ORGANIC CHEMISTRY

Chemistry of Heterocyclic Compounds

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Introduction
Organic compounds can have a variety of structures. These structures can be acyclic or cyclic. The cyclic systems containing only carbon atoms are called carbocyclic and the cyclic systems containing carbons and at least one other element are called heterocyclic. Though a number of heteroatoms are known to be part of the heterocyclic rings, the most common heteroatoms are nitrogen, oxygen or sulphur. A heterocyclic ring may contain one or more heteroatoms which may or may not be same. Also the rings may be saturated or unsaturated. Nearly half of the known organic compounds contain at least one heterocyclic ring. Many heterocyclic compounds occur naturally and are actively involved in biology e.g., nucleic acids (purine and pyrimidine bases), vitamins (Thiamine B1, Riboflavin B2, Nicotinamide B3, Pyridoxol B6 and Ascorbic acid C), heme and chlorophyll, penicillins, cephalosporins, macrolides etc. The study of heterocyclic chemistry is a vast and expanding area of chemistry because of their applications in medicine, agriculture, photodiodes and other fields.

Heterocyclic compounds may be classified as aliphatic and aromatic heterocycles. The aliphatic heterocycles are the cyclic analogues of amines, ethers and thioethers and their properties are influenced by the ring strain. The three and four membered aliphatic heterocyclic rings are more strained and reactive compared to five and six membered rings. The common aliphatic heterocyclic compounds are aziridine (I), oxirane (II), thiirane (III), azetidine (IV), oxetane (V), thietane (VI), pyrrolidine (VII), tetrahydrofuran (VIII), tetrahydrothiophene (IX) and piperidine (X).

The heterocycles which show aromatic behavior as in benzene are called the aromatic heterocyclic compounds. These compounds follow the Hückel’s rule which states that cyclic conjugated and planar systems having \((4n+2)\) \(\pi\) electrons are aromatic. The aromatic nature of five and six-membered heterocycles is discussed in Sec. 1. Some simple aromatic heterocyclic compounds are pyrrole (XI), furan (XII), thiophene (XIII), imidazole (XIV), pyrazole (XV), oxazole (XVI), thiazole (XVII) and pyridine (XVIII).
**Aromaticity and Physico-Chemical Properties**

**π Electron Theory and the Hückel 4n+2 Rule:** In a conjugated planar system, the σ framework is formed by sp² hybrid orbitals of carbon with 1s orbitals of hydrogen. Each carbon having one perpendicular p-orbital then forms π bonds with adjacent atoms. Similarly for the cyclic planar conjugated rings, the σ framework is formed by sp² hybrid orbitals of carbon and 1s orbitals of hydrogen. The p-orbitals on each carbon atom perpendicular to the plane of the ring then interact with each other. The energies of π molecular orbitals of a regular polygon with even number of atoms follows the pattern shown in Fig. 1. In this pattern, there is lowest level and the higher levels are in pairs of the same energy (degenerate levels/degenerate energy).

![Fig. 1](image1)

If the electro pairs are filled into the energy level pattern (Fig. 1), a closed-shell structure will result only when the number of electron pairs is odd (total number of electrons is 4n+2). However, if the number of electron pairs is even (total number of electrons is 4n), the last pair will occupy the degenerate orbital pair so that one electron is present in each degenerate orbital with parallel spins (Fig. 2 and 3). As a consequence, cyclic systems with 4n π electrons undergo deformation and lose the planarity and hence the extended conjugation. The difference of π energy calculated for an open chain CₙHₙ₊₂ conjugated polyene and cyclic CₙHₙ conjugated polyene is known as resonance energy. Therefore cyclic conjugated polyenes are aromatic if they are thermodynamically more stable than the corresponding open-chain analogs and it is antiaromatic if it is less stable. Molecules which show neither stabilization nor destabilization are known as non-aromatic.

![Fig. 2](image2)  \[\text{Energy}\]

![Fig. 3](image3)  \[\text{Energy}\]
Pyrrole, Furan and Thiophene

Pyrrole (XI), furan (XII) and thiophene (XIII) are the simplest of the five membered aromatic heterocyclic compounds having one heteroatom. Planar unsaturated heterocycles containing five atoms can be considered aromatic system if they have an uninterrupted cycle of p-orbitals containing six electrons in all. Pyrrole, furan and thiophene are examples of this type. In all these heterocycles, four carbon atoms and the heteroatom are sp\(^2\) hybridized. The p-orbital of each carbon atom contributes one electron and forms π-bond with adjacent carbon. The three σ-bonds of the sp\(^2\) hybridized heteroatom lie in the plane of the molecule. The third p-orbital, which is orthogonal to the plane of the atoms, contributes its lone pair of electrons. This p-orbital of the heteroatom with an electron pair interacts with other four p-orbitals of carbons resulting into a cyclic π electron system involving five p-orbitals and six π-electrons in three bonding molecular orbitals \(\pi_1, \pi_2\) and \(\pi_3\). Therefore each of these compounds has three pairs of delocalized π-electrons. Two of the pairs are shown as π-bonds in the structure and one pair is shown as non-bonding electrons on the heteroatom. Hence these five sp\(^2\) hybridized atoms form planar six electron delocalized π-cloud, which is responsible for the aromatic character of these rings (Fig. 4). It can be seen from the

![Fig. 4](image)

structures of furan and thiophene, which contain bivalent oxygen and sulfur respectively, that they have a second pair of non-bonding electrons also which is not involved in the π-cloud (Fig. 4).

The resonance structures of pyrrole show that nitrogen donates electrons to the ring (Fig. 5) and thereby increases the electron density of the ring. In fact introduction

![Fig. 5](image)

of the heteroatom in the ring brings about splitting of \(\pi_2\) and \(\pi_3\) orbitals. This splitting of degenerate \(\pi_2\) and \(\pi_3\) orbitals can also be viewed as representing a partial localization of the lone pair on nitrogen. The calculated π-electron distribution of pyrrole is shown in Fig. 6. It is evident from the resonance structures given above and the data in Fig. 6 that the ring

![Fig. 6](image)

system is electron rich since six electrons are distributed over five atoms. Therefore all the carbon atoms have greater π-electron density than benzene, which has equivalent resonance structures with no charge separation.
Similarly furan and thiophene are also aromatic in nature and can be represented by the similar delocalized structures as in pyrrole wherein one of the lone pairs on oxygen or sulphur contributes to the aromatic sextet. However, unlike pyrrole, the delocalization is not as extensive in furan because of high electronegativity of oxygen and so the lone pairs are held more tightly by the oxygen. Thiophene with the least electronegative heteroatom is regarded as aromatic and has the highest resonance energy whereas furan has the least resonance energy. All these heterocycles have lower resonance energies than benzene. The resonance energies of pyrrole, thiophene and furan are 88, 121 and 67 KJ/mol, respectively. Therefore, the order of aromaticity is

Thiophene > Pyrrole > Furan

All these compounds undergo electrophilic substitution e.g., nitration, sulfonation, halogenation, Friedel-crafts reaction etc. characteristic of aromatic compounds. These are more reactive than benzene towards electrophilic substitution because of the increased electron density on each carbon in the ring. Therefore, the attack of the electrophile which is the rate determining step is more facile with these heterocycles. Unlike pyrrole, furan and thiophene do not undergo protonation. Pyrrole is an extremely weak base because its pair of non-bonding electrons are part of the $\pi$-cloud ($K_b = 2.5 \times 10^{-14}$). Therefore, if pyrrole is protonated, it loses its aromaticity as the non bonding electrons are no more available for delocalization to form the aromatic sextet. The number of five membered aromatic heterocycles is much larger than that of the six membered aromatic heterocycles. This is because one of the heteroatoms in the ring can be divalent and so more heteroatoms can be incorporated into the five-membered rings than six-membered rings. Pyrrole, thiophene and furan are colourless liquids and boil at 130°C, 84°C and 32°C respectively. High boiling point of pyrrole is due to hydrogen bonding between pyrrole molecules.

**Pyridine**

All six membered fully unsaturated heterocycles are related to benzene as these can be represented by replacement of one or more CH groups by a trivalent heteroatom. The simplest six membered aromatic heterocycle is pyridine (XVIII). Pyridine ring consists of five carbon atoms and a nitrogen atom. Pyridine is a planar molecule. The ring is a slightly distorted hexagon as the C–N bonds are shorter than C–C bonds. All the carbons and nitrogen are $sp^2$ hybridized which form $\sigma$-bonds with adjacent atoms having $\sim120^\circ$ bond angles. Each atom has a p-orbital orthogonal to the ring which undergoes delocalization to form 6$\pi$-electron cyclic loop (Fig. 7).

**Fig. 7 : Pyridine (XVIII)**
Pyridine has two uncharged resonance structures like benzene and three charged structures as shown in Fig. 8. Its resonance energy is 117 KJ/mol and the dipole moment is 1.57 μ. The lone pair of electrons on sp\(^2\) hybridized nitrogen is responsible for the basicity of pyridine and it behaves like a tertiary amine. Pyridine is a stronger base than pyrrole as its lone pair is not involved in delocalization (K\(_b\) = 2.3 \times 10^{-9}). Its aromaticity is not affected by protonation unlike pyrrole which loses aromaticity upon protonation. The lone pair of nitrogen in pyridine is sp\(^2\) hybridized which is more electronegative than the sp\(^3\) hybridized nitrogen. Therefore pyridine is less basic than amines and anilines. Pyridine is less basic than its saturated analog piperidine (K\(_b\) = 2 \times 10^{-3}) because the lone pair of nitrogen in piperidine is sp\(^3\) hybridized and hence less electronegative than pyridine and more available for protonation. Heterocycles in which other benzenoid CH groups are replaced with nitrogen, also behave similarly. Pyridine is a colourless liquid which boils at 115°C.

**Benzo-fused Heterocycles**

**Heterocycles with fused five membered rings:** Five membered aromatic heterocycles namely pyrrole, furan and thiophene fused with benzene ring give rise to various possible structures given below:

- **INDOLE (XIX)**
  - Benzo[b]pyrrole
- **ISOINDOLE (XX)**
  - Benzo[c]pyrrole
- **INDOLIZINE (XXI)**
- **DIBENZOPYRROLE (XXII)**
  - (Carbazole)
- **BENZOFURAN (XXIII)**
  - Benzo[b]furan
- **ISOBENZOFURAN (XXIV)**
  - Benzo[c]furan
- **DIBENZOFURAN (XXV)**
- **BENZOTHIOPHENE (XXVI)**
  - Benzo[b]thiophene
- **ISOBENZOTHIOPHENE (XXVII)**
  - Benzo[c]thiophene
- **DIBENZOTHIOPHENE (XXVIII)**

Indole, benzofuran and benzo-thiophene are planar aromatics which contain 10π-electrons including the non-bonding electron pair of heteroatom as in monocyclic heterocycles. These 10π-electrons are delocalized over the ring. Because of the involvement of non-bonding lone
pair of heteroatom in aromatization, it makes the 5-membered rings more prone to attack by electrophilic reagents.

**Indole:** Indole is a pleasant smelling solid which melts at 52°C and is used as a perfume base. It is a planar aromatic molecule with conjugated 10π-electrons contributed by eight carbon atoms and a lone pair contributed by nitrogen. Its resonance energy is 47-49 kcal/mol. Because of the involvement of lone pair of nitrogen, charge separated canonical forms can be written for indole as shown in Fig. 9.

![Fig. 9](image)

**Quinoline and Isoquinoline: Heterocycles with Fused Six Membered Rings:** Quinoline (XXIX) and isoquinoline (XXX) are two fused heterocycles derived by fusion of pyridine ring with a benzene ring. Both ring systems occur naturally and were originally isolated from coal tar. Quinoline is high boiling liquid (b.p. 237°C) and smells like pyridine while isoquinoline is a low melting solid (m.p. 26.5°C, b.p. 243°C). Both quinoline and isoquinoline are planar 10π-electron aromatic systems in which all atoms are sp² hybridized and contribute one electron each in orthogonal p-orbitals for delocalization over the rings.

Both quinoline and isoquinoline are aromatic with resonance energies of 198 and 143 KJ/mol respectively as depicted by various contributing structures in Fig. 10 and Fig. 11, respectively. The first three structures (i-iii) of both quinoline and isoquinoline are of

![Fig. 10](image)
lower energy and contribute significantly to aromatic character compared to charge separated structures (iv and v). Quinoline and isoquinoline are weak bases but slightly more basic than pyridine but less basic than anilines since the nitrogen in quinoline and isoquinoline is more electronegative being sp\(^2\) hybridized compared to sp\(^3\) hybridized nitrogen of anilines. Isoquinoline has higher dipole moment (2.60D) compared to quinoline (2.10D).

**Methods of Preparation**

**Synthesis of Furan, Pyrrole and Thiophene**

(i) Furfural can be prepared by dehydration and cyclization of pentoses. Furfural undergoes decarbonylation to give furan (eq. 1).

\[
\begin{align*}
\text{CHO} & \quad \text{(CHOH)}_3 \quad \text{HCl} \quad \Delta \\
\text{CHO} & \quad \text{CaCO}_3 \\
& \quad \text{625K} \\
\text{CHO} & \quad \text{Furan} \\
\end{align*}
\]  
\[\text{...(1)}\]

(ii) The Paal-Knorr method for synthesis of furans involves cyclization of 1,4-diketones with acid catalysts such as sulphuric acid, phosphorus (V) oxide, zinc chloride, acidic ion-exchange resin etc. while pyroles and thiophenes can be obtained by heating 1,4-diketones with ammonia (or primary amines) and phosphorus pentasulphide respectively (eq. 2).

\[
\begin{align*}
\text{R}_1 \quad \text{R}_2 & \quad \text{O} \quad \text{O} \quad \text{R}_1 \quad \text{R}_2 \\
\text{RNH}_2 & \quad \text{P}_2\text{S}_5 \\
& \quad \text{Catalyst} \\
& \quad \text{R}_1 \quad \text{R}_2 & \quad \text{R}_1 \quad \text{R}_2 \\
& \quad \text{Pyrrole} & \quad \text{Thiophene} \\
& \quad \text{...}(2) \\
\end{align*}
\]

(iii) 3-Substituted furans can be prepared by cyclization of Z-butene-1,4-diols with pyridinium chlorochromate (PCC) (eq. 3).
(iv) Pyrrole can be produced from a mixture of furan, ammonia and steam on alumina at 675K (eq. 4).

\[
\text{Cyclohexene} \xrightarrow{\text{NH}_3, \text{steam}} \text{Pyrrole}
\]

(v) The Knorr synthesis is the most widely used method for the synthesis of pyrroles. Two moles of ethyl acetoacetate are used (eq. 5).

\[
2 \text{MeCOCH}_2\text{COOEt} \xrightarrow{(i) \text{NaNO}_2, \text{AcOH}} \xrightarrow{(ii) \text{Zn–AcOH}} \text{Pyrrole}
\]

(vi) Pyrrole and thiophene can also be prepared by passing a mixture of ethyne and ammonia or hydrogen sulphide through a red hot tube (eq. 6).

\[
2 \text{HC}≡\text{CH} \xrightarrow{\text{NH}_3, \Delta} \text{Pyrrole}
\]

\[
2 \text{HC}≡\text{CH} \xrightarrow{\text{NH}_3, \Delta} \text{Thiophene}
\]

1,3-Diynes and hydrogen sulfide can also be converted to substituted thiophenes (eq. 7).

\[
\text{RC}≡\text{C}≡\text{CR} \xrightarrow{\text{H}_2\text{S}, \text{Ba(OH)}_2} \text{Thiophene}
\]

(vii) Cyclization of 1,2-diketones with diylide (eq. 8) is also used to prepare different thiophenes.

\[
\text{1,2-Diketone} + \text{Ph}_3\text{P}⁺\overline{\text{S}}⁺\text{Ph}_3 \rightarrow \text{Thiophene}
\]

**Synthesis of Pyridine**

Pyridine and picolines (methylpyridine) are found in coal-tar. Picolines can be oxidised to corresponding pyridine carboxylic acids and converted to other pyridine derivatives.
(i) **Hantzsch Synthesis**: One of the most useful methods for the synthesis of pyridine derivatives is Hantzsch synthesis. The Hantzsch synthesis involves the reaction of two molecules of β-ketoester or other activated methylene compounds with an aldehyde in the presence of ammonia to give dihydro-pyridine which can be oxidised to give pyridine derivative (eq. 9). There are several modification of the Hantzs ch synthesis.

\[
2 \text{MeCOCH}_2\text{COOEt} + \text{HCHO} + \text{NH}_3 \rightarrow \text{Me} \begin{array}{c}
\text{OOC} \\
\text{Me}
\end{array} \begin{array}{c}
\text{COOEt}
\end{array} \begin{array}{c}
\text{Me} \\
\text{Me}
\end{array} \begin{array}{c}
\text{COOEt}
\end{array} \begin{array}{c}
\text{Me}
\end{array} 
\]  

(ii) **Ring expansion**: Pyrrole undergoes ring expansion after reaction with dichlorocarbene to give 3-chloropyridine (eq. 10).

\[
\text{H}_3\text{C}=\text{CHCl}, \text{NaOH} \rightarrow \text{H}_3\text{C} \begin{array}{c}
\text{N}
\end{array} \begin{array}{c}
\text{Cl}
\end{array} \begin{array}{c}
\text{Cl}
\end{array} \begin{array}{c}
\text{H}
\end{array} \begin{array}{c}
\text{N}
\end{array} \begin{array}{c}
\text{Cl}
\end{array} \begin{array}{c}
\text{Cl}
\end{array} \begin{array}{c}
\text{N}
\end{array} \begin{array}{c}
\text{H}
\end{array} 
\]

(iii) **Synthesis of pyridones**: Pyridones may be prepared by the action of ammonia or amines with pyrones (eq. 11). Aromatic amines do not give good yields.

\[
\text{O} \begin{array}{c}
\text{O}
\end{array} \text{O} + \text{RNH}_2 \rightarrow \text{N} \begin{array}{c}
\text{R}
\end{array} 
\]

**Synthesis of Indole**

(i) **Fischer-Indole Synthesis**: The most important synthesis of indole is the Fischer-indole Synthesis which has been investigated very widely. The Fischer-indole synthesis is carried out by heating phenyl hydrazone or substituted phenyl hydrazone of an aldehyde or ketone. The reaction is catalyzed by zinc chloride, polyphosphoric acid, sulphuric acid or boron trifluoride and proceeds with elimination of a molecule of ammonia (eqs. 12-13).

\[
\text{Me} \begin{array}{c}
\text{Me}
\end{array} \begin{array}{c}
\text{N}
\end{array} \begin{array}{c}
\text{H}
\end{array} \begin{array}{c}
\text{Me}
\end{array} \begin{array}{c}
\text{N}
\end{array} \begin{array}{c}
\text{Me}
\end{array} \begin{array}{c}
\text{N}
\end{array} \begin{array}{c}
\text{Me}
\end{array} \rightarrow \text{Me} \begin{array}{c}
\text{Me}
\end{array} \begin{array}{c}
\text{N}
\end{array} \begin{array}{c}
\text{Me}
\end{array} \begin{array}{c}
\text{N}
\end{array} \begin{array}{c}
\text{Me}
\end{array} 
\]

\[
\text{Me} \begin{array}{c}
\text{Ph}
\end{array} \begin{array}{c}
\text{N}
\end{array} \begin{array}{c}
\text{H}
\end{array} \begin{array}{c}
\text{Ph}
\end{array} \begin{array}{c}
\text{N}
\end{array} \begin{array}{c}
\text{H}
\end{array} \begin{array}{c}
\text{Ph}
\end{array} \begin{array}{c}
\text{N}
\end{array} \begin{array}{c}
\text{H}
\end{array} 
\]
Different mechanisms have been proposed depending on reaction conditions and nature of hydrazone. The most acceptable mechanism is given in Scheme 1.

Scheme 1

Unsymmetrical phenyl hydrazones give a mixture of two differently substituted indoles, the ratio of which depends on steric factors and reaction conditions (eq. 14).

(ii) Madelung Synthesis: Reaction of \( o \)-toluidine with acyl chloride gives \( o \)-acylamino toluene which can be cyclized with strong bases followed by dehydration to give indole or 2-substituted indoles (eq. 15).
(iii) **Bischler Synthesis:** The Bischler synthesis involves reaction of aniline or substituted aniline with $\alpha$-halo ketone or aldehyde to give $\alpha$-aryl aminoketone or aldehyde which can be cyclized by heating with an acid or zinc chloride to give substituted indoles (eq. 16).

\[
\text{NH}_2 + \text{O} = \text{C} - \text{Me} \xrightarrow{\text{HCl}, \Delta} \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{...(16)}
\]

**Synthesis of Quinoline**

(i) **The Skraup Synthesis:** The Skraup synthesis consists of heating an aniline derivative having free ortho position with glycerol and sulphuric acid and an oxidising agent like nitrobenzene corresponding to aniline (eq. 17). The acid acts as a dehydrating agent and an acid catalyst. The reaction proceeds in the following manner (Scheme 2). Dehydration of glycerol gives acrolein which undergoes Michael addition with aniline followed by electrophilic attack of protonated carbonyl group. The cyclized intermediate undergoes subsequent dehydration and oxidation to give quinoline. Oxidation has been reported with other oxidising agents as well. Quinolines with substituent in the benzene ring may be obtained by starting from substituted anilines. $\alpha$- and $\beta$-Substituted anilines give 8- and 6-substituted quinolines respectively (eqs. 18-19), while $m$-substituted aniline gives a mixture of 5- and 7-substituted quinolines (eq. 20). If the reaction is carried out in presence of substituted $\alpha,\beta$-unsaturated aldehyde or ketone, instead of acrolein generated *in situ*, quinoline with substituent in heterocyclic ring is obtained.

**Scheme 2**
(ii) **Friedlander Synthesis:** This synthesis involves heating a mixture of \( o \)-aminobenzaldehyde or \( o \)-aminoacetophenone with an aldehyde or ketone having an active methylene group in presence of a base (eq. 21).

\[
\text{CHO} + \text{CH}_3\text{CHO} \xrightarrow{\text{NaOH} \Delta} \text{N} \quad \text{...(21)}
\]

(iii) **Knorr Quinoline Synthesis:** 2-Substituted quinolines can also be prepared by heating aniline with \( \beta \)-keto esters in presence of an acid (eq. 22).

\[
\text{NH}_2 + \text{RCOCH}_2\text{COOC}_2\text{H}_5 \xrightarrow{\text{H}_2\text{SO}_4 \Delta} \text{N} \quad \text{...(22)}
\]

(iv) **Combes Synthesis:** When aniline is heated with 1,3-diketones in presence of an acid, 2,4-disubstituted quinoline is obtained (eq. 23).

\[
\text{NH}_2 + \text{RCOCH}_2\text{COR} \xrightarrow{\text{conc. H}_2\text{SO}_4 \Delta} \text{N} \quad \text{...(23)}
\]
**Synthesis of Isoquinoline**

(i) **Bischler-Napieralski Synthesis:** The Bischler-Napieralski synthesis involves reaction of β-phenyl ethylamine with acyl halide to give β-phenyl ethylamide which undergoes cyclodehydration in presence of POCl₃, P₂O₅, H₃PO₄ or ZnCl₂ to give 3,4-dihydroisoquinoline. Dehydrogenation of 3,4-dihydroquinoline over Pd, S or Se yields 1-substituted isoquinoline (Scheme 3). There are various modifications of the method. The two modifications are Pictat-Gams synthesis (eq. 24) in which a hydroxy group is introduced in the starting β-phenyl ethylamine and Pictet-Spengler synthesis (eq. 25) in which the β-phenyl ethylamine is reacted with an aldehyde to give an imine which is cyclized in presence of an acid to give tetrahydroisoquinoline.

(ii) **Pomeranz-Fritsch Reaction:** This is carried out by condensation of an aromatic aldehyde with an amino acetal which is then cyclized in presence of sulphuric acid to give isoquinoline (eq. 26).
Reactions of Heterocycles

Reactions of Pyrrole, Furan and Thiophene

(i) Electrophilic Substitution Reactions: Pyrrole, furan and thiophene undergo electrophilic substitution reactions like nitration, sulphonation, halogenation etc. characteristic of aromatic rings. It has already been described in Sec. 1.1 that carbons in 5-membered heterocyclic rings have higher electron density compared to benzene and hence undergo electrophilic substitution more readily than benzene (eq. 28). The electrophilic substitution takes place preferentially at 2-position (C-2).

\[ \text{Step} \quad \text{Slow} \quad + \quad \text{Y}^+ \quad \xrightarrow{\text{Step}} \quad \text{H}^+ \quad \xrightarrow{-\text{H}^+} \quad \text{XXXI} \quad \text{XXXII} \quad \text{...(28)} \]

The attack of an electrophile on pyrrole, for example, will lead to formation of 2- and 3-substitution products by way of carbocations XXXI and XXXII, respectively (Fig. 12). The substitution occurs preferably at C-2 position because the

\[ \text{Fig. 12} \]
intermediate obtained by attack at this position is more stable than the intermediate obtained by attack at C-3. The positive charge in intermediate XXXI is more delocalized than intermediate XXXII and hence is more stable and preferred intermediate.

The electrophilic substitution at C-2 in furan and thiophene can also be accounted in the same manner. Furan is not as reactive as pyrrole in electrophilic substitution reactions because the oxygen in furan is more electronegative than nitrogen in pyrrole and therefore does not enhance the electron density of carbons as much as pyrrole. Thiophene is less reactive than furan towards electrophilic substitution because the p-electrons of sulphur are in 3p orbital which overlaps less effectively than the 2p orbital of nitrogen or oxygen with 2p orbitals of carbon. The relative reactivities towards electrophilic substitution follows the order:

\[
\begin{align*}
\text{N} & > \text{O} > \text{S} \\
\end{align*}
\]

Some typical examples of electrophilic substitution of pyrrole, furan and thiophene are given below (Fig. 12).
Both the Mannich reaction (reaction with Me₂NH, H₂CO and H⁺) and azo coupling fail with furan, showing its lower reactivity compared with pyrrole.

(ii) Reduction: Pyrrole, furan and thiophene can be reduced to pyrrolidine (eq. 29), tetrahydrofuran (eq. 30) and tetrahydrothiophene (eq. 31), respectively by catalytic hydrogenation.
(iii) **Diels-Alder Reaction**: Furan is least aromatic of the three heterocycles and therefore behaves as a diene in a number of Diels-Alder reactions (eq. 32).

Pyrrole and thiophene do not undergo Diels-Alder reactions. However, N-carbomethoxy pyrrole reacts with highly reactive dienophiles e.g., dimethylacetylene dicarboxylate (DMAD) to give Diels-Alder product (eq. 33). The electron withdrawing group reduces the availability of nitrogen lone pair for the ring and so it behaves more like a diene. Pyrrole and N-alkyl pyrrole undergo Michael-type addition reactions (eq. 34).
(iv) **Ring Expansion of Pyrrole:** Pyrrole adds on dichlorocarbene generated *in situ* from chloroform and base to give a bicyclic compound which undergoes ring expansion to give 3-chloropyridine (Scheme 4).

**Scheme 4**

**Reactions of Pyridine**

(i) **Electrophilic Substitution Reactions:** Pyridine is a six-membered aromatic heterocycle and undergoes electrophilic substitution (eq. 35) e.g., nitration, sulfonation, halogenation, formylation etc. but the ring

is highly deactivated (about million times) compared to benzene because the more electronegative nitrogen pulls the electrons towards itself, thus reducing the electron density on the ring carbons.

The electrophilic substitution takes place at C-3 in pyridine. This orientation can be explained by comparing the relative stabilities of the intermediates arising from attack at C-3, C-4 or C-2 (Fig. 13). The electrophilic attack at C-3 gives a carbocation which is hybrid of three resonance structures in which the positive charge is on the carbon atoms only.
The electrophilic attacks at C-4 or C-2 also give an ion which is hybrid of three
resonances structures but one of the resonance structures in each contains positively
charged nitrogen which is a sextet and so unstable and hence does not contribute
significantly to the resonance hybrid. Thus the resonance hybrid resulting from
electrophilic attack at C-3 is more stable and the preferred site of electrophilic attack.

Some typical examples of electrophilic substitutions in pyridine are given below
(Fig. 14). All these reactions involve substitution of a pyridinium cation. Friedel-crafts
alkylation and acylation does not proceed with pyridine. Alkyl halides on heating with
pyridine give pyridinium salts. Nitration also gives poor yields.
(ii) **Nucleophilic Substitution Reactions:** Pyridine undergoes nucleophilic substitution reactions much more readily than benzene because the ring has lower electron density than benzene due to electron withdrawal by nitrogen which is also responsible for its lower reactivity towards electrophiles. The high reactivity of pyridine towards nucleophilic substitution can cause displacement of even powerful hydride (H⁻) ion, e.g., the reaction of pyridine with sodamide gives 2-aminopyridine and is known as Chichibabin reaction (eq. 36).

\[
\text{Pyridine} + \text{NaNH}_2 \rightarrow \text{2-aminopyridine} \quad \cdots(36)
\]

The nucleophilic substitution in pyridine takes place at C-2 and C-4 positions compared to electrophilic substitution at C-3. Attack of nucleophile at C-2, C-3 and C-4 gives different resonating structures (Scheme 5).

It is obvious from the above structures that nucleophilic attack at C-2 and C-4 gives hybrid of three resonance structures in which one of the contributory structures contains negative charge on nitrogen which is more electronegative atom and therefore contributes significantly towards its stabilization unlike nucleophilic attack at C-3 in which the negative charge is present on only carbon atoms. Since the intermediate resulting from nucleophilic attack at C-2 and C-4 is more stable, nucleophilic substitution at these positions is preferred. Other nucleophilic substitution reactions of pyridine are given below (eqs. 37-38). If the leaving group at C-2 and C-4 are different, the incoming nucleophile will preferentially substitute for the weaker base (the better leaving group) (eqs. 39-40).
Reactions of Indole

Indole is a very weak base like pyrrole because of the involvement of lone pair of nitrogen in aromatization. However, in dilute solutions it undergoes protonation of nitrogen to give indolium cation in which the aromaticity of benzene ring is retained (eq. 41). Indole does not undergo easy alkylation of nitrogen unlike amines for the same reason.

\[
\text{Indole} + \text{H}^+ \rightleftharpoons \text{Indolium cation} \quad \ldots(41)
\]

(i) **Electrophilic Substitution of Indole**: The electron density of carbons in heterocyclic ring of indole is higher due to contribution from nitrogen as in case of pyrrole. Therefore, the heterocyclic ring of indole is more reactive towards electrophiles compared to its benzene ring. The electrophilic substitution in indole takes place at C-3 and not at C-2 as in pyrrole. This can be explained from the following observations. Electrophilic attack at C-2 and C-3 gives different intermediates as shown below (Scheme 6):
The carbocation resulting from electrophilic attack at C-2 is less favourable than the carbocation resulting from electrophilic attack at C-3 because though the former has more resonance structures, the aromaticity is completely lost whereas in the latter intermediate, the positive charge resides on heterocyclic ring carbon or the nitrogen atom without affecting the benzene ring. Some typical examples of electrophilic substitution of indole are given below (Fig. 15):

\[
\begin{align*}
\text{EtONO}_2, \text{NaOMe} & \quad \text{CHO} \\
\text{POCl}_3, \text{Me}_2\text{N.CH} & \quad \text{SO}_3\text{H} \\
\text{SO}_3, \text{Pyridine} & \quad \Delta \\
\text{PhN}_2^+ \text{Cl}^- & \quad \text{aq. KOH} \\
\text{N-Chlorosuccinimide,} & \\
\text{MeOH or NaOCl, base} & \\
\text{N-Bromosuccinimide,} & \quad \text{Cl} \\
\text{CCl}_4, \Delta & \\
\text{EtONO}_2, \text{NaOMe} & \quad \text{NO}_2
\end{align*}
\]

**Fig. 15**

Acylation of indole at C-3 does not take place as the reaction with acyl halide leads to acylation of nitrogen. If C-3 of indole is blocked, then electrophilic substitution takes place at C-2 and if both C-2 and C-3 are blocked, then electrophilic substitution takes place preferably at C-6 in aromatic ring.

(ii) **Oxidation and Reduction of Indole**: Indoles are easily oxidized by air and give a mixture of products. The C₂⁻C₃ double bond of indole is labile and can be easily cleaved by ozonolysis, peracids and sodium hypoiodeate etc. Indole gives a resinous material whereas 3-substituted or 2,3-disubstituted indoles undergo C₂⁻C₃ cleavage as in case of ozonolysis (eqs. 42-43).

\[
\begin{align*}
\text{R} & \quad \text{NaIO}_3 \\
\text{H} & \\
\text{NH–CHO} & \quad \text{COR}, \text{NH–CHO}
\end{align*}
\]

...(42)
Indoles can be selectively reduced in five membered ring or six membered ring. The five membered ring is reduced by a number of reagents in acidic media e.g., Zn, Sn, BH$_3$-NMe$_3$ complex (eq. 44) while six membered ring can be reduced by Birch reduction using Li-ammonia in ethanol to give 4,7-dihydroindole (eq. 45).

(iii) Reaction with Carbenes: Indole and substituted indoles undergo addition of dihalocarbene on electron rich C$_2$-C$_3$ double bond to give an intermediate which undergoes ring expansion to give 3-chloroquinoline or 3-membered ring cleavage to give 3-substituted indole derivative (eq. 46).

Reactions of Quinoline and Isoquinoline
Quinolines and isoquinolines behave similar to pyridine. Both are weakly basic and undergo protonation of nitrogen without affecting the aromaticity of the ring. Quaternary ammonium salts are formed on nitrogen by alkylation.

(i) Electrophilic Aromatic Substitution: The nitrogen of the quinoline and isoquinoline has deactivating effect on the ring towards electrophilic substitution as in case of pyridine as discussed earlier. However electrophilic substitution of quinoline and isoquinoline requires less vigorous conditions than pyridine. Electrophilic substitution of protonated quinoline and isoquinoline takes place on the carbocyclic ring at C-5 or C-8 positions. Some typical examples of electrophilic substitution in quinoline (Fig. 16) and isoquinoline (Fig. 17) are given below.
Quinoline and isoquinoline undergo reaction with nitric acid in presence of acetic anhydride to give 3-nitroquinoline and 4-nitroisoquinoline, respectively (eqs. 47-48).

\[ \text{HNO}_3, \text{Ac}_2\text{O} \quad \Delta \quad \text{HNO}_3, \text{Ac}_2\text{O} \quad \Delta \]
(ii) **Nucleophilic Aromatic Substitution:** Quinoline and isoquinoline undergo facile nucleophilic substitution as in pyridine. Quinoline undergoes Chichibabin reaction to give 2-aminoquinoline (eq. 49) while isoquinoline undergoes Chichibabin reaction to give 1-amino isoquinoline (eq. 50). Isoquinoline undergoes substitution faster than quinoline. The reaction proceeds in a manner analogous to pyridine.

\[
\begin{align*}
\text{Quinoline} & \xrightleftarrows{\text{NaNH}_2, \text{liq. NH}_3} \text{2-aminoquinoline} \quad \text{(eq. 49)} \\
\text{Isoquinoline} & \xrightleftarrows{\text{NaNH}_2, \text{liq. NH}_3} \text{1-aminoisoquinoline} \quad \text{(eq. 50)}
\end{align*}
\]

(iii) **Reductions:** Quinoline can be selectively reduced at 1,2-bond by reaction with lithium aluminium hydride but the 1,2-dihydro quinolines are unstable and disproportionate easily to give quinoline and 1,2,3,4-tetrahydroquinoline (eq. 51). Quinoline can be converted to 1,2,3,4-tetrahydroquinoline by catalytic hydrogenation or with tin and hydrochloric acid (eq. 52).

\[
\begin{align*}
\text{Quinoline} & \xrightarrow{\text{LiAlH}_4} \text{1,2-dihydroquinoline} \quad \text{(eq. 51)} \\
\text{Quinoline} & \xrightarrow{\text{Pt, H}_2 \text{ or Sn, HCl}} \text{1,2,3,4-tetrahydroquinoline} \quad \text{(eq. 52)}
\end{align*}
\]

Isoquinoline can also be converted to 1,2-dihydro or 1,2,3,4-tetrahydroisoquinoline with diethyl aluminium hydride and sodium-ethanol, respectively (eq. 53).

\[
\begin{align*}
\text{Isoquinoline} & \xrightarrow{\text{Et}_2\text{AlH}} \text{1,2-dihydroisoquinoline} \quad \text{(eq. 53)} \\
\text{Isoquinoline} & \xrightarrow{\text{Na-EtOH}} \text{1,2,3,4-tetrahydroisoquinoline}
\end{align*}
\]
(iv) **Oxidations:** Quinoline and isoquinoline undergo oxidative cleavage with alk. potassium permanganate to give pyridine-2,3-dicarboxylic acid (eq. 54) and pyridine-3,4-dicarboxylic acid (eq. 55), respectively. However, pyridine-2,3-dicarboxylic acid is not stable and undergoes decarboxylation to give nicotinic acid (eq. 54). Quinoline and isoquinoline both form N-oxides when treated with hydrogen peroxide in acetic acid or with organic peracids.

\[
\text{alk. KMnO}_4 \rightarrow \begin{array}{c}
\text{COOH} \\
\text{COOH}
\end{array} \rightarrow \begin{array}{c}
\text{COOH} \\
\text{COOH}
\end{array} \quad \text{...(54)}
\]

\[
\text{alk. KMnO}_4 \rightarrow \begin{array}{c}
\text{COOH} \\
\text{COOH}
\end{array} \quad \text{...(55)}
\]

**Suggested Readings:**

1. Organic Chemistry by I.L. Finar
3. An Introduction to Chemistry of Heterocyclic Compounds by R.M. Acheson
4. Heterocyclic Chemistry by R.K. Bansal