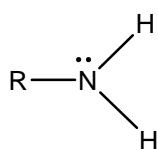


AMINES

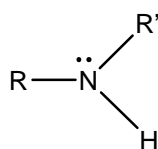
Amines are basic nitrogen containing organic compounds thought to be derived from ammonia by the replacement of one or more hydrogen atoms bonded to nitrogen by alkyl or aryl groups.

Classification and Nomenclature of Amines

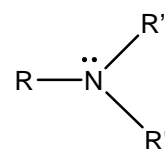
Amines are classified as primary, secondary or tertiary depending upon the degree of substitution at the nitrogen atom. An amine with one alkyl/aryl group attached to nitrogen is a primary amine. If there are two or three alkyl/aryl groups bonded to nitrogen, then the said amines are classified as secondary and tertiary respectively.



Primary

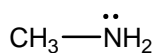


Secondary

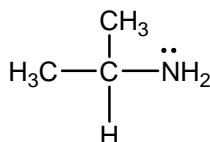


Tertiary

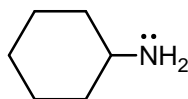
Primary Amines



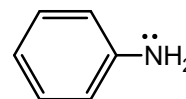
Methylamine



Isopropylamine

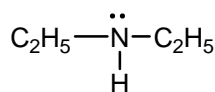


Cyclohexylamine

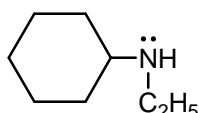


Phenylamine
(aniline)

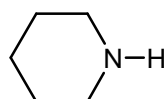
Secondary Amines



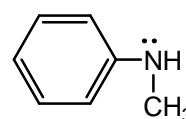
Diethylamine



N-cyclohexylethylamine

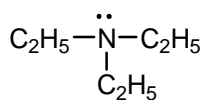


Piperidine

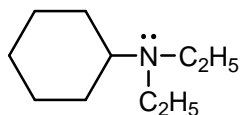


N-methylaniline

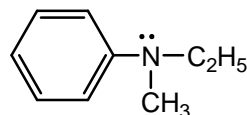
Tertiary Amines



Triethylamine

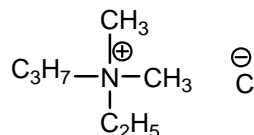
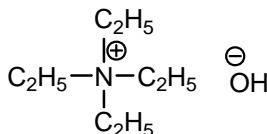
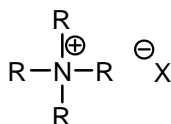


N,N-cyclohexyldiethylamine



N-ethyl-N-methylaniline

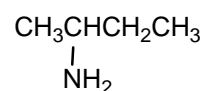
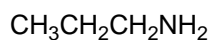
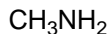
Besides, the above three amines in which the nitrogen is bonded to one, two or three alkyl/aryl substituents. There is another class of compound in which nitrogen may also be bonded to four alkyl/aryl groups. Such category of compounds are called **quaternary ammonium salts**. The nitrogen atom, which bears a positive charge in these compounds is named as an ammonium ion



Quaternary ammonium salt Tetraethylammonium hydroxide Ethyldimethylpropylammonium chloride

Amines are named by following two methods:

- In the common nomenclature system primary aliphatic amines are named as **alkylamines**. In this system the name of the amine is obtained by adding the suffix amine to the alkyl group bonded to the nitrogen atom eg ethylamine.
 - In the systematic nomenclature (IUPAC) they are named as **alkanamines**, with the alkyl group being named as alkane and the word -e ending being replaced by amine
- Primary amines



Common name
(Systematic name)

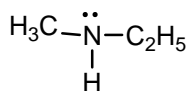
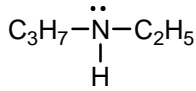
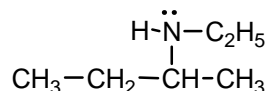
Methyl amine
(methanamine)

Propyl amine
(Propanamine)

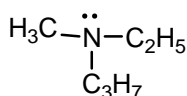
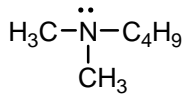
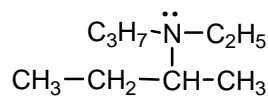
1-methylpropylamine
(2-butanamine)

Secondary and tertiary amines are however named as N-Substituted derivatives of primary amines. The largest alkyl group is taken to be the parent molecule whereas the smaller alkyl group is taken to be a substituent. The prefix N-is added as a locant to identify that the substituent is bonded to the nitrogen atom and not to the carbon atom. If there are two, three or four identical groups then the prefix di, tri or tetra may be used.

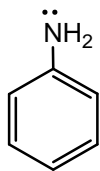
Secondary amines

N-methylethylamine
(N-methylethanamine)N-ethylpropylamine
(N-ethylpropan-1-amine)N-ethylbutyl-2-amine
(N-ethylbutan-2-amine)

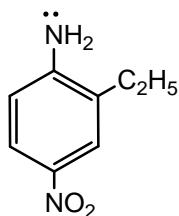
Tertiary amines

Ethylmethylpropylamine
(N-ethyl-N-methylpropan-1-amine)Butyldimethylamine
(N,N-dimethylbutan-1-amine)Ethylpropylbutyl-2-amine
(N-ethyl-N-propylbutan-2-amine)

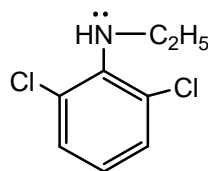
IUPAC nomenclature retains the common name aniline for the amino substituted derivative of benzene. Substituted derivatives of aniline are numbered beginning from carbon that bears the amino group.



Aniline

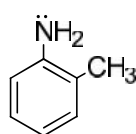


2-ethyl-4-nitroaniline

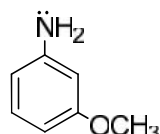


2,6-dichloro-N-ethylaniline

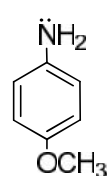
Many aromatic amines like toluidines and anisides are still known by their historical names.



o-Toluidine
(2-Methylaniline)

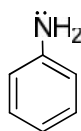


m-Anisidine
(3-Methoxyaniline)

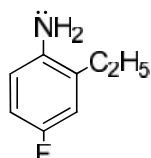


p-Anisidine
(4-Methoxyaniline)

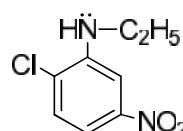
Aromatic amines have also been named as arenamines. Thus aniline the parent compound of the aromatic family is listed as benzenamine.



Aniline
(benzenamine)

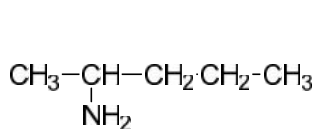


2-ethyl-4-fluoroaniline
(2-ethyl-4-fluorobenzenamine)

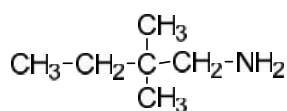


2-chloro-5-nitro-N-ethylaniline
(2-chloro-5-nitro-N-ethylbenzenamine)

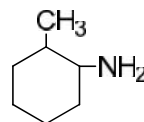
Substitutive nomenclature: The most widely used system of substitutive amine nomenclature is the one adopted by Chemical Abstracts- a comprehensive index of chemical literature. In this system the compounds are named as follows:



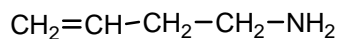
pentan-2-amine



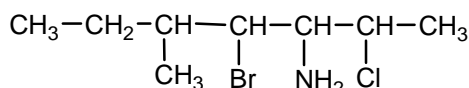
2,2-dimethylbutan-1-amine



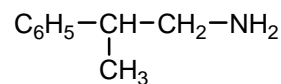
2-methylcyclohexanamine



but-3-en-1-amine



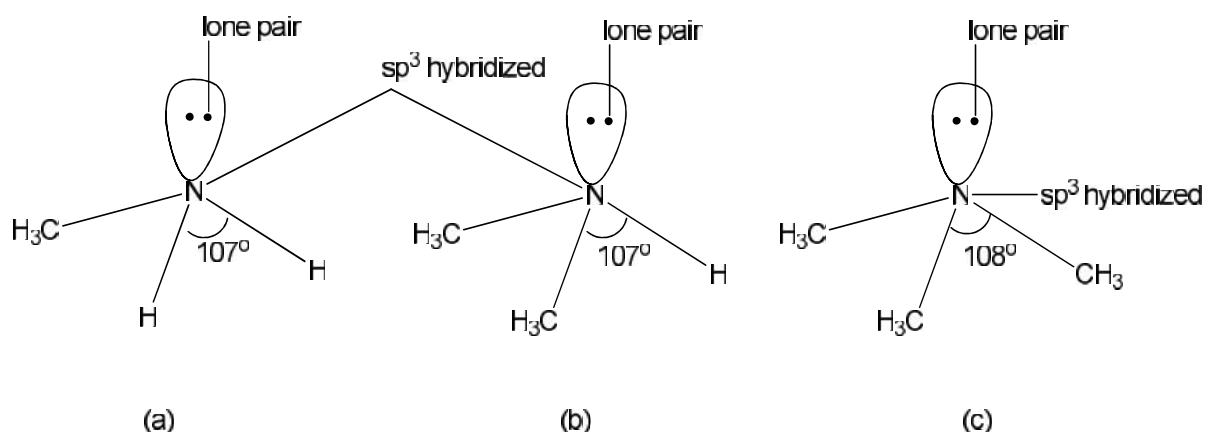
4-bromo-2-chloro-5-methylheptan-3-amine



2-phenylpropan-1-amine

Structure and stereochemistry of Amines

Alkyl amines have structure quite similar to ammonia. The geometry of the sp^3 hybridized nitrogen atom bonded to three atoms or groups is trigonal pyramidal (or approximately tetrahedral) with nitrogen at the apex of the pyramid. Depending upon the composition of the amine, the three sp^3 hybridized orbitals form sigma bond with the hydrogen atom or the carbon atom of the alkyl group that are directed downwards to form the triangular base of the pyramid. Since the lone pair of electron on nitrogen is considered the fourth group, which makes the arrangement of "groups" around nitrogen to be approximately tetrahedral.

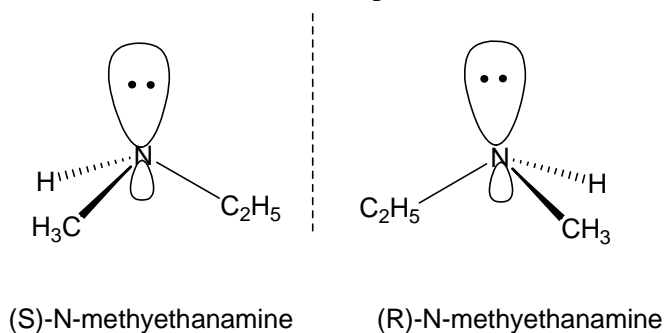


hybrid orbital description of (a) p-amine (b) s-amine (c) t-amine

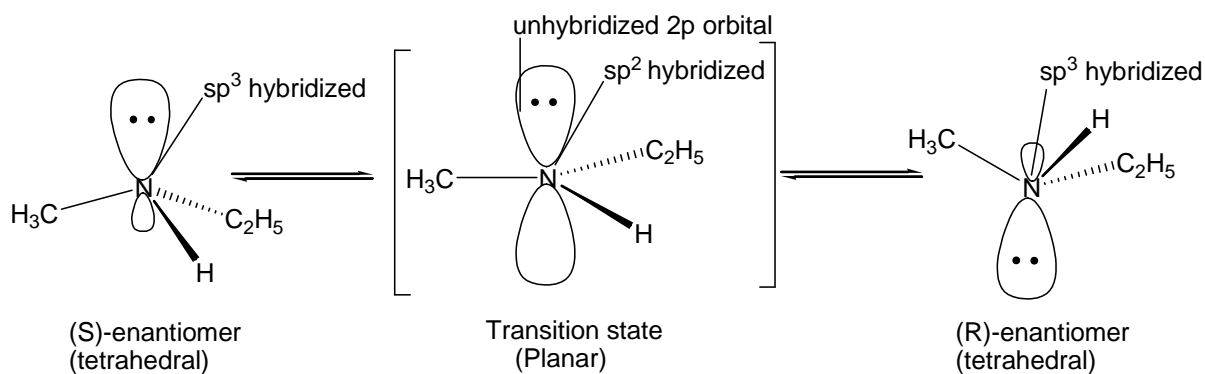
Due to the presence of lone pair of electron there is repulsion between lone pair and bond pair, as a result the bond angle between the two adjacent hydrogen atoms or alkyl groups in primary and secondary amines decreases from tetrahedral angle of 109.5° to 107° . But in case of tertiary amine the C-N-C bond angle is 108° . The C-N bond distance in all types of aliphatic amines is 1.47\AA .

Arylamines also have a pyramidal arrangement of bonds around nitrogen, but the pyramid as in the case of aniline is somewhat shallower.

As a consequence of the tetrahedral geometry of the tertiary amines, in which all the alkyl groups bonded to the nitrogen are different, as in the case of ethylmethyl amine. Then this molecule is chiral and can exist in a pair of enantiomers



It has been observed that though these tertiary amines are chiral but they optically inactive because the enantiomers cannot be resolved as they undergo rapid interconversion by a process called **pyramidal inversion**. During the process there is rapid oscillation of nitrogen atom from one side of the plane to another. In the transition state of this inversion process there is rehybridization of the nitrogen to planar sp^2 geometry with the lone pair of electron lying in the unhybridized 2p orbital. Nitrogen completes the inversion process and becomes sp^3 hybridized again.



Basicity of Amines

All amines possess a lone pair of electron on the nitrogen atom. The basic character of these compounds depends upon how readily this lone pair of electron is available for coordination with a proton. Greater the tendency to donate the lone pair of electron, stronger the base. The basicity of amine is usually expressed by the following basicity constant K_b also known as the base dissociation constant.



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

Larger the K_b value, stronger the base. For convenience the strength of base is usually indicated by its pK_b value.

$$pK_b = -\log K_b$$

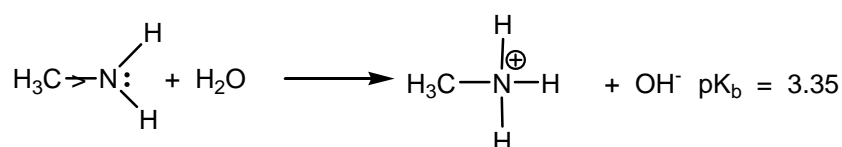
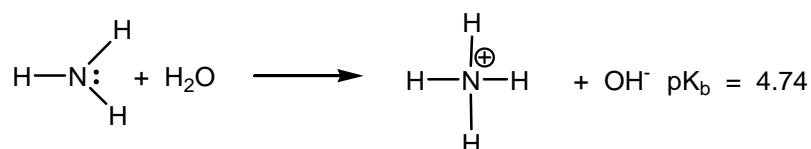
Smaller the pK_b value, stronger will be the base.

In reaction (1) any structural feature that stabilizes the ammonium ion (relative to the free base), the amine would be a stronger base, whereas any structural feature that stabilizes the free amine (relative to ammonium ion), the amine would be a weaker base. Thus basicity of amines is largely dependent on the following factors

- (i) + I and -I effect of alkyl groups
- (ii) Hybridization
- (iii) Steric effects

(iv) Resonance

Basicity of aliphatic amines: (+I effect of alkyl groups): In case of methylamine, the methyl group because of its +I effect helps to stabilize the positive charge on nitrogen (makes the lone pair of electron easily available for protonation). The positive charged ammonium ion is dispersed better because it has a methyl group instead of hydrogen. This stabilization lowers the potential energy of methyl ammonium cation, thus making it a stronger base than ammonia.



Thus more the alkyl groups are attached to positively charged nitrogen, the more stable the alkyl ammonium cation becomes and more basic the amine would be. As a result in gaseous phase tertiary amines are stronger bases in comparison to secondary amines which in turn would be stronger bases than primary amine.

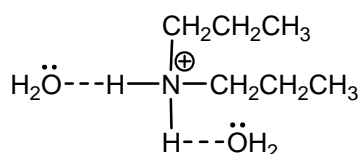
Basicity in gaseous phase: $(\text{CH}_3)_3\text{N} > (\text{CH}_3)_2\text{NH} > \text{CH}_3\text{NH}_2 > \text{NH}_3$

Effect of hydrogen bonding and steric effect:

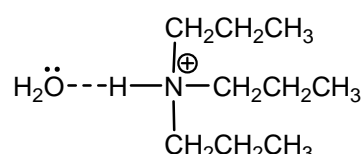
Thus it can be said that the basicity of amine in gaseous phase depends largely on the +I effect of the alkyl group. But this basicity order of amines does not hold true in aqueous solution. In aqueous phase tertiary amines are weaker bases even in comparison to primary amines. This altered order of amine basicity in solution is due to solvation effect.

Basicity in aqueous phase: $(\text{CH}_3\text{CH}_2)_2\text{NH} > \text{CH}_3\text{CH}_2\text{NH}_2 > (\text{CH}_3\text{CH}_2)_3\text{N} > \text{NH}_3$

Alkyl substitution increases the ability of ammonium cation to disperse its positive charge but it decreases its ability to form hydrogen bond with water molecules. In case of secondary amines the dialkylammonium cation formed still has two hydrogens to undergo hydrogen bonding, whereas in case of tertiary amines, the trialkylammonium cation has only one hydrogen available for hydrogen bonding. As a result trialkylammonium cation is less stabilized in comparison to dialkylammonium cation. Besides this, the steric hindrance of the three-alkyl groups on t-amine also prevents the lone pair of electron to be attacked by H^+ ions. Hence secondary amines are stronger bases than tertiary amines.

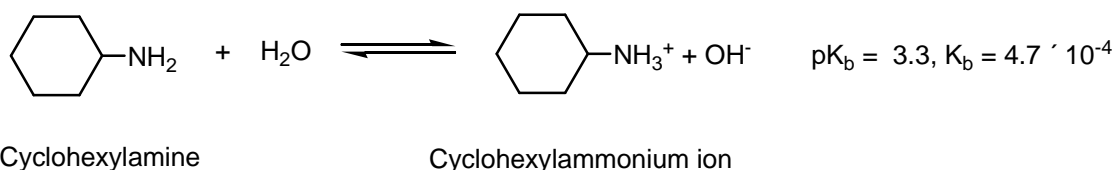
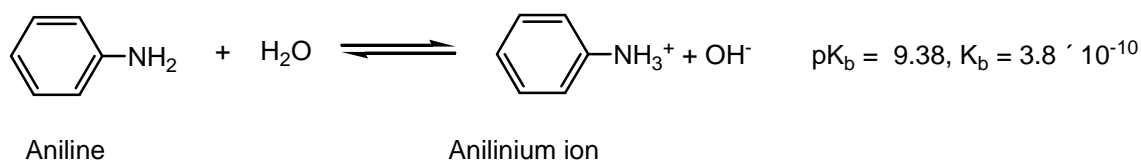


Dipropylammonium cation
(two hydrogen available for bonding)

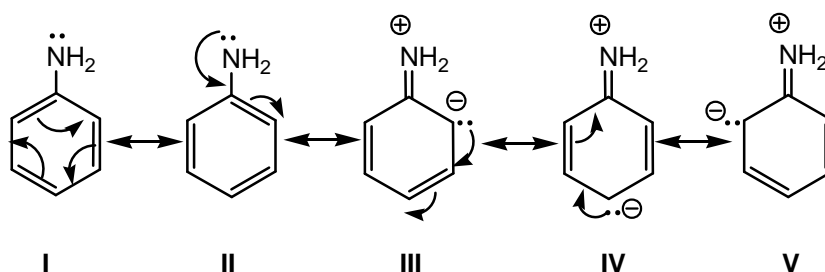


Tripropylammonium cation
(only one hydrogen available for bonding)

Basicity of Aromatic amines: (Effect of resonance) Aromatic amines are weaker bases in comparison to aliphatic amines. The pK_b value for aniline is 9.38 whereas for non-aromatic cyclic amine, cyclohexylamine, this value is 3.3.

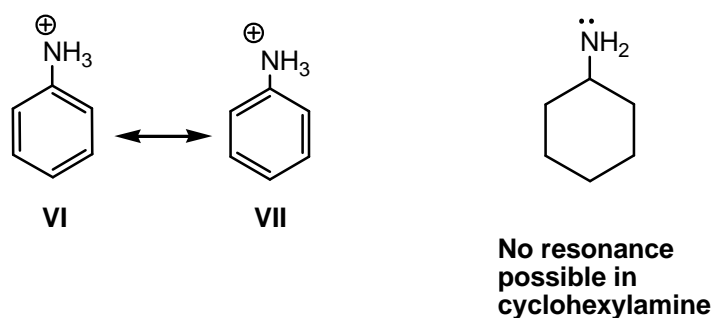


The decreased basicity of aniline and other aromatic amine is due to delocalization of lone pair of electron on nitrogen over ortho and para positions of the aromatic ring. As a result of this delocalization, the lone pair is less available for protonation. Due to this resonance stabilization, the resonance energy for aniline (39 kcal/mol) is even more than benzene (36 kcal/mole). No such resonance stabilization is possible in cyclohexylamine, as a result the lone pair of electron is readily available for protonation, hence more basic in comparison to aromatic amines.



Aniline on protonation forms the anilinium ion. Since the lone pair of electron has been utilized in the formation of N-H bond, only two resonance structures (VI and VII) are possible for anilinium ion. The greater stabilization of aniline (five resonance structures) in comparison to anilinium ion (two resonance structures) means that lone pair of electron on nitrogen of aniline is not readily available for protonation to form anilinium ion. Thus

resonance stabilization not only lowers the basicity of aniline in comparison to anilinium ion, but it lowers its basicity in comparison to cyclohexylamine, in which no resonance is possible.

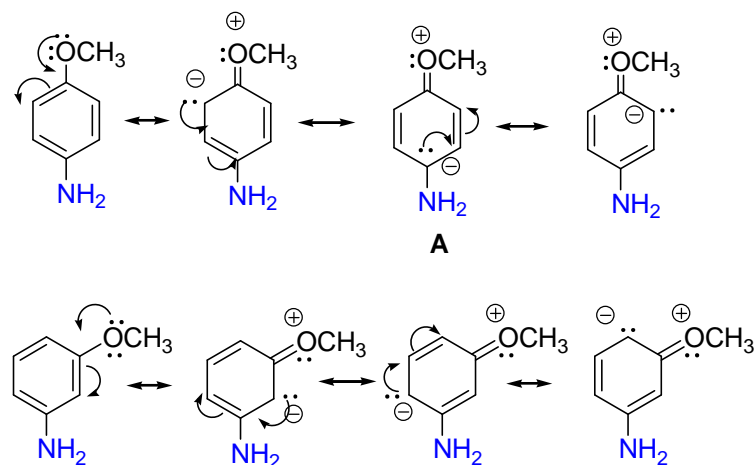


Effect of hybridization: Another reason for the reduced basicity of the aromatic amines in comparison to cyclohexylamine or other aliphatic amines is due to the fact that carbon atom to which the amino group is bonded in aromatic amines is sp^2 hybridized whereas in case of cyclohexylamines or other aliphatic amines the carbon bearing the amino groups are sp^3 hybridized. Because of greater s character the sp^2 hybridized carbon to which the aromatic amino group is bonded is more electronegative in comparison to sp^3 hybridized carbon of cyclohexylamine or other aliphatic amines. In fact the benzene ring of the aromatic amines acts as an electron withdrawing group (pulls the lone pair of electron on nitrogen towards itself) in comparison to cyclohexane ring of cyclohexylamine and alkyl group of aliphatic amines.

(+I and -I effect of the groups): Depending upon the type of substituent, substituted aromatic amines can be more basic or lesser basic in comparison to aniline. In general electron-donating substituents such as $-\text{CH}_3$, $-\text{NH}_2$, $-\text{OCH}_3$, OH which increase the reactivity of the aromatic ring towards electrophilic substitution reaction also increase the basicity of the aromatic amines.

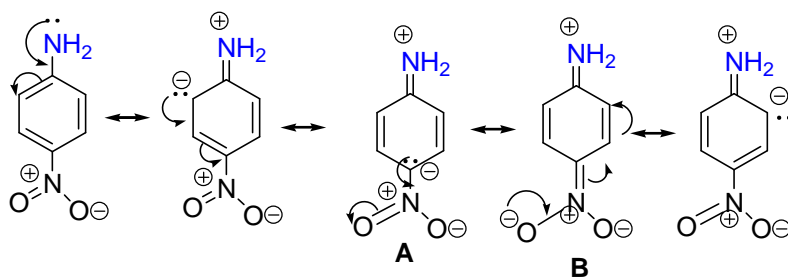
Electron donating substituents because of their +I effect tend to increase the electron density on nitrogen, as a result the lone pair of electron is easily available for protonation. Besides the electron donating substituents tend to dispel the positive charge of the substituted anilinium ion, thereby increasing their stability relative to the parent amine. As a result of this combined effect the basicity of aromatic amines containing electron donating substituents are more basic in comparison to the parent amine.

The increase in basicity of aniline and other arylamine derivatives is due to the presence of electron releasing substituent carrying lone pair of electron at o and p position, which make their lone pair easily available to the benzene ring due to mesomeric effect. Besides it has been observed that the base enhancing effect is more pronounced at para position than at ortho position. It is for this reason that p-methoxy aniline is more basic in comparison to m-methoxy aniline. The reason behind this enhanced basicity of p-methoxy aniline being that one of its resonance structure (A) carries a negative on the carbon to which the amino group is bonded. This resonance structure tends to increase the electron density on nitrogen atom. But no such resonance structure is possible for m-methoxy aniline.

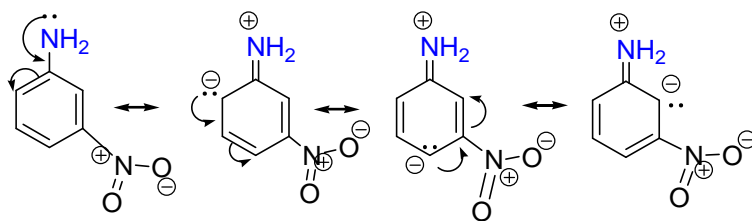


Electron-withdrawing substituents like $-\text{Cl}$, $-\text{NO}_2$, $-\text{CN}$, CO decrease the basicity of the aromatic amine. The decrease in basicity is due to the electron withdrawing inductive effect of these groups, as a result of which the lone pair of electron on nitrogen is not easily available for protonation, hence decreased basicity. Besides the electron withdrawing substituents tend to increase the positive charge on the substituted anilium ion, thereby decreasing its stability relative to aniline.

It has been observed that decrease in basicity is more pronounced when electron withdrawing substituents is present at p- position than when it is present at m-position. It is for this reason that p-nitroaniline (4-nitroaniline) is a weaker base in comparison to m-nitroaniline (3-nitroaniline)



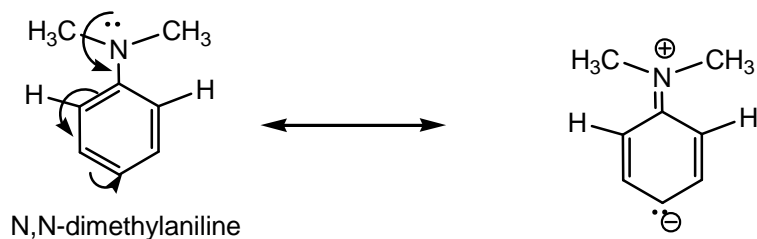
In case p-nitroaniline the decrease in basicity is caused by the combination of inductive as well as resonance effect. As a result of which delocalization of lone pair of electron on the nitrogen of the amino group not only involves the carbon of the aromatic ring but also the oxygen of the nitro group (structure B). Hence the lone pair of electron is less readily available for protonation-decreased basicity. In case of m-nitroaniline, no such resonance structure (as structure B) is possible, only electron withdrawing inductive effect operates, which makes the lone pair of electron comparatively more readily available for protonation-hence increased basicity.

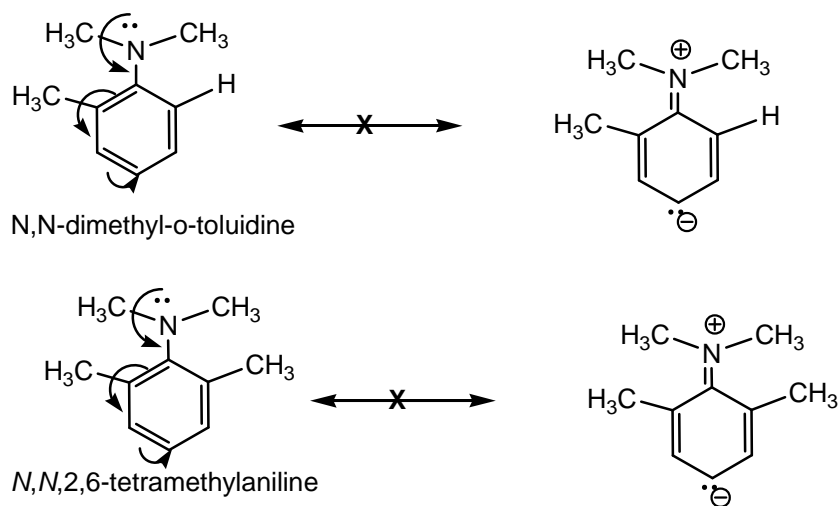


Depending upon the type of substituent, substituted aromatic amines can be more basic or lesser basic in comparison to aniline. In general when hydrogen atom of the amino group in primary aromatic amines is substituted by electron releasing groups like methyl, ethyl, propyl etc, the basicity of the resultant aromatic amine increases. It is for this reason N-methylaniline and N,N-dimethylaniline are more basic in comparison to aniline (Table). If however the hydrogen atom is substituted by an electron withdrawing group, basicity decreases. Thus diphenylamine is a weaker base in comparison to aniline.

Steric effects: Steric effects indirectly effects the basicity of aromatic amines by interfering with their resonance stabilization. For resonance to take place it is essential that all atoms must be in one plane. Any factor that prevent atoms from attaining coplanarity, reduces resonance, thereby reducing the chances for the availability of the lone pair of electron on nitrogen and in turn resulting in the increase in base strength. It is for this reason steric inhibition of resonance results in increase in the basic strength of N,N-dimethyl-o-toluidine or N,N,2,6-tetramethylaniline relative to N,N-dimethylaniline.

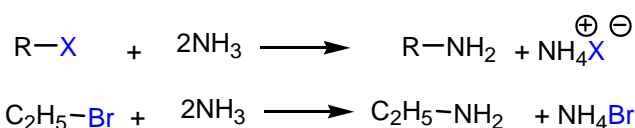
The increased basicity of N,N-dimethyl-o-toluidine or N,N,2,6-tetramethylaniline is due to the fact that the bulky o-methyl/s push the methyl group on nitrogen out of the plane of the aromatic ring, because of which the p-orbital on nitrogen containing the lone pair of electron is no longer parallel to the p-orbitals of the aromatic ring. As a result coplanarity is prevented thereby preventing delocalization of lone pair of electron on nitrogen over ortho and para position of the aromatic ring. The lone pair of nitrogen in turn is easily available for protonation. However no such steric factor operates in N,N-dimethylaniline, the lone pair of electron on nitrogen can easily be delocalized on to the aromatic ring and is thus unavailable for protonation. It is for this reason N,N-dimethyl-o-toluidine or N,N,2,6-tetramethylaniline is more basic in comparison to N,N-dimethylaniline



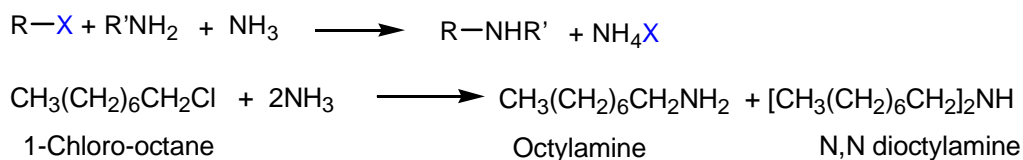


Preparation of Amines

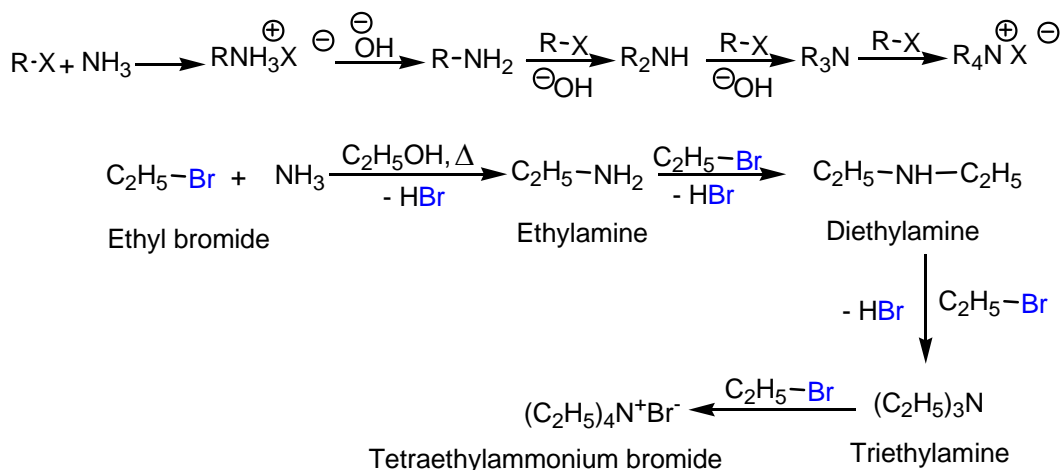
(i) **Alkylation of ammonia:** Alkyl amines, primary, secondary or tertiary are prepared by heating alkyl halide with ethanolic solution of ammonia in a sealed tube at 100°C . If ammonia is used in excess, primary amine is the major product.



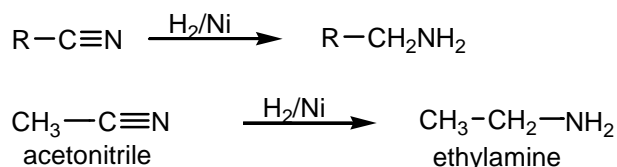
Primary amine produced during the reaction is itself a good nucleophile and it competes with ammonia. It is for this reason that a mixture of primary and secondary amines is produced.



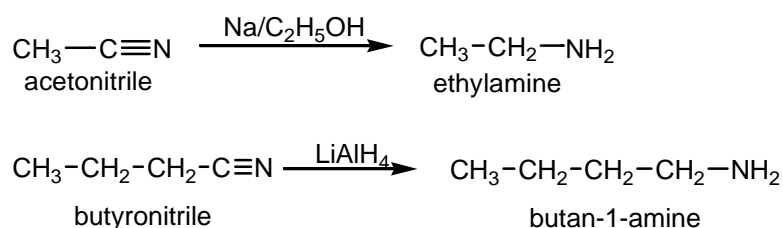
If alkyl halide is used in excess, primary amine formed further reacts with alkyl halide to form secondary, tertiary and finally quaternary ammonium salt. This reaction is known as **Hoffmann ammonolysis** of alkyl halides



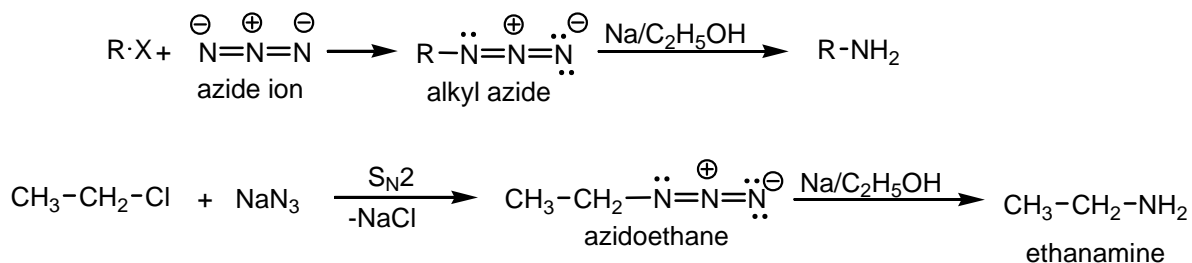
(ii) Reduction of nitriles: Another important method for the preparation of primary alkyl amines involves reaction of nitrile with hydrogen. In the presence of catalyst, usually Raney nickel. The reaction involves addition of two molecules of hydrogen across the triple bond, leading to the generation of primary amine.



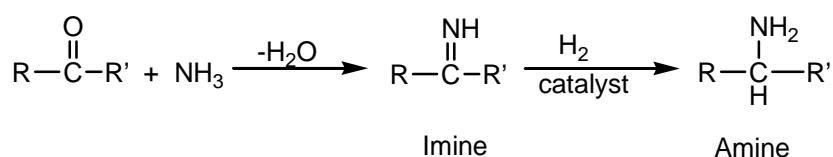
The reduction of nitriles can also be carried out with sodium/alcohol (Mandus reaction) or lithium aluminium hydride

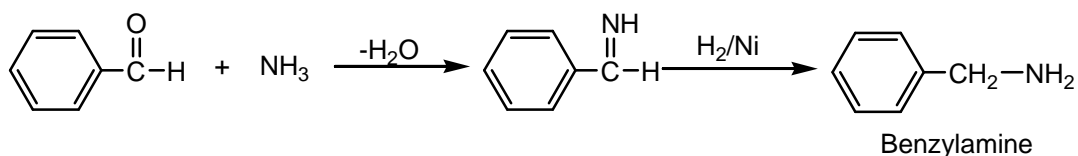


(iii) Reduction of azide: Alkyl azide on reduction yields alkylamines. This reduction reaction can easily be carried out by a variety of reagent including lithium aluminium hydride. The method involves converting alkyl halide to alkyl azide and then reducing the azide to primary amine by treating it with sodium and alcohol or lithium aluminium hydride.

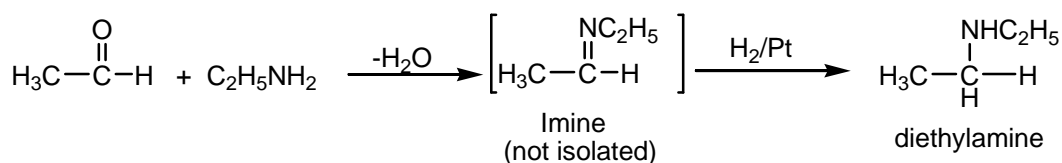


(iv) Reductive amination: Reduction of imine derivative of aldehyde or ketone to amines is commonly known as reductive amination. The overall reaction involves the conversion of carbonyl compound to an imine, often referred to as **Schiff base**, resulting in the formation of carbon-nitrogen bond, followed by its reduction to amines. Reduction of imine is achieved by lithium aluminium hydride, sodium borohydride, sodium cyanoborohydride, sodium and alcohol or by catalytic hydrogenation.

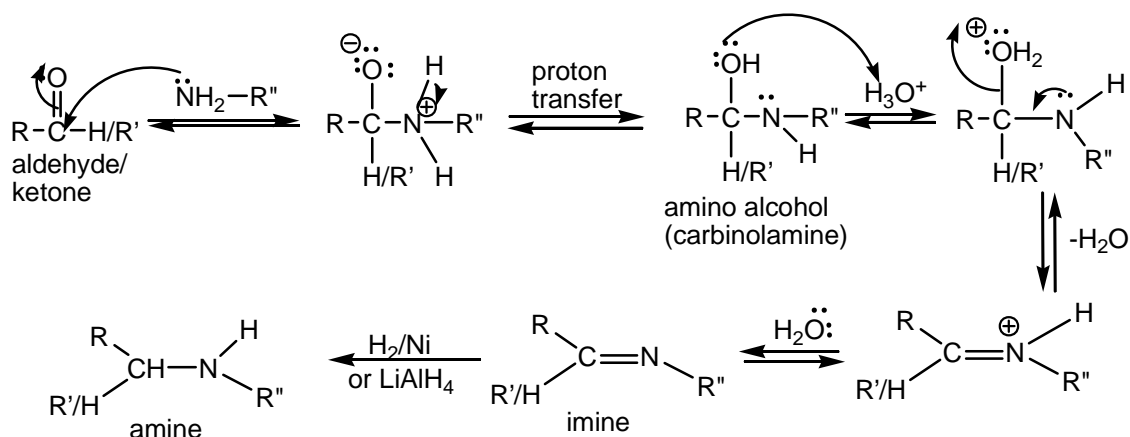




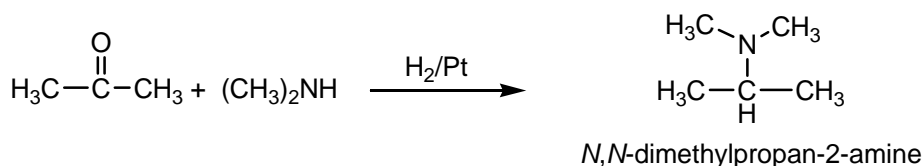
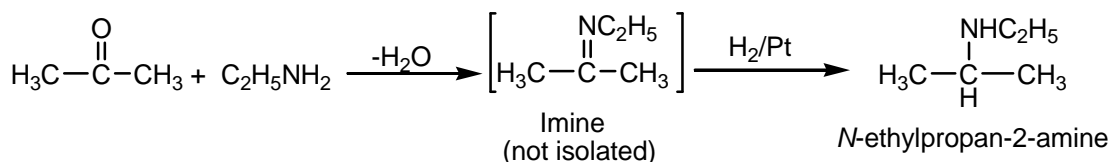
The synthetic utility of the reaction can be gauged from the fact that the reaction can be carried out in a single step by hydrogenating the solution containing both ammonia/amine and carbonyl compound along with hydrogenation catalyst. The intermediate imine formed during the reaction is not isolated but it is reduced under the conditions of the reaction, because imines are reduced much more rapidly than carbonyl compounds.



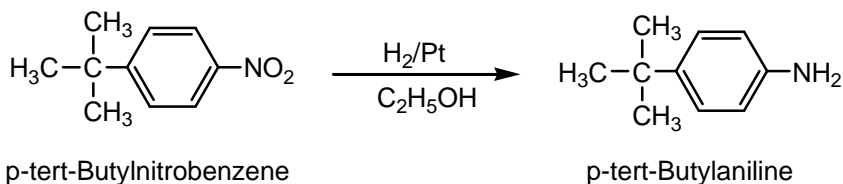
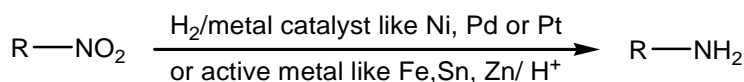
Mechanism:



All category of amines are synthesized by this process. When reaction is carried out with ammonia, the product is primary amine, with primary amine the product is secondary amine and with secondary amine the product is tertiary amine.

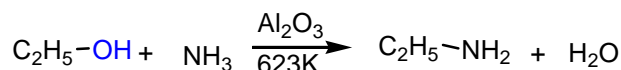
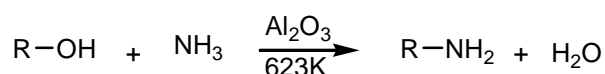


(v) Reduction of Nitro compounds: Nitro group can easily be reduced to primary amines either by catalytic hydrogenation or with a combination of finely divided metal powder and mineral acid.

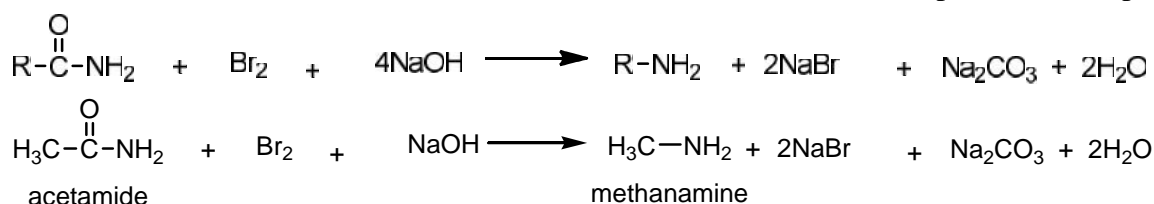


For details see nitro chapter

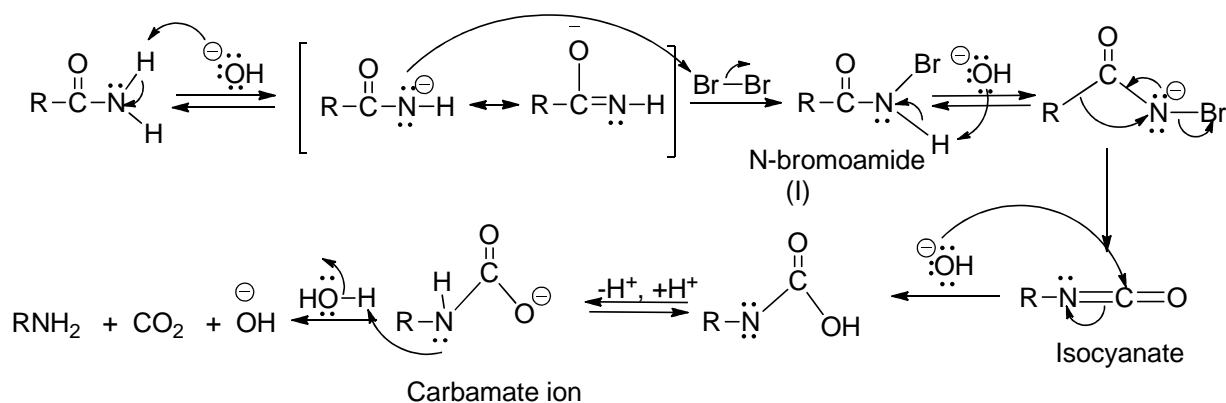
(vi) Ammonolysis of alcohols : By heating a mixture of alcohol and ammonia in a sealed tube in presence of copper chromite or alumina as catalyst, a mixture of primary, secondary and tertiary alcohol are obtained.



(vii) Hoffmann rearrangement: The reaction involves treatment of primary amide with bromine or chlorine in the presence of alkali to yield primary amine. The amine formed by this method contains one carbon less than the parent compound.

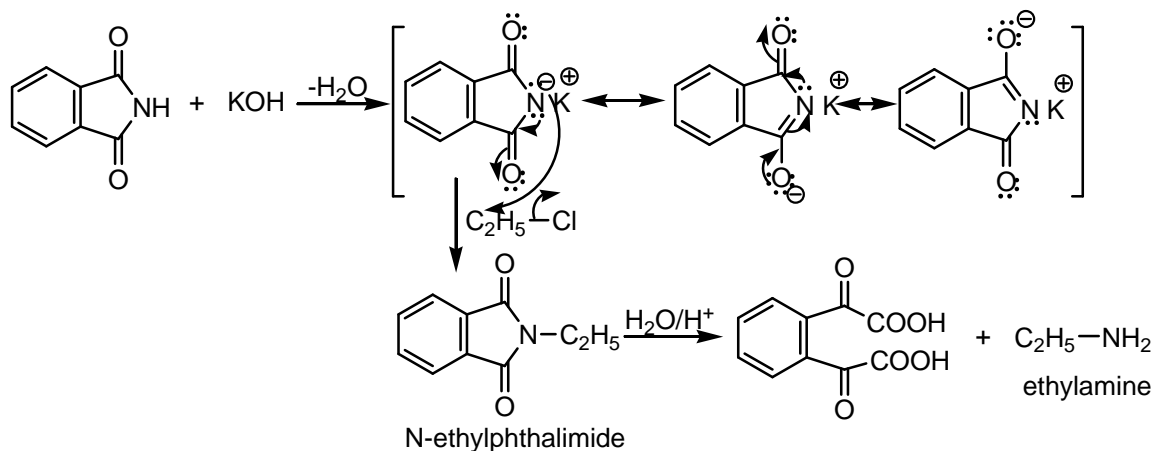


Mechanism:



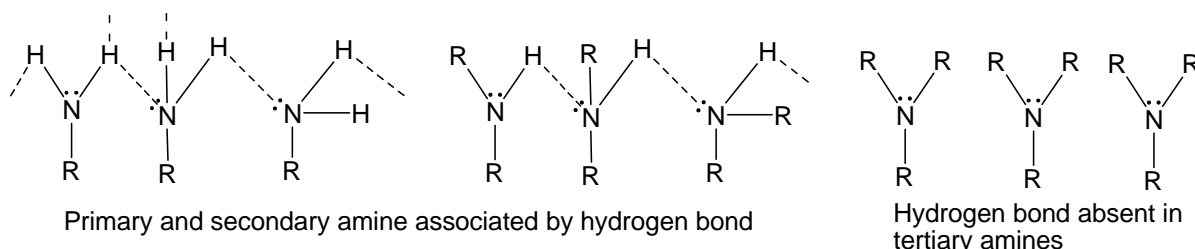
(x) Gabriel Phthalimide synthesis: The reaction is one of the convenient method for the synthesis of aliphatic as well as aralkyl primary amines. The reaction starts with the conversion of phthalimide to its potassium salt by reacting it with potassium hydroxide. The

salt formed has a negatively charged nitrogen atom, which acts as a nucleophile and attack the alkyl group of the alkyl halide in an S_N2 type process an imide-a diacyl derivative of amine. Hydrolysis by aqueous acid or base yields the desired amine.



Physical properties: Lower aliphatic amines are colourless gases at room temperature, those with more than two carbon atoms are volatile liquid, while the higher ones are colourless solids. Lower aliphatic amines possess fishy or fish like odour.

Amines are polar compounds because the nitrogen of the C-N bond is more electronegative in comparison to carbon. The nitrogen of this C-N bond carries a lone pair of electron, besides the primary amine have two and secondary amine have one polar N-H bond. As a result primary and secondary amines are capable of forming intermolecular hydrogen bonds, so these amines have higher boiling point in comparison to alkanes of comparable molecular mass.

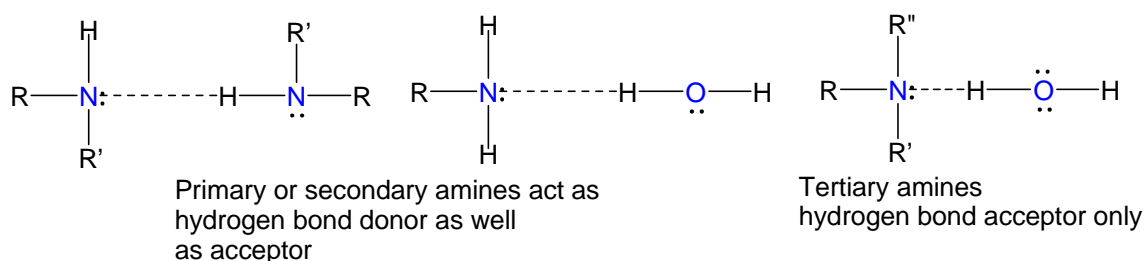


But as nitrogen is less electronegative as oxygen, the N-H bond is less polar in comparison to O-H bond. Hydrogen bond between amine molecules are weaker than those between alcohols. Amines therefore have lower boiling point than alcohols.

Primary amines, which have two N-H bonds, the hydrogen bonding is more prominent in comparison to secondary amines, which have one N-H bond. But tertiary amines has no N-H bond, hence no hydrogen bonding. Consequently among the isomeric amines, primary amines have the highest boiling point and tertiary amines the lowest.

Primary and secondary amines with low molecular mass are soluble in water. In fact those, which are gases at room temperature are sold as solution in water, in the same way as ammonia, which is usually supplied as ammonia solution. The nitrogen atom of amines readily accepts proton from water to form cation, which then co-associates with water due to

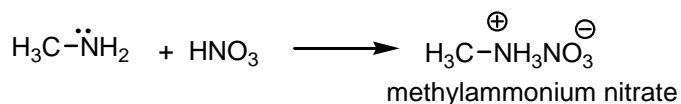
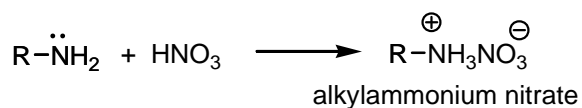
hydrogen bonding. Tertiary amines on the other hand do not have any hydrogen atom attached to nitrogen and so cannot form any hydrogen bond with themselves, but they can form hydrogen bond with water by using the lone pair on nitrogen. Tertiary amines are therefore less soluble in water in comparison to primary and secondary amines of comparable molecular weights.



Chemical reactions: The chemical reactivity of amines is chiefly determined by the presence of lone pair of electron on nitrogen and its ability to attack electrophilic centres.

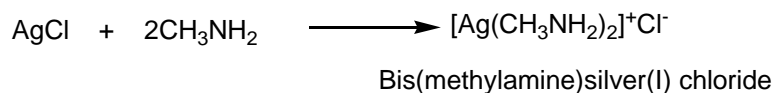
Amines as base

(a) Reaction with acids: Due to the presence of lone pair of electron on nitrogen, amines are lewis bases and they react with mineral acids to form soluble ammonium salts

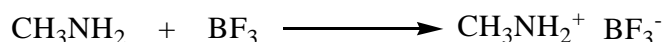


These amine salts are crystalline compounds with sharp melting point and soluble in water.

(b) Reaction with metal ions: Amines react with transition metal ions to form coordination compounds

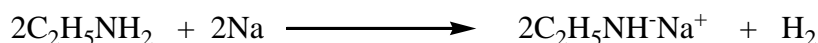


(c) Reaction with Lewis acids: Amines which act as lewis base also react with lewis acids

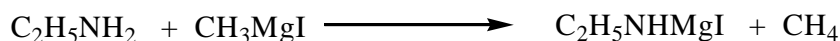


Amines as acid

(a) Reaction with active metals: Hydrogen of the primary and secondary amines are weakly acidic and on reaction with sodium and lithium metal, sodium and lithium salt are formed and hydrogen gas is released

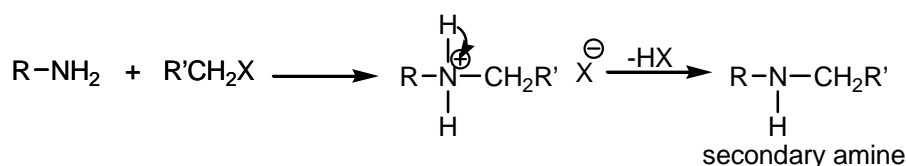


(b) Reaction with Grignard reagent: Grignard reagent being a strong base deprotonated amines very easily

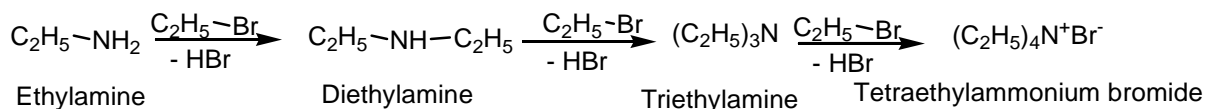


Nucleophilic substitution reaction

(a) Alkylation: Reaction of an amine with alkyl halide, result in alkylation of the nitrogen. The reaction takes place by $\text{S}_{\text{N}}2$ mechanism with the amine acting as a nucleophile.

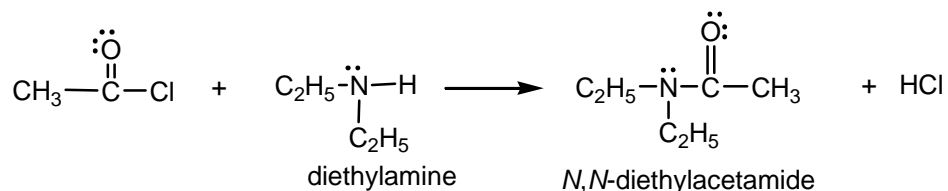


The initial product of the reaction is infact an alkylammonium ion and if N-H bond is still available then further alkylation may take place. It is for this reason that primary amine on reaction with alkyl halide yields secondary amine. Secondary amine on alkylation yields tertiary amine. The reaction may not stop at this stage and tertiary amine may itself be alkylated, yielding quaternary ammonium salts. Hence this procedure is also known as **exhaustive alkylation**. However if the alkyl halide used is methyl iodide, then the process is commonly referred to **exhaustive methylation**

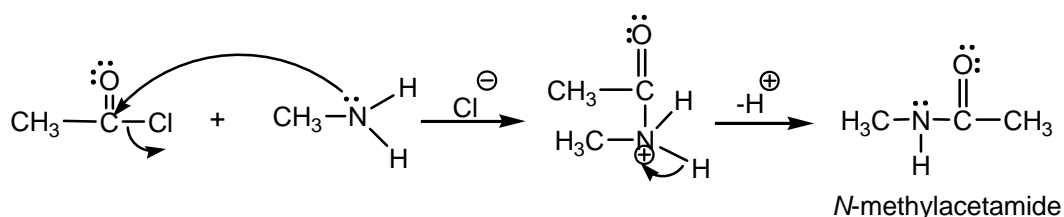


Since a mixture of product results, thus alkylation of amines is not a good method for introducing alkyl group into an amine.

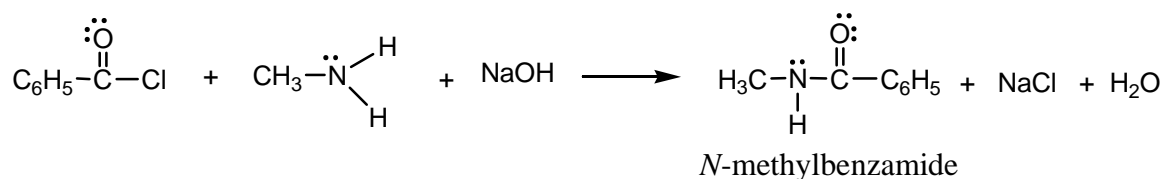
(b) Acylation: Primary and secondary amines undergo nucleophilic acyl substitution reaction when treated with acyl halides or anhydrides forming N-substituted amides



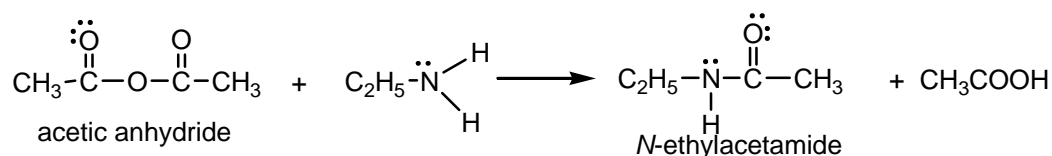
Mechanism:



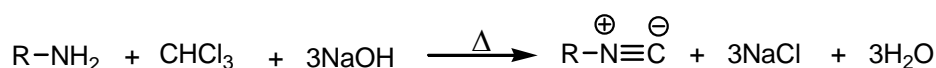
Benzoylation of amines is carried out by treating amine with benzoyl chloride in presence of aqueous alkali.



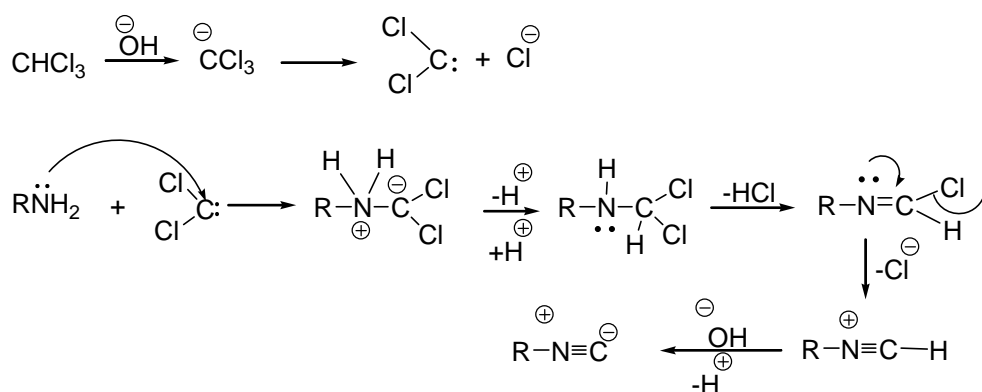
Acylation of amines to substituted amides is also achieved by treating them with carboxylic anhydrides.



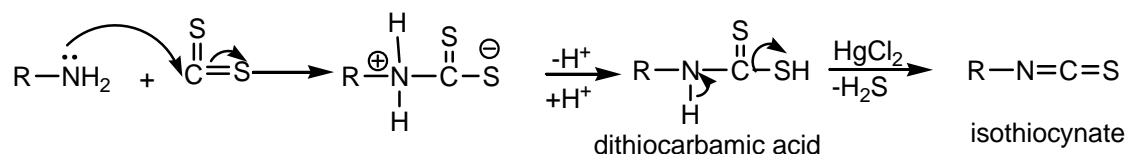
(c) Carbylamine reaction : Primary amines react with chloroform in presence of alkali to form isonitrile or carbylamines, which have extremely unpleasant nauseating odour. This reaction is therefore used as a qualitative diagnostic for primary amines.



Mechanism:



(d) Reaction with carbon disulphide: Primary amines on reaction with carbon disulphide forms dithiocarbamic acid, which on treatment with mercuric chloride yields alkyl isocyanate, which have pungent odour similar to mustard oil.

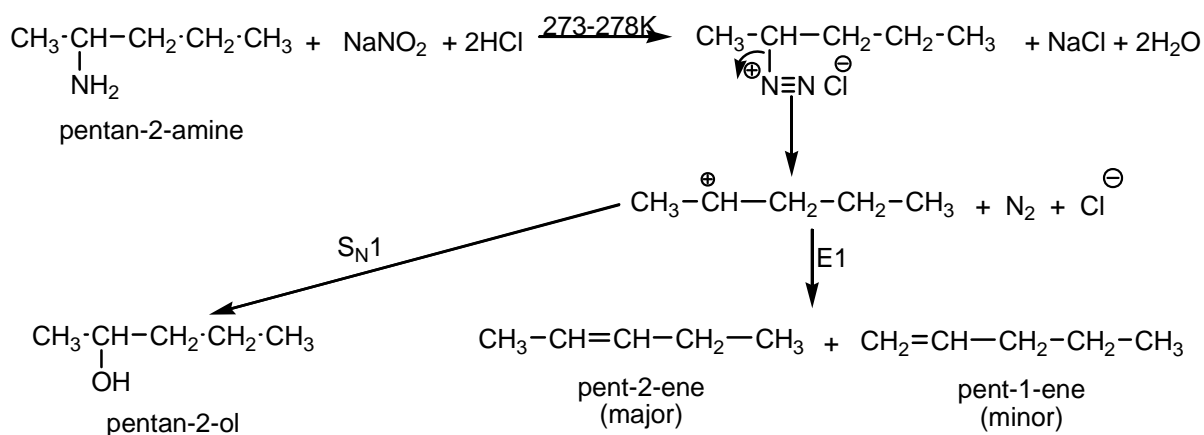


(e) Reaction with nitrous acid: All amines react with nitrous acid, however the product formed depends upon the category of amine used in the reaction. Nitrous acid used in the

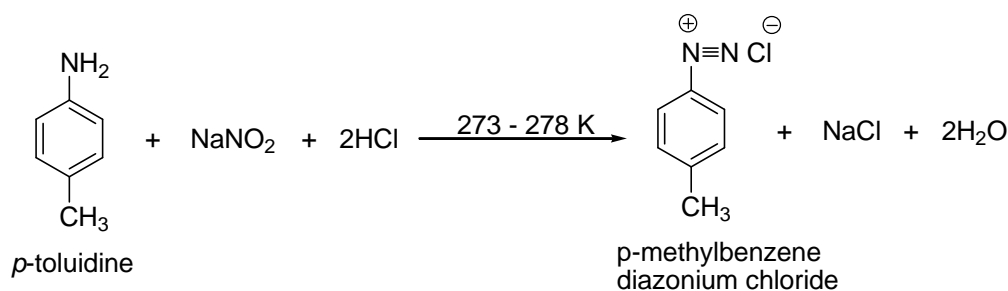
reaction is unstable, as a result it is generated in situ by treatment of sodium nitrite with strong acid such as HCl or H₂SO₄.

Aliphatic primary amines react with nitrous acid forming diazonium salts. This process of conversion of primary amine to its diazonium salt is known as **diazotization**.

Diazonium salts of aliphatic primary amine are highly unstable even at lower temperatures, as a result as soon as they are formed they decompose, liberating nitrogen to form carbocation. The carbocation may undergo substitution and elimination reaction to give alcohol and alkene respectively. As a result diazotization of aliphatic primary amine of little or no importance, and their reaction are also of no importance.

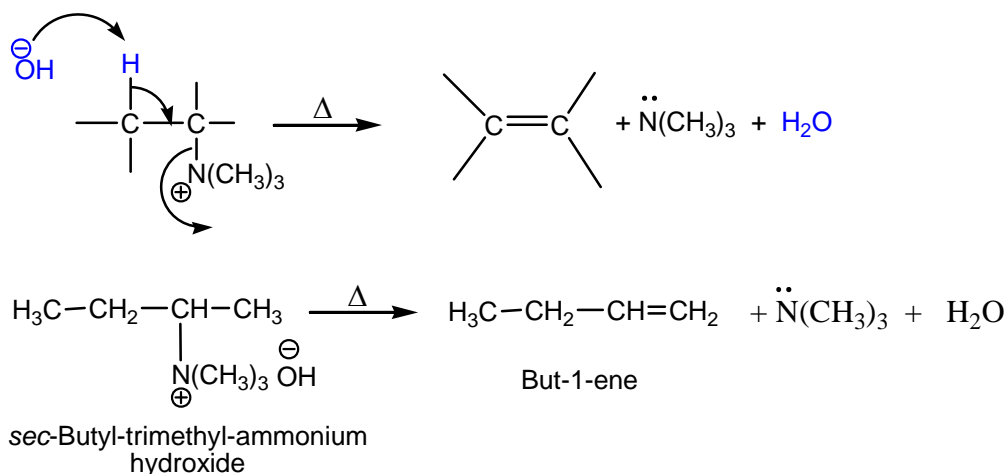


Though diazonium salts of primary aromatic amines are also unstable, but they are far more stable in comparison to diazonium salts of aliphatic primary amines and they do not decompose when the temperature of the reaction mixture is kept below 278K.

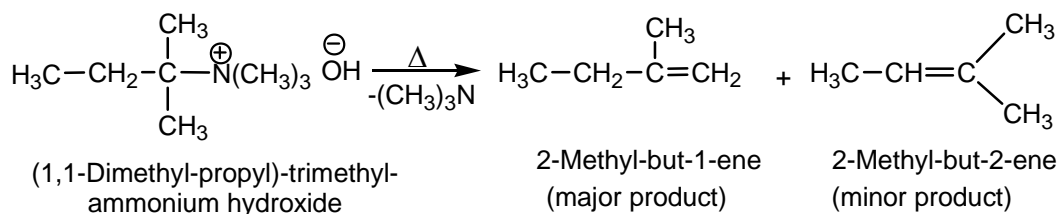


For detail see diazonium chapter

(f) Hoffmann elimination: When quaternary ammonium hydroxides are heated in presence of aqueous silver oxide, they undergo elimination yielding a tertiary amine and an olefin. The reaction commonly known as **Hoffmann elimination** takes place by E2 mechanism with preference for anti-elimination.

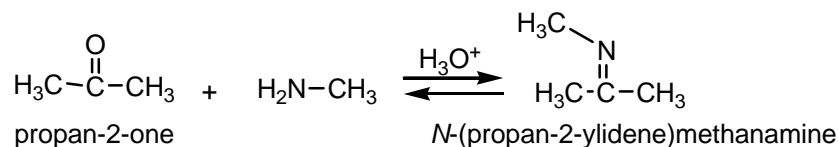


Hoffmann elimination reaction being highly regioselective, the reaction proceeds in the direction that gives the least substituted alkene as the predominant product. This is known as **Hoffmann rule** and the least substituted alkene is known as **Hoffmann product**

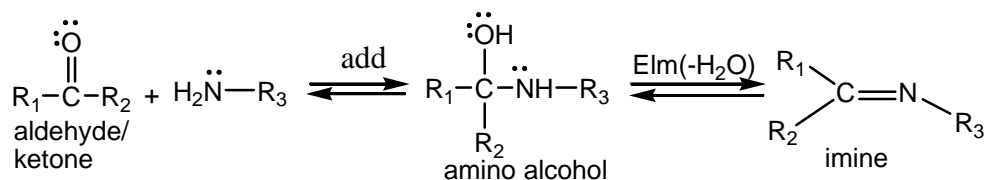


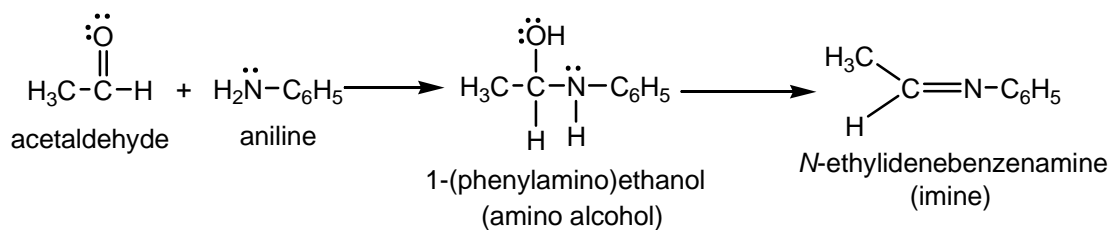
Nucleophilic addition reaction

(a) Reaction with aldehydes and ketones: (i) Reaction with primary amines: Primary amines react with aldehydes and ketones to yield imines commonly called Schiff's bases.

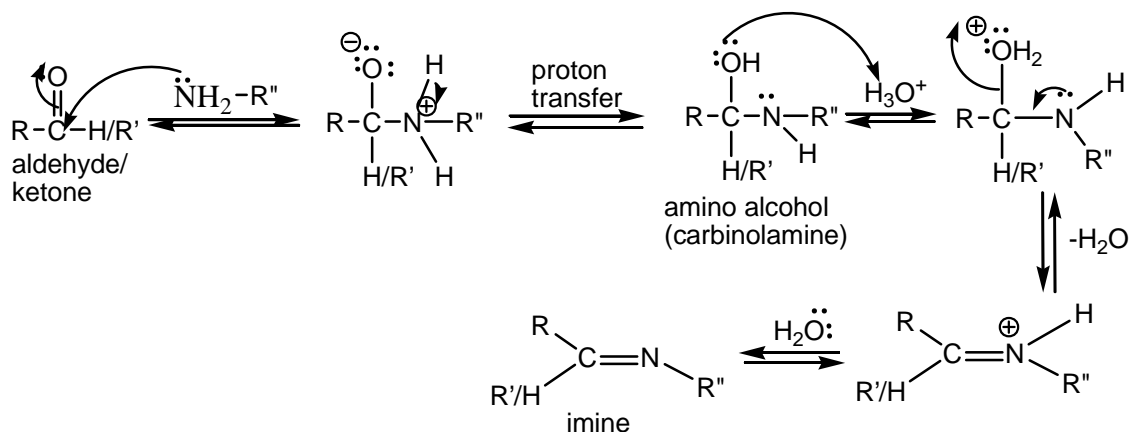


This reaction actually takes place in two steps. In the first step the amine derivative adds to the carbonyl group to form amino alcohol or carbinolamine. In the next step, a molecule of water is eliminated from carbinolamine yielding imine derivative also called Schiff bases, named after a German chemist Hugo Schiff, who first described its synthesis.

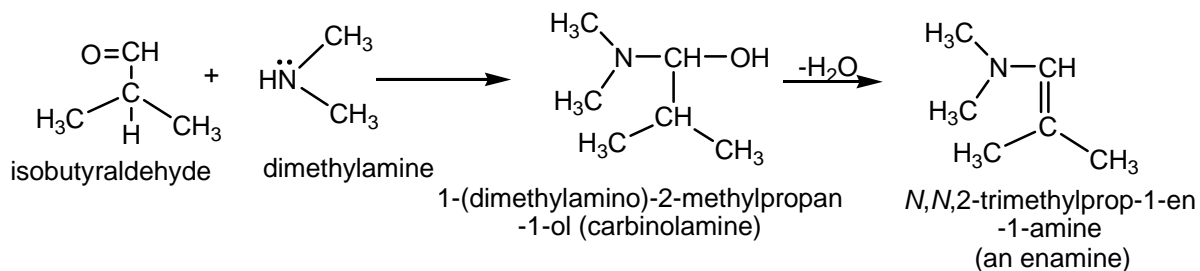




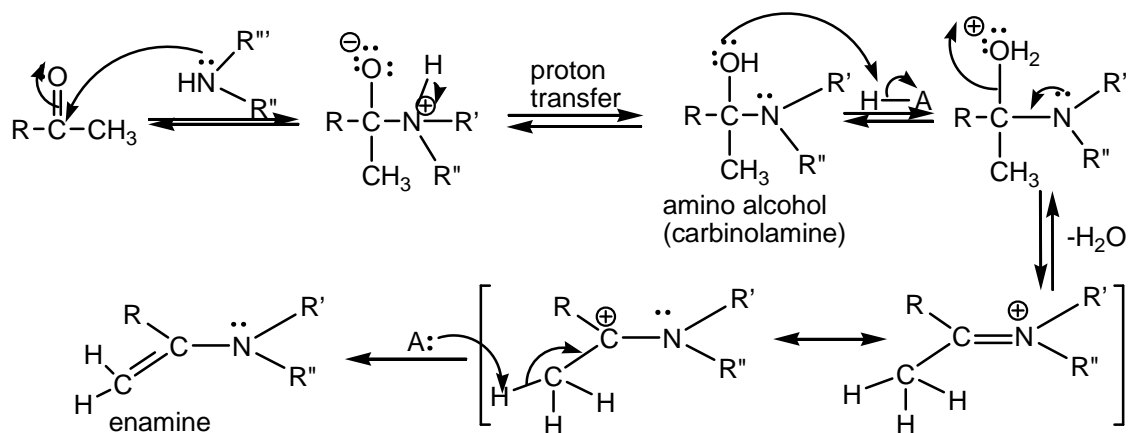
Mechanism:



(ii) Reaction with secondary amines: Aldehydes and ketones containing α -hydrogen react with secondary amines in the presence of acid to form enamines- a vinyl amine (compounds in which amino group is bonded to carbon that is part of a double bond)



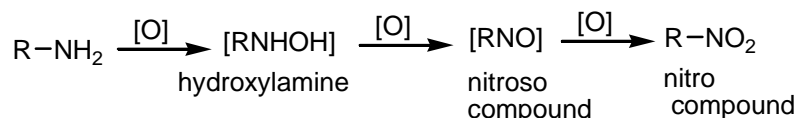
Mechanism:



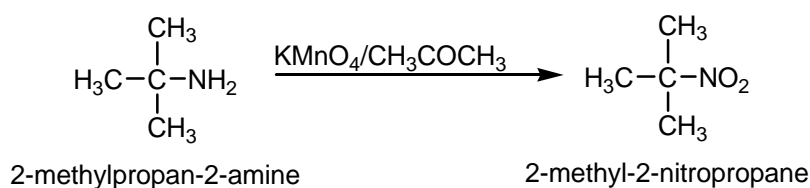
Oxidation reactions

(a) Oxidation: All types of amines are oxidized, however the product depends upon the type of amine and the oxidant used

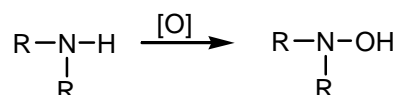
Primary amines on oxidation through a series of steps yield nitro compounds



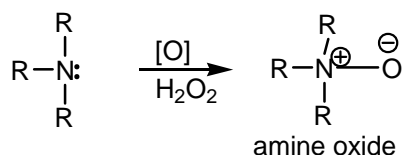
Primary amines in which the amino group is bonded to a tertiary carbon can be oxidized with potassium permanganate in aqueous acetone to nitro compound in 70-85% yield



Secondary amines on oxidation yield dialkylhydroxylamines



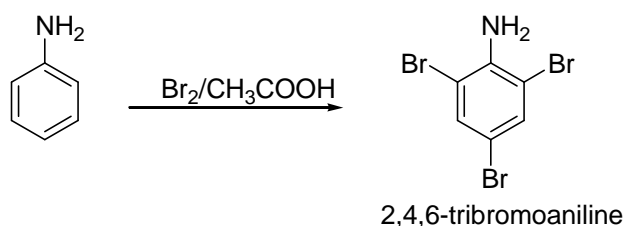
Tertiary amines on oxidation yield amine oxide. The bond between the nitrogen and oxygen must be drawn with positive on nitrogen and negative charge on oxygen (in older version the bond was written as N O, because of the donation of electron from nitrogen).



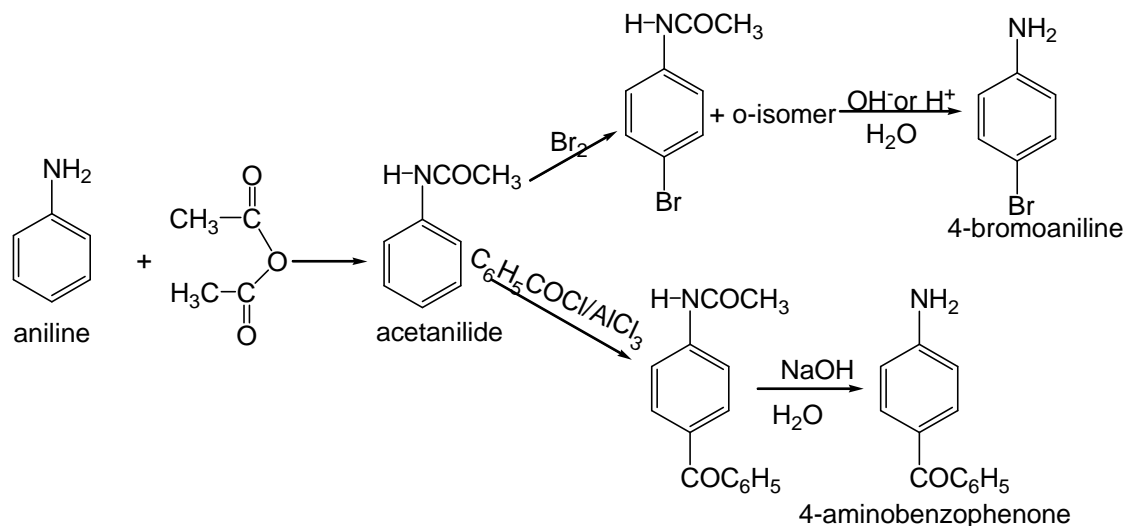
Electrophilic Aromatic substitution reaction in Amines

Besides the reactions of the amino group, aryl amines also undergo electrophilic aromatic substitution reaction. Amino group activates the aromatic ring for further electrophilic substitution reaction because of the delocalization of the lone pair of electron on the nitrogen atom over to the benzene ring.

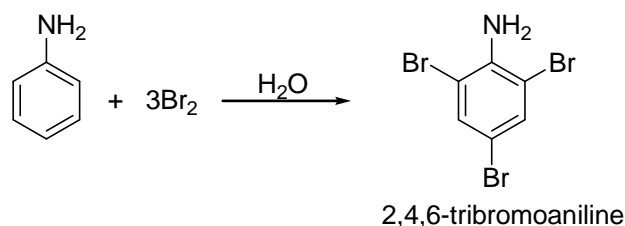
The amino group is thus activating and ortho-para directing. The group is so activating that it is difficult to prevent its polysubstitution. For example bromination of aniline instead of o-bromo aniline and p-bromo aniline yields a single 2,4,6-tribromoaniline.



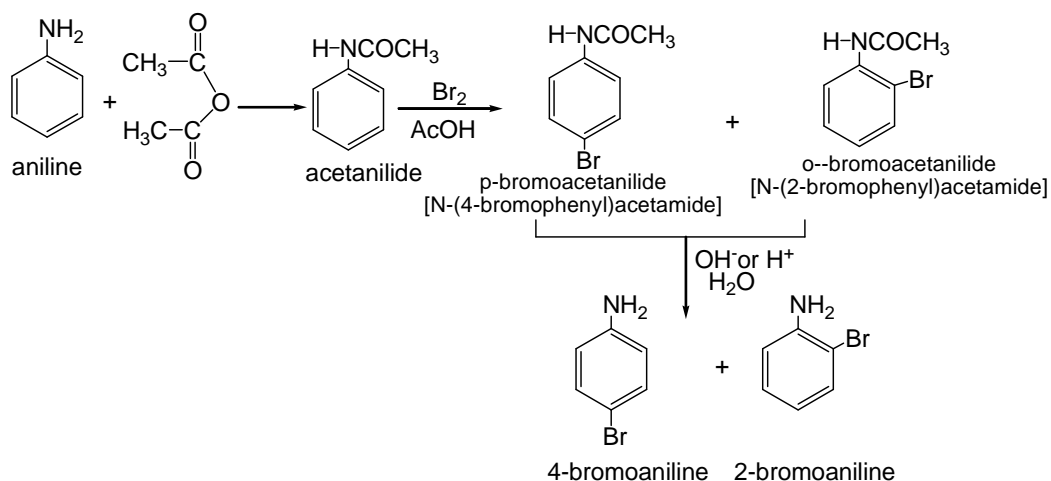
Another point to remember about the amino substituted benzenes is that their Friedel Craft reactions are not successful and this is due to the fact that the amino group being basic forms complex with the lewis acid, thereby preventing the reaction to take place. Hence in order to obtain a monosubstituted and Friedel Craft alkylated and acylated product the activation of amino group is reduced by converting it into acetyl amide group (anilide) by treating it with acetic anhydride or acetyl chloride.



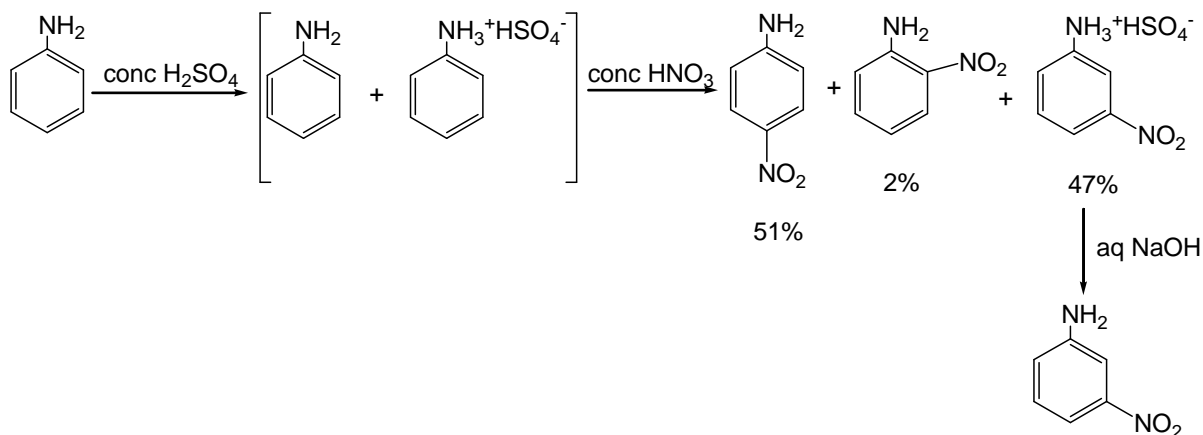
(i) Halogenation: Due to strong activating nature of the amino group, halogenations of aromatic amines can take place even in the absence of lewis acid catalyst and the halogen will be introduced at the para and both the ortho positions.



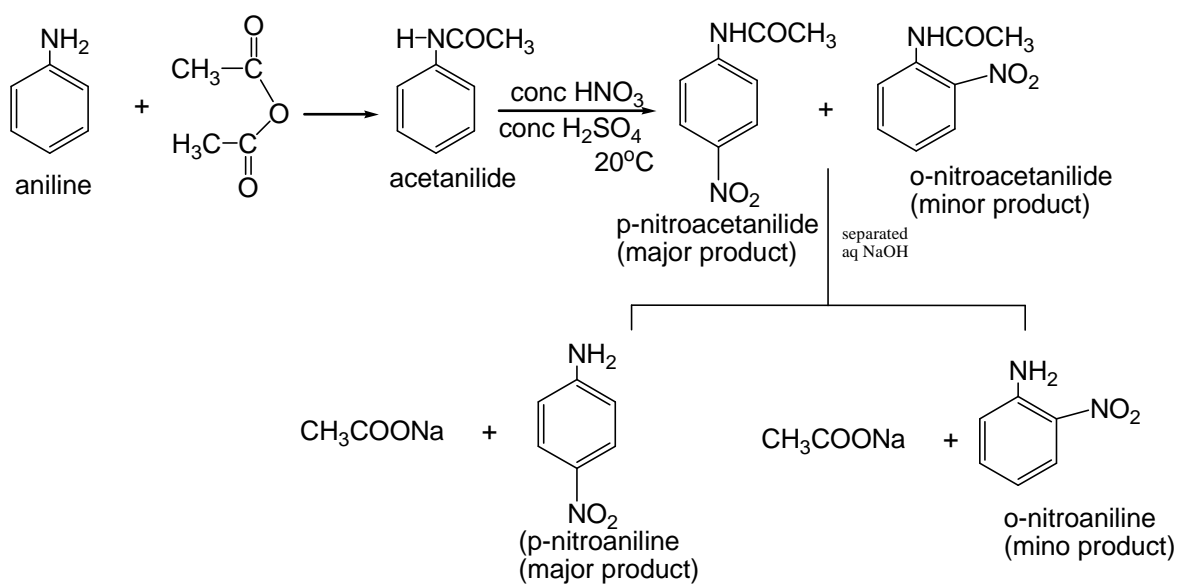
However if the demand is for the monohalogenated derivative, then the amino group is first protected by converting it into acetyl amide group (anilide) by treating it with acetic anhydride or acetyl chloride. Halogenation is then carried out and subsequently the acetyl group is hydrolyzed to yield the monohalogenated amine derivative.



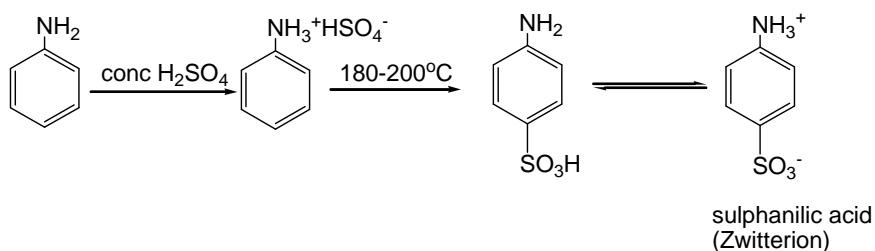
(ii) Nitration: Direct nitration of aryl amines is difficult since nitric acid is not only a nitrating agent but it is also a good oxidizing agent and it oxidizes aryl amines to dark coloured “tars”. However under controlled conditions the nitration yields a mixture of p-nitroaniline and m-nitroaniline.



However nitration on arylamines is best carried out by protecting the amino group and then carrying out the nitroation process, followed by hydrolysis yielding p-nitroaniline and o-nitroaniline.



Sulphonation: Aniline on reaction with equimolar amount of concentrated sulphuric acid initially gives anilinium hydrogen sulphate, which when heated at higher temperatures (180-200°C), undergoes rearrangement to yield p-aminobenzene sulphonic acid (sulphanilic acid)



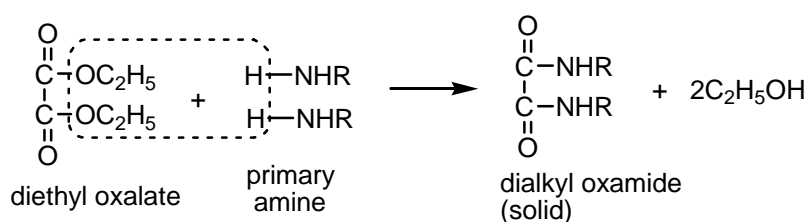
Separation of primary, secondary and tertiary amines

There are a number of methods of synthesis which usually give a mixture of primary, secondary and tertiary amines alongwith quaternary ammonium salts. Thus methods have to be adopted in order to separate the mixture into individual components. In the first step of the separation the mixture is distilled with KOH, whereby quaternary ammonium salts being non-volatile remains in the flask and the mixture of amines distill over. This amine mixture can however be separated by one of the following methods

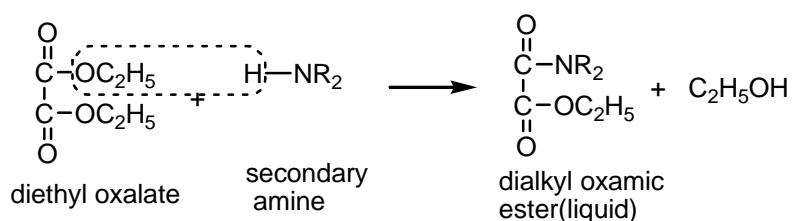
(i) **Fractional distillation:** As the boiling points of primary, secondary and tertiary amines are far apart, hence the three class of amines can be separated into individual components by fractional distillation. This is also one of the industrial method of separation of amines a now highly efficient fractionating columns are available.. For example the three class of amine- ethylamine ($C_2H_5NH_2$, b.p $16.5^\circ C$), diethylamine [$(C_2H_5)_2NH$, b.p $55^\circ C$] and triethylamine [$(C_2H_5)_3N$, b.p $89^\circ C$] can be separated by this method

(ii) **Hoffmann method:** In this method the mixture of amines is heated with diethyl oxalate. The three amines react differently

(a) Primary amines on reaction with diethyl oxalate forms dialkyl oxamide, which are generally solid



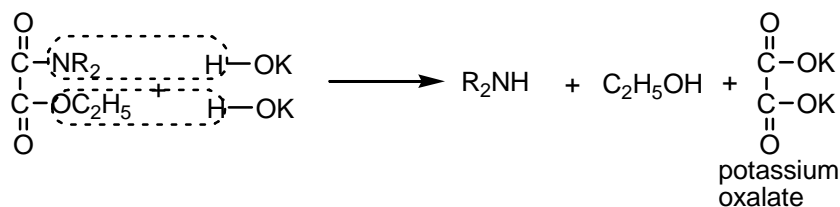
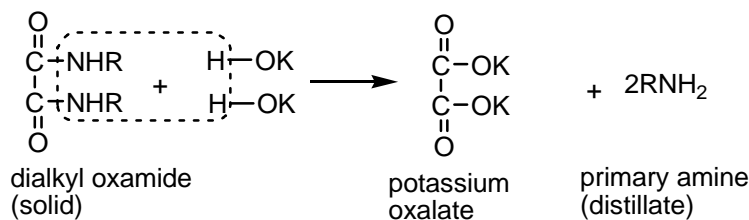
(b) Secondary amines on reaction with diethyl oxalate forms N,N-dialkyl oxamic ester, which are generally oily liquids



(c) Tertiary amines do not react with diethyl oxalate as they do not possess any replaceable hydrogen atoms.

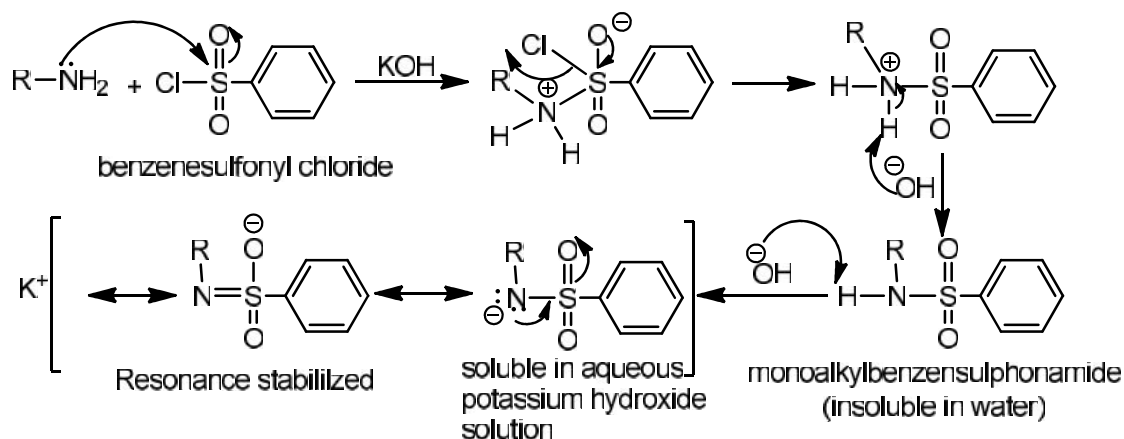
Recovery of amines: The mixture of amines after reaction with diethyl oxalate contain a mixture of substituted oxamide (solid), oxamic ester (liquid) and unreacted tertiary amine. This mixture is now distilled, tertiary amine being more volatile distill off and is collected. The residual mixture containing the substituted oxamide (solid) and oxamic ester (liquid), may be separated by simple filtration and then treated separately with strong alkali, whereby

the corresponding amines are generated.

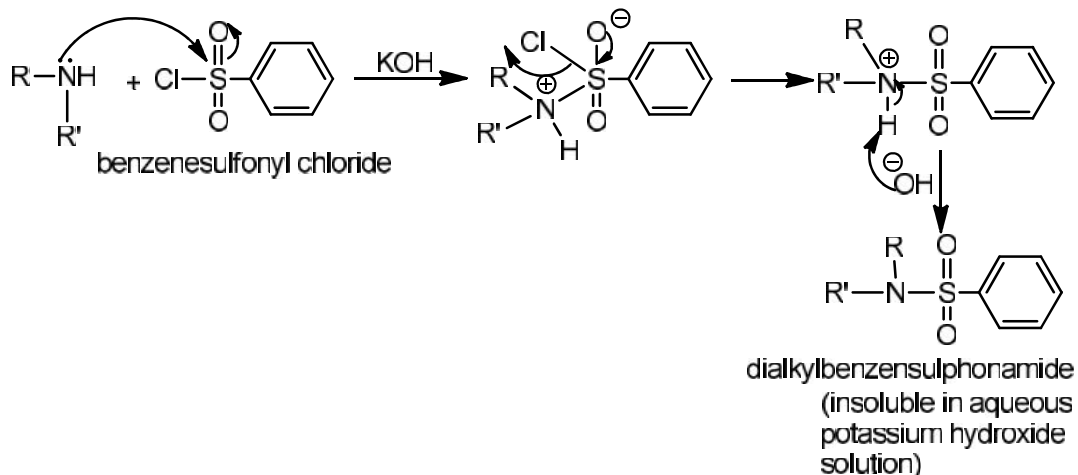


(iii) Hinsberg separation of amines: A chemical method developed by Oscar Hinsberg in 1890, is not only an excellent method for the detection and distinguishing the three category of amines but it also helps in their separation. The process involves reacting mixture of amines with Hinsberg reagent (aqueous sodium or potassium hydroxide and benzene sulphonyl chloride). Primary amine forms soluble sulphonamide salt which precipitates after addition of dilute hydrochloric acid. Secondary amine forms an insoluble sulphonamide, whereas tertiary amine does not react. It is important to note that instead of benzene sulphonyl chloride, p-toluene sulphonyl chloride can also be used.

(i) Primary amine in the presence of base reacts with benzene sulphonyl chloride to form monoalkyl benzenesulphonamide, which is soluble in aqueous alkali solution. Benzenesulphonyl group being a strong electron withdrawing group, as a result the proton bonded to nitrogen is acidic and can easily be removed by the base, leading to the generation of resonance stabilized anion, which makes it soluble in aqueous alkali solution..

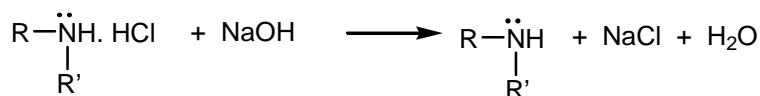
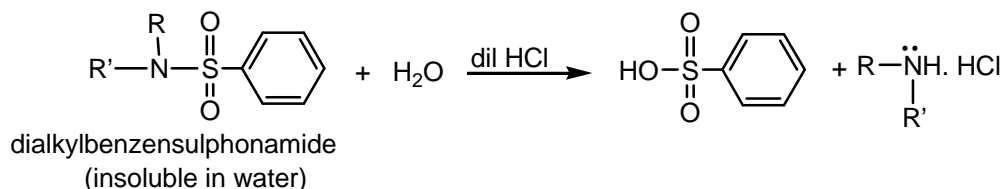
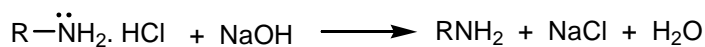
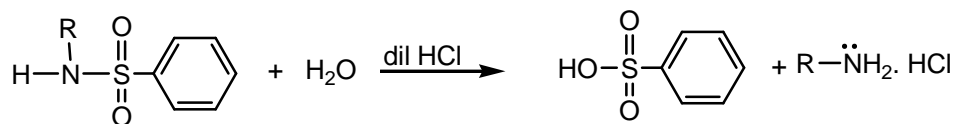
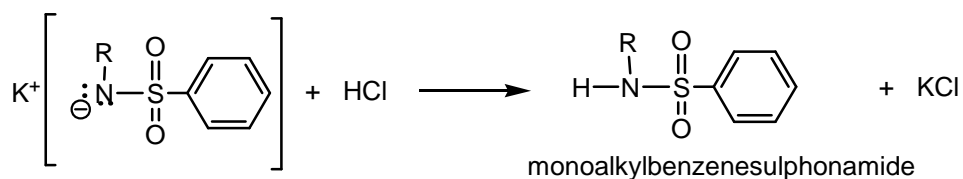


(ii) Secondary amine in the presence of base reacts with benzene sulphonyl chloride to form dialkyl benzenesulphonamide. It is insoluble in aqueous potassium hydroxide solution and as it does not contain any hydrogen atom on nitrogen, it therefore cannot ionize to give anionic species, hence insoluble.



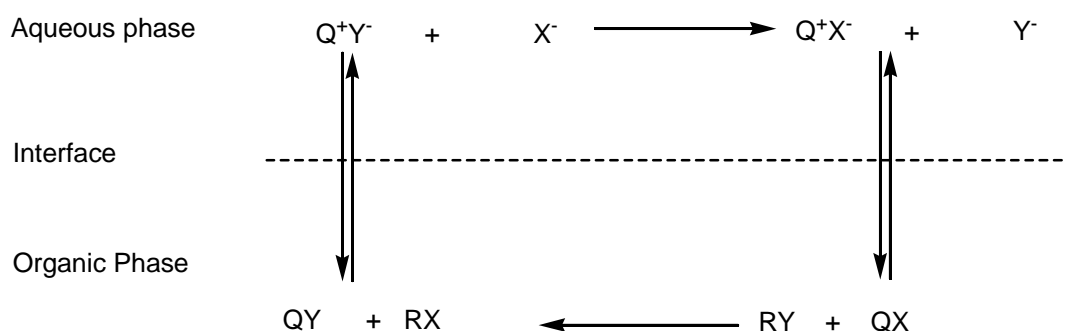
(iii) Tertiary amine does not react with benzenesulphonyl chloride

The reaction mixture obtained after reaction of the mixture of amines with benzenesulphonyl chloride is then distilled, unreacted tertiary amine distills over and is recovered. The remaining mixture is then filtered, sulphonamide of primary amine, which is soluble in water is obtained as a filtrate, whereas sulphonamide of secondary amine, which is insoluble in water is obtained as a residue on the filter paper. The two sulphonamides thus separated can be hydrolyzed by acid to get their respective salts. The salts can thus be hydrolyzed by base to recover the respective amines.



Phase transfer catalyst

According to collision state theory for a reaction to take place it is necessary for the reacting species to collide with one another or they should be accessible to each other. However, a number of reactions cannot take place because the reacting species cannot collide as they are separated by an interface i.e. both the reacting species are not soluble in the same phase. For example 1-chlorooctane cannot react with sodium cyanide because 1-chlorooctane is not soluble in water. This problem has thus been solved by the use of PHASE TRANSFER CATALYSIS (PTC) technique. In this technique each reactant is dissolved in an appropriate solvent and the two solvent solutions are mixed. These solvents are normally immiscible with one another. Now a phase transfer catalyst is added, which facilitates the transport of one reactant into another phase. The most commonly used phase transfer catalysts are quaternary ammonium salts, which are soluble in the aqueous phase, undergo anion exchange with the anion of the reactant (X^-) dissolved in the aqueous phase. The new ion pair formed (Q^+X^-) can cross the liquid-liquid interface due to its lipophilic nature and thus diffuse into the organic phase (this step being phase transfer). In the organic phase the diffused ion pair (Q^+X^-) being nucleophilic undergoes nucleophilic substitution reaction with the organic reagent to form the desired product (RX). The phase transfer catalyst subsequently returns to the aqueous phase and the cycle continues.

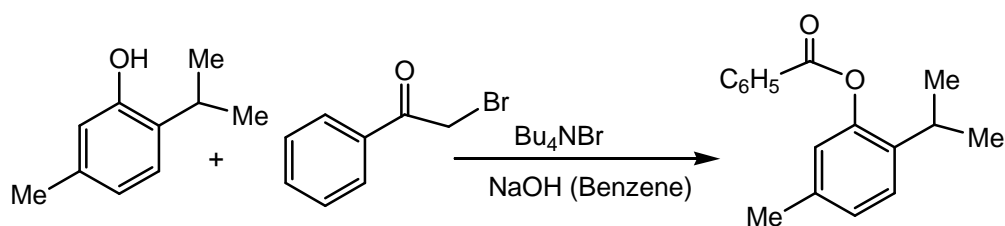


The most commonly used phase transfer catalysts are quaternary ammonium salts. Some of the common quaternary ammonium salts used as phase transfer catalysts are tetra-n-butylammonium chloride [TBAC, $(n-C_4H_9)_4N^+Cl^-$], tetrabutylammonium bromide [TBAB, $(n-C_4H_9)_4N^+Br^-$], triethylbenzylammonium chloride [TEBA, $(C_6H_5CH_2N^+(C_2H_5)_3)Cl^-$].

Application of Phase transfer catalyst

Phase transfer catalyst finds wide application in organic synthesis. There are numerous examples where this methodology has been adopted for the synthesis of compounds which could not be synthesized by the conventional methods.

Alkylation



Advantage of Phase transfer catalysis over conventional procedures

- (i) There is no use of expensive anhydrous or aprotic solvents
- (ii) The reaction can be carried out at lower temperatures
- (iii) Greater region and chemoselectivity is achieved in these reactions
- (iv) The yield of the product formed is high and lesser chances of side reactions