STEREOCHEMISTRY II

SEM-1, CC-1B
PART-11, PPT-11

Part-11: Racemization

CONTENTS

- *Racemic Compounds/Racemic Modifications*
- *Racemization*
- *Racemization through*

1. *Radical Intermediate formation (Thermal Racemization)*
2. *Cationic Intermediate formation*
3. *Anionic Intermediate formation*
4. *Reversible formation of Stable Inactive Intermediate*

Dr. Kalyan Kumar Mandal
Associate Professor
St. Paul's C. M. College
Kolkata

Stereochemistry (PART-11, PPT-11)

Racemization

***Racemic* Compounds/*Racemic* Modifications**

A mixture of equal parts of enantiomers is called a *racemic modification*. A *racemic modification* is optically inactive. When enantiomers are mixed together, the optical rotation caused by a molecule of one isomer is exactly cancelled by an equal and opposite rotation caused by a molecule of its enantiomer. The prefix ± is used to specify the *racemic* nature of the particular sample, as, for example, (±)-lactic acid or (±)-2-methyl-1-butanol.

A *racemic modification* or *racemate* is a 1:1 mixture of (+) and (-) enantiomers so that the overall optical rotation is zero. This corresponds to an enantiomeric excess of 0%, or an enantiomeric ratio of 1. As *racemate* is an equimolar mixture of a pair of enantiomers, it does not exhibit optical activity. *Racemates* are denoted by the symbol (±) or (*d*,*l*). The chemical name or formula of a *racemate* is distinguished from those of the enantiomers by the prefix (±)- or *rac*- (or *racem*) or by the symbols *RS* and *SR*.

***Racemic* Modifications**

The individual molecules of most substances are optically active if they are *dissymmetric* (although this statement has some doubtful operational significance as the optical activity of an individual molecule has never been observed and possibly never will be). Nevertheless, the substance in bulk may not be optically active, because it may be constituted of approximately equal numbers of *dextrorotatory* (+) and *levorotatory* (-) molecules so that the average rotation is zero.

Such an assembly of molecules, one half of which are mirror images of the other half, is called a *"racemic modification"* (the term *"dl"* is frequently used) and is denoted by the symbol (±). The term *"racemic modification"* evidently does not apply to individual molecules; rather it is a statistical concept which arises when large numbers of molecules are considered.

Racemization

Racemization (Pasteur, 1953) is the process of production of *racemic* modification (*racemate*) starting with one of the pure enantiomers. *Racemates* have the same constitutions as the pure enantiomers. Racemization involves the progressive loss of optical activity with time, usually in accord with a well-defined kinetic process. Since the two enantiomers have the same free energy, the equilibrium mixture will correspond to a 50-50 composition, i.e., it will be a *racemic modification*.

In practice, spectra of *racemic* and enantiomeric forms are indistinguishable, though in principle this will only be true at infinite dilution. In the solid state the difference between a *racemate* and one enantiomer has features in common with a large box filled with (a) pairs of

shoes and (b) left shoes only. Thus, the packing in the two instances is not the same. This is reflected in different melting points and densities of the *racemate* and either enantiomer; these properties are the same for the two enantiomers.

When equimolecular quantities of two enantiomers of a *chiral* molecule are mixed together or formed in a reaction, the resultant mixture is called a *racemic modification*. Since the differentiation of stereoisomers is made at the molecular level, *racemic modifications* do not really represent a separate class of stereoisomers although they differ from the corresponding pure enantiomers in certain physical properties especially in the solid state. In addition, they do not show any optical rotation, the rotation due to one enantiomer being exactly cancelled by an equal and opposite rotation of the other enantiomer (external compensation).

The difference in properties between a *racemic modification* and the corresponding pure enantiomer arises from the difference in the intermolecular associations which govern the molecular packing in the crystal lattice and the intermolecular association in the liquid state or in concentrated solution. The packing of stereoisomers of the same chirality, e.g., (+ +) or (- -) and of opposite chirality, e.g., (+ -) in two crystals would be different.

The two crystals are thus diastereomerically related and behave so as long as the intermolecular interactions are appreciable. Under this condition, they will have different physical and spectroscopic properties. In dilute solutions or in the gaseous form, the molecular species are usually well segregated, i.e., the intermolecular interactions become negligible and as a result, the differences in physical and spectroscopic properties between a *racemate* and the corresponding pure enantiomers are minimized (except for optical activity).

Racemic compounds, or *dl* pairs, arise from (a) mixing the enantiomers in a 1:1 molar ratio, (b) synthesis in the absence of a biassing influence that would cause one enantiomer to predominate, and (c) deliberate racemization of enantiomers by interconversion. It should be noted that on a molar basis a *racemate* is more stable than either enantiomer on account of the entropy of mixing. The entropy of mixing, $\Delta_{mix}S$, for the two enantiomers A and B present in equal amounts is given by equation (1):

$$\Delta_{mix}S = -nR(x_A \ln x_A + x_B \ln x_B) \text{ ---------- (1)}$$

where n = total number of moles present, and x_A and x_B represent the mole fractions of A and B. The contribution of the entropy of mixing to the free energy of mixing is given by equation (2):

$$T\Delta_{mix}S = -nRT(x_A \ln x_A + x_B \ln x_B) \text{ ----------(2)}$$

For n = 1, and $x_A = x_B = 0.5$ and a room temperature of 298 K, the entropy of mixing has the value of $\Delta_{mix}S = R \ln 2 = 5.77$ J mol^{-1} degree^{-1} and $T\Delta_{mix}S = 1.72$ kJ mol^{-1}. The entropy of mixing is thus a positive quantity. This is the amount by which a mole of *racemate* is more stable than a mole of either enantiomer. Conceptually, a *racemic* modification consisting of two molecular species corresponds to a more random or less orderly system than the enantiomeric form which consists of a single molecular species.

Formation of *Racemic* Modifications: By Mixing

The most obvious and trivial way of forming a *racemic modification* is by intimate mixing of exactly equal amount of the *dextrorotatory* (+) and *levorotatory* (-) isomers. This process is associated with an entropy of mixing, since *racemic modification* represents a more random state of affairs than the separate enantiomers.

In the case of *racemic modification*, $\Delta_{mix}S$ = -R ln1/2 = R ln2 = 1.4 cal. deg^{-1}. mol^{-1}. The free-energy in producing the *racemi*c modification from the enantiomers is, therefore $\Delta G = \Delta H - T\Delta S$ = -0.42 kcal mol^{-1} (1.72 kJ mol^{-1}) at room temperature (assuming that mixing is a thermoneutral process, i.e., ΔH = 0. This is certainly the case if ideal behavior is encountered). The entropy of mixing is positive because racemization by mixing (like any mixing) leads from a more ordered to a more random (or disordered) state.

This means that the conversion of pure enantiomers into the *racemic* modification-a process known as racemization-is thermodynamically favourable and a spontaneous process.

Formation of *Racemic* Modifications: By Synthesis

Any synthesis of dissymmetric molecules, starting from either symmetric molecules or a *racemic modification* and using no optically active reagents or catalysts and no asymmetric physical influence, always produces a *racemic modification*, i.e., an equal number of the two enantiomeric types of product molecules. This point may be looked at the two common ways of producing an asymmetric carbon in a molecule: by displacement and by addition.

The displacement method is exemplified by the bromination of propionic acid to α-bromopropionic acid by the Hell-Volhard-Zelinsky method (Figure 1). Since each of the two α-hydrogens bears the same relationship (In reality, the two relations are of the mirror-image type) to the other and to the rest of the molecule, each is replaced at the same rate as the other and equal numbers of (+) and (-) molecules of α-bromopropionic acid result.

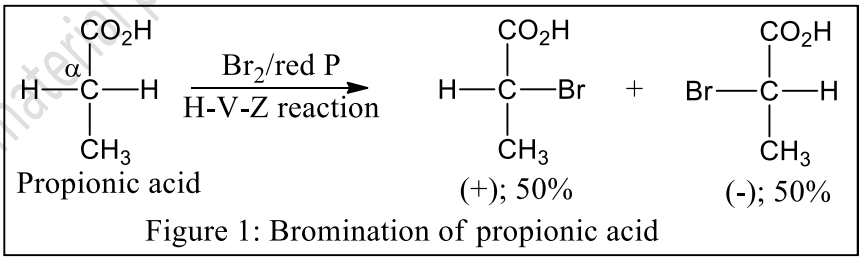


Figure 1: Bromination of propionic acid

Formation of *Racemic* Modifications: Racemization

Racemization is the process of producing a *racemic modification* starting with one of the pure enantiomers. Since the two enantiomers have the same free-energy, the equilibrium mixture will correspond to a 50-50 composition; i.e., it will be a *racemic modification*. Since the concentration of the pure enantiomer is reduced to one-half of its original value when

racemization occurs, the free-energy change associated with racemization is ΔG = RT in1/2 = -RT ln2.

It will be seen that this is equal to the free-energy change associated with forming a *racemic modification* by mixing. In mixing, one starts with equal amounts of the (+) and (-) forms, in racemization with either form by itself; however, this makes no difference to the free-energy change. Given that racemization is an energetically favoured process, the question remains whether a convenient pathway can be found for equilibrium to be established, or, in other words, whether the activation energy for interconversion of the enantiomers is prohibitively high or not.

Thermal Racemization: Through Radical Intermediates

One general method of racemizing an optically active material is by breaking, temporarily, one of the four bonds to an asymmetric carbon. If, in the subsequent re-formation of the bond, the group separated exchanges places with one of the remaining groups, the dissymmetric molecule is converted to its enantiomer. Therefore, this process involves the formation of a *racemic* modification from a pure enantiomer.

If the bond is to be broken homolytically, i.e., in such a way that one of the electrons of the bond stays with carbon and the other with the group separated, considerable energy (namely, that equivalent to the bond-dissociation energy) must be expanded and high temperatures are required. The racemization of a α-phenethyl chloride, $PhCH(Cl)CH_3$, upon distillation at atmospheric pressure may be of this type. This process passes through the formation of a carbon free-radical as reactive intermediate.

The homolytic cleavage of C-Cl bond of α-phenethyl chloride (A; Figure 2) leads to the formation of a resonance stabilized benzylic radical (B). Recombination of the *achiral* carbon free-radical intermediate with the hydrogen radical then gives *racemic modification*. There is loss of asymmetry on going from optically active α-phenethyl chloride to the intermediate radical (B) which is enantiotopic. Therefore, recombination can take place from both faces of the planar radical intermediate (B) giving a 1:1 mixture of the starting compound and its enantiomer. Figure 2 illustrates the thermal racemization process.

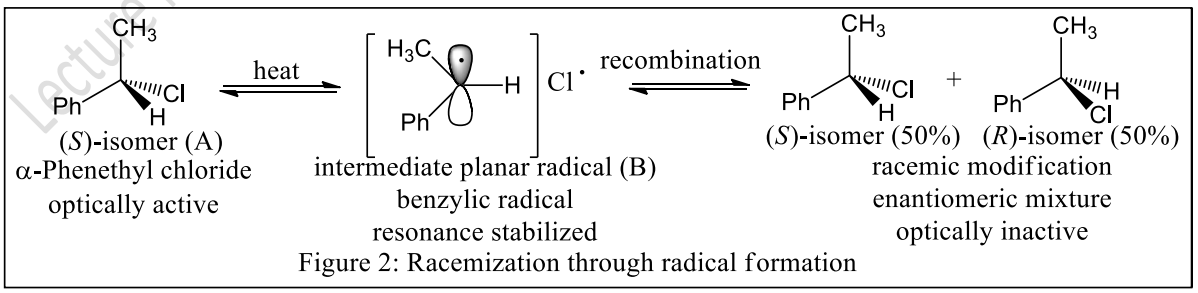


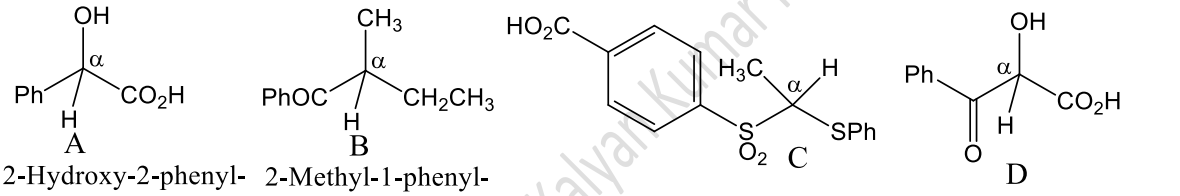
Figure 2: Racemization through radical formation

Base Catalyzed Racemization: Racemization through the Anionic Intermediate

The process of racemization involving anion formation occurs with heterolytic cleavage. The process involves the temporary separation of a mildly acidic hydrogen. The base used to remove the proton is, in most cases, methoxide or ethoxide. Only those compounds (A-D in Figure 3) having an acidic hydrogen attached to the *asymmetric carbon* are racemized by base.

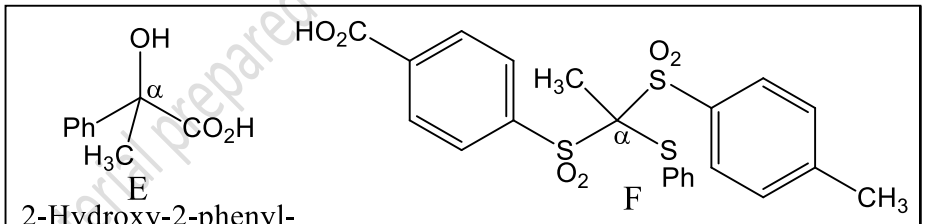
The more labile and acidic the hydrogen, the greater, in general, is the ease of racemization. Where there is no acidic hydrogen attached to the asymmetric carbon (E and F; Figure 4) no base-catalyzed racemization occurs. Atrolactic acid (E) does not undergo racemization in presence of base. In this case, carbanion formation is not possible due to the absence of acidic hydrogen on *chiral* centre. The hydrogen on the *asymmetric carbon* in the disulphone (F; Figure 5) is so acidic and the compound is therefore converted to the carbanion so readily that all attempts to resolving it have failed.

Base Catalyzed Racemization



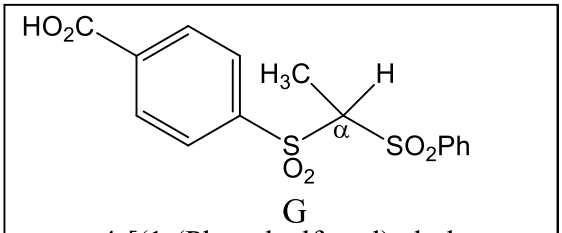
2-Hydroxy-2-phenyl-acetic acid (Mandelic acid) | 2-Methyl-1-phenyl-butan-1-one | 4-[(1-(Phenylthio)ethyl-sulfonyl]benzoic acid | 2-Benzoylpropanoic acid

Figure 3: Compounds undergoing base-catalyzed racemization



2-Hydroxy-2-phenyl-propanoic acid (Atrolactic acid) | 4-[(1-(Phenylthio)-1-tosylethyl-sulfonyl]benzoic acid

Figure 4: Compounds does not undergo base-catalyzed racemization



4-[(1-(Phenylsulfonyl)ethyl-sulfonyl]benzoic acid

Figure 5: Compound failed to resolve

Base Catalyzed Racemization: Racemization through the Anionic Intermediate

Racemization by base involves the carbanion as reactive intermediate. It was shown that the rate of racemization of optically active phenyl *sec*-butyl ketone (A; Figure 6) in dioxan-D_2O medium using NaOD as base was equal to the rate of deuterium exchange. It is important to note that the rate of racemization by sodium acetate is equal to the rate of bromination in the presence of same catalyst.

These observations are rationalized readily by assuming that all three base-catalyzed processes (racemization, deuterium-exchange, and halogenation) proceed through a common intermediate-an anion (carbanion or enolate ion) which is formed in a *rate-determining step*. Figure 6 illustrates the mechanism of racemization as well as deuteration under base-catalyzed conditions. The enolate ion intermediate has enantiotopic faces, hence protonation/deuteration occurs from both the faces with equal readiness.

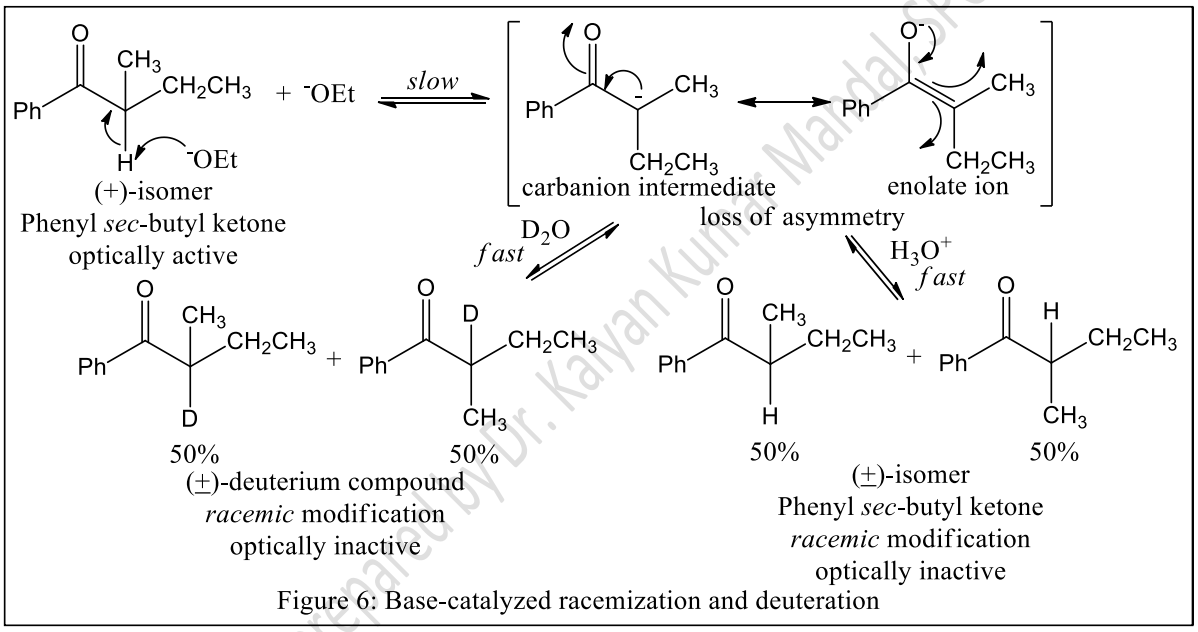
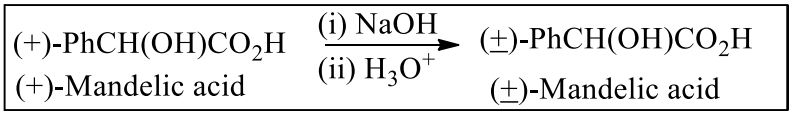


Figure 6: Base-catalyzed racemization and deuteration

If an acidic hydrogen is bonded to a *chiral* centre, adjacent to a π-electron system, then racemization may be achieved through carbanion formation. The hydrogen is lost as proton (H^+) being promoted by base. Carbanion undergoes delocalization with an adjacent π-electron system so that parent *chiral* carbon can become planar at an intermediate form. Recombination of the *achiral* intermediate with the proton then gives *racemic modification*.



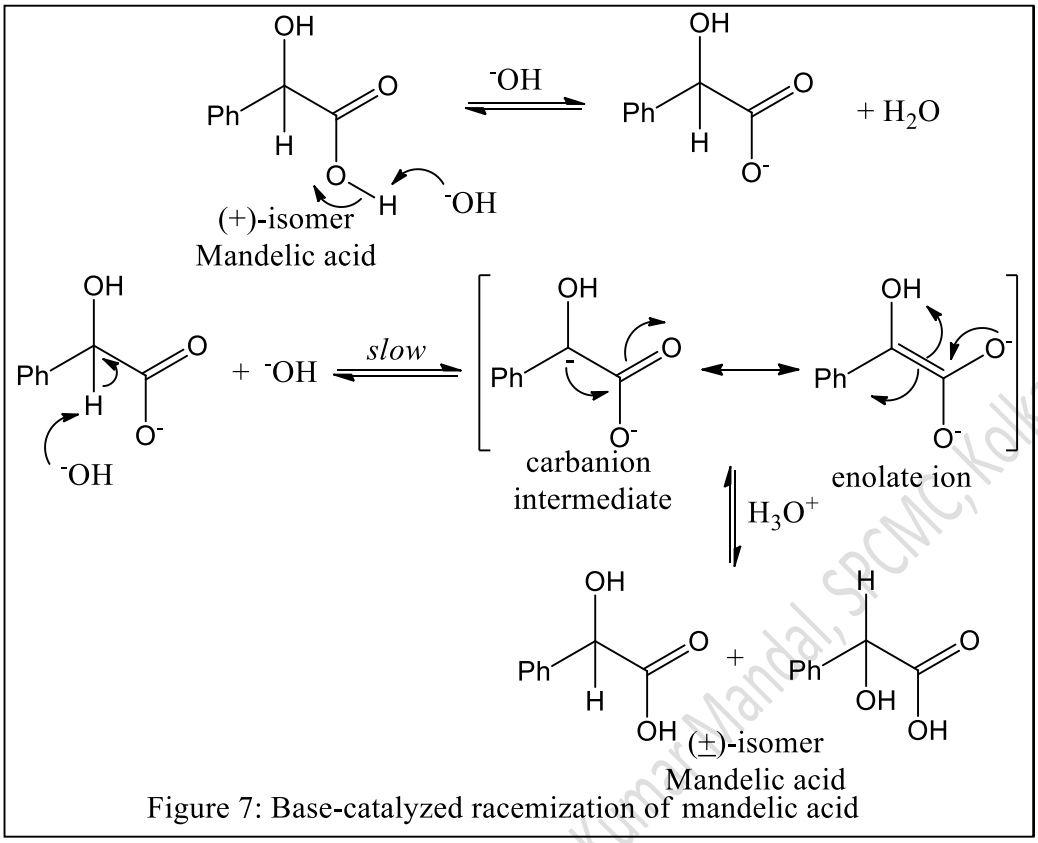


Figure 7: Base-catalyzed racemization of mandelic acid

Acid Catalyzed Racemization: Racemization through the Cationic Intermediate

Aldehydes or ketones containing acidic hydrogen atom(s) on the asymmetric carbon atom (α- to the carbonyl group) readily undergo racemization in presence of acid. Since the α-hydrogen of these compounds are acidic, they undergo tautomeric change to form an *enol* readily in presence of acid. Phenyl *sec*-butyl ketone (A; Figure 8) undergoes racemization under this condition. The *enol* (B) of the optically active phenyl *sec*-butyl ketone is optically inactive, but opposite faces of this *enol* are enantiotopic. Therefore, recombination with proton gives a mixture of compounds in equal amounts which are enantiomeric to each other.

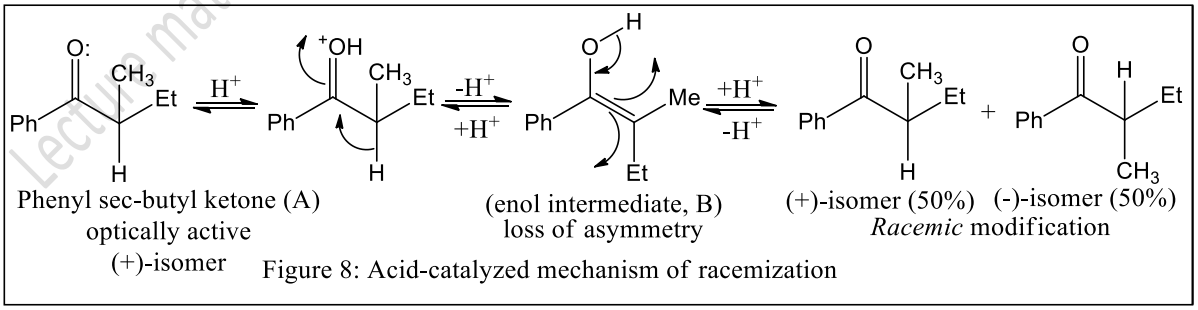


Figure 8: Acid-catalyzed mechanism of racemization

Another way of bringing about racemization by the cationic intermediate is explained in Figure 9. Usually, this type of racemization is brought about by a Lewis acid which the leaving group.

Examples are the racemization of α-phenethyl chloride by means of antimony pentachloride ($SbCl_5$). Mercuric chloride, zinc chloride, and stannic chloride are also effective catalysis for the racemization of α-phenethyl chloride. Racemization of α-phenethyl chloride in presence of antimony pentachloride ($SbCl_5$) can be achieved through the formation of a planar benzylic type carbocation (*achiral*) by the heterolytic cleavage of a ligand attached to the *chiral* carbon. The ligand must be a good leaving group.

The Lewis acid abstracts the leaving group and facilitates the formation of the carbocation. In the given example, carbocation formation is also facilitated because benzylic carbocation is considerably resonance stabilized. Since carbon atom of carbocation is sp^2 hybridized, it is planar and can recombine with the ligand from either of the two enantiotopic faces of the planar carbocation with equal probability to form both the enantiomers in equal quantities.

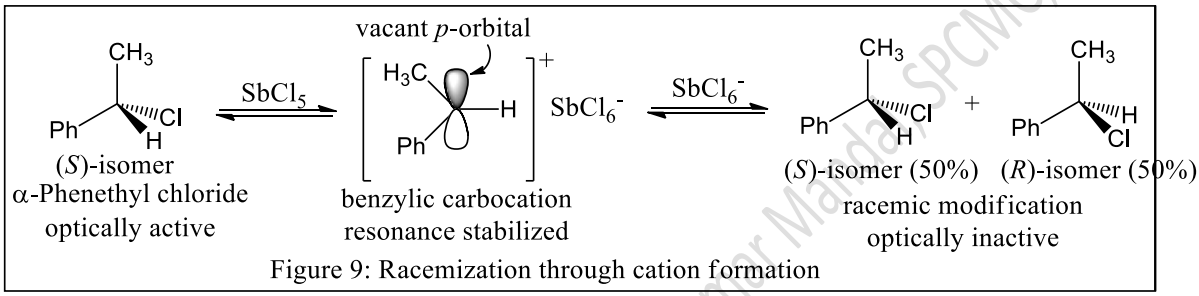


Figure 9: Racemization through cation formation

Racemization through the Reversible Formation of Stable Inactive Intermediate

The carbocations and the carbanions involved in the racemization processes so far are true intermediates but of very short half-life. In contrast, the following example will be concerned with the reversible formation of symmetric intermediates which are stable entities in their own right. An example of such type is the racemization of α-phenethyl chloride upon dissolution in liquid sulphur dioxide or formic acid. This has been shown to proceed by a dehydrohalogenation-hydrohalogenation process (Figure 10).

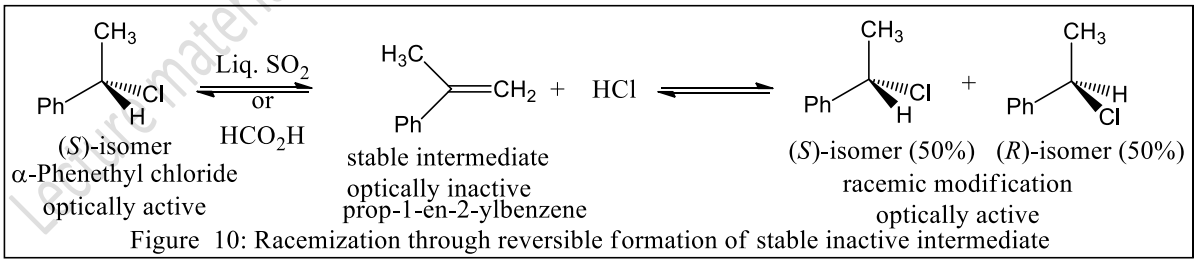


Figure 10: Racemization through reversible formation of stable inactive intermediate