STEREOCHEMISTRY II

SEM-1, CC-1B
PART-12, PPT-12

Part-12: Resolution

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Stereochemistry (PART-12, PPT-12)

Resolution

Racemic Modifications

The *racemic modification* is an equimolecular mixture of a pair of enantiomers independent of whether it is crystalline, liquid or gases. The *racemic modification* is optically inactive due to external compensation, i.e., (+)-rotation of one enantiomer is compensated by the (-)-rotation of the other. Since *racemic modification* is a mixture, it can be separated into pure enantiomers.

Chiral compounds synthesized from *achiral* starting materials and reagents are generally *racemic* (i.e., a 50:50 mixture of enantiomers). Separation of *racemates* into their component enantiomers is a process called resolution. Since enantiomers have identical physical properties, such as solubility and melting point, resolution is extremely difficult. Diastereomers, on the other hand, have different physical properties, and this fact is utilised to achieve resolution of *racemates*.

Resolution

Resolution is the method of separation of *racemic* modification into pure enantiomers. The most commonly used procedure for separating enantiomers is to convert them to a mixture of diastereomers that will have different physical properties: melting point, boiling point, solubility, etc.

For example, if a *racemic* or *dl-mixture* of enantiomers of an acid is converted to a salt with a *chiral* base (say, *d*-isomer), the salt will be a mixture of two diastereomers, (*d*-acid.*d*-base) and (*l*-acid.*d*-base). These diastereomeric salts are *not* identical and they are not mirror images. Therefore, they will differ to some degree in their physical properties, and a separation by physical methods, such as crystallization, may be possible.

Resolution Through the Formation of Diastereomers

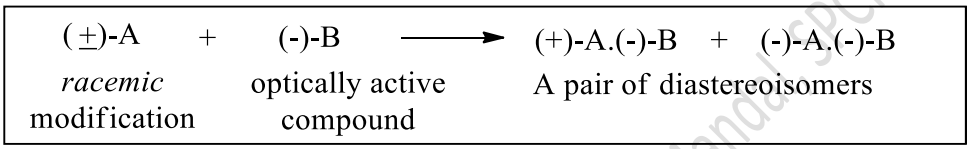
Because the physical properties of enantiomers are identical, they seldom can be separated by simple physical methods, such as fractional crystallization or distillation. It is only under the influence of another *chiral* substance that enantiomers behave differently, and almost all methods of resolution of enantiomers are based upon this fact.

The basis of chemical method of separation consists in converting the enantiomers of a *racemic* modification into a pair of diastereomers. The *racemic modification* is treated with an *optically active* substance (enantimer of a *chiral* substance) and the diastereomers thereby formed are separated by fractional crystallization or by chromatography. The separated diastereomers are then individually treated with suitable reagent to regenerate the pure enantiomer.

Resolution of *Racemic* Acids

The principle involves in the resolution of a *racemic acid*, (±)-A with an optically pure base, such as, (-)-Brucine which combines with the *racemic* acid giving two diasteromeric salts. Being diastereomeric, the two salts differ in physical properties, such as solubility, boiling point, fractional crystallization, adsorption coefficient, etc. The diastereomeric salts are then separated on the basis of the suitable physical properties. Decomposition of the salt with mineral acids would give (+)-A and (-)-A in enantiomerically pure form.

Resolving agents that can be used to resolve *racemic* acids into optically pure enantiomer are optically active naturally occurring alkaloids, like (-)-Brucine, (-)-Strychnine, (-)-Ephedrine, (+)-Cinchonine, (+)-Cinchonidine, (-)-Morphine, etc.



Scheme for the Resolution of Racemic Acids

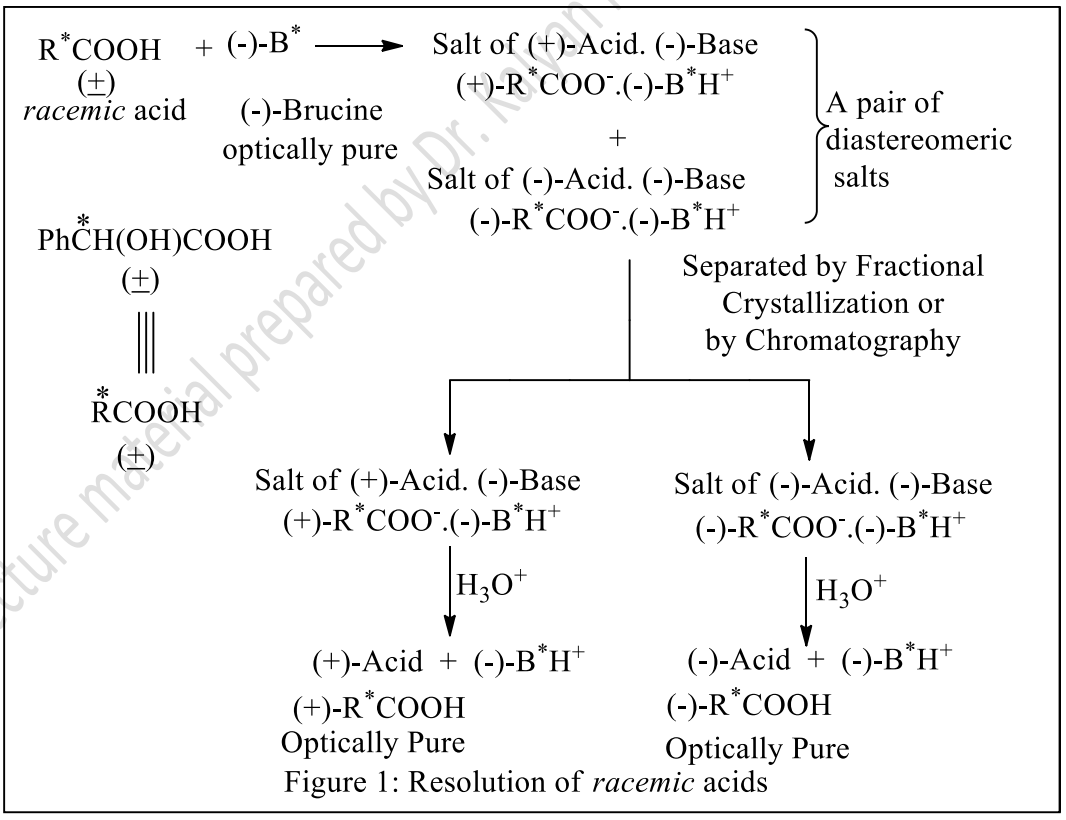


Figure 1: Resolution of *racemic* acids

Resolution of *Racemic* Acids

Racemic bases are resolved by using optically active acids as *chiral* reagent. The active acids used as an active resolving agent are (+)-Camphor-10-sulphonic acid, (+)-Bromocamphorsulphonic acid, (+)-Camphoric acid, (+)-Tartaric acid, (-)-Malic acid, (-)-Mandelic acid, (+)-Glutamic acid, etc.

The principle involves in the resolution of a *racemic base*, (±)-B with an optically pure acid, such as, (+)-Camphor-10-sulphonic acid which combines with the *racemic* base giving two diasteromeric salts. Being diastereomeric, the two salts differ in physical properties such as solubility, boiling point, fractional crystallization, adsorption coefficient, etc. The diastereomeric salts are then separated on the basis of the suitable physical properties. Decomposition of the salt with mineral bases would give (+)-B and (-)-B in enantiomerically pure form.

Scheme for the Resolution of *Racemic* Bases

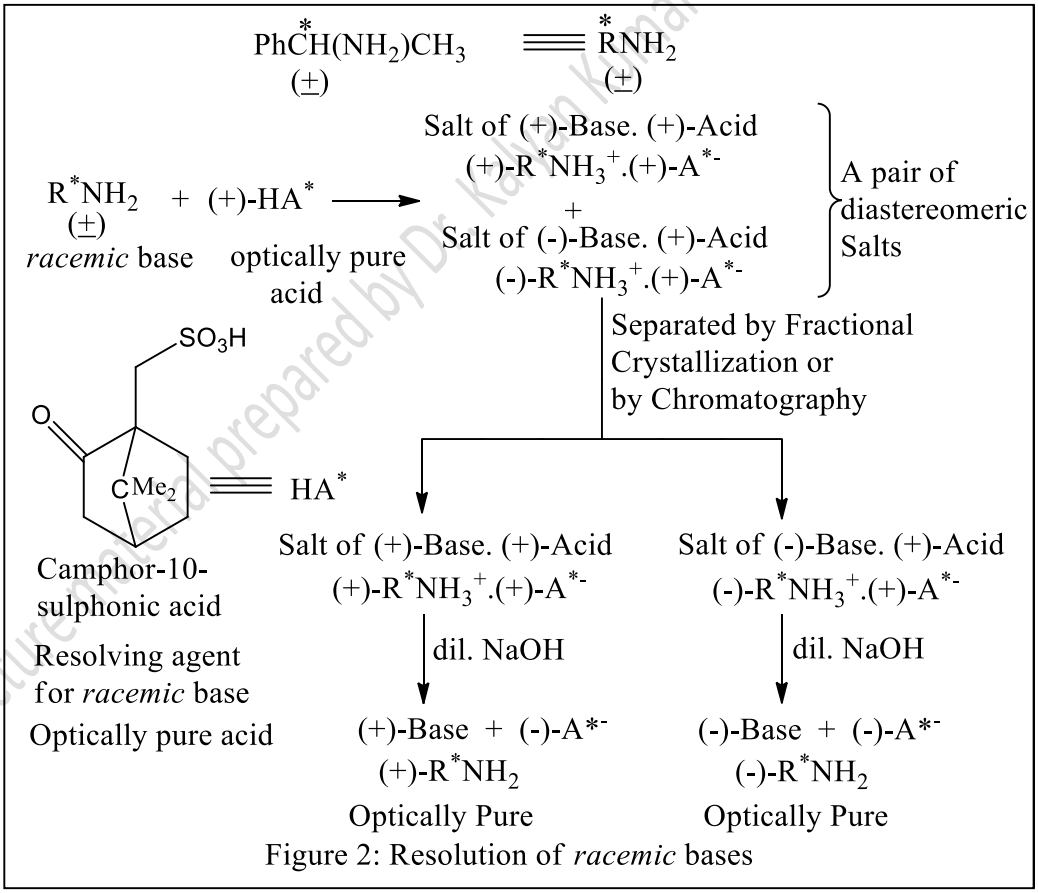


Figure 2: Resolution of *racemic* bases

Resolution of *Racemic* Alcohol

The *racemic* alcohols [(±)-R^*OH], cannot be resolved directly like a *racemic* acid and base, as there is no suitable resolving agent available to do so. The *racemic* alcohol, prior to resolution, is first converted into a half-ester of a dicarboxylic acid, such as succinic acid or phthalic acid by heating with succinic anhydride or phthalic anhydride respectively in presence of pyridine.

The resulting half-esters have a free carboxyl function and are then resolved as typical acids, e.g., by means of the optically pure base (-)-Brucine. The pure diastereomeric salts, obtained after fractional crystallization are decomposed by dilute aqueous hydrochloric acid (actual procedure involves dissolution of the salt in methanol, pouring into dilute aqueous hydrochloric acid and extraction of the phthalate precipitated with ether) to the corresponding half-esters.

The half-ester is then either saponified by treatment with hot aqueous sodium hydroxide, (*there is a chance of *racemization* by base), or, the alcohol is recovered from the half-ester by reduction using lithium aluminium hydride as the reducing agent.

The phthalyl alcohol formed as a by-product in the case of hydride reduction of acid phthalates is very high boiling so that the resolved alcohol can usually separate from it by vacuum distillation. The by-product in the reduction of succinates is the very water-soluble 1,4-butanediol. Figure 3 illustrates the resolution process.

An alternative method of resolving alcohols is to convert them to esters of optically active acids. The usefulness of this method is limited because relatively few esters are satisfactorily crystalline. Tartranilic acid, menthyl isocyanate may be used to resolve *racemic* alcohols.

Scheme for the Resolution of *Racemic* Alcohols

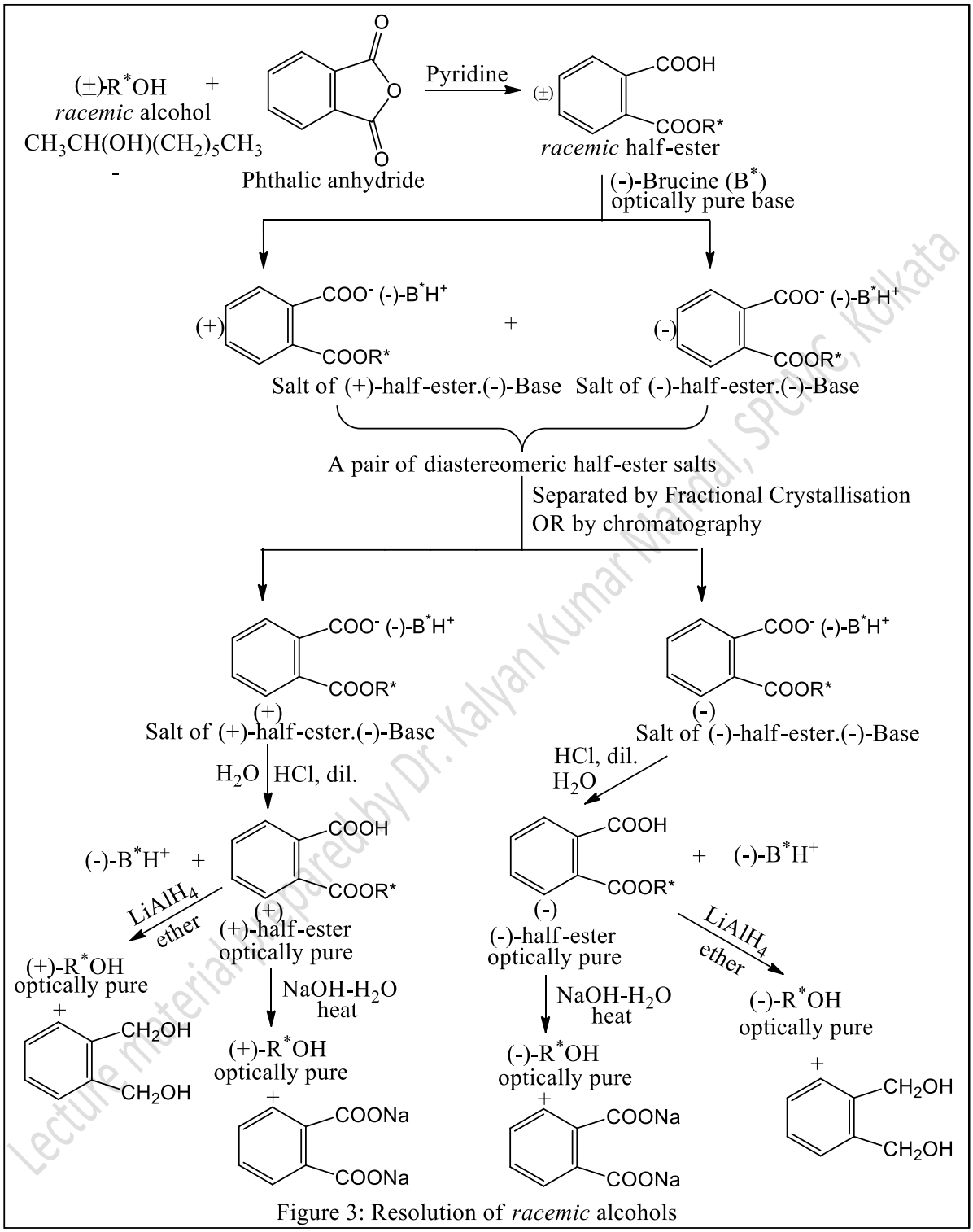


Figure 3: Resolution of *racemic* alcohols

Optical Purity

An optically pure compound is one, which is 100% one enantiomer. During synthesis of optically active compounds, it is often found that enantiomeric mixtures of different percentage composition have been produced. To express the enantiomeric composition of such a mixture, the term optical purity has been introduced. Optical purity of a *racemic* modification is zero. Optical purity (Op) of a *chiral* compound is expressed as the fraction or percentage ratio of the rotation observed and the maximum rotation (rotation of a pure enantiomer). Optical purity is also called enantiomeric excess (*ee*).

Optical purity: The absolute value of the ratio of the observed specific rotation of a sample made up only of two enantiomers to the corresponding specific rotation of one pure enantiomer, expressed as a percentage. For example, if one enantiomeric mixture is 30% optically pure with respect to d-form, then the rest 70% is a *racemic* modification. That is, % composition of this mixture is *d*-isomer = (30 + 35) % = 65% and *l*-isomer = 35%.

The specific rotation, [α], is highest for an enantiomerically pure compound and any contamination with the optical antipode lowers at, usually, proportionately. The ratio of the observed optical rotation of a sample consisting of a mixture of enantiomers to the optical rotation of one pure enantiomer, expressed as a percentage is the measure of the optical purity.

$$\% \text{ Optical Purity} = \frac{\text{Speccific rotation of enantiomeric mixture}}{\text{Speccific rotation of pure enantiomer}} \times 100$$

$$= \frac{[\alpha]_{obs}}{[\alpha]_{max}} \times 100$$

$[\alpha]_{max}$ indicates the specific rotation of pure enantiomer.

For example, let the *specific rotation* of an enantiomeric mixture is (+)-25° and that of pure enantiomer is (+)-50°, then the optical purity of the enantiomeric mixture is equal to 25°/50° x 100% = 50% with respect to (+)-enantiomer. This means that in the enantiomeric mixture, the excess of (+)-enantiomer is 50% and remaining 50% exists as *racemic modification*. Thus, the composition of enantiomeric mixture is, (+)-enantiomer = (50 + 25) % = 75% and (-)-enantiomer = (100 – 75) % = 25%. The mole-fraction of (+)-enantiomer to (-)-enantiomer = 75%: 25% = 3: 1

Enantiomeric Excess (*ee*)

In a mixture of a pure enantiomer (*d*- or *l*- / *R*- or *S*-) and a *racemat*e (*dl* or *RS*), enantiomeric excess is the percent excess of the enantiomer over the *racemate* and is considered to be the same as optical purity. Enantiomeric excess can be calculated from the expression:

$$ee = \frac{[\alpha]_{obs}}{[\alpha]_{max}} \times 100 = \frac{[d] - [l]}{[d] + [l]} \times 100 = \frac{[R] - [S]}{[R] + [S]} \times 100$$

Where [*d*] and [*l*] or [*R*] and [*S*] represent the mole fractions of the individual enantiomers *d*- and *l*- *or R- and S*- respectively so that [*d*] + [*l*] = 1 or [*R*] + [*S*] = 1. The % of *d*- and *l*- or *R*- and *S*-enantiomers can be calculated from the above equation as follows:

$$\% \text{ of } d\text{-enantiomer (or } l\text{-enantiomer)} = ee + \% \text{ of } l\text{-enantiomer (or } d\text{-enantiomer)}$$
$$= ee + 100 - \% \; d\text{-enantiomer (or } l\text{-enantiomer)}$$
$$= \frac{ee + 100}{2} \quad \text{(for the major enantiomer)}$$
$$\text{Similarly, } \% \text{ of } l\text{-enantiomer (or } d\text{-enantiomer)} = \frac{100 - ee}{2} \quad \text{(for the minor enantiomer)}$$

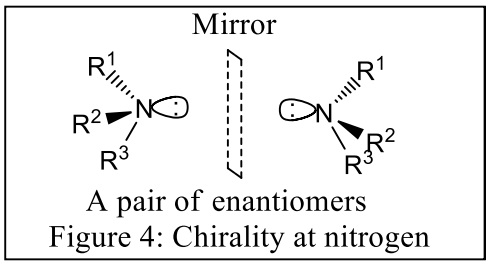
Problem on Optical Purity

Pure (-)-enantiomer of an optically active compound (X) has a specific rotation of $[\alpha]^{20}_{d}$ = -42.8°. What is the optical purity of a sample of X which shows a specific rotation of (-)-21.4°? How much of each enantiomer is present in the enantiomeric mixture?

Answer: 100% pure (-)-enantiomer has a specific rotation (-)- 42.8° and that of enantiomeric mixture is (-)-21.4°. Therefore, ee = (-21.4° / -42.8°) x 100% = 50% [with respect to (-)-enantiomer]. Therefore, (100 – 50) % = 50% of the mixture is *racemic*. Since, optical purity of the mixture is 50% with respect to (-)-enantiomer, enantiomeric mixture contains (50 + 25) % = 75% of the (-)-enantiomer and the remaining 25% of the (+)-enantiomer.

Invertomerism of *Chiral* Trialkylamines

Invertomer: Either of two conformers that interconvert by inversion at an atom possessing a nonbonding electron pair. Invertomerism is exhibited by a pair of non-resolvable enantiomers formed by inversion process. Although tertiary amines are pyramidal and structure of the type $R^1R^2R^3N$ are *chiral*, enantiomers cannot normally be resolved owing to rapid interconversion between them by inversion at the nitrogen. The frequency of inversion is found to about 10^{10} per second. Figures 4 illustrates the changes in invertomerism.



A pair of enantiomers
Figure 4: Chirality at nitrogen

Features

- The molecule "turns inside out".
- The process involves a rapid oscillation of the nitrogen atom and its substituent.
- The molecule passes through a planar transition state.
- Nitrogen inversion provides a low energy pathway for racemization, usually making *chiral* resolution impossible.
- Figure 5 shows the geometrical changes involve in invertomerism process.

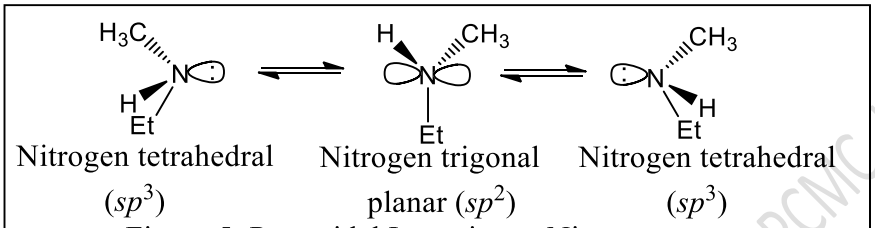


Figure 5: Pyramidal Inversion at Nitrogen atom

An amine such as ethyl methyl amine (illustrated in Figure 5) has a tetrahedral (sp^3) nitrogen atom and the nitrogen lone pair occupies an sp^3 orbital. However this tetrahedral amine structure is not static, rather the nitrogen atom inverts. The lone pair disappears from one face, moves through the nucleus, and reappears on the opposite face. Therefore, the lone pair is tunnelling through the nucleus. These structures are enantiomers but non-resolvable.

When Nitrogen is substituted by halogen, the barrier to N-inversion increases considerably and isolation of invertomers are possible. The inversion barrier also increases as the substituents become more electronegative. In certain cyclic compounds, this inversion can be slowed down sufficiently to allow the isolation of enantiomers.

N-Chloro-2-methylaziridine are separable as optically active enantiomers. The energy barrier for inversion is quite high (73 kJ mol^{-1}) because of highly strained transition state involving sp^2 nitrogen. Figure 6 shows different examples of *chiral* amines which are resolvable. The inversion process of the following *chiral* nitrogen compounds involves very high activation energy that makes the process extremely slow.

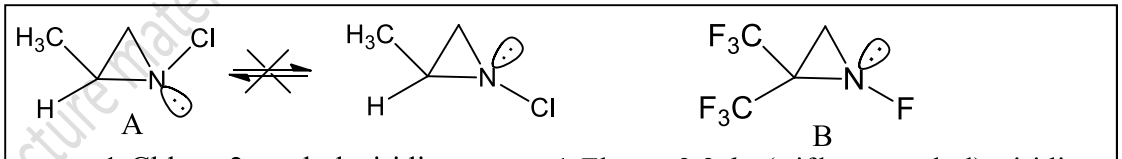


Figure 6: *Chiral* amines which are resolvable

The relatively high barrier of rotation for aziridine compounds (A; Figure 6) is due to a highly strained transition state involving an sp^2 hybridized nitrogen (for which the normal valency angle is 120°) constrained to an endocyclic bond angle of approximately 60°.

As the normal bond angle is increased in passing from three-membered to seven-membered heterocycles, the free energy of activation for N-inversion gradually decreases. Optical activity due to restricted rotation arises in case of certain substituted nitrogen compounds. Figure 7 shows a few nitrogen compounds where pyramidal inversion has been observed for compound A whereas for the other two (for B and C) this process is extremely slow making them resolvable into distinct entities.

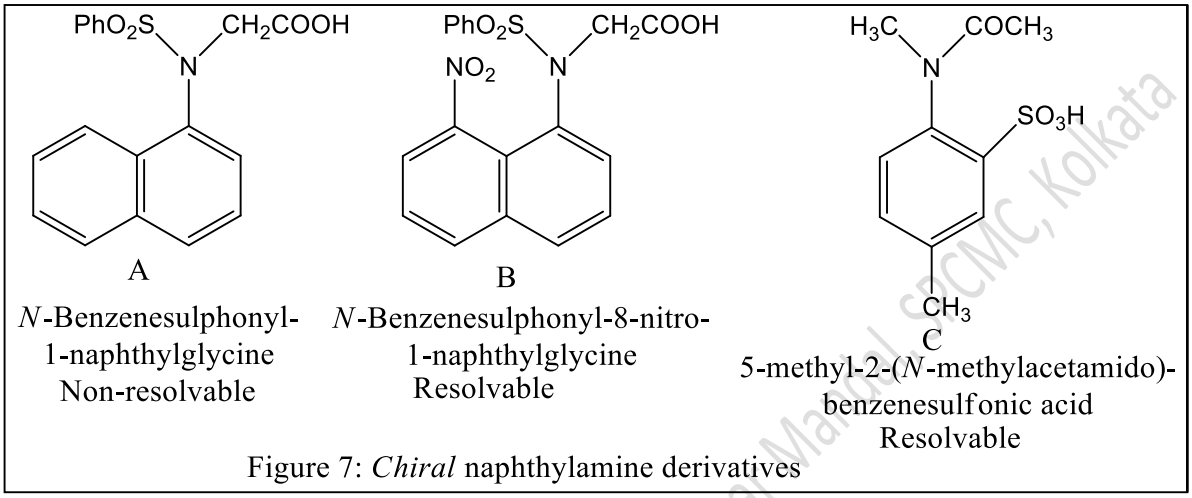


Figure 7: *Chiral* naphthylamine derivatives

In both compounds, B and C the optical activity arises from the restricted rotation about the C-N bond (the C being the ring carbon to which the N is attached). The groups attached to the amino nitrogen atom do not find room in the plane of the naphthalene nucleus and cannot readily pass through that plane. Compound A, on the other hand, is *chiral* but non-resolvable. Here, pyramidal inversion process is fast, and hence difficult to resolve.

Quaternary Ammonium Salts

For quaternary ammonium salts, $[N\mathit{abcd}]^{+}X^{-}$, if it is assumed that the charge on the nitrogen atom has no effect on the configuration of the cation, the cation can be considered as a five-point system similar to that of carbon in compounds of the type C*abcd*. If the cation is planar, it would not be resolvable. It would be resolvable, if the configuration is pyramidal or tetrahedral. Compounds such as A (Figure 8) and the related amine oxide (B) are thus resolvable into optically active enantiomers.

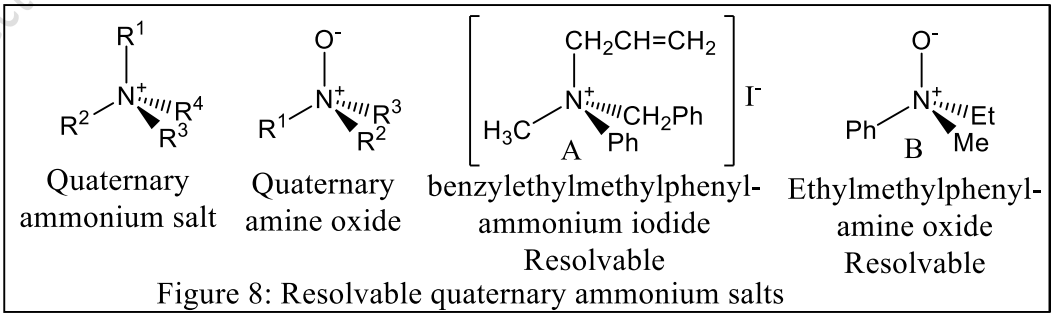


Figure 8: Resolvable quaternary ammonium salts