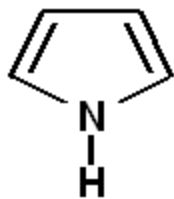


Five-membered Heterocycles

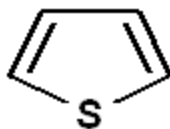
Pyrrole, Furan and Thiophene

Five Membered Heterocycles-Introduction

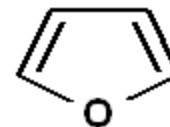
- ❖ The main reason for the study of pyrrole came from the work on the structure of haem; the blood respiratory pigment, and the chlorophyll; the green photosynthetic pigment of plants.
- ❖ Thiophen occur in plants in association with polyacetylenes with which they are biogenetically closely linked.
- ❖ Furan occurs widely in secondary plant metabolites, especially in terpenoids.
- ❖ Unsubstituted pyrrole, furan, and thiophene are usually obtained from petroleum



Pyrrole

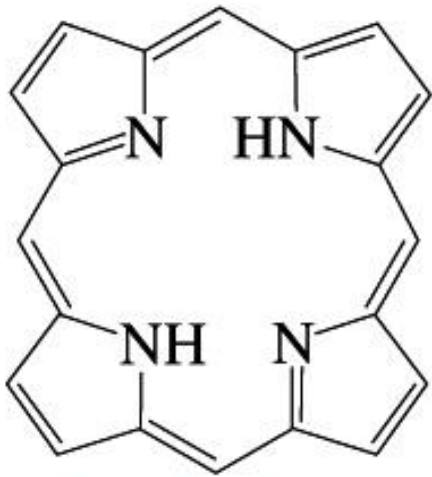


Thiophene

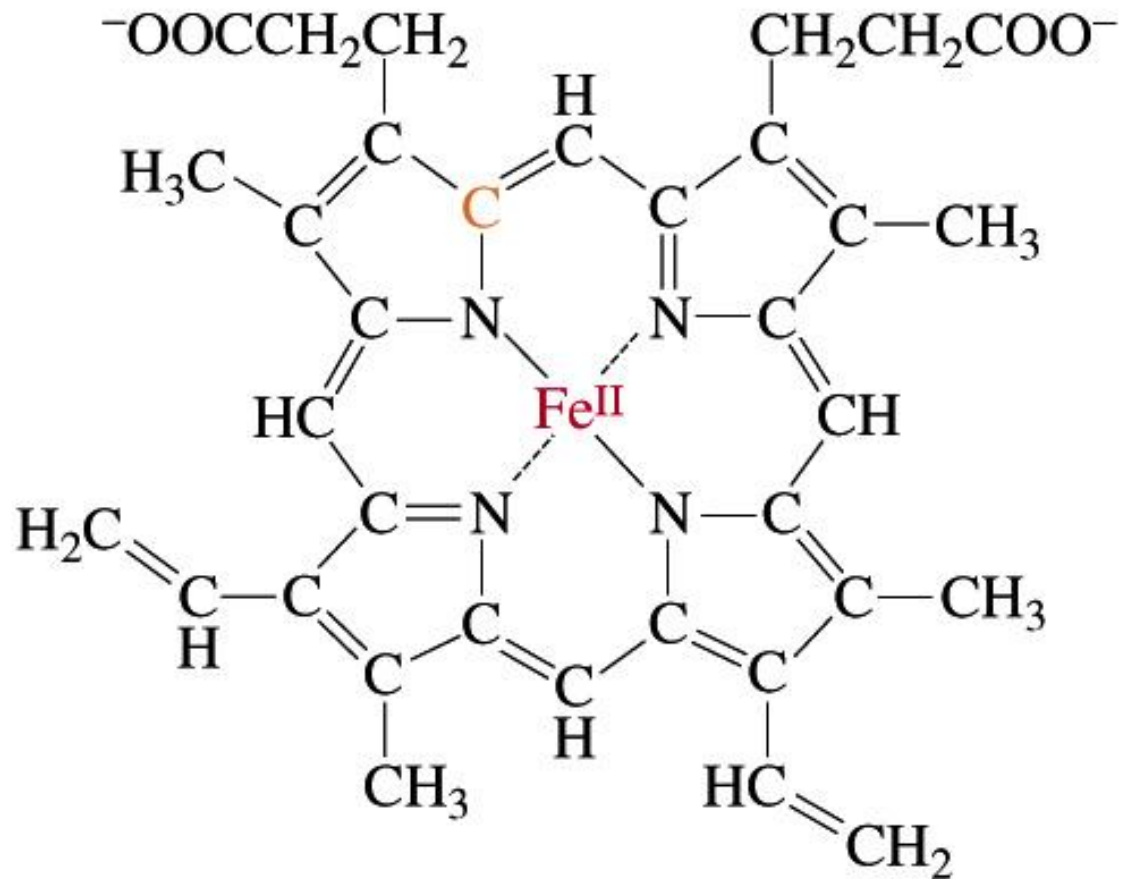


Furan

Porphyrin



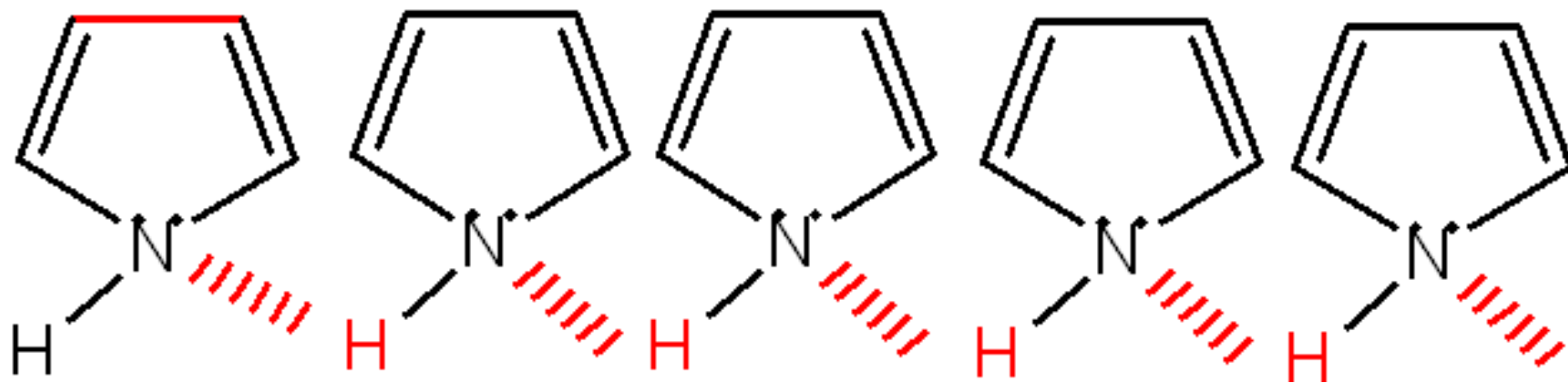
a porphyrin ring system



iron protoporphyrin IX
heme

General Characteristics

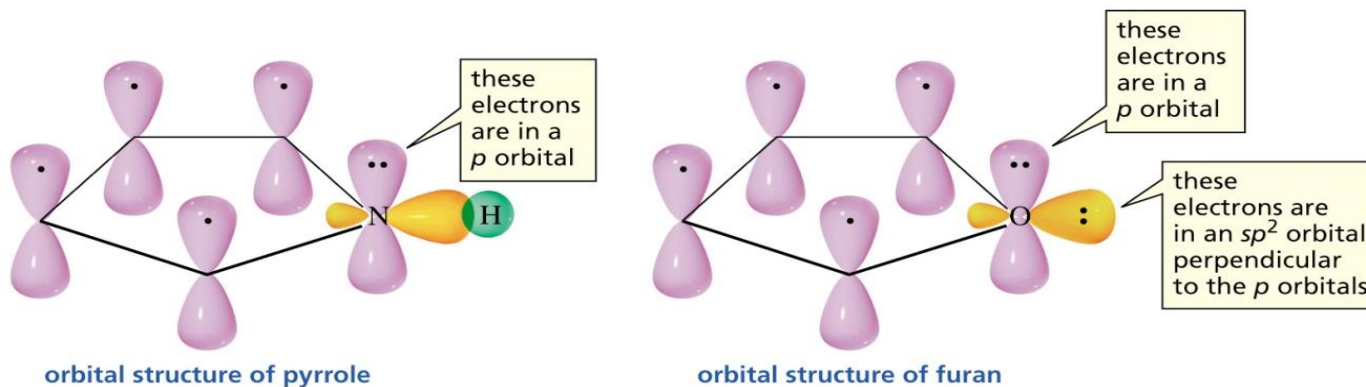
- ❖ Pyrrole, furan and thiophene are colorless liquids of boiling points 126° , 32° , and 84° respectively.
- ❖ **Pyrrole** has a relatively **high boiling point** as compared to furan and thiophene, this is due to the presence of intermolecular hydrogen bonding in pyrrole.



Structure and Aromaticity

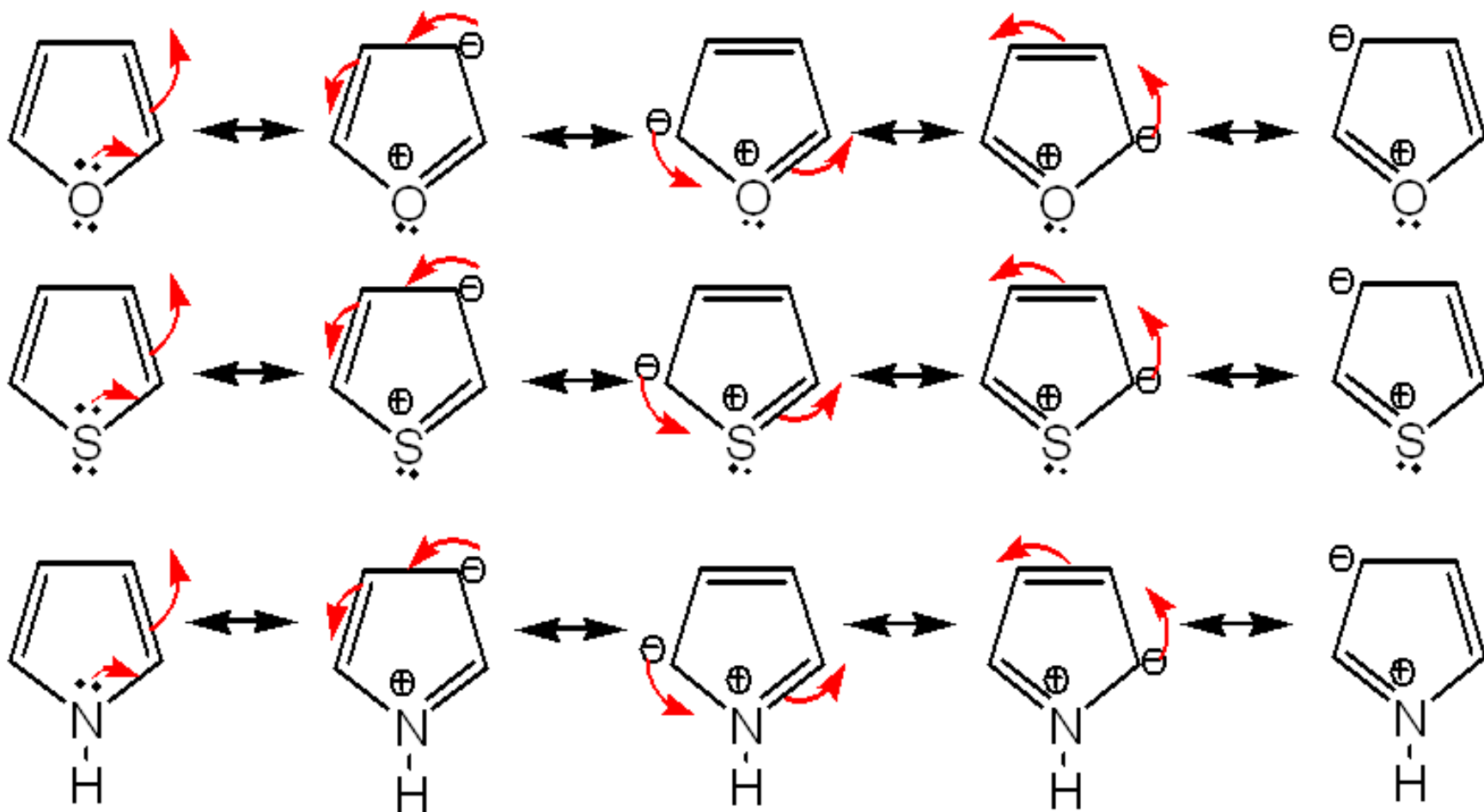
Pyrrole, furan and thiophene are aromatic because:

1) they fulfill the criteria for aromaticity, the extent of delocalization of the nonbonding electron pair is decisive for the aromaticity, thus the grading of aromaticity is in the order of: furan < pyrrole < thiophene < benzene this order is consistent with the order of electronegativity values for oxygen (3.44), nitrogen (3.04) and thiophene (2.56).



Evidences of aromatic character in pyrrole

- 2) They tend to react by electrophilic substitution due appearance of -ve charge on carbon atoms due to delocalization as shown in the following resonance structures

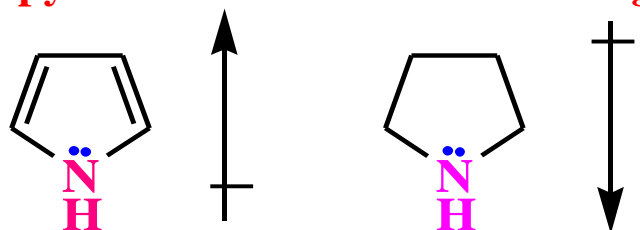


Evidences of aromatic character in pyrrole

- 1) All ring bonds are intermediates between single and double bonds.
- 2) It tends to react by electrophilic substitution
- 3) Its exceptional **lack of basicity** and **strong acidity** as a secondary amine compared to the aliphatic analog (pyrrolidine). This can be explained on the basis of participation of N lone pair in aromatic sextet (see the previous resonance structures) thus the dipole moment of

pyrrole compared with pyrrolidine is reverted and thus protonation occurs at carbons not at N

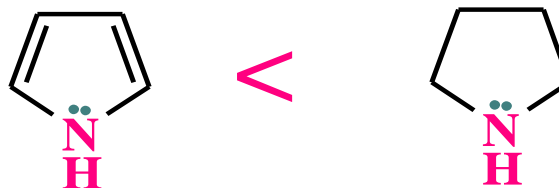
Dipole moment of pyrrole and its saturated analog



Pyrrole

Pyrrolidine

Basicity of pyrrole and its saturated analog



Pyrrole
aromatic 2° amine

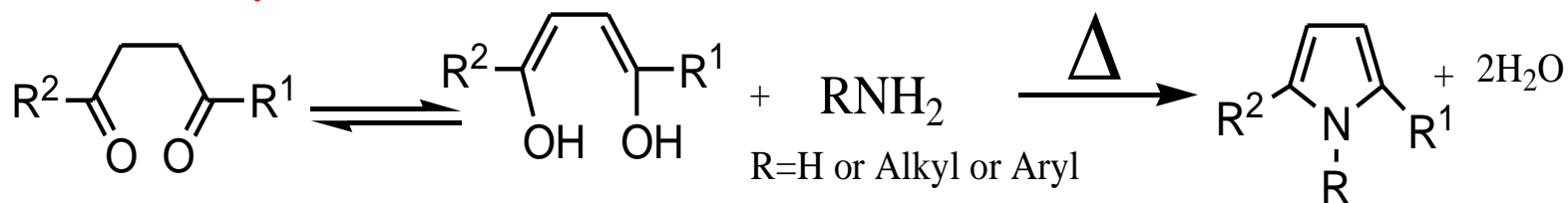
Pyrrolidine
Aliphatic 2° amine

Synthesis of Pyrrole

1) From 1,4-dicarbonyl compounds (Paal-Knorr Synthesis)

- Generally Substituted pyrrole may be synthesized through the cyclization of 1,4-diketones in combination with ammonia (NH_3) or amines, The ring-closure is proceeded by dehydration (condensation), which then yields the two double bonds and thus the aromatic π system. The formation of the energetically favored aromatic system is one of the driving forces of the reaction.

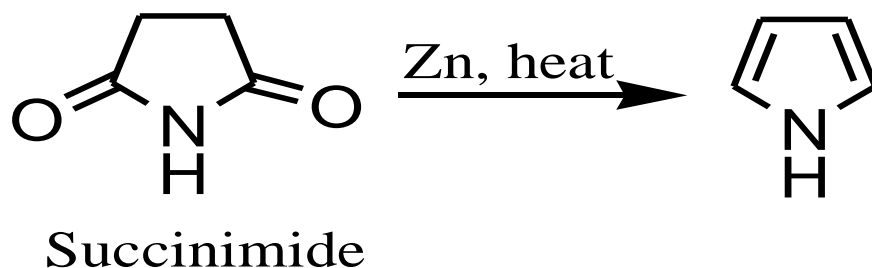
Paal-Knorr Synthesis



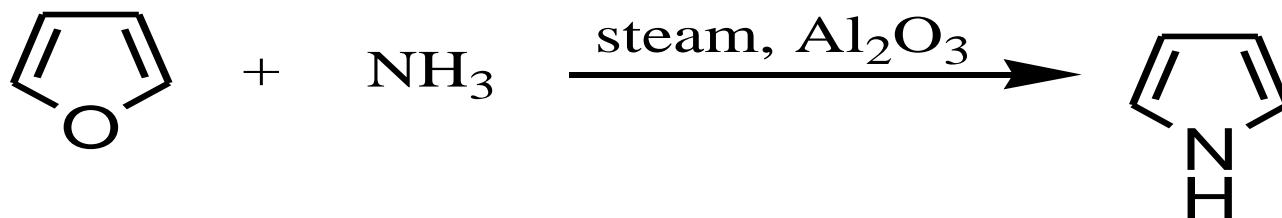
1,4-Dicarbonyl compound

Synthesis of Pyrrole

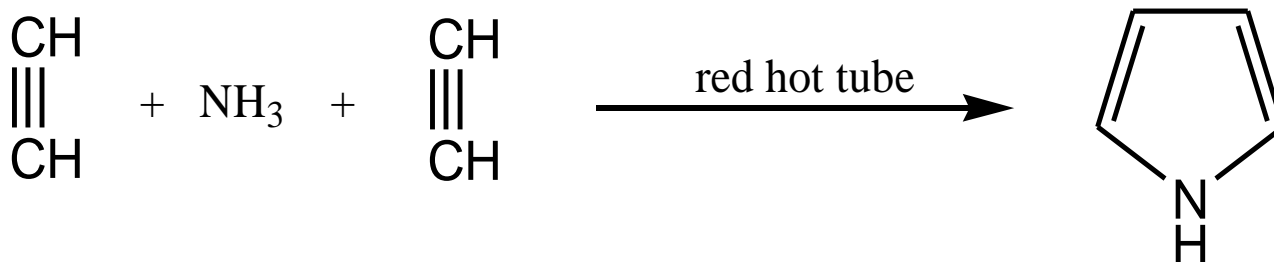
2) Pyrrole is obtained by distillation of succinimide over zinc dust.



3) By heating a mixture of furan, ammonia and steam over alumina catalyst



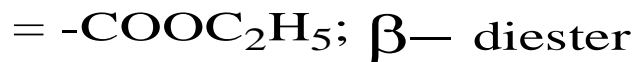
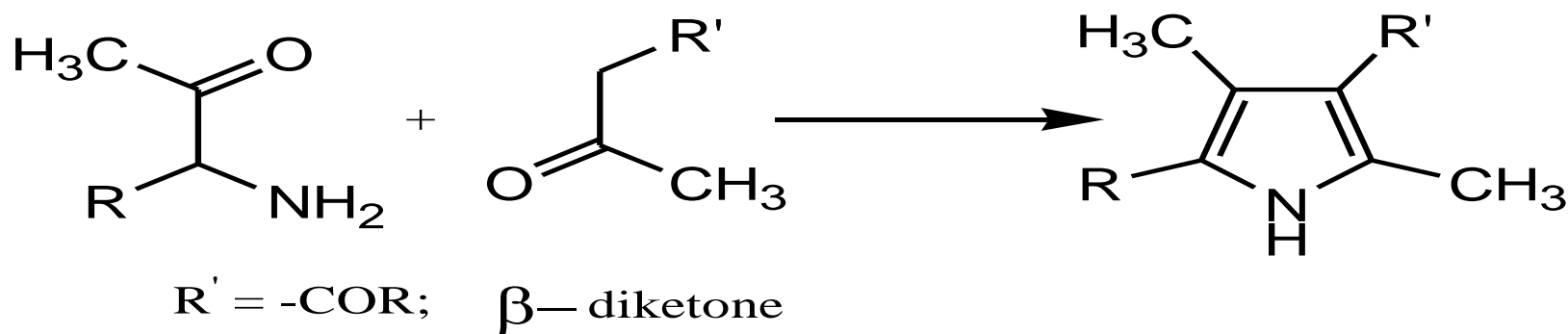
4) By passing a mixture of acetylene and ammonia over red hot tube.



Synthesis of Pyrrole

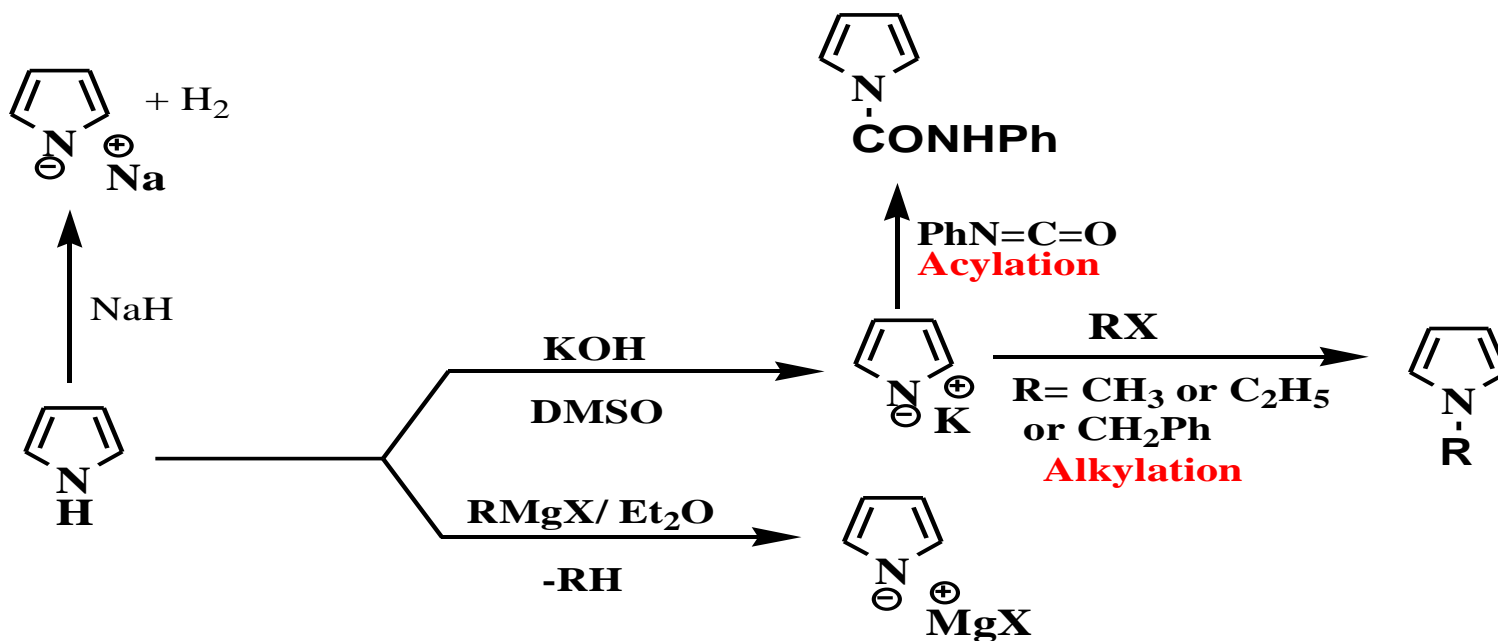
5) Knorr-pyrrole synthesis:

This involves the condensation of α -amino ketones with a β -diketone or a β -ketoester to give a substituted pyrrole.



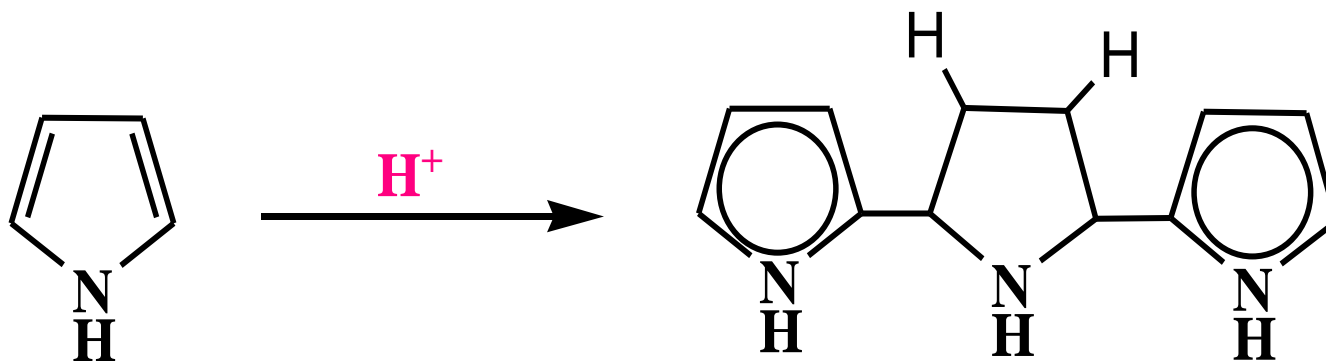
Acidic properties of pyrrole

❖ Due to participation of N lone pair in aromaticity), **pyrrole** has **exceptionally strong acidic properties** for a secondary amine for instance it can react with strong bases or Grignard reagent or potassium metal in inert solvents, and with sodium amide in liquid ammonia, to give salt-like compounds which can be used to alkylate or acylate the nitrogen atom as shown below:



Sensitivity of pyrrole to acids

- ❖ Pyrrole is sensitive to strong acids.
- ❖ This is due to protonation occurs at one of C-3 and the resulting protonated molecule will add to another unprotonated pyrrole molecule this continues to give pyrrole trimer.
- ❖ This reaction is considered as electrophilic addition to pyrrole



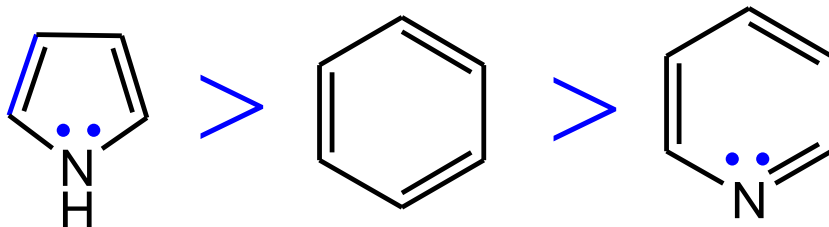
pyrrole trimer

Pyrrole is unstable in strongly acid solution because the protonated pyrrole polymerizes

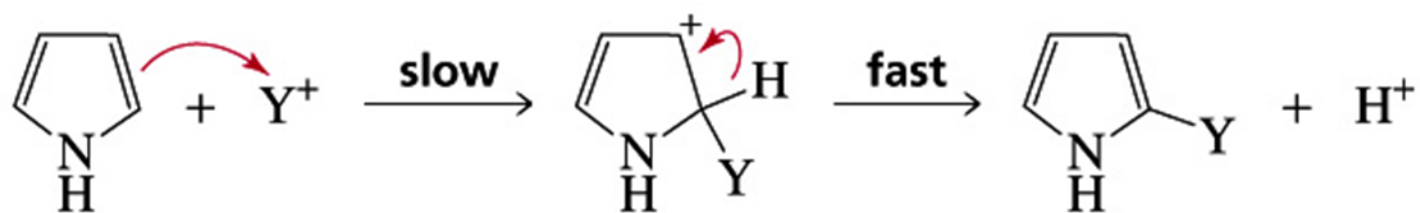
Electrophilic substitution in pyrrole

- ❖ As expected for aromatic compound, pyrrole can react by electrophilic (NO_2^+) substitution.
- ❖ In comparison to benzene pyrrole is more reactive thus the substitution is easier and milder reagents can be used.
- ❖ The increased reactivity is a result of resonance which pushes the electrons from the N-atom into the ring making the c-atoms of pyrrole ring more electron rich than in case of benzene. In fact pyrrole resembles most reactive benzene derivatives (phenols and amines) (see previous slide for resonance structures of pyrrole).
- ❖ Consequently, there are some modifications in usual electrophilic reagents, for instance, sulphonating and nitrating reagents have been modified to avoid the use of strong acids (induce polymerization). Also reaction with halogens requires no Lewis acid.

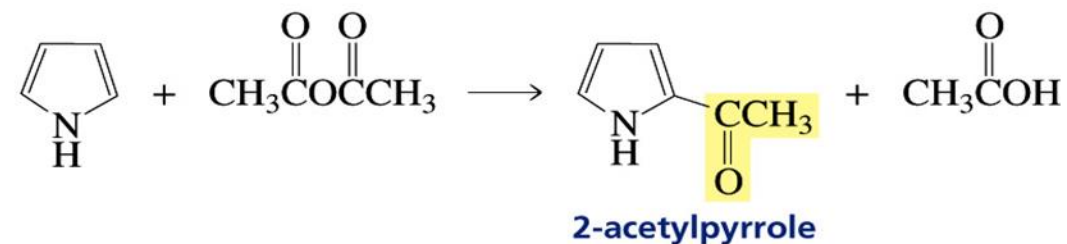
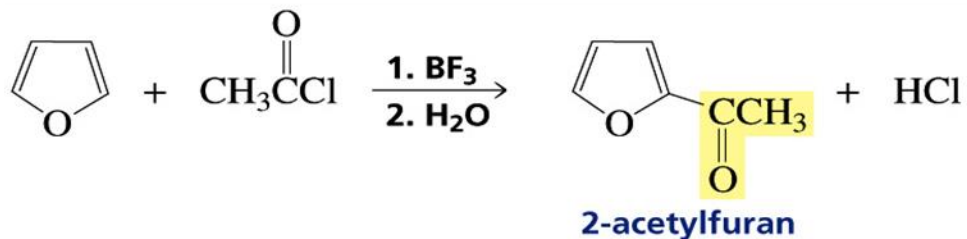
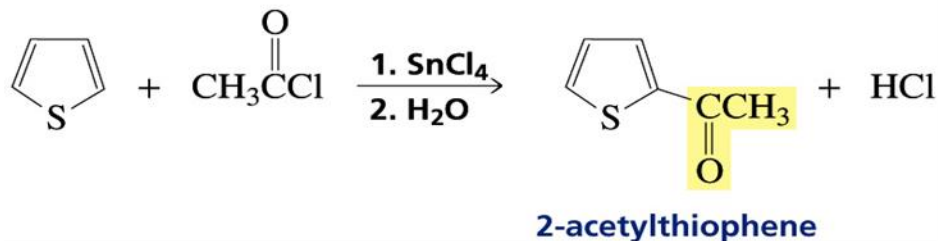
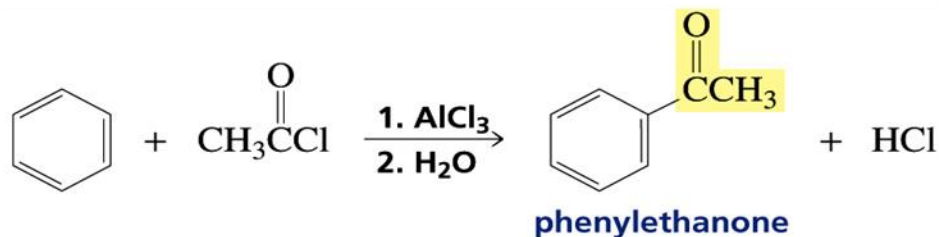
Reactivity in electrophilic substitution



mechanism for electrophilic aromatic substitution

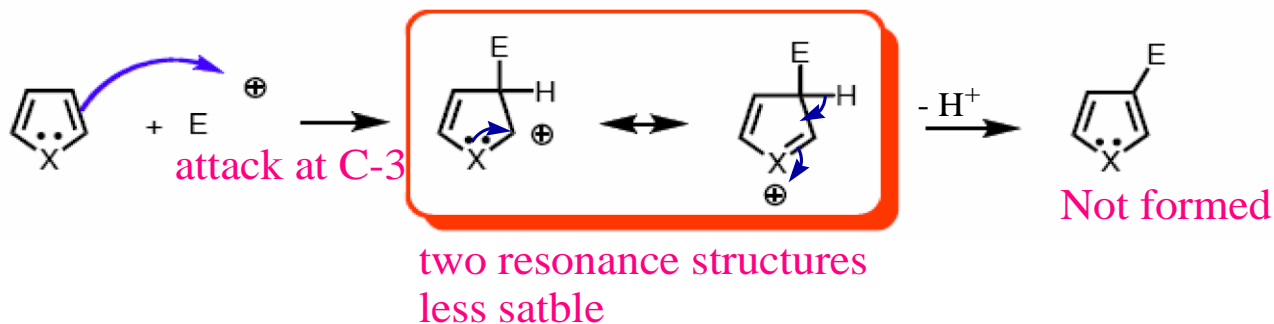
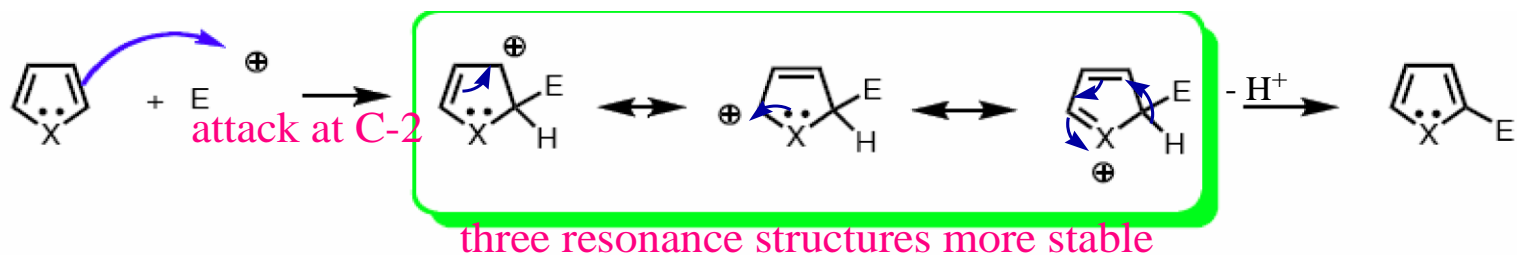


The relative reactivities of the five-membered-ring heterocycles in Friedel–Crafts reaction

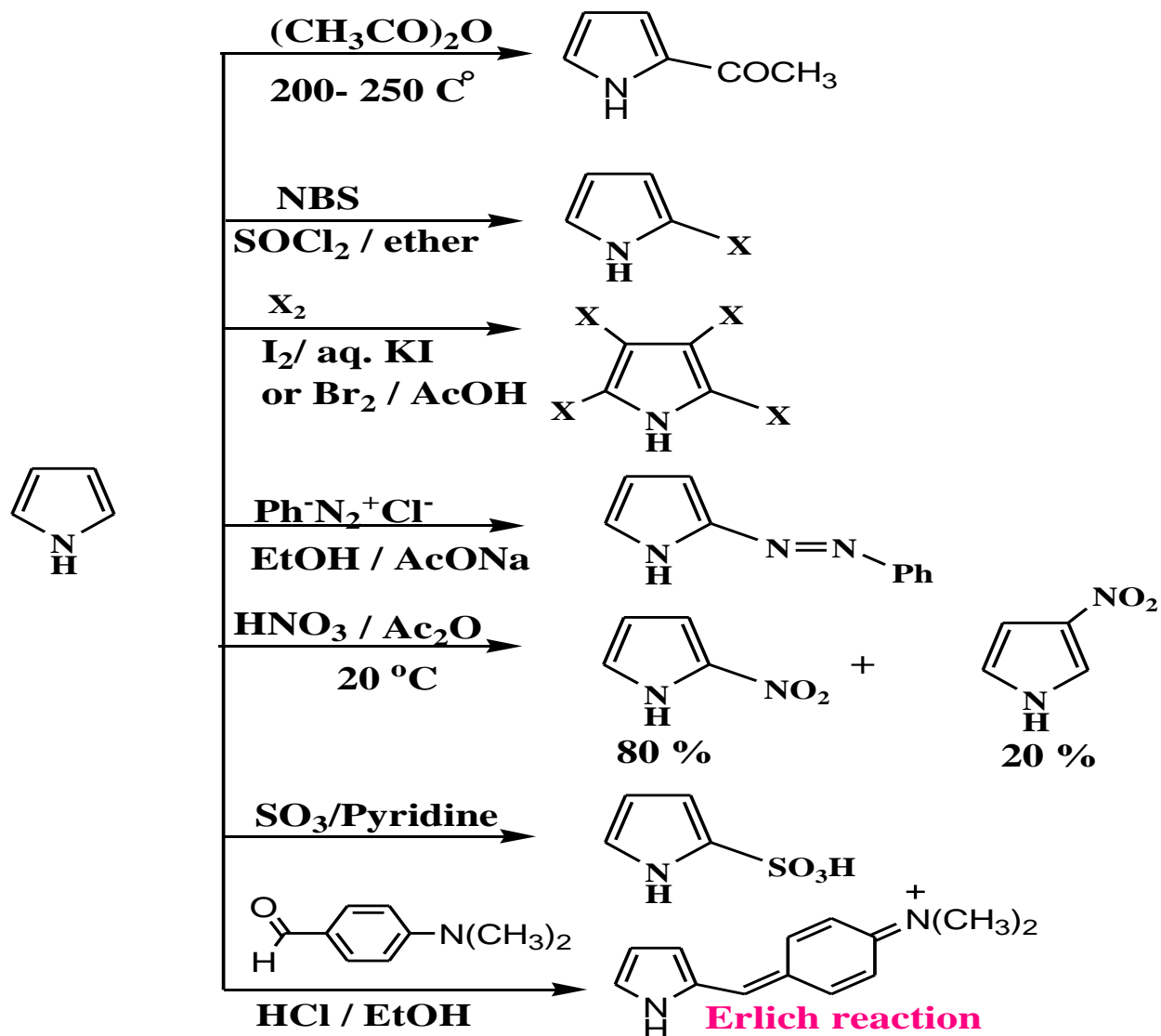


Orientation of Electrophilic Substitution in Pyrrole

- ❖ Electrophilic substitution normally occurs at a carbon atoms instead of at the nitrogen as explained before.
- ❖ Also it occurs preferentially at C-2 (the position next to the heteroatom) rather than at C-3 (if position 2- is occupied it occurs at position 3).
- ❖ This is due to attack at C-2 gives more stable intermediate (it is stabilized by three resonance structure) than the intermediate resulted from C-3 attack (it is stabilized by two resonance structure).

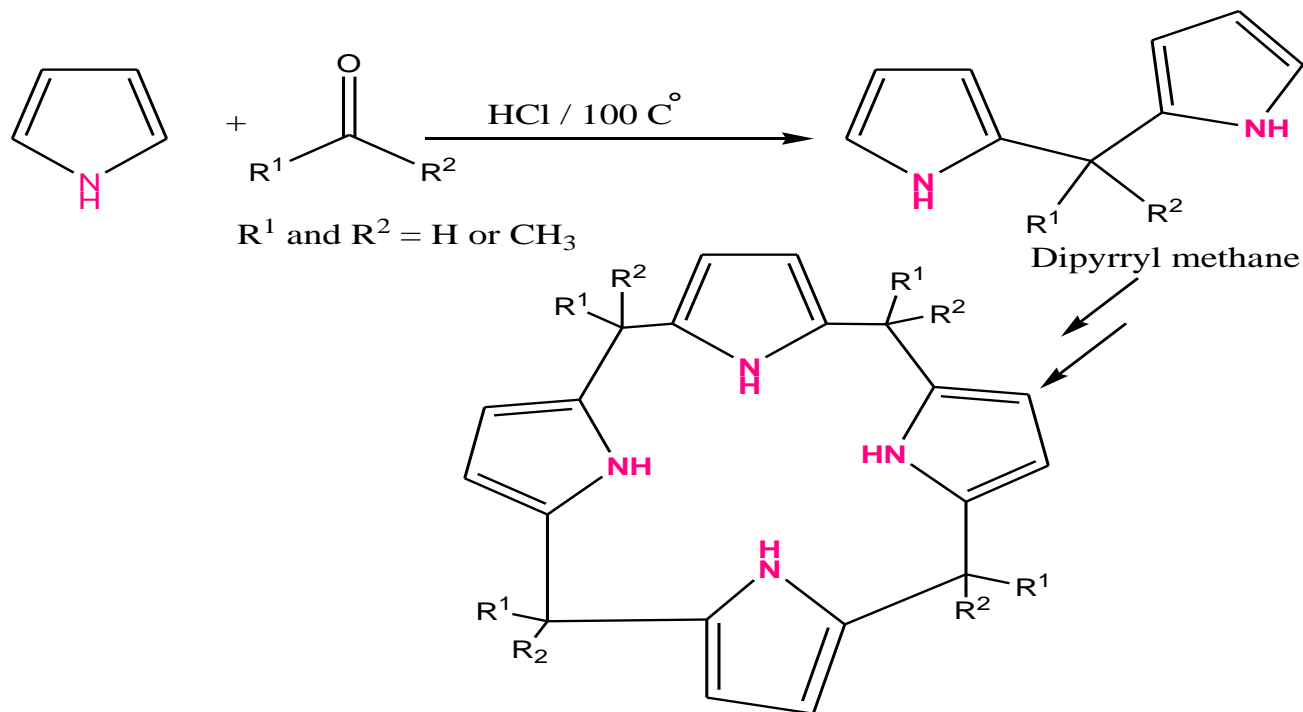


Electrophilic Substitution Reactions of Pyrrole



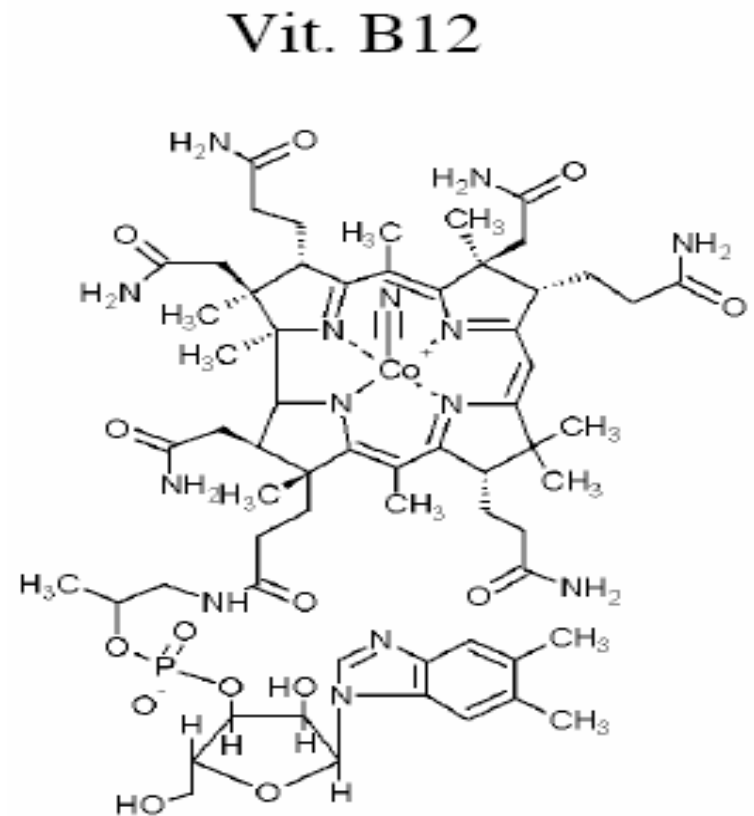
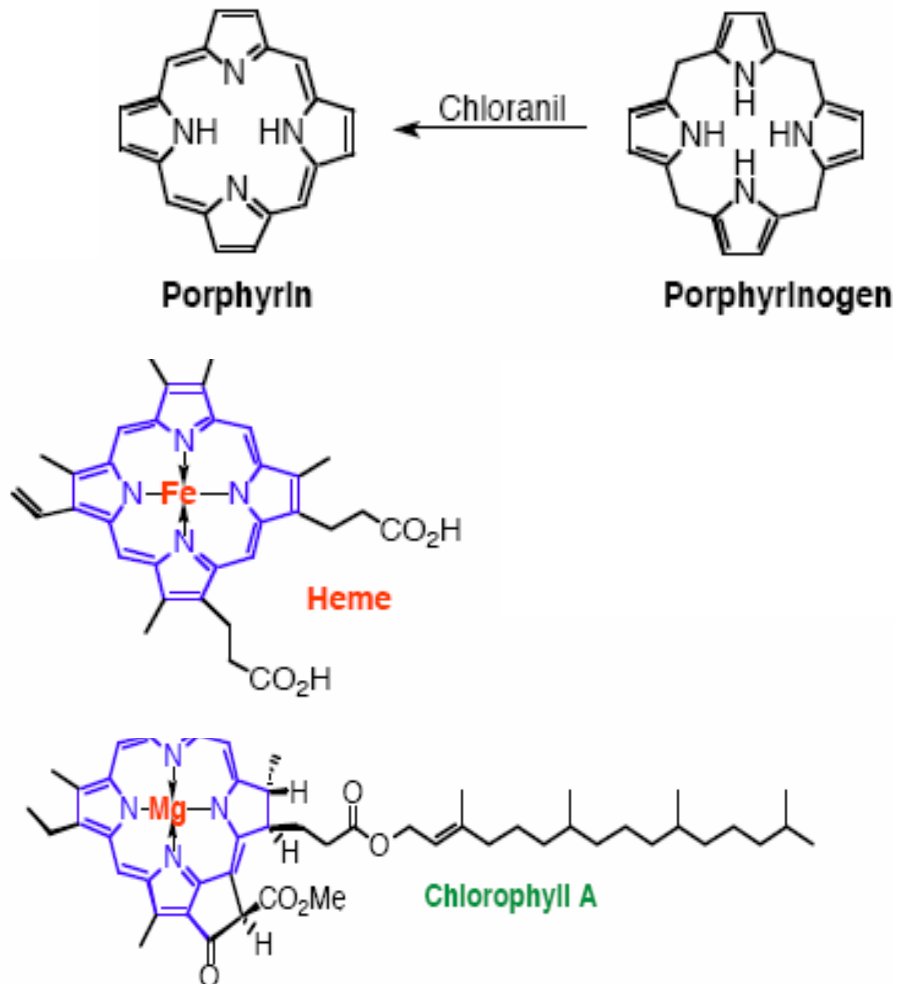
Reaction of pyrrole with aldehydes and ketones

- ❖ Aldehydes and ketones condense with unsubstituted pyrrole at α -position in acidic medium to give **dipyrlyl methane**. The condensation may continue to give **tetramer (4 pyrrole rings connected by methine bridge)**. The tetramers are known as **porphyrinogens**, they are stable, planar structures that can accommodate a wide range of metal ions.

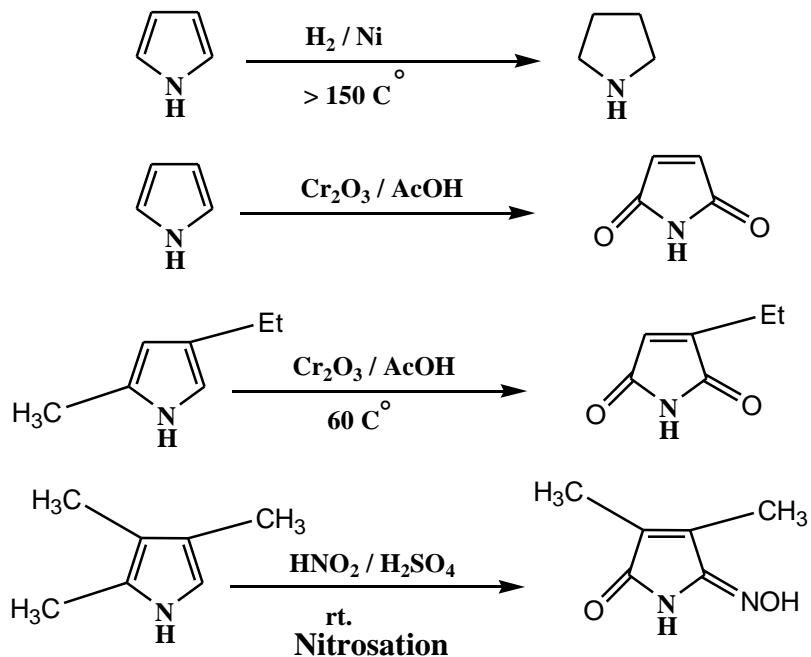


Application in Porphyrine Synthesis

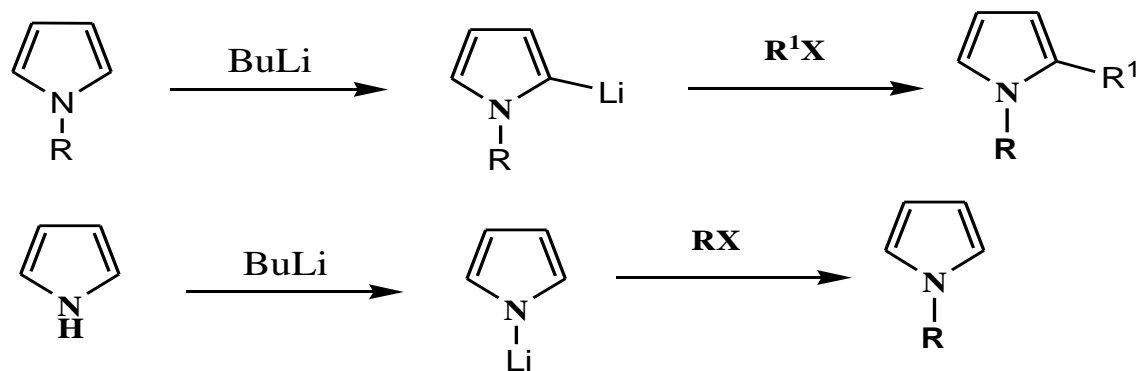
❖ Oxidation of porphyrinogen results in structures known as **porphyrins** that found in many natural compounds such as haem in animal kingdom and in chlorophyll in plant.



Oxidation-Reduction of Pyrrole

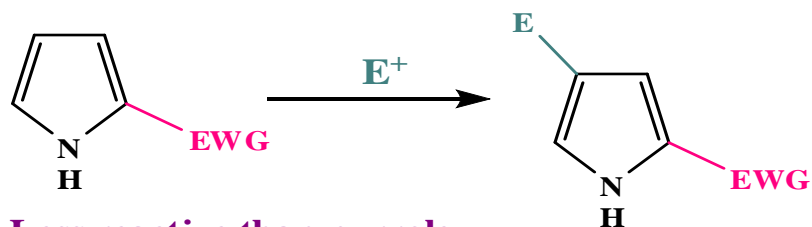


Lithiation of Pyrrole and N alkyl pyrrole



Second electrophilic substitution

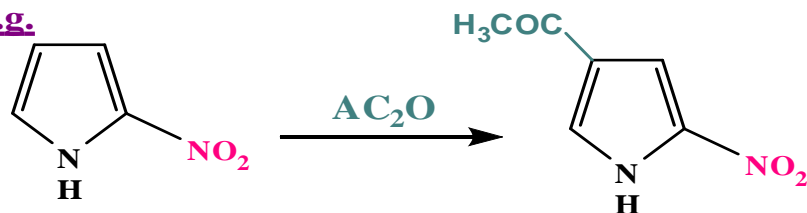
a) Monosubstituted pyrrole with electron withdrawing group



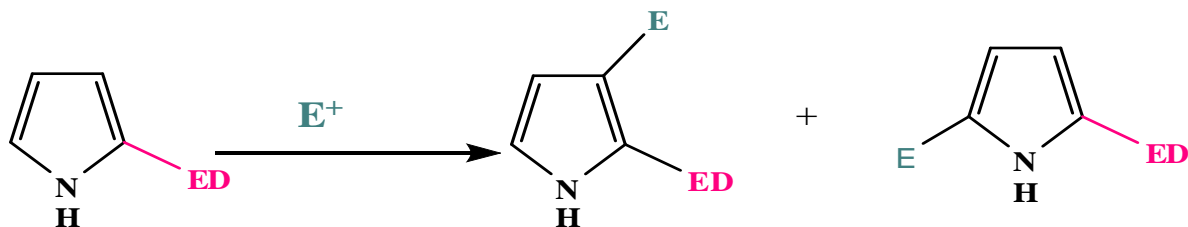
(incoming E^+ directed to *m*-position i.e. position 4)

Less reactive than pyrrole

e.g.



b) Monosubstituted pyrrole with electron donating group

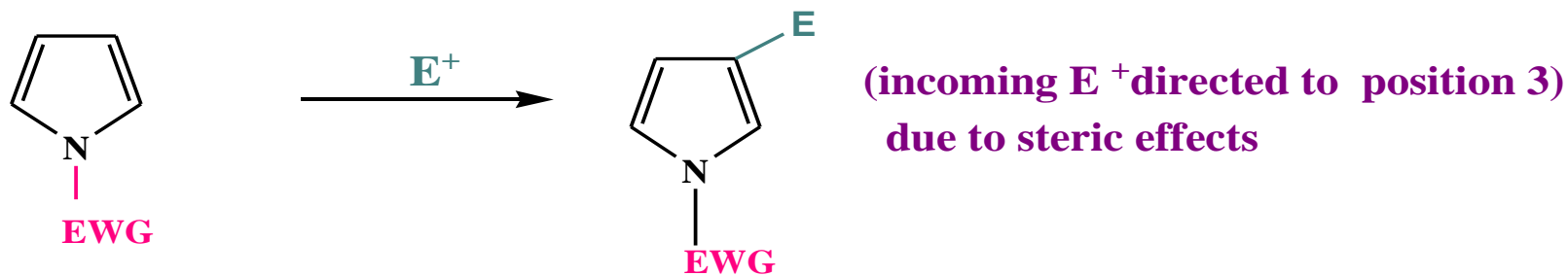


More reactive than pyrrole

(incoming E^+ directed to *p* or *o*-positions i.e. position 3 or 5)

Second electrophilic substitution

c) N-substituted pyrrole with electron withdrawing group



e.g.

