DIRECTORATE OF DISTANCE & CONTINUING EDUCATION

MANONMANIAM SUNDARANAR UNIVERSITY

TIRUNELVELI- 627 012

OPEN AND DISTANCE LEARNING (ODL) PROGRAMMES

(FOR THOSE WHO JOINED THE PROGRAMMES FROM THE ACADEMIC YEAR 2025–2026)

B. Sc. Chemistry Course material

Core IX

Organic Chemistry - I

Course Code JMCH51

Prepared by

Dr. S. NAGARAJAN

Assistant Professor

Department of Chemistry

Manonmaniam Sundaranar University

Tirunelveli – 627 012

ORGANICCHEMISTRY-I

UNIT-I

Stereo chemistry: Fischer Project on, New man and Sawhorse Projection formulae and their inter conversions; Geometrical isomerism: cis–trans, syn-anti isomerism, E/Z notations. Optical Isomerism: Optical activity, specific rotation, asymmetry, enantiomers, distereo isomers, meso structures– molecules with one and two chiral centres, racemization–methods of race misation; resolutionmethods of resolution. C.I.P rules. R and S notations for one and two chirality (stereo genic) centres. Molecules with no asymmetric carbon atoms – allenes an d biphenyls. Conformational analysis of ethane and butane.

UNIT-II

Chemistry of Nitrogen Compounds–I: Nitroalkanes Nomenclature, isomerism, preparation from alkyl halides, halo acids, alkanes; physical properties; reactions– reduction, halogenations, Grignard reagent, Pseudo acid character. Nitro- acid nitro tautomerism. Aromatic nitro compounds Nomenclature, preparation–nitration, from diazonium salts, physical properties; reactions –reduction of nitrobenzene in different medium, Electrophilic substitution reactions, TNT. Amines: Aliphatic amines Nomenclature, isomerism, preparation – Hofmanns' degradation reaction, Gabriel's phthalimide synthesis, Curtius Schmidt rearrangement. Physical properties, reactions– alkylation, acylation, carbylamine reaction, Man nich reaction, oxidation, basicity of amines.

UNIT-III

Chemistry of Nitrogen Compounds-II: Aromatic amines – Nomenclature, preparation – from nitro compounds, Hofmann's method; Schmidt reaction, properties - basic nature, ortho effect; reactions – alkylation, acylation, carbylamine reaction, reaction with nitrous acid, aldehydes, oxidation, Electrophilic substitution reactions, diazotization and coupling reactions; sulphanilic acid-zwitterion formation. Distinction between primary, secondary and tertiary amines -aliphatic and aromatic Diazonium compounds. Diazomethane, Benzene diazonium chloride -preparations and synthetic applications. Dyes Theory of colour and constitution; classification based on structure and application; preparation–Martius yellow, aniline yellow, methyl orange, alizarin, indigo, malachite green. Dyes Industry, Food colour and additives.

UNIT-IV

Heterocyclic compounds: Nomenclature and classification. General characteristics-aromatic character and reactivity. Five- member heterocyclic compounds Pyrrole – preparation –from succinimide, Paal Knorr synthesis; reactions – reduction, basic character, acidic character, electrophilic substitution reactions, ring opening. Furan – preparation from mucic acid and pentosan; reactions – hydrogenation, reaction with oxygen, Diels Alder reactions, formation of thiophene and pyrrole; Electrophilic substitution reaction. Thio phene synthesis–from acetylene; reactions–reduction; oxidation; Electrophilic substitution reactions.

UNIT-V

Six-member edheterocyclic compounds: Pyridine – synthesis -from acetylene, Physical properties; reactions -basic character, oxidation, reduction, electrophilic substitution reactions; nucleophilic substitution – uses, Condensedring systems. Quinoline – preparation – Skraup synthesis and Friedlander's synthesis; reactions – basic nature, reduction, oxidation; electrophilic substitutions; nucleophilic substitutions – Chichibabin reaction Iso quinoline – preparation by the Bischler – Napieralski reaction, reduction, oxidation; electrophilic substitution.

Recommended Text:

1. M.K.Jain, S.C.Sharma, Modern Organic Chemistry,Vishal Publishing, fourth reprint, 2009.
2. S.M. Mukherji, and S.P. Singh, Reaction Mechanism in Organic Chemistry, Macmillan India Ltd., third edition, 2009.
3. Arun Bah land B. S. Bahl, Advanced organic chemistry, New Delhi, S. Chand & Company Pvt. Ltd., Multicolour edition,2012.
4. P.L. Soni and H. M. Chawla, Text Book of Organic Chemistry, Sultan Chand & Sons, New Delhi, twenty ninth edition, 2007.
5. C.N. Pillai, Text Book of Organic Chemistry, Universities Press (India) Private Ltd., 2009.

UNIT–I

STEREOCHEMISTRY

Introduction

Stereochemistry is the branch of organic chemistry that deals with the study of the three-dimensional arrangement of atoms or groups in molecules and the effect of this spatial arrangement on the physical, chemical, and biological properties of compounds. Although molecular formulas and structural formulas provide information about the types of atoms present and their connectivity, they do not adequately represent the actual spatial orientation of atoms in space. Stereochemistry bridges this gap by explaining how molecules exist and behave in three dimensions.

The importance of stereochemistry arises from the fact that many organic compounds having the same molecular formula and structural connectivity exhibit different properties due to differences in spatial arrangement. Such compounds are known as stereoisomers. Differences in stereochemistry can significantly influence melting point, boiling point, solubility, optical activity, reactivity, and biological action. For example, two stereoisomers of a drug may exhibit entirely different pharmacological effects.

Configuration and Conformation

In stereochemistry, it is essential to distinguish between configuration and conformation. Configuration refers to the fixed spatial arrangement of atoms or groups in a molecule that can be changed only by breaking and reforming chemical bonds. Isomers differing in configuration are known as configurational isomers and include enantiomers, diastereomers, and geometrical isomers.

Conformation, on the other hand, refers to different spatial arrangements of a molecule that arise due to rotation about single (σ) bonds, without breaking any bonds. Different conformations interconvert readily at room temperature and are called conformational isomers or conformers. The study of conformations and their relative stabilities forms an important part of stereochemistry.

Types of Stereoisomerism

Stereoisomerism can be broadly classified into conformational isomerism and configurational isomerism.

Conformational isomerism arises due to free rotation around carbon–carbon single bonds. Molecules such as ethane and butane exist in different conformations like staggered and eclipsed forms, which differ in energy and stability. These conformations are best represented using Newman and Sawhorse projections.

Configurational isomerism arises due to restricted rotation, usually caused by the presence of double bonds, rings, or chiral centers. Configurational isomers cannot interconvert without bond cleavage. This category includes:

- **Geometrical isomerism** (cis–trans, E/Z)
- **Optical isomerism** (enantiomers, diastereomers, meso compounds)

Chirality and Asymmetry

A key concept in stereochemistry is chirality. A molecule is said to be chiral if it is not superimposable on its mirror image. Such molecules exist as a pair of mirror-image forms called enantiomers. The presence of chirality is commonly associated with an asymmetric or chiral carbon atom, which is a carbon atom bonded to four different atoms or groups.

However, chirality is not restricted only to molecules containing asymmetric carbon atoms. Certain molecules without any chiral carbon, such as allenes and substituted biphenyls, can also exhibit chirality due to their unique three-dimensional arrangements. The absence of a plane of symmetry is a fundamental requirement for chirality.

Optical Activity

One of the most important consequences of chirality is optical activity. Optically active substances have the ability to rotate the plane of plane-polarized light. Depending on the direction of rotation, substances are classified as dextrorotatory (clockwise rotation) or levorotatory (anticlockwise rotation). Optical activity is measured using a polarimeter and expressed as specific rotation, which is a characteristic property of a compound.

Compounds that rotate plane-polarized light equally but in opposite directions are known as enantiomers. When equal amounts of two enantiomers are present, the mixture becomes optically inactive and is called a racemic mixture.

Representation of Three-Dimensional Molecules

Since molecules exist in three dimensions but are represented on a two-dimensional surface such as paper, several projection formulae have been developed to express their spatial arrangements clearly. The most important among them are:

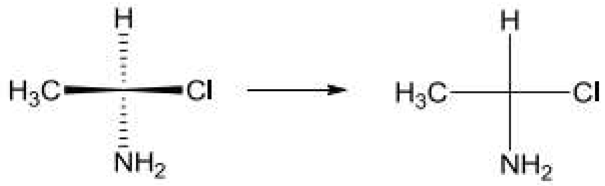
- **Fischer projection**
- **Newman projection**
- **Sawhorse projection**

Each projection formula has specific rules and conventions and is useful for a particular type of stereochemical analysis. Fischer projections are mainly used for configurational analysis of chiral molecules, whereas Newman and Sawhorse projections are employed for conformational analysis of molecules involving rotation about single bonds. Understanding these projection methods and their interconversions is essential for the study of stereochemistry.

Fischer Projection

The **Fischer projection** is a planar representation of three-dimensional molecules and is mainly used for compounds containing **chiral centres**, such as carbohydrates, amino acids, and hydroxy acids. This method was introduced by Emil Fischer and follows specific conventions to represent the spatial orientation of substituents around a tetrahedral carbon atom.

In a Fischer projection, the **carbon chain is written vertically,** and the most oxidized carbon atom is placed at the top of the projection. Each intersection of horizontal and vertical lines represents a carbon atom, usually a stereogenic centre. The fundamental rule of Fischer projection is that **horizontal bonds project out of the plane of the paper towards the observer**, while **vertical bonds project behind the plane of the paper away from the observer**.



Fischer projections represent molecules in a fixed **eclipsed conformation**, where substituents on adjacent carbon atoms appear to eclipse each other. Because of this, Fischer projections do not depict the actual three-dimensional shape or the most stable conformation of the molecule. However, they are extremely useful for comparing stereoisomers and assigning relative configurations.

Certain operations are permitted in Fischer projections without altering the configuration of the molecule. A **180° rotation in the plane of the paper** does not change the configuration, whereas rotation by 90° or turning the projection upside down changes the configuration and leads to an incorrect representation. Interchanging any two substituents at a stereogenic centre results in inversion of configuration.

Uses of Fischer projection

- To represent chiral molecules clearly
- To compare enantiomers and diastereomers
- To assign D/L notation
- To study optical isomerism

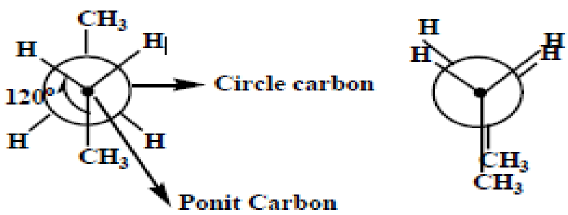
Limitations

- Does not represent true three-dimensional geometry
- Represents only eclipsed conformations
- Not suitable for conformational analysis

Newman projection

This method used in organic chemistry to represent the three-dimensional arrangement of atoms in a molecule by viewing it directly along the axis of a selected bond, most commonly a carbon–carbon single bond. In this representation, the carbon atom closer to the observer is known as the **front (proximal) carbon** and is depicted by a **dot**, while the carbon atom farther from the observer is called the **rear (distal) carbon** and is shown as a **circle**.

The substituents attached to each carbon are arranged around these symbols at angles of **120°**, which reflects the tetrahedral geometry of sp^3-hybridized carbon atoms and allows clear visualization of the **dihedral angle** between bonds. Newman projection serves as an alternative to sawhorse and wedge–dash representations and provides a clearer view of bond orientation along a specific axis. This projection was introduced by **Melvin Spencer Newman in 1952** to overcome the limitations of Fischer projections, which cannot effectively represent molecular conformations. Newman projections can be applied not only to simple acyclic molecules but also to more complex systems, including substituted chains and cyclic structures, making them an important tool for understanding molecular geometry.



Newman representation formula of butane

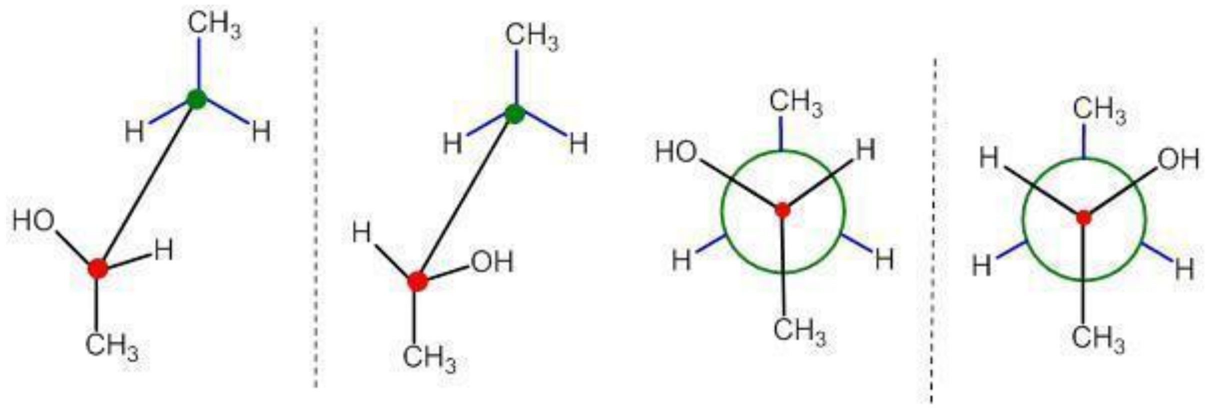
When the number of carbon atoms in a molecule increases, the Newman projection becomes comparatively more complex. For instance, in the case of **butane**, Newman projections can be drawn to represent different conformations such as **eclipsed, gauche, and anti**, all of which are conformational isomers that interconvert by rotation about a single bond. In this representation, the **front dot corresponds to the second carbon atom** of the butane chain, while the **rear circle represents the third carbon atom**. The Newman projection effectively compresses the bond between these two carbon atoms, allowing the relative spatial arrangement of substituent groups to be clearly visualized along the chosen bond axis.

Uses of Newman projection

- To study conformational isomerism
- To compare relative stability of conformations
- To understand torsional strain
- To analyze rotation about single bonds

Sawhorse Projection

A sawhorse projection is a three-dimensional representation used to illustrate the arrangement of atoms around a carbon–carbon single bond. Unlike the Newman projection, where the bond axis is viewed end-on, the sawhorse projection explicitly displays the bond as a diagonal line, allowing both carbon atoms to be seen simultaneously. This representation provides a clearer picture of how substituents are oriented in space. The groups attached to each carbon are drawn at approximately ±120° relative to the carbon–carbon bond, reflecting tetrahedral geometry.



Sawhorse and Newman representations for the 2 enantiomers of 2-Butanol

Sawhorse projections are commonly used to depict different conformational states, particularly staggered and eclipsed arrangements. In the staggered conformation, substituents on adjacent carbons are offset by about 60°, minimizing repulsive interactions, whereas in the eclipsed conformation the substituents align directly with one another, leading to increased steric and torsional strain. Because the spatial relationships between groups are more clearly visible, sawhorse projections are especially useful for comparing molecular structures and identifying stereochemical relationships such as enantiomerism or diastereomerism. The term "sawhorse" originates from the visual similarity between the eclipsed form and a carpenter's sawhorse. In simple molecules like ethane, this projection effectively demonstrates the difference between staggered and eclipsed conformations.

Uses of Sawhorse projection

- To visualize three-dimensional molecular structure
- To represent staggered and eclipsed conformations
- To compare stereochemical relationships

- To assist in interconversion between projections

Interconversion of Projection Formulae

A clear understanding of the interrelationship among different projection formulae is essential for interpreting the stereochemical aspects of organic molecules. Since the same molecule can be represented using Fischer, Newman, or Sawhorse projections, it is necessary to know how to convert one form into another without altering the configuration of the molecule. These interconversions involve only rotations of the molecule in space and not the breaking or rearrangement of bonds. The general procedures followed for such interconversions are described below.

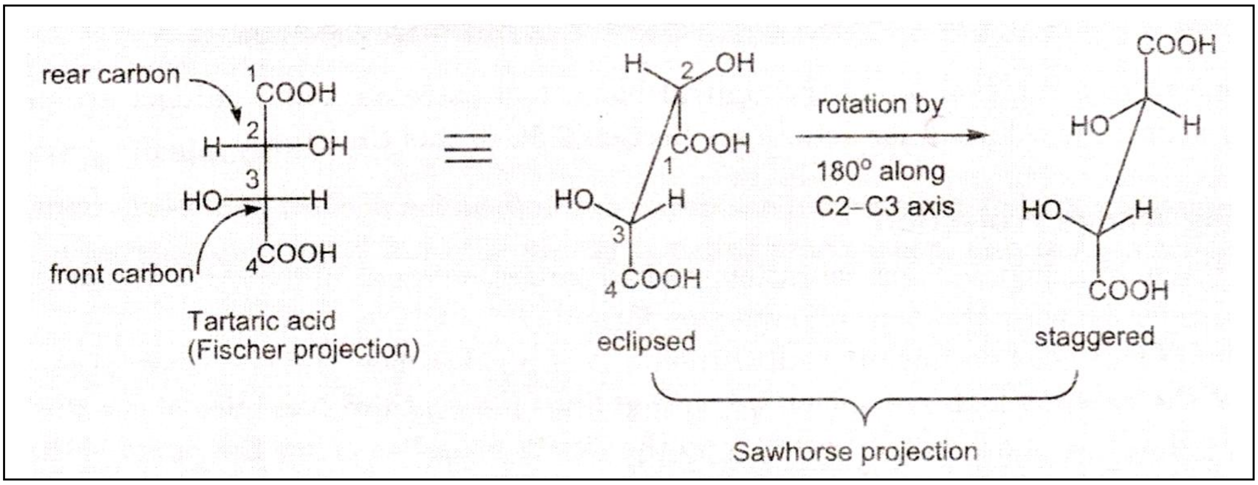
Interconversion of Fischer Projection and Sawhorse Projection

(i) Fischer Projection to Sawhorse Projection

A Fischer projection can be transformed into a sawhorse projection by following a systematic approach. In a Fischer projection, the substituents on adjacent carbon atoms are considered to be in an eclipsed arrangement. To begin the conversion, the Fischer projection is imagined to lie in a horizontal plane such that the vertical bonds point upward and downward, away from the observer. The lowest numbered chiral carbon is oriented facing the viewer.

This orientation initially gives an eclipsed sawhorse form, corresponding to the Fischer projection. To obtain the more stable and realistic representation, one of the two carbon atoms is then rotated by 180° about the carbon–carbon bond. This rotation converts the eclipsed form into a staggered sawhorse projection, which represents the relaxed conformation of the molecule.

Using this method, the Fischer projection of optically active tartaric acid can be accurately converted into its staggered sawhorse representation without any change in stereochemical configuration.

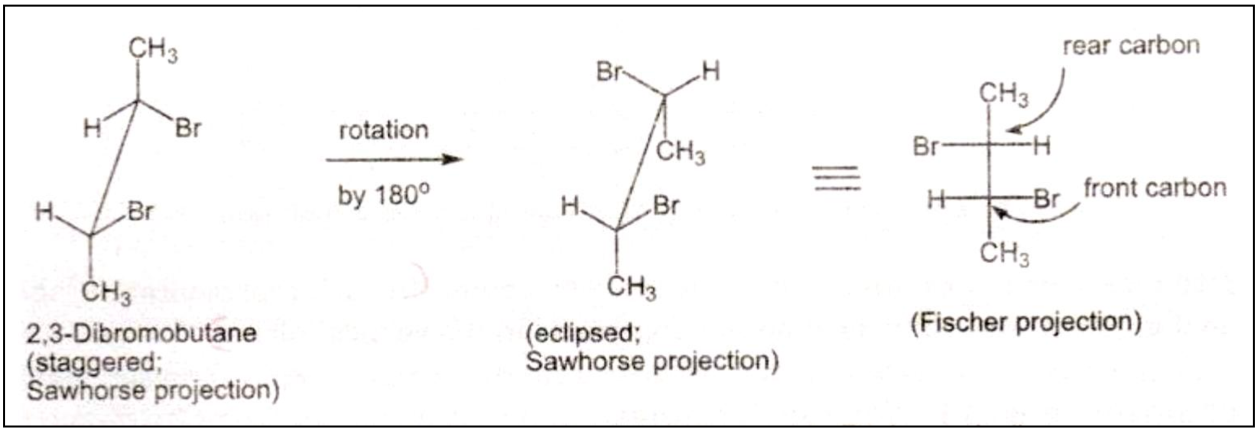


Conversion of Fisher projection into sawhorse projection

(ii) Sawhorse Projection to Fischer Projection

The conversion of a sawhorse projection back into a Fischer projection follows the reverse sequence. First, the given staggered sawhorse projection is converted into an eclipsed form by rotating one carbon atom around the carbon–carbon bond. This step is necessary because Fischer projections correspond to eclipsed arrangements.

The eclipsed structure is then placed in a vertical plane, ensuring that the two substituents pointing upward are directed away from the observer. These groups are then represented on the vertical line of the Fischer projection. The remaining substituents are placed on the horizontal line, projecting toward the observer.



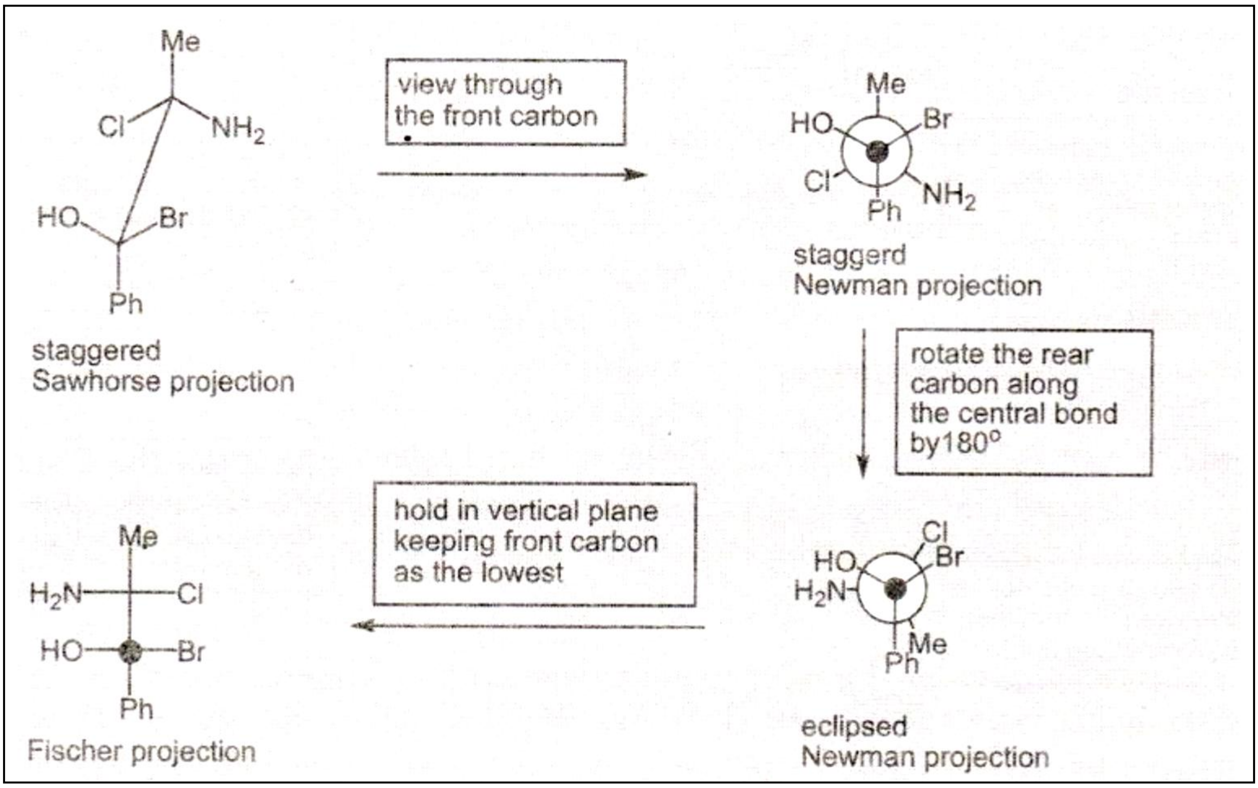
Conversion of sawhorse projection into Fisher projection

By applying this method, the sawhorse projection of compounds such as **2,3-dibromobutane** can be correctly translated into their Fischer projections while preserving the original configuration.

Interconversion of Sawhorse Projection and Fischer Projection via Newman Projection

(i) Sawhorse Projection to Newman Projection and then Fischer Projection

The conversion of a sawhorse projection into a Newman projection is relatively straightforward. The molecule is viewed along the carbon–carbon bond from the direction of the front carbon, making the bond itself invisible. This produces a staggered Newman projection corresponding to the given sawhorse structure.



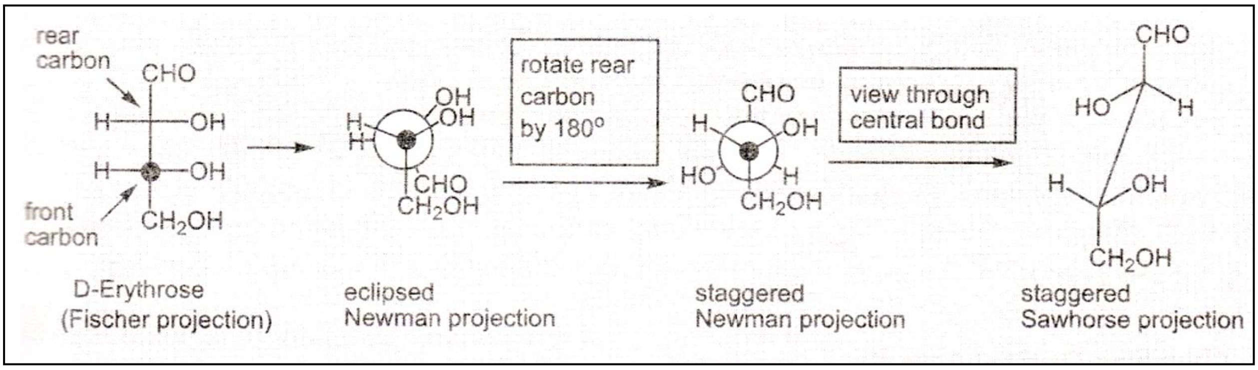
Conversion of Sawhorse Projection and Fischer Projection via Newman Projection

To proceed further, the rear carbon is rotated by 180°, converting the staggered Newman projection into an eclipsed Newman projection, which is required for Fischer representation. The molecule is then oriented in a vertical plane, such that the central carbon–carbon bond lies vertically and the front carbon becomes the lower carbon in the structure.

Once this orientation is achieved, the substituents projecting away from the observer are placed on the vertical line, while those projecting toward the observer are placed on the horizontal line, giving the correct Fischer projection.

(ii) Fischer Projection to Newman Projection and then Sawhorse Projection:

In this method, the Fischer projection is first converted into a Newman projection. The molecule is viewed along the bond passing through the lowest chiral carbon, which becomes the front carbon. Since Fischer projections represent eclipsed conformations, the initial Newman projection obtained is also eclipsed. Next, the eclipsed Newman projection is converted into a staggered conformation by rotating the rear carbon through 60°. This staggered Newman projection represents a more stable arrangement. Finally, the molecule is viewed obliquely along the same carbon–carbon bond to obtain the corresponding sawhorse projection. This sequence of conversions is commonly illustrated using molecules such as D-erythrose, where Fischer, Newman, and sawhorse projections can be interconverted smoothly without disturbing the stereochemical integrity.



Conversion of Sawhorse Projection and Fischer Projection via Newman Projection

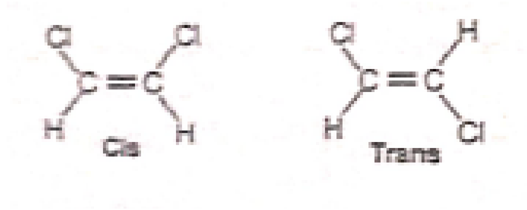
These interconversion techniques are extremely important for understanding stereochemistry, conformational analysis, and reaction mechanisms. Mastery of Fischer, Newman, and sawhorse projection interconversions enables accurate identification of stereoisomers, prediction of molecular stability, and correct interpretation of three-dimensional molecular structures from two-dimensional drawings.

Geometrical Isomerism: *Cis–Trans Isomerism*

Cis–Trans Isomerism

Cis–trans isomerism is a type of geometrical isomerism that arises due to restricted rotation about a carbon–carbon double bond or within a cyclic structure. When two similar groups are present on the same side of the double bond or ring, the isomer is called **cis**, and when they are present on opposite sides, the isomer is called **trans**.

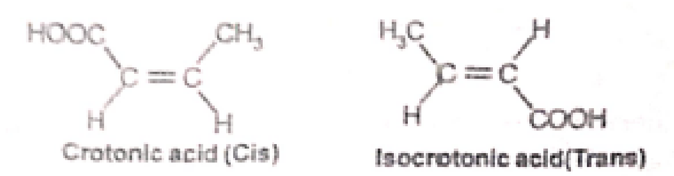
Examples of Cis–Trans Isomerism: 1, 2 dicholoroethene



(ii) Crotonic acid and Isocrotonic acid

Crotonic acid and isocrotonic acid exhibit cis–trans isomerism due to the presence of a carbon–carbon double bond.

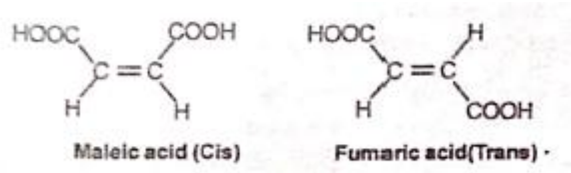
- **Crotonic acid (cis)**: In crotonic acid, the –COOH group and the $–CH_3$ group are present on the **same side** of the C=C double bond. Hence, it is the **cis isomer.**
- **Isocrotonic acid (trans)**: In isocrotonic acid, the –COOH group and the $–CH_3$ group are present on **opposite sides** of the C=C double bond. Therefore, it is the **trans isomer.**



(iii) Maleic acid and Fumaric acid

Maleic acid and fumaric acid are geometrical isomers differing in the arrangement of –COOH groups around the double bond.

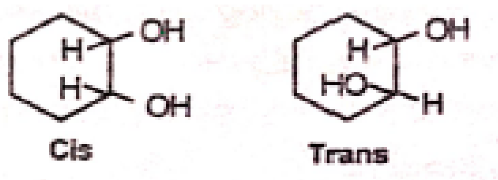
- **Maleic acid (cis)**: In maleic acid, both –COOH groups are present on the **same side** of the carbon–carbon double bond, making it the **cis form**.
- **Fumaric acid (trans)**: In fumaric acid, the two –COOH groups are present on **opposite sides** of the double bond, hence it is the **trans form.**



(iv) Cyclohexane-1,2-diol

Cyclohexane-1,2-diol shows cis–trans isomerism due to restricted rotation in the cyclic structure.

- **Cis-cyclohexane-1,2-diol**:
  In the cis form, both –OH groups are attached to adjacent carbon atoms and lie on the **same side** of the cyclohexane ring.
- **Trans-cyclohexane-1,2-diol**:
  In the trans form, the –OH groups are attached to adjacent carbon atoms but are present on **opposite sides** of the ring.

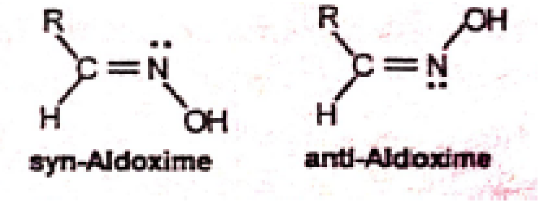


Syn–Anti Isomerism

The terms **syn** and **anti** are used in place of **cis** and **trans**, respectively, to designate geometrical isomerism in oximes and azo compounds.

In the case of aldoximes, the syn isomer is the one in which the hydrogen atom and the hydroxyl (–OH) group are present on the same side of the carbon–nitrogen double bond (C=N). The anti isomer is the one in which the hydrogen atom and the hydroxyl group lie on opposite sides of the C=N bond.

- **Syn-aldoxime**: Hydrogen and –OH groups are on the same side of the C=N bond.
- **Anti-aldoxime**: Hydrogen and –OH groups are on opposite sides of the C=N bond.



In the case of unsymmetrical ketoximes, the designation of syn and anti is made with respect to the relative positions of the –OH group and the larger alkyl group, and the assignment is considered arbitrary.

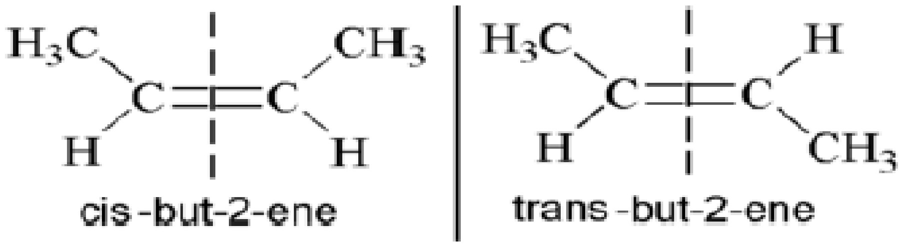
Thus, in ethyl methyl ketoxime, two geometrical isomers are possible:

- **Syn-ethyl methyl ketoxime**: The –OH group and the ethyl group are on the same side of the C=N bond.
- **Anti-ethyl methyl ketoxime**: The –OH group and the ethyl group are on opposite sides of the C=N bond.

This type of isomerism arises due to restricted rotation about the C=N double bond, leading to different spatial arrangements of substituents.

E/Z Notation

In stereochemistry, geometrical isomerism was traditionally described using the **cis–trans notation**, where *cis* indicates that similar groups are located on the same side of a double bond and *trans* indicates that they are on opposite sides. This system works well for simple alkenes in which each carbon of the double bond is attached to one identical substituent. However, in many alkenes this approach becomes inadequate. Alkenes are **planar molecules** due to the presence of a carbon–carbon double bond, and **rotation about the double bond is not possible**. Once a substituent is positioned on one side of the double bond, it remains fixed on that side. While the cis–trans notation is suitable for simple cases, it fails when an alkene contains **three or four different substituents** attached to the double-bonded carbon atoms.



For example, in *but-2-ene*, the cis–trans system works clearly. When the two methyl groups are on the same side of the double bond, the compound is named **cis-but-2-ene**. When the methyl groups lie on opposite sides, the compound is called **trans-but-2-ene**. In such cases, cis–trans notation is both simple and correct. However, difficulties arise in more substituted alkenes such as *3-methylpent-2-ene*. In these molecules, it is no longer clear which groups should be compared using cis and trans terminology. To overcome this limitation, the **E/Z nomenclature system** is used. This system is derived from the German words **Zusammen** (together) and **Entgegen** (opposite) and is based on a set of priority rules known as the **Cahn–Ingold–Prelog (CIP) rules**.

To apply the E/Z system, the double bond is first considered as having two sides—left and right. On each carbon of the double bond, the two attached substituents are assigned priorities based on their **atomic numbers**, with the atom of higher atomic number receiving higher priority. If the directly attached atoms are the same, priority is determined by moving outward along the chain until a difference is found. In *(Z)-3-methylpent-2-ene*, the higher-priority substituents on both sides of the double bond are located on the **same side**. Since the high-priority groups are together, the alkene is designated as the **Z isomer**. A helpful way to remember this is that "Z" stands for *together*.

(E)-3-methylpent-2-ene and (Z)-3-methylpent-2-ene

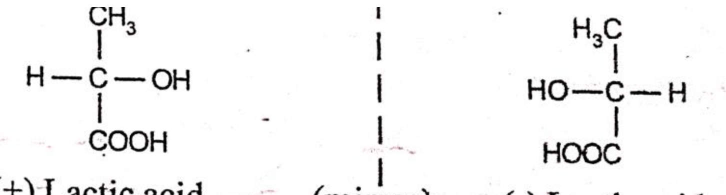
In *(E)-3-methylpent-2-ene*, the priority assignments on the left side of the double bond remain the same, but on the right side the higher-priority substituent is positioned on the opposite side. As a result, the higher-priority groups are **on opposite sides** of the double bond, and the alkene is assigned the **E configuration**, meaning *opposite*. Although the E/Z system may initially seem complex, it provides a **clear and unambiguous method** for describing the geometry of all alkenes, regardless of the number or nature of substituents. With regular practice, identifying and assigning E and Z configurations becomes straightforward and reliable.

Optical Isomerism (Enantiomerism)

Optical isomerism is a type of stereoisomerism in which compounds have the same structural formula but differ in their spatial configurations and exhibit equal and opposite optical activity towards plane-polarised light. Such isomers rotate the plane of polarised light either to the right or to the left by the same magnitude.

Compounds showing optical isomerism exist as pairs of non-superimposable mirror images, and these isomers are known as optical isomers or enantiomers. Although enantiomers possess identical physical and chemical properties in an achiral environment, they differ in the direction of rotation of plane-polarised light. An enantiomer that rotates plane-polarised light to the right is denoted by the symbol **(+)** or dextro, while the one that rotates it to the left is denoted by **(−)** or laevo.

Example:
(+) Lactic acid and (−) lactic acid form a pair of optical isomers (enantiomers), as they have identical structures but rotate plane-polarised light in opposite directions.

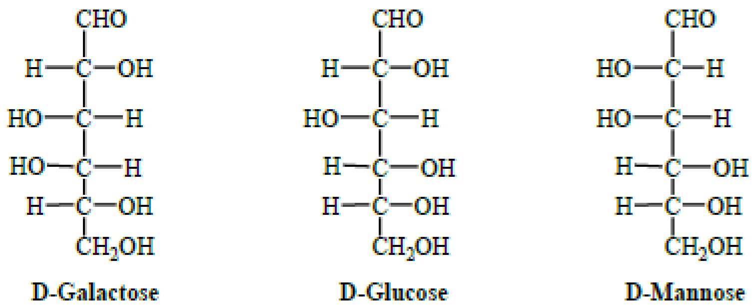


(+) Lactic acid (mirror) (-) Lactic acid

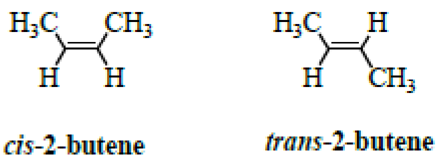
Diastereomers:
Diastereomers are those stereoisomers that are not mirror image of each other, in other words you can understand the diastereomers are stereoisomers that are not enantiomers. Diastereomers are non-enantiomeric stereoisomers with two or more stereo centers. The pair

of stereoisomer that differs in the arrangement of atoms/groups bonded with at least one stereo centre is called diastereomers.

Example: D-Galactose, D-Glucose and D-Mannose are the non-mirror image stereoisomer of each other. Therefore are called diastereomers.



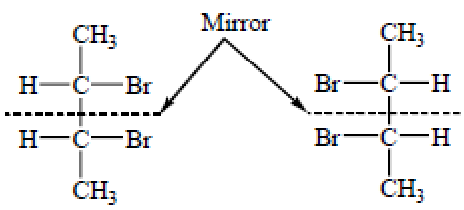
Example: *cis*- and *trans*-2-butenes are non-mirror image stereoisomers of each other hence are called diastereomers.



Meso compounds:

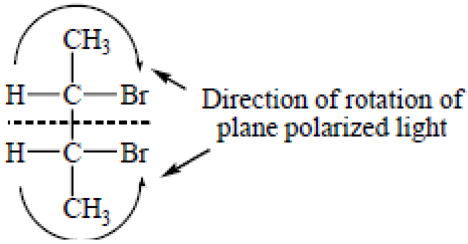
A compound with two or more carbon stereo centre but also having a plane of symmetry is called *meso* compounds. All the carbon centers have four different atoms/groups but the compound can be divided in to two equal halves which are super imposable mirror image.

Example 24: 2,3-dibromobutane have two stereocentres, but the molecule have two symmetric ends therefore it can be divided in to two equal halves. In other words the molecule have plane of symmetry

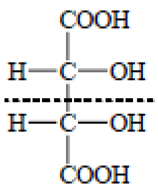


2,3-Dibromobutane

The 2,3-dibromobutane have non super imposable mirror image but this molecule have an internal plane of symmetry hence this molecule is optically inactive or achiral. This molecule will not be able to rotate the plane polarized light in any direction. If one half of the molecule will rotate the plane polarized light towards right hand direction with some degrees; the other half will rotate the plane polarized light towards left hand direction with same degrees of rotation. Thus the net rotation of the plane polarized light is zero. Such molecules are called meso compounds



Another example of meso compound is one of the stereo isomeric forms of Tartaric acid (2, 3-dihydroxysuccinic acid). The molecule is optically inactive because it has internal plane of symmetry



meso-Tartaric acid

Elements of Symmetry (Symmetry Elements)

The **symmetry elements of a molecule** are of **four types**:

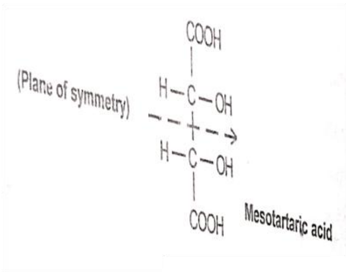
(i) Plane of symmetry
(ii) Centre of symmetry
(iii) Axis of symmetry
(iv) Alternating axis of symmetry

(i) Plane of Symmetry

A plane of symmetry is a plane that cuts a molecule into two equal halves such that the two halves are mirror images of each other.

Example: *Mesotartaric acid*

Mesotartaric acid possesses a plane of symmetry that divides the molecule into two identical mirror-image halves. Due to the presence of this plane of symmetry, the molecule is optically inactive.

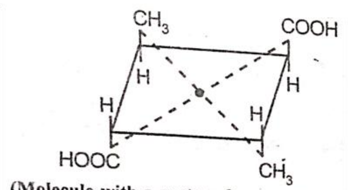


(ii) Centre of Symmetry

A centre of symmetry is a point in a molecule such that a line drawn from any atom on one side of the point, when produced to an equal distance on the opposite side, meets an identical atom or group.

Example: 2,4-Dimethylcyclobutane-1,3-dicarboxylic acid

This molecule contains a centre of symmetry, as identical groups are present at equal distances on opposite sides of a central point.



(Molecule with a centre of symmetry)

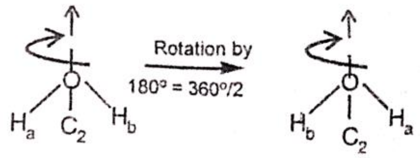
2,4-Dimethylcyclobutane-1,3-dicarboxylic acid

(iii) Axis of Symmetry

An axis of symmetry is an imaginary axis passing through a molecule such that rotation of the molecule through a complete rotation (360°) about this axis results in more than one identical configuration.

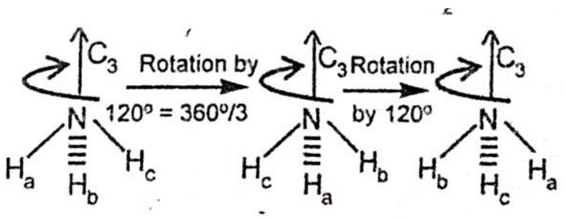
Examples:

- **H_2O molecule** has a two-fold axis of symmetry (C_2). Rotation of the molecule by 180° (360°/2) gives an identical structure.



H_2O molecule

- **NH_3 molecule** has a three-fold axis of symmetry (C_3). Rotation of the molecule by 120° (360°/3) produces identical structures.



NH_3 molecule

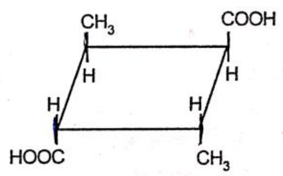
(iv) Alternating Axis of Symmetry

An alternating axis of symmetry is an axis through which, if a molecule is rotated by a certain angle and then reflected across a plane at right angles to the axis, an identical structure is obtained.

- A one-fold alternating axis corresponds to a plane of symmetry.
- A two-fold alternating axis corresponds to a centre of symmetry.

Example: 2,4-Dimethylcyclobutane-1,3-dicarboxylic acid

This molecule possesses a two-fold alternating axis of symmetry, as rotation followed by reflection gives an identical structure.



2,4-Dimethylcyclobutane-1,3-dicarboxylic acid

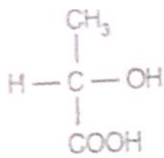
Symmetry or Symmetric molecule

An object or a molecule having any one of symmetry elements i.e. plane of symmetry, centre of symmetry, axis of symmetry, Alternating Axis of Symmetry is known as symmetry molecule. Ex. 2,4-Dimethylcyclobutane-1,3-dicarboxylic acid is symmetry molecule because it has a Alternating Axis of Symmetry.

Asymmetry or Asymmetric Molecule

A molecule or an object having no element of symmetry of any kind is called an asymmetric molecule or asymmetric object. Asymmetric molecules cannot be superimposed on their mirror images and therefore show optical activity.

Example: *(+) Lactic acid*



(+) Lactic acid

Lactic acid has no plane of symmetry, centre of symmetry, or axis of symmetry and hence exists as an asymmetric molecule.

1.6 Dissymmetry or Dissymmetric Molecule

Molecules possessing only a few elements of symmetry are known as dissymmetric molecules. Dissymmetric molecules may have an axis of symmetry, but they do not possess a plane of symmetry. Like asymmetric molecules, dissymmetric molecules cannot be superimposed on their mirror images and hence can exhibit optical activity.

1.6 Optical Activity

Substances that have the ability to rotate the plane of plane-polarised light are said to be optically active, and this property is known as optical activity.

- Substances that rotate the plane of polarised light to the right (clockwise direction) are called dextrorotatory and are denoted by the symbol **d** or **(+)**.
- Substances that rotate the plane of polarised light to the left (anticlockwise direction) are called laevorotatory and are denoted by the symbol **l** or **(−)**.

Example: *(+) Lactic acid* is an optically active compound.

1.7 Optical Rotation

The optical rotation is the angle through which the plane of polarization is rotated when polarized light passes through a layer of liquid. Optical activity is the ability of a compound to rotate the plane of polarized light. This property arises from an interaction of the electromagnetic radiation of polarized light with the unsymmetric electric fields generated by the electrons in a chiral molecule

A compound is said to be optically active when the linearly polarized light is being rotated when it is passing through it. The optical rotation is the angle through which the plane of polarization is rotated when polarized light passes through a layer of a liquid. Optical rotation is the effect which is determined by the concentration of chiral molecules and their molecular structure in a substance. Every optical active substance has its own specific rotation.

Optical Rotation Theory

The optical rotation that is the rotation of the plane of polarized light is shown below.

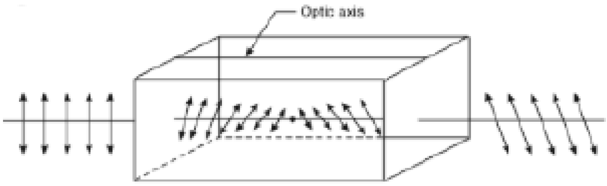
Optical Rotation

The ability to rotate the plane of polarization of plane-polarized light by a certain substance is called optical activity. Substances that have the ability to rotate the plane of the polarized light passing through them are called optically active substances. Quartz and cinnabar are examples of optically active crystals while aqueous solutions of sugar, tartaric acid are optically active solutions.

Optically active substances are classified into two types.

1. **Dextrorotatory substances –** Substances that rotate the plane of polarization of the light towards the right are known as right-handed or dextrorotatory.

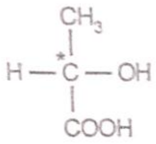
2. Laevorotatory substances – Substances which rotate the plane of polarization of the light toward the left are known as left-handed or **Laevorotatory.**



Optical Rotation

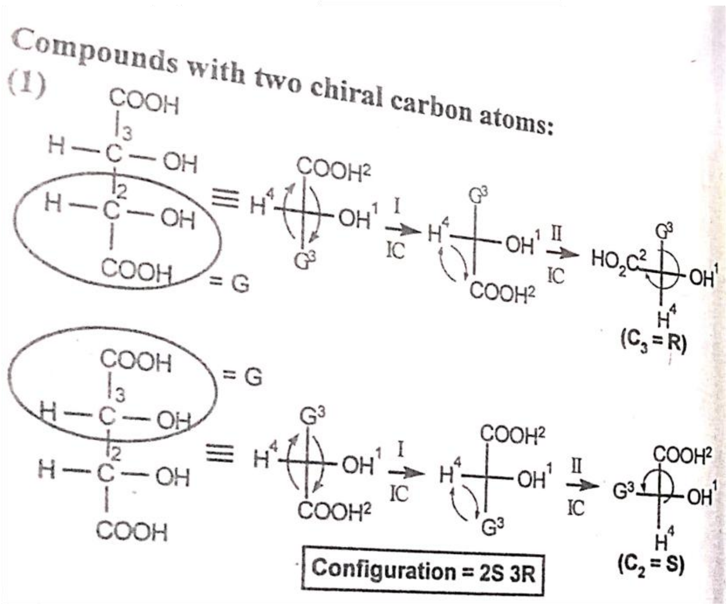
Chiral Centre or Asymmetric Centre

A **carbon atom surrounded by four different atoms or groups** is known as a **chiral centre** or **asymmetric centre**. Such a carbon atom is represented by the symbol **C***.



(C* = Chiral centre)

(+) Lactic acid



Example:

In **(+) lactic acid**, the carbon atom attached to **–CH_3, –H, –OH and –COOH** groups is a chiral centre (C*). This asymmetry is responsible for the optical activity of lactic acid.

1.11 Racemisation

Definition:

The process of converting an **optically active compound** into an **optically inactive racemic modification** is known as **racemisation**.

1.12 Methods of Racemisation

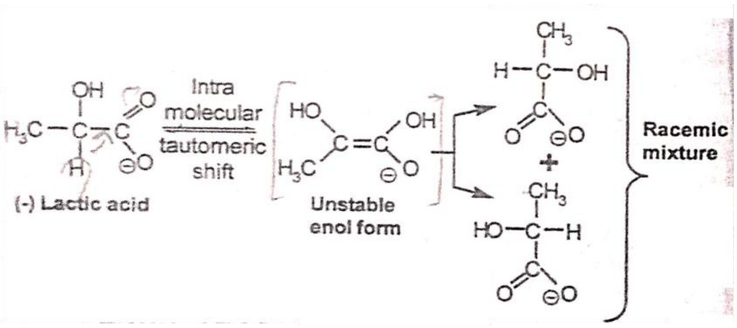
Racemisation occurs through **intramolecular rearrangements** caused by **heat, light, or catalysts**. Some compounds undergo racemisation **spontaneously at room temperature**, a process known as **auto-racemisation**.

(a) Racemisation Using Catalyst

Racemisation readily occurs in compounds where the **asymmetric carbon atom is attached to a hydrogen atom** and can undergo **tautomeric change**.

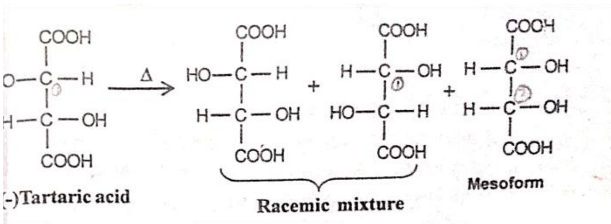
Example:

Racemisation of **(−) lactic acid** occurs in **aqueous NaOH** through **enolisation.** The compound forms an unstable enol intermediate, which on reverting back produces **both (+) and (−) forms**, resulting in a **racemic mixture**.



(b) Racemisation by Heating

When **tartaric acid** is heated, it is converted into a **racemic mixture** as well as a **meso form**. This occurs due to rearrangement of the configuration around the asymmetric carbon atoms.



Resolution

Definition

Resolution is the process of separation of a racemic modification into its two enantiomers. When the two enantiomers are separated in unequal amounts, the process is known as partial resolution.

Methods of Resolution

Several methods are employed for the resolution of racemic mixtures, which are described below.

(i) Biochemical separation

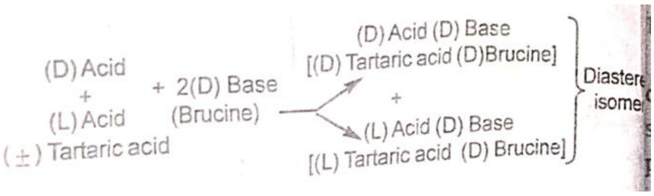
Some microorganisms such as bacteria or moulds show selective action toward one enantiomer when grown in a dilute solution of a racemic compound. As a result, one enantiomer is destroyed faster, while the other remains unchanged.

Example:
When *Penicillium glaucum* is allowed to grow in a solution of racemic ammonium tartrate, it preferentially decomposes the (+) enantiomer, leaving behind the (–) enantiomer.

(ii) Conversion into diastereoisomers

In this method, a racemic mixture is treated with an optically active reagent, converting its enantiomers into diastereoisomeric compounds. Since diastereoisomers have different physical properties, they can be separated by fractional crystallisation. Generally, racemic acids are resolved using optically active bases, and racemic bases are resolved using optically active acids.

Example:
Racemic tartaric acid reacts with optically active brucine to form two different diastereoisomeric salts, which can be separated due to their different solubilities.



(iii) Mechanical separation

Mechanical separation is applicable only when the racemic compound forms distinct crystalline enantiomers. These crystals can be physically separated based on their shape.

Example:
Pasteur successfully resolved sodium ammonium tartrate by crystallising its racemic solution below 27°C and manually separating the (+)- and (–)-crystals by hand picking.

(iv) Preferential crystallisation (seeding)

In this technique, a supersaturated solution of a racemate is seeded with a crystal of one enantiomer. This added crystal promotes the crystallisation of the same enantiomer from the solution, leaving the other enantiomer in solution. Using this method, racemic mixtures such as (±) glutamic acid and (±) aspartic acid can be resolved. Seeding may also be carried out with another optically active substance having a similar crystal structure.

Example:
The resolution of (±) sodium ammonium tartrate can be achieved by seeding the solution with asparagine.

R–S Notation (Absolute Configuration)

A definite and universally applicable nomenclature system was needed to specifying the absolute configuration of each chiral centre in a molecule. Cahn and coworkers (1956, 1966) have proposed a new and universally applicable nomenclature pattern for the determination of absolute configuration of any chiral molecule. This is known as the R/S system or *Cahn-Ingold-Prelog* (CIP) nomenclature. It involves following two steps.

1. In first step we need to assign the priority to the four different atoms/groups attached to a chiral centre.
2. Priorities to the groups/atoms can be assigned as per the **sequence rule**.

3. After assigning the priority to the atoms/groups attached to the chiral centre, the molecule is oriented in such a way that the lowest priority group is directed away to the observer.

4. Now the arrangement of the remaining atoms/groups is viewed by following deceasing order of priorities from highest priority to lowest priority.

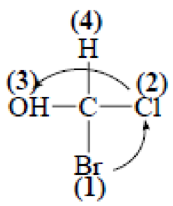
5. While viewing the atoms/groups in their decreasing order if your eyes follow the clockwise direction then the chiral centre will have *R* configuration; whereas if your eyes follow anticlockwise direction the chiral centre will have *S* configuration.

6. When a molecule has two or more than two chiral centers then the same process should be followed to assign their configuration.

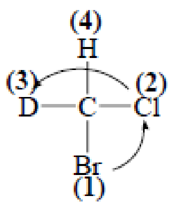
Cahn–Ingold–Prelog (CIP) Rules

To assign the priorities to all four different groups/atoms attached with the chiral centre following sequence rule should be followed. The sequence rule is given by the three scientists *Cahn-Ingold-Prelog* therefore it is also called the CIP rule. The sequence rules are arbitrary but consistent. The main observations of sequence rules are listed below.

1. If all the atoms directly attached to the chiral centre are different, the sequence of priorities is determined by their atomic number. The atom with higher atomic number is given higher priority. If two atoms are isotopes of same element, the isotope with higher mass number has the higher priority.



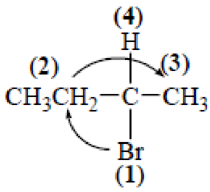
Bromochloromethanol
1-2-3 order is anticlockwise
the configuration is *S*



Deuterium (D) is an isotope of Hydrogen with mass number 2 hence get higher priority than H

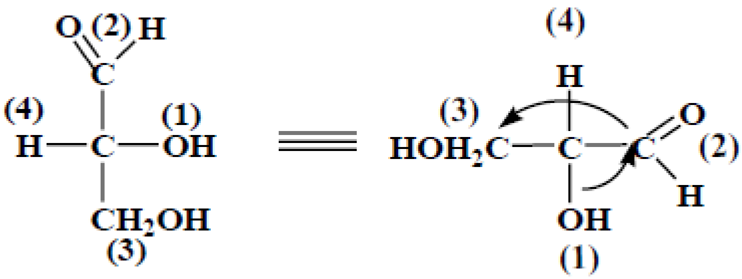
Deuterio bromochloromethane
1-2-3 order is anticlockwise
the configuration is *S*

2. If two or more atoms attached to the chiral centre having same atomic number, the priorities are assigned by comparing the atomic numbers of the next atoms attached to each group/atom.



2-bromobutane
1-2-3 order is clockwise
configuration is *R*

3. If the atoms or groups attached to the centre atom are further linked with some other atoms via double and triple bonds. Then the double or triple bonded atoms are considered to be duplicate or triplicate. As per sequence rule the triple bond gets priority over double bond, similarly double bond gets priority over single bond.

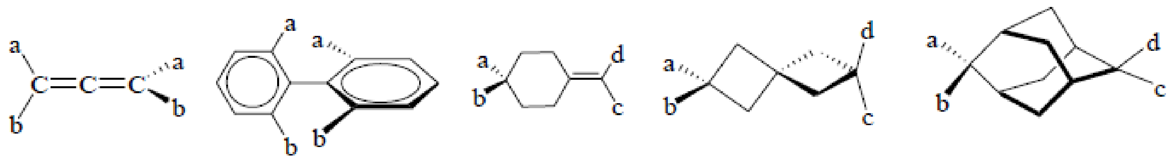


2,3-dihydroxypropanal
1-2-3 order is anticlockwise
configuration is *S*

Molecules with no asymmetric carbon atoms

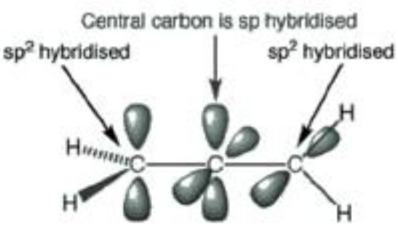
Axial chirality is a type of chirality is produced in a molecule when there is no chiral centre present in the molecule. As discussed, in order to produce chirality it is not necessary for all of the substituents to be different. However, it is sufficient to have each substituent different from its nearest neighbour.

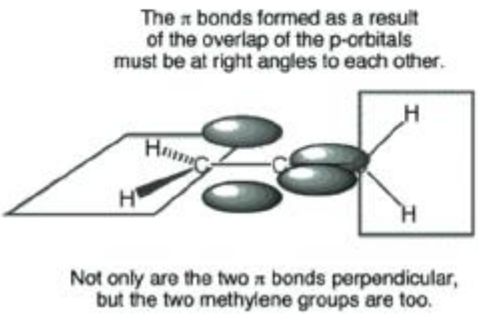
When four atoms/groups attached to a central atom are located on the corners of tetrahedron the central atom is termed as chiral centre. If the chiral centre is replaced by a linear grouping like C-C or C=C=C, the tetrahedron geometry get extended along the axis of the grouping and thus generates a chiral axis. Depending on the nature of groups attached with the carbon atoms, some examples of molecules with chiral axis are allenes, biphenyls, alkylidenecycloalkanes, spiranes, adamentanes etc.; are shown below



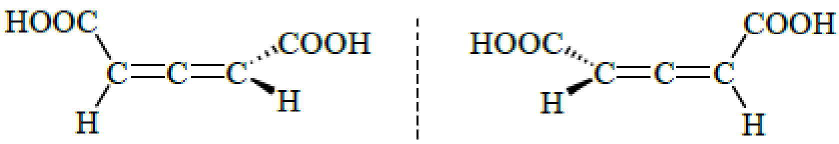
Allene **Biphenyl** **alkylidenecycloalkane** **Spirane** **Adamantane**

Allenes: Allenes are compounds with two or more double bonds side-by-side. Such bonds are called *cumulated double bonds.* The central carbon of allene forms two sigma bonds and two pi bonds. The central carbon is *sp*-hybridized and the two terminal carbons are s*p2*-hybridized. The two π-bonds attached to the central carbon are perpendicular to each other. The geometry of the π-bonds causes the groups attached to the end carbon atoms to lie in perpendicular planes. The bond angle formed by the three carbons is 180°, indicating linear geometry for the carbons of allene.





Stereochemistry of Allenes: When three or more adjacent carbon atoms in a molecule are bonded by double bonds, the compounds is called cumulene or said to have cumulative double bonds. Allene is the simplest example of this class. Allenes are chiral and they have nonsuperimposable mirror images and exist as enantiomers although they have no chiral centre.

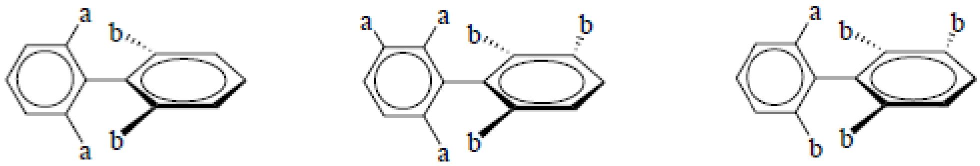


Nonsuperimposable Mirror images
(Enantiomeric Pair)

Stereochemistry of Biphenyls: Stereoisomers obtained due to the restricted rotation about carbon-carbon single bond are called atropisomers and the phenomenon is called atropisomerism. Such compounds also have the chirality due to the axis. Suitably substituted biphenyls exhibit enantiomerism due to the presence of chiral axis. This enantiomerism arises due to atropisomerism *i.e.* restricted rotation around C-C bond between two phenyl rings. This steric hindrance of substituents at *ortho*- position of the each ring is responsible for such restricted rotation. To maintain the maximum stability, molecule orients itself in such a manner so that both the *ortho*- substituted phenyl rings lie in different plane.

Biphenyl shows the enantiomerism when the molecule has the following properties.

a) Each ring must be unsymmetrically substituted. Each of the rings should not contain any kind of symmetry element.



I II III

nonresolvable Biphenyl (optically inactive due to plane of symmetry)

resolvable Biphenyls (optically active due to absence of symmetry elements)

b) Suitable substitution (at least one substitution) at *ortho*- position must be there at each rings.

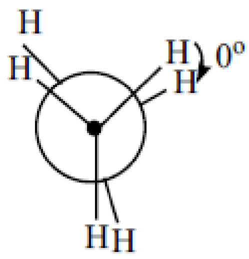
c) *othro*- substituents must be larger in size (-Cl, -Br, -I, -COOH, $-NO_2$, $-NHCOCH_3$, -SO3H, -R groups etc.).

The smaller groups at *othro*- position make the compounds planar in nature and thus do not exhibit atropisomerism.

a) Each ring must be unsymmetrically substituted. Each of the rings should not contain any kind of symmetry element.

Conformational Analysis of Ethane:

When ethane molecule rotates around carbon-carbon single bond, two extreme conformations (one is highly stable and other is highly unstable) are obtained. The highly stable conformation of ethane is called '*staggered conformation*' and the highly unstable conformation of ethane is called '*eclipsed conformation*'. In between these two extreme conformations (*i.e.* staggered and eclipsed), an infinite number of conformations are also possible.



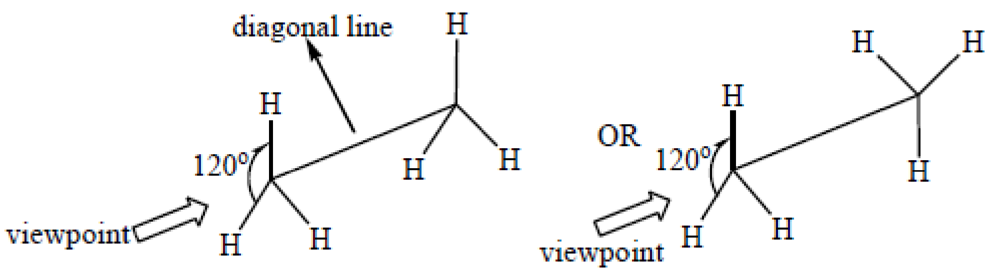
Eclipsed conformation

Staggered conformation: A conformation with a 60° dihedral angle is known as staggered conformation. The angle between the atoms attached to the front and rear carbon atom is called dihedral angle.

Eclipsed conformation: A conformation with a 0° dihedral angle is known as eclipsed conformation.

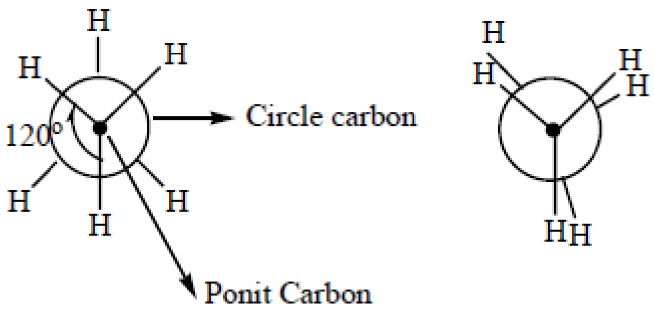
In staggered conformation the atoms are located at maximum possible distance from each other hence they are in their most relaxed spatial arrangement thus the staggered conformation is considered as the most stable conformation; whereas, in eclipsed conformation the atoms are located at minimum distance, hence due to repulsion between the atoms the eclipsed conformation is considered as the least stable (high energy) conformation. There are two methods for the representation of staggered and eclipsed conformations, **a**) the Sawhorse representation formula and, **b**) the Newman representation formula.

a) **The Sawhorse representation formula:** In sawhorse representation formula the spatial arrangement of all the atoms/groups on two adjacent carbon atoms. The bond between adjacent carbon atoms is represented by a diagonal line and rest of the atoms are located on each carbon at +120° or -120° angles to each other. The sawhorse representation is shown as:



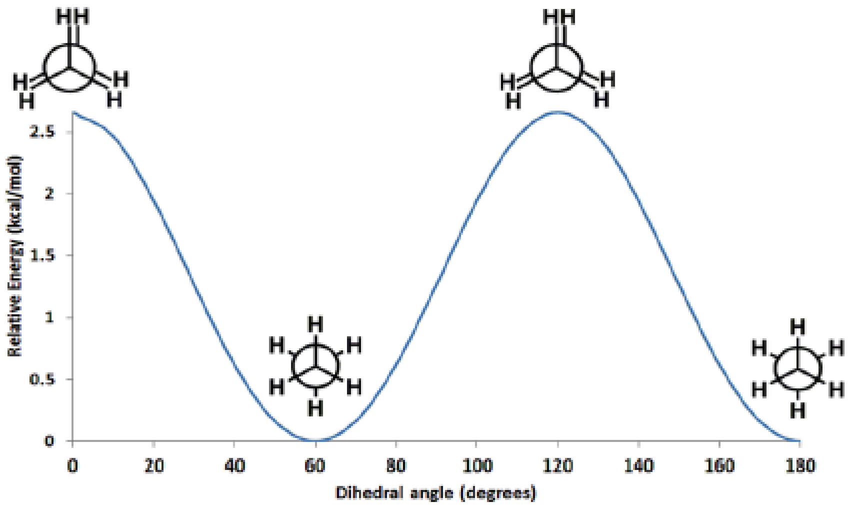
Sawhorse representation formula

b) **The Newman representation** formula is a planar representation of the sawhorse formula. The molecule is viewed along the axis of a carbon-carbon bond. The carbon atom in front of the viewer is represented by a dot (●), whereas the carbon atom away to the viewer is represented by circle. The rest of the atoms/groups are located on each carbon atoms at +120° or -120° angles to each other as shown below:



Newman representation formula

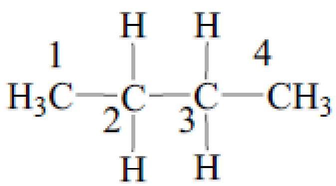
The different conformations of ethane are not equally stable. The staggered form in which the hydrogen atoms are 'perfectly staggered' (dihedral angle is 60°) is the most stable conformation. This is because, in this conformation the all carbon hydrogen (C-H) bonds are located at maximum possible distance to each other, and hence they feel minimum repulsive energy from each other. In eclipsed conformation of ethane, the hydrogen atoms attached to each carbon are directly opposing to each other. This result the minimum separation of the atoms or groups, and hence they feel maximum repulsive energy from each other. The eclipsed conformation therefore, of highest energy and has the lowest stability. A graph plot for the energy profile for various conformations of ethane is shown on below figure



Energy profile diagram of conformational isomer of ethane

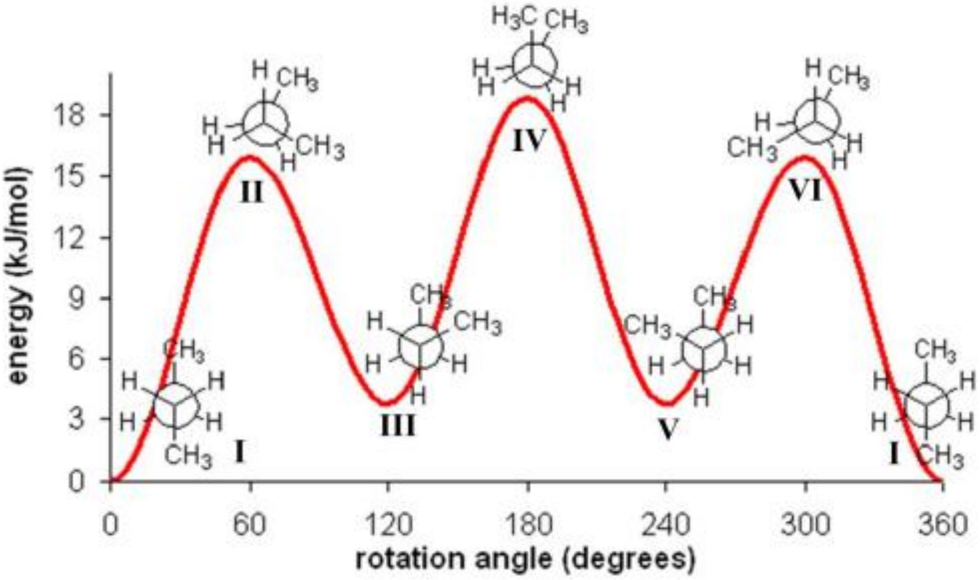
Conformational Analysis of *N*-Butane:

n-Butane (C_4H_{10}) has three carbon-carbon single bonds; therefore the molecule can rotate about each of them. The rotation about C2 and C3 bond will provide the symmetrical conformations. To study the conformational analysis of *n*-butane, we must consider it as a derivative of ethane molecule, where one hydrogen at each carbon of ethane is replaced by methyl group ($-CH_3$).



Butane molecule

Various conformation of *n*-butane can be obtained by rotation about C2 and C3 bond are shown in figure:



Energy profile diagram of conformational isomer of *n*-butane

n-butane has three staggered conformations (**I, III** and **V**). Conformer **I**, in which two methyl groups are as far as possible, and hence is more stable than other two staggered conformers (*i.e.* **III** and **V**), because conformer **I**, has minimum repulsive energy. In conformer **I,** both the methyl groups are located opposite to each other. The most stable conformer of *n*-butane, in which both the methyl groups are located opposite to each other is called the *anti-conformer*, whereas other two staggered conformers (*i.e.* **III** and **V**) are called *gauche conformer*. Due to difference in steric strain (repulsion between dihedral atoms/groups) the repulsive energy of *anti* and *gauche* conformers are also different. Three eclipsed conforms (**II**, **IV** and **VI**) are also exits for *n*-butane, in which the dihedral atoms/groups are in front of each other (*i.e.* dihedral angle is 0°). The fully eclipsed conformer **IV,** in which the two methyl groups are closest to each other, has maximum steric strain; hence it is of higher energy than the other eclipsed conformers (**II** and **VI)**.Thus the relative stabilities of the six conformers of *n*-butane in their decreasing order is given as follows:

Anti > Gauche > Eclipsed > Fully eclipsed

UNIT II

CHEMISTRY OF NITROGEN COMPOUNDS-I

Nitroalkanes

Nitroalkanes are represented by the formula, R-NO_2 where R is an alkyl group (CnH2n+1-). Nitroalkanes are further classified into primary, secondary, tertiary nitroalkanes on the basis of type of carbon atom to which the nitro (-NO_2) group is attached.

Nomenclature of nitroalkanes

In the IUPAC nomenclature, the nitroalkanes are named by adding prefix nitro before the name of alkane, the position of the nitro group is indicated by number.

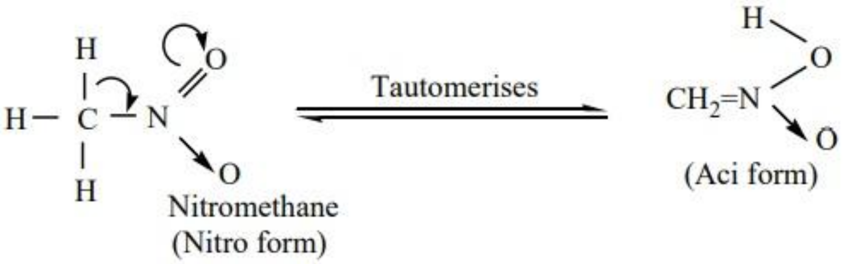
Compound (Common Name, Structural Formula, IUPAC Name)	Prefix with Position Number	Root Used	Primary Suffix	Secondary Suffix
AcetonitrileCH_3-CNEthane nitrile	–	Eth	ane	nitrile
PropiononitrileCH_3CH_2-CNPropanenitrile	–	Prop	ane	nitrile
Butyronitrile$CH_3CH_2CH_2$-CNButanenitrile	–	But	ane	nitrile
IsobutyronitrileCH_3-CH-CH_2-CN2-methylpropanenitrile CH_3	2-methyl–	prop	ane	nitrile
BenzonitrileC_6H_5-CNBenzene carbonitrile	–	Benzene	carbo	nitrile
3-Cyanobutanoic acidH_3C-CH-CH_2-COOH CN	3-Cyano	but	ane	oic acid
2-Bromo-3-chloro-3-methyl pentanenitrileCH_3-C(C_2H_5)(Cl)-CH_2-CN Br	2-Bromo-3-chloro-3-methyl	pent	ane	nitrile

Isomerism

Nitroalkanes exhibit chain and position isomerism among their own class and functional isomerism with alkyl nitrites and special type tautomerism can also exist in nitro alkanes having an α-H atom. For example, nitro compounds having the molecular formula $C_4H_9NO_2$ exhibit the following isomerisms.

Isomerism	Structural Formula of Isomers
Chain isomerism:They differ in the length of the carbon chain.	$CH_3CH_2CH_2CH_2$—NO_2 (1-nitrobutane) and CH_3CHCH_2—NO_2 CH_3 (2-methyl-1-nitropropane)
Position isomerism:They differ in the position of the nitro group.	$CH_3CH_2CH_2CH_2$—NO_2 (1-nitrobutane) $CH_3CHCH_2CH_3$ NO_2 (2-nitrobutane) CH_3C—NO_2 CH_3 CH_3 (2-methyl-2-nitropropane)
Functional isomerism:Nitroalkanes exhibit functional isomerism with alkyl nitrites	$CH_3CH_2CH_2CH_2$—NO_2 (1-nitrobutane) and $CH_3CH_2CH_2CH_2$—O—N=O (butyl nitrite)

Tautomerism: Primary and secondary nitroalkanes, having α-H , also show an equilibrium mixture of two tautomers namely nitro – and aci – form



Tertiary nitro alkanes donot exhibit tautomerism due to absence of α-H atom.

S.No.	Nitro form	Aci – form
1.	Less acidic	More acidic
2.	Dissolves in NaOH slowly	Dissolves in NaOH instantly
3.	Decolourises $FeCl_3$ solution	With $FeCl_3$ gives reddish brown colour
4.	Electrical conductivity is low	Electrical conductivity is high

Acidic nature of nitro alkanes

The α-H atom of 1 & 2 nitroalkanes show acidic character because of the electron with drawing effect of NO2 group. These are more acidic than aldehydes, ketones, ester and cyanides. Nitroalkanes dissolve in NaOH solution to form a salt. Aci – nitro derivatives are more acidic than nitro form. When the number of alkyl group attached to α carbon increases, acidity decreases. due to +I effect of alkyl groups.

$$CH_3-NO_2 > CH_3CH_2-NO_2 > \begin{matrix} CH_3 \searrow \\ \quad CH-NO_2 \\ CH_3 \nearrow \end{matrix}$$

__**Preparation of nitroalkanes**__

1) From alkyl halides: (Laboratory method)

a) Alkyl bromides (or) iodides on heating with ethanolic solution of potassium nitrite gives nitroethane.

$$\underset{\text{Ethyl bromide}}{CH_3CH_2\text{-}Br} + KNO_2 \xrightarrow[SN^2]{\text{ethanol}/\Delta} \underset{\text{Nitroethane}}{CH_3CH_2\text{-}NO_2} + KBr$$

The reaction follows SN2 mechanism.

This method is not suitable for preparing nitrobenzene because the bromine directly attached to the benzene ring cannot be cleaved easily.

2) Vapour phase nitration of alkanes: (Industrial method)

Gaseous mixture of methane and nitric acid passed through a red hot metal tube to give nitromethane.

$$\underset{\text{Methane}}{CH_{4(g)}} + HNO_{3\,(g)} \xrightarrow[\text{Red hot Si tube}]{675\text{ K}} \underset{\text{nitro methane}}{CH_3\text{-}NO_2} + H_2O$$

Except methane, other alkanes (upto n – hexane) give a mixture of nitroalkanes due to C-C cleavage. The individual nitro alkanes can be separated by fractional distillation.

$$\underset{\text{Ethane}}{CH_3\text{-}CH_3} + HNO_3 \xrightarrow{675\ K} \underset{\text{Nitroethane(73\%)}}{CH_3CH_2\text{-}NO_2} + \underset{\text{Nitromethane (27\%)}}{CH_3NO_2}$$

3) From a- halocarboxylic acid

α- choloroacetic acid when boiled with aqueous solution of sodium nitrite gives nitromethane.

$$\underset{\alpha\text{ - chloro acetic acid}}{Cl\text{ - }CH_2\text{-}COOH} + NaNO_2 \xrightarrow[SN^2]{H_2O/Heat} \underset{\text{Nitromethane}}{CH_3\text{-}NO_2} + CO_2 + NaCl$$

4) Oxidation of tert – alkyl amines

tert – butyl amine is oxidised with aqueous KMnO4 to give tert – nitro alkanes.

$$\underset{\text{tert-butylamine}}{CH_3-\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}-NH_2} + 3[O] \xrightarrow{KMnO_4} \underset{\text{2 - methyl - 2 - nitro propane}}{CH_3-\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}-NO_2} + H_2O$$

5) Oxidation of Oximes

Oxidation of acetaldoxime and acetoneoxime with trifluoroperoxy acetic acid gives nitroethane (1º) and 2 – nitropropane (2 º) respectively.

$$\underset{\text{Acetaldoxime}}{CH_3\text{-}CH{=}N\text{-}OH} \xrightarrow[{[O]}]{CF_3COOOH} \underset{\text{Nitroethane}}{CH_3CH_2\text{-}NO_2}$$

<u>Physical properties of nitro alkane</u>

The lower nitroalkanes are colourless pleasant smelling liquids, sparingly soluble in water, but readily soluble in organic solvents like benzene, acetone etc… They have high boiling points because of their highly polar nature. Alkylnitrites have lower boiling points than nitro alkanes.

Chemical properties of nitroalkanes

Nitroalkanes undergo the following common reactions.

i. Reduction ii. Hydrolysis iii. Halogenations

i. Reduction of nitroalkanes

Reduction of nitroalkanes has important synthetic applications. The various reduction stages of nitro group are given below.

$$\underset{\text{nitromethane}}{CH_3-NO_2} \xrightarrow[-H_2O]{+2[H]} \underset{\text{nitroso methane}}{CH_3-N=O} \xrightarrow{+2[H]} \underset{\text{N - methyl hydroxylamine}}{CH_3-NHOH} \xrightarrow[-H_2O]{+2[H]} \underset{\text{methylamine}}{CH_3-NH_2}$$

The final product depends upon the nature of reducing agent as well as the pH of the medium.

$$\underset{\text{Nitromethane}}{CH_3-NO_2} \xrightarrow[6[H]]{Sn/HCl} \underset{\text{Methyl amine}}{CH_3-NH_2} + 2H_2O \quad \text{(acid medium)}$$

$$\underset{\text{Nitromethane}}{CH_3-NO_2} \xrightarrow[4[H]]{Zn\,/\,NH_4Cl} \underset{\text{N - methyl hydroxylamine}}{CH_3-NHOH} + H_2O \quad \text{(neutral medium)}$$

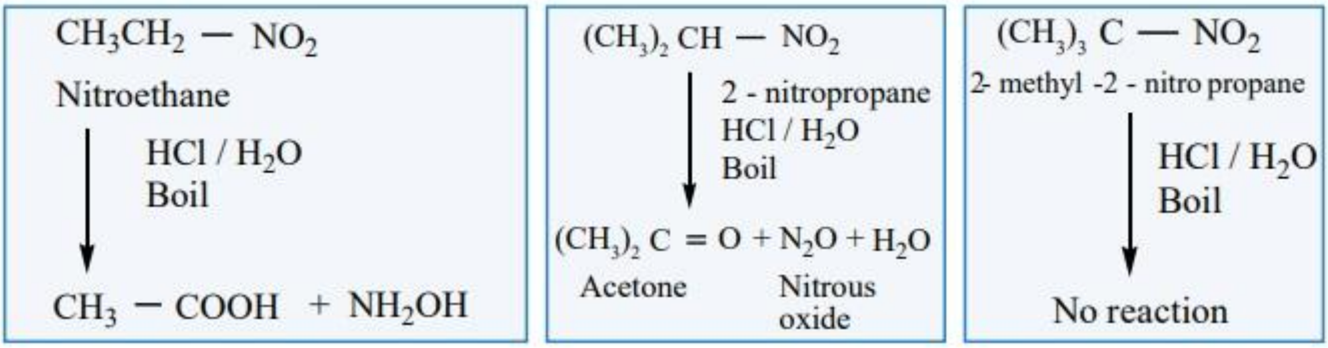
Reduction of alkyl nitrites

Ethylnitrite on reduction with Sn / HCl gives ethanol

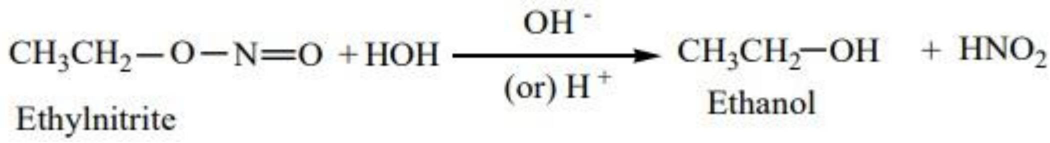
$$CH_3CH_2\text{-}O\text{-}N=O + 6[H] \xrightarrow{Sn\,/\,HCl} CH_3CH_2\text{-}OH + NH_3 + H_2O$$

ii. Hydrolysis of nitroalkanes

Hydrolysis can be effected using conc. HCl or conc. H2SO4 . Primary nitroalkanes on hydrolysis gives carboxylic acid, and the secondary nitroalkanes give ketones. The tertiary nitroalkanes have no reaction.

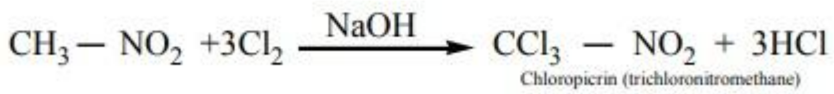


On the other hand, the acid or base hydrolysis of ethyl nitrite gives ethanol.



iii. Halogenation of nitroalkanes

Primary and secondary nitroalkanes on treatement with Cl2 or Br2 in the presence of NaOH give halonitroalkanes. The α - H atom of nitroalkanes are successively replaced by halogen atoms.



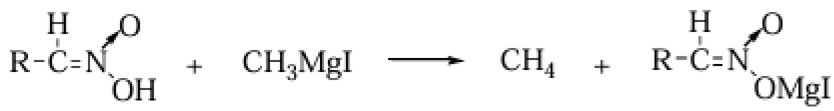
Toxicity

Nitroethane is suspected to cause genetic damage and be harmful to the nervous system.

Reaction with Grignard Reagent:

When a nitroalkane is present in its aci form—a tautomeric form where the nitro group exists as R−C(=N−OH)R-C(=N-OH)R−C(=N−OH)—it exhibits acidic behavior due to the highly labile hydrogen attached to the –OH group. This makes it susceptible to reaction with strong nucleophiles and bases, such as Grignard reagents. In this reaction**,** methylmagnesium iodide (CH_3MgI)**,** a typical Grignard reagent, interacts with the aci-nitro compound. The highly basic methyl group of the Grignard reagent abstracts the acidic proton from the –OH group of the aci-nitro form. This proton transfer results in the formation of methane (CH_4) as a gaseous byproduct.

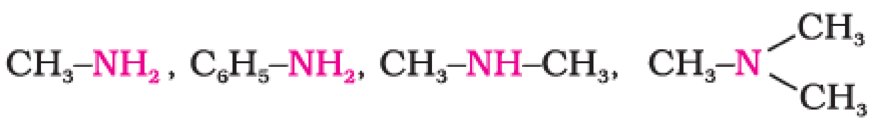
Simultaneously, the deprotonated nitronate anion binds to the magnesium of the Grignard reagent, yielding a stable complex known as a magnesium nitronate **(**R−C(=N−O)OMgIR**-**C(=N-O)OMgIR−C(=N−O)OMgI**)**. This reaction highlights the dual role of Grignard reagents as both nucleophiles and strong bases, and it illustrates the unique reactivity of nitro compounds in their acidic (aci) form. The reaction converts a nitro compound into its magnesium-bound nitronate while liberating methane, a process that is widely employed in organic synthesis to manipulate nitro functionality under mild conditions.



Aci form
of nitroalkane

Aliphatic Amines

Aliphatic amines are organic compounds derived from ammonia in which one or more hydrogen atoms are replaced by alkyl groups. Depending on the number of alkyl groups attached to the nitrogen atom, they are classified as primary, secondary, and tertiary amines. The nitrogen atom in aliphatic amines is sp^3 hybridised and contains a lone pair of electrons, which accounts for their basic nature and chemical reactivity.



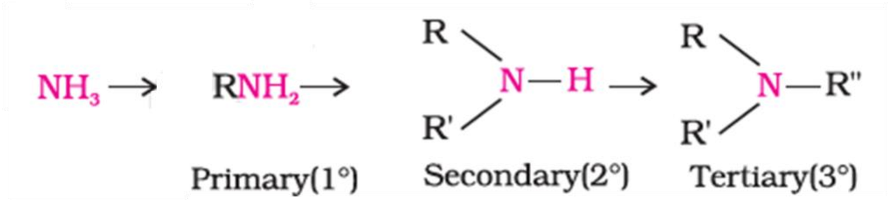
Nomenclature of Aliphatic Amines

Aliphatic amines are named using both common and IUPAC systems. In the common system, the alkyl group attached to the nitrogen atom is named first, followed by the word *amine*, such as methylamine or ethylamine. In the IUPAC system, the longest carbon chain bonded to the nitrogen atom is selected as the parent chain, and the suffix *amine* replaces the final "e" of the corresponding alkane. When alkyl substituents are attached directly to nitrogen, the prefix **N-** is used to indicate their position.

Amine (Structure)	Common Name	IUPAC Name
$CH_3–CH_2–NH_2$	Ethylamine	Ethanamine
$CH_3–CH_2–CH_2–NH_2$	*n*-Propylamine	Propan-1-amine
$CH_3–CH(NH_2)–CH_3$	Isopropylamine	Propan-2-amine
$CH_3–NH–CH_2–CH_3$	Ethylmethylamine	*N*-Methylethanamine
$(CH_3)_3N$	Trimethylamine	*N*,*N*-Dimethylmethanamine
$(C_2H_5)_2N–CH_2–CH_2–CH_2–CH_3$	*N*,*N*-Diethylbutylamine	*N*,*N*-Diethylbutan-1-amine
$NH_2–CH_2–CH=CH_2$	Allylamine	Prop-2-en-1-amine
$NH_2–(CH_2)_6–NH_2$	Hexamethylenediamine	Hexane-1,6-diamine

Isomerism in Aliphatic Amines

Aliphatic amines exhibit different types of isomerism. Chain isomerism arises due to variation in the carbon skeleton, while position isomerism occurs when the amino group occupies different positions in the carbon chain. Functional isomerism is also common, where primary, secondary, and tertiary amines have the same molecular formula but differ in their functional arrangement.



Preparation of Aliphatic Amines

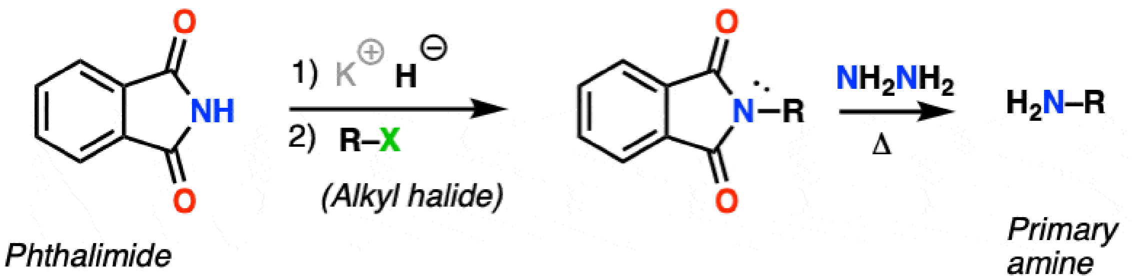
Hofmann's Degradation Reaction

In this method, a primary amide is treated with bromine in the presence of aqueous alkali to produce a primary aliphatic amine containing one carbon atom less than the parent amide. This reaction is particularly useful for the preparation of pure primary amines.

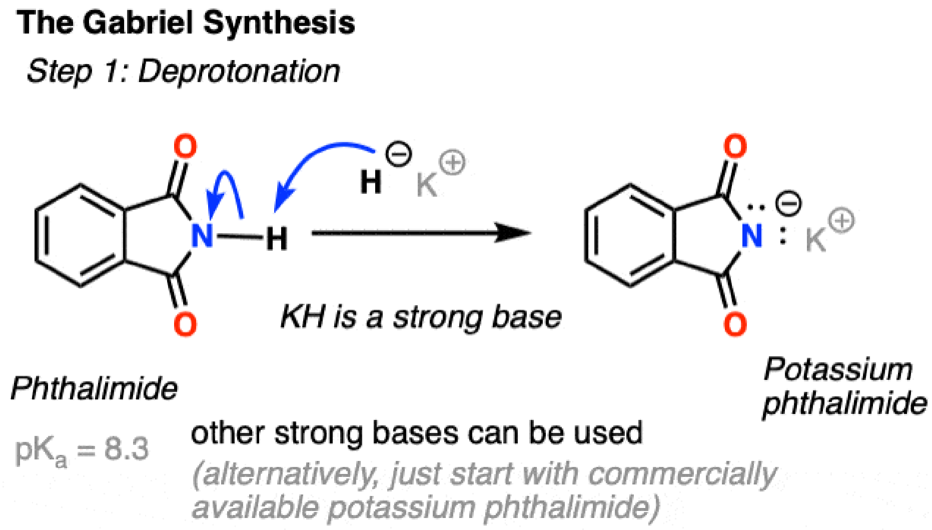
$$R - \overset{\overset{\displaystyle O}{\|}}{C} - NH_2 + Br_2 + 4NaOH \rightarrow R\text{-}NH_2 + Na_2CO_3 + 2NaBr\ 2H_2O$$

Gabriel's Phthalimide Synthesis

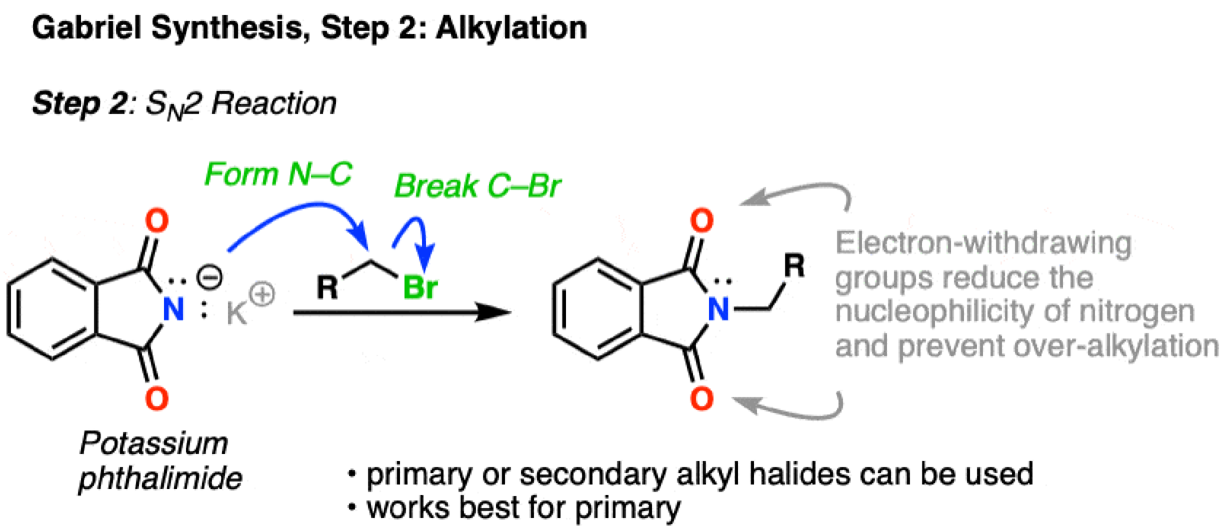
Gabriel's synthesis involves the reaction of potassium phthalimide with an alkyl halide followed by hydrolysis to yield a primary aliphatic amine. This method is suitable only for the preparation of primary amines and does not give secondary or tertiary amines.



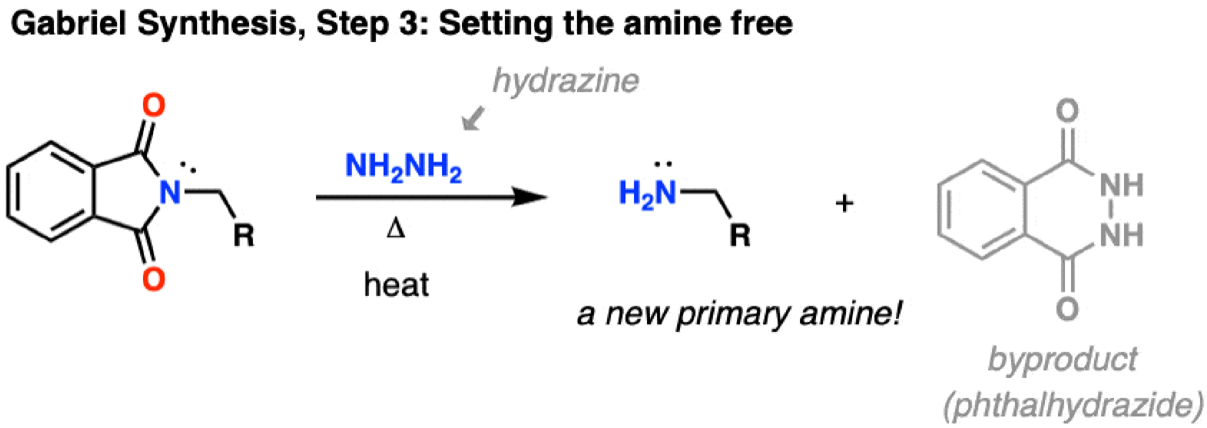
In the Gabriel synthesis we start with a molecule called "phthalimide". In phthalimide, a nitrogen is flanked by two carbonyl groups. This means that the N-H is a lot more acidic than it normally would be, because the resulting anion will be resonance stabilized. (Its pK_a is 8.3). A common choice of base is a hydride base such as KH, which results in potassium phthalimide and a molecule of hydrogen (H_2).



Once phthalimide is deprotonated with a strong base like NaH, $NaNH_2$, KH (or many others) the next step is to add an alkyl halide. The nitrogen nucleophile will then attack the alkyl halide in an S_N2 reaction, and form an N-C bond.

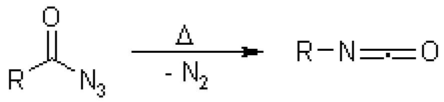


The third step is to liberate the amine! This is done through addition of NH_2NH_2 (hydrazine), which ends up adding to the carbonyl carbon, and through a sequence of steps, the amine ends up as the leaving group.

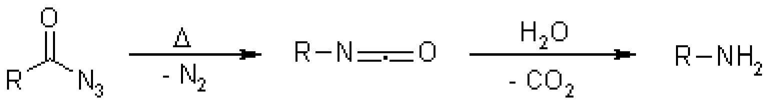


Curtius Rearrangement

The Curtius Rearrangement is the thermal decomposition of carboxylic azides to produce an isocyanate. These intermediates may be isolated, or their corresponding reaction or hydrolysis products may be obtained.

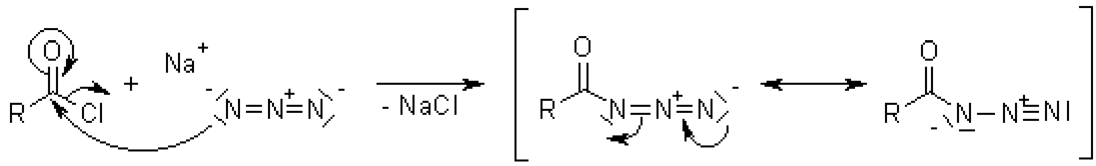


The reaction sequence - including subsequent reaction with water which leads to amines - is named the Curtius Reaction. This reaction is similar to the Schmidt Reaction with acids, differing in that the acyl azide in the present case is prepared from the acyl halide and an azide salt.

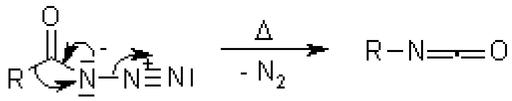


Mechanism of the Curtius Rearrangement

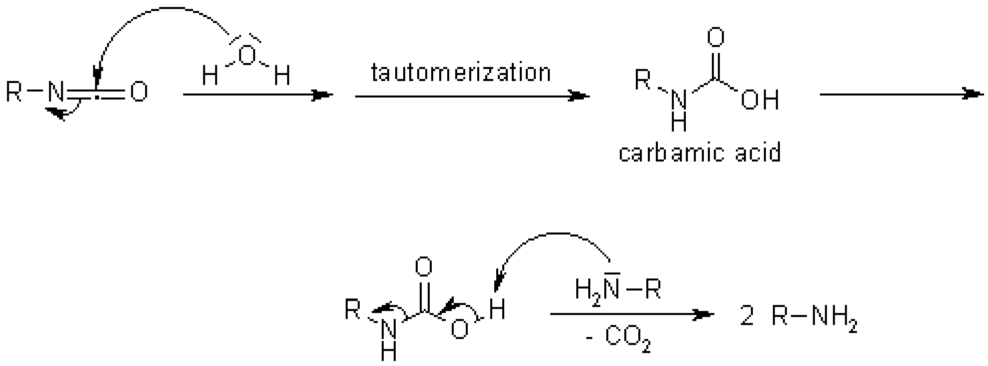
Preparation of azides:



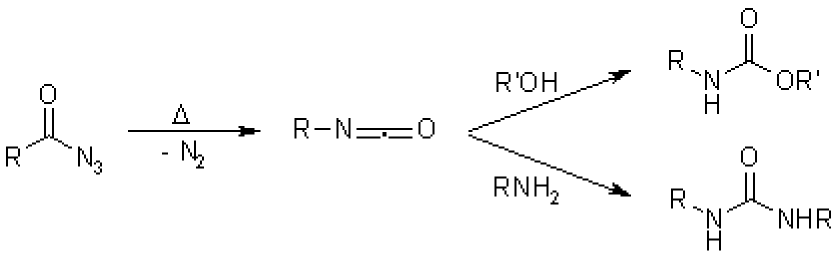
Decomposition:



Reaction with water to the unstable carbamic acid derivative which will undergo spontaneous decarboxylation:



Isocyanates are versatile starting materials:



Isocyanates are also of high interest as monomers for polymerization work and in the derivatisation of biomacromolecules.

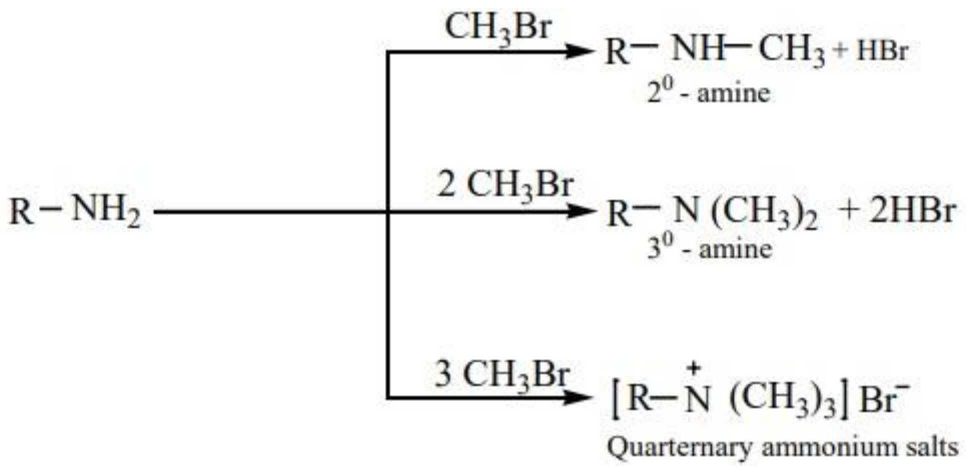
Physical Properties of Aliphatic Amines

Lower aliphatic amines are generally gases or liquids with a strong ammoniacal or fishy odour, while higher members are solids. Primary and secondary amines exhibit intermolecular hydrogen bonding, resulting in higher boiling points than hydrocarbons of comparable molecular mass. Aliphatic amines of lower molecular mass are soluble in water due to hydrogen bonding with water molecules, though solubility decreases as the alkyl chain length increases.

Chemical Reactions of Aliphatic Amines

Alkylation

Aliphatic amines react with alkyl halides to form higher substituted amines and, ultimately, quaternary ammonium salts.

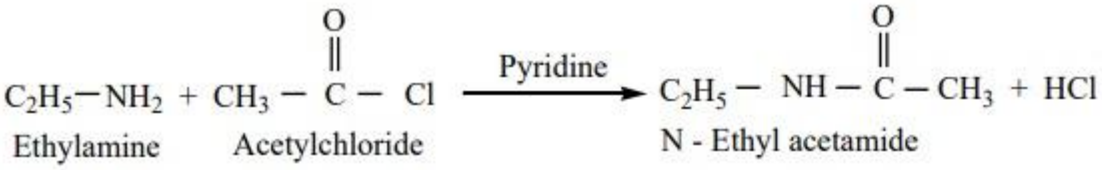


Acylation

Primary and secondary aliphatic amines undergo acylation when treated with acid chlorides or acid anhydrides, forming amides. Tertiary amines do not undergo this reaction due to the absence of replaceable hydrogen.

Ethylamine amines react with acetyl chloride (or) acetic anhydride in presence of pyridine to form N – alkyl acetamide.

Example



Carbylamine Reaction

Primary aliphatic amines react with chloroform and alcoholic potassium hydroxide to form isocyanides, which possess an unpleasant odour. This reaction serves as a qualitative test for primary amines.

Ethylamine amines react with chloroform and alcoholic KOH to give isocyanides (carbylamines), which has an unpleasant smell. This reaction is known as carbylamine test. This test used to identify the primary amines.

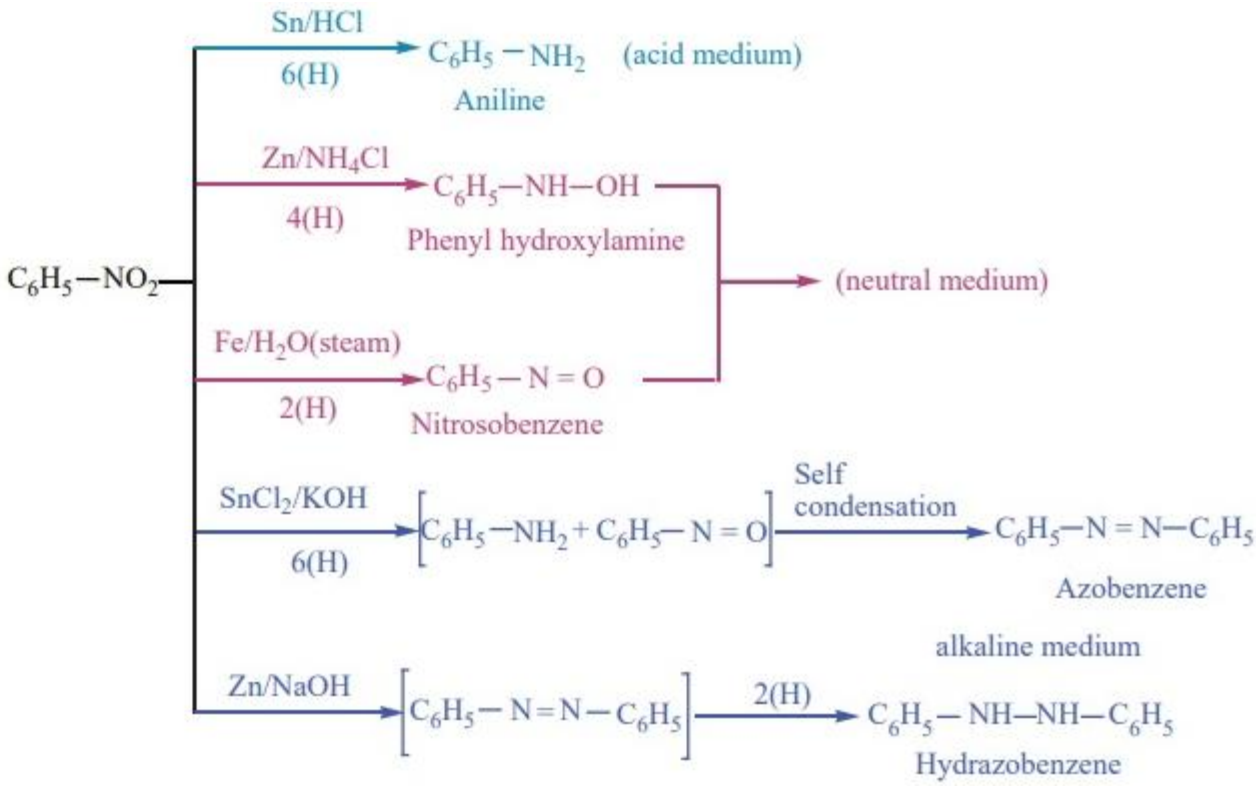
$$\underset{\text{Ethylamine}}{C_2H_5 - NH_2} + \underset{\text{Chloroform}}{CHCl_3} + 3KOH \longrightarrow \underset{\text{Ethylisocyanide}}{C_2H_5 - NC} + 3KCl + 3H_2O$$

Mannich Reaction

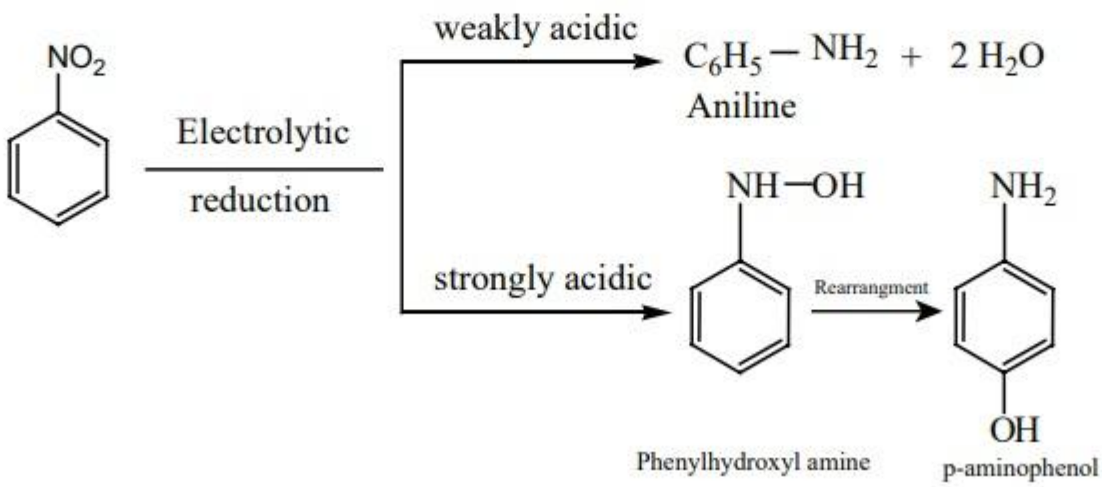
Primary and secondary nitro compounds also undergo Mannich reaction. This is the condensation between formaldehyde, ammonia or 1º or 2º amine and a compound containing at least one active hydrogen atom. The active hydrogen atom is replaced by an aminomethyl group or substituted aminomethyl group.

$$R_2CHNO_2 + HCHO + R'_2NH \xrightarrow{NaOEt} \begin{array}{c} R_2CNO_2 \\ | \\ CH_2NR'_2 \end{array}$$

Reactions of nitrobenzene



Electrolytic reduction:

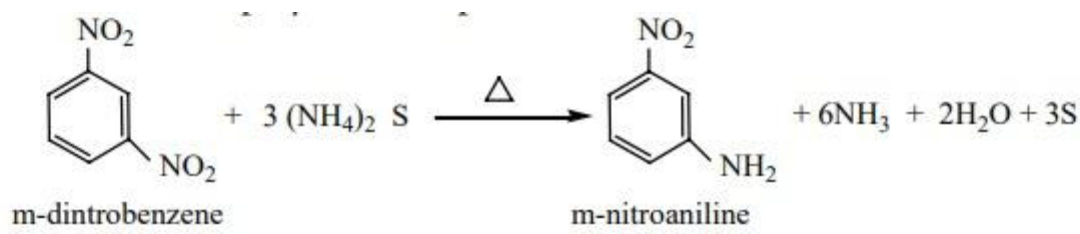


Reduction of catalytic and metal hydrides

Nitrobenzene reduction with Ni (or) Pt, (or) LiAlH4 to give aniline

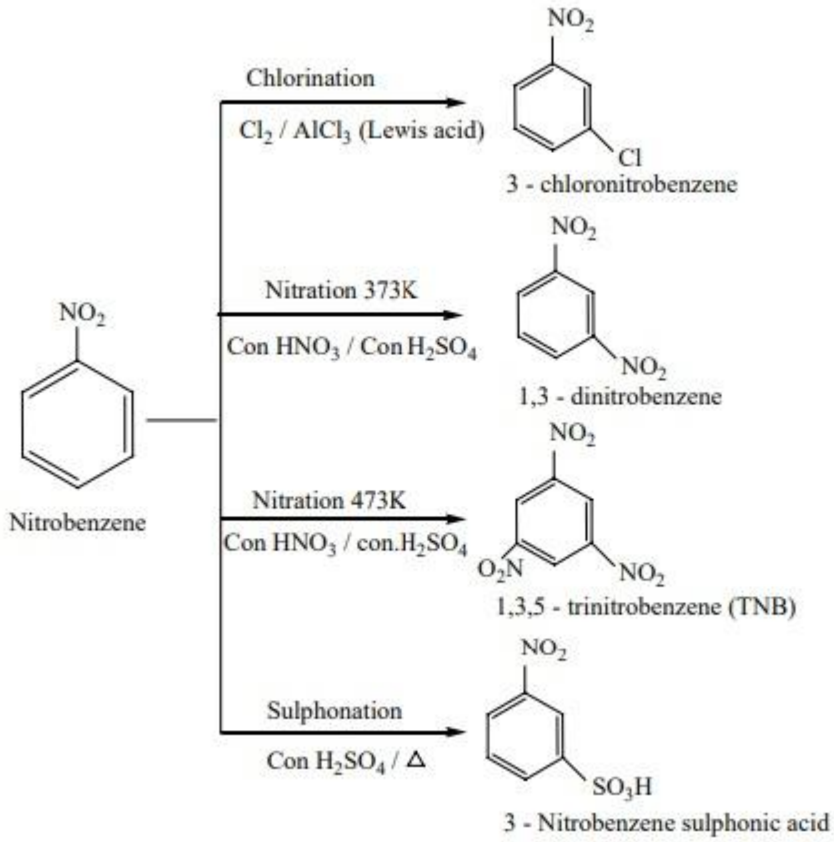
$$C_6H_5 - NO_2 + 6\,[H] \xrightarrow[\text{(or) LiAH}_4]{\text{Ni (or) Pt / H}_2} C_6H_5 - NH_2 + 2\,H_2O$$

Selective reduction of polynitro compounds



Electrophilic substitution reaction

The electrophilic substitution reactions of nitrobenzene are usually very slow and vigorous reaction condition have to be employed (- NO2 group is stongly deactivating and m – directing).



Nitrobenzene does not undergo Friedel – Crafts reactions due to the strong deactivating nature of -NO_2 group.

UNIT III

CHEMISTRY OF NITROGEN COMPOUNDS-II

AROMATIC AMINES

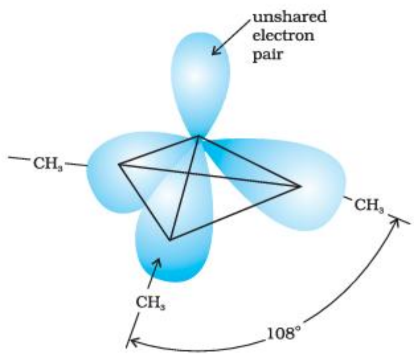
Introduction

Amines are organic compounds that may be regarded as derivatives of ammonia, in which one, two, or all three hydrogen atoms of the ammonia molecule are substituted by alkyl and/or aryl groups. Based on the extent of substitution, different classes of amines are formed. For example:

$$CH_3{-}NH_2,\ C_6H_5{-}NH_2,\ CH_3{-}NH{-}CH_3,\ CH_3{-}N\begin{matrix}CH_3\\CH_3\end{matrix}$$

Structure of Amines:

Similar to ammonia, the nitrogen atom in amines is trivalent and possesses one lone pair of electrons. Consequently, the nitrogen atom in amines undergoes *sp³* hybridisation and exhibits a pyramidal molecular geometry. Of the four *sp³*-hybridised orbitals, three participate in σ-bond formation by overlapping with the orbitals of hydrogen or carbon atoms, depending on the nature of the amine. The remaining *sp³* orbital accommodates the lone pair of electrons. The presence of this lone pair causes greater electron–electron repulsion, resulting in a reduction of the bond angle below the ideal tetrahedral value of 109.5°. For example, in trimethylamine, the C–N–C bond angle is approximately 108°, as illustrated in the figure below



Nomenclature:

Arylamines are characterized by the direct attachment of the amino group ($-NH_2$) to an aromatic ring. The simplest arylamine, $C_6H_5NH_2$, is commonly known as *aniline*, which is also an accepted IUPAC name. Under strict IUPAC nomenclature, arylamines are named by replacing the 'e' of the arene with the suffix *amine*; thus, $C_6H_5NH_2$ is systematically named *benzenamine*. The common and IUPAC names of selected alkylamines and arylamines are summarized in the table.

Amine (Structure)	Common Name	IUPAC Name
C_6H_5–NH_2	Aniline	Aniline or Benzenamine
o-CH_3–C_6H_4–NH_2	*o*-Toluidine	2-Methylaniline
p-Br–C_6H_4–NH_2	*p*-Bromoaniline	4-Bromobenzenamine or 4-Bromoaniline
C_6H_5–$N(CH_3)_2$	*N,N*-Dimethylaniline	*N,N*-Dimethylbenzenamine

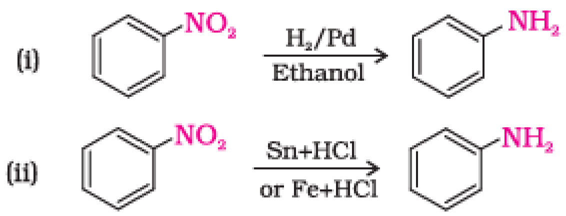
Prepartion of Amines

Amines can be synthesized using a variety of laboratory and industrial methods, depending on the nature of the starting materials and the type of amine required. The commonly employed methods for the preparation of amines are described below.:

1.Reduction of nitro compounds

(i) Nitro compounds can be converted into the corresponding amines through reduction using hydrogen gas in the presence of finely divided metal catalysts such as nickel, palladium, or platinum. Alternatively, reduction may also be carried out using metals in an acidic medium. Nitroalkanes undergo similar reduction reactions to yield the corresponding alkanamines.

(ii) Among the various methods, reduction employing iron filings and hydrochloric acid is commonly preferred. This preference arises because the ferrous chloride ($FeCl_2$) formed during the reaction undergoes hydrolysis, thereby regenerating hydrochloric acid. As a result, only a limited quantity of hydrochloric acid is required to initiate and sustain the reduction process.



2. Hoffmann bromamide degradation reaction

Hofmann introduced a method for the synthesis of primary amines by treating amides with bromine in an aqueous or ethanolic solution of sodium hydroxide. This reaction, known as Hofmann degradation or Hofmann rearrangement, involves the migration of an alkyl or aryl group from the carbonyl carbon of the amide to the nitrogen atom. As a result of this rearrangement, the primary amine obtained contains one carbon atom fewer than the parent amide.

$$R-\overset{\overset{\displaystyle O}{\|}}{C}-NH_2 + Br_2 + 4NaOH \longrightarrow R-NH_2 + Na_2CO_3 + 2NaBr + 2H_2O$$

Properties

Lower aliphatic amines exist as gases and are characterised by a strong, fishy odour. Primary aliphatic amines containing three or more carbon atoms are generally liquids, whereas amines with still higher molecular masses occur as solids. Aniline and other arylamines are typically colourless when freshly prepared; however, they tend to develop coloration upon storage due to slow oxidation by atmospheric oxygen.

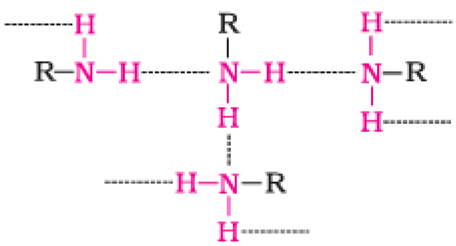
Lower aliphatic amines exhibit appreciable solubility in water because they are capable of forming hydrogen bonds with water molecules. Nevertheless, as the molar mass of the amine increases, its solubility in water decreases. This reduction in solubility is attributed to the increasing size of the hydrophobic alkyl group, which outweighs the hydrophilic influence of the amino group. Consequently, higher aliphatic amines are nearly insoluble in water.

By comparing the electronegativity values of nitrogen in amines (3.0) and oxygen in alcohols (3.5), the relative solubility behaviour of amines and alcohols in water can be predicted. For example, when butan-1-ol and butan-1-amine are compared, the alcohol is more soluble in water due to its greater polarity and stronger hydrogen-bonding capability.

Amines are, however, readily soluble in many organic solvents such as alcohol, ether, and benzene. Alcohols are more polar than amines and form stronger intermolecular hydrogen bonds, which influences their physical properties. Primary and secondary amines undergo intermolecular association through hydrogen bonding between the nitrogen atom of one molecule and the hydrogen atom of another. This association is more pronounced in primary amines than in secondary amines, as primary amines possess two hydrogen atoms available for hydrogen bond formation. In contrast, tertiary amines do not exhibit intermolecular hydrogen bonding due to the absence of hydrogen atoms attached to nitrogen.

As a result of these differences in intermolecular hydrogen bonding, the boiling points of isomeric amines follow the order:
Primary amines > Secondary amines > Tertiary amines.

The intermolecular hydrogen bonding present in primary amines is illustrated in the accompanying figure.

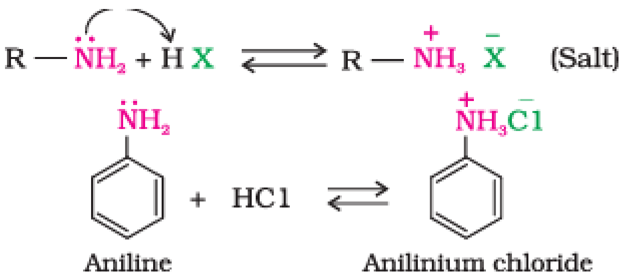


Intermolecular hydrogen bonding in primary amines

Basic character of amines

The reactivity of amines arises from the difference in electronegativity between the nitrogen and hydrogen atoms, along with the presence of a lone pair of electrons on the nitrogen atom. In addition, the number of hydrogen atoms bonded to nitrogen significantly influences the chemical behaviour of amines. As a result, primary (1°), secondary (2°), and tertiary (3°) amines exhibit distinct reaction patterns. Owing to the availability of an unshared electron pair, amines act as nucleophiles in many chemical reactions.

Amines exhibit basic character and readily react with acids to form corresponding ammonium salts.



These salts, upon treatment with strong bases such as sodium hydroxide, regenerate the original free amines. Amine salts are generally soluble in water but insoluble in non-polar organic solvents like ether. This property forms the basis for the separation of amines from non-basic organic compounds that are insoluble in water. The formation of ammonium salts upon reaction with mineral acids further confirms the basic nature of amines.

$$R\overset{+}{N}H_3\,\bar{X} + \bar{O}H \longrightarrow R\ddot{N}H_2 + H_2O + \bar{X}$$

The basicity of amines can also be explained using the Lewis acid–base concept, as the lone pair of electrons on the nitrogen atom enables amines to donate an electron pair, thereby behaving as Lewis bases. A quantitative measure of basic strength is provided by the base dissociation constant (Kb) and its logarithmic expression, pKb. A higher value of Kb or a lower value of pKb indicates a stronger base.

$$R - NH_2 + H_2O \rightleftharpoons R - \overset{+}{N}H_3 + \bar{O}H$$

$$K = \frac{[R - \overset{+}{N}H_3][\bar{O}H]}{[R - NH_2][H_2O]}$$

$$\text{or } K[H_2O] = \frac{[R - \overset{+}{N}H_3][\bar{O}H]}{[R - NH_2]}$$

$$\text{or} \quad K_b = \frac{[R - \overset{+}{N}H_3][\bar{O}H]}{[R - NH_2]}$$

$$pK_b = -\log K_b$$

Ammonia has a pKb value of 4.75. Aliphatic amines are generally stronger bases than ammonia due to the electron-releasing (+I) effect of alkyl groups, which increases the electron density on the nitrogen atom. Consequently, the pKb values of aliphatic amines typically fall in the range of 3.0 to 4.22. In contrast, aromatic amines are weaker bases than ammonia because the aryl group withdraws electron density from the nitrogen atom through resonance, thereby reducing its availability for protonation.

The pKb values of selected amines are listed below:

Name of amine	**pKb**
Methanamine	3.38
N-Methylmethanamine	3.27
N,N-Dimethylmethanamine	4.22

Ethanamine	3.29
N-Ethylethanamine	3.00
N,N-Diethylethanamine	3.25
Benzenamine	9.38
Phenylmethanamine	4.70
N-Methylaniline	9.30
N,N-Dimethylaniline	8.92

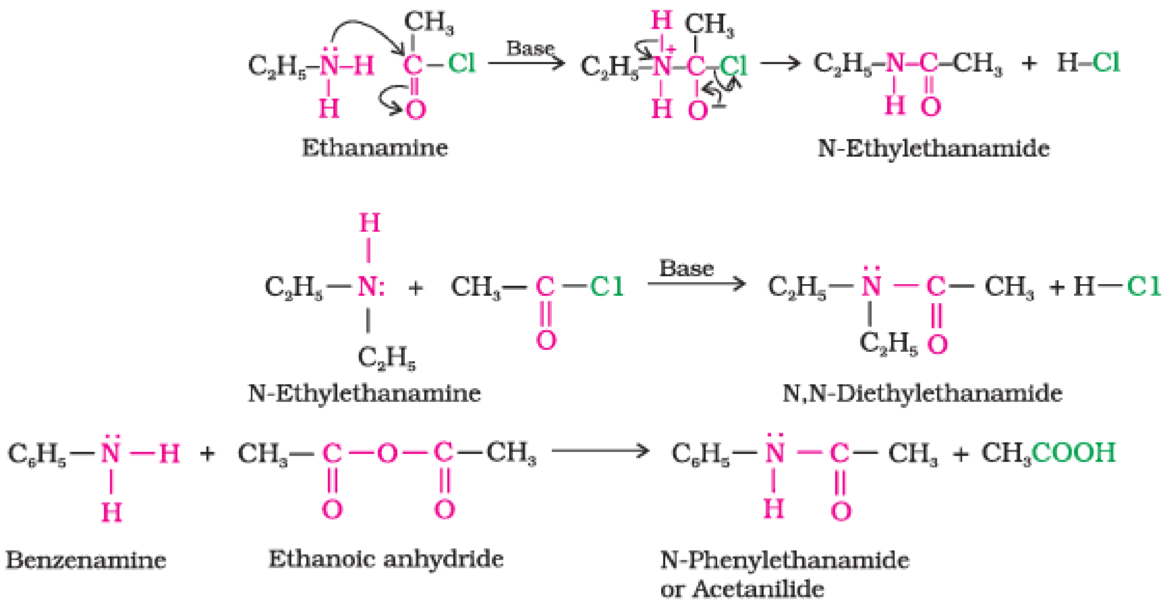
While interpreting the basicity of amines solely on the basis of the inductive (+I or –I) effects of substituents, it is important to consider additional factors. Effects such as solvation, steric hindrance, and resonance also play significant roles in determining the overall basic strength of amines.

Reactions

1. **Acylation**

   Primary and secondary aliphatic as well as aromatic amines undergo nucleophilic substitution reactions with acid chlorides, acid anhydrides, and esters. This transformation is referred to as **acylation**. During this process, an acyl group replaces one hydrogen atom attached to the nitrogen atom of the $–NH_2$ or –NH– group of the amine. The compounds formed as a result of this reaction are known as **amides**.

   Acylation reactions are typically carried out in the presence of a base stronger than the amine, such as pyridine. The base serves to neutralise the hydrogen chloride produced during the reaction, thereby preventing protonation of the amine and driving the equilibrium towards the formation of the amide.



Amines also undergo reaction with benzoyl chloride (C_6H_5COCl). This specific type of acylation reaction is referred to as **benzoylation**, in which the benzoyl group is introduced onto the nitrogen atom of the amine.

$$\underset{\text{Methanamine}}{CH_3NH_2} + \underset{\text{Benzoyl chloride}}{C_6H_5COCl} \rightarrow \underset{\text{N – Methylbenzamide}}{CH_3NHCOC_6H_5} + HCl$$

2. **Carbylamine reaction**

   When aliphatic or aromatic primary amines are heated with chloroform and ethanolic potassium hydroxide, they form isocyanides (carbylamines), which possess an extremely unpleasant odour. Secondary and tertiary amines do not undergo this reaction. This reaction, known as the carbylamine reaction or isocyanide test, is therefore used as a qualitative test for the identification of primary amines.

$$R{-}NH_2 + CHCl_3 + 3KOH \xrightarrow{\text{Heat}} R{-}NC + 3KCl + 3H_2O$$

3. **Reaction with nitrous acid**

   Three classes of amines react differently with nitrous acid which is prepared in situ from a mineral acid and sodium nitrite. (a) Primary aliphatic amines react with nitrous acid to form aliphatic diazonium salts which being unstable, liberate nitrogen gas quantitatively and alcohols. Quantitative evolution of nitrogen is used in estimation of amino acids and proteins.

$$R{-}NH_2 + HNO_2 \xrightarrow{NaNO_2 + HCl} [R{-}\overset{+}{N_2}\overset{-}{Cl}] \xrightarrow{H_2O} ROH + N_2 + HCl$$

(b) Aromatic amines react with nitrous acid at low temperatures (273-278 K) to form diazonium salts, a very important class of compounds used for synthesis of a variety of aromatic compounds.

$$C_6H_5-NH_2 \xrightarrow[273-278\ K]{NaNO_2 + 2HCl} C_6H_5-\overset{+}{N_2}\overset{-}{Cl} + NaCl + 2H_2O$$

Aniline — Benzenediazonium chloride

Secondary and tertiary amines react with nitrous acid in a different manner.

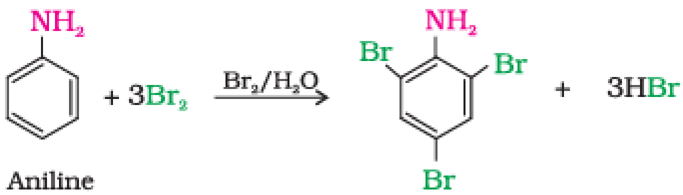
Electrophilic substitution

(a) Bromination

The presence of the amino (–NH_2) group increases the electron density at the ortho and para positions of the aromatic ring through its strong electron-donating effect. As a result, the –NH_2 group acts as a powerful activating substituent and directs incoming electrophiles to the ortho and para positions.

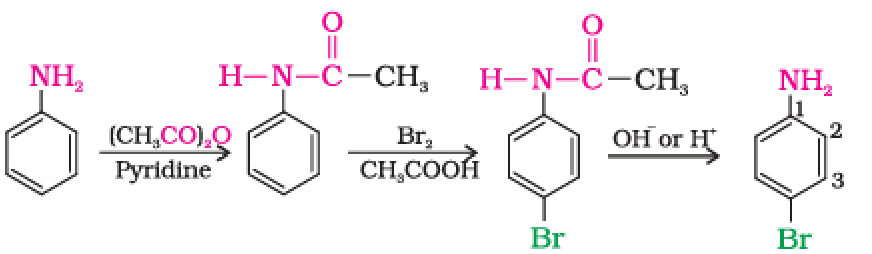
(a) Bromination:

Aniline reacts readily with bromine water at room temperature, leading to rapid substitution at the ortho and para positions and forming a white precipitate of **2,4,6-tribromoaniline**.



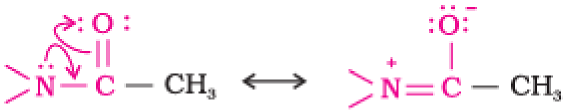
Aniline — 2,4,6-Tribromoaniline

A major difficulty encountered in electrophilic substitution reactions of aromatic amines arises from their excessively high reactivity. Owing to the strong activating influence of the –NH_2 group, substitution predominantly occurs at the ortho and para positions, often leading to polysubstitution. To regulate this activating effect, the amino group is temporarily protected by acetylation using acetic anhydride. The electrophilic substitution is then carried out on the resulting amide, followed by hydrolysis of the substituted amide to regenerate the corresponding substituted amine.



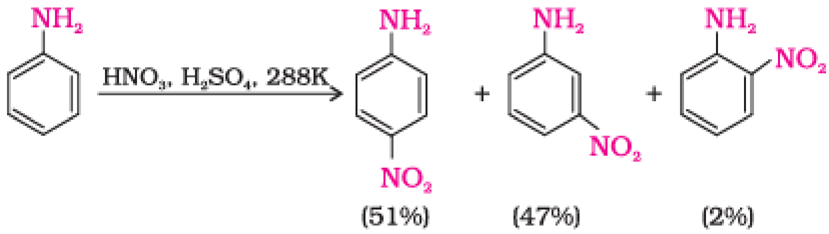
Aniline — *N*-Phenylethanamide — (Major) — 4-Bromoaniline

In acetanilide, the lone pair of electrons on the nitrogen atom is not entirely free because it participates in resonance with the carbonyl group of the $–COCH_3$ moiety. This delocalization reduces the availability of nitrogen's electrons to interact with the aromatic ring. As a result, the $–NHCOCH_3$ group exerts a weaker activating influence on the benzene ring compared to a simple amino ($–NH_2$) group, where the nitrogen's lone pair can fully engage in resonance with the ring.

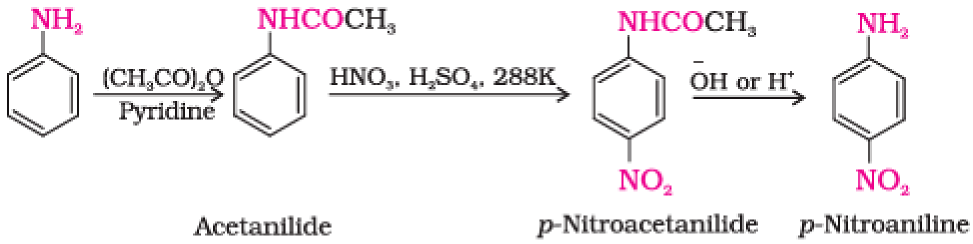


(b) Nitration:

Direct nitration of aniline yields tarry oxidation products in addition to the nitro derivatives. Moreover, in the strongly acidic medium, aniline is protonated to form the anilinium ion which is meta directing. That is why besides the ortho and para derivatives, significant amount of meta derivative is also formed.

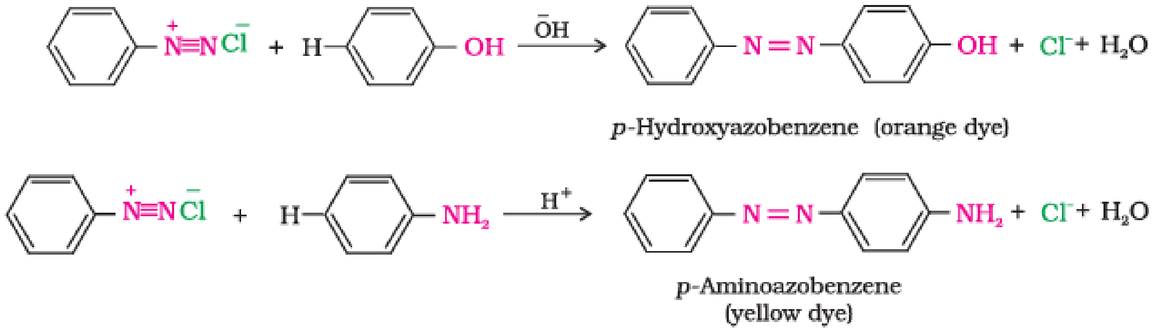


However, by protecting the $–NH_2$ group by acetylation reaction with acetic anhydride, the nitration reaction can be controlled and the p-nitro derivative can be obtained as the major product.



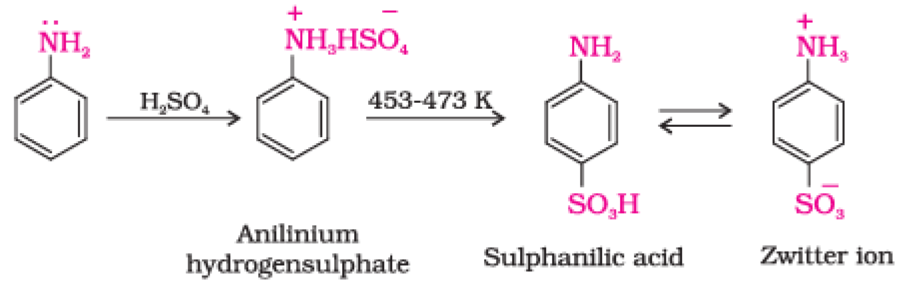
(c) Reactions involving retention of diazo group coupling reactions

The azo products obtained have an extended conjugate system having both the aromatic rings joined through the –N=N– bond. These compounds are often coloured and are used as dyes. Benzene diazonium chloride reacts with phenol in which the phenol molecule at its para position is coupled with the diazonium salt to form p-hydroxyazobenzene. This type of reaction is known as coupling reaction. Similarly the reaction of diazonium salt with aniline yields p-aminoazobenzene. This is an example of electrophilic substitution reaction



(d) Sulphonation (sulphanilic acid-zwitterion formation):

Aniline reacts with concentrated sulphuric acid to form anilinium hydrogensulphate which on heating with sulphuric acid at 453-473K produces p-aminobenzene sulphonic acid, commonly known as sulphanilic acid, as the major product.



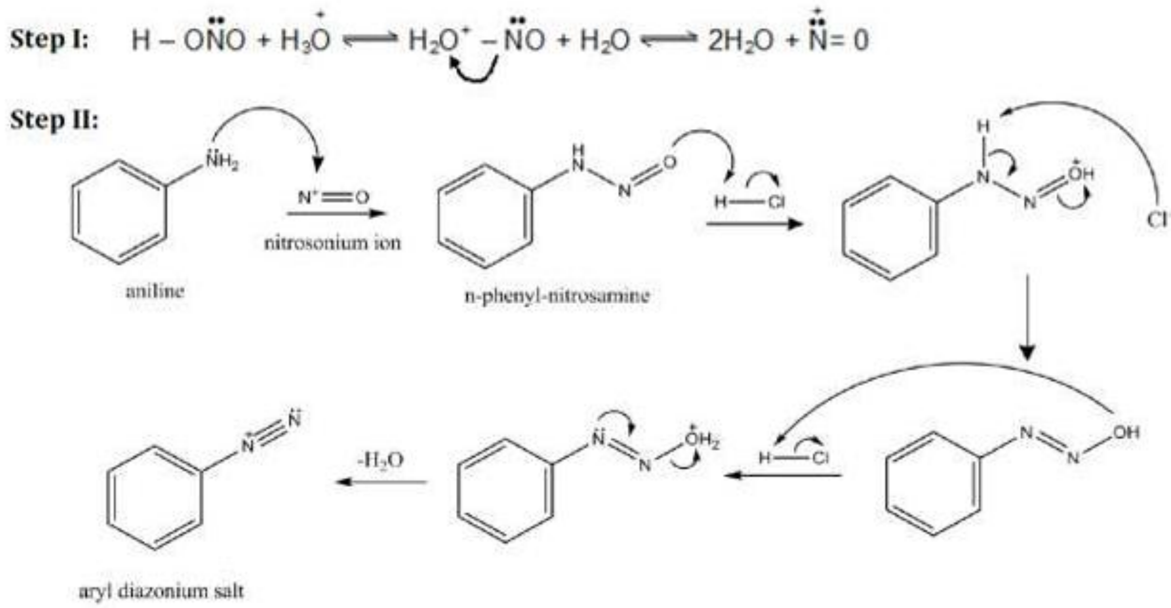
Aniline does not undergo Friedel-Crafts reaction (alkylation and acetylation) due to salt formation with aluminium chloride, the Lewis acid, which is used as a catalyst. Due to this, nitrogen of aniline acquires positive charge and hence acts as a strong deactivating group for further reaction

Benzene diazonium chloride -preparations

Benzenediazonium chloride is prepared by the reaction of aniline with nitrous acid at 273-278K. Nitrous acid is produced in the reaction mixture by the reaction of sodium nitrite with hydrochloric acid. The conversion of primary aromatic amines into diazonium salts is known as diazotisation. Due to its instability, the diazonium salt is not generally stored and is used immediately after its preparation.

$$C_6H_5NH_2 + NaNO_2 + 2HCl \xrightarrow{273-278K} C_6H_5\overset{+}{N_2}\overset{-}{Cl} + NaCl + 2H_2O$$

Mechanism



Importance of synthetic application;

From the above reactions, it is clear that the diazonium salts are very good intermediates for the introduction of –F, –Cl, –Br, –I, –CN, –OH,–NO_2 groups into the aromatic ring. Aryl fluorides and iodides cannot be prepared by direct halogenation. The cyano group cannot be introduced by nucleophilic substitution of chlorine in chlorobenzene but cyanobenzene can be easily obtained from diazonium salt. Thus, the replacement of diazo group by other groups is helpful in preparing those substituted aromatic compounds which cannot be prepared by direct substitution in benzene or substituted benzene.

Uses:

- Azo-compounds are highly coloured, they are widely used in dyeing industries, such as: i) Methyl orange ii) Direct brown 138 iii) Sunset yellow FCF
- Methyl orange - used as acid-base indicators due to the different colors of their acid and salt forms
- Artist's paints – clays, yellow to red range
- Dye in food and textiles Uses and important of azo dye
- Examples of azo dyes used in food: E102: Tartrazine, E107 : Yellow 2G, E110 : Sunset Yellow, E122 : Azorubine, E123: Amaranth, E124 : Ponceau 4R, E129 : Allura Red & E151 : Brilliant Black.

DYES –

Theory of Colour And Constitution

Dyes are organic substances that impart colour to materials such as fibres, paper, and leather in a durable manner. The colour shown by a dye depends on its chemical constitution. When white light falls on a coloured compound, certain wavelengths are absorbed while the remaining wavelengths are reflected or transmitted, producing the observed colour. Absorption in the visible region occurs due to electronic transitions within the molecule, which are made possible by conjugated systems and specific functional groups.

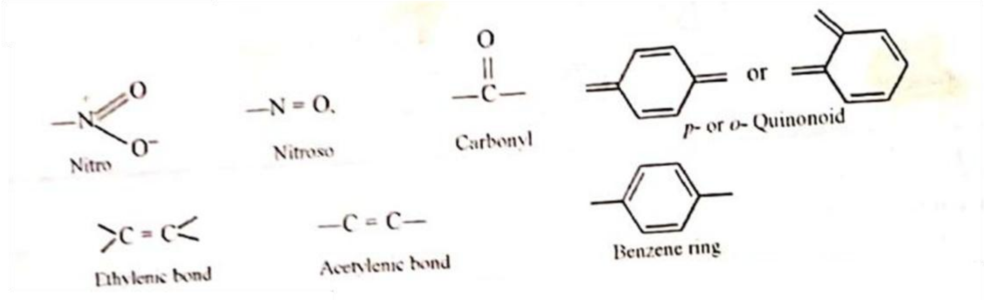
Wavelength (nm)	Colour absorbed	Colour reflected
400–435	Violet	Yellow-green
435–480	Blue	Yellow
480–490	Green-blue	Orange
490–500	Blue-green	Orange
500–560	Green	Purple
560–580	Yellow-green	Violet
580–595	Yellow	Blue
595–605	Orange	Green-blue
605–750	Red	Blue-green

Colour in organic molecules is mainly associated with π-electron systems. The presence of alternating single and multiple bonds lowers the energy difference between electronic states, allowing absorption of visible light. Structural changes that increase conjugation generally deepen colour, while loss of conjugation leads to fading or disappearance of colour.

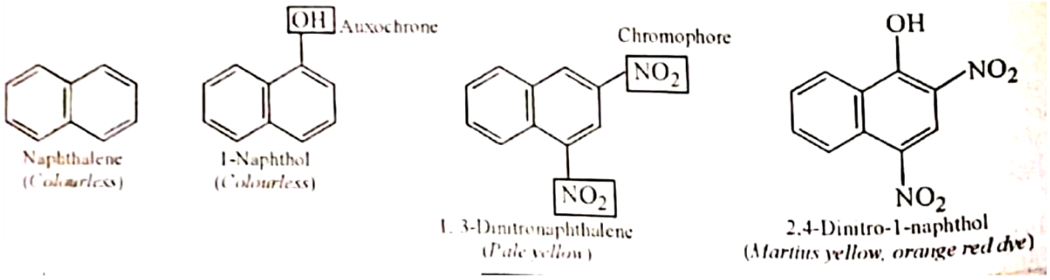
Chromophore–Auxochrome Theory

According to the chromophore–auxochrome theory proposed by Witt, colour in organic compounds is due to chromophores, while dyeing properties are improved by auxochromes. A chromophore is an unsaturated group capable of absorbing light in the visible region. Compounds containing chromophores are usually coloured but may not necessarily act as dyes.

Common chromophores include the azo group (–N=N–), nitro group (–NO_2), nitroso group (–NO), carbonyl group (–C=O), ethylenic group (–C=C–), and cyano group (–C≡N). The introduction of such groups into an otherwise colourless molecule generally produces colour.



Auxochromes are groups that intensify colour and impart dyeing ability when attached to a chromophore. They increase solubility and enhance the affinity of the dye for fibres. Typical auxochromes include –OH, –NH_2, –NHR, –NR_2, –SO_3H, and –COOH. The combined presence of chromophore and auxochrome results in stronger colour and better fixation on substrates.



For instance, benzene is colourless. Introduction of a nitro group produces nitrobenzene, which is pale yellow. Further introduction of an amino group forms p-nitroaniline, which exhibits a much deeper colour due to the auxochromic effect.

Modern Theories or Electronic Theory of Colour

Two electronic theories have been proposed to explain the origin of colour in organic compounds. These are the **Valence Bond (V.B.) theory** and the **Molecular Orbital (M.O.) theory**. The essential difference between these two approaches lies in the treatment of electrons. In valence bond theory, electrons are considered in paired form, whereas in molecular orbital theory, electrons may be treated individually.

Valence Bond Theory

According to the valence bond theory, the electron pairs present in a molecule in its ground state remain in continuous oscillation. When such a molecule is exposed to a beam of light, it absorbs a photon of suitable energy and gets excited. The wavelength of light absorbed depends on the energy gap between the ground state and the excited state. A smaller energy difference corresponds to absorption of light with a longer wavelength.

To explain the valence bond theory of colour, let us consider the ethylene molecule. Ethylene can be regarded as a resonance hybrid of two limiting structures (I) and (II):

$$CH_2 = CH_2 \leftrightarrow CH_2^+ - CH_2^-$$

In the ground state, the molecule is represented mainly by structure (I), while in the excited state, structure (II) contributes more significantly. The energy difference between these two states is quite large, and therefore ethylene absorbs light of very short wavelength.

In general, the following conclusions can be drawn:

1. Resonance involving charged structures reduces the energy of both the ground state and the excited state.
2. Charged resonance forms stabilize the excited state to a greater extent than the ground state.
3. As the number of electrons participating in resonance increases, the energy gap between the ground and excited states decreases.

From the above points, it follows that as conjugation in a molecule becomes more extensive, the contribution of charged resonance structures increases. This leads to a reduction in the energy difference between the ground and excited states, resulting in absorption of light at longer wavelengths. When the absorbed wavelength lies within the visible region, the compound appears coloured.

For example:

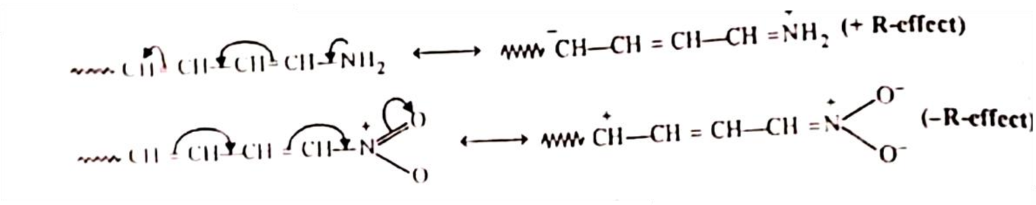
- **Ethylene ($CH_2 = CH_2$)** absorbs at $\lambda_{max} \approx 175$ nm and is colourless.
- **1,3-Butadiene ($CH_2 = CH–CH = CH_2$)** absorbs at $\lambda_{max} \approx 217$ nm and is colourless.

- **1,3,5-Hexatriene ($CH_2 = CH–CH = CH–CH = CH_2$)** absorbs at $\lambda_{max} \approx 258$ nm and is colourless.
- **1,10-Diphenyl-1,3,5,7,9-decapentaene** absorbs at $\lambda_{max} \approx 424$ nm and appears orange.

It should be noted that the colour observed for a compound is the **complementary colour** of the light that is absorbed.

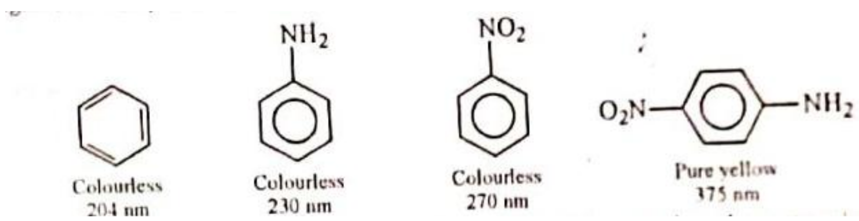
Further, the presence of electron-donating groups (that is, groups showing +I or +R effect) or electron-withdrawing groups (groups showing –I or –R effect) at the terminal positions of a conjugated system leads to an extension of conjugation. This occurs because the lone pair of electrons present on the heteroatom interacts with the π-electrons of the conjugated system. As a result, the contribution of charged resonance structures to the overall resonance hybrid increases.

When an electron-donating group such as $–NH_2$ is present, it donates electron density through the +R effect, stabilizing the charged resonance form. Similarly, when an electron-withdrawing group such as $–NO_2$ is present, it withdraws electron density through the –R effect and also enhances the contribution of charged structures.



Due to this increased contribution of charged resonance forms, the energy difference between the ground state and the excited state decreases. Consequently, the wavelength of light absorbed becomes longer, and when this wavelength falls within the visible region, the compound appears coloured.

For example:



Steric Effects and Colour

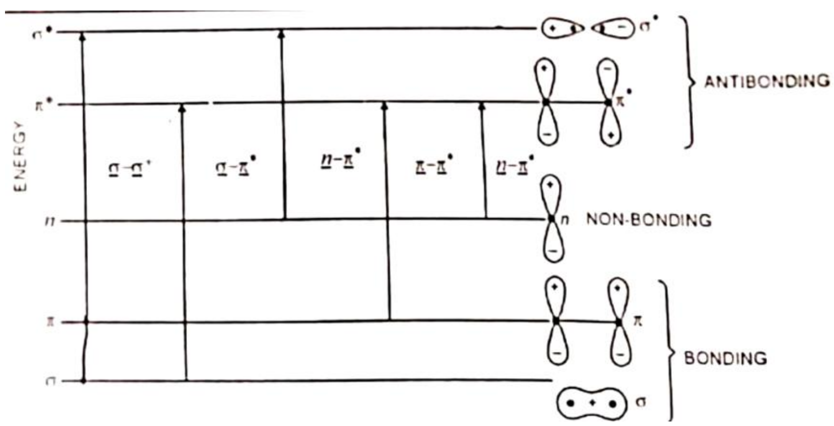
Resonance is most effective when the molecular system is either completely or nearly planar. When steric hindrance is present, planarity is disturbed and resonance is reduced. As a result, the intensity of colour decreases, and in some cases, the compound may even become colourless.

Molecular Orbital Theory

According to molecular orbital theory, when a molecule absorbs a photon of light, one electron is promoted from a bonding orbital or a non-bonding orbital to an antibonding orbital. Depending on the type of electron involved, different electronic transitions are possible.

A transition in which a bonding σ-electron is excited to an antibonding σ*-orbital is known as a **σ → σ*** transition. Similarly, a **π → π*** transition involves the excitation of a bonding π-electron to an antibonding π*-orbital. An **n → π*** transition involves the excitation of a lone-pair (non-bonding) electron to an antibonding π*-orbital.

The n → π* type of transition is commonly observed in molecules containing heteroatoms with multiple bonds, such as >C=O, >C=S, and >C=N systems.



Electronic transition in molecules

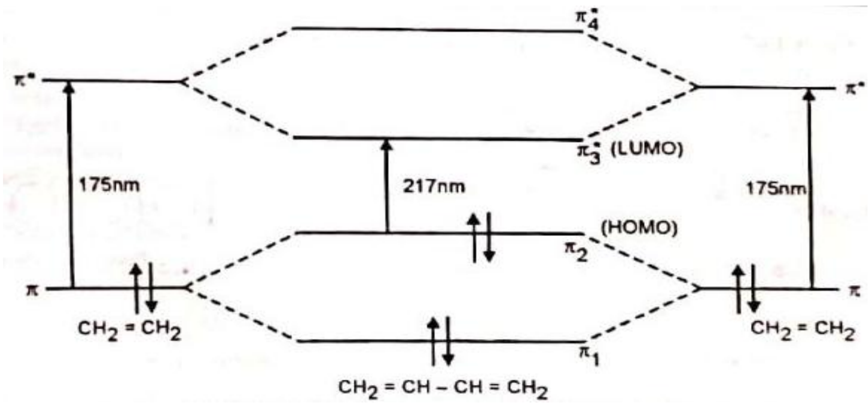
The relative energy levels of the various electronic transitions follow the order:

$$\sigma\rightarrow\sigma^* > \sigma\rightarrow\pi^* > n\rightarrow\sigma^* > \pi\rightarrow\pi^* > n\rightarrow\pi^*$$

Among these transitions, only **$\pi \rightarrow \pi^*$** and **$n \rightarrow \pi^*$** occur within the usual ultraviolet region (200–400 nm). Of these two, **$\pi \rightarrow \pi^*$** transitions are considerably more intense than **$n \rightarrow \pi^*$** transitions and therefore play a major role in the development of colour. As the extent of conjugation increases, absorption due to $\pi \rightarrow \pi^*$ transitions shifts towards longer wavelengths and may eventually reach the visible region, resulting in colour.

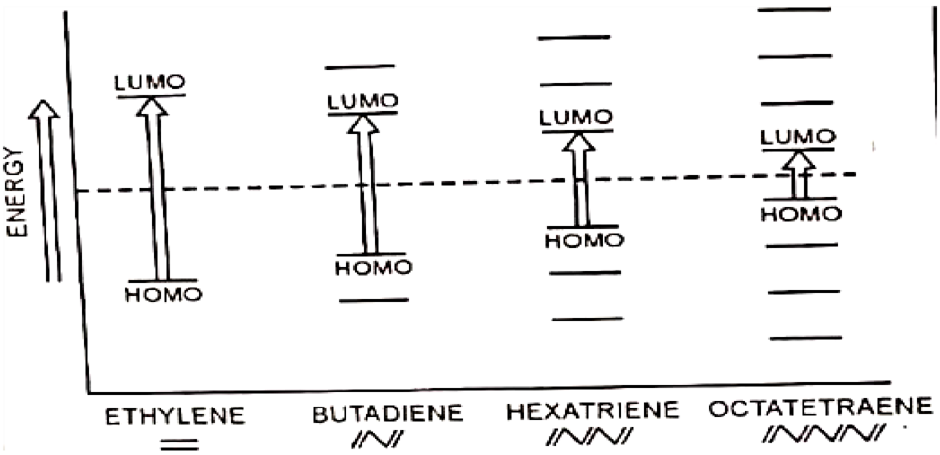
In ethylene, two types of electronic transitions are possible, namely **$\sigma \rightarrow \sigma^*$** and **$\pi \rightarrow \pi^*$**. The longest wavelength absorption band corresponds to the $\pi \rightarrow \pi^*$ transition and occurs at about 175 nm ($\varepsilon \approx 5000$). Since this absorption lies in the ultraviolet region, ethylene appears colourless. In the case of butadiene, the $\pi \rightarrow \pi^*$ transition occurs at $\lambda_{max} \approx 217$ nm ($\varepsilon \approx 21000$). This shows that conjugation shifts the absorption to longer wavelengths, although it still remains outside the visible region. However, the intensity of absorption increases significantly.

A double bond consists of two molecular orbitals: one bonding and one antibonding. When two double bonds become conjugated, four molecular orbitals are formed. Among these, two orbitals (π_1 and π_2) are bonding orbitals and are each occupied by a pair of electrons, while the remaining two orbitals (π_3^* and π_4^*) are antibonding in nature, as illustrated in below Fig.



Thus, it is evident that the energy of the **highest occupied molecular orbital (HOMO)**, that is π_2, increases, while the energy of the **lowest unoccupied molecular orbital (LUMO),** that is π_3^*, decreases. Consequently, the energy levels involved in the **$\pi \rightarrow \pi^*$** transition move closer to each other and a smaller amount of energy is required for excitation. In other words, the energy gap between π_2 and π_3^* orbitals in **1,3-butadiene** is much smaller than the corresponding energy gap between the π and π^* orbitals in **ethylene**. As a result, 1,3-butadiene absorbs light of longer wavelength (217 nm) compared to ethylene (175 nm). Further, as the energy levels approach each other, interaction in the excited state increases, leading to an increase in the molar absorptivity (ε_{max}).

In a similar manner, when three double bonds are brought into conjugation, the energy difference between the HOMO and LUMO becomes even smaller (as indicated by the arrows in below Fig.), and the wavelength of absorption increases further.



As conjucation increases the energy gap between HOMO and LUMO decreases and adsorption shifts to the longer wavelengths

Dyes

A **dye** is defined as a specialized coloring agent designed for application to a substrate via solution or dispersion. Unlike pigments, which typically sit on the surface, dyes are intended to integrate with the material's structure. This process is versatile, extending beyond traditional textiles—such as cotton, silk, and synthetic polymers like nylon—to include organic materials like leather, hair, and even cosmetic bases.

Critical Criteria for Dye Efficacy

For a coloring substance to be academically and industrially recognized as a viable dye, it must demonstrate more than just aesthetic appeal. It must satisfy three fundamental functional requirements:

- The substance must exhibit a suitable and consistent color, derived from its molecular ability to absorb specific wavelengths of light.

- A primary requirement is the dye's capacity for "fixation." It must possess the chemical affinity to bond with the fibers either through direct molecular attraction or via a secondary chemical process ensuring the color remains embedded rather than superficial.
- Perhaps the most rigorous requirement is durability. A professional-grade dye must remain "fast" when exposed to environmental stressors. This includes photostability (resistance to UV light) and chemical resistance to surfactants, detergents, and organic solvents used in both aqueous washing and professional dry-cleaning processes.

Classification of Dyes

Dyes can be categorized in several ways, as outlined below:

1. Natural and Synthetic Dyes: Historically, humans have obtained dyes from plants to color textiles. Such dyes are termed natural dyes. Examples include **indigo**, which produces a blue color, and **alizarin**, which yields red. India has been a major producer and exporter of indigo. However, natural dyes are limited in the range of shades they provide. Today, most dyes are **synthetic**, offering a wider variety of colors. Many synthetic dyes are **aromatic compounds derived from coal-tar**, which is why they are also referred to as **coal-tar dyes**.

2. Classification of Dyes Based on Chemical Constitution (Chemical Classification): In this approach, dyes are grouped according to their chemical structure or the functional group responsible for their color. Major classes include **azo dyes, nitro dyes, nitroso dyes, triphenylmethane dyes, anthraquinone dyes, indigoid dyes, phthalocyanine dyes,** and **acridine dyes**, among others.

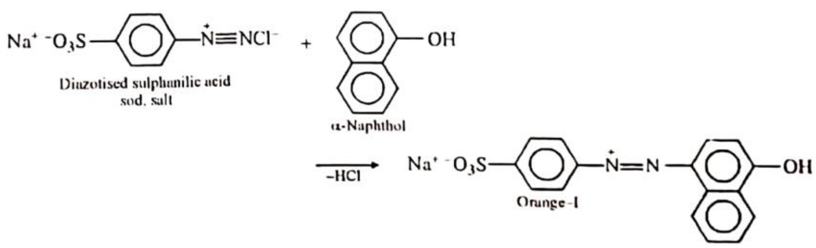
3. Classification of Dyes Based on Application: The method of applying a dye depends on the nature of both the dye and the fiber. There are four primary ways in which a dye molecule can attach to a fiber:

1. **Covalent bonds**
2. **Hydrogen bonds**
3. **Ionic bonds**
4. **Van der Waals forces**

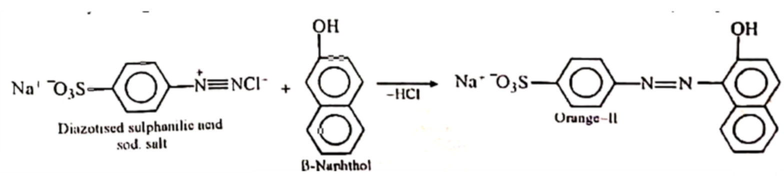
Based on these application methods, dyes are further categorized.

(i) Acid Dyes: Acid dyes are sodium salts of azo dyes containing **sulphonic acid (-SO_3H)** and **carboxylic acid (-CO_2H)** groups. These dyes are applied from acidic solutions and are mainly used on wool, silk, nylon, and other polyamide fibers. Nylon exhibits higher affinity for acid dyes due to its free amino groups, whereas cotton does not bind well and cannot be dyed with these dyes. Common acid dyes include **orange-I, orange-II, methyl orange,** and **congo red**.

For instance, **orange-I** is produced by coupling diazotized sulphanilic acid with **α-naphthol**, resulting in a versatile dye used in textiles.



orange-I is produced by coupling diazotized sulphanilic acid with **β-naphthol**, resulting in a versatile dye used in textiles.



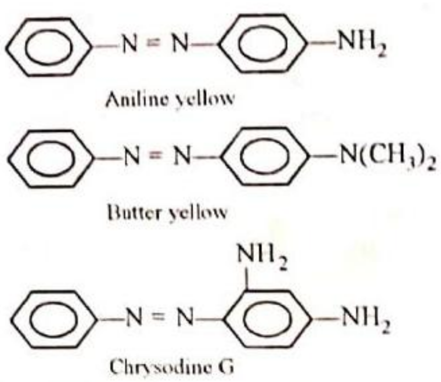
Basic Dyes

Basic dyes are a specific category of dyes consisting of salts of colored bases. These dyes contain amino groups $(NH)_2$ or substituted amino groups which function as auxochromes. This class primarily includes **azo** and **triphenylmethane** dyes.

The process by which basic dyes color a substrate involves specific chemical interactions:

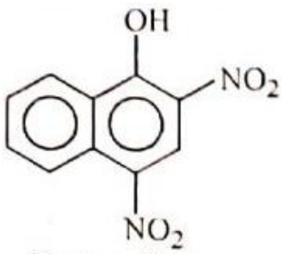
- **Cation Formation**: In an acidic solution, the amino groups in the dye molecules form water-soluble cations.
- **Ionic Bonding**: These cations react with anionic sites located on the fabric, allowing the dye to bind to the material.
- **Substrate Compatibility**: These dyes are particularly effective for modified or reinforced nylons and polyesters.

Common examples of basic dyes mentioned include:



2. Direct or Substantive Dyes

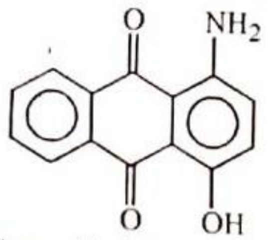
Direct dyes are water-soluble substances characterized by their ease of application. These dyes can be applied directly to the fabric from an aqueous solution. They are most suitable for fabrics capable of forming hydrogen bonds with the dye molecules. They are typically used for dyeing cotton, wool, rayon, and nylon. Well-known examples of this class include **Congo red** and **Martius yellow**.



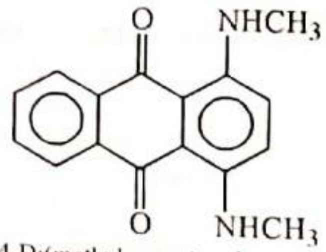
Martius yellow

3. Disperse Dyes

Disperse dyes are **water-insoluble dyes** that are applied to textile fibres in the form of a fine aqueous dispersion. Since these dyes have very low solubility in water, they are dispersed using soaps or other dispersing agents, often in the presence of stabilizing substances such as phenol or cresol. These dyes are mainly used for dyeing **synthetic fibres** such as nylon, polyester, cellulose acetate and polyacrylonitrile. Most disperse dyes belong to the class of **anthraquinone dyes**, which provide bright shades and good fastness properties on synthetic fibres. Important examples of disperse dyes include *Celliton Fast Pink B* and *Celliton Fast Blue B*.



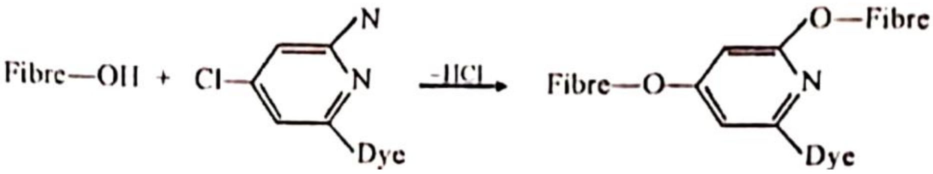
1-Amino-4-hydroxyanthraquinone
(*Celliton fast pink B*)



1,4-Di(methylamino) anthraquinone
(*Celliton fast blue B*)

4. Fibre Reactive Dyes

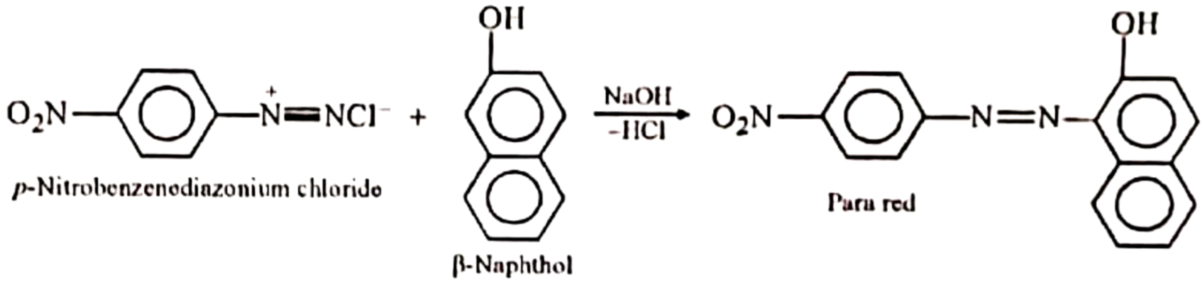
Fibre reactive dyes are those dyes which contain **reactive functional groups** capable of forming **covalent bonds** directly with the fibre. These dyes react with the **hydroxyl groups of cellulose fibres** or the **amino groups of protein fibres**, resulting in the formation of strong chemical bonds between the dye molecule and the fibre. Due to this permanent chemical linkage, fabrics dyed with fibre reactive dyes show **excellent colour fastness** and long service life. Fibres such **as cotton, wool and silk** are commonly dyed using this class of dyes.



Dyes derived from **2,4-dichloro-1,3,5-triazine** are important examples of fibre reactive dyes. During the dyeing process, one chlorine atom is replaced by the fibre group, with the elimination of hydrochloric acid.

5. Ingrain Dyes or Insoluble Azo Dyes

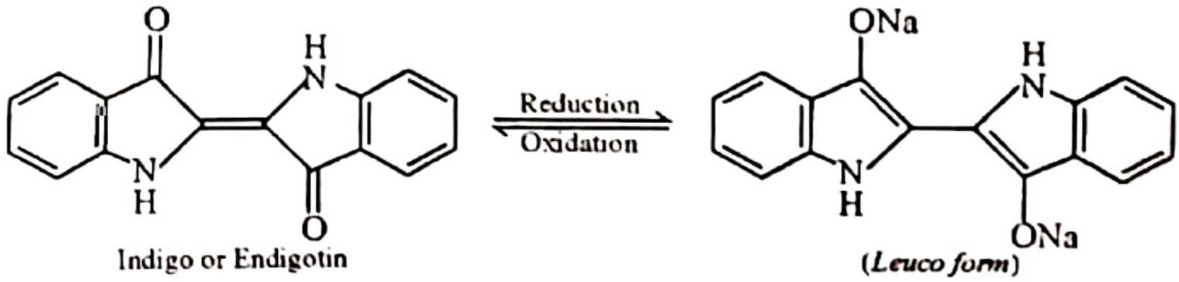
Ingrain dyes, also known as **insoluble azo dyes**, constitute nearly **60% of the total dyes used** in the textile industry. These dyes are produced **directly on the fibre** by coupling a diazonium salt with phenols, naphthols, arylamines or aminophenols that are adsorbed on the fabric surface. Since the dye is held on the fabric mainly by **surface adsorption** rather than strong chemical bonding, the colour obtained is **not very fast.** Ingrain dyes are used for dyeing **cellulose fibres, silk, polyester, nylon, polypropylene, polyurethanes, polyacrylonitrile and leather.**



A well-known example of an ingrain dye is **Para Red**, which is formed by coupling *p-nitrobenzenediazonium chloride* with *β-naphthol* in alkaline medium. Azo dyes are also used in **cosmetics, drugs, biological stains and chemical indicators.** However, due to their toxic nature, their use in foodstuffs has been discontinued.

6. Vat Dyes

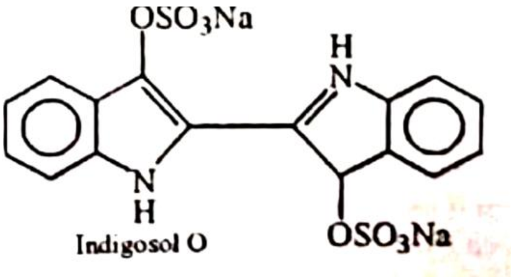
Vat dyes are **insoluble in water** and therefore cannot be used directly for dyeing. Before application, these dyes are reduced to a **soluble, colourless form known as the leuco form** by treating them with reducing agents such as **sodium hydrosulphite** in alkaline medium.



Under these conditions, the leuco form shows strong affinity for **cellulose fibres**, particularly cotton. After the fabric is impregnated with the leuco solution, it is exposed to air or treated with mild oxidizing agents such as chromic acid or perboric acid. This converts the soluble leuco form back into the **insoluble coloured dye**, which becomes firmly fixed within the fibre. A well-known example of a vat dye is **indigo**, which is widely used for dyeing cotton fabrics.

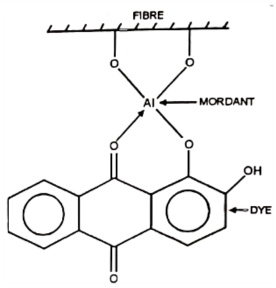
Indigosol Dyes

Indigosol dyes are **water-soluble derivatives of indigo**. Unlike vat dyes, they dissolve readily in water and possess good affinity for cellulose fibres. After absorption by the fibre, these dyes are rapidly and quantitatively oxidized to indigo directly on the fabric. Indigosol O is an important example of this class of dyes and is especially suitable for dyeing **wool and cellulose fibres.**



6. Mordant Dyes

Mordant dyes are those dyes which **do not dye the fabric directly** but require the use of a **mordant**. A mordant is a substance that acts as a **binding agent between the fibre and the dye**, thereby helping in the fixation of the dye on the fabric. In the case of **acid dyes**, metal ions such as aluminium, chromium or iron are commonly used as mordants, whereas for **basic dyes**, organic substances like **tannic acid** serve as mordants. Mordant dyes are mainly employed for dyeing **wool fibres**.



Alizarin aluminium fibre complex

In the dyeing process, the fabric is first soaked in a solution of a suitable metal salt (mordant). The mordanted fabric is then immersed in the dye solution. During this process**, insoluble coloured complexes**, known as **lakes**, are formed on the fibre. Initially, the metal ions become attached to the fibre, and subsequently, the dye molecules bind to the metal ions through **coordinate or covalent bonds**.

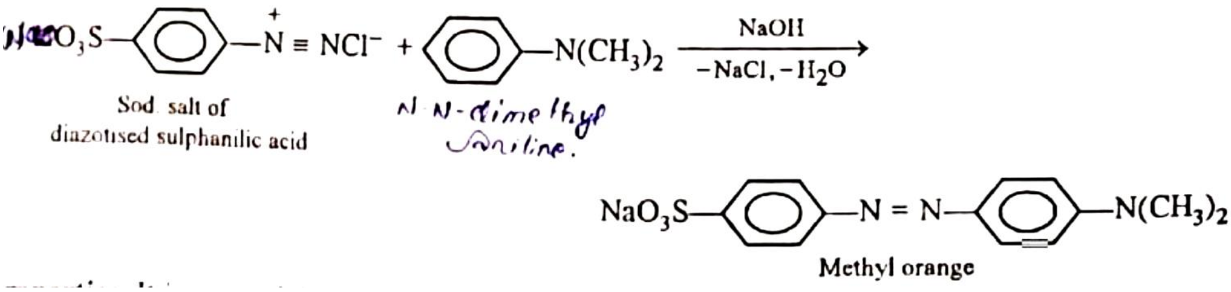
The same dye can produce **different colours with different metal ions**. For example, **alizarin** gives:

- rose-red (Turkey red) colour with aluminium ions,
- blue colour with barium ions,
- brownish-red colour with chromium ions,
- violet colour with magnesium ions, and
- red colour with strontium ions.

Methyl Orange (Helianthin)

Synthesis

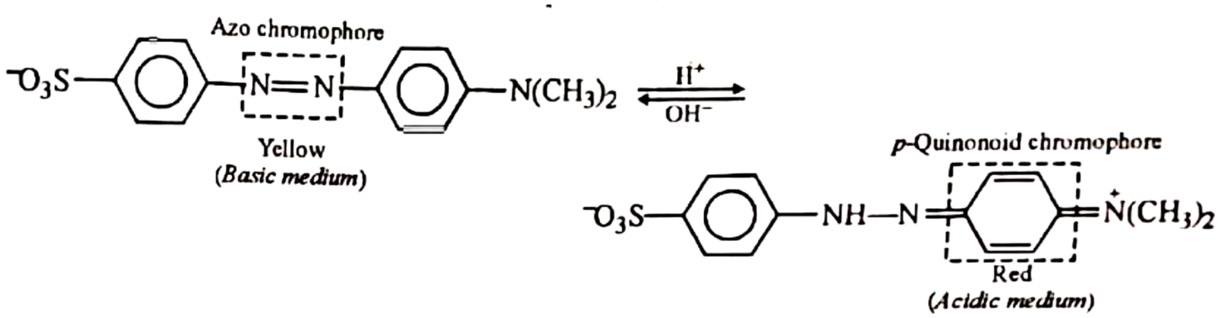
Methyl orange is prepared by coupling **N,N-dimethylaniline** with **diazotised sulphanilic acid** in alkaline medium. The coupling reaction results in the formation of methyl orange as the sodium salt.



Properties and Uses

Methyl orange is an **acid dye** used for wool and silk, but its colour fades on exposure to light and washing. Therefore, it is not commonly used as a textile dye. Instead, it is widely used as an **acid–base indicator**.

It appears **yellow in alkaline solutions (pH above 4.4)** and **red in acidic solutions (pH below 3.1)**. The colour change is due to a structural transformation of the dye molecule. In alkaline medium, the dye exists in the **azo form**, whereas in acidic medium, it exists in the **p-quinonoid form**.



Alizarin

Alizarin is one of the most important anthraquinonoid dyes. It occurs naturally in the roots of the madder plant (*Rubia tinctorum*) in the form of its glucoside known as ruberythric acid.

Hydrolysis of Ruberythric Acid

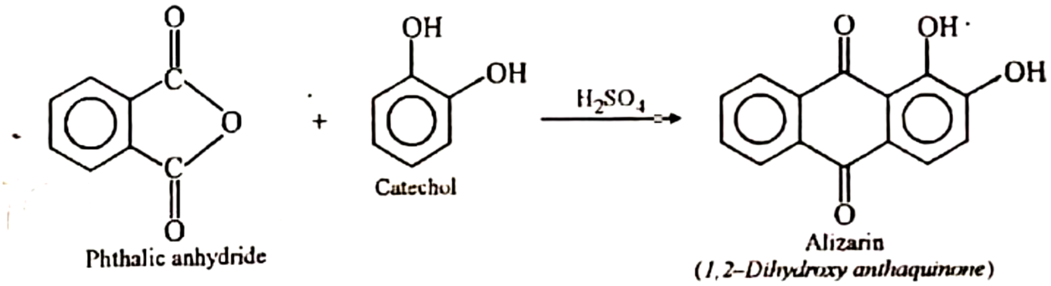
On hydrolysis in the presence of an acid or enzyme, ruberythric acid breaks down to yield alizarin and glucose. Alizarin is chemically 1,2-dihydroxyanthraquinone.

$$\underset{\text{Ruberthyric acid}}{C_{26}H_{28}O_{14}} + 2H_2O \xrightarrow[(\textit{Hydrolysis})]{H^+ \text{ or Enyzyme}} \underset{\text{Alizarin}}{C_{14}H_6O_2(OH)_2} + \underset{\text{Glucose}}{2C_6H_{12}O_6}$$

Structure of Alizarin

The structure of alizarin has been established based on the following evidences:

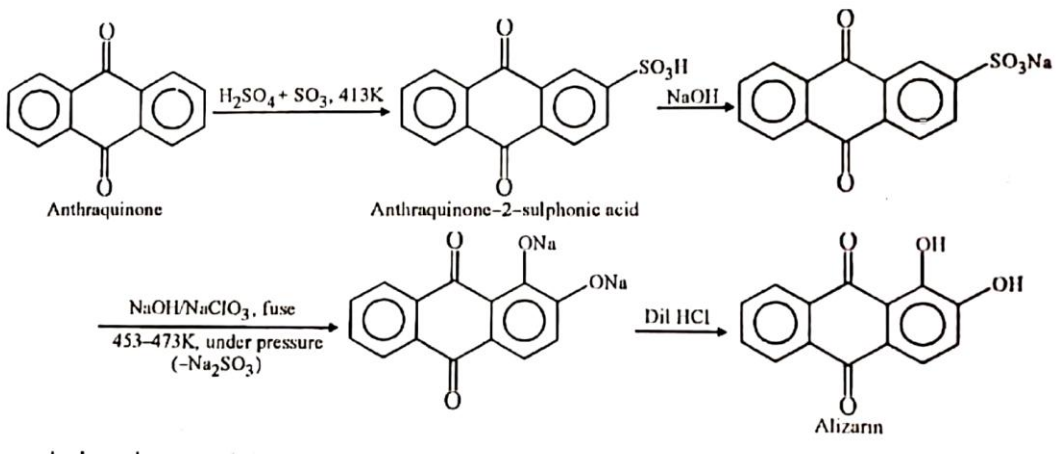
1. Elemental analysis and molecular weight determination show that the molecular formula of alizarin is $C_{14}H_8O_4$.
2. On reduction with zinc dust at about 673 K, alizarin gives anthracene, indicating that alizarin is a derivative of anthracene.
3. When treated with acetic anhydride, alizarin forms a diacetate, showing the presence of two hydroxyl (–OH) groups.
4. Alizarin can be synthesised by the condensation of phthalic anhydride with catechol in the presence of concentrated sulphuric acid at about 453 K. This confirms that alizarin is a dihydroxy derivative of anthraquinone, with both hydroxyl groups present in the same benzene ring.



Manufacture of Alizarin

Alizarin is manufactured from anthraquinone by the following sequence of reactions:

1. **Sulphonation**
   Anthraquinone is sulphonated with fuming sulphuric acid (oleum) at about 413 K to form anthraquinone-2-sulphonic acid.
2. **Fusion with Alkali**: The sodium salt of anthraquinone-2-sulphonic acid is fused with sodium hydroxide in the presence of a calculated amount of sodium or potassium chlorate at 453–473 K under pressure. During this process, sulphonic acid groups are replaced by hydroxyl groups.
3. **Acidification**
   The fused mass is acidified with dilute hydrochloric acid, resulting in the formation of alizarin.

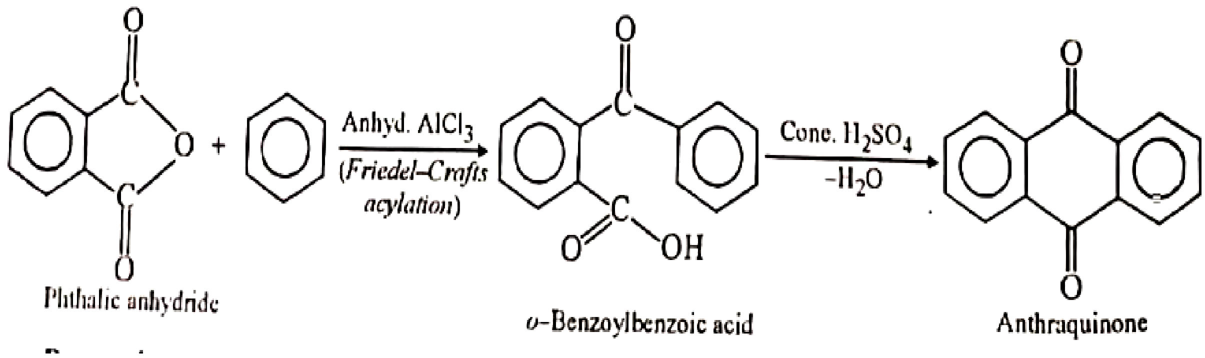


The function of sodium or potassium chlorate in this process is to supply oxygen required for the oxidation of C–H bonds into C–OH groups.

Preparation of Anthraquinone

Anthraquinone required for the manufacture of alizarin is prepared from benzene and phthalic anhydride by the following steps:

1. Friedel–Crafts Acylation: Phthalic anhydride reacts with benzene in the presence of anhydrous aluminium chloride to form o-benzoylbenzoic acid.
2. Cyclisation and Dehydration: On treatment with concentrated sulphuric acid, o-benzoylbenzoic acid undergoes cyclisation and dehydration to yield anthraquinone.



Properties of Alizarin

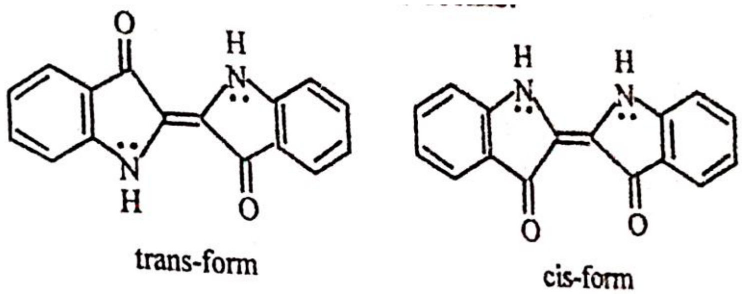
1. Alizarin forms ruby-red crystals and melts at about 563 K.
2. It is insoluble in water and alcohol, but dissolves in alkalies to give a purple solution.
3. It sublimes on heating.
4. Alizarin is a mordant dye, and the colour of the dye lake depends on the metal ion used:
   - Aluminium salts give red (Turkey red),
   - Ferric salts give violet-black,
   - Chromium salts give brown-violet lakes. Aluminium and iron lakes are mainly used for cotton dyeing and printing, whereas aluminium and chromium lakes are used for wool dyeing.

Uses of Alizarin

Alizarin is widely used as a mordant dye and is also used as a purgative in medicine.

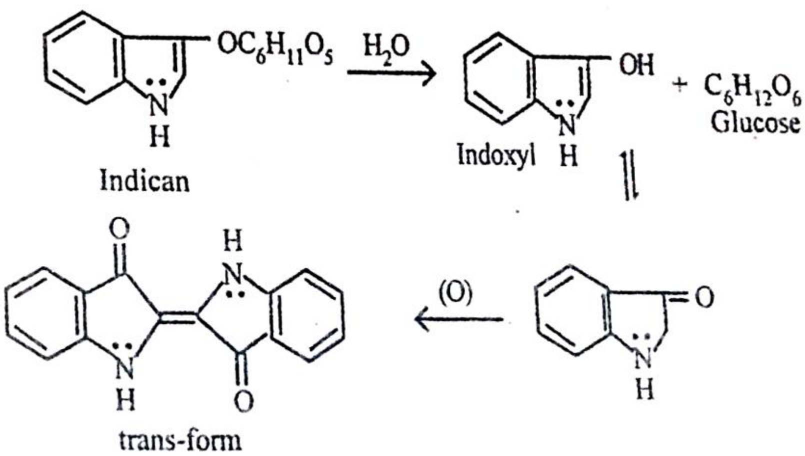
Indigo

Natural indigo is obtained from plants such as *Indigofera tinctoria* and the European plant *Isatis tinctoria*. Natural indigo is a mixture of several related dyes, of which the chief component *indigotin* is designated as indigo. X-ray analysis has shown that indigotin possesses the trans-configuration, which is the more stable of the two possible forms (trans and cis).



Preparation of Indigo from Natural Sources

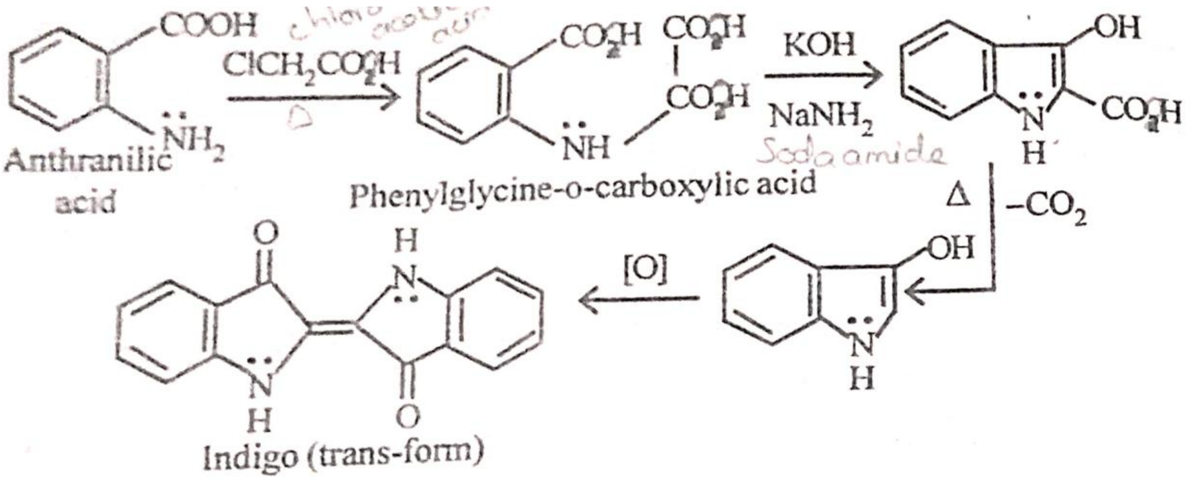
The appropriate plants are **cut shortly before flowering** and treated with **water at 25–30 °C in wooden tanks.** The **enzymes present in the leaves** hydrolyse the glucoside **indican** into **indoxyl and glucose**. The liquid extract is then **agitated in the presence of lime in open vats**, during which **indoxyl is oxidised to indigotin**, forming **insoluble blue flakes**. The crude indigotin thus obtained is **boiled with water, filtered, and dried** to give the **natural dye indigo.**



Heumann’s Commercial Synthesis of Indigo

Anthranilic acid is heated with chloroacetic acid to form phenylglycine-o-carboxylic acid. This compound is then heated with a mixture of potassium hydroxide (KOH) and sodamide ($NaNH_2$) to produce indoxylic acid. Indoxylic acid undergoes decarboxylation to form indoxyl.

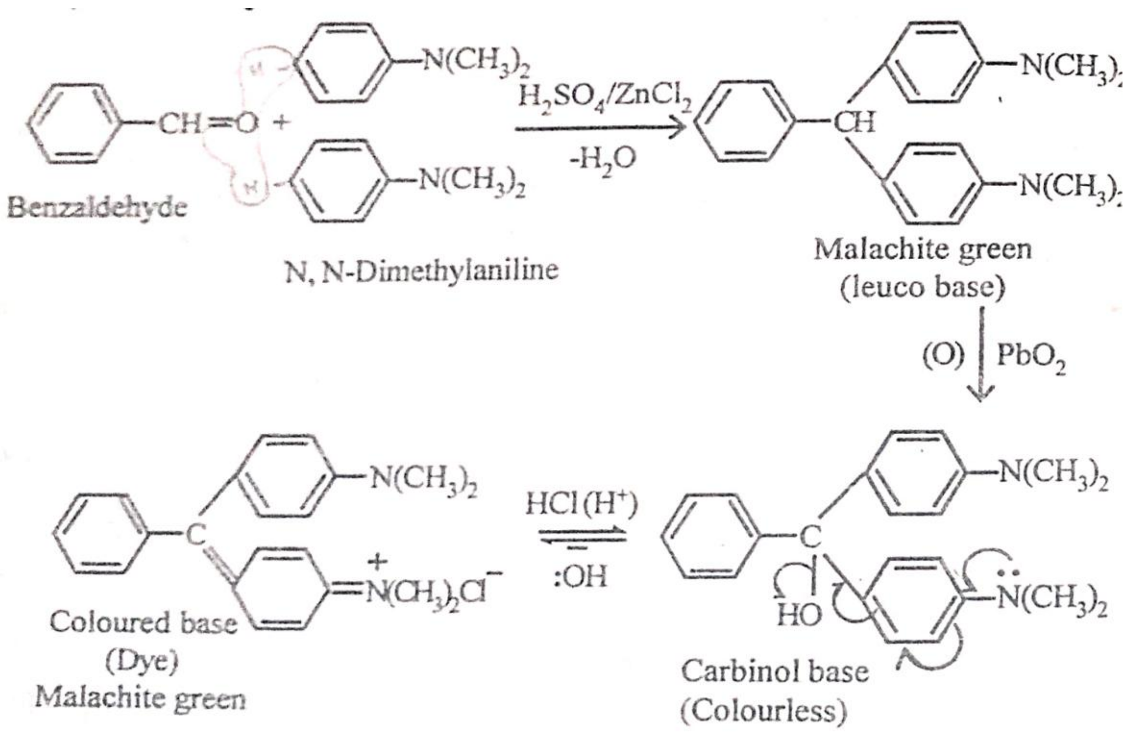
On exposure to air, indoxyl is oxidised to indigotin (indigo).



Malachite Green

Preparation

Malachite green is prepared by **condensing benzaldehyde with N,N-dimethylaniline** in the presence of **concentrated sulphuric acid and zinc chloride**, followed by loss of water.



Uses of Malachite Green

Malachite green is used:

1. **For directly dyeing silk, wool, jute and leather**
2. **For dyeing cotton after mordanting**
3. **For staining host tissue in plants infected with fungi**
4. **For staining bacterial spores**, with **safranine as counter-stain**
5. **As a spot test reagent for detecting sulphurous acid and cerium**
6. **As a topical antiseptic for bacterial and mycotic infections**

Dyes Industry

The dyes industry is an important branch of chemical industry that deals with the manufacture and application of dyes used for colouring textiles, leather, paper, plastics, inks, paints, cosmetics and several other materials. Dyes are coloured organic compounds that have the ability to attach themselves to a substrate and impart a permanent colour under conditions of use. The industry originally developed from coal-tar chemistry and later expanded with the use of petroleum-based aromatic intermediates.

The raw materials used in the dyes industry mainly include aromatic compounds such as benzene, toluene, naphthalene, aniline, phenols and naphthols. These substances undergo various chemical transformations like nitration, sulphonation, halogenation and reduction to form dye intermediates. Colour development in dyes is achieved through reactions such as diazotisation and coupling, condensation and oxidation. After synthesis, dyes are isolated, purified, dried, ground and standardised before being marketed.

Based on their chemical nature and method of application, dyes are classified into acid dyes, basic dyes, direct dyes, reactive dyes, vat dyes and disperse dyes. Each class of dye has specific industrial applications. For example, acid dyes are mainly used for wool and silk, reactive dyes for cotton and cellulose fibres, vat dyes such as indigo for denim, and disperse dyes for synthetic fibres like polyester. The dyes industry supports large-scale textile production and plays a major role in employment generation and export earnings.

Environmental pollution is a major concern in the dyes industry due to the discharge of coloured effluents and toxic aromatic compounds. To overcome these problems, modern dye industries adopt effluent treatment plants, waste minimisation techniques and eco-friendly dyeing processes. Research is also focused on developing biodegradable and less hazardous dyes to meet environmental regulations.

Food Colours and Additives

Food colours and additives form an essential part of the food processing industry. Food colours are substances added to foods to enhance or restore their colour, improve visual appeal and maintain uniformity in appearance. During food processing and storage, natural colour may be lost, and the addition of permitted colours helps to make food products more attractive to consumers.

Food colours may be classified as natural or synthetic. Natural food colours are obtained from plant, animal or mineral sources, such as curcumin from turmeric, chlorophyll from green plants and carotenoids from fruits and vegetables. These colours are generally safer but may suffer from limitations such as lower stability, higher cost and limited colour range. Synthetic food colours are chemically manufactured and provide bright, uniform and stable colours. However, their use is strictly regulated because excessive intake may lead to adverse health effects.

Food additives are substances added in small quantities to improve the quality, shelf life, flavour, texture and safety of food products. Preservatives prevent microbial growth, antioxidants retard oxidation, emulsifiers and stabilisers improve texture and consistency, flavouring agents enhance taste and aroma, and artificial sweeteners provide sweetness with reduced caloric value. The use of food colours and additives is controlled by regulatory authorities such as the Food Safety and Standards Authority of India and international organisations like the WHO and FAO.

The food colours and additives industry plays a crucial role in the modern food supply chain by ensuring product stability, safety and consumer acceptance. Strict regulations and continuous research ensure that these substances are used responsibly, balancing industrial needs with public health and safety

UNIT-IV

HETEROCYCLIC COMPOUNDS

Intoduction

Heterocyclic compounds constitute an important group of cyclic organic substances in which the ring system contains at least one atom other than carbon, known as a heteroatom. The most commonly encountered heteroatoms in these compounds are nitrogen, oxygen, and sulfur. Heterocyclic compounds are widely distributed in nature and are found in a large number of plant and animal products. In fact, nearly half of the naturally occurring organic compounds possess heterocyclic structures. Many biologically significant substances belong to this class of compounds. Alkaloids, natural colorants, pharmaceutical drugs, proteins, enzymes, and other biomolecules frequently contain heterocyclic rings as essential structural components. Because of their structural diversity and chemical behavior, heterocyclic compounds play a crucial role in both biological systems and synthetic chemistry.

Heterocyclic compounds can be broadly classified on the basis of their electronic configuration into saturated and unsaturated types. Saturated heterocyclic compounds exhibit chemical behavior similar to their open-chain analogues, though their cyclic nature influences steric effects. Examples of this category include piperidine and tetrahydrofuran, which resemble conventional amines and ethers, respectively. Unsaturated heterocyclic compounds, particularly those containing five- and six-membered rings, have been studied extensively due to their stability and lack of ring strain. Important unstrained unsaturated heterocycles include pyridine, pyrrole, furan, thiophene, and their fused derivatives. Benzo-fused heterocyclic systems such as quinoline, isoquinoline, indole, benzothiophene, and benzofuran are also of great significance.

Heterocyclic compounds find extensive applications in pharmaceuticals, agrochemicals, and veterinary medicines. Many compounds essential to human life, including hormones, alkaloids, antibiotics, essential amino acids, hemoglobin, vitamins, dyes, and pigments, possess heterocyclic frameworks. In this unit, study about the fundamental aspects of commonly occurring five- membered heterocyclic compounds such as pyrrole, furan, thiophene, with emphasis on their structure, properties, and chemical behavior.

Classification of Heterocyclic compounds

Heterocyclic compounds can be classified into two major groups based on their structural features and electronic arrangement: **aliphatic heterocyclic compounds** and **aromatic heterocyclic compounds**.

Aliphatic heterocyclic compounds consist of cyclic amines, cyclic amides, cyclic ethers, and cyclic thioethers. When these compounds contain only single bonds within the ring, they are known as **saturated heterocycles**. The properties of aliphatic heterocycles are primarily influenced by the degree of ring strain present in the molecule. Typical examples of aliphatic heterocyclic compounds are illustrated in Figure 1.

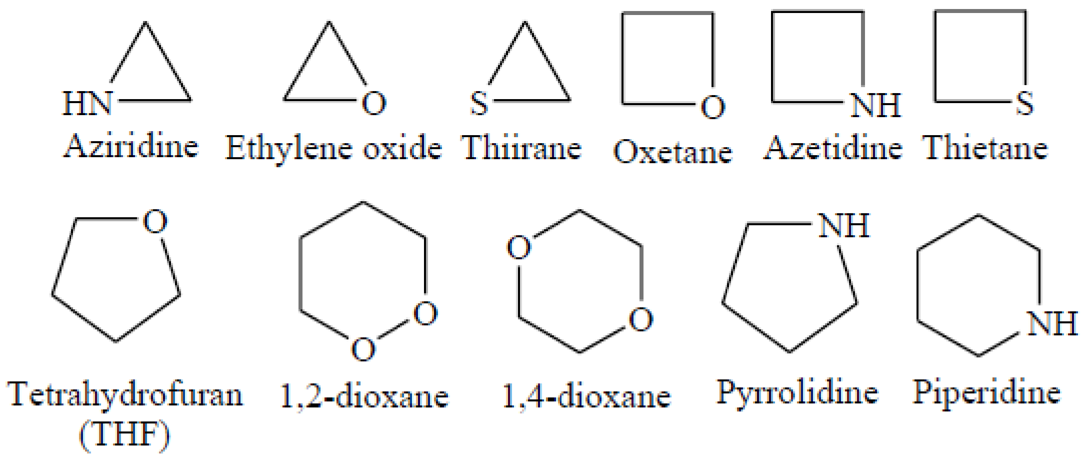


Figure 1. Examples of aliphatic heterocyclic compounds

Aromatic heterocyclic compounds, on the other hand, are structurally similar to benzene and exhibit aromatic behavior. These compounds possess planar, cyclic structures with conjugated double bonds and follow **Hückel's rule,** which states that aromatic systems must contain $(4n + 2)$ π-electrons. The delocalization of these π-electrons provides additional stability to aromatic heterocycles. Representative examples of aromatic heterocyclic compounds are shown in Figure 2.

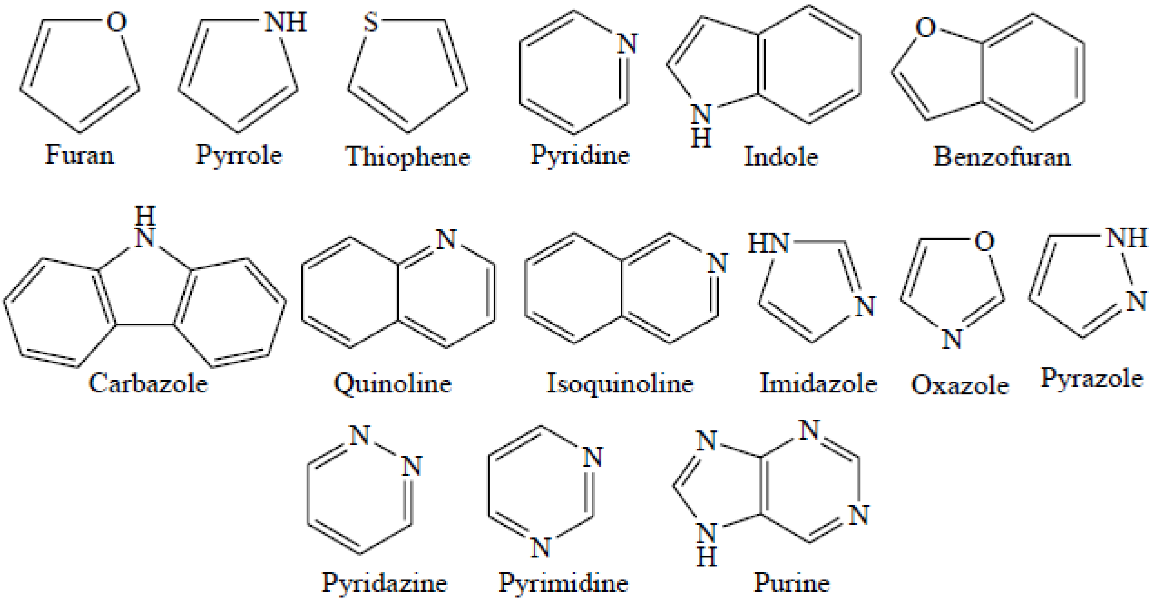


Figure 2. Examples of aromatic heterocyclic compounds

A heterocyclic ring may consist of three or more atoms and can exist in either saturated or unsaturated form. Such rings may contain one or more heteroatoms, which can be identical or different in nature. Owing to this wide structural diversity, heterocyclic compounds can be broadly grouped into three main categories.

Five-Membered Heterocyclic Compounds

Five-membered heterocycles can be viewed as derivatives of benzene in which one carbon–carbon double bond is replaced by a heteroatom possessing a lone pair of electrons. Based on the number of heteroatoms present in the ring, these compounds are further classified into two types.

(a) **Five-membered heterocycles containing one heteroatom:** This group includes compounds in which a single heteroatom is present in the ring. Typical examples are furan, thiophene, and pyrrole, as illustrated in Figure 3.

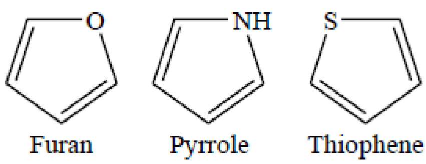


Figure 3. Five member heterocyclic compounds with one hetero atom

(b) Five-membered heterocycles containing more than one heteroatom: In this category, the ring contains two or more heteroatoms, which may be the same or different. Common examples include pyrazole, imidazole, thiazole, oxazole, triazole, and tetrazole, as shown in Figure 4.

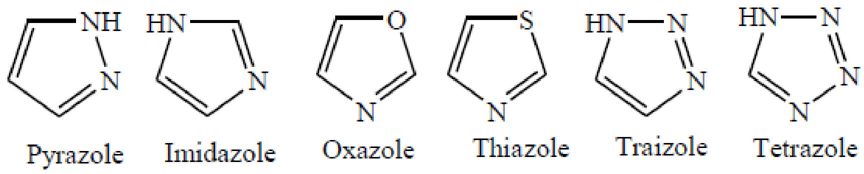


Figure 4. Five member heterocyclic compounds with two hetero atom

Six-Membered Heterocyclic Compounds

Six-membered heterocyclic compounds are considered to be derived from benzene by replacing one carbon atom with an isoelectronic heteroatom. Similar to five-membered heterocycles, these compounds can also be subdivided based on the number of heteroatoms present.

(a) Six-membered heterocycles with one heteroatom: Examples of this class include pyridine, pyran, and thiopyran, as depicted in Figure 5.

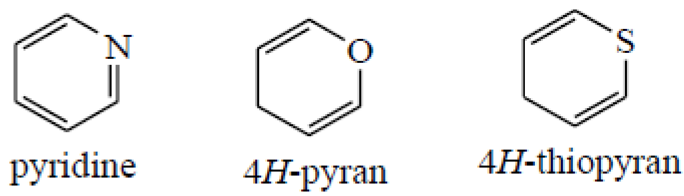


Figure 5. Six member heterocyclic compounds with one hetero atom

(b) Six-membered heterocycles with more than one heteroatom: This group comprises compounds such as pyridazine, pyrimidine, and pyrazine, which contain two or more heteroatoms within the ring (Figure 6).

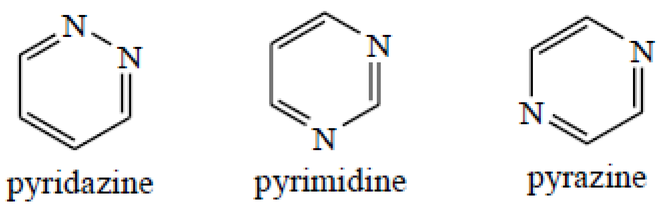


Figure 6. Six member heterocyclic compounds with more than one hetero atom

NOMENCLATURE OF HETEROCYCLIC COMPOUNDS

Heterocyclic compounds constitute an important class of organic compounds in which one or more atoms of the ring are heteroatoms such as nitrogen, oxygen, or sulphur. Because of the large number and structural diversity of heterocyclic systems, a well-defined and systematic method of naming is essential for their clear identification. The nomenclature of heterocyclic compounds is broadly classified into **two main systems**:

(i) Trivial (Common) nomenclature
(ii) Systematic nomenclature

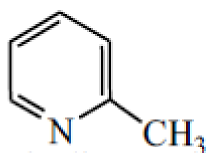
Although many heterocyclic compounds are still commonly known by their traditional names, systematic nomenclature provides precise structural information and is recommended by IUPAC.

1. Trivial (Common) Nomenclature

The trivial system of nomenclature originated during the early development of organic chemistry, when compounds were often named based on their source, method of isolation, or characteristic properties, rather than their structure.

1.1 Naming Based on Source

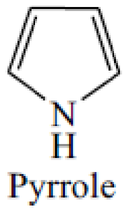
Some heterocyclic compounds were named according to the natural source from which they were first isolated. For example, picoline derives its name from coal tar, with the term originating from the Latin word *pictus*, meaning tar-like.



Picoline

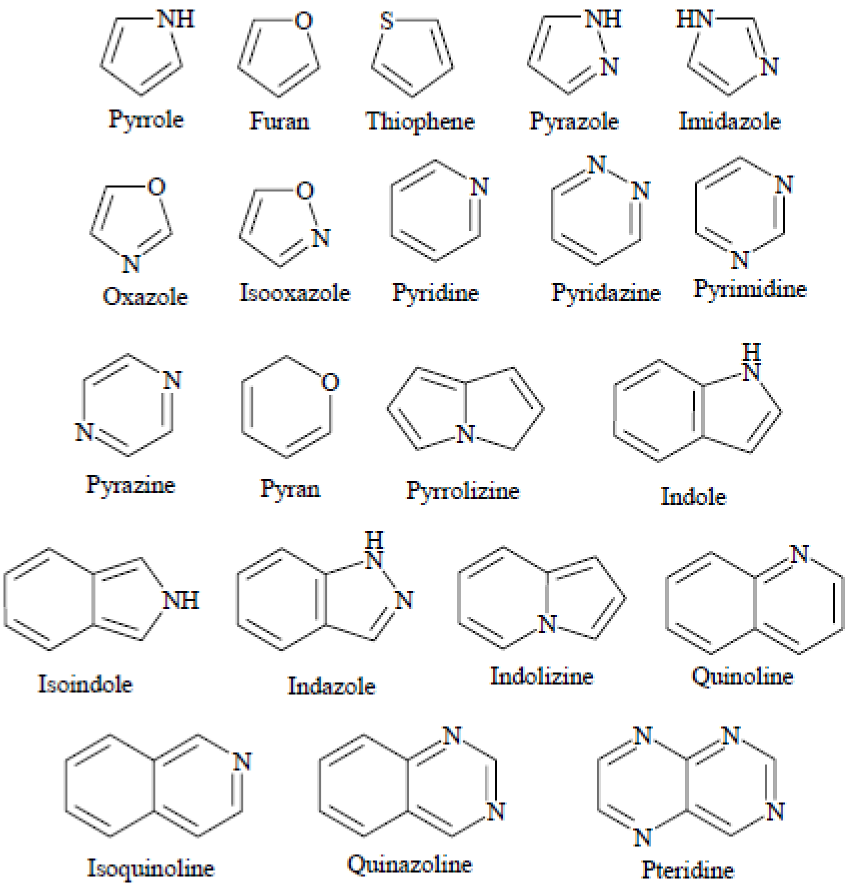
1.2 Naming Based on Properties

In certain cases, names were assigned based on distinctive chemical behavior. For instance, pyrrole was named from Greek words referring to its ability to produce a reddish coloration when a pine splint soaked in hydrochloric acid is exposed to it.



1.3 Importance and Limitations of Trivial Nomenclature

Trivial names played a significant role in the historical development of heterocyclic chemistry and many of these names are still accepted by IUPAC. However, this system has a major limitation: it does not provide any information about ring size, heteroatoms, or degree of saturation. For this reason, trivial nomenclature is largely supplemented by systematic naming methods.



Some heterocyclic compounds with recognized trivial names

Systematic Method of Nomenclature

The systematic method is the most commonly adopted approach for naming monocyclic heterocyclic compounds, particularly those containing three- to ten-membered ring systems. These compounds may exhibit different degrees of saturation and may contain one or more heteroatoms within the ring. Systematic nomenclature is valuable because it conveys essential structural details of heterocyclic compounds in a precise and logical manner.

Among the various systems developed, the method recommended by IUPAC for heterocyclic compounds is the Hantzsch–Widmann system of nomenclature. This system clearly defines the nature, position, number, type of heteroatoms, and the size of the ring present in a heterocyclic structure. In general, the systematic name of a heterocyclic compound is constructed using the format:

Name = Prefix + Stem + Suffix

The following guidelines are important when applying the systematic nomenclature to heterocyclic compounds:

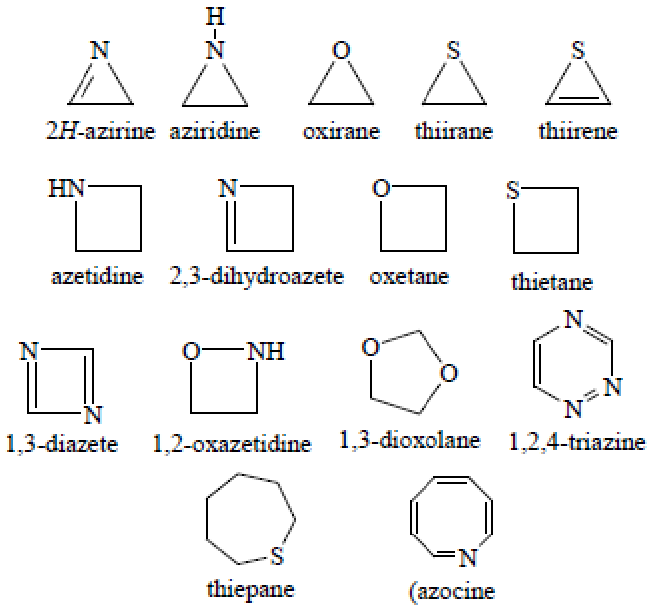
1. In this system, the name of a heterocyclic compound is formed by combining a **prefix**, which identifies the heteroatom present, with a **stem**, which denotes the ring size as well as the degree of saturation or unsaturation, followed by an appropriate **suffix**. A list of commonly used prefixes is provided in Table 1. When a prefix is followed by a vowel, the terminal letter "a" of the prefix is omitted for ease of pronunciation.
2. The naming of a heterocyclic compound begins with the heteroatom that appears first in the priority list given in Table 1.
3. When two or more different heteroatoms are present in the same heterocyclic ring, their prefixes are arranged in the order of priority as specified in the table.
4. If multiple heteroatoms of the same type are present in a heterocycle, their number is indicated using numerical prefixes such as di-, tri-, and so on.
5. The position of a saturated atom in the ring is indicated numerically using the prefix **H-** as part of the compound's name. When more than one numbering option is possible, the position assigned is the one with the lowest possible number.
6. The size of a monocyclic heterocyclic ring, particularly those containing three to ten atoms, is specified by the **stem**. Common stem names used in nomenclature are listed in Table 2.

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 1: 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

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

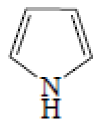


Examples of some heterocyclic compounds with systematic names

Structure and Aromaticity of Pyrrole

The structure and aromatic nature of pyrrole can be explained using the following points.

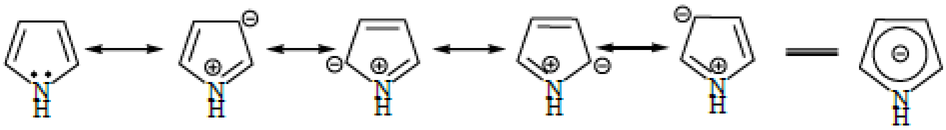
1. Pyrrole has the molecular formula **C_4H_5N**, this indicates that the molecule consists of four carbon atoms, five hydrogen atoms, and one nitrogen atom.



Pyrrole

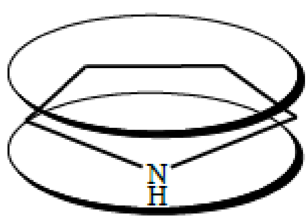
2. The structure of pyrrole can be proposed by considering the valency of the atoms involved. Carbon is tetravalent, while nitrogen is trivalent. Based on this, pyrrole is represented as a five-membered ring containing four carbon atoms and one nitrogen atom, with alternating single and double bonds.
3. Pyrrole does not normally undergo simple addition reactions like alkenes. This behavior is due to the participation of the lone pair of electrons on the nitrogen atom in conjugation with the ring π-electrons. The delocalization of this lone pair increases the stability of the molecule and prevents the double bonds from behaving like isolated double bonds.

4. Pyrrole is considered an aromatic compound because it satisfies **Hückel's rule of aromaticity**, which states that a compound must contain **(4n + 2) π-electrons**. In pyrrole, the four π-electrons from the two double bonds and two electrons from the lone pair of nitrogen together make six π-electrons, fulfilling this rule. The aromatic character and enhanced stability of pyrrole are further supported by the presence of several resonance structures. The actual structure of pyrrole is a resonance hybrid of all these contributing forms.



5. The involvement of the nitrogen lone pair in conjugation also implies that pyrrole must be a **planar molecule**. Planarity allows effective overlap of orbitals for delocalization. This is achieved because all the carbon atoms and the nitrogen atom in pyrrole are **sp^2 hybridized**.
6. In pyrrole, the nitrogen atom has three sp^2 hybrid orbitals, each containing one electron. Two of these sp^2 orbitals form σ-bonds with adjacent carbon atoms in the ring, while the third sp^2 orbital forms a σ-bond with a hydrogen atom. The unhybridized p-orbital of nitrogen contains a lone pair of electrons. Each carbon atom is also sp^2 hybridized, forming σ-bonds with neighboring carbon atoms and hydrogen atoms. The unhybridized p-orbitals of carbon and nitrogen overlap to form a continuous, delocalized π-electron cloud.

This delocalized electron cloud extends above and below the plane of the five-membered ring, providing aromatic stability to pyrrole, as shown in below Figure.

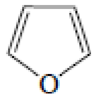


Delocalized electron cloud above and below the pyrrole ring

Structure and Aromaticity of Furan

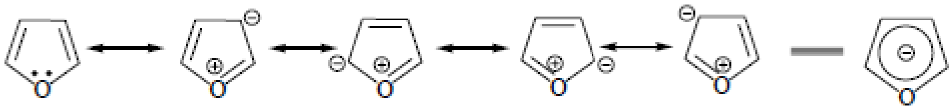
The structure and aromatic nature of furan can be explained based on the following discussion.

1. Furan has the molecular formula **C_4H_4O**, this indicates that the molecule consists of four carbon atoms, four hydrogen atoms, and one oxygen atom.



Furan

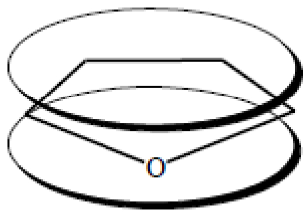
2. The structure of furan can be proposed by considering the normal valencies of the atoms involved. Carbon is tetravalent, while oxygen is divalent. Based on these valency requirements, furan is represented as a five-membered cyclic structure containing four carbon atoms and one oxygen atom with alternating single and double bonds.
3. Similar to pyrrole, furan does not undergo typical addition reactions like simple alkenes under ordinary conditions. This behavior arises because one of the lone pairs of electrons on the oxygen atom participates in conjugation with the π-electron system of the ring. This delocalization increases the stability of the molecule and prevents the double bonds from reacting independently.
4. Furan is regarded as an aromatic compound because it satisfies **Hückel's rule of aromaticity**, which requires the presence of **(4n + 2) π-electrons**. In furan, four π-electrons are contributed by the two double bonds, and two π-electrons are donated by one lone pair of the oxygen atom, giving a total of six π-electrons. The aromatic character and enhanced stability of furan are further confirmed by the existence of several resonance structures. The actual structure of furan is a resonance hybrid of these contributing forms.



5. The involvement of the oxygen lone pair in conjugation also implies that furan must possess a **planar structure** to allow effective overlap of orbitals. This planarity is achieved because all the atoms in the furan ring are **sp^2 hybridized**.
6. In furan, the oxygen atom uses two of its sp^2 hybrid orbitals to form σ-bonds with the adjacent carbon atoms in the ring. The third sp^2 hybrid orbital contains one lone pair of electrons. The unhybridized p-orbital of oxygen holds the second lone pair of electrons,

which participates in the delocalized π-system. Each carbon atom is also sp^2 hybridized, forming σ-bonds with neighboring atoms and hydrogen atoms. The unhybridized p-orbitals of carbon and oxygen overlap to produce a continuous, delocalized π-electron cloud.

This delocalized electron cloud extends above and below the plane of the five-membered ring, providing aromatic stability to furan, as illustrated in below Figure.

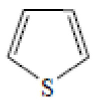


Delocalized electron cloud above and below the furan ring

Structure and Aromaticity of Thiophene

The structure and aromatic character of thiophene can be explained as follows.

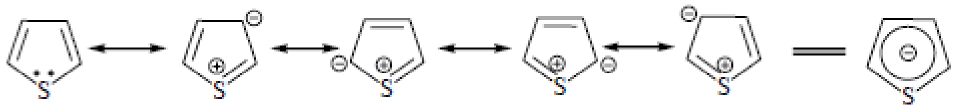
1. Thiophene has the molecular formula $\mathbf{C_4H_4S}$. This shows that the molecule is composed of four carbon atoms, four hydrogen atoms, and one sulphur atom.



Thiophene

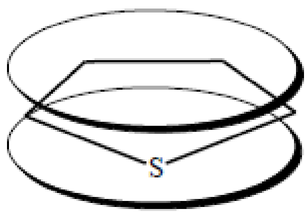
2. The structure of thiophene can be proposed by considering the usual valencies of the atoms involved. Carbon is tetravalent, while sulphur is divalent. Based on these valency requirements, thiophene is represented as a five-membered cyclic structure consisting of four carbon atoms and one sulphur atom, with alternating single and double bonds.
3. Similar to pyrrole and furan, thiophene does not undergo typical addition reactions like simple alkenes under normal conditions. This behavior is due to the participation of one of the lone pairs of electrons on the sulphur atom in conjugation with the π-electron system of the ring. The delocalization of this lone pair provides additional stability to the molecule and reduces the reactivity of the double bonds.

4. Thiophene is classified as an aromatic compound because it obeys **Hückel's rule of aromaticity**, which requires the presence of **(4n + 2) π-electrons**. In thiophene, four π-electrons come from the two double bonds, and two π-electrons are donated by one lone pair of the sulphur atom, giving a total of six π-electrons. The aromatic nature and enhanced stability of thiophene are further supported by the existence of several resonance structures. The actual structure of thiophene is therefore a resonance hybrid of all its contributing forms.



5. The involvement of the sulphur lone pair in conjugation also implies that the thiophene molecule must be **planar** to allow effective orbital overlap. This planarity is achieved because all the atoms in the thiophene ring are **sp² hybridized**.
6. In thiophene, the sulphur atom uses two of its sp² hybrid orbitals to form σ-bonds with the adjacent carbon atoms in the ring. The third sp² hybrid orbital contains one lone pair of electrons. The unhybridized p-orbital of sulphur contains the second lone pair of electrons, which participates in the delocalized π-system. Each carbon atom in the ring is also sp² hybridized and forms σ-bonds with neighboring carbon atoms and hydrogen atoms. The unhybridized p-orbitals of carbon and sulphur overlap to form a continuous delocalized π-electron cloud.

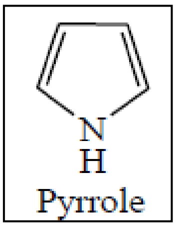
This delocalized electron cloud extends above and below the plane of the five-membered ring, providing aromatic stability to thiophene, as illustrated in below Figure.



Delocalized electron cloud above and below the thiophene ring

Pyrrole

Pyrrole is a five-membered heterocyclic aromatic compound containing one nitrogen atom as the heteroatom. It is an important structural unit in many biologically significant molecules such as haemoglobin, chlorophyll, bile pigments, and vitamin B_{12}. Pyrrole is a colorless liquid with a boiling point of about 131 °C and possesses a characteristic odor. Compared to other five-membered heterocycles like furan and thiophene, pyrrole has a higher boiling point due to intermolecular hydrogen bonding arising from the presence of the N–H group. Structurally, pyrrole is planar and aromatic, and all the atoms in the ring are sp^2-hybridized.

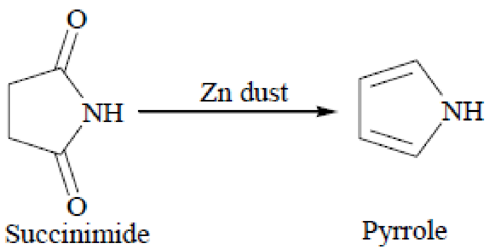


The aromatic nature of pyrrole arises from the delocalization of six π-electrons over the ring. The lone pair of electrons on the nitrogen atom participates in the conjugated π-electron system, thereby completing the aromatic sextet and stabilizing the molecule. This participation of the lone pair significantly affects the chemical behavior of pyrrole, particularly its basic and acidic properties.

Preparation of Pyrrole

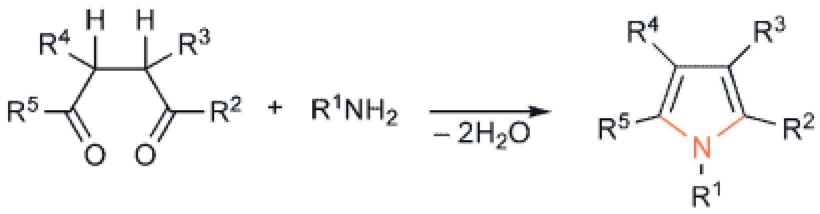
Preparation from Succinimide

Pyrrole can be prepared by heating succinimide with zinc dust. In this method, zinc acts as a reducing agent and removes the oxygen atoms from the carbonyl groups of succinimide. As a result, deoxygenation occurs, followed by rearrangement to form the pyrrole ring. This reaction demonstrates the conversion of a cyclic imide into an aromatic nitrogen-containing heterocycle.

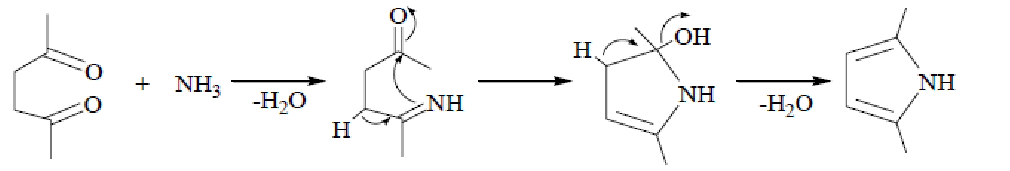


Paal–Knorr Synthesis of Pyrrole

The Paal–Knorr synthesis is one of the most important and commonly used methods for the preparation of pyrrole and its derivatives. In this method, a 1,4-dicarbonyl compound is heated with ammonia or a primary amine under acidic conditions.



Initially, ammonia attacks one of the carbonyl groups of the 1,4-diketone to form an imine intermediate. This is followed by nucleophilic attack on the second carbonyl group, leading to cyclization. Subsequent elimination of two molecules of water results in aromatization of the ring and formation of pyrrole. This method is particularly valuable because substituted pyrroles can be synthesized by choosing suitable 1,4-dicarbonyl compounds.



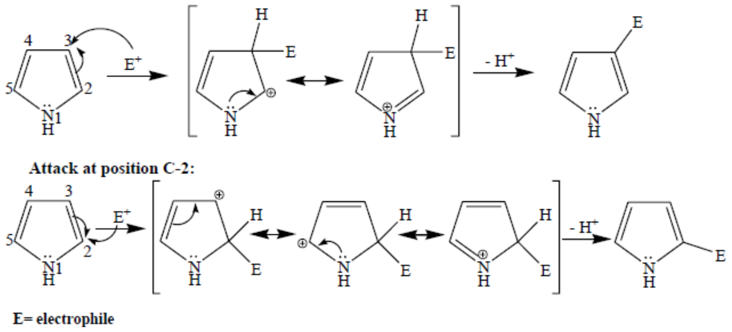
Hexane-2,5-dione

2,5-dimethylpyrrole

Properties of Pyrrole

Physical Properties of Pyrrole

Pyrrole is a colorless liquid with a boiling point of approximately 131 °C. It is highly sensitive to atmospheric oxygen and moisture. When exposed to air, pyrrole gradually darkens in color, turning brown, and eventually undergoes polymerization to form resinous products. In terms of solubility, pyrrole is only slightly soluble in water but is completely miscible with organic solvents such as ether and ethanol. The presence of an N–H group allows pyrrole to engage in intermolecular hydrogen bonding, which contributes to its relatively high boiling point compared to other five-membered heterocyclic compounds.



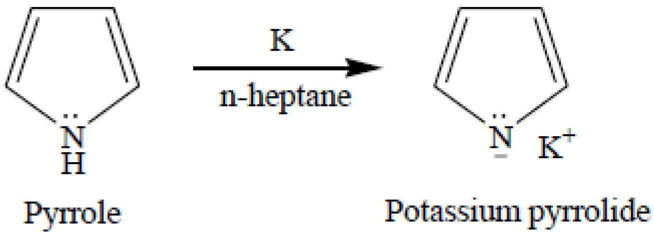
Chemical Properties of Pyrrole

Pyrrole is an aromatic heterocyclic compound and is considerably more reactive than benzene toward electrophilic substitution reactions. Its enhanced reactivity arises from the contribution of the nitrogen lone pair to the aromatic π-electron system, which increases the overall electron density of the ring. Due to its aromatic nature, pyrrole undergoes characteristic electrophilic substitution reactions such as halogenation, nitration, sulphonation, Friedel–Crafts acylation, and related reactions.

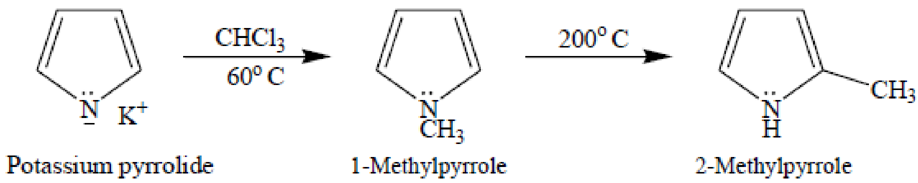
Electrophilic substitution in pyrrole occurs predominantly at the C-2 (α) position. When an electrophile attacks the C-2 position, the resulting σ-complex is stabilized by three resonance structures. In contrast, electrophilic attack at the C-3 (β) position generates an intermediate stabilized by only two resonance forms. Because the C-2 substituted intermediate is more resonance-stabilized, substitution preferentially takes place at this position. Consequently, nearly all electrophilic substitution reactions of pyrrole follow a similar mechanism and yield C-2 substituted products.

Acidic Character of Pyrrole

In pyrrole, the lone pair of electrons on the nitrogen atom participates in the aromatic sextet, which makes it unavailable for protonation. As a result, pyrrole does not exhibit basic behavior typical of amines. However, pyrrole shows weak acidic character due to the presence of an N–H proton.



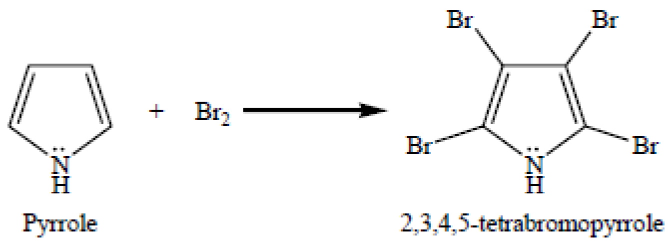
When pyrrole is heated with potassium metal in n-heptane, the N–H proton is removed to form potassium pyrrolide. This reaction does not disturb the aromaticity of the ring, making deprotonation possible. Potassium pyrrolide is a stable compound and reacts with alkyl halides at around 60 °C to form N-alkyl pyrroles. These N-alkyl derivatives can undergo rearrangement under suitable conditions to give C-alkyl pyrroles.



Electrophilic Substitution Reactions of Pyrrole

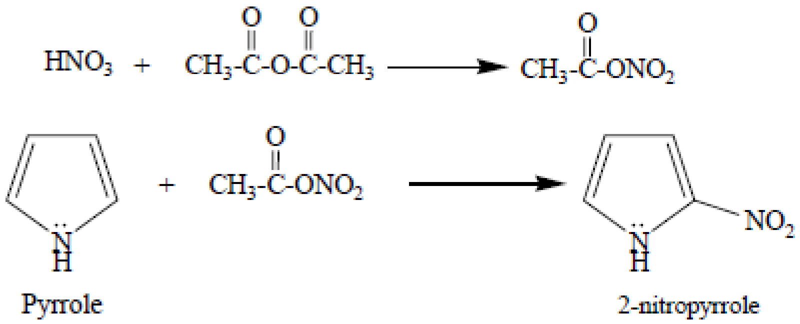
Halogenation

Pyrrole reacts readily with halogens such as chlorine, bromine, and iodine. Due to its high reactivity, halogenation often leads to multiple substitution. For example, reaction of pyrrole with bromine results in the formation of tetrabromopyrrole.



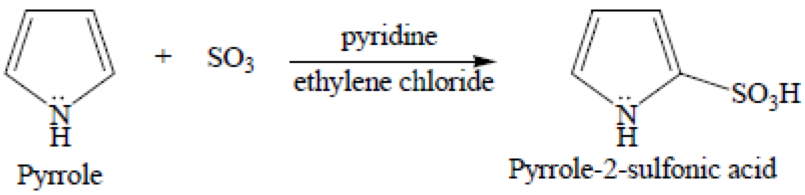
Nitration

Nitration of pyrrole is carried out under mild conditions using nitric acid in acetic anhydride. This combination generates acetyl nitrate in situ, which serves as the nitrating agent. The nitronium ion ($-NO_2^+$) acts as the electrophile and substitutes at the C-2 position of the pyrrole ring.



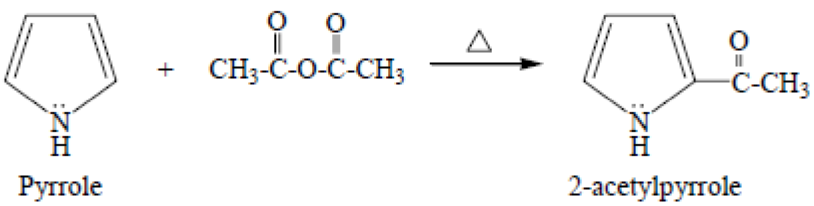
Sulphonation

Sulphonation of pyrrole is achieved by treating it with a sulfur trioxide–pyridine complex in an inert solvent such as ethylene chloride. The reaction proceeds via electrophilic substitution at the C-2 position to form pyrrole-2-sulfonic acid.



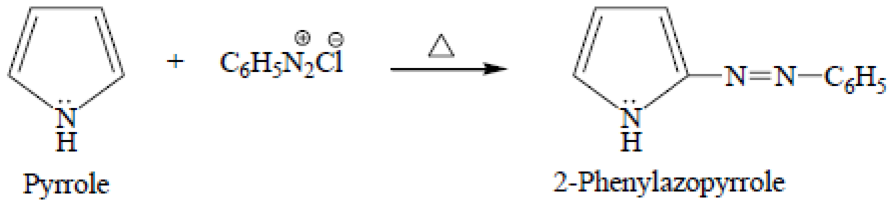
Friedel–Crafts Acylation

Pyrrole undergoes Friedel–Crafts acylation with acetic anhydride upon heating. This reaction leads to substitution at the C-2 position, producing 2-acetylpyrrole as the major product.



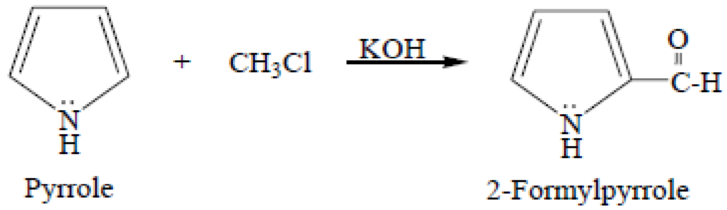
Diazotization Reaction

Pyrrole reacts with benzenediazonium chloride in acidic medium to form 2-phenylazopyrrole. This reaction involves electrophilic substitution by the diazonium ion at the C-2 position of the pyrrole ring.



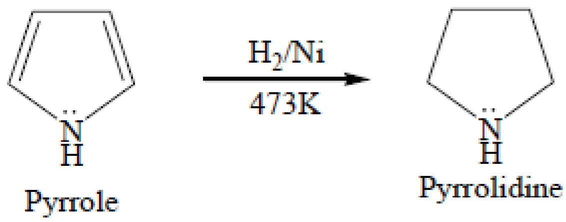
Reimer–Tiemann Reaction

In the presence of chloroform and potassium hydroxide, pyrrole undergoes the Reimer–Tiemann reaction to produce 2-formylpyrrole. This reaction proceeds through an electrophilic substitution mechanism involving the dichlorocarbene intermediate.



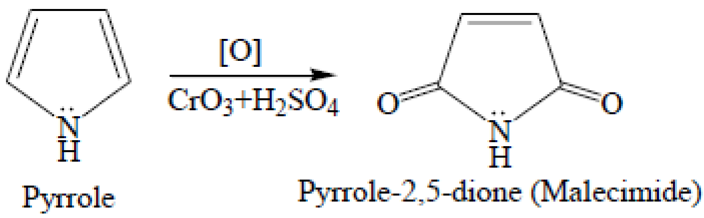
Reduction of Pyrrole

Pyrrole can be reduced to pyrrolidine (tetrahydropyrrole) by catalytic hydrogenation using hydrogen gas in the presence of Raney nickel at high temperature (around 473 K). During this process, the aromaticity of the ring is destroyed, resulting in a fully saturated heterocycle.



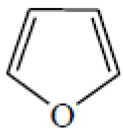
Oxidation of Pyrrole

When pyrrole is oxidized with chromium trioxide in sulfuric acid, it is converted into maleimide. This oxidation involves cleavage and rearrangement of the pyrrole ring under strongly oxidative conditions.



FURAN

Furan is a five-membered heterocyclic aromatic compound containing one oxygen atom as the heteroatom. It is an important member of the heterocyclic family and serves as a key intermediate in organic synthesis and industrial chemistry. Furan is a colorless, volatile liquid with a characteristic ether-like odor.



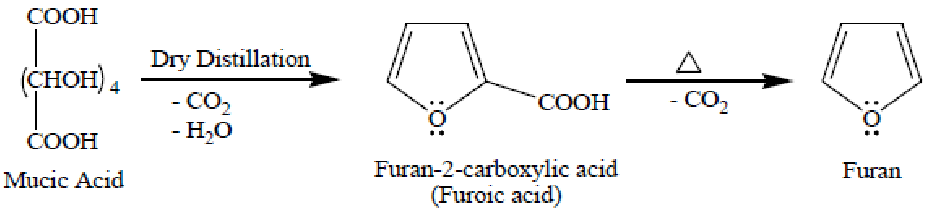
Furan

Structurally, furan is planar and aromatic, with six π-electrons delocalized over the ring. One lone pair of electrons on the oxygen atom participates in the aromatic π-electron system, while the second lone pair remains non-bonding. Due to this electron donation, furan exhibits aromatic behavior but is less aromatic and more reactive than benzene.

Preparation of Furan

Preparation from Mucic Acid

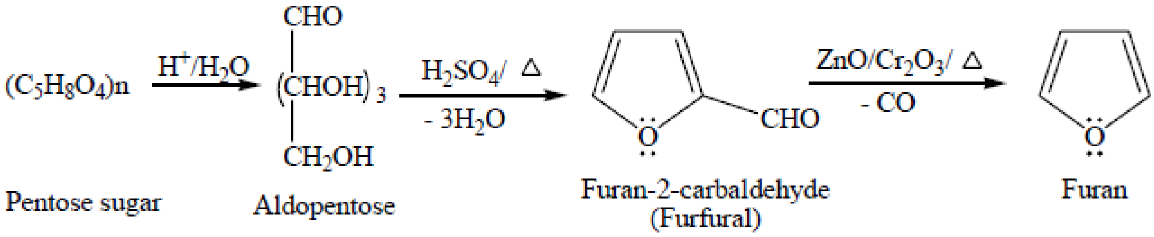
Furan can be prepared by the thermal decomposition of mucic acid. When mucic acid is heated in the presence of concentrated sulfuric acid, it undergoes dehydration followed by decarboxylation to form furan.



In this reaction, mucic acid first loses water molecules to form intermediate compounds, which subsequently eliminate carbon dioxide. The final product formed is furan. This method highlights the conversion of carbohydrate-derived acids into heterocyclic aromatic compounds.

Preparation from Pentosan

Furan is also prepared from pentosan, a polysaccharide obtained from agricultural waste such as rice husk, corn cobs, or wood. When pentosan is heated with dilute mineral acids, it undergoes hydrolysis to produce pentoses such as xylose or arabinose. These sugars further undergo dehydration to form furfural. On decarbonylation of furfural, furan is obtained.



This method is of industrial importance as it utilizes renewable biomass resources for the synthesis of furan.

Reactions of Furan

Hydrogenation

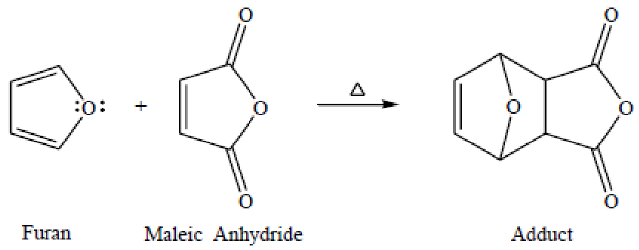
Furan undergoes catalytic hydrogenation when treated with hydrogen gas in the presence of catalysts such as nickel or palladium. Under controlled conditions, hydrogenation leads to the formation of tetrahydrofuran (THF), a saturated five-membered heterocyclic compound. During this reaction, the aromatic nature of furan is destroyed, and the π-electron system is fully reduced. Tetrahydrofuran is an important industrial solvent widely used in polymer and pharmaceutical industries.

Reaction with Oxygen

Furan reacts readily with oxygen due to its high electron density and relatively weak aromatic stabilization. When exposed to air, especially in the presence of light, furan undergoes slow oxidation to form peroxides. Under controlled oxidation conditions, furan can react with oxygen to yield maleic anhydride. This reaction demonstrates the susceptibility of the furan ring toward oxidative cleavage.

Diels–Alder Reaction

Furan readily participates in Diels–Alder reactions because of its conjugated diene system. It acts as a diene and reacts with electron-deficient dienophiles such as maleic anhydride. The reaction occurs smoothly at room temperature or under mild heating to form a bicyclic adduct. This cycloaddition reaction is reversible in nature and illustrates the dienic character of furan despite its aromaticity.



Formation of Thiophene and Pyrrole

Formation of Thiophene

When furan is heated with phosphorus pentasulfide (P_2S_5), the oxygen atom in the ring is replaced by sulfur, resulting in the formation of thiophene. This reaction is an example of heteroatom replacement within a heterocyclic ring.

Formation of Pyrrole

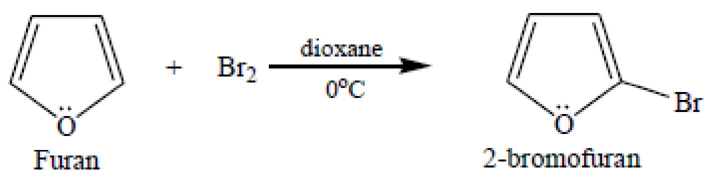
Furan can be converted into pyrrole by heating it with ammonia in the presence of alumina at high temperature. In this process, the oxygen atom of furan is replaced by a nitrogen atom, leading to the formation of pyrrole. This reaction further emphasizes the interconversion of five-membered heterocycles.

Electrophilic Substitution Reactions of Furan

Furan undergoes electrophilic substitution reactions due to the availability of π-electrons donated by the oxygen atom. However, because furan is less aromatic than benzene, these reactions occur under much milder conditions. Harsh reagents often cause ring cleavage instead of substitution. Electrophilic substitution in furan occurs predominantly at the C-2 (α) position. When an electrophile attacks the C-2 position, the resulting intermediate carbocation is stabilized by two resonance structures. In contrast, electrophilic attack at the C-3 position results in an intermediate with only one stabilizing resonance form. As a result, substitution at the C-2 position is energetically favored. Typical electrophilic substitution reactions of furan include halogenation, nitration, and sulphonation, all of which are carried out under carefully controlled, mild conditions to avoid destruction of the ring.

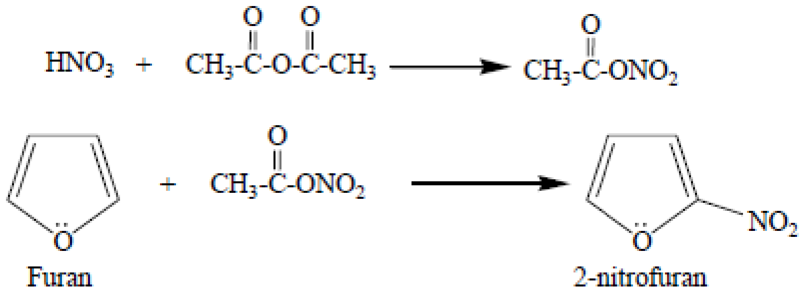
Halogenation

Furan undergoes halogenation with halogens such as chlorine, bromine, and iodine under mild conditions. The substitution takes place predominantly at the C-2 position of the furan ring. For instance, when furan reacts with bromine, 2-bromofuran is formed as the major product



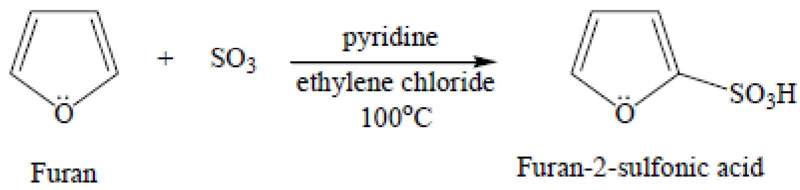
Nitration

Nitration of furan is carried out using nitric acid in the presence of acetic anhydride. In this reaction, nitric acid reacts with acetic anhydride to generate acetyl nitrate, which serves as the effective nitrating agent. The nitro group introduced acts as an electrophile and substitutes at the C-2 position of the furan ring.



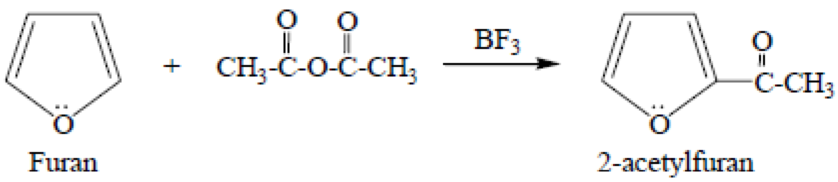
Sulphonation

Sulphonation of furan is achieved by treating it with a sulfur trioxide–pyridine complex in ethylene chloride at about 100 °C. The reaction proceeds through electrophilic substitution, leading to the formation of sulfonated furan derivatives, mainly substituted at the C-2 position.



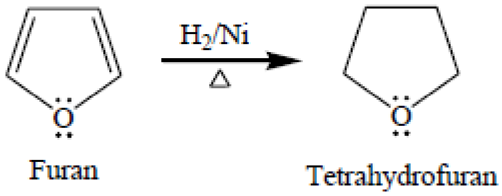
Friedel–Crafts Acylation

Furan undergoes Friedel–Crafts acylation when reacted with acetic anhydride in the presence of a Lewis acid catalyst such as boron trifluoride (BF_3). This reaction results in the formation of 2-acetylfuran as the principal product due to substitution at the α-position.



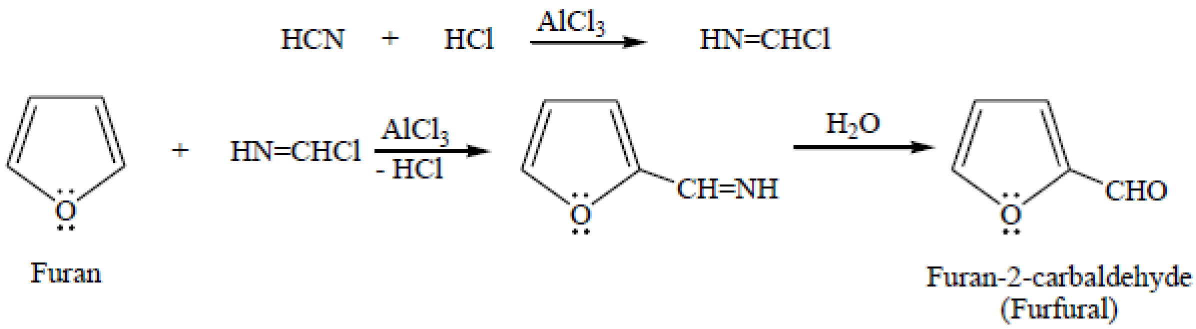
Reduction

On catalytic hydrogenation, furan is reduced to tetrahydrofuran (THF). This reaction is carried out using hydrogen gas in the presence of suitable catalysts such as nickel or palladium. Tetrahydrofuran is an important solvent and is widely used as an alternative to ether, particularly in Grignard reactions.



Gattermann–Koch Synthesis

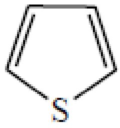
When furan is treated with a mixture of hydrogen cyanide and hydrogen chloride in the presence of a Lewis acid catalyst such as aluminum chloride, formylation of the furan ring occurs. The reaction yields furfural as the final product, with the formyl group introduced at the C-2 position.



Furan is an aromatic five-membered heterocyclic compound with distinctive chemical properties arising from the participation of the oxygen lone pair in aromaticity. It can be prepared from mucic acid and pentosan through dehydration and decarboxylation processes. Furan undergoes hydrogenation, oxidation, Diels–Alder reactions, and interconversion reactions leading to thiophene and pyrrole. Its electrophilic substitution reactions occur mainly at the C-2 position under mild conditions. Due to its reactivity and versatility, furan is an important compound in both laboratory and industrial chemistry.

THIOPHENE

Thiophene is a five-membered heterocyclic aromatic compound containing one sulfur atom as the heteroatom. It is a colorless liquid with a characteristic benzene-like odor and exhibits remarkable chemical stability compared to other five-membered heterocycles such as pyrrole and furan.



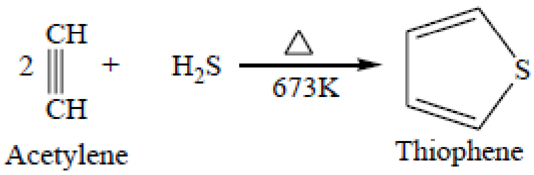
Thiophene

Thiophene is aromatic in nature and contains six π-electrons, which satisfy Hückel's rule of aromaticity. One pair of electrons from the sulfur atom participates in the delocalized π-electron system, contributing to the aromatic stabilization of the ring. Due to this stabilization, thiophene closely resembles benzene in its chemical behavior and undergoes substitution reactions rather than addition reactions.

Synthesis of Thiophene

Synthesis from Acetylene

Thiophene can be synthesized by passing a mixture of acetylene and sulfur vapors through a heated tube at high temperature. Under these conditions, acetylene reacts with sulfur to form thiophene.

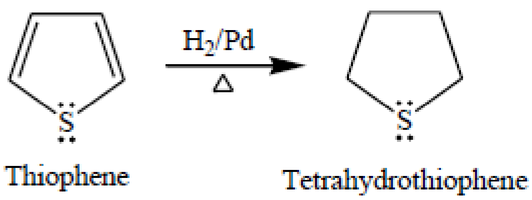


In this reaction, acetylene molecules undergo cyclization in the presence of sulfur, resulting in the formation of the five-membered thiophene ring. This method demonstrates the construction of a heterocyclic ring system from simple unsaturated hydrocarbons.

Reactions of Thiophene

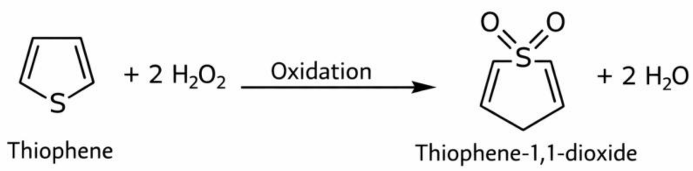
Reduction

Thiophene undergoes reduction under catalytic hydrogenation conditions. When treated with hydrogen gas in the presence of catalysts such as nickel at elevated temperature and pressure, thiophene is reduced to tetrahydrothiophene. During this process, the aromatic character of the ring is destroyed, and the π-electron system becomes fully saturated. However, thiophene is more resistant to reduction than pyrrole and furan due to its greater aromatic stability.



Oxidation

Thiophene can be oxidized under strong oxidative conditions. When treated with oxidizing agents such as hydrogen peroxide or potassium permanganate, thiophene undergoes oxidation at the sulfur atom to form thiophene-1,1-dioxide (thiophene sulfone). In more vigorous oxidation, ring cleavage may occur, leading to open-chain products. The oxidation reactions highlight the susceptibility of the sulfur atom toward oxidation.

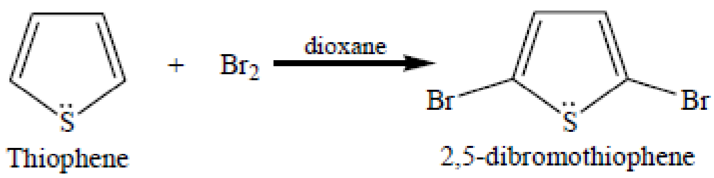


Electrophilic Substitution Reactions of Thiophene

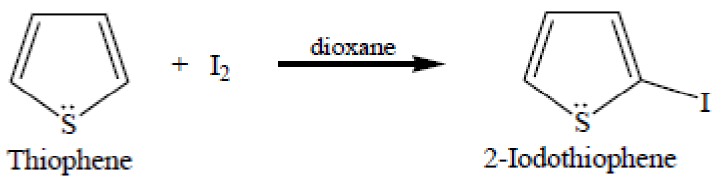
Thiophene readily undergoes electrophilic substitution reactions due to the presence of a delocalized π-electron system. These reactions occur preferentially at the C-2 (α) position of the thiophene ring because the intermediate formed during electrophilic attack at this position is more resonance-stabilized than that formed by attack at the C-3 position.

Halogenation

Thiophene reacts with halogens such as chlorine, bromine, and iodine under suitable conditions. In the absence of a halogen carrier, bromination of thiophene results in substitution at the α-positions, leading to the formation of 2,5-dibromothiophene.

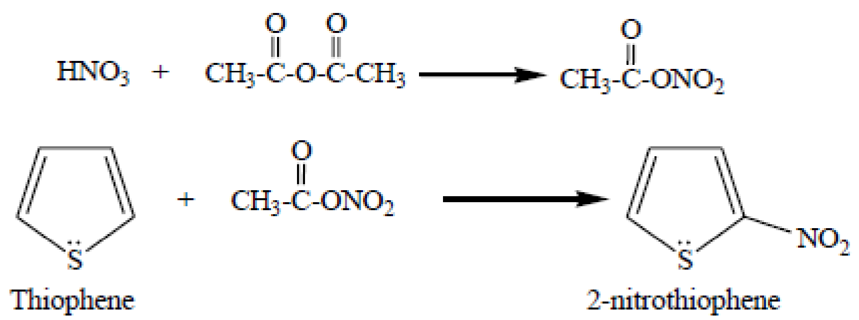


Iodination of thiophene, however, requires an oxidizing agent. When thiophene is treated with iodine in the presence of yellow mercuric oxide, substitution occurs at the C-2 position to yield 2-iodothiophene.



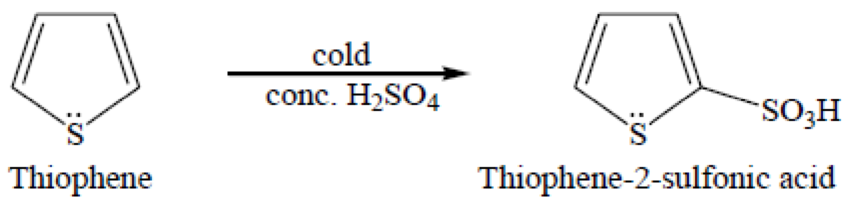
Nitration

Nitration of thiophene is carried out using fuming nitric acid in the presence of acetic anhydride. In this reaction, nitric acid and acetic anhydride generate acetyl nitrate, which serves as the active nitrating species. The nitro group acts as the electrophile and substitutes at the C-2 position, forming 2-nitrothiophene as the major product.



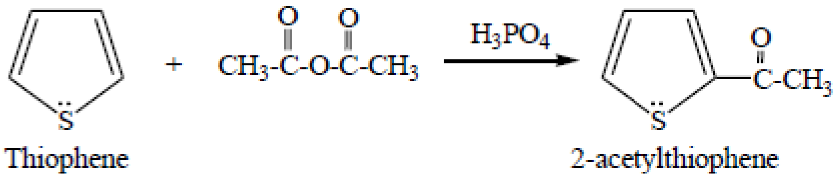
Sulphonation

Sulphonation of thiophene is achieved by treating it with cold concentrated sulfuric acid. Under these conditions, electrophilic substitution occurs at the α-position, resulting in the formation of thiophene-2-sulphonic acid.



Friedel–Crafts Acylation

Thiophene undergoes Friedel–Crafts acylation when reacted with acetic anhydride in the presence of phosphoric acid. This reaction introduces an acetyl group at the C-2 position of the ring, producing 2-acetylthiophene as the main product.



UNIT-V

SIX-MEMBERED HETERO CYCLIC COMPOUNDS

Introduction

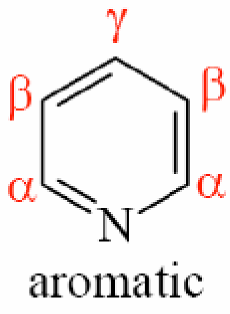
Six-membered heterocyclic compounds constitute an important class of organic molecules in which one or more atoms of a six-membered ring are heteroatoms such as nitrogen, oxygen, or sulfur, instead of carbon. These compounds may be aromatic or non-aromatic and play a central role in heterocyclic chemistry due to their structural diversity and wide range of chemical reactivity. Among them, nitrogen-containing heterocycles are particularly significant, as they form the core of many naturally occurring substances and synthetic materials.

A prominent example of six-membered aromatic heterocycles is pyridine, where a nitrogen atom replaces one carbon atom in the benzene ring. Such substitution markedly alters the electronic distribution within the ring, influencing properties such as basicity, reactivity, and substitution patterns. Other important six-membered heterocycles include diazines (pyrimidine, pyridazine, and pyrazine), many of which are essential components of biologically active molecules such as nucleic acids, vitamins, and pharmaceuticals.

Six-membered heterocyclic compounds are widely encountered in natural products, agrochemicals, dyes, and medicinal agents. Their chemistry is governed by the nature and position of the heteroatom(s), which affects aromaticity, stability, and reaction mechanisms. Because of their importance in both fundamental organic chemistry and applied fields such as medicinal and industrial chemistry.

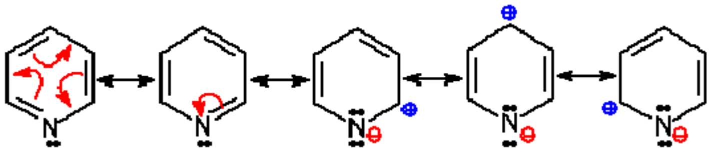
Pyridine

Pyridine is a six-membered aromatic heterocyclic compound containing one nitrogen atom in the ring and has the molecular formula C_5H_5N. Structurally, it can be considered as benzene in which one CH group is replaced by a sp^2-hybridized nitrogen atom. Pyridine occurs naturally in coal tar and bone oil and is an important parent compound of many nitrogen-containing heterocycles.



Structure for Pyridine

Pyridine is aromatic because it possesses six π-electrons circulating in a planar, cyclic conjugated system and follows Hückel's (4n+2) rule. The nitrogen atom contributes one electron to the aromatic sextet through its p-orbital. The lone pair of electrons on nitrogen occupies an sp^2 orbital that lies in the plane of the ring and is orthogonal to the π-system. Hence, this lone pair does not participate in aromaticity but remains available for protonation, which accounts for the basic nature of pyridine.

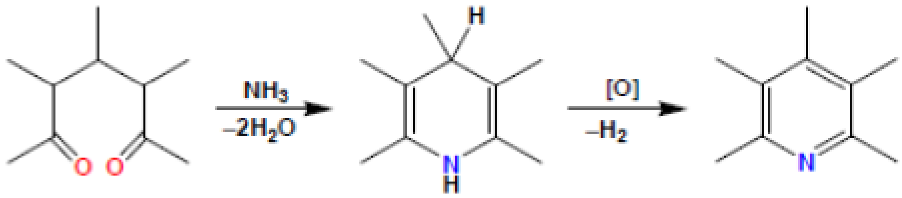


Due to the higher electronegativity of nitrogen compared to carbon, electron density is withdrawn from the ring. As a result, carbon atoms at the 2-, 4-, and 6-positions acquire partial positive charge, while the nitrogen atom carries partial negative charge. The 3- and 5-positions remain comparatively neutral, which strongly influences the orientation of substitution reactions.

2. Synthesis of Pyridine

(i) Synthesis from 1,5-Dicarbonyl Compounds

Pyridine can be synthesized by cyclization of 1,5-dicarbonyl compounds in the presence of ammonia or ammonium acetate. The reaction proceeds through condensation, cyclization, and subsequent aromatization to yield substituted pyridines.

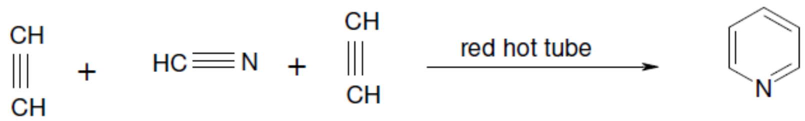


Mechanism:

1. Formation of imine intermediates by reaction of carbonyl groups with ammonia.
2. Intramolecular cyclization to form a dihydropyridine framework.
3. Oxidation leading to the aromatic pyridine ring.

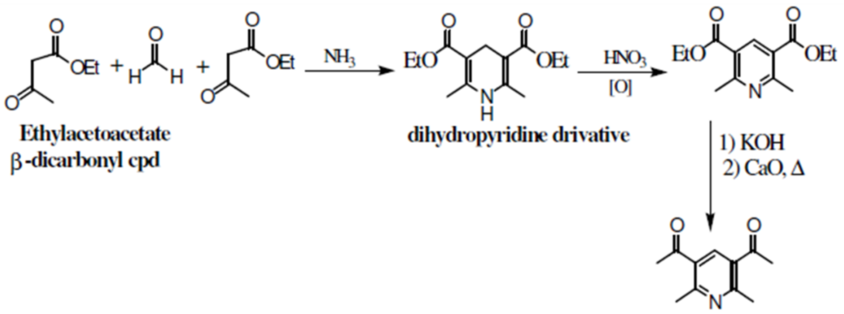
(ii) Bönnemann Cyclization

In the Bönnemann method, pyridine is synthesized using transition-metal-catalyzed cyclization reactions involving nitriles and alkynes. This method is particularly useful for the preparation of highly substituted pyridine derivatives.



(iii) Hantzsch Pyridine Synthesis

The Hantzsch synthesis involves the condensation of two equivalents of a β-dicarbonyl compound (such as ethyl acetoacetate), one equivalent of an aldehyde, and ammonia.



Reaction sequence:

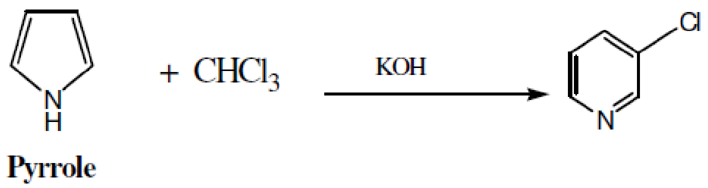
1. Initial formation of a dihydropyridine intermediate.

2. Oxidation of the dihydropyridine (using nitric acid or air oxidation) to yield the corresponding pyridine derivative.

This method is widely used for the synthesis of substituted pyridines.

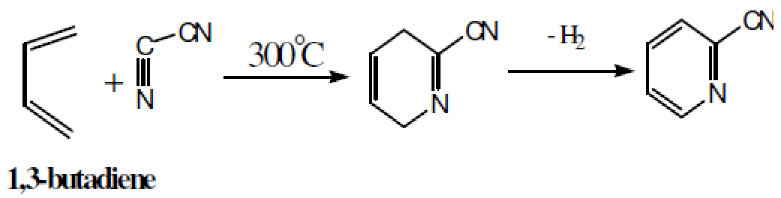
(iv) Synthesis from Pyrrole

Pyridine can be obtained from pyrrole by reaction with chloroform and potassium hydroxide, followed by rearrangement and oxidation steps.



(v) Diels–Alder Approach

Reaction of 1,3-butadiene with activated nitriles at elevated temperature (~300 °C) followed by dehydrogenation affords pyridine derivatives. This route demonstrates the utility of cycloaddition strategies in heterocyclic synthesis.



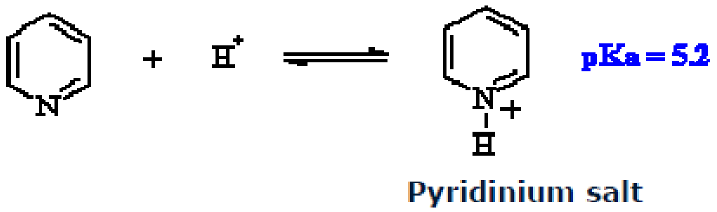
3. Physical Properties

Pyridine is a colorless liquid with a characteristic unpleasant odor. It is completely miscible with water and most organic solvents. Pyridine has a boiling point of approximately 115 °C. The molecule is planar and aromatic, contributing to its thermal stability and distinctive reactivity.

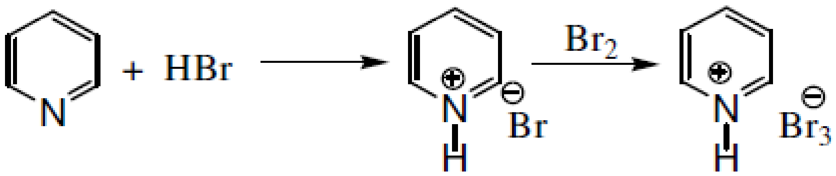
4. Chemical Reactions of Pyridine

(i) Basic Character

Pyridine behaves as a weak base because the lone pair on nitrogen is available for protonation. It readily reacts with hydrogen to form pyridinium salts.

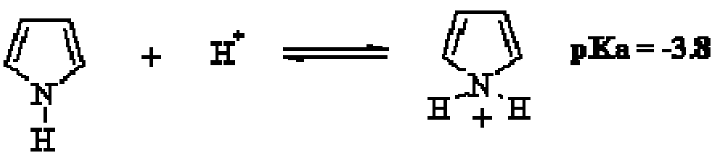


Pyridinium salts undergoes in several reactions characteristic of amines, including interactions with Brønsted acids such as chromic acid and hydrobromic acid.



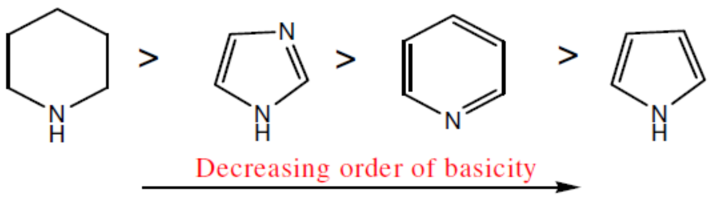
Examples:

When compared with pyrrole, pyridine exhibits much higher basicity because the nitrogen lone pair in pyridine does not take part in maintaining aromaticity and is therefore readily available for protonation. In contrast, the lone pair on the nitrogen atom in pyrrole is involved in the aromatic π-electron system; protonation at nitrogen disrupts this aromaticity, making such protonation energetically unfavorable



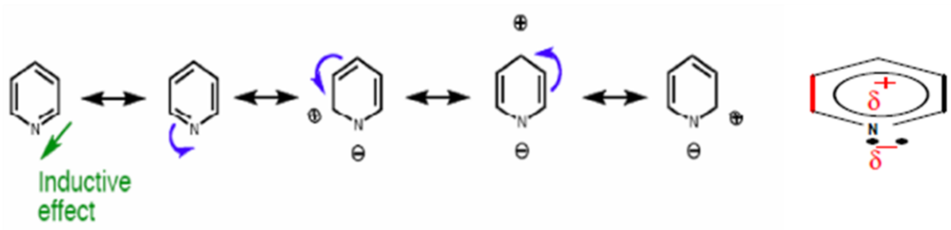
- **Pyridine vs imidazole**: In comparison with imidazole, pyridine shows lower basicity because, upon protonation, the positive charge in imidazole can be delocalized over two nitrogen atoms. In pyridine, however, the positive charge is distributed over the ring, which disturbs the aromatic stabilization and reduces its basic strength.

- **Pyridine vs aliphatic amines**: Pyridine is less basic than comparable aliphatic amines because the nitrogen atom in pyridine is sp^2-hybridized and therefore more electronegative. As a result, its lone pair resides in an sp^2 orbital and is held more tightly by the nucleus. In contrast, aliphatic amines contain an sp^3-hybridized nitrogen with a lone pair in an sp^3 orbital, which is less tightly bound and hence more readily available for protonation.

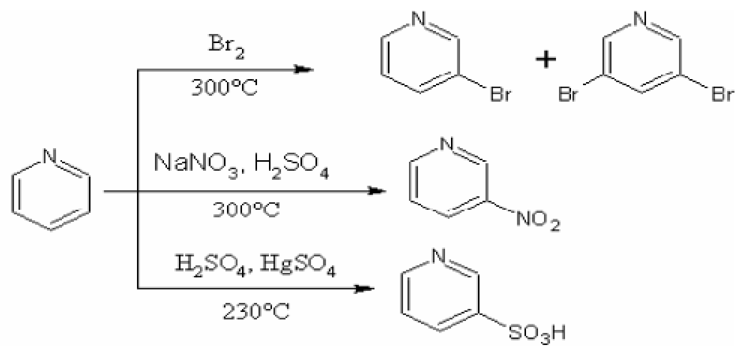


(ii) Electrophilic Substitution Reactions

Pyridine is highly deactivated toward electrophilic substitution because the electronegative nitrogen atom withdraws electron density from the ring. Consequently, pyridine behaves like a strongly deactivated benzene derivative.



- Electrophilic substitution occurs, if at all, at the 3-position.
- Reactions require harsh conditions and generally give low yields.
- Pyridine does not undergo Friedel–Crafts alkylation or acylation.



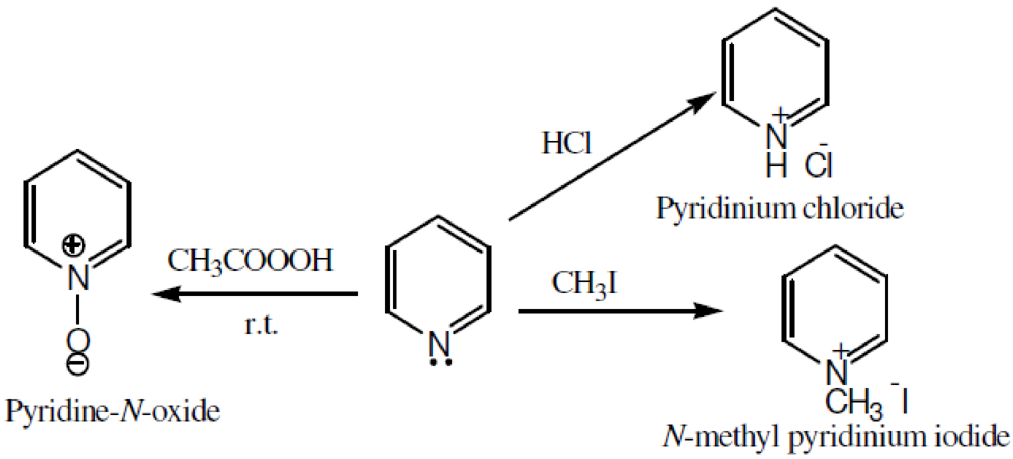
Attack at the 2- or 4-positions would generate highly unstable σ-complexes with positive charge adjacent to nitrogen, whereas substitution at the 3-position avoids this destabilization.

(iii) Pyridine as a Nucleophile (Reactions at Nitrogen)

As a tertiary amine, pyridine can act as a nucleophile and reacts readily with electrophiles.

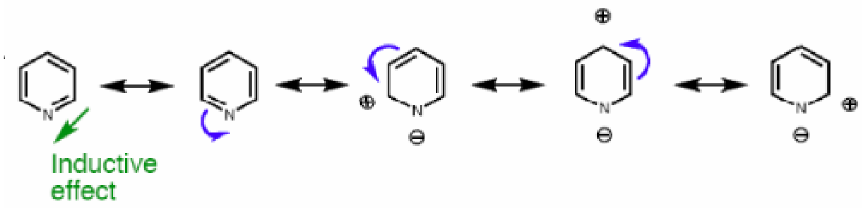
Examples:

- Reaction with acids to form pyridinium salts.
- Alkylation with methyl iodide to form N-alkylpyridinium salts.
- Oxidation with peracids produces pyridine-N-oxide.

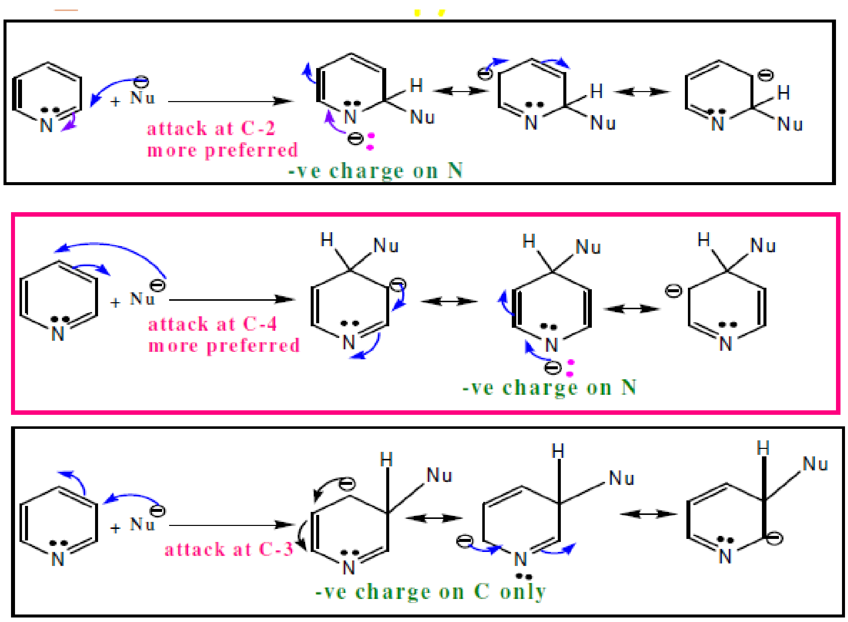


(iv) Nucleophilic Substitution on the Ring Carbon

Pyridine reacts with nucleophiles more easily than benzene because the ring nitrogen strongly withdraws electron density, making the ring electron-deficient, similar to benzene containing a powerful electron-withdrawing substituent. Resonance considerations show that the carbon atoms at the 2-, 4-, and 6-positions carry partial positive charge. As a result, nucleophilic substitution occurs most readily at the 2-position, then at the 4-position, and is least favored at the 3-position.



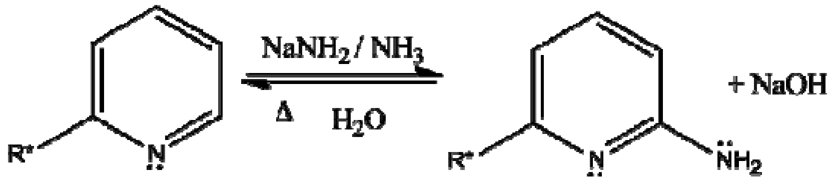
Moreover, nucleophilic attack at the 2-, 4-, or 6-positions leads to intermediates in which the negative charge can be delocalized onto the nitrogen atom, providing additional stabilization. In contrast, attack at the 3- or 5-position produces intermediates where the negative charge remains localized on carbon atoms only, making such pathways less favorable



This preference arises because attack at the 2- or 4-positions produces resonance intermediates in which the negative charge can be delocalized onto the nitrogen atom.

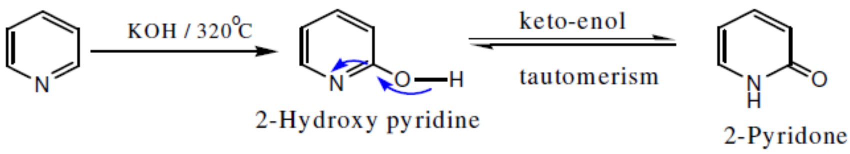
Important reactions:

- **Chichibabin reaction:** Treatment of pyridine with sodamide introduces an amino group at the 2-position, forming 2-aminopyridine.



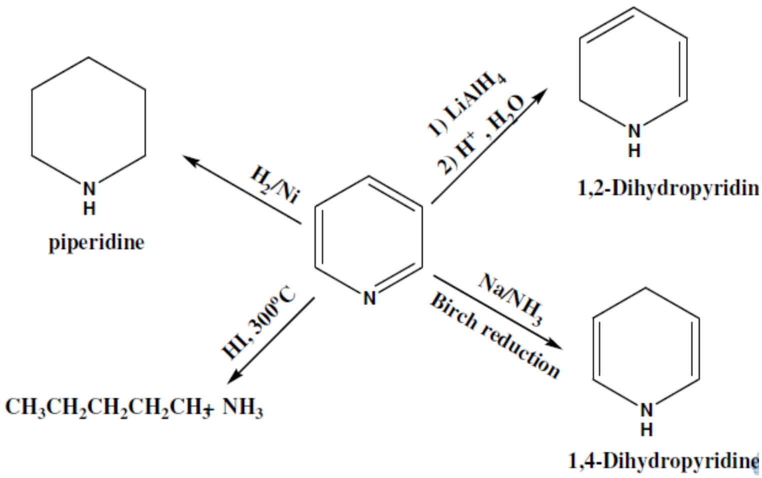
- **Reaction with organolithium reagents:** n-Butyllithium reacts with pyridine to give 2-butylpyridine.

- **Reaction with KOH at high temperature:** Produces 2-hydroxypyridine, which exists in equilibrium with its keto form (2-pyridone).



(v) Reduction Reactions

- Partial reduction using lithium aluminium hydride or catalytic hydrogenation yields dihydropyridines.
- Birch reduction (Na/NH_3) produces 1,4-dihydropyridine.
- Complete catalytic hydrogenation gives piperidine.



(vi) Oxidation Reactions

Pyridine undergoes oxidation primarily at the nitrogen atom rather than the ring.

- Oxidation with peracids or hydrogen peroxide yields pyridine-N-oxide.

Properties of pyridine-N-oxide:

- Exhibits increased reactivity toward both electrophilic and nucleophilic substitution at the 2- and 4-positions.
- Serves as an important intermediate for functionalization of the pyridine ring.

For example, nitration of pyridine is difficult and occurs at the 3-position in low yield. However, nitration of pyridine-N-oxide occurs preferentially at the 4-position, and subsequent reduction removes the oxygen atom to regenerate substituted pyridine.

5. Uses of Pyridine

Pyridine is widely used as:

- A solvent for polar reactions
- A base and acid scavenger in organic synthesis
- A starting material for pharmaceuticals, agrochemicals, dyes, and vitamins

6. Condensed Ring Systems

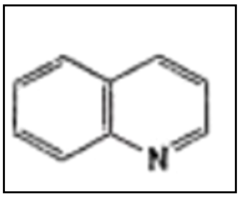
Pyridine serves as a fundamental building block for condensed heterocyclic systems such as quinoline and isoquinoline, in which a benzene ring is fused to the pyridine nucleus. These systems exhibit modified chemical reactivity due to extended conjugation and are of great importance in medicinal chemistry.

7. Summary

Pyridine is a six-membered aromatic nitrogen heterocycle characterized by weak basicity, resistance toward electrophilic substitution, and enhanced nucleophilic substitution at specific positions. Its versatile chemistry, ease of functionalization through N-oxide intermediates, and role as a precursor to condensed heterocycles make pyridine a cornerstone of heterocyclic chemistry.

Quinoline

Quinoline is a fused bicyclic nitrogen heterocycle formed by the condensation of a benzene ring with a pyridine ring across the 2,3-positions. It was originally isolated from coal tar and can also be obtained by the alkaline distillation of quinine. The quinoline framework is widely distributed in natural alkaloids such as quinine and in several important pharmaceutical agents, including antimalarial drugs (e.g., chloroquine) and analgesics. Owing to its aromatic, planar structure and the presence of a ring nitrogen atom, quinoline exhibits chemical behavior characteristic of both benzene and pyridine.

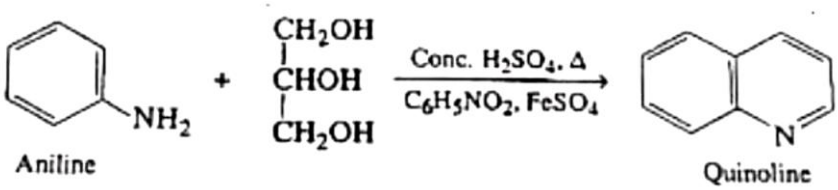


Structure for Quinoline

2. Methods of Formation of Quinoline and Its Derivatives

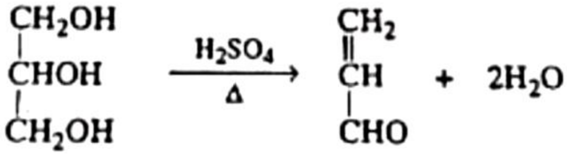
(i) Skraup Synthesis

The Skraup synthesis is the most important and industrially useful method for preparing quinoline and substituted quinolines. In this method, a primary aromatic amine possessing at least one free ortho position is heated with an α,β-unsaturated carbonyl compound or its precursor (commonly glycerol) in the presence of concentrated sulfuric acid. Nitrobenzene is added as a mild oxidizing agent, while ferrous sulfate is often included to moderate the reaction and prevent excessive oxidation.

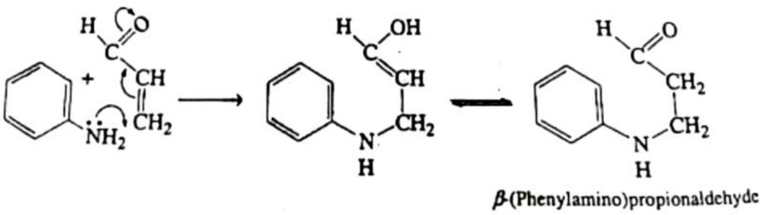


Mechanism:

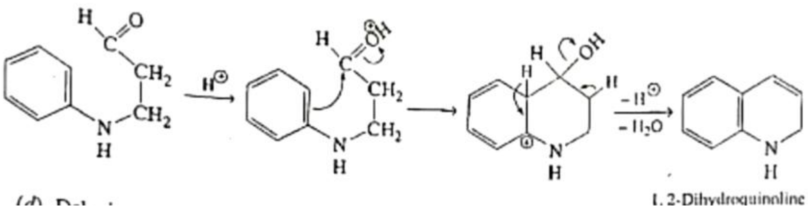
1. **Formation of acrolein:** Under strongly acidic conditions, glycerol undergoes dehydration to generate acrolein (CH_2=CH–CHO).



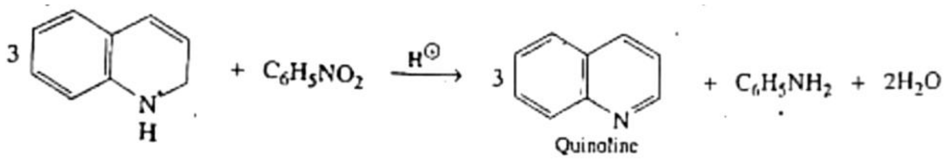
2. **Michael addition:** Aniline adds to the β-carbon of acrolein via Michael addition, producing β-(phenylamino)propionaldehyde.



3. **Cyclization:** Intramolecular cyclization occurs through electrophilic attack of the aromatic ring at the aldehydic carbon, forming a dihydroquinoline intermediate.



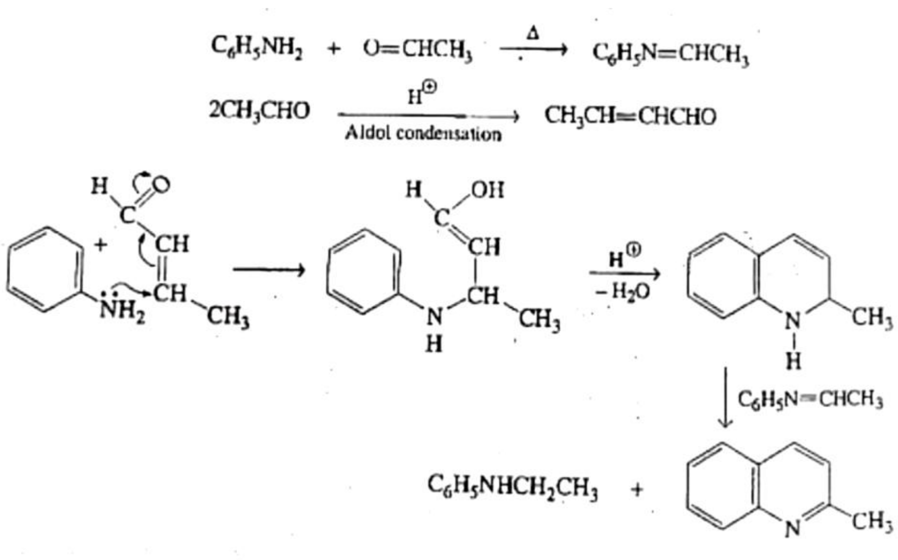
4. **Reduction:** The initially formed dihydroquinoline is reduced by nitrobenzene to yield fully aromatic quinoline.



Direct use of acrolein is avoided because it polymerizes readily; therefore, glycerol is preferred as an in situ source of acrolein. By choosing appropriately substituted anilines, a wide variety of quinoline derivatives can be synthesized.

(ii) Doebner–Miller Synthesis

The Doebner–Miller reaction is a modification of the Skraup synthesis and is particularly suitable for the preparation of quinoline homologues. In this method, a primary aromatic amine is condensed with an aldehyde in the presence of hydrochloric acid.



2-Methylquinoline

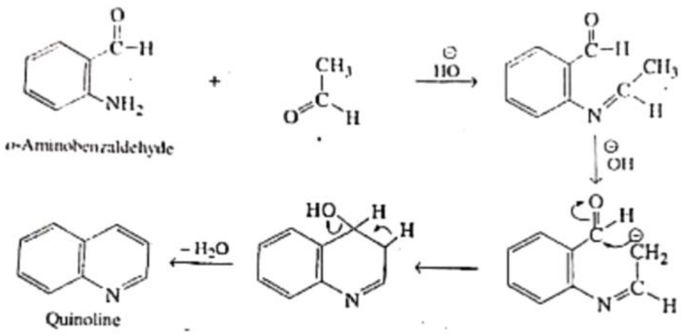
Mechanistic outline:

1. The aldehyde undergoes self-condensation under acidic conditions to form an α,β-unsaturated aldehyde.
2. The aromatic amine adds to this unsaturated aldehyde, forming an intermediate similar to that in the Skraup reaction.
3. Subsequent cyclization and oxidation lead to the formation of substituted quinolines.

(iii) Friedländer Synthesis

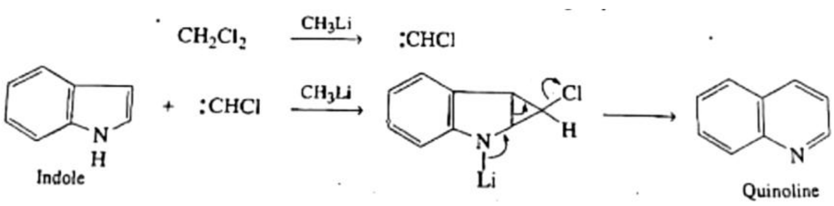
The Friedländer synthesis involves the base-catalyzed condensation of an o-aminobenzaldehyde (or o-aminoketone) with a carbonyl compound containing an active methylene group. The amino group of o-aminobenzaldehyde reacts with the carbonyl compound to form a Schiff base. Intramolecular aldol-type condensation occurs between the aryl carbonyl group and the activated methylene group. Dehydration of the resulting intermediate produces the quinoline ring system.

This method is particularly valuable for synthesizing quinolines bearing substituents at specific positions.



(iv) Synthesis of Quinoline from Indole (Ring Expansion)

Quinoline can also be obtained through ring expansion of indole. Treatment of indole with methyllithium in methylene chloride generates a reactive chloromethylene intermediate.

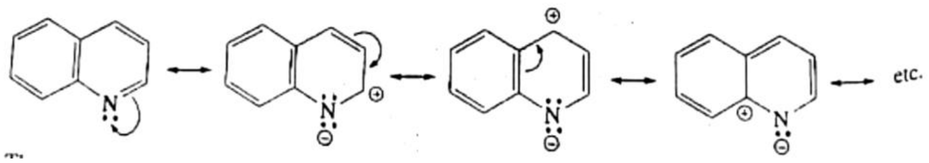


Mechanism:

1. Formation of chloromethylene species in situ.
2. Addition of this intermediate to the indole nucleus.
3. Rearrangement accompanied by ring expansion leads to the formation of the quinoline system.

3. Physical Properties

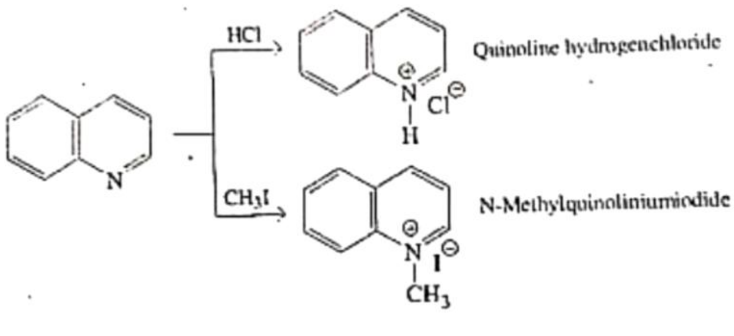
Quinoline is a colorless to pale yellow liquid with a boiling point of approximately 238 °C. It possesses an unpleasant odor and is volatile with steam. Quinoline is sparingly soluble in water but readily soluble in organic solvents such as alcohol and ether. Structurally, quinoline is planar and fully conjugated, containing ten π-electrons, and therefore obeys Hückel's (4n+2) rule for aromaticity. The resonance energy of quinoline is about 47 kcal mol^{-1}, indicating significant aromatic stabilization.



4. Chemical Reactions of Quinoline

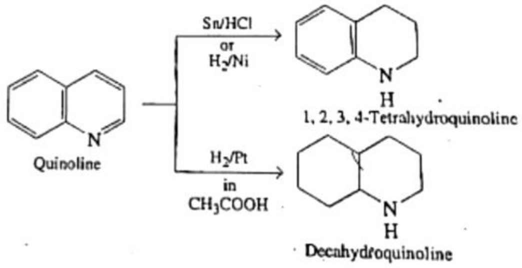
(i) Basic Character

The nitrogen atom in quinoline possesses a lone pair of electrons in a 2p orbital oriented perpendicular to the π-electron system. This lone pair does not participate in aromaticity, making quinoline a tertiary base. Consequently, it forms salts with inorganic acids and reacts with alkyl halides such as methyl iodide to give quaternary ammonium salts, for example, N-methylquinolinium iodide.



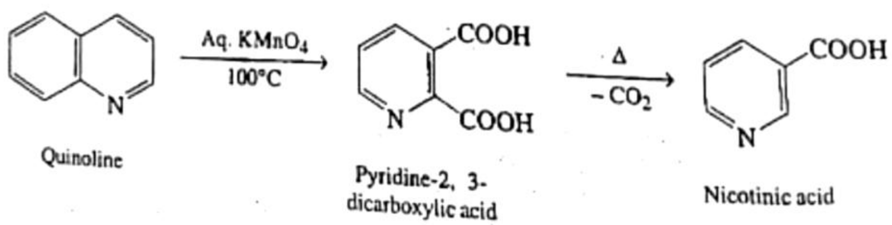
(ii) Reduction

- Reduction with tin and hydrochloric acid or catalytic hydrogenation over nickel produces 1,2,3,4-tetrahydroquinoline.
- More vigorous catalytic hydrogenation using platinum in acetic acid leads to complete saturation of the ring system, yielding decahydroquinoline.

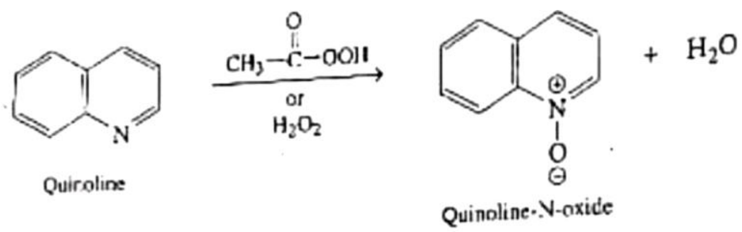


(iii) Oxidation

(a) **Strong oxidation:** Oxidation with alkaline potassium permanganate cleaves the benzene ring to form quinolinic acid (pyridine-2,3-dicarboxylic acid), which on decarboxylation yields nicotinic acid.

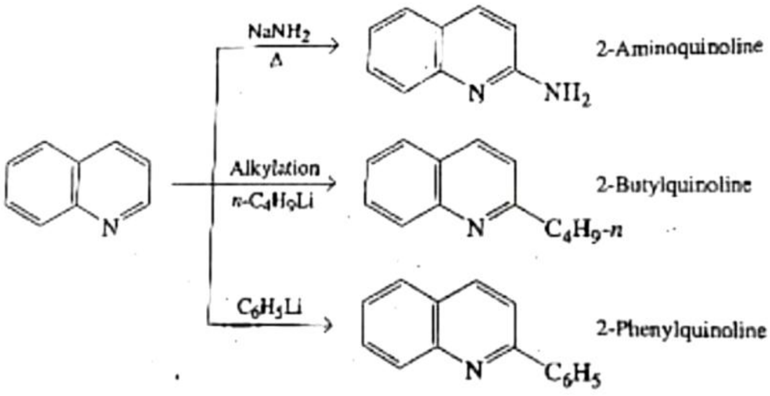


(b) **Mild oxidation:** Treatment with peracids or hydrogen peroxide converts quinoline into quinoline-N-oxide through oxidation of the ring nitrogen.

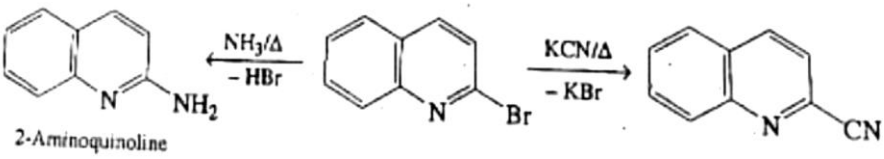


(iv) Nucleophilic Substitution Reactions

(a) **Chichibabin reaction:** Heating quinoline with sodamide introduces an amino group at the 2-position, giving 2-aminoquinoline. Reaction with organolithium reagents such as phenyllithium or n-butyllithium similarly yields 2-substituted quinolines.

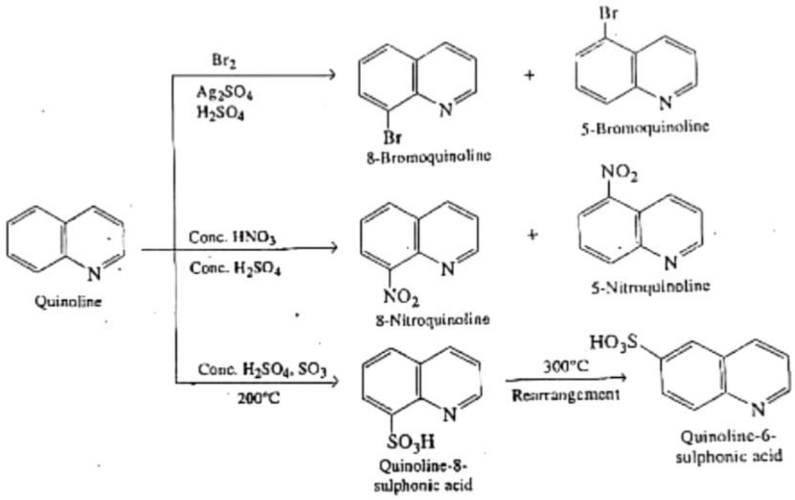


(b) **Substitution in haloquinolines:** Halogen atoms present at the 2- or 4-positions of quinoline are readily displaced by nucleophiles, leading to various substituted derivatives.

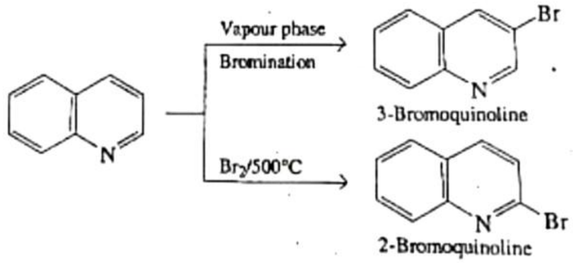


(v) Electrophilic Substitution Reactions

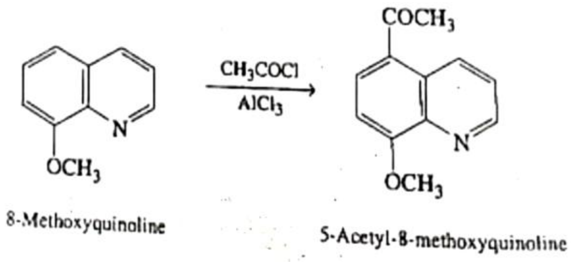
Quinoline undergoes electrophilic substitution reactions such as nitration, sulfonation, halogenation, and Friedel–Crafts reactions. However, the nitrogen atom strongly deactivates the pyridine ring toward electrophilic attack. As a result, substitution occurs mainly in the benzene ring, preferentially at the 8-position, with minor substitution at the 5-position.



In vapor-phase bromination, substitution occurs at the 3-position, whereas at high temperatures (around 500 °C), bromination yields 2-bromoquinoline.



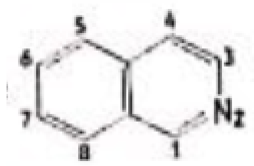
Quinoline derivatives containing activating groups on the benzene ring can also undergo Friedel–Crafts acylation reactions.



Quinoline is an important fused heterocyclic system displaying dual chemical behavior derived from both benzene and pyridine. Its synthesis through reactions such as Skraup, Doebner–Miller, Friedländer, and ring-expansion methods, along with its characteristic reactions, makes quinoline a central structure in heterocyclic chemistry and pharmaceutical science.

Isoquinoline

Isoquinoline is a fused bicyclic nitrogen heterocycle in which a benzene ring is condensed with a pyridine ring at the β,γ-positions. For this reason, isoquinoline is also referred to as β,γ-benzopyridine. Unlike most heterocycles, the numbering of the isoquinoline ring does not begin at the heteroatom. Isoquinoline is encountered as a degradation product of several naturally occurring alkaloids such as papaverine and narcotine. Industrially, it is obtained from coal tar and bone oil. Because of its aromatic structure and ring nitrogen atom, isoquinoline exhibits chemical behavior similar to that of quinoline, though with distinct positional reactivity.



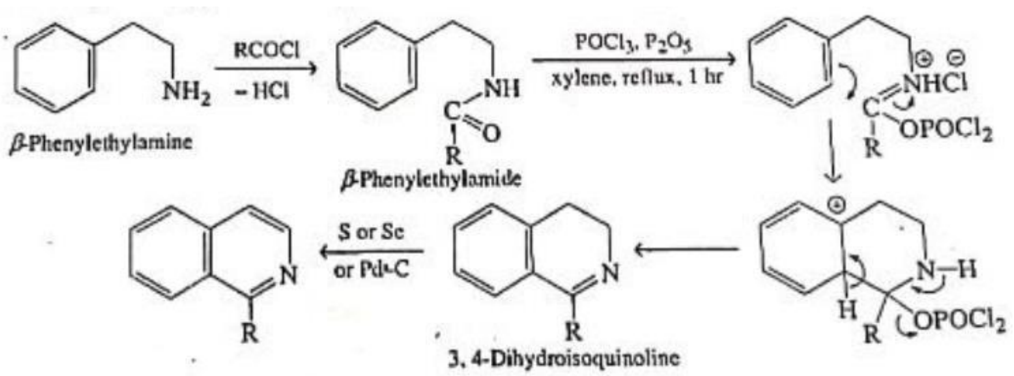
2. Methods of Formation of Isoquinoline and Its Derivatives

(i) Bischler–Napieralski Synthesis

The Bischler–Napieralski synthesis is one of the most important methods for constructing the isoquinoline nucleus. In this reaction, an acyl derivative of β-phenylethylamine is cyclodehydrated by heating with a strong dehydrating agent such as phosphorus pentoxide or phosphorus oxychloride in an inert solvent.

Reaction sequence:

1. Cyclodehydration of the amide produces 3,4-dihydroisoquinoline.
2. Subsequent dehydrogenation using sulfur or selenium converts the dihydro compound into the corresponding isoquinoline.

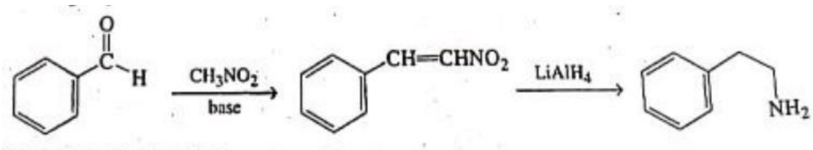


Mechanism:

- The dehydrating agent initially attacks the oxygen atom of the amide group, increasing the electrophilicity of the carbonyl carbon.
- Intramolecular electrophilic substitution occurs when the activated aromatic ring attacks this carbon, resulting in ring closure.
- Loss of water leads to the formation of 3,4-dihydroisoquinoline.

- Final oxidation removes two hydrogen atoms to generate the fully aromatic isoquinoline system.

The required β-phenylethylamine is generally prepared from aromatic aldehydes through reductive amination followed by appropriate functional group transformations.

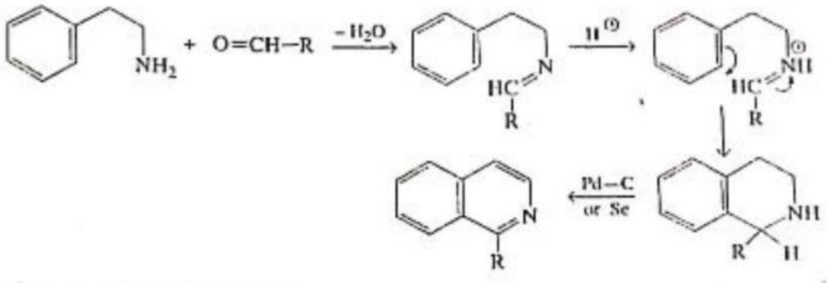


(ii) Pictet–Spengler Reaction

The Pictet–Spengler reaction involves the condensation of a β-arylethylamine with an aldehyde under acidic conditions, usually in the presence of hydrochloric acid at elevated temperature.

Reaction sequence:

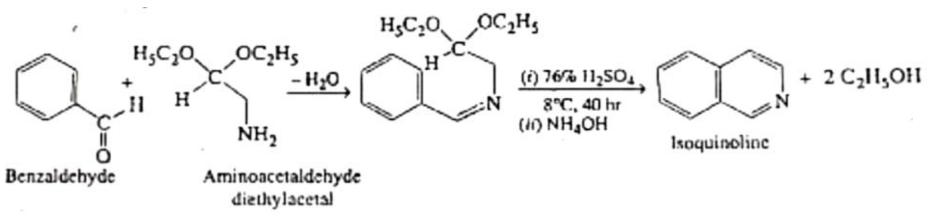
1. Condensation of the amine with the aldehyde forms an imine.
2. Protonation of the imine increases its electrophilicity.
3. Intramolecular electrophilic aromatic substitution leads to cyclization, forming 1,2,3,4-tetrahydroisoquinoline.
4. Dehydrogenation with palladium–carbon or selenium yields isoquinoline.



The reaction proceeds through iminium ion formation followed by intramolecular electrophilic attack of the aromatic ring, closely resembling the cyclization step of the Bischler–Napieralski synthesis.

(iii) Pomeranz–Fritsch Synthesis

The Pomeranz–Fritsch synthesis provides a direct route to the isoquinoline ring. In this method, an aromatic aldehyde is condensed with an aminoacetal to form a Schiff base.



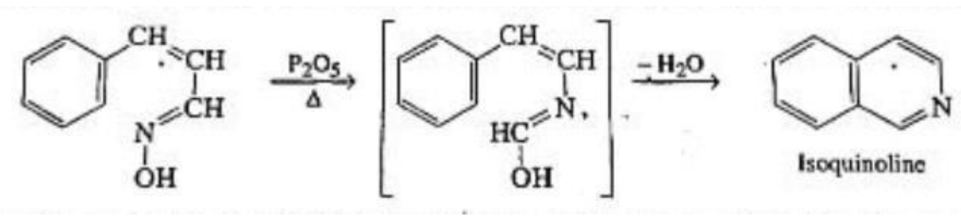
Mechanism:

1. Formation of a Schiff base through condensation of the aldehyde and aminoacetal.
2. Acid-catalyzed cyclization of the Schiff base.
3. Elimination of alcohol molecules followed by aromatization to yield isoquinoline.

This method is particularly useful for synthesizing unsubstituted or simply substituted isoquinolines.

(iv) Dehydration of Cinnamaldehyde Oxime

Isoquinoline can also be synthesized by dehydrating cinnamaldehyde oxime using phosphorus pentoxide.

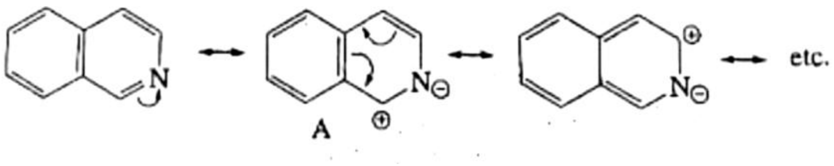


Mechanism:

- The oxime first undergoes Beckmann rearrangement under dehydrating conditions.
- The rearranged intermediate cyclizes intramolecularly.
- Subsequent loss of small molecules and aromatization results in the formation of isoquinoline.

3. Physical Properties

Isoquinoline is a colorless liquid with a boiling point of about 243 °C. It has an unpleasant odor and is volatile in steam. Isoquinoline is sparingly soluble in water but readily soluble in organic solvents such as alcohol and ether. It is moderately basic with a pKa value of approximately 6.1. The molecule is planar and aromatic, and its stability arises from resonance delocalization over the fused ring system. Among the resonance structures, the form retaining maximum benzenoid character contributes most significantly to the resonance hybrid.



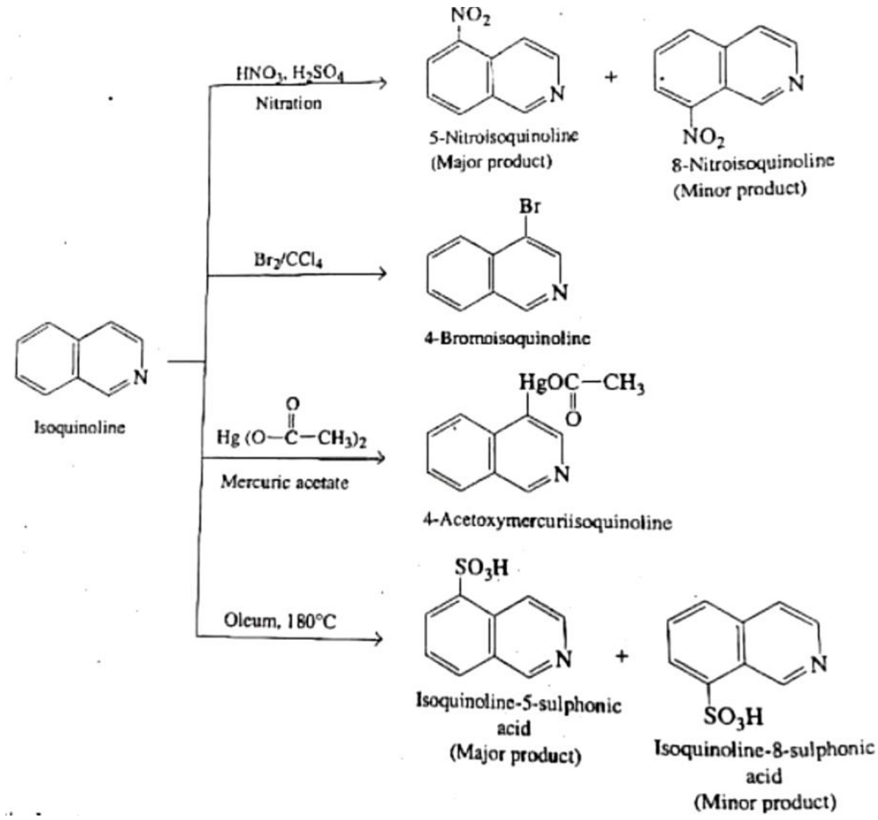
4. Chemical Reactions of Isoquinoline

(i) Electrophilic Substitution Reactions

Due to protonation of the ring nitrogen, the pyridine portion of isoquinoline is strongly deactivated toward electrophilic substitution. As a result, electrophilic attack occurs primarily on the benzene ring.

- Substitution predominantly takes place at the 5-position.
- Minor substitution may occur at the 8-position.

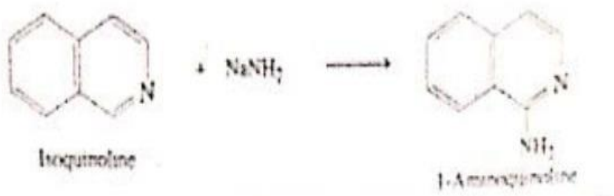
For example, nitration and sulfonation mainly yield 5-substituted isoquinoline derivatives. However, reactions such as mercuration (using mercuric acetate) and bromination in carbon tetrachloride preferentially produce 4-substituted isoquinoline.



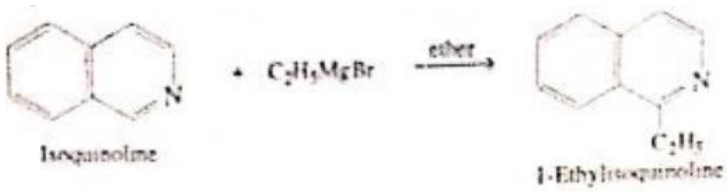
(ii) Nucleophilic Substitution Reactions

Nucleophilic substitution in isoquinoline occurs mainly at the 1-position.

- Heating isoquinoline with sodamide results in the formation of 1-aminoisoquinoline via the Chichibabin reaction.

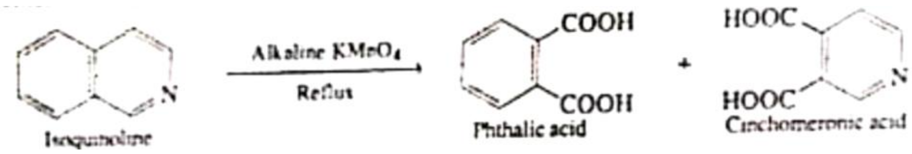


- Treatment with Grignard reagents introduces alkyl groups at the 1-position, yielding 1-alkylisoquinoline derivatives.



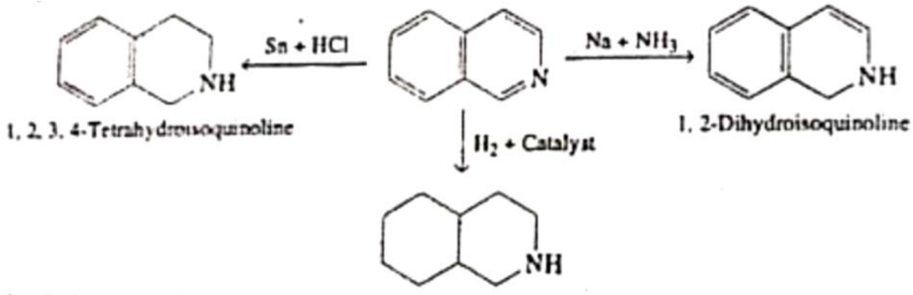
(iii) Oxidation

- Oxidation with alkaline potassium permanganate cleaves the ring system to give a mixture of phthalic acid and cinchomeronic acid.
- Mild oxidation using perbenzoic acid converts isoquinoline into isoquinoline-N-oxide by oxidation of the ring nitrogen.



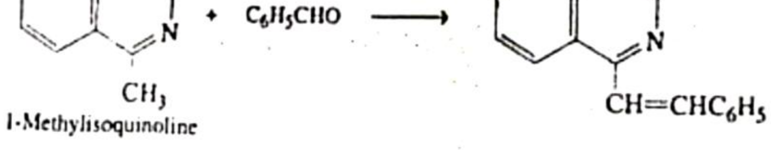
(iv) Reduction

- Reduction with sodium in liquid ammonia produces 1,2-dihydroisoquinoline.
- Treatment with tin and hydrochloric acid yields 1,2,3,4-tetrahydroisoquinoline.
- Catalytic hydrogenation results in octahydroisoquinoline.



(v) Side-Chain Reactivity

Alkyl groups located at positions ortho or para to the ring nitrogen exhibit enhanced acidity and reactivity. Consequently, such side chains undergo typical condensation reactions. For example, 1-methylisoquinoline reacts with benzaldehyde to form the corresponding styryl derivative.



Isoquinoline is an important benzofused nitrogen heterocycle that shares many chemical features with quinoline while displaying distinct regioselectivity in substitution reactions. Its synthesis through methods such as Bischler–Napieralski, Pictet–Spengler, Pomeranz–Fritsch, and oxime dehydration reactions, along with its characteristic electrophilic, nucleophilic, oxidation, and reduction reactions, makes isoquinoline a key system in heterocyclic and medicinal chemistry.