

## Unit 2. Amines

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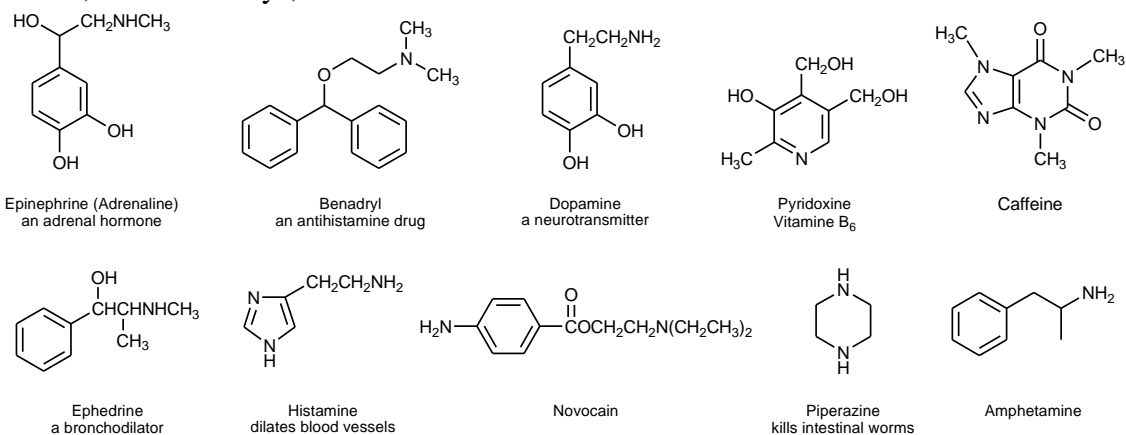
### Learning Objectives:

After completing this unit the student should be able to:

- draw and name the amines.
- describe the trends in various physical and chemical properties of amines.
- assign the basicity and acidity of nitrogen compounds.
- compare the basicity of amines with other common bases, and explain how their basicity varies with hybridization, aromaticity, resonance, and induction.
- distinguish primary, secondary and tertiary amines.
- propose single-step and multistep syntheses of amines from compounds containing other functional groups.
- Write and understand mechanism of reactions of amines with ketones, aldehydes, acid chlorides, nitrous acid, alkyl halides, and oxidizing agents.
- describe the importance of diazonium salts in the synthesis of a series of aromatic compounds including azo dyes.

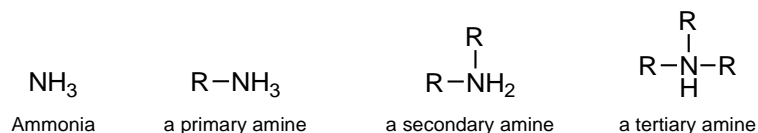
## Amines

Amines are organic derivatives of ammonia. They are derived by replacing one or more hydrogens of ammonia molecule by alkyl /aryl group(s) and are characterized by their fishy odour. Amines and carbonyl compounds are the most abundant and have the richest chemistry. Amines occur widely among proteins, vitamins, alkaloids and hormones in all living organisms. In addition, cyclic amine bases are constituents of nucleic acids. The majority of pharmaceutical agents contain amine functional groups, and many of the common coenzymes necessary for biological catalysis are amines. Because of their high degree of biological activity, many amines are used as drugs and medicines. **Adrenaline** and **ephedrine**, for example, are used to increase blood pressure. Ephedrine is potent dilator of the air passages of the lungs also. **Histamine** dilates blood vessels. **Benadryl**, a well-known antihistaminic drug, is tertiary amine. **Neurotransmitters** (e.g. **dopamine**) pass impulses around the brain by bridging the gaps between the brain cells. **Pyridoxine** is vitamin B<sub>6</sub>. **Piperazine** kills intestinal worms. Synthetic amines are also widely known. **Novocain**, a synthetic amino compound, is used as an anaesthetic in dentistry. Quaternary ammonium salts are used as surfactants. Diazonium salts are intermediates in the preparation of a variety of aromatic compounds including dyes. At the same time, many neurologically active compounds are also amines: **amphetamine** is a central nervous system stimulant. This is also used clinically as appetite suppressant. **Caffeine**, a naturally occurring amine, a bitter-tasting compound found in coffee, tea, cola beverages, and chocolate, is a mild stimulant, increases heart rate, dilates airways, and stimulates the secretion of stomach acid.

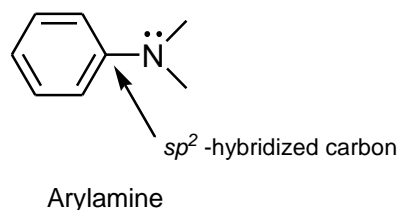
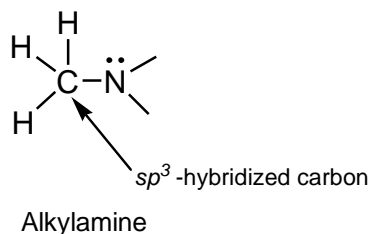


### 2.1. Classification and Nomenclature

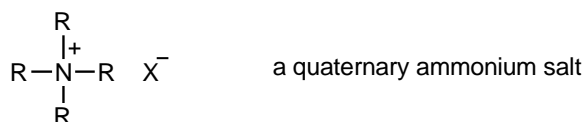
- Amines are classified as primary, secondary and tertiary amine according to the number of substitution (alkyl/aryl) groups attached to the nitrogen. An amine with one carbon attached to nitrogen is a *primary amine*, an amine with two is a *secondary amine*, and an amine with three is a *tertiary amine*.



- Amines are said to be ‘simple’ when all the alkyl or aryl groups are the same, and ‘mixed’ when they are different.
- Amines are also classified on the basis of nature of substitution as **alkylamines** and **arylamines**. In alkylamines the nitrogen is attached to  $sp^3$ -hybridized carbon while in arylamines the nitrogen is attached to a  $sp^2$ -hybridized carbon of a benzene or benzene-like ring.

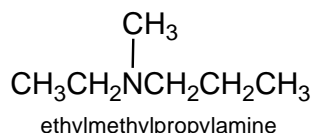
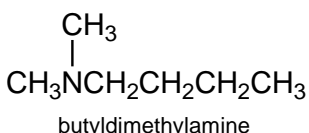
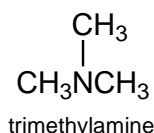
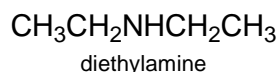
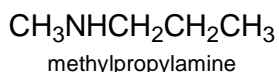
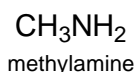


- Compounds containing a nitrogen atom with four attached groups with a formal positive charge on nitrogen are called quaternary ammonium salts.



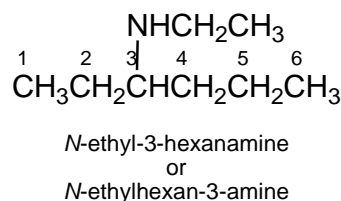
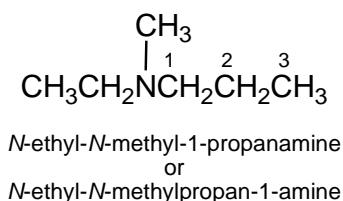
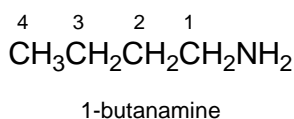
### Common name:

- The common name of an amine consists of the names of the alkyl groups bonded to the nitrogen, in alphabetical order, followed by “amine.”
- The entire name is written as one word (unlike the common names of alcohols, ethers, and alkyl halides, in which “alcohol,” “ether,” and “halide” are separate words).
- Prefixes “di” and “tri” are used in case of secondary and tertiary amines.

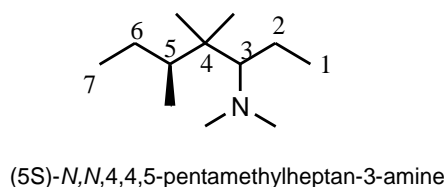
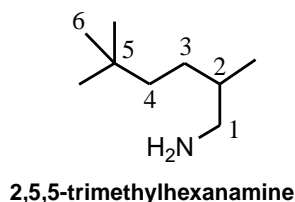
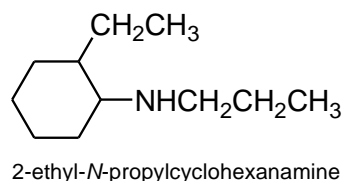
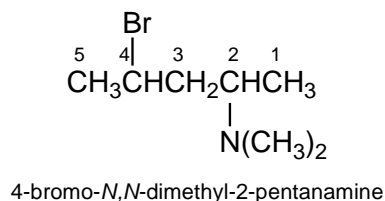
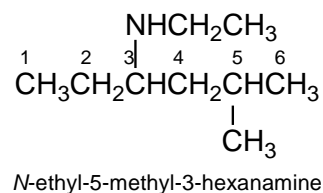
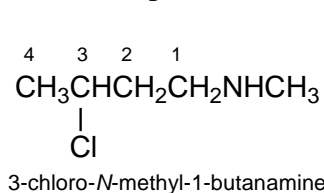


### Systematic (IUPAC) name:

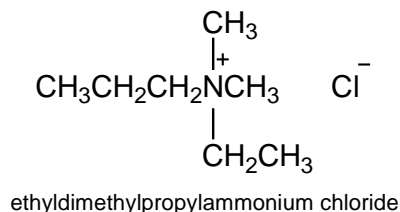
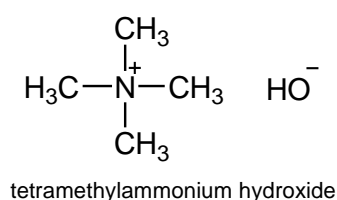
- The –e ending in alkane is changed to **–amine**.
- The locator shows the position of amine along the main chain.
- Other substituents on the main chain are given numerical locators.
- Substituents on amino group are given prefix *N* (italic)- to indicate the position of the substituent (as located on nitrogen):



- The substituents attached to the nitrogen or to the parent hydrocarbon are listed in alphabetical order. The chain is numbered in the direction that gives the functional group suffix the lowest possible number.



- Quaternary ammonium salts** of amines are named as the names of the alkyl substituents in alphabetical order, followed by “ammonium” (all in one word), and then the name of the counterion as a separate word.

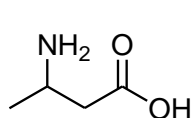


### Polyfunctional Amines:

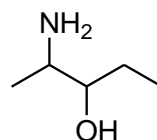
- In polyfunctional compounds the order of decreasing precedence, to determine which functional group is the principal one, is:

Acids, aldehydes, ketones, alcohol, amines

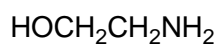
- Therefore, in most of the polyfunctional compounds, an amine group is designated by using the prefix “amino”. The substituents are given the lowest number possible.



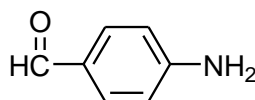
3-aminobutanoic acid



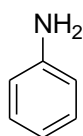
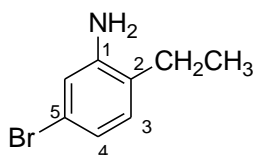
2-amino-3-pentanol



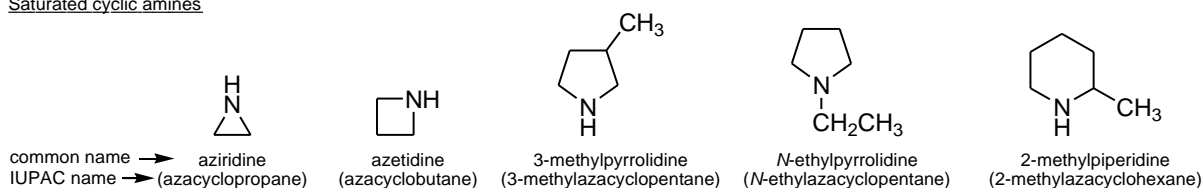
2-aminoethanol

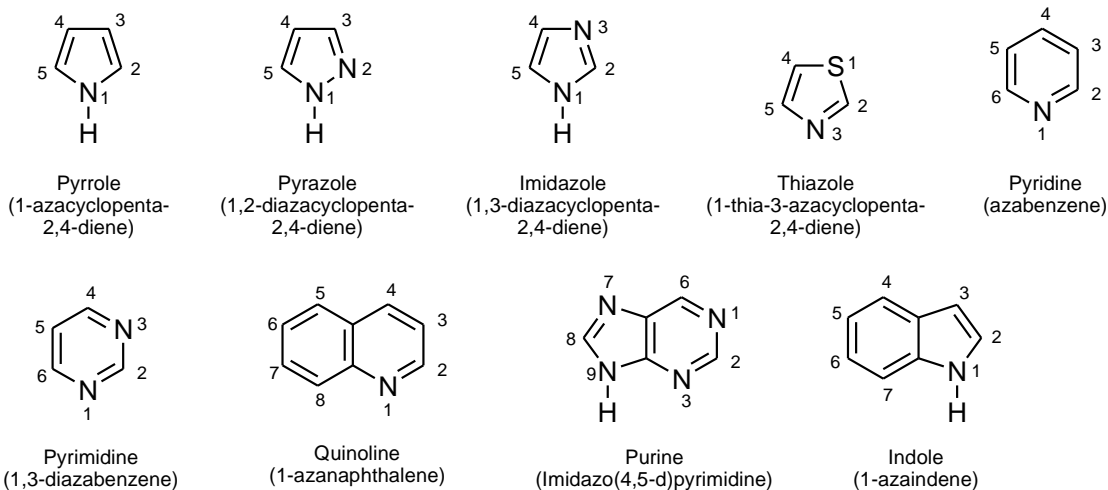
*p*-aminobenzaldehyde

- **Arylamines** are often named as derivatives of aniline.
- Substituted derivatives of aniline are numbered beginning at the carbon that bears the amino group.
- Substituents are given the lowest number possible and listed in alphabetical order.

**Aniline****5-Bromo-2-ethylaniline**

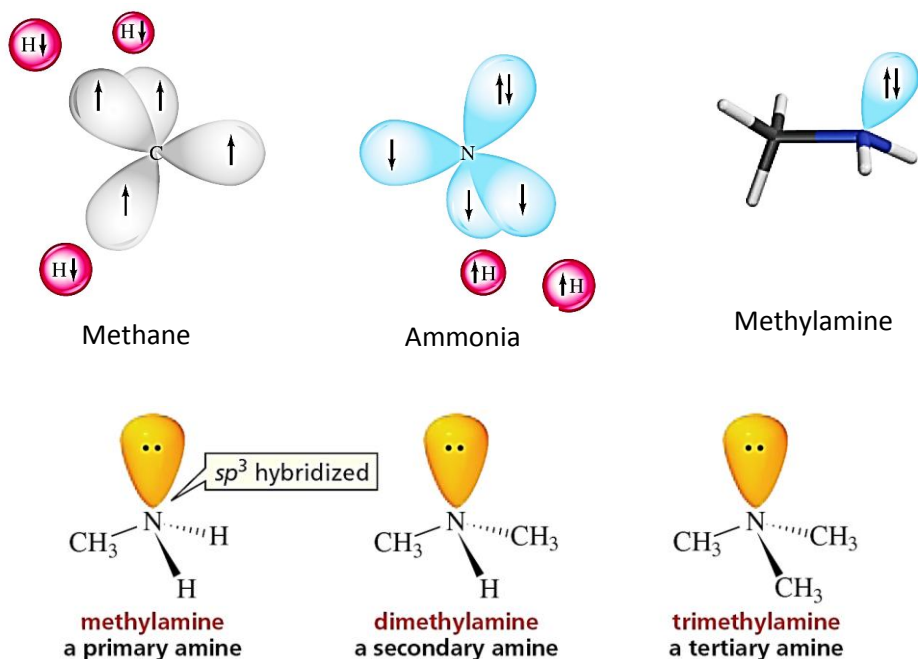
- In IUPAC nomenclature, saturated cyclic amines are named as a cycloalkane and unsaturated cyclic amines as cycloalkene. The prefixes *aza*-, *diaza*-, and *triaza*- are used to indicate the number of nitrogen atoms present in the ring.
- Heterocyclic amines all have common names.
- A nitrogen atom in the ring or the highest atomic weight heteroatom is designated position 1 and numbering proceeds to give the lowest overall set of locants to the heteroatoms.

Saturated cyclic amines

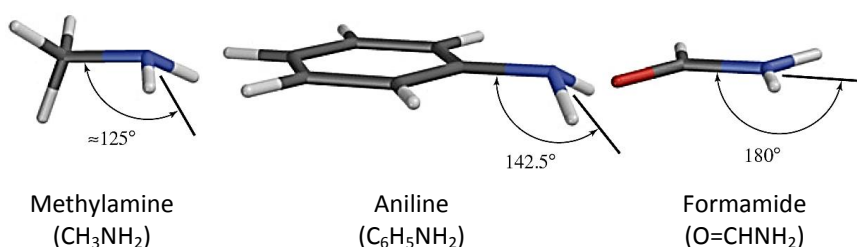
Unsaturated cyclic amines

## 2.2. Structure and bonding

**Alkylamines:** The nitrogen atom of most alkylamines is like that of ammonia; it is approximately  $sp^3$  hybridized. The three alkyl groups (or hydrogen atoms) occupy corners of a tetrahedron; the  $sp^3$  orbital containing the unshared electron pair is directed toward the other corner describing the shape of the amine by the location of the atoms as being **trigonal pyramidal**. This unshared pair (lone pair) of electrons is involved in reactions in which amines act as bases or nucleophiles. The bond angles are close to  $109.5^\circ$  (tetrahedral angle). The H–N–H angle ( $108^\circ$ ) for trimethylamine, for example, is slightly smaller than tetrahedral angle whereas the C–N–H angle ( $112^\circ$ ) is slightly larger. The C–N bond distance of 147 pm lies between typical C–C bond distance in alkanes (153 pm) and C–O bond distance in alcohols (143 pm).

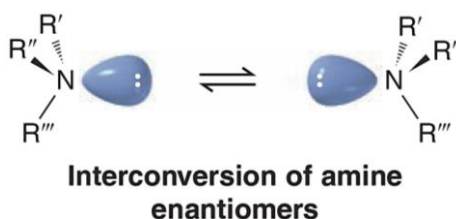


**Arylamines:** Aniline, like alkylamines, has a pyramidal arrangement of bonds around nitrogen, but its pyramid is somewhat shallower. Hybridization of N in aniline lies between  $sp^3$  and  $sp^2$ . For  $sp^3$ -hybridized nitrogen as in simple alkylamines, the angle between the carbon–nitrogen bond and the bisector of the H–N–H angle is  $125^\circ$ , while in formamide ( $sp^2$ -hybridized nitrogen) it is  $180^\circ$ . In aniline it is  $142.5^\circ$ , suggesting a hybridization somewhat closer to  $sp^3$  than to  $sp^2$ . The structure of aniline reflects a compromise between two modes of binding the nitrogen lone pair. Lone pair of N can be delocalized into ring best if N is  $sp^2$  and lone pair is in a  $p$  orbital. Lone pair bound most strongly by N if pair is in an  $sp^3$  orbital of N, rather than  $p$ . As a result of these two opposing forces, nitrogen adopts an orbital hybridization that is between  $sp^3$  and  $sp^2$ . Delocalization of the nitrogen lone pair decreases the electron density at nitrogen while increasing it in the  $p$  system of the aromatic ring. As the extent of electron delocalization into the ring increases, the geometry at nitrogen flattens. *p*-Nitroaniline, for example, is planar.



### Configuration:

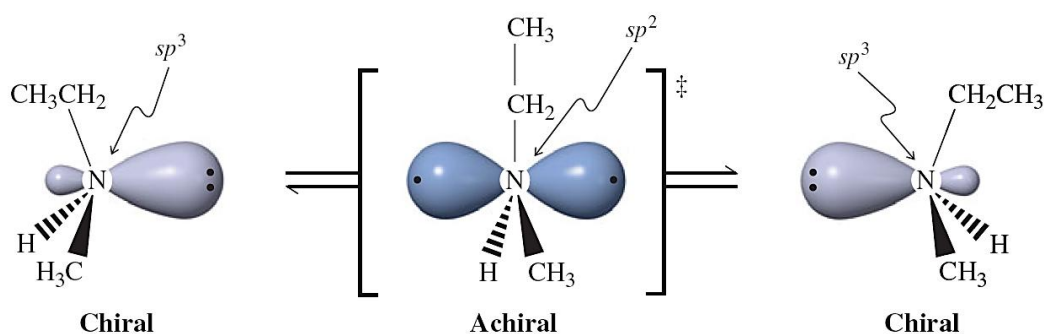
If the alkyl groups of a tertiary amine are all different, the amine will be chiral. Unlike chiral carbon compounds, however, chiral amines can't usually be resolved because the two enantiomeric forms rapidly interconvert by a **pyramidal, amine** or **nitrogen** inversion at room temperature as the energy required for inversion is very low (about 6 kcal/mol).



It can be compared to an umbrella that turns inside out in a windstorm. In the transition state for the inversion, the nitrogen atom momentarily becomes planar,  $sp^2$  geometry with the unshared electron pair occupying a  $p$  orbital, followed by rehybridization of the planar intermediate to tetrahedral,  $sp^3$  geometry. The “inverted” and “non-inverted” amine molecules are enantiomers, but they cannot be separated because the inversion is rapid.





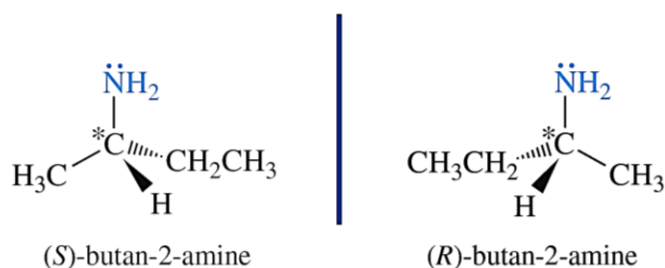


### Exceptions

There are certain special cases where amines are chiral.

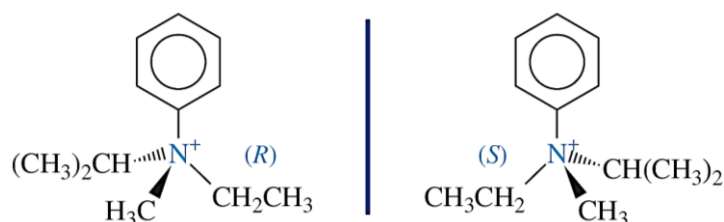
Case 1: Amines which are chiral because of chiral carbon atoms.

Example: Butan-2-amine



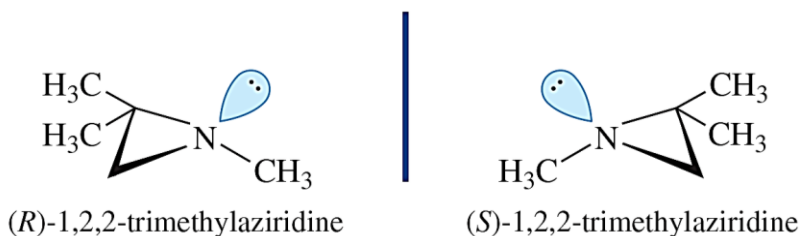
Case 2: Ammonium salts cannot undergo nitrogen inversion because they do not have an unshared pair. Therefore, those quaternary ammonium salts with four different groups are chiral and can be resolved into separate (relatively stable) enantiomers:

Example:



Case 3: Certain amines unable to attain  $sp^2$  hybridisation required for nitrogen inversion.

Example: aziridines where nitrogen atom is in ring and therefore are unable to obtain required bond angle of  $120^\circ$ .



## 2.3. Properties of Amines: Physical and chemical properties

### 2.3.1. Physical state:

Primary amines with three or more carbon atoms are liquid and still higher ones are solid.

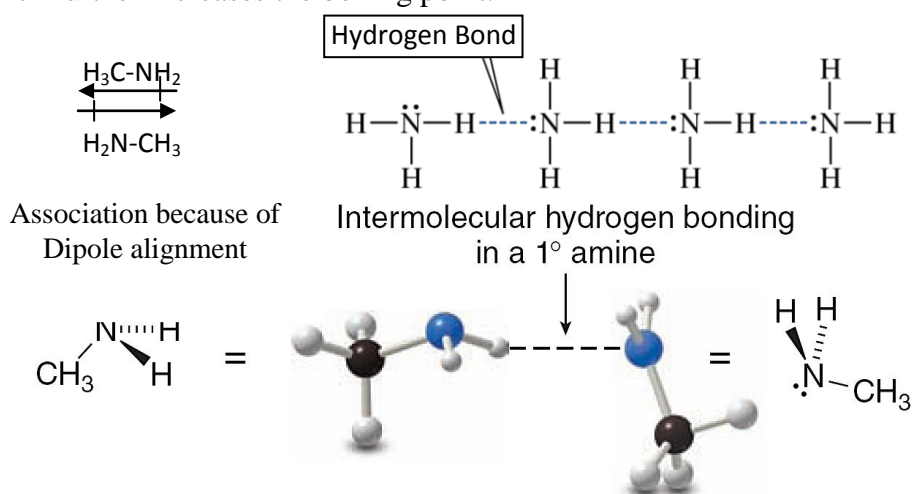
- ✓ Aniline and other arylamines are usually colourless but get coloured on storage due to atmospheric oxidation.

### 2.3.2. Odour and toxicity:

- ✓ Low-molecular-weight amines such as trimethylamine have a distinctive fishlike aroma, while diamines such as cadaverine (1,5-pentanediamine) and putrescine (1,4-butanediamine) have the appalling odors.
- ✓ Aromatic amines are generally very toxic; they are readily absorbed through the skin, often with fatal results.

### 2.3.3. Boiling Point:

- ✓ The polar nature of a substance can affect physical properties such as boiling point. Amines are moderately polar substances - more polar than alkanes but less polar than alcohols. Therefore, they aggregate in solution. Boiling requires overcoming the intermolecular attraction forces between the dipoles. Moreover, amines form hydrogen-bonded oligomers in solution, effectively increasing the molecular weight which further increases the boiling point.

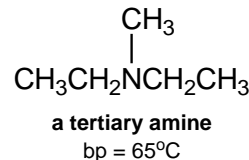
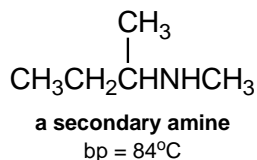
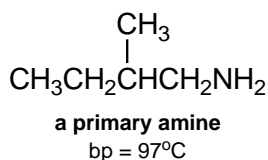


- ✓ The hydrogen bonds between amine molecules are weaker than the hydrogen bonds between alcohol molecules because nitrogen is less electronegative than oxygen. An amine, therefore, has higher boiling point than an alkane and a lower boiling point than an alcohol with a similar molecular weight.

$\text{CH}_3\text{CH}_2\text{CH}_3$	$\text{CH}_3\text{CH}_2\text{NH}_2$	$\text{CH}_3\text{CH}_2\text{OH}$
<b>Propane</b>	<b>Ethylamine</b>	<b>Ethanol</b>
$\mu = 0 \text{ D}$	$\mu = 1.2 \text{ D}$	$\mu = 1.7 \text{ D}$
bp $-42^\circ\text{C}$	bp $17^\circ\text{C}$	bp $78^\circ\text{C}$

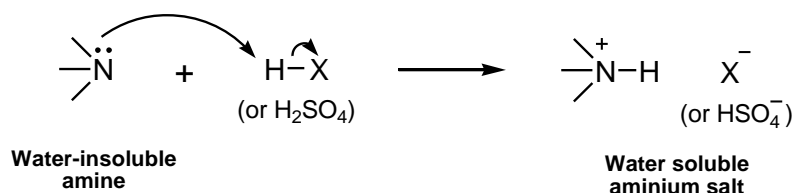
- ✓ Because primary amines have two N–H bonds, hydrogen bonding is more significant in primary amines than in secondary amines. Tertiary amines cannot form hydrogen

bonds between their own molecules because they do not have hydrogen attached to the nitrogen. Consequently, among isomeric amines, the primary amines have higher boiling points than secondary amines and secondary amines have higher boiling points than tertiary amines.

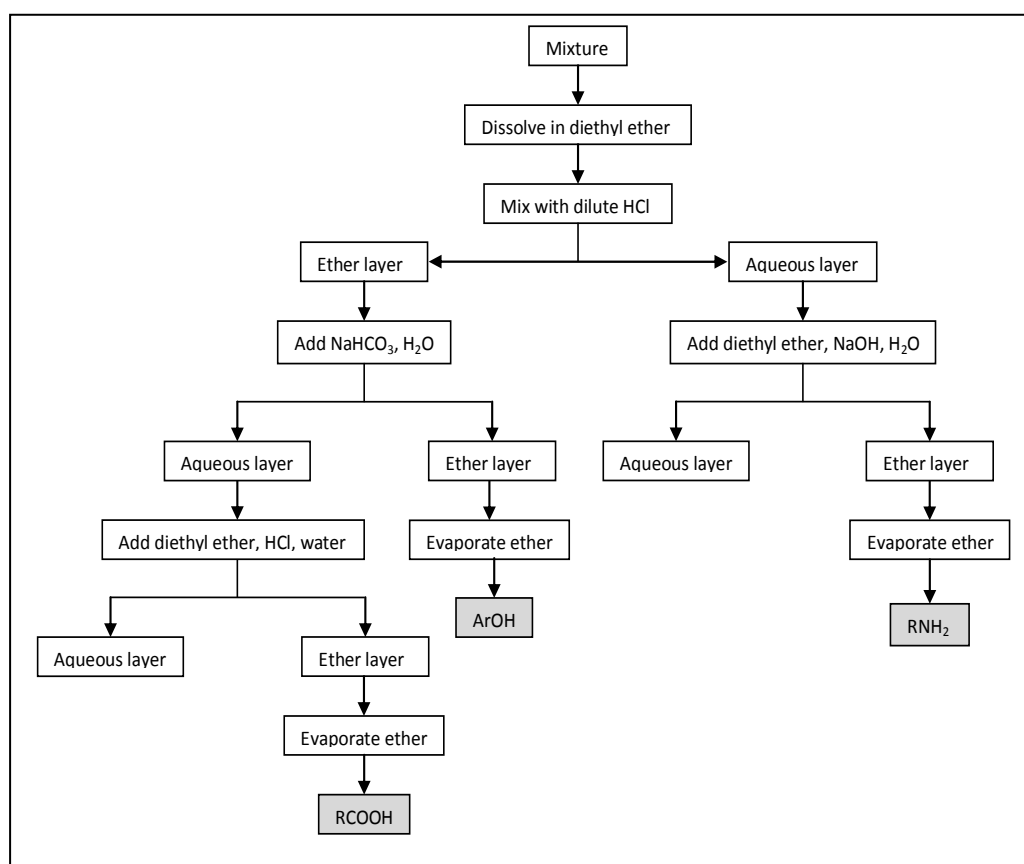


### 2.3.4. Solubility:

- ✓ Amines are soluble in organic solvents like alcohol, ether and **benzene**.
- ✓ Like alcohols, amines with fewer than five carbon atoms, including tertiary amines, are generally water soluble. However, solubility decreases with increase in molar mass of amines due to increase in size of the hydrophobic alkyl part. Higher amines are essentially insoluble in water.
- ✓ With the same number of carbons, the primary amines are more soluble than secondary amines because primary amines have two hydrogens that can engage in hydrogen bonding with water. Tertiary amines, like primary and secondary amines, have lone-pair electrons that can accept hydrogen bonds, but unlike primary and secondary amines, tertiary amines do not have hydrogens to donate for hydrogen bonds. Tertiary amines, therefore, are less soluble in water than are secondary amines with the same number of carbons.
- ✓ The simplest arylamine, aniline, is a liquid at room temperature and has a boiling point of  $184^\circ\text{C}$ . Almost all other arylamines have higher boiling points. Aniline is only slightly soluble in water (3 g/100 mL). Substituted derivatives of aniline tend to be even less water-soluble.
- ✓ **Solubility of Amines in Aqueous Acids:**
  - Almost all alkyl aminium chloride, bromide, iodide, and sulfate salts are soluble in water. Thus, primary, secondary, or tertiary amines that are not soluble in water will dissolve in dilute aqueous HCl, HBr, HI, and  $\text{H}_2\text{SO}_4$ .
  - Solubility in dilute acid provides a convenient chemical method for distinguishing and separating amines from non-basic compounds that are insoluble in water. The amine can be extracted into aqueous acid (dilute HCl) and then recovered by making the aqueous solution basic and extracting the amine into ether or  $\text{CH}_2\text{Cl}_2$ .



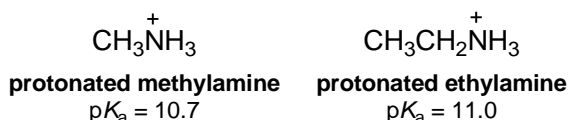
Example: A mixture of a carboxylic acid ( $\text{RCOOH}$ ,  $pK_a 5$ ), a primary aliphatic amine ( $\text{RNH}_2$ ,  $pK_a 10.8$ ) and a phenol ( $\text{ArOH}$ ,  $pK_a 10$ ) can be separated by acid-base neutralization reaction as a flow chart given below. Assume that these compounds are insoluble in water and soluble in diethyl ether.



## 2.4. Basicity of Nitrogen compounds

- The strength of a base is a measure of a compound's affinity for a proton. Therefore, a negatively charged base is more likely to pick up a proton than a neutral one. A compound in which the negative charge is delocalized is going to be less basic than one with a more concentrated, localized charge, and so on.
- In case of neutral bases (e.g. amines) the basicity is because of the lone pair on nitrogen. Two factors determine the strength of a base. First the accessibility of lone pair – greater the electron density on the nitrogen, the better its ability to attract protons. Second the stabilization of resultant positive moiety by delocalization or by solvent.
- It is common to compare basicities quantitatively by using the  $pK_a$ 's of their conjugate acids rather than their  $pK_b$ 's. The weaker the conjugate acid, the higher its  $pK_a$  and the stronger the base.

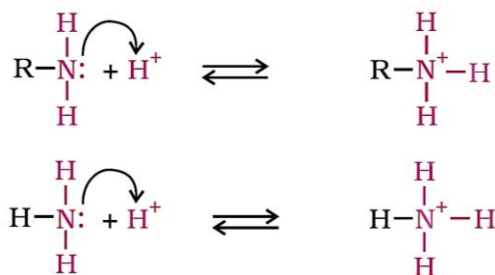
For example, protonated methylamine is a stronger acid than protonated ethylamine, which means that methylamine is a weaker base than ethylamine.



- Basicity of compounds increases when it is attached to electron releasing groups making the lone pair on nitrogen easily available for protonation. Conjugation with an electron-donating group produces even stronger bases.
- The lone pair on nitrogen is *less* available for protonation and the basicity of the compound decreases, if:
  - The nitrogen atom is attached to an electron-withdrawing group
  - The lone pair is in an  $sp$  or  $sp^2$  hybridized orbital
  - The lone pair is conjugated with an electron-withdrawing group
  - The lone pair is involved in maintaining the aromaticity of the molecule

### Alkylamines versus ammonia:

Let us consider the reaction of an alkanamine and ammonia with a proton to compare their basicity.



Due to the electron releasing nature of alkyl group, it (R) pushes electrons towards nitrogen and thus makes the unshared electron pair more available for sharing with the proton of the acid. Moreover, the substituted ammonium ion formed from the

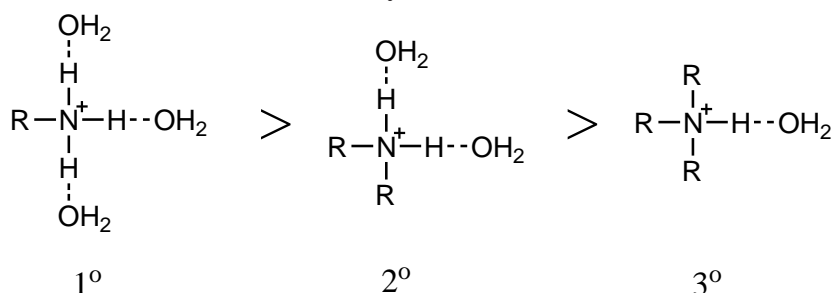
amine gets stabilized due to dispersal of the positive charge by the +I effect of the alkyl group. Hence, alkylamines are stronger bases than ammonia. Thus, the basic nature of aliphatic amines should increase with increase in the number of alkyl groups. This trend is followed in the gaseous phase. The order of basicity of amines in the gaseous phase follows the expected order:



However, the trend is not regular in the aqueous state as evident by their  $pK_b$  values.

Name of amine	$pK_b$
Methanamine	3.38
<i>N</i> -Methylmethanamine	3.27
<i>N,N</i> -Dimethylmethanamine	4.22
Ethanamine	3.29
<i>N</i> -Ethylethanamine	3.00
<i>N,N</i> -Diethylethanamine	3.25

In the aqueous phase, the substituted ammonium cations get stabilized not only by electron releasing effect of the alkyl group (+I) but also by solvation with water molecules. The greater the size of the ion, lesser will be the solvation and the less stabilized is the ion. The order of stability of ions is as follows:

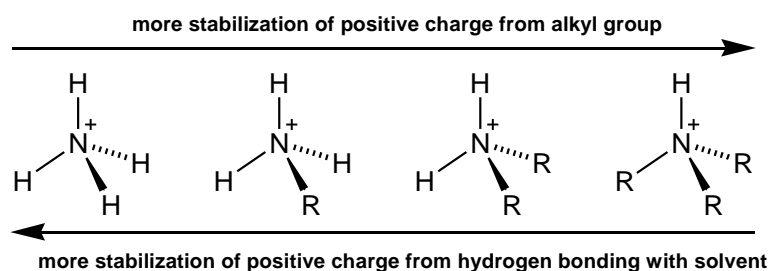


**Decreasing order of extent of H-bonding in water and order of stability of ions by solvation**

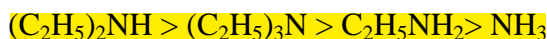
Greater is the stability of the substituted ammonium cation, stronger should be the corresponding amine as a base. Thus, the order of basicity of aliphatic amines should be:



This is opposite to the inductive effect based order.



Secondly, when the alkyl group is small, like  $-\text{CH}_3$  group, there is no steric hindrance to H-bonding. In case the alkyl group is bigger than  $\text{CH}_3$  group, there will be steric hindrance to H-bonding. Therefore, the change of nature of the alkyl group, e.g., from  $-\text{CH}_3$  to  $-\text{C}_2\text{H}_5$  results in change of the order of basic strength. The order of basic strength in case of methyl substituted amines and ethyl substituted amines in aqueous solution is as follows:

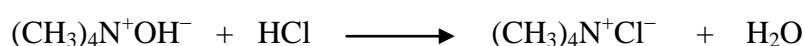


$\text{p}K_{\text{aH}}$  values for primary, secondary and tertiary amines:

R	$\text{p}K_{\text{aH}} \text{RNH}_2$	$\text{p}K_{\text{aH}} \text{R}_2\text{NH}$	$\text{p}K_{\text{aH}} \text{R}_3\text{N}$
Me	10.6	10.8	9.8
Et	10.7	11.0	10.8
<i>n</i> -Pr	10.7	11.0	10.3
<i>n</i> -Bu	10.7	11.3	9.9

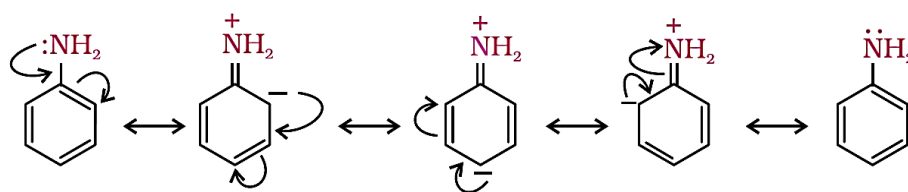
Thus, there is a subtle interplay of the inductive effect, solvation effect and steric hindrance of the alkyl group which decides the basic strength of alkyl amines in the aqueous state.

Quaternary ammonium halides—because they do not have an unshared electron pair on the nitrogen atom—cannot act as bases. Quaternary ammonium hydroxides, however, are strong bases. As solids, or in solution, they consist *entirely* of quaternary ammonium cations ( $\text{NR}_4^+$ ) and hydroxide ions ( $\text{OH}^-$ ); they are, therefore, strong bases—as strong as sodium or potassium hydroxide. Quaternary ammonium hydroxides react with acids to form quaternary ammonium salts:



#### ▪ Arylamines:

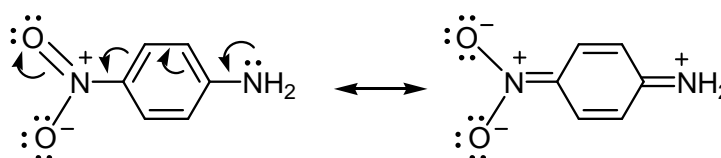
In case of alkylamines the total effect of various factors is small, and most alkylamines are very similar in basicity. Arylamines, however, are mostly about a million times weaker as bases than ammonia and alkylamines. Aniline is a weaker base than cyclohexyl amine by roughly a million fold. Electron withdrawing groups (e.g. benzene ring) decrease the electron density on nitrogen, and therefore, the basicity of the compound. Aromatic amines are weaker bases than ammonia because the lone pair on nitrogen is *less* available for protonation. The  $-\text{NH}_2$  group is attached directly to the benzene ring which results in the unshared electron pair on nitrogen atom to be in conjugation with the benzene ring and thus making it less available for protonation.



Conjugation of the amino group of an arylamine with a second aromatic ring, then a third, reduces its basicity even further. Diphenylamine is 6300 times less basic than aniline, whereas triphenylamine is scarcely a base at all, being estimated as  $10^8$  times less basic than aniline and  $10^{14}$  times less basic than ammonia.

$\text{C}_6\text{H}_5\text{NH}_2$ Aniline ( $K_b$ $3.8 \times 10^{-10}$ ; $\text{p}K_b$ 9.4)	$(\text{C}_6\text{H}_5)_2\text{NH}$ Diphenylamine ( $K_b$ $6 \times 10^{-14}$ ; $\text{p}K_b$ 13.2)	$(\text{C}_6\text{H}_5)_3\text{N}$ Triphenylamine ( $K_b \approx 10^{-19}$ ; $\text{p}K_b \approx 19$ )
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In substituted anilines, it is observed that electron releasing groups like  $-\text{OCH}_3$ ,  $-\text{CH}_3$  increase basic strength whereas electron withdrawing groups like  $-\text{NO}_2$ ,  $-\text{SO}_3\text{H}$ ,  $-\text{X}$ ,  $-\text{COOH}$  decrease it. Extended conjugation further reduces the basicity. For example, *p*-nitroaniline is less basic than aniline by the factor of 3800 which resulted by extensive delocalization of the unshared electron pair of the amine group to the nitro group.

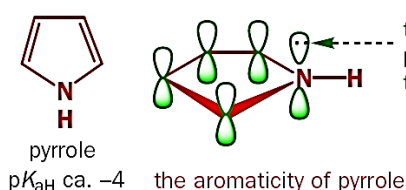
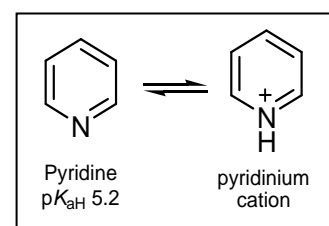


Electron delocalization in *p*-nitroaniline

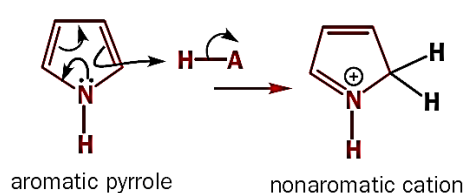
#### ▪ Heterocyclic compounds:

In pyridine the nitrogen is  $sp^2$  hybridized. The non-bonding electron pair is localized on the nitrogen atom, but increasing *s*-character brings it closer to the nitrogen nucleus, reducing its tendency to bond to a proton.

Very low basicity of pyrrole is due the exceptional delocalization of the nitrogen electron pair associated with its incorporation in an aromatic ring. The cation formed after protonation is no longer aromatic because the conjugation is interrupted by a saturated  $\text{CH}_2$  group and so pyrrole is not at all basic ( $\text{p}K_{\text{aH}}$  about  $-4$ ).

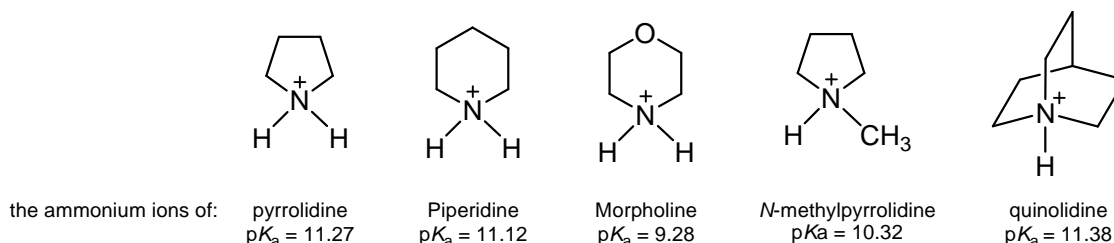


this lone pair is in a p orbital contributing to the  $6\pi$  electrons in the aromatic ring

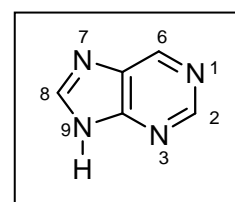




Physical and chemical properties of saturated heterocycles containing five or more atoms are similar to that of acyclic compounds with the same heteroatom. For example, pyrrolidine, piperidine, and morpholine are typical secondary amines, and *N*-methylpyrrolidine and quinuclidine are typical tertiary amines. The conjugate acids of these amines have  $pK_a$  values expected for ammonium ions.



Purine has three basic, pyridine-like nitrogens with lone-pair electrons in  $sp^2$  orbitals in the plane of the ring. The remaining purine nitrogen is non-basic and pyrrole-like, with its lone-pair electrons as part of the aromatic  $\pi$  electron system.

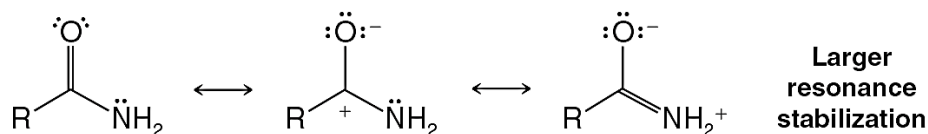
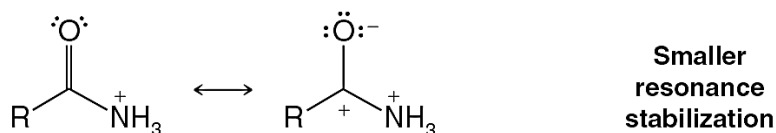


▪ **Nitriles:**

Nitriles are much harder to protonate as the lone pair being in  $sp$  hybridized orbital is more tightly held. This explains why the lone pair of the nitrile group is not at all basic and needs a strong acid to protonate it.

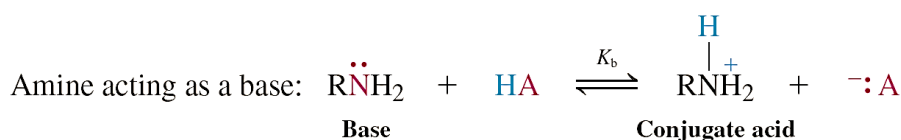
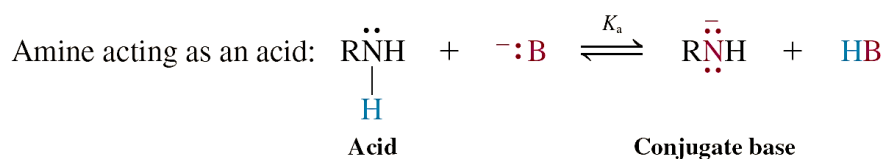
▪ **Amides:**

Amides are less basic than amines. A more important factor accounting for amides being weaker bases than amines is the powerful electron-withdrawing effect of the carbonyl group of the amide. Moreover, in amides the nitrogen is  $sp^2$  hybridized and its lone pair is in the  $p$  orbital which overlaps effectively with the carbonyl group. This delocalization makes the lone pair less available for protonation and thus makes amides much less basic. Instead of nitrogen, protonation occurs at carbonyl oxygen atom because the positive charge on the oxygen atom after protonation can be delocalized to the nitrogen atom making the cation much more stable. If the nitrogen is protonated, the positive charge could not be delocalized on to the oxygen but would have to stay localized on the nitrogen, which would make the cation less stable. Furthermore, the nitrogen in amides being attached to electron deficient carbon of carbonyl group makes its protonation energetically unfavourable.

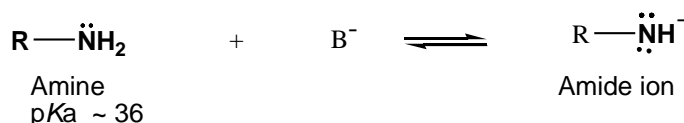
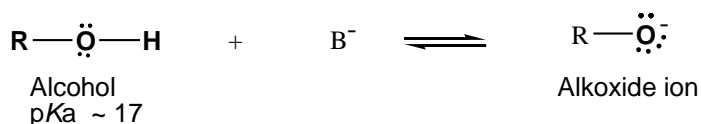
**Amide****N-Protonated Amide**

## 2.5. Acidity of Nitrogen compounds

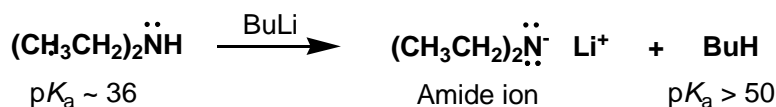
- The strength of an acid depends on the stability of the conjugate base—the more stable the conjugate base, the stronger the acid. The stability of conjugate base depends on:
  - the electronegativity of the element carrying the negative charge—the more electronegative the element, the more stable the conjugate base, and
  - The delocalization of negative charge – the more delocalized the negative charge, the more stable the base.
- Amines** can act as an acid and donate a proton, as well as a base and accept a proton.



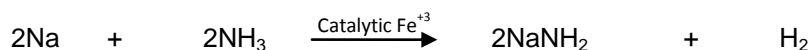
- ✓ The same factors that decreased the basicity of amines increase their acidity.  $\text{pK}_a$  is being used as a measure of the acidity of the amine itself.
- ✓ Primary and secondary amines are very weak Bronsted acids – much weaker than alcohols. Removal of a proton from an alcohol provides alkoxide bearing negative charge on oxygen while the removal of proton from amines gives an amide ( $\text{RNH}^-$ ) bearing negative charge on nitrogen. Nitrogen being less electronegative than oxygen is less favoured to carry negative charge.



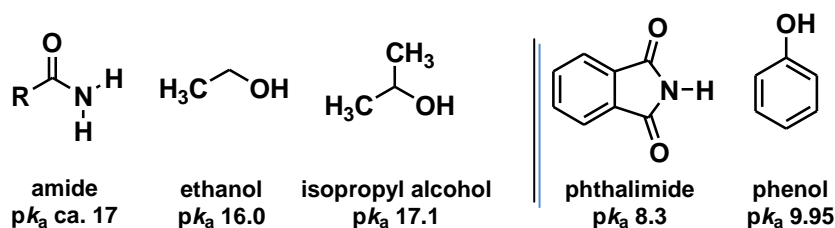
- ✓ Only very strong bases such as Alkylolithium reagents can remove a proton from an amine to give the amide ion, which is itself much stronger conjugate base of the parent amine.



- ✓ An alternative synthesis of amide ions is the treatment of amines with alkali metals. Alkali metals dissolve in amines with the evolution of hydrogen and the formation of amine salts.



- ✓ Therefore, the amines are good bases and relatively poor acids.
- **Amides** (acyl compounds,  $\text{RCONH}_2$ ) are weakly acidic (about the same as alcohols), and **imides** are definitely acidic (about the same as phenols).



## 2.6. Preparation of 1<sup>o</sup>, 2<sup>o</sup> and 3<sup>o</sup> amines

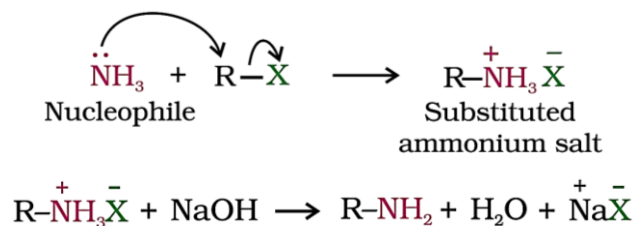
Following types of reactions are used to prepare an amine:

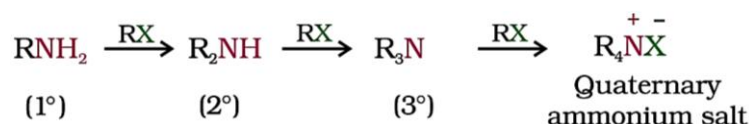
- **Nucleophilic substitution of alkyl halide** using nitrogen nucleophiles
- **Reduction** of other nitrogen-containing functional groups
- **Reductive amination** of aldehydes and ketones
- **Hofmann and Curtius Rearrangement**

### 2.6.1. Through Nucleophilic substitution reaction:

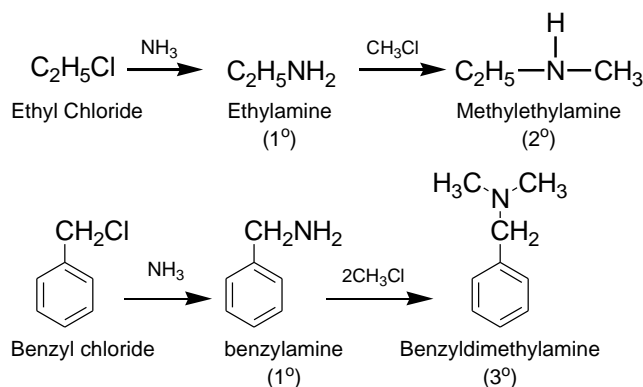
#### Ammonolysis of alkyl halides

An alkyl or benzyl halide on reaction with aqueous or an ethanolic solution of ammonia undergoes nucleophilic substitution reaction in which the halogen atom is replaced by an amino ( $-\text{NH}_2$ ) group. This process of cleavage of the  $\text{C}-\text{X}$  bond by ammonia molecule is known as **ammonolysis**. The reaction is carried out in a sealed tube at  $100^\circ\text{C}$ ; the salts of amines are produced, which on the treatment with strong base give free amines. The primary amine thus obtained behaves as a nucleophile and can further react with alkyl halide to form secondary and tertiary amines, and finally quaternary ammonium salt.





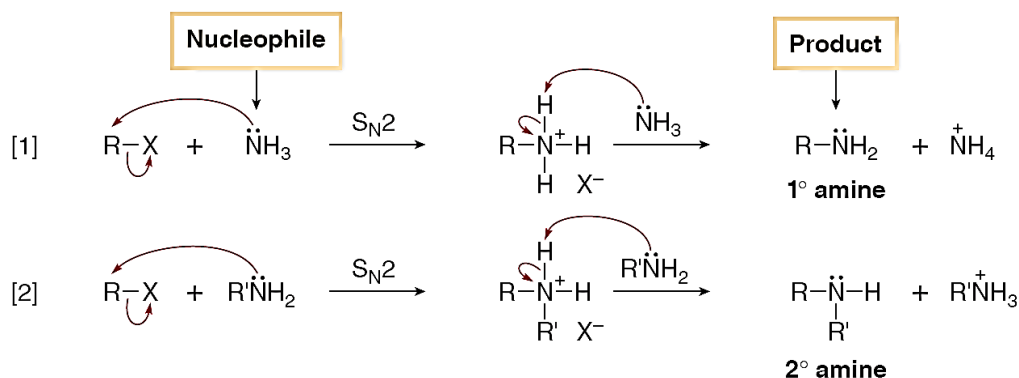
### Examples

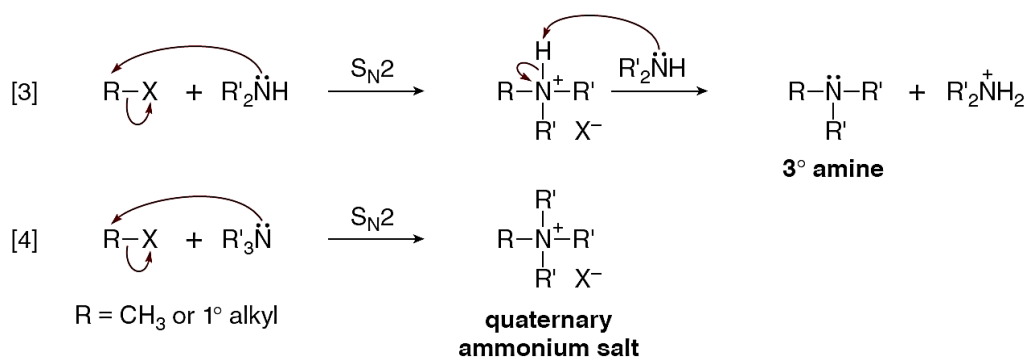


Ammonolysis has the **disadvantage** of yielding a mixture of primary, secondary and tertiary amines and also a quaternary ammonium salt. Because primary amine formed by nucleophilic substitution still has a non-bonded electron pair, making it a nucleophile as well. It will react with remaining alkyl halide to form salt of 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 and so on. The reaction stops at the formation of quaternary ammonium salt as it does not have any electron pair to react with alkyl halide.

### Mechanism:

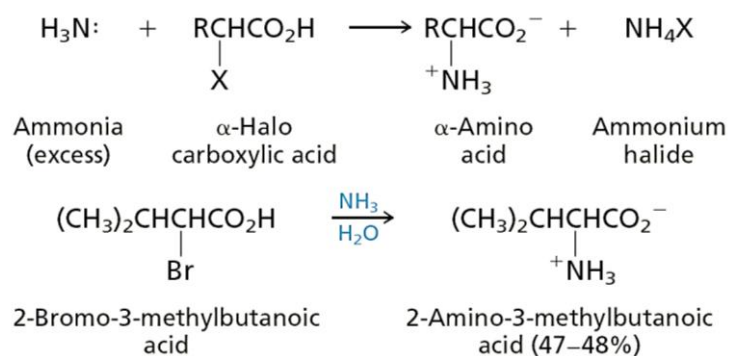
Ammonia is a very good nucleophile and readily undergoes alkylation when treated with an alkyl halide. The reaction follows  $\text{S}_{\text{N}}2$  process followed by deprotonation to give primary amine. The primary amine is even a better nucleophile and thus reacts further with another molecule of alkyl halide to yield secondary, then tertiary amine, and finally quaternary ammonium salt.





Therefore, this method can be used for the formation of primary amine by using ammonia in very large excess, and for preparing quaternary ammonium salts by using large excess of alkyl halide. However, monoalkylation is difficult to achieve because each successive alkylation makes the nitrogen atom more nucleophilic, thus a mixture of products generally achieved.

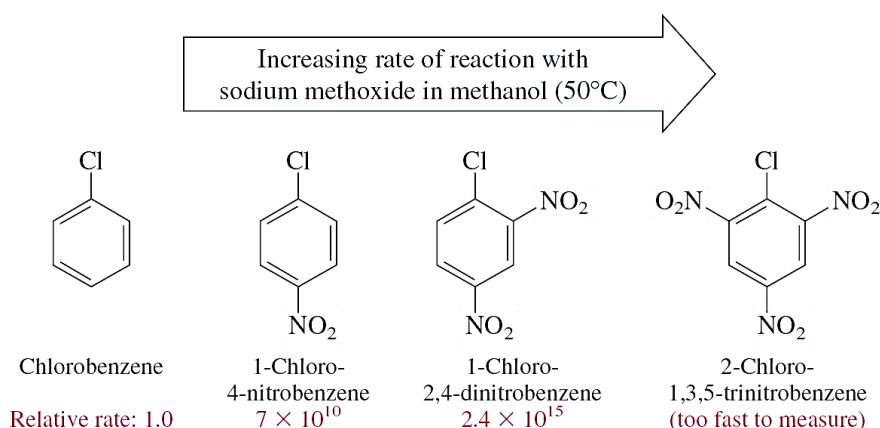
This is a good method for the preparation of  $\alpha$ -amino acids.



Because the reaction follows an  $\text{S}_{\text{N}}^2$  mechanism, the primary alkyl halides favour the reaction. The order of reactivity of halides with amines is:

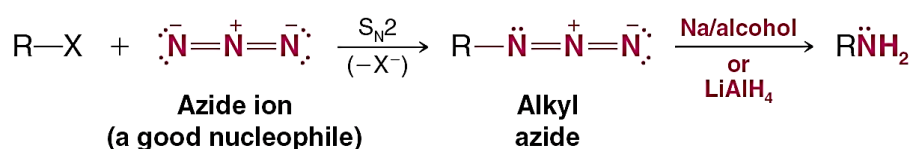


Aryl halides do not normally react with ammonia under these conditions. Aryl halides undergo these reactions only (i) if a nitro group, or other strongly electron-withdrawing groups, is present *ortho* or *para* to the halogen, or (ii) if a high temperature or a strong basic reagent is used. *m*-Chloronitrobenzene is much more reactive than chlorobenzene, however, it is thousands of times less reactive than either *o*- or *p*-chloronitrobenzene. The effect of *o*- and *p*-nitro substituents is cumulative:



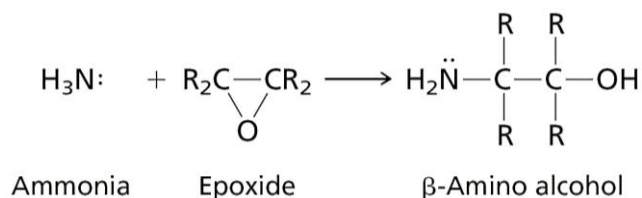
### Formation of alkyl azide followed by reduction

Nucleophilic substitution of alkyl halides by sodium azide to form alkyl azide followed by reduction with sodium and alcohol or with lithium aluminum hydride is a much better method for the preparation of primary amines. Azide reacts only once with alkyl halides because the product, an alkyl azide, is no longer nucleophilic.



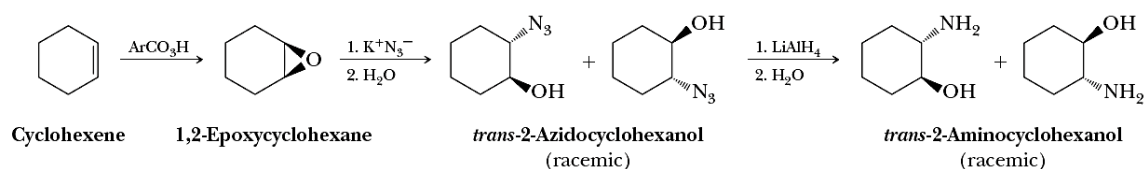
### Nucleophilic ring opening of epoxides by ammonia or Azide ion

The strained ring of an epoxide is opened on nucleophilic attack by ammonia and amines to give  $\beta$ -amino alcohols.



Azide can also react with epoxides. Azide attacks at either end of the three-membered ring to give the  $\beta$ -azidoalcohol which on reduction with  $\text{LiAlH}_4$  provides  $\beta$ -aminoalcohol.

Example: conversion of cyclohexene to *trans*-2-aminocyclohexanol

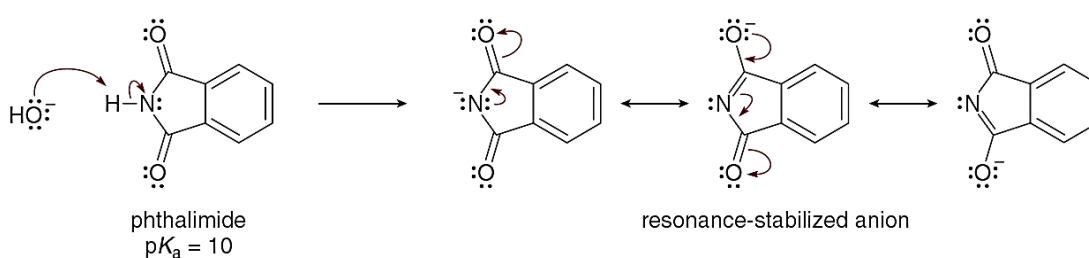


Cyclohexene is converted to epoxide by the reaction with peroxyacids. Stereospecific nucleophilic attack by azide ion anti to the leaving oxygen of the epoxide ring followed by reduction of the azide with lithium aluminium hydride gives racemic *trans*-2-aminocyclohexanol.

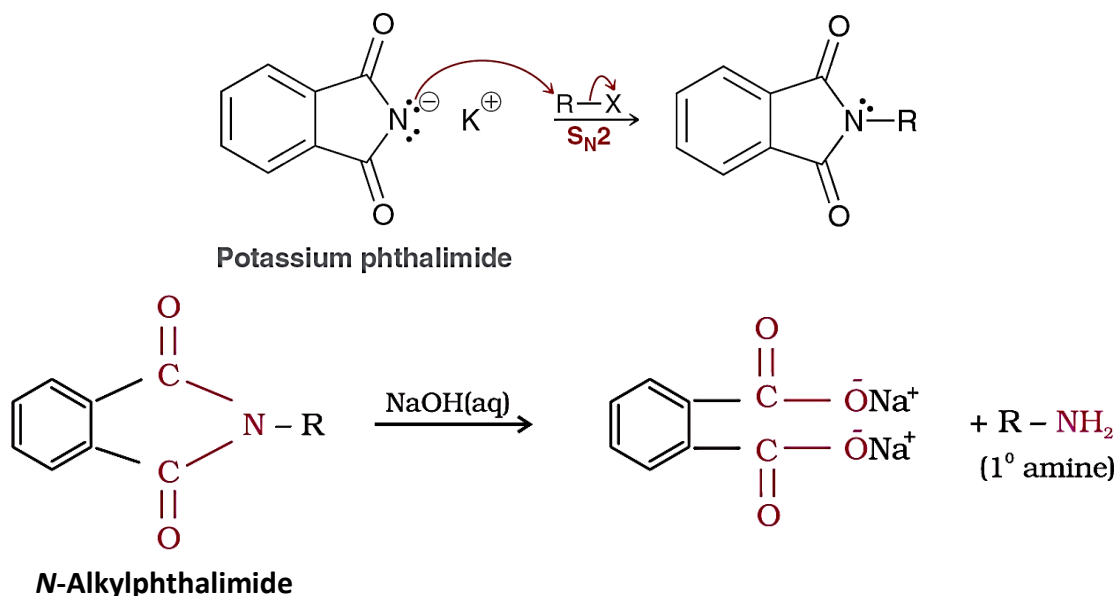
### Gabriel Synthesis

The Gabriel synthesis converts an alkyl halide into a 1° amine by a two-step process – nucleophilic substitution followed by hydrolysis. This avoids the complications of multiple alkylation because phthalimide can undergo only a single alkylation, therefore, the formation of secondary and tertiary amines does not occur. This makes the Gabriel synthesis a valuable procedure for the laboratory preparation of primary amines.

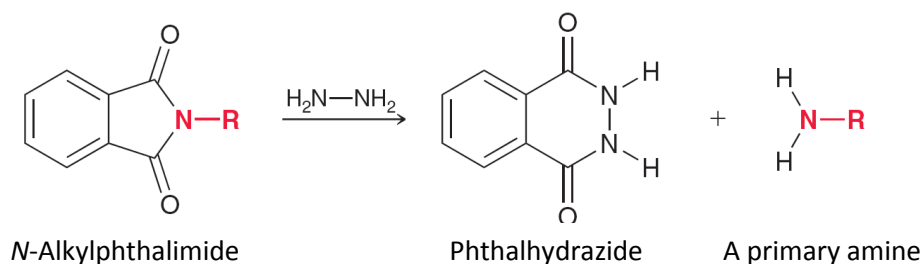
The treatment of phthalimide with ethanolic potassium hydroxide forms potassium salt of phthalimide. The N–H bond of phthalimide is relatively acidic because it is flanked by two electron-withdrawing C=O groups; and the anion resulting from the loss of proton is stabilized through resonance. Thus this proton can easily be abstracted by hydroxide.



The potassium salt of phthalimide has a negatively charged nitrogen atom, which acts as a nucleophile toward primary alkyl halides in  $\text{S}_{\text{N}}2$  process. The *N*-alkylphthalimide so formed on alkaline hydrolysis produces the corresponding primary amine, but the hydrolysis is often difficult.



A more effective and convenient method of cleaving the two amide bonds is by treating *N*-alkylphthalimide with hydrazine in refluxing ethanol to give a primary amine and phthalhydrazide:



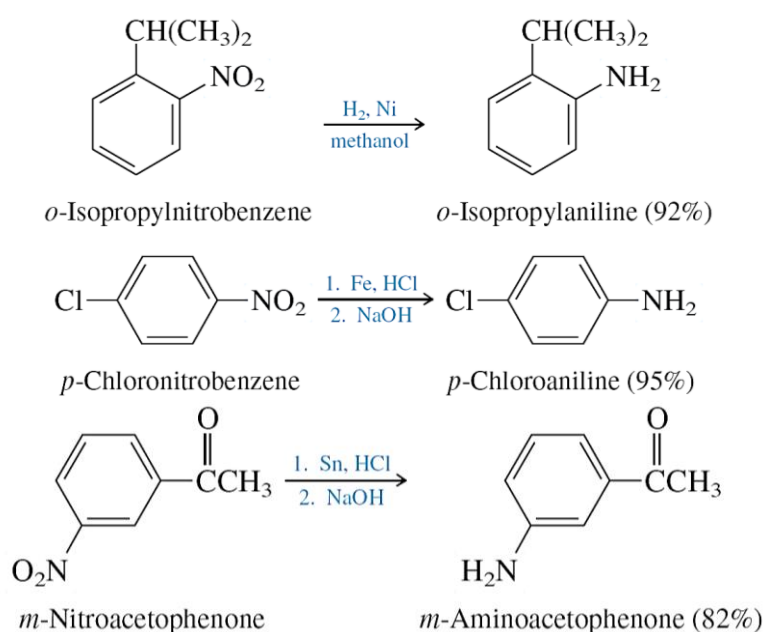
Aromatic primary amines cannot be prepared by this method because aryl halides do not undergo nucleophilic substitution with the anion formed by phthalimide.

### 2.6.2. Reduction of other nitrogen-containing functional groups

Reduction of a nitro and a nitrile compound furnishes a primary amine while reduction of amides produces primary, secondary, or tertiary amines. Depending on the circumstances, different reducing agents are used for reduction. Catalytic hydrogenation over platinum works well if any other reducible groups, such as C=C bonds or carbonyl groups, are not present elsewhere in the molecule. In that case, Tin(II) chloride is preferred as it is very mild reducing agent and cannot reduce other reducible groups. Iron and zinc chloride ( $\text{ZnCl}_2$ ) are also effective when used in acidic aqueous solution.

#### Reduction of Nitro compounds

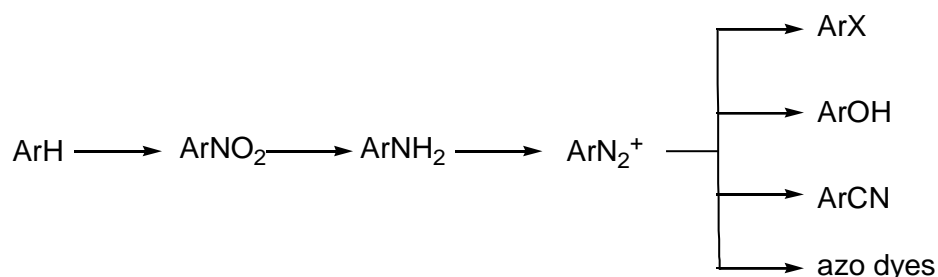
Nitro compounds are reduced to amines by a variety of reducing agents. This method is most widely used for the preparation of aromatic amines. The reaction is carried out by passing hydrogen gas in the presence of finely divided nickel, palladium or platinum and also by reduction with metals in acidic medium. Nitroalkanes can also be similarly reduced to the corresponding alkylamines.





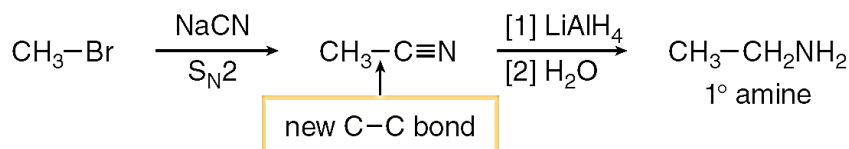
Reduction with iron scrap and hydrochloric acid is preferred because  $\text{FeCl}_2$  formed gets hydrolyzed to release hydrochloric acid during the reaction. Thus, only a small amount of hydrochloric acid is required to initiate the reaction.

Reduction of nitro compounds to amines is an essential step in the synthesis of various aromatic compounds. Nitro compounds are readily obtained by direct nitration. The amines formed by reduction can easily be converted into diazonium salts which can produce different compounds.



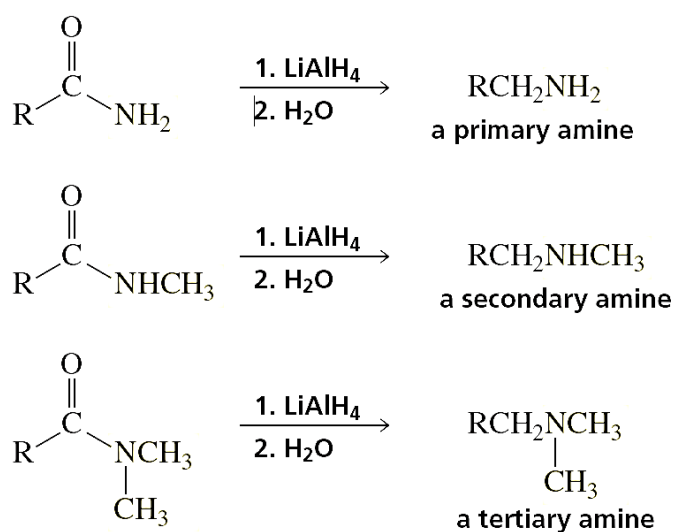
### Reduction of Nitriles

Nitriles on reduction with lithium aluminium hydride ( $\text{LiAlH}_4$ ) or catalytic hydrogenation produce primary amines. This reaction is used for increasing the length of carbon chain. A cyano group is readily introduced by  $\text{S}_{\text{N}}2$  substitution of alkyl halides with  $-\text{CN}$ . This provides a two-step method to convert an alkyl halide to a primary amine with one more carbon atom.

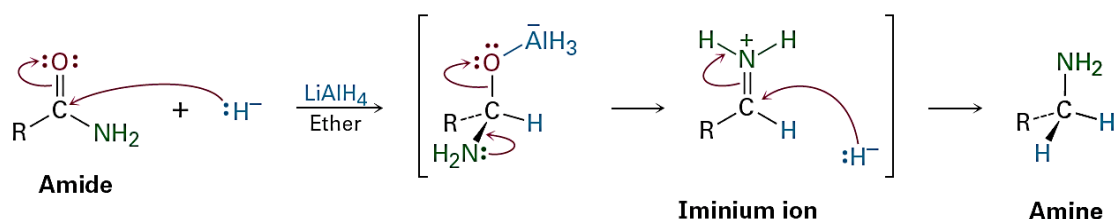


### Reduction of Amides

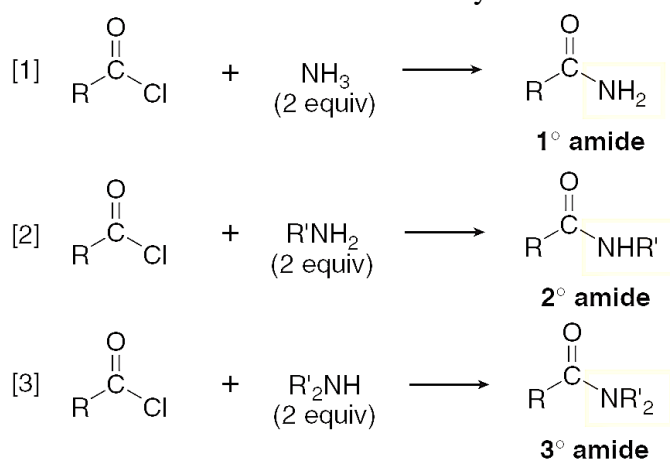
The amides on reduction with lithium aluminium hydride yield amines. **Reduction 1°, 2°, and 3° amides provides 1°, 2°, and 3° amines**, respectively. Thus, primary amines are obtained from primary amide; *N*-substituted amides yield secondary amines; and the *N,N*-disubstituted amides provide tertiary amines.

**Mechanism:**

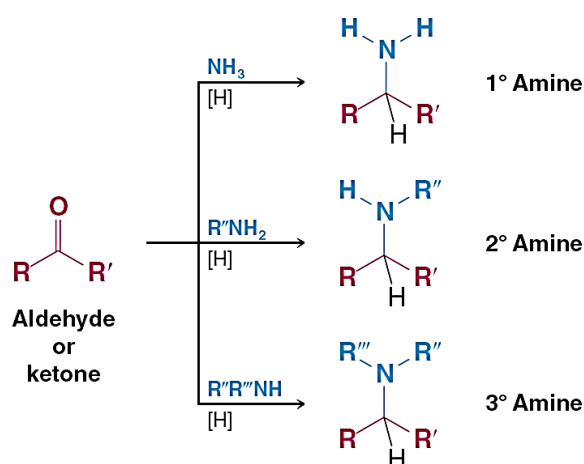
A nucleophilic addition of  $\text{LiAlH}_4$ , with hydride ion adding to the carbonyl carbon and aluminum making complex with carbonyl oxygen generates a tetrahedral intermediate. The amino group is a poor leaving group, however, the carbonyl oxygen complexed with aluminum acts as a fair leaving group, which makes an imine or iminium ion. Further nucleophilic attack of hydride ion gives amine.



This is a versatile method for the preparation of amines because the amides can easily be prepared from acid chloride, acid anhydride and esters by nucleophilic addition-elimination reactions of ammonia or an amine at an acyl carbon.

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

Many aldehydes ( $\text{RCHO}$ ) and ketones ( $\text{R}_2\text{CO}$ ) are converted into amines by reductive amination of aldehydes or ketones (or *reductive alkylation* of the amine) i.e. reduction in the presence of ammonia. The reaction is a two-step process that converts aldehydes and ketones into  $1^\circ$ ,  $2^\circ$ , and  $3^\circ$  amines. First step is the nucleophilic addition-elimination reaction of ammonia or amines on to the carbonyl group of aldehydes or ketones, and the second step is the reduction of the  $\text{C}=\text{N}$  bond formed in the first step. Reduction can be accomplished catalytically in presence of  $\text{H}_2$  and Raney nickel or by use of sodium cyanoborohydride,  $\text{NaBH}_3\text{CN}$  or Sodium triacetoxyborohydride,  $\text{NaBH}(\text{OAc})_3$ . Because of the electron withdrawing cyano group in sodium cyanoborohydride, it is milder than sodium borohydride and reduces the imine, not the carbonyl group. Primary, secondary, and tertiary amines can be prepared by this method.



Primary amines are formed by nucleophilic addition of ammonia to the carbonyl group of aldehydes and ketones to form carbinolamines, which on dehydration under the conditions of their formation give imines. Similarly, the addition of primary amines to carbonyl group yields *N*-substituted imines. Secondary amines yield enamines. Imines, *N*-substituted imines and enamines on reduction yield primary, secondary and tertiary amines, respectively.

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

Reductive amination is quite valuable from synthetic point of view because the reaction is carried out in a single operation. The carbonyl compound, ammonia (or amines) and hydrogenating agent are taken in one reaction solution. The intermediate imine is not isolated but undergoes reduction under the conditions of its formation.

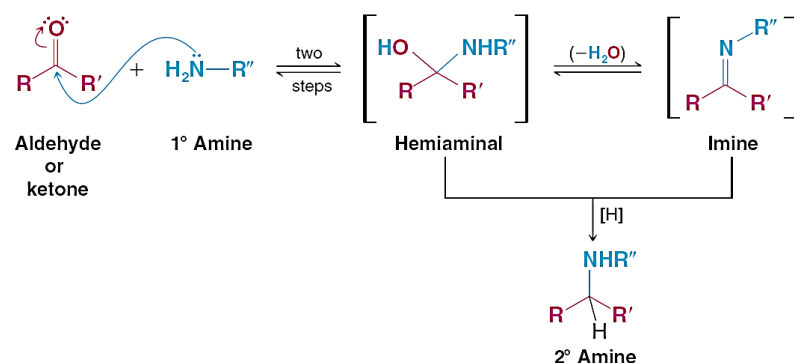
### Mechanism:

The mechanism will be discussed in unit-3 in detail. The key steps are –

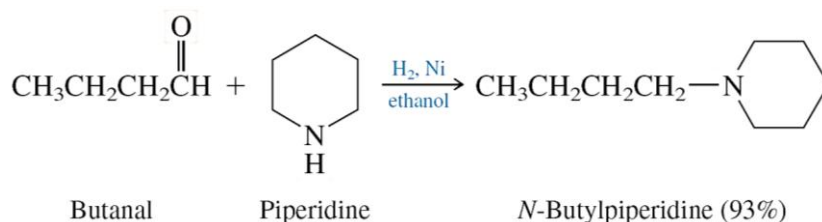
**Part 1: Nucleophilic attack of ammonia or amine (formation of imine).** The nucleophilic attacks of ammonia on carbonyl carbon; followed by protonation of

carbonyl oxygen generates an intermediate carbinolamine (or hemiaminal). Carbinolamine loses water to yield imine.

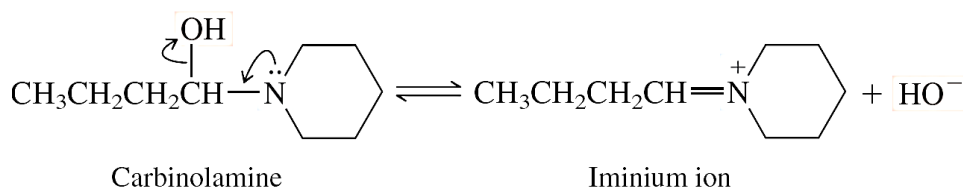
**Part 2: Reduction of imine (Formation of amine).** The catalytic or metal hydride reduction of imine yields amine.



Tertiary amines can also be prepared by reductive amination from carbonyl compound and secondary amines, although a neutral imine is not possible in this case.

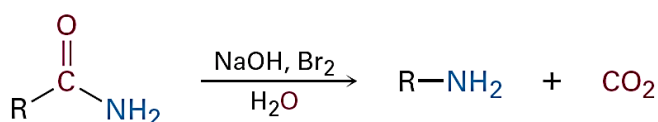


Possibly, the reaction proceeds through carbinolamine or an iminium ion.

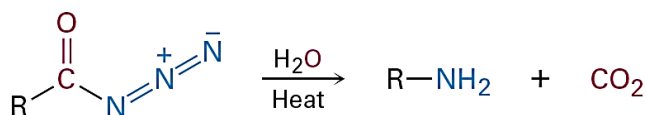


#### 2.6.4. Hofmann and Curtius rearrangement

Carboxylic acid derivatives can be converted into primary amines with loss of one carbon atom by both the Hofmann rearrangement and the Curtius rearrangement. Both involve the similar mechanisms. The differences in two reactions are that (i) Hofmann rearrangement involves a primary amide while the Curtius rearrangement involves an acyl azide, and (ii) Hofmann rearrangement is carried out in aqueous conditions under which isocyanate and carbamic acid are not stable and therefore, cannot be isolated; Curtius rearrangement is carried out in nonaqueous conditions under which isocyanate is stable and can be isolated.

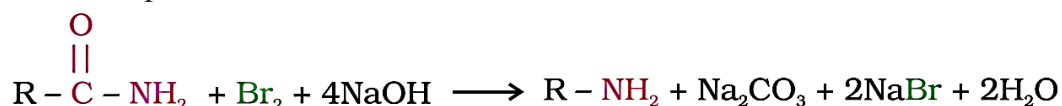
**Hofmann rearrangement**

An amide

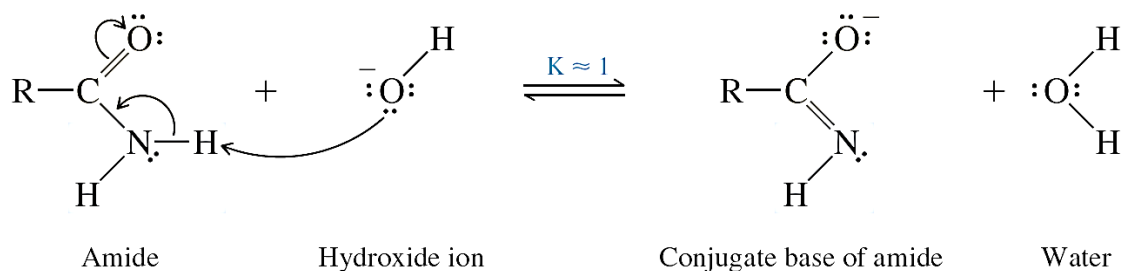
**Curtius rearrangement**

An acyl azide

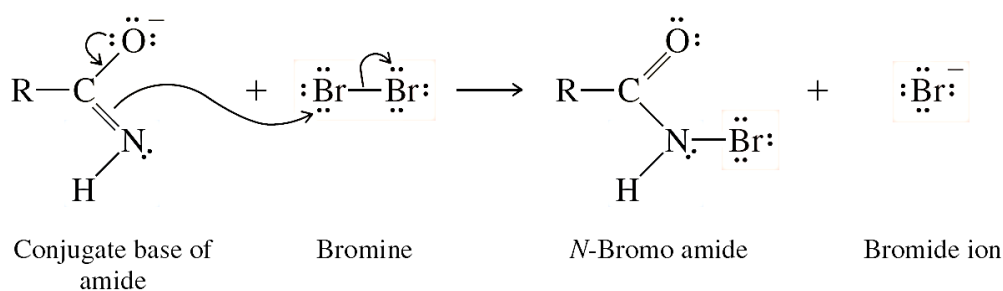
The **Hofmann degradation** involves the treatment of a primary amide with bromine in an aqueous or ethanolic solution of sodium hydroxide. An *N*-bromo amide is an intermediate; it rearranges to an isocyanate by the migration of alkyl or aryl group from carbonyl carbon of the amide. The isocyanate on addition of water followed by decarboxylation produces a primary amine. The amine so formed contains one carbon less than that present in the amide.

**Mechanism:**

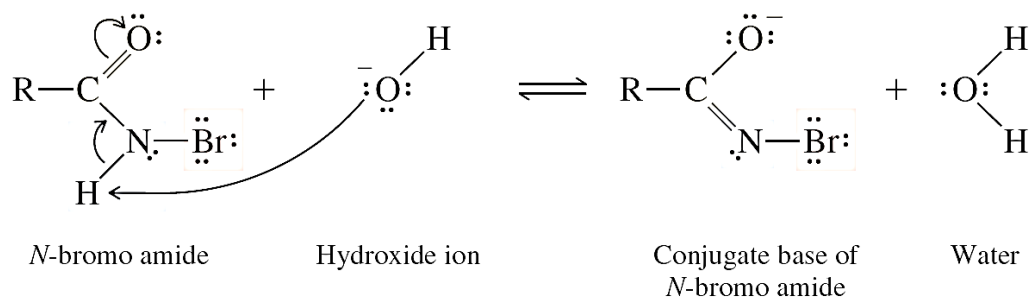
**Step 1: Deprotonation of amide (formation of amidate ion).** The amido hydrogens are acidic because of electron-withdrawing acyl group. A base abstracts an acidic N-H proton to generate amide ion (a conjugate base), which is stabilized by delocalization of electrons.



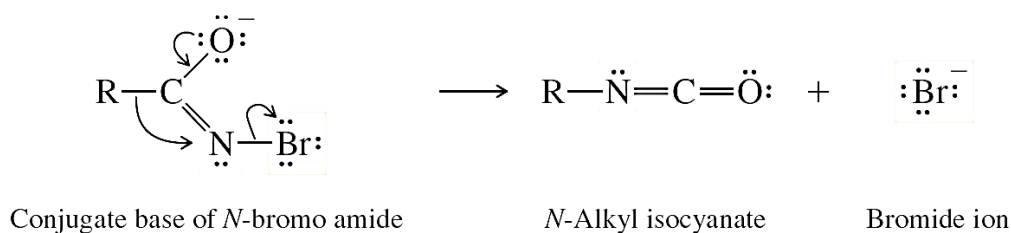
**Step 2: Halogenation (formation of *N*-bromo amide).** The conjugate base of amide reacts with bromine to give *N*-bromo amide, much like  $\alpha$ -halogenation of aldehyde and ketone enolates.



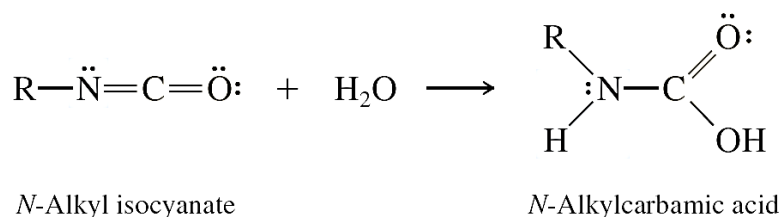
**Step 3: Deprotonation of *N*-bromo amide.** The attachment of electron-withdrawing bromine further enhances the acidic nature of the amido hydrogen. Thus, *N*-bromo amide is even more acidic than amide. Therefore, base abstracts another proton to form conjugate base of *N*-bromo amide, which is stabilized by electron delocalization.



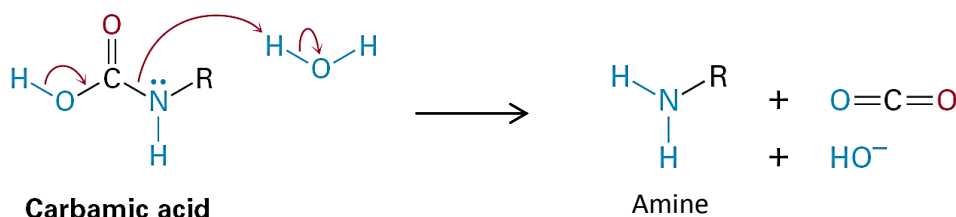
**Step 4: Rearrangement of conjugate base of *N*-bromo amide.** The conjugate base of *N*-bromo amide, containing a weak nitrogen-halogen bond and a good leaving group, undergoes loss of halide ion accompanied by migration of the R-group from the carbonyl carbon to nitrogen to give isocyanate.



**Step 5: Addition of water (formation of carbamic acid).** The *sp*-hybridized carbonyl carbon in the isocyanate is highly electrophilic and is attacked by water to produce an unstable carbamic acid.

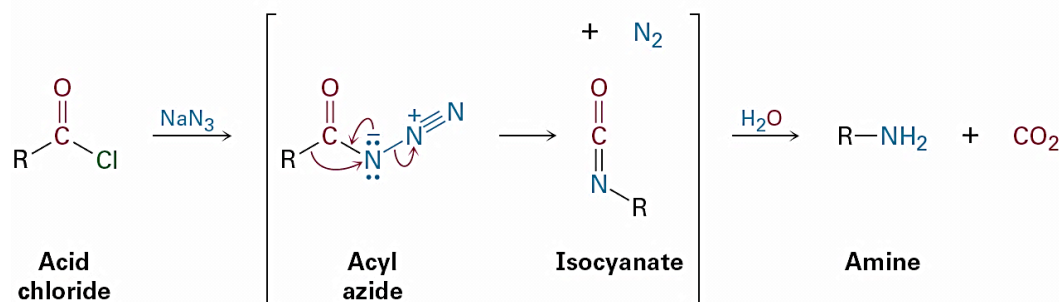


**Step 6: Decarboxylation (Formation of amine).** *N*-Alkylcarbamic acid is unstable and spontaneously loses CO<sub>2</sub> resulting in the formation of amine.

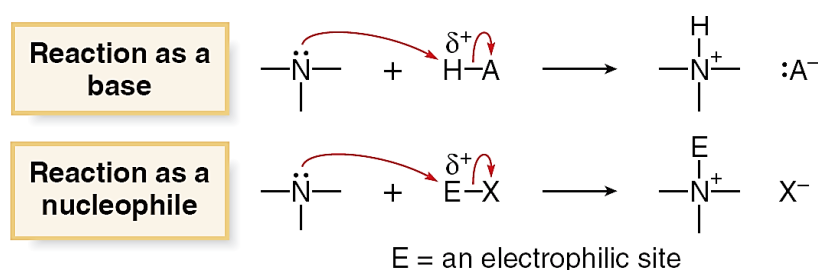


As two hydrogen atoms are used in first three steps, the Hofmann rearrangement is limited to primary amides, RCONH<sub>2</sub>. The reaction occurs with *retention of*

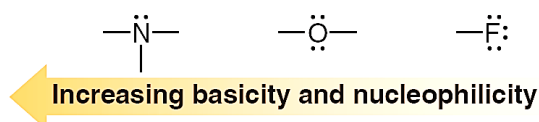
**Curtius rearrangement** occurs with acyl azides which are easily prepared by the reaction of acyl chloride with sodium azide. On heating, nitrogen departs from acyl azide and, like in Hofmann degradation, R-group migrates from the acyl carbon to the nitrogen atom to generate isocyanate.  $N_2$  is the best of all possible leaving groups since it is highly stable, is virtually nonbasic, and being a gas, removes itself from the medium. The isocyanate on hydrolysis and decarboxylation produces amine.



Most of the reactions of amines are because of the lone pair of electrons on nitrogen. Amines behave as bases in presence of Bronsted acid and as nucleophile with compounds having electrophilic centre.



As the electronegativity increases across the row in periodic table, the tendency of losing electrons decreases- means the basicity and nucleophilicity decreases. Therefore nitrogen is more basic and more nucleophilic than oxygen and fluorine.



In addition alkylamines being more basic than arylamines, are also more nucleophilic.

Amines undergo following reactions in general:

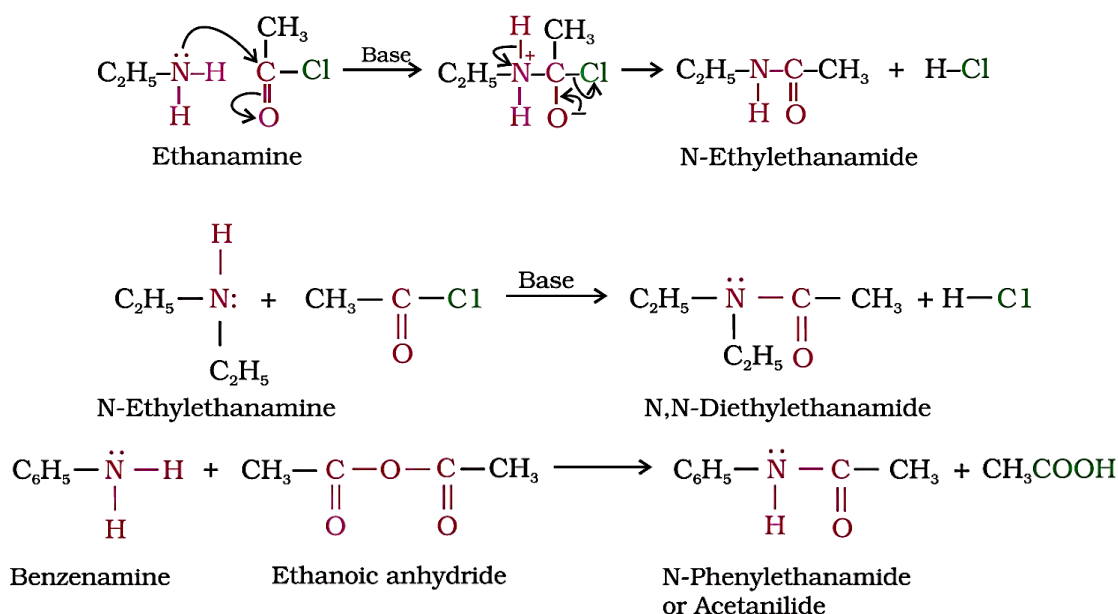
We have already discussed earlier in this chapter under section 2.6.1 (Ammonolysis of alkyl halides) that primary, secondary, and tertiary amines can be alkylated by reaction

with a primary alkyl halide. Primary and secondary amines often give mixtures of products; however tertiary amines are cleanly alkylated to give quaternary ammonium salts.

### 2.7.2. Acylation:

Aliphatic and aromatic primary and secondary amines (but not tertiary) can be acylated by nucleophilic substitution reaction with acid chlorides, anhydrides and esters. The hydrogen atom of  $-NH_2$  or  $>N-H$  group is replaced by the acyl group to produce amides. The reaction is carried out in presence of a base stronger than the amine, like pyridine, which removes HCl so formed and shifts the equilibrium to the right hand side.

As the amides are much less nucleophilic and less reactive than the starting amine, further acylation of the nitrogen does not take place.



### 2.7.3. Benzoylation:

Similar to acylation, amines undergo benzoylation also. They react with benzoyl chloride ( $\text{C}_6\text{H}_5\text{COCl}$ ) to give benzamide.



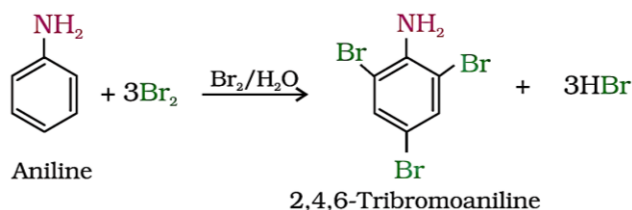
### 2.7.4. Electrophilic substitution of aryl amines:

Arylamines are **difunctional compounds** as they contain two functional groups, the amine group and the aromatic ring. The reactivity of the amine group is affected by its aryl substituent, and the reactivity of the ring is affected by its amine substituent. The electron delocalization in the ring reduces the basicity of amine and the nucleophilicity of arylamine nitrogen increases the electron density in the aromatic ring and makes arylamines extremely reactive toward electrophilic aromatic substitution.  $-NH_2$ ,  $-NHR$

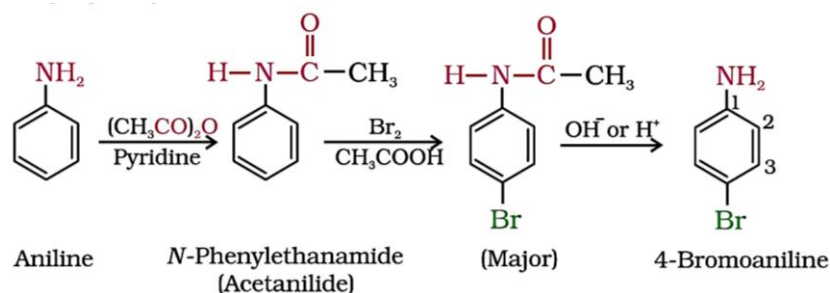


and  $-NR_2$  groups in arylamines are *ortho*, *para*-directing and exceedingly powerful activating groups. These substituents are such powerful activators that electrophilic aromatic substitution is only rarely performed directly on arylamines.

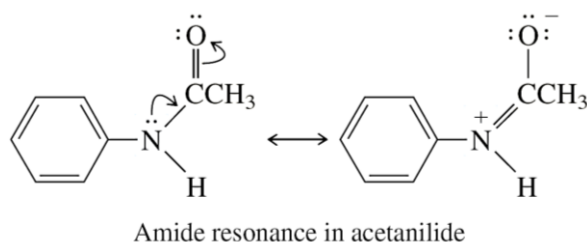
- (a) **Bromination:** Aniline reacts with bromine water at room temperature to give a white precipitate of 2,4,6-tribromoaniline.



The main problem encountered during electrophilic substitution reactions of aromatic amines is that of their very high reactivity. The preparation of monosubstituted aniline derivative can only be done by protecting the  $-NH_2$  group by acetylation with acetic anhydride, then carrying out the desired substitution followed by hydrolysis of the substituted amide to the substituted amine.

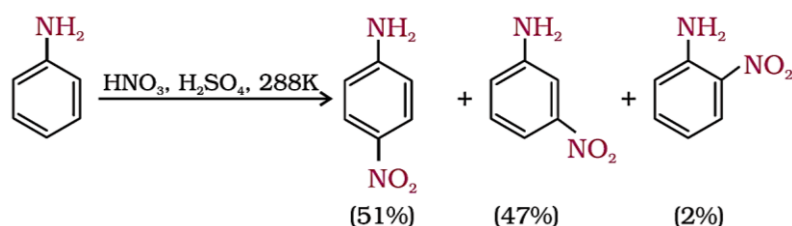


The lone pair of electrons on nitrogen of acetanilide interacts with oxygen atom due to resonance as shown below:

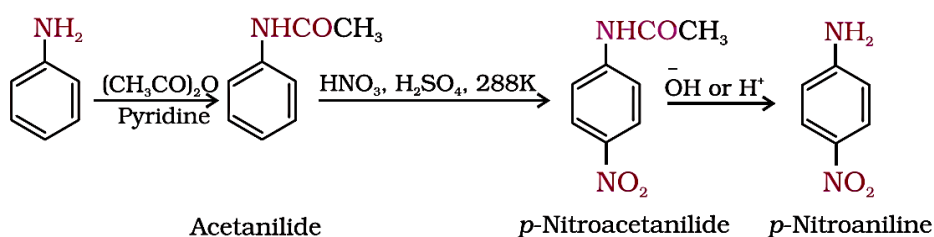


Hence, the lone pair of electrons on nitrogen is less available for donation to benzene ring by resonance. Therefore, activating effect of  $-NHCOCH_3$  group is less than that of amino group.

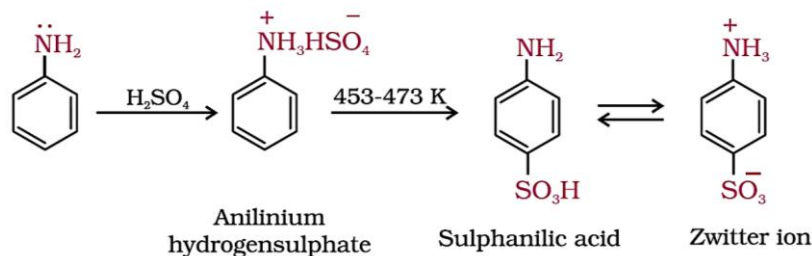
- (b) **Nitration:** Direct nitration of aniline and other arylamines is difficult to carry out and is accompanied with oxidation that leads to the formation of dark-colored “tars.” Moreover, in the strongly acidic medium, aniline is protonated to form the anilinium ion which is *meta* directing. Therefore, besides the *ortho* and *para* derivatives, significant amount of *meta* derivative is also formed.



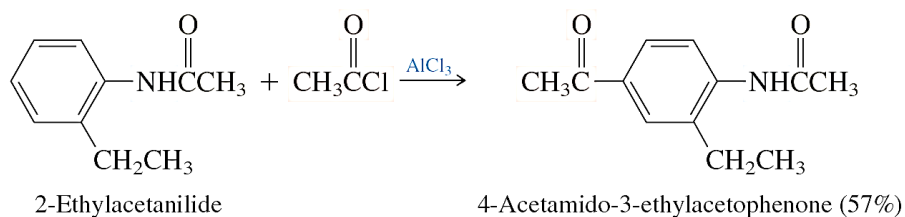
Therefore, it is advisable to first protect the amino group by acylation with either acetyl chloride or acetic anhydride. By protecting the  $\text{-NH}_2$  group by acetylation the nitration reaction can be controlled and the *p*-nitro derivative can be obtained as the major product. After the *N*-acetyl-protecting group has served its purpose, it may be removed by hydrolysis, liberating the amino group.



- (c) **Sulphonation:** Aniline reacts with concentrated sulphuric acid to form anilinium hydrogen sulphate which on heating with sulphuric acid at 453-473°K produces *p*-aminobenzenesulphonic acid, commonly known as sulphanilic acid, as the major product.



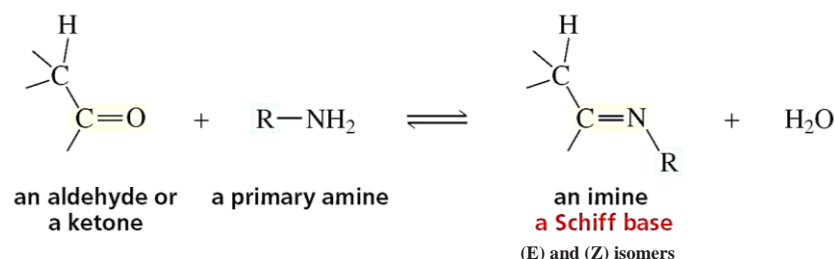
- (d) **Friedel-Crafts reactions:** Friedel-Crafts reactions are normally not successful when attempted on an arylamine, because of the formation of acid-base complex with  $\text{AlCl}_3$  catalyst. Due to this, nitrogen of arylamines acquires a positive charge and hence acts as a strong deactivating group for further reaction. However, Friedel-Craft reaction can be carried out readily once the amino group is protected.



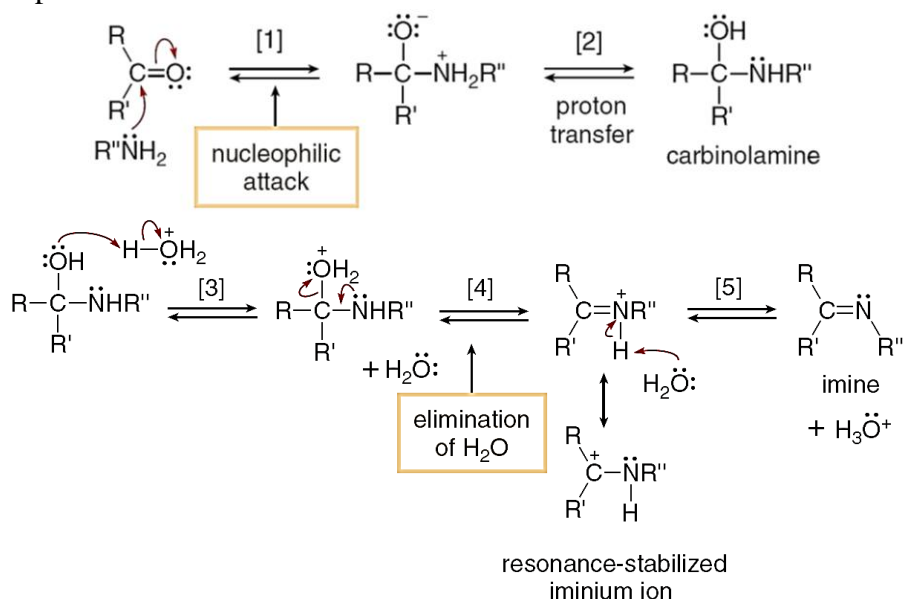
### 2.7.5. Nucleophilic addition – elimination reactions:

(a) **Reaction of Primary amines with aldehydes and ketones:**

Nucleophilic addition of primary amines to ketonic group yields unstable carbinolamine which on elimination of water produces imine,  $R_2C=NR$ , often called **Schiff's bases**. The overall reaction is the replacement of  $C=O$  with  $C=NR$ . The reaction is acid-catalysed and the product is the mixture of (E) and (Z) isomers.

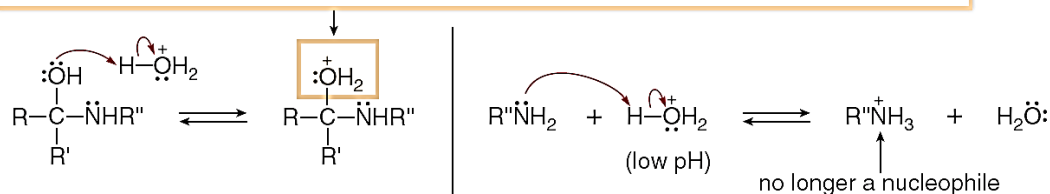
**Mechanism:**

The nucleophilic addition of the primary amine to the carbonyl group followed by transfer of a proton from nitrogen to oxygen yields a neutral tetrahedral *carbinolamine*. Protonation of the carbinolamine oxygen by an acid catalyst generates a better leaving group ( $-OH_2^+$ ) and E1-like loss of water produces a resonance-stabilized iminium ion. Finally, the loss of a proton from nitrogen yields the final product imine.

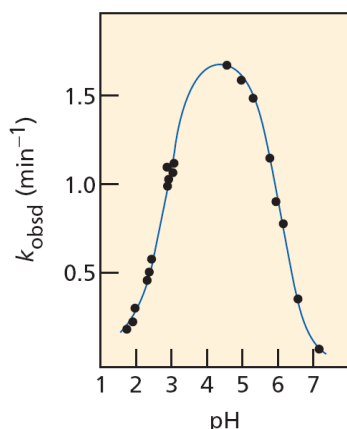


The reaction is fastest between pH 4 and 5 and is slow at very low or very high pH. Mild acid is required to protonate  $-OH$  of carbinolamine to convert it to more strong leaving group ( $-OH_2^+$ ). However, strong acidic conditions decrease the reaction rate because the amine is protonated and thus the lone pair is not available to function as a nucleophile. At very low concentration of hydronium ion, the reaction becomes slow because the concentration of the protonated carbinolamine becomes lower.

Protonation makes a good leaving group...but at low pH, the basic amine is protonated.



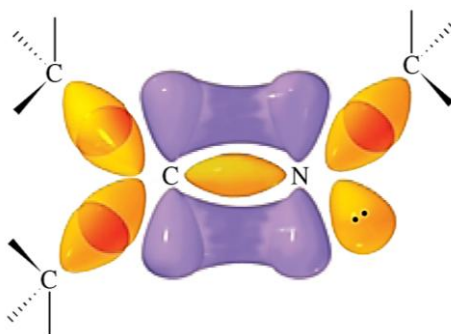
A plot of the observed rate constant for the reaction of acetone with hydroxylamine as a function of the pH of the reaction mixture is shown below.



This type of plot is called a **pH-rate profile**. The pH-rate profile in the figure is a bell-shaped curve with the maximum rate occurring at about pH 4.5. As the acidity increases below pH 4.5, the rate of the reaction decreases because more and more of the amine becomes protonated. As a result, less and less of the amine is present in the nucleophilic non-protonated form. As the acidity decreases above pH 4.5, the rate decreases because less and less of the tetrahedral intermediate is present in the reactive protonated form. Imine formation is reversible: In

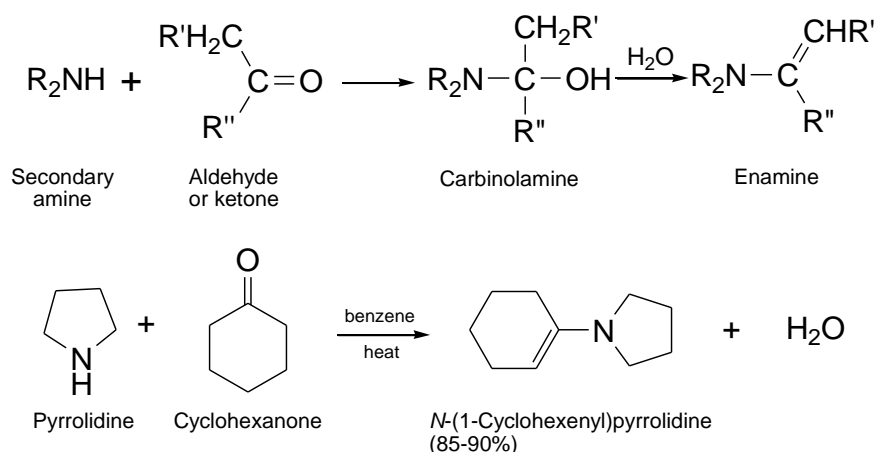
acidic aqueous solutions, imines are hydrolyzed back to the carbonyl compound and amine. In an acidic solution, the amine is protonated and, therefore, is unable to react with the carbonyl compound to reform the imine.

**Structure of imine:** The imine is  $sp^2$  hybridized; the two  $sp^2$  orbitals are bonded to imine carbon and the substituent (R) making  $\sigma$ -bonds and the third orbital possesses a lone pair. The  $p$ -orbitals of carbon and nitrogen overlap sideways to form  $\pi$ -bond.



#### (b) Reaction of Secondary amines with aldehydes and ketones:

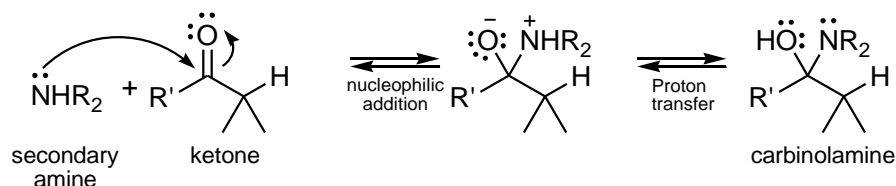
Reaction of a secondary amine,  $\text{R}_2\text{NH}$  with an aldehyde or ketone yields an enamine (ene + amine). Like imine formation, the enamine formation is also acid-catalyzed.



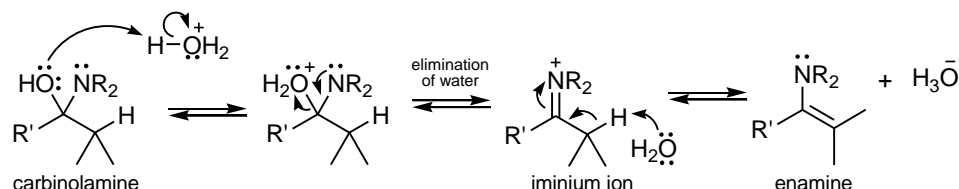
### Mechanism:

The process is identical to imine formation up to the iminium ion stage, but at this point there is no proton on nitrogen that can be lost to form a neutral imine product. Instead, a proton is lost from the *neighboring* carbon (the  $\alpha$ -carbon), yielding an enamine. The reaction involves the nucleophilic attack of secondary amines to carbonyl carbon followed by proton transfer from nitrogen to oxygen results in the formation of neutral carbinolamine. Thereafter, protonation of  $-\text{OH}$  group of carbinolamine generates a better leaving group ( $-\text{OH}_2^+$ ). Elimination of water leads to the formation of resonance-stabilized iminium ion. As nitrogen doesn't have any hydrogen, the removal of hydrogen from the adjacent carbon forms enamine.

**Step 1** – Nucleophilic addition of secondary amine to carbonyl group of aldehyde or ketone followed by proton transfer from nitrogen to oxygen produces carbinolamine.

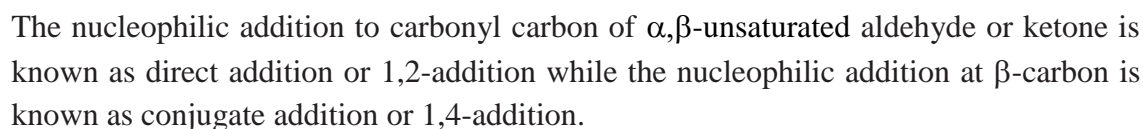


**Step 2** – Protonation of hydroxyl by acid catalyst to make it a better leaving group followed by the elimination of water yields an intermediate iminium ion. Iminium ion loses a proton from  $\alpha$ -carbon atom to make an enamine and regenerate the acid catalyst.



### 2.7.6. Conjugate addition reaction

Conjugated carbonyl compounds have two electrophilic sites: the carbonyl carbon and the  $\beta$ -carbon:

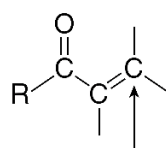

$$\text{Y:} + \text{RCH=CH-CR} \begin{array}{c} \text{:}\ddot{\text{O}} \\ \parallel \end{array} \longrightarrow \text{RCH=CH-CR} \begin{array}{c} \text{:}\ddot{\text{O}}^- \\ | \\ \text{Y} \end{array} \xrightarrow{\text{H}_3\text{O}^+} \text{RCH=CH-CR} \begin{array}{c} \text{OH} \\ | \\ \text{Y} \end{array}$$
$$\begin{array}{c}
 \text{Y:} + \text{RCH}=\text{CH}-\overset{\text{O}}{\parallel}{\text{CR}} \longrightarrow \left[ \underset{\text{Y}}{\text{RCH}}-\ddot{\text{C}}\text{H}-\overset{\text{O}}{\parallel}{\text{CR}} \longleftrightarrow \underset{\text{Y}}{\text{RCH}}-\text{CH}=\overset{\text{O}^-}{\text{CR}} \right] \\
 \text{resonance contributors} \\
 \downarrow \text{H}_3\text{O}^+ \\
 \underset{\text{Y}}{\text{RCH}}-\text{CH}_2-\overset{\text{O}}{\parallel}{\text{CR}} \rightleftharpoons \underset{\text{Y}}{\text{RCH}}-\text{CH}=\overset{\text{OH}}{\text{CR}} \\
 \text{keto tautomer} \qquad \qquad \text{enol tautomer}
 \end{array}$$
$$\begin{array}{c} \text{CH}_3 \quad \text{O} \\ | \quad || \\ \text{CH}_3\text{C}=\text{CHCH} \end{array} + \begin{array}{c} \text{CH}_3\text{NH} \\ | \\ \text{CH}_3 \end{array} \longrightarrow \begin{array}{c} \text{CH}_3 \quad \text{O} \\ | \quad || \\ \text{CH}_3\text{C}-\text{CH}_2\text{CH} \\ | \\ \text{NCH}_3 \\ | \\ \text{CH}_3 \end{array}$$

**1,2-Addition**

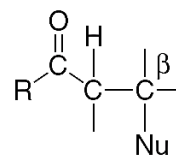
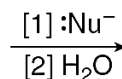
The nucleophile attacks at the carbonyl carbon.

$$\text{R}-\overset{\overset{\text{O}}{\parallel}}{\underset{\uparrow}{\text{C}}}-\text{C}(\text{R})=\text{C}(\text{R}) \xrightarrow[\text{[2] H}_2\text{O}]{\text{[1] :Nu}^-} \text{R}-\overset{\overset{\text{OH}}{\mid}}{\underset{\underset{\text{Nu}}{\mid}}{\text{C}}}-\text{C}(\text{R})=\text{C}(\text{R})$$

allylic alcohol

**1,4-Addition  
(conjugate addition)**

The nucleophile attacks at the  $\beta$  carbon.

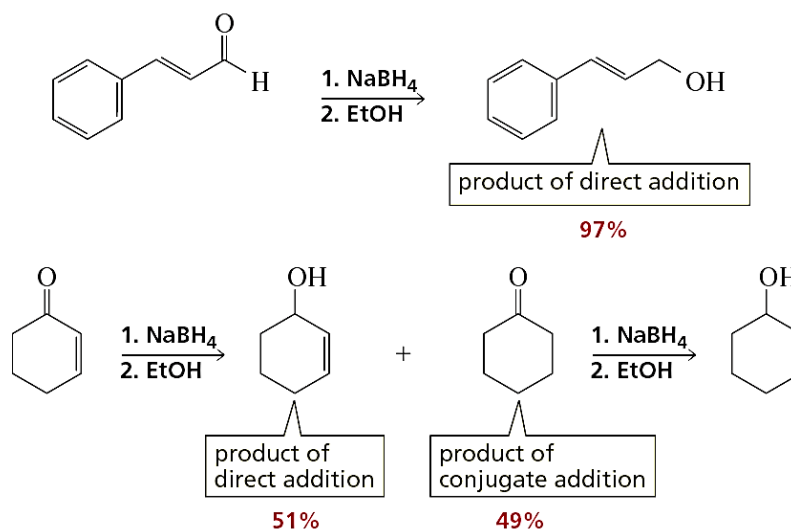


a carbonyl compound with a new substituent on the  $\beta$  carbon

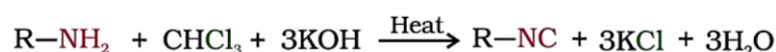
Whether the nucleophilic addition to an  $\alpha,\beta$ -unsaturated aldehyde or ketone is performed through the direct addition or the conjugate addition depends on the nature of the nucleophile, the structure of the carbonyl compound, and the conditions under which the reaction is carried out.

In case when nucleophile is a weak base (e.g. halide ions, cyanide ion, thiols, alcohols, and amines), conjugate addition is preferred because weak bases give unstable addition product and thus makes the reaction reversible; conjugate addition is not reversible, and the conjugate addition product is more stable.

Compounds with reactive carbonyl groups form primarily direct addition products, whereas compounds with less reactive carbonyl groups form primarily conjugate addition products. For example, aldehydes have more reactive carbonyl groups than do ketones, so sodium borohydride forms primarily direct addition products with aldehydes. Compared with aldehydes, ketones form less of the direct addition product and more of the conjugate addition product.

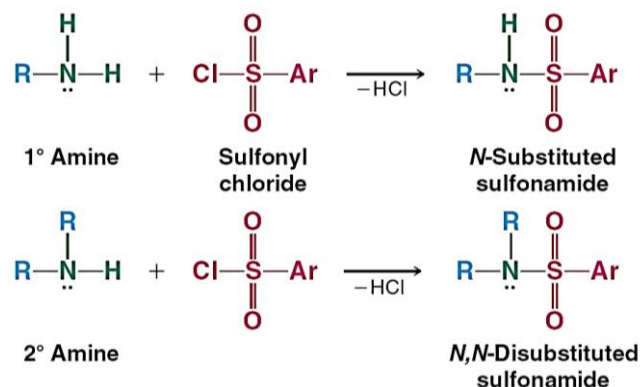
**2.7.7. Carbylamine reaction:**

Carbylamine reaction or isocyanide test is specific for primary amines and is used to test primary amines. Aliphatic and aromatic primary amines on heating with chloroform and ethanolic potassium hydroxide form isocyanides or carbylamines which are foul smelling substances. Secondary and tertiary amines do not show this reaction.

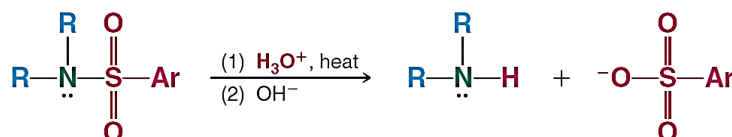


### 2.7.8. Reaction with sulfonyl chloride:

The reaction of primary and secondary amines with sulfonyl chlorides results to sulfonamide.



Sulphonamides are hydrolyzed back to amines on heating with aqueous acids.

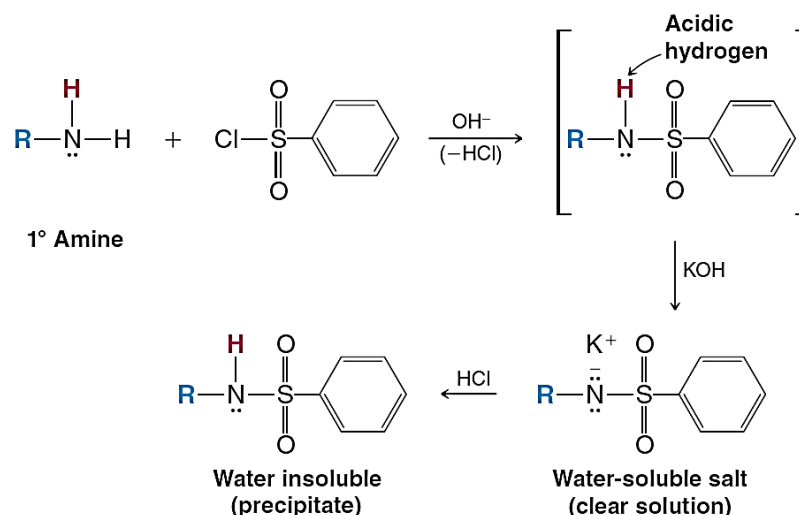


Benzenesulphonyl chloride ( $\text{C}_6\text{H}_5\text{SO}_2\text{Cl}$ ), which is also known as Hinsberg's reagent, is used to distinguish primary, secondary and tertiary amines, and also for separation of a mixture of amines. However, these days benzenesulphonyl chloride is replaced by *p*-toluenesulphonyl chloride.

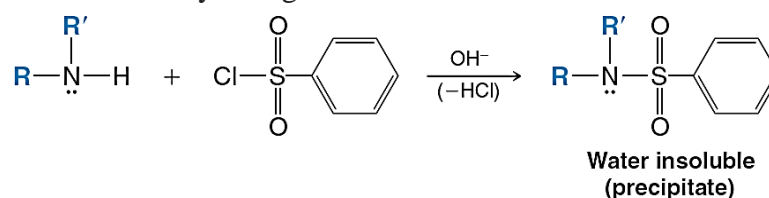
The test is done in two steps:

- (i) A mixture of a small amount of amine and Hinsberg's reagent is shaken with excess KOH.
- (ii) After allowing time for the reaction to take place, the mixture is acidified.
  - a. Primary amines give clear solution in first step. The reaction of benzenesulphonyl chloride with primary amines yields N-ethylbenzenesulphonyl amides. The hydrogen attached to nitrogen in sulphonamide is strongly acidic due to the presence of strong electron withdrawing sulphonyl group. Hence, it undergoes acid-base reaction with excess KOH to form potassium salts which is soluble in water. In second step, acidification of potassium salt results to precipitate of water-insoluble N-ethylbenzenesulphonyl amides.





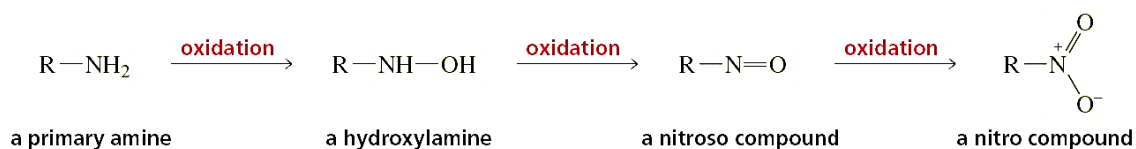
- b. Secondary amines give precipitate of N,N-diethylbenzenesulphonamide in first step. Since N, N-diethylbenzenesulphonamide does not contain any hydrogen atom attached to nitrogen atom, it does not dissolve in aqueous KOH. Second step of the reaction does not make any changes.



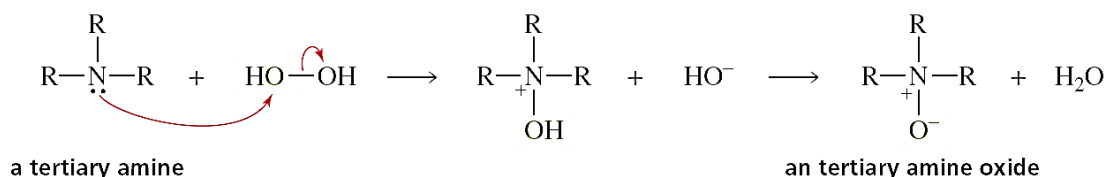
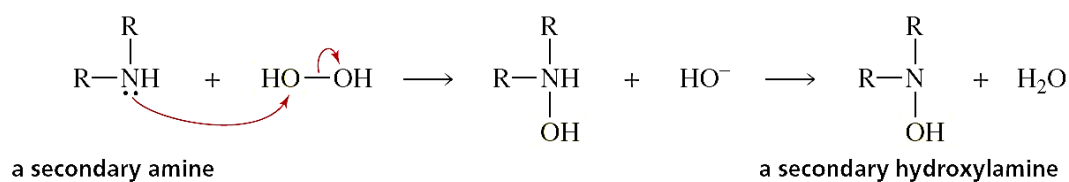
- c. Tertiary amines do not react with benzenesulphonyl chloride. However, in second step, the acid reacts with tertiary amines to form a water-soluble salt and a clear solution is obtained.

### 2.7.9. Oxidation of amines:

All amines including arylamines are easily oxidized by oxidizing agents like hydrogen peroxide and peroxyacids, however, sometimes they are oxidized just by being exposed to air. Primary amines are oxidized to hydroxylamines to nitroso compounds and finally to nitro compounds.



Secondary and tertiary amines are oxidized to hydroxylamines and amine oxides, respectively.

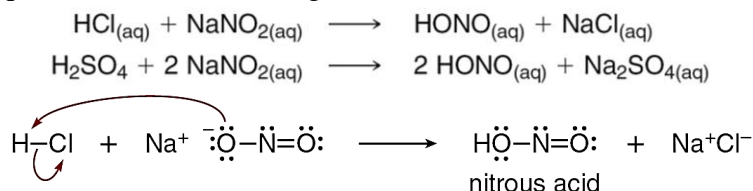


Therefore, to protect the drugs having amino group, they are converted to salts mainly as hydrochlorides and then stored and sold as salts.

In case of arylamines, oxidation is not confined to the amino group but also occurs in the ring. The amino group is electron donating, hence makes the ring electron rich and thus susceptible to oxidation. Therefore, the oxidation of other functional groups on an aromatic ring cannot usually be accomplished when an amino group is present on the ring, because oxidation of the ring takes place first.

## 2.8. Reactions with Nitrous Acid

Nitrous acid is a weak, unstable acid and generally formed *in situ* by the reaction of  $\text{NaNO}_2$  with aqueous solution of strong mineral acids.

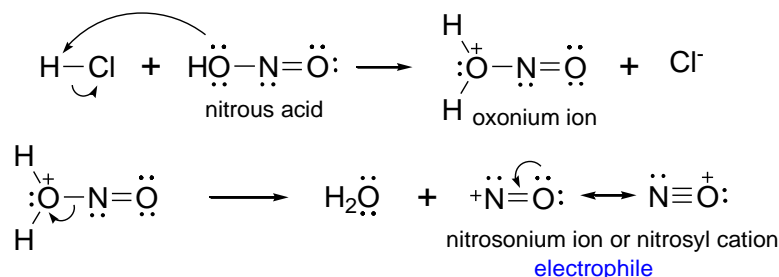


In presence of acid, nitrous acid decomposes to  $^+\text{NO}$ , the nitrosonium ion or nitrosyl cation which acts as electrophile and reacts with the nucleophilic nitrogen atom of amines.

### Mechanism:

*Step 1*- Protonation of the  $-\text{OH}$  group of nitrous acid forms oxonium ion.

*Step 2*- Elimination of water generates nitrosonium ion or nitrosylation, which is hybrid of two resonating structures.



All classes of amines react with nitrous acid although the reaction products are different in each class of amines. The reaction is used to distinguish primary, secondary and tertiary amines.

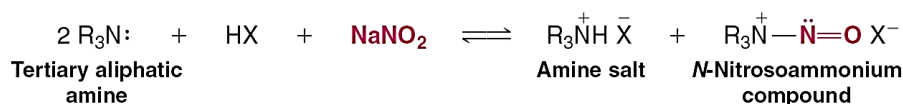
1°amine + HONO (cold acidic solution) → nitrogen gas evolution from a clear solution

2°amine + HONO (cold acidic solution) → an insoluble oil (N-nitrosamine)

3°amine + HONO (cold acidic solution) → a clear solution (ammonium salt formation)

### 2.8.1. Reaction of 3° Amines with nitrous acid

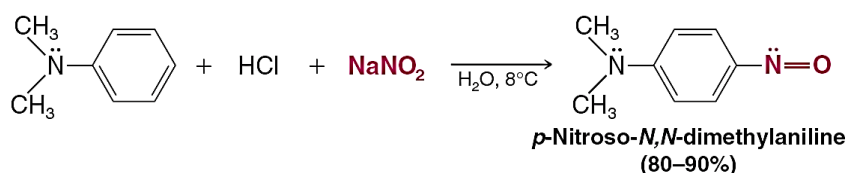
The reaction of **tertiary aliphatic amines** with nitrous acids establishes an equilibrium among the tertiary amine, its salts and an *N*-nitrosoammonium compound:



*N*-nitrosoammonium compounds are stable at low temperature; however, they are decomposed at higher temperature and in aqueous acid. These salts of tertiary amines are water-soluble; therefore, a clear solution is obtained in the reaction.

**Tertiary arylamines** react with nitrous acid to give blue or green aromatic *C*-nitroso compounds, the substitution products because the lone pair at nitrogen is in conjugation with the benzene ring and thus is not available for nitrosation reaction at nitrogen. The substitution takes place almost exclusively at the *para* position, if available, if not, at the *ortho* position.

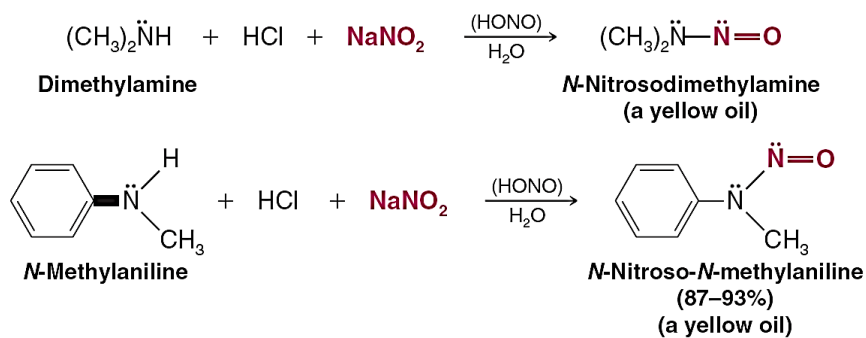
Example:



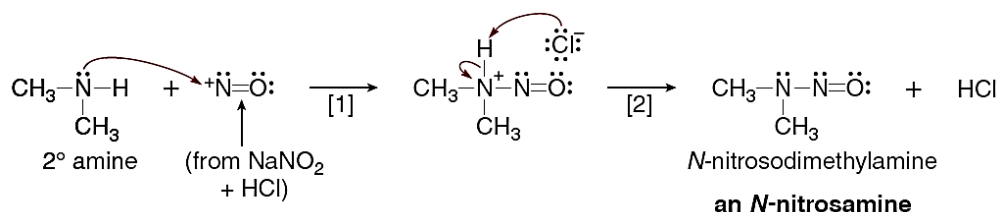
Nitrosonium cation is a relatively weak electrophile and attacks only very strongly activated aromatic rings. Therefore, tertiary arylamines and phenols undergo *C*-nitrosation reaction, whereas most of the other benzene derivatives do not.

### 2.8.2. Reaction of 2° Amines with nitrous acid

Both alkyl and aryl secondary amines react with nitrous acid to produce *N*-nitroso amines (more often called *N*-nitrosamines) as oily yellow liquids. Many of the nitrosamines are carcinogenic and are produced in our body by the enzyme-catalysed reduction of nitrate to nitrite which reacts with secondary amines to yield nitrosamines.

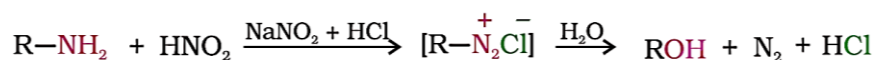


The reaction proceeds by the nucleophilic attack of amino group of amines on nitrosylation followed by loss of proton.



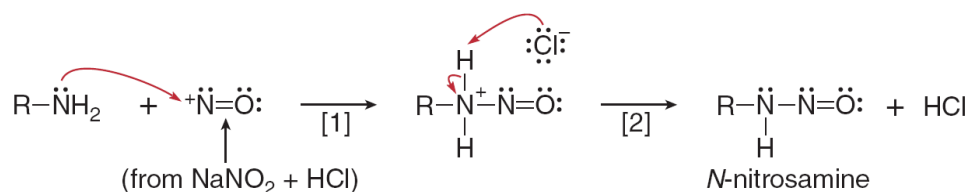
### 2.8.3. Reaction of 1° Amines with nitrous acid

The *N*-nitrosamines of primary amines, being unstable, cannot be isolated and they react further with acid to produce diazonium salts. The reaction is called *diazotization*.

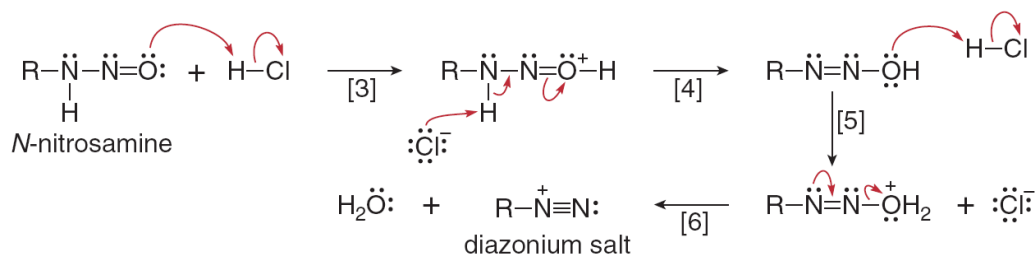


#### Mechanism:

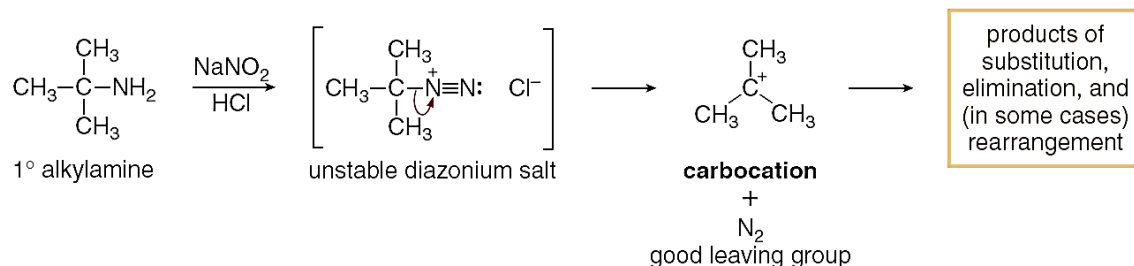
**Part 1: Formation of *N*-nitrosamine.** Nucleophilic attack of amino group on  $^+\text{NO}$  followed by loss of a proton gives *N*-nitrosamine.



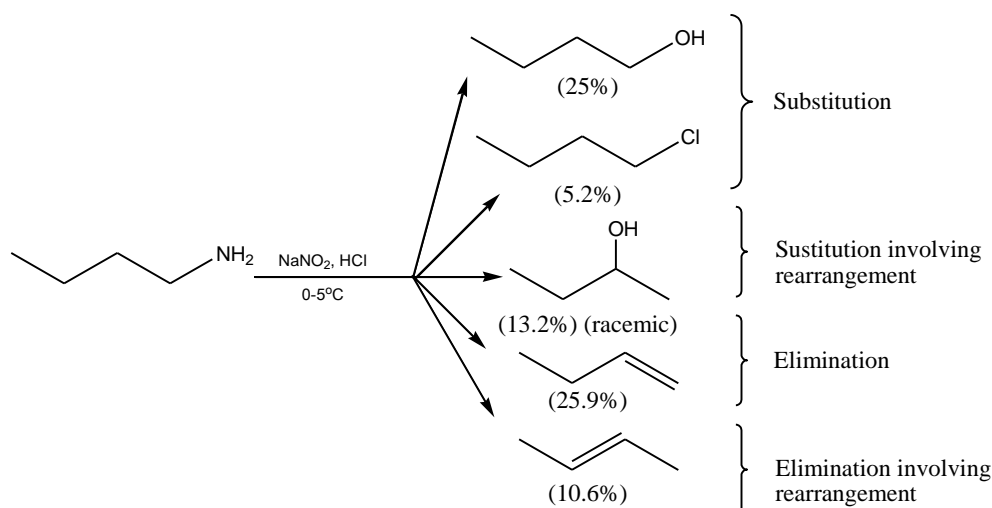
**Part 2: Loss of water (Formation of diazonium salt).** The unstable *N*-nitrosamine tautomerizes to a diazohydroxide in a reaction that is similar to keto-enol tautomerization. Then, in the presence of acid, the diazohydroxide loses water to form the diazonium ion.



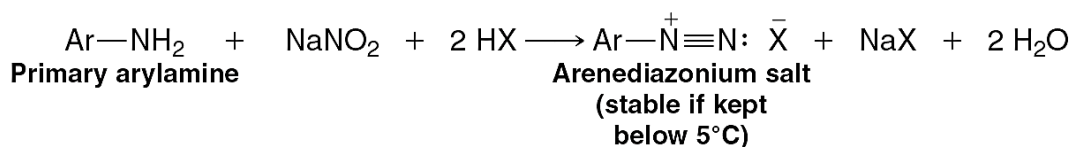
**Aliphatic diazonium salts** are highly unstable and even at low temperature decompose spontaneously to yield carbocations by losing nitrogen, a very good leaving group. The reaction is called deamination reaction. The carbocations further give a mixture of compounds through substitution, elimination and rearrangement reactions. Therefore, the diazotization of primary aliphatic amines has very little synthetic significance, although, from the analytical point of view, the reaction has been studied extensively to prove the behavior of carbocations. Further advantage of the reaction is that the evolution of nitrogen is quantitative.



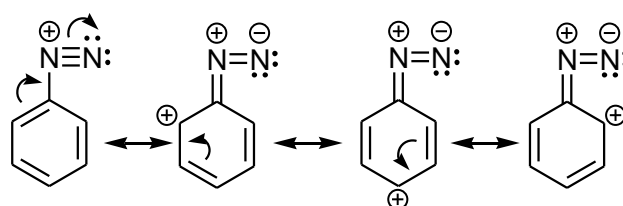
Example:



The most important reaction of amines with nitrous acid, by far, is the reaction of **primary arylamines**. Unlike aliphatic diazonium salts, **primary aryl diazonium salts** are appreciably stable at 0°C and can be kept in solution for short periods without decomposition.



The stability of primary aryl diazonium ion can be explained on the basis of resonance:



**Primary aryl diazonium salts** are very useful synthetic intermediates and significantly used in the synthesis of substituted aromatic compound because the diazonium group, can easily be replaced by a variety of other functional groups.

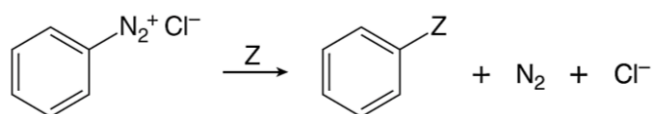
		Products	
$\text{Ar}-\text{N}^+\equiv\text{N}$	$\xrightarrow{\text{H}_3\text{O}^+, \text{ warm}}$	$\text{Ar}-\text{OH}$	phenols
	$\xrightarrow{\text{CuCl}}$	$\text{Ar}-\text{Cl}$	aryl chlorides
	$\xrightarrow{\text{CuBr}}$	$\text{Ar}-\text{Br}$	aryl bromides
	$\xrightarrow{\text{CuCN}}$	$\text{Ar}-\text{C}\equiv\text{N}$	benzonitriles
	$\xrightarrow{\text{HBF}_4}$	$\text{Ar}-\text{F}$	aryl fluorides
	$\xrightarrow{\text{KI}}$	$\text{Ar}-\text{I}$	aryl iodides
	$\xrightarrow{\text{H}_3\text{PO}_2}$	$\text{Ar}-\text{H}$	(deamination)
	$\xrightarrow{\text{H}-\text{Ar}'}$	$\text{Ar}-\text{N}=\text{N}-\text{Ar}'$	azo dyes

Sandmeyer reaction  
 Schiemann reaction

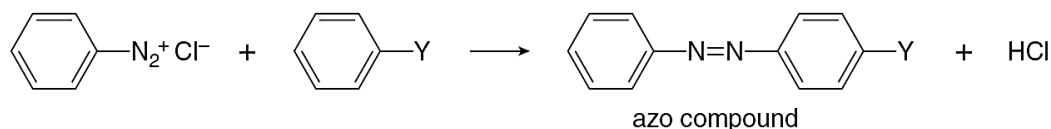
## 2.9. Reactions of Aryl Diazonium Intermediates

Most of the aryl diazonium salts are stable in aqueous solutions around 0-10°C. They decompose above these temperatures, and may explode if they are isolated and allowed to dry. However, most of the replacement reactions are carried out simply by adding another reagent (CuCl, CuBr, KI, etc.) to the reaction mixture without isolating the diazonium salts. The reactions of diazonium salts can be broadly divided into two categories:

(A) Reactions involving displacement of nitrogen by another group



(B) Reactions involving coupling of a diazonium salt with another benzene derivative to form an azo compound, a compound having a nitrogen-nitrogen double bond.

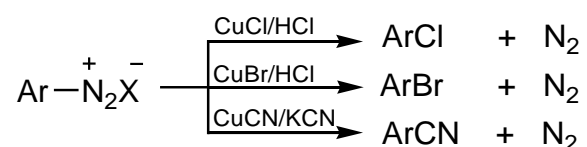


$\text{Y} = \text{NH}_2, \text{NHR}, \text{NR}_2, \text{OH}$  (a strong electron-donor group)

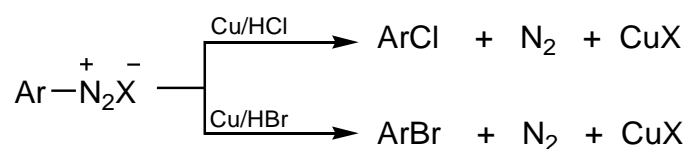
### 2.9.1. Reactions involving displacement of nitrogen:

Diazonium group being a very good leaving group is substituted by other groups such as  $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{I}^-$ ,  $\text{CN}^-$  and  $\text{OH}^-$  which displace nitrogen from the aromatic ring. The nitrogen formed escapes from the reaction mixture as a gas.

- (A) **Replacement by halide or cyanide ion:** The  $\text{Cl}^-$ ,  $\text{Br}^-$  and  $\text{CN}^-$  nucleophiles can easily be introduced in the benzene ring in the presence of  $\text{Cu(I)}$  ion. This reaction is called **Sandmeyer reaction**. The Sandmeyer reaction fails when attempted with  $\text{CuI}$  or  $\text{CuF}$ .

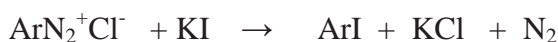


Alternatively, chlorine or bromine can also be introduced in the benzene ring by treating the diazonium salt solution with corresponding halogen acid in the presence of copper powder. This is referred as **Gatterman reaction**.

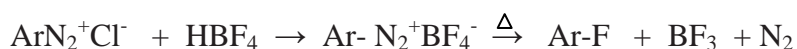


The yield in Sandmeyer reaction is found to be better than in Gatterman reaction.

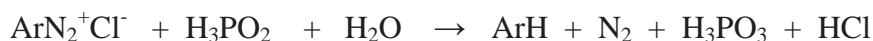
- (B) **Replacement by iodide ion:** Iodine is not easily introduced into the benzene ring directly; however, iodobenzene can be prepared by treating the diazonium salt solution with potassium iodide.



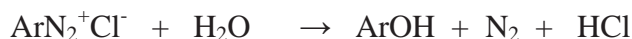
- (C) **Replacement by fluoride ion:** When arenediazonium chloride is treated with fluoroboric acid, arenediazonium fluoroborate is precipitated which is isolated, dried and heated until decomposes to yield aryl fluoride. The reaction is called **Schiemann reaction**.



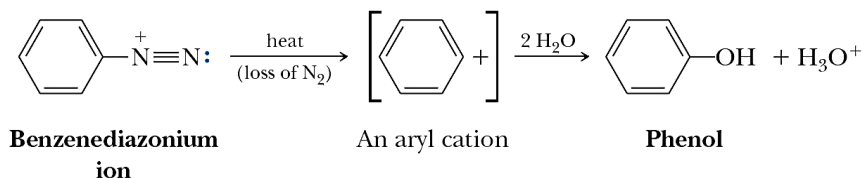
- (D) **Replacement by H:** Certain mild reducing agents like hypophosphorous acid (phosphinic acid) or ethanol reduce diazonium salts to arenes and themselves get oxidised to phosphorous acid and ethanal, respectively. The reactions of this type are called **reductive deamination**.



- (E) **Replacement by hydroxyl group:** If the temperature of the diazonium salt solution is allowed to raise upto  $283^\circ\text{K}$ , the salt gets hydrolysed to phenol. Thus the aromatic amines can be converted to phenols by first forming the arenediazonium salt in aqueous sulphuric acid and then heating the solution.

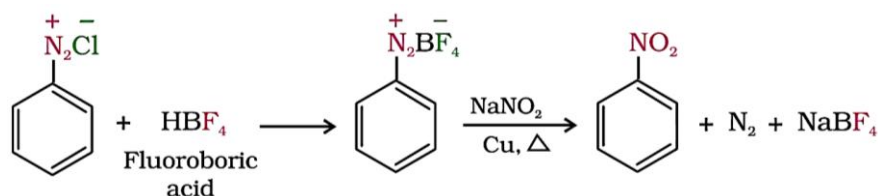


An aryl cation is formed as an intermediate in the decomposition of an arenediazonium ion in water, which then undergoes reaction with water to form the phenol.



Sulphuric acid is normally used instead of hydrochloric acid in the diazotization step so as to minimize the competition with water for capture of the cationic intermediate. Hydrogen sulphate anion ( $\text{HSO}_4^-$ ) is less nucleophilic than chloride.

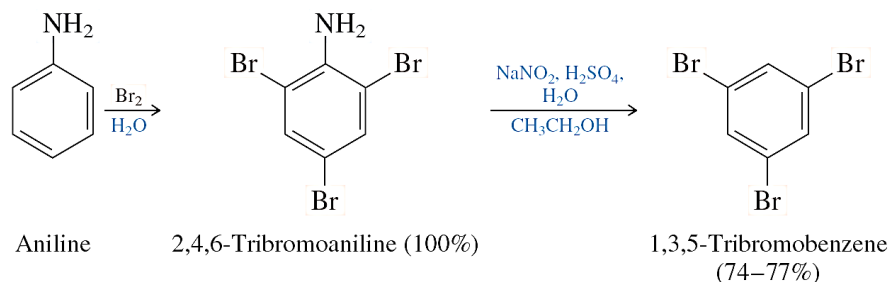
- (F) *Replacement by  $-\text{NO}_2$  group*: When diazoniumfluoroborate is heated with aqueous sodium nitrite solution in the presence of copper, the diazonium group is replaced by  $-\text{NO}_2$  group.



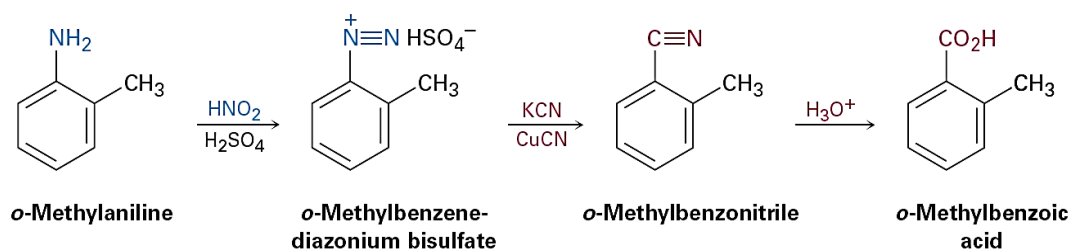
From the above reactions, it is clear that the diazonium salts are very good intermediates for the introduction of  $-\text{F}$ ,  $-\text{Cl}$ ,  $-\text{Br}$ ,  $-\text{I}$ ,  $-\text{CN}$ ,  $-\text{OH}$ ,  $-\text{NO}_2$  groups into the aromatic ring. Aryl fluorides and iodides cannot be prepared by direct halogenations. The cyano group cannot be introduced by nucleophilic substitution of chlorine in chlorobenzene but cyanobenzene can be easily obtained from diazonium salt. Thus, the replacement of diazo group by other groups is helpful in preparing those substituted aromatic compounds which cannot be prepared by direct substitution in benzene or substituted benzene.

Secondly, compounds that have substitution patterns not directly available by electrophilic aromatic substitution can be prepared e.g. synthesis of 1,3,5-tribromobenzene. This compound cannot be obtained by direct bromination of benzene, because bromine is *ortho*, *para*-director. Instead, advantage is taken of the powerful activating and *ortho*, *para*-directing effects of the amino group in aniline. Bromination of aniline yields 2,4,6-tribromoaniline in quantitative yield. Diazotization of the resulting 2,4,6-tribromoaniline and reduction of the diazonium salt gives the desired 1,3,5-tribromobenzene.



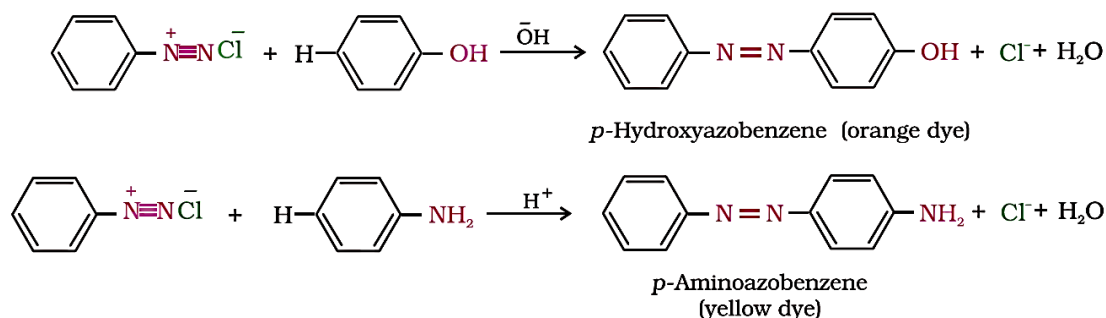


Another example is the synthesis of *o*-methylbenzoic acid. This product can't be prepared from *o*-xylene by the usual side-chain oxidation route because both methyl groups would be oxidized. Instead, Sandmeyer reaction of *o*-methylbenzenediazonium bisulfate with CuCN yields *o*-methylbenzonitrile, which can be hydrolyzed to give *o*-methylbenzoic acid.



## 2.9.2. Coupling Reactions of Aryl Diazonium Salts

A reaction of aryl diazonium salts that does not involve loss of nitrogen takes place when they react with phenols and arylamines. Benzene diazonium chloride reacts with phenol in which the phenol molecule at its *para* position is coupled with the diazonium salt to form *p*-hydroxyazobenzene. Similarly the reaction of diazonium salt with aniline yields *p*-aminoazobenzene. Diazonium ions are relatively weak electrophiles but have sufficient reactivity to attack strongly activated aryl aromatic rings. The reaction is called **diazo coupling** as both the aromatic rings joined through the *azo* ( $-\text{N}=\text{N}-$ ) function. Because of extended conjugate system, these compounds are often coloured and are used as dyes. This is an example of electrophilic substitution reaction.

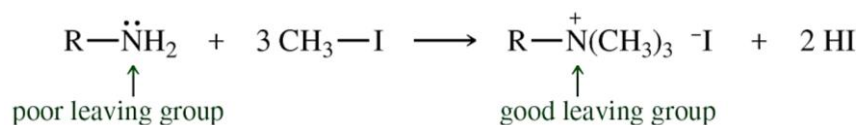


## 2.10. Elimination Reactions of Amines

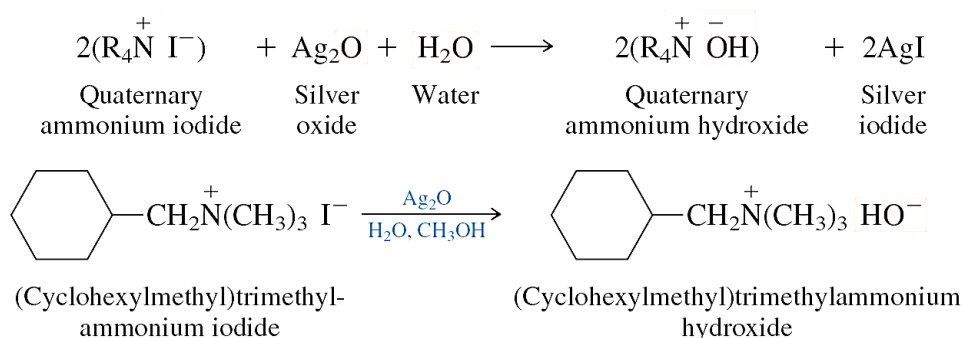
### 2.10.1. Hoffmann Elimination

Like alcohols and alkyl halides, amines can also be converted to alkenes by elimination reaction to give alkenes. However, an amine cannot undergo elimination directly

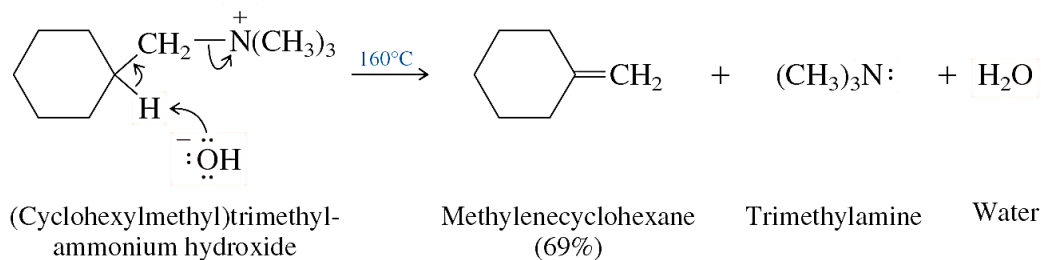
because the leaving group, an amide ion ( $\text{NH}_2^-$  or  $\text{NHR}^-$ ), is a very strong base and a poor leaving group. An amino group can be converted to a good leaving group by exhaustive methylation, which converts it to a quaternary ammonium salt that can leave as a neutral amine. Exhaustive methylation is usually accomplished using methyl iodide.



Elimination of the quaternary ammonium salt generally takes place by the E2 mechanism, which requires a strong base. To provide the base, the quaternary ammonium iodide is converted to the hydroxide salt by treatment with silver oxide.



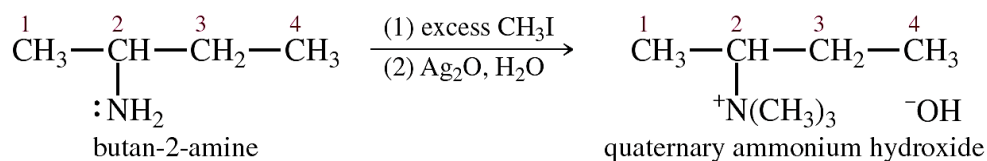
The heating of the quaternary ammonium hydroxide results in E2 elimination to form an alkene. This thermal decomposition of a quaternary ammonium hydroxide to an alkene is known as the **Hofmann elimination**. Thus, the mechanism of the Hofmann elimination is a one-step, concerted E2 reaction using an amine as the leaving group.



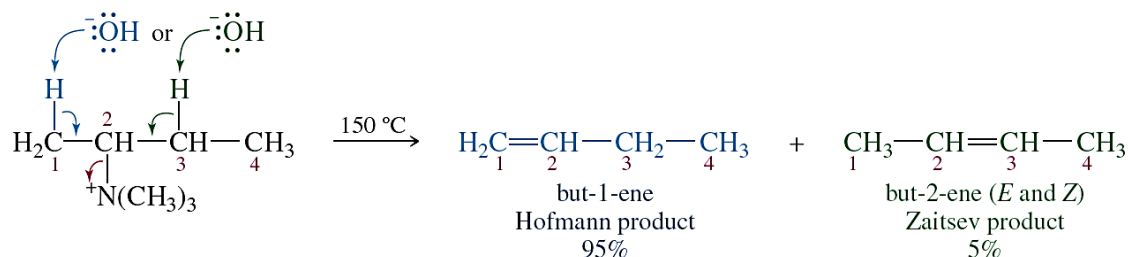
### Example:

Butan-2-amine on exhaustive methylation is converted to the hydroxide salt which upon heating forms a mixture of but-1-ene and but-2-ene.

*Exhaustive methylation and conversion to the hydroxide salt:*

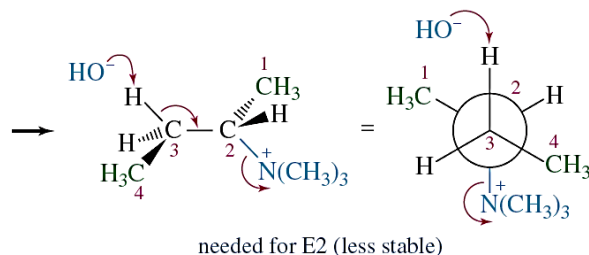


*Heating and Hofmann elimination*

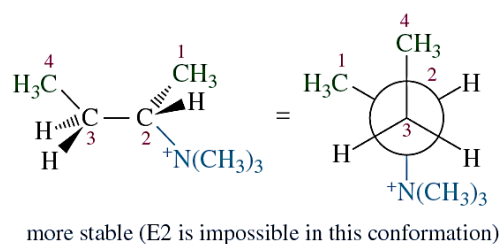


The eliminations in case of alkyl halides usually follow Zaitsev's rule; that is, the most substituted product predominates because the most-substituted alkene is usually the most stable. In the Hofmann elimination, however, the product is commonly the *least*-substituted alkene. This is because of the bulky leaving group. E2 mechanism requires an anti-coplanar arrangement of the proton and the leaving group. The extremely large trialkylamine leaving group in the Hofmann elimination often interferes with this coplanar arrangement.

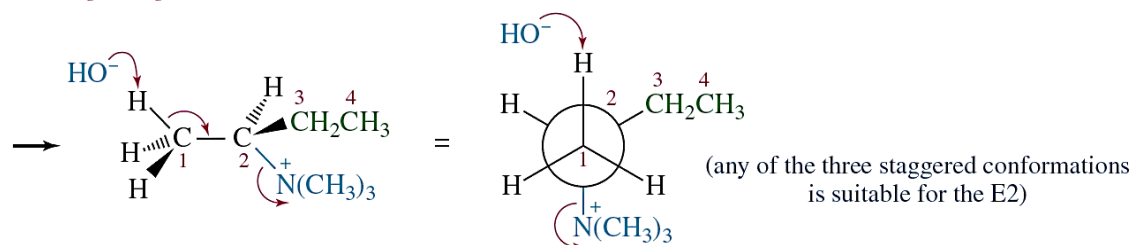
Looking along the C2—C3 bond



The most stable C2—C3 conformation



Looking along the C1—C2 bond



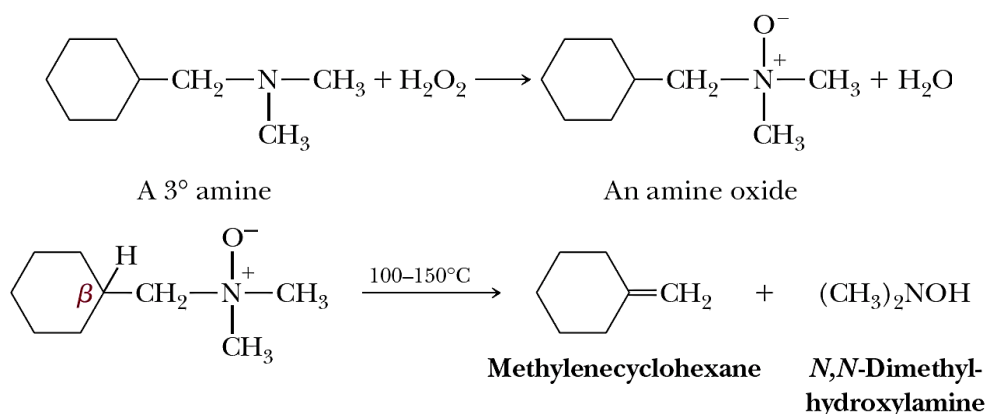
### Hofmann vs Zaitsev

Both Hofmann and Zaitsev eliminations are always preferentially anti. If only one  $\beta$ -hydrogen is anti to the leaving group, then that one will be removed. If more than one  $\beta$ -hydrogen is anti, then there will be competition between Hofmann and Zaitsev elimination.

- Eliminations involving a negatively charged leaving group, for example  $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{I}^-$ , and  $\text{OTs}^-$ , almost always follow Zaitsev's rule, unless a bulky base is used.
- Eliminations involving a neutral leaving group, for example  $\text{N}(\text{CH}_3)_3$  and  $\text{S}(\text{CH}_3)_2$ , almost always follow Hofmann's rule.
- The bulkier the base, the greater the percentage of Hofmann product; compare for example,  $(\text{CH}_3)_3\text{CO}^-\text{K}^+$ , which gives mostly Hofmann elimination with  $\text{CH}_3\text{O}^-\text{Na}^+$ , which gives mostly Zaitsev's elimination.

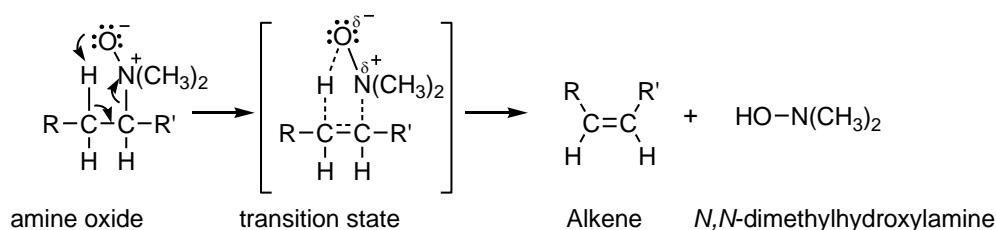
### 2.10.2. Cope Elimination

Treatment of a tertiary amine with hydrogen peroxide results in oxidation of the amine to an amine oxide. Amine oxides undergo a reaction similar to the Hofmann elimination reaction. A tertiary amine rather than a quaternary ammonium ion undergoes elimination. An amine oxide with at least one  $\beta$ -hydrogen on heating undergoes thermal decomposition to form an alkene and an *N,N*-dialkylhydroxylamine. The reaction is known as **Cope elimination**. The Cope elimination reaction occurs under milder conditions than does a Hofmann elimination reaction.



### Mechanism:

Cope elimination is a one-step, concerted internal elimination using amine oxide as both the base and the leaving group. *Syn* stereochemistry is required for the Cope elimination.

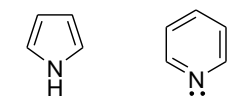
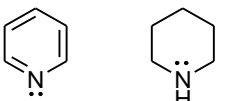


If two or more *syn*  $\beta$ -hydrogens can be removed in Cope elimination, there is little preference for one over another except when the double bond is conjugated with an aromatic ring. Therefore, as a method of preparation of alkenes, Cope eliminations are best used where only one alkene is possible.

## 2.11. Summary

- Amines can be considered as derivatives of ammonia obtained by replacement of hydrogen atoms with alkyl or aryl groups. They are classified as primary ( $\text{R-NH}_2$ ), secondary ( $\text{R}_2\text{NH}$  or  $\text{R-NHR}'$ ), or tertiary ( $\text{R}_3\text{N}$ ,  $\text{RNR}'\text{R}''$  or  $\text{R}_2\text{NR}'$ ), depending on whether one, two, or three hydrogens of ammonia have been replaced.
- Secondary and tertiary amines are known as simple amines if the alkyl or aryl groups are the same and mixed amines if the groups are different.
- All amines having  $\leq 5$  C's are water soluble because they can hydrogen bond with  $\text{H}_2\text{O}$ .

- Higher amines having  $\geq 5$  C's are soluble in organic solvents and insoluble in water because the non polar alkyl portion is too large to dissolve in the polar water solvent.
- Boiling point of primary and secondary amines are higher than that of similar compounds (like ethers) which are incapable of hydrogen bonding, however lower than alcohols that have stronger intermolecular hydrogen bonds.
- Tertiary amines being incapable of hydrogen bonding have lower boiling point than the primary and secondary amines of comparable molecular weight.
- Like ammonia, all the three types of amines have one unshared electron pair on nitrogen atom due to which they behave as **Lewis bases**.
- Factors that determine Amines' Basicity:

	Factor	Example
1.	Inductive effect: electron releasing and withdrawing groups, respectively, increase and decrease basic character of amines	<ul style="list-style-type: none"> <li>• <math>\text{RNH}_2</math>, <math>\text{R}_2\text{NH}</math>, and <math>\text{R}_3\text{N}</math> are more basic than <math>\text{NH}_3</math>.</li> <li>• <i>p</i>-Toluidine is more basic than aniline while <i>p</i>-nitroaniline is less basic than aniline.</li> </ul>
2.	Resonance effect: Delocalisation of lone pair on N decreases basicity	<ul style="list-style-type: none"> <li>• Arylamines (<math>\text{C}_6\text{H}_5\text{NH}_2</math>) are less basic than alkylamines (<math>\text{RNH}_2</math>)</li> <li>• Amides (<math>\text{RCONH}_2</math>) are much less basic than amines (<math>\text{RNH}_2</math>).</li> </ul>
3.	Aromaticity: If lone pair on N becomes part of the aromatic $\pi$ -system, basicity decreases.	<ul style="list-style-type: none"> <li>• Pyrrole is less basic than pyridine.</li> </ul> <div style="text-align: center;">  <p style="display: flex; justify-content: space-around; margin: 0;"> <span>less basic</span> <span>more basic</span> </p> </div>
4.	Hybridisation effect: increasing the percent s-character in the orbital with the lone pair decreases basicity.	<ul style="list-style-type: none"> <li>• Pyridine is less basic than piperidine.</li> </ul> <div style="text-align: center;">  <p style="display: flex; justify-content: space-around; margin: 0;"> <span>less basic</span> <span>more basic</span> </p> </div>

- Amines undergo **amine inversion** through a transition state in which the  $sp^3$  nitrogen becomes  $sp^2$  nitrogen. Secondary or tertiary amines with three different groups bonded to nitrogen are chiral, but they cannot usually be resolved because at room temperature they undergo a process called **pyramidal inversion** that rapidly interconverts the two enantiomers.
- Quaternary ammonium ions have four alkyl and/or aryl groups bonded to nitrogen, resulting in a positively charged species. As they don't have any lone pair on nitrogen, they are not basic.
- Reactions of amines are governed by availability of the unshared pair of electrons on nitrogen. Influence of the number of hydrogen atoms at nitrogen atom on the type of reactions and nature of products is responsible for identification and distinction

between primary, secondary and tertiary amines. *p*-Toluenesulphonyl chloride is used for the identification of primary, secondary and tertiary amines.

- Presence of amino group in aromatic ring enhances reactivity of the aromatic amines. Reactivity of aromatic amines can be controlled by **acylation** process, i.e., by treating with acetyl chloride or acetic anhydride.
- **Aryl diazonium salts**, usually obtained from arylamines, undergo replacement of the diazonium group with a variety of nucleophiles to provide advantageous methods for producing aryl halides, cyanides, phenols and arenes by reductive removal of the diazo group.
- Coupling reaction of aryl diazonium salts with phenols or arylamines give rise to the formation of **azo dyes**.

## 2.12. Exercises

2.12.1. Write IUPAC names of the following compounds and classify them into primary, secondary and tertiary amines.

- (i)  $(\text{CH}_3)_2\text{CHNH}_2$       (ii)  $\text{CH}_3(\text{CH}_2)_2\text{NH}_2$       (iii)  $\text{CH}_3\text{NHCH}(\text{CH}_3)_2$   
(iv)  $(\text{CH}_3)_3\text{CNH}_2$       (v)  $\text{C}_6\text{H}_5\text{NHCH}_3$       (vi)  $(\text{CH}_3\text{CH}_2)_2\text{NCH}_3$   
(vii) *m*- $\text{BrC}_6\text{H}_4\text{NH}_2$

2.12.2. Arrange the following :

- (i) In decreasing order of the  $\text{p}K_b$  values:  
 $\text{C}_2\text{H}_5\text{NH}_2$ ,  $\text{C}_6\text{H}_5\text{NHCH}_3$ ,  $(\text{C}_2\text{H}_5)_2\text{NH}$  and  $\text{C}_6\text{H}_5\text{NH}_2$
- (ii) In increasing order of basic strength:  
 $\text{C}_6\text{H}_5\text{NH}_2$ ,  $\text{C}_6\text{H}_5\text{N}(\text{CH}_3)_2$ ,  $(\text{C}_2\text{H}_5)_2\text{NH}$  and  $\text{CH}_3\text{NH}_2$
- (iii) In increasing order of basic strength:  
Aniline, *p*-nitroaniline and *p*-toluidine
- (iv) In increasing order of boiling point:  
 $\text{C}_2\text{H}_5\text{OH}$ ,  $(\text{CH}_3)_2\text{NH}$ ,  $\text{C}_2\text{H}_5\text{NH}_2$
- (v) In increasing order of solubility in water:  
 $\text{C}_6\text{H}_5\text{NH}_2$ ,  $(\text{C}_2\text{H}_5)_2\text{NH}$ ,  $\text{C}_2\text{H}_5\text{NH}_2$

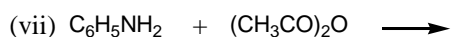
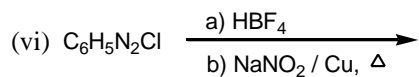
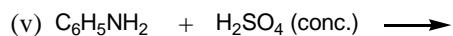
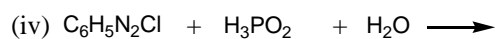
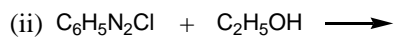
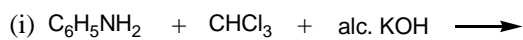
2.12.3. Write a chemical test to distinguish primary, secondary and tertiary amines and also write the chemical equations involved.

2.12.4. How to do the following conversions:

- (i) Benzoic acid to aniline
- (ii) Benzene to *m*-chlorophenol
- (iii) Nitrobenzene to benzoic acid
- (iv) Aniline to *p*-bromoaniline
- (v) Benzamide to toluene

(vi) Nitrobenzene to benzene

2.12.5. Complete the following reactions:



2.12.6. Explain the following

- (i) Aniline is less basic than methylamine.
- (ii) Ethylamine is soluble in water while aniline is not.
- (iii) Pyridine is less basic than piperidine while more basic than pyrrole.
- (iv) Arylamines do not undergo Friedel-Craft reaction.
- (v) Diazonium salts of arylamines are more stable than those of aliphatic amines.