Heterocyclic Compounds

Heterocycles form the largest class of organic compounds. In fact, many natural products and most drugs contain heterocyclic rings. The colors of flowers and plants, antibiotics known to all as penicillins, compounds that transport the oxygen we breathe to our vital organs, and the components of DNA responsible for the genetic code are all heterocyclic compounds.

From an organic chemist's viewpoint, **heteroatoms** are atoms other than carbon or hydrogen that may be present in organic compounds. The most common heteroatoms are oxygen, nitrogen, and sulfur. In heterocyclic compounds, one or more of these heteroatoms replaces carbon in a ring.

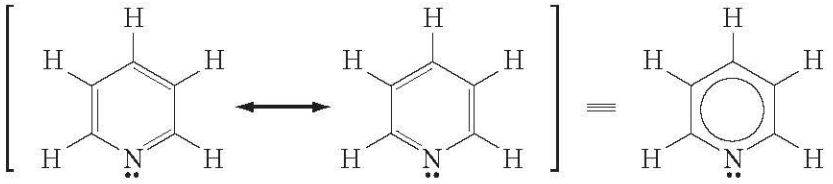
Heterocycles can be divided into two subgroups: nonaromatic and aromatic.

Pyridine: Bonding and Basicity

Heterocycles are cyclic organic compounds in which one or more carbon atoms is replaced by **heteroatoms**, atoms other than C or H.

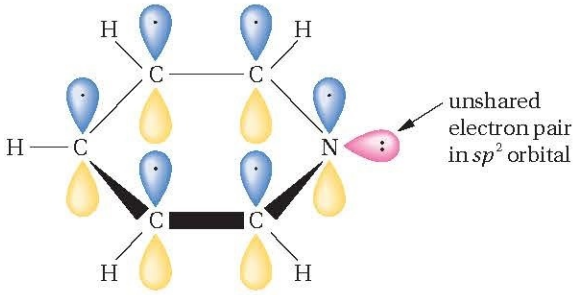
Pyridine is a benzene ring in which one CH unit has been replaced by an N atom.

Pyridine has a structure similar to that of benzene, except that one CH unit is replaced by a nitrogen atom. As with benzene, pyridine is a resonance hybrid of Kekulé-type structures



Pyridine is a resonance hybrid of these two contributing structures

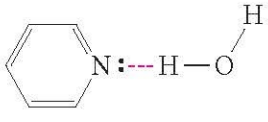
The orbital pictures for benzene and pyridine are similar. The nitrogen atom, as with the carbons, is sp^2-hybridized, with one electron in a p orbital perpendicular to the ring plane. Thus, the nitrogen contributes one electron to the six electrons that form the aromatic pi cloud above and below the ring plane. On the other hand, the unshared electron pair on nitrogen lies in the ring plane (as with the C—H bonds) in an sp^2 orbital.



bonding in pyridine

Because of the similarities in bonding, pyridine resembles benzene in shape. It is planar, with nearly perfect hexagonal geometry. It is aromatic and tends to undergo substitution rather than addition reactions.

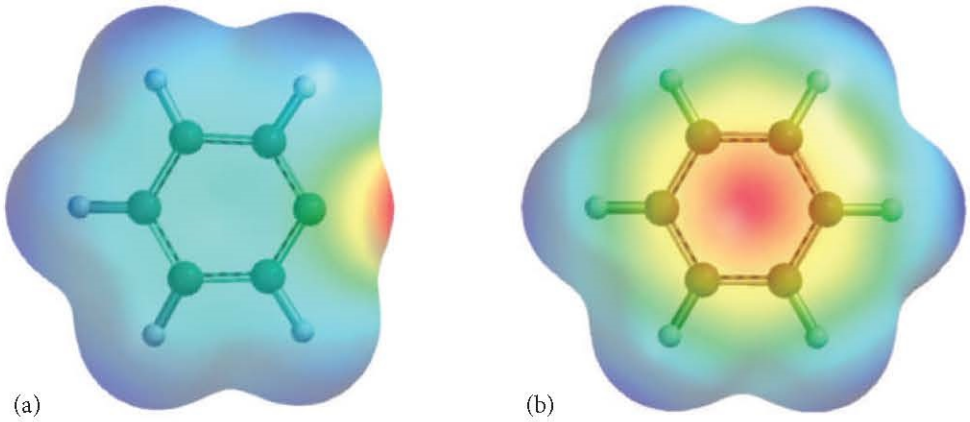
But the substitution of nitrogen for carbon changes many of the properties. Like benzene, pyridine is miscible with most organic solvents, but unlike benzene, pyridine is also completely miscible with water! One explanation lies in its hydrogen-bonding capability



Another reason is that pyridine is much more polar than benzene. The nitrogen atom is electron-withdrawing compared to carbon; hence, there is a shift of electrons away from the ring carbons and toward the nitrogen, making it partially negative and the ring carbons partially positive (Figure 13.1). This polarity enhances the solubility of pyridine in polar solvents like water, and also increases the boiling point of pyridine (115°C) relative to benzene (80°C).

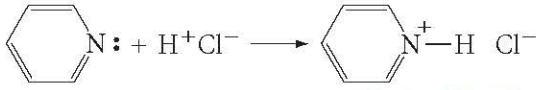
Pyridine is weakly basic. It is a much weaker base than aliphatic amines, mainly because of the different hybridization of the nitrogen (sp^2 in pyridine and sp^3 in aliphatic amines). The greater s-character of the orbital containing the basic nonbonded lone pair (one-third s in pyridine and one-fourth s in aliphatic amines) means that the unshared electron pair is held closer to the nitrogen nucleus in pyridine, decreasing its basicity.

Figure
Electrostatic potential maps of (a) pyridine and (b) benzene.



Pyridinium salts are formed when pyridine reacts with strong acids.

Pyridine does react with strong acids to form **pyridinium salts**. For this reason, pyridine is often used as a scavenger in acid-producing reactions;



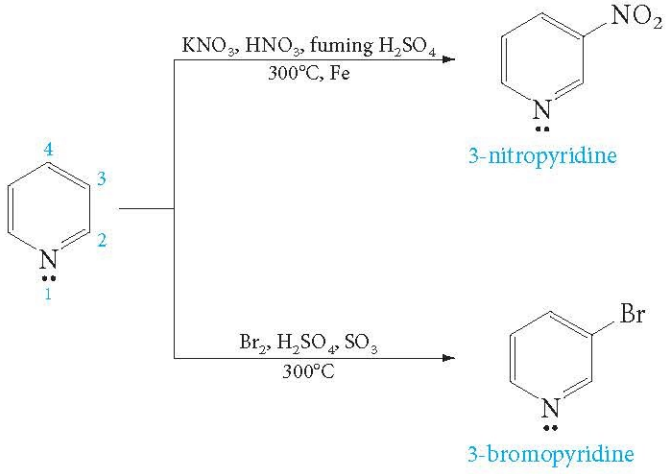
pyridinium chloride
$pK_a = 5.29$

PROBLEM 13.1 Write an equation for the reaction of pyridine with

a. cold sulfuric acid (H_2SO_4) b. cold nitric acid (HNO_3)

Substitution in Pyridine

Though aromatic, *pyridine is very resistant to electrophilic aromatic substitution* and undergoes reaction only under drastic conditions. For example, nitration or bromination requires high temperatures and strong acid catalysis.



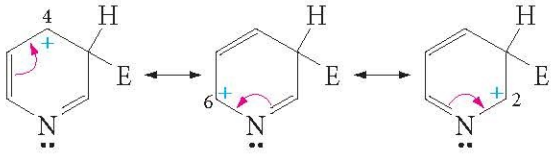
One reason for this sluggishness is that electron withdrawal by the nitrogen makes the ring partially positive and therefore not receptive to attack by electrophiles, which are also positive . A second reason is that, under the acidic conditions for these reactions, most of the pyridine is protonated and present as the positively charged pyridinium ion, which is even more unlikely to be attacked by electrophiles than is neutral pyridine.

When substitution does occur, electrophiles attack pyridine mainly at C-3. The cationic intermediate (review Sec. 4.9) is *least unfavorable* in this case, because it does not put a positive charge on the electron-deficient nitrogen (especially bad if the nitrogen is protonated).

EXAMPLE

Draw all contributors to the resonance hybrid for electrophilic attack at C-3 of pyridine.

Solution

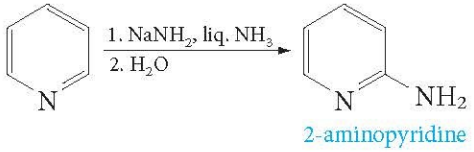


For substitution at C-3, the "pyridinonium ion" positive charge is delocalized to C-2, C-4, and C-6, but not to the nitrogen.

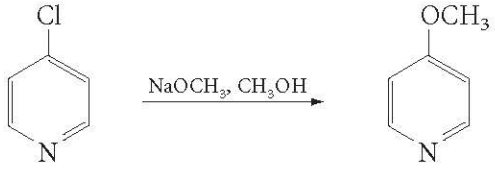
PROBLEM 13.2 Repeat Example 13.1, but for electrophilic substitution at C-2 or C-4 of pyridine. Explain why substitution at C-3 (eq. 13.2) is preferred.

Although resistant to electrophilic substitution, pyridine undergoes **nucleophilic aromatic substitution**. The pyridine ring is partially positive (due to electron withdrawal by the nitrogen) and is therefore susceptible to attack by nucleophiles. Here are two examples:

In **nucleophilic aromatic substitution** reactions of pyridine, a nucleophile displaces a hydride or halide ion from the aromatic ring.



2-aminopyridine

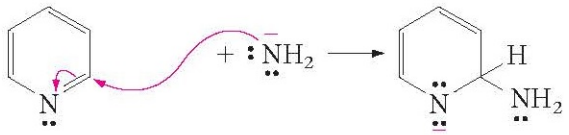


4-chloropyridine 4-methoxypyridine

EXAMPLE

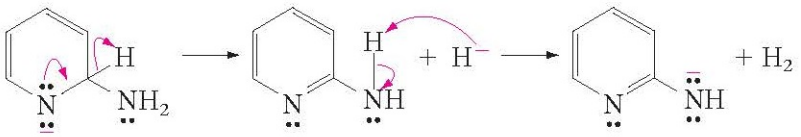
Write a mechanism for eq. 13.3.

Solution Attack of amide ion at C-2 gives an anionic intermediate with the negative charge mainly on nitrogen.

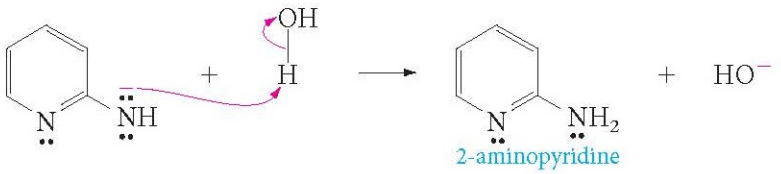


You can think of this as nucleophilic addition to a C=N bond, analogous to addition of nucleophiles to a C=O bond (Sec. 9.6).

To restore aromaticity, hydride ion is displaced. The hydride then attacks the amino group to give hydrogen gas and an amide-type anion (see eq. 11.17).



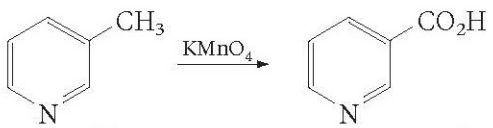
In the final step, this ion is protonated by water.



2-aminopyridine

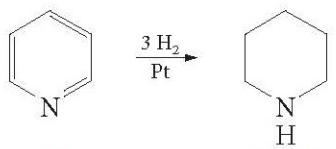
PROBLEM Write a mechanism for eq. 13.4.

Pyridine and alkylpyridines are found in coal tar. The monomethyl pyridines (called picolines) undergo side-chain oxidation to carboxylic acids . For example, 3-picoline gives nicotinic acid (or niacin), a vitamin essential in the human diet to prevent the disease *pellagra*.



3-picoline nicotinic acid

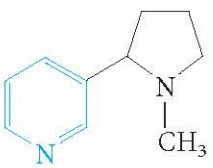
Pyridine can be reduced by catalytic hydrogenation to the fully saturated secondary amine piperidine.

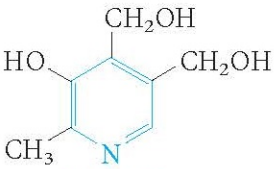


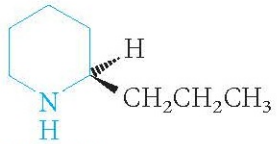
pyridine piperidine

The pyridine and piperidine rings are found in many natural products. Examples are **nicotine** (the major alkaloid in tobacco, used as an agricultural insecticide and

highly toxic to humans), pyridoxine (vitamin B_6, a coenzyme), and coniine (the toxic principle of poison hemlock, taken by Socrates).


nicotine


pyridoxine


(+)-coniine

PROBLEM Naturally occurring coniine is the (+)-isomer shown. What is its configuration, *R* or *S*?

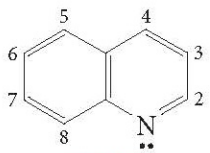
PROBLEM Naturally occurring nicotine is the (*S*)-(−) isomer. Locate the stereogenic center, and draw the three-dimensional structure.

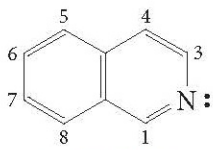
PROBLEM Nicotine contains two nitrogens, one in a pyridine ring and one in a pyrrolidine ring. It reacts with *one* equivalent of HCl to form a crystalline salt, $C_{10}H_{15}N_2Cl$. Draw its structure. Nicotine also reacts with *two* equivalents of HCl to form another crystalline salt, $C_{10}H_{16}N_2Cl_2$. Draw its structure.

Other Six-Membered Heterocycles

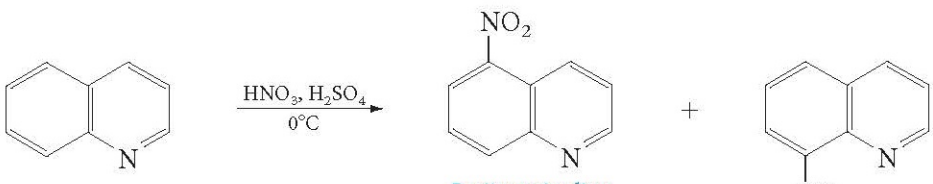
The pyridine ring can be fused with benzene rings to produce polycyclic aromatic heterocycles. The most important examples are **quinoline** and **isoquinoline**,

Quinoline and **isoquinoline** are naphthalene analogs in which an N atom replaces a CH unit at C-1 or C-2.


quinoline
bp 237°C

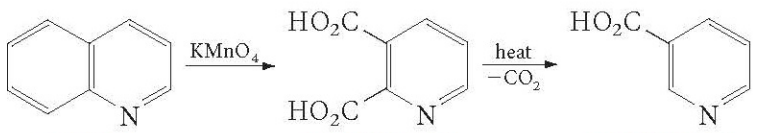

isoquinoline
bp 243°C, mp 26.5°C

Electrophilic substitution in these amines occurs in the carbocyclic ring, illustrating the inactivity toward electrophiles of the pyridine ring relative to the benzene ring.



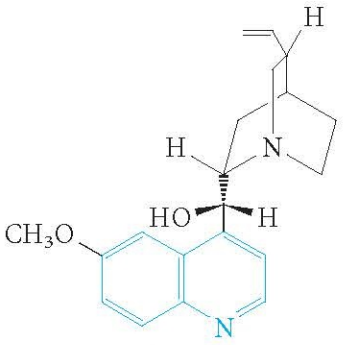
5-nitroquinoline
8-nitroquinoline

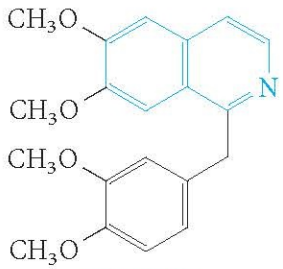
The stability of the pyridine ring is also illustrated by its resistance to oxidation. Thus, when quinoline is treated with potassium permanganate, the benzene ring is oxidized.



quinoline quinolinic acid nicotinic acid

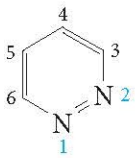
The quinoline and isoquinoline rings occur in many natural products. Good examples are quinine (which occurs in cinchona bark and is used to treat malaria) and papaverine (present in opium and used as a muscle relaxant).

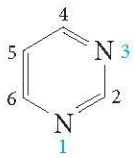

quinine

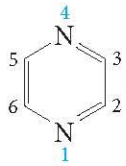

papaverine

It is logical to ask: If we can replace one CH with N in a benzene ring to create pyridine, can we replace more than one of the benzene CH groups with nitrogens? The answer is yes. For example, there are *three* **diazines**.

Diazines are six-membered ring heterocycles containing two N atoms. In **pyrimidines**, the N atoms are located at ring positions 1 and 3.

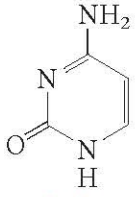

pyridazine
(bp 208°C)

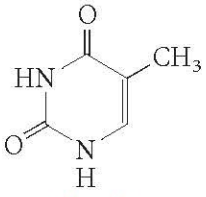

pyrimidine
(bp 134°C)

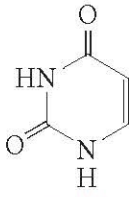

pyrazine
(bp 118°C)

Cytosine, **thymine**, and **uracil** are pyrimidines, and they are important bases in nucleic acids DNA and RNA.

Of these, the most important are the **pyrimidines**, derivatives of which (**cytosine**, **thymine**, and **uracil**) are important bases in nucleic acids DNA and RNA (see Chapter 18).

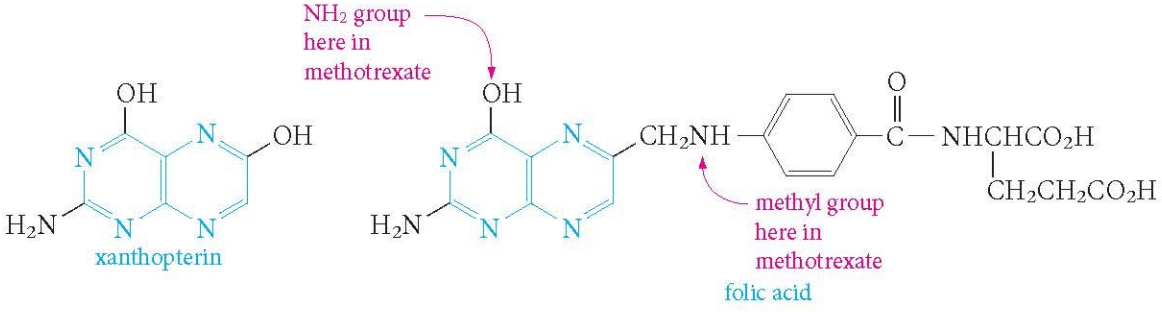

cytosine


thymine


uracil

Triazines and tetrazines are also known, but neither pentazine nor hexazine (which would really not be a heterocycle, since it would contain only one element and be an allotrope of nitrogen) is known.

Similar analogs of naphthalene with more than one nitrogen are also known. The pteridine ring, with nitrogens replacing C-1, C-3, C-5, and C-8 in naphthalene, is present in many natural products, such as the butterfly wing pigment xanthopterin and the blood-forming vitamin B9, which is also called folic acid. The analog of folic acid, but with an NH_2 group in place of the OH group on the pteridine ring and a methyl group on the first nitrogen in the side chain, is useful in cancer chemotherapy (it is called methotrexate).



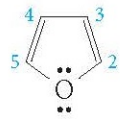
xanthopterin

folic acid

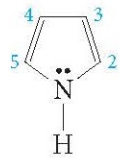
Five-Membered Heterocycles: Furan, Pyrrole, and Thiophene

Furan, **pyrrole**, and **thiophene** are important five-membered ring heterocycles with one heteroatom.

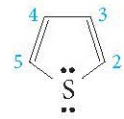
Furan, **pyrrole**, and **thiophene** are five-membered ring aromatic heterocycles containing one heteroatom (O, N, and S, respectively) in the ring.



furan
(bp 32°C)



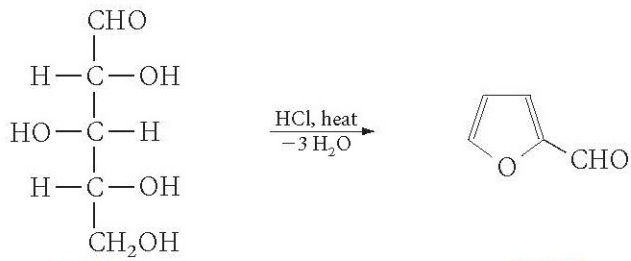
pyrrole
(bp 131°C)



thiophene
(bp 84°C)

Numbering begins with the heteroatom and proceeds around the ring.

The most important commercial source of furans is furfural (2-furaldehyde), obtained by heating oat hulls, corn cobs, or straw with strong acid. These naturally occurring materials are polymers of a five-carbon sugar, which is dehydrated by the acid to furfural.



a pentose
(5-carbon sugar)

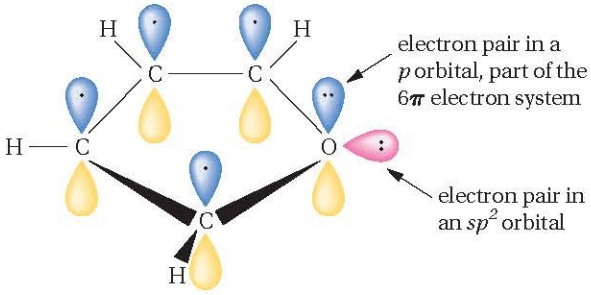
furfural
(2-furaldehyde)

Pyrrole is obtained commercially by distillation of coal tar or from furan, ammonia, and a catalyst. Thiophene is obtained by heating a mixture of butanes and butenes with sulfur.

As drawn, the structures of these heterocycles look as if they ought to be dienes, but in fact, these ring systems are aromatic; they behave like benzene in many ways, particularly in their tendency to undergo electrophilic aromatic substitution. The reasons for this behavior will become clear if we examine the bonding in these molecules.

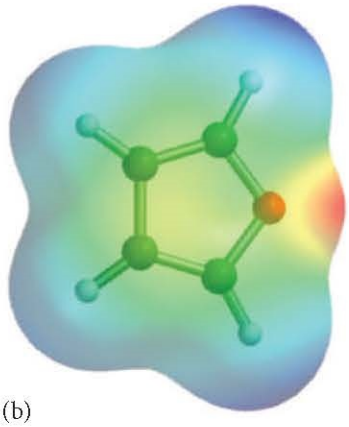
Furan has a planar, pentagonal structure in which each ring atom is sp^2-hybridized (Figure 13.2). Each ring atom uses two of these orbitals to form sigma bonds with its neighbors. Each carbon also uses one sp^2 orbital to form a sigma bond in the ring plane with a hydrogen atom and has one electron in a p orbital perpendicular to the ring plane, exactly analogous to the carbons in benzene. Now look at the oxygen. It has an unshared electron pair in an sp^2 orbital in the ring plane and *two electrons in a p orbital perpendicular to the ring plane.* These two electrons overlap with those in the p orbitals on the carbons to form a 6π electron cloud above and below the ring plane, just as in benzene. The bonding in pyrrole and thiophene is similar to that in furan.

Some striking differences are seen between five-membered ring heterocyclic compounds and their six-membered ring counterparts. For example, pyrrole is an exceedingly weak base compared to pyridine . Its conjugate acid has a pK_a of −4.4 compared with a pK_a of 5.29 for pyridinium (see eq. 13.1). How can this be explained? In pyrrole, the unshared electron pair on nitrogen is part of the aromatic 6π system.



orbital structure of furan

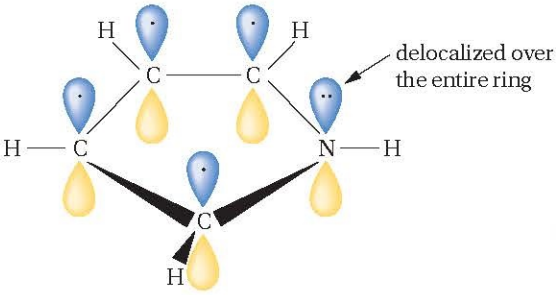
(a)



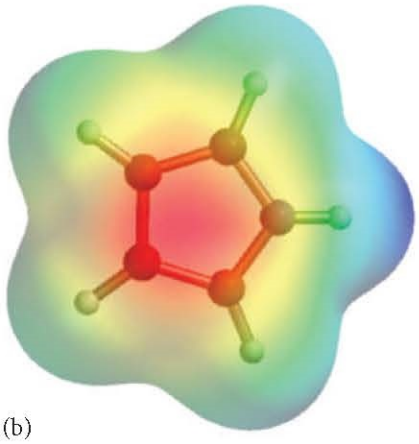
(b)

Figure
(a) Bonding in furan and (b) electrostatic potential map.

Protonation of the nitrogen of pyrrole destroys the aromatic system, thus forfeiting its resonance energy. Hence pyrrole is a very weak base. In fact, pyrrole can be protonated by very strong acids, but it is *protonated on the carbon* rather than on the nitrogen! In pyridine, the electron pair on nitrogen is not part of the aromatic π system and is available for protonation.



(a)



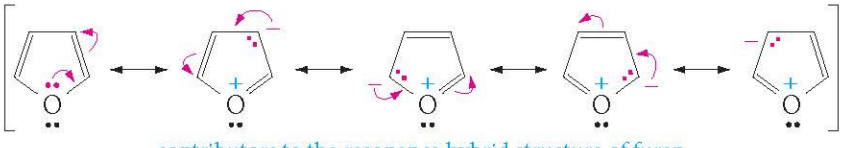
(b)

Figure 13.3
(a) Bonding in pyrrole and (b) electrostatic potential map that illustrates how pyrrole is an electron-rich relative to furan.

PROBLEM What is the structure of the cation derived from protonation of pyrrole at C-2?

Another important difference between five- and six-membered aromatic heterocycles is that, in the five-membered heterocycles, the heteroatom contributes *two* electrons to the aromatic 6π systems, whereas in six-membered heterocycles, the heteroatom contributes only *one* electron to that system. This difference has important consequences for the chemical behavior of the two types of heterocycles.

Before we consider those consequences, let us examine the bonding in furan in another way. We can write these heterocycles as a resonance hybrid in which an electron pair from the heteroatom is delocalized to all ring atoms.

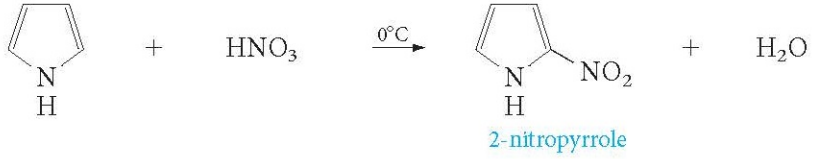


contributors to the resonance hybrid structure of furan

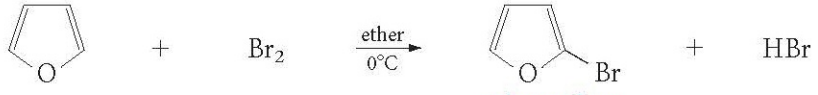
Notice that four of these structures are dipolar and place a *negative* charge on the ring carbons. As might be expected, this enhances their susceptibility to attack by electrophiles.

Electrophilic Substitution in Furan, Pyrrole, and Thiophene

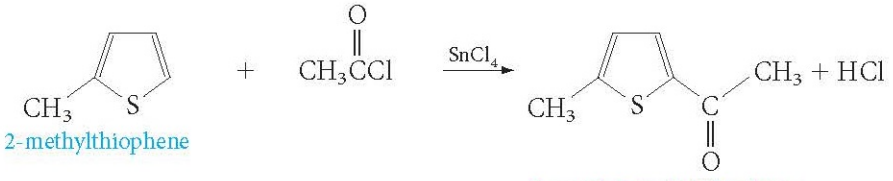
Furan, pyrrole, and thiophene are all much more reactive than benzene toward electrophilic substitution. Each reacts predominantly at the 2-position (and, if that position is already substituted, at the 5-position). Here are typical examples:



2-nitropyrrole



2-bromofuran

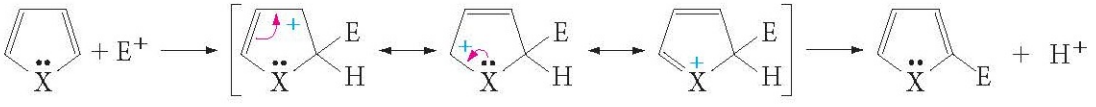


2-methylthiophene

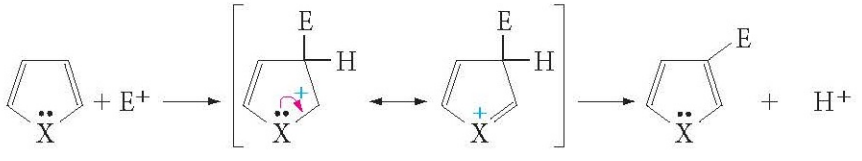
2-acetyl-5-methylthiophene

The reason for predominant attack at C-2 (instead of the other possibility, C-3) becomes clear if we examine the carbocation intermediate in each case:

Attack of electrophile at C-2 (X = NH, O, or S):



Attack of electrophile at C-3:



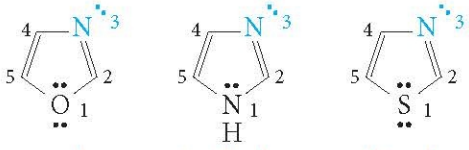
Attack at C-2 is preferred because, in the carbocation intermediate, the positive charge can be delocalized over *three* atoms, whereas attack at C-3 allows delocalization of the charge over only two positions.

PROBLEM Write out the steps in the mechanism for bromination of furan (eq. 13.11).

Other Five-Membered Heterocycles: Azoles

Azoles are five-membered heterocycles with an O, N, or S atom at position 1 and an N atom at position 3.

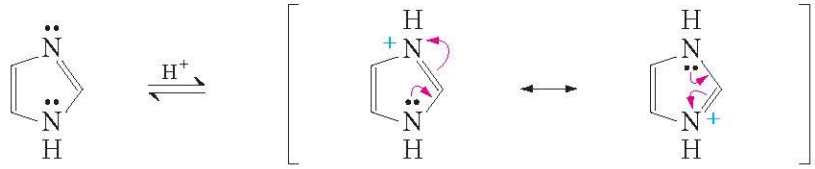
It is possible to introduce a second heteroatom (and even a third and fourth) into five-membered heterocycles. The most important of these are the **azoles**, in which the second heteroatom, located at position 3, is nitrogen.



Analogs in which the two heteroatoms are adjacent are also known.

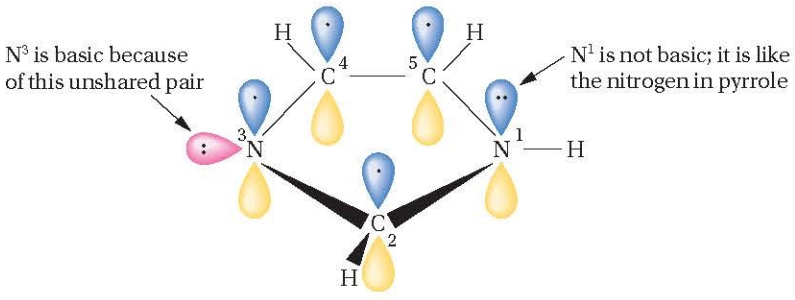
As with pyridine, these heterocycles can be thought of as derived by replacing an aromatic CH group by N. The unshared electron pair on this nitrogen (at position 3) is therefore *not* part of the 6π aromatic system, as seen in the orbital picture for imidazole in Figure 13.4.

Consequently, the N-3 nitrogen is basic and can be protonated. The imidazolium ion is very stable because the positive charge can be delocalized equally over both nitrogens. Imidazole is even more basic than pyridine, and as a consequence, the pK_a of the imidazolium ion (7.0) is greater than the pK_a of the pyridinium ion (5.3).



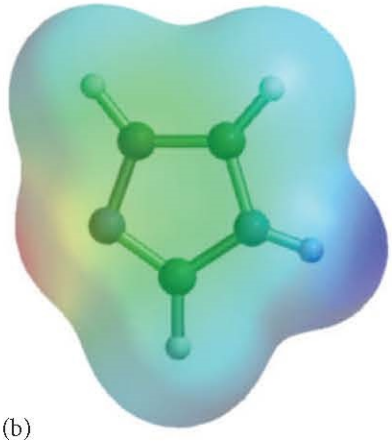
(13.15)

resonance in the imidazolium ion



bonding in imidazole

(a)



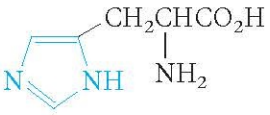
(b)

Figure

(a) Bonding in imidazole and (b) electrostatic potential map illustrating the difference in properties of the two nitrogen atoms.

These ring systems occur in nature. For example, the imidazole skeleton is present in the amino acid histidine, where it plays an important role in the reactions of many enzymes. Decarboxylation of histidine gives **histamine**, a toxic substance present in combination with proteins in body tissues. It is released as a consequence of allergic hypersensitivity or inflammation (for example, in hay fever sufferers). Many **antihistamines**, compounds that counteract the effects of histamine, have been developed. One of the better known of these is the drug benadryl (diphenylhydramine).

Antihistamines are compounds that counteract the effects of the toxin **histamine**, which contains an imidazole ring.

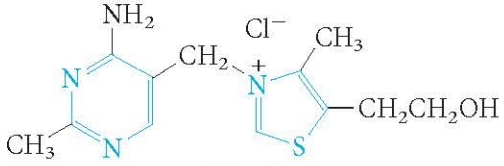


histidine

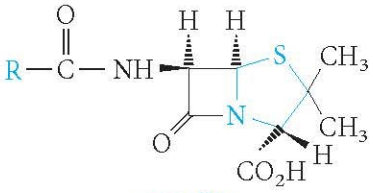
histamine

benadryl
(an antihistamine)

The thiazole ring occurs in thiamin (vitamin B_1), a coenzyme required for certain metabolic processes and hence essential to life (thiamin also contains a pyrimidine ring). In its reduced form, the tetrahydrothiazole ring appears in penicillins, which are important antibiotics.



thiamin
(vitamin B_1)

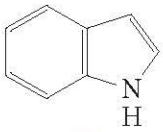


penicillin

Fused-Ring Five-Membered Heterocycles: Indoles and Purines

Another aromatic or heteroaromatic ring can be fused to the double bonds of five-membered heterocycles. For example, **indole** has a benzene ring fused to the C-2–C-3 bond of pyrrole.

The **indole** ring system, consisting of a benzene ring fused to the C-2–C-3 bond of pyrrole, occurs in many natural products.

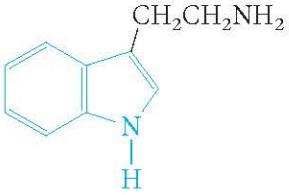


indole

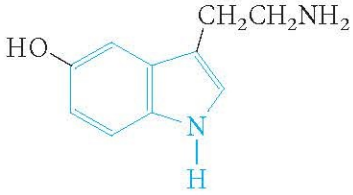
The indole ring system, which occurs in several important natural products, is usually biosynthesized from the amino acid tryptophan, one of the protein building blocks. Indole itself and its 3-methyl derivative, skatole, are formed during protein decay.

Decarboxylation of tryptophan gives tryptamine. Several compounds with this skeleton have a profound effect on the brain and nervous system. One example is serotonin (5-hydroxytryptamine), a neurotransmitter and vasoconstrictor active in the central nervous system.

tryptophan

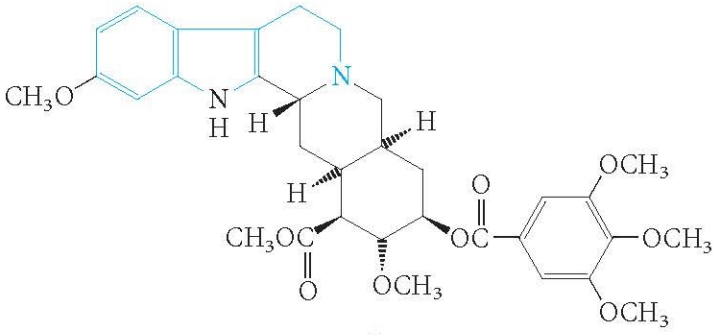


tryptamine

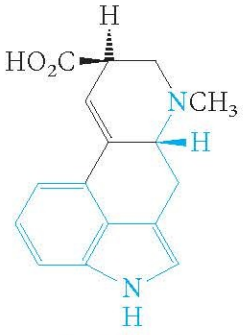


serotonin

The tryptamine skeleton is disguised but present (shown in color) in more complex molecules. Reserpine, present in Indian snake root (*Rauwolfia serpentina*) that grows wild on the foothills of the Himalayas, has been used medically for centuries. It lowers blood pressure and is used to calm schizophrenics and improve their accessibility to psychiatric treatment. Lysergic acid is present in the fungus *ergot*, which grows on rye and other grains. Conversion of the carboxyl group to its diethylamide gives the extremely potent hallucinogen LSD.



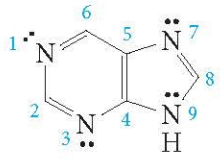
reserpine



lysergic acid

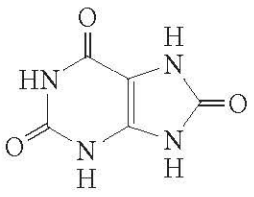
Purines contain a pyrimidine ring fused to an imidazole ring.

The **purines** are another biologically important class of fused-ring heterocycles. They contain a pyrimidine ring fused to an imidazole ring.

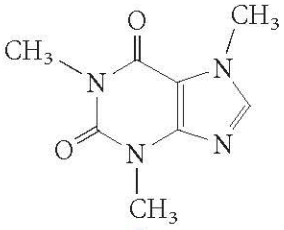


purine
(mp 217°C)

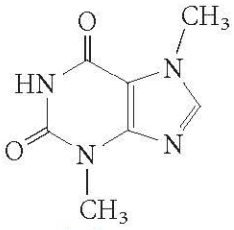
Uric acid is present in the urine of all carnivores and is the main product of nitrogen metabolism in the excrement of birds and reptiles. The disease gout results from deposition of sodium urate (the salt of uric acid) in joints and tendons. Caffeine, present in coffee, tea, and cola beverages, and theobromine (in cocoa) are also purines.



uric acid



caffeine

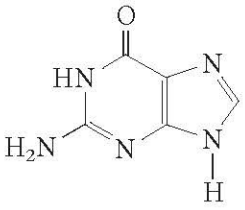


theobromine

Adenine and **guanine** are purines, and they are present in nucleic acids DNA and RNA.

Perhaps the most important purines in nature are **adenine** and **guanine**, two of the nitrogen bases that are present in nucleic acids (DNA and RNA; for further details, see Chapter 18).

adenine



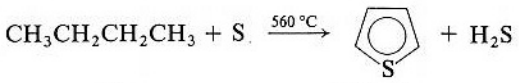
guanine

Many nitrogen heterocycles play a role in medicine. One leading actor in this field is morphine.

Source of pyrrole, furan, and thiophene

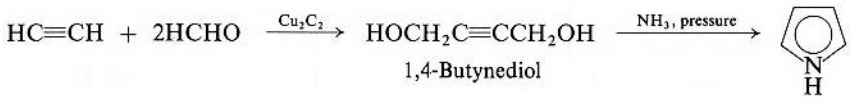
Pyrrole and thiophene are found in small amounts in coal tar. During the fractional distillation of coal tar, thiophene (b.p. 84 °C) is collected along with the benzene (b.p. 80 °C); as a result ordinary benzene contains about 0.5% of thiophene, and must be specially treated if *thiophene-free benzene* is desired.

Thiophene can be synthesized on an industrial scale by the high-temperature reaction between *n*-butane and sulfur.

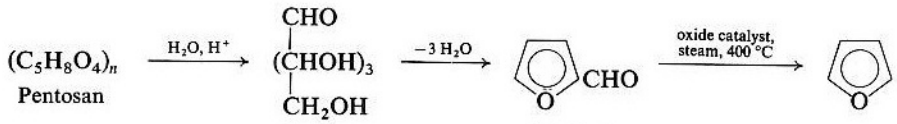


n-Butane Thiophene

Pyrrole can be synthesized in a number of ways. For example:

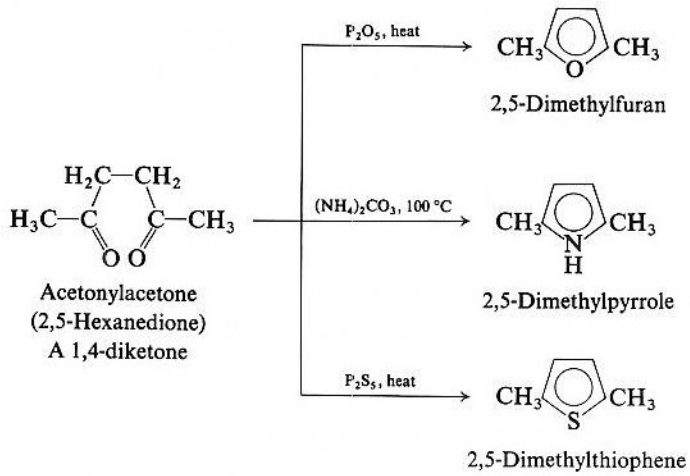


1,4-Butynediol Pyrrole



Pentosan Pentose Furfural (2-Furancarboxaldehyde) Furan

Certain substituted pyrroles, furans, and thiophenes can be prepared from the parent heterocycles by substitution (see Sec. 30.4); most, however, are prepared from open-chain compounds by ring closure. For example:



Acetonylacetone (2,5-Hexanedione) A 1,4-diketone

2,5-Dimethylfuran

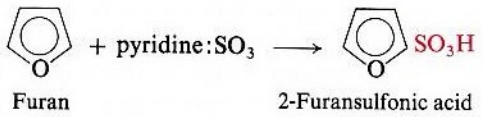
2,5-Dimethylpyrrole

2,5-Dimethylthiophene

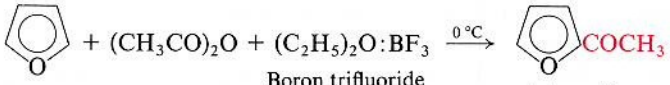
Electrophilic substitution in pyrrole, furan, and thiophene. Reactivity and orientation

Like other aromatic compounds, these five-membered heterocycles undergo nitration, halogenation, sulfonation, and Friedel–Crafts acylation. They are much more reactive than benzene, and resemble the most reactive benzene derivatives (amines and phenols) in undergoing such reactions as the Reimer–Tiemann reaction, nitrosation, and coupling with diazonium salts.

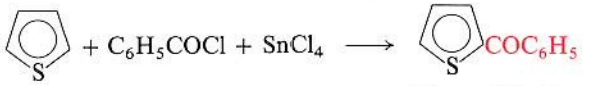
Reaction takes place predominantly at the 2-position. For example:



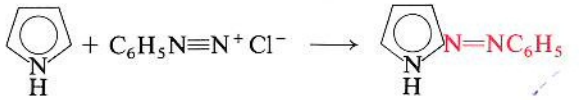
Furan — 2-Furansulfonic acid



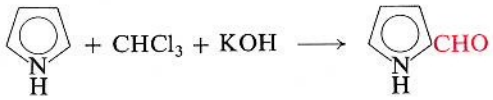
Furan — Boron trifluoride etherate — 2-Acetylfuran



Thiophene — 2-Benzoylthiophene



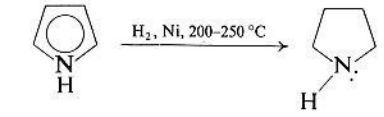
Pyrrole — 2-(Phenylazo)pyrrole



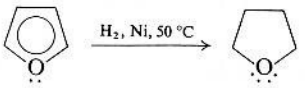
Pyrrole — 2-Pyrrolecarboxaldehyde (*Low yield*)

Saturated five-membered heterocycles

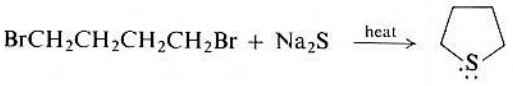
Catalytic hydrogenation converts pyrrole and furan into the corresponding saturated heterocycles, *pyrrolidine* and *tetrahydrofuran*. Since thiophene poisons most catalysts, *tetrahydrothiophene* is made instead from open-chain compounds.



Pyrrole ($K_b \sim 10^{-14}$) Pyrrolidine ($K_b \sim 10^{-3}$)



Furan Tetrahydrofuran

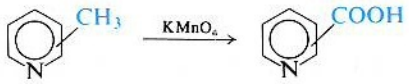


Tetrahydrothiophene

30.7 Source of pyridine compounds

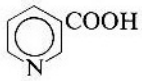
Pyridine is found in coal tar. Along with it are found a number of methylpyridines, the most important of which are the monomethyl compounds, known as *picolines*.

Oxidation of the picolines yields the pyridinecarboxylic acids.



Picoline (2-, 3-, or 4-) — Pyridinecarboxylic acid (2-, 3-, or 4-)

The 3-isomer (*nicotinic acid* or *niacin*) is a vitamin. The 4-isomer (*isonicotinic acid*) has been used, in the form of its hydrazide, in the treatment of tuberculosis.



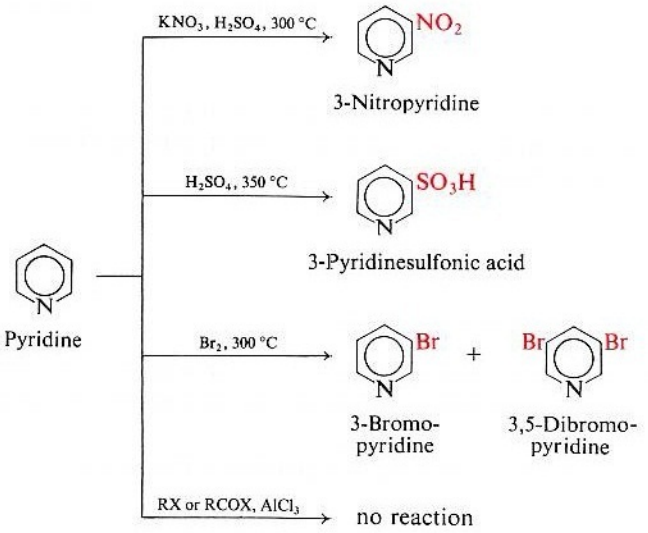
Nicotinic acid
Niacin
3-Pyridinecarboxylic acid
Anti-pellagra factor

Isonicotinic acid hydrazide
(Isoniazid)

Electrophilic substitution in pyridine

Toward electrophilic substitution pyridine resembles a highly deactivated benzene derivative. It undergoes nitration, sulfonation, and halogenation only under very vigorous conditions, and does not undergo the Friedel–Crafts reaction at all.

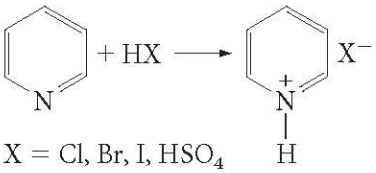
Substitution occurs chiefly at the 3- (or β-) position.



REACTION SUMMARY

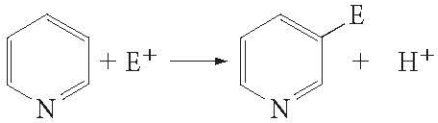
1. Reactions of Pyridine and Related Six-Membered Ring Aromatic Heterocycles

a. Protonation (Sec. 13.1)

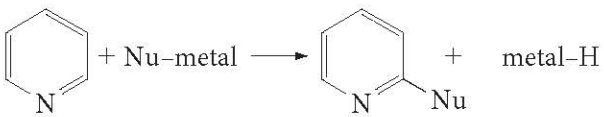


X = Cl, Br, I, HSO_4

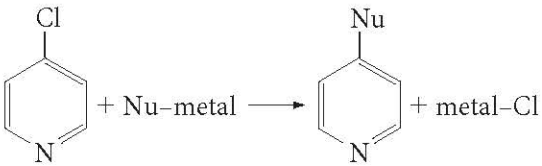
b. Electrophilic Aromatic Substitution (Sec. 13.2)



c. Nucleophilic Aromatic Substitution (Sec. 13.2)

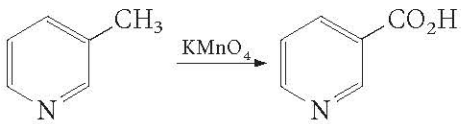


Examples: Nu—metal = H_2N—Na, Ph—Li

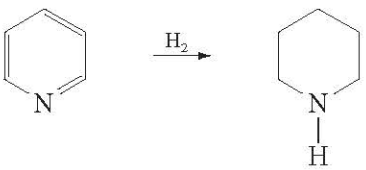


Example: Nu—metal = CH_3O—Na

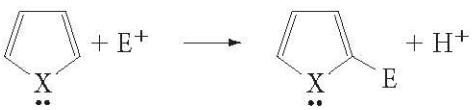
d. Alkyl Side Chain Oxidation (Sec. 13.2)



e. Ring Reduction (Sec. 13.2)



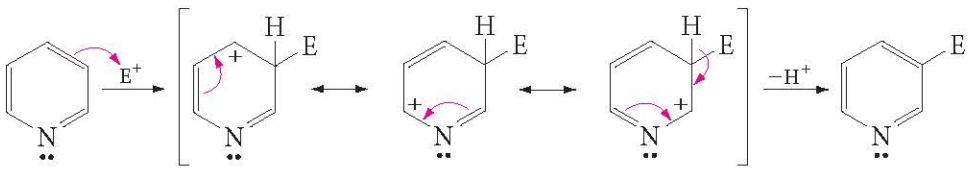
2. Electrophilic Aromatic Substitution Reactions of Five-Membered Ring Aromatic Heterocycles (Sec. 13.5)



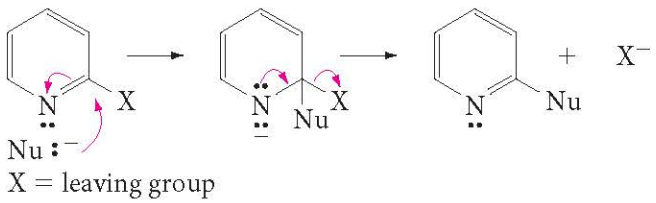
X = O, S, N—H

MECHANISM SUMMARY

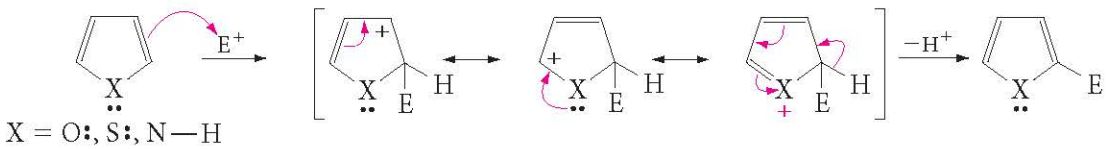
1. Electrophilic Aromatic Substitution of Pyridine (Sec. 13.2)



2. Nucleophilic Aromatic Substitutions of Pyridines (Sec. 13.2)



3. Electrophilic Aromatic Substitution of Five-Membered Ring Heterocycles (Sec. 13.5)



ADDITIONAL PROBLEMS

OWL Interactive versions of these problems are assignable in OWL.

Reactions of Pyridine and Related Six-Membered Ring Heterocycles

13.9 In addition to the Kekulé-type contributors to the pyridine resonance hybrid shown on page 391, there are three minor dipolar contributors. Draw their structures. Do they suggest a reason why pyridine is deactivated (relative to benzene) toward reaction with electrophiles and a reason why substitution, when it does occur, takes place at the 3-position?

13.10 Although nitration of pyridine requires a temperature of 300°C (eq. 13.2), 2,6-dimethylpyridine is readily nitrated at 100°C. Write an equation for the reaction, and explain why milder conditions suffice.

13.11 Pyridine reacts with phenyllithium to give a good yield of 2-phenylpyridine. Write an equation and a mechanism for the reaction.

13.12 Oxidation of nicotine (page 395) with $KMnO_4$ gives nicotinic acid (page 394). Write an equation for the reaction.

13.13 Draw the product of the reaction of nicotinic acid with

a. catalytic sulfuric acid and excess methanol **b.** $LiAlH_4$, then H_3O^+ **c.** H_2 (excess) with Pt

13.14 Write equations for the reaction of coniine (page 395) with

a. hydrochloric acid
b. benzyl iodide (1 equivalent)
c. allyl iodide (2 equivalents)
d. acetic anhydride

13.15 Explain why nitration of quinoline (eq. 13.7) occurs mainly at C5 and C8.

13.16 Write an equation for each of the following reactions:

a. quinoline (page 395) + HCl
b. nitration of quinoline
c. quinoline + $NaNH_2$
d. quinoline + phenyllithium
e. quinoline + CH_3I

Properties and Reactions of Five-Membered Ring Heterocycles

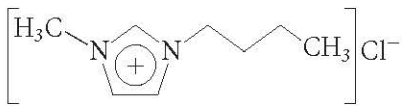
13.17 Write equations for the reactions of furan with

a. Br_2
b. HNO_3
c. CH_3COCl (acetyl chloride), $SnCl_4$

13.18 Write equations for the reactions 2-methylfuran with the reagents shown in Problem 13.16.

13.19 Although electrophilic substitution occurs at C2 in pyrrole, it occurs predominantly at C3 in indole. Suggest an explanation.

13.20 As we saw in Chapter 10 in "A Word about . . . Green Chemistry" (page 299), ionic liquids are used as alternatives for other organic solvents. Suggest a synthetic scheme to prepare 1-butyl-3-methylimidazolium chloride from imidazole (Sec. 13.6).



13.21 Draw a molecular orbital picture of the bonding in oxazole (Sec. 13.6), using the bonding in imidazole as an example. Do you expect oxazole to be more or less basic than pyrrole? Explain.

Structure, Nomenclature, and Properties of Heterocycles

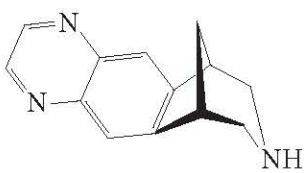
13.22 Using structures for the parent compounds given in the text, write the structural formula for

a. 2,4-difluorofuran
b. 2-bromothiophene
c. 4-methoxyquinoline
d. 5-hydroxyisoquinoline
e. 2-isopropylimidazole
f. 3-pyridinecarboxylic acid
g. 3,4-diethylpyrrole
h. 5-hydroxyindole
i. 4-chloropyridinium bromide
j. 4-aminopyrimidine

13.23 What is the configuration (*R* or *S*) of the hydroxyl-bearing carbon atom in codeine (page 405)?

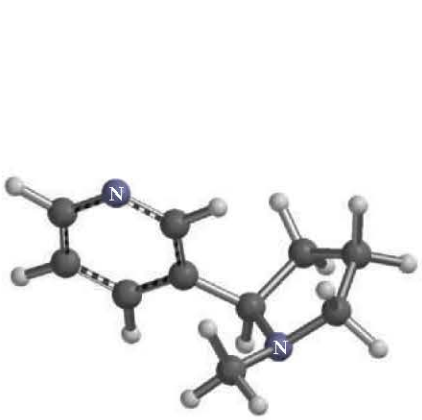
13.24 The water solubility of morphine (page 405) is only 0.2 g/L, but morphine hydrochloride has a water solubility of 57 g/L. Write equations to show how morphine could be extracted and isolated from opium.

13.25 Nitrogen is present in many pharmaceutical drugs, as described in "A Word About . . . Morphine and Other Nitrogen-Containing Drugs" (pages 405–406). Varenicline is a drug inspired by morphine and is a prescription medication used to aid in smoking cessation.

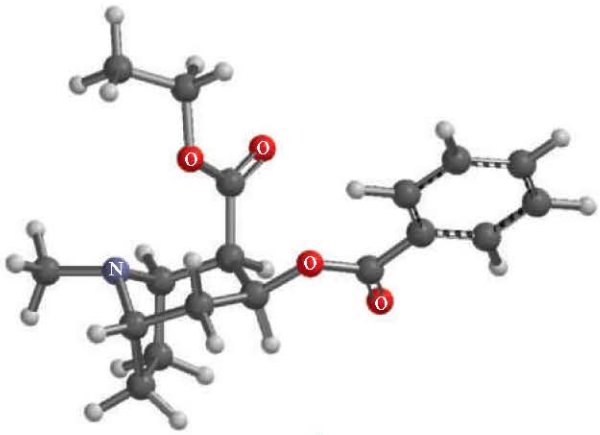


What is your prediction of the pK_a values for the conjugate acids of each of the nitrogens in varenicline?

13.26 Identify the stereogenic centers in nicotine and cocaine shown below, and assign an absolute configuration (*R* or *S*) for each center.



nicotine



cocaine

13.27 Lysergic acid (page 404) has two nitrogens. Which do you expect is the more basic, and why?

Hydroxypyridines, Hydroxypyrimidines, and Related Heterocycles

13.28 In contrast with phenol, which exists almost entirely in the enol form, 2-hydroxypyridine exists mainly in the keto form. Draw the structures, and suggest a reason for the difference.

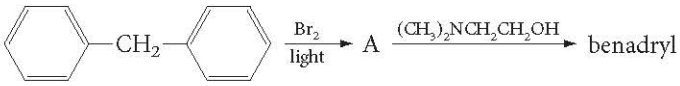
13.29 The RNA base **uracil** is a pyrimidine derivative, usually depicted in its keto form (page 396). The enol tautomer readily undergoes electrophilic substitution, unlike most pyrimidines.

a. Draw the structure of the enol tautomer of uracil.
b. Draw the product of the nitration of uracil with HNO_3. Where on the ring is the nitronium (NO_2^+) ion most likely to attack (see Chapter 4)?

13.30 Uric acid (page 404) has four hydrogens. Which do you expect to be the most acidic, and why?

Puzzle Problem

13.31 Benadryl can be synthesized in two steps from diphenylmethane, according to the following sequence:



a. What is the structure of A?
b. How can the aminoalcohol needed for the second step be synthesized from ethylene oxide?
c. Write a mechanism for each step.

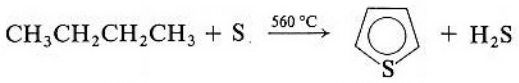
13.32 The structure of porphine is shown on page 402 as part of the "A Word About . . . Porphyrins: What Makes Blood Red and Grass Green?" There are two different kinds of nitrogens in porphine.

a. Which one is more basic? Explain.
b. If porphine is treated with two equivalents of a very strong base, what would be the product?

Source of pyrrole, furan, and thiophene

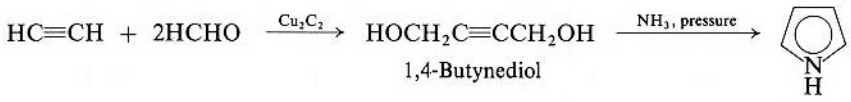
Pyrrole and thiophene are found in small amounts in coal tar. During the fractional distillation of coal tar, thiophene (b.p. 84 °C) is collected along with the benzene (b.p. 80 °C); as a result ordinary benzene contains about 0.5% of thiophene, and must be specially treated if *thiophene-free benzene* is desired.

Thiophene can be synthesized on an industrial scale by the high-temperature reaction between *n*-butane and sulfur.

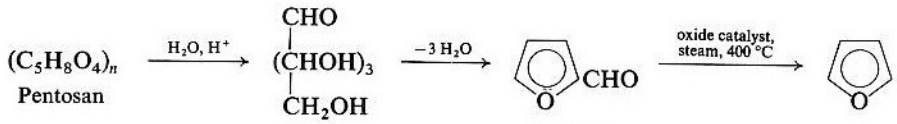


n-Butane Thiophene

Pyrrole can be synthesized in a number of ways. For example:

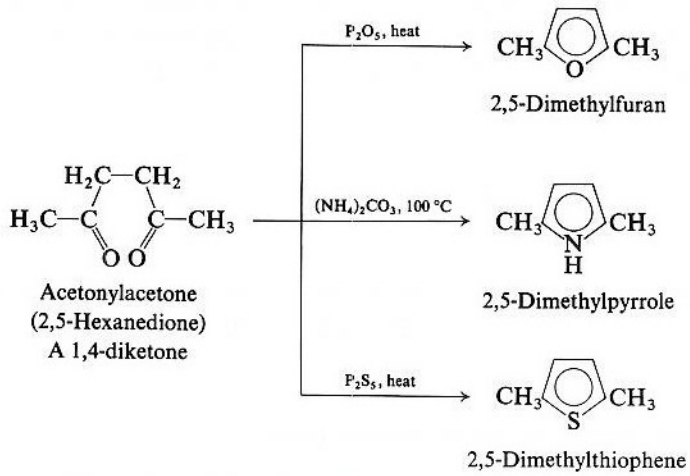


1,4-Butynediol Pyrrole



Pentosan Pentose Furfural (2-Furancarboxaldehyde) Furan

Certain substituted pyrroles, furans, and thiophenes can be prepared from the parent heterocycles by substitution (see Sec. 30.4); most, however, are prepared from open-chain compounds by ring closure. For example:



Acetonylacetone (2,5-Hexanedione) A 1,4-diketone

2,5-Dimethylfuran

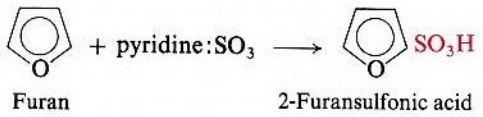
2,5-Dimethylpyrrole

2,5-Dimethylthiophene

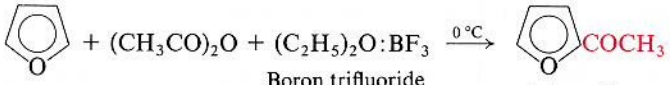
Electrophilic substitution in pyrrole, furan, and thiophene. Reactivity and orientation

Like other aromatic compounds, these five-membered heterocycles undergo nitration, halogenation, sulfonation, and Friedel–Crafts acylation. They are much more reactive than benzene, and resemble the most reactive benzene derivatives (amines and phenols) in undergoing such reactions as the Reimer–Tiemann reaction, nitrosation, and coupling with diazonium salts.

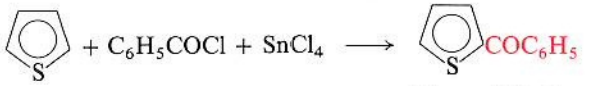
Reaction takes place predominantly at the 2-position. For example:



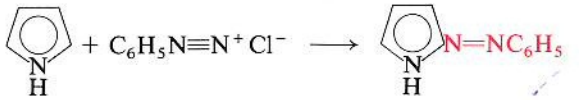
Furan — 2-Furansulfonic acid



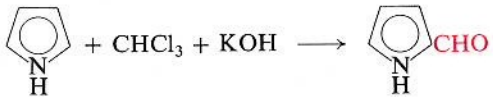
Furan — Boron trifluoride etherate — 2-Acetylfuran



Thiophene — 2-Benzoylthiophene



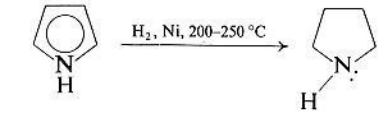
Pyrrole — 2-(Phenylazo)pyrrole



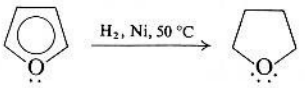
Pyrrole — 2-Pyrrolecarboxaldehyde (*Low yield*)

Saturated five-membered heterocycles

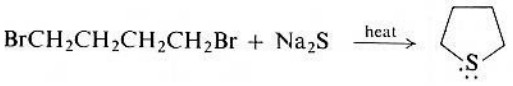
Catalytic hydrogenation converts pyrrole and furan into the corresponding saturated heterocycles, *pyrrolidine* and *tetrahydrofuran*. Since thiophene poisons most catalysts, *tetrahydrothiophene* is made instead from open-chain compounds.



Pyrrole ($K_b \sim 10^{-14}$) Pyrrolidine ($K_b \sim 10^{-3}$)



Furan Tetrahydrofuran

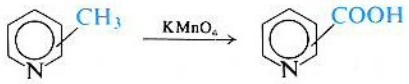


Tetrahydrothiophene

30.7 Source of pyridine compounds

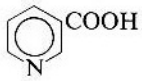
Pyridine is found in coal tar. Along with it are found a number of methylpyridines, the most important of which are the monomethyl compounds, known as *picolines*.

Oxidation of the picolines yields the pyridinecarboxylic acids.



Picoline (2-, 3-, or 4-) — Pyridinecarboxylic acid (2-, 3-, or 4-)

The 3-isomer (*nicotinic acid* or *niacin*) is a vitamin. The 4-isomer (*isonicotinic acid*) has been used, in the form of its hydrazide, in the treatment of tuberculosis.



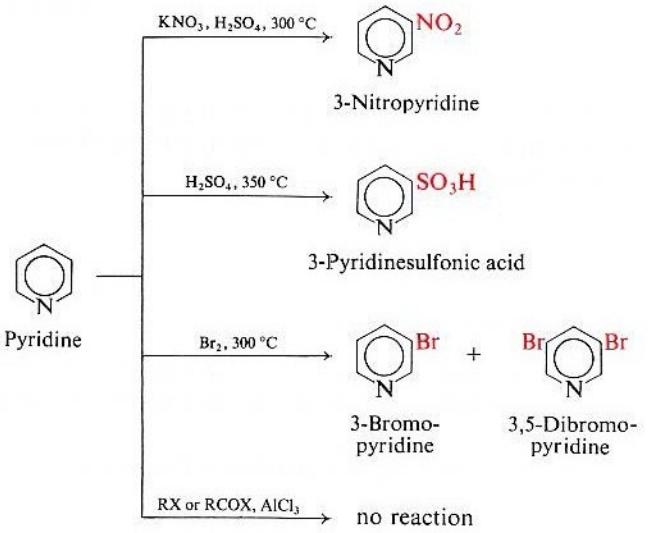
Nicotinic acid
Niacin
3-Pyridinecarboxylic acid
Anti-pellagra factor

Isonicotinic acid hydrazide
(Isoniazid)

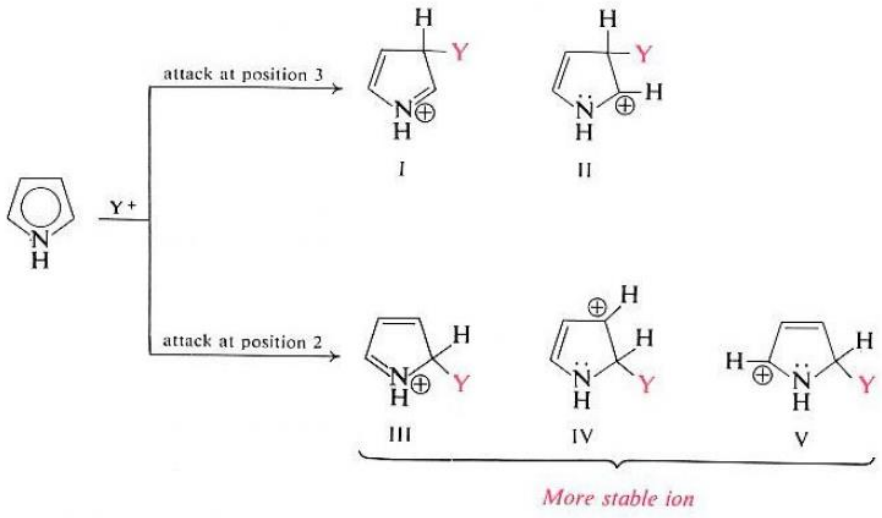
Electrophilic substitution in pyridine

Toward electrophilic substitution pyridine resembles a highly deactivated benzene derivative. It undergoes nitration, sulfonation, and halogenation only under very vigorous conditions, and does not undergo the Friedel–Crafts reaction at all.

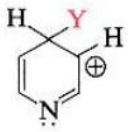
Substitution occurs chiefly at the 3- (or β-) position.



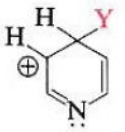
Electrophilic aromatic substitution in pyrrole occurs at 2 position. Explain ?



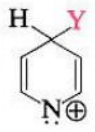
Electrophilic aromatic substitution in pyridine occurs at 3 position. Explain ?



I



II

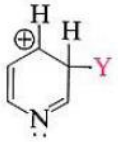


III

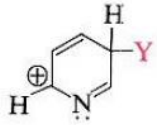
Especially unstable: nitrogen has sextet

Electrophilic attack at 4-position

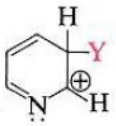
Attack at the 3-position yields an ion that is a hybrid of structures IV, V, and VI.



IV



V



VI

Electrophilic attack at 3-position