CHAPTER

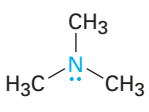
12

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

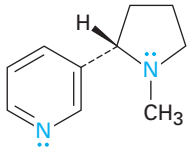
Amines

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.

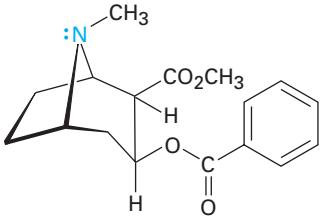
Amines occur widely in both plants and animals. Trimethylamine, for instance, occurs in animal tissues and is partially responsible for the distinctive odor of fish; nicotine is found in tobacco; and cocaine is a stimulant found in the South American coca bush. In addition, amino acids are the building 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

OWL

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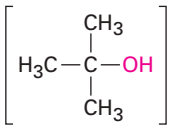
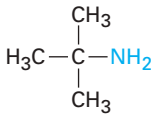
acids already mentioned, the majority of pharmaceutical agents contain amine functional groups, and many of the common coenzymes necessary for biological catalysis are amines.

12.1 Naming Amines

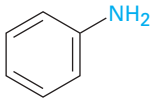
Amines can be either alkyl-substituted (**alkylamines**) or aryl-substituted (**arylamines**) and can be classed as *primary* (RNH_2), *secondary* (R_2NH), or *tertiary* (R_3N), depending on the number of organic substituents attached to nitrogen. For example, methylamine (CH_3NH_2) is a primary alkylamine and trimethylamine [$(CH_3)_3N$] is a tertiary alkylamine. 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.



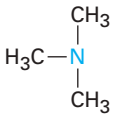
***tert*-Butyl alcohol**
(a tertiary alcohol)



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

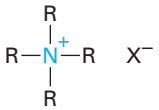


Aniline
(a primary arylamine)



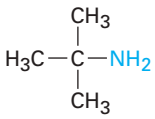
Trimethylamine
(a tertiary alkylamine)

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**.

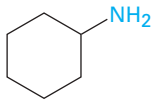


A quaternary ammonium salt

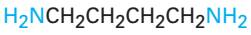
Primary amines, RNH_2, are named in the IUPAC system by adding the suffix *-amine* to the name of the organic substituent.



***tert*-Butylamine**

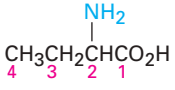


Cyclohexylamine

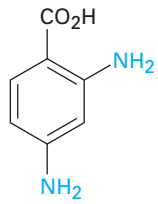


Butane-1,4-diamine

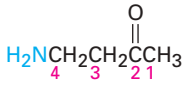
Amines with more than one functional group are named by considering the $-NH_2$ as an *amino* substituent on the parent molecule.



2-Aminobutanoic acid

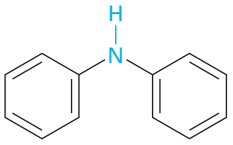


2,4-Diaminobenzoic acid

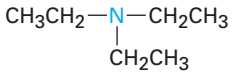


4-Aminobutan-2-one

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

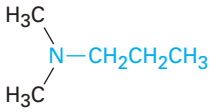


Diphenylamine

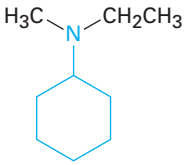


Triethylamine

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

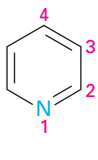


***N,N*-Dimethylpropylamine**

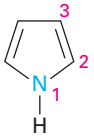


***N*-Ethyl-*N*-methylcyclohexylamine**

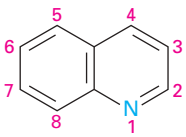
Heterocyclic amines—compounds in which the nitrogen atom occurs as part of a ring—are also common, and each different heterocyclic ring system has its own parent name. The heterocyclic nitrogen atom is always numbered as position 1.



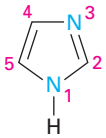
Pyridine



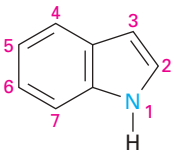
Pyrrole



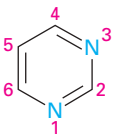
Quinoline



Imidazole



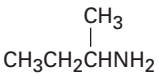
Indole



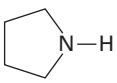
Pyrimidine

Problem 12.1 Classify each of the following compounds as either a primary, secondary, or tertiary amine:

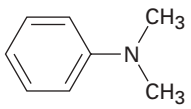
(a)



(b)



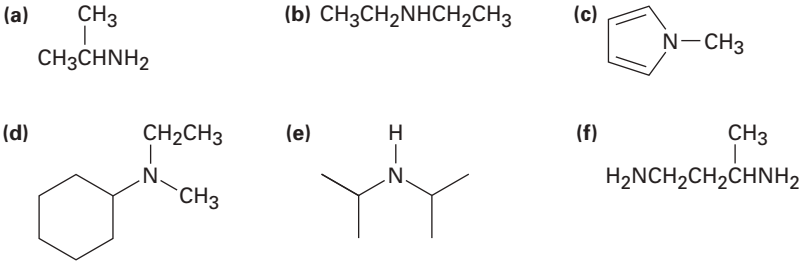
(c)



Problem 12.2 Draw structures of compounds that meet the following descriptions:

(a) A secondary amine with one isopropyl group
(b) A tertiary amine with one phenyl group and one ethyl group
(c) A quaternary ammonium salt with four different groups bonded to nitrogen

Problem 12.3 Name the following compounds:



Problem 12.4 Draw structures corresponding to the following IUPAC names:

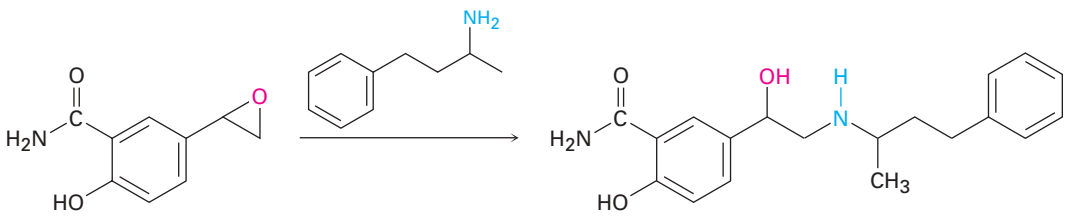
(a) Triethylamine
(b) *N*-Methylaniline
(c) Tetraethylammonium bromide
(d) *p*-Bromoaniline
(e) *N*-Ethyl-*N*-methylcyclopentylamine

12.2 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 very close to the 109° tetrahedral value—108° in trimethylamine, for example.

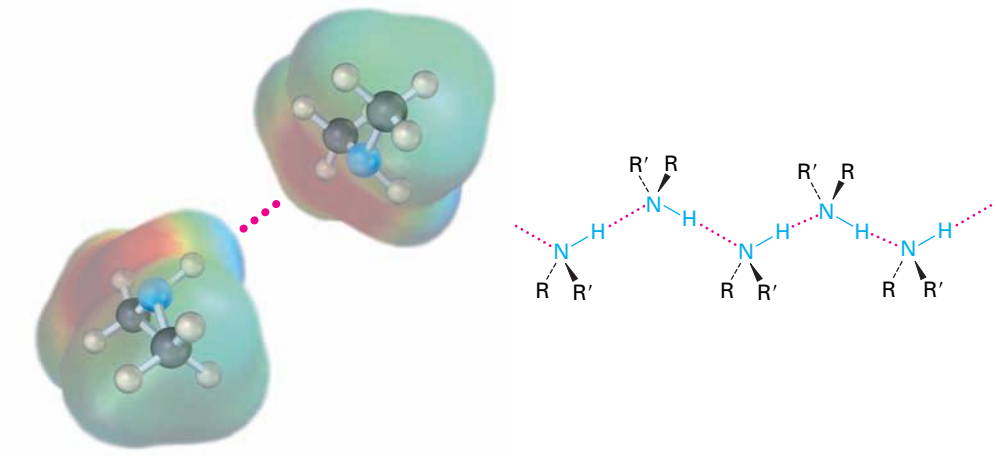
Trimethylamine

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 beta-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

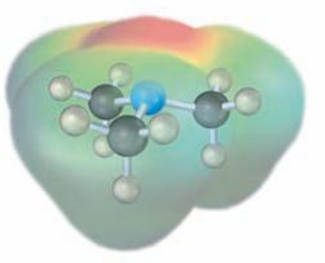
Like alcohols, amines with fewer than five carbon atoms are generally water-soluble. Also like alcohols, primary and secondary amines form hydrogen bonds and are highly associated. As a result, amines have higher boiling points than alkanes of similar molecular weight.

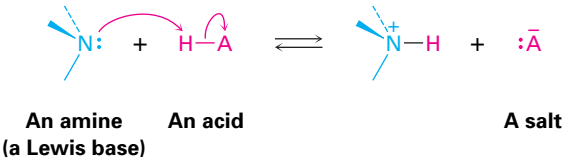


One other characteristic property of amines is their odor. Low-molecular-weight amines such as trimethylamine have a distinctive fish-like aroma, while diamines such as putrescine (butane-1,4-diamine) have odors as putrid as their common names suggest.

12.3 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 therefore react with acids to form acid–base salts, and they react with electrophiles in many of the polar reactions seen in past chapters.





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 1.10), the base strength of an amine can be measured by defining an analogous **basicity constant K_b**. The larger the

K_b and the smaller the pK_b, the more favorable the proton-transfer equilibrium and the stronger the base.

For the reaction

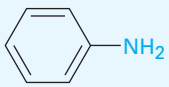
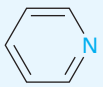
$$RNH_2 + H_2O \rightleftharpoons RNH_3^+ + OH^-$$

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

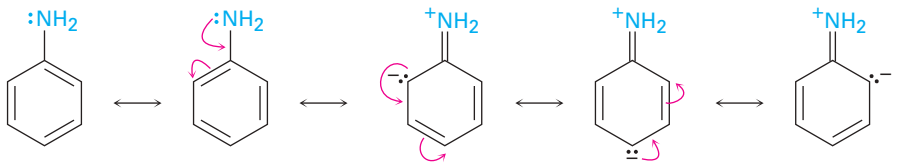
$$pK_b = -\log K_b$$

Table 12.1 gives the pK_b values of some common amines. As indicated, substitution has relatively little effect on alkylamine basicity; most simple alkylamines have pK_b's in the narrow range 3 to 4. Arylamines, however, are weaker bases than alkylamines by a factor of about 10^6, as is the heterocyclic amine pyridine.

Table 12.1 Basicity of Some Common Amines

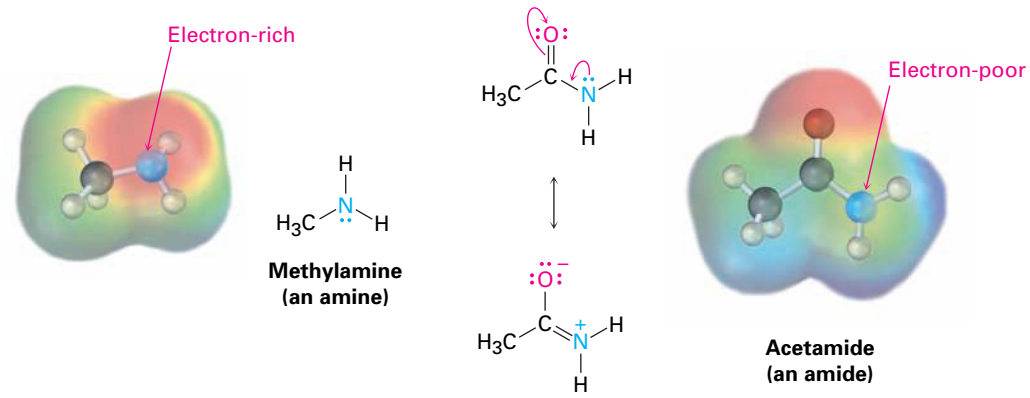
Name	Structure	pK_b
Ammonia	NH_3	4.74
Primary alkylamine		
Methylamine	CH_3NH_2	3.36
Ethylamine	$CH_3CH_2NH_2$	3.25
Secondary alkylamine		
Diethylamine	$(CH_3CH_2)_2NH$	3.02
Tertiary alkylamine		
Triethylamine	$(CH_3CH_2)_3N$	3.24
Arylamine		
Aniline		9.37
Heterocyclic amine		
Pyridine		8.75

The decreased basicity of arylamines relative to alkylamines is due to the fact that the nitrogen lone-pair electrons in an arylamine are shared by orbital overlap with the *p* orbitals of the aromatic ring through five resonance forms and are less available for bonding to an acid.



In contrast to amines, *amides* ($RCONH_2$) are nonbasic. Amides aren't protonated by aqueous acids, and they are poor nucleophiles. The main reason for this decreased basicity of amides relative to amines is that the nitrogen lone-pair electrons are shared by orbital overlap with the neighboring carbonyl-group

π orbital. 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, however, so protonation is disfavored. Electrostatic potential maps show clearly this decreased electron density on the amide nitrogen.



It's often possible to take advantage of its basicity to purify an amine. If a mixture of an amine (basic) and a ketone (neutral) is dissolved in an organic solvent and aqueous HCl is added, the basic amine dissolves in the acidic water as its ammonium ion, while the neutral ketone remains in the organic solvent. Separation of the water layer and neutralization of the ammonium ion by addition of NaOH then provides the pure amine (Figure 12.1).

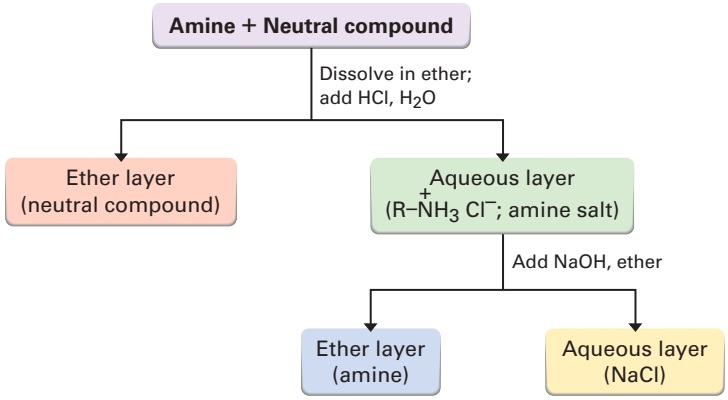
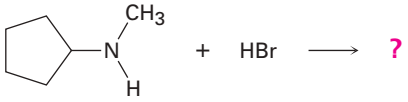


Figure 12.1 Separation and purification of an amine from a mixture.

Problem 12.5 Predict the product of the following reaction:



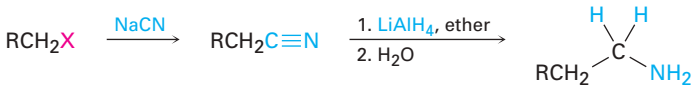
Problem 12.6 Which compound in each of the following pairs is more basic?

(a) $CH_3CH_2NH_2$ or $CH_3CH_2CONH_2$ **(b)** NaOH or $C_6H_5NH_2$
(c) CH_3NHCH_3 or $CH_3NHC_6H_5$ **(d)** CH_3OCH_3 or $(CH_3)_3N$

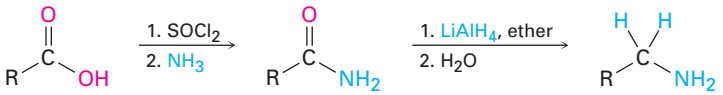
12.4 Synthesis of Amines

Reduction of Nitriles and Amides

We've already seen how amines can be prepared by reduction of amides (Section 10.10) and nitriles (Section 10.11) with $LiAlH_4$. The two-step sequence of S_N2 reaction of an alkyl halide with cyanide ion, followed by reduction, is a good method for converting an alkyl halide into a primary amine having one more carbon atom than the original halide. Amide reduction provides a method for converting a carboxylic acid into an amine having the same number of carbon atoms.



Alkyl halide **1° amine**



Carboxylic acid **1° amine**

Worked Example 12.1

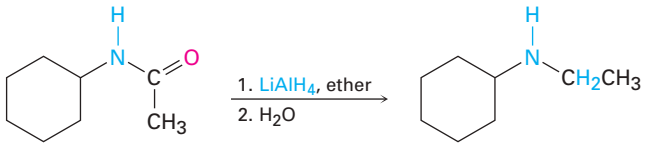
Synthesizing an Amine from an Amide

What amide would you use to prepare *N*-ethylcyclohexylamine?

Strategy

Reduction of an amide with $LiAlH_4$ yields an amine in which the amide carbonyl group has been replaced by a methylene (CH_2), $RCONR_2 \rightarrow RCH_2NR_2$. Since *N*-ethylcyclohexylamine has only one CH_2 attached to nitrogen (in the ethyl group), the product must come from reduction of *N*-cyclohexylacetamide.

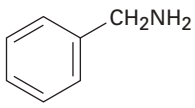
Solution



***N*-Cyclohexylacetamide** ***N*-Ethylcyclohexylamine**

Problem 12.7 Propose structures for amides that might be precursors of the following amines:

(a) $CH_3CH_2CH_2NH_2$ **(b)** $NH(CH_2CH_2CH_3)_2$ **(c)**



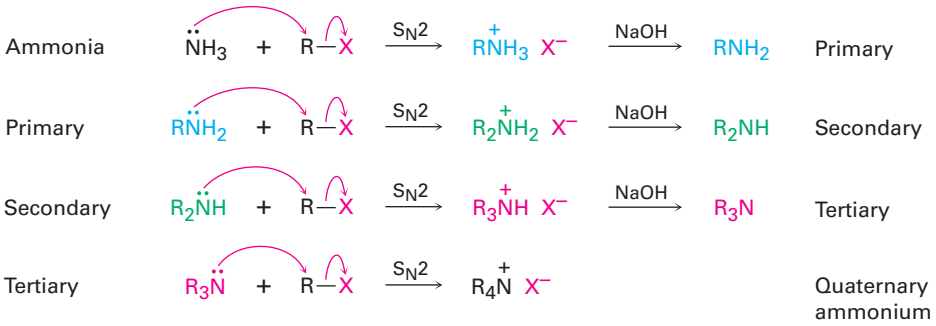
Problem 12.8 Propose structures for nitriles that might be precursors of the following amines:

(a) $CH_3CH(CH_3)CH_2CH_2NH_2$

(b) Benzylamine, $C_6H_5CH_2NH_2$

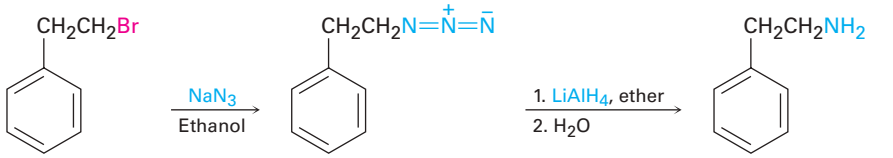
S_N2 Alkylation Reactions of Alkyl Halides

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 (Section 7.5). 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, yielding quaternary ammonium salts, $R_4N^+ X^-$.



Unfortunately, none of these reactions stops cleanly after a single alkylation has occurred. Because ammonia and primary amines have similar reactivity, the initially formed monoalkylated amine often undergoes further reaction to yield a mixture of mono-, di-, and trialkylated products.

A better method for preparing primary amines from alkyl halides is to use azide ion, N_3^-, as the nucleophile rather than ammonia. 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.



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

Worked Example 12.2 Synthesizing an Amine from an Alkyl Halide

How could you prepare diethylamine from ammonia and an alkyl halide?

Strategy Look at the starting material (NH_3) and the product $(CH_3CH_2)_2NH$, and note the difference. Since two ethyl groups have become bonded to the nitrogen atom, the reaction must involve ammonia and 2 equivalents of an ethyl halide.

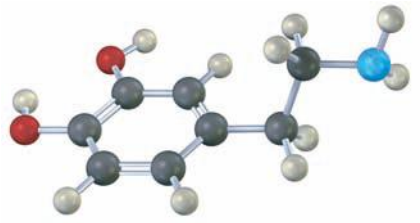
Solution

$$2\ CH_3CH_2Br + NH_3 \longrightarrow (CH_3CH_2)_2NH$$

Problem 12.9 How could you prepare the following amines from ammonia and appropriate alkyl halides?

(a) Triethylamine **(b)** Tetramethylammonium bromide

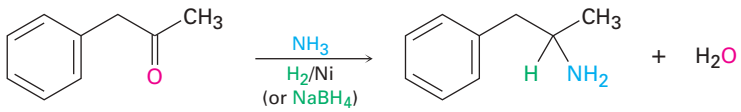
Problem 12.10 What alkyl halide would you use to synthesize dopamine, a neurotransmitter involved in regulation of the central nervous system?



Dopamine

Reductive Amination of Aldehydes and Ketones

Amines can be synthesized from an aldehyde or ketone in a single step by reaction 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 phenylpropan-2-one with ammonia, using hydrogen gas over a nickel catalyst as the reducing agent. In the laboratory, $NaBH_4$ is often used as the reducing agent rather than H_2 and nickel.

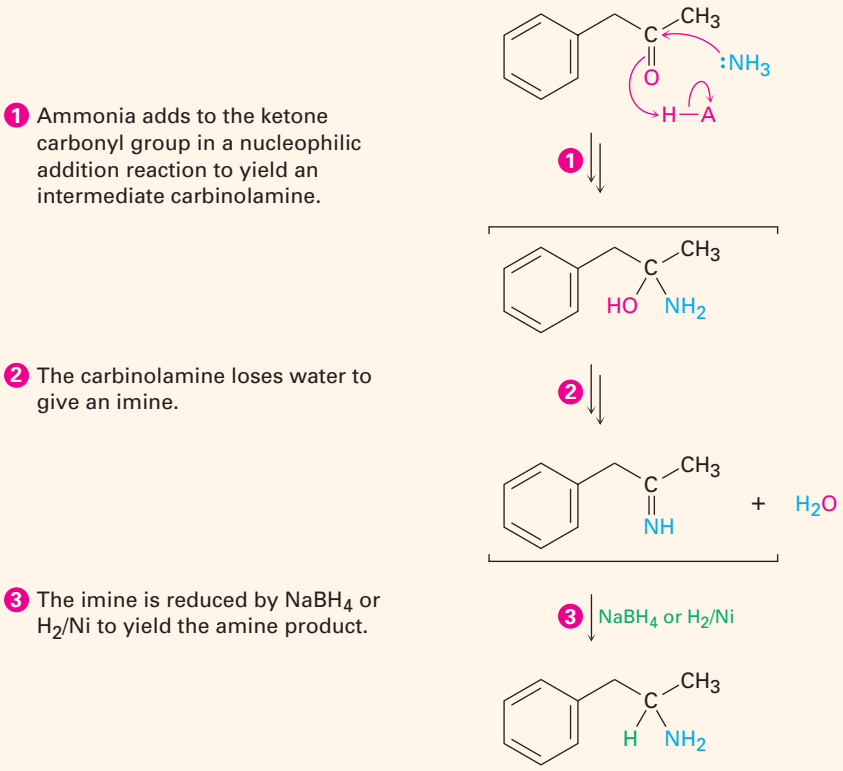


Phenylpropan-2-one **Amphetamine**

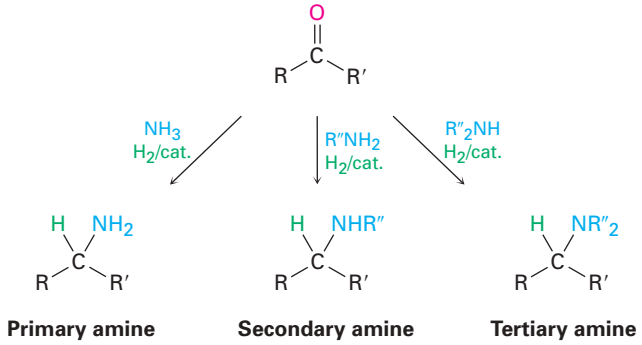
Reductive amination takes place by the pathway shown in Figure 12.2. An imine intermediate is first formed by a nucleophilic addition reaction (Section 9.9), and the C=N bond of the imine is then reduced to the amine, much as the C=O bond of a ketone can be reduced to an alcohol.

MECHANISM

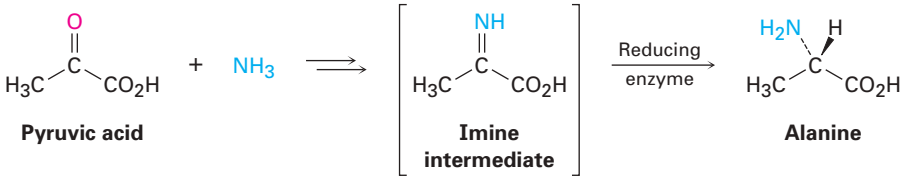
Figure 12.2 Mechanism of reductive amination of a ketone to yield an amine. The imine-forming step was discussed in Section 9.9.



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

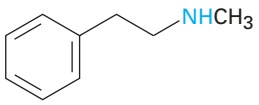


We'll see in Section 17.5 that a closely related reductive amination occurs in the biological pathways by which some amino acids are synthesized. The amino acid alanine, for instance, arises by reaction of pyruvic acid and ammonia to give an intermediate imine that is then enzymatically reduced.



Worked Example 12.3 Synthesizing an Amine Using a Reductive Amination

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

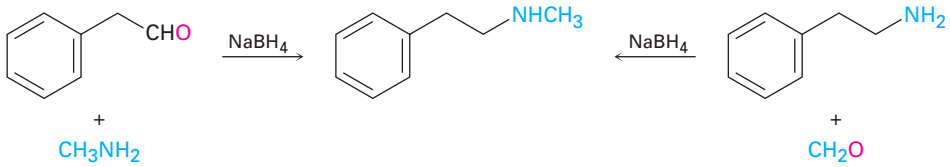


***N*-Methyl-2-phenylethylamine**

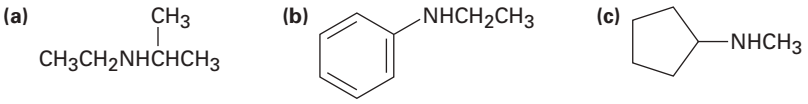
Strategy

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, there are two combinations that can lead to the product: phenylacetaldehyde plus methylamine or formaldehyde plus 2-phenylethylamine. In general, it's better to choose the combination with the simpler amine component—methylamine in this case—and to use an excess of that amine as reactant.

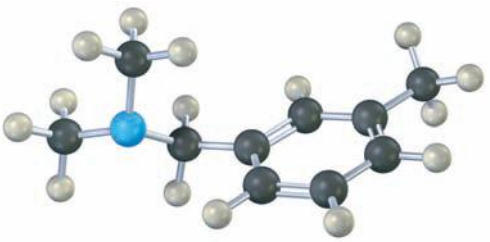
Solution



Problem 12.11 How could you prepare the following amines using reductive amination reactions? Show all precursors if more than one is possible.



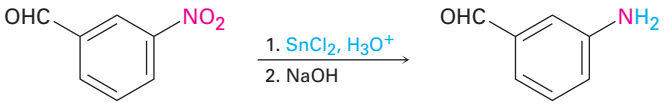
Problem 12.12 How could you prepare the following amine using a reductive amination reaction?



Reduction of Nitrobenzenes

Arylamines are prepared by nitration of an aromatic starting material, followed by reduction of the nitro group (Section 5.4). The reduction step can be carried out in different ways, depending on the circumstances. Catalytic hydrogenation

over platinum works well but is sometimes incompatible with the presence elsewhere in the molecule of other reducible groups, such as C=C bonds. Iron, tin, and stannous chloride ($SnCl_2$) in aqueous acid are also effective.



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

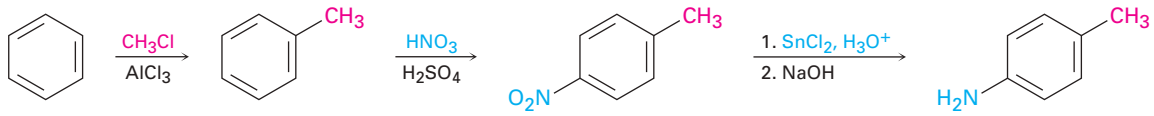
Worked Example 12.4 Synthesizing an Aromatic Amine

How could you synthesize *p*-methylaniline from benzene? More than one step is needed.

Strategy

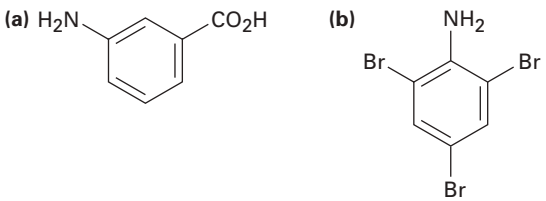
A methyl group is introduced onto a benzene ring by a Friedel–Crafts reaction with $CH_3Cl/AlCl_3$ (Section 5.5), and an amino group is introduced onto a ring by nitration and reduction. Because a methyl group is ortho- and para-directing (Section 5.7), it would be best to introduce the methyl group first followed by nitration and reduction.

Solution



Benzene **Toluene** ***p*-Nitrotoluene** ***p*-Methylaniline**

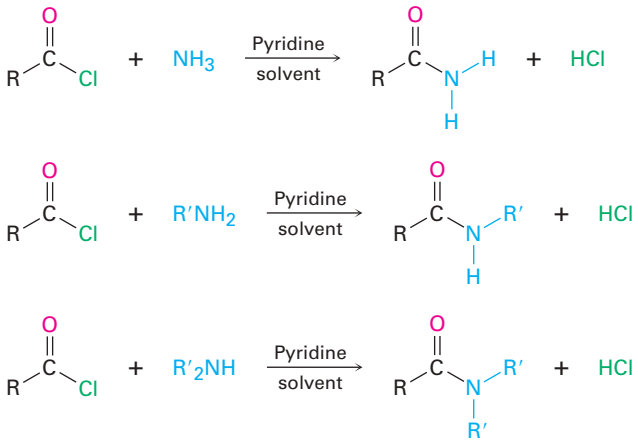
Problem 12.13 How could you synthesize the following amines from benzene? More than one step is required in each case.



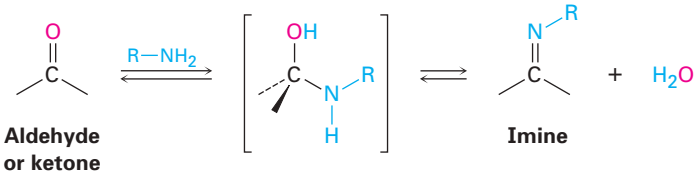
12.5 Reactions of Amines

We've already discussed the two most general reactions of alkylamines—alkylation and acylation. As we saw in the previous section, primary, secondary, and tertiary amines can be alkylated by reaction with alkyl halides. Primary and secondary (but not tertiary) amines can also be acylated by

nucleophilic acyl substitution reactions with acid chlorides (Section 10.7) or acid anhydrides (Section 10.8) to give amides.

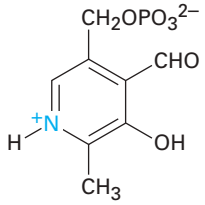


In addition, we've seen that primary amines react with aldehydes and ketones to give imines (Section 9.9).

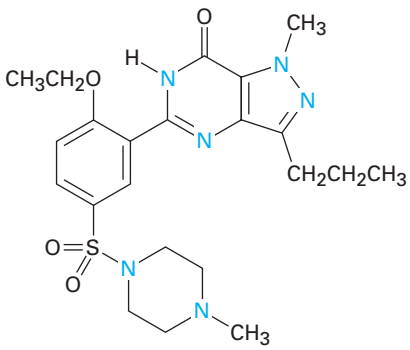


12.6 Heterocyclic Amines

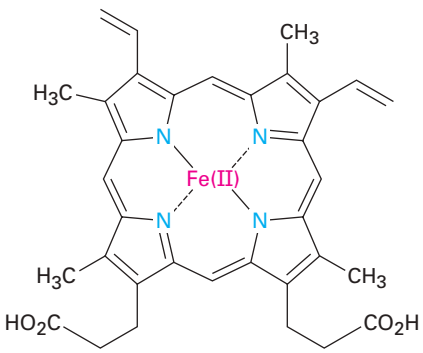
A **heterocycle**, as noted in Section 5.9 in connection with a discussion of aromaticity, contains atoms of two or more different elements in its ring, usually carbon along with nitrogen, oxygen, or sulfur. Heterocyclic amines are particularly common in organic chemistry, and many have important biological 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

For the most part, heterocyclic amines have the same chemistry as their open-chain counterparts. In certain cases, though, particularly when the ring is unsaturated, heterocycles have unique properties. Let's look at several examples.

Pyrrole

Pyrrole is a five-membered heterocyclic amine with two double bonds and one nitrogen. As we saw in Section 5.9, pyrrole is aromatic. Even though it has a five-membered ring, pyrrole has six π electrons in a cyclic, conjugated π-orbital system, just as benzene does. Each of the four carbon atoms contributes one π electron, and the sp^2-hybridized nitrogen atom contributes two more—its lone pair. The six π electrons occupy p orbitals with lobes above and below the plane of the ring, as shown in Figure 12.3. Because the lone-pair electrons on nitrogen are shared in the aromatic ring, they are not available for donation to an acid and pyrrole is nonbasic. Note in Figure 12.3 how the nitrogen atom is neutral (green) rather than electron-rich (red).

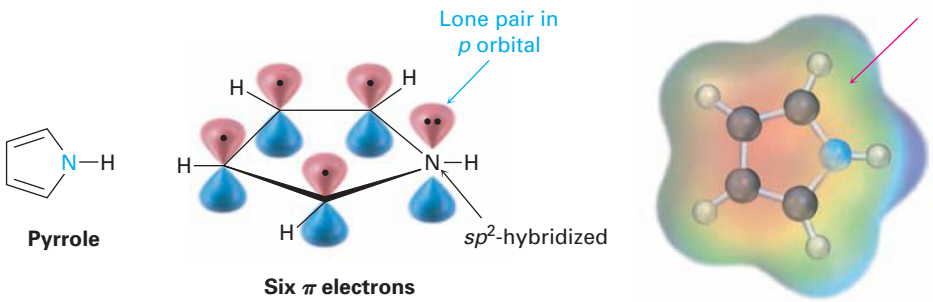
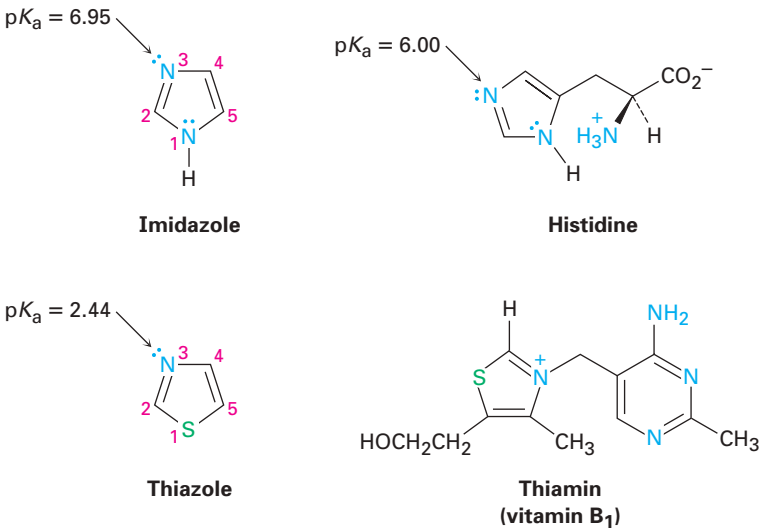


Figure 12.3 Pyrrole, an aromatic heterocycle, has a π electron structure similar to that of benzene. The nitrogen atom is nonbasic.

Other common five-membered aromatic heterocycles 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 12.14 Pyrrole undergoes typical electrophilic substitution reactions on the carbon next to nitrogen in the ring. What products would you expect to obtain from reaction of *N*-methylpyrrole with the following reagents?

(a) Br_2 **(b)** CH_3Cl, $AlCl_3$ **(c)** CH_3COCl, $AlCl_3$

Problem 12.15 Review the mechanism of the nitration of benzene (Section 5.4), and propose a mechanism for the nitration of pyrrole.

Pyridine

Pyridine is the nitrogen-containing heterocyclic analog of benzene. Like benzene, pyridine is a flat, aromatic molecule with bond angles of approximately 120°. Also like benzene, pyridine is aromatic with six π electrons in a cyclic, conjugated π-orbital system. The sp^2-hybridized nitrogen atom and the five carbon atoms each contribute one π electron to the cyclic, conjugated p orbitals of the ring.

Unlike the situation in pyrrole, the lone-pair electrons on the pyridine nitrogen atom are not part of the π orbital system but instead occupy an sp^2 orbital in the plane of the ring (Figure 12.4). As a result, the pyridine lone-pair electrons are available for donation to an acid and pyridine is therefore basic. Compare the electrostatic potential maps of pyrrole (Figure 12.3) and pyridine (Figure 12.4) to see this difference in basicity.

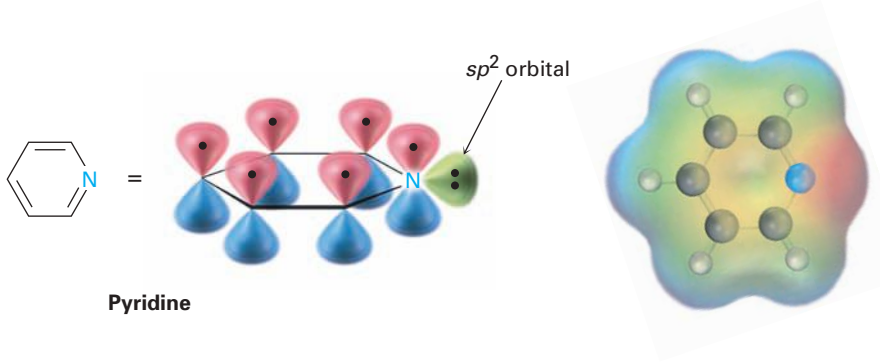
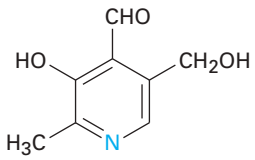


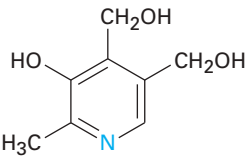
Figure 12.4 Electronic structure of pyridine, a nitrogen-containing analog of benzene.

Although less basic than typical alkylamines, pyridine (pK_b = 8.75) is nevertheless used in a variety of organic reactions when a base catalyst is required. You might recall, for instance, that the reaction of an acid chloride with an alcohol to yield an ester is commonly done in the presence of pyridine (Section 10.7).

Substituted pyridines, such as the B_6 complex vitamins pyridoxal and pyridoxine, are important biologically. Present in yeast, cereal, and other foodstuffs, the B_6 vitamins are necessary for the synthesis of some amino acids.

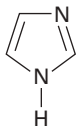


Pyridoxal



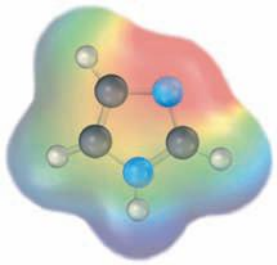
Pyridoxine

Problem 12.16 The five-membered heterocycle imidazole contains two nitrogen atoms, one "pyrrole-like" and one "pyridine-like." Draw an orbital picture of imidazole, and indicate the orbital in which each nitrogen has its electron lone pair.



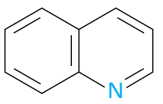
Imidazole

Problem 12.17 Which nitrogen atom in imidazole (Problem 12.16) is more basic according to the following electrostatic potential map? Why?

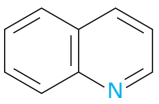


Fused-Ring Aromatic Heterocycles

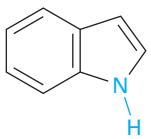
Fused-ring heterocycles like quinoline, isoquinoline, and indole are more complex than simple monocyclic compounds. All three have a benzene ring and a heterocyclic ring sharing a common bond. These and many other fused-ring systems occur widely in nature, and many members of the class have useful biological properties. Quinine, a quinoline derivative found in the bark of the South American cinchona tree, is an important antimalarial drug. *N,N*-Dimethyltryptamine, which contains an indole ring, is a powerful hallucinogen.



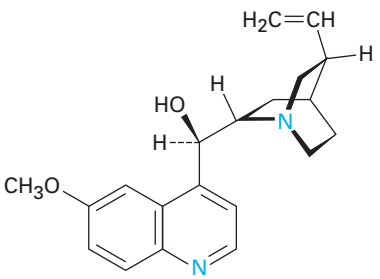
Quinoline



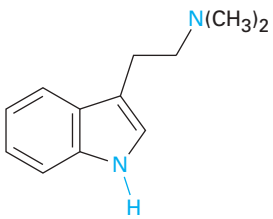
Isoquinoline



Indole



Quinine (antimalarial)



***N,N*-Dimethyltryptamine (hallucinogenic)**

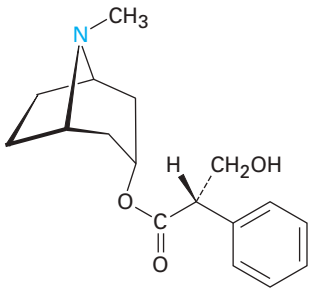
Problem 12.18 Which nitrogen atom in the hallucinogenic indole alkaloid *N,N*-dimethyltryptamine do you think is more basic? Explain.

12.7 Alkaloids: Naturally Occurring Amines

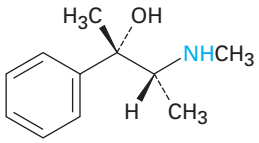
Naturally occurring amines derived from plant sources were once known as "vegetable alkali" because their aqueous solutions are slightly basic, but they are now referred to as **alkaloids**. The study of alkaloids provided much of the impetus for the growth of organic chemistry in the 19th century and remains today a fascinating area of research.

Approximately 30,000 different alkaloids are known, varying widely in structure from the simple to the enormously complex. The odor of rotting fish, for example, is largely caused by the simplest alkaloid, methylamine. In fact, the use of acidic lemon juice to mask fish odors is just an acid–base reaction of the citric acid in lemons with methylamine to form the nonvolatile methylammonium salt.

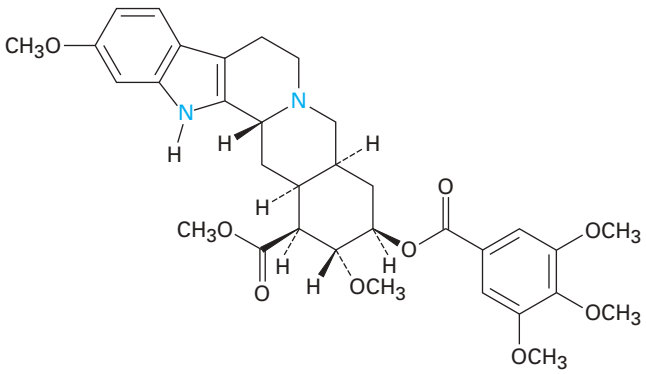
Many alkaloids have pronounced biological properties, and many of the pharmaceutical agents used today are alkaloids from natural sources. As only a few examples, atropine, an antispasmodic agent used for the treatment of colitis, is obtained from the flowering plant *Atropa belladonna,* commonly called the deadly nightshade. Ephedrine, a bronchodilator and decongestant, is obtained from the Chinese plant *Ephedra sinica.* Reserpine, a tranquilizer and antihypertensive, comes from powdered roots of the semitropical plant *Rauwolfia serpentina.*



Atropine



Ephedrine



Reserpine

A recent report from the U.S. National Academy of Sciences estimates that less than 1% of all living species have been characterized. Thus, alkaloid chemistry today remains an active area of research, and innumerable substances with potentially useful properties remain to be discovered.

INTERLUDE

Green Chemistry

© Modern Landscapes/Alamy

Let's hope disasters like this are never repeated.

Organic chemistry in the 20th century changed the world, giving us new medicines, insecticides, adhesives, textiles, dyes, building materials, composites, and all manner of polymers. But these advances did not come without a cost: every chemical process produces wastes that must be dealt with, including reaction solvents and toxic by-products that might evaporate into the air or be leached into groundwater if not disposed of properly. Even apparently harmless by-products must be safely buried or otherwise sequestered. As always, there's no such thing as a free lunch; with the good also comes the bad.

It may never be possible to make organic chemistry completely benign, but awareness of the environmental problems caused by many chemical processes has grown dramatically in recent years, giving rise to a movement called *green chemistry*. Green chemistry is the design and implementation of chemical products and processes that reduce waste and attempt to eliminate the generation of hazardous substances. There are 12 principles of green chemistry.

Prevent waste—Waste should be prevented rather than treated or cleaned up after it has been created.

Maximize atom economy—Synthetic methods should maximize the incorporation of all materials used in a process into the final product so that waste is minimized.

Use less hazardous processes—Synthetic methods should use reactants and generate wastes with minimal toxicity to health and the environment.

Design safer chemicals—Chemical products should be designed to have minimal toxicity.

Use safer solvents—Minimal use should be made of solvents, separation agents, and other auxiliary substances in a reaction.

Design for energy efficiency—Energy requirements for chemical processes should be minimized, with reactions carried out at room temperature if possible.

Use renewable feedstocks—Raw materials should come from renewable sources when feasible.

Minimize derivatives—Syntheses should be designed with minimal use of protecting groups to avoid extra steps and reduce waste.

Use catalysis—Reactions should be catalytic rather than stoichiometric.

Design for degradation—Products should be designed to be biodegradable at the end of their useful lifetimes.

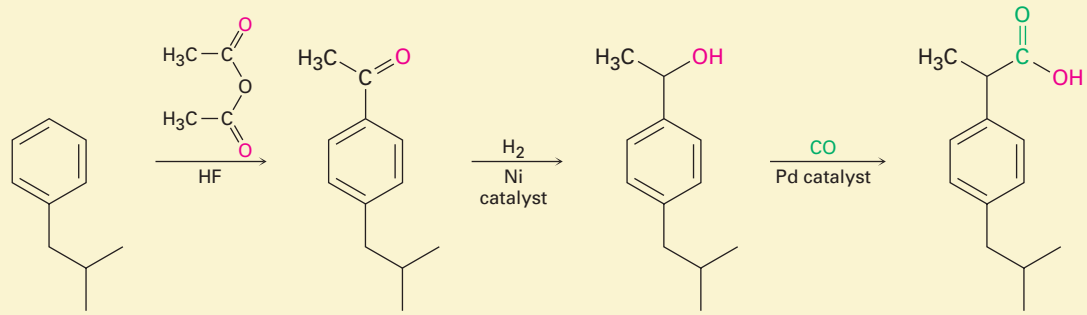
Monitor pollution in real time—Processes should be monitored in real time for the formation of hazardous substances.

Prevent accidents—Chemical substances and processes should minimize the potential for fires, explosions, or other accidents.

continued

INTERLUDE

The foregoing 12 principles won't all be met in most real-world applications, but they provide a worthy goal to aim for and they can make chemists think more carefully about the environmental implications of their work. Real success stories are already occurring, and more are in progress. Approximately 7 million pounds per year of ibuprofen (6 billion tablets!) is now made by a "green" process that produces approximately 99% less waste than the process it replaces. Only three steps are needed, the anhydrous HF solvent used in the first step is recovered and reused, and the second and third steps are catalytic.



Isobutylbenzene **Ibuprofen**

Summary and Key Words

alkaloid 421
alkylamine 405
amine 404
arylamine 405
basicity constant, K_b 408
heterocycle 417
quaternary ammonium salt 405
reductive amination 413

We've now seen all the common functional groups that occur throughout organic and biological chemistry. Of those groups, amines are among the most abundant. 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 catalysis 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. Bonding in amines is similar to that in ammonia: the nitrogen atom is sp^3-hybridized, the three substituents are directed to three corners of a regular tetrahedron, and the lone pair of electrons occupies the fourth corner of the tetrahedron.

The chemistry of amines is dominated by the presence of the lone-pair electrons on nitrogen, which make amines both basic and nucleophilic. **Arylamines** are generally weaker bases than **alkylamines** because their lone-pair electrons are shared by orbital overlap with the aromatic π electron system.

The simplest method of amine synthesis involves S_N2 reaction of ammonia or an amine with an alkyl halide. Alkylation of ammonia yields a primary

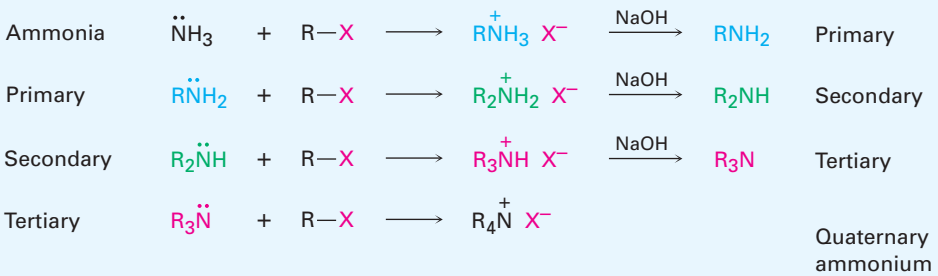
amine; alkylation of a primary amine yields a secondary amine; and so on. Amines can also be prepared from amides and nitriles by reduction with $LiAlH_4$ and from aldehydes and ketones by **reductive amination** with ammonia and a reducing agent. Arylamines are prepared by nitration of an aromatic ring followed by reduction of the nitro group. Many of the reactions that amines undergo are familiar from previous chapters. Thus, amines react with alkyl halides in S_N2 reactions and with acid chlorides in nucleophilic acyl substitution reactions.

Heterocyclic amines, compounds in which the nitrogen atom is in a ring, have a great diversity in their structures and properties. Pyrrole, pyridine, indole, and quinoline all show aromatic properties.

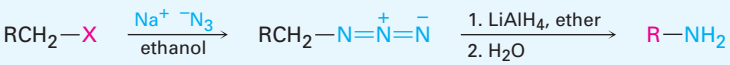
Summary of Reactions

1. Synthesis of amines (Section 12.4)

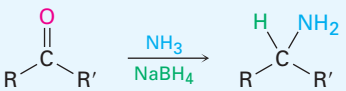
(a) S_N2 reaction of alkyl halides



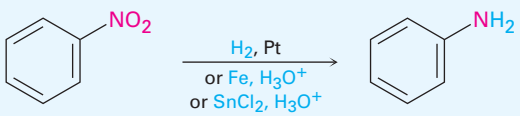
(b) Reduction of azides



(c) Reductive amination of aldehydes and ketones



(d) Reduction of nitrobenzenes



Exercises

Visualizing Chemistry

(Problems 12.1–12.18 appear within the chapter.)

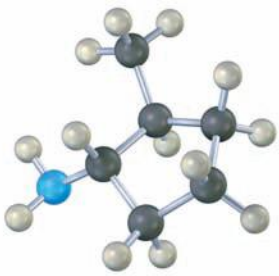
OWL

Interactive versions of these problems are assignable in OWL.

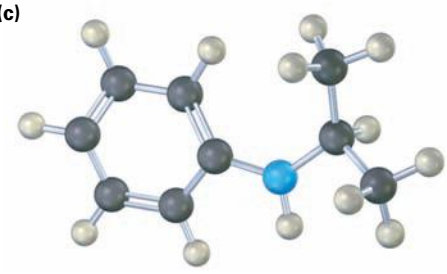
12.19 Name the following amines, and identify each as primary, secondary, or tertiary:

(a)

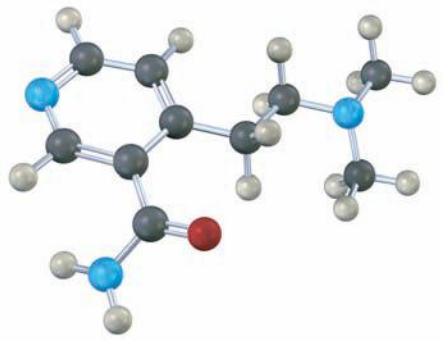
(b)



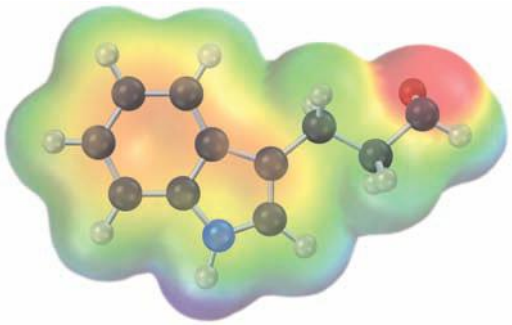
(c)

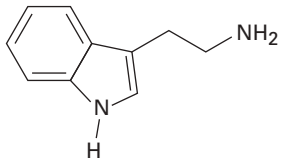


12.20 The following compound contains three nitrogen atoms. Rank them in order of increasing basicity.



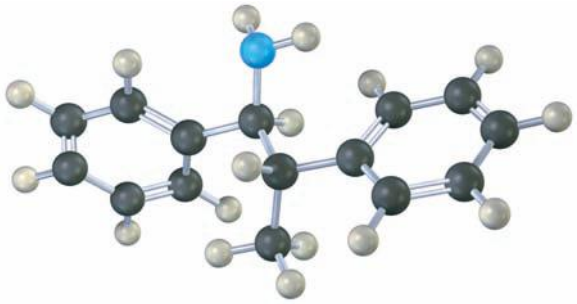
12.21 Which nitrogen atom in the alkaloid tryptamine is more basic? Explain.



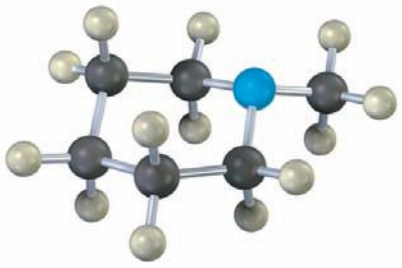


Tryptamine

12.22 Name the following amine, including *R,S* stereochemistry, and draw the product of its reaction with (i) CH_3CH_2Br and (ii) CH_3COCl.



12.23 The following molecule can be prepared by reaction between a primary amine and a *dihalide.* Identify the two reactants, and write the reaction.

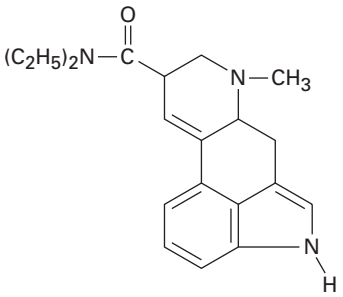


Additional Problems

Naming Amines

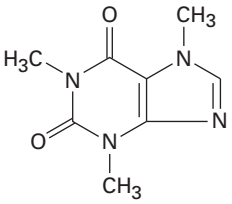
12.24 Classify each of the amine (not amide) nitrogen atoms in the following substances as primary, secondary, or tertiary:

(a)



Lysergic acid diethylamide

(b)

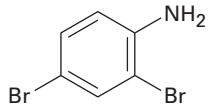


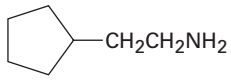
Caffeine

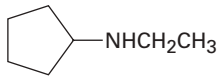
12.25 Draw structures corresponding to the following IUPAC names:

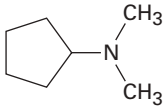
(a) *N,N*-Dimethylaniline
(b) *N*-Methylcyclohexylamine
(c) (Cyclohexylmethyl)amine
(d) (2-Methylcyclohexyl)amine
(e) 3-(*N,N*-Dimethylamino)propanoic acid

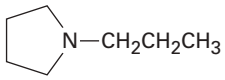
12.26 Name the following compounds:

(a) 

(b) 

(c) 

(d) 

(e) 

(f) $H_2NCH_2CH_2CH_2CN$

12.27 There are eight isomeric amines with the formula $C_4H_{11}N$. Draw them, name them, and classify each as primary, secondary, or tertiary.

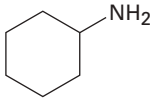
12.28 Mescaline, a powerful hallucinogen derived from the peyote cactus, has the systematic name 2-(3,4,5-trimethoxyphenyl)ethylamine. Draw its structure.

12.29 Propose structures for amines that fit the following descriptions:
(a) A secondary arylamine
(b) A 1,3,5-trisubstituted arylamine
(c) An achiral quaternary ammonium salt
(d) A five-membered heterocyclic amine

Reactions and Synthesis

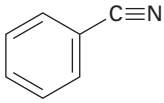
12.30 Show the products of the following reactions:

(a) $CH_3CH_2CH_2NH_2 \xrightarrow{CH_3Br}$?

(b) 

$\xrightarrow{HBr}$?

(c) $CH_3CH_2\overset{\overset{O}{\|}}{C}NH_2 \xrightarrow[2.\ H_2O]{1.\ LiAlH_4}$?

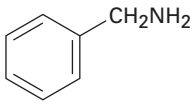
(d) 

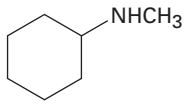
$\xrightarrow[2.\ H_2O]{1.\ LiAlH_4}$?

12.31 How might you prepare the following amines from ammonia and any alkyl halides needed?

(a) $CH_3CH_2CH_2CH_2CH_2CH_2NH_2$

(b) $(CH_3)_4N^+\ I^-$

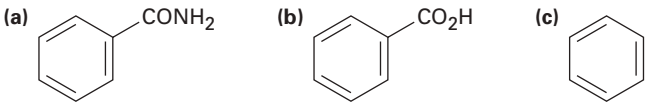
(c) 

(d) 

12.32 How might you prepare the following amines from 1-bromobutane?
(a) Butylamine **(b)** Dibutylamine **(c)** Pentylamine

12.33 How might you prepare each of the amines in Problem 12.32 from butan-1-ol?

12.34 How would you prepare benzylamine, $C_6H_5CH_2NH_2$, from each of the following starting materials?



12.35 How might you prepare pentylamine from the following starting materials?

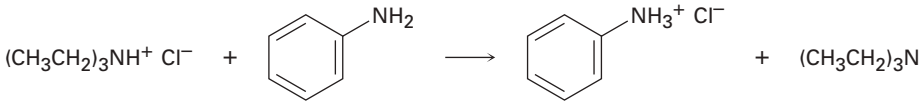
(a) Pentanamide **(b)** Pentanenitrile **(c)** Pentanoic acid

Basicity

12.36 Which compound is more basic, $CH_3CH_2NH_2$ or $CF_3CH_2NH_2$? Explain.

12.37 Which compound is more basic, *p*-aminobenzaldehyde or aniline?

12.38 Which compound is more basic, triethylamine or aniline? Does the following reaction proceed as written?



12.39 Suppose you were given a mixture of toluene, aniline, and phenol. Describe how you would separate the mixture into its three pure components.

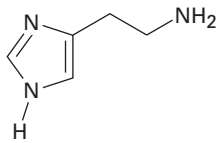
12.40 Would you expect diphenylamine to be more basic or less basic than aniline? Explain.

General Problems

12.41 Hexane-1,6-diamine, one of the starting materials used for the manufacture of nylon 66, can be synthesized by a route that begins with the addition of Cl_2 to buta-1,3-diene (Section 4.8). How would you carry out the complete synthesis?

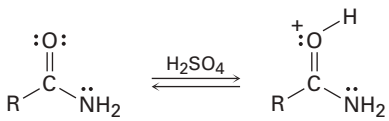
12.42 Another method for making hexane-1,6-diamine (see Problem 12.41) starts from adipic acid (hexanedioic acid). How would you carry out the synthesis?

12.43 Histamine, whose release in the body triggers nasal secretions and constricted airways, has three nitrogen atoms—one "pyrrole-like," one "pyridine-like," and one alkylamine. List them in order of increasing basicity, and explain your ordering.



Histamine

12.44 Protonation of an amide using strong acid occurs on oxygen rather than on nitrogen. Explain, using resonance structures of *O*-protonated and *N*-protonated products.



12.45 Give the structures of the major organic products you would obtain from the reaction of *m*-methylaniline with the following reagents:
(a) Br_2 (1 mol) **(b)** CH_3I (excess) **(c)** CH_3COCl, pyridine

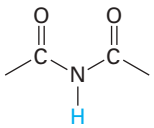
12.46 Furan, the oxygen-containing analog of pyrrole, is aromatic in the same way that pyrrole is. Draw an orbital picture of furan, and show how it has six electrons in its cyclic conjugated π orbitals.

Furan

12.47 How can you explain the observation that *p*-nitroaniline is less basic than aniline by a factor of 40,000? (See Section 5.7.)

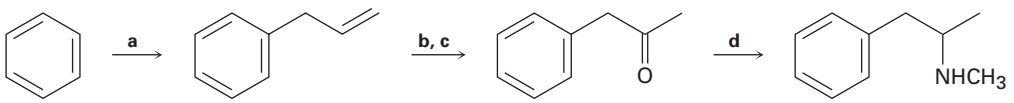
12.48 In light of your answer to Problem 12.47, which would you expect to be more basic, aniline or *p*-methoxyaniline? Explain.

12.49 We've seen that amines are basic and amides are neutral. *Imides,* compounds with two carbonyl groups flanking an N–H, are actually acidic. Show by drawing resonance structures of the anion resulting from deprotonation why imides are acidic.



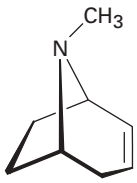
An imide

12.50 Fill in the missing reagents **a** through **d** in the following synthesis of racemic methamphetamine from benzene.



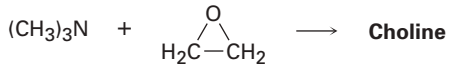
(*R,S*)-Methamphetamine

12.51 Atropine, $C_{17}H_{23}NO_3$, is a poisonous alkaloid isolated from the leaves and roots of the deadly nightshade, *Atropa belladonna*. In small doses, atropine acts as a muscle relaxant: 0.5 ng (1 nanogram = 10^{-9} g) is sufficient to cause pupil dilation. On reaction with aqueous NaOH, atropine yields tropic acid, $C_6H_5CH(CH_2OH)CO_2H$, and tropine, $C_8H_{15}NO$. Tropine, an optically inactive alcohol, yields tropidene on dehydration. Propose a structure for atropine.

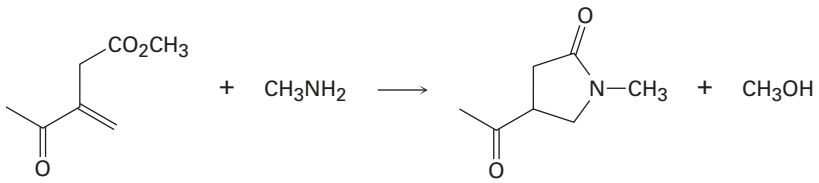


Tropidene

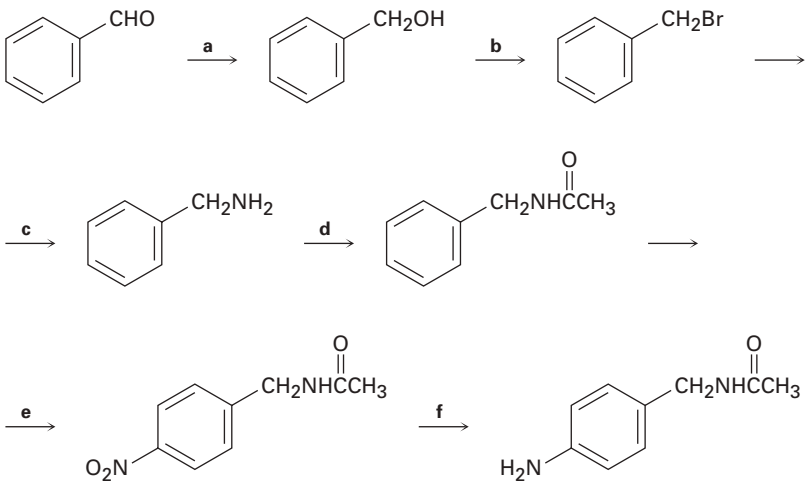
12.52 Choline, a component of the phospholipids in cell membranes, can be prepared by S_N2 reaction of trimethylamine with ethylene oxide. Show the structure of choline, and propose a mechanism for the reaction.



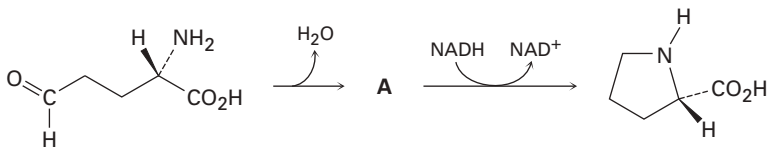
12.53 The following transformation involves a conjugate nucleophilic addition reaction (Section 9.10) followed by an intramolecular nucleophilic acyl substitution reaction (Section 10.5). Show the mechanism.



12.54 Fill in the missing reagents **a** through **f** in the following scheme:



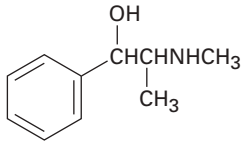
12.55 The amino acid proline is biosynthesized from glutamate semialdehyde by the following transformation, where NADH is the biological reducing agent nicotinamide adenine dinucleotide. What is the likely structure of intermediate **A**, and how is it formed?



Glutamate 5-semialdehyde **Proline**

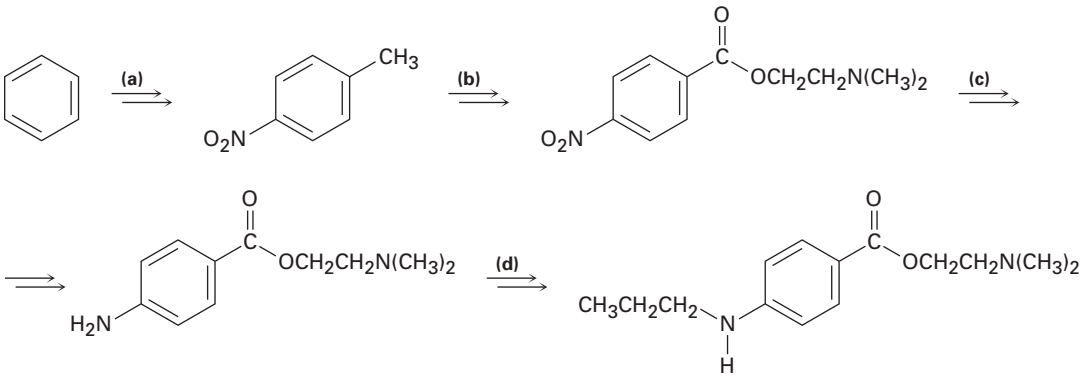
IN THE MEDICINE CABINET

12.56 How might you use a reductive amination to synthesize ephedrine, an amino alcohol that is widely used for the treatment of bronchial asthma?



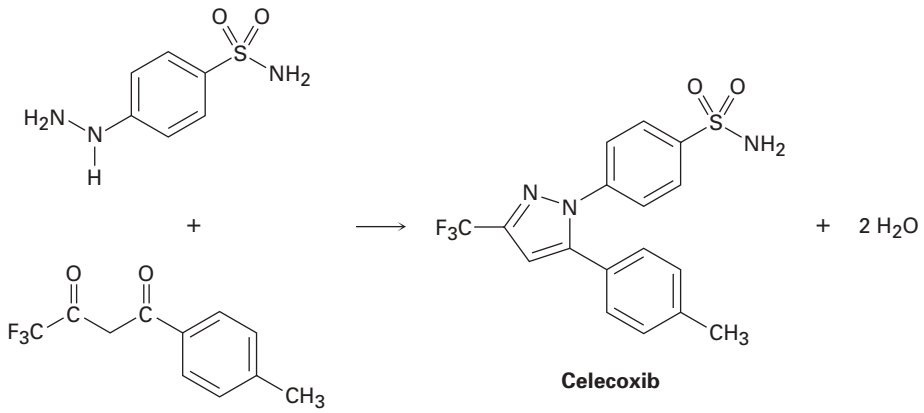
Ephedrine

12.57 Tetracaine, a substance used as a spinal anesthetic, can be prepared from benzene by the following route. Show how you could accomplish each of the transformations **(a)** through **(d)**.



Tetracaine

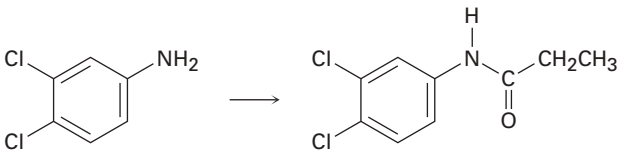
12.58 The anti-inflammatory drug celecoxib, marketed as Celebrex, is widely used for treatment of rheumatoid arthritis. Draw a mechanism for the following step used in celecoxib synthesis.



Celecoxib

IN THE FIELD

12.59 Propanil, marketed under names such as Stampede and Chem-Rice, is commonly used to prevent weeds in rice fields. How would you prepare propanil from 3,4-dichloroaniline? Show the mechanism of your reaction.



3,4-Dichloroaniline **Propanil**

12.60 Paraquat, a broad-spectrum weed killer, is prepared using the following step. What is the structure of paraquat?