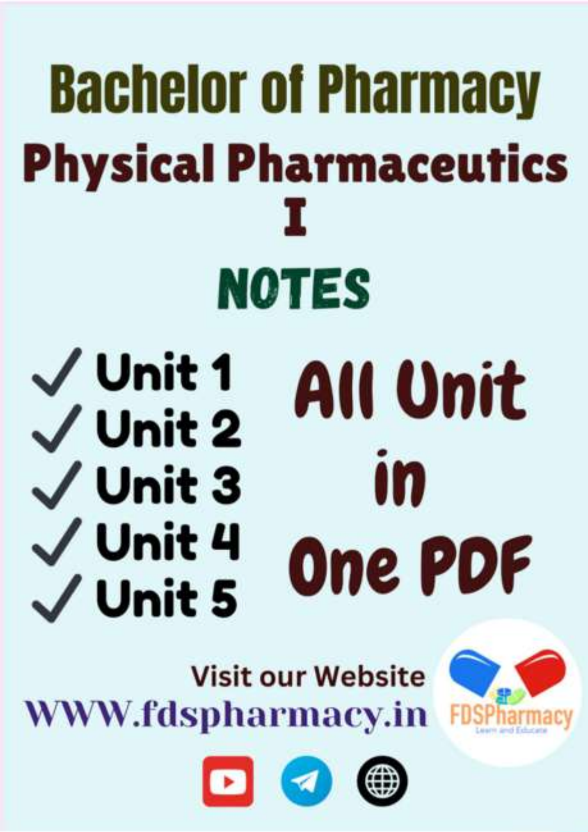


Diploma in Pharmacy

Bachelor of Pharmacy

PHARMACEUTICAL ORGANIC CHEMISTRY - II

UNIT 2

TOPIC :

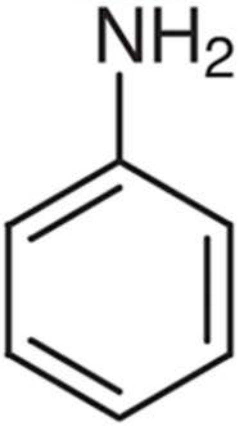
- **Aromatic Amines*-** Basicity of amines, effect of substituents on basicity, and synthetic uses of aryl diazonium salts

Aromatic Amines

- ✓ Aromatic amines are derivatives of aromatic hydrocarbons in which one or more hydrogen atoms of the benzene ring are replaced by an amino group (-NH_2).
- ✓ Alternatively, they can be considered as derivatives of ammonia (NH_3), where one or more hydrogen atoms of ammonia are replaced by an aryl (aromatic) group.
- ✓ In aromatic amines, the amino group is directly bonded to the aromatic ring.

General Structure:

→ Ar-NH_2, where Ar represents an aromatic ring such as benzene, naphthalene, etc.

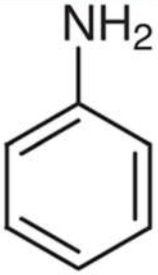


Types of Aromatic Amines:

Aromatic amines are classified based on the number of aryl groups attached to the nitrogen atom:

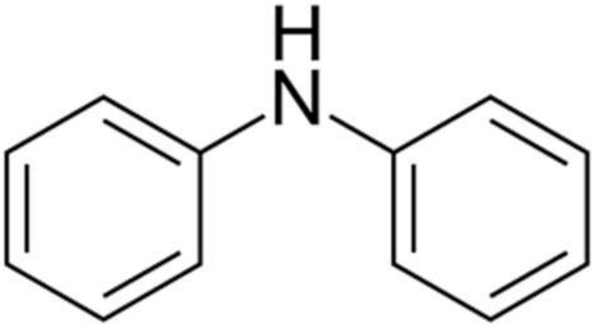
1. Primary Aromatic Amines (1°)

- In these amines, one hydrogen atom of ammonia is replaced by an aromatic group.
- General formula: $Ar–NH_2$
- Example:
    - Aniline or Phenylamine
      Structure:



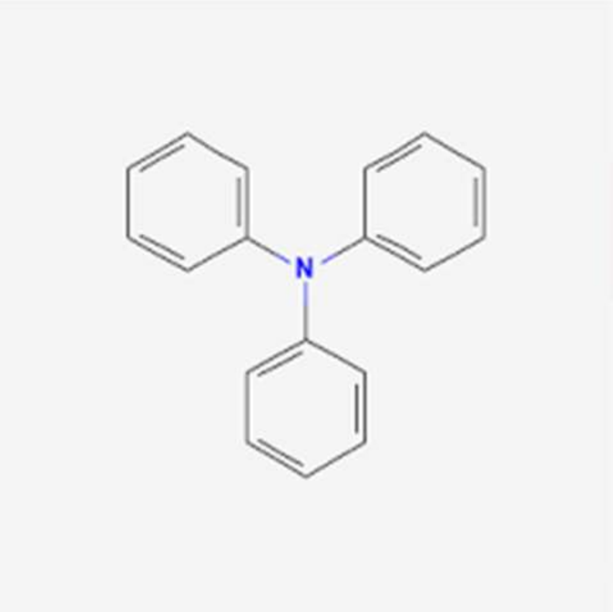
2. Secondary Aromatic Amines (2°)

- In these amines, two hydrogen atoms of ammonia are replaced by two aryl groups.
- General formula: Ar–NH–Ar
- Example:
    - Diphenylamine
      Structure:



3. Tertiary Aromatic Amines (3°)

- In these amines, all three hydrogen atoms of ammonia are replaced by three aryl groups.
- General formula: Ar_3N
- Example:
    - Triphenylamine
      Structure:



Methods of Preparation of Aromatic Amines

Aromatic amines can be synthesized by using the following methods:

1. Reduction of Nitro Compounds

- This is the most common method for preparing aromatic amines.
- Aromatic nitro compounds like nitrobenzene are reduced in the presence of a reducing agent such as:
    - Tin (Sn) + Hydrochloric acid (HCl), or
    - Iron (Fe) + HCl, or
    - Catalytic hydrogenation (H_2 + Pd/C)

General Reaction:

$$\mathrm{Ar{-}NO_2} \xrightarrow[\mathrm{HCl}]{\mathrm{Sn}} \mathrm{Ar{-}NH_2}$$

Example:

Nitrobenzene → Aniline

$$\mathrm{C_6H_5NO_2} + 6[H] \xrightarrow{\mathrm{Sn/HCl}} \mathrm{C_6H_5NH_2} + 2H_2O$$

Mechanism: Nitro group is reduced stepwise to a nitroso group, then hydroxylamine, and finally to an amine.

Product: Aniline

2. Hofmann Rearrangement Reaction (Hofmann Degradation)

- Hofmann rearrangement is a chemical reaction in which an aromatic amide is treated with bromine (Br_2) and sodium hydroxide (NaOH) to form a primary aromatic amine with one less carbon atom.

General Reaction:

$$\mathrm{Ar{-}CONH_2} + Br_2 + 4NaOH \rightarrow \mathrm{Ar{-}NH_2} + Na_2CO_3 + 2NaBr + 2H_2O$$

Example:

Conversion of Benzamide to Aniline

$$\mathrm{C_6H_5CONH_2} \xrightarrow[\mathrm{NaOH}]{\mathrm{Br_2}} \mathrm{C_6H_5NH_2}$$

Benzamide → Aniline

Basicity of Aromatic Amines

→ Amines are basic in nature because the nitrogen atom in the $-NH_2$ group contains a lone pair of electrons, which can be donated to accept a proton (H^+).

→ According to Lewis theory, a base is a species that donates an electron pair — therefore, aromatic amines act as Lewis bases.

→ When an aromatic amine reacts with an acid, it forms a salt by accepting a proton:

$$\mathrm{Ar{-}NH_2} + HCl \rightarrow \mathrm{Ar{-}NH_3^+}Cl^-$$

Comparison with Other Amines:

- Although aromatic amines (like aniline) are basic, their basicity is weaker than aliphatic amines and ammonia (NH_3).
- This is because of two main factors:
  1. Hybridization of the Carbon Atom
  2. Resonance Effect

1. Effect of Hybridization:

- In aromatic amines, the nitrogen atom is attached to an sp^2-hybridized carbon (i.e., benzene ring).
- In aliphatic amines, nitrogen is bonded to an sp^3-hybridized carbon (like CH_3-).
- sp^2-hybridized carbon is more electronegative than sp^3 carbon, so it pulls the electron density towards itself, reducing the availability of the nitrogen's lone pair for protonation.

  Result: Basicity decreases in aromatic amines.

2. Resonance Effect in Aromatic Amines:

- In compounds like aniline, the lone pair of electrons on nitrogen participates in resonance with the benzene ring.
- This delocalization of the nitrogen lone pair into the aromatic π-system reduces its availability to accept a proton.

Resonating structures:

$$\mathrm{Ph{-}NH_2 \leftrightarrow Ph{=}NH{-}^{-} \leftrightarrow Ph{-}N{=}}$$

Hence, resonance reduces electron density on nitrogen, making aniline less basic

Basicity Order of Amines:

Increasing Order of Basicity:

$$\text{Aromatic Amine (Aniline)} < \text{Ammonia } (\mathrm{NH_3}) < \text{Aliphatic Amine } (\mathrm{CH_3NH_2})$$

$$C_6H_5NH_2 < NH_3 < CH_3NH_2$$

Effect of Substituents on the Basicity of Aromatic Amines

→ The basicity of aromatic amines like aniline is influenced by substituents present on the aromatic ring. These substituents affect the availability of the lone pair on the nitrogen atom by either withdrawing or releasing electron density through inductive or resonance effects.

Types of Substituents:

There are mainly two types of substituent groups:

1. Electron-Withdrawing Groups (–I effect)

- These groups pull electron density away from the benzene ring and the nitrogen atom.
- As a result, they reduce the electron density on the nitrogen, making its lone pair less available for protonation.
- Hence, basicity decreases.

Examples:

- $-NO_2$ (nitro group)
- –CN (cyano group)
- –COOH (carboxylic acid group)
- $-SO_3H$ (sulfonic acid group)

Effect:

- Strong electron-withdrawing groups decrease basicity.
- The stronger the –I or –R (resonance withdrawing) effect, the weaker the base.

2. Electron-Releasing Groups (+I or +R effect)

- These groups donate electrons to the ring and nitrogen atom.
- This increases the electron density on the nitrogen atom, making the lone pair more available for accepting a proton.
- Hence, basicity increases.

Examples:

- $-CH_3$ (methyl group)
- –OH (hydroxyl group)
- $-OCH_3$ (methoxy group)
- $-NH_2$ (amino group)

Effect:

- These groups enhance basicity of aromatic amines.
- The stronger the +I or +R effect, the stronger the base.

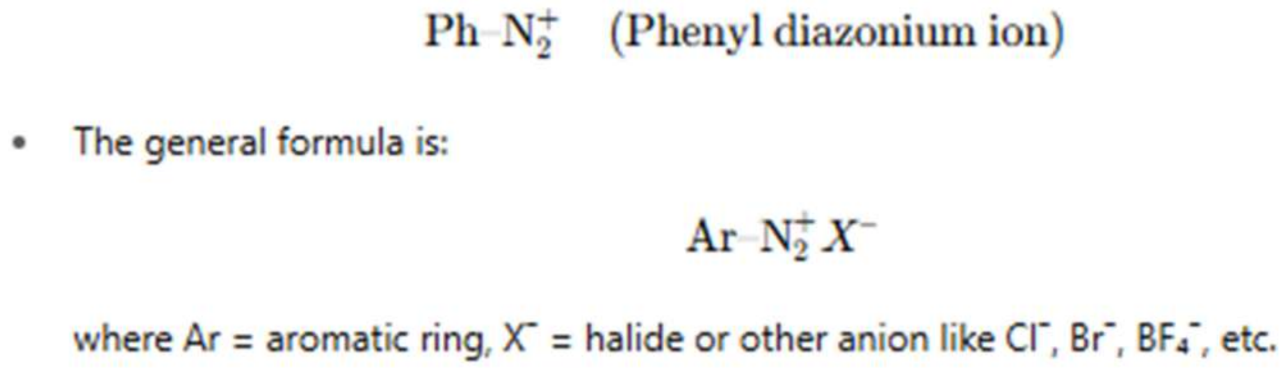
Aryl Diazonium Salts

- The word "diazo" is derived from two parts:
  - "Di" meaning two
  - "Azo" (from nitrogen) meaning nitrogen atoms
- An aryl diazonium salt is an organic compound that contains a diazonium group ($-N_2^+$) attached to an aromatic ring.

$$Ar-N_2^+ X^-$$

- These salts are important intermediates in organic chemistry and are commonly used to synthesize various aromatic compounds, including dyes, azo compounds, and substituted aromatic derivatives.

Structure of Aryl Diazonium Ion:



$Ph-N_2^+$ (Phenyl diazonium ion)

- The general formula is:

$$Ar-N_2^+ X^-$$

where Ar = aromatic ring, X^- = halide or other anion like Cl^-, Br^-, BF_4^-, etc.

Preparation of Aryl Diazonium Salts (Diazotization Reaction):

The preparation involves **two steps**:

Step 1: Formation of Nitrous Acid (HNO_2)

- Sodium nitrite ($NaNO_2$) reacts with hydrochloric acid (HCl) **in situ** to generate nitrous acid.

$$\mathrm{NaNO_2 + HCl \rightarrow HNO_2 + NaCl}$$

Step 2: Reaction with Aromatic Amine

- Nitrous acid reacts with an aromatic primary amine (e.g., aniline) at low temperatures (0–5°C) to form the aryl diazonium salt.

$$\mathrm{C_6H_5NH_2 + HNO_2 + HCl \rightarrow C_6H_5N_2^{+}Cl^{-}} + 2H_2O$$

Aniline → Benzenediazonium chloride

Conditions Required:

- **Low temperature** (0–5°C) is essential to stabilize the diazonium salt.
- The reaction is generally carried out in **aqueous acidic medium**.

Synthetic Uses of Aryl Diazonium Salts:

1. Dye Manufacturing:
    - Used in the synthesis of azo dyes, which are brightly colored and used in textile, paper, and food industries.
2. Sandmeyer Reaction:
    - Replacement of the diazonium group with halogens (Cl, Br) using CuCl or CuBr.
3. Gattermann Reaction:
    - Replacement with halogens (Cl, Br) using Cu powder and HCl/HBr.
4. Synthesis of Phenols:
    - Reaction with water to form phenol.
5. Synthesis of Aromatic Cyanides:
    - Reaction with CuCN gives aromatic nitriles.
6. Synthesis of Fluorobenzene:
    - Reaction with HBF_4 gives Ar–F.