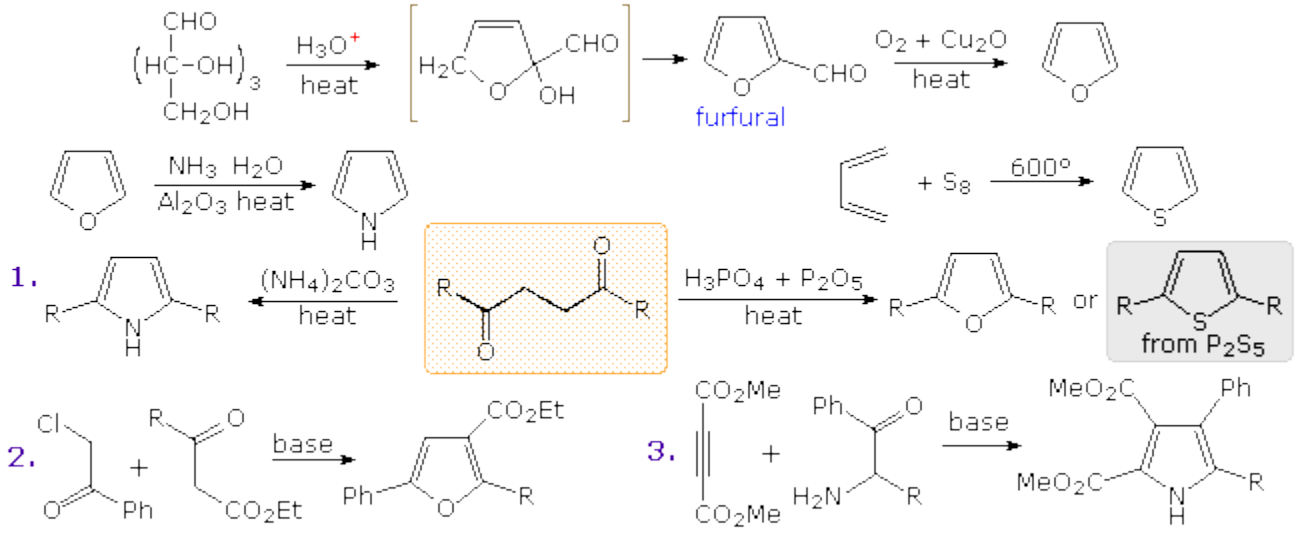
Preparation and Reactions of Heterocyclic Compounds II

Five-Membered Rings

Preparation

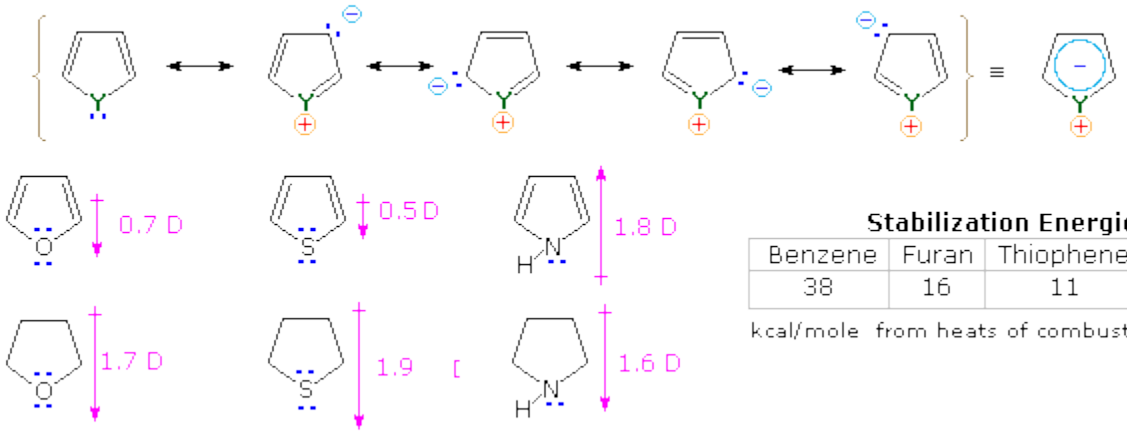
Commercial preparation of furan proceeds by way of the aldehyde, furfural, which in turn is generated from pentose containing raw materials like corncobs, as shown in the uppermost equation below. Similar preparations of pyrrole and thiophene are depicted in the second row equations. Equation 1 in the third row illustrates a general preparation of substituted furans, pyrroles and thiophenes from 1,4-dicarbonyl compounds, known as the Paal-Knorr synthesis. Many other procedures leading to substituted heterocycles of this kind have been devised. Two of these are shown in reactions 2 and 3. Furan is reduced to tetrahydrofuran by palladium-catalyzed hydrogenation. This cyclic ether is not only a valuable solvent, but it is readily converted to 1,4-dihalobutanes or 4-haloalkylsulfonates, which may be used to prepare pyrrolidine and thiolane.
Dipolar cycloaddition reactions often lead to more complex five-membered heterocycles.



Indole is probably the most important fused ring heterocycle in this class. By clicking on the above diagram three examples of indole synthesis will be displayed. The first proceeds by an electrophilic substitution of a nitrogen-activated benzene ring. The second presumably takes place by formation of a dianionic species in which the $ArCH_2(-)$ unit bonds to the deactivated carbonyl group. Finally, the Fischer indole synthesis is a remarkable sequence of tautomerism, sigmatropic rearrangement, nucleophilic addition, and elimination reactions occurring subsequent to phenylhydrazone formation. This interesting transformation involves the oxidation of two carbon atoms and the reduction of one carbon and both nitrogen atoms.

Reactions

The chemical reactivity of the saturated members of this class of heterocycles: tetrahydrofuran, thiolane and pyrrolidine, resemble that of acyclic ethers, sulfides, and 2º-amines, and will not be described here. 1,3-Dioxolanes and dithiolanes are cyclic acetals and thioacetals. These units are commonly used as protective groups for aldehydes and ketones, and may be hydrolyzed by the action of aqueous acid.
It is the "aromatic" unsaturated compounds, furan, thiophene and pyrrole that require our attention. In each case the heteroatom has at least one pair of non-bonding electrons that may combine with the four π-electrons of the double bonds to produce an annulene having an aromatic sextet of electrons. This is illustrated by the resonance description at the top of the following diagram. The heteroatom **Y** becomes sp^2-hybridized and acquires a positive charge as its electron pair is delocalized around the ring. An easily observed consequence of this delocalization is a change in dipole moment compared with the analogous saturated heterocycles, which all have strong dipoles with the heteroatom at the negative end. As expected, the aromatic heterocycles have much smaller dipole moments, or in the case of pyrrole a large dipole in the opposite direction. An important characteristic of aromaticity is enhanced thermodynamic stability, and this is usually demonstrated by relative heats of hydrogenation or heats of combustion measurements. By this standard, the three aromatic heterocycles under examination are stabilized, but to a lesser degree than benzene.
Additional evidence for the aromatic character of pyrrole is found in its exceptionally weak basicity (pK_a ca. 0) and strong acidity (pK_a = 15) for a 2º-amine. The corresponding values for the saturated amine pyrrolidine are: basicity 11.2 and acidity 32.



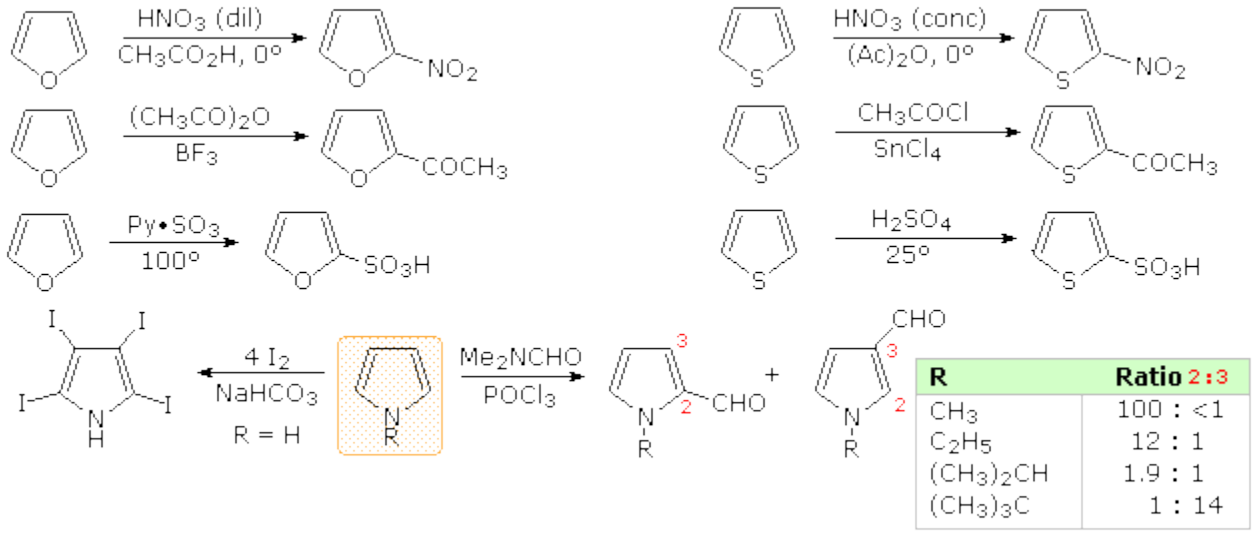
Stabilization Energies

Benzene	Furan	Thiophene	Pyrrole
38	16	11	16

kcal/mole from heats of combustion

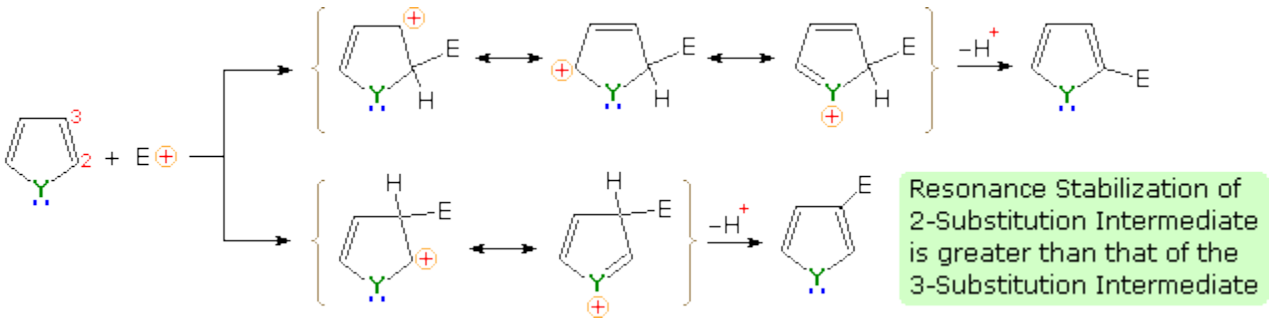
Another characteristic of aromatic systems, of particular importance to chemists, is their pattern of reactivity with electrophilic reagents. Whereas simple cycloalkenes generally give addition reactions, aromatic compounds tend to react by substitution. As noted for benzene and its derivatives, these substitutions take place by an initial electrophile addition, followed by a proton loss from the "onium" intermediate to regenerate the aromatic ring. The aromatic five-membered heterocycles all undergo electrophilic substitution, with a general reactivity order: pyrrole >> furan > thiophene > benzene. Some examples are given in the

following diagram. The reaction conditions show clearly the greater reactivity of furan compared with thiophene. All these aromatic heterocycles react vigorously with chlorine and bromine, often forming polyhalogenated products together with polymers. The exceptional reactivity of pyrrole is evidenced by its reaction with iodine (bottom left equation), and formation of 2-acetylpyrrole by simply warming it with acetic anhydride (no catalyst).



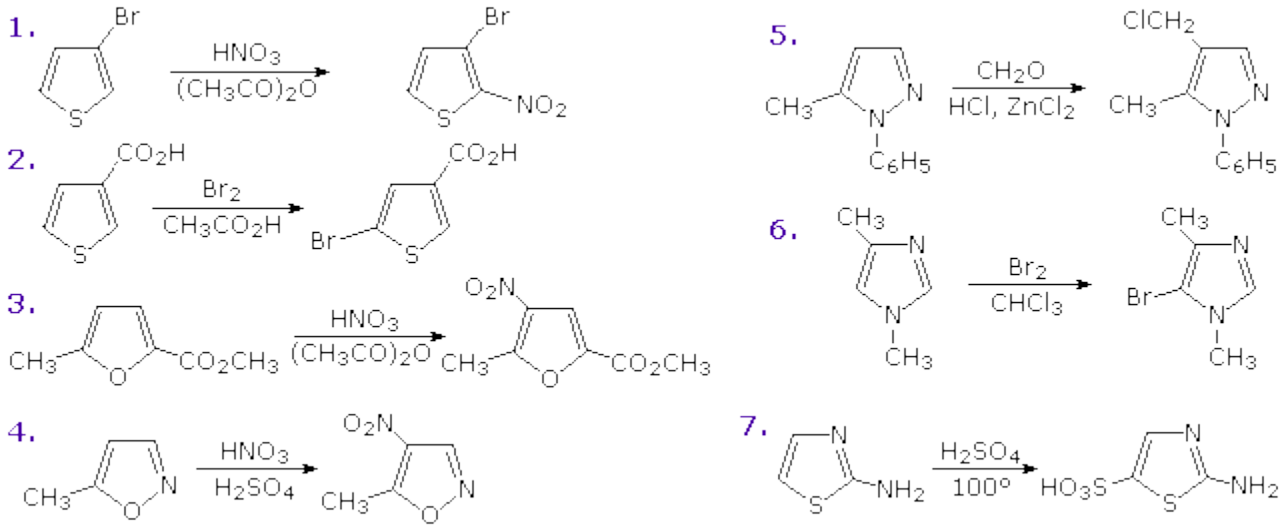
R	Ratio 2:3
CH_3	100 : <1
C_2H_5	12 : 1
$(CH_3)_2CH$	1.9 : 1
$(CH_3)_3C$	1 : 14

There is a clear preference for substitution at the 2-position (α) of the ring, especially for furan and thiophene. Reactions of pyrrole require careful evaluation, since N-protonation destroys its aromatic character. Indeed, N-substitution of this 2º-amine is often carried out prior to subsequent reactions. For example, pyrrole reacts with acetic anhydride or acetyl chloride and triethyl amine to give N-acetylpyrrole. Consequently, the regioselectivity of pyrrole substitution is variable, as noted by the bottom right equation. An explanation for the general α-selectivity of these substitution reactions is apparent from the mechanism outlined below. The intermediate formed by electrophile attack at C-2 is stabilized by charge delocalization to a greater degree than the intermediate from C-3 attack. From the Hammond postulate we may then infer that the activation energy for substitution at the former position is less than the latter substitution.



Functional substituents influence the substitution reactions of these heterocycles in much the same fashion as they do for benzene. Indeed, once one understands the ortho-para and meta-directing character of these substituents, their directing influence on heterocyclic ring

substitution is not difficult to predict. The following diagram shows seven such reactions. Reactions 1 & 2 are 3-substituted thiophenes, the first by an electron donating substituent and the second by an electron withdrawing group. The third reaction has two substituents of different types in the 2 and 5-positions. Finally, examples 4 through 7 illustrate reactions of 1,2- and 1,3-oxazole, thiazole and diazole. Note that the basicity of the sp^2-hybridized nitrogen in the diazoles is over a million times greater than that of the apparent sp^3-hybridized nitrogen, the electron pair of which is part of the aromatic electron sextet.

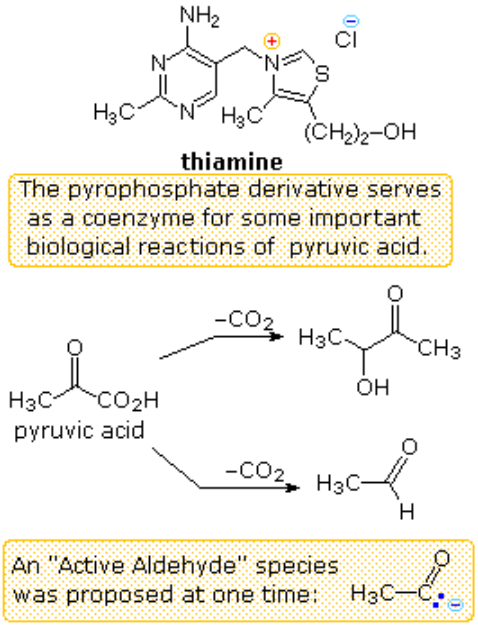


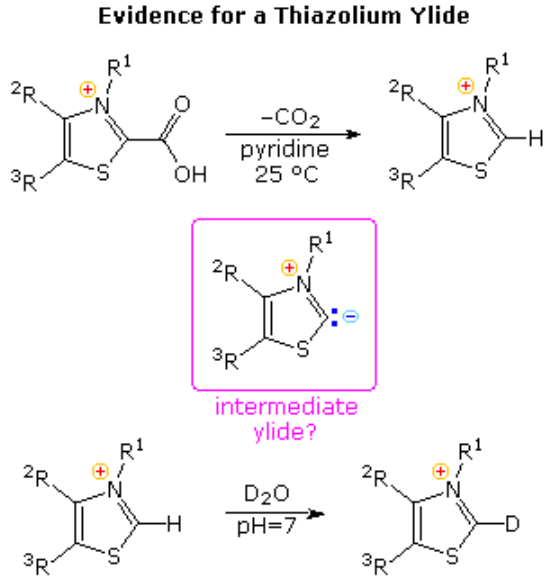
Other possible reactions are suggested by the structural features of these heterocycles. For example, furan could be considered an enol ether and pyrrole an enamine. Such functions are known to undergoacid-catalyzed hydrolysis to carbonyl compounds and alcohols or amines. Since these compounds are also heteroatom substituted dienes, we might anticipate Diels-Alder cycloaddition reactions with appropriate dienophiles. These possibilities will be illustrated above by clicking on the diagram. As noted in the upper example, furans may indeed be hydrolyzed to 1,4-dicarbonyl compounds, but pyrroles and thiophenes behave differently. The second two examples, shown in the middle, demonstrate typical reactions of furan and pyrrole with the strong dienophile maleic anhydride. The former participates in a cycloaddition reaction; however, the pyrrole simply undergoes electrophilic substitution at C-2. Thiophene does not easily react with this dienophile.

The bottom line of the new diagram illustrates the remarkable influence that additional nitrogen units have on the hydrolysis of a series of N-acetylazoles in water at 25 ºC and pH=7. The pyrrole compound on the left is essentially unreactive, as expected for an amide, but additional nitrogens markedly increase the rate of hydrolysis. This effect has been put to practical use in applications of the acylation reagent1,1'-carbonyldiimidazole (Staab's reagent).

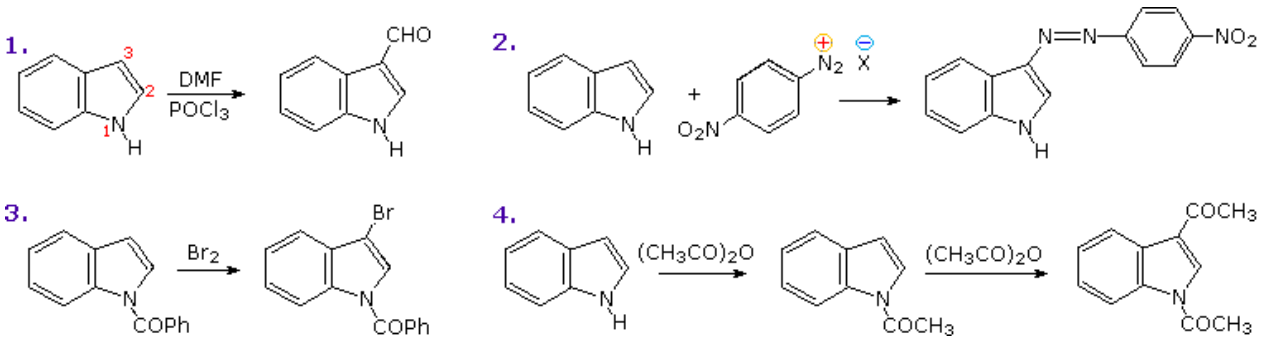
Another facet of heterocyclic chemistry was disclosed in the course of investigations concerning the action of thiamine (following diagram). As its pyrophosphate derivative, thiamine is a coenzyme for several biochemical reactions, notably decarboxylations of

pyruvic acid to acetaldehyde and acetoin. Early workers speculated that an "active aldehyde" or acyl carbanion species was an intermediate in these reactions. Many proposals were made, some involving the aminopyrimidine moiety, and others, ring-opened hydrolysis derivatives of the thiazole ring, but none were satisfactory. This puzzle was solved when R. Breslow (Columbia) found that the C-2 hydrogen of thiazolium salts was unexpectedly acidic (pK_a ca. 13), forming a relatively stable ylide conjugate base. As shown, this rationalizes the facile decarboxylation of thiazolium-2-carboxylic acids and deuterium exchange at C-2 in neutral heavy water.
Appropriate thiazolium salts catalyze the conversion of aldehydes to acyloins in much the same way that cyanide ion catalyzes the formation of benzoin from benzaldehyde, **the benzoin condensation**. By clicking on the diagram, a new display will show mechanisms for these two reactions. Note that in both cases an **acyl anion equivalent** is formed and then adds to a carbonyl function in the expected manner. The benzoin condensation is limited to aromatic aldehydes, but the use of thiazolium catalysts has proven broadly effective for aliphatic and aromatic aldehydes. This approach to acyloins employs milder conditions than the reduction of esters to enediol intermediates by the action of metallic sodium .





The most important condensed ring system related to these heterocycles is indole. Some electrophilic substitution reactions of indole are shown in the following diagram. Whether the indole nitrogen is substituted or not, the favored site of attack is C-3 of the heterocyclic ring. Bonding of the electrophile at that position permits stabilization of the onium-intermediate by the nitrogen without disruption of the benzene aromaticity.

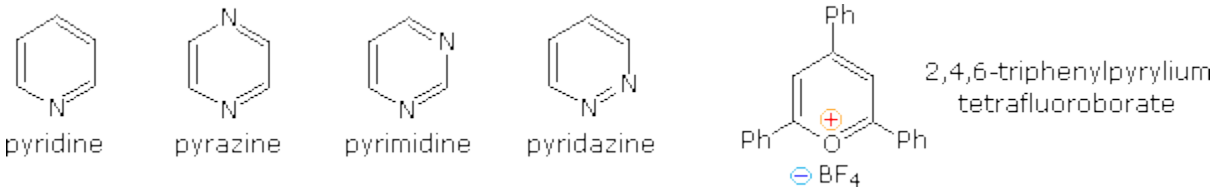


Six-Membered Rings

Properties

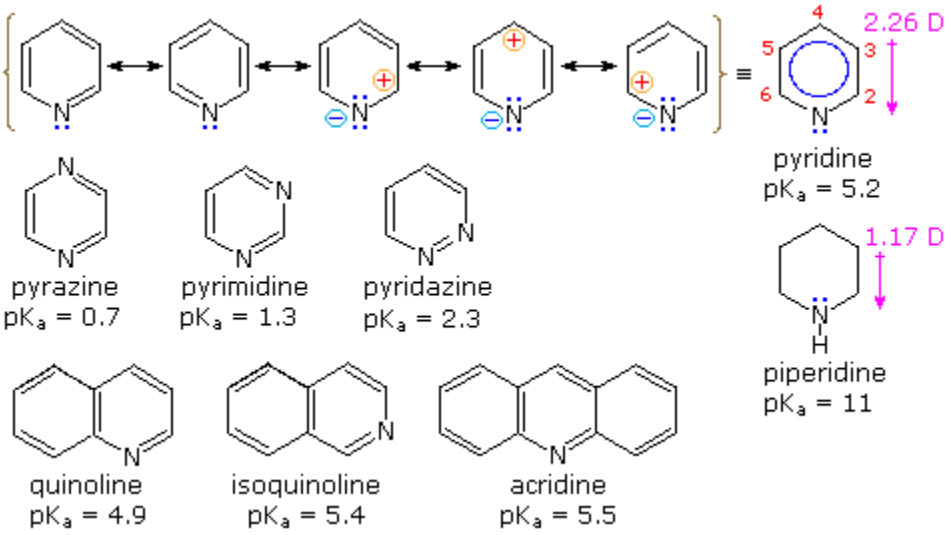
The chemical reactivity of the saturated members of this class of heterocycles: tetrahydropyran, thiane and piperidine, resemble that of acyclic ethers, sulfides, and 2º-amines, and will not be described here. 1,3-Dioxanes and dithianes are cyclic acetals and thioacetals. These units are commonly used as protective groups for aldehydes and ketones, as well as synthetic intermediates, and may be hydrolyzed by the action of aqueous acid. The reactivity of partially unsaturated compounds depends on the relationship of the double bond and the heteroatom (e.g. 3,4-dihydro-2H-pyran is an enol ether).

Fully unsaturated six-membered nitrogen heterocycles, such as pyridine, pyrazine, pyrimidine and pyridazine, have stable aromatic rings. Oxygen and sulfur analogs are necessarily positively charged, as in the case of 2,4,6-triphenylpyrylium tetrafluoroborate.



From heat of combustion measurements, the aromatic stabilization energy of pyridine is 21 kcal/mole. The resonance description drawn at the top of the following diagram includes charge separated structures not normally considered for benzene. The greater electronegativity of nitrogen (relative to carbon) suggests that such canonical forms may contribute to a significant degree. Indeed, the larger dipole moment of pyridine compared with piperidine supports this view. Pyridine and its derivatives are weak bases, reflecting the sp^2 hybridization of the nitrogen. From the polar canonical forms shown here, it should be apparent that electron donating substituents will increase the basicity of a pyridine, and that substituents on the 2 and 4-positions will influence this basicity more than an equivalent 3-substituent. The pK_a values given in the table illustrate a few of these substituent effects. Methyl substituted derivatives have the common names picoline (methyl pyridines), lutidine (dimethyl pyridines) and collidine (trimethyl pyridines). The influence of 2-substituents is

complex, consisting of steric hindrance and electrostatic components. 4-Dimethylaminopyridine is a useful catalyst for acylation reactions carried out in pyridine as a solvent. At first glance, the sp^3 hybridized nitrogen might appear to be the stronger base, but it should be remembered that N,N-dimethylaniline has a pK_a slightly lower than that of pyridine itself. Consequently, the sp^2 ring nitrogen is the site at which protonation occurs.



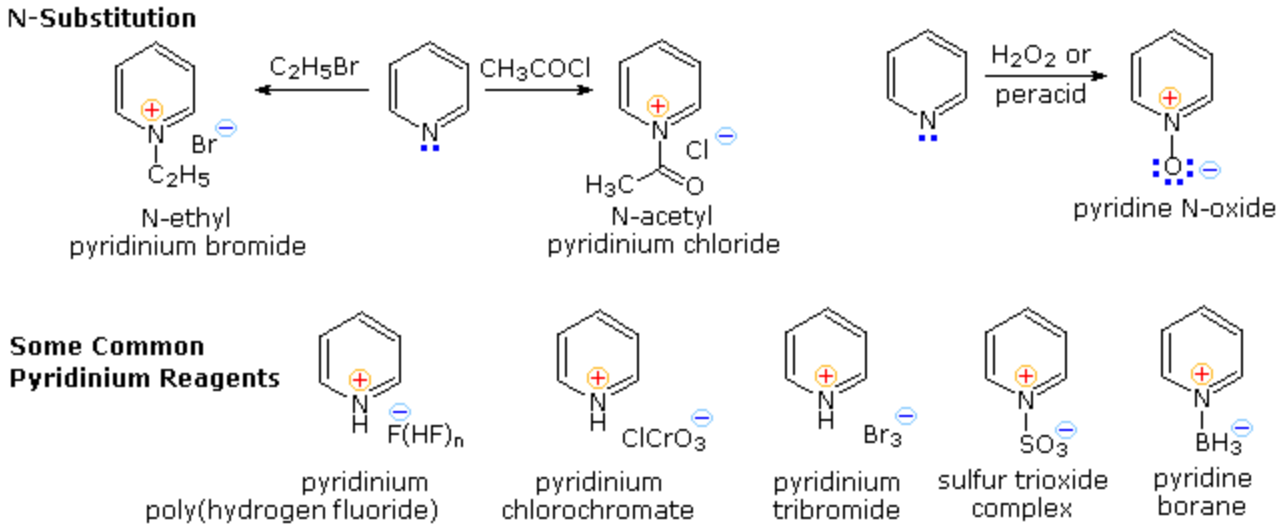
Pyridine Basicities

Substituent(s)	pK_a
4-methyl	6.0
3-methyl	5.7
2,6-dimethyl	6.7
2,4,6-trimethyl	7.5
2,6-di-*t*-butyl	3.6
3-methoxy	4.9
4-methoxy	6.5
4-dimethylamino	9.7
2-chloro	0.7
4-chloro	3.8
2,6-dichloro	−2.9

The diazines pyrazine, pyrimidine and pyridazine are all weaker bases than pyridine due to the inductive effect of the second nitrogen. However, the order of base strength is unexpected. A consideration of the polar contributors helps to explain the difference between pyrazine and pyrimidine, but the basicity of pyridazine seems anomalous. It has been suggested that electron pair repulsion involving the vicinal nitrogens destabilizes the neutral base relative to its conjugate acid.

Electrophilic Substitution of Pyridine

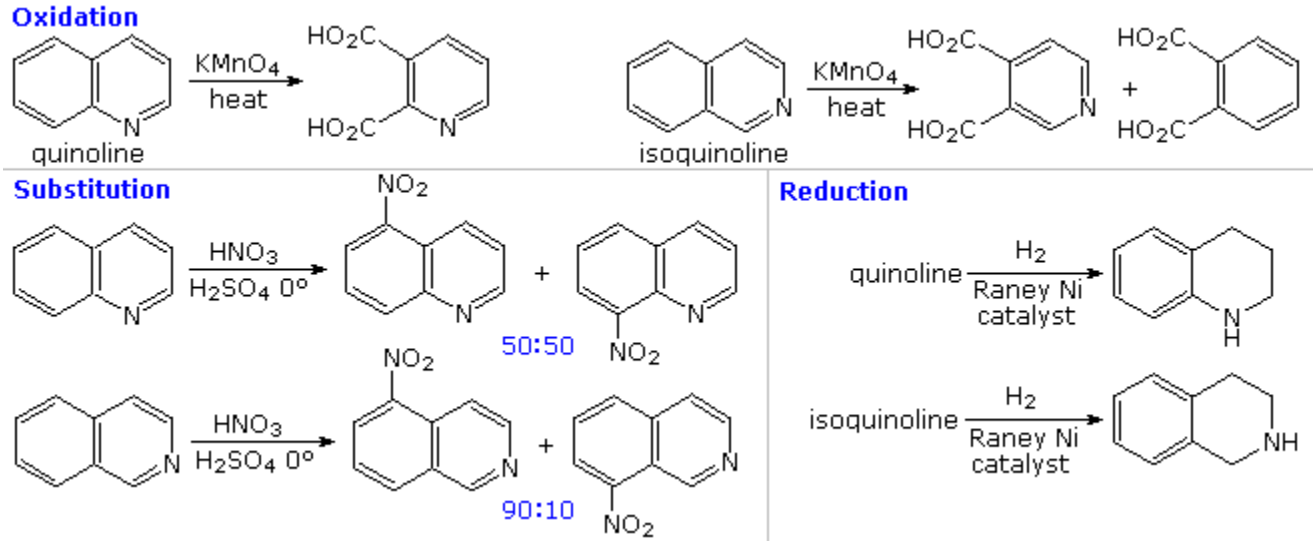
Pyridine is a modest base (pK_a=5.2). Since the basic unshared electron pair is not part of the aromatic sextet, as in pyrrole, pyridinium species produced by N-substitution retain the aromaticity of pyridine. As shown below, N-alkylation and N-acylation products may be prepared as stable crystalline solids in the absence of water or other reactive nucleophiles. The N-acyl salts may serve as acyl transfer agents for the preparation of esters and amides. Because of the stability of the pyridinium cation, it has been used as a moderating component in complexes with a number of reactive inorganic compounds. Several examples of these stable and easily handled reagents are shown at the bottom of the diagram. The poly(hydrogen fluoride) salt is a convenient source of HF for addition to alkenes and conversion of alcohols to alkyl fluorides, pyridinium chlorochromate (PCC) and its related dichromate analog are versatile oxidation agents and the tribromide salt is a convenient source of bromine. Similarly, the reactive compounds sulfur trioxide and diborane are conveniently and safely handled as pyridine complexes. Amine oxide derivatives of 3º-amines and pyridine are readily prepared by oxidation with peracids or peroxides, as shown by the upper right equation. Reduction back to the amine can usually be achieved by treatment with zinc (or other reactive metals) in dilute acid.



From the previous resonance description of pyridine, we expect this aromatic amine to undergo electrophilic substitution reactions far less easily than does benzene. Furthermore, as depicted above by clicking on the diagram, the electrophilic reagents and catalysts employed in these reactions coordinate with the nitrogen electron pair, exacerbating the positive charge at positions 2,4 & 6 of the pyridine ring. Three examples of the extreme conditions required for electrophilic substitution are shown on the left. Substituents that block electrophile coordination with nitrogen or reduce the basicity of the nitrogen facilitate substitution, as demonstrated by the examples in the blue-shaded box at the lower right, but substitution at C-3 remains dominant. Activating substituents at other locations also influence the ease and regioselectivity of substitution. By clicking on the diagram a second time, three examples will shown on the left. The amine substituent in the upper case directs the substitution to C-2, but the weaker electron donating methyl substituent in the middle example cannot overcome the tendency for 3-substitution. Hydroxyl substituents at C-2 and C-4 tautomerize to pyridones, as shown for the 2-isomer at the bottom left. Pyridine N-oxide undergoes some electrophilic substitutions at C-4 and others at C-3. The coordinate covalent N–O bond may exert a push-pull influence, as illustrated by the two examples on the right. Although the positively charged nitrogen alone would have a strong deactivating influence, the negatively charged oxygen can introduce electron density at C-2, C-4 & C-6 by π-bonding to the ring nitrogen. This is a controlling factor in the relatively facile nitration at C-4. However, if the oxygen is bonded to an electrophile such as SO_3, the resulting pyridinium ion will react sluggishly and preferentially at C-3.

The fused ring heterocycles quinoline and isoquinoline provide additional evidence for the stability of the pyridine ring. Vigorous permanganate oxidation of quinoline results in predominant attack on the benzene ring; isoquinoline yields products from cleavage of both rings. Note that naphthalene is oxidized to phthalic acid in a similar manner. By contrast, the heterocyclic ring in both compounds undergoes preferential catalytic hydrogenation to yield tetrahydroproducts. Electrophilic nitration, halogenation and sulfonation generally take place at C-5 and C-8 of the benzene ring, in agreement with the preceding description of similar

pyridine reactions and the kinetically favored substitution of naphthalene at C-1 (α) rather than C-2 (β).



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