ORGANIC CHEMISTRY

Organic Compounds containing Nitrogen

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CONTENTS
Introduction
Preparation of Nitroalkanes
Chemical Reactions of Nitroalkanes
Nitro Arenes
Picric Acid
Amines
Diazonium Salts
Introduction
Due to different tautomeric forms of nitrous acid (H - O - N = O ⇌ H - N = O) two kinds of alkyl derivatives are formed, e.g. R - O - NO (alkyl nitrites) and R - NO₂ (nitro alkanes). They are functional isomers.

Alkyl nitrites may be considered as esters of nitrous acid with alcohols.

While nitro alkanes may be considered as nitro derivatives of alkanes.

The reaction which most clearly indicates their respective structures is reduction.

When alkyl nitrites are reduced, an alcohol and ammonia or hydroxylamine is formed. This shows that the alkyl group in nitrites is attached to an oxygen atom

\[ R \cdot NO \xrightarrow{Reduction} ROH + NH_3 + H_2O \]
On the other hand, when nitroalkanes are reduced, a primary amine is formed. This shows that the alkyl group is attached to the nitrogen atom, since the structure of a primary amine is R—NH₂

\[ R \cdot NO_2 \xrightarrow{Reduction} R \cdot NH_2 + 2H_2O \]

Structure
The structure of the nitro-compounds is depicted as follows:

R—N\( \overset{O}{\null} \)O

The dipole moments, however, indicate that they are resonance hybrids as follows:

R—N\( \overset{O}{\null} \)O ↔ R—N\( \overset{+}{\null} \)O

From the Molecular Orbital point of view, the nitro-group is conjugated and delocalization of bonds increases its stability (the two oxygen atoms are equivalent just like the two oxygen atoms of the carboxylate ion (-COO⁻)).

Preparation of Nitro alkanes
1. By direct nitration of alkanes: Two techniques are used:
   (a) liquid-phase nitration: The hydrocarbon is heated with concentrated nitric acid under pressure at 140°. This is a slow reaction and a large amount of polynitro-compounds is also produced. Unlike for the aromatic hydrocarbons, the nitrating mixture (mixture of nitric and sulphuric acid) is not suitable for nitrating alkanes.
(b) Vapour-phase nitration: The hydrocarbon is heated with nitric acid (or with oxides of nitrogen) at 150 – 475°C; (the temperature varies for different hydrocarbon). Here, the nitro derivatives of the smaller hydrocarbon, in addition to the nitro derivative of the starting one, are also formed. For example, propane on vapour phase nitration gives 1-nitropropane, 2-nitropropane, nitroethane and nitromethane.

\[
\text{CH}_3\cdot\text{CH}_2\cdot\text{CH}_3 + \text{HNO}_3 \xrightarrow{400\degree} \text{CH}_3\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{NO}_2 + \text{CH}_3\cdot\text{CH}(\text{NO}_2)\cdot\text{CH}_3 + \text{CH}_3\cdot\text{CH}_2\cdot\text{CNO}_2 + \text{CH}_3\cdot\text{NO}_2
\]

Out of the two nitration techniques, Vapour-phase nitration is more satisfactory than liquid-phase nitration.

**General rules of vapour phase nitration of alkanes (and cycloalkanes), as given by Hass and Shechter (1947):**

i. Polynitro compounds are formed only from alkanes of fairly high molecular weight. Smaller alkanes give mainly mono-nitro alkanes.

ii. The ease of replacement of the hydrogen atom by nitro group is:
   - tertiary hydrogen > secondary hydrogen > primary hydrogen.
   - At higher temperature, however, the ease of replacement is almost equal.

iii. An alkyl group present in the alkane can also be replaced by a nitro-group, i.e., chain fission takes place. For example, isopentane yields nine nitroparaffins. The fission reaction increases as the temperature rises.

iv. Oxidation always accompanies nitration, resulting in the formation of nitro-compounds and a mixture of acids, aldehydes, ketones, alcohols, nitrites, nitroso-compounds, nitroolefins, polymers, carbon monoxide and carbon dioxide. Catalysts such as copper, iron, platinum oxide, etc., accelerate oxidation rather than nitration.

**Mechanism:** Proceeds by a free radical mechanism.

\[
\begin{align*}
\text{CH}_3 - \text{CH}_2 \cdot \text{CH}_3 + \text{NO}_2 & \xrightarrow{HNO_2} \text{CH}_3 - \text{CH}_2 \cdot \text{CH}_2 \cdot \text{NO}_2 + \text{HNO}_2 \\
\text{CH}_3 - \text{CH}_2 \cdot \text{CH}_2 \cdot \text{NO}_2 & \xrightarrow{\text{H}_2 \cdot \text{O}} \text{CH}_3 - \text{CH}_2 \cdot \text{NO}_2 + \text{CH}_3 - \text{CH}_2 \cdot \text{ONO} \\
\text{CH}_3 - \text{CH}_2 \cdot \text{ONO} & \xrightarrow{\text{H}_2 \cdot \text{O}} \text{CH}_3 - \text{CH}_2 \cdot \text{O} + \text{NO} \cdot \\
\text{CH}_3 - \text{CH}_2 \cdot \text{O} \cdot \xrightarrow{\text{CH}_3 \cdot \text{O}} \text{CH}_3 \cdot \text{O} + \text{CH}_2 \cdot \text{O} \\
\text{CH}_3 \cdot \text{O} + \text{CH}_2 \cdot \text{O} & \xrightarrow{\text{NO}_2} \text{CH}_3 - \text{NO}_2
\end{align*}
\]

2. From alkyl halides: By heating an alkyl halide with silver nitrite in aqueous ethanolic solution.

\[
\text{R} - \text{X} + \text{AgNO}_2 \longrightarrow \text{R} - \text{NO}_2 + \text{R} - \text{O} - \text{N} = \text{O} + \text{AgX}
\]

**Explanation:** This reaction is an example of a nucleophilic substitution reaction.

Nitrite ion (O\(^-\) - N =O) is an ambidient nucleophile, since, it has two sites through which it can attack the alkyl halide and attach through nitrogen to give nitro alkanes whereas through oxygen gives nitrites. i.e.,
Alkali metal nitrites are ionic compounds, therefore, NaNO₂, or KNO₂ attacks chiefly through negative charge on the oxygen to form alkyl nitrites. In contrast, silver nitrite is covalent compound and, hence, the more nucleophilic nitrogen through its lone pair of electrons attacks and as a result, nitro compounds are formed as major products.

This method is only useful for the preparation of primary nitroalkanes. With the secondary halides the yield is very low, and with tertiary halides even lower.

This method has been modified by Kornblum et al for the synthesis of primary and secondary nitro-compounds. Here, the alkyl halide is reacted with sodium nitrite in the presence of di-methyl formamide as solvent, and urea which increases the solubility of sodium nitrite. Here, nitro alkanes are obtained (55 – 62 %) together with alkyl nitrites (25 – 33 %).

Alkyl bromides and iodides are most satisfactory; the chlorides react too slowly to be useful.

3. From halogeno-acetic acid: Nitromethane is prepared by boiling an aqueous solution of sodium nitrite with sodium salt of halogeno acetic acid. e.g.,

\[
\text{CH}_2\text{Cl} - \text{COONa} + \text{NaNO}_2 \rightarrow \text{NaCl} + [\text{CH}_3(\text{NO}_2) - \text{CO}_2\text{H}] \rightarrow \text{CH}_3 - \text{NO}_2 + \text{CO}_2
\]

Initially, an unstable intermediate nitro acetic acid is formed, which readily decarboxylates to give nitromethane. The loss of carbon dioxide is facilitated by the electron withdrawing nitro-group.

This method, however, cannot be used for preparing higher nitroalkanes.

4. From α-nitro alkenes: By the hydrolysis of α-nitro-alkenes with water, acid or alkali, e.g., 2-methyl-1-nitroprop-1-ene gives acetone and nitromethane in almost quantitative yield.

\[
(\text{CH}_3)_2\text{C} = \text{CH} - \text{NO}_2 + \text{H}_2\text{O} \rightarrow (\text{CH}_3)_2\text{C} = \text{O} + \text{CH}_3 - \text{NO}_2
\]

5. From primary amines were nitrogen is joined to tertiary alkyl group: Tertiary nitro compounds can be obtained by the oxidation of primary amines containing amino group linked to tertiary carbon, with acidified potassium permanganate:
6. By alkylation of lower nitro alkanes: An important method for alkylation of lower nitro alkanes is by treating them with Butyl lithium followed by an appropriate alkyl halide.

\[
R_3C - NH_2 \xrightarrow{K_MnO_4} R_3C - NO_2
\]

\(\text{e.g.,}\)

\[
\begin{align*}
(\text{CH}_3)_2C - NH_2 & \xrightarrow{[\text{O}]} (\text{CH}_3)_2C - NO_2 \\
\text{2-Methyl} & \quad \text{2-Methyl 2-nitropropane}
\end{align*}
\]

**Chemical reactions of Nitro alkanes**

1. **Reduction:** The various reduction stages of the nitro group are as given below.

\[
\begin{align*}
\text{NO}_2 & \rightarrow \text{N}==\text{O} \rightarrow \text{NH}==\text{OH} \rightarrow \text{NH}_2 \\
\text{Nitro} & \quad \text{Nitros} \quad \text{Hydroxyl} \quad \text{Amine}
\end{align*}
\]

The extent of reduction depends on the nature of the reducing agent as well as on the pH of the medium.

a) **Catalytic reduction:** Both aliphatic and aromatic nitro compounds are reduced to primary amines when reacted with \(\text{H}_2/\text{Ni}\) or \(\text{H}_2/\text{Pt}\) or \(\text{H}_2/\text{Pd}\).

\[
R - NO_2 \xrightarrow{H_2/Ni, or Pt} R - NH_2 + 2H_2O
\]

\(\text{e.g.}\)

\[
\text{CH}_3\text{CH}_2\text{NO}_2 \xrightarrow{\text{H}_2/\text{Ni}, \Delta} \text{CH}_3\text{CH}_2\text{NH}_2
\]

b) **Reduction with LiAlH}_4 (Lithium aluminium hydride):** Nitroalkanes are reduced to primary amines.

\[
R - NO_2 \xrightarrow{\text{LiAlH}_4} R - NH_2
\]

\(\text{e.g.}\)

\[
\text{CH}_3\text{CH}_2\text{NO}_2 \xrightarrow{\text{LiAlH}_4} \text{CH}_3\text{CH}_2\text{NH}_2
\]
c) **Reduction in acidic medium:** Aliphatic nitro compounds are reduced to primary amines by metal and acid, e.g. Zn/HCl, Fe/HCl or Sn/HCl

\[
R - \text{NO}_2 \xrightarrow{\text{Metal/Acid}} R - \text{NH}_2
\]

E.g.,

\[
\begin{align*}
\text{CH}_3\text{NO}_2 \xrightarrow{\text{Fe/HCl}} & \text{CH}_3\text{NH}_2 \\
\text{CH}_3\text{—CH—CH}_3 \xrightarrow{\text{Sn/HCl}} & \text{CH}_3\text{—CH—CH}_3
\end{align*}
\]

d) **Reduction in neutral medium:** In neutral medium, the nitro group is reduced to \(\text—\text{NHOH}\), thus giving substituted hydroxylamines as the product.

\[
R - \text{NO}_2 \xrightarrow{\text{Zn/NH}_4\text{Cl}} R - \text{NH—OH}
\]

E.g.,

\[
\text{CH}_3\text{CH}_2\text{NO}_2 \xrightarrow{\text{Zn/NH}_4\text{Cl}} \text{CH}_3\text{CH}_2\text{NHOH}
\]

These hydroxylamines on warming with ammoniacal silver nitrate solution (Tollen's reagent) get oxidised to nitroso compounds and reduce Tollen's reagent to metallic silver (which deposits as a silver mirror). This reaction is used to test nitro compounds and is known as the **Baker-Mulliker test**.

e) **With stannous chloride and HCl:** When stannous chloride and hydrochloric acid are used as the reducing agent, nitro compounds are converted into a mixture of hydroxylamine derivative and oxime:

\[
R - \text{CH}_2 - \text{NO}_2 \xrightarrow{\text{SnCl}_2\text{/HCl}} R - \text{CH}_2 - \text{NH—OH} + R - \text{CH} = \text{N—OH}
\]

2. **Hydrolysis of nitro alkanes:** Primary nitro-alkanes are hydrolysed by boiling hydrochloric acid or by sulphuric acid to give a mixture of carboxylic acid and hydroxylamine:

\[
R - \text{CH}_2 - \text{NO}_2 + H_2O \xrightarrow{\text{HCl}} R - \text{COOH} + \text{NH}_2OH
\]

Secondary nitro-alkanes are hydrolysed by boiling hydrochloric acid to give a mixture of ketone and nitrous oxide:

\[
2R_2\text{CH} - \text{NO}_2 \xrightarrow{\text{HCl}} 2R_2\text{C} = \text{O} + N_2\text{O} + H_2O
\]

Tertiary nitro-alkanes do not undergo hydrolysis.

3. **Salt formation with bases:** These nitro-compounds dissolve in aqueous sodium hydroxide to form salts.

**Explanation:** Primary and secondary nitro-compounds, i.e., those containing \(\alpha\)-hydrogen atoms, exhibit tautomerism:

\[
\begin{align*}
\text{R} \cdot \text{CH}_2\cdot \text{N} \xrightleftharpoons[O^-]{O^+} & \text{R} \cdot \text{CH} \xrightleftharpoons[O^-]{O^+} \\
\text{I) (II)} & \text{OH}
\end{align*}
\]
The nitro-form (I) is also known the *pseudo-acid* form; (II) is known as the *aci*-form or *nitronic acid*.

This is called the *nitro-acinitro system of tautomerism*. The equilibrium is almost completely on the left, as the nitro-form is more stable due to resonance.

In the formation of salt, the hydroxide ion removes the α-hydrogen atom from the nitro-form. The removal of the proton is made possible by the strong –I effect of the nitro-group and the resulting anion is resonance stabilised.

\[
\text{CH}_3\text{N}^+\text{O}^− + \text{OH}^− \rightarrow \text{H}_2\text{O} + \text{CH}_2\text{N}^+\text{O}^− \quad \leftrightarrow \quad \text{CH}_2\text{N}^+\text{O}^− \quad \text{(IIa)}
\]

**Reactions of sodium salt of nitro alkanes:**

a. When the sodium salt is acidified at low temperature, there is a slow formation of yellow oily nitro-form.

b. When the sodium salt solution is acidified with 50 % sulphuric acid at room temperature, an aldehyde (from a primary nitro-compound) and a ketone (from a secondary nitro-compound) is obtained.

E.g. (R’ is either an alkyl group or a hydrogen atom):

\[
2\text{RR′C}\cdot\text{NO}_2\text{Na} + 2\text{H}_2\text{SO}_4 \rightarrow 2\text{RR′CO} + \text{N}_2\text{O} + 2\text{NaHSO}_4 + \text{H}_2\text{O} \quad (85\%)
\]

This reaction is called as the Nef carbonyl synthesis.

c. When treated with stannous chloride and hydrochloric acid, the sodium salt of the nitronic acid is reduced to the aldoxime or ketoxime :

\[
2\text{RR′C}\cdot\text{NO}_2\text{Na} \quad \text{SnCl}_2/\text{HCl} \quad \text{RR′C}\cdot\text{NOH}
\]

These oximes can be readily converted into the parent carbonyl compound by steam distillation or by direct hydrolysis with acid.

4. **Halogenation:** When primary and secondary nitro-alkanes are reacted with halogen in the presence of base, –halogenation takes place.

\[
\text{R}_2\text{C}≡\text{NO}_2\text{Na} + \text{Br}_2 + \text{NaOH} \rightarrow \text{R}_2\text{C} - \text{NO}_2 + \text{NaBr}
\]

Primary nitro-alkanes can form the mono- as well as dibromo-derivatives, but secondary nitroalkanes form only the monobromo derivative. Nitromethane can form the tribromo-derivative. The trichloro-derivative of nitro methane is called *chloropicrin*. 
When liquid or gaseous nitro-compounds are treated with halogen in the absence of alkali, then all the α-, β-, γ-, halogeno-nitroalkanes are formed.

\[
\text{CH}_3\text{CH}_2\text{NO}_2 + \text{Cl}_2 \rightarrow \text{CH}_3\text{CHClNO}_2 + \text{CH}_2\text{ClCH}_2\text{NO}_2
\]

E.g.,

5. Reaction with Nitrous acid: Nitro-compounds react with nitrous acid, the product formed depending on the nature of the alkyl group.

**Primary nitro-alkanes** form nitrolic acids, which dissolve in sodium hydroxide to give red solutions.

\[
\text{R-CH}_2\text{NO}_2 + \text{HO-NO} \rightarrow \text{R-C} \overset{\text{NO}}{\text{NO}} + \text{H}_2\text{O}
\]

**Secondary nitro-alkanes** form pseudonitroles; which are blue in colour. (the blue colour is probably due to the presence of the nitroso-group)

\[
\text{R}_2\text{CH-NO}_2 + \text{HO-NO} \rightarrow \text{R}_2\text{C} \overset{\text{NO}}{\text{NO}}_2 + \text{H}_2\text{O}
\]

**Tertiary nitro-alkanes** do not react with nitrous acid since they have no α-hydrogen atom.

These reactions with nitrous acid are the basis of the ‘red, white and blue’ test for the differentiation between different monohydric alcohols (Victor Meyer Test). In this test,

a) Treat alcohol with P + I\(_2\) to get alkyl iodide.
b) Alkyl iodide is then converted to nitroalkane by treating with AgNO\(_2\).
c) The nitroalkane is treated with HNO\(_3\) (NaNO\(_2\) + HCl).
d) Finally, the solution is made alkaline with aqueous NaOH (or KOH) solution.

- A blood red colouration indicates primary alcohol.
- A blue colouration indicates secondary alcohol.
- Colourless solution indicates tertiary alcohol.
5. **Aldol type condensations**: Owing to the presence of active $\alpha$-hydrogen atoms, primary and secondary nitro-compounds undergo condensation with aldehydes; this is similar to Aldol condensation. The $\alpha$-carbanion is formed from the nitro alkanes (having $\alpha$-hydrogen atom), which attack as a nucleophile to the carbonyl carbon atom of aldehydes.

E.g., Nitromethane condenses with benzaldehyde in the presence of ethanolic potassium hydroxide to form $\omega$-nitrostyrene.

\[
C_2H_5CHO + CH_2NO_2 \xrightarrow{KOH} C_6H_5CH=CHNO_2 + H_2O
\]

Similarly, nitroethane condenses with formaldehyde in the presence of aqueous potassium hydrogen carbonate to form the bis-hydroxy-methyl compound, 2-methyl-2-nitropropane-1,3-diol.

\[
CH_2CH_2NO_2 + 2HCHO \xrightarrow{KHCO_3} CH_2C\xrightarrow{NO_2}CH_2OH \xrightarrow{CH_2OH}
\]

6. **Mannich Reaction**: Primary and secondary nitro-compounds undergo this reaction. This is the condensation between formaldehyde, ammonia or a primary or secondary amine (preferably as the hydrochloride), and a compound containing at least one active hydrogen atom.

In this reaction, the active hydrogen atom is replaced by an amino-methyl group or substituted amino-methyl group:

\[
R_2CHNO_2 + HCHO + NH_4Cl \longrightarrow R_2C\xrightarrow{NO_2}CH_2NH_2\cdot HCl + H_2O
\]

This reaction provides a means of preparing a large variety of compounds, e.g., nitro-amines, diamines, etc.

**Nitro Arenes (Aromatic Nitro Compounds)**

**Introduction**

Aromatic nitro compounds are named by prefixing nitro to the name of the arene in which the $-NO_2$ group is substituted.

- Nitrobenzene
- 2-Nitrotoluene
- 1,3-Dinitrobenzene ($m$-Dinitrobenzene)
- 4-Nitrophenol

**Methods of preparation**

1. **From diazonium salts**: Diazonium salts when treated with nitrous acid in the presence of cuprous oxide, form nitro compounds.
2. **By direct nitration:** Nitroarenes are prepared by the *nitration* of the arene. E.g. nitrobenzene is prepared by reacting benzene with a mixture of concentrated nitric acid and concentrated sulphuric acid (known as the *nitrating mixture*).

**Mechanism:**

1. **The formation of the electrophile:** The electrophile is the "nitronium ion" or the "nitryl cation", \( \text{NO}_2^+ \). This is formed by reaction between the nitric acid and the sulphuric acid.

\[
\text{HNO}_3 + 2\text{H}_2\text{SO}_4 \rightarrow \text{NO}_2^+ + 2\text{HSO}_4^- + \text{H}_3\text{O}^+
\]

2. The electrophile attacks the benzene ring.

3. This is followed by the removal of proton, abstracted by an \( \text{HSO}_4^- \) ion.

**Chemical reactions of Nitro arenes**

Nitro group is an electron-withdrawing group and by resonance (-M or –R) and inductive effect
(-I), it withdraws electrons from the benzene ring and deactivates it to the attack of electrophiles. Further, a partial positive charge develops on the ortho- and para- positions.

The various resonating structures and resonance hybrids are as follows:

Electrophilic attack: Hence, an electrophile seeking to attack at the most electron-rich position(s), will attack the meta-position and not the ortho- and para- positions. Nitro group deactivates all positions for attack by an electrophile, but it does so more strongly for the ortho and para positions (by –R/M effect and –I effect) than the meta position (only by –I effect).

Nucleophilic attack: Generally, nucleophiles do not react with benzene but the presence of nitro group makes it susceptible to be attacked by nucleophiles. The nucleophile seeking to attack at the most electron-deficient position(s), will attack the ortho and para-position and not at the meta-positions.

1. Electrophilic substitution reactions: It takes place at the meta-position and drastic conditions are required to do so.

   a. Nitration: Is carried out by reacting with a mixture of concentrated nitric acid and concentrated sulphuric acid (known as the nitrating mixture).

   b. Sulphonation: Is carried out by reacting with a mixture of concentrated sulphuric acid and SO₃ (known as the sulphonating mixture).

   c. Chlorination: Is carried out by reacting with chlorine in the presence of Lewis acids like
d. Friedel Craft’s reaction: The presence of nitro group in the benzene nucleus deactivates it and reduces the electron density appreciably at $o$- and $p$-positions by resonance effect.

Compounds having deactivating and $m$-directing groups do not undergo Friedel-Craft's reaction and hence nitro compounds also do not show this reaction. In fact nitrobenzene is used as a solvent in Friedel-Craft's reaction as much because of its capability to dissolve AlCl$_3$ by forming a co-ordination complex and also because of its inertness towards the Friedel-Craft's reaction.

2. Nucleophilic substitution reactions

a. Aromatic Nucleophilic substitution
i. Nucleophilic substitution at vacant ortho and para positions: It takes place at the ortho and para- positions, e.g, Nitrobenzene when fused with KOH forms a mixture of $o$- and $p$-nitrophenol on acidification.

ii. Replacement (Nucleophilic substitution) of halogen group located at ortho and/or para positions to nitro group: When the $-\text{NO}_2$ group is present at the $o$- and $p$- positions (not in the $m$ - position) with respect to 'X' atom (halogen atom) in the benzene ring, it greatly activates the halogens towards nucleophilic substitution reaction. Moreover, greater the number of such activating group in the $o$ - and $p$ - positions with respect to 'X' atom, greater is the reactivity of haloarenes in nucleophilic substitution reaction.
It can be observed clearly, that the substitution has become easier with an increase in the number of NO$_2$ groups. Also note that, here, the vacant ortho and para position does not undergo nucleophilic substitution. This is because, although the ortho and para positions are electron deficient, but the halogen is a better leaving group than hydrogen atom.

**Mechanism: Aromatic nucleophilic substitution**

$S_N Ar$ mechanism [addition/elimination]: This is the most important of the mechanisms for nucleophilic aromatic substitution reactions. The experimental evidence indicates that there are two steps and so it is often referred to as the *addition/elimination mechanism*.

**Step 1: Addition step:** The reaction begins with attack by the nucleophile on the ring carbon bearing the leaving group. This produces an anionic intermediate. This ion, known as the *Meisenheimer complex*, is resonance stabilized.
Second step: Elimination step: The ring undergoes rearomatization with the loss of the Leaving Group. The first step, in which the ring loses its aromatic stabilization and the anion is produced is the slow or Rate Determining Step (RDS). However, the reaction as shown above would not proceed to yield product! Resonance stabilization alone is not sufficient for the anionic intermediate to form. It must be stabilized by strong electron-withdrawing groups in positions ortho and/or para to the leaving group.

The most important electron-withdrawing group \((G)\) for these reactions is the Nitro group \((-\text{NO}_2\)). It will activate the ring for NAS reaction with strong nucleophiles at moderate temperatures \((80-100^\circ\text{C})\).

The support for the \(S_NAr\) mechanism comes from the fact that the Meisenheimer complex has been trapped. Also the nature of the Leaving Group has little effect on the course of the reaction.

Like all anionic leaving groups, the group in the nucleophilic aromatic substitution reaction leaves with a pair of electrons so it must be a species that is able to bear a negative charge. In the first case \([a\ (i)]\), it is hydrogen leaving as hydride ion, which is a poor leaving group and the reaction does not take place easily. In the second case \([a\ (ii)]\), it is the halogen atoms leaving as halide ions, good leaving groups and thus the reaction proceeds readily.

b. Reactions of alkyl groups located at ortho and/or para positions to nitro group:
The presence of nitro group at \(o\)- or \(p\)-position with respect to an alkyl group alters the properties of the alkyl groups significantly.

Normally, the hydrogen atoms of alkyl groups attached to the benzene ring are not acidic or active. Hence, the alkyl groups do not participate in condensation reaction with aldehydes and ketones. If however, nitro groups are present in \(o\)- or \(p\)-position then the benzylic \(C - H\)
bonds get activated and the benzyl carbon can participate in condensation reaction.
e.g.

\[
\begin{align*}
\text{O}_2\text{N} &\quad \text{CH}_3 + \text{O} \quad = \quad \text{CH}_6\text{H}_5 \\
\rho &- \text{Nitrotoluene} \\
\text{O}_2\text{N} &\quad \text{CH} = \text{CH} \quad \text{CH} \quad \text{CH} \\
\rho &- \text{Nitrostilbene}
\end{align*}
\]

**d. Replacement of nitro group:** Nitro group is firmly linked to the aromatic nucleus and is not normally displaced by other groups. However, in polynitro compounds having nitro groups at ortho or \(p\)-position causes nucleophilic substitution of a nitro group. E.g.,

\[
\begin{align*}
\text{NO}_2 &\quad \text{NaNH}_2(\text{alcoholic}) \quad \Delta \quad \text{NH}_2 \\
\rho &- \text{Dinitrobenzene} \\
\text{NO}_2 &\quad \text{KOH}(\text{alcoholic})/\Delta \quad 2.\text{H}^+ \\
\rho &- \text{Nitrophenol}
\end{align*}
\]

**3. Reduction**
Different products are formed when nitrobenzene is reduced under different conditions. Reduction of nitro groups proceeds in the following stages.

- **1. Reduction in Acidic medium:** With metals and acid (Sn or Zn and HCl or TiCl₃) or by catalytic hydrogenation (H₂ in presence of Ni or Pt), nitrobenzene forms aniline.
  \[
  \text{C}_6\text{H}_5\text{NO}_2 \quad \text{[H]} \quad \text{H}^+ \quad \text{C}_6\text{H}_5\text{NH}_2
  \]

- **2. Reduction in Neutral medium:**
  a) With iron and steam, the nitro group is reduced to nitroso group.
b) On reduction with Zn/Sn and NH\(_4\)Cl or CaCl\(_2\) in neutral medium, it gets reduced to phenyl hydroxylamine

\[
C_6H_5NO_2 + 2Zn + 4NH_4Cl \rightarrow C_6H_5NHO + 2ZnCl_2 + 4NH_3 + H_2O
\]

Phenylhydroxyl amine

These phenyl hydroxylamines are reducing agents and reduce Tollens's reagent to form silver mirror. The reaction is used as a test for nitro group and is known as the Mulliken-Barker Test.

3. **Reduction in Alkaline medium:** Reduction of nitro group in alkaline medium first forms nitrosobenzene and phenyl hydroxylamine. These react with each other in alkaline medium to first form azoxybenzene, then azobenzene and finally hydrazobenzene.

![Chemical structure diagram](image)

The end product depends on the nature of the reducing agent. Reduction of nitrobenzene by methanolic sodium methoxide forms azoxybenzene. Nitrobenzene when reduced with alkaline sodium stannite or zinc and methanolic NaOH forms azobenzene. When reduced with Zn dust and KOH, nitrobenzene forms hydrazobenzene.

4. **Electrolytic reduction:** Electrolytic reduction of nitrobenzene in strongly acidic solution first forms phenyl hydroxylamine which in acidic solution rearranges, by migration of -OH group to \(p\)-position to form \(p\)-aminophenol.

![Chemical structure diagram](image)

In **strongly alkaline medium**, reduction of nitrobenzene first forms hydrazobenzene which rearranges to form benzidine used in the formation of azo dyes (Benzidine rearrangement). The reaction involves a cleavage of N - N bond in hydrazobenzene with the migration of phenyl group to \(p\)-position.
5. **Selective Reduction of Nitro group:** In the presence of other reducible groups like - CH = CH₂ or - CHO etc. on the ring, the nitro group may be selectively reduced to amino group using alkaline FeSO₄.

\[
\text{C}_6\text{H}_5\text{NO}_2 \xrightarrow{\text{Electrolytic reduction (alkaline)}} \text{Hydrazobenzene} \\
\text{Benzidine} \xrightarrow{\text{Rearrangement}} \text{Benzidine}
\]

\[
\text{CH} = \text{CH}_2 \xrightarrow{\text{alk.FeSO}_4} \text{NH}_2
\]

\(\alpha\)-Nitrostyrene \(\xrightarrow{\text{alk.FeSO}_4}\) \(\alpha\)-Amino styrene

\[
\text{CH} = \text{O} \xrightarrow{\text{alk.FeSO}_4 \text{ or SnCl}_2 \text{HCl}} \text{NH}_2
\]

\(p\)-Nitrobenzaldehyde \(\xrightarrow{\text{alk.FeSO}_4 \text{ or SnCl}_2 \text{HCl}}\) \(p\)-Amino benzaldehyde

When **two nitro groups** are present at \(m\)-position, one of them may be selectively reduced to nitro group using ammonium hydrogen sulphide \([(\text{NH}_4)_2\text{S}]\) or sodium polysulphide \([\text{Na}_2\text{S}_x]\) as the reducing agent.

\[
\text{O} \xrightarrow{\text{(NH}_4)_2\text{S} \text{ or N}_2\text{S}_x} \text{NH}_2
\]

\(p\)-Dinitrobenzene

6. **Reduction with Metal Hydrides like NaBH₄ and LiAlH₄:** LiAlH₄ reduces nitrobenzene to azobenzene while NaBH₄ reduces it to aniline.
Picric acid (2,4,6-trinitro-phenol)
Also known as Picronitric acid, Carbazotic acid, nitroxantic acid

Picric Acid is used in electric batteries, leather industry, dyes, pigments, inks, paints, manufacture of colored glass, textile mordants, as a laboratory reagent, in matches and explosives. It consists of pale yellow, odorless, intensely bitter crystals of density 1.763 and melting point 122 – 123°C. It explodes at 300°C.

Preparation:
1. From phenol: When phenol is treated with concentrated nitric acid in the presence of conc. sulphuric acid, picric acid is formed.

\[
\text{OH} + \text{Concentrated HNO}_3 \rightarrow O_2N\text{-OH-NO}_2
\]

Picric acid (2,4,5-Trinitrophenol)

2. From picryl chloride: Picryl chloride when treated with water at 40°C, it produces picric acid.

\[
\text{O}_2\text{N-Cl-NO}_2 \xrightarrow{\text{H}_2\text{O}, 40^\circ \text{C}} \text{O}_2\text{N-H-NO}_2 + \text{HCl}
\]

3. From Phenol derivatives such as Salicylic and Acetylsalicylic acids: In place of phenol, salicylic acid or acetyl salicylic acids are nitrated. The sulfuric acid breaks down the acetylsalicylic acid to acetic and salicylic acid.
Salicylic acid with heat source converts to carbolic acid (phenol) and carbon dioxide; (in presence of water from 98% H\textsubscript{2}SO\textsubscript{4})

The phenol so produced undergoes nitration to give picric acid.

**Reactions:**

1. **Picrates:** Are charge-transfer complexes of picric acid.

Picric acid combines with electron rich compounds such as amines, phenols, naphthalene, anthracene, etc in 1:1 ratio to yield molecular compounds (picrates), which usually possess characteristic melting points.
2. Halogenation: Reaction with SOCl₂ or PCl₅ gives picryl chloride. Halogen acids have no affect on it.

![Reaction Diagram]

Amines
Introduction
Amines are organic compounds that are structurally related to inorganic ammonia and are basic in nature. They can be thought of as derivatives of ammonia in which one, two or all the three hydrogen atoms have been replaced by alkyl or aryl groups. They are classified into primary (1°), secondary (2°) or tertiary (3°) amines, depending on whether nitrogen is joined to one, two or three alkyl or aryl groups respectively.

\[
\begin{align*}
\text{NH}_3 & \quad \text{Primary (1°) amine} \\
& \Rightarrow \text{R NH}_2 \\
& \Rightarrow \text{R}_2 \text{NH} \\
& \Rightarrow \text{R}_3 \text{N} \quad \text{Secondary (2°) amine} \\
& \Rightarrow \text{Tertiary (3°) amine}
\end{align*}
\]

The characteristic functional groups for primary, secondary and tertiary amines are -- NH₂, \( \text{NH} \) and \( \text{N} \) respectively.

Another class of compounds, besides the primary, secondary and tertiary amines, is the quaternary ammonium salts. In these salts, nitrogen is quaternary, i.e. joined to four alkyl groups. They can be considered to be derivatives of ammonium salts, in which all the four hydrogen (H) atoms are replaced by alkyl or aryl groups.

\[
\begin{align*}
\text{Ammonium salt} & \Rightarrow \text{Replace four H atoms by alkyl groups} \\
\left[\text{NH}_4\right]^+ \times X^{-} & \Rightarrow \left[\text{NR}_4\right]^+ \times^{-} \\
\text{Tetraalkyl ammonium salt}
\end{align*}
\]

Here, X may be Cl⁻, Br⁻, I⁻, HSO₄⁻ or OH⁻.
Examples
\[
\begin{align*}
\text{Tetramethyl ammonium chloride} & \Rightarrow (\text{CH}_3)_4 \text{N}^+ \text{Cl}^- \\
\text{Tetraphenyl ammonium bromide} & \Rightarrow (\text{C}_6\text{H}_5)_4 \text{N}^+ \text{Br}^- \\
\text{Tetraethyl ammonium iodide} & \Rightarrow (\text{CH}_3\text{CH}_2)_4 \text{N}^+ \text{I}^- 
\end{align*}
\]
Amines are further classified into aliphatic amines and aromatic amines.

**Nomenclature**

**Aliphatic Amines**

In aliphatic amines, the nitrogen atom is bonded to one, two or three alkyl chains.

In the **common system**, the aliphatic amines are named by using a prefix for the alkyl chain or the group, followed by the word **amine**. They are also called **aminoalkanes**. For example

\[
\begin{align*}
\text{CH}_3\text{NH}_2 & \text{ is methylamine or aminomethane.} \\
\text{(CH}_3\text{)}_2\text{NH} & \text{ is dimethylamine or N-methylaminomethane.} \\
\text{CH}_3\text{NHC}_2\text{H}_3 & \text{ is ethylmethylamine or N-methylaminoethane.} \\
\text{(CH}_3\text{)}_3\text{N} & \text{ is trimethylamine or N,N-dimethylaminomethane.}
\end{align*}
\]

In the **IUPAC system**, they are considered to be amino derivatives of corresponding alkanes. Thus, they are named **alkanamines**, if \(-\text{NH}_2\) is the highest **priority group**. If there is another group with higher priority in the molecule, then the prefix **-amino** is used. An alkanamine is obtained by dropping \(-\text{e}\) from the name of the parent alkane, and adding the suffix **amine** to it. For example

\[
\begin{align*}
\text{CH}_3\text{NH}_2 & \text{ is methanamine} \\
\text{CH}_3\text{CH}_2\text{NH}_2 & \text{ is ethanamine} \\
\text{CH}_3 - \text{CH} - \text{CH}_3 & \text{ is propan-2-amine} \\
\text{CH}_3 - \text{CH}_2 - \text{CH}_2 - \text{NH}_2 & \text{ is propan-1-amine}
\end{align*}
\]

Secondary and tertiary amines are named **N-alkylalkanamine** and **N,N-dialkylalkanamine** respectively, where alkanamine refers to the parent alkanamine which has the largest number of carbon atoms. For example

\[
\begin{align*}
\text{(CH}_3\text{)}_2\text{NH} & \text{ is N-methylmethanamine} \\
\text{(CH}_3\text{)}_3\text{N} & \text{ is N,N-dimethylmethanamine} \\
\text{CH}_3\text{CH}_2\text{NHCH}_3 & \text{ is N-methylethananine} \\
\text{CH}_3\text{CH}_2\text{N(CH}_3\text{)}_2 & \text{ is N,N-dimethylethananine} \\
\text{(CH}_3\text{CH}_2\text{)}_2\text{NCH}_3 & \text{ is N-ethyl-N-methylethananine}
\end{align*}
\]
Aliphatic Heterocyclic amines
Here, the Nitrogen is a part of the aliphatic cyclic ring. For example,

\[
\begin{align*}
\text{piperidine} & \quad \text{pyrrolidine}
\end{align*}
\]

Aromatic amines
Aromatic amines can be classified into the following two types:
Aryl amines: Aryl amines have the nitrogen atom bonded to one or more aryl groups directly.
Example

\[
\begin{align*}
\text{Aniline} & \quad \text{Diphenylamine} & \quad \text{Triphenylamine}
\end{align*}
\]

Aromatic Heterocyclic amines: Here, the Nitrogen is a part of an aromatic cyclic ring. For example,

\[
\begin{align*}
\text{indole} & \quad \text{pyridine} & \quad \text{pyrimidine} & \quad \text{pyrrole} & \quad \text{imidazole}
\end{align*}
\]

Aralkyl amines
Aralkyl amines have the nitrogen atom bonded to the side chain of aromatic ring systems.
Example

\[
\begin{align*}
\text{Benzylamine}
\end{align*}
\]
Physical properties

1. **Physical state and smell**: The lower aliphatic amines are colourless gases, while those with four carbons or higher members are liquids. Methylamine and ethylamine have an ammoniacal smell but higher amines have a fishy smell. They are all lighter than water.

Aromatic amines are generally very toxic; they are readily absorbed through the skin, often with fatal results. Aromatic amines are very easily oxidized by air, and although most are colorless when pure, they are often encountered discolored by oxidation products.

2. **Boiling points**: Like ammonia, amines are polar compounds and, except for tertiary amines, can form intermolecular hydrogen bonds. As a result of this, amines have higher boiling points than the non-polar compounds of similar molecular masses.

<table>
<thead>
<tr>
<th>Compound</th>
<th>CH₂CH₃</th>
<th>CH₃OH</th>
<th>CH₃NH₂</th>
<th>CH₃CH₂CH₃</th>
<th>CH₃CH₂OH</th>
<th>CH₃CH₂NH₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular mass (g mol⁻¹)</td>
<td>30</td>
<td>32</td>
<td>31</td>
<td>44</td>
<td>46</td>
<td>45</td>
</tr>
<tr>
<td>Boiling Point (°C)</td>
<td>-88.6°</td>
<td>65°</td>
<td>-6.0°</td>
<td>-42°</td>
<td>78.5°</td>
<td>16.6°</td>
</tr>
</tbody>
</table>

However, they have lower boiling points than those of corresponding alcohols or carboxylic acids. This is because the O - H bond is more polar than the N - H bond and, thus, hydrogen bonds are stronger in alcohols and acids than in amines.

Among the isomeric amines, tertiary amines show no hydrogen bonding and have the lowest boiling points. Primary amines have the highest boiling points due to a more extensive hydrogen bonding. Chain branching reduces boiling points by 10 to 15 °C.
<table>
<thead>
<tr>
<th>Compound</th>
<th>CH$_3$(CH$_2$)$_2$NH$_2$</th>
<th>CH$_3$CH$_2$NHCH$_3$</th>
<th>(CH$_3$)$_2$CHNH$_2$</th>
<th>(CH$_3$)$_3$N</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Molecular mass (g mol$^{-1}$)</strong></td>
<td>59</td>
<td>59</td>
<td>59</td>
<td>59</td>
</tr>
<tr>
<td><strong>Boiling Point (°C)</strong></td>
<td>48°</td>
<td>37°</td>
<td>34°</td>
<td>3°</td>
</tr>
</tbody>
</table>

3. **Solubility**: Amines of all three classes are capable of forming hydrogen bonds with water. As a result, amines of lower molecular masses (upto 6 carbon atoms) are soluble in water due to hydrogen bonding. With an increase in molecular mass, the solubility in water decreases. The higher amines are soluble in non-polar solvents like benzene, ether, etc.

Amines are soluble in less polar solvents like ether, alcohol, benzene, etc.

The water solubility of 1º and 2º-amines is similar to that of comparable alcohols. As expected, the water solubility of 3º-amines and ethers is also similar.

**Salts of amines**: Aqueous mineral acids or carboxylic acids readily convert amines into their salts, which are readily soluble in water.

**Structure and Stereochemistry of Amines**
Nitrogen uses $sp^3$ orbitals, which are directed to the corners of a tetrahedron. Three of these orbitals overlap s orbitals of hydrogen or carbon; the fourth contains an unshared pair of electrons. Amines, thus are like ammonia, **pyramidal**, and with very nearly the same bond angles.
For example, trimethylamine has bond angle $108^\circ$.

\[
\begin{align*}
\ldots & \quad \text{N} \quad 108^\circ \\
\text{CH}_3 & \quad \text{CH}_3 \quad \text{CH}_3
\end{align*}
\]

From their 3-D visualisation, one can see that a molecule in which nitrogen carries three different groups is not super impossible on its mirror image; it is chiral and should exist in two enantiomeric forms (I and II) each of which if separated from the other is expected to show optical activity. *But no that’s not true! Why?*

Such enantiomers have not yet been isolated—for simple amines—and spectroscopic studies have shown why: the energy barrier between the two pyramidal arrangements about nitrogen is ordinarily so low that they are rapidly interconverted. This is very similar to the rapid rotation about carbon–carbon single bond, which prevents the isolation of conformational enantiomers.
Hence, the rapid inversion about nitrogen prevents isolation of enantiomers like I and II. This phenomenon is referred as inversion. Hence, an unshared pair of electrons of nitrogen cannot ordinarily serve as a fourth group to maintain configuration.

The quaternary ammonium salts, in which four alkyl groups are attached to nitrogen atom are tetrahedral. Here all four sp³ orbitals of nitrogen are used to form bonds.

Quaternary ammonium salts in which nitrogen is attached to four different groups have been found to exist as configurational enantiomers, and are capable of showing optical activity.

Amine Salts as Phase Transfer Catalysts
As the chemical industry strives to improve process efficiency, safety and reduce environmental impact, Phase Transfer Catalysis (PTC) has become recognized as a useful tool to achieve these goals.

The PTC methodology involves a substrate (which is soluble in the organic layer) and an anionic reagent (often a nucleophile), which is dissolved in the aqueous layer. The substrate and the anion are then brought together by a catalyst, which transports the anion into the organic phase where reaction can take place with the substrate.

Quaternary ammonium and phosphonium salts with their unique capability to dissolve in both aqueous and organic liquids are the catalysts of choice for most phase transfer applications. The ammonium derivatives are the most commonly used, but the phosphonium based phase transfer catalysts offer other interesting properties as well, like higher thermal stability. Other phase transfer catalysts include crown ethers and polyethyleneglycols (PEG).

Applications: Some examples of well-known phase transfer catalyzed reactions include:
- Nucleophilic substitution reactions, like halogenations and cyanations
- Alkylation and condensation reactions
- Oxidations and reductions
- Elimination reactions
- Wittig and Wittig-Horner reactions

Advantages as compared to other systems:
There are several advantages of the phase transfer catalysis system over single-phase systems, such as:
- An increased reaction rate
- A lower reaction temperature
Avoiding the need for expensive anhydrous or aprotic solvents.
- The use of water together with an organic solvent as reaction medium.

Interestingly, some reactions are known to occur in a PTC-system that does not work in a normal system. The efficiency of phase transfer catalysis is influenced by the bulkiness of the groups attached to the phase transfer catalyst, its lipophilicity as well as that of its counter ion.

**Why is it required?**

Phase-Transfer Catalysis is useful primarily for performing reaction between anions (and certain neutral molecules such as $\text{H}_2\text{O}_2$ and transition metal complexes such as $\text{RhCl}_3$) and organic substrates. PTC is needed because many anions (in the form of their salts, such as NaCN) and neutral compounds are soluble in water and not in organic solvents, whereas the organic reactants are not usually soluble in water. The name phase-transfer catalysis does what it says...the catalyst acts as a shuttling agent by extracting the anion or neutral compound from the aqueous (or solid) phase into the organic reaction phase (or interfacial region) where the anion or neutral compound can freely react with the organic reactant already located in the organic phase.

Reactivity is further enhanced, sometimes by orders of magnitude (!), because once the anion or neutral compound is in the organic phase, it has very little (if any) hydration or solvation associated with it, thereby greatly reducing the energy of activation, thus increasing reactivity.

Since the catalyst is often a **quaternary ammonium salt** (e.g., tetrabutyl ammonium, $[\text{C}_4\text{H}_{9}4\text{N}^+]$), also called the "quat" and symbolized by $Q^+$, the ion pair $Q^+X^-$ ($X^-$ being the anion to be reacted) is a much looser ion pair than say $\text{Na}^+X^-$. This looseness of the ion pair is a third key reason for enhanced reactivity, which will ultimately lead to increased productivity (reduced cycle time) in commercial processes. At the end of the reaction, an anionic leaving group is usually generated. This anionic leaving group is conveniently brought to the aqueous (or solid) phase by the shuttling catalyst, thus facilitating the separation of the waste material from the product. This mechanism is called the "extraction mechanism" of phase-transfer catalysis and is shown in Figure 1.

**The Extraction Mechanism (Starks, 1971)**

![Extraction Mechanism Diagram](image)

The extraction mechanism easily accounts for the benefits of PTC which include the following and other benefits:

1. **achieving high reactivity** : reactants are in the same phase with less hydration in a loose ion pair.
2. **extreme flexibility in choosing or eliminating solvent**: a properly chosen quaternary ammonium catalyst can extract almost any anion into almost any organic medium, including into the product or into one of the organic reactants resulting in a solvent-free process.

3. **reducing the excess of water-sensitive reactants**: such as phosgene, benzoyl chloride, esters and dimethyl sulfate since they are protected in the bulk organic phase from the aqueous phase by interfacial tension.

4. **higher selectivity**: lower energy of activation allows reduction of reaction temperature and time.

5. **the use of inexpensive and less hazardous bases**: hydroxide is easily transferred and activated in nearly all organic solvents.

**Some Reactions**: There are hundreds of commercial applications of Phase-Transfer Catalysis and they were commercialized due to the competitive advantages which they truly provide. A few are as follows:

1. **Continuous Dehydrohalogenation to Produce a Large Scale Monomer**

   ![Chemical Reaction](cocoalkyl bis[beta-hydroxypropyl] ammonium Cl 1115 ppm 20.5% NaOH 99.2%)

2. **Thiolation (Methyl Mercaptan)**

   ![Chemical Reaction](NH N N NH CHSH BuNBr 2 mole% 20% NaOH o-xylene 4.5h, 100°C 96%)

3. **Etherification (O-Alkylation)**

   ![Chemical Reaction](OH + (CH3)2SO BuNCH2PhCl 1-10 mol% 0.3M NaOH CH2Cl2 2-12h, r.t. 93%)

4. **High Yield Solvent-Free Hazardous Nucleophilic Displacement**

   ![Chemical Reaction](Cl Cl NaN3 BuNBr 1.6 mole% 2.4 equiv Na3 no solvent 94%)
5. Oxidation (Hypochlorite)

\[
\text{CH}_3\text{O} + \text{CH}_3\text{OH} + 10\% \text{NaOCl} \rightarrow \text{Bu_4NHSO_4, 5 mol\% \text{ethyl acetate, 28 min, r.t.}} \rightarrow \text{CH}_3\text{O} + \text{H} \]

6. Oxidation (Air)

\[
\text{CH}_3 \quad + \quad \text{air (12-15 atm)} \quad \xrightarrow{\text{CoCl}_2 \cdot 6\text{H}_2\text{O, 0.2 mol\%, no solvent}} \quad \text{COOH} \]

7. Cyanation

\[
\text{C}_4\text{H}_8 + \text{NaCN} \rightarrow \text{C}_4\text{H}_8 + \text{NaCl} \]

8. Michael Addition

\[
\text{F}_2\text{C} = \text{C} + \text{Ph}_3\text{NCH}_2\text{Cl} \rightarrow \text{LDA, THF(dry), 1h, -78°C} \rightarrow \text{F}_2\text{C} = \text{C} \quad \text{84\%} \]

9. Chiral Alkylation
Basicity of Amines
Like ammonia, the primary, secondary and tertiary amines has a lone pair of electrons on the nitrogen atom and thus, is basic in character.

Also, like ammonia, amines are converted into their salts by aqueous mineral acids and are liberated from their salts by aqueous hydroxides. Like ammonia, therefore, amines are more basic than water and less basic than hydroxide ion:

$$RNH_3^+ + OH^- \rightarrow RNH_2 + H_2O$$

It is convenient to compare basicities of amines by measuring the extent to which they accept hydrogen ion from water; the equilibrium constant for this reaction on combining with $[H_2O]$ gives the basicity constant, $K_b$.

$$RNH_2 + H_2O \leftarrow K_b \rightarrow RNH_3^+ + OH^-$$

$$K_b = K_{eq}[H_2O] = \frac{[RNH_3^+][OH^-]}{[RNH_2]}$$

Each amines has its characteristic $K_b$; the larger the $K_b$, the stronger the base. It can also be expressed in terms of $pK_b$ values ($pK_b = -\log K_b$). Smaller the value of $pK_b$, stronger is the base.

Note: The principal base in an aqueous solution of an amine (or of ammonia, for that matter) is the amine itself, not hydroxide ion. Measurement of $[OH^-]$ is simply a convenient way to compare basicities.

Factors affecting the basicity:
1. the atom having the lone pair of electrons (here, nitrogen atom) should be less electronegative, so that the lone pair is readily donated.
2. After accepting the proton, the conjugate acid should be stabilized.

Both the above conditions, in general, are enhanced by electron donating groups. Hence, electron donating groups increase the basicity; and electron withdrawing groups decrease the basicity.

a. Amines are stronger bases than alcohols, ethers, esters, etc.
It is because, nitrogen is less electronegative than oxygen, the lone pair is easily donated and can better accommodate the positive charge of the ion.

b. Alkyl amines are stronger bases than ammonia
This can be explained in terms of an electron donating inductive effect of the alkyl groups. Alkyl groups, by their electron donating effect, increase the electron density of nitrogen and hence, make the lone pair of nitrogen more easily available to be given to acids. Further, the electron
donating alkyl group(s) stabilises the alkyl ammonium ion formed and, thus, shifts the equilibrium in the forward direction.

\[
\begin{align*}
R & \overset{\text{ donate electrons}}{\longrightarrow} N^+ + H^+ \quad \overset{\text{stabilizes ions, makes unshared pair more available}}{\longleftrightarrow} \quad R \overset{\text{donates electrons}}{\longrightarrow} N-H^+
\end{align*}
\]

Aliphatic amines of all three classes have \(K_b\) values of about \(10^{-3}\) to \(10^{-4}\) (0.001 to 0.0001); they are thus somewhat stronger bases than ammonia (\(K_b = 1.8 \times 10^{-5}\)).

c. Basic strength of primary, secondary and tertiary amines

The difference in basicity among primary, secondary, and tertiary aliphatic amines are due to a combination of salvation and polar factors.

1. In gas phase: Among primary, secondary and tertiary aliphatic amines, the number of electron donating alkyl groups are maximum in tertiary amines and minimum in primary amines. The basic strength should be expected to increase from primary to tertiary. This is the order observed in the gas phase.

\[
R_3N > R_2NH > RNH_2
\]

(3°) (2°) (1°)

2. In solution phase: However, the order of basicity in an aqueous solution is found to be

\[
R_2NH > RNH_2 > R_3N
\]

(2°) (1°) (3°)

This can be explained as follows:

The basic strength in aqueous solutions depends not only upon the electron releasing effects but also upon the steric effect and the hydration effect (or solvation effect).

a. Steric Effect: The steric effect refers to the crowding of bulky alkyl groups around the N atom, which hinder the attack of the hydrated proton (\(H_3O^+\)) on the amine and thus, decrease its basic strength. The steric effect is maximum in case tertiary amines. This can be visualized with the help of inversion happening in all the amines, but primary and secondary amines have two or one smaller hydrogen atoms attached to them, thus less steric hindrance.

b. Solvation Effect: The solvation or hydration effect refers to the stabilisation of the protonated amine (conjugate acid) by water molecules. The water molecules form H bonds with the protonated amine and release hydration energy. In the case of primary amines, hydration energy is maximum and in tertiary amines, it is the least. The resultant of all the factors usually causes the 2° amine to be more basic than the 1° amine, followed by the 3° amine.
c. Aryl amines are weaker bases than ammonia: This can be explained in terms of the electron withdrawing resonance and inductive effect of the aryl groups, which decrease the electron density of nitrogen and hence, make the lone pair of nitrogen less available to be given to acids. Aromatic amines have $K_b$ values of $10^{-9}$ or less, they are thus weaker bases than ammonia ($K_b = 1.8 \times 10^{-5}$).

Other explanations:
Comparing the structures of aniline and the anilinium ion with the structures of ammonia and the ammonium ion, we find that ammonia and the ammonium ion are each represented satisfactorily by a single structure:

\[
\begin{align*}
\text{Ammonia:} & \quad H \quad N \quad H \\
\text{Ammonium ion:} & \quad H \quad N \quad H^+ \\
\end{align*}
\]

Aniline and anilinium ion contain the benzene ring and therefore are hybrids of the Kekule structure I and II, and III and IV respectively.

\[
\begin{align*}
\text{Aniline:} & \quad \begin{bmatrix}
H \\
\text{N:H} \\
\text{I}
\end{bmatrix} + H^+ \\
\text{Anilinium ion:} & \quad \begin{bmatrix}
H^+ \\
\text{N:H} \\
\text{II}
\end{bmatrix}
\end{align*}
\]

The resonance at the first look, presumably stabilizes both amine and ion to the same extent. It lowers the energy content of each by the same number of kilocalories per mole, and hence does not affect the difference in their energy contents, that is, does not affect $G$ of protonation (or ionization). If there were no other factors involved, then, we might expect the basicity of aniline to be about the same as the basicity of ammonia.

But looking carefully, there are additional structures to be considered. Due to the resonance effect (+R effect of $\text{-NH}_2$ group), aniline is hybrid not only of structures I and II but also of structures V, VI and VII. On the other hand, similar comparable structures of the anilinium ion cannot be made.

This is because $\text{-NH}_3^+$ is neither $+R$ group (as there is no lone pair available for delocalization into the benzene ring) nor $-R$ group (as nitrogen will exceed its valency if it withdraws electrons from the benzene ring).

\[
\begin{align*}
\text{Aniline:} & \quad \begin{bmatrix}
H \quad N \quad H \\
\text{V}
\end{bmatrix} \\
\text{Anilinium ion:} & \quad \begin{bmatrix}
H \quad N \quad H \\
\text{VI}
\end{bmatrix} \\
\end{align*}
\]

Contribution from the three structures V, VI and VII stabilizes aniline in a way that is not possible for anilinium ion; resonance thus lowers the energy content of aniline more than it
lowers the energy content of the anilinium ion. The net effect is to shift the equilibrium in the
direction of less ionization, that is, to make $K_b$ smaller

The low basicity of aromatic amines is thus due to the fact the amine is stabilized by resonance
to a greater extent than is the ion.

**Order of basicity of some common compounds:**

<table>
<thead>
<tr>
<th>Compound</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \text{NH}_2 )</td>
<td>( \text{O}_2\text{N} )</td>
<td>( \text{NH}_3 )</td>
<td>( \text{CH}_3\text{C}≡\text{N} )</td>
<td></td>
</tr>
<tr>
<td>( pK_b )</td>
<td>3.0</td>
<td>3.3</td>
<td>3.3</td>
<td>4.7</td>
<td>12.2</td>
</tr>
</tbody>
</table>

From the table, it is clear that
1. **amides are less basic than amines:** This is due to the delocalization of lone pair of nitrogen on more electronegative oxygen atom.
2. **Acetonitrile is least basic:** This is due to the sp character of N, less electronegative than the sp$^2$ or sp$^3$ hybridised nitrogen (as in imines and amines).
3. **Pyridine is more basic than pyrrole:** This is because, the lone pair is available on the nitrogen of pyridine, but not in pyrrole. In pyrrole, the lone pair is deocalised for exhibiting the aromatic character.

d. **Effect of substituents on basicity of aromatic amines:** Substituents on the ring have a marked effect on the basicity of aromatic amines. For example, \( p \)-nitroaniline is only 1/4000 as basic as aniline.

**Table: Basicity Constants Of Substituted Anilines**

\[
K_b \text{ of aniline} = 4.2 \times 10^{-10}
\]

<table>
<thead>
<tr>
<th>S.N.o.</th>
<th>Substituent</th>
<th>( K_b )</th>
<th>Substituent</th>
<th>( K_b )</th>
<th>Substituent</th>
<th>( K_b )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( p - \text{NH}_2 )</td>
<td>( 140 \times 10^{-10} )</td>
<td>( m - \text{NH}_2 )</td>
<td>( 10 \times 10^{-10} )</td>
<td>( o - \text{NH}_2 )</td>
<td>( 3 \times 10^{-10} )</td>
</tr>
<tr>
<td>2</td>
<td>( p - \text{OCH}_3 )</td>
<td>( 20 \times 10^{-10} )</td>
<td>( m - \text{OCH}_3 )</td>
<td>( 2 \times 10^{-10} )</td>
<td>( o - \text{OCH}_3 )</td>
<td>( 3 \times 10^{-10} )</td>
</tr>
<tr>
<td>3</td>
<td>( p - \text{CH}_3 )</td>
<td>( 12 \times 10^{-10} )</td>
<td>( m - \text{CH}_3 )</td>
<td>( 5 \times 10^{-10} )</td>
<td>( o - \text{CH}_3 )</td>
<td>( 2.6 \times 10^{-10} )</td>
</tr>
<tr>
<td>4</td>
<td>( p - \text{Cl} )</td>
<td>( 1 \times 10^{-10} )</td>
<td>( m - \text{Cl} )</td>
<td>( 0.3 \times 10^{-10} )</td>
<td>( o - \text{Cl} )</td>
<td>( 0.05 \times 10^{-10} )</td>
</tr>
<tr>
<td>5</td>
<td>( p - \text{NO}_2 )</td>
<td>( 0.001 \times 10^{-10} )</td>
<td>( m - \text{NO}_2 )</td>
<td>( 0.029 \times 10^{-10} )</td>
<td>( o - \text{NO}_2 )</td>
<td>( 0.00006 \times 10^{-10} )</td>
</tr>
</tbody>
</table>
From the table, it can be seen that
1. an electron releasing substituent like $–\text{CH}_3$ increases the basicity of aniline
2. an electron-withdrawing substituent like $–\text{X}$ or $–\text{NO}_2$ decreases the basicity.

A given substituent affects the basicity of an amine and the acidity of a carboxylic acid in opposite ways. This is to be expected, since basicity depends upon ability to accommodate a positive charge, and acidity depends upon ability to accommodate a negative charge.

Here also, like in ortho substituted benzoic acid, ortho effect is operative. Electron-releasing substituents weaken basicity when they are ortho to the amino group, and electron-withdrawing substituents do so to a much greater extent from the ortho position than from meta or para position.

e. Guanidine is a very strong base: Although lone pair delocalization generally reduces the basicity of amines, a dramatic example of the reverse effect is found in the compound guanidine ($\text{pK}_a = 13.6$). Here, as shown below, resonance stabilization of the base is small, due to charge separation, while the conjugate acid is stabilized strongly by charge delocalization. Consequently, aqueous solutions of guanidine are nearly as basic as are solutions of sodium hydroxide.

Preparation

1. Reduction of nitro compounds: Both aliphatic and aromatic nitro compounds on reduction give primary amines.
Nitro compounds can be reduced in two general ways:

(a) by catalytic hydrogenation using molecular hydrogen.
A solution of the nitro compound in alcohol is shaken with finely divided nickel or platinum under hydrogen gas.

For example:

\[
\begin{align*}
\text{NHCOCH}_3 \text{NO}_2 & \quad \xrightarrow{H_2, \text{Pt}} \quad \text{NHCOCH}_3 \text{NH}_2 \\
\text{o-Nitroacetanilide} & \quad \text{o-Aminoacetanilide}
\end{align*}
\]

Similarly,

\[
\begin{align*}
\text{COOC}_2\text{H}_5 \text{NO}_2 & \quad \xrightarrow{H_2, \text{Pt}} \quad \text{COOC}_2\text{H}_5 \text{NH}_2 \\
\text{Ethyl } p\text{-nitrobenzoate} & \quad \text{Ethyl } p\text{-aminobenzoate}
\end{align*}
\]

This method cannot be used when the molecule also contains some other easily hydrogenated group, such as a carbon-carbon double bond.

(b) by chemical reduction, usually by a metal and acid.
Done by adding hydrochloric acid to a mixture of the nitro compound and a metal, usually granulated tin. In the acidic solution, the amine is obtained as its salt; the free amine is liberated by the addition of base, and is steam-distilled from the reaction mixture.

\[
\begin{align*}
\text{CH}_3 \text{NO}_2 & \quad \xrightarrow{\text{Sn, HCl, heat}} \quad \text{(NH}_3\text{)}^+\text{SnCl}_6^{2-} \\
\text{p-Nitrotoluene} & \quad \text{p-Toluidine}
\end{align*}
\]

The crude amine is generally contaminated with some unreduced nitro compound, from which it can be separated by taking advantage of the basic properties of the amine; the amine is soluble in aqueous mineral acid, and the nitro compound is not.

Similarly,

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{CH}_2\text{NO}_2 & \quad \xrightarrow{\text{Fe, HCl}} \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{NH}_2 \\
1\text{-Nitropropane} & \quad n\text{-Pr oplia min e}
\end{align*}
\]
Reduction of aromatic nitro compound is by far the most useful method of preparing amines, since it uses readily available starting materials, and yields the most important kind of amines, primary aromatic amines. These amines can be converted into aromatic diazonium salts, which are among the most versatile class of organic compounds known. The sequence

\[ \text{nitro compound} \rightarrow \text{amine} \rightarrow \text{diazonium salt} \]

provides the best possible route to synthesise various kinds of aromatic compounds.

2. Reduction of alkyl cyanides: When alkyl or aryl cyanides are reduced with H\textsubscript{2}/Ni or LiAlH\textsubscript{4} or Na - C\textsubscript{2}H\textsubscript{5}OH, they give primary amines. When the reduction is carried out using Na - C\textsubscript{2}H\textsubscript{5}OH, it is known as Mendius's reaction.

\[ R - C \equiv N \xrightarrow{\text{Reduction}} R - CH\textsubscript{2}NH\textsubscript{2} \]

\[ Ar - C \equiv N \xrightarrow{\text{Reduction}} Ar - CH\textsubscript{2}NH\textsubscript{2} \]

Examples:

\[ \text{CH}_3\text{CN} \xrightarrow{\text{LiAlH}_4} \text{CH}_3\text{CH}_2\text{NH}_2 \]

\[ \text{C}_2\text{H}_5\text{CN} \xrightarrow{\text{Na,C}_2\text{H}_5\text{OH}} \text{C}_2\text{H}_5\text{CH}_2\text{NH}_2 \]

\[ \text{CH}_2\text{Cl} \xrightarrow{\text{NaCN}} \text{CH}_3\text{CN} \xrightarrow{\text{H}_2, \text{Ni, 140°C}} \text{CH}_2\text{CH}_2\text{NH}_2 \]

Synthesis via reduction of nitriles has the special feature of increasing the length of a carbon chain, producing a primary amine that has one more carbon atom than the alkyl halide from which the nitrile was made.

3. By ammonolysis: Alkyl halides react with alcoholic ammonia to form amines. The reactivity of various halides in this reaction is as follows:

\[ R - I > R - Br > R - Cl \]

The reaction is generally carried out either by allowing the reactants to stand together at room
temperature or by heating them under pressure. Displacement of halogen by \( \text{NH}_3 \) yields the amine salt, from which the free amine can be liberated by treatment with hydroxide ion.

\[
\text{RX} + \text{NH}_3 \rightarrow \text{RNH}_3^+ \text{X}^-
\]

\[
\text{RNH}_3^+ \text{X}^- + \text{OH}^- \rightarrow \text{RNH}_2 + \text{H}_2\text{O} + \text{X}^-
\]

Ammonolysis of halides is a nucleophilic substitution reaction. The organic halide is attacked by the nucleophilic ammonia molecule in the same way that it is attacked by hydroxide ion, alkoxide ion, cyanide ion, acetylide ion, and water:

As with other reactions of this kind, elimination tends to compete with substitution: ammonia can attack hydrogen to form alkene as well as attack carbon to form amine. Ammonolysis thus gives the highest yields with primary halides (where substitution predominates) and is virtually worthless with tertiary halides (where elimination predominates).

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} \xrightarrow{\text{NH}_3} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_3^+\text{Br}^- \quad \text{Substitution}
\]

\[
\text{CH}_3 \quad \text{C} \quad \text{CH}_3 \xrightarrow{\text{NH}_3} \text{CH}_3 \quad \text{C} \equiv \text{CH}_2 + \text{NH}_4\text{Br} \quad \text{Elimination}
\]

Because of their generally low reactivity, aryl halides are converted into amines only (a) if the ring carries \(-\text{NO}_2\) groups, (a strongly electron-withdrawing group), at positions ortho and para to the halogen, or (b) if a high temperature (and pressure) or a strongly basic reagent is used.

Examples:

Toluene \( \rightarrow \) Benzyl chloride \( \rightarrow \) Benzylamine

\[
\text{CH}_3\text{CH}_2\text{COOH} \xrightarrow{\text{Br}_2} \text{CH}_3\text{CHCOOH} \xrightarrow{\text{NH}_3} \text{CH}_3\text{CHCOOH}
\]

Propionic acid \( \rightarrow \) \(\alpha\)-Bromopropionic acid \( \rightarrow \) Alanine

\[
\text{CH}_2 = \text{CH}_2 \xrightarrow{\text{Cl}_2} \text{CICH}_2\text{CH}_2\text{Cl} \xrightarrow{2\text{NH}_3} \text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_2
\]

Important disadvantage of this synthesis is the formation of more than one class of amine.

The primary amine salt, formed by the and the free primary amine; the following equilibrium thus exists;
The free primary amine, like the ammonia from it was made, is a nucleophilic reagent; it too can attack the alkyl halide, to yield the salt of a secondary amine:

\[
\text{RNH}_2 + RX \rightarrow R_2\text{NH}_2^+X^- \quad \text{secondary amine}
\]

The secondary amine, which is in equilibrium, with its salt, can in turn attack the alkyl halide to form the salt of a tertiary amine:

\[
R_2\text{NH}_2 + RX \rightarrow R_3\text{NH}_2^+X^- \quad \text{tertiary amine}
\]

Finally, the tertiary amine can attack the alkyl halide to form a compound of the formula \( R_4\text{N}^+X^- \), called a quaternary ammonium salt.

\[
R_3\text{N} + RX \rightarrow R_4\text{N}^+X^- \quad \text{quaternary ammonium salt}
\]

In the presence of excess ammonia, the yield of primary amine is more.

**4. Reductive amination of aldehydes and ketones**

\[
\begin{align*}
\text{C}==\text{O} + \text{NH}_3 & \xrightarrow{H_2, \text{Ni} \text{ or NaBH}_3\text{CN}} \text{CH} \text{NH}_2 & 1^\circ \text{ amine} \\
& + \text{RNH}_2 \xrightarrow{H_2, \text{Ni} \text{ or NaBH}_3\text{CN}} \text{CH} \text{NHR} & 2^\circ \text{ amine} \\
& + \text{R}_2\text{NH} \xrightarrow{H_2, \text{Ni} \text{ or NaBH}_3\text{CN}} \text{CH} \text{NR}_2 & 3^\circ \text{ amine}
\end{align*}
\]

**Reductive amination** means reduction in the presence of ammonia.
Primary amines may be prepared by passing a mixture of an aldehyde (or a ketone) and a large excess of ammonia and hydrogen over nickel at 150°C or by use of sodium cyanohydridoborate, NaBH₃CN.

Reaction involves reduction of an intermediate compound (an imine, \( \text{RCH} = \text{NH} \) or \( \text{R}_2\text{C} = \text{NH} \)) that contains a carbon-nitrogen double bond.
If a primary amine is used in place of ammonia, it will produce a 2° amine. If a secondary amine, it will produce a 3° amine. Reductive amination has been used successfully with a wide variety of aldehydes and ketones, both aliphatic and aromatic.

**Examples:**

\[
\begin{align*}
\text{CH}_3 - \text{C} = \text{CH}_3 + \text{NH}_3 + \text{H}_2 \overset{\text{Ni}}{\rightarrow} & \quad \text{CH}_3 - \text{CH} - \text{CH}_3 \\
\text{Acetone} & \quad \text{Isopropylamine (1°)}
\end{align*}
\]

\[
\begin{align*}
\text{(CH}_3\text{)}_2\text{CH} = \text{O} + \text{NH}_2 & \overset{\text{NaBH}_3\text{CN}}{\rightarrow} \text{NCH}_2\text{CHC(CH}_3\text{)}_2 \\
\text{Isobutyraldehyde} & \quad \text{Aniline (1°)}
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3\text{C} = \text{O} + \text{(CH}_3\text{)}_2\text{NH} + \text{H}_2 & \overset{\text{Ni}}{\rightarrow} \text{CH}_3\text{CH} - \text{N} - \text{CH}_3 \\
\text{Acetaldehyde} & \quad \text{Dimethylethylamine (3°)}
\end{align*}
\]

\[
\begin{align*}
\text{CH}=\text{CH}_3 & \overset{\text{NH}_2, \text{NaBH}_3\text{CN}}{\rightarrow} \text{CH} - \text{CH}_3 \\
\text{Acetophenone} & \quad \alpha\text{-Phenylethylamine}
\end{align*}
\]

Reductive amination of ketones yields amines containing a sec-alkyl group in good yields; such amines are otherwise difficult to obtain by ammonolysis because of the tendency for sec-alkyl halides to undergo elimination.

For example, cyclohexanone is converted into cyclohexylamine by reductive amination, whereas ammonolysis of bromocyclohexane yields only cyclohexene.
Although the yields are poor. This is because, during reductive amination, the aldehyde or ketone can react not only with ammonia but also with the primary amine that has already been formed, and thus yield a certain amount of secondary amine.

$$R \quad C \quad O \quad H_2N \quad CH_2R \quad \rightarrow \quad \left[ R \quad C \quad N \quad CH_2R \right] \quad \text{reduction} \quad \rightarrow \quad RCH_2 \quad N \quad CH_2R$$

Although, the tendency for the reaction to go beyond the desired stage can be fairly well limited by the proportions of reactants employed.

5. Gabriel's phthalimide synthesis: Gabriel's phthalimide synthesis is used to prepare pure primary aliphatic amines and thus provides an indirect method of carrying on the transformation of RX to RNH$_2$, without the formation of secondary or tertiary amines as byproducts. In this method, phthalimide is first converted into potassium phthalimide (a salt) by a reaction with KOH (or NaOH). Then, potassium phthalimide gives N-alkyl-phthalimide on treatment with alkyl halide, which gives a primary amine on hydrolysis with hydrochloric acid.

Example:
6. By **Hoffmann's bromamide reaction**: Acid amides give primary amines on reaction with bromine, in the presence of an alkali, at about 343 K. The amine formed in this reaction has one carbon atom less than the parent compound.

![Chemical reaction](image)

In another way,

![Chemical reaction](image)

Examples:

- \( \text{CH}_3\text{CONH}_2 \overset{\text{Br}_2/\text{KOH}}{\Delta} \rightarrow \text{CH}_3\text{NH}_2 \)
- \( \text{CH}_3\text{CH}_2\text{CH}_2\text{CONH}_2 \overset{\text{Br}_2/\text{KOH}}{\Delta} \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{NH}_2 \)

Hofmann degradation of amides has the special feature of **yielding a product containing one less carbon than the starting material**.

**Mechanism**: The reaction is believed to proceed by the following steps:

**Step (1)**: is the halogenation of an amide. The N-haloamide can be isolated if no base is present. Furthermore, if the N-haloamide isolated in this way is then treated with base, it is converted into the amine.

![Chemical reaction](image)

**Step (2)**: is the abstraction of a the proton (hydrogen ion) attached to nitrogen, by the hydroxide ion, felicitated by presence of the electron-withdrawing bromine which increases the acidity of the amide. Unstable salts have actually been isolated in certain of these reactions.

![Chemical reaction](image)

**Step (3)**: involves the separation of a halide ion, which leaves behind an electron-deficient nitrogen atom.
Step (4): the actual rearrangement occurs.

Step (3) and (4) are generally believed to occur simultaneously, the attachment of R to nitrogen helping to push out halide ion.

Step (5): is the hydrolysis of an isocyanate (R – N = C = O) to form an amine and carbonate ion. This is a known reaction of isocyanates. If the Hofmann degradation is carried out in the absence of water, an isocyanate can actually be isolated.

Hofmann rearrangement thus, involves a 1, 2-shift, very similar to rearrangement of carbocations. In the rearrangement of carbocations, a group migrates with its electrons to an electron-deficient carbon; here, the alkyl group migrates with its electrons to an electron-deficient nitrogen.

The strongest support for the mechanism just outlined is the fact that many of the proposed intermediates have been isolated, and that these intermediates have been shown to yield the products of the Hofmann degradation.

The mechanism is also supported by the fact that analogous mechanisms account satisfactorily for observations made on a large number of related rearrangements. Furthermore, the actual rearrangement step fits the broad pattern of 1, 2-shifts to electron-deficient atoms.

This is an example of an intramolecular rearrangement.

**Stereochemistry at the migrating group in Hofmann’s rearrangement:** Rearrangement proceeds with complete retention of configuration about the chiral center of the migrating group. For example, when optically active α-phenylpropionamide undergoes the Hofmann degradation, α-phenylethylamine of the same configuration and of essentially the same optical purity is obtained.
Important features of this rearrangement in terms of stereochemistry are:

1. Nitrogen takes the same relative position of the chiral carbon that was originally occupied by the carbonyl carbon.
2. The chiral carbon does not break away from the carbonyl carbon until it has started to attach itself to nitrogen. If the group were actually to become free during its migration, we would expect considerable loss of configuration and hence a partially recemic product.

Hence, the migrating group moves from carbon to nitrogen via a transition state, I, in which carbon is pentavalent:

The migrating group steps from atom to atom; it does not jump.

The stereochemistry of all 1, 2-shifts has this common feature: complete retention of configuration in the migrating group.

Timing of the steps in Hofmann’s rearrangement:

As mentioned earlier, steps (3) and (4) of the mechanism are believed to be simultaneous, that is that loss of bromide ion and migration occur in the same step:

There are two reasons for this belief:

a. The chances of formation of a highly unstable intermediate in which an electronegative element like nitrogen has only a sextet of electrons are very-very rare. Such a particle should be even less stable than primary carbocations, which are seldom formed.

b. Due to the effect of structure on reactivity.
An electron deficient atom is most commonly generated by the departure of a leaving group which takes the bonding electrons with it. The migrating group here is, obviously, a nucleophile, and so the rearrangement is an intramolecular nucleophilic substitution.

As the nucleophilic substitution can be of two types: SN$_2$ and SN$_1$; Similarly, the same possibilities exist for a rearrangement.

**In SN$_1$ like mechanism**, the migrating group will wait for the departure of the leaving group before it moves.

**In SN$_2$- like mechanism**, the neighbouring group helps to push out the leaving group in a single step reaction. When the migrating groups helps to expel the groups leaving group, it is said to give anchimeric assistance (Greek; anchi + mercos, adjacent parts).

let’s come back to the Hofmann degradation, it has been found that when the migrating group is aryl, the rate of the degradation is increased by the presence of electron-releasing substitutents in the aromatic ring; thus substituted benzamides show the following order of reactivity.

```
CONH$_2$  \( \xrightarrow{\text{ohe}} \)  NH$_2$
```

G: \( -\text{OCH}_3 > -\text{CH}_3 > -\text{H} > -\text{Cl} > -\text{NO}_2 \)

*How could electron donation speed up Hofmann’s degradation?* It must be affecting the rate of migration. Migration of an aryl group takes place via a structure shown below which is more stable if aryl ring is joined to electron donating group. Hence, the substituents affect the rate of rearrangement and hence the migratory aptitude.
The electron releasing substituents speed up Hofmann degradation by speeding up rearrangement. But, under what conditions can this happen? Consider the steps (3) and (4). Loss of bromide ion (3) could be fast and reversible, followed by slow rearrangement (4). Hence, the rearrangement is the slowest and rate determining step. Also there is evidence which show that steps (3) and (4) take place simultaneously.

Hence, a concentrated mechanism (3, 4). Attachment of the migrating groups helps to push out bromide ion. As the amount of anchimeric assistance varies so does the observed rate of reaction.

Also, the sequence (3) and (4) corresponds to an $S_{N}1$ mechanism; the concerted reaction (3, 4) corresponds to a $S_{N}2$ mechanism. Dependence of overall rate on the nature of the nucleophile is consistent with the $S_{N}2$ like mechanism, but not with the $S_{N}1$ like mechanism.

**Similar other reactions:**

This reaction is one of the four reactions involving the rearrangement of Acyl Nitrenes to Isocyanates

Although the nitrogen atom of a nitrene has no formal charge, it is electron deficient and serves as a locus for 1,2-rearrangements. Acyl nitrenes may be generated from different amide-like starting compounds. Once formed, acyl nitrenes quickly rearrange to relatively stable isocyanate isomers, which may be isolated or reacted with hydroxylic solvents. The most common application of this rearrangement is for the synthesis of amines. Thus, addition of water to the ketene-like isocyanates produces an unstable carbamic acid that decomposes to an amine and carbon dioxide.
Hofmann Route: Primary amides are converted to N-halogenated derivatives by the action of HOX or X₂ in alkaline solution. Excess base generates a conjugate base of the product.

Lossen Route: A hydroxamic acid derivative (RCONHOH) is made by reacting an ester with hydroxyl amine. The hydroxamic acid is O-acylated and then converted to its conjugate base.

Curtius Route: An acyl azide (RCON₃) is prepared in one of two ways. (i) Reaction of an acyl chloride with sodium azide, or (ii) Reaction of an ester with excess hydrazine, followed by reaction of the acylhydrazide product (RCONHNH₂) with cold nitrous acid. Acyl azides decompose to isocyanates on heating.

Schmidt Route: A variant of the Curtius procedure in which a carboxylic acid is heated with hydrazoic acid (HN₃) and an acid catalyst.

7. Other methods of preparation:

From alcohols (industrial method): Aliphatic amines of low molar mass are prepared on a large scale by passing a mixture of an alcohol and ammonia in the vapour phase, over heated alumina or thoria at 300-400°C. This method also results in a mixture of primary, secondary and tertiary amines. If ammonia is in excess, primary amine is the major product.

\[ \text{ROH} + \text{NH}_3 \xrightarrow{\text{Al}_2\text{O}_3 \text{ or ThO}_2, \text{300-400}^\circ\text{C}} \text{RNH}_2 \xrightarrow{\Delta} \text{R}_2\text{NH} \xrightarrow{\Delta} \text{R}_3\text{N} \]

2. Reduction of oximes: Primary amines can be obtained by the reduction of oximes of aldehydes and ketones with LiAlH₄ or H₂/Ni.

\[ \text{R} \text{C} \equiv \text{N} \text{OH} \xrightarrow{\text{LiAlH}_4} \text{R} \text{CH} \equiv \text{NH}_2 + \text{H}_2\text{O} \]

Primary amine

\[ \text{CH}_3 \text{C} \equiv \text{N} \text{OH} \xrightarrow{\text{LiAlH}_4} \text{CH}_3 \text{CH}_2 \equiv \text{NH}_2 + \text{H}_2\text{O} \]

Ethanamine
3. **By reduction of amides:** Amides get reduced to primary, secondary or tertiary amines by Na/C₂H₅OH or LiAlH₄.

\[
    \text{R\textsuperscript{\text{-}}C\textsuperscript{\text{-}}NH\text{₂} \xrightarrow{\text{LiAlH₄}} \text{RCH₂NH₂ (1\text{°})}}
\]

\[
    \text{R\textsuperscript{\text{-}}C\textsuperscript{\text{-}}NH\text{\text{-}}R' \xrightarrow{\text{LiAlH₄}} \text{RCH₂NHR' (2\text{°})}}
\]

\[
    \text{R\textsuperscript{\text{-}}C\textsuperscript{\text{-}}N\text{\text{-}}R' \xrightarrow{\text{LiAlH₄}} \text{RCH₂N\text{-}N\text{-}R (3\text{°})}}
\]

**Reactions**

All the three classes of amines contain nitrogen that bears an unshared pair of elections. *The tendency of nitrogen to share this pair of electrons underlies the entire chemical behaviour of amines*: their basicity, their actions as nucleophiles – in both aliphatic and acyl substitution – and the unusually high reactivity of aromatic rings bearing amino or substituted amino groups.

With certain reagents the product that is actually obtained can vary, depending upon the class of the amines. Here also the first step is the nucleophilic attack; it is just that what finally happens depends upon how many hydrogen the nitrogen carries, that is, upon the class of the amine.

1. **Reaction with metal ions:** Lower aliphatic amines form coordination complexes with metal ions like Ag\(^+\) and Cu\(^{2+}\). For example, copper sulphate forms a deep blue solution with ethylamine.

\[
    \text{CuSO₄ + 4C₂H₅NH₂} \rightarrow [\text{Cu(C₂H₅NH₂)}₄]^{2+} + \text{SO₄}^{2-} \quad \text{(Deep blue solution)}
\]

2. **Alkylation: (Reaction with alkyl halides):** Both aliphatic and aromatic amines react with alkyl halides to form amines of higher classes.

\[
    \text{RNH₂} \xrightarrow{\text{RX}} \text{R₂NH} \xrightarrow{\text{RX}} \text{R₃N} \xrightarrow{\text{RX}} \text{R₄N⁺X⁻}
\]

\[
    \text{ArNH₂} \xrightarrow{\text{RX}} \text{ArNHR} \xrightarrow{\text{RX}} \text{ArNR₂} \xrightarrow{\text{RX}} \text{ArNR₃⁺X⁻}
\]

**Examples**

- \(\text{C₂H₅NH₂ + C₂H₅I} \rightarrow (\text{C₂H₅})₂\text{NH} + \text{HI}\)
- \((\text{C₂H₅})₂\text{NH} + \text{C₂H₅I} \rightarrow (\text{C₂H₅})₃\text{N} + \text{HI}\)
- \((\text{C₂H₅})₃\text{N} + \text{C₂H₅I} \rightarrow (\text{C₂H₅})₄\text{N}⁺\text{I}⁻\)
3. Reaction with aldehydes and ketones: Primary amines react with aliphatic and aromatic aldehydes or ketones to form imines known as Schiff's bases.

Examples:

- Ethylamine + Acetaldehyde → C$_2$H$_5$-N=C-CH$_3$
- Methylamine + Acetone → CH$_3$-N=C-CH$_3$

Secondary amines react to form enamines.

Tertiary amines do not react with aldehydes or ketones.
4. Conversion into amides:

a. Acylation: Acylation is the process of replacement of the H atom of the amino group by the acyl group \( R - C = O \).

Primary and secondary amines react with acid chlorides or acid anhydrides to form N-substituted amides.

Tertiary amines do not give this reaction, as they do not have an H atom on nitrogen.

Examples:

\[
\text{CH}_3\text{NH}_2 + \text{CH}_3\text{COCl} \rightarrow \text{CH}_3\text{NCOCH}_3 + \text{HCl}
\]

b) Benzylation: Benzylation is the process of replacement of the H atom of the amino group by the benzyol group \( \text{C}_6\text{H}_5\text{CO} \). Primary and secondary amines react with benzyol chloride \( \text{C}_6\text{H}_5\text{COCl} \), in the presence of a base-like pyridine to form benzyol derivatives.

\[
\text{C}_2\text{H}_5\text{NH}_2 + \text{C}_6\text{H}_5\text{COCl} \xrightarrow{\Delta, \text{Pyridine}} \text{C}_2\text{H}_5\text{NHCOCH}_6\text{H}_5
\]

\[
(\text{CH}_3)_2\text{NH} + \text{C}_6\text{H}_5\text{COCl} \xrightarrow{\Delta, \text{Pyridine}} (\text{CH}_3)_2\text{NCOCH}_6\text{H}_5
\]

When the acetylation or benzylation of compounds containing active hydrogen such as alcohols, phenols or amines is carried out with acetylchloride or benzyolchloride respectively, in the presence of aqueous NaOH as a base, it is called a Schotten-Baumann reaction. The
reaction takes place at room temperature.

c. **Sulphonylation**: Primary, secondary and tertiary amines react differently with benzene sulphonyl chloride and this forms the basis for the **Hinsberg test** to differentiate between different types of amines.

In this test, amine is treated with benzene sulphonyl chloride in the presence of cold aqueous sodium hydroxide (NaOH).

**Primary amines** produce N-alkylsulphonamide, which contains acidic hydrogen and hence, dissolves in a sodium hydroxide (NaOH) solution to form the soluble sodium salt. The acidification of the solution gives a precipitate of N-alkylsulphonamide.

![Reaction of primary amine with benzene sulphonyl chloride](image)

Secondary amines yield N,N-dialkylsulphonamide, which has no acidic hydrogen and precipitates immediately, as it is incapable of forming soluble sodium salts with sodium hydroxide (NaOH).

![Reaction of secondary amine with benzene sulphonyl chloride](image)

Tertiary amines, having no available hydrogen attached to nitrogen, do not react and remain insoluble materials, which, on acidification, form a soluble quaternary salt.

![Reaction of tertiary amine with benzene sulphonyl chloride](image)

Tertiary amines, although basic and hence nucleophilic, fail to yield amides, presumably because they cannot lose a proton (to stabilize the product) after attaching themselves to carbon or to sulfur. Here is a reaction which requires not only that amines be nucleophilic, but also that they
possess a hydrogen atom attached to nitrogen.

**Like simple amides, substituted amides undergo hydrolysis.** The products are the corresponding acid and the amine, although one or the other is obtained as its salt, depending upon the acidity or alkalinity of the medium.

![Chemical reaction diagram](image1.png)

**Sulfonamides are hydrolyzed more slowly than amides of carboxylic acids.** This is because, nucleophilic attack on a trigonal acyl carbon is relatively unhindered; it involves the temporary attachment of the fourth group, the nucleophilic reagent. Nucleophilic attack on tetrahedral sulfonyl sulfur is relatively hindered; it involves the temporary attachment of the fifth group. Also, the tetrahedral carbon of the acyl intermediate makes use of the permitted octet of electrons; although sulfur may be able to use more than eight electrons in covalent bonding, this is a less stable system than the octet. Thus both steric and electronic factors tend to make sulfonyl compounds less reactive than acyl compounds.

![Chemical reaction diagram](image2.png)

6. **Ring substitution in aromatic amines**
The lone pair on nitrogen atom of the -NH₂ group is delocalised in the benzene ring. As a result, the overall electron density of the benzene ring is increased and it becomes activated for attack by electrophiles and deactivated for attack by nucleophiles. The resonance effect makes the ortho- and para- positions comparatively richer in electrons than meta-positions. An electrophile, thus preferentially attacks the ortho- and para-positions.
Thus, aryl amines undergo electrophilic substitution in the benzene ring readily and the -NH₂ group directs the incoming electrophile to its ortho- and para- positions.

\[
\begin{align*}
-\text{NH}_2 & \quad \text{Activate strongly and direct orth, para} \\
-\text{NHR} & \quad \text{in electrophilic aromatic substitution} \\
-\text{NR}_2 &
\end{align*}
\]

The acetamido group -NHCOCH₃, is also activating and ortho, para directing, but less powerfully so than a free amino group. Electron withdrawal by oxygen of the carbonyl group makes the nitrogen of an amide a much poorer source of electrons than the nitrogen of an amine. Electrons are less available for sharing with a hydrogen ion, and therefore amides are much weaker bases than amines: amides of carboxylic acids do not dissolve in dilute aqueous acids. Electrons are less available for sharing with an aromatic ring, and therefore an acet-amido group activates an aromatic ring less strongly than an amino group.

More precisely, electron withdrawal by carbonyl oxygen destabilizes a positive charge on nitrogen, whether this charge is acquired by protonation or by electrophilic attack on the ring.

**In electrophilic substitution, the chief problem encountered with aromatic amines is that**

(a) they are *too reactive.*

(b) With some electrophiles, the attack may first occur at the nitrogen thus making it positively charged and *meta directing* for the electrophilic attack (e.g. nitration of aniline)

a) **Bromination:** When aniline is treated with bromine or chlorine water, halogenation occurs to give tribromo- or trichloroaniline. In halogenation, substitution tends to occur at every available ortho or para position.

To get monosubstituted products, the phenyl ring of aniline is *deactivated by acetylation* of the -NH₂ group.
b) **Nitration**: Direct nitration of aniline with HNO\(_3\) and H\(_2\)SO\(_4\) yields \(m\)-nitroaniline as the major product.

Nitric acid not only nitrates, but oxidizes the highly reactive ring as well, with loss of much material as tar. Furthermore, in the strongly acidic nitration medium, the amine is converted into the anilinium ion; substitution is thus controlled not by the \(-\text{NH}_2\) group but by the \(-\text{NH}_3^+\) group which, because of its positive charge and –I effect (electron withdrawing), directs much of the substitution to the *meta* position.

In order to prepare \(o\)- and \(p\)-nitroaniline, the \(-\text{NH}_2\) group of aniline is protected by acetylation. The products are \(o\)- and \(p\)-nitroacetanilide, which, on hydrolysis, give \(o\)- and \(p\)-nitroaniline.

c) **Sulphonation**: Primary aromatic amines can be sulphonated without prior protection of the \(-\text{NH}_2\) group, as sulphuric acid is a weaker oxidising agent than nitric acid. Aniline, on reaction with concentrated sulphuric acid, gives aniline hydrogen sulphate, which, on heating, forms sulphamic acid, which undergoes rearrangement to finally give sulphanilic acid or \(p\)-aminobenzenesulphonic acid.
Sulfanilic acid; it is an important and interesting compound. Its properties are not those we would expect of a compound containing an amino group and a sulfonic acid group. Both aromatic amines and aromatic sulfonic acids have low melting points. On the other hand, sulfanilic acid has such a high melting point that on being heated it decomposes (at 280 – 300°C) before its melting point can be reached.

Sulfonic acid are generally very soluble in water; indeed, we have seen that the sulfonic acid group is often introduced into a molecule to make it water-soluble. Sulfanilic acid is insoluble in organic solvents. Sulfanilic acid is soluble in aqueous bases but insoluble in aqueous acids. These properties of sulfanilic acid are understandable when we realize that sulfanilic acid actually has the structure I which contains the $\text{–NH}_3^+$ and $\text{–SO}_3^–$ groups. Sulfanilic acid is a salt, but a rather special kind, called a dipolar ion (sometimes called a zwitterions, from the German, Zwitter, hermaphrodite).

It is the product of reaction between an acidic group and a basic group that are part of the same molecule. The hydrogen ion is attached to nitrogen rather than oxygen simply because the $\text{–NH}_2$ group is a stronger base than the $\text{–SO}_3^–$ group.

Hence, sulphanilic acid has

1. a high melting point and insolubility in organic solvents
2. insolvability in water is not surprising, since many salts are insoluble in water.
3. In alkaline solution, the strongly basic hydroxide ion pulls hydrogen ion away from the weakly basic $\text{–NH}_2$ group to yield the $p$ – aminobenzenesulfonate ion (II), which, like most sodium salts, is soluble in water.
4. In aqueous acidic medium, the sulfanilic acid structure is not charged, and therefore the compound remains insoluble; sulfonic acid are strong acids and their anions (very weak bases) show little tendency to accept hydrogen ion from $\text{H}_3\text{O}^+$.

![Diagram of sulfanilic acid and its derivatives](image-url)
**d) Nitrosation:** Tertiary dialkyl, aryl amines undergo nitrosation at para position, when treated with nitrous acid.

\[
\text{N(CH}_3\text{)}_2 + \text{NaNO}_2, \text{HCl} \rightarrow \text{N(CH}_3\text{)}_2 \text{NO}
\]

\(N,N\) – Dimethyl amine \(p\) – Nitroso – \(N,N\) – dimethylaniline

**e) Azo dye formation:** Aromatic amines give azo dyes when treated with diazonium salts, at 0-5°C.

\[
\text{CH}_3\text{N} = \text{N} + \text{N}_2\text{Cl}^+ \xrightarrow{\text{acid}} \text{CH}_3\text{N} = \text{N} + \text{HCl} + \text{N}_2
\]

\(N,N\) – Dimethylaniline Benzenediazonium chloride An azo compound

**7. Reactions with nitrous acid.**
Primary, secondary and tertiary amines react with nitrous acid to give different products.

**Primary aliphatic amines** react with nitrous acid to form alcohol and nitrogen gas.

\[
\text{RNH}_2 \xrightarrow{\text{HONO}} \text{[R -- N = N]} \xrightarrow{\text{H}_2\text{O}} \text{N}_2 + \text{mixture of alcohols (and alkenes)}
\]

Example:

\[
\text{C}_2\text{H}_5\text{NH}_2 \xrightarrow{\text{HNO}} \text{C}_2\text{H}_5\text{OH} + \text{N}_2 + \text{H}_2\text{C}
\]

**Primary aromatic amines** react with nitrous acid at low temperatures (0 - 5°C) to give aromatic diazonium salts. This reaction is called diazotisation.

\[
\text{ArNH}_2 \xrightarrow{\text{HONO}} \text{Ar -- N = N} \quad \text{Diazonium salt}
\]

Example:

\[
\text{NH}_2 \quad \xrightarrow{\text{0-5°C}} \quad \text{N}_2\text{Cl}^- + \text{NaCl} + \text{2H}_2\text{O}
\]

**Secondary aliphatic and aromatic amines** react with nitrous acid to form yellow, oily nitrosoamines that are insoluble in the aqueous solution.
On heating the nitrosoamine with a little phenol and concentrated sulphuric acid, it produces a red solution which turns blue on treatment with sodium hydroxide. This is known as **Liebermann's nitrosoamine test**. Example

\[ (\text{CH}_3\text{)}_2\text{NH} + \text{HNO}_2 \rightarrow \text{CH}_3\text{N} = \text{NO} + \text{H}_2\text{O} \]

**Tertiary aliphatic amines** form nitrites on reaction with nitrous acid.

\[ \text{R}_3\text{N} + \text{HNO}_2 \rightarrow [\text{R}_3\text{NH}]^+ \text{NO}_2^- \]

Example

\[ (\text{C}_2\text{H}_5\text{)}_3\text{N} + \text{HNO}_2 \rightarrow [ (\text{C}_2\text{H}_5\text{)}_3\text{NH}]^+ \text{NO}_2^- \]

**Tertiary aromatic amines** undergo electrophilic substitution in the ring to give \( p \)-nitroso derivatives.

\[ \text{NR}_2 \xrightarrow{\text{HONO}} \text{O} = \text{N} \text{NR}_2 \quad p-Nitroso compound \]

Example:

\[ \text{N,N-Dimethylaniline} + \text{HNO}_2 \rightarrow \text{p-Nitroso-N,N-dimethylaniline} \]

Ring nitrosation is an electrophilic substitution reaction, in which the attacking reagent is either the nitrosonium ion, \( ^+\text{NO} \), or some species (like \( \text{H}_2\text{O} = \text{NO} \) or \( \text{NOCl} \)) that can easily transfer \( ^+\text{NO} \) to the ring. The nitrosonium ion is very weakly electrophilic compared with the reagents involved in nitration, sulfonation, halogenation, and the Friedel-Crafts reaction.
Nitrosation occurs only in rings bearing the powerfully activating dialkylamino (−NR₂) or hydroxyl (−OH) group.

7. Reaction with Diethyl Oxalate (Hofmann's Reagent)
Primary amines react with diethyl oxalate to form solid oxamide. Secondary amines react with diethyloxalate to form a liquid oxamic ester. Tertiary amines do not react.

Diethyl oxalate may therefore be used to distinguish and separate primary, secondary and tertiary amine (no reaction) as these oxamide and oxamic ester on hydrolysis regenerate primary and secondary amines respectively.

8. Carbylamine reaction
Primary aliphatic and aromatic amines react with chloroform in the presence of an alcoholic solution of potassium hydroxide, to give offensive (foul) smelling isocyanides (or carbylamines).

\[
\begin{align*}
R-\text{NH}_2 + CHCl_3 + 3KOH & \rightarrow R-N=C + 3KCl + 3H_2O \\
C_2H_5NH_2 \xrightarrow{CHCl_3,KOH} & C_2H_5N=C
\end{align*}
\]
The reaction is used as a test for primary amine.

**Mechanism:**
The reaction of chloroform with alkali forms dichlorocarbene by α-elimination. This neutral electrophile attacks the electron rich nitrogen of amino followed by elimination of two HCl molecules to form the bad smelling isocyanide.

\[
\text{H} + \text{H} - \text{CCl}_3 \xrightarrow{\text{H}_2\text{O}} \text{Cl} - \text{C} - \text{Cl} \xrightarrow{-\text{Cl}} \text{Cl} - \text{C} - \text{Cl} \xrightarrow{\text{Cl}} \text{Dichlorocarbene}
\]

\[
\text{R} - \text{NH}_2 + \text{CCl}_2 \xrightarrow{+\text{H}_2\text{O}} \text{R} - \text{N}^+ - \text{C} - \text{Cl}_2 \xrightarrow{-2\text{HCl}} \text{R} - \text{N} \xrightarrow{\text{H}^+} \text{Alkylcarbylamine}
\]

Hydrolysis of alkyl carbylamine with acid, regenerates the amine and the bad smell of isocyanide disappears.

\[
\text{R} - \text{NC} + 2\text{H}_2\text{O} \xrightarrow{\text{H}^+} \text{R} - \text{NH}_2 + \text{HCOOH}
\]

**9. With carbon disulphide**
Primary aliphatic and aromatic amines react with CS\(_2\) in the presence of HgCl\(_2\) to give alkyl isothiocyanates.

\[
\text{RNH}_2 + \text{CS}_2 + \text{HgCl}_2 \rightarrow \text{R} - \text{N} = \text{C} = \text{S} + \text{HgS} + 2\text{HCl}
\]

Example

\[
\text{CH}_3\text{NH}_2 + \text{CS}_2 + \text{HgCl}_2 \rightarrow \text{CH}_3 - \text{N} = \text{C} = \text{S} + \text{HgS} + 2\text{HCl}
\]

Isothiocyanates have a characteristic smell of mustard oil and thus, the reaction is called **Hoffmann's mustard oil reaction**.

**10. With Grignard's reagent**
Primary and secondary (both aliphatic and aromatic) amines react with Grignard's reagent to form alkanes. The alkane formed from the alkyl part of the Grignard's reagent is

\[
\text{RNH}_2 + \text{R'} \text{MgX} \rightarrow \text{R'H} + \text{MgX} \{(\text{NHR})\}
\]
11. Oxidation
Different types of amines give different types of oxidation products.

**Primary aliphatic amines:** With acidified KMnO₄, primary amines joined to primary alkyl group give aldehydes, primary amines joined to secondary alkyl group give ketones and primary amines joined to tertiary alkyl group give nitroalkanes.

\[
\begin{align*}
R\text{CH}_2\text{NH}_2 & \xrightarrow{[O]} R\text{CH} = \text{NH} \xrightarrow{\text{H}_2\text{O}/\text{H}^+} R\text{CHO} + \text{NH}_3 \\
R\text{CH}_2\text{NH}_2 & \xrightarrow{[O]} R\text{C} = \text{NH} \xrightarrow{\text{H}_2\text{O}/\text{H}^+} R\text{C} = \text{O} + \text{NH}_3 \\
R\text{C} = \text{NH}_2 & \xrightarrow{[O]} R\text{C} = \text{NO}_2
\end{align*}
\]

**Secondary aliphatic and aromatic amines,** on oxidation with KMnO₄, give etraalkylhydrazines and with H₂O₂ or peracid, give dialkylhydroxylamines.

\[
\begin{align*}
R\text{NH} & \xrightarrow{\text{KMnO}_4} R\text{NNR} \\
R\text{NH} & \xrightarrow{\text{H}_2\text{O}_2 \text{ or Peracid}} R\text{N} = \text{OH}
\end{align*}
\]

**Tertiary amines** form amine oxides when oxidised with H₂O₂ or peracids.

\[
\begin{align*}
R\text{N} & \xrightarrow{\text{H}_2\text{O}_2 \text{ or Peracid}} R\text{N} = \text{O}
\end{align*}
\]

**Primary Aromatic amines** are readily oxidised. They undergo slow aerial oxidation and thus become dark in colour. Vigorous oxidation of primary aromatic amines with potassium dichromate and sulphuric acid results in the formation of quinones.

\[
\begin{align*}
\text{Aniline} & \xrightarrow{\text{K}_2\text{Cr}_2\text{O}_7/\text{H}_2\text{SO}_4} \text{p-Benzoquinone}
\end{align*}
\]

**Oxidation of aniline:** Aniline is highly sensitive to oxidation and under different conditions forms different products.
12. **Hofmann’s elimination from quaternary ammonium salts.**

When quaternary ammonium hydroxides are strongly heated, alkenes are formed.

\[
\begin{align*}
\text{Quaternary ammonium ion} & \xrightarrow{\text{OH}^-, \text{heat}} \text{Alkene} + R_3N + H_2O \\
\end{align*}
\]

The quarternary ammonium halides are first converted to corresponding ammonium hydroxides by reacting with moist silver oxide (or AgOH).

**Examples:**

- Tetraethyl ammonium chloride:
  \[
  \text{AgOH} \rightarrow (C_2H_5)_4N^+\text{OH}^- \rightarrow \Delta \rightarrow CH_2 = CH_2 + (C_2H_5)_3N + H_2O
  \]
  Ethene

- NH

\[
\begin{align*}
\text{excess} & \rightarrow \text{I}^+\text{(CH}_3\text{)}_3 \\
\Delta & \rightarrow \text{Major product}
\end{align*}
\]
Elimination reactions of 4°-ammonium salts are termed **Hofmann eliminations**. It is an E2-like elimination of a 3°-amine.

The amines are converted to quarternary ammonium salts by treating them with excess methyl iodide. Let us consider the following reaction.

This reaction illustrates **two important features of the Hofmann elimination:**

1. Simple amines are easily converted to the necessary 4°-ammonium salts by exhaustive alkylation, usually with methyl iodide (methyl has no beta-hydrogen atom and cannot compete in the elimination reaction).

2. When a given alkyl group has two different sets of beta-hydrogens available to the elimination process, the major product is often the alkene isomer having the less substituted double bond.

The tendency of Hofmann eliminations to give the less-substituted double bond isomer is commonly referred to as the **Hofmann Rule**, and contrasts strikingly with the **Saytzeff’s rule** formulated for dehydrohalogenations and dehydrations. Hence, **Hofmann rule** is anti-Saytzeff rule.

To understand why the base-induced elimination of 4°-ammonium salts behaves differently from that of alkyl halides it is necessary to reexamine the nature of the E2 transition state described for dehydrohalogenation The energy diagram shown earlier for a single-step bimolecular E2 mechanism is as shown below:
Both polar and steric factors have been proposed to account for Hofmann orientation.

**Polar factors:** In the dehydrohalogenation, there is *variable transition state* theory of E2 elimination. We are speaking remember, of a one step elimination; both the C — H and C — X bonds are being broken in the same transition state. But there is a whole spectrum of E2 transition states which differ in the relative *extent* to which the two bonds are broken.

At the center of the spectrum is the transition state; for elimination from alkyl halides: both C — H and C — X bonds are broken to a considerable extent, the transition state has considerable alkene character, and orientation is Saytzeff.

But, if breaking of the C — H bond greatly exceeds breaking of the C — X bond, there is little alkene character to the transition state, but instead the development of negative charge on the carbon losing the proton. In this case, the transition state has *carbanion character*, and its stability is controlled as we might expect, by dispersal or intensification of the negative charge: electron-withdrawing groups stabilize, and electron-releasing groups destabilize. At one end of the spectrum, then, we have the carbanion like transition state.

**Hofmann orientation in the E2 elimination from quaternary ammonium salts:** Here, the transition state has considerable carbanion character, at least partly because powerful electron withdrawal by the positively charged nitrogen favors development of negative charge. There is preferential abstraction of a proton from the carbon that can best accommodate the partial negative charge: in the example given from the primary carbon rather than the secondary. A primary carbanion formation is preferred over the secondary, which in turn is favoured over tertiary. (this is the order of stability of carbanions!)

**Steric factors:** The large size of the leaving group, \( {R_3N} \), gives crowding in the transition state; a proton on the less substituted carbon is more accessible, and is preferentially abstracted by the base.

It seems likely that both factors, polar and steric are involved.

**The stereochemistry of Hofmann elimination is commonly *anti*,** but less so than we formerly believed. *Syn*-Elimination is important for certain cyclic compounds, and can be made important even for open chain compounds by the proper choice of base and solvent.

**More examples:**
Separation of Amines

For separation of amines from a mixture of primary, secondary and tertiary amines, the following methods are used:

a) Fractional distillation
b) Hinsberg method using benzene sulphonyl chloride.

A mixture of primary, secondary and tertiary amines is treated with benzene sulphonyl chloride in the presence of excess of aqueous sodium hydroxide (or potassium hydroxide).

A precipitate is obtained. It is the N,N-dialkyl-benzenesuphonamide obtained from secondary amine. This is filtered and on hydrolysis gives pure secondary amine.

The filtrate from above is then acidified. A precipitate is obtained. It is N-alkyl-benzene suphonamide obtained from primary amine. This is filtered and on hydrolysis gives pure primary amine.

The filtrate contains salt of tertiary amine, which on treatment with dilute base (NaOH or KOH) gives pure tertiary amine.

(Refer to Hinsberg reaction)

Test for amines

1. Hinsberg test : Primary, secondary and tertiary amines (aliphatic and aromatic) can be distinguished by this test. The amine is treated with benzene sulphonyl chloride in the presence of excess of aqueous sodium hydroxide (or potassium hydroxide).

A clear solution in aqueous sodium hydroxide, which, on acidification, gives an insoluble material, indicates a primary amine.

\[ \text{RNH}_2 + \text{CH} = \text{SO}_2 - \text{C}_6 \text{H}_5 \xrightarrow{\text{NaOH}} \text{RNH}_2 + \text{SO}_2 \text{C}_6 \text{H}_5 \xrightarrow{\text{HCl}} \text{RNH}_2 \text{SO}_2 \text{C}_6 \text{H}_5 \]

A precipitate which is insoluble in NaOH solution and which remains insoluble on acidification, indicates a secondary amine.
Tertiary amines do not react with benzene sulphonyl chloride. An insoluble compound in NaOH solution, which dissolves by the addition of acid, indicates a tertiary amine.

\[
R_3N + \text{Cl} = \text{SO}_2 \rightarrow \text{C}_6\text{H}_5 \xrightarrow{\text{NaOH}} R_2N = \text{SO}_2 \rightarrow \text{C}_6\text{H}_5 \xrightarrow{\text{HCl}} \text{Insoluble (insoluble)}
\]

\[N, N-\text{Dialkylbenzene-sulphoramide}\]

2. **Carbylamine test:** This test is used to identify primary amines (aliphatic as well as aromatic). In this test, the compound is warmed with chloroform in the presence of an alcoholic solution of potassium hydroxide. The primary amines give offensive-smelling isocyanides.

\[
\text{RNH}_2 + \text{CHCl}_3 + 3\text{KOH} \rightarrow \text{RN} \equiv \text{C} + 3\text{KCl} + 3\text{H}_2\text{O}
\]

3. **Nitrous acid test:** This test is used to differentiate between primary aliphatic amines and primary aromatic amines. Primary aliphatic amines react with nitrous acid to give alcohols and nitrogen, while primary aromatic amines react with nitrous acid, 0-5°C to give crystalline diazonium salts and at room or higher temperature, to give phenols and nitrogen. Phenols give a dark colouration with neutral FeCl₃.

\[
\text{RNH}_2 + \text{HONO} \rightarrow [\text{R} = \text{N} = \text{N} \equiv \text{OH}] \rightarrow \text{R} \equiv \text{OH} + \text{N}_2 \uparrow
\]

**Diazonium salts**

**Preparation:** When aliphatic primary amines are treated with HNO₂ (prepared *in situ* by reacting NaNO₂ and HCl) we obtain alcohols with the liberation of N₂.

When the same reaction is carried out with aromatic 1° amine we can isolate the intermediate
diazonium salts, specially if the reaction is carried out at low temperatures (0 - 5°C). The extra stability of aromatic diazonium salts can be attributed to resonance because of which we have a double bond character between the carbon atom and the N₂ molecule as shown below.

Reactions
Due to their instability, these diazonium salts generally lose nitrogen and the diazonium group is substituted by some other group. These reactions are of great synthetic importance as a large variety of compounds can be prepared through diazonium salts. Even in cases where the directive influence of a group already present does not allow the preparation of some compound (e.g. presence of methyl group in nucleus will not allow formation of m-derivatives in halogenation, nitration or sulphonation) these compounds can be prepared through diazonium salts. Such reactions of diazonium salts, where this group is replaced by some other group may be classified into two categories depending on their mechanism.

(a) replacement, in which nitrogen is lost as N₂, and some other atom or group becomes attached to the ring in its place
(b) coupling in which the nitrogen is retained in the product

(A) Reaction Where The Diazonium Group Is Replaced

1. Where The Substitution Is Catalysed By Cuprous Ion
The reaction is believed to proceed through a free radical mechanism involving the formation of a phenyl radical. Important amongst such reactions are:

1. Replacement of Diazonium Group by Hydrogen: Diazonium salts reacts with reagents like HCHO or C₂H₅OH or sodium stannite to displace diazonium group by hydrogen but the best reagent is hypophosphorus acid in presence of cuprous salts.

\[ \text{C₆H₅N⁺ + H₃PO₃ + H₂O} \underset{\text{Cu}}{\rightarrow} \text{C₆H₆ + H₃PO₄ + HCl} \]

Benzene diazonium                 Benzene chloride
Example:

\[
\begin{align*}
\text{NH}_3\text{Cl} & \quad \xrightarrow{\text{NaNO}_2, \text{H}_2\text{SO}_4} \quad \text{N}_2\text{H}_4^+\text{HSO}_4^- \\
\text{Cl} & \quad \text{Cl} \\
\text{Dichloroaniline} & \quad \text{m-Dichlorobenzene}
\end{align*}
\]

The diazonium salt is simply allowed to stand in the presence of the hypophosphorous acid; nitrogen is lost, and hypophosphorous acid is oxidized to phosphorous acid:

2. **Replacement of Diazonium Group by Alkoxy Group:** Reaction with alcohols on heating forms alkoxy derivatives by free radical mechanism.

\[
\text{C}_6\text{H}_5^-\text{N}^+\equiv\text{NX}^- + \text{R} - \text{OH} \rightarrow \text{C}_6\text{H}_5^-\text{O} - \text{R} + \text{HX} + \text{N}_2
\]

3. **Replacement of Diazonium Group by Phenyl Group (Gomberg Reaction):** The reaction of diazonium salts with liquid aromatic hydrocarbons like benzene results in the displacement of diazonium group by phenyl group in a free radical mechanism.

\[
\text{C}_6\text{H}_5^-\text{N}^+\equiv\text{NX}^- \xrightarrow{\text{N}_2 / \text{C}_6\text{H}_5^-} \text{C}_6\text{H}_5^-\text{C}_6\text{H}_5
\]

**Diphenyl**

4. **Replacement of Diazonium Group by Acyloxy group:** When an aqueous solution of a diazonium salt is heated with aliphatic acids it forms esters by a free radical mechanism.

\[
\text{C}_6\text{H}_5\text{N}^+\equiv\text{NX}^- + \text{CH}_3\text{COOH} \rightarrow \text{C}_6\text{H}_5\text{OOCCH}_3 + \text{HX} + \text{N}_2
\]

**Phenylacetate**

5. **Replacement by Halogen (Sandmeyer's Reaction):** When an aqueous solution of diazonium salt is warmed with cuprous chloride or bromide dissolved in corresponding halogen acid the diazonium group is replaced by chlorine or bromine.

\[
\text{C}_6\text{H}_5\text{N}^+\equiv\text{NX}^- + \text{HCl} \xrightarrow{\text{CuCl}} \text{C}_6\text{H}_5\text{Cl} + \text{HX} + \text{N}_2
\]

It has been observed in this reaction that it is the halogen of cuprous halide which enters the benzene ring and proceeds as follows:

\[
\text{HCl} + \text{CuCl} \rightarrow \text{CuCl}_2^- + \text{H}^+
\]

\[
\text{C}_6\text{H}_5\text{N}^+\equiv\text{N} + \text{CuCl}_2^- \rightarrow \text{C}_6\text{H}_5^- + \text{CuCl}_2 + \text{N}_2
\]

\[
\cdot\text{C}_6\text{H}_5\text{H}^+ + \text{Cl}^- - \text{Cu} - \text{Cl} \rightarrow \text{C}_6\text{H}_5\text{Cl} + \text{CuCl}
\]

Alternatively when diazonium salts are heated with halogen acids in the presence of Cu, the diazonium group is replaced by halogen. The reaction is known as **Gattermann's Reaction**.

A special case of Sandmeyer reaction is the use of HCN/CuCN or HCN/Cu to replace diazonium group by cyano group.

\[
\text{C}_6\text{H}_5\text{N}^+\equiv\text{NX}^- + \text{HCN} \xrightarrow{\text{Cu/CuCN}} \text{C}_6\text{H}_5^-\text{CN} + \text{HX} + \text{N}_2
\]

**Phenyl cyanide**

**or Benzonitrile**
**Examples:**

\[
\text{CH}_3\text{NH}_2 \xrightarrow{\text{NaNO}_2, \text{HCl}} \text{CH}_3\text{N}_2^+\text{Cl}^- \xrightarrow{\text{CuCl}} \text{CH}_3\text{Cl} + \text{N}_2
\]

*o-Toluidine → o-Toluenediazonium chloride → o-Chlorotoluene*

\[
\text{CH}_3\text{NH}_2 \xrightarrow{\text{NaNO}_2, \text{H}_2\text{SO}_4} \text{CH}_3\text{N}_2^+\text{H}_2\text{SO}_4^- \xrightarrow{\text{CaBr}} \text{CH}_3\text{Br} + \text{N}_2
\]

*o-Toluidine → o-Bromotoluene*

\[
\text{CH}_3\text{NH}_2 \xrightarrow{\text{NaNO}_2, \text{HCl}} \text{CH}_3\text{N}_2^- \xrightarrow{\text{CuCN}} \text{CH}_3\text{CN} + \text{N}_2
\]

*o-Toluidine → o-Tolunitrile*

---

**II. When The Substitution Is Nucleophilic**

The loss of nitrogen from diazonium salt, gives rise to a phenyl carbocation, which is then attached by a nucleophile resulting in an overall S_N1 reaction.

1. **Replacement of Diazonium Group by the Hydroxy Group**: When aqueous solution of diazonium salt is boiled, it forms phenol by the loss of nitrogen.

   \[
   \text{C}_6\text{H}_5\text{N}^+\equiv \text{N}^- + \text{H}_2\text{O} \xrightarrow{\text{H}^+} \text{C}_6\text{H}_5\text{OH} + \text{H}^+ + \text{N}_2
   \]

   The mechanism of the reaction is S_N1.

   \[
   \text{C}_6\text{H}_5\text{N}^+\equiv \text{N}^- \xrightarrow{\text{Slow}} \text{C}_6\text{H}_5^- \xrightarrow{\text{H}_2\text{O}} \text{C}_6\text{H}_5\text{OH}_2^- \xrightarrow{\text{H}^+} \text{C}_6\text{H}_5\text{OH}
   \]

   Phenol

   **Example:**

   \[
   \text{CH}_3\text{NH}_2 \xrightarrow{\text{NaNO}_2, \text{H}_2\text{SO}_4} \text{CH}_3\text{N}_2^+\text{H}_2\text{SO}_4^- \xrightarrow{\text{H}_2\text{O}, \text{H}^+, \text{heat}} \text{CH}_3\text{OH} + \text{N}_2
   \]

   *o-Toluidine → o-Cresol*

2. **Replacement of Diazonium Group by Iodine**: Aqueous solution of diazonium salts react with KI to form iodobenzene. This reaction follows a S_N1 mechanism.

   \[
   \text{C}_6\text{H}_5\text{N}^+\equiv \text{N}^- + \text{KI} \xrightarrow{\Delta} \text{C}_6\text{H}_5\text{I} + \text{K}^+ + \text{N}_2
   \]

   **Example:**

   \[
   \text{NH}_2 \xrightarrow{\text{NaNO}_2, \text{H}_2\text{SO}_4} \text{N}_2^+\text{HSO}_4^- \xrightarrow{\text{KI}} \text{I} + \text{N}_2
   \]

   Aniline → Iodobenzene
3. Replacement of Diazonium Group by Fluorine (Baltz - Schiemann Reaction): Diazonium salts on reaction with HBF₄, form a precipitate of diazonium fluoroborate \( \text{C}_6\text{H}_5^- \cdot \text{N}^+ = \overset{\text{N}}{\text{BF}}_4^- \). These on gentle heating decompose to give fluorobenzene, nitrogen and boron trifluoride.

\[
\text{C}_6\text{H}_5\text{N}^+ + \text{BF}_4^- \xrightarrow{\Delta} \text{C}_6\text{H}_5\text{F}^- + \text{BF}_3 + \text{N}_2
\]

The reaction occurs by \( \text{S}_\text{N}1 \) mechanism.

**Example:**

\[
\begin{align*}
\text{NH}_2 & \xrightarrow{\text{NaNO}_2, \text{HCl}} \text{N}_2^+\text{Cl}^- & \xrightarrow{\text{HBF}_4} \text{N}_2^+\text{BF}_4^- & \xrightarrow{\text{heat}} \text{F}^- + \text{N}_2 + \text{BF}_3
\end{align*}
\]

4. Replacement of Diazonium Group by Nitro Group: Diazonium salts when heated with sodium nitrite in presence of cuprous oxide form nitro compounds.

\[
\text{C}_6\text{H}_5\text{N}^+ \equiv \overset{\text{N}}{\text{X}}^- + \text{NaNO}_2 \xrightarrow{\text{Cu}_2\text{O}} \text{C}_6\text{H}_5\text{NO}_2 + \text{NaX} + \text{N}_2
\]

A better method is to heat benzene diazonium fluoroborate with \( \text{NaNO}_2 \) and copper when nitrobenzene is formed in good yield.

\[
\text{C}_6\text{H}_5\text{N}^+ \equiv \text{NBF}_4^- + \text{NaNO}_2 \xrightarrow{\text{Cu}} \text{C}_6\text{H}_5\text{NO}_2 + \text{NaBF}_4 + \text{N}_2
\]

5. Replacement of Diazonium Group by Thiol Group: Diazonium salts on reaction with \( \text{H}_2\text{S} \) form thiophenol by \( \text{S}_\text{N}1 \) reaction

\[
\text{C}_6\text{H}_5\text{N}^+ \equiv \overset{\text{N}}{\text{X}}^- + \text{H}_2\text{S} \rightarrow \text{C}_6\text{H}_5\text{SH} + \text{N}_2 + \text{H}_2\text{X}
\]

**Thiophenol**

6. Replacement of Diazonium Group by - NCO or - NCS Group: When diazonium salts are reduced with \( \text{KNCO} \) or \( \text{KNCS} \) they form phenyl isocyanate and phenyl thioisocyanates respectively.

\[
\text{N}_2 + \text{HX} + \text{C}_6\text{H}_5\text{NCS} \xrightarrow{\text{KNCS}} \text{C}_6\text{H}_5\text{N}^+ \equiv \overset{\text{N}}{\text{X}}^-
\]

\[
\text{C}_6\text{H}_5\text{NCO} + \text{HX} + \text{N}_2
\]

**Phenyl isocyanate**

\[
\text{C}_6\text{H}_5\text{NCS} + \text{HX} + \text{N}_2
\]

**Phenyl thioisocyanate**

(b) Reaction Where The Diazonium Group Is Retained

There are few reactions of diazonium salts in which both the nitrogen atoms are retained. They are:

1. **Reaction with Alkali:** On treatment with NaOH diazonium salts are first converted to diazohydroxides and then to sodium diazotes which exhibit geometrical isomerism due to presence of - N = N -

\[
\text{H}_5\text{C}_6 - \overset{\text{N}^-}{\text{H}} \xrightarrow{\text{NaOH}} \text{H}_5\text{C}_6 - \overset{\text{N}^-}{\overset{\text{H}}{\text{O}}} \xrightarrow{\text{NaOH}} \text{H}_5\text{C}_6 - \overset{\text{N}^-}{\overset{\text{O}^-}{\text{H}}} \equiv \text{N}^+ - \overset{\text{O}^-}{\text{H}}^- \text{Na}^+
\]

**Diazonium ion**

**Diazohydroxide**

**Sodium diazote**
2. **Reduction to Hydrazines**: When benzene diazonium chloride is reduced with stannous chloride and hydrochloric acid or sodium bisulphate the product is phenyldiazide hydrochloride.

\[
\text{C}_6\text{H}_5\text{N}^+\equiv\text{NCl}^- + 4\,[\text{H}] \xrightarrow{\text{SnCl}_2/\text{HCl}} \text{C}_6\text{H}_5\text{NNH}_2\text{HCl}
\]

Phenyldiazide hydrochloride

However, reduction with Zn and HCl converts them to aniline.

\[
\text{C}_6\text{H}_5\text{N}^+\equiv\text{NCl}^- + \,[\text{H}] \xrightarrow{\text{Zn/HCl}} \text{C}_6\text{H}_5\text{NH}_2 + \text{NH}_4\text{Cl}
\]

3. **Coupling Reaction - formation of Azo Dyes**: Diazonium salts react with aromatic compounds joined to strongly electron donating groups like –OH, -NH\textsubscript{2}, -NR\textsubscript{2} etc to form coloured substance called azo dyes by coupling at p- or o-position of the aromatic compound (an amine or phenol).

\[
\text{Ar}–\text{N}_2^+\text{X}^- + \text{G} \xrightarrow{\text{weakly alkaline}} \text{Ar}–\text{N}=\text{N}–\text{G} \\
\text{G must be a strongly electron-releasing group:} \\
\text{OH, NR}_2, \text{NHR, NH}_2
\]

**Example:**

\[
\text{N}_2^+\text{Cl}^- + \text{OH} \xrightarrow{\text{weakly alkaline}} \text{N}=\text{N}–\text{OH}
\]

Benzenediazonium chloride Phenol $p$- Hydroxyazobenzene $p$- (Phenylazo)phenol

**Mechanism:**
The mechanism is basically that of electrophilic aromatic substitution where the diazonium is the electrophile.

\[
\text{N}=\text{N}–\text{H} \xrightarrow{\text{O}^-} \text{N}=\text{N}–\text{H} \xrightarrow{\text{NaOH}} \text{N}=\text{N}–\text{H} \xrightarrow{\text{Na}^+} \text{N}=\text{N}–\text{H}
\]

Azo dye

\[
\text{N}^+\equiv\text{N} + \text{H} \xrightarrow{\text{Cl}^-} \text{N}^+\equiv\text{N} + \text{H} \xrightarrow{\text{- HCl}} \text{N}^+\equiv\text{N} + \text{H} \xrightarrow{\text{Cl}^-} \text{N}^+\equiv\text{N} + \text{H}
\]

$\text{p}$- Aminoazobenzene

These azo dyes and diazoamino compounds are bright yellow, red or orange colour dyes insoluble in water. This reaction is therefore used as a test for aromatic amines having - NH\textsubscript{2}
group in the nucleus. Such amines on diazotisation with NaNO₂ and HCl at low temperatures followed by the reaction with phenol (or Naphthol) form bright coloured dyes (Dye test).

**Effect of high acidity on the amine or phenol with which the diazonium salt is reacting:**

1. **On amine:** Acid converts an amine into its ion, which, because of the positive charge, is relatively unreactive toward electrophilic aromatic substitution. Hence less reactive to be attacked by the weakly electrophilic diazonium ion.

   Higher is the acidity, higher is the proportion of amine that exists as its ion, and the lower the rate of coupling.

   
   ![Diagram of amine reaction](image)

2. **On phenol:** A phenol is appreciably acidic; in aqueous solutions it exists in equilibrium with phenoxide ion:

   
   ![Diagram of phenol reaction](image)

   The fully developed negative charges makes −O⁻ much more powerfully electron releasing than —OH; the phenoxide ion is therefore much more reactive than the un-ionized phenol toward electrophilic aromatic substitution.

   The higher the acidity of the medium, the higher the proportion of phenol is un-ionized, and the lower the rate of coupling.

   Hence, for both amines and phenols, the coupling is favoured by low acidity.

   **The conditions under which coupling proceeds most rapidly:**

   1. The solution must not be so alkaline that the concentration of diazonium ion is too low.
   2. It must not be so acidic that the concentration of free amine or phenoxide or phenoxide ion is too low.
   3. Amines couple fastest in mildly acidic solutions, and phenols couple fastest in mildly alkaline solution.