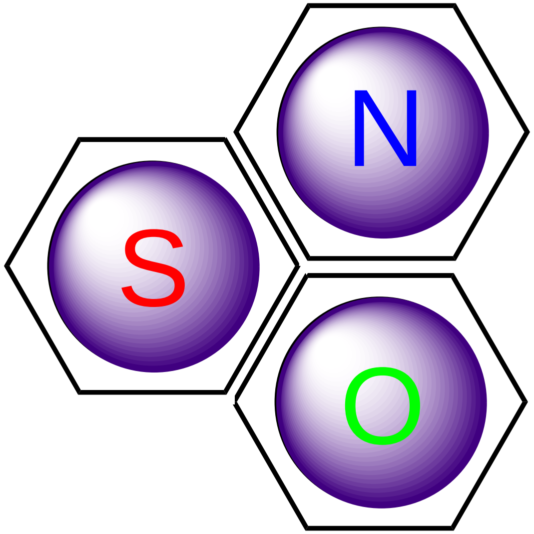


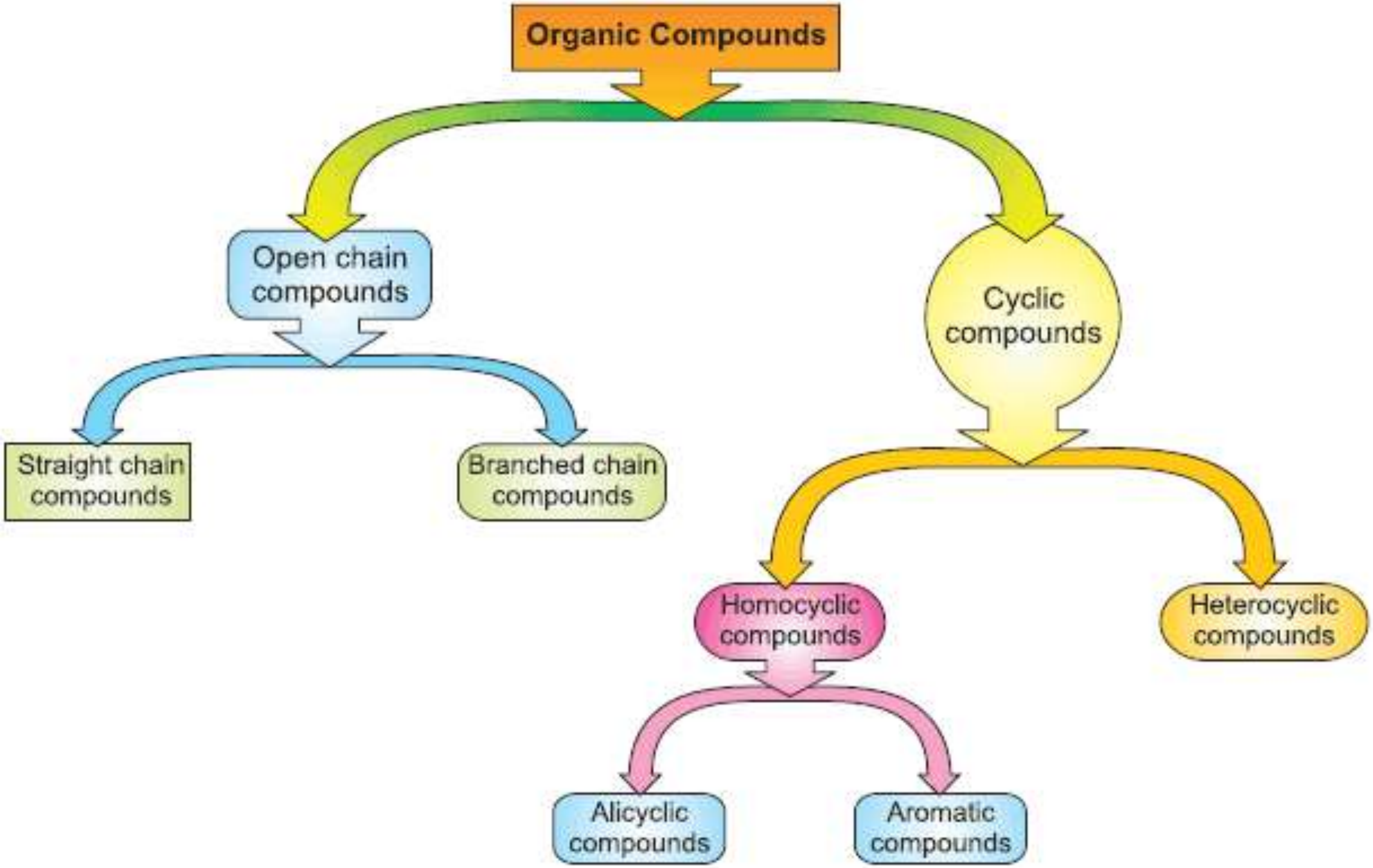
Five-membered Heterocycles

Pyrrole, Furan and Thiophene

Heterocyclic Chemistry

Dr Gohar Taqi Kazimi

Classification of Organic Compounds



Organic Compounds

Open chain compounds

Cyclic compounds

Straight chain compounds

Branched chain compounds

Homocyclic compounds

Heterocyclic compounds

Alicyclic compounds

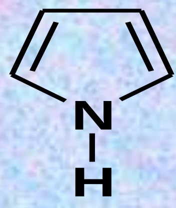
Aromatic compounds

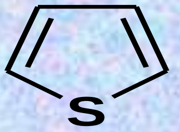
Heterocyclic Compounds

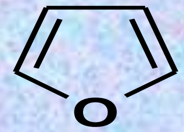
- **Definition:** Cyclic compounds which have one atom other than carbon in a ring are called heterocyclic compounds. The most commonly found hetrocyclic compounds contain sulfur, oxygen or nitrogen, as the heteroatom. The ring may be aromatic or non-aromatic.
- The most stable hetrocyclic compounds are those having 5 or 6 membered rings.
- Heterocycles form one half of natural organic compounds and include many important natural materials like alkaloids,dyes, proteins, enzymes and pharmaceuticals like penicillin G.

Five Membered Heterocycles-Introduction

- These can be considered to be derived from benzene by replacement of a (C=C) by a hetero atom with an unshared pair of electron.
- These are further divided into two types.
- Compounds having only one hetero atoms


Pyrrole


Thiophene


Furan

- Compounds having more than one hetero atoms

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.

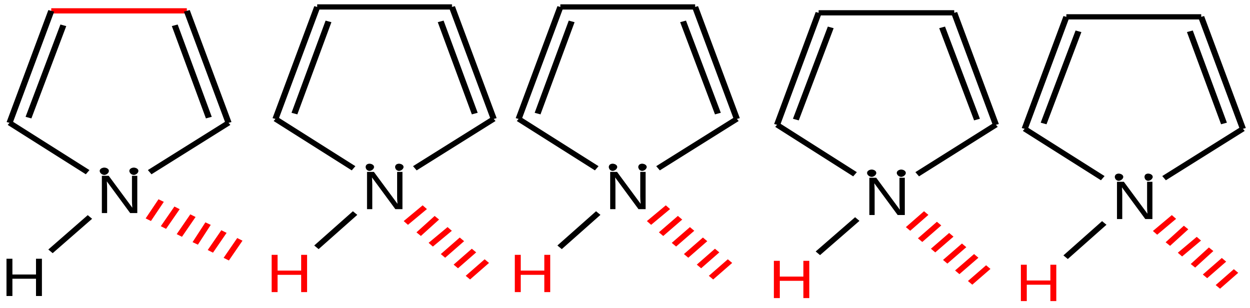
Thiophen does occur in plants in association with polyacetylenes with which they are biogenetically closely linked.

Furan occurs widely in secondary plant metabolites, especially in terpenoids.

Unsubstituted pyrrole, furan, and thiophene are usually obtained from petroleum

General Characteristics

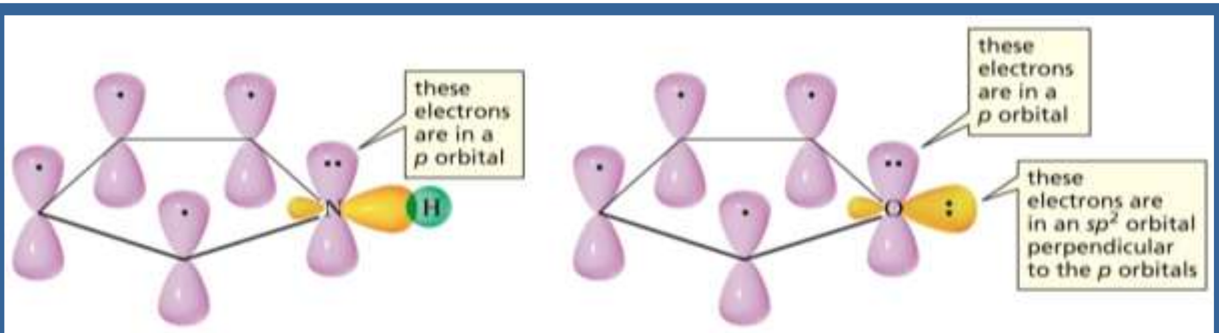
- Pyrrole, furan and thiophene are colorless liquids of boiling points 126°, 32°, and 84° respectively.
- Pyrrole has a relatively high boiling point as compared to furan and thiophene, this is due to the presence of intermolecular hydrogen bonding in pyrrole.



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).

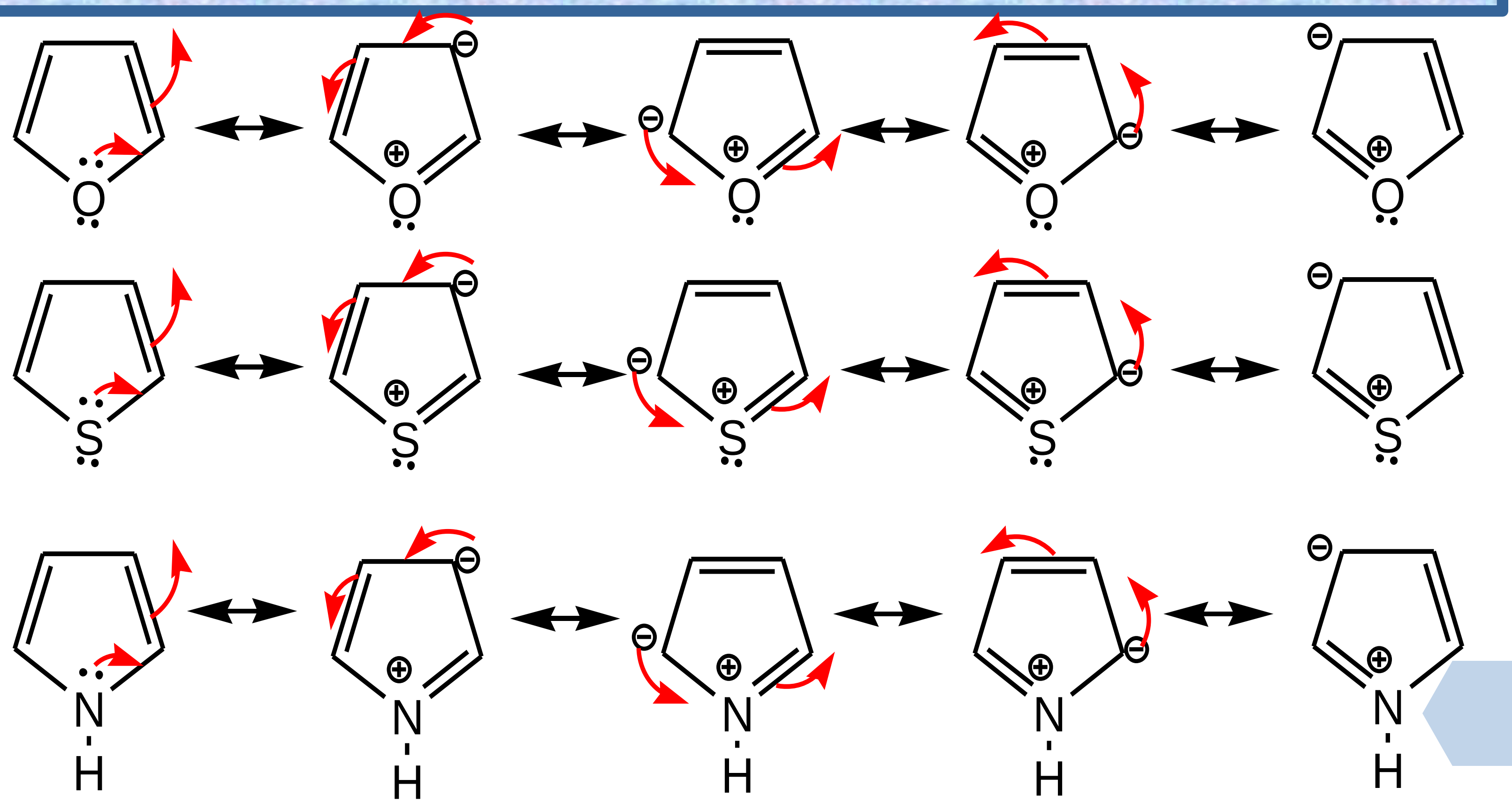


orbital structure of pyrrole

orbital structure of furan

Structure and Aromaticity

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



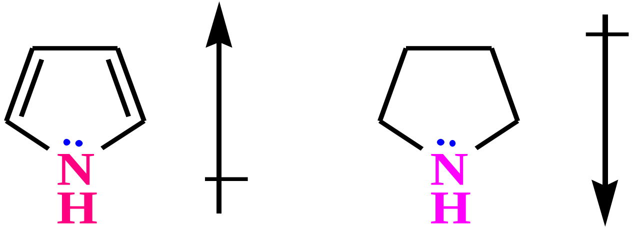
Evidences of aromatic character in pyrrole

1) All ring bonds are intermediates between single & 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 pyrolidine is reverted and thus protonation occurs at carbons not at N

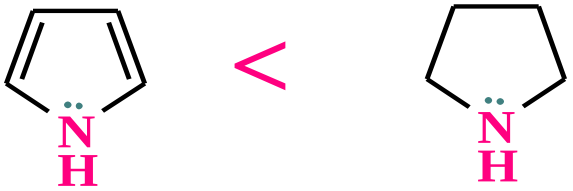
Dipole monent of pyrrole and its saturated analog



Pyrrole

Pyrrolidine

Basicity of pyrrole and its saturated analog



Pyrrole
aroamtic 2° amine

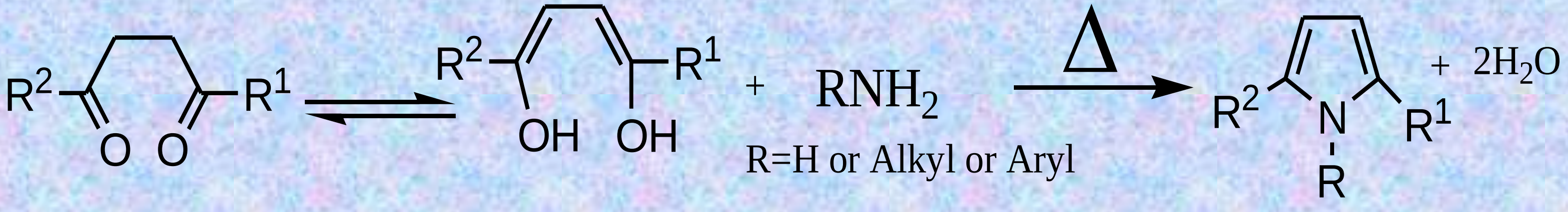
Pyrrolidin
Aliphatic 2° amine

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

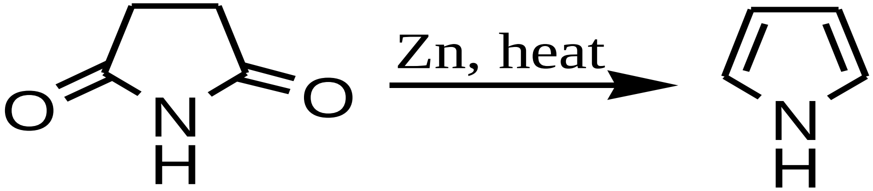


R=H or Alkyl or Aryl

1,4-Dicarbony compound

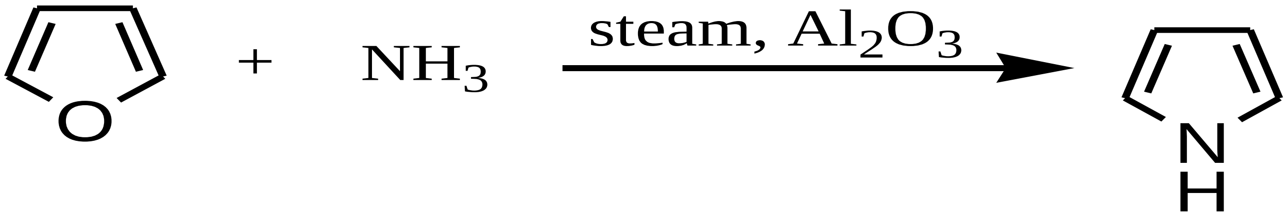
Synthesis of Pyrrole

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



Succinimide

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

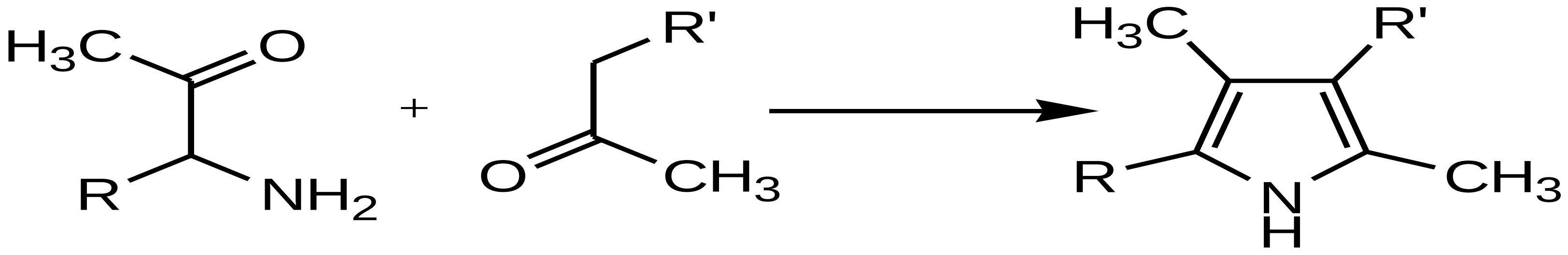


4) By passing a mixture of acetylene and ammonia over red hot tube.

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.

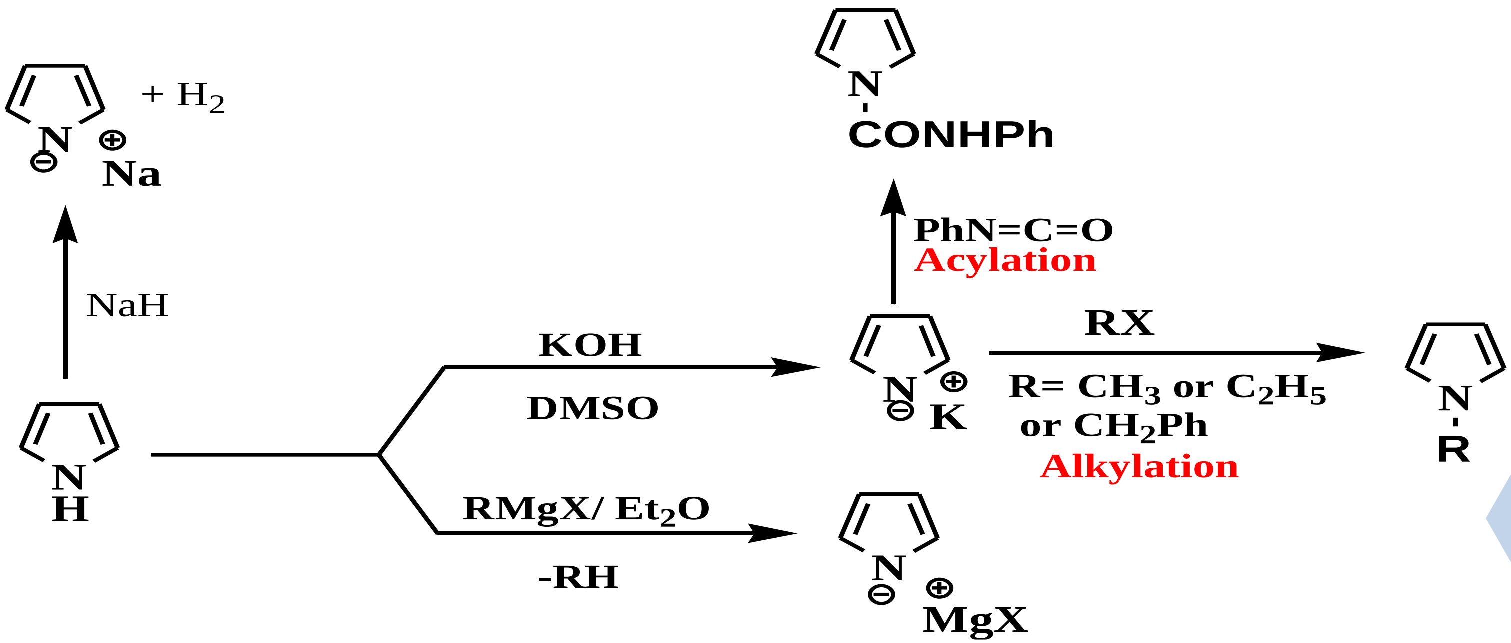


R' = -COR; β— diketone

= -$COOC_2H_5$; β— diester

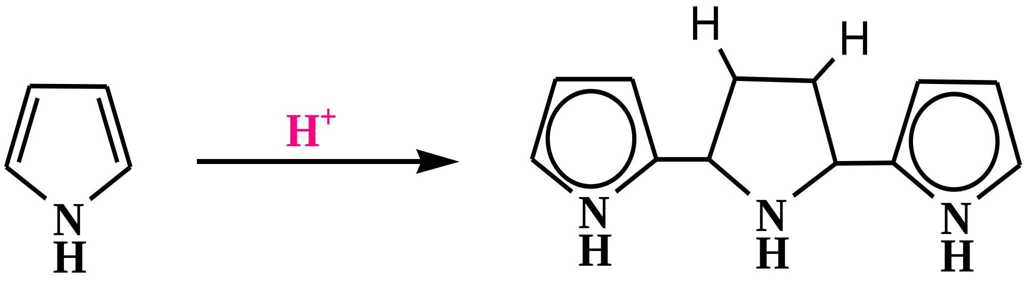
Acidic properties of pyrrole

❖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 an 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

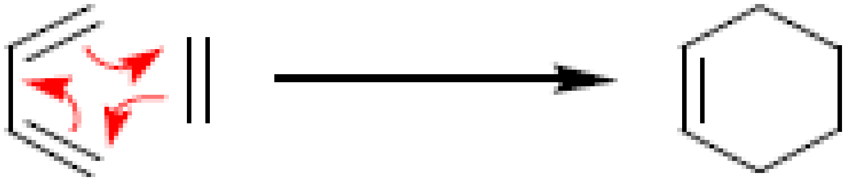


pyrrole trimer

Cycloaddition reactions (Diels Alder Reaction)

❖**Cycloaddition reaction** is one in which two reactants add together with formation of 2 new C-C bonds at the same time to give a cyclic product e.g. Diels-Alder reaction.

❖**Diels – Alder reaction** involves addition of a compound containing a double or a triple bond (2 π e it is Called **dienophile**) across the 1,4- position of a conjugated system (4π e, 1,3-**diene**), with the formation of a six membered ring.

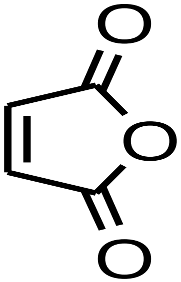


❖The heterocyclic compounds can react as a 1,3-diene in D. A. reaction with reactive dienophiles (e.g. maleic anhydride, or benzyne) or with less reactive dienophiles (e.g. acrylonitrile) in presence of catalyst.

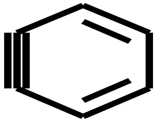
Cycloaddition reactions of pyrrole (Diels Alder Reaction)

- The diene can be activated by E.D.G while the dienophile by EWG.
- Thus N-alkyl pyrrole and N-amino pyrrole are more reactive than pyrrole itself in D.A reaction but less reactive than furan (the least aromatic 5- membered heterocycle thus the most reactive in addition) .
- The order of reactivity in D.A reaction is as follows which is the reverse of aromaticity order:

Furan > N-alkyl pyrrole > Pyrrole > Thiophene.



Maleic anhydride



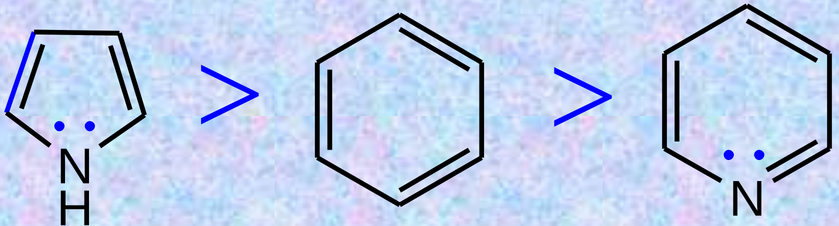
Benzyne

Acrylonitrile

Electrophilic substitution in pyrrole

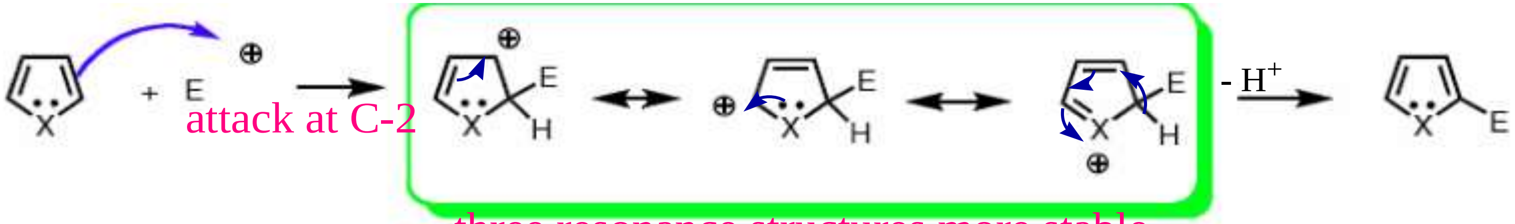
- As expected for aromatic compound, pyrrole can react by electrophilic substitution.
- In comparison to benzene pyrrole is more reactive thus the substitution is easier and milder reagents can be used.
- The increased reactivity is a result of resonance which pushes the electrons from the N-atom into 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 slide 4 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



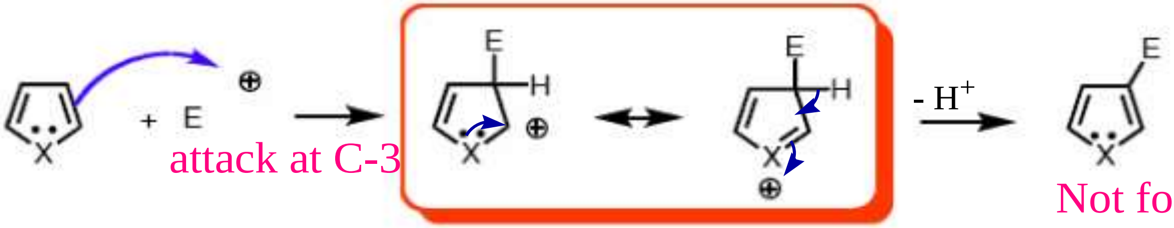
Orientation of Electrophilic Substitution in Pyrrole

- 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).



attack at C-2

three resonance structures more stable

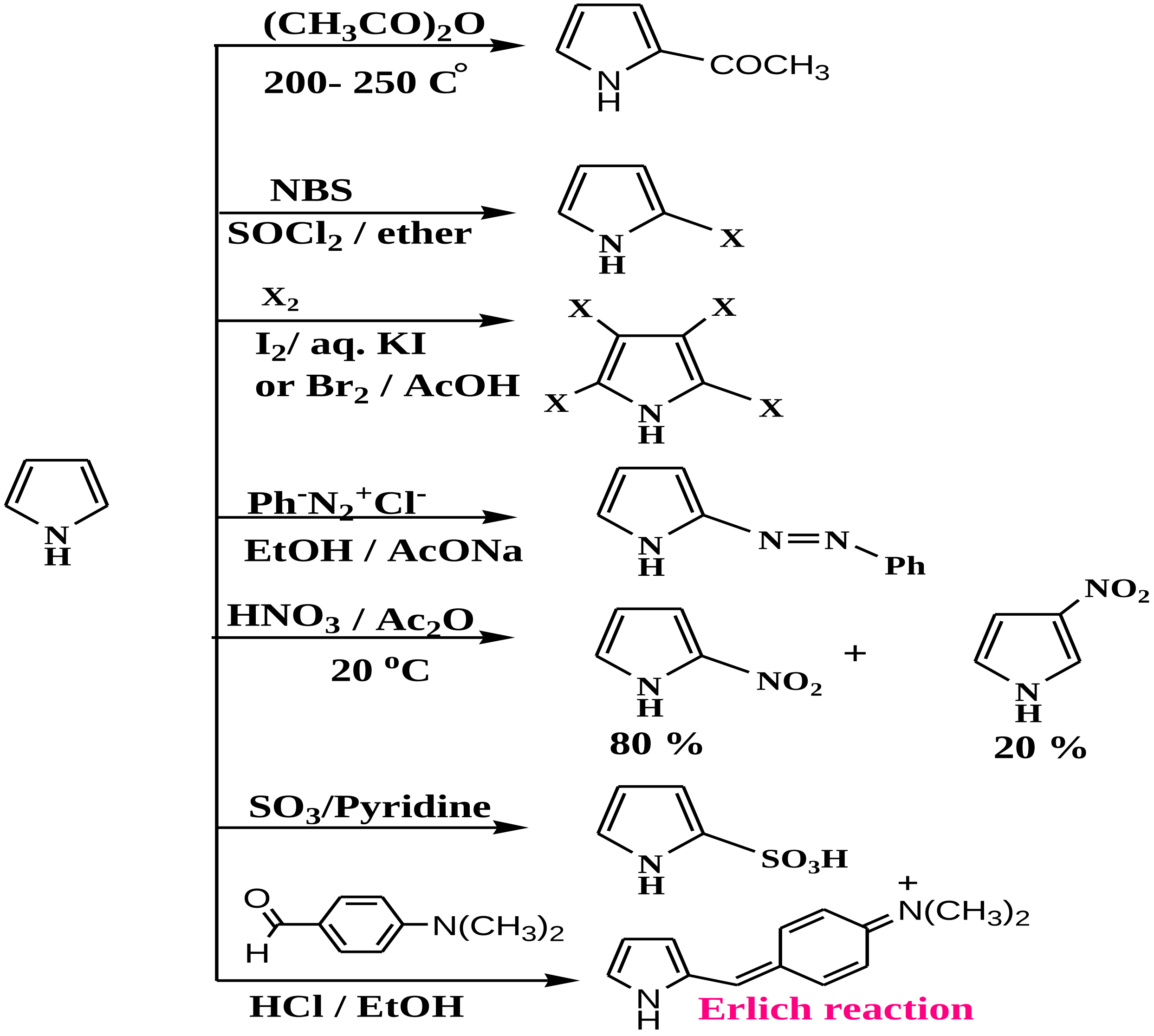


attack at C-3

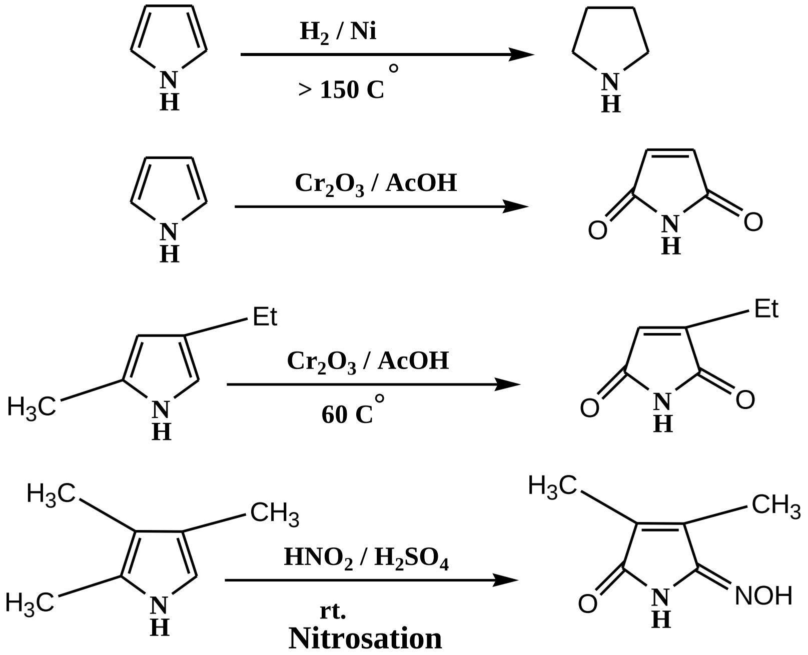
two resonance structures less satble

Not formed

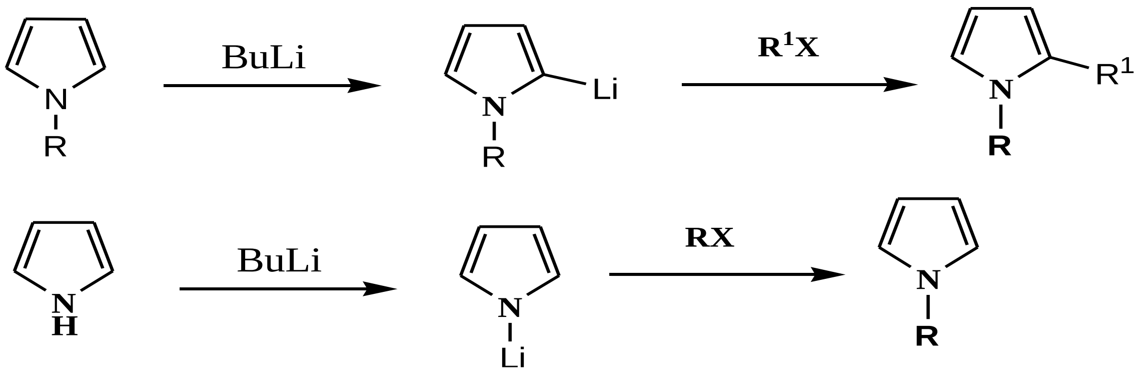
Electrophilic Substitution Reactions of Pyrrole



Oxidation-Reduction of Pyrrole

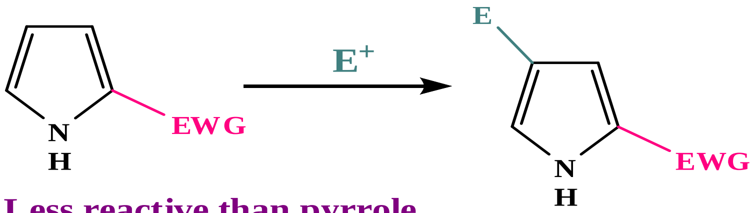


Lithiation of Pyrrole and N alkyl pyrrole



Second electrophilic substitution

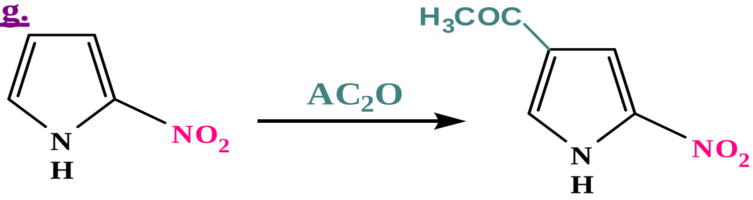
a) Monosubstituted pyrrole with electron withdrawing group



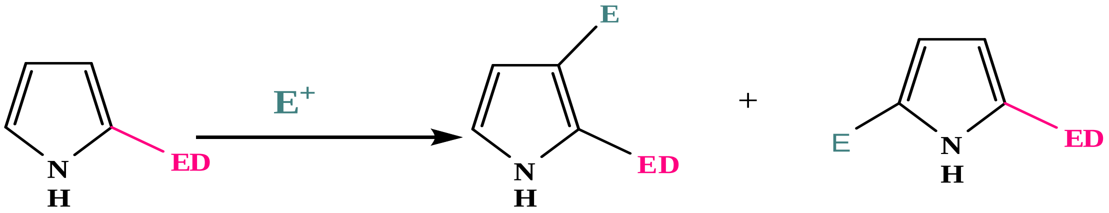
(incoming E $^+$directed to *m*-position i.e. position 4)

Less reactive than pyrrole

e.g.



b) Monosubstituted pyrrole with electron donating group

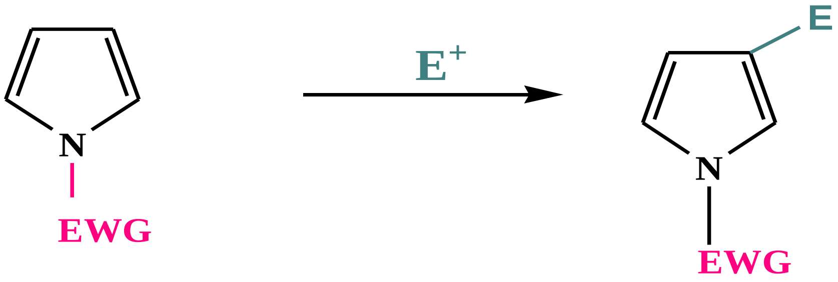


More reactive than pyrrole

(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



(incoming E $^+$directed to position 3) due to steric effects

e.g.