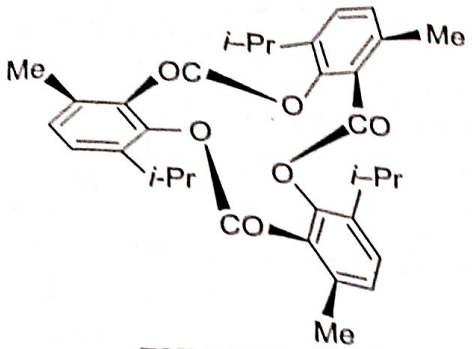


TOT (tri-O-Thymotide)

TOT (tri-O-Thymotide) is racemic when guest free. In the presence of a guest it forms clathrate inclusion complexes which are conglomerates, with TOT as (P)-(+)-right handed propeller or (M)-(–)-left handed propeller.

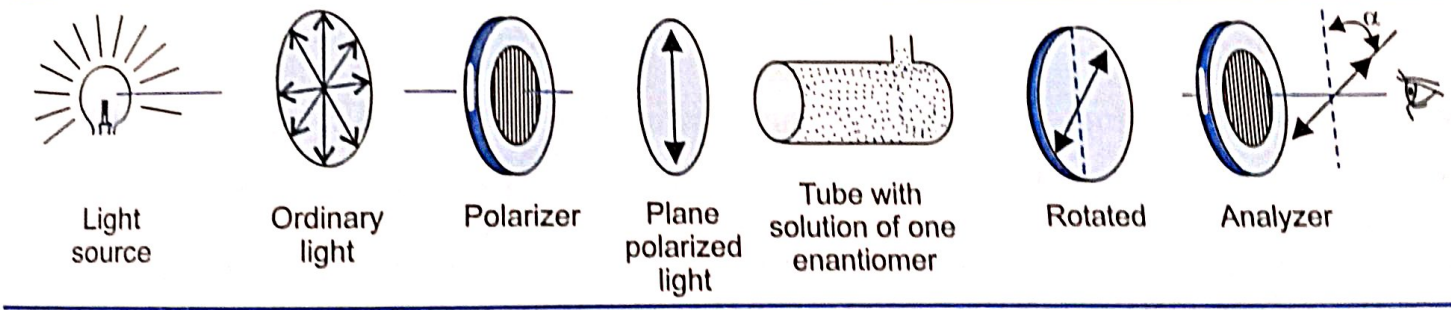
SCHEME 1.86d

(iv) Other methods of resolution

Optically active diisopinocamphenyl borane (see scheme 2.39) can be used to resolve racemic olefins. The reagent adds to one enantiomer and the other is unchanged. Chiral allylic alcohols have been resolved with chiral epoxidizing agents made from tartarate complexes of titanium (see scheme 2.52). One enantiomer is epoxidized while the other remains unchanged.

1.10A MEASUREMENT OF OPTICAL ACTIVITY

Light is a wave phenomenon in which vibrations take place at right angles to the direction in which the light travels. Infinite number of planes pass through the line of propagation and in ordinary light vibration take place in all these planes. Plane polarized light is light in which vibrations take place in only one plane, and this is realised by passing ordinary light through a polarizer which forms an important component of a polarimeter (Fig. 1.3). Plane polarized



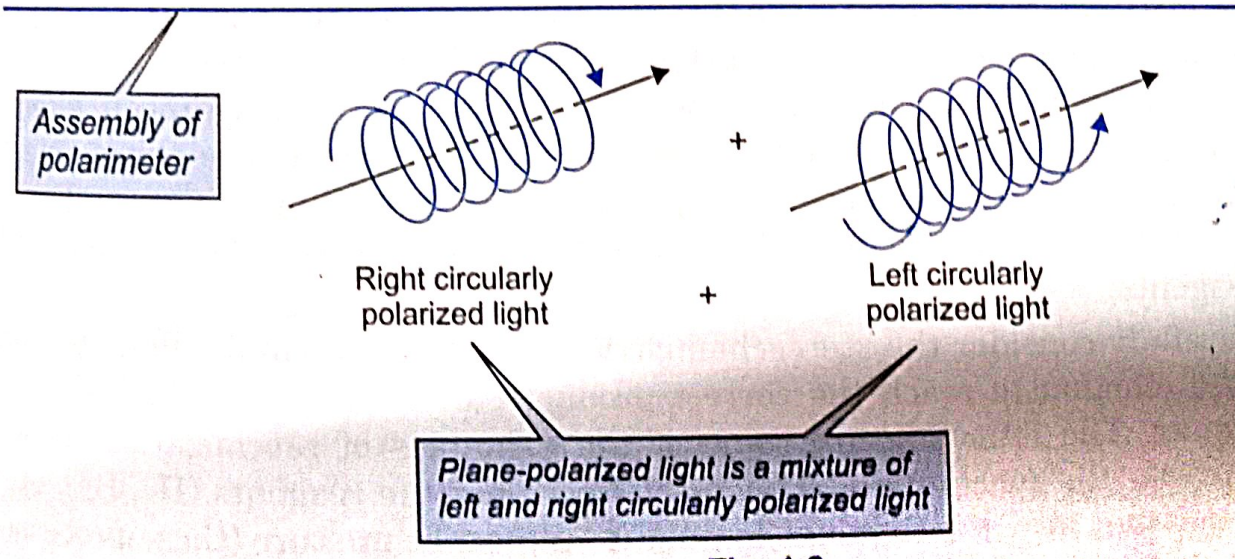


Fig. 1.3

light is a vector sum of left and right circularly polarised light, which propagates through space as left and right handed helices. These two forms of light represent two enantiomers, and therefore, the two enantiomers of a compound interact with it in opposite ways.

An optically active compound is one which rotates the plane of polarized light. An optically active substance which rotates the plane-polarized light to the right (clock-wise) is said to be dextrorotatory often abbreviated by the letter *d*, and its optical rotation is given a (+) sign. A substance is said to be levorotatory (often abbreviated by the letter *l*) if it rotates plane-polarized light to the left (counter-clockwise), and its optical rotation is given a (−) sign.

Optical rotation is a function of concentration, sample thickness, temperature, wavelength of polarized light, etc. It is usually recorded in the literature in terms of specific rotation $[\alpha]_\lambda^t$.

where t = temperature measurement in °C
λ = wavelength of polarized light
(usually sodium D line, 5893 Å)
α = observed angle of rotation in degrees
l = sample thickness in decimeters
c = concentration of solution in g/100 ml

1.11 RACEMIC MIXTURE AND RACEMIZATION

Recemic mixture or a recemate is an equimolar mixture of two enantiomers. Since a recemic mixture contains equal numbers of *dextrorotating* and *levorotating* molecules, the net optical rotation is zero. A racemic mixture is often symbolized by (±) or (*dl*).

The process whereby a pure enantiomer is converted into a racemic mixture is called racemization. Racemization may be accomplished in a trivial sense by simply mixing equal amounts of two pure enantiomers. Racemization may also result from the following chemical interconversions.

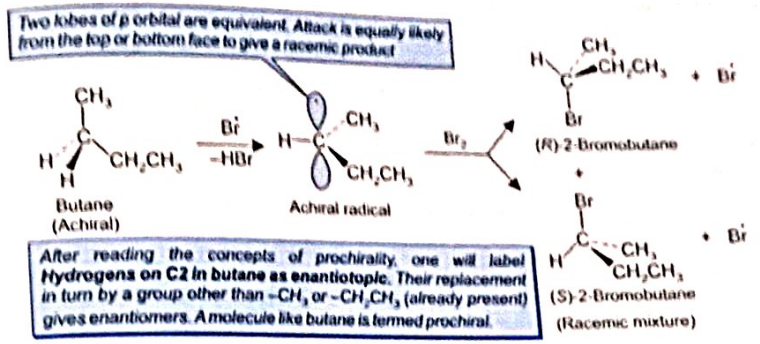
(A) Formation of Enantiomers (Recemization During Reactions That Create Stereocenters)

Several organic reactions can yield a chiral product from an achiral starting material. Thus the addition of hydrogen to the carbon-oxygen double bond of 2-butanone (achiral compound) in the presence of a catalyst creates a stereocenter. The two enantiomers of 2-butanol (achiral compound) however, are produced in equal amounts—the product is racemic (see, Scheme 1.85). The hydrogen has exactly an equal chance of attacking above or below the plane of the double bond in 2-butanone molecule (see, scheme 2.16). There is no reason why the hydrogen should prefer one approach over the other ; as long as there is nothing else that is chiral in the reaction, the enantiomeric products are formed in equal amounts. According to a general principle optically active products cannot be formed when optically inactive substances react with optically inactive reagents.

One should carefully consider the stereochemistry of the reactants and follow through the mechanism of the reaction to reach the correct products. One may focus the step that creates the stereocenter. The following are some of the examples of racemization during reactions in which neither the reactants (C=O, C=C, C^+ etc.) nor the reagents (H_2, Br_2, etc.) are chiral. Addition to either face is equivalent to produce a racemic mixture (these processes are described as having no enantioselectivity).

(*i*) Mechanism Involving a Radical Intermediate—Bromination of Butane

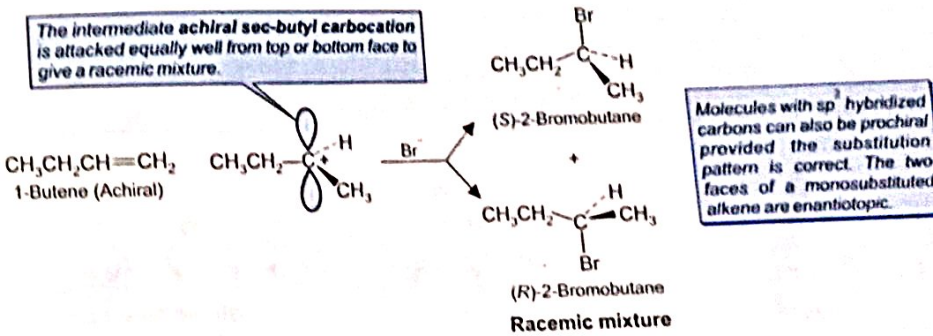
The radical bromination of butane (achiral molecule) at C2 yields a chiral molecule (scheme 1.87), however, the product is obtained in a racemic form. Abstraction of either methylene hydrogen at C2 by bromine gives an achiral radical. Reaction of Br_2 with this radical is equally likely at either the top or the bottom face, a situation which gives a racemic mixture of products (the C2 hydrogens are enantiotopic).



SCHEME 1.87

(*ii*) Mechanism Involving a Carbocation—Addition of HBr to 1-Butene

This addition proceeds via the intermediate formation of a planar carbocation (scheme 1.88) to give again a racemic mixture of products.

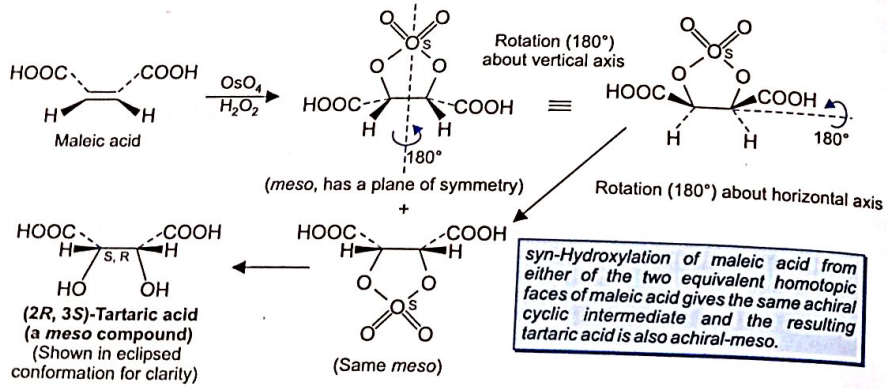


SCHEME 1.88

(*iii*) Mechanisms Involving Stable Cyclic Intermediates—Syn Addition to Diastereomeric Substrates

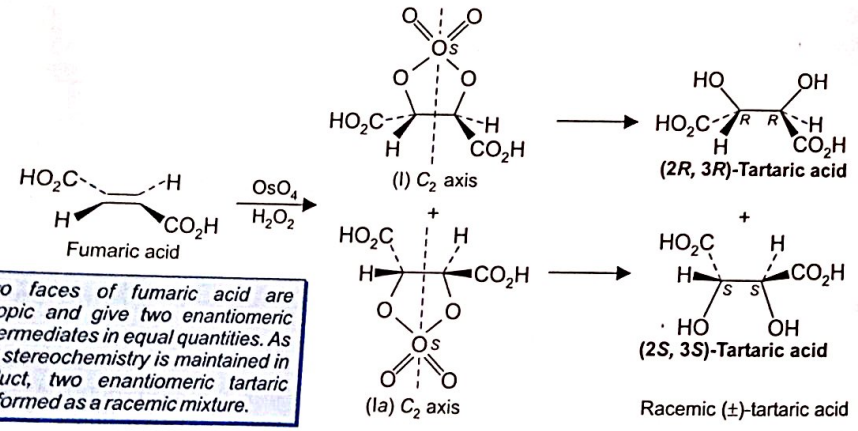
The *syn*-hydroxylation of maleic acid gives *meso* tartaric acid [see, scheme 1.40 where att
from one face is shown, the attack from the other face of the double bond is equally poss
and takes place, to give again the same *meso* tartaric acid (the two faces of maleic acid
equivalent *i.e.*, homotopic)]. Infact the *syn*-hydroxylation proceeds through the cyclic osn

ester which in the case of maleic acid (scheme 1.89) is achiral having a σ plane. Attack on either face of the double bond in maleic acid gives the same achiral intermediate. Its decomposition directly leads to the product and thus the resulting tartaric acid must also be achiral *i.e., meso*. Fumaric acid on the other hand can give two enantiomeric cyclic intermediates (I and Ia, with C_2 axis scheme 1.90) in equal amounts and since the stereochemistry is again maintained in the product, the tartaric acid thus obtained is chiral but in the form of a racemic mixture of two optically active enantiomeric forms.



SCHEME 1.89

This result may well be compared with e.g., bromination of E-and Z-2-butenes where a Z alkene gives a racemic mixture while the E isomer gives the meso compound, this being the result of anti addition (see scheme 1.100). During syn hydroxylation, the initial geometry of the alkene is maintained in the product, during bromination it is maintained up to the formation of bromonium ion only and disturbed during its S_N2 opening of the bromonium ion.



SCHEME 1.90

(B) Racemization from One Enantiomer

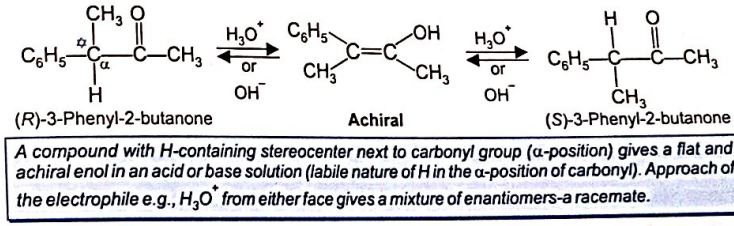
(a) By Rotation About a Single Bond

The biphenyls and related compounds, in which optical activity is due to the restriction of rotation about a single bond, racemize when enough thermal energy is employed for the energy barrier between the enantiomers to be surmounted at a practicable rate (see Scheme 1.118). Amine inversion is yet another example of recemization.

Cyclic compounds which exist in enantiomeric conformations *e.g.*, *cis*-1, 2-dimethyl-cychlohexane (see Scheme 4.33) undergo racemization *via* ring inversion and apparently do not involve any achiral intermediate or transition state.

(b) Via an Enol or Enolate Anion

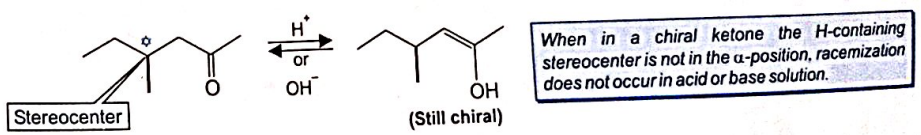
Racemization occurs in those compounds, in which a carbonyl function is attached to a stereocenter that also carries a hydrogen. When (*R*)-3-phenyl-2-butanone is dissolved in aqueous ethanol that contains NaOH or HCl, the optical rotation of the solution gradually drops to zero, to yield a racemic mixture of the (*R*) and (*S*) enantiomers (scheme 1.91). This rate of racemization is found to be proportional to the concentration of ketone and the concentration of NaOH or HCl. Racemization thus, occurs by way of the intermediate enol form in which the former stereogenic carbon becomes planar (achiral). As racemization involves the formation of the enol form, the rates of racemization and enolization are found to be exactly equal.



Rate = k[Ketone][H^+] or k'[Ketone][OH^-]

SCHEME 1.91

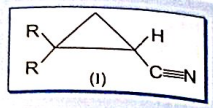
Racemization of an optically active ketone occurs only if the stereocenter is α to the carbonyl group. If the aldehyde or ketone is chiral because of asymmetry at some other carbon, the enol form is also chiral, enolization in such a case does not lead to racemization (scheme 1.92).



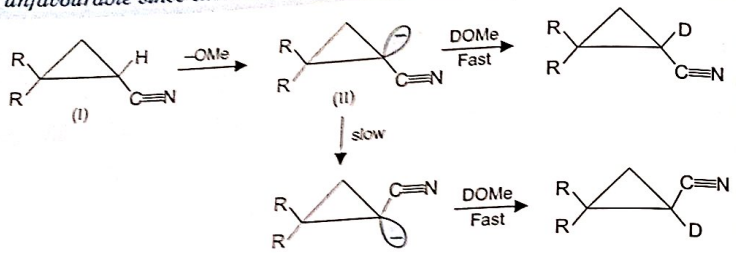
SCHEME 1.92

EXERCISE 1.14

Groups others than the carbonyl group also activate the adjacent protons which are easily removed by base, examples are nitro compounds, sulfones and nitriles. Thus the optically active nitrile (I) is expected to racemize when treated with base. However, (I) undergoes deuterium exchange 4000 times faster than it racemizes on treatment with sodium methoxide in deuteriomethanol. Explain.

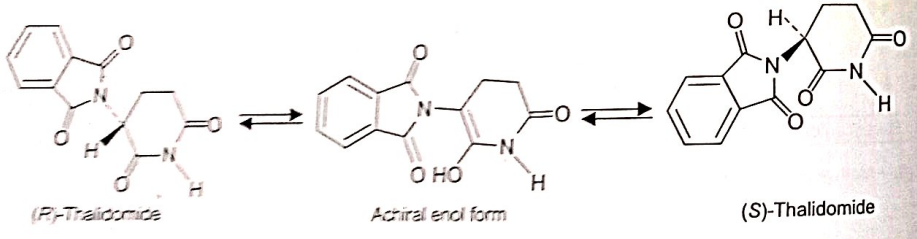


ANSWER. *The inversion of carbanion (II) formed by the abstraction of a proton from the position adjacent to the nitrile group with base is difficult since the nitrile group has to become coplanar with the cyclopropane ring and this flipping process is unfavourable since excessive strain energy will be involved. (scheme 1.92a)*



SCHEME 1.92a

Racemization is often a facile process which is troublesome as well as it has nuisance value. The presence of both the enantiomers of thalidomide in a drug formulation led to birth defects in the children of some women who took the substance during pregnancy. Even if the pure (*R*) form was given to patients, the mutagenic (*S*)-isomer was formed by racemization under physiological conditions because the stereocenter is α to a carbonyl group (scheme 1.93). Similarly amino acids can undergo racemization due to the presence of a stereocenter α to the carbonyl group in these compounds. In proteins, the peptide bonds render this structural feature prone to racemization, however, it does not occur under physiological conditions.

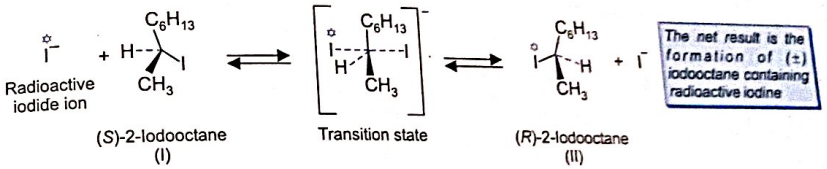


SCHEME 1.93

(C) By Substitution Reactions

(*i*) S_N2 reactions

Normally in an S_N2 reaction the incoming nucleophile (*e.g.*, OH^- in scheme 1.28*e*, eq. I) initiates the reaction from the back while Br^- leaves the molecule from the front in a concerted process. The stereocenter, thus undergoes an inversion of configuration with respect to the stereochemistry of substrate. In case the incoming nucleophile and the out going leaving group are same as in the case of reaction of optically active 2-iodoctane (Scheme 1.94) with sodium iodide, the reaction becomes reversible and an equilibrium is set up between the two enantiomers (I and II, scheme 1.94) leading to racemization. Conclusive proof that inversion of configuration occurs during an S_N2 reaction was provided by studying the reaction between optically active 2-iodooctane and radioactive iodide ions. This is one of the simplest possible types of bimolecular substitution reacton, and involves replacement of iodide ions by radioactive iodide ions so that product and starting material are chemically identical. The process also involves inversion of configuration, and is thus accompanied by a loss of optical activity. It was seen that the rate of loss of optical activity is twice the rate of incorporation of radioactive iodide ions [*i.e.*, the inversion rate is half the rate of racemization since for every pair of S isomers only one is inverted to give the racemate].



(Racemization via an S_N2 reaction)

SCHEME 1.94

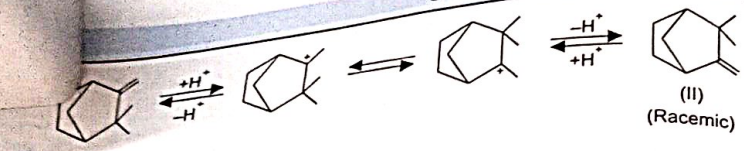
In case the process involved an achiral intermediate, like a carbocation, the rate of racemization will be equal to the rate of incorporation of radioactivity. On the another hand, in an S_N2 reaction every substitution (eq. I, scheme 1.28*e*) involves inversion. Racemization is, therefore, complete when half of the material gets inverted (and has incorporated radioactivity) so that the rate of racemization is twice the rate of incorporation of radioactivity. This experiment provides the most convincing proof to date that an S_N2 reaction is accompanied by inversion of configuration.

(*ii*) S_N1 reaction

Although many S_N1 reactions proceed with racemization, many others result in more inversion of configuration in the product than retention. This is due to initial ion pair formation where the leaving group blocks the front side of the carbocation to favour inversion. It is only when the leaving group diffuses away leaving the carbocation in free form that the nucleophile can attack equally well from either side to result in equal amounts of inversion and retention (see scheme 3.37).

(*iii*) During a molecular rearrangement

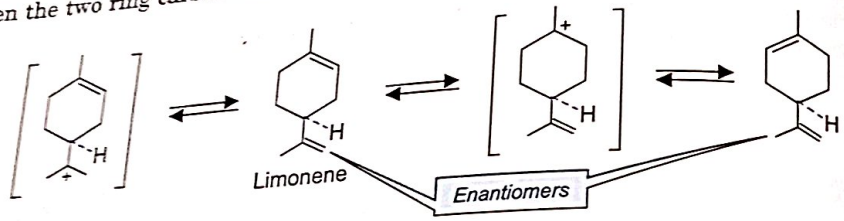
Optically active monoterpenoid camphene undergoes racemization on treatment with acid. The reaction of (I, scheme 1.95) with a proton leads to the formation of a carbocation which undergoes a methyl shift with its bonding pair of electrons to give another carbocation, the loss of a proton gives (II) which is the mirror image of (I, scheme 1.95).



Racemization of monoterpenoid camphene on treatment with acid

SCHEME 1.95

Another example is in the racemization of limonene on treatment with an acid (scheme 1.96). This also is a protonation deprotonation reaction. One may note that during protonation of endocyclic double bond the cation becomes achiral, consequently the distinction between the two ring carbon substituents is lost (scheme 1.96).



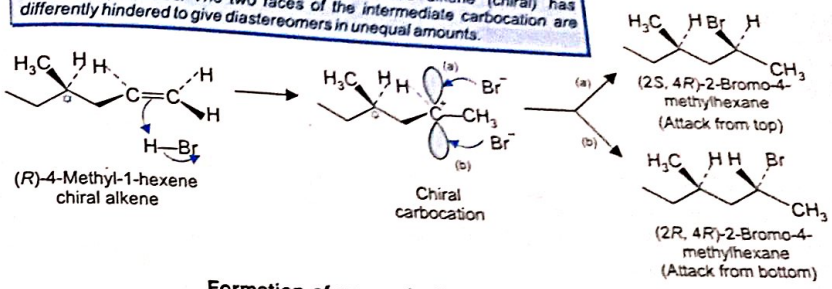
SCHEME 1.96

1.12 SOME STEREOCHEMICAL REACTIONS NEAR A STEREOCENTER (FORMATION OF DIASTEREOMERS)

Several reactions *e.g.*, electrophilic addition of HBr to monosubstituted alkene (see, scheme 1.88, achiral reactants) or the radical bromination of butane at C2 (see, scheme 1.87) introduce chirality in the molecule, however, the product obtained is racemic. In these reactions a planar sp^2 hybridized and therefore, achiral intermediates (a carbocation and a radical respectively) are formed. The two faces are equally susceptible to attack on two equivalent reaction sites to result in racemic products.

The presence of a stereocenter in the starting substrate affects the outcome of the reaction to give an unequal mixture of product diastereomers. Thus the addition of HBr to (*R*) enantiomer of 4-methyl-1-hexene proceeds through a carbocation (scheme 1.97).

Unlike a monosubstituted alkene, e.g. but-1-ene which has two enantiotopic faces (see, scheme 1.88), this monosubstituted alkene (chiral) has diastereotopic faces. The two faces of the intermediate carbocation are differently hindered to give diastereomers in unequal amounts.

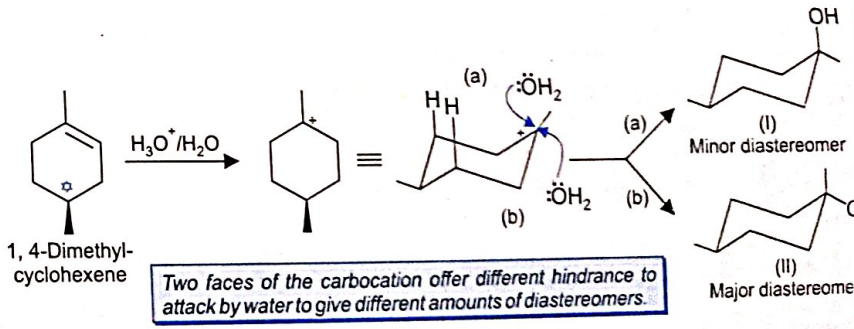


Formation of unequal mixture of diastereomers

SCHEME 1.97

Because there is a stereocenter in the carbocation intermediate, it is a chiral speci and therefore, it does not have a plane of symmetry. One face of the carbocation will be mo sterically hindered than the other, the incoming bromide ion will therefore, have greater cess to the less sterically hindered face. As a result of this the two diastereomers will formed in unequal amounts. The reaction is termed as stereoselective since more of stereoisomer is formed than the other, however, precisely this is a diastereoselective reac since the stereoisomer produced in excess is a diastereomer (for further details see u asymmetric synthesis—also see schemes (1.105–1.107). The reaction (scheme 1.97) crea new stereocenter, thus two stereoisomers are formed. These stereoisomers are diastereois since, one of the stereocenters (initially present) has the same configuration in both other (newly created) has the opposite configuration. This also is the basis of Crams r addition to diastereotopic ketones (see, scheme 2.23b).

During acid catalyzed addition of water to 1, 4-dimethyl-cyclohexene (the pres a stereocenter) the two faces of the intermediate carbocation are not identical (schem Attack of water from the axial direction is hindered by the two axial hydrogen atom



SCHEME 1.98

therefore, slower to give the minor diastereomer (I, scheme 1.98) and the addition of the equatorial face dominates and the major product is the diasteromer (II, sche where the hydroxyl group is *trans* to the methyl group at C4. Both the diastereoiso achiral (plane of symmetry).