

Six-Membered Heteroaromatic Rings (six-atom, six- π -electron aromatic heterocycles)

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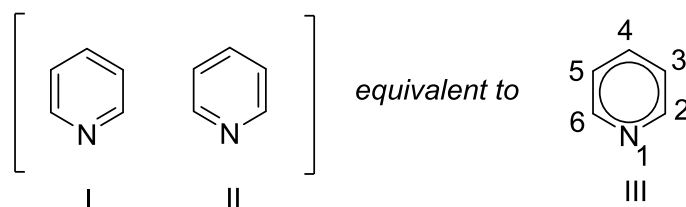
Reference Text Book:

- R.T. Morrison, R.N. Boyd and S.K. Bhattacharjee "Organic Chemistry" 7th ed. Pearson Education Inc. India (2011).

Structure of Pyridine

Of the six-membered aromatic heterocycles, we shall take up only one, pyridine. Pyridine is classified as aromatic on the basis of its properties. It is flat, with bond angles of 120° ; the four carbon-carbon bonds are of the same length, and so are the two carbon-nitrogen bonds. It resists addition and undergoes electrophilic substitution. Its heat of combustion indicates resonance energy 23 kcal/mole.

Pyridine can be considered a hybrid of the Kekule structures I and II. We shall represent it as structure III, in which the circle represents the aromatic sextet.



In electronic configuration, the nitrogen of pyridine is considerably different from the nitrogen of pyrrole. In pyridine the nitrogen atom, like each of the carbon atoms, is bonded to other members of the ring by the use of sp^2 orbitals, and provides one electron for the π cloud. The third sp^2 orbital of each carbon atom is used to form a bond to hydrogen; the third sp^2 orbital of nitrogen simply contains a pair of electrons, which are available for sharing with acids (Fig. 1). Because of this electronic configuration, the nitrogen atom makes pyridine a much stronger base than pyrrole, and affects the reactivity of the ring in a quite different way, as we shall see.

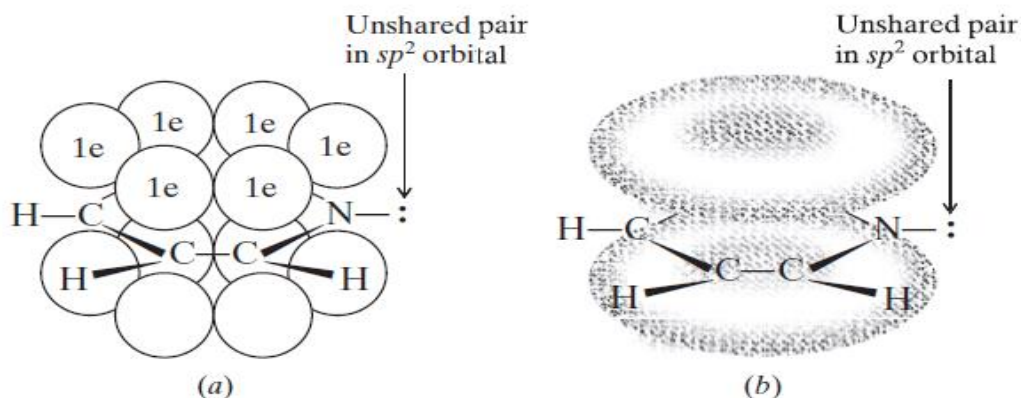
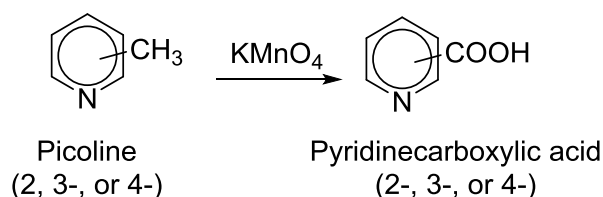


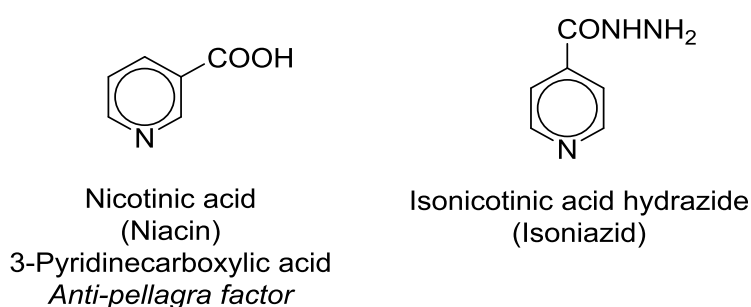
Figure 1 Pyridine molecule. (a) One electron in each p orbital; two electrons in an sp^2 orbital of nitrogen. (b) The p orbital overlap to form π clouds above and below the plane of the ring; two unshared electrons are still in an sp^2 orbital of nitrogen.

Source of pyridine compounds

Pyridine is found in coal tar. Along with it are found a number of methyl pyridines, the most important of which are the mono methyl compounds, known as picolines. Oxidation of the picolines yields the pyridine carboxylic acids.



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.



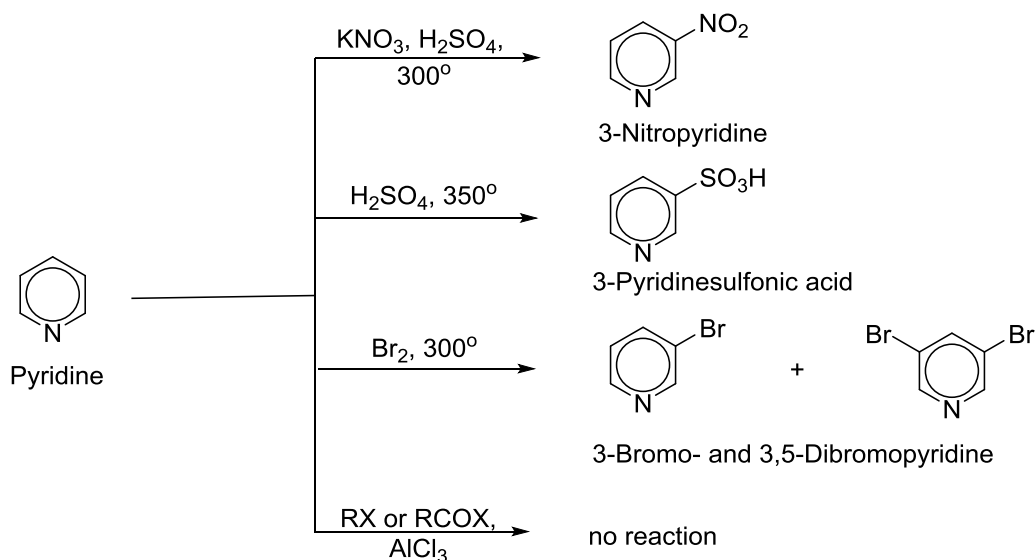
Reactions of pyridine

The chemical properties of pyridine are those we would expect on the basis of its structure. The ring undergoes the substitution, electrophilic and nucleophilic, typical of aromatic rings; our interest will lie chiefly in the way the nitrogen atom affects these reactions.

There is another set of reactions in which pyridine acts as a base or nucleophile; these reactions involve nitrogen directly and are due to its unshared pair of electrons.

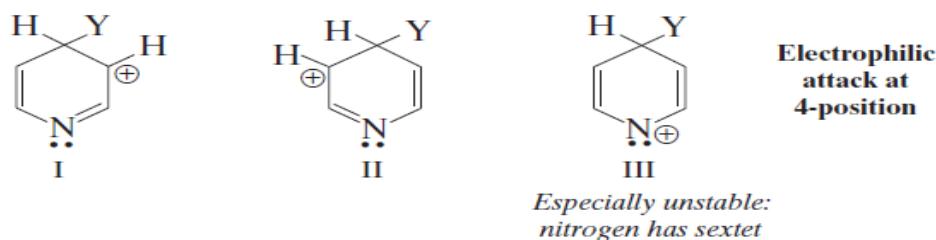
Electrophilic substitution in pyridine

Unlike benzene, pyridine undergoes electrophilic aromatic substitution reactions with difficulty. 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.

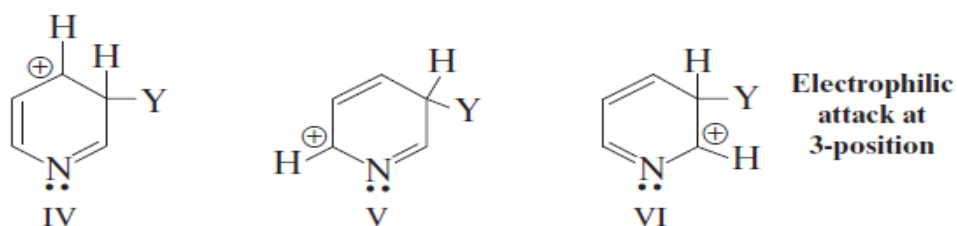


Let us see if we can account for the reactivity and orientation on our usual basis of stability of the intermediate carbocation.

Attack at the 4-position yields a carbocation that is a hybrid of structures I, II, and III.



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



(Attack at the 2-position resembles attack at the 4-position just as *ortho* attack resembles *para* attack in the benzene series.)

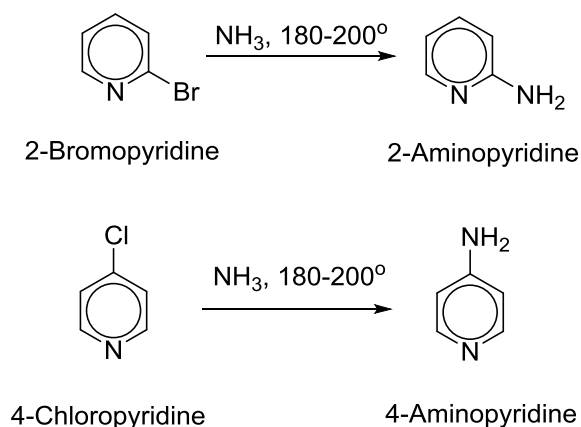
All these structures are less stable than the corresponding ones for attack on benzene, because of electron withdrawal by the nitrogen atom. As a result, pyridine undergoes substitution more slowly than benzene.

Of these structures, III is *especially* unstable, since in it the electronegative nitrogen atom has only a sextet of electrons. As a result, attack at the 4-position (or 2-position) is especially slow, and substitution occurs predominantly at the 3-position.

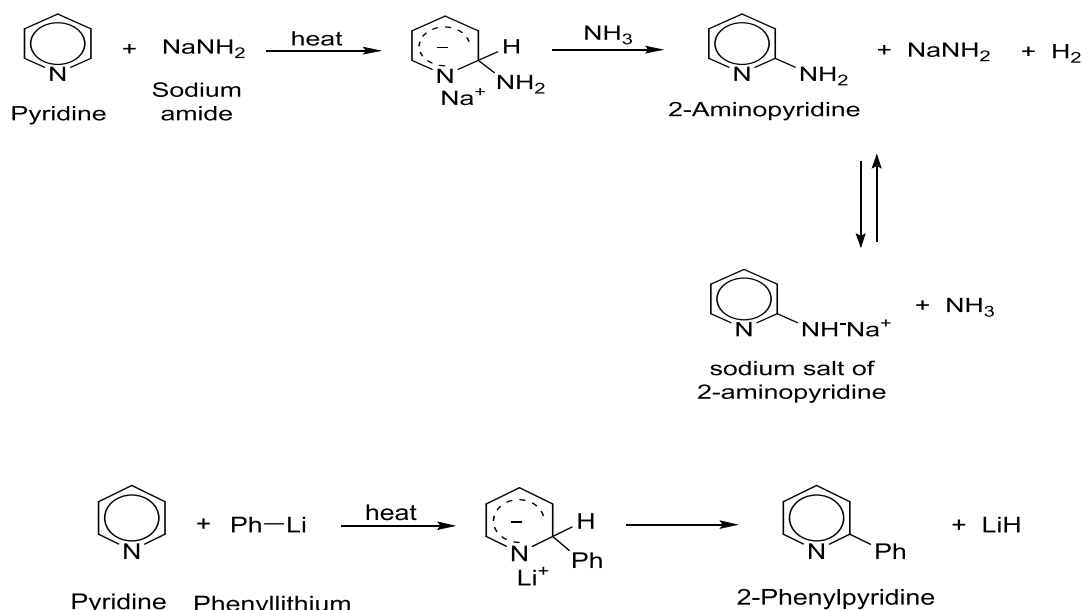
It is important to see the difference between substitution in pyridine and substitution in pyrrole. In the case of pyrrole, a structure in which nitrogen bears a positive charge is especially stable since every atom has an octet of electrons; nitrogen accommodates the positive charge simply by sharing four pairs of electrons. In the case of pyridine, a structure in which nitrogen bears a positive charge (III) is especially unstable since nitrogen has only a sextet of electrons; nitrogen *shares* electrons readily, but as an electronegative atom it resists the *removal* of electrons.

Nucleophilic Substitution in Pyridine

Here, as in electrophilic substitution, the pyridine ring resembles a benzene ring that contains strongly electron-withdrawing groups. Nucleophilic substitution takes place readily, particularly at the 2- and 4-positions. For example:

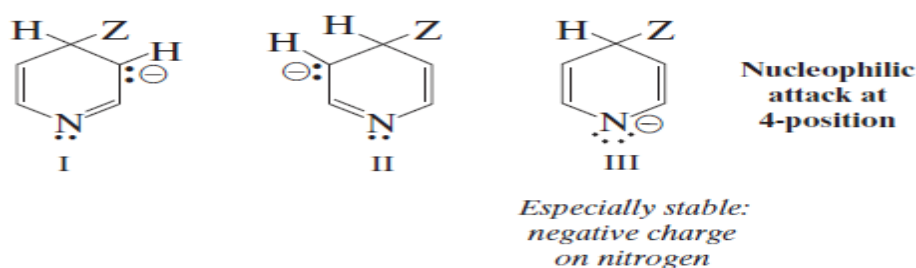


The reactivity of pyridine toward nucleophilic substitution is so great that even the powerfully basic hydride ion, H^- , can be displaced. Two important examples of this reaction are amination by sodium amide (**Chichibabin reaction**), and alkylation or arylation by organolithium compounds.

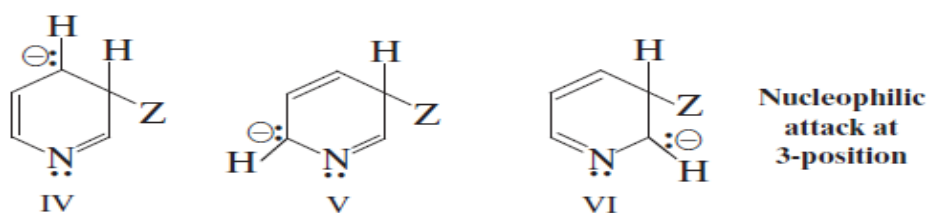


As we have seen, nucleophilic aromatic substitution can take place by a mechanism that is quite analogous to the mechanism for electrophilic substitution. Reaction proceeds by two steps; the rate of the first step, formation of a charged particle, determines the rate of the overall reaction. In electrophilic substitution, the intermediate is positively charged; in nucleophilic substitution, the intermediate is negatively charged. The ability of the ring to accommodate the charge determines the stability of the intermediate and of the transition state leading to it, and hence determines the rate of the reaction.

Nucleophilic attack at the 4-position yields a carbanion that is a hybrid of structures I, II, and III:



Attack at the 3-position yields a carbanion that is a hybrid of structures IV, V, and VI:

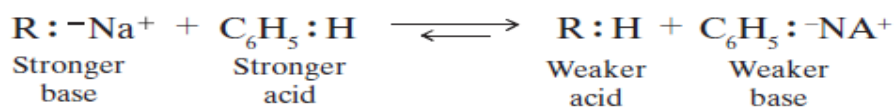


(As before, attack at the 2-position resembles attack at the 4-position.)

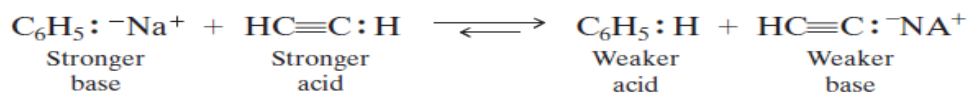
All these structures are more stable than the corresponding ones for attack on a benzene derivative, because of electron withdrawal by the nitrogen atom. Structure III is *especially* stable, since the negative charge is located on the atom that can best accommodate it, the electronegative nitrogen atom. It is reasonable, therefore, that nucleophilic substitution occurs more rapidly on the pyridine ring than on the benzene ring, and more rapidly at the 2- and 4-positions than at the 3-position. The same electronegativity of nitrogen that makes pyridine unreactive toward electrophilic substitution makes pyridine highly reactive toward nucleophilic substitution.

Basicity of pyridine

- Pyridine is a base with $K_b = 2.3 \times 10^{-9}$. It is thus much stronger than pyrrole ($K_b = 2.5 \times 10^{-14}$) but much weaker than aliphatic amines ($K_b = 10^{-4}$).
- Pyridine has a pair of electrons (in an sp^2 orbital) that is available for sharing with acids; pyrrole has not, and can accept an acid only at the expense of the aromatic character of the ring.
- The fact that pyridine is a weaker base than aliphatic amines is more difficult to account for, but at least it fits into a pattern. Let us turn for a moment to the basicity of the carbon analogs of amines, the carbanions.
- Benzene is a stronger acid than an alkane, as shown by its ability to displace an alkane from its salts; this, of course, means that the phenyl anion, C_6H_5^- , is a weaker base than an alkyl anion, R^- .

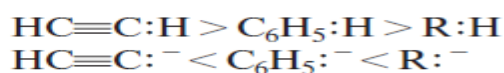


In the same way, acetylene is a stronger acid than benzene, and the acetylide ion is a weaker base than the phenyl anion.



Thus we have the following sequences of acidity of hydrocarbons and basicity of their anions:

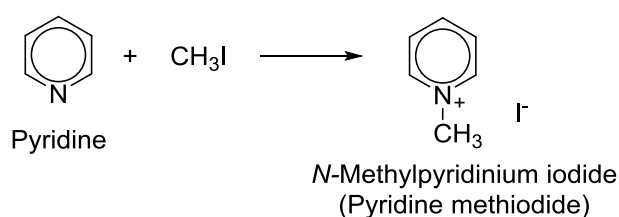
Acidity
Basicity



A possible explanation for these sequences can be found in the electronic configuration of the carbanions. In the alkyl, phenyl, and acetylide anions, the unshared pair of electrons occupies respectively an sp^3 , an sp^2 , and an sp orbital.

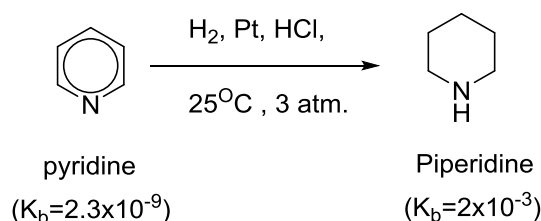
The availability of this pair for sharing with acids determines the basicity of the particular anion. As we proceed along the series sp^3 , sp^2 , sp , the p character of the orbital decreases and the s character increases.

- Now, an electron in a p orbital is at some distance from the nucleus and is held relatively loosely; an electron in an s orbital, on the other hand, is close to the nucleus and is held more tightly.
- Of the three anions, the alkyl ion is the strongest base since its pair of electrons is held most loosely, in an sp^3 orbital. The acetylide ion is the weakest base since its pair of electrons is held most tightly, in an sp orbital.
- Pyridine bears the same relationship to an aliphatic amine as the phenyl anion bears to an alkyl anion. The pair of electrons that gives pyridine its basicity occupies an sp^2 orbital; it is held more tightly and is less available for sharing with acids than the pair of electrons of an aliphatic amine, which occupies an sp^3 orbital.
- Pyridine is widely used in organic chemistry as a water-soluble base, as, for example, in the Schotten–Baumann acylation procedure.
- Like other amines, pyridine has nucleophilic properties, and reacts with alkyl halides to form quaternary ammonium salts.



Reduction of pyridine

Catalytic hydrogenation of pyridine yields the aliphatic heterocyclic compound **piperidine**. $C_5H_{11}N$.



Piperidine ($K_b = 2 \times 10^{-3}$) has the usual basicity of a secondary aliphatic amine, a million times greater than that of pyridine; again, clearly, a fundamental change in structure has taken place (see Fig. 2). Like pyridine, piperidine is often used as a basic catalyst in such reactions as the Michael addition.

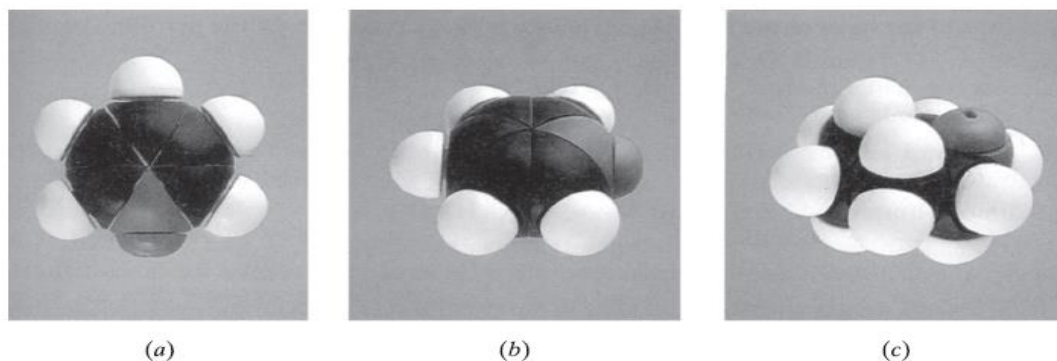
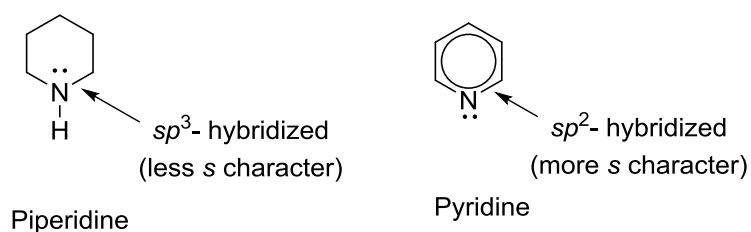


Figure 2 Electronic configuration and molecular shape: (a) and (b) pyridine, aromatic; (c) piperidine, aliphatic. Here again we see the contrast between aromatic and aliphatic structures reflected in a contrast in molecular shape. Pyridine has the shape of benzene with an unshared pair of electrons taking the place of one hydrogen. Piperidine has the familiar shape of chair cyclohexane with an unshared pair occupying an equatorial—or, in another conformation, an axial—position.



Like the pyrrolidine ring, the piperidine and pyridine rings are found in a number of alkaloids, including *nicotine*, *strychnine*, *cocaine*, and *reserpine*.

