

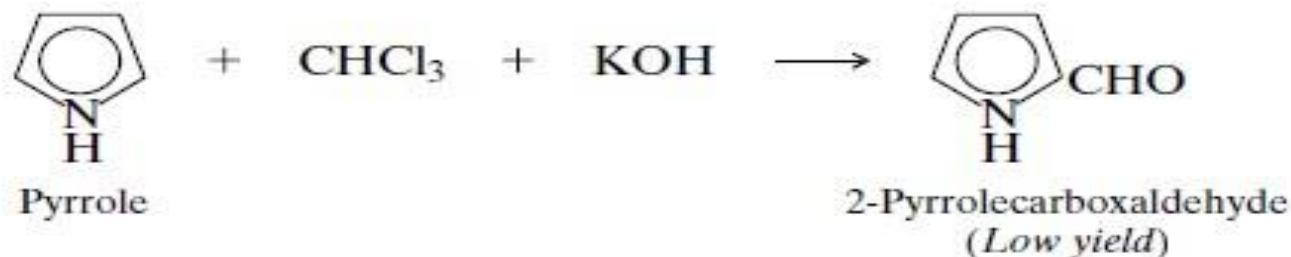
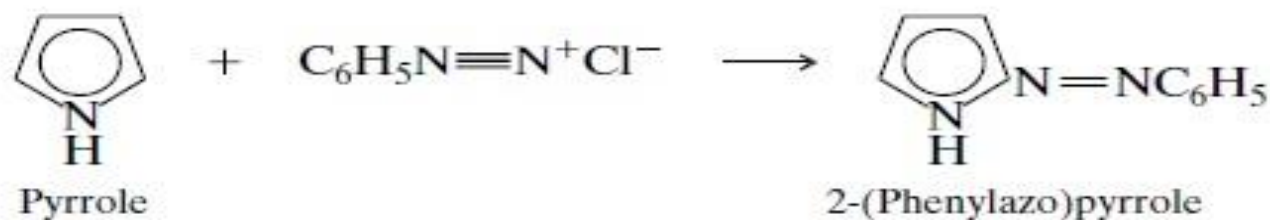
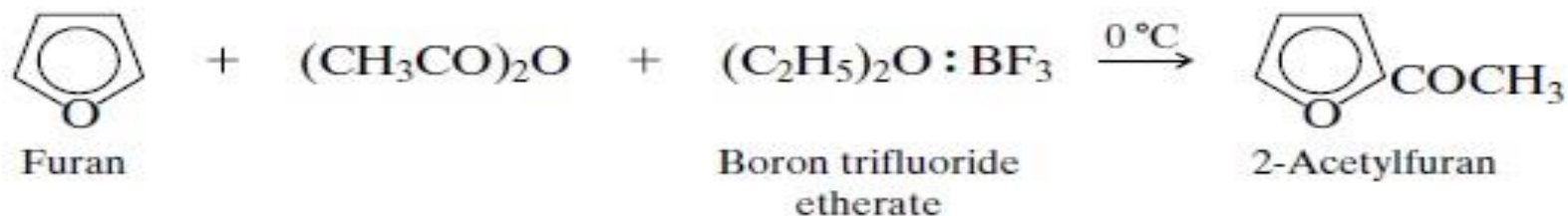
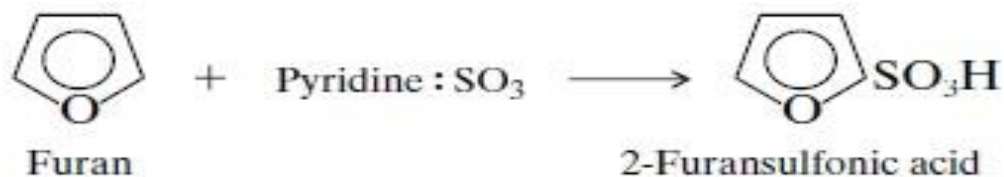
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**Electrophilic substitution in pyrrole, furan, and thiophene.
Reactivity and orientation**

lec.Doctor yahya saad yaseen

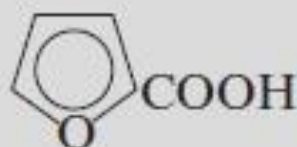
Electrophilic substitution in pyrrole, furan, and thiophene. Reactivity and orientation

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:



In some of the examples we notice modifications in the usual electrophilic reagents. The high reactivity of these rings makes it cases, as, for example, the weak Lewis acid stannic chloride in the Friedel-Crafts acylation of thiophene. The sensitivity to protic acids of furan (which undergoes ring opening) and pyrrole (which undergoes polymerization) makes it necessary to modify the usual sulfonating agent. Possible to use milder reagents in many

Problem 16.3 Furan undergoes ring opening upon treatment with sulfuric acid; it reacts almost explosively with halogens. Account for the fact that 2-furoic acid, however, can be sulfonated (in the 5-position) by treatment with fuming sulfuric acid, and brominated (in the 5-position) by treatment with bromine at 100°C.

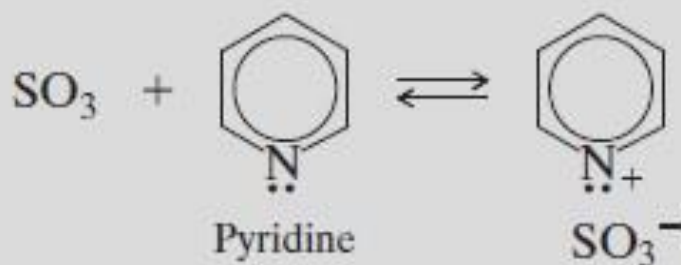


2-Furoic acid

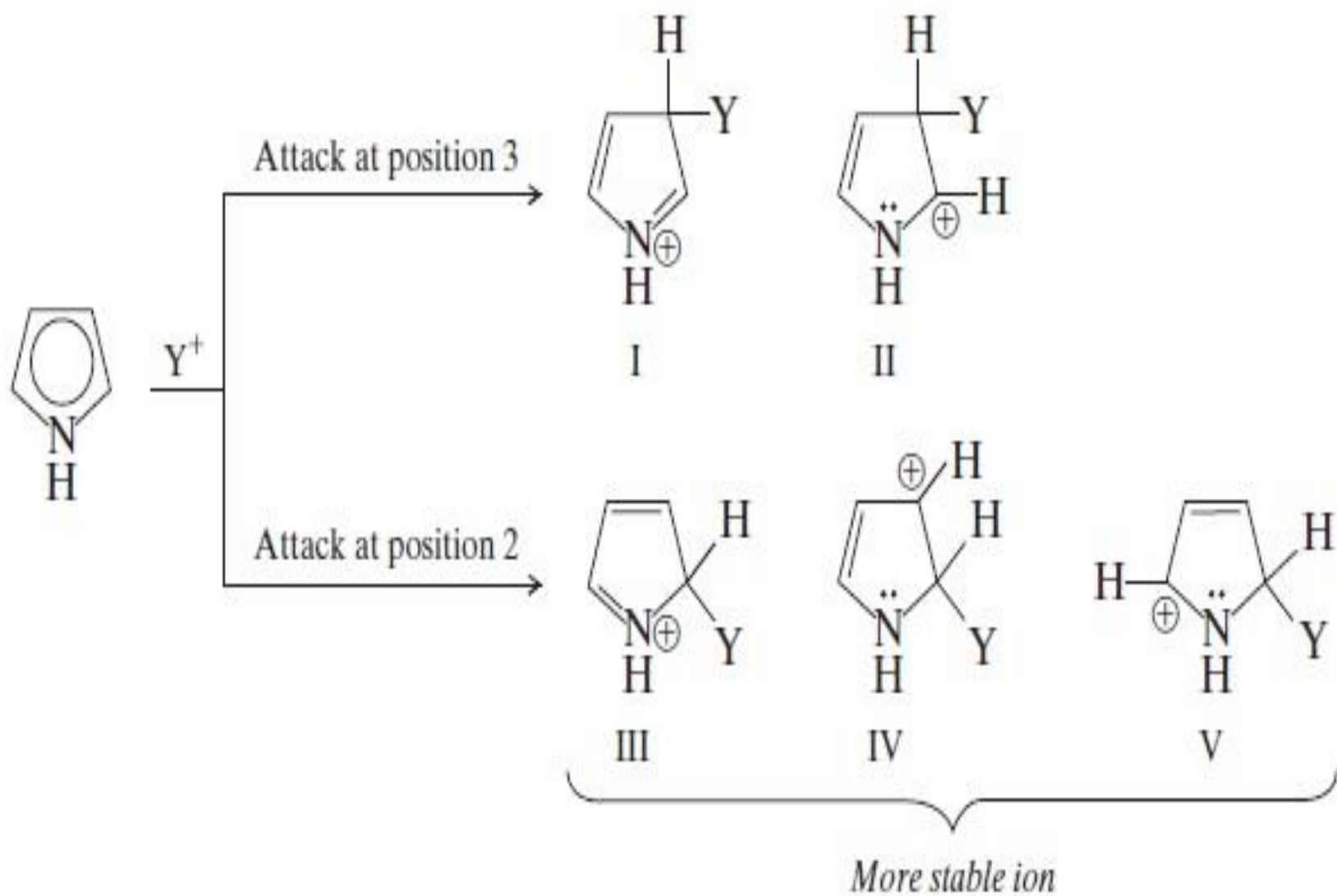
Problem 16.4 Upon treatment with formaldehyde and acid, ethyl 2,4-dimethyl-3-pyrrolecarboxylate is converted into a compound of formula $C_{19}H_{26}O_4N_2$. What is the most likely structure for this product? How is it formed?

Problem 16.5 Predict the products from the treatment of furfural (2-furancarboxaldehyde) with concentrated aqueous NaOH.

Problem 16.6 Sulfur trioxide dissolves in the tertiary amine pyridine to form a salt. Show all steps in the most likely mechanism for the sulfonation of an aromatic compound by this reagent.



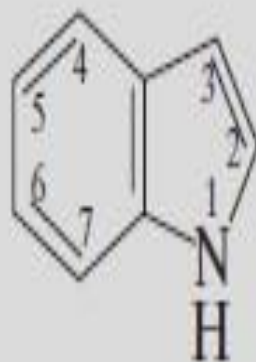
Study of electrophilic aromatic substitution, we found that we account for orientation on the following basis: the σ complex of the electrophilic reagent controlling step is the attachment yield to the aromatic ring, which takes place in such a way as the most stable intermediate carbocation. Let us apply this approach to the reactions of pyrrole.



Attack at position 3 yields a carbocation that is a hybrid of structures I and II. Attack at position 2 yields a carbocation that is a hybrid not only of structures III and IV (analogous to I and II) but also of structure V; the extra stabilization conferred by V makes this ion the more stable one.((((attack at position 2 is faster because the developing positive charge is accommodated by *three* atoms of the ring instead of by only two.))))))

Pyrrole is highly reactive, compared with benzene,???? because of contribution from the relatively stable structure III. (((In III every atom has an octet of electrons; nitrogen accommodates the positive charge simply by *sharing* four pairs of electrons)))). It is no accident that pyrrole resembles aniline in reactivity: both owe their high reactivity to the ability of nitrogen to share four pairs of electrons. Orientation of substitution in furan and thiophene, as well as their high reactivity, can be accounted for in a similar way.

Problem 16.7 The heterocycle *indole*, commonly represented as formula VI, is found in coal tar and in orange blossoms.



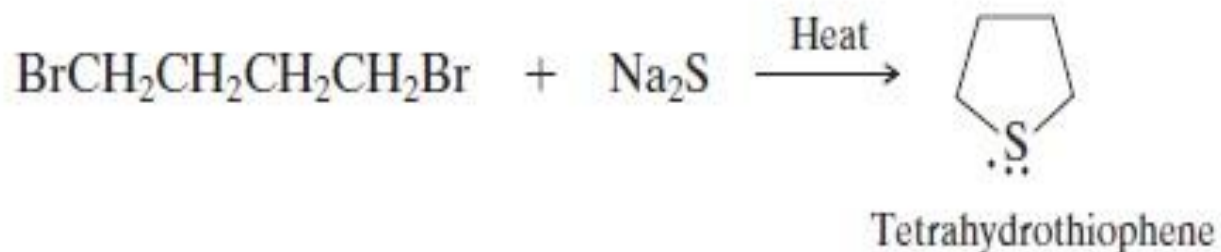
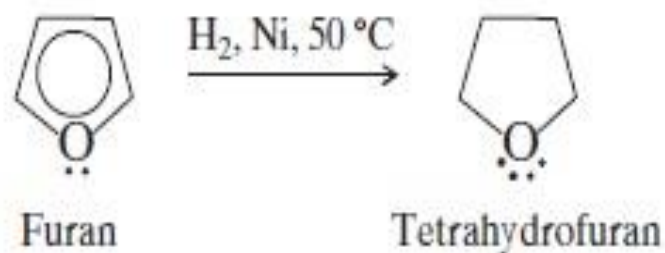
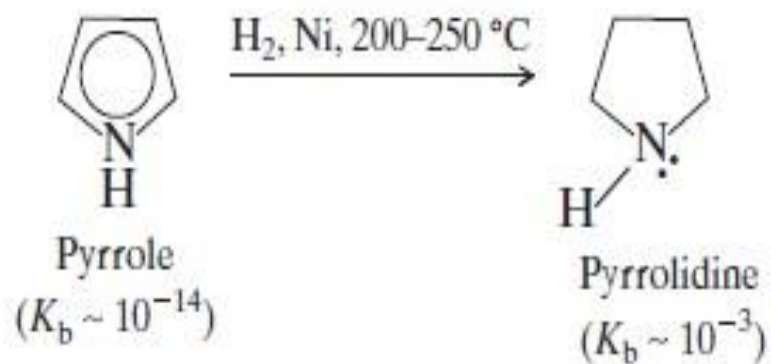
VI
Indole

It undergoes electrophilic substitution, chiefly at position 3. Account (a) for the aromatic properties of indole, and (b) for the orientation in electrophilic substitution.

NONAROMATIC HETEROCYCLES

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.

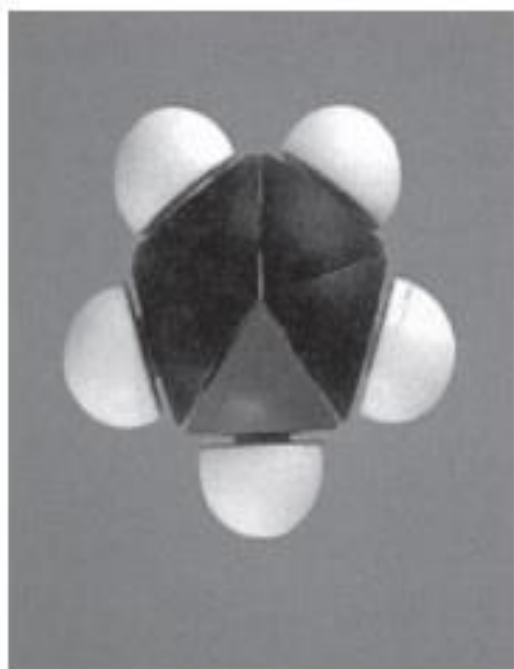


Saturation of these rings destroys the aromatic structure and, with it, the aromatic properties. The properties of a secondary aliphatic amine, an aliphatic ether, or an aliphatic sulfide. With nitrogen's extra pair of electrons now available for sharing

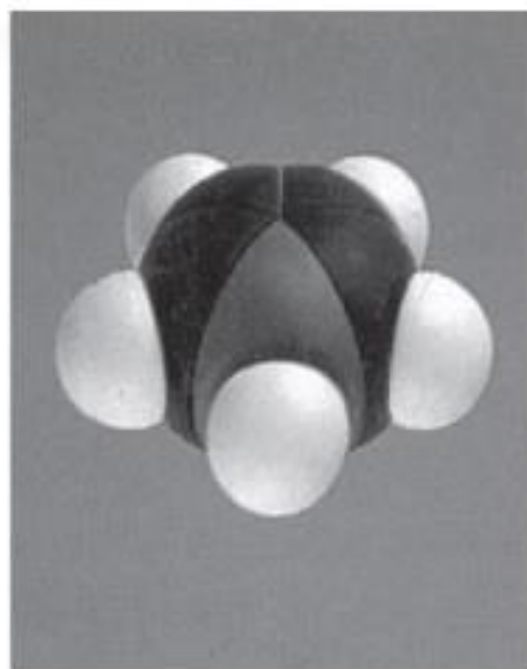
with acids, pyrrolidine ($K_b \sim 10^{-3}$) has the normal basicity of an aliphatic amine.

Hydrogenation of pyrrole increases the base strength by a factor of 10^{11} (100 billion);

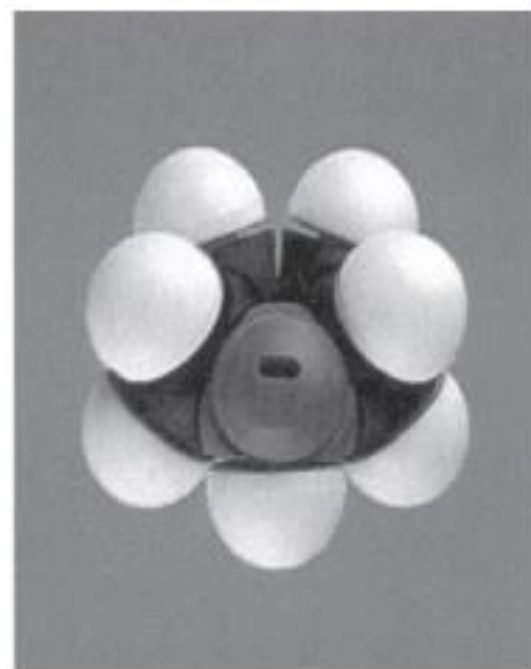
clearly a fundamental change in structure has taken place. (See Fig. 16.2.)



(a)



(b)



(c)

Figure 16.2 Electronic configuration and molecular shape: (a) and (b) pyrrole, aromatic; (c) pyrrolidine, aliphatic.

The fundamental difference in structure is reflected by the striking difference in shape between the two molecules. As we see, pyrrole has the characteristic aromatic shape: flat, like benzene—or, closer yet, like the cyclopentadienyl anion, with which it is isoelectronic. Pyrrolidine, on the other hand, is clearly aliphatic, and closely resembles cyclopentane, with an unshared pair of electrons taking the place of one hydrogen atom.

Tetrahydrofuran is an important solvent, used, for example, in reductions with lithium aluminum hydride, in the preparation of arylmagnesium chlorides, and in hydroborations. Oxidation of tetrahydrothiophene yields *tetramethylene sulfone* (or *sulfolane*), also used as an aprotic solvent.



Tetramethylene sulfone
(Sulfolane)

We have encountered pyrrolidine as a secondary amine commonly used in making enamines. The pyrrolidine ring occurs naturally in a number of alkaloids, providing the basicity that gives these compounds their name (*alkali-like*).

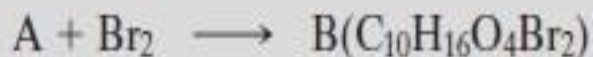
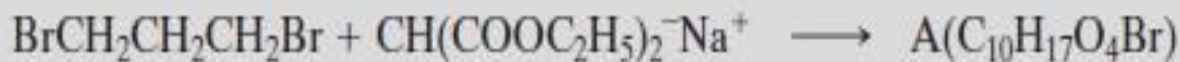
Problem 16.9 Predict the products of the treatment of pyrrolidine with:

- (a) aqueous HCl
- (b) aqueous NaOH
- (c) acetic anhydride
- (d) benzenesulfonyl chloride + aqueous NaOH
- (e) methyl iodide, followed by aqueous NaOH
- (f) repeated treatment with methyl iodide, followed by Ag_2O and then strong heating

Problem 16.10 The alkaloid *hygrine* is found in the coca plant. Suggest a structure for it on the basis of the following evidence:

Hygrine ($\text{C}_8\text{H}_{15}\text{ON}$) is insoluble in aqueous NaOH but soluble in aqueous HCl. It does not react with benzenesulfonyl chloride. It reacts with phenylhydrazine to yield a phenylhydrazone. It reacts with NaOI to yield a yellow precipitate and a carboxylic acid ($\text{C}_7\text{H}_{13}\text{O}_2\text{N}$). Vigorous oxidation by CrO_3 converts hygrine into *hygrinic acid* ($\text{C}_6\text{H}_{11}\text{O}_2\text{N}$).

Hygrinic acid can be synthesized as follows:



**"THANK YOU"
IN JAPANESE**

