UNIT 4: HETEROCYCLIC COMPOUNDS- I

CONTENTS

4.1 OBJECTIVES

In this unit learner will be able to

- Know about the most important simple heterocyclic ring systems containing heteroatom and their systems of nomenclature and numbering.
- Understand and discuss the reactivity and stability of hetero aromatic compounds.
- Study the important synthetic routes and reactivity for five and six member hetero aromatic compounds.
- Understand the important physical and chemical properties of five and six member hetero aromatic compounds.
- Know about the applications of these hetero aromatic compounds in the synthesis of important industrial and pharmaceutical compounds

4.2 INTRODUCTION

Heterocyclic compound is the class of cyclic organic compounds those having at least one hetero atom (*i.e.* atom other than carbon) in the cyclic ring system. The most common heteroatoms are nitrogen (N), oxygen (O) and sulphur (S). Heterocyclic compounds are frequently abundant in plants and animal products; and they are one of the important constituent of almost one half of the natural organic compounds known. Alkaloids, natural dyes, drugs, proteins, enzymes etc. are the some important class of natural heterocyclic compounds. Heterocyclic compounds can be easily classified based on their electronic structure. Heterocyclic compounds are primarily classified as saturated and unsaturated. The saturated heterocyclic compounds behave like the acyclic derivatives with modified steric properties. Piperidine and tetrehydrofuran are the conventional amines and ethers of this category. However, unsaturated heterocyclic compounds of 5- and 6- member rings have been studied extensively because of their unstrained nature. The unstrained unsaturated heterocyclic compounds include Pyridine, Thiophene, Pyrrole, Furan and their benzo fused derivatives. Quinoline, Isoquinoline, Indole, Benzothiophene, and Benzofuran are some important example of benzo fused heterocycles. Heterocyclic compounds have a wide application in pharmaceuticals, agrochemicals and veterinary products. Many heterocyclic compounds are very useful and essential for human life. Various compounds such as hormones, alkaloids antibiotic, essential amino acids, hemoglobin, vitamins, dyestuffs and pigments have heterocyclic structure.

In the present unit, students would be able to learn about the common five and six membered heterocyclic compounds, such as Pyrrole, Furan, Thiophene, Pyridine and Piperidine etc.

4.3 CLASSIFICATION OF HETEROCYCLIC COMPOUNDS

Based on the structural and electronic arrangement the heterocyclic compounds may be classified into two categories.

i. Aliphatic heterocyclic compounds
ii. Aromatic heterocyclic compounds

The aliphatic heterocyclic compounds are the cyclic amines, cyclic amides, cyclic ethers and cyclic thioethers. Aliphatic heterocycles those do not contain double bonds are called saturated heterocycles. The properties of aliphatic heterocycles are mainly affected by the ring strain. Examples of aliphatic heterocyclic compounds are shown in figure 1.

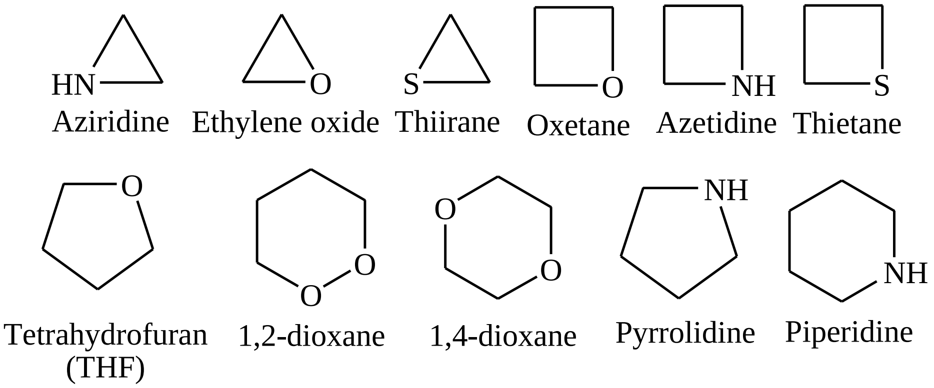


Figure 1. Examples of aliphatic heterocyclic compounds

However, aromatic heterocyclic compounds are analogous of benzene. The aromatic heterocyclic compounds also follow the Huckel’s rule. According to Huckel’s rule an aromatic compounds must be cyclic in nature with planar geometry due to conjugate double bonds and must have (4n+2)π electrons. Examples of aromatic heterocyclic compounds are shown in figure 2.

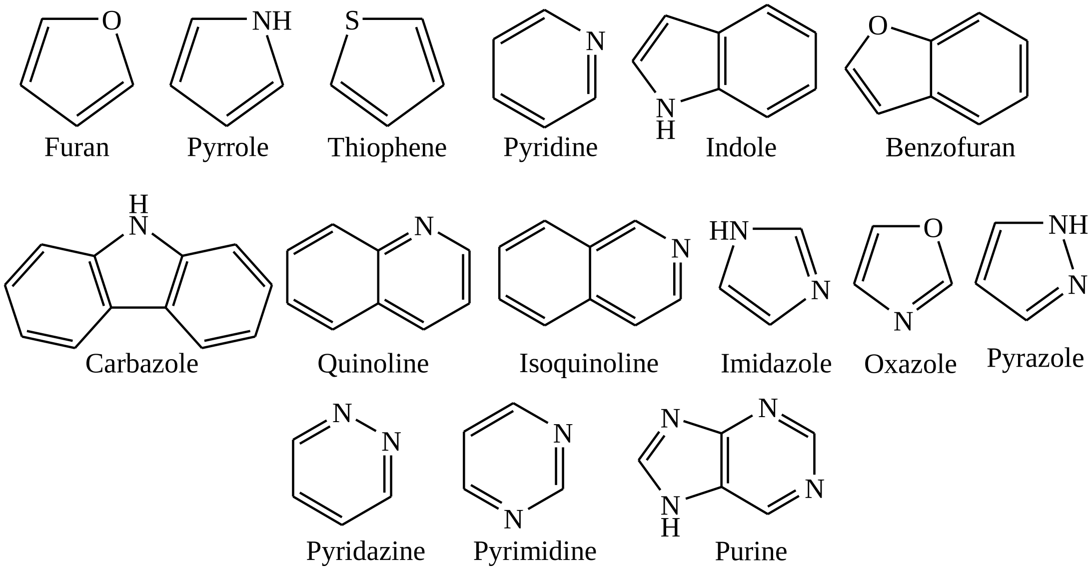


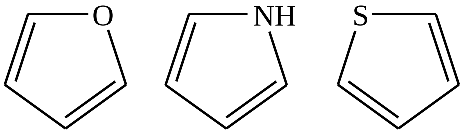
Figure 2. Examples of aromatic heterocyclic compounds

A hetero cyclic ring may comprise of three or more than three atoms, which may be saturated or unsaturated. Also heterocyclic ring may contain more than one heteroatom which may be either similar or different.

Based on the variety of structure, the heterocyclic compounds may also be divided in to three categories.

1. Five membered heterocyclic compounds: These heterocyclic compounds may be considered to be derived from benzene by replacing one C=C bond by a hetero atom with a lone pair of electron. Based on number of hetero atom present in the cyclic ring this class of heterocyclic compounds may be further subdivided in to following categories.

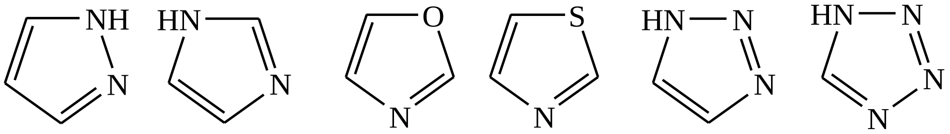
a). Heterocyclic compounds with one hetero atom: Common examples of this class of compounds are furan, thiophene and pyrrole (Figure 3).



Furan Pyrrole Thiophene

Figure 3. Five member heterocyclic compounds with one hetero atom

b). Heterocyclic compounds with more than one hetero atom: These hetero atoms may be same or different. Common examples of this category of heterocyclic compounds are pyrazole, imidazole, thiazole, oxazole, triazole and tetrazole etc (Figure 4).

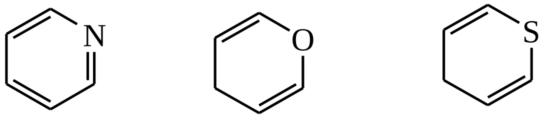


Pyrazole Imidazole Oxazole Thiazole Traizole Tetrazole

Figure 4. Five member heterocyclic compounds with two hetero atom

2. Six membered heterocyclic compounds: This class of compounds may be considered to be derived from the replacement of a carbon atom of benzene by an iso-electronic atom. Similar to the five membered heterocyclic compounds, the six membered heterocyclic compounds may also be subdivided in to following categories.

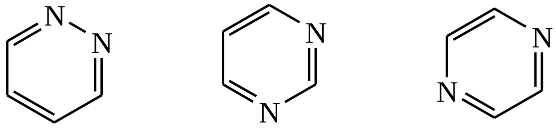
a). Heterocyclic compounds with one hetero atom: Common examples of this class of compounds are pyridine, pyran, thiopyran etc (Figure 5).



pyridine 4*H*-pyran 4*H*-thiopyran

Figure 5. Six member heterocyclic compounds with one hetero atom

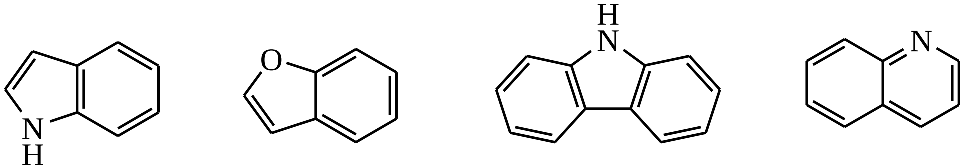
b). Heterocyclic compounds with more than one hetero atom: Common examples of this class of compounds are pyridazine, pyrimidine, pyrazine etc (Figure 6).



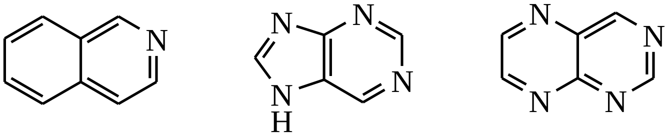
pyridazine pyrimidine pyrazine

Figure 6. Six member heterocyclic compounds with more than one hetero atom

3. Fused or condensed heterocyclic compounds: This class of compound may consist two or more fused rings which may be partly carbocyclic and partly heterocyclic, common examples of this category of heterocyclic compounds are Indole, Quinoine, Isoquionoline, Cabazole etc; or may be completely heterocyclic, common examples of this category of heterocyclic compounds are purine, pteridine etc (Figure 7).



Indole Benzofuran Carbazole Quinoline



Isoquinoline Purine Pteridine

Figure 7. Fused or condensed heterocyclic compounds

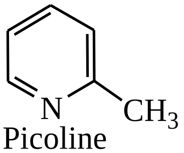
4.4 NOMENCLATURE OF HETEROCYCLIC COMPOUNDS

The nomenclature of heterocyclic compounds is divided in to two categories, a) Trivial method of nomenclature and, b) Systematic method of nomenclature. However, most of the heterocyclic compounds are known by their common trivial names.

4.4.1 TRIVIAL METHOD OF NOMENCLATUTRE:

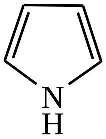
During the early days of organic chemistry, names of the heterocyclic organic compounds were given based on their occurrence, their first preparation and some characteristic properties.

Heterocyclic compounds were named on the basis of their source from which the compound was obtained. Thus the name depended on the source of the compound. For example picoline; picoline is derived from coaltar. This is based on Lattin word *pictus* means *tarry*.



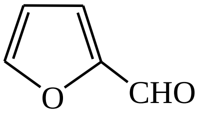
Picoline

Heterocyclic compounds were also named on the basis of their characteristic properties. For example, pyrrole; which is basic in nature; the name of pyrrole was originated from the Greek word for fiery red because of characteristic colour which the compound gives with pine splint dipped in hydrochloric acid.



Pyrrole

Similarly, the name Furfural is given based on it’s source. Furfural means barn oil. Furfural was isolated from the distillation of barn.



Furfural

The trivial nomenclature was the first nomenclature method which has a significant role in the development of heterocyclic chemistry. However, this system has some disadvantages too. The trivial system does not give any structural information about the compound. At present just over 60 trivial names survive and recognized by IUPAC system of nomenclature. These recognized names are, however, significant because they are used as basis for constructing other compounds, more systematic names for polycyclic compounds and/or their derivatives. Examples of heterocyclic compounds with recognized trivial names are shown in figure 8.

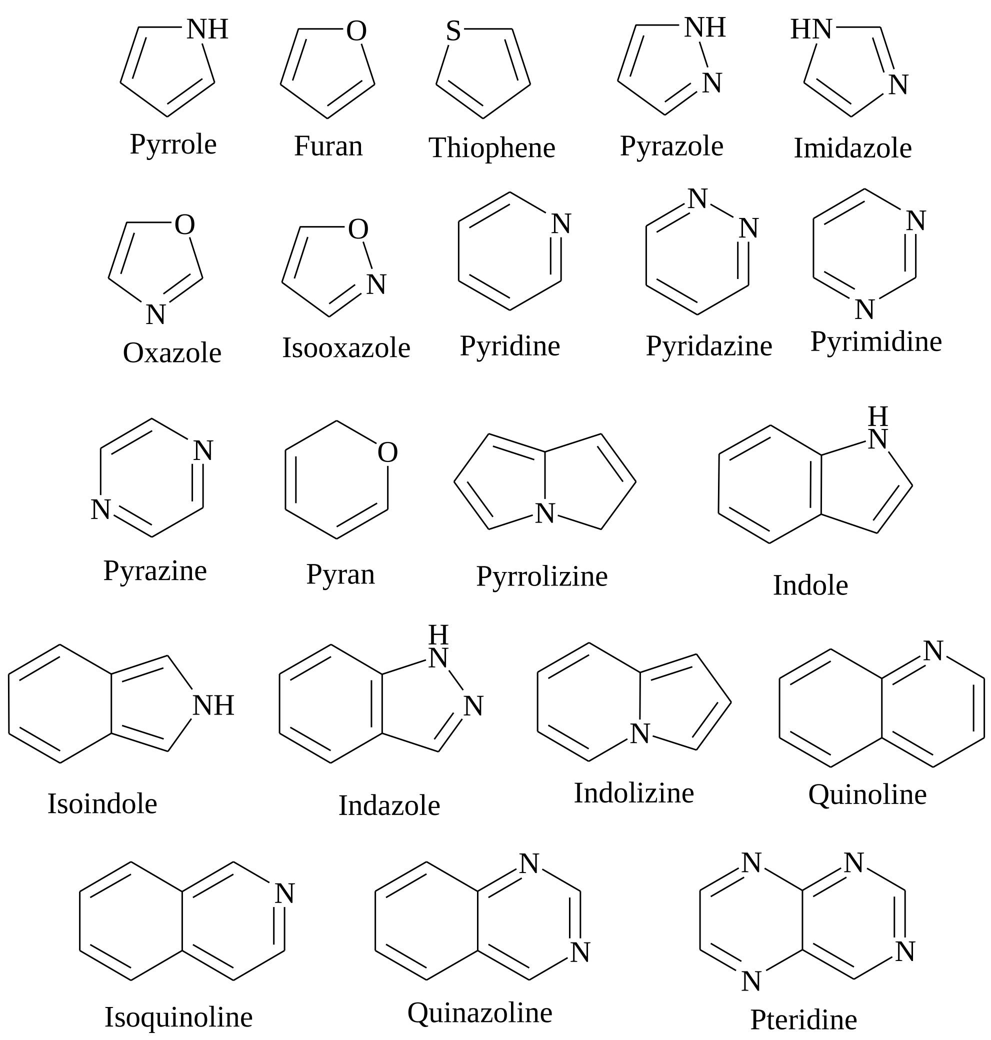


Figure 8. Some heterocyclic compounds with recognized trivial names

4.4.2 SYSTENATIC METHOD OF NOMENCLATUTRE:

This is most widely used nomenclature system for monocyclic heterocyclic compounds especially for three to ten membered ring systems. These members have various degree of unsaturation containing one or more heteroatoms. The systematic nomenclature gives important structural information. The most relevant system that is recommended by IUPAC for nomenclature of heterocyclic compounds is the ***Hantzch-Widmann system*** of nomenclature. This nomenclature system specifies the nature, position, ring size, number, and types of heteroatoms present in any heterocyclic compounds. This systematic method generally derived the nomenclature using the following syntax;

Name: Prefix + Stem + Suffix

Following are the important points to be remembered during the systematic nomenclature of heterocyclic compounds.

1. In this nomenclature the nomenclature of heterocyclic compounds are assigned by combining ‘prefix’ (that indicate the heteroatom present) with ‘stem’ (that indicate the ring size as well as the saturation and unsaturation in the ring) and ‘suffixes’. The common prefixes are shown in Table 1. It should be noted that final ‘a’ is dropped when prefix is followed by vowel.
2. Nomenclature of heterocyclic compound starts with the heteroatom appears first in the table 1.
3. If more than two different heteroatoms are present in any heterocyclic compound the prefixes are listed in order in which they are appear in above table (Table 1).
4. If there are two or more than two hetero atoms of same types are present in a heterocyclic compound they are indicated by di-, tri- etc.
5. The position of saturated atom is numerically indicated with prefix ‘*H*-’ as a part of the name of the ring system. It should be noted that where, there is a choice of numbering, the indicated position is given the lowest possible number.
6. The size of a monocyclic ring (three to ten membered rings) is indicated by stem. The common ‘stem’ nomenclature is given in Table 2.

Table 1: Common Prefix for Heteroatoms (arranged in the preferential order)

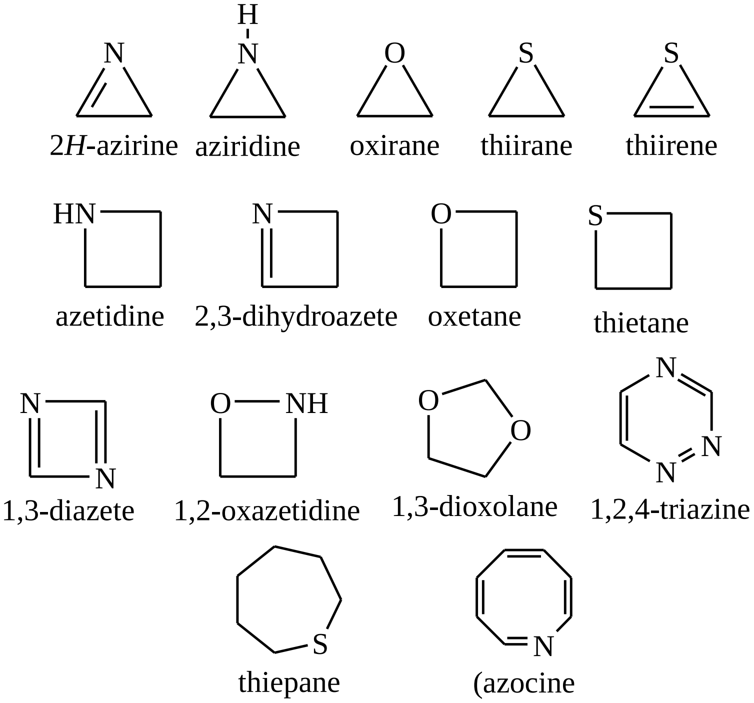
S. No.	**Heteroatom**	**Symbol**	**Prefix**
1	Oxygen	O	Oxa
2	Sulphur	S	Thia
3	Selenium	Se	Selena
4	Nitrogen	N	Aza
5	Phosphorous	P	Phospha
6	Arsenic	As	Arsa
7	Antimony	Sb	Stiba
8	Bismuth	Bi	Bisma
9	Silicon	Si	Silia

10	Tin	Sn	Stanna
11	Lead	Pb	Plumba
12	Boron	B	Bora
13	Mercury	Hg	Mercura

Table 2: Common Prefix for Heteroatoms (arranged in the preferential order)

S.No	Ring Size	Unsaturated Ring	Saturated Ring
1	3	iren	Irane
2	4	ete	Etane
3	5	ole	Olane
4	6	ine	Inane
5	7	epine	Epane
6	8	ocine	Ocane
7	9	onine	Onane
8	10	ecine	Ecane

Some examples of heterocyclic compounds with systematic nomenclature are shown in figure 9.



2*H*-azirine aziridine oxirane thiirane thiirene

azetidine 2,3-dihydroazete oxetane thietane

1,3-diazete 1,2-oxazetidine 1,3-dioxolane 1,2,4-triazine

thiepane (azocine

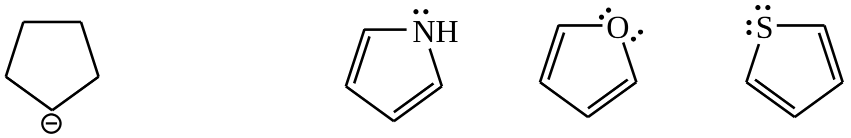
Figure 9. Examples of some heterocyclic compounds with systematic names

4.5 MOLECULAR ORBITAL PICTURE OF HETEROCYCLIC COMPOUNDS

Molecular orbital theory is widely used to interpret the structure of aromatic and hetero-aromatic compounds. According to Huckel approximation the electrons in the p-orbitals are treated separately from those electrons which are involved in the formation of the bonds in the plane of the ring. The six p-orbitals are combined to give six delocalized π molecular orbitals (3 π bonding molecular orbitals and 3 antibonding π molecular orbitals). Each of the six π -molecular orbitals can accommodate a maximum of two electrons. The 3 bonding π -molecular orbitals are of lower energies than the 3 antibonding π -molecular orbitals. Thus the electrons will be filled in lower 3 bonding π -molecular orbitals first. We will be discussing here the π -molecular orbitals of pyrrole and pyridine as model compounds of five and six membered heterocyclic compounds.

4.5.1 MOLECULAR ORBITAL PICTURE OF PYRROLE:

Five membered heterocyclic compounds with conjugated double bond can be considered as aromatic if the delocalization of π electrons is possible. Pyrrole, furan, thiophene etc are the most common examples of this class of compounds. These five membered heterocyclic compounds are structural homologue of cyclopentadienyl anion (Figure 10).



Cyclopentadienyl Anion Pyrrole Furan Thiophene

Figure 10. Examples of cyclopentadienyl anion structural homologue heterocyclic compounds

Pyrrole is the most fundamental member of this family. It is an aromatic compound with all 5 *sp^2*- hybridized atoms. The lone pair of heteroatom (*e.g.* N in the case of pyrrole) participates in the delocalization and constitutes an aromatic compound with 4n+2 π electrons (Huckel rule of aromaticity). The molecular orbital diagram of pyrrole is shown on figure 11.

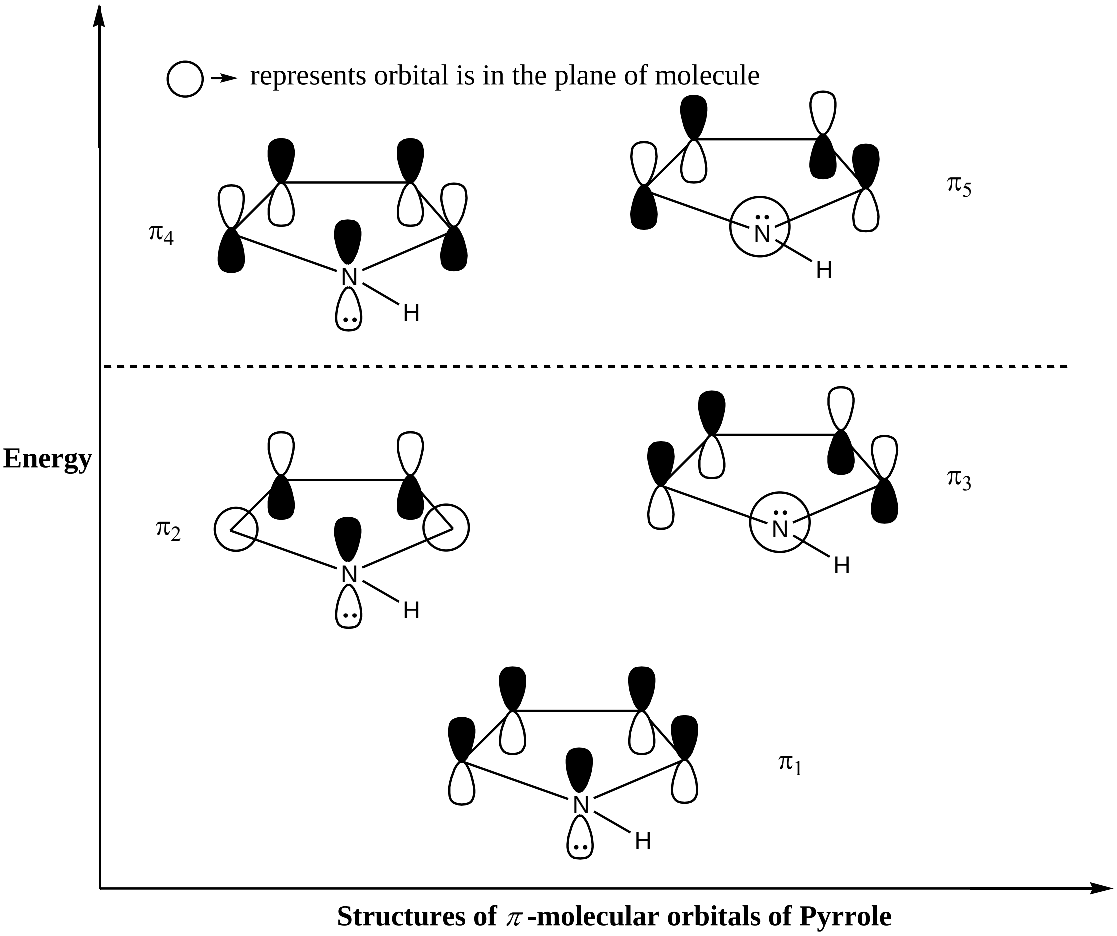


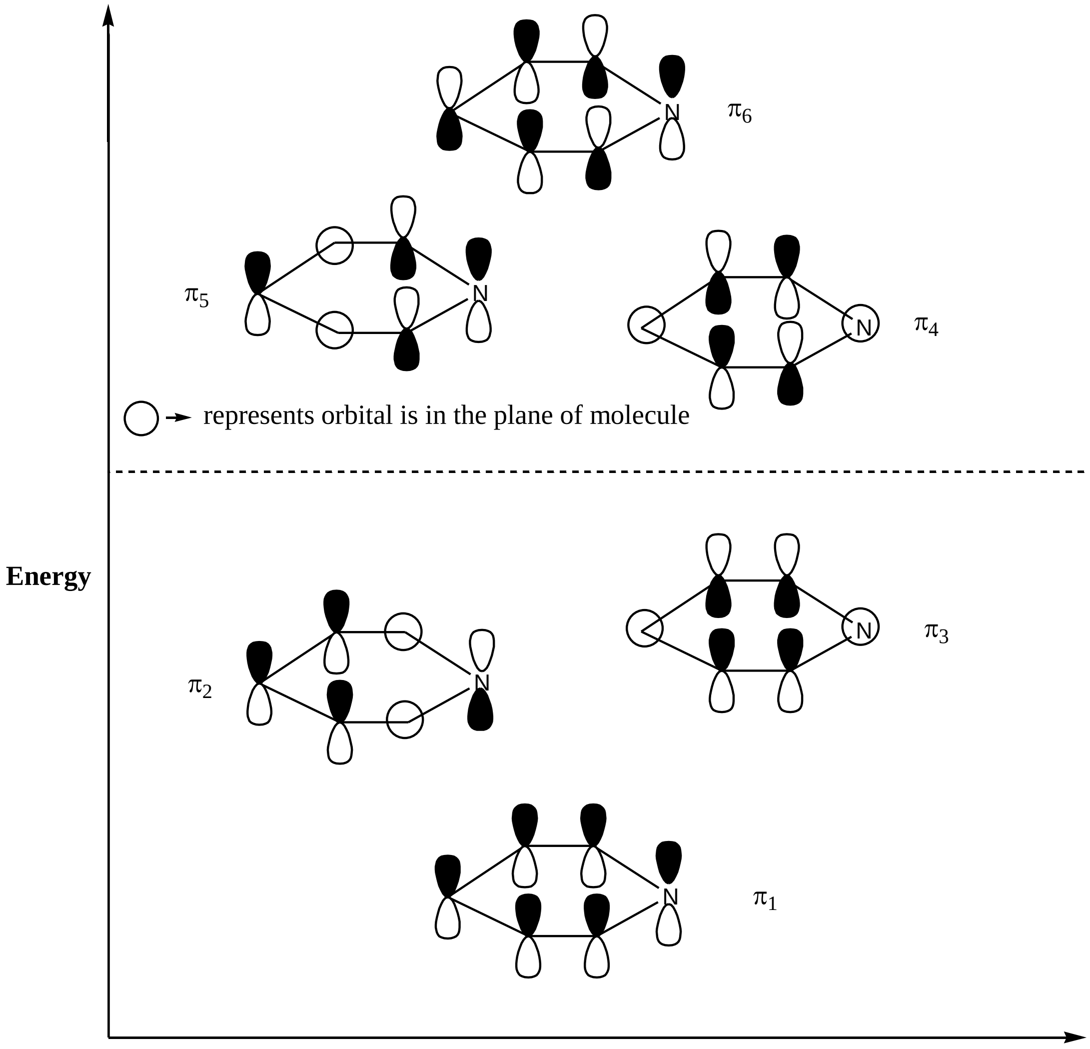
Figure 11. π -Molecular orbital of Pyrrole

If we recall the π -molecular orbital of benzene that we have studied in undergraduate chemistry course of semester one; where you could see that the π -molecular orbitals of benzene follow the rule of degeneracy (set of orbitals with same energy, same symmetry and similar orientation). However, the introduction of heteroatom by replacement of ring carbon leads the formation of non-degenerated set of π -molecular orbital. For example, we can see from the figure 11, splitting of the π_2 and π_3 levels; the orbital π_2 has a large orbital coefficient on nitrogen (due to more electro negativity of nitrogen than carbon) and thus lower in energy than $\pi_{3.}$ The π_3 molecular orbital, in which the lone pair of the nitrogen atom lies on the perpendicular plane of the *p*-orbitals of ring carbon atoms helps to create two nodal points, hence, do not participate in the formation of ring current. Thus the nitrogen atom of π_3 has less orbital coefficient that π_2. In the five membered heterocyclic compounds six- π electron are distributed over five atoms therefore the carbon atoms of such heterocyclic compounds have more electron density than that of benzene. Among the five constituting atoms of pyrrole, the nitrogen has maximum electron density than four carbon atoms this is because of the more electro-negativity of nitrogen.

Similar description may also be made for the other five membered heterocyclic compounds like Furan and Thiophene.

4.5.2 MOLECULAR ORBITAL PICTURE OF PYRIDINE:

Six membered heterocyclic compounds (with one heteroatom) are structural analogous to that of benzene but with a heteroatom replacing one of the carbon atom of the benzene ring. Pyridine is the most common example of this class of heterocyclic compounds. Pyridine is a planar molecule like benzene, since all the carbon atoms and nitrogen atom of the pyridine are of *sp*^{2}-hybridized. The lone pair of electrons of nitrogen atom lies in the plane of the ring. Pyridine is also an aromatic compound with (4n+2) π -electrons (Huckel rule of aromaticity). The molecular orbital diagram of pyridine is shown on figure 12.



Orbital representation of π–molecular orbital of Pyridine

Figure 12. π -Molecular orbital of

Pyridine

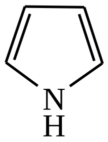
The six p-orbitals are combined together to give six delocalized π -molecular orbitals. Each π -molecular orbital can contain two electrons. Out of six π -molecular orbitals three are called bonding π -molecular orbital and three are called antibonding π -molecular orbital. All six π -electrons are accommodated by three bonding π -molecular orbital. Similar to pyrrole, the π -molecular orbital of pyridine also have lower energy in comparison to benzene, this is because of the presence of nitrogen atom in place of a ring carbon. As already discussed in the previous section that the due to more electro-negativity of nitrogen than carbon the electron density at nitrogen atom is greater than the carbon, thus nitrogen have comparatively larger orbital coefficient than carbon, therefore, the π -molecular orbital of pyridine are of lower energy than that of benzene. Similar to pyrrole, in pyridine also the introduction of heteroatom by replacement of ring carbon leads the formation of non-degenerated set of π -molecular orbital. For example, we can see from the figure 12, splitting of the π_2 and π_3 levels; the orbital π_2 has a large orbital coefficient on nitrogen (due to more electro negativity of nitrogen than carbon) and thus lower in energy than π_3 (figure 12).

4.6 STRUCTURE AND AROMATICITY OF PYRROLE, FURAN, THIOPHENE AND PHRIDINE

4.6.1 STRUCTURE AND AROMATICITY OF PYRROLE:

Structure and aromaticity of pyrrole can be discussed according to following points.

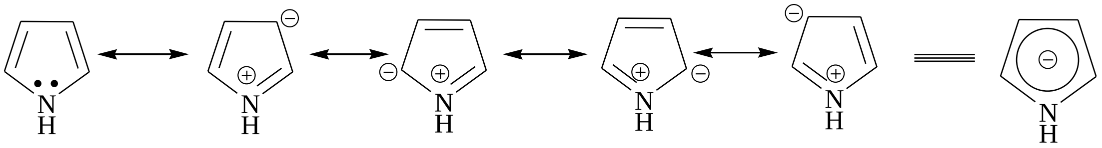
1. The molecular weight determination method and related analytical studies revealed that the molecular formula of Pyrrole would be C_4H_5N.
2. The possible structure of pyrrole can be given by considering the tetravalency of carbon and trivalency of nitrogen, and it is shown below



Pyrrole

3. Pyrrole usually does not explain the simple addition reactions like alkenes under normal conditions. This is because of the delocalization of lone pair of nitrogen atom through conjugation. This delocalization provides extra stability to the double bonds of pyrrole.

Also the proposed structure of pyrrole is considered as an aromatic compound since it follows the Huckel's aromaticity rules (4n+2 electron rule). The aromatic nature and extra-stability of pyrrole can also be supported by the formation of its different resonating structures as shown in below figure. The structure of pyrrole is the resonance hybrid of all resonating structures.



4. The delocalization of lone pair of nitrogen in pyrrole through conjugation also suggests that the pyrrole molecule should have planar geometry. This is only possible when the orbitals of carbon and nitrogen in pyrrole are *sp*^{2}- hybridized. The three *sp*^{2}- hybridized orbitals of nitrogen contain one- one electron in each *sp*^{2}- hybridized orbital. The unhybridized *p*-orbital of nitrogen contains lone pair of electrons. Two *sp*^{2}- hybridized orbitals of nitrogen atom forms □-bond with two carbon atoms of the ring whereas the third *sp*^{2}- hybridized orbital of nitrogen atom forms □-bond with hydrogen atom. Similarly each *sp*^{2}- hybridized carbon forms two □-bonds with neighboring carbon atoms and one □-bond with hydrogen atom. The unhybridized orbitals of each carbon contain one electron. These unhybridized orbitals of carbon and nitrogen form a delocalized electron cloud above and below the pentagonal ring of pyrrole. The delocalized electron cloud is shown in figure 13.

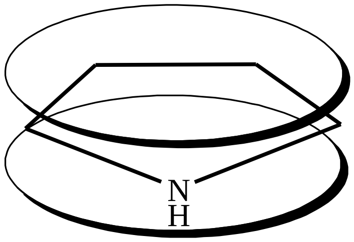


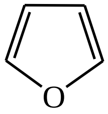
Figure 13. Delocalized electron cloud above and below the pyrrole ring

4.6.2 STRUCTURE AND AROMATICITY OF FURAN:

Structure and aromaticity of furan can be discussed according to following points.

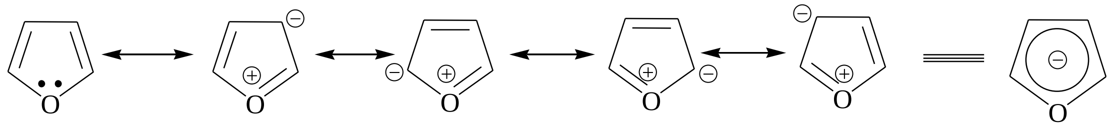
1. The molecular weight determination method and related analytical studies revealed that the molecular formula of Furan would be C_4H_4O.

2. The possible structure of Furan can be given by considering the tetravalency of carbon and bivalency of oxygen, and it is shown below



Furan

3. Like Pyrrole, due to delocalization of one of the lone pair of electron of oxygen in furan, it also does not explain the fundamental addition reactions like simple alkenes under normal condition. The proposed structure of furan is also considered as an aromatic compound since it follows the Huckel's aromaticity rules (4n+2 electron rule). The aromatic nature and extra-stability of furan is also supported by the formation of its different resonating structures as shown in below figure. The structure of furan is the resonance hybrid of all resonating structures.



4. The delocalization of lone pair of oxygen in furan through conjugation also suggests that the furan molecule should have planar geometry. This is only possible when the orbitals of carbon and oxygen in furan are *sp*^{2}- hybridized. The two *sp*^{2}- hybridized orbitals of oxygen contain one- one electron in each *sp*^{2}- hybridized orbital; however, third *sp*^{2}- hybridized orbital contains one lone pair of electron. The unhybridized *p*-orbital of oxygen contains two electrons. Two *sp*^{2}- hybridized orbitals of oxygen atom forms π -bond with two carbon atoms of the ring, whereas the third *sp*^{2}- hybridized orbital of oxygen atom accommodate lone pair of electron. Similarly each *sp*^{2}- hybridized carbon forms two π -bonds with neighboring atoms and one π -bond with hydrogen atom. The unhybridized orbitals of each carbon contain one electron. These unhybridized orbitals of carbon and oxygen form a delocalized electron cloud above and below the pentagonal ring of furan. The delocalized electron cloud is shown in figure 14.

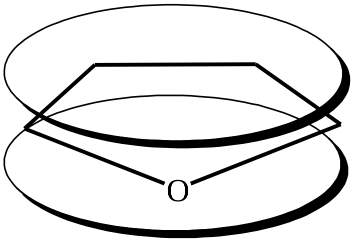
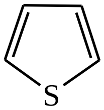


Figure 14. Delocalized electron cloud above and below the furan ring

4.6.3 STRUCTURE AND AROMATICITY OF THIOPHENE:

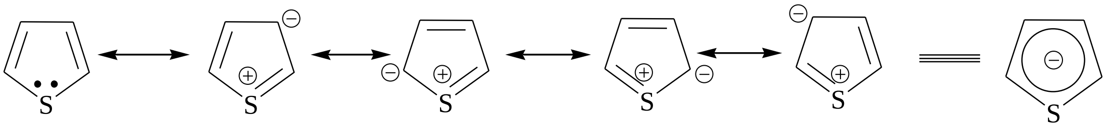
Structure and aromaticity of Thiophene can be discussed according to following points.

1. The molecular weight determination method and related analytical studies revealed that the molecular formula of Thiophene would be C_4H_4S.
2. The possible structure of Thiophene can be given by considering the tetravalency of carbon and bivalency of sulphur, and it is shown below



Thiophene

3. Like Pyrrole, due to delocalization of one of the lone pair of electron of oxygen in thiophene, it also does not explain the fundamental addition reactions like simple alkenes under normal condition. The proposed structure of thiophene is also considered as an aromatic compound since it follows the Huckel's aromaticity rules (4n+2 electron rule). The aromatic nature and extra-stability of thiophene is also supported by the formation of its different resonating structures as shown in below figure. The structure of thiophene is the resonance hybrid of all resonating structures.



4. The delocalization of lone pair of sulphur in furan through conjugation also suggests that the thiophene molecule should have planar geometry. This is only possible when the orbitals of carbon and sulphur in thiophene are sp^2- hybridized. The two sp^2- hybridized orbitals of sulphur contain one- one electron in each sp^2- hybridized orbital; however, third sp^2- hybridized orbital contains one lone pair of electron. The unhybridized *p*-orbital of sulphur contains two electrons. Two sp^2- hybridized orbitals of sulphur atom forms π -

bond with two carbon atoms of the ring, whereas the third *sp^2*- hybridized orbital of sulphur atom accommodate lone pair of electron. Similarly each *sp^2*- hybridized carbon forms two π -bonds with neighboring atoms and one π -bond with hydrogen atom. The unhybridized orbitals of each carbon contain one electron. These unhybridized orbitals of carbon and sulphur form a delocalized electron cloud above and below the pentagonal ring of thiophene. The delocalized electron cloud is shown in figure 15.

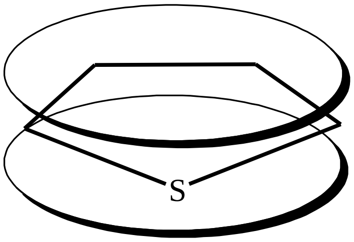


Figure 15. Delocalized electron cloud above and below the thiophene ring

4.6.4 STRUCTURE AND AROMATICITY OF PYRIDINE:

Structure and aromaticity of Thiophene can be discussed according to following points.

1. The molecular weight determination method and related analytical studies revealed that the molecular formula of Pyridine as C_5H_5N.
2. Pyridine was found to be basic in nature since it forms salt with acids

$$\underset{\text{Pyridine}}{C_5H_5N} \quad + \quad HCl \longrightarrow \underset{\text{Pyridinium hydrochloride}}{C_5H_5N.HCl}$$

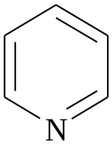
3. Pyridine does not react with acetyl chloride and nitrous acid it confirms that pyridine does not have primary or secondary amino group. The above fact also confirms that the pyridine is a mono-acidic tertiary base.
4. Pyridine also reacts with equimolar amount of methyl iodide to form a quaternary ammonium salt.

$$\underset{\text{Pyridine}}{C_5H_5N} \quad + \quad CH_3I \longrightarrow \underset{\text{N-methyl pyridinium iodide}}{[C_5H_5N^+ (CH_3)]I^-}$$

5. The molecular formula also indicates that it is a highly unsaturated compound; however, pyridine does not give the simple addition reactions like alkenes.
6. Pyridine is also found stable towards the oxidizing agents.
7. Pyridine exhibits aromatic character like benzene and give electrophilic substitution reactions such as halogenation, nitration and sulphonation.

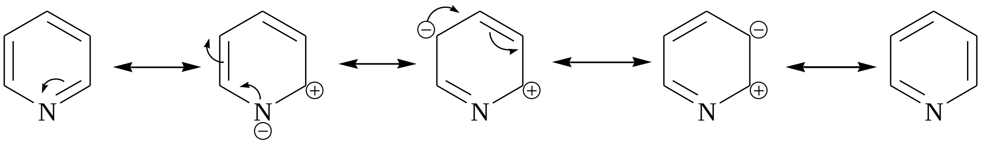
Last two reactions confirm the aromatic character of pyridine.

8. Based on above observations the possible structure of Pyridine can be given by considering the tetravalency of carbon and trivalency of nitrogen, and it is shown below



pyridine

This structure is considered to be the resonance hybrid of the following structures.



Resonance in pyridine molecule is supported by the following points:

i. All the carbon, nitrogen and hydrogen atoms lie in the same plane all the carbon and nitrogen atoms of pyridine are sp^2 hybridized.

ii. Each sp^2- hybridized carbon forms two π -bonds with neighboring atoms and one □-bond with hydrogen atom.

iii. The unhybridized p-orbital of each carbon atom is involved to form the □-bond with neighboring atoms.

iv. The two of three sp^2- hybridized orbitals of nitrogen contain one- one electron in each sp^2- hybridized orbital; however, the third sp^2- hybridized orbital of nitrogen contains lone pair of electron. The unhybridized p orbital of nitrogen contains one electron which is involved to form π -bond with any of the neighboring carbon atoms.

v. All the carbon-carbon bonds in pyridine are of equal length (*i.e.* 1.39 Å).

vi. The carbon-nitrogen bonds are also of equal length (1.37 Å).

vii. These properties resists the pyridine from simple addition reaction of C=C double bond. Since in pyridine there is no true C=C double bond.

viii. The resonating structures represent that the more electron density at C-3, hence electrophilic substitution in pyridine takes place at C-3.

9. The delocalized electron cloud in pyridine is shown in figure 16.

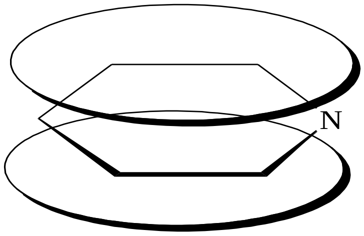


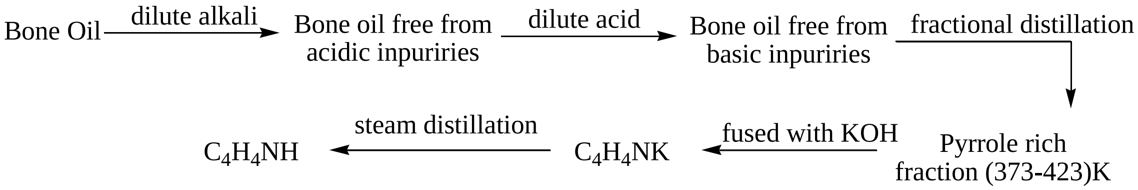
Figure 16. Delocalized electron cloud above and below the pyridine ring

4.7 METHODS OF PREPARATION AND CHEMICAL REACTIONS

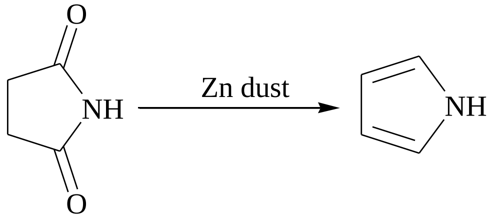
4.7.1 METHODS OF PREPARATION OF PYRROLE:

Following are the general methods of preparation of pyrrole:

- **i. From bone oil:** Bone oil is rich of pyrrole. The basic and acidic impurities of Bone oil are removed by sequential treatment of it with dilute acidic and dilute basic solutions. The treated Bone oil is then subjected for fractional distillation, the fraction obtained between 373K and 423K is collected. The collected fraction is then purified with KOH to obtained potassiopyrrole. Steam distillation of potassiopyrrole gives pure pyrrole.



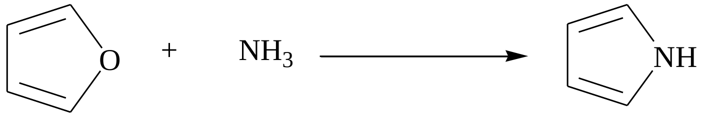
- **ii. From succinimide:** Succinimide when is distilled with Zn dust it reduces the succinimide to pyrrole.



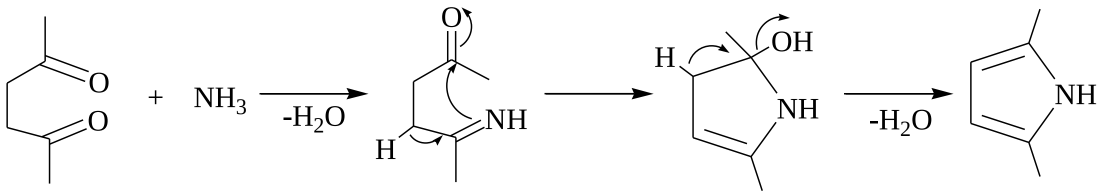
Succinimide

Pyrrole

- **iii. From Furan:** Industrially pyrrole is prepared by passing a mixture of furan and ammonia over alumina over 400° C.



iv. Pall-Knorr synthesis: In this method, when a 1,4-diketone is heated with ammonia or a primary amine it gives the corresponding pyrrole derivatives.



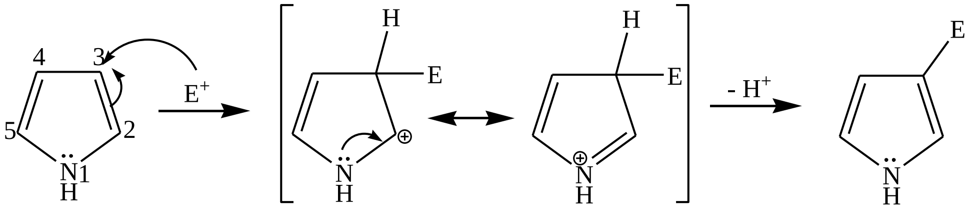
4.7.2 PROPERTIES OF PYRROLE:

i. **Physical Properties of pyrrole:** Pyrrole is a colorless liquid with boiling point 131° C. It is highly sensitive to air, when pyrrole is exposed to air it turns brown and gradually resinifies. Pyrrole is slightly soluble in water but completely miscible in ether and ethanol.

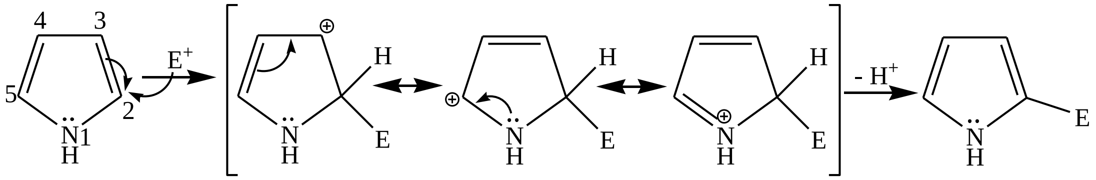
ii. **Chemical Properties:** Pyrrole is an aromatic compound and more reactive than benzene. Because of the aromatic nature pyrrole gives all characteristic reactions (electrophilic substitution reactions) of aromatic compounds such as halogenation, nitration, sulphonation, Friedel-Crafts reactions etc.

Pyrrole undergoes electrophilic substitution at the position C-2. Approach of the electrophile at position C-2 leads the formation of three resonating structures; however, only two resonating structures are obtained when the electrophile approaches at position C-3. Thus the intermediate obtained by the approach of electrophile at position C-2 is more stable than the intermediate obtained by the approach of electrophile at position C-3. This is the reason that electrophilic attack occurs at position C-2. Following mechanism is suggested for the electrophilic attack at position C-2.

Attack at position C-3:



Attack at position C-2:

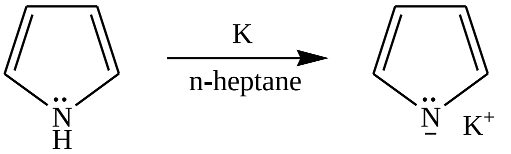


E= electrophile

All the electrophilic substitution reactions of pyrrole occur at position C-2 and follow the similar mechanism as shown above.

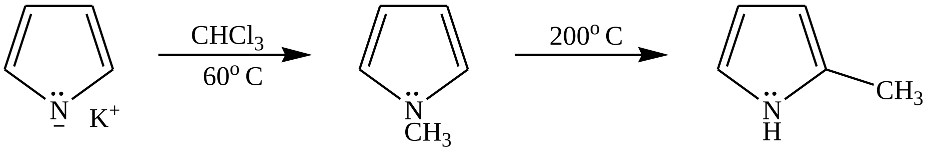
a) **Acidic Character of Pyrrole:** The lone pair of nitrogen usually participates in resonance and thus makes the pyrrole aromatic. That is the reason, the lone pair of nitrogen could not be available free to react with a proton.

However, pyrrole can behave as a weak acid. When pyrrole is heated with potassium in n-heptane as solvent, stable potassium pyrrolide is formed.



Pyrrole Potassium pyrrolide

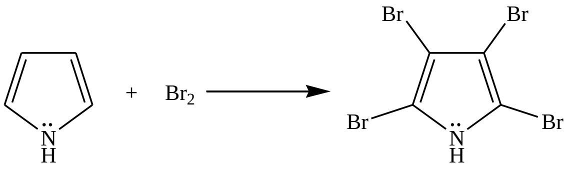
Potassium pyrrolide when reacts with alkyl halide at 60° C to give *N*-alkyl pyrrole. The *N*-alkyl pyrrole can easily rearrange to C-alkyl pyrrole.



Potassium pyrrolide 1-Methylpyrrole 2-Methylpyrrole

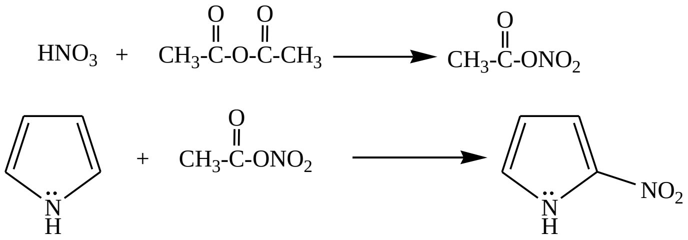
b) **Electrophilic Substitution Reactions of Pyrrole:** Pyrrole undergoes electrophilic substitution reactions at position C-2.

i. **Halogenation:** Pyrrole reacts with halogens [X_2 (X_2 = Cl_2, Br_2 and I_2)] to give tetrahalopyrrole. For example, Reaction of bromine with pyrrole gives tetrabromopyrrole.



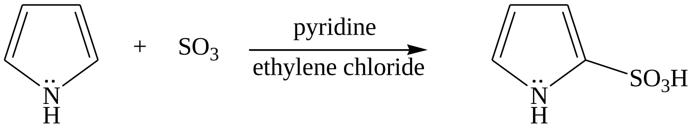
Pyrrole 2,3,4,5-tetrabromopyrrole

ii. **Nitration:** Nitration of pyrrole is achieved by reacting it with HNO_3 in acetic anhydride. The reaction of HNO_3 and acetic anhydride resulted acetyl nitrate in which $–NO_2$ acts as an electrophile.



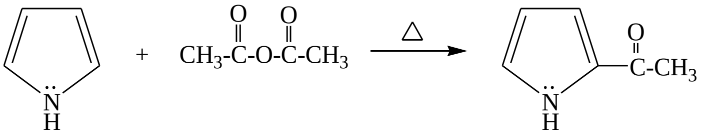
Pyrrole 2-nitropyrrole

iii. **Sulphonation:** Sulphonation of pyrrole is achieved by reacting it with sulfur trioxide (SO_3) – pyridine mixture in ethylene chloride.



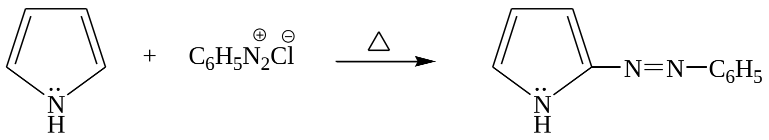
Pyrrole Pyrrole-2-sulfonic acid

iv. **Friedel-Crafts Acylation:** Reaction of pyrrole with acetic anhydride under heating condition gives 2-acetylpyrrole.

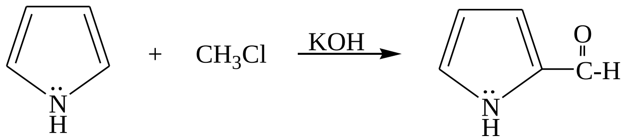


Pyrrole 2-acetylpyrrole

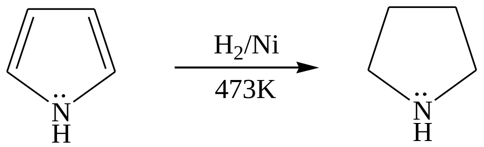
v. **Diazotization:** Pyrrole reacts with benzenediazonium chloride in acidic medium to give 2-phenylazopyrrole.



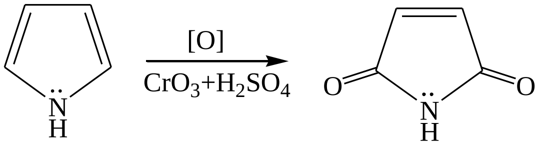
vi. Reimer-Tiemann Reaction: Pyrrole reacts with Chloroform in presence of KOH to give 2-Formylpyrrole. This reaction is known as Reimer-Tiemann reaction. It also takes place through electrophilic substitution reaction mechanism.



c) Reduction: Pyrrole can be reduced to pyrrolidine (tetrahydropyrrole) by H_2 gas in Raney Ni at very high temperature (473K).



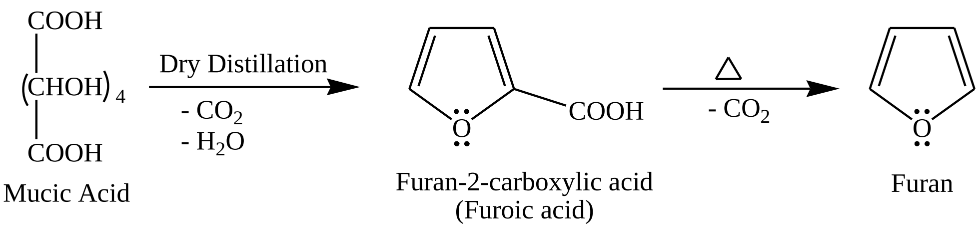
d) Oxidation: Pyrrole when oxidized with Chromium trioxide in H_2SO_4, it gives Malecimide.



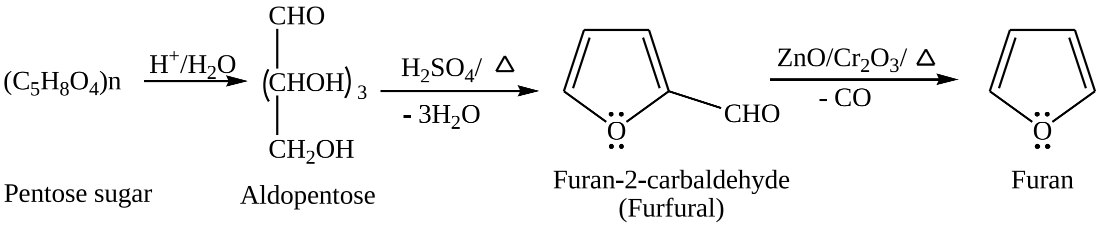
4.7.3 METHODS OF PREPARATION OF FURAN:

Following are the general methods of preparation of Furan:

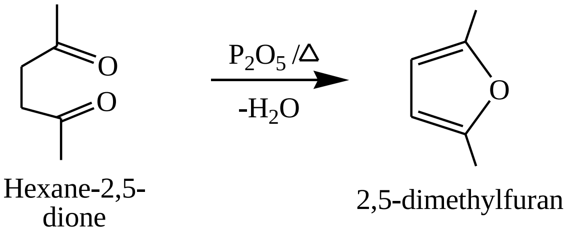
i. From Mucic acid: Dry distillation of mucic acid first gives Furoic acid which on decarboxylation by heating gives Furan.



ii. **From Furfural:** Furan is synthesized from furfural which is obtained by acid-hydrolysis of pentose sugars.



iii. **Paal-Knorr Synthesis:** Dehydration of 1,4-diketone with P_2O_5 (phosphorous Pentaoxide) gives derivatives of Furan.

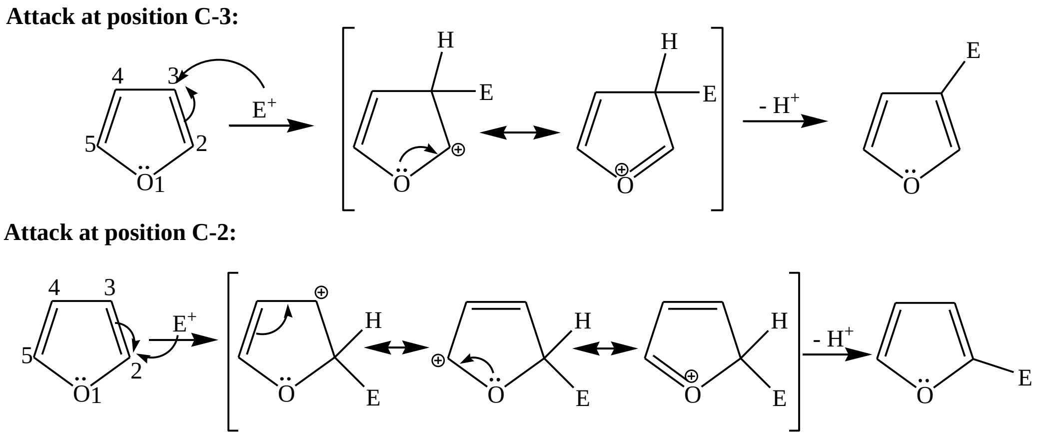


4.7.4 PROPERTIES OF FURAN:

i. **Physical Properties of Furan:** Furan is colorless liquid. Its boiling point is 31.4° C. It has an odor similar to Chloroform. It is insoluble in ether but soluble in most of the organic solvents.

ii. **Chemical Properties of Furan:** furan is an aromatic compound and more reactive than benzene. Because of the aromatic nature, furan gives all characteristic reactions (electrophilic substitution reactions) of aromatic compounds such as halogenation, nitration, sulphonation, Friedel-Crafts reactions etc.

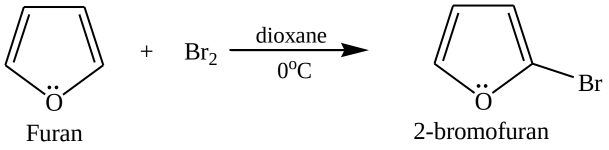
Similar to pyrrole, furan also undergoes electrophilic substitution at the position C-2. Approach of the electrophile at position C-2 leads the formation of three resonating structures; however, only two resonating structures are obtained when the electrophile approaches at position C-3. Thus the intermediate obtained by the approach of electrophile at position C-2 is more stable than the intermediate obtained by the approach of electrophile at position C-3. This is the reason that electrophilic attack occurs at position C-2. Following mechanism is suggested for the electrophilic attack at position C-2.



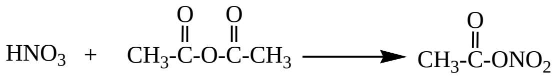
E= electrophile

a) Electrophilic Substitution Reactions of Furan: Furan undergoes electrophilic substitution reactions at position C-2.

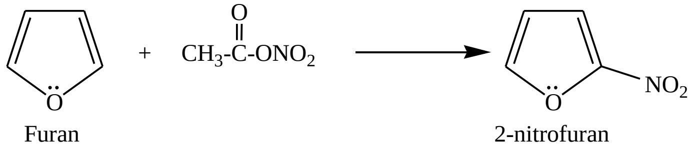
i. Halogenation: Furan reacts with halogens [X_2 (X_2 = Cl_2, Br_2 and I_2)] to give 2-halofuran. For example, reaction of bromine with Furan gives 2-bromofuran.



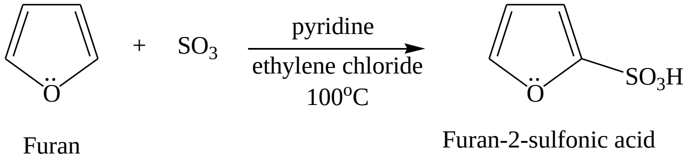
ii. Nitration: Nitration of furan is achieved by reacting it with HNO_3 in acetic anhydride. The reaction of HNO_3 and acetic anhydride resulted acetyl nitrate in which $-NO_2$ acts as an electrophile.



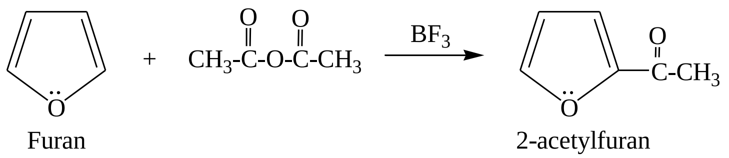
$$HNO_3 + CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3 \longrightarrow CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}ONO_2$$



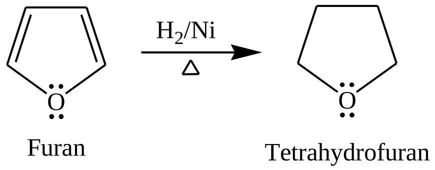
iii. Sulphonation: Sulphonation of Furan is achieved by reacting it with sulfur trioxide (SO_3) – pyridine mixture in ethylene chloride at 100° C.



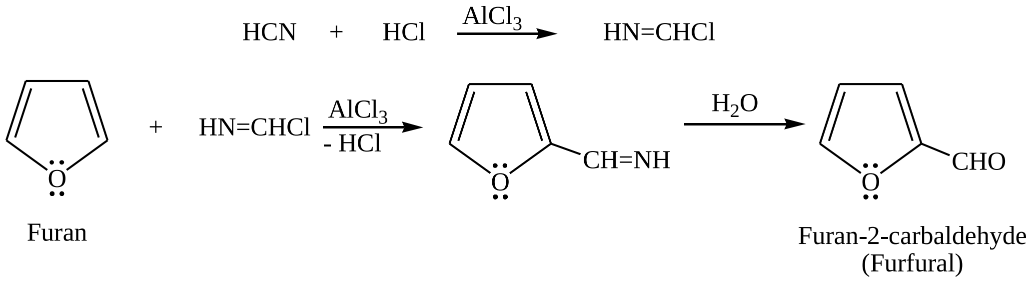
iv. **Friedel-Crafts Acylation:** Reaction of furan with acetic anhydride in presence of BF_3 gives 2-acetylfuran.



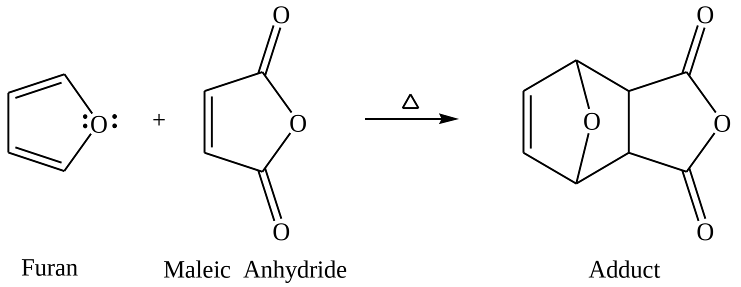
b) Reduction: On catalytic hydrogenation of furan, the tetrehydrofuran (THF) is obtained. THF is used as a solvent in place of ether in the Grignard reactions.



c) Gattermann Koch Synthesis: When furan is treated with a mixture of HCN and HCl in the presence of Lewis acid catalyst AlCl3, furfural is obtained as final product.



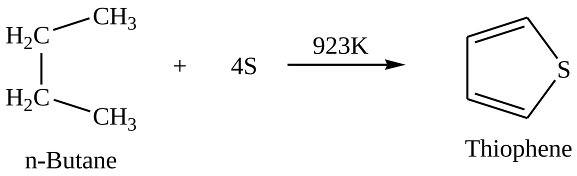
d) Diels-Elder Reaction: Furan is the only heterocyclic compound which undergoes Diels-Elder reaction. Diels-Elder reaction is a cycloaddtion reaction of 4π-system to 2π-system.



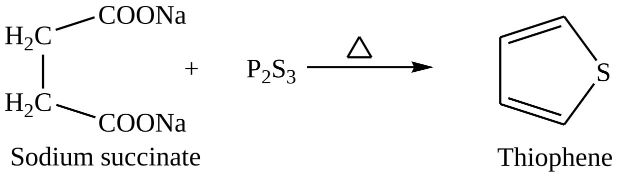
4.7.5 METHODS OF PREPARATION OF THIOPHENE:

Following are the general methods of preparation of thiophene

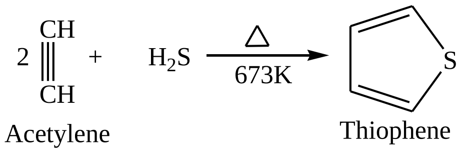
i. **From *n*-Butane:** Thiophene is obtained when n-butane is heated with elemental sulphur at very high temperature (923K).



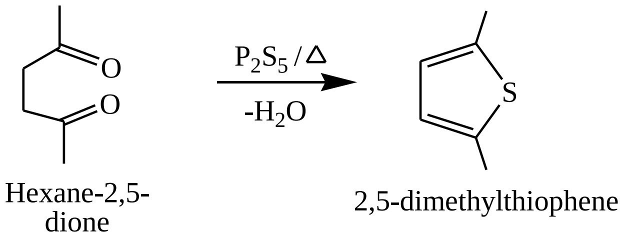
- **ii. Laboratory Method:** When sodium succinate is heated with phosphorous sulphide, thiophene is obtained.



- **iii. Industrial Method:** Industrially, thiophene is prepared by passing a mixture of acetylene and hydrogen sulphide through a tube containing alumina (Al_2O_3) at 673K.



- **iv. Pall-Knorr synthesis of thiophene derivatives:** In this method, dehydration of 1,4-diketone with P_2S_5 (phosphorous Pentasulphide) gives derivatives of thiophene.

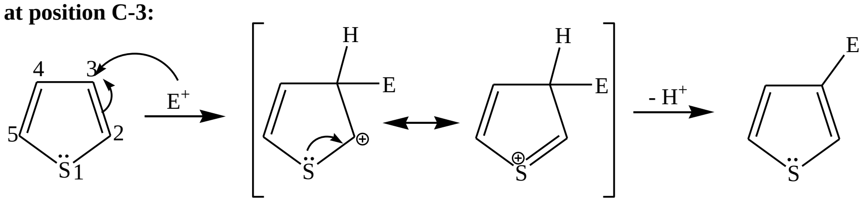


4.7.6 PROPERTIES OF THIOPHENE:

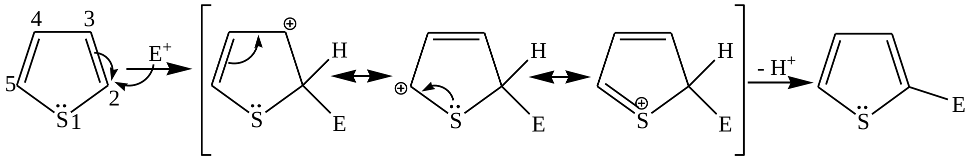
- **i. Physical Properties of thiophene:** Thiophene is colorless liquid. Boiling point of thiophene is 357 K. It smells like benzene. It is soluble in alcohol and ether but insoluble in water.
- **ii. Chemical Properties of thiophene:** Thiophene is an aromatic compound and more reactive than benzene. Because of the aromatic nature, thiophene gives all characteristic reactions (electrophilic substitution reactions) of aromatic compounds such as halogenation, nitration, sulphonation, Friedel-Crafts reactions etc.

Similar to pyrrole and furan; thiophene also undergoes electrophilic substitution at the position C-2. Approach of the electrophile at position C-2 leads the formation of three resonating structures; however, only two resonating structures are obtained when the electrophile approaches at position C-3. Thus the intermediate obtained by the approach of electrophile at position C-2 is more stable than the intermediate obtained by the approach of electrophile at position C-3. This is the reason that electrophilic attack occurs at position C-2. Following mechanism is suggested for the electrophilic attack at position C-2.

Attack at position C-3:



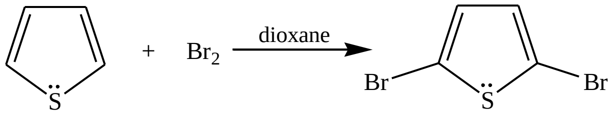
Attack at position C-2:



E= electrophile

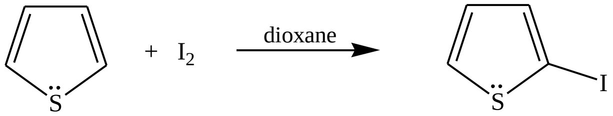
a) Electrophilic Substitution Reactions of Thiophene: Thiophene undergoes electrophilic substitution reactions at position C-2.

i. Halogenation: Thiophene reacts with halogens [X_2 (X_2 = Cl_2, Br_2 and I_2)] to give 2-halofuran. For example, reaction of bromine with Thiophene in absence of any halogen carrier gives 2,5-dibromothiophene.



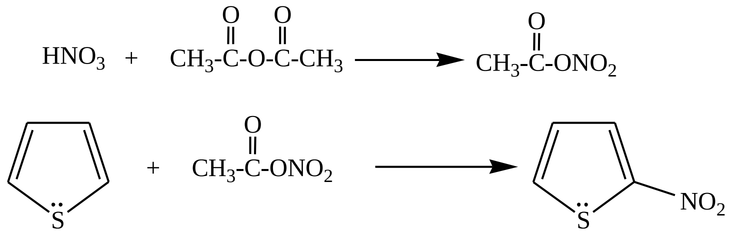
Thiophene
2,5-dibromothiophene

However, Iodination of thiophene in presence of yellow mercuric oxide gives 2-iodothiophene.



Thiophene
2-Iodothiophene

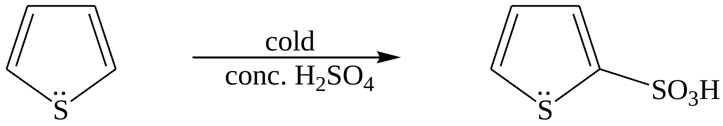
ii. Nitration: 2-Nitrothiophene is obtained when nitration of thiophene is performed by reacting it with fuming HNO_3 in acetic anhydride. The reaction of HNO_3 and acetic anhydride resulted acetyl nitrate in which $–NO_2$ acts as an electrophile.



$$HNO_3 + CH_3\text{-}\overset{\overset{O}{\|}}{C}\text{-}O\text{-}\overset{\overset{O}{\|}}{C}\text{-}CH_3 \longrightarrow CH_3\text{-}\overset{\overset{O}{\|}}{C}\text{-}ONO_2$$

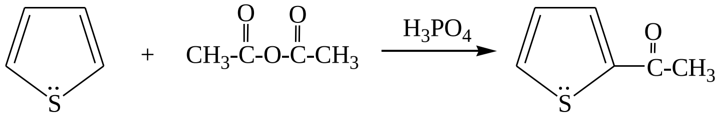
Thiophene 2-nitrothiophene

iii. Sulphonation: Sulphonation of thiophene is achieved by reacting it with cold concentrated H_2SO_4. Thiophene-2-sulphonic acid is obtained as product.



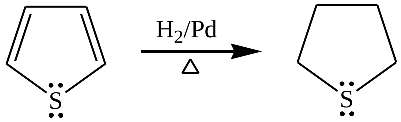
Thiophene Thiophene-2-sulfonic acid

iv. Friedel-Crafts Acylation: Reaction of thiophene with acetic anhydride in presence of H_3PO_4 gives 2-acetylthiophene.



Thiophene 2-acetylthiophene

b) Reduction: On catalytic hydrogenation of thiophene, the tetrehydrothiophene (Thiophane) is obtained.

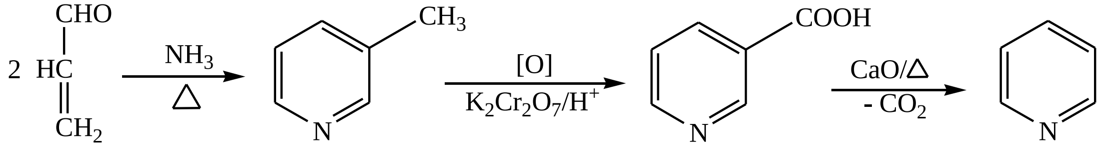


Thiophene Tetrahydrothiophene

4.7.7 METHODS OF PREPARATION OF PYRIDINE:

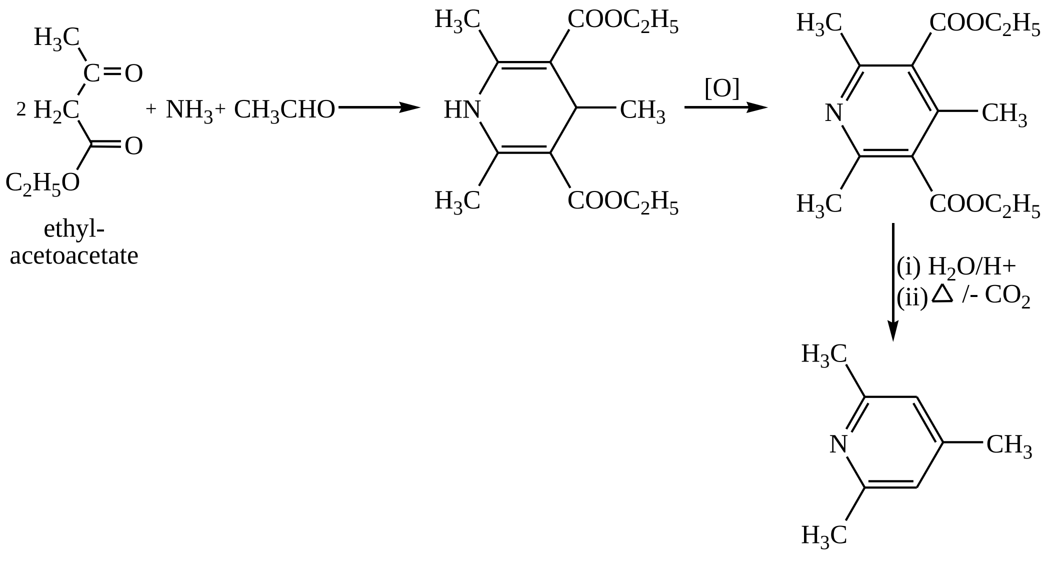
Following are the general methods of preparation of pyridine:

i. From acroline: Pyridine can be prepared by the reaction of acroline and ammonia according to following reaction steps.

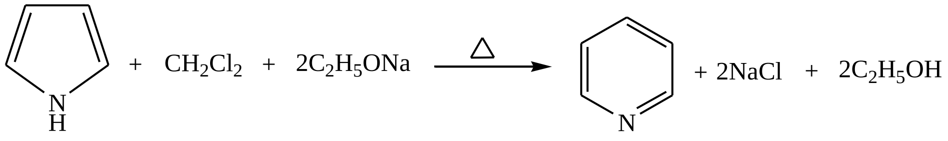


Acrylaldehyde 3-Methylpyridine Nicotinic acid Pyridine

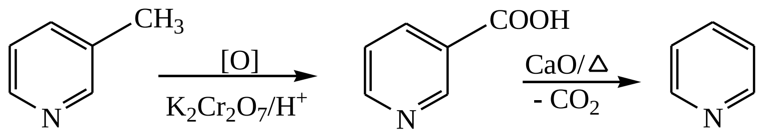
ii. Hantzsch Synthesis (1882): In this method, the condensation of a beta-dicarbonyl compound, ammonia and an aldehyde lead the formation of 1,4-dihydropyridine derivative. The 1,4-dihydro pyridine derivative on oxidation with HNO_3 yields the formation of pyridine derivative.



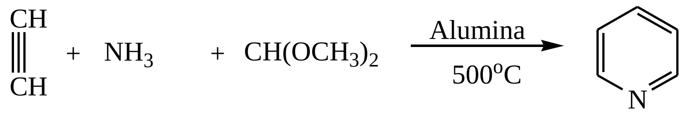
iii. From pyrrole: Pyrrole when heated with methylene chloride in presence of sodium ethoxide, pyridine is formed.



iv. From Picoline: Beta-picoline on oxidation with potassium dichromate and sulphuric acid gives nicotinic acid, which on decarboxylation with calcium oxide gives pyridine.



v. Industrial Method: Industrially pyridine is prepared by heating the acetylene, ammonia and formaldehyde dimethylacetal in the presence of alumina at 500° C.



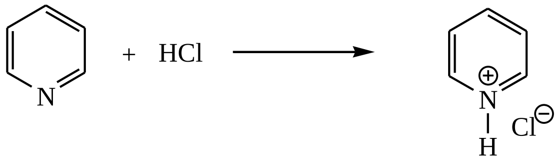
Acetylene Pyridine

4.7.8 PROPERTIES OF PYRIDINE:

i. **Physical Properties of Pyridine:** Pyridine is a colourless liquid. Its boiling point is 115.5° C. It has a characteristic unpleasant odor. It is soluble in water and most organic solvents.

ii. **Chemical properties of Pyridine:** Chemical properties of pyridine are discussed as follow:

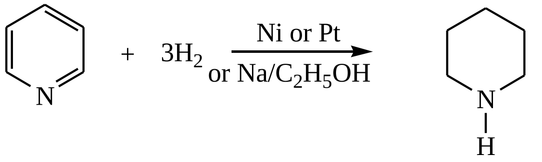
a. Basic character of pyridine: Pyridine is basic in nature. Its pK_b is 8.75. It reacts with strong acids to form salts.



Pyridine Pyridinium Chloride

The basic nature of pyridine is due to the freely available lone pair of electrons in sp^2 hybridized orbital pyridine, which does not participate in the formation of delocalized π -molecular orbital. Pyridine is less basic in comparison to aliphatic amines whereas, it is more basic than aniline and pyrrole. This is because the lone pair of electrons in aliphatic amines exists in sp^3 hybridized orbital, however, in case of pyridine the lone pairs of electrons exists in sp^2 hybridized orbital. Electrons are held more tightly by the nucleus in a sp^2 hybridized orbital than an sp^3 hybridized orbital. Hence the lone pair of electrons in pyridine is less available for protonation. The less basicity of pyrrole and aniline can be explained in terms of non-availability of these lone pair of electrons on nitrogen atom. These lone pair of electrons is involved in the formation of delocalized π -molecular orbital.

b. Reduction: Under catalytic hydrogenation of pyridine hexahydropyridine is formed. It is also known as Piperidine.

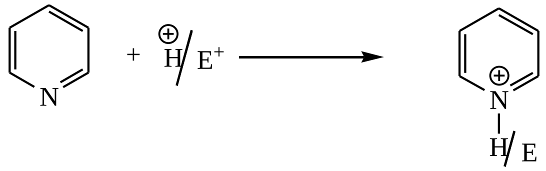


Pyridine Piperidine

c. **Electrophilic substitution Reactions:** Pyridine is also an aromatic compound. It is less aromatic than benzene and pyrrole. Pyridine usually considered a highly deactivated aromatic nucleus towards electrophilic substitution reactions. Therefore highly vigorous reaction conditions should be used for these reactions to take place. The low reactivity of pyridine towards the electrophilic substitution reactions is due to the following reasons:

- The higher electro negativity of nitrogen atom reduces electron density on the ring, thus deactivate the ring.
- Pyridine is highly sensitive to acidic medium; it readily forms pyridinium cation with a positive charge on nitrogen atom. Similarly, electrophile itself may also react with pyridine to form corresponding pyridinium ion. This positive charge on nitrogen atom decreases electron density on nitrogen atom, consequently, the electron density on ring also decreases.

However, the effect of such deactivation is comparatively lower at position C-3. The position C-3 is thus, comparatively, the position of highest electron density in pyridine.

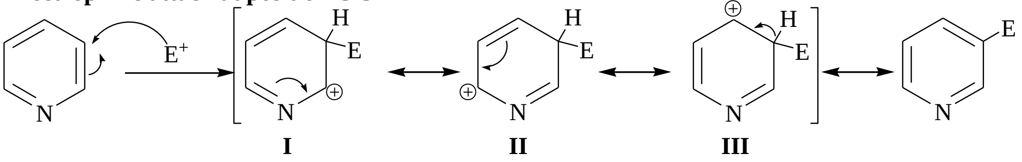


Pyridine

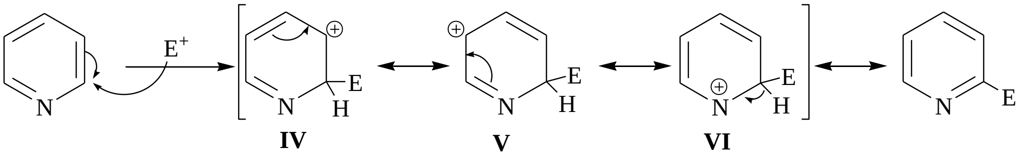
Pyridinium cation

This is the reason that the pyridine undergoes electrophilic substitution at position C-3. Pyridine also gives electrophilic substitution like halogenation, nitration and sulphonation only under drastic conditions. Pyridine does not give Friedel-crafts reaction. Approach of the electrophile at position C-3 leads the formation of three resonating structures (I, II and III); similarly, approach of electrophile at position C-2 also leads the formation of three resonating structures (IV, V and VI). However, out of the three contributing resonating structures for the intermediate ion resulting from the attack of electrophile at position C-2, structures VI is considered as an unstable resonating form because in resonating structure VI the more electronegative nitrogen atom bears a +ve charge. Because of the unstable nature of one of the resonating structure of the intermediate ion formed during the attack of electrophile at position C-2 than that of the formed during the attack of electrophile at position C-3, the electrophilic substitution in pyridine at position C-3 is always favoured. Following mechanism is suggested for the electrophilic attack at position C-3.

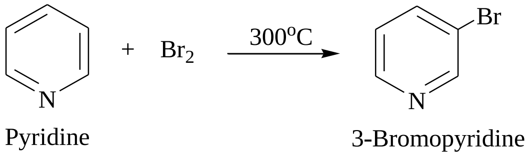
Electrophilic attack at position C-3



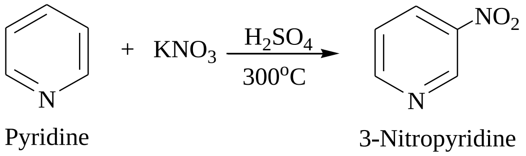
Electrophilic attack at position C-2



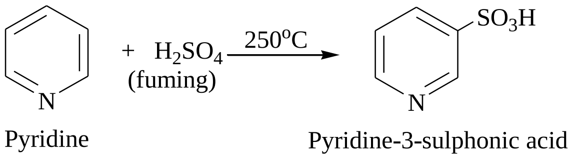
i. **Bromination:** Pyridine reacts with Bromine at high temperature to give 3-Bromopyridine.



ii. **Nitration:** 3-Nitropyridine is obtained when nitration of pyridine is performed by reacting it with KNO_3 in concentrated H_2SO_4 at 300°C. The reaction of KNO_3 and concentrated H_2SO_4 resulted–NO_2 which acts as an electrophile.

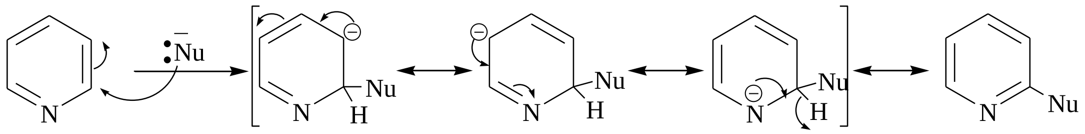


iii. **Sulphonation:** Sulphonation of pyridine is achieved by reacting it with fuming H_2SO_4 at 250°C. Pyridine-3-sulphonic acid is obtained as product.



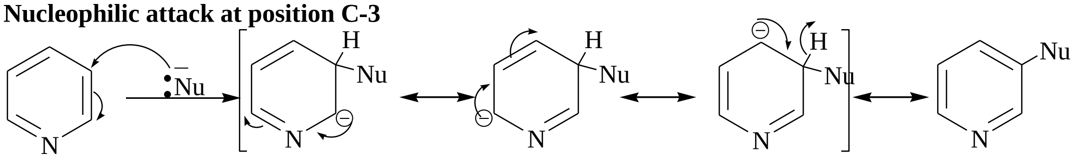
d. **Nucleophilic Substitution Reactions:** As we have discussed in previous section that pyridine generally deactivated the aromatic ring towards electrophilic substitution reaction. The deactivation of aromatic ring towards electrophilic substitution resulted due to the electron withdrawing nature of nitrogen atom. Due to such deactivation, pyridine also gives nucleophilic substitution reaction. Nucleophilic substitution in pyridine ring occurs at position C-2. Approach of the nucleophilic at position C-2 leads the formation of three resonating structures (I, II and III); similarly, approach of nucleophilic at position C-3 also leads the formation of three resonating structures (IV, V and VI). The resonating structures for intermediate resulting from the attack of nucleophile at position C-2 are more stable than those of position C-3, since more electronegative nitrogen atom hold –ve charge in one of the resonating structure (III) obtained from the attack of nucleophile at position C-2. Hence, the nucleophilic substitution in pyridine at position C-2 is always favored. Following mechanism is suggested for the electrophilic attack at position C-2.

Nucleophilic attack at position C-2



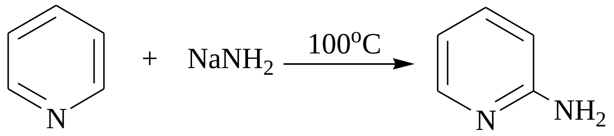
I **II** **III**

Nucleophilic attack at position C-3



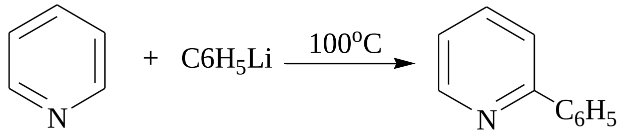
IV **V** **VI**

i. **Reaction with Sodium amide:** Pyridine reacts with sodium amide to give 2-aminopyridine via nucleophilic substitution.



Pyridine Pyridin-2-amine

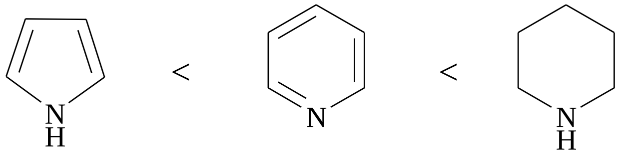
ii. **Reaction with Phenyllithium:** Pyridine reacts with phenyllithium (an organometallic compound) to give 2-phenylpyridine.



Pyridine 2-Phenylpyridine

4.8 COMPARISON OF BASICITY OF PYRROLE, PYRIDINE AND PIPERIDINE

From experimental studies it is observed that the pK_b values of pyrrole, pyridine and Piperidine are ~14, ~8.7 and ~2.7, respectively. Based on the suggested pK_b values the piperidine in found as a stronger base than pyridine and pyrrole. Pyrrole is the weakest base among these three heterocyclic bases. The order of basicity of pyrrole, pyridine and piperidine is as given below:



Pyrrole $pK_b = 14$

Pyridine $pK_b = 8.7$

Piperidine $pK_b = 2.7$

The above order of basicity of pyrrole, pyridine and piperidine can be justified in terms of the structure of these compounds. As we know that the basicity of nitrogen compounds depends upon the availability of lone pair of electron on nitrogen atom. In pyrrole, the lone pair of electron on nitrogen atom exists in the sp^2 hybridized orbital of nitrogen and participates in the delocalization, hence does not freely available to cause the basic character of pyrrole. Similar to pyrrole, the lone pair of electron on nitrogen atom of pyridine also exists in the sp^2 hybridized orbital; however, it does not participate in the delocalization and available freely to cause the basic character. Although the lone pair of electron on nitrogen atom of pyridine available freely but due to more electronegative character of sp^2 hybridized nitrogen atom (50% s-character) this lone pair is tightly bonded with nucleus, hence, less available for protonation. However, in piperidine, the lone pair of electron of nitrogen atom lies in sp^3 hybridized orbital of nitrogen. These electrons are less tightly bonded with nucleus. Therefore, these electrons are readily available for protonation. Thus, piperidine is the strongest base among the three.

4.9 SUMMARY

- Heterocyclic compounds are those organic cyclic compounds which contains a hetero atom (N, O, S) as the part of ring.
- A hetero cyclic ring may comprise of three or more than three atoms, which may be saturated or unsaturated.
- Heterocyclic ring may contain more than one heteroatom which may be either similar or different.
- Heterocyclic compounds may be aliphatic or aromatic in nature.
- The aliphatic heterocyclic compounds are the cyclic amines, cyclic amides, cyclic ethers and cyclic thioethers.

- Aliphatic heterocycles those do not contain double bonds are called saturated heterocycles.
- The properties of aliphatic heterocycles are mainly affected by the ring strain.
- Aromatic heterocyclic compounds are analogous of benzene.
- The aromatic heterocyclic compounds also follow the Huckel's rule (*i.e.* aromatic compounds must be cyclic in nature with planar geometry due to conjugate double bonds and must have (4n+2)π electrons).
- The nomenclature of heterocyclic compounds is divided in to two categories, a) Trivial method of nomenclature and, b) Systematic method of nomenclature.
- The trivial nomenclature was the first nomenclature method which has a significant role in the development of heterocyclic chemistry.
- When heterocyclic compounds are named on the basis of their source from which the compound was obtained. This nomenclature pattern in known as trivial nomenclature.
- The trivial system does not give any structural information about the compound.
- Systematic nomenclature is the most widely used nomenclature system for monocyclic heterocyclic compounds especially for three to ten membered ring systems.
- The systematic nomenclature gives important structural information.
- The most relevant systematic nomenclature that is recommended by IUPAC for nomenclature of heterocyclic compounds is the ***Hantzch-Widmann system*** of nomenclature.
- This nomenclature system specifies the nature, position, ring size, number, and types of heteroatoms present in any heterocyclic compounds.
- Molecular orbital model of heterocyclic compounds reveals that the heterocyclic compounds have less aromatic character in comparison to benzene and its derivatives.
- Molecular orbital model of heterocyclic compounds also suggested why there is asymmetrical electron density occurs in heterocyclic compounds.
- Due to less aromatic character then benzene, the rate of electrophilic substitution reactions of heterocyclic compounds is slower than benzene.
- Pyrrole, furan and thiophene undergo electrophilic substitution at position C-2.
- Pyridine undergoes electrophilic substitution at position C-3.
- Pyridine generally deactivated the aromatic ring towards electrophilic substitution reaction.

- The deactivation of aromatic ring towards electrophilic substitution resulted due to the electron withdrawing nature of nitrogen atom.
- Due to such deactivation, pyridine also gives nucleophilic substitution reaction.
- Nucleophilic substitution in pyridine ring occurs at position C-2.
- Among the three nitrogenous heterocyclic compounds (*i.e.* Pyrrole, Pyridine and Piperidine), Piperidine is the most basic; whereas, pyrrole is the least basic heterocyclic compound.

4.10 TERMINAL QUESTION

Q1. What do you understand by heterocyclic compounds?

Q2. Why systematic nomenclature is more useful than trivial nomenclature of Heterocyclic compounds?

Q3. Discuss the aromaticity of pyrrole.

Q4. Why pyridine is more basic than pyrrole?

Q5. Discuss the general mechanism of electrophilic substitution reaction of pyrrole.

Q6. Why pyridine also gives nucleophilic substitution reactions?

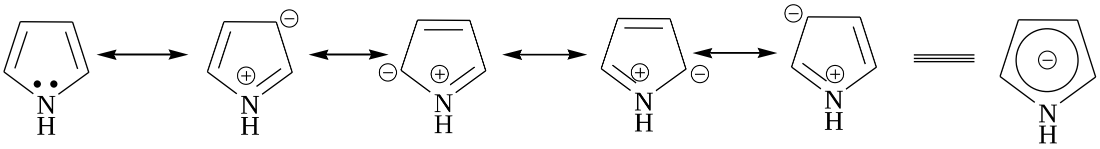
4.11 ANSWERS

A1. Heterocyclic compound is the class of cyclic organic compounds those having at least one hetero atom (*i.e.* atom other than carbon) in the cyclic ring system. The most common heteroatoms are nitrogen (N), oxygen (O) and sulphur (S). Heterocyclic compounds are frequently abundant in plants and animal products; and they are one of the important constituent of almost one half of the natural organic compounds known. Alkaloids, natural dyes, drugs, proteins, enzymes etc. are the some important class of natural heterocyclic compounds. Heterocyclic compounds have a wide application in pharmaceuticals, agrochemicals and veterinary products. Many heterocyclic compounds are very useful and essential for human life. Various compounds such as hormones, alkaloids antibiotic, essential amino acids, hemoglobin, vitamins, dyestuffs and pigments have heterocyclic structure.

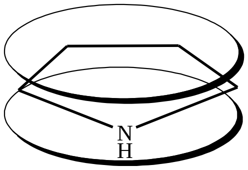
A2. The systematic nomenclature is more useful than trivial nomenclature because the systematic nomenclature gives important structural information. The most relevant system that is recommended by IUPAC for nomenclature of heterocyclic compounds is the *Hantzch-Widmann* *system* of nomenclature. This nomenclature system specifies the nature, position, ring size, number, and types of heteroatoms present in any heterocyclic compounds. This systematic method generally derived the nomenclature using the following syntax;

Name: Prefix + Stem + Suffix

A3. Pyrrole usually does not explain the simple addition reactions like alkenes under normal conditions. This is because of the delocalization of lone pair of nitrogen atom through conjugation. This delocalization provides extra stability to the double bonds of pyrrole. Also the proposed structure of pyrrole is considered as an aromatic compound since it follows the Huckel's aromaticity rules (4n+2 electron rule). The aromatic nature and extra-stability of pyrrole can also be supported by the formation of its different resonating structures as shown in below figure. The structure of pyrrole is the resonance hybrid of all resonating structures.



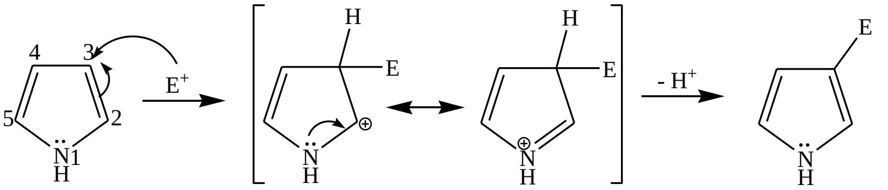
1. The delocalization of lone pair of nitrogen in pyrrole through conjugation also suggests that the pyrrole molecule should have planar geometry. This is only possible when the orbitals of carbon and nitrogen in pyrrole are *sp*^{2}- hybridized. The three *sp*^{2}- hybridized orbitals of nitrogen contain one- one electron in each *sp*^{2}- hybridized orbital. The unhybridized *p*-orbital of nitrogen contains lone pair of electrons. Two *sp*^{2}- hybridized orbitals of nitrogen atom forms π-bond with two carbon atoms of the ring whereas the third *sp*^{2}- hybridized orbital of nitrogen atom forms π -bond with hydrogen atom. Similarly each *sp*^{2}- hybridized carbon forms two π -bonds with neighboring carbon atoms and one π -bonds with hydrogen atom. The unhybridized orbitals of each carbon contain one electron. These unhybridized orbitals of carbon and nitrogen form a delocalized electron cloud above and below the pentagonal ring of pyrrole. The delocalized electron cloud is shown in figure.



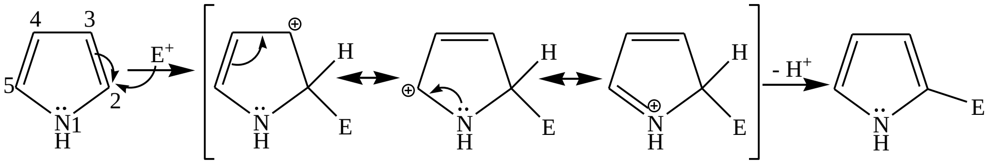
A4. As we know that the basicity of nitrogen compounds depends upon the availability of lone pair of electron on nitrogen atom. In pyrrole, the lone pair of electron on nitrogen atom exists in the *sp*^{2} hybridized orbital of nitrogen and participates in the delocalization, hence does not freely available to cause the basic character of pyrrole. Similar to pyrrole, the lone pair of electron on nitrogen atom of pyridine also exists in the *sp*^{2} hybridized orbital; however, it does not participate in the delocalization and available freely to cause the basic character. Therefore, pyridine is more basic than pyrrole.

A5. Pyrrole undergoes electrophilic substitution at the position C-2. Approach of the electrophile at position C-2 leads the formation of three resonating structures; however, only two resonating structures are obtained when the electrophile approaches at position C-3. Thus the intermediate obtained by the approach of electrophile at position C-2 is more stable than the intermediate obtained by the approach of electrophile at position C-3. This is the reason that electrophilic attack occurs at position C-2. Following mechanism is suggested for the electrophilic attack at position C-2. All the electrophilic substitution reactions of pyrrole occur at position C-2 and follow the similar mechanism as shown below.

Attack at position C-3:



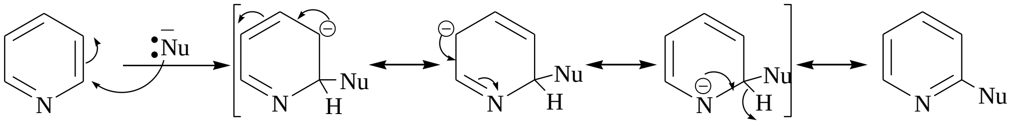
Attack at position C-2:



E= electrophile

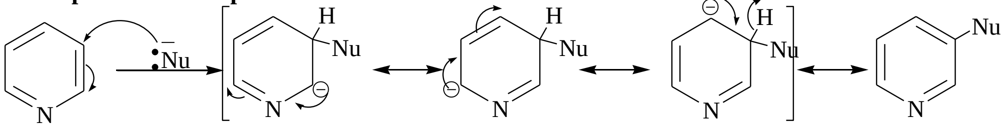
A6. Pyridine generally deactivated the aromatic ring towards electrophilic substitution reaction. The deactivation of aromatic ring towards electrophilic substitution resulted due to the electron withdrawing nature of nitrogen atom. Due to such deactivation, pyridine also gives nucleophilic substitution reaction. Nucleophilic substitution in pyridine ring occurs at position C-2. Approach of the nucleophilic at position C-2 leads the formation of three resonating structures (I, II and III); similarly, approach of nucleophilic at position C-3 also leads the formation of three resonating structures (IV, V and VI). The resonating structures for intermediate resulting from the attack of nucleophile at position C-2 are more stable than those of position C-3, since more electronegative nitrogen atom hold –ve charge in one of the resonating structure (III) obtained from the attack of nucleophile at position C-2. Hence, the nucleophilic substitution in pyridine at position C-2 is always favored. Following mechanism is suggested for the electrophilic attack at position C-2.

Nucleophilic attack at position C-2



I **II** **III**

Nucleophilic attack at position C-3



IV **V** **VI**

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