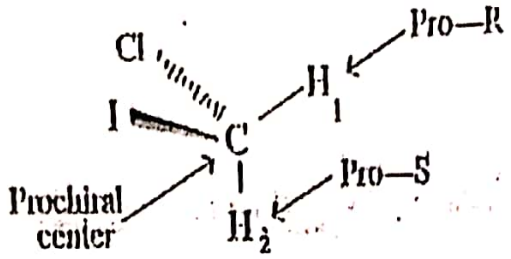
Q. 13. (a) What are equivalent (homotopic) groups ?

(b) Define a prochiral center ? How the hydrogens or any other ligands attached to a prochiral centre are designated ?

Ans. (a) Atoms (including H's) or group of atoms that can be interchanged by an axis of rotation C_n $(\infty > n > 1)$, analogous to homotopic or equivalent hydrogen atoms but generalized to cover other atoms. In cis-dichloroethylene one has the following group of equivalent atoms—2 H's, 2 Cl's, 2 C's 2 CHCl's i.e. in (Z)-dichloro ethylene, all the like atoms and groups are homotopic.

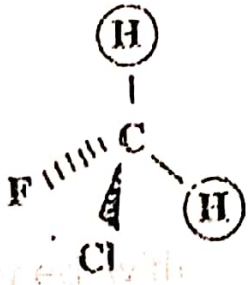
(b) When a centre in a molecule bears enantiotopic atoms or groups *i.e.*, ligands, the centre is said to be prochiral, i.e, when a molecule contains enantiotopic ligands it is termed prochiral and vice versa.



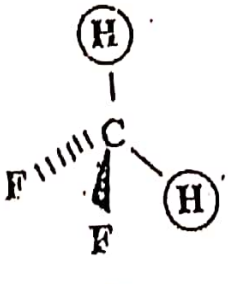
Chloroiodomethane
Prochirality

Enantiotopic ligands can be specified by the modified application of the (R, S) system. The ligand to be labelled is arbitrarily assigned a higher priority over the other. The sequence rules are than applied in the usual way. A clockwise path demands that the ligand should be labelled pro-R and an anticlockwise path specifies it as pro-S. The application of these rules to ICH_2Cl gives H_1 as pro-R (H_2 lowest priority with $I > Cl > H_2$) and H_2 as pro-S.

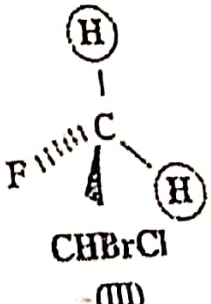
Q. 15. (a) Characterize the protons encircled in compounds as being stereohomotopic, enantiotopic or diastereotopic—



(I)



(II)



(III)

Page No.

(b) How enantiotopic and diastereotopic faces are named?

Ans. (a) Compound (I) The protons are enantiotopic. Replacement of one of the enantiotopic atoms by another ligand affords enantiomeric molecules.

Compound (II) The protons are homotopic.

Compound (III) –The protons are diastereotopic. There is a chiral centre already present in this compound. In a prochiral assembly CX_2WY, X atoms or groups are diastereotopic if either W or Y is chiral.

(b) These faces can be named by an extension of the Cahn-Ingold Prelog rule.

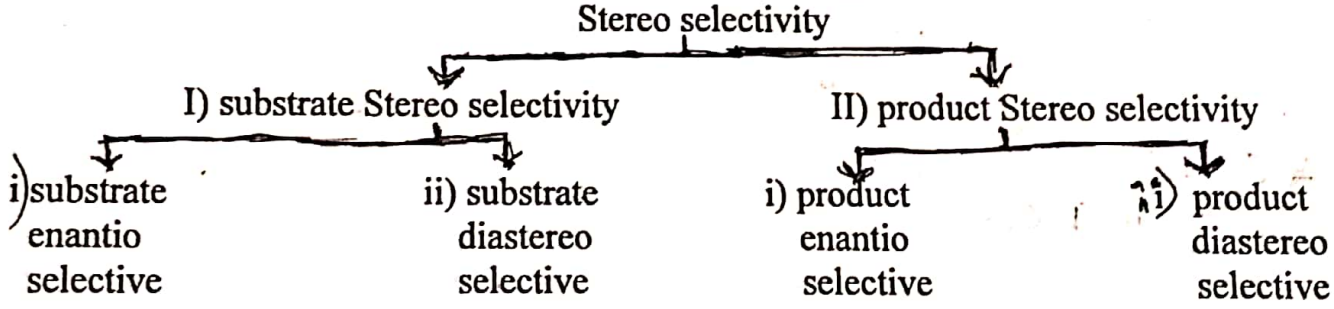
re-face (rectus)
(clockwise arrangement)

si-face (sinister)
(anticlockwise arrangement)

The order of precedence is $a > b > c$.

Stereo selectivity :

Stereo selectivity of reactions are classified as following:



I) substrate Stereo selectivity:

→ reaction starts with mixture of stereo isomers
→ in reactions different property (discrimination) shown by substances towards reagent (i.e., Reacting reagent prefers only one substance to other)

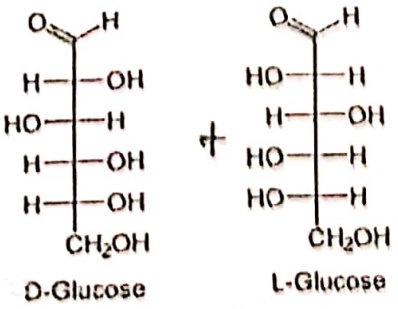
Ex : A + B $\xrightarrow{\text{reagent}}$ product
(stereo isomers) (reagent prefered Either A or B only)

i) substrate enantio selectivity:

→ reaction starts with mixture of enantiomers
→ in reactions different property (discrimination) shown by enantiomers towards reagent (i.e., Reacting reagent prefers only one enatiomer to other)

ex : e 1 + e 2 —reagent→ product
(enantiomers) (reagent prefered Either e 1 or e 2 only)

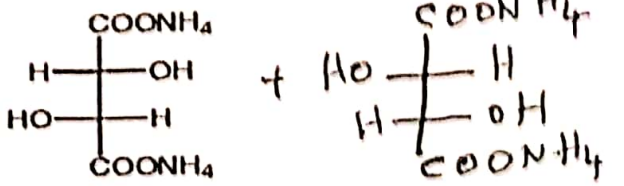
Ex 1:



Yeast → L-Glucose

> yeast prefered D – glucose only in the above reaction

Ex 2:



Penicillium glaucum → (−) Amm. tartrate

(±) – (Amm. tartrate)

> in the above reaction pencillium glaucum prefered (+) ammpnium tartarate only

→ chirality may retains or destroys
If chirality retains then ⇒ products are optically active
if destroyed then ⟶ products optically inactive

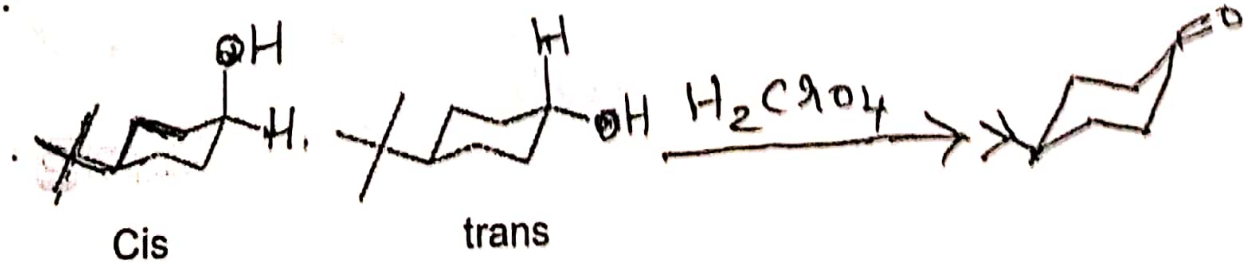
(#)

ii) substrate diastereo selectivity:

→ reaction starts with mixture of diastereomers
→ in reactions different property (discrimination) shown by diastereomers towards Reagent (i.e., Reacting reagent prefers only one diastereomer to other)

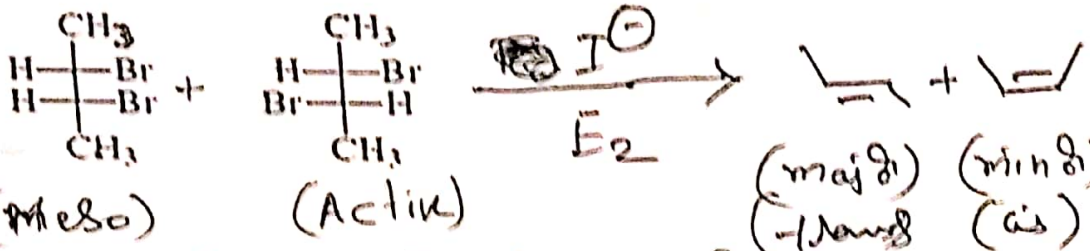
ex : d 1 + d 2 —reagent⇢ product
(enantiomers) (reagent prefered Either d 1 or d 2 only)

Ex 1:



.> here cis isomer is faster towards chromic acid

Ex 2 :



(Meso) (Actik) (majo) (mino) (trans) (cis)

→ trans Product formed is majo due T.S Energies..

(#)

II) product Stereo selectivity:

→ reaction produces un equal amounts of stereo isomers
→ reaction starts not by mixture of substrates
→ symmetry of substrate should be with stereo hetrotopic (enantiotopic or diastreotopic) Units

Ex :

A ⟶ X + Y

(with Stereo hetrotopic units) (unequal amounts streo isomers)

→ most of the reactions are product selective

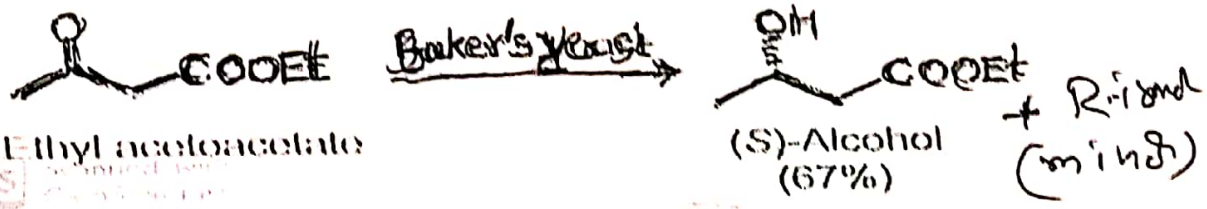
i) product enantio selectivity:

→ reaction produces un equal amounts of stereo isomers
→ reaction starts not by mixture of substrates
→ symmetry of substrate should be with stereo enantiotopic Units

ex:

(with A enantiotopic units) ⟶ $C_1 + C_2$ (un-equal amounts)

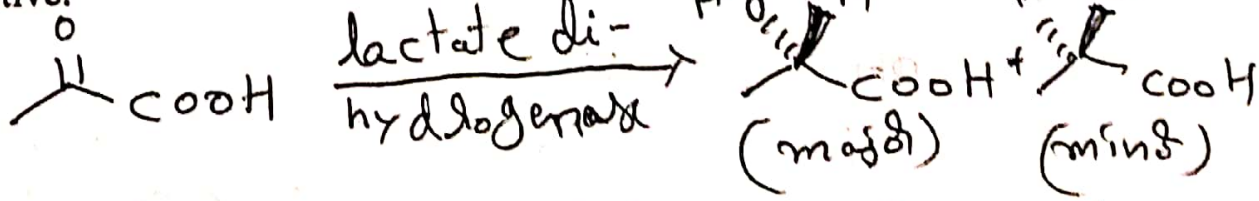
Ex 1:



Ethyl acetoacetate (S)-Alcohol (67%)

> here recimic mixture is not formed (I.e., 50 % : 50 %) so the reaction is product Enatio selective.

Ex 2 :



(majo) (mino)

> in the above reaction lactate dihydrogenase producing one of enantiomer as major Product

(#)

ii) product diastereo selectivity:

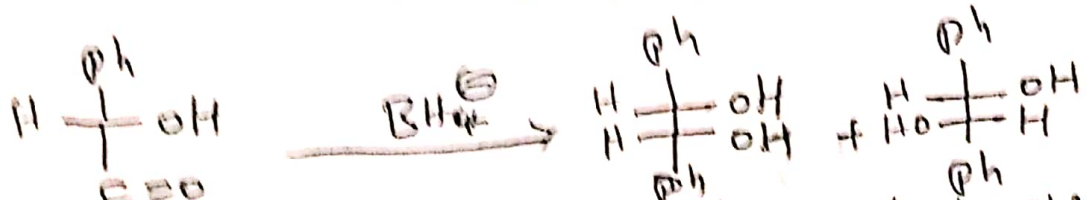
→ reaction produces un equal amounts of stereo isomers
→ reaction starts not by mixture of substrates
→ symmetry of substrate should be with stereo hetrotopic (enantiotopic or diastreotopic) Units

Ex :

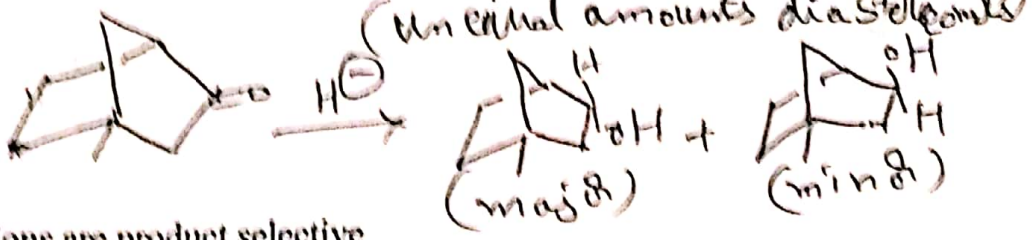
$$A \longrightarrow X + Y$$

(with Stereo hetrotopic units) (unequal amounts streo isomers)

Ex 1:



Ex 2 :



(#) :

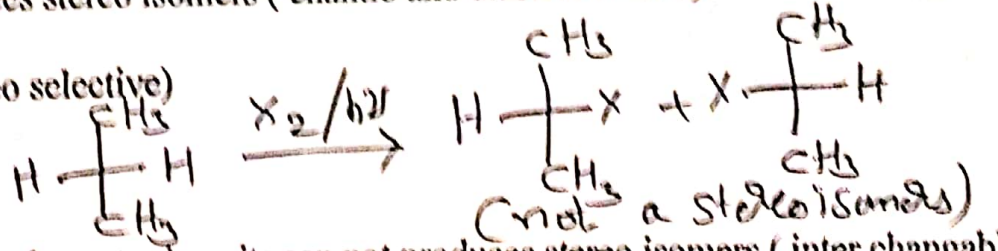
→ most of the reactions are product selective
Reason : transition state energies of resulting products are not same

A) symmetry criteria :

I) <u>product Stereo selectivity:</u>

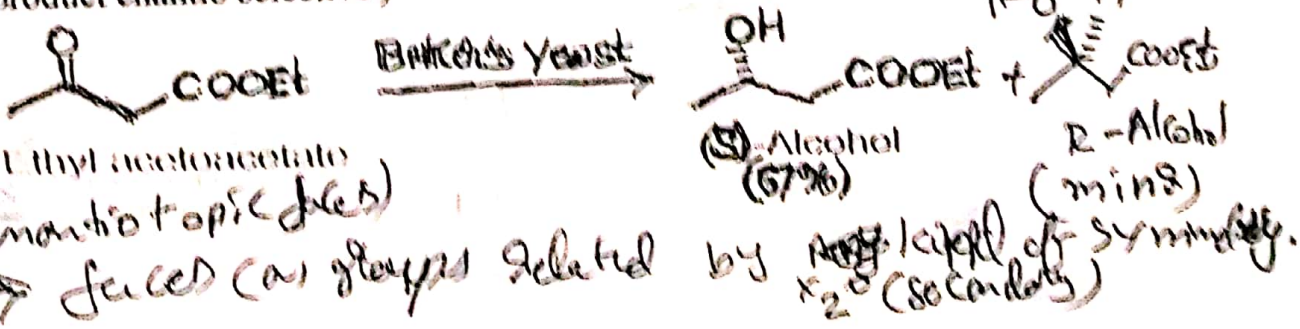
→ if substrate is not with stereo hetrotopic (enantiotopic or diastreotopic) Units not produces stereo isomers (enantio and diastero ismers)

For Ex : (Non stereo selective)



→ molecules having homotopic units can not produces stereo isomers (inter changable symmetry)

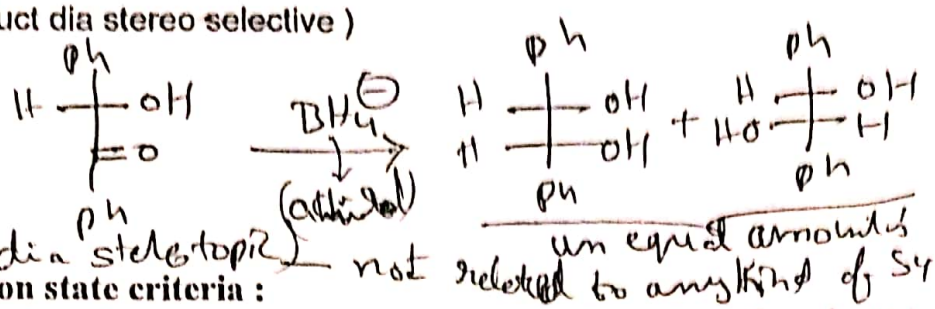
ex : 1 (product enantio selective)



Ethyl acetoacetate

- here bakers yeast is chiral - related.
- if ethyl acetoacetate is treated with achiral borohydride not a stereo selective (enantio) reaction

ex 2 : (product dia stereo selective)

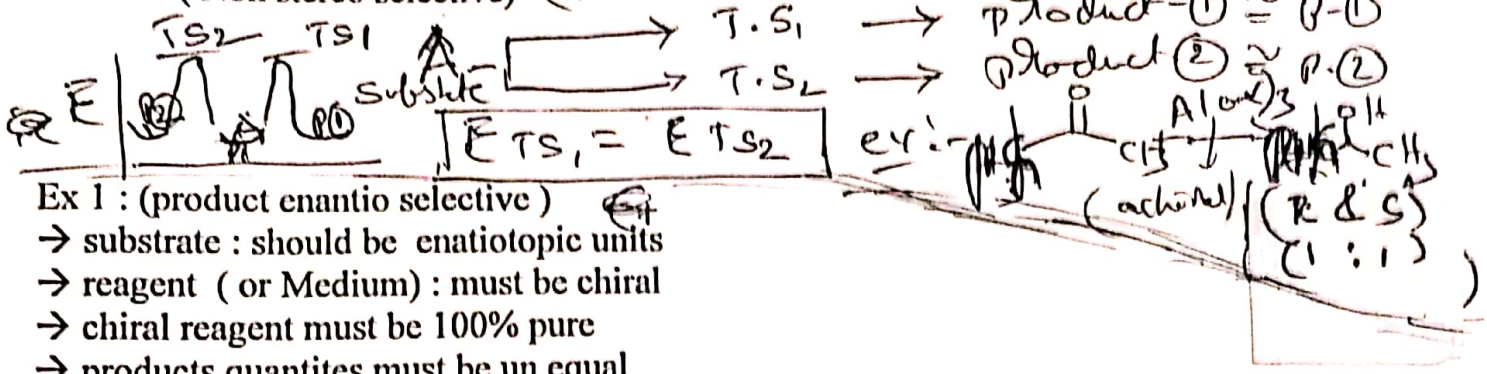


B) Transition state criteria :

→ every reaction shows transition state before the formation of product(s)

→ if produces more than one product then each product has its own translation

For ex : (Non stereo selective) (i.e due to same thermodynamic states).



Ex 1 : (product enantio selective)

→ substrate : should be enatiotopic units

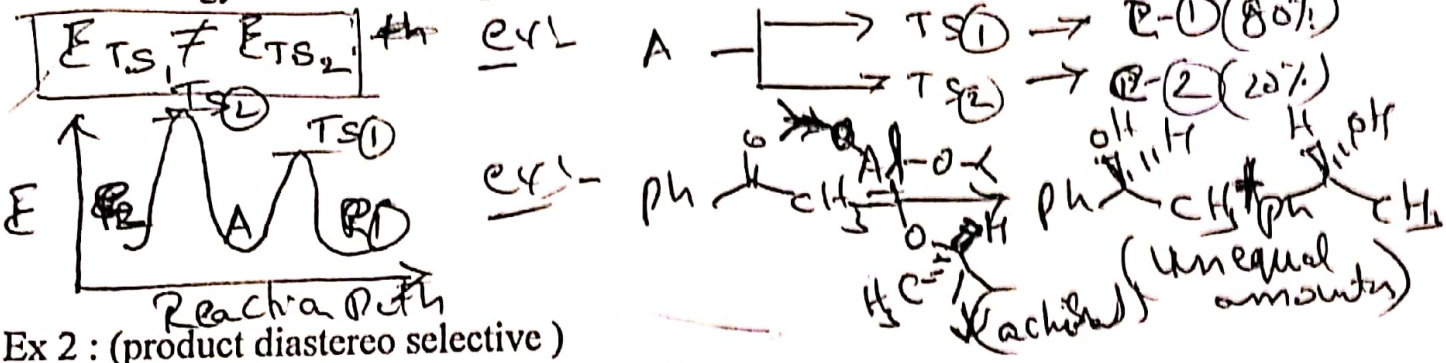
→ reagent (or Medium) : must be chiral

→ chiral reagent must be 100% pure

→ products quantites must be un equal

→ resuling products transition state energy must be unequl

→ low energy transition state path of reaction coordinates results the major product



Ex 2 : (product diastereo selective)

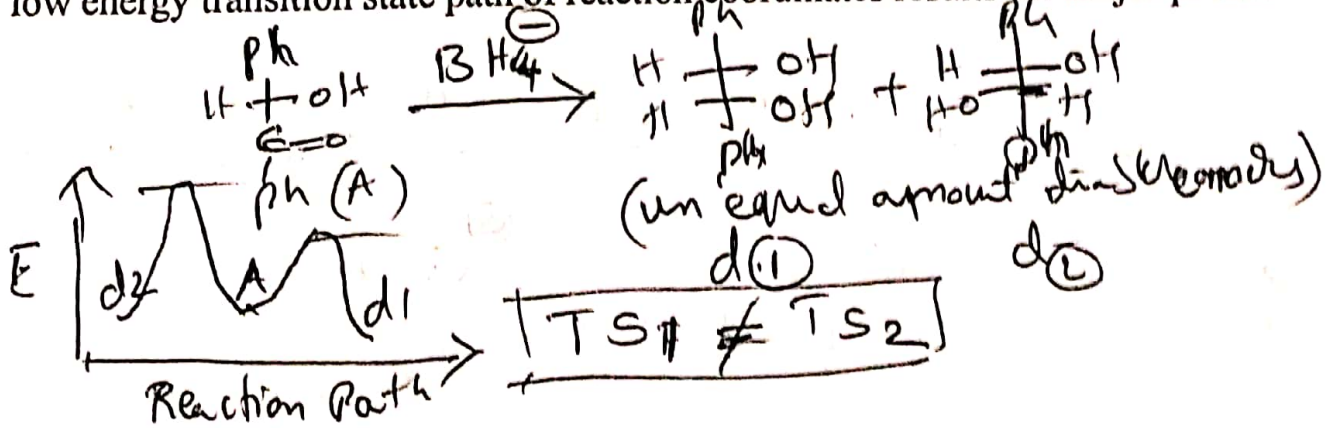
→ substrate : should be diastereotopic units

→ reagent : chiral as well as achiral results the product selectivity

→ products quantites must be un equal

→ resuling products transition state energy must be unequl

→ low energy transition state path of reaction coordinates results the major product



Optical activity

Compounds which rotate the plane of plane polarised light are called optically active compounds and this property is known as **optical activity.** If the compound rotates the plane of polarisation to the right (clockwise), it is said to be *dextrorotatory* (Latin : *dexter* = right) and is denoted by (+), or *d*. If the rotation is to the left (anticlockwise), the compound is said to be *laevorotatory* (Latin : *laevus* = left) and is denoted by (−), or *l*. Now the notations *d* and *l* are not used.

The optical rotation is detected and measured by an instrument called polarimeter. The degree of rotation depends on the nature of the compound, the temperature, the solvent, the concentration of the solution, the lenght of the polarimeter tube, and on the wavelength of the light used. It is, therefore, necessary to introduce some standard by which rotating power of different compounds may be compared. Thus, the measurement of optical activity is reported in terms of **specific rotation** [α], or molecular rotation [*M*].

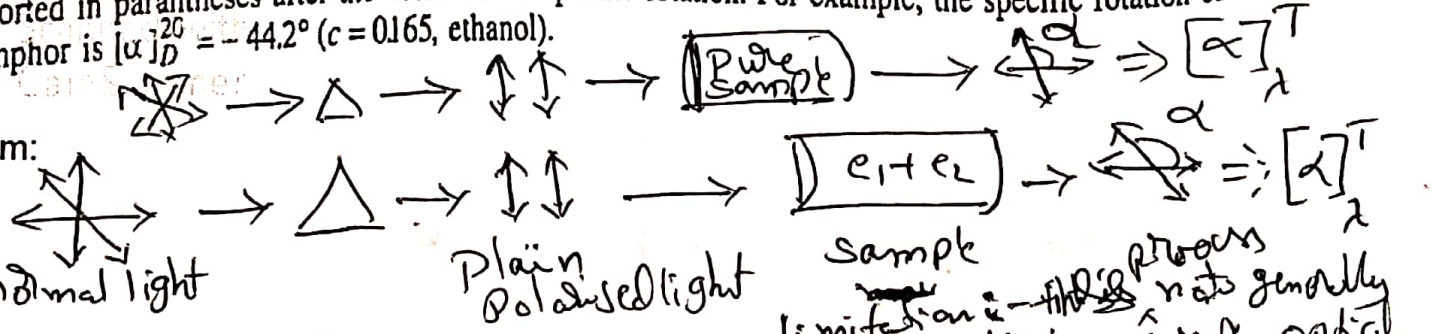
$$[\alpha]^{t}_{\lambda} = \frac{\alpha}{lc}$$

where [α] = specific rotation
t = temperature of the measurement
λ = wavelength of the light used (usually sodium *D* line, 5893 Å)
α = observed angle of rotation
l = the length of sample tube in decimeter
c = the concentration of the sample in g/mL of solution

For example, the specific rotation of cane sugar (sucrose) in water is $[\alpha]^{20}_{D} = +66.4°$

In most cases, the concentration of the sample in g/mL of solution and the solvent used are reported in parantheses after the value of the specific rotation. For example, the specific rotation of camphor is $[\alpha]^{20}_{D} = -44.2°$ (c = 0.165, ethanol).

Diagram:



limitation: polarimeters rots generally used to measure optical activity sample must be more quantity & 100% pure are required.

Differences between enantiomers and diastereomers:

TABLE 1.2. Comparative properties of diastereomers and enantiomers

Diastereomers	Enantiomers
1. are not mirror image isomers;	1. are mirror image isomers;
2. have different physical properties;	2. have identical physical properties;
3. show similar but not identical chemical properties (will typically react at different rates);	3. show identical chemical properties (will react at the same rates);
4. can be easily separated by fractional distillation, chromatography, etc.	4. cannot be separated by classic physical methods.

17.5 Enantiomeric Excess or Optical Purity

Enantiomers rotate the plane of plane polarized light by equal amounts in opposite direction. The net specific rotation of their mixture (Racemic mixture) will be zero. A sample of pure chiral compound uncontaminated by its enantiomer is said to be optically pure. But in some cases, mixtures are neither optically pure nor racemic mixtures. In such cases, their optical purity or percent enantiomeric excess is determined.

~~Racemic mixture~~

Optical purity : While working in the field of asymmetric synthesis, one needs to report not only the chemical yield but also the **optical yield** or **optical purity (o.p.)**. The percent optical yield or optical purity of a sample is calculated as:

$$\% \text{ optical purity (\% o.p.)} = \frac{[\alpha] \text{ of sample}}{[\alpha] \text{ of pure enantiomer}} \times 100$$

Assuming a linear relationship between $[\alpha]$ and concentration, which is true for most cases, the percent optical purity is equal to the percent excess of one enantiomer over the other :

$$\% \text{ o.p.} = \text{percent enantiomeric excess (\% e.e.)} = \frac{[R]-[S]}{[R]+[S]} \times 100 = \%R - \%S$$

Thus, it is usual to assume that : % o.p. = % e.e.

For a racemic mixture, the optical purity is zero. Effectiveness of asymmetric synthesis is estimated by the optical purity of the product obtained.

Ex : (1) substrate ----------→ e 1 (98.2 %) + e 2 (1.8 %)

% of e .e. = 98.2 – 1.8

= 96.4 %

Ex: (2) if a enantiomeric mixture is having 60% e.e then find the % of major enantiomer.

Ans: $\%$ of major enantiomer $= \frac{100 + \%\text{ of e.e}}{2}$

$= \frac{100+60}{2} = \frac{160}{2} = 80$

Method (II): e.e % = 60%

⇒ racemic mixture % = 40%

⇒ 20% R + 20% S

⇒ major enantiomer % } = 60 + 20

= 80%

A mixture, which is 50% optically pure contains 75% of one enantiomer and 25% of the other.

Optical purity means the excess of one enantiomer in a partially racemised or partially resolved sample which expressed as the percentage of total.

Optical purity of a test sample can be mathematically expressed as

$$\text{Optical purity} = \frac{\text{Specific rotation of the test sample}}{\text{Specific rotation of pure enantiomer}} \times 100$$

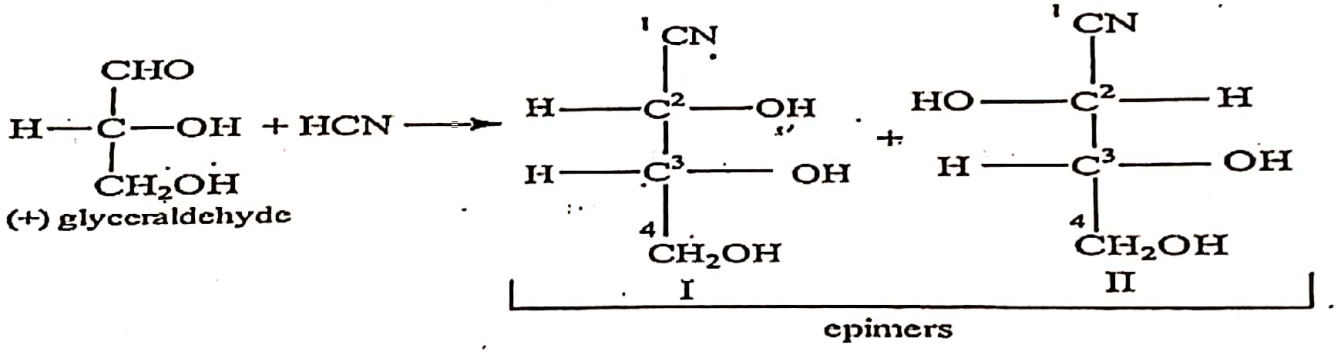
The specific rotation of pure (S)-2- butanol is $+13.5^0$, if the rotation of sample is $+ 9.54^0$, then O.P $= \frac{9.54^0}{13.5^0} \times 100 = 70.7\%$.

Diastereomeric excess means the excess of one diastereomer in a mixture of the two diastereomers formed when a new asymmetric centre is created in an optically active molecule.

Diastereomers are optically active isomers which do not bear the relation of an object and its mirror image.

When a new optically active substance is prepared from a optically active substance by the introduction of a new asymmetric centre, two diastereomers result and one of which will be in excess over the other.

Ex:- When Glyceraldehyde is treated with HCN, two epimers (Epimers are diastereo-isomers, which carry more than one chiral carbon atom and differ in configuration at a single chiral carbon) are obtained.



Compounds I & II are epimers as they differ from each other in configuration at C_2-atom only.

In this reaction, the chiral carbon in (+) glyceraldehyde (C_3) remains intact and a new chiral carbon is generated by the addition of HCN, resulting in the formation of two diastereomers and the diastereomers will be formed at different rates and one diastereomer will be excess than other.

*Diastereomeric excess (% d.e.) = % of major diastereomer (D_1) – % of minor diastereomer (D_2)

$$\%\ d.e. = \frac{[D_1] - [D_2]}{[D_1] + [D_2]} \times 100$$

Ex : substrate ⟶ d 1 (98.2 %) + d 2 (1.8 %)

% of d .e. = 98.2 -- 1.8

= 96.4 % ⇒ reaction is diastereo selectivity

What is the "e/e" ratio?
"e/e" refers to the ratio of one enantiomer to the other in a compound. For example, in prep chiral HPLC, the "pure" enantiomer may be 98% e/e

For example:
Process I :

Substrate ⟶ e_1 (major) 90 % + e_2 (minor) 10 %

Optical purity in terms of e/e ratio = % of e_1 major / % of e_2 minor = 90/ 10 = 9

process II :

Substrate ⟶ e_1 (major) 80 % + e_2 (minor) 20 %

Optical purity in terms of e/e ratio = % of e_1 major / % of e_2 minor = 80/ 20 = 4

final conclusion : Process I is Highly enantioselective reaction than process II

Chiral solating agents :

→ One method of NMR analysis for enantiomer composition is to record the spectra in a chiral environment, such as a chiral solvent or a chiral solvating agent.

→ This method is based on the diastereomeric interaction between the substrate and the chiral environment applied in the analysis.

→ The first example found in the literature was the use of this method in distinguishing the enantiomers of 2,2,2-tri¯uoro-1-phenylethanol. This was realized by recording the 19F NMR of the compound in (–) -a-phenethylamine.

→ The ee values could also be determined by studying the 1H NMR.

→ Mostly in the presence of certain chiral compounds, namely, chiral solvating agents. In these cases, the determination was achieved based on the diastereomeric interaction between the substrate and the chiral solvating agent. Sometimes, the observed chemical shift dfference is very small, making the analysis difficult. This problem may be overcome by using a higher held NMR spectrometer or recording the spectra at lower temperature.

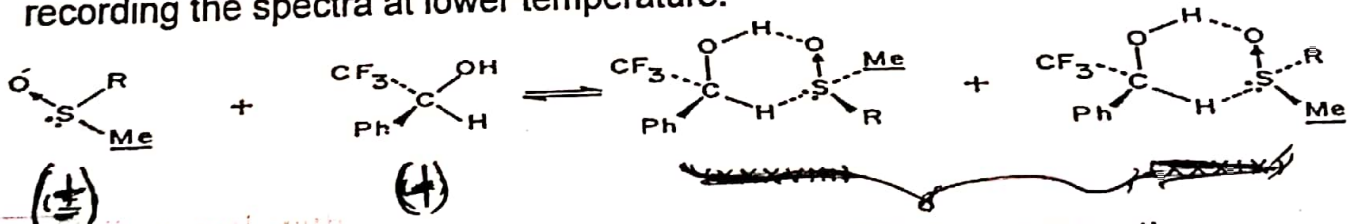
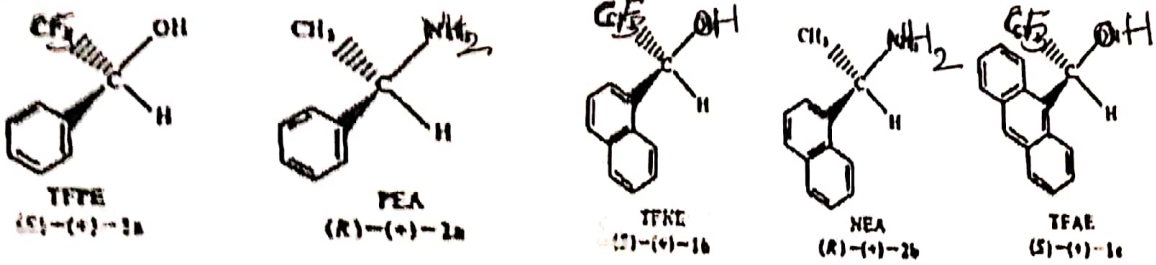


Figure 7.18 Diastereomeric associates with CSA through H-bonding

without chiral Solvating agent(or) Solvent.

by the CSA

Exmples :



Chiral shift reagents :

→ Lanthanide complexes can serve as weak Lewis acids In nonpolar solvents (e.g., CDCl3, CCl4, or CS2)

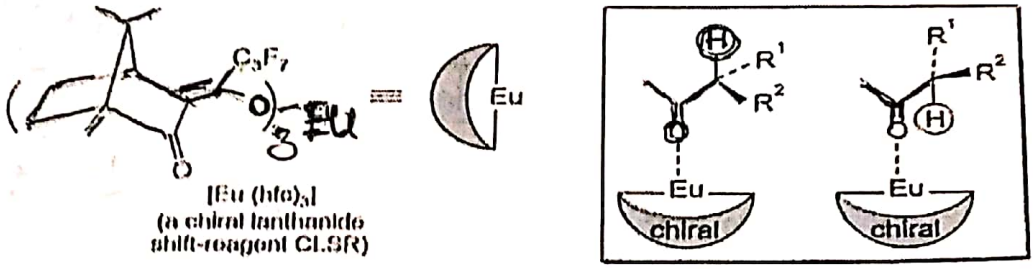
→ these paramagnetic salts are able to bind Lewis bases, such as amides, amines, esters, ketones, and sulfoxids.

→ So the lanthanide complexs (camphor derivates etc,,) intracts with two enantiomers and forms diasteriomeric complexs

→ As a result, protons, carbons, and other nuclei are usually deshielded relative to their positions in the uncomplexed substrates, and the chemical shifts of those nuclei are altered.

The extent of this alteration depends on the strength of the complex and the distance of the nuclei from the paramagnetic metal ion.

Therefore, the NMR signals of different types of nuclei are shifted to different extents, and this leads to spectral simplication.

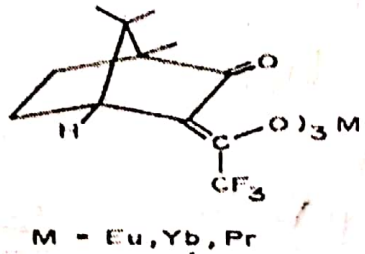


[Eu (hfc)$_3$]
(a chiral lanthanide shift-reagent CLSR)

The signals of circled hydrogen atoms will be shifted down field and will have different chemical shifts

SCHEME 1.152

Examples :



without Chiral shift reagent

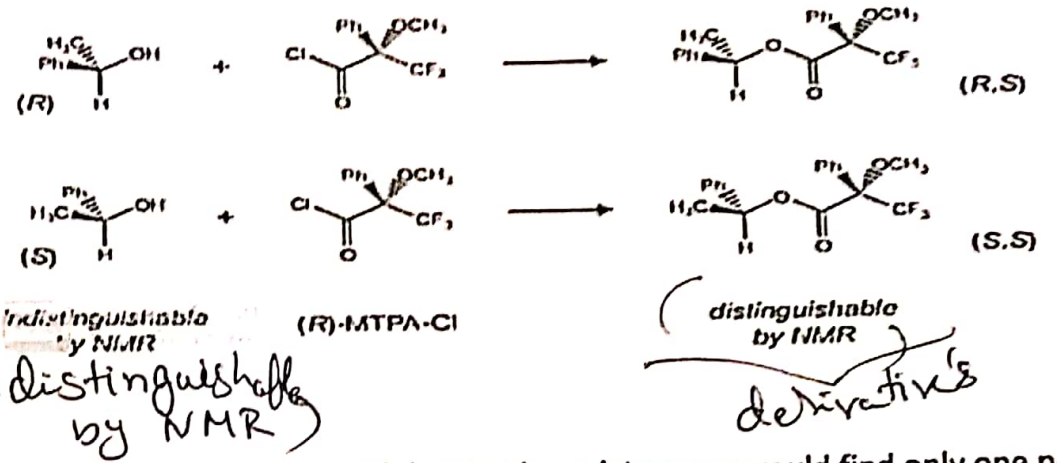
by the chiral Shift reagent (here diastereomers enantiomers observed)

Chiral NMR ; Chiral deralvatizing agents :

One of the method for this is the use of NMR.

In general to analyse the enantiomers mixture convert the non racemic mixture of enantiomers in to diasteromers (derivatives) with optically pure reagent and then only by the resulting mixture we can properly analyse enatiomers by help of nmr spectrum.

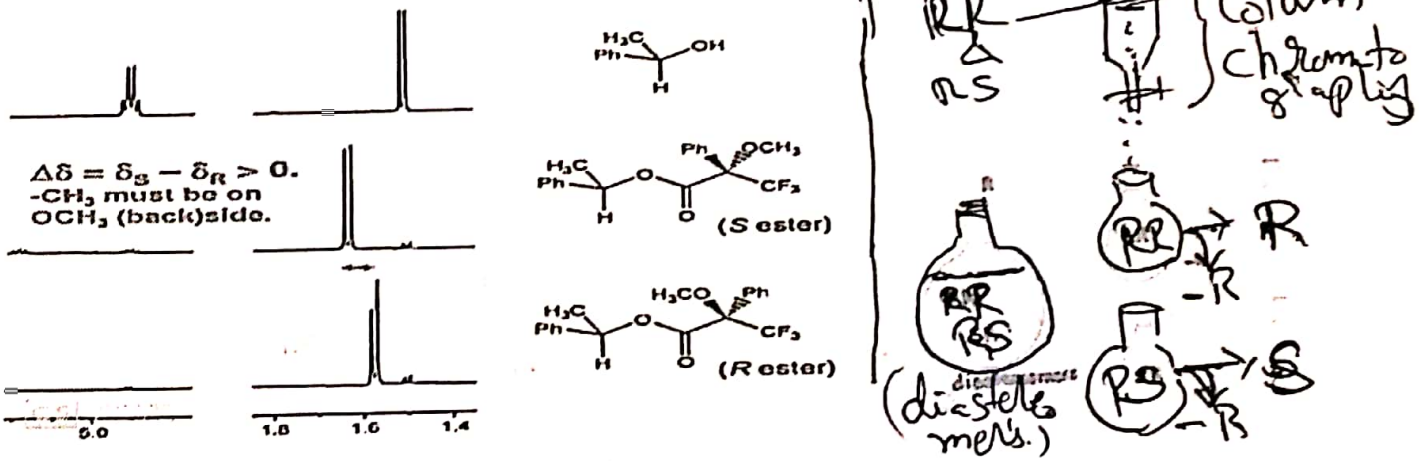
Ex:



If we examine the NMR spetrum of the starting mixture we would find only one peak for CH 3 Protons.

But the ester are not enantiomers and each CH 3 gives its own doublet

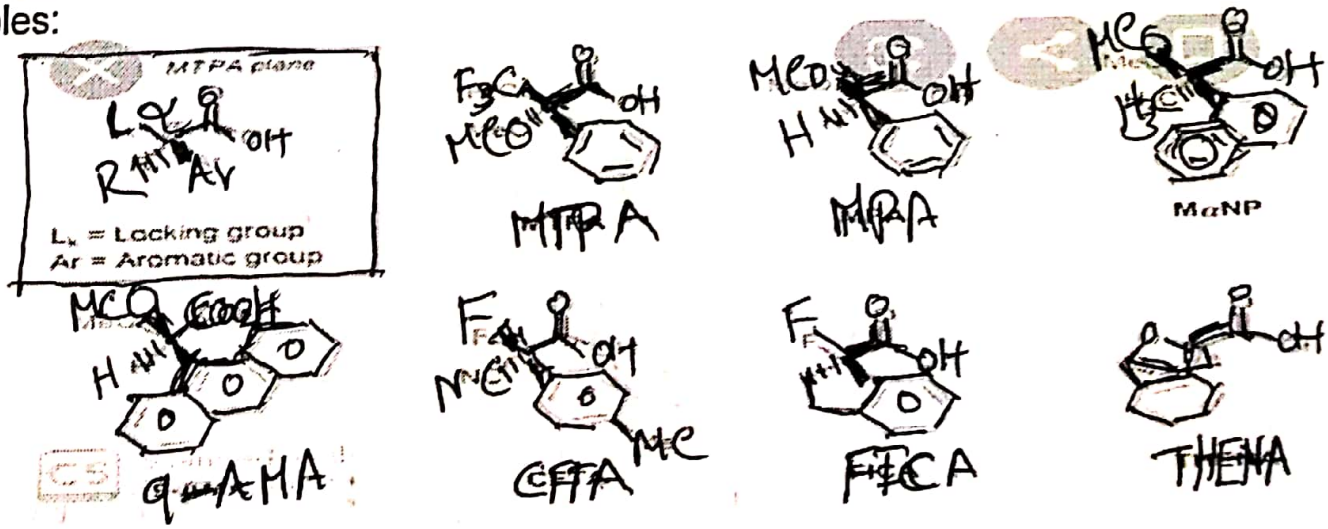
From the intensity of the two peaks the relative proportions of the two diastereomers can be determined



→ Utilising derivating reagent mustbe enantiomerically pure for converting the racimic mixture in to derivative

→ moschers acid : α -methoxy- α -phenyl- α-trifluoromethyl acetic acid in both the (R)- and (S)-forms are most popular derivating agents for amines and for alcohols

Examples:



Chiral HPLC :

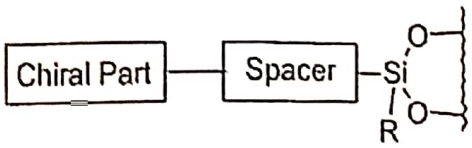
Chromatography :

This method is of limited use. This process involves the addition of a racemic solution over an optically active adsorbent and collecting two enantiomers from adsorbates.

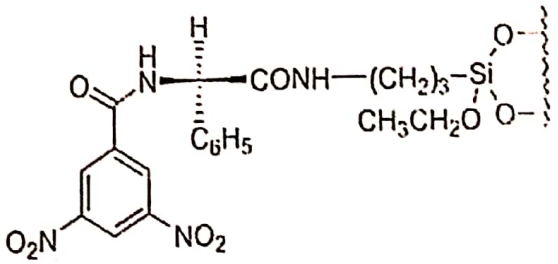
Liquid Chromatography :

The development of rapid, simple liquid chromatographic methods for determining the enantiomeric purity of chiral compounds is probably one of the most important developments in the study of asymmetric synthesis

. Initially, chiral stationary phases for chiral liquid chromatography were designed for preparative purposes, mostly based on the concept of ``three-point recognition". Pirkle and other scientists developed a series of chiral stationary phases that usually contain an aryl-substituted chiral compound connected to silica gel through a spacer.



36a (general structure)



36b (used for the separation of amino acids)

Figure 1–14. Chiral stationary phase for high-performance liquid chromatography.

Figure 1–14 depicts the general concept and an actual example of such a chiral stationary phase.

Another chiral stationary phase is modified cyclodextrin. Cyclodextrins arecyclic chiral carbohydrates composed of six, seven, or eight glucopyranose units designated as a-, b- , and g-cyclodextrin, respectively. Cyclodextrins are cylinder-shaped molecules with an axial void cavity. Their outer surface is hydrophilic, and therefore they are soluble in water. The cavity is nonpolarand can include other nonpolar molecules of appropriate dimensions and bind them through hydrophobic interactions.

The complexation of cyclodextrin is highly selective. The inclusion processes are influenced mainly by the hydrophobicity and shape of the guest molecules. Specifically, the guest molecules must at the cyclodextrin cavity. Complexation processes occurring in solution are reversible, and the equilibration in solution is relatively fast. For these reasons, cyclodextrin immobilized on silica gel is also used for chromatographic separation of chiral compounds, especially for compounds containing aromatic groups. An aromatic group on the substrate is essential for getting enantioselective binding through interaction with the glycosidic oxygen atoms. A substrate without an aromatic group will occupy random positions within the cavity and consequently lose enantioselectivity.

Mobile Phase

The general criteria for the selection of a good mobile eluting phase are :

1. It should dissolve the sample,
2. It should keep the column stable,
3. It should be very pure,
4. It should be compatible with the detector,
5. It should satisfy a number of special criteria (e.g., the mobile and stationary phases must be immiscible with one another, active fluorides should be avoided when using glass columns and the eluant should not contain dissolved gases,) and
6. The viscosity should not be high.

Mostly all solvents are suitable to Hplc stationary phases & the mostly using sovents :

Chloroform-hexane	Hexane-chloroform
iso-Octane-isoPrOH	CH_2Cl_2
Hexane	iso-Octane-alcohols
Hexane-isoPrOH	Hexane-alcohols
Acetone	Tetrahydrofuran-alcohols
Chloroform-isoPrOH	

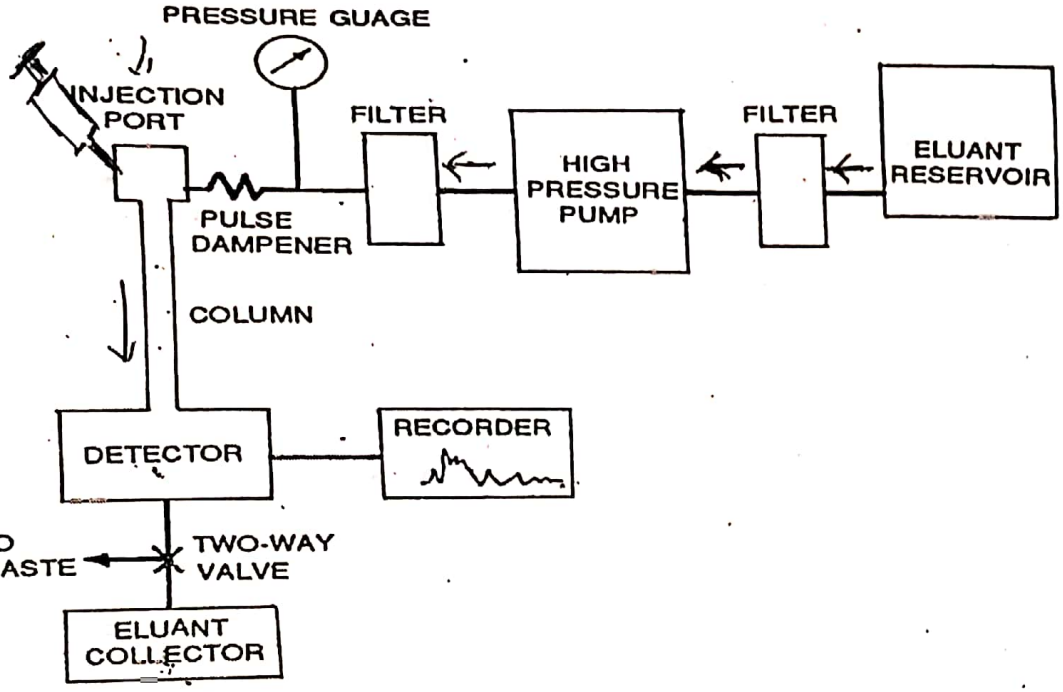
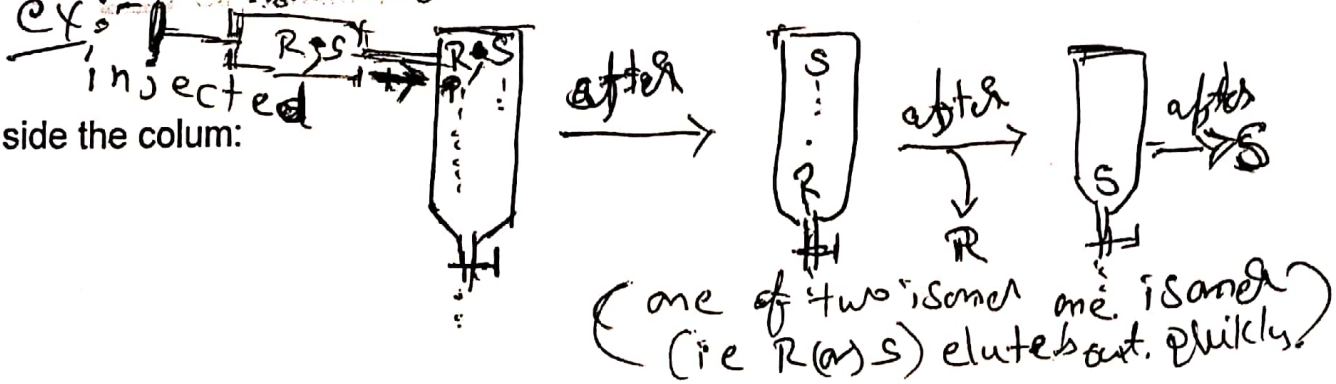


Fig. XI.1 High Performance Liquid Chromatography (schematic)

In side the colum:



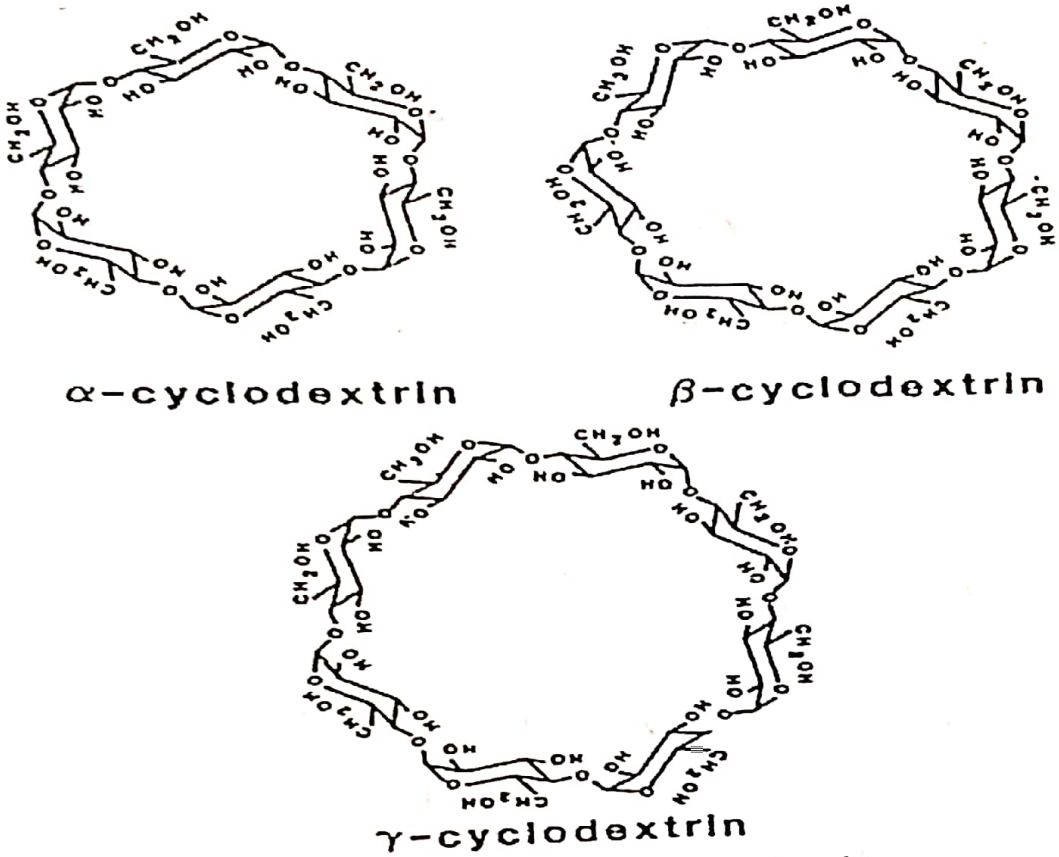


Fig. XI.4 Structure of α-, β-, and γ- cyclodextrings.

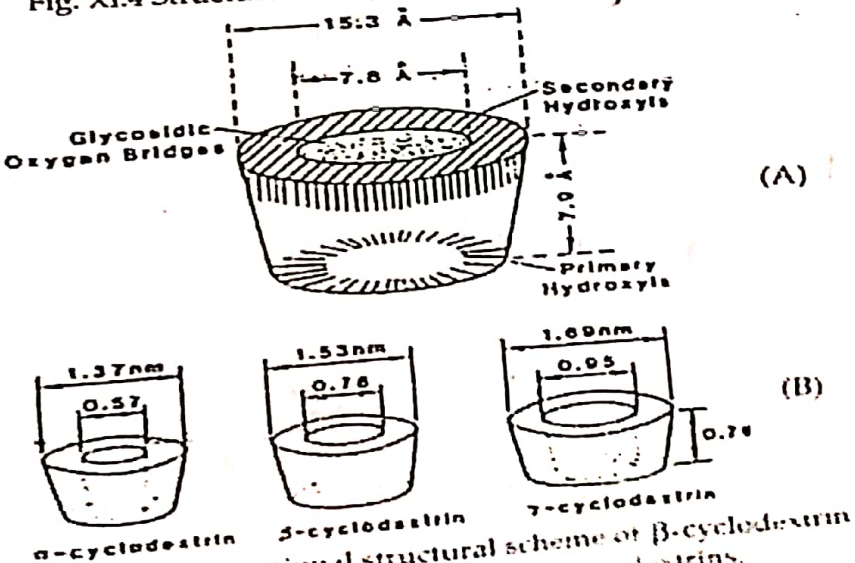


Fig. XI.5 (A) Functional structural scheme of β-cyclodextrin
(B) Molecular dimensions of cyclodextrins.

Model questions:

write a short note about the following

i) Homotpic and Heterotopic groups and faces. (10 M)

ii) Pro-R and pro-S, Re and Si (5 M)

iii) Substrate stereo selectivity and product stereo selectivity.

iv) Chiral shift reagents and chiral HPLC (v) Write about chiral NMR (3 M)

vi) Write about enantiomeric excess and specific rotation (3 M)

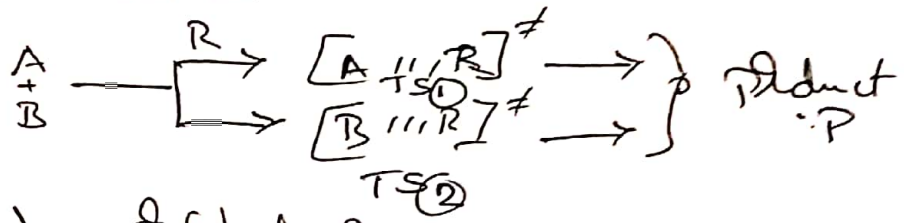
(#) Symmetry & Transition State's Criteria:

(i) Substrate Stereo selectivity:

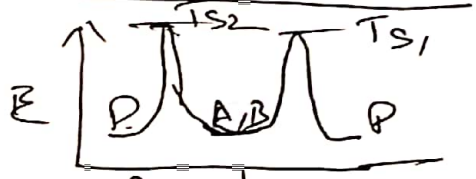
A + B (Substrates) $\xrightarrow{R\ (Reagent)}$ P

→ Reagent A & B both (Symmetric) Substrates structures are same. then rxn is non-stereo selective.

→



→ energy profile diagram:



$E_{TS(1)} = E_{TS(2)}$

⇒ Non-Stereo selective

Case (ii): if A = e_1 ; B = e_2 ; $E_{TS(1)} \neq E_{TS(2)}$

enantiomers

then out two enantiomeric substrate only one is preferred R. then rxn is enantio substrate-selective.

→ energy profile diagram:

Case (iii): Similarly if A = d_1 ; B = d_2

Substrate diastereomers

rxn is diastereo selective.

→ energy profile diagram