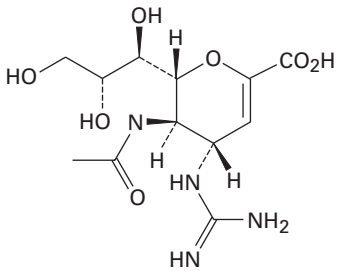
Figure 25.12 Release of a newly formed virion from an infected cell occurs when neuraminidase, present on the surface of the virion, cleaves the bond holding the virion to a sialic acid molecule in a glycoprotein receptor on the infected cell.

So what can be done to limit the severity of an influenza pandemic? Development of a vaccine is the only means to limit the spread of the virus, but work can't begin until the contagious strain of virus has appeared. Until that time,

the only hope is that an antiviral drug might limit the severity of infection. Oseltamivir, sold as Tamiflu, and zanamivir, sold as Relenza, are two of only a handful of known substances able to inhibit the neuraminidase enzyme. With the enzyme blocked, newly formed virions are not released, and spread of the infection within the body is thus limited. You might notice in Figure 25.12 the similarity in shape between *N*-acetylneuraminic acid and both oseltamivir and zanamivir, which allows the drugs to bind to and block the action of neuraminidase. Unfortunately, the H1N1 swine flu virus developed almost complete resistance to oseltamivir within a year of appearing, so chemists will have to work hard to keep ahead.



Oseltamivir (Tamiflu)



Zanamivir (Relenza)

A DEEPER LOOK Sweetness

Say the word *sugar* and most people immediately think of sweet-tasting candies, desserts, and such. In fact, most simple carbohydrates do taste sweet but the degree of sweetness varies greatly from one sugar to another. With sucrose (table sugar) as a reference point, fructose is nearly twice as sweet, but lactose is only about one-sixth as sweet. Comparisons are difficult, though, because perceived sweetness varies depending on the concentration of the solution being tasted and on personal opinion. Nevertheless, the ordering in Table 25.1 is generally accepted.

The real thing comes from sugarcane fields like this one.

Table 25.1 Sweetness of Some Sugars and Sugar Substitutes

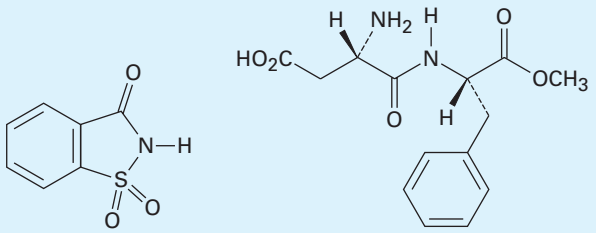
Name	Type	Sweetness
Lactose	Disaccharide	0.16
Glucose	Monosaccharide	0.75
Sucrose	**Disaccharide**	**1.00**
Fructose	Monosaccharide	1.75
Aspartame	Synthetic	180
Acesulfame-K	Synthetic	200
Saccharin	Synthetic	350
Sucralose	Semisynthetic	600
Alitame	Semisynthetic	2000

(continued)

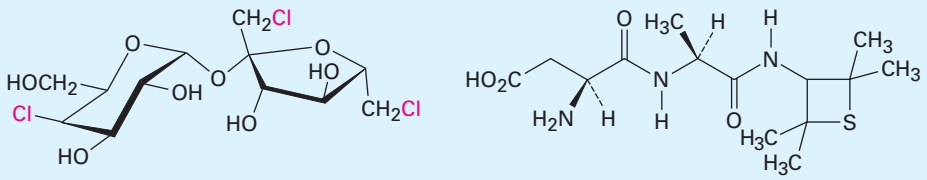
(continued)

The desire of many people to cut their caloric intake has led to the development of synthetic sweeteners such as saccharin, aspartame, acesulfame, and sucralose. All are far sweeter than natural sugars, so the choice of one or another depends on personal taste, government regulations, and (for baked goods) heat stability. Saccharin, the oldest synthetic sweetener, has been used for more than a century, although it has a somewhat metallic aftertaste. Doubts about its safety and potential carcinogenicity were raised in the early 1970s, but it has now been cleared of suspicion.

Acesulfame potassium, one of the most recently approved sweeteners, is proving to be extremely popular in soft drinks because it has little aftertaste. Sucralose, another recently approved sweetener, is particularly useful in baked goods because of its stability at high temperatures. Alitame, marketed in some countries under the name Aclame, is not approved for sale in the United States. It is some 2000 times as sweet as sucrose and, like acesulfame-K, has no aftertaste. Of the five synthetic sweeteners listed in Table 25.1, only sucralose has clear structural resemblance to a carbohydrate, although it differs dramatically in containing three chlorine atoms. Aspartame and alitame are both dipeptides.



Saccharin **Aspartame** **Acesulfame potassium**



Sucralose **Alitame**

Summary

Key words

aldaric acid, 1021
alditol, 1020
aldonic acid, 1020
aldose, 1002
amino sugar, 1024
α anomer, β anomer, 1012
anomeric center, 1012

Now that we've now seen all the common functional groups and reaction types, our focus has changed to looking at the major classes of biological molecules. **Carbohydrates** are polyhydroxy aldehydes and ketones. They are classified according to the number of carbon atoms and the kind of carbonyl group they contain. Glucose, for example, is an aldohexose, a six-carbon aldehydo sugar. **Monosaccharides** are further classified as either D **sugars** or L **sugars**, depending on the stereochemistry of the chirality center farthest from the carbonyl group. Carbohydrate stereochemistry is frequently depicted using **Fischer projections**, which represent a chirality center as the intersection of two crossed lines.

Monosaccharides normally exist as cyclic hemiacetals rather than as open-chain aldehydes or ketones. The hemiacetal linkage results from reaction of the carbonyl group with an −OH group three or four carbon atoms away. A five-membered cyclic hemiacetal is called a **furanose**, and a six-membered cyclic hemiacetal is called a **pyranose**. Cyclization leads to the formation of a new chirality center called the **anomeric center** and the production of two diastereomeric hemiacetals called **alpha (α) and beta (β) anomers**.

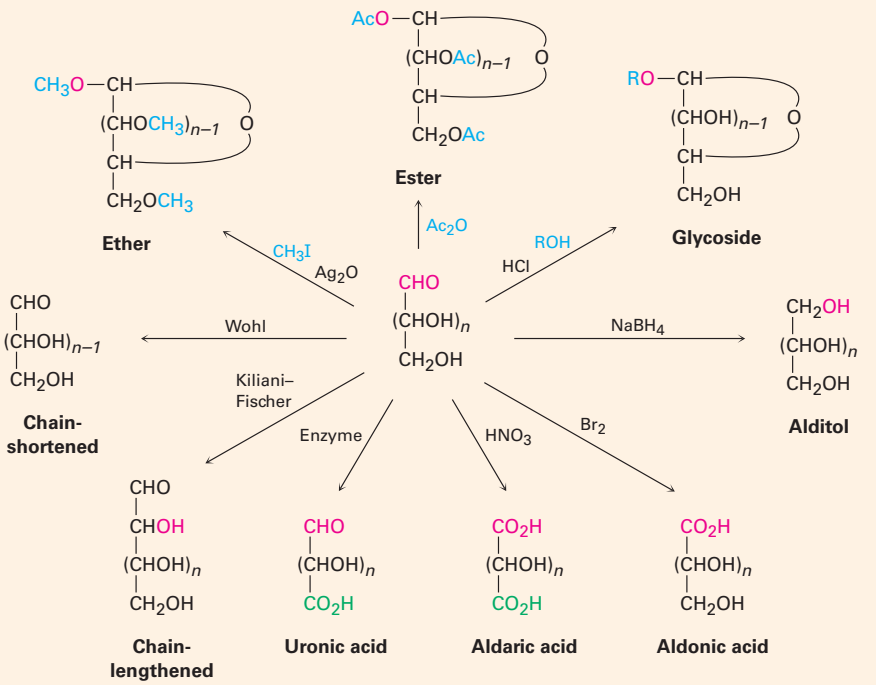
Much of the chemistry of monosaccharides is the familiar chemistry of alcohols and aldehydes/ketones. Thus, the hydroxyl groups of carbohydrates form esters and ethers. The carbonyl group of a monosaccharide can be reduced with $NaBH_4$ to form an **alditol**, oxidized with aqueous Br_2 to form an **aldonic acid**, oxidized with HNO_3 to form an **aldaric acid**, oxidized enzymatically to form a **uronic acid**, or treated with an alcohol in the presence of acid to form a **glycoside**. Monosaccharides can also be chain-lengthened by the multistep **Kiliani–Fischer synthesis** and can be chain-shortened by the **Wohl degradation**.

Disaccharides are complex carbohydrates in which simple sugars are linked by a glycoside bond between the **anomeric center** of one unit and a hydroxyl of the second unit. The sugars can be the same, as in maltose and cellobiose, or different, as in lactose and sucrose. The glycosidic bond can be either α (maltose) or β (cellobiose, lactose) and can involve any hydroxyl of the second sugar. A 1→4 link is most common (cellobiose, maltose), but others such as 1→2 (sucrose) are also known. **Polysaccharides**, such as cellulose, starch, and glycogen, are used in nature as structural materials, as a means of long-term energy storage, and as cell-surface markers.

Key words—cont'd

carbohydrate, 1000
complex carbohydrate, 1001
D sugar, 1007
deoxy sugar, 1024
disaccharide, 1025
Fischer projection, 1002
furanose, 1012
glycoside, 1016
ketose, 1002
L sugar, 1007
monosaccharide, 1001
mutarotation, 1013
polysaccharide, 1028
pyranose, 1011
reducing sugar, 1020
simple sugar, 1001
uronic acid, 1021

Summary of Reactions



Exercises

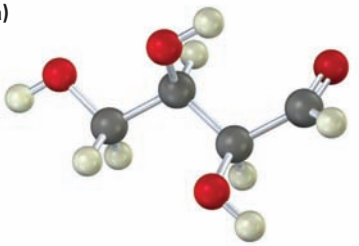
OWL Interactive versions of these problems are assignable in OWL for Organic Chemistry.

Visualizing Chemistry

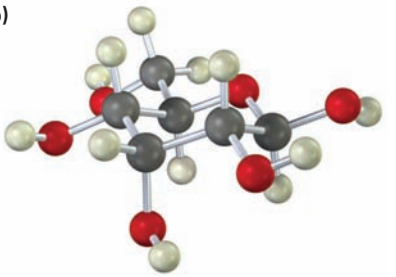
(Problems 25.1–25.25 appear within the chapter.)

25.26 Identify the following aldoses, and tell whether each is a D or L sugar:

(a)

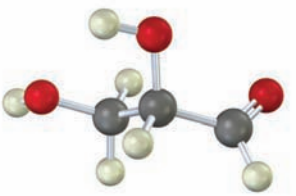


(b)



25.27 Draw Fischer projections of the following molecules, placing the carbonyl group at the top in the usual way. Identify each as a D or L sugar.

(a)



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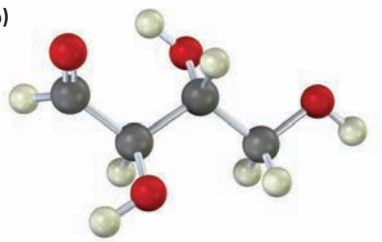
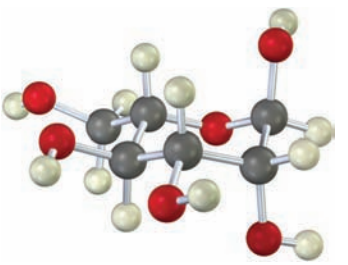
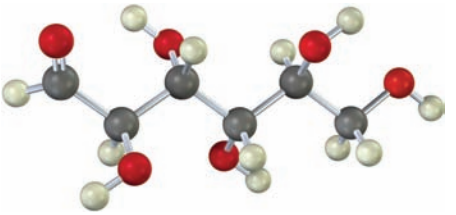


25.28 The following structure is that of an L aldohexose in its pyranose form. Identify it, and tell whether it is an α or β anomer.



25.29 The following model is that of an aldohexose:

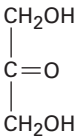


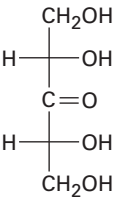
(a) Draw Fischer projections of the sugar, its enantiomer, and a diastereomer.
(b) Is this a D sugar or an L sugar? Explain.
(c) Draw the β anomer of the sugar in its furanose form.

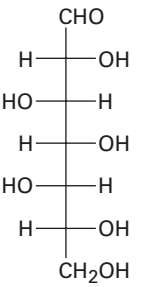
Additional Problems

Carbohydrate Structures

25.30 Classify each of the following sugars. (For example, glucose is an aldohexose.)

(a)


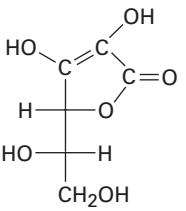
(b)


(c)


25.31 Write open-chain structures for the following:
(a) A ketotetrose
(b) A ketopentose
(c) A deoxyaldohexose
(d) A five-carbon amino sugar

25.32 What is the stereochemical relationship of D-ribose to L-xylose? What generalizations can you make about the following properties of the two sugars?
(a) Melting point
(b) Solubility in water
(c) Specific rotation
(d) Density

25.33 Does ascorbic acid (vitamin C) have a D or L configuration?

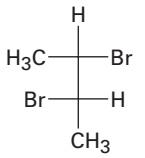


Ascorbic acid

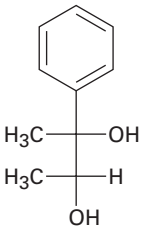
25.34 Draw the three-dimensional furanose form of ascorbic acid (Problem 25.33), and assign *R* or *S* stereochemistry to each chirality center.

25.35 Assign *R* or *S* configuration to each chirality center in the following molecules:

(a)



(b)



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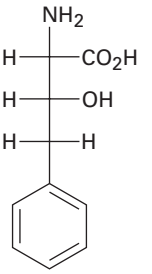
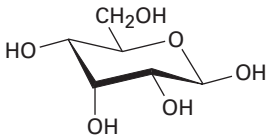


25.36 Draw Fischer projections of the following molecules:

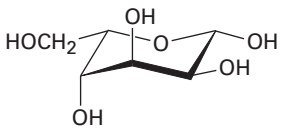
(a) The *S* enantiomer of 2-bromobutane
(b) The *R* enantiomer of alanine, $CH_3CH(NH_2)CO_2H$
(c) The *R* enantiomer of 2-hydroxypropanoic acid
(d) The *S* enantiomer of 3-methylhexane

25.37 Draw Fischer projections for the two D aldoheptoses whose stereochemistry at C3, C4, C5, and C6 is the same as that of D-glucose at C2, C3, C4, and C5.

25.38 The following cyclic structure is that of allose. Is this a furanose or pyranose form? Is it an α or β anomer? Is it a D or L sugar?

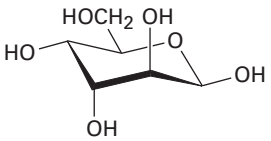


25.39 What is the complete name of the following sugar?

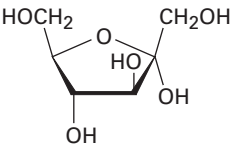


25.40 Write the following sugars in their open-chain forms:

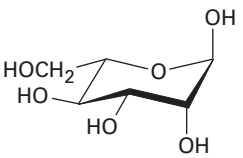
(a)



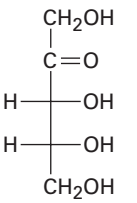
(b)



(c)



25.41 Draw D-ribulose in its five-membered cyclic β-hemiacetal form.



Ribulose

25.42 Look up the structure of D-talose in Figure 25.3, and draw the β anomer in its pyranose form. Identify the ring substituents as axial or equatorial.

Carbohydrate Reactions

25.43 Draw structures for the products you would expect to obtain from reaction of β-D-talopyranose with each of the following reagents:

(a) $NaBH_4$ in H_2O **(b)** Warm dilute HNO_3 **(c)** Br_2, H_2O
(d) CH_3CH_2OH, HCl **(e)** CH_3I, Ag_2O **(f)** $(CH_3CO)_2O$, pyridine

25.44 How many D-2-ketohexoses are possible? Draw them.

25.45 One of the D-2-ketohexoses is called *sorbose*. On treatment with $NaBH_4$, sorbose yields a mixture of gulitol and iditol. What is the structure of sorbose?

25.46 Another D-2-ketohexose, *psicose,* yields a mixture of allitol and altritol when reduced with $NaBH_4$. What is the structure of psicose?

25.47 L-Gulose can be prepared from D-glucose by a route that begins with oxidation to D-glucaric acid, which cyclizes to form two six-membered-ring lactones. Separating the lactones and reducing them with sodium amalgam gives D-glucose and L-gulose. What are the structures of the two lactones, and which one is reduced to L-gulose?

25.48 Gentiobiose, a rare disaccharide found in saffron and gentian, is a reducing sugar and forms only D-glucose on hydrolysis with aqueous acid. Reaction of gentiobiose with iodomethane and Ag_2O yields an octamethyl derivative, which can be hydrolyzed with aqueous acid to give 1 equivalent of 2,3,4,6-tetra-*O*-methyl-D-glucopyranose and 1 equivalent of 2,3,4-tri-*O*-methyl-D-glucopyranose. If gentiobiose contains a β-glycoside link, what is its structure?

General Problems

25.49 All aldoses exhibit mutarotation. For example, α-D-galactopyranose has $[\alpha]_D = +150.7$, and β-D-galactopyranose has $[\alpha]_D = +52.8$. If either anomer is dissolved in water and allowed to reach equilibrium, the specific rotation of the solution is +80.2. What are the percentages of each anomer at equilibrium? Draw the pyranose forms of both anomers.

25.50 What other D aldohexose gives the same alditol as D-talose?

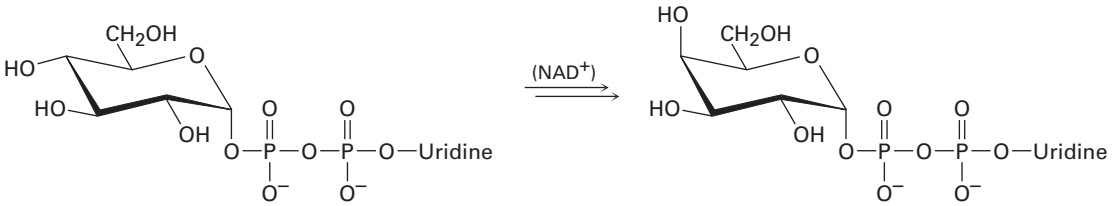
25.51 Which of the eight D aldohexoses give the same aldaric acids as their L enantiomers?

25.52 Which of the other three D aldopentoses gives the same aldaric acid as D-lyxose?

25.53 Draw the structure of L-galactose, and then answer the following questions:

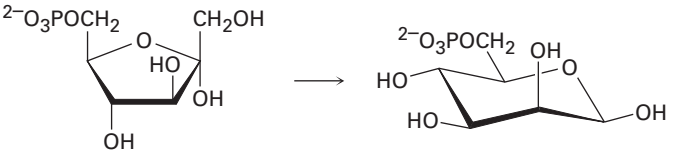
(a) Which other aldohexose gives the same aldaric acid as L-galactose on oxidation with warm HNO_3?
(b) Is this other aldohexose a D sugar or an L sugar?
(c) Draw this other aldohexose in its most stable pyranose conformation.

25.54 Galactose, one of the eight essential monosaccharides (Section 25.7), is biosynthesized from UDP-glucose by galactose 4-epimerase, where UDP = uridylyl diphosphate (a ribonucleotide diphosphate; Section 28.1). The enzyme requires NAD^+ for activity (Section 17.7), but it is not a stoichiometric reactant, and NADH is not a final reaction product. Propose a mechanism.



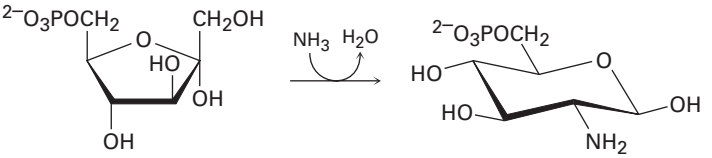
UDP-Glucose **UDP-Galactose**

25.55 Mannose, one of the eight essential monosaccharides (Section 25.7), is biosynthesized as its 6-phosphate derivative from fructose 6-phosphate. No enzyme cofactor is required. Propose a mechanism.



Fructose 6-phosphate **Mannose 6-phosphate**

25.56 Glucosamine, one of the eight essential monosaccharides (Section 25.7), is biosynthesized as its 6-phosphate derivative from fructose 6-phosphate by reaction with ammonia. Propose a mechanism.



Fructose 6-phosphate **Glucosamine 6-phosphate**

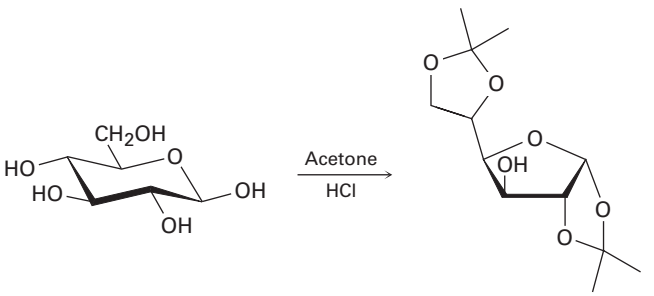
25.57 Amygdalin, or laetrile, is a cyanogenic glycoside isolated in 1830 from almond and apricot seeds. Acidic hydrolysis of amygdalin liberates HCN, along with benzaldehyde and 2 equivalents of D-glucose. If amygdalin is a β-glycoside of benzaldehyde cyanohydrin with gentiobiose (Problem 21.56), what is its structure?

25.58 Trehalose is a nonreducing disaccharide that is hydrolyzed by aqueous acid to yield 2 equivalents of D-glucose. Methylation followed by hydrolysis yields 2 equivalents of 2,3,4,6-tetra-*O*-methylglucose. How many structures are possible for trehalose?

25.59 Trehalose (Problem 25.58) is cleaved by enzymes that hydrolyze α-glycosides but not by enzymes that hydrolyze β-glycosides. What is the structure and systematic name of trehalose?

25.60 Isotrehalose and neotrehalose are chemically similar to trehalose (Problems 25.58 and 25.59) except that neotrehalose is hydrolyzed only by β-glycosidase enzymes, whereas isotrehalose is hydrolyzed by both α- and β-glycosidase enzymes. What are the structures of isotrehalose and neotrehalose?

25.61 D-Glucose reacts with acetone in the presence of acid to yield the nonreducing 1,2:5,6-diisopropylidene-D-glucofuranose. Propose a mechanism.



1,2:5,6-Diisopropylidene-D-glucofuranose

25.62 D-Mannose reacts with acetone to give a diisopropylidene derivative (Problem 25.61) that is still reducing toward Tollens' reagent. Propose a likely structure for this derivative.

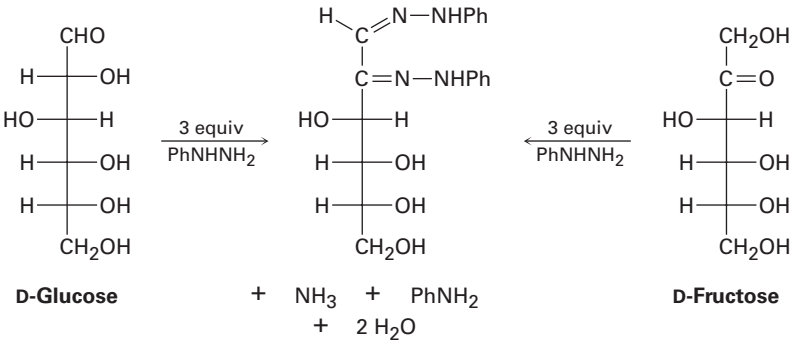
25.63 Glucose and mannose can be interconverted (in low yield) by treatment with dilute aqueous NaOH. Propose a mechanism.

25.64 Propose a mechanism to account for the fact that D-gluconic acid and D-mannonic acid are interconverted when either is heated in pyridine solvent.

25.65 The *cyclitols* are a group of carbocyclic sugar derivatives having the general formulation 1,2,3,4,5,6-cyclohexanehexol. How many stereoisomeric cyclitols are possible? Draw them in their chair forms.

25.66 Compound **A** is a D aldopentose that can be oxidized to an optically inactive aldaric acid **B**. On Kiliani–Fischer chain extension, **A** is converted into **C** and **D**; **C** can be oxidized to an optically active aldaric acid **E**, but **D** is oxidized to an optically inactive aldaric acid **F**. What are the structures of **A–F**?

25.67 Simple sugars undergo reaction with phenylhydrazine, $PhNHNH_2$, to yield crystalline derivatives called *osazones*. The reaction is a bit complex, however, as shown by the fact that glucose and fructose yield the same osazone.



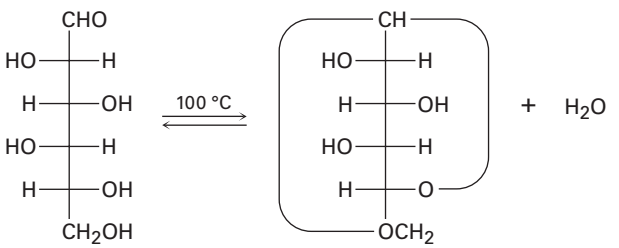
(a) Draw the structure of a third sugar that yields the same osazone as glucose and fructose.

(b) Using glucose as the example, the first step in osazone formation is reaction of the sugar with phenylhydrazine to yield an imine called a *phenylhydrazone*. Draw the structure of the product.

(c) The second and third steps in osazone formation are tautomerization of the phenylhydrazone to give an enol, followed by elimination of aniline to give a keto imine. Draw the structures of both the enol tautomer and the keto imine.

(d) The final step is reaction of the keto imine with 2 equivalents of phenylhydrazine to yield the osazone plus ammonia. Propose a mechanism for this step.

25.68 When heated to 100 °C, D-idose undergoes a reversible loss of water and exists primarily as 1,6-anhydro-D-idopyranose.



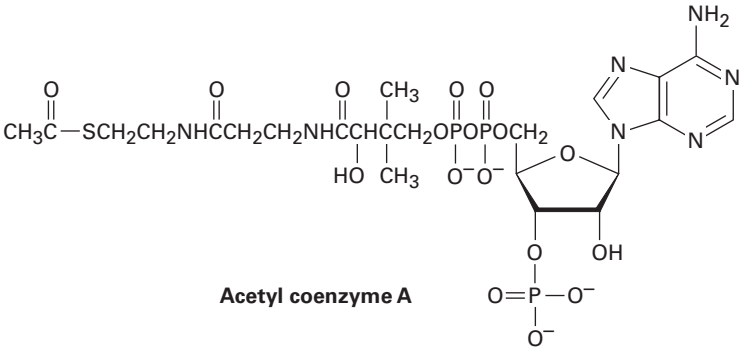
(a) Draw D-idose in its pyranose form, showing the more stable chair conformation of the ring.

(b) Which is more stable, α-D-idopyranose or β-D-idopyranose? Explain.

(c) Draw 1,6-anhydro-D-idopyranose in its most stable conformation.

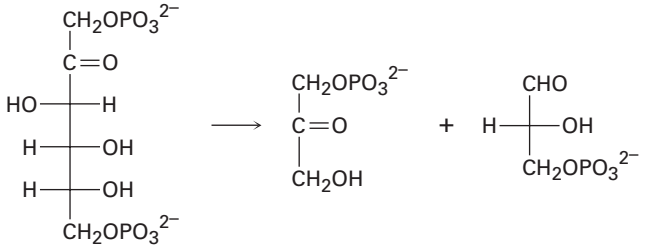
(d) When heated to 100 °C under the same conditions as those used for D-idose, D-glucose does not lose water and does not exist in a 1,6-anhydro form. Explain.

25.69 Acetyl coenzyme A (acetyl CoA) is the key intermediate in food metabolism. What sugar is present in acetyl CoA?



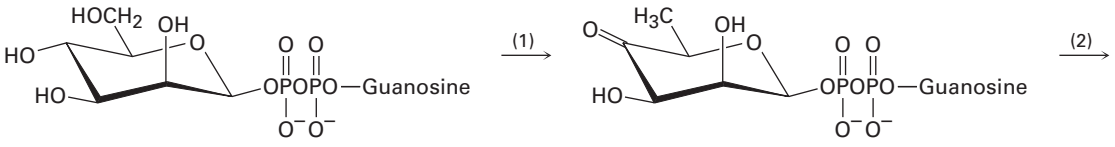
Acetyl coenzyme A

25.70 One of the steps in the biological pathway for carbohydrate metabolism is the conversion of fructose 1,6-bisphosphate into dihydroxyacetone phosphate and glyceraldehyde 3-phosphate. Propose a mechanism for the transformation.

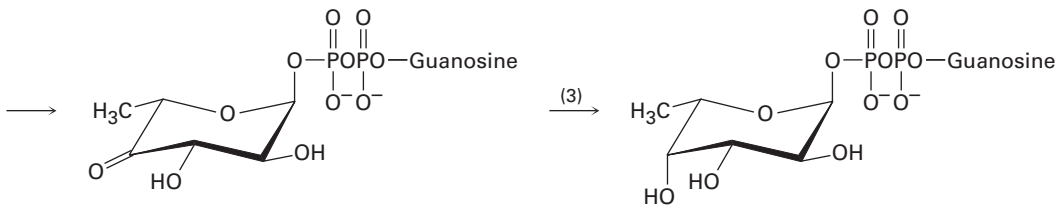


Fructose 1,6-bisphosphate | **Dihydroxyacetone phosphate** | **Glyceraldehyde 3-phosphate**

25.71 L-Fucose, one of the eight essential monosaccharides (Section 25.7), is biosynthesized from GDP-D-mannose by the following three-step reaction sequence, where GDP = guanosine diphosphate (a ribonucleoside diphosphate; Section 28.1):



GDP-D-Mannose



GDP-L-Fucose

(a) Step 1 involves an oxidation to a ketone, a dehydration to an enone, and a conjugate reduction. The step requires $NADP^+$, but no NADPH is formed as a final reaction product. Propose a mechanism.

(b) Step 2 accomplishes two epimerizations and utilizes acidic and basic sites in the enzyme but does not require a coenzyme. Propose a mechanism.

(c) Step 3 requires NADPH as coenzyme. Show the mechanism.