

# STEREOCHEMISTRY

→ Chiral centers are tetrahedral atoms

(usually C) that have four different substituents

→ Stereogenic center or stereocenter is any

point in a molecule, though not necessarily

an atom, which can exhibit stereoisomerism.

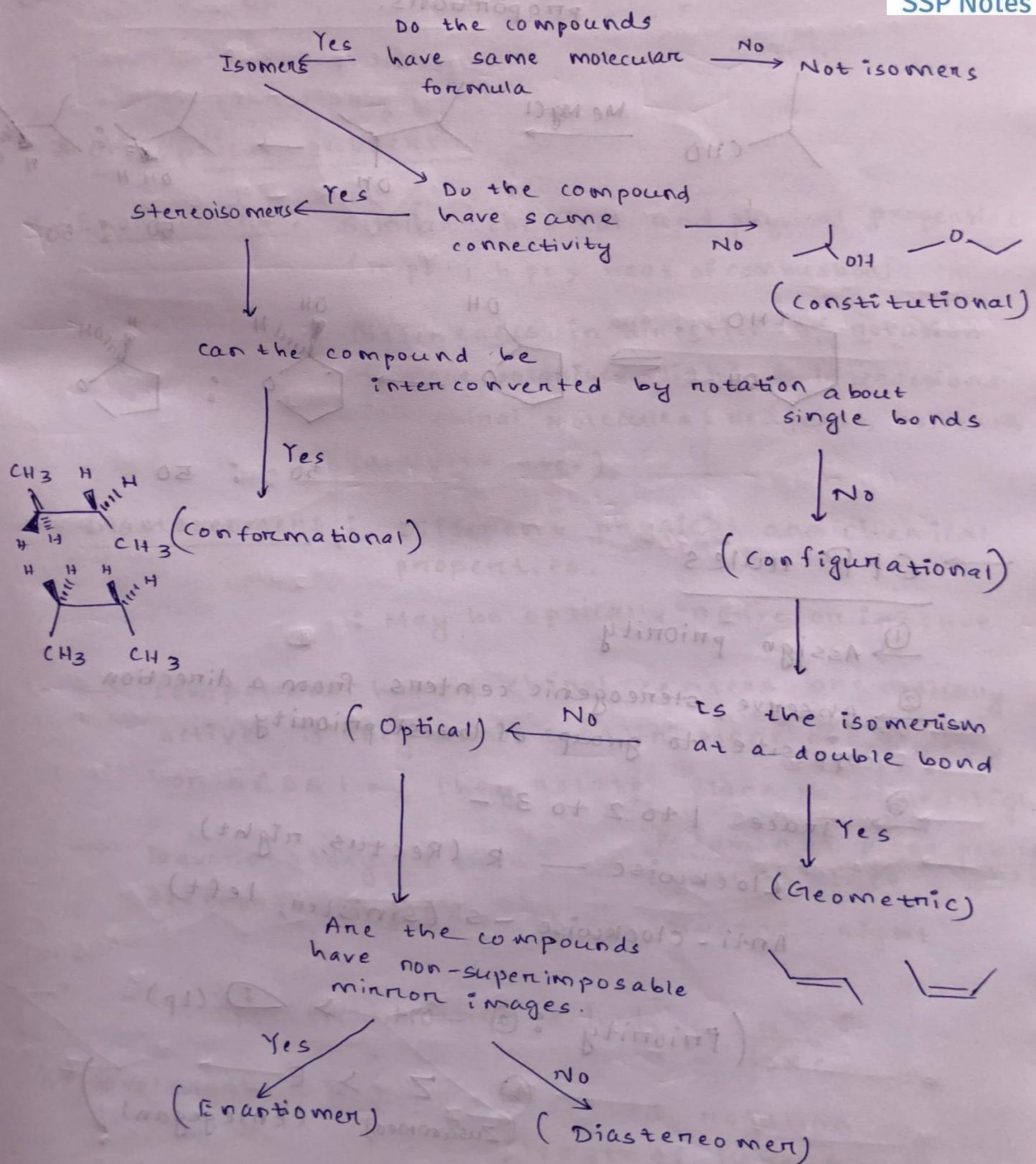
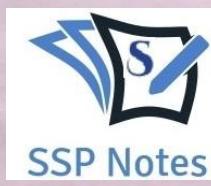
→ A racemic mixture is a mixture of two enantiomers in equal proportions.

→ Laboratory produced chiral molecule from achiral substrates (Strecker synthesis for alanine) are racemic mixtures, while those found in nature are enantiomerically pure (mostly).

→ Stereoisomers that are not mirror images of one another are called diastereomers

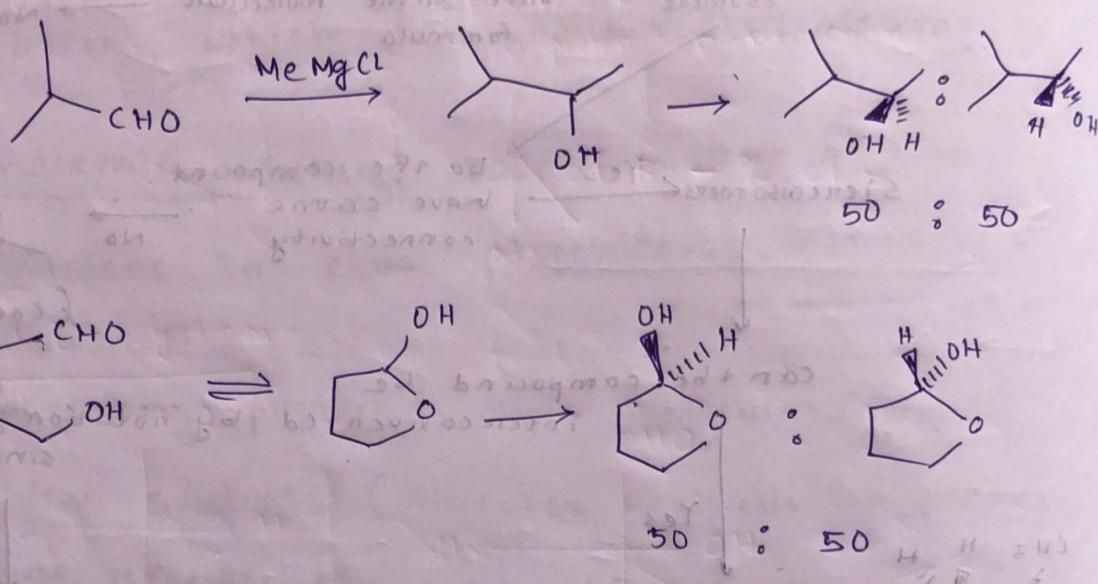
→ Static stereochemistry : Stereochemistry of molecules

Dynamic stereochemistry : Stereochemistry of reactions



→ Chirality is removed if an object / molecule acquires a pos on a COS (inversion center)

→ Racemic mixture - A racemic mixture is a mixture of two enantiomers in equal proportions.



### CIP Rules

① Assign priority

② Observe stereogenic centers from a direction opposite to group of lowest priority

③ Trace 1 to 2 to 3 -

Clockwise — R (Rectus, right)

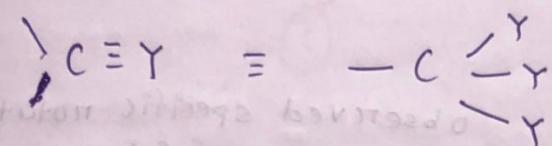
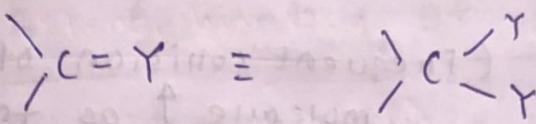
Anti-clockwise — S (Sinister, left)

(Priority : @ - OH > ⚡ (LP))

(b) Z > E

(Zusammen) (Entgegengesetzt)

④ In case of alenes (odd-numbered) and BINAP (cases), don't required the lowest (4) substituent to be down viewed or positive



### \* Chiroptical properties

Enantiomers : Similar chemical and physical properties (m.pt., b.pt; heat of combustion)

: Differences in direction of rotation of plane polarised light & interactions with chiral molecules (reagents, solvents, catalysts etc.)

Diastereomers : Different physical and chemical properties.

: May be optically (active) or inactive

→ Compounds having chiral centers are optically active if they do not contain plane of symmetry or a CDOS i.e., they rotate plane polarised light

→ laevorotatory (l or -) - towards left  
dextrorotatory (d or +) - towards right

$$\text{Specific rotation} = [\alpha]_D^T = \frac{\alpha}{l \times c}$$

$\lambda$  → wavelength

$\alpha$  = observed rotation

$l$  = length of tube (in dm)

$c$  = conc. of solution (in g/mL)

$$\alpha \propto \frac{1}{\text{Temp.}}$$

(frequent collision of molecule ↑ as temp. ↑)

Optical purity  
(enantiomeric excess, ee)

$$\text{Optical purity} = \frac{\text{observed specific rotation} (\alpha_{\text{obs}}) \times 100}{\text{specific rotation of the pure enantiomer} (\alpha_{\text{max}})}$$

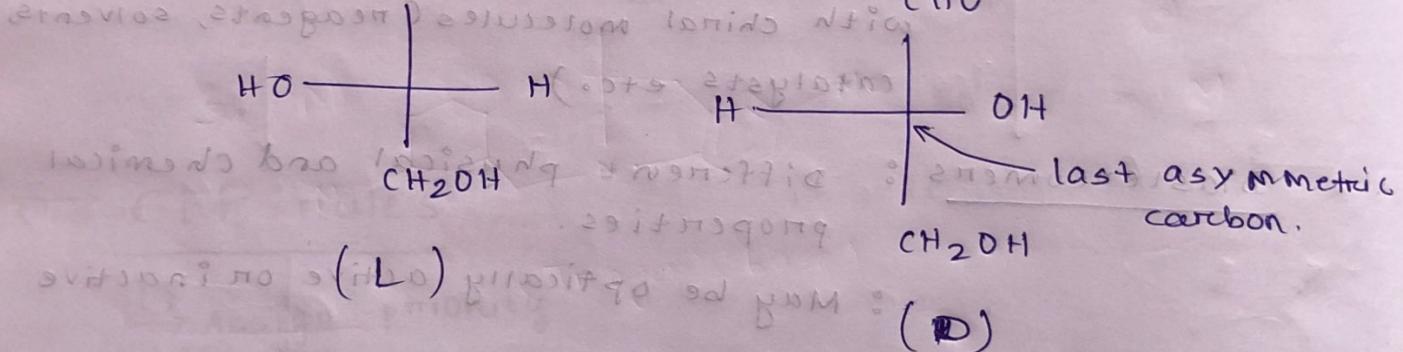
~~enantiomeric excess = % of R - % of S~~

~~= % of R - % of S~~



### D and L system

CHO & HO both have to be added to



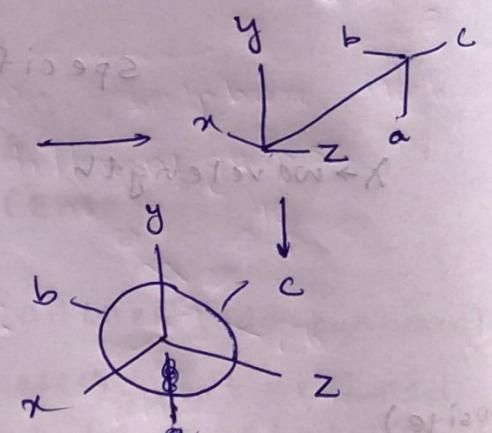
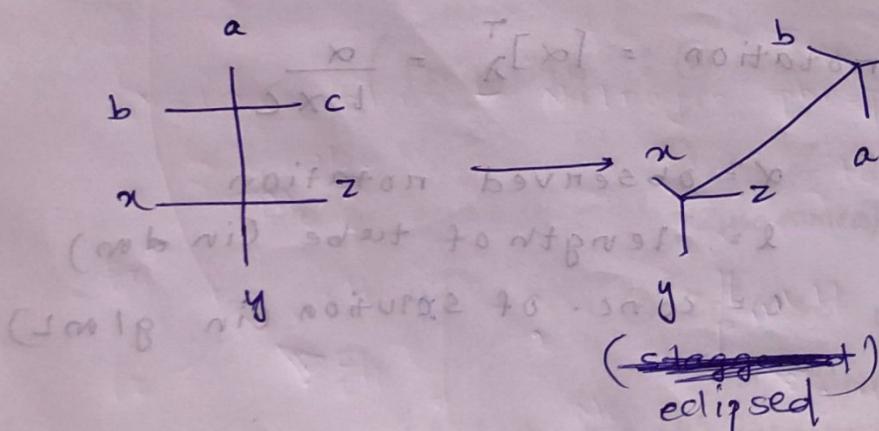
→ wedge-dash

→ Fischer

→ sawhorse

→ Newmann

to understand steric relations

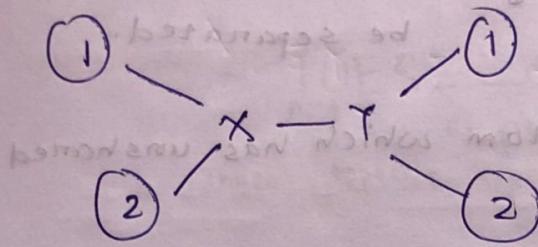


# \* Z/E Geometry of Double Bonds

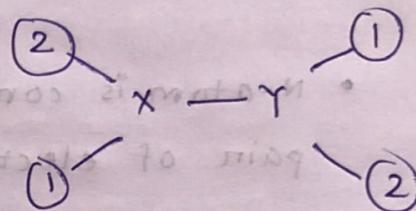


(for olefinic compounds)

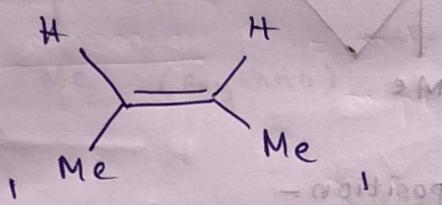
SSP Notes



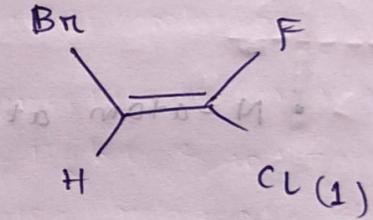
Z (zusammen, together)



E (entgegen, opposite)



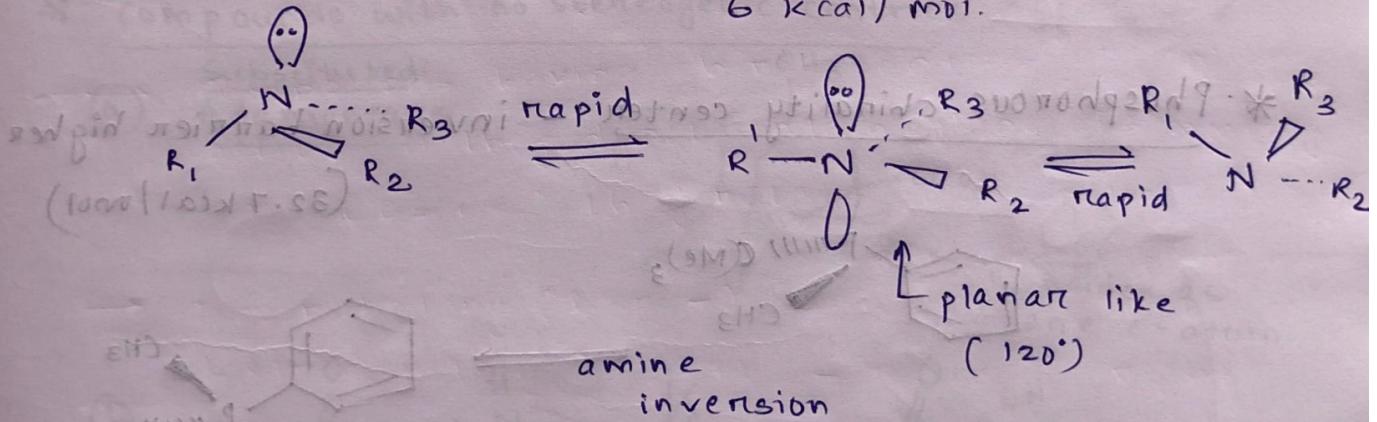
(Z)-2-butene



(E)-1-bromo-1-fluoroethene

## \* Nitrogen chirality

6 kcal/mol.



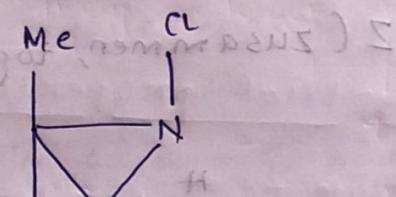
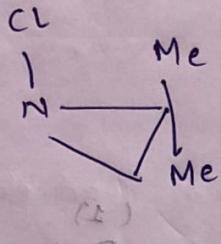
→ inversion is very fast and difficult to separate -  $2 \times 10^{11}$  interconversions/sec.

For 5/6-membered rings N-acts not as chiral centre

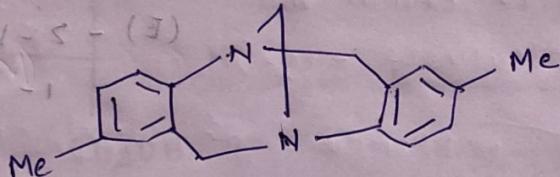
For 3-membered rings N-act as chiral centre as no inversion.

- Inversion becomes slow when -
  - N is three-membered ring - two enantiomers can be separated.

- N-atom is connected to atom which has unshared pair of electron.

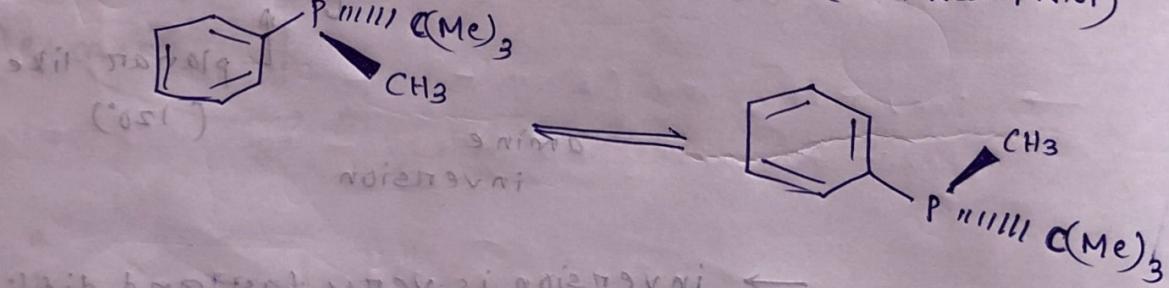


- N-atom at bridgehead position -

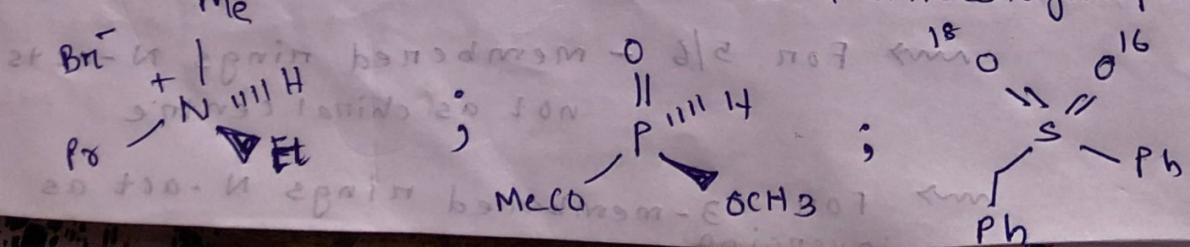


(Triogen's base)

\* Phosphorous chirality centers - inversion barrier higher (32.7 kcal/mol)



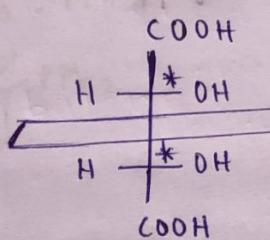
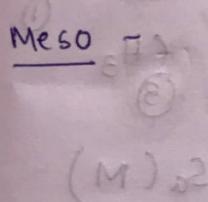
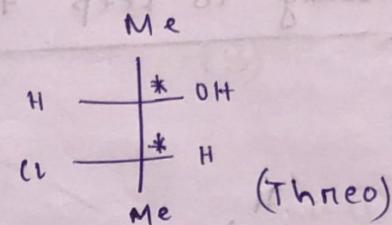
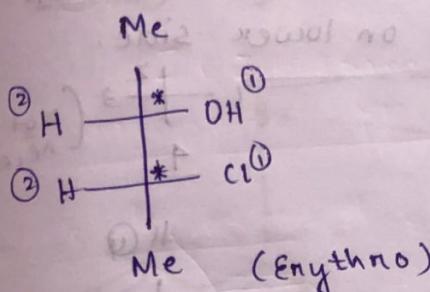
\* Stereocenters - Nitrogen, phosphorous, sulphur- attached to 4 different groups



Diastereomers may be chiral or achiral.

- Threo / erythro → it requires vertical projection of main chain.

TOES ← some  
↑ ↑  
Erythro  
Threo opposite

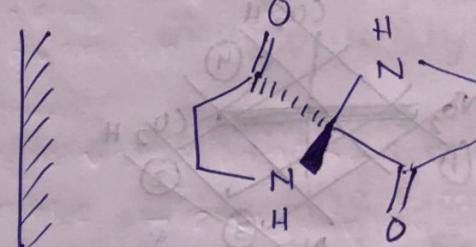
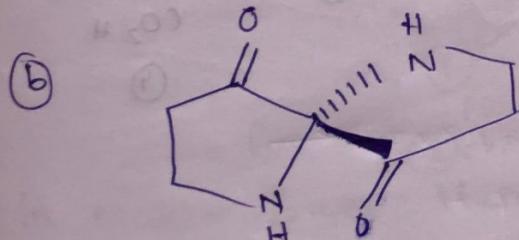
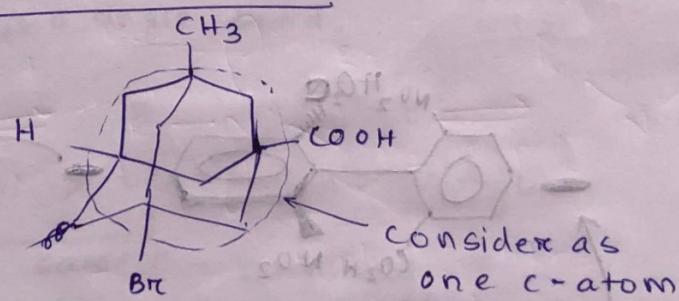


(Tartaric Acid)

Meso - (POS)

\* Compounds with no stereogenic centres

a) Substituted Adamantane



enantiomers  
(but in soln., racemic mix.)

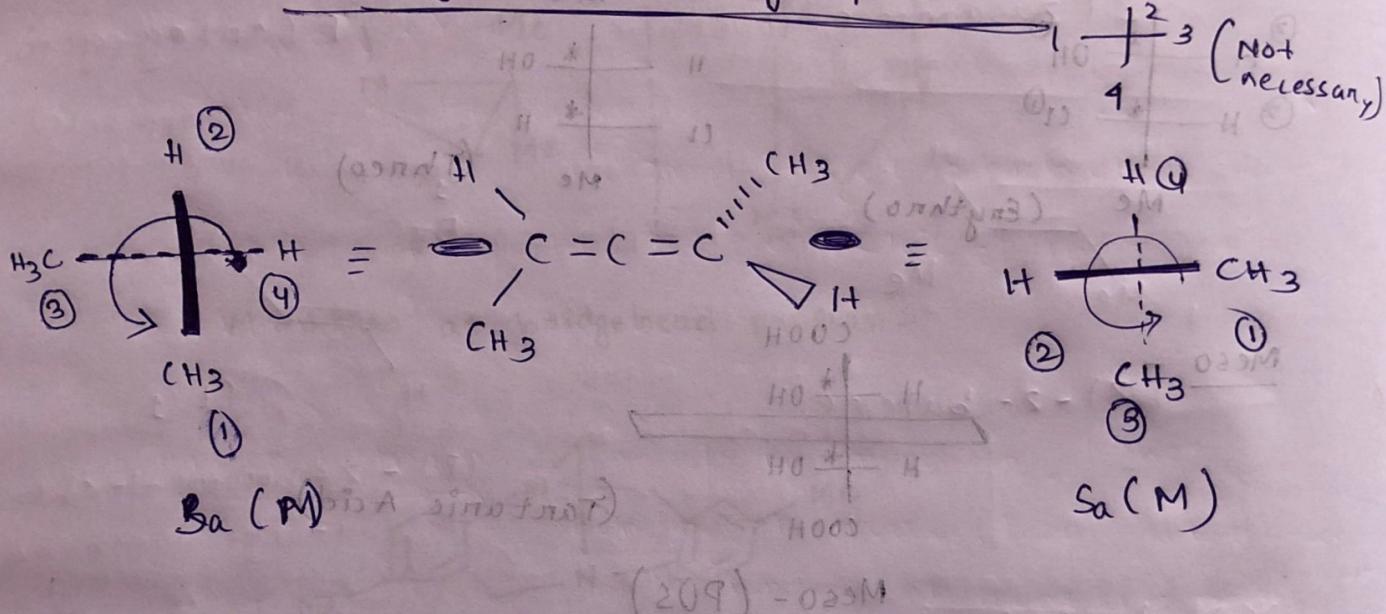
\* Allene - R<sub>a</sub> on P(plus) & S<sub>a</sub> or M(minus)

Axial

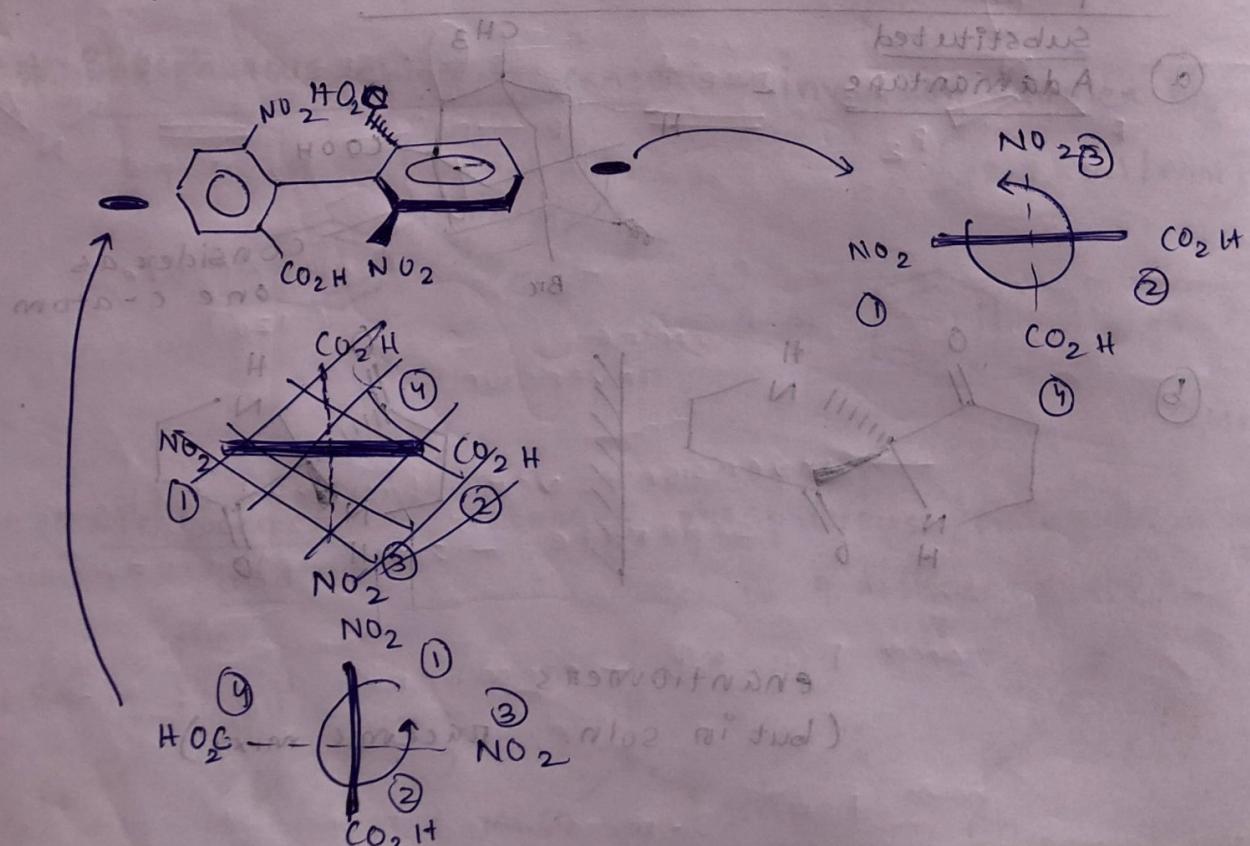
→ CIP rules

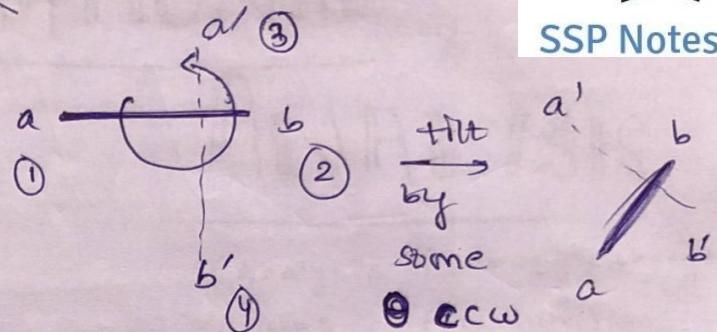
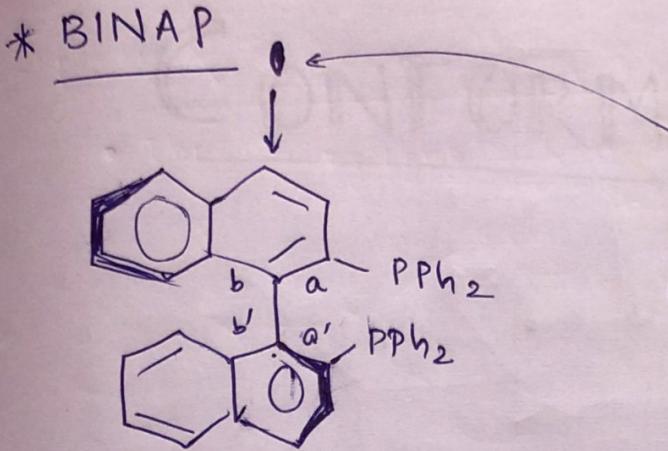
→ Near groups have higher precedence over far groups

→ The chiral axis is viewed end-on and it is not necessary to keep '4th group on lower side.

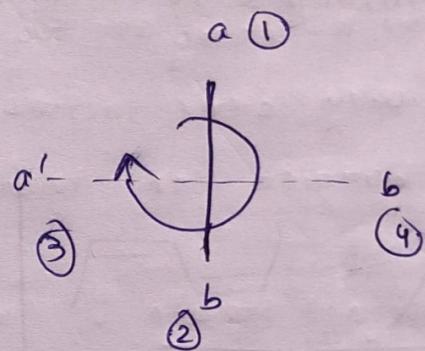
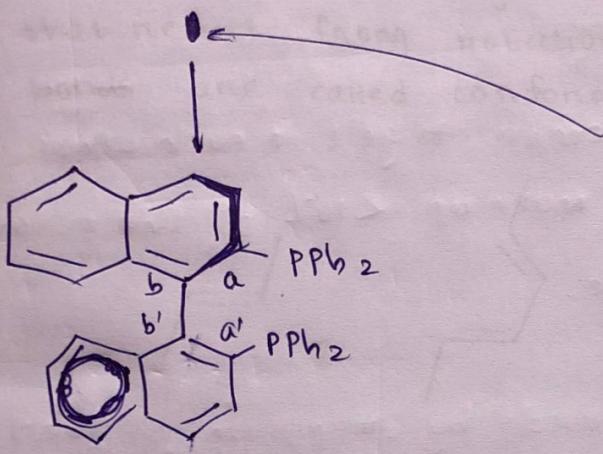


### \* Biphenyl





(S)



(R)

→ Atropisomers are stereoisomers arising because of hindered rotation about a single bond.

→ CIP: -Ph > -C≡CH > tert-but. > vinyl  
 ↑  
 same C - numbers  
 (i.e. more unsaturation,  
 more priority)

→ In meso-form there is nothing like enantiomer (Class Test Famous)  
 (1) pos internal;  
 (2) chiral centre cancelling each other across pos  
 → for meso

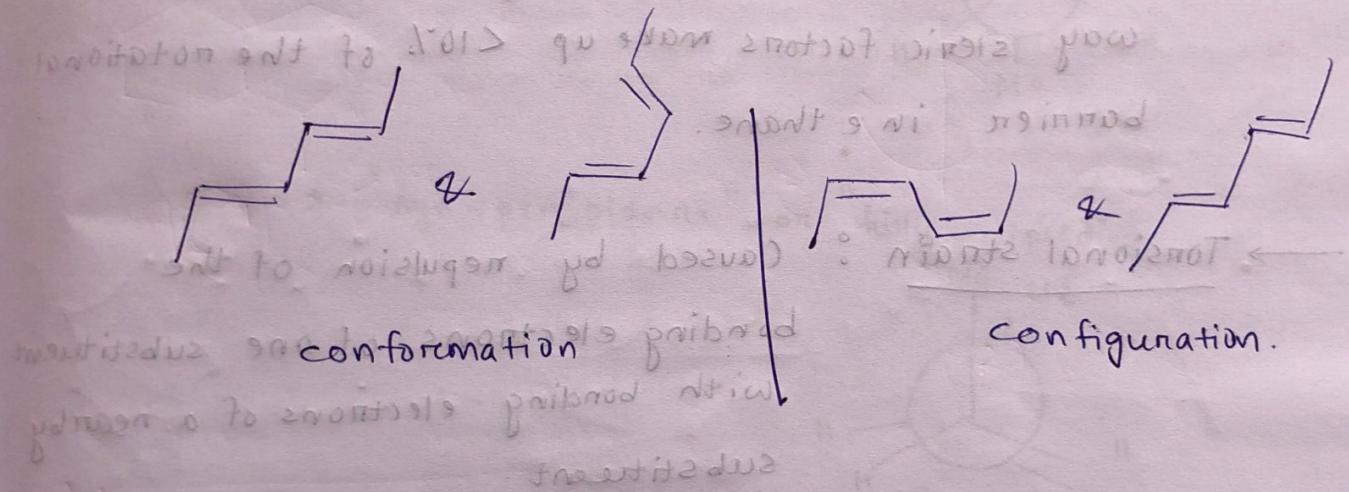
→ S-axis: Take a C-axis; rotate about it; then place mirror ⊥ to the axis and check if same is coming or not.

# CONFORMATIONAL

## ANALYSIS

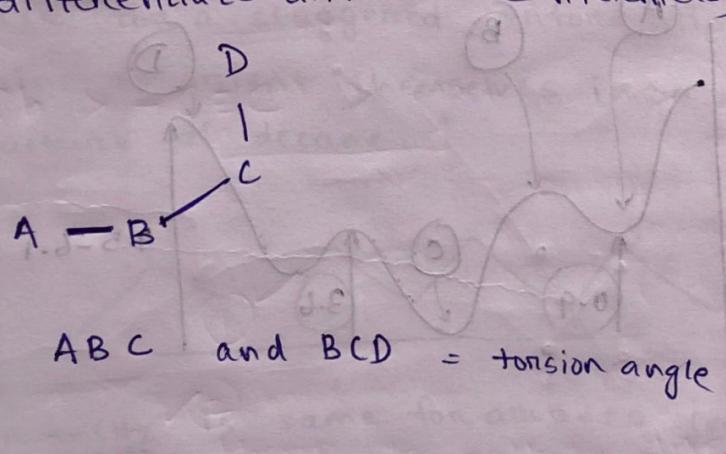
(Analysis of energy change during conformation)

- The different arrangements of the atoms in space that result from rotations of groups about single bonds are called conformations of a molecule.



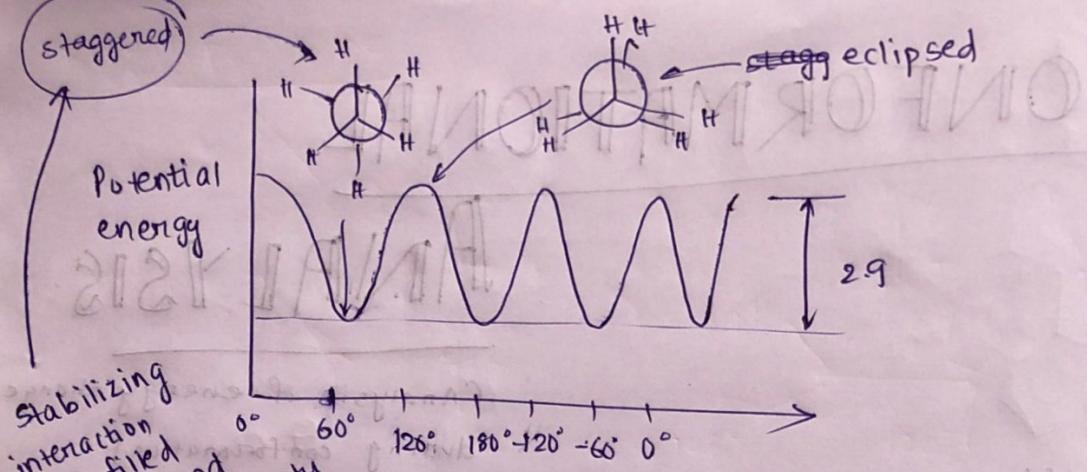
### \* Dihedral / Torsion angle

(to differentiate different conformers)



→ Angle b/w Plane ABC and BCD = torsion angle

→ S.O.S. : Take a point & rotate about it

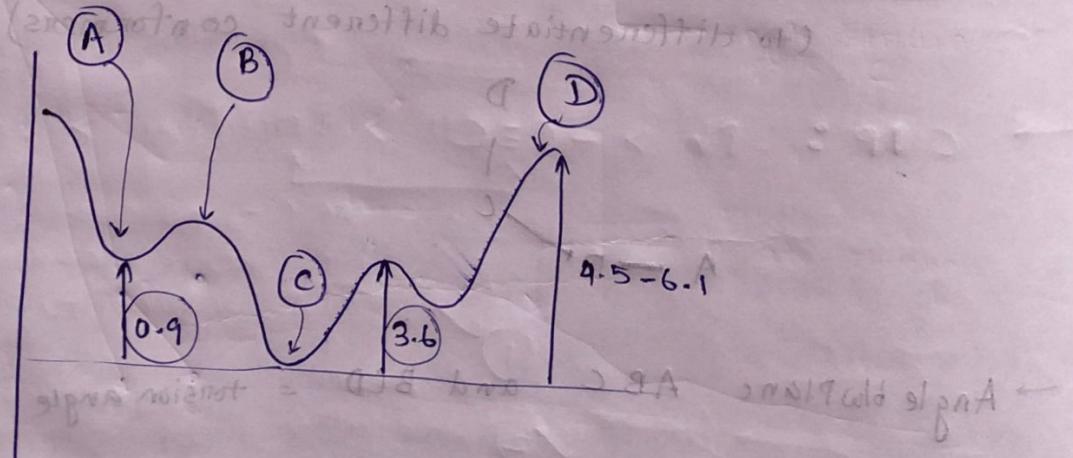


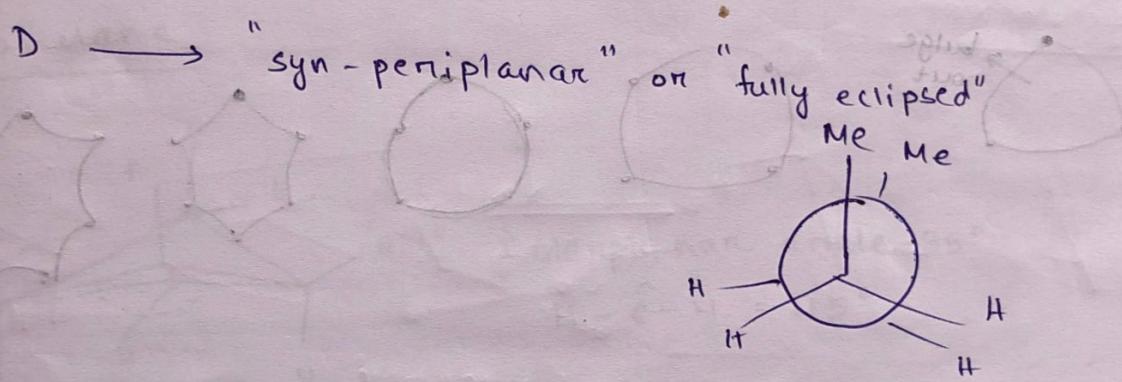
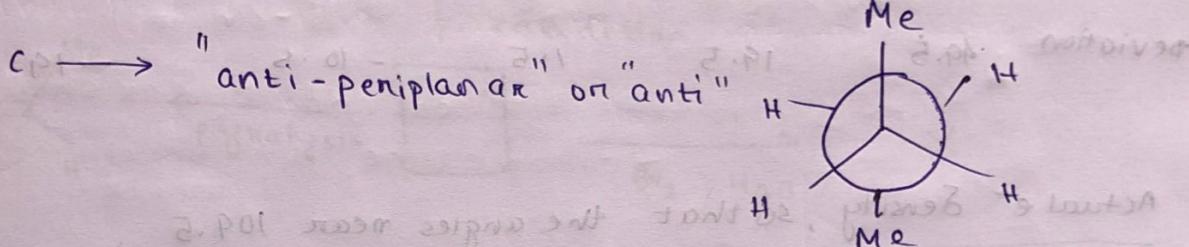
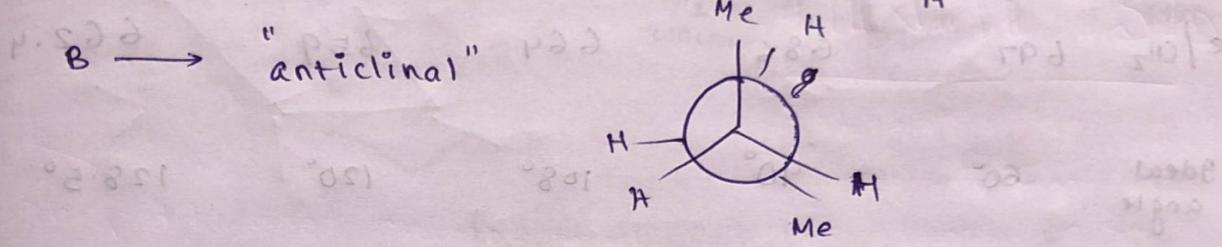
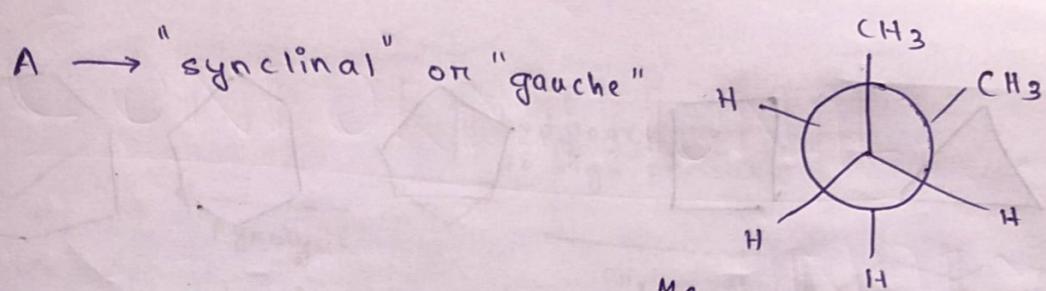
Q. Why above stability order?

→ The H-atoms are too small to get in each other's way steric factors make up <10% of the rotational barriers in ethane.

→ Torsional strain: Caused by repulsion of the bonding electrons of one substituent with bonding electrons of a nearby substituent.

→ Butane

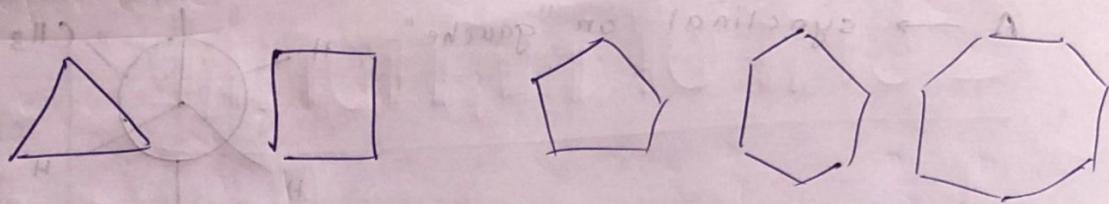




\* The preference for a staggered conformation causes carbon chains to orient themselves in a zig-zag fashion, see structure of decane.



Combustion  
 → Energy per  $-\text{H}_2$  is same for alkanes (nearly) but different for cycloalkanes.



$\text{ce}/\text{CH}_2$  697

686

664

659

662.4

ideal  
angle

60°

90°

108°

120°

128.5°

Deviation

49.5

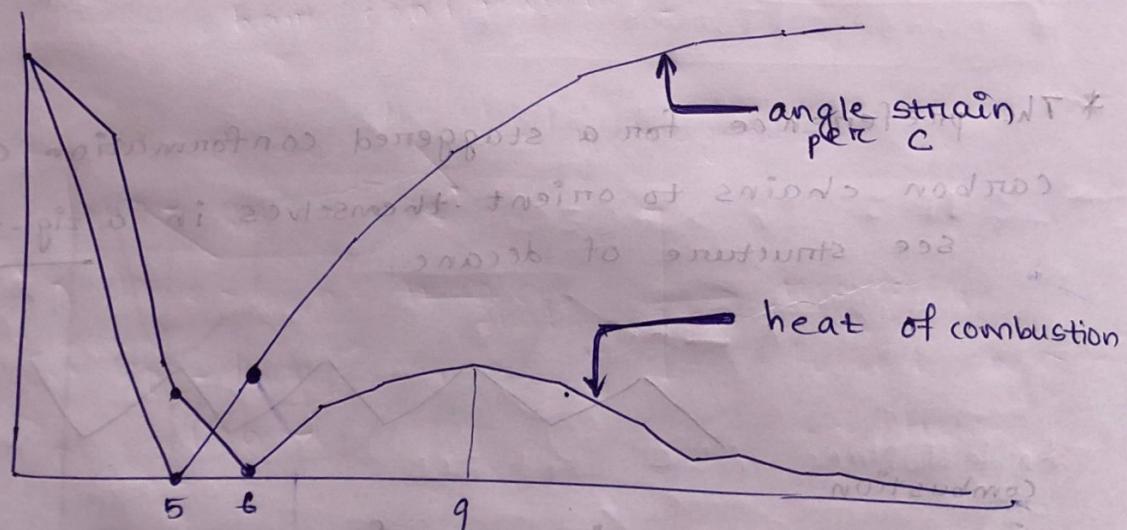
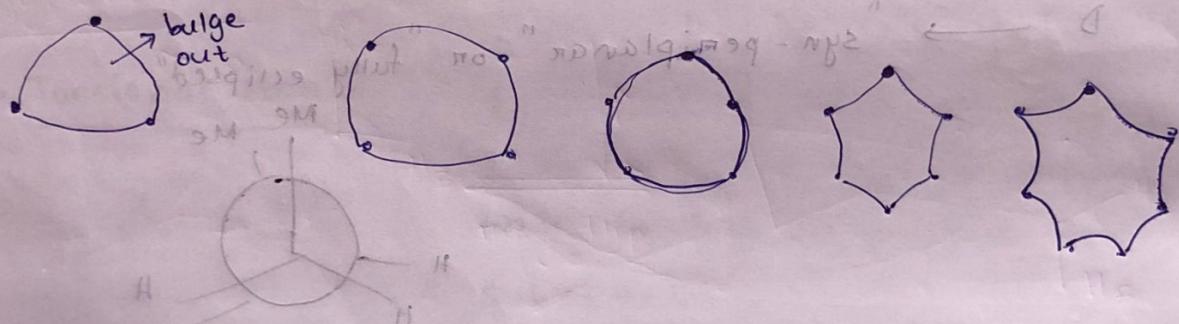
19.5

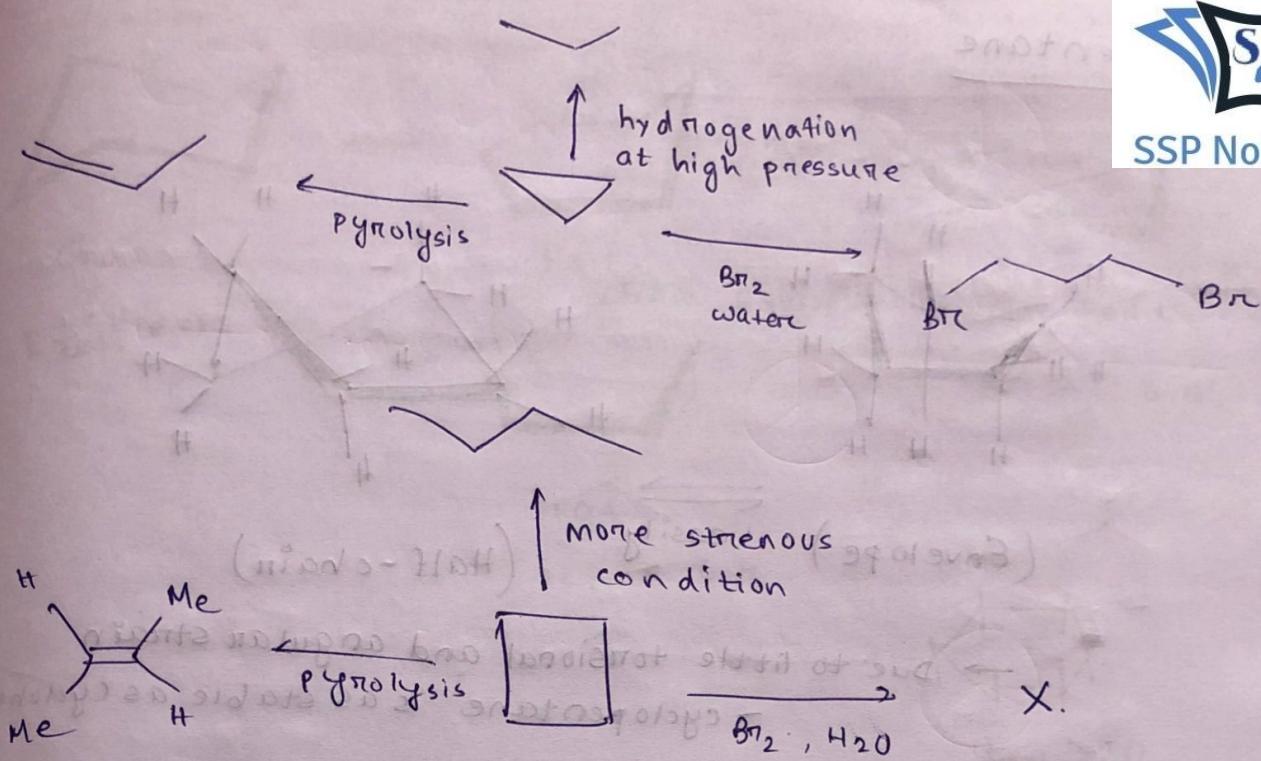
1.5

-10.5

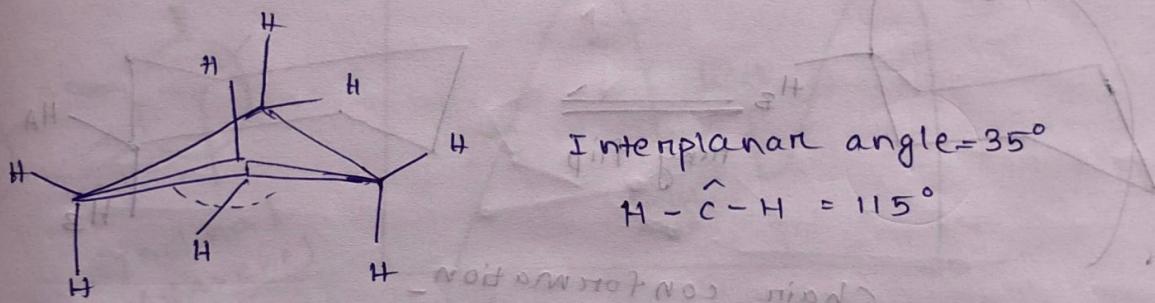
-19

Actual  $e^-$  density, so that the angles near 109.5 ,



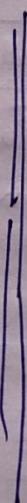


### \* Cyclobutane



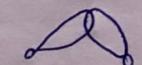
External orbitals : 33% s & 67% p  $\rightarrow \text{sp}^2$

Internal orbitals : 17% s & 83% p  $\rightarrow \text{sp}^5$



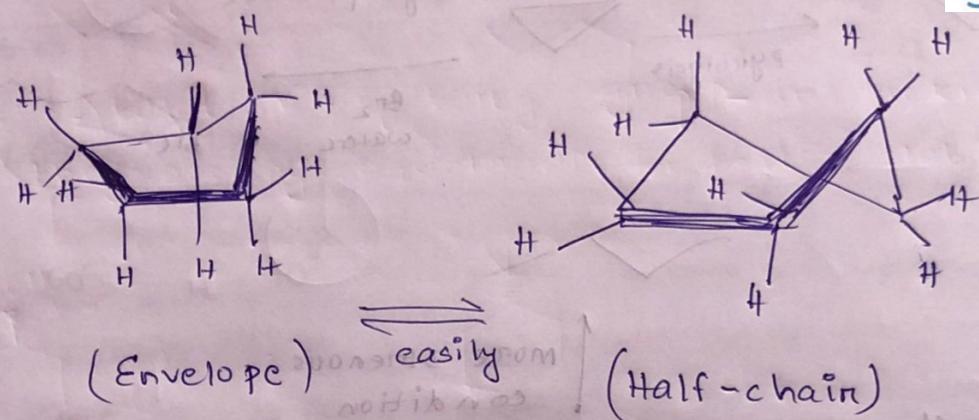
$e^-$  density diverges away from ring by  $21^\circ$

Good overlap



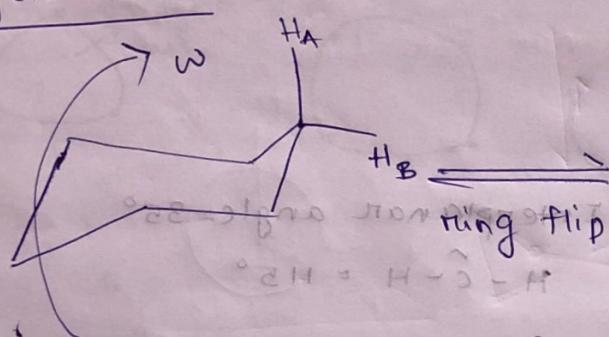
Poor overlap.

## \* Cyclopentane

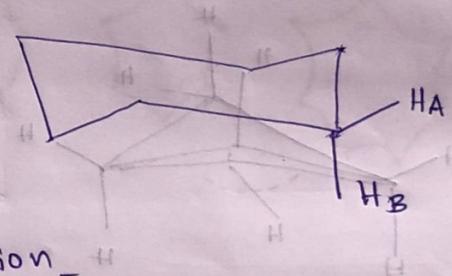


→ Due to little torsional and angular strain  
— cyclopentane is as stable as cyclohexane

## \* Cyclohexane

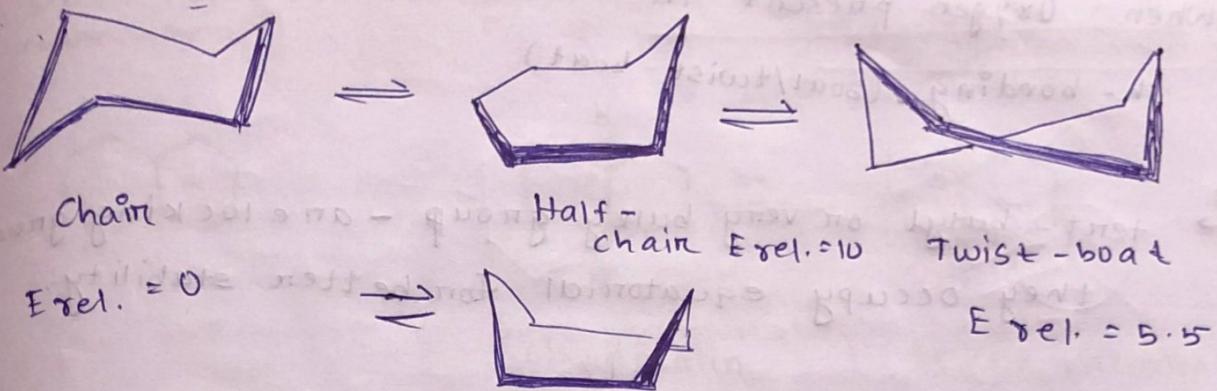


Chair conformation -

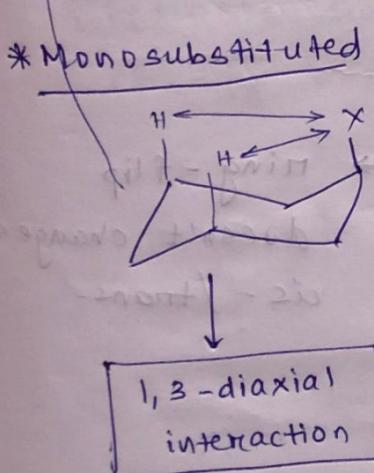
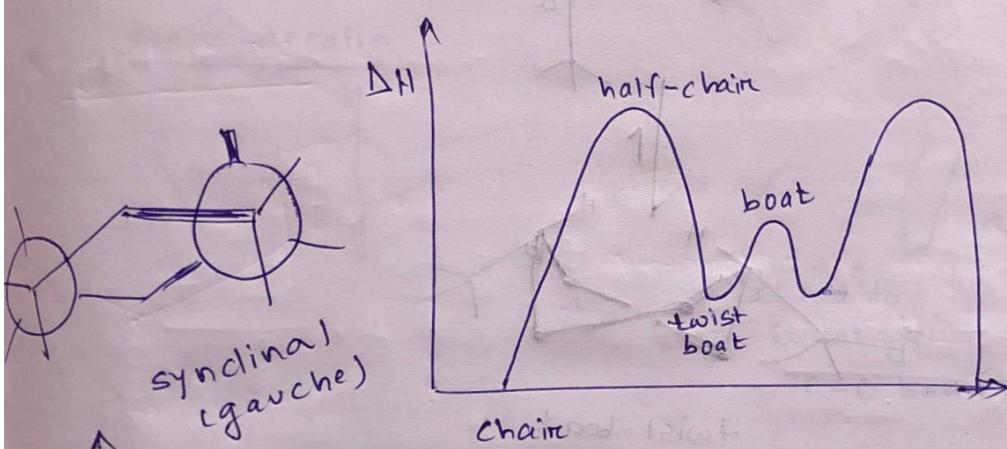


Boat conformation -

## ① Newman projection -



Boat  $E_{\text{rel.}} = 6.5$

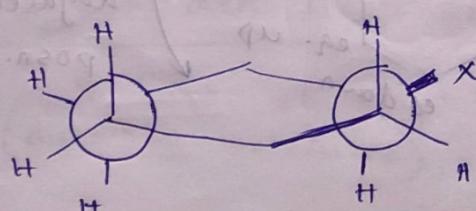


cyclohexane

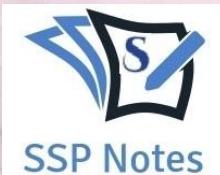
\* One Me-axial has two gauche interaction

This conformation is lower in energy.

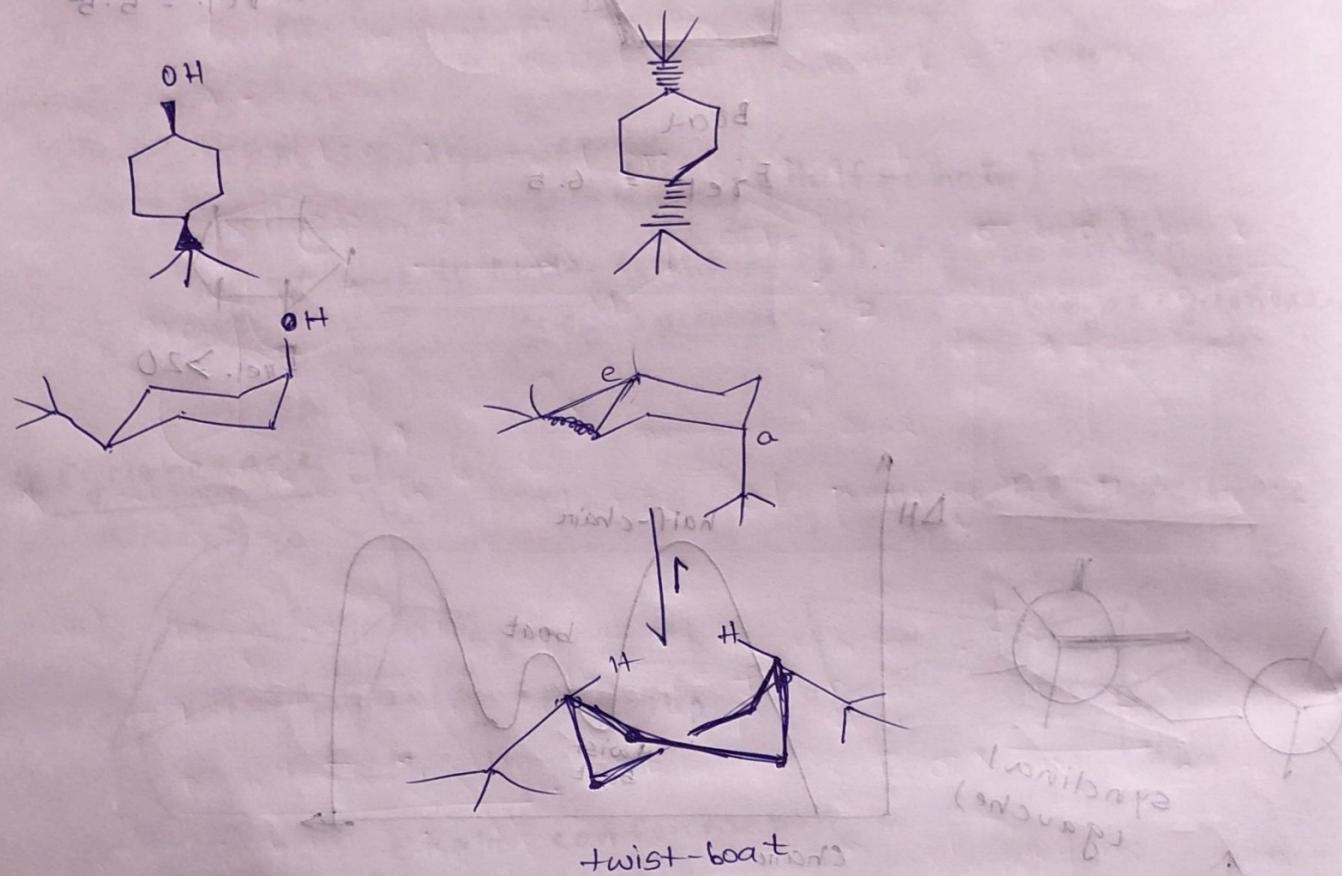
In Newmann's projection, bonds are anti-periplanar



→ When Oxygen present in the substituent, check for  
 Pref. ② h-bonding. (boat/twist-boat)

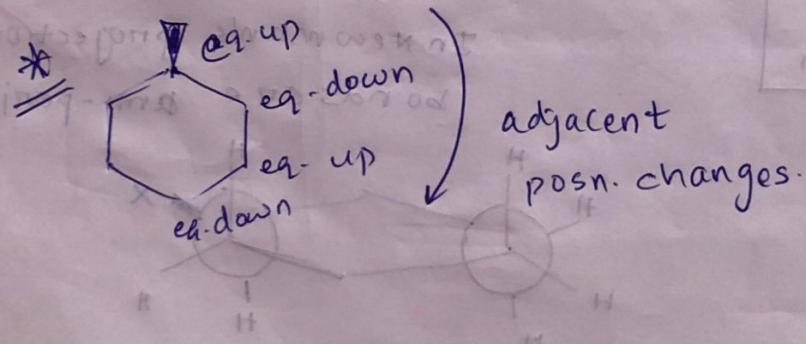


Pref. ① tent-butyl or very bulky group - are locking group, they occupy equatorial for better stability



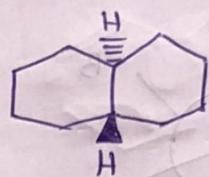
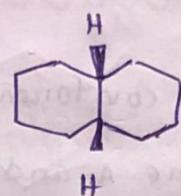
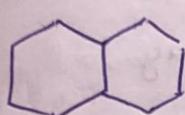
check up-down { up-up = cis  
 not a axial-equatorial } down-down = ~~cis~~ cis  
 up-down = trans

bot flip doesn't change cis-/trans-



Dixib-SI  
 not possible

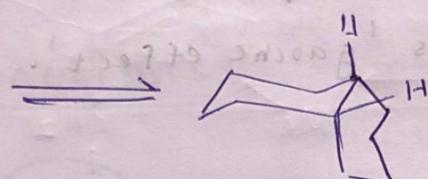
# \* Decalin



cis-decalin

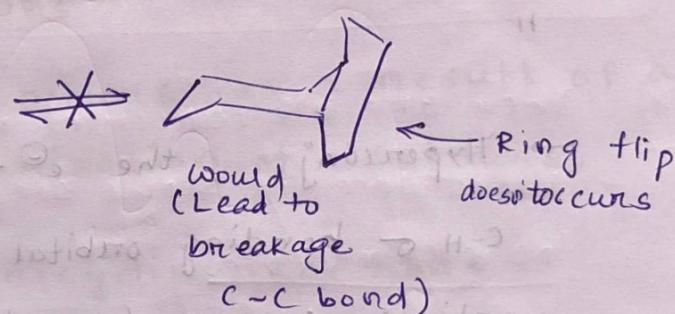
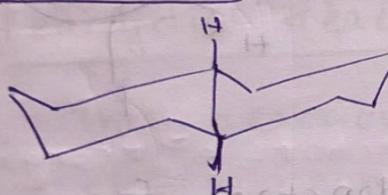
trans-decalin

cis-decalin

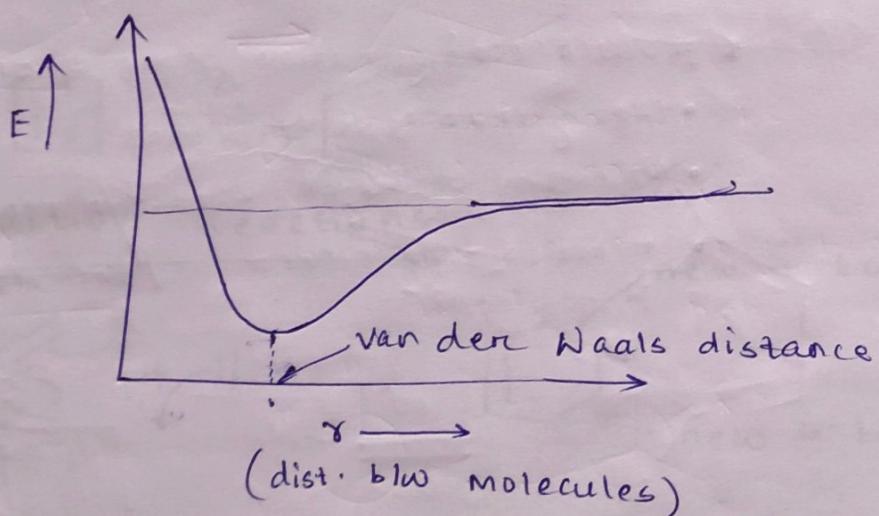


Ring flip ✓ occurs

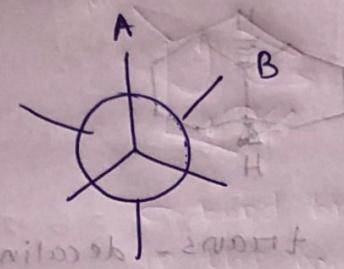
trans-decalin



→ The van der Waals radius → one-half the distance between two equivalent atoms at the point of the energy minimum.



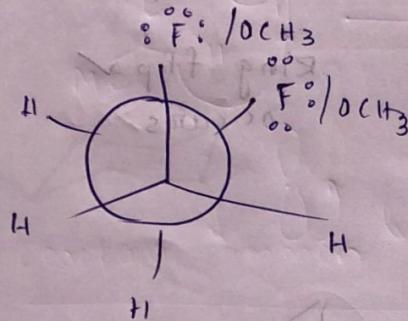
## \* Gauche-Effect:



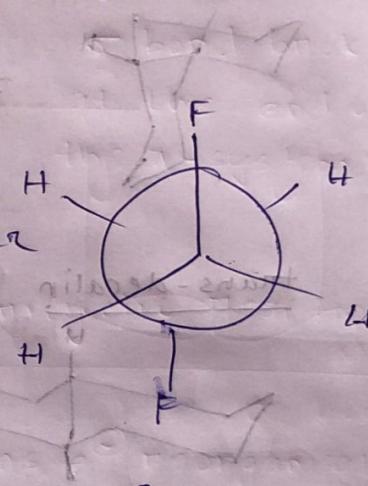
In a conformational array where A and B are second-row electronegative atoms such as N, O, F on unshared  $e^-$  pairs,

the often observed preference for gauche-

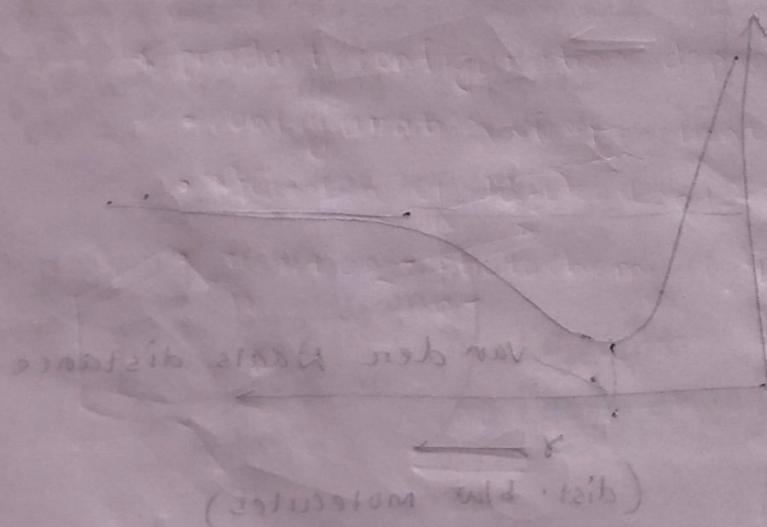
conformation is 'gauche effect'.



is preferred over



Hypconj. the  $e^-$  donation from C-H  $\sigma$  bonding orbital to C-F  $\sigma^*$  anti-bonding orbital = source of stabilization of gauche-isomer.



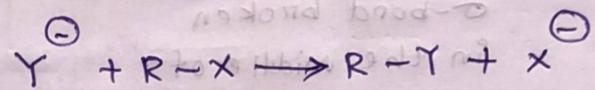
# PERICYCLIC REACTIONS

\* Three classes of organic Reactions



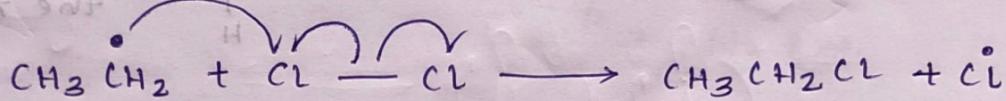
## a) Polar reactions

(ions involved)



R = aliphatic as well as aromatic

## b) Radical reactions

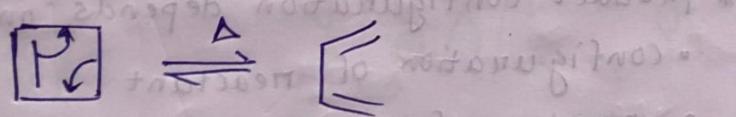
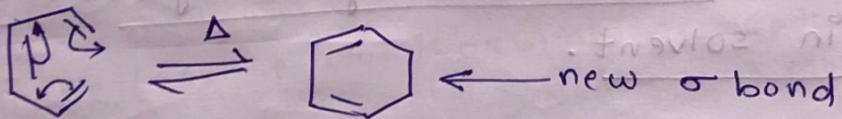


## c) Pericyclic reactions

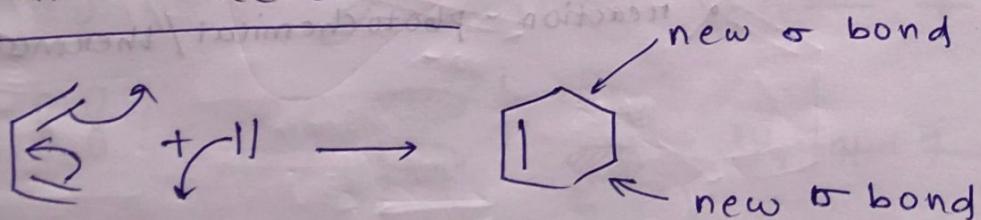
This reaction occurs as a result of a cyclic neorganizat<sup>n</sup> of electrons.

## \* Three types of pericyclic reactions

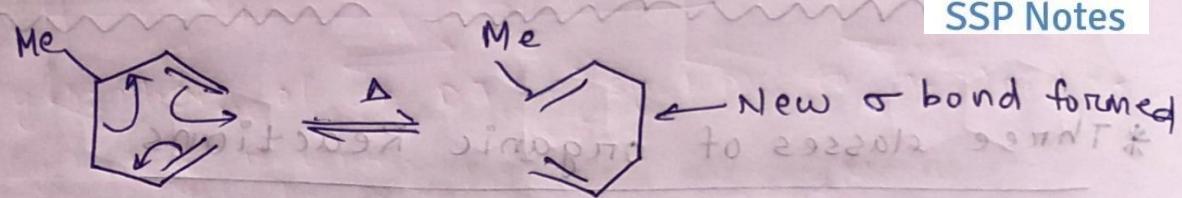
### Electrocyclic reactions



### Cycloaddition reactions



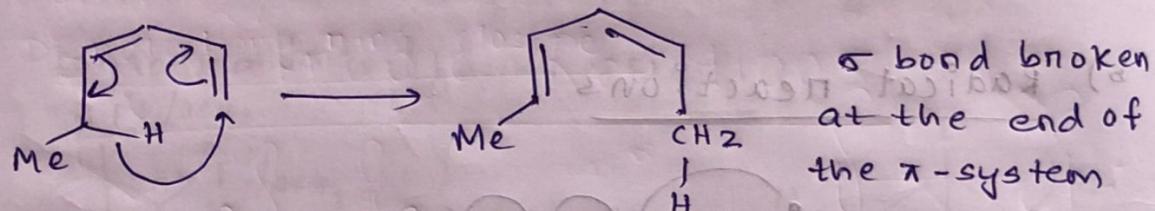
### c) Sigmatropic reactions



$\sigma$ -bond broken

in the middle of  $\pi$ -system.

$\pi$ -system.



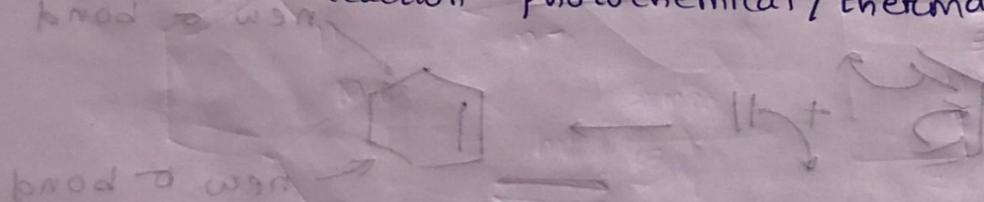
#### \* Certain common features of polycyclic reactions

- They are all concerted reactions, e.g. reorganisation takes place in single step, there is one TS and no intermediates.
- Highly stereospecific.
- Rxn. not affected by catalysts or by a change in solvent.



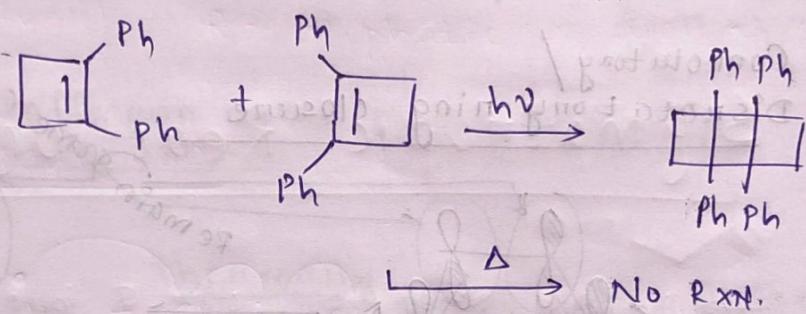
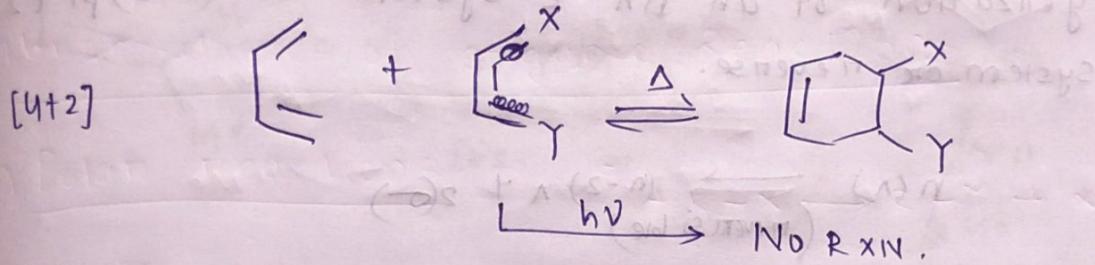
\* product configuration depends on -

- configuration of reactant
- number of double bonds in reactant
- reaction - photochemical / thermal.



$[4+2]$  cycloaddition → thermally induced

$[2+2]$  cycloaddition → photochemically induced

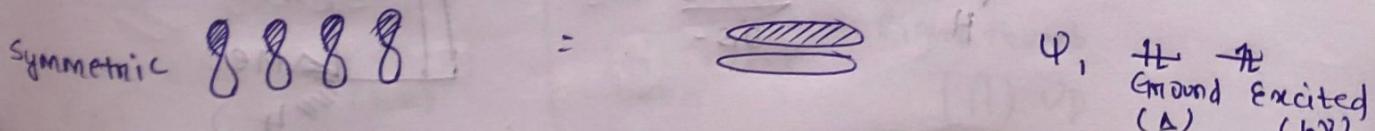
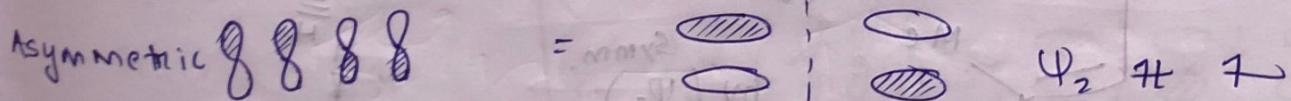
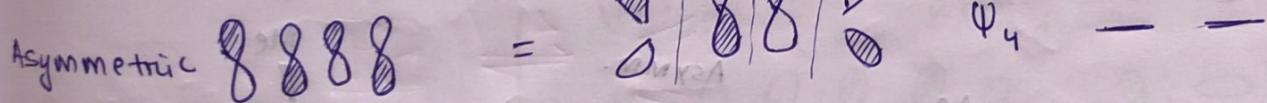


### \* Conservation of Orbital Symmetry Theory

\* In phase orbital overlap in pericyclic reactions.

- The occupied orbitals of different molecules repel.
- +ve and -ve charges attract each other.
- Occupied orbitals of one molecule and the unoccupied orbitals of the other (HOMO, LUMO) interact with each other.

\* 1,3-Butadiene (Four p-atomic orbitals overlap to give four  $\pi$  molecular orbitals)

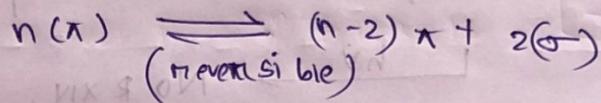


# 1 Electrocyclic Reactions

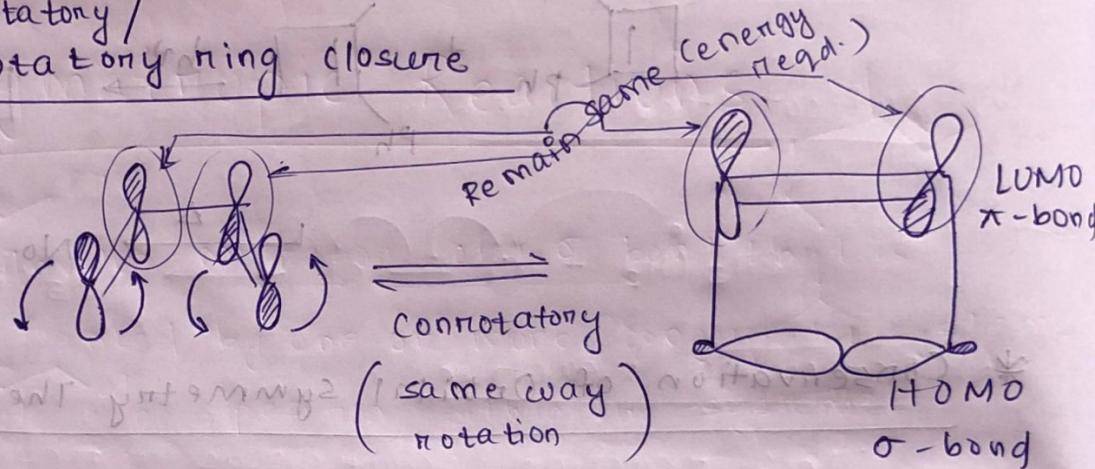


SSP Notes

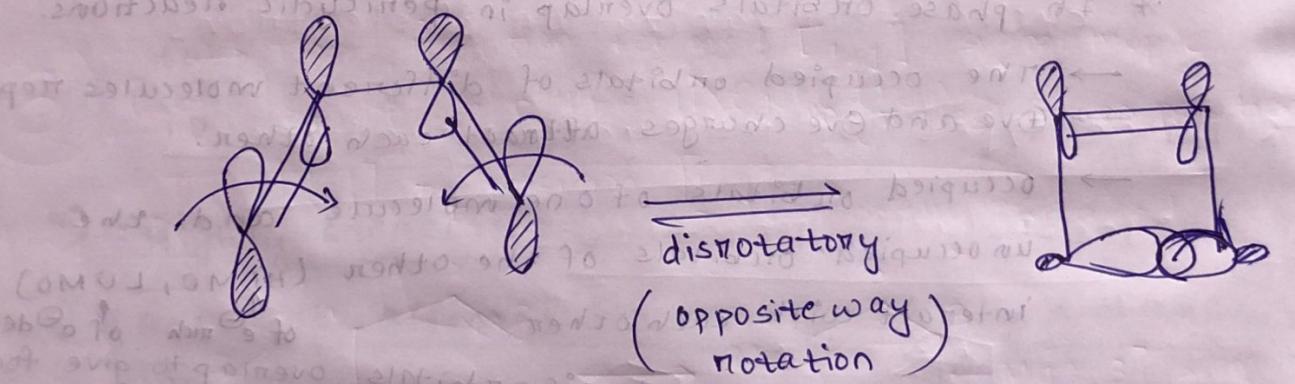
cyclization of an  $n\pi$   $e^\ominus$  system to  $(n-2)\pi^\circ + 2\sigma^\ominus$  system or reverse.



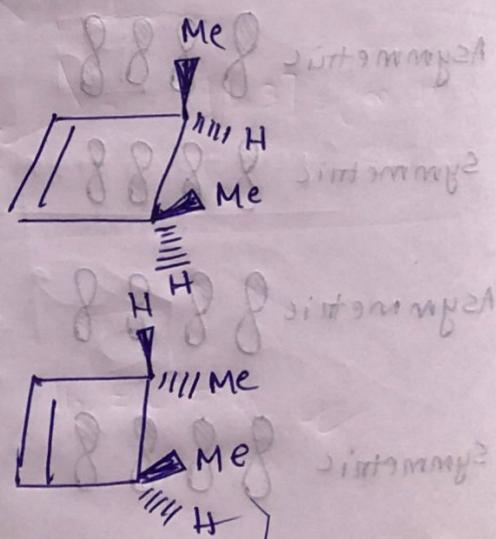
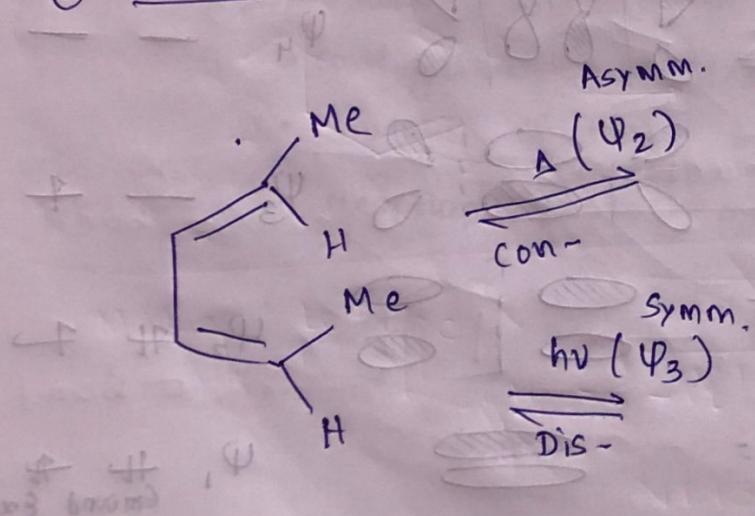
## a) Conrotatory / Disrotatory ring closure

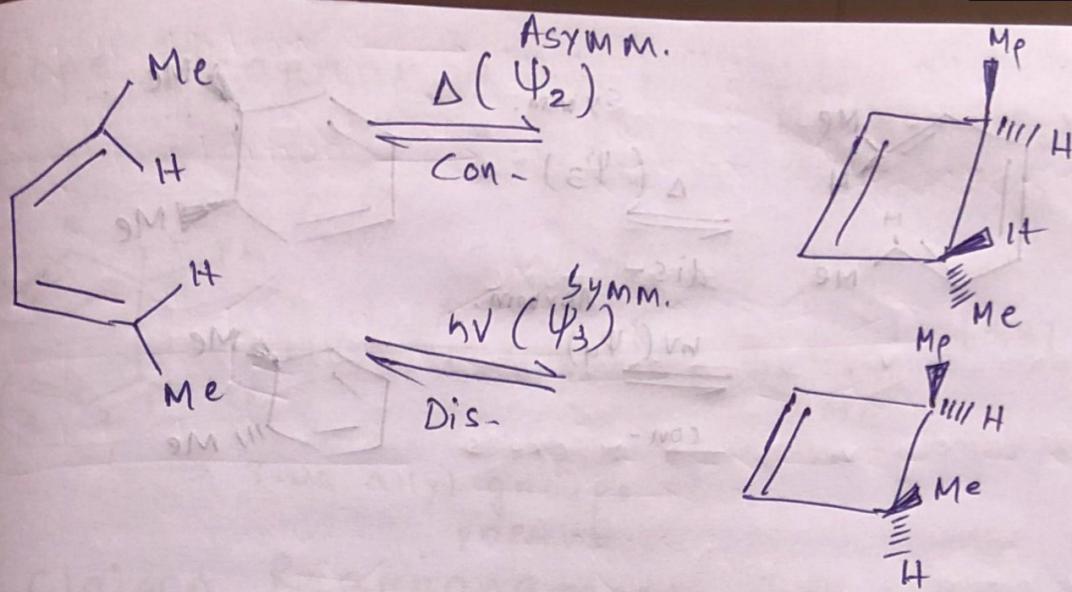


conrotatory disrotatory in general starting from HOMO



## b) Examples





① Woodward-Hoffmann rules : cyclohexadiene

No. of  
π-electrons

Thermally  
allowed, photochemically  
forbidden

Thermally  
forbidden,  
photochemically  
allowed

$4n + 2$       Con-

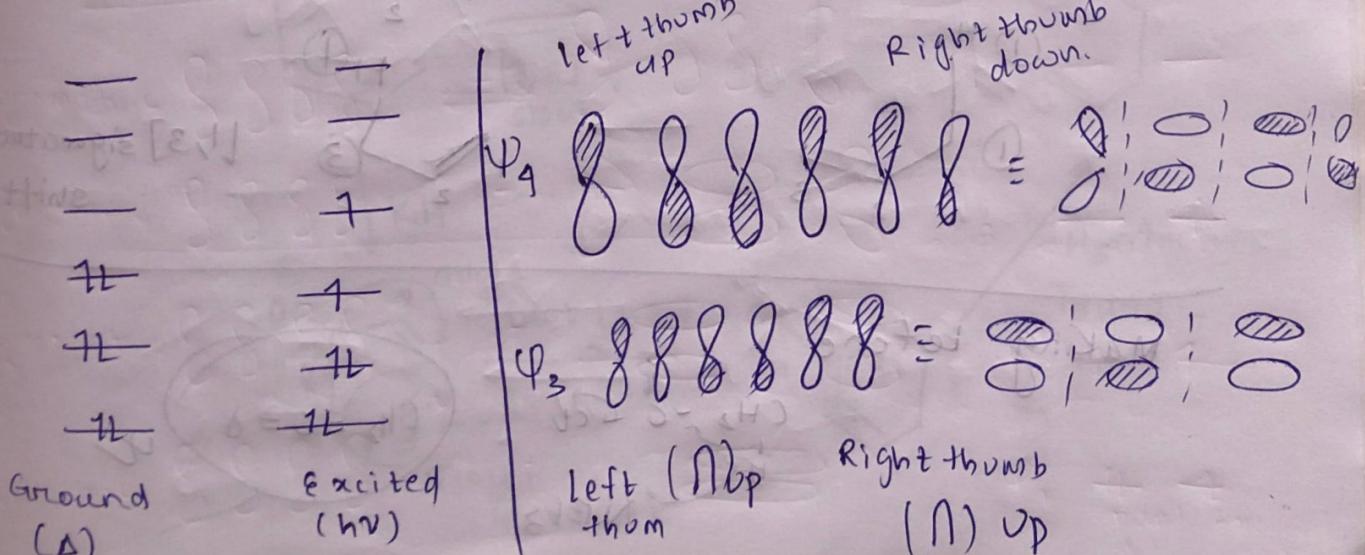
Dis-

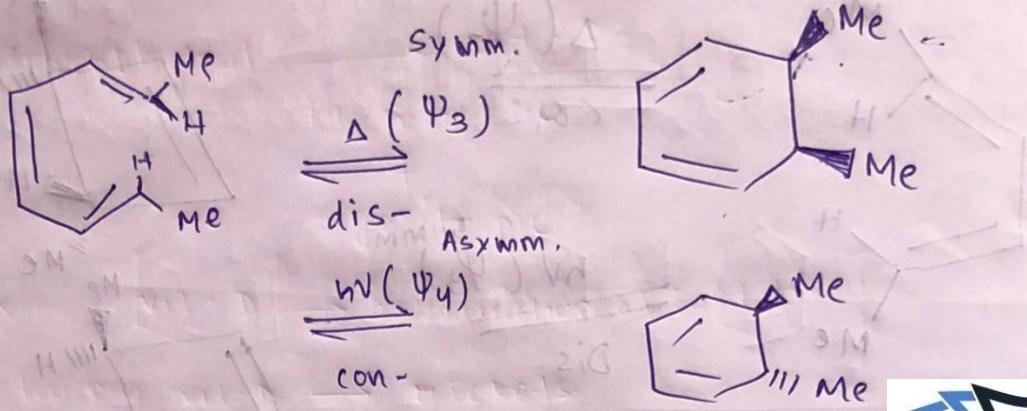
Con-

② 1,3,5-Hexatriene ( $\text{H}_3\text{C}-\text{CH}=\text{CH}-\text{CH}=\text{CH}-\text{CH}_3$ )

$\Psi_1, \Psi_3, \Psi_5 \rightarrow$  Symmetrical

$\Psi_2, \Psi_4, \Psi_6 \rightarrow$  Asymmetrical



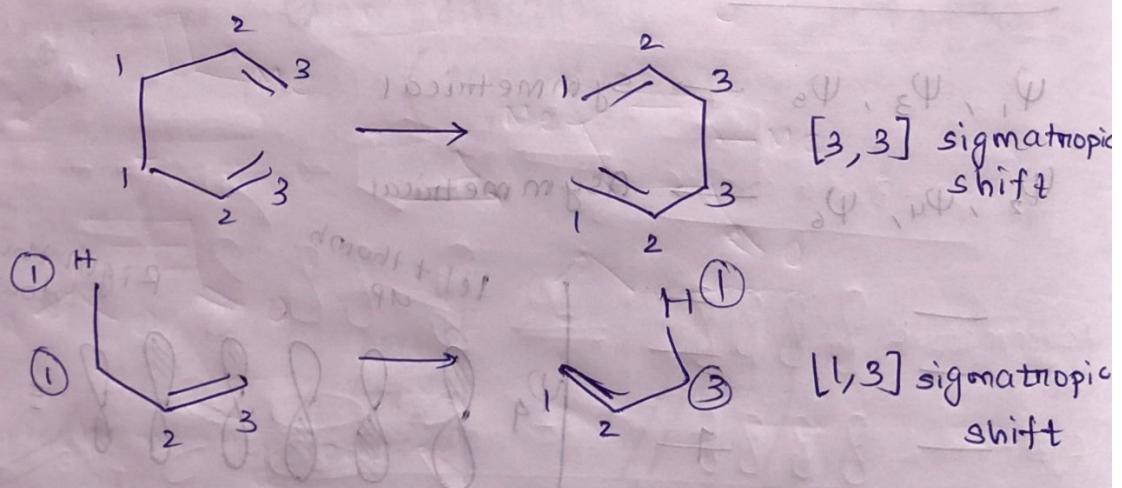


②

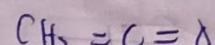
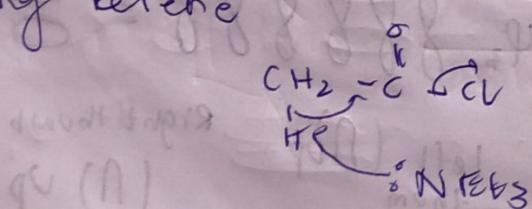
## Sigmatropic Reactions

→ Involve migration of a  $\sigma$  bond that is flanked by one or more conjugated systems to a new position within the system.

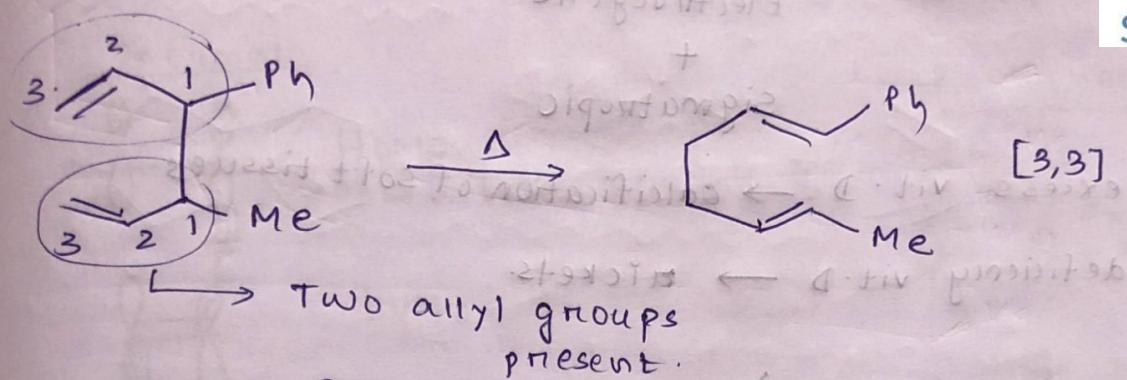
→ This reaction termed  $[i,j]$  sigmatropic shift when the bond migrates from position  $[i,i]$  to position  $[i,j]$ .



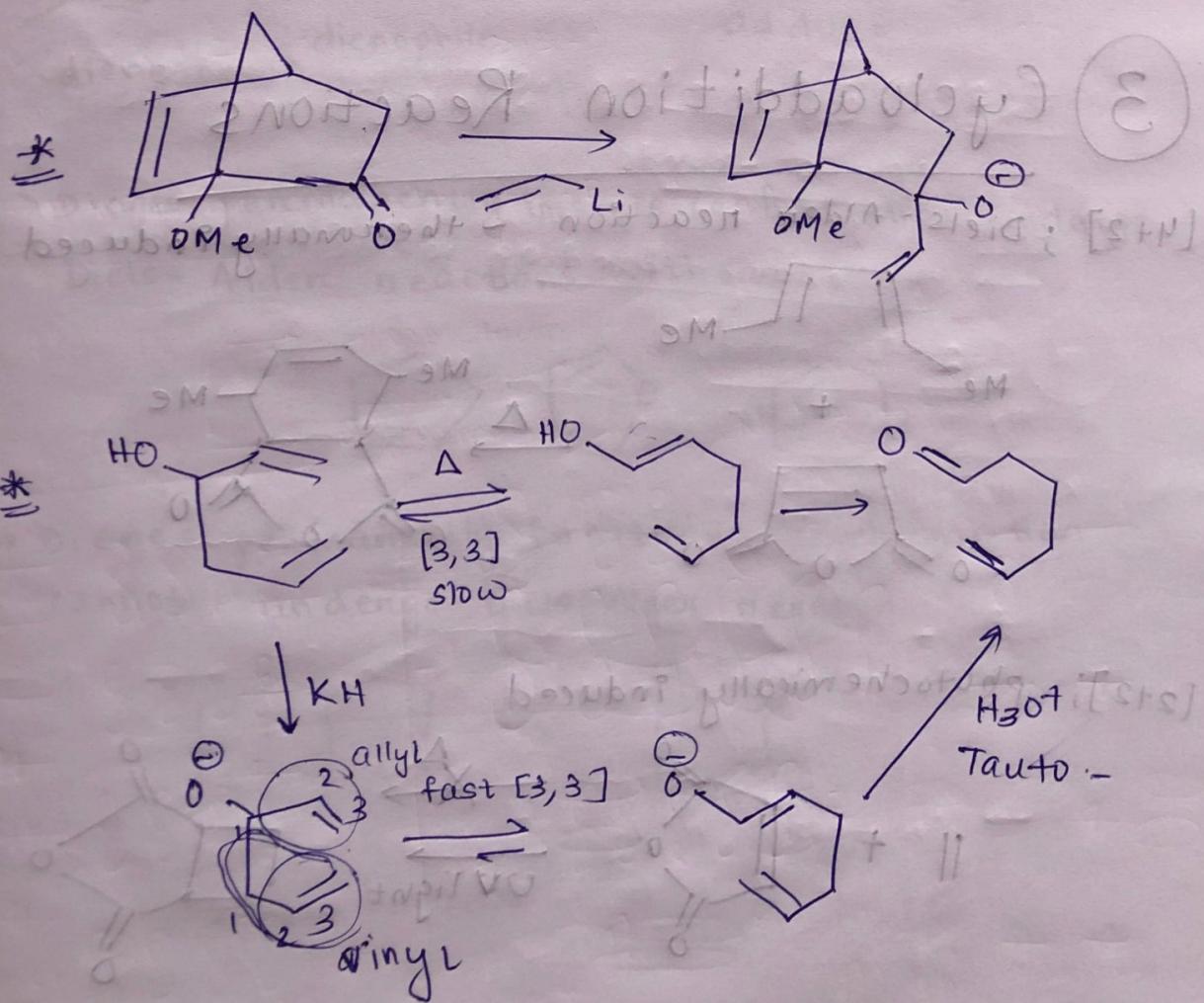
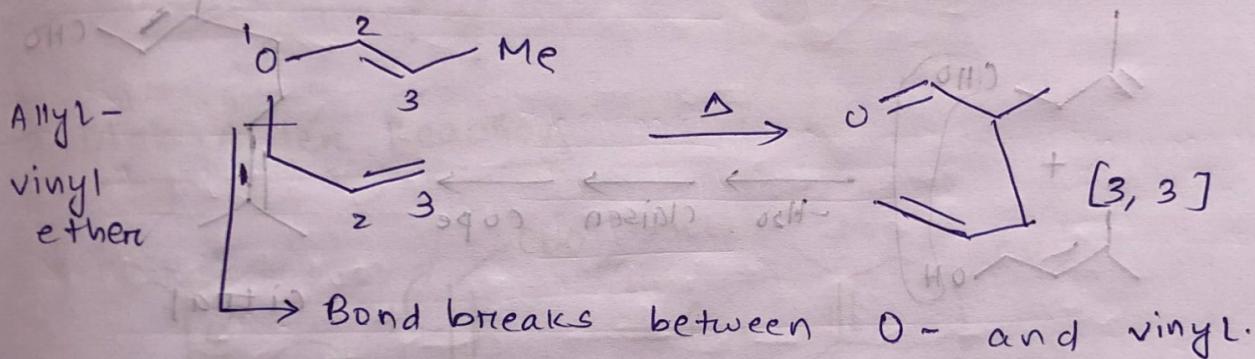
Making ketene

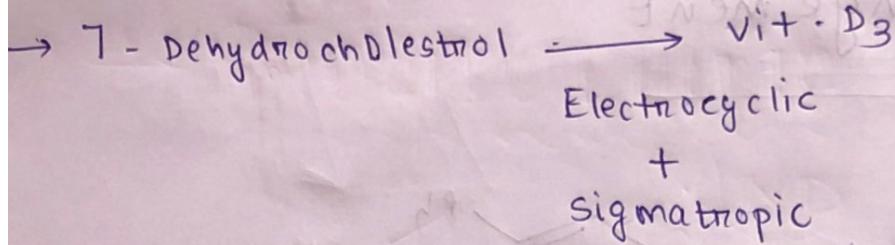


# A Cope Rearrangement



# A Claisen Rearrangement

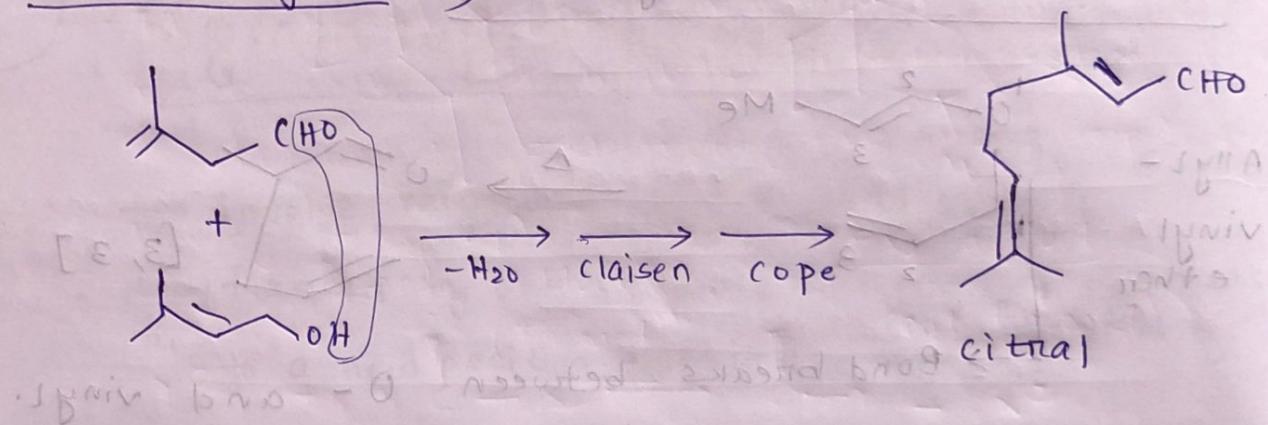




excess vit. D → calcification of soft tissues

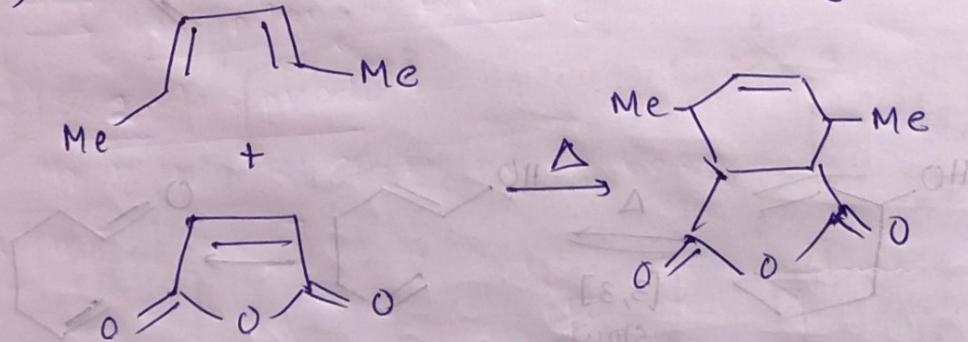
deficiency vit. D → rickets.

(\*Check citral synthesis)

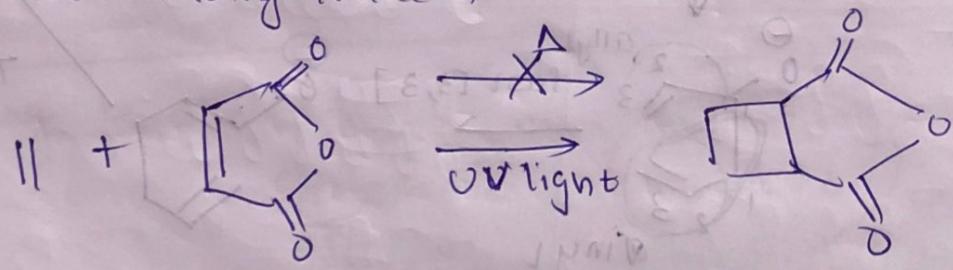


### ③ Cycloaddition Reactions

[4+2] ; Diels-Alder reaction ~ thermally induced

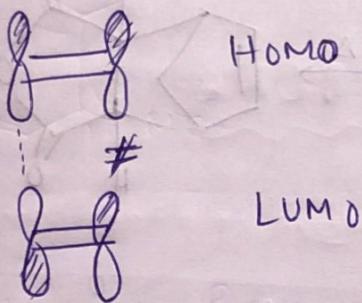


[2+2]; photochemically induced

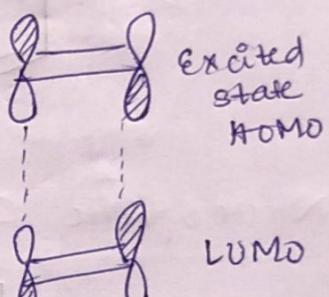


→ HOMO of one reactant should react with LUMO of other.

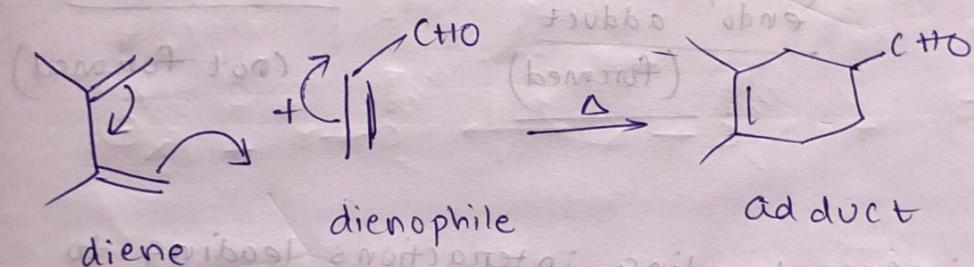
Thermal



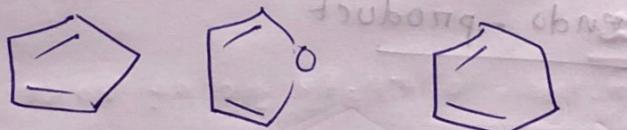
Photochemical



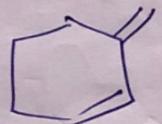
→ Diels-Alder Reaction



→ Dienes permanently in s-cis conformation undergo Diels-Alder reactions with ease.

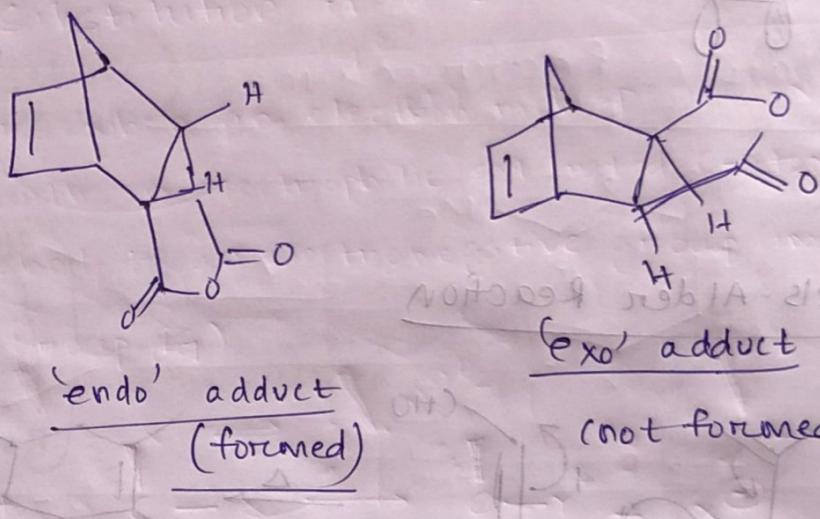
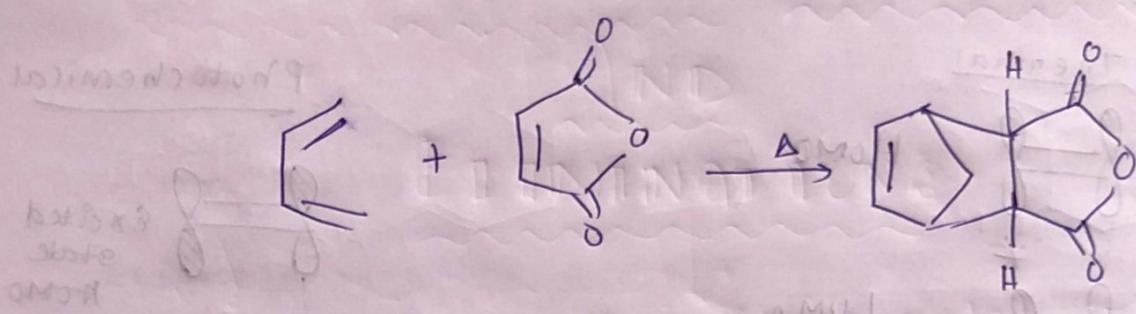


→ Dienes permanently in s-trans conformation cannot undergo Diels-Alder reaction.



endo-rule

→ 'endo' adduct forms in Diels-Alder reaction.



3) → primary bonding interactions leading to new  $\sigma$ -bonds.

→ secondary bonding interactions leading to endo-product

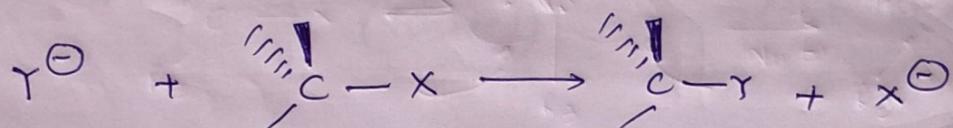


# NUCLEOPHILIC AND ELIMINATIONS



\* Nucleophilic Substitution at a saturated carbon

→ It occurs when an electron rich species,  $\text{Nu}^-$ , reacts with an electrophilic saturated C-atom which is attached to an electronegative group (imp.), the leaving group (LG)



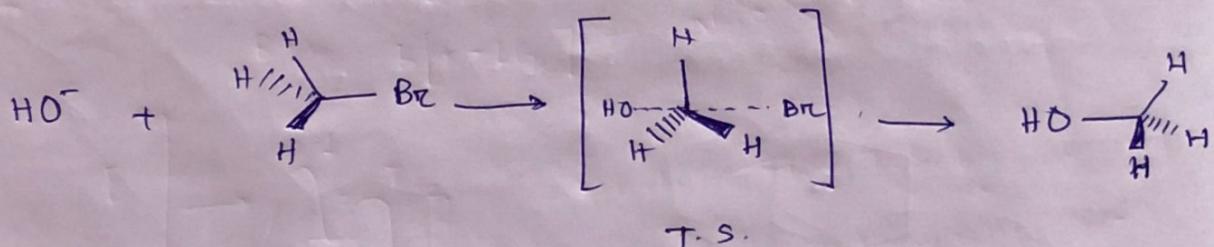
a)  $S_N1$  ( LG goes first and  $\text{Nu}^-$  comes later)

b)  $S_N2$  ( $\text{Nu}^-$  attacks and LG goes simultaneously)

(\*)  $S_N2$

Hydrolysis of  $\text{CH}_3\text{Br}$  in aq. base -

$$\text{Rate} = k [\text{HO}^-] [\text{CH}_3\text{Br}]$$

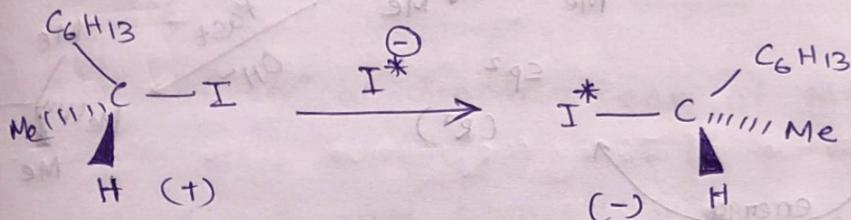


→ An approach by  $\text{OH}^-$  along the line of centers of the C & Br is that of lowest.

→ Walden inversion occurs

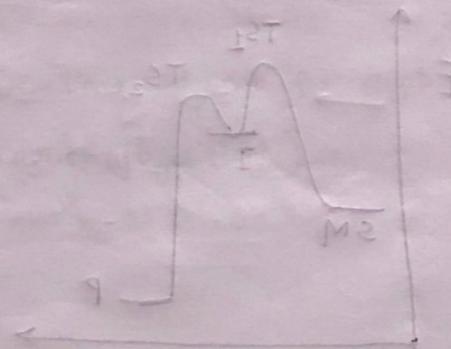
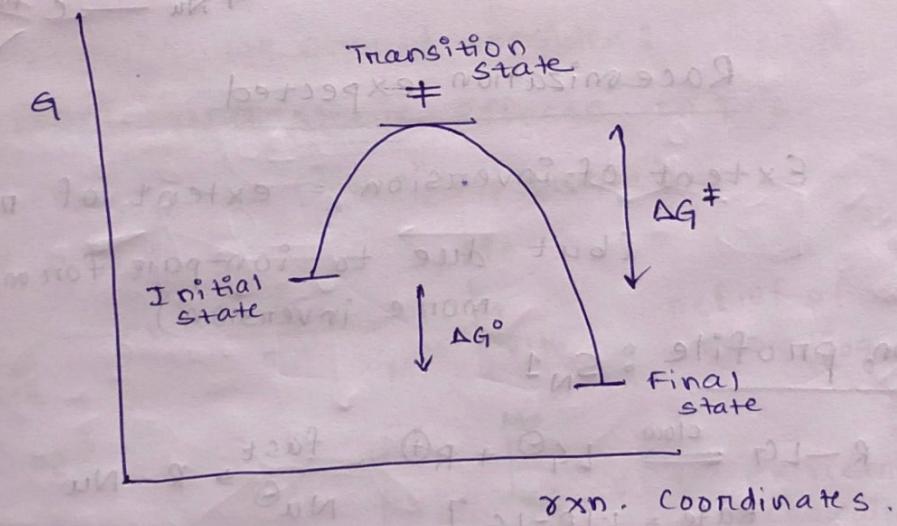
⇒ Inversion of configuration does not mean R going to S or vice versa. It means bond formation takes place opposite to that of bond breaking...

inversion of umbrella in stereo.



Rate of racemization = twice the rate of inversion or incorporation

→ Reaction profile  $\text{S}_{\text{N}}^2$

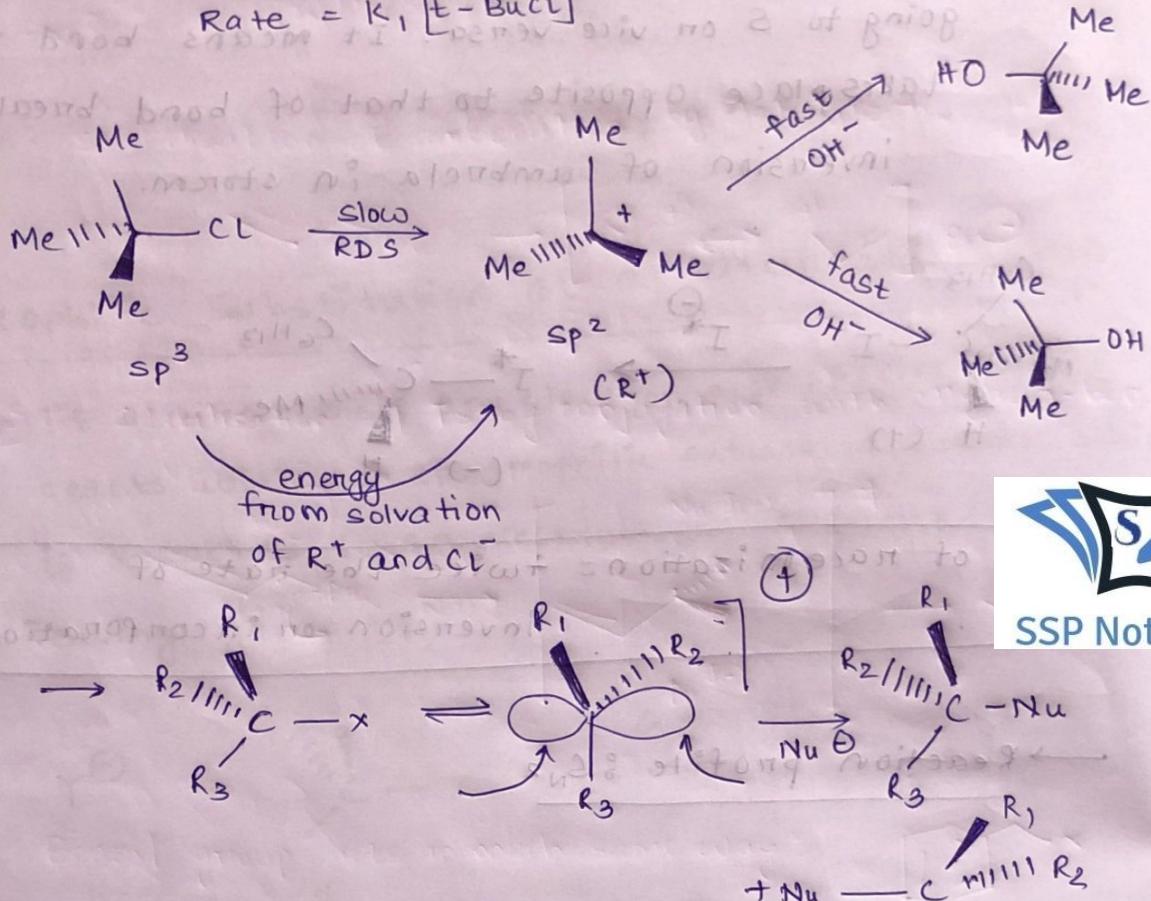


\*

### $S_N1$

Hydrolysis of tert-butyl chloride by base proceeds -

$$\text{Rate} = K_1 [t\text{-BuCl}]$$

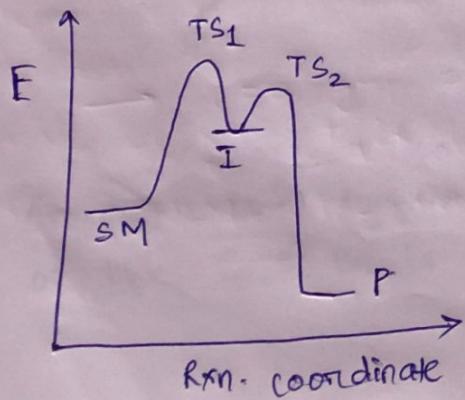
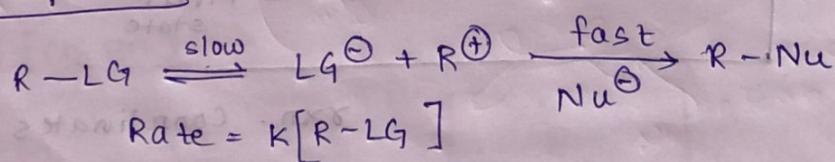


Raceination + expected

Extent of inversion = extent of retention

(but due to ion-pair formation; more inversion)

Reaction profile :  $S_N1$



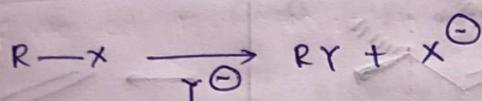
## \* Factors Affecting $S_N1$ & $S_N2$



SSP Notes

- 1) The structure of the substrate
- 2) conc. ; reactivity of  $Nu^-$ .
- 3) The effect of solvent
- 4) The nature of leaving group (nucleofuge)
- 5) stereochemical implications of mechanism.

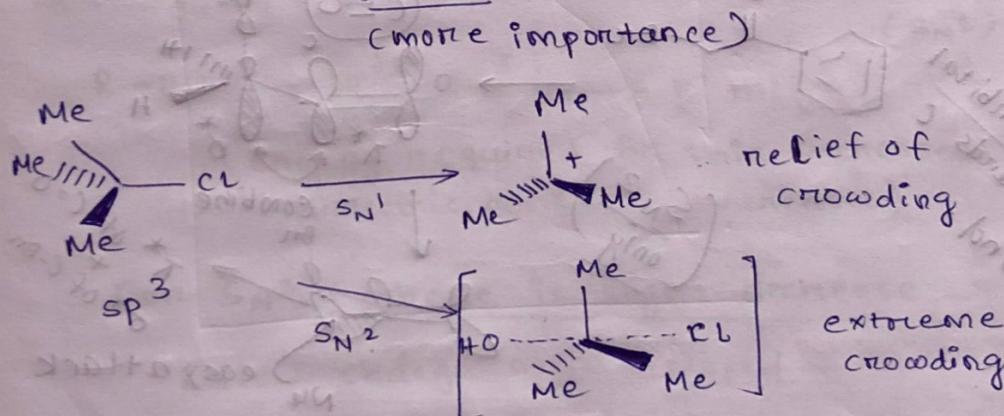
### \* Effect of substrate structure



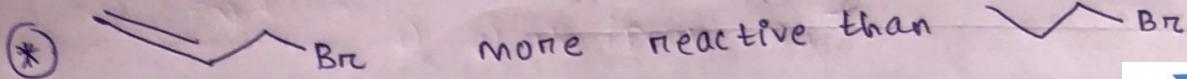
$S_N2$  : Methyl > Primary > Secondary >> Tertiary (Unreactive)

$S_N1$  : Tertiary >> Secondary > Primary > Methyl.

→ To explain we should consider:  
electronic and steric effects on T.S.



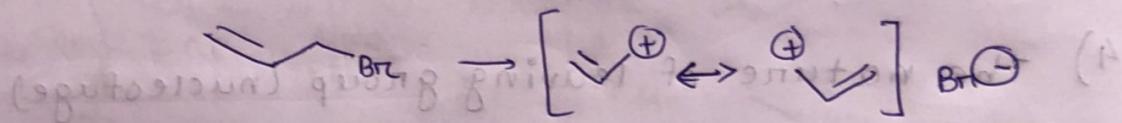
→ stability of carbocation - important for  $S_N1$   
(inductive + hyperconjugation)



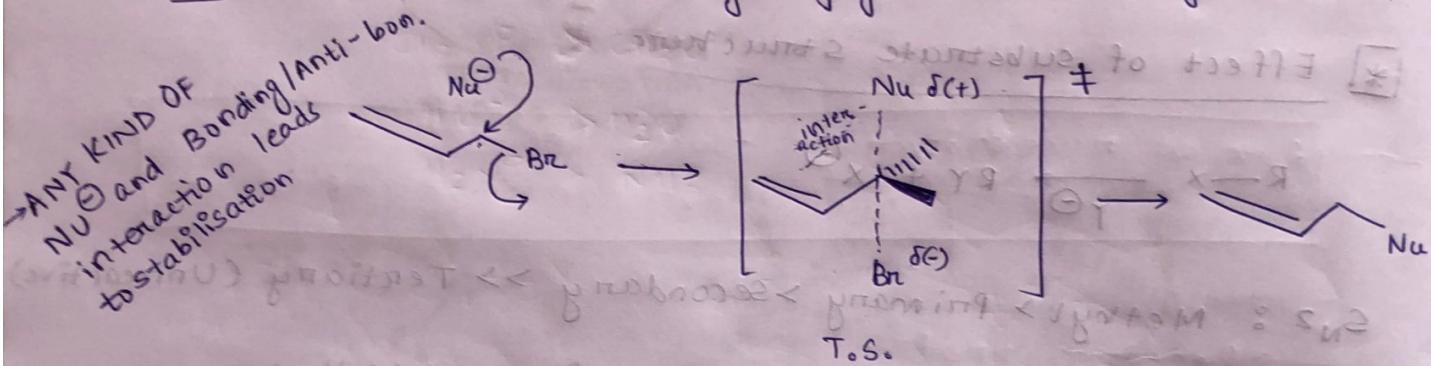
( $S_N1$  /  $S_N2$ )

Only to protonate;

$S_N1$ : stabilisation of carbocation by delocalization



$S_N2$ : stabilisation of TS by conjugation with allylic  $\pi$ -bond

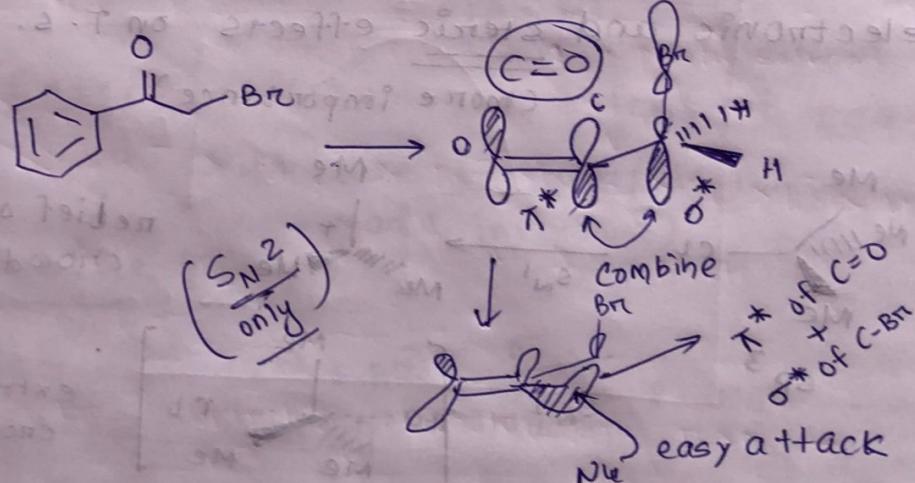


Benzyl group acts in much same way:

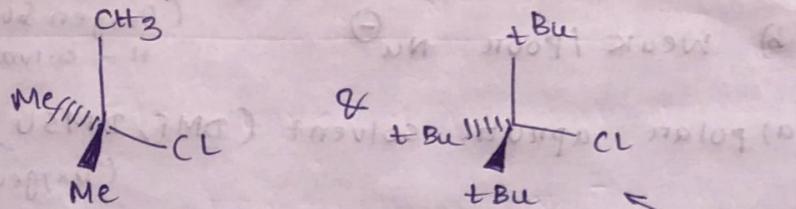


Imp.

$\text{Nu}^-$  attacks anti-bonding orbital which is towards C bond in  $-\text{C}-\text{X}$



$\text{C}=\text{O}$  grp. stabilises the T.S. by overlap of its  $\pi^*$  orbital with full  $p_{\sigma}$  orbital of the C-atom under attack.

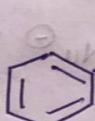
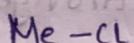


600 times

faster

(steric acceleration)

slight shift to right



500

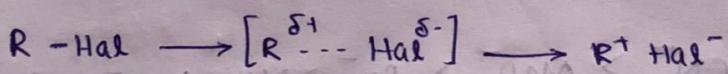
$\text{H}_2\text{O}^+$

$\text{Cl}^-$

C=O grp. stabilises TS by overlap of its  $\pi^*$  orbital with full p-orbital of the C-atom under attack.

### Solvent effect

→ Increase in dielectric constant and/or ion-solvating ability result in a marked increase in reaction rate. ( $\text{S}_{\text{N}}^1$ )



(Energy required for this decreases as dielectric constant increases)

For  $\text{S}_{\text{N}}^2$ ; there is slight decrease -

- New charge not developed
- Existing charge is dispersed in the T.S. compared to starting material.

→  $\text{S}_{\text{N}}^2$  from polar protic solvent to polar aprotic solvent;  
rate increases (to max  $\text{S}_{\text{N}}^2$ )



- MeOH solvates  $\text{Na}^+$  and  $\text{N}_3^-$
- DMSO solvates  $\text{Na}^+$ ;  $\text{N}_3^-$  is free to attack.

$\rightarrow S_N 1 :$

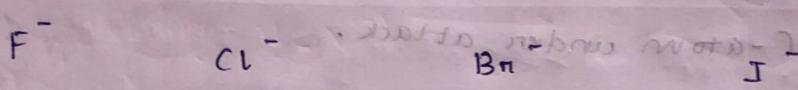
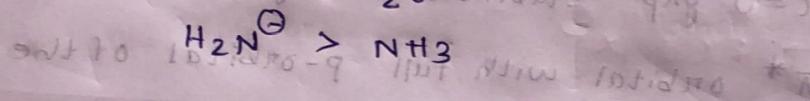
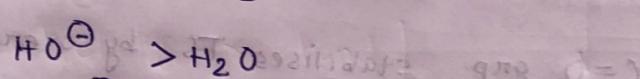
- a) polar protic solvent ( $H_2O / MeOH / EtOH$ )
- b) Weak / Poor  $Nu^-$  (Oxygen solvates cation  
H - solvates anion)

$S_N 2 :$

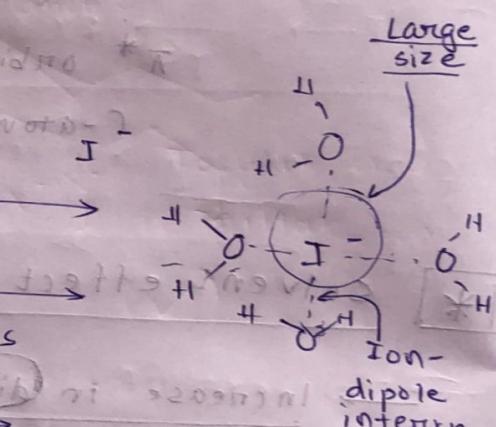
- a) polar aprotic solvent (DMF, DMSO)  
(Oxygen solvates cation)
- b) strong & High conc.  $Nu^-$  ( $MeO^-$ ;  $HO^-$  etc.)

## \* Effect of Nucleophile

→ A negatively charged  is always stronger than its conjugate acid.



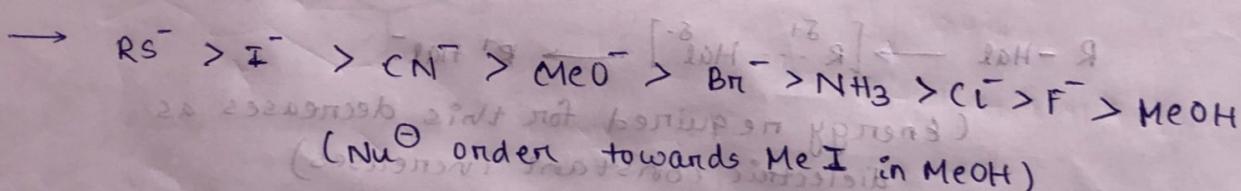
Basicity decreases



Nucleophilicity decreases

in gas phase insoluble

Nucleophilicity increases in a protic solvent



- Two main factors controlling bimolecular rxn.

1) Electrostatic attraction of opposite charges

(substitution at vacant site)

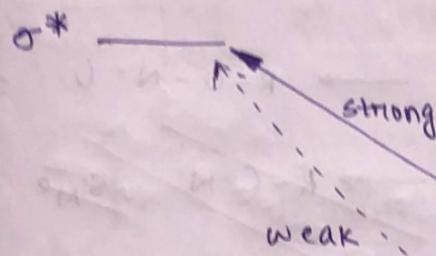
11) HOMO of  $\text{N}_u^{\ominus} + \text{LUMO}$

ii) HOMO of  $\text{Nu}^-$  + LUMO of  $\text{E}^+$  interactions  
 $(\text{S}_{\text{N}}^2 \text{ rxn. at saturated } \text{sp}^3 \text{ carbon})$



$R-X$

$R_2C=O$



Sulphur

Oxygen

$\pi^*$

$\pi$



$\sigma$   $\uparrow\downarrow$

second phase

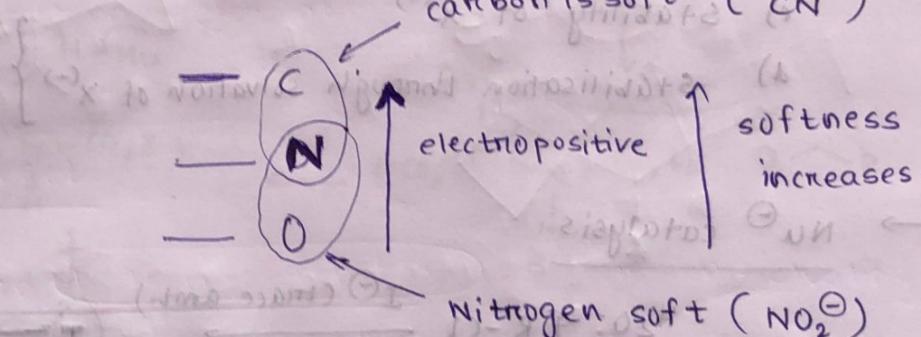
$R-X$

soft

$\left\{ \begin{array}{l} \text{hard } X = \text{a little to a} \\ \text{little to slightly} \end{array} \right.$

$\sigma^*$  —————  
 no soft part  
 no soft part

$\sigma$   $\uparrow\downarrow$



$\Rightarrow$

Hard  $Nu^-$

→ small with closely held electrons with high charge density

→ Like to attack  $>C=O$  at

→  $RO^-$ ,  $\bar{NH}_2$ ,  $\bar{R}, F, Cl^-$

→ Electrostatic interactions

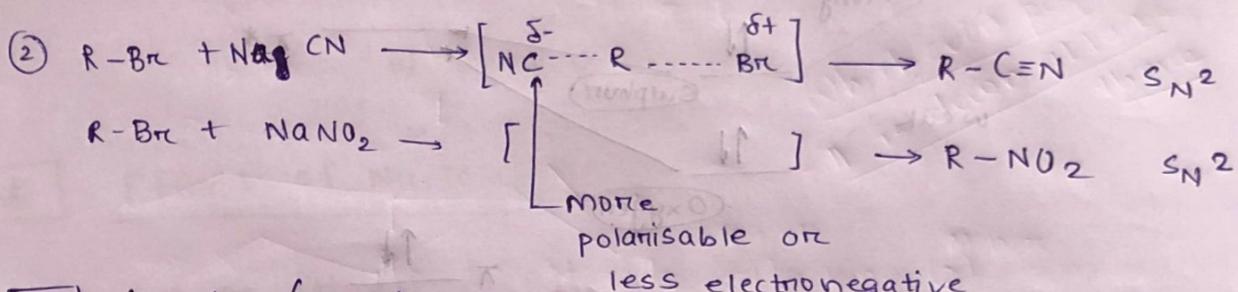
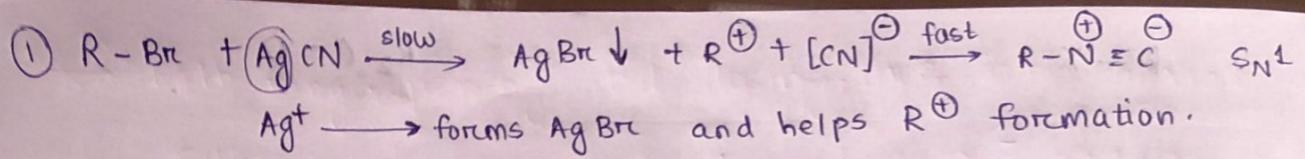
Soft  $Nu^-$

→ Diffused high energy electrons.

→ Like to attack at saturated carbon.

→  $RS^-$ ,  $I^-$ ,  $R_3P, RSH$

→ HOMO - LUMO interactions.

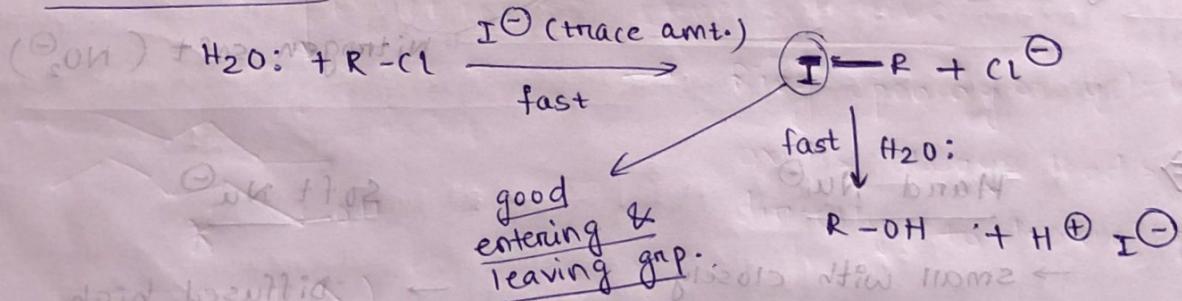


### \* Leaving Groups

→ Weaker the base better the leaving group.

- a) strength of  $\text{R}-\text{X}$  bond
  - b) polarisability of bond
  - c) stability of  $\text{X}^{(-)}$
  - d) stabilisation through solvation of  $\text{X}^{(-)}$
- } Halides       $\text{X} = \text{F}, \text{Cl}, \text{Br}, \text{I}$
- } Tosylate or  
Triflate ion.

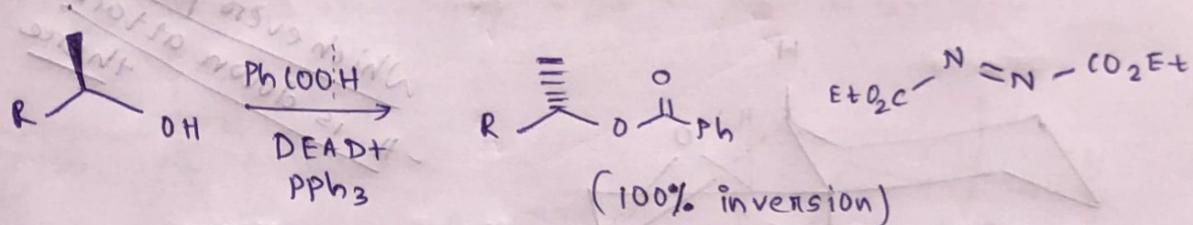
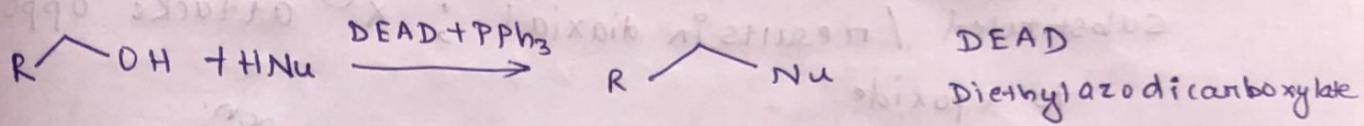
→  $\text{Nu}^-$  catalysis



→ To displace weak LG :  $\text{OH}^-$ ,  $\text{NH}_2^-$  (soft bases);  $\text{H}^+$  is needed →  $\text{OH}^-$  to  $\text{H}_2\text{O}$  (Good LG)

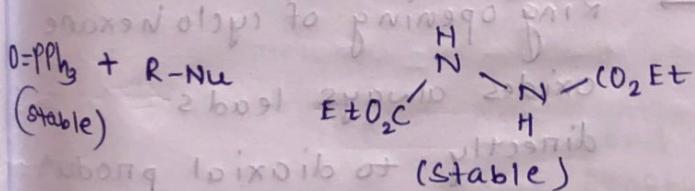
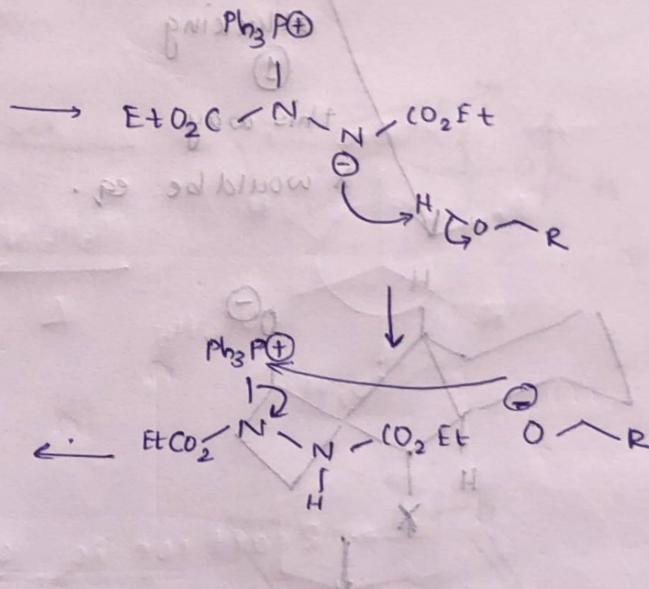
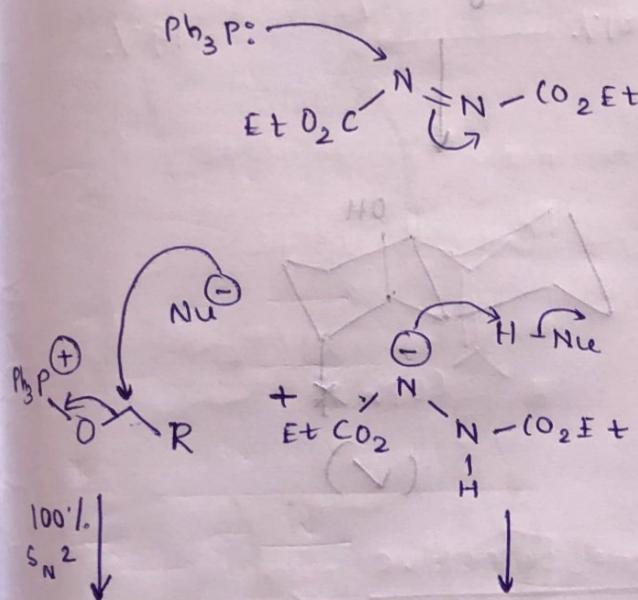
$\text{NH}_2^-$  to  $\text{NH}_3$  (Good LG)

## \* Mitsunobu Reaction



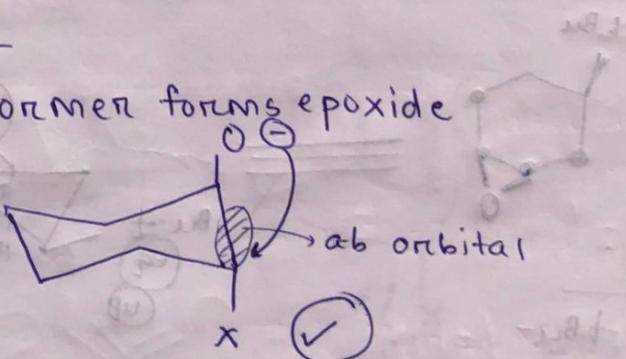
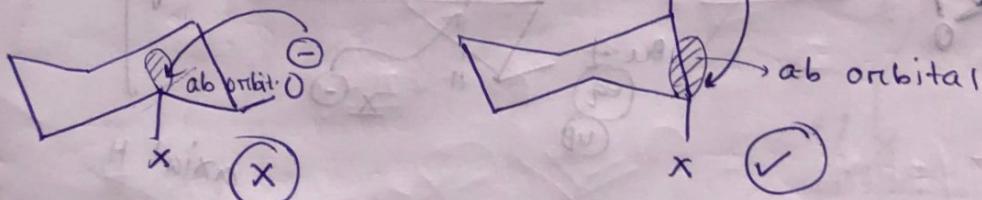
Normal esterification = retention.

### Mech.

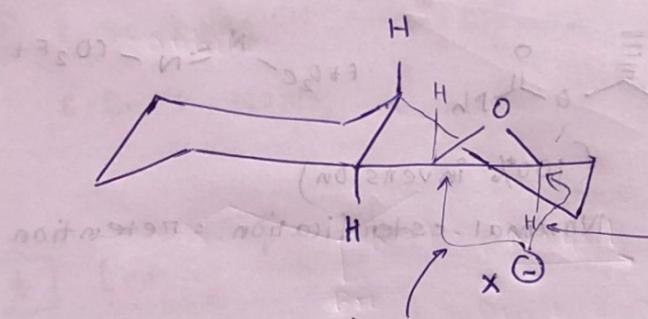


## \* Epoxide formation

→ only diaxial conformer forms epoxide

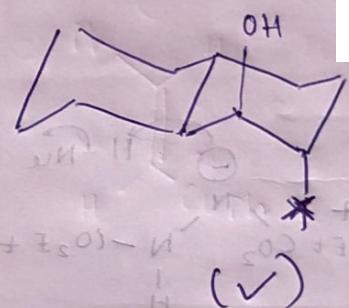
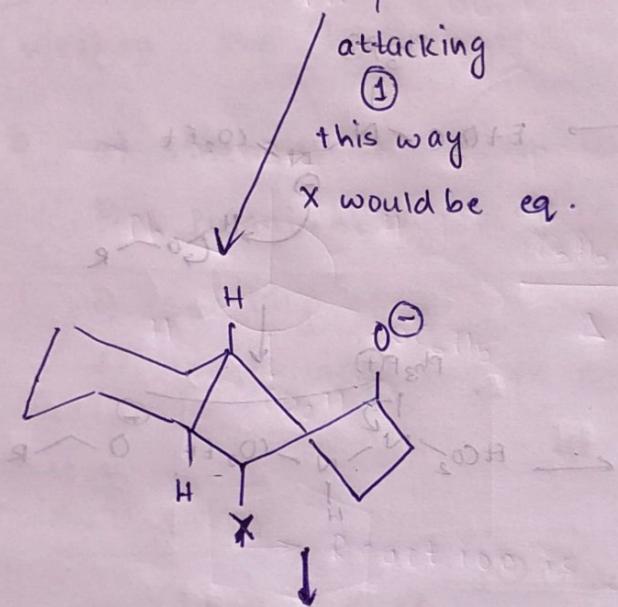


→ Both ring opening and closing are for diaxial substituted / results in diaxial ;  $\text{X}^-$  attacks opposite to epoxide.

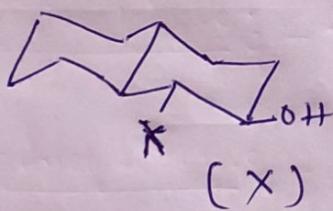


Which ever posn.  
- H is down attacks  
there

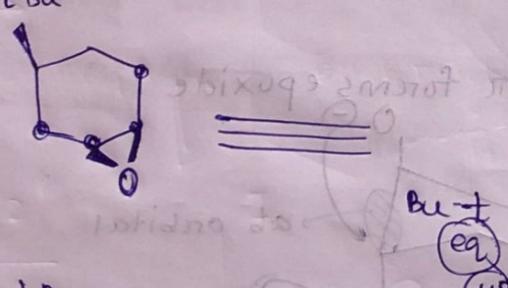
attacking ②  
this way  $\text{X}$  would be axial



→ Ring opening of cyclohexane oxides always leads directly to diaxial products

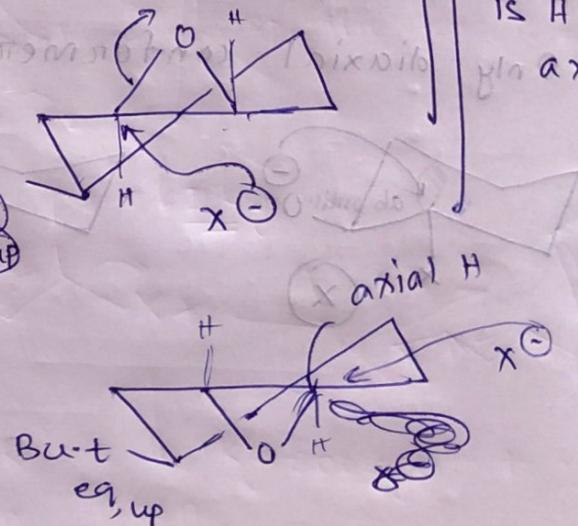
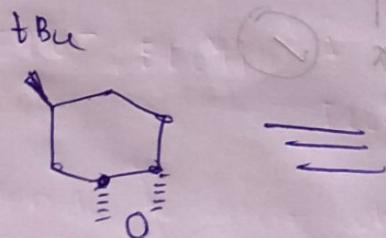


a)



Find where  
is H at  
in axial.

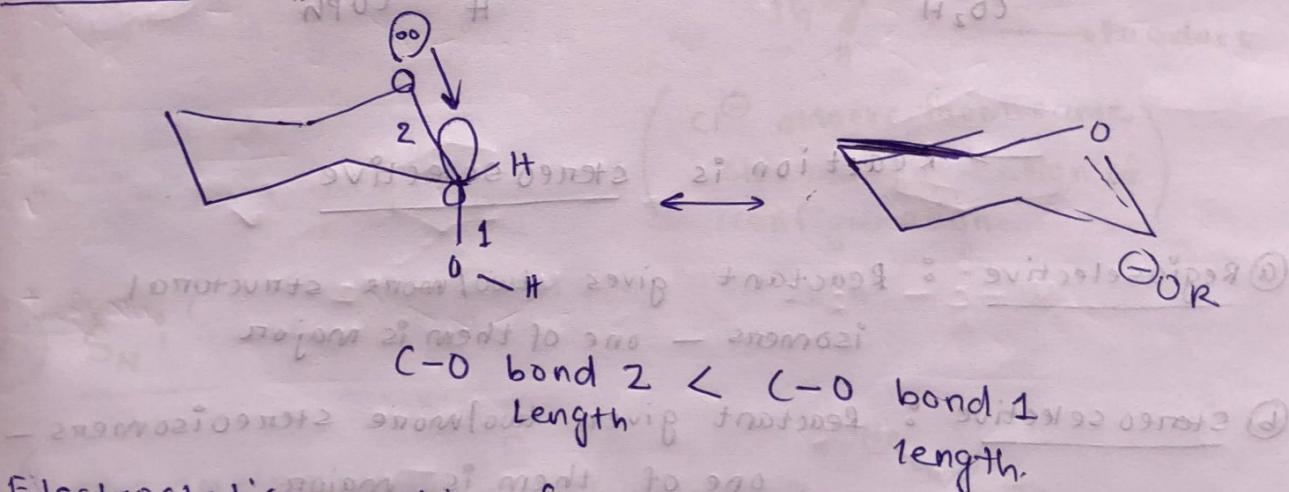
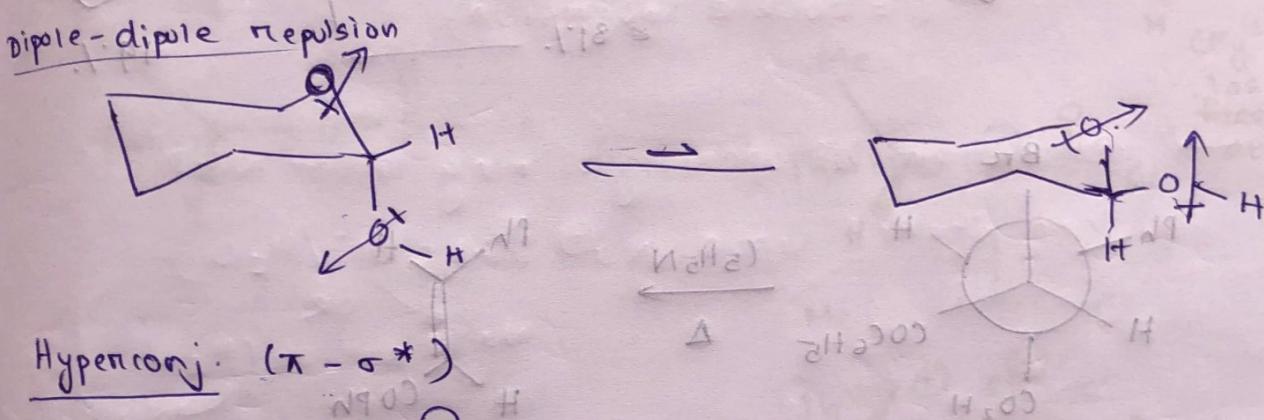
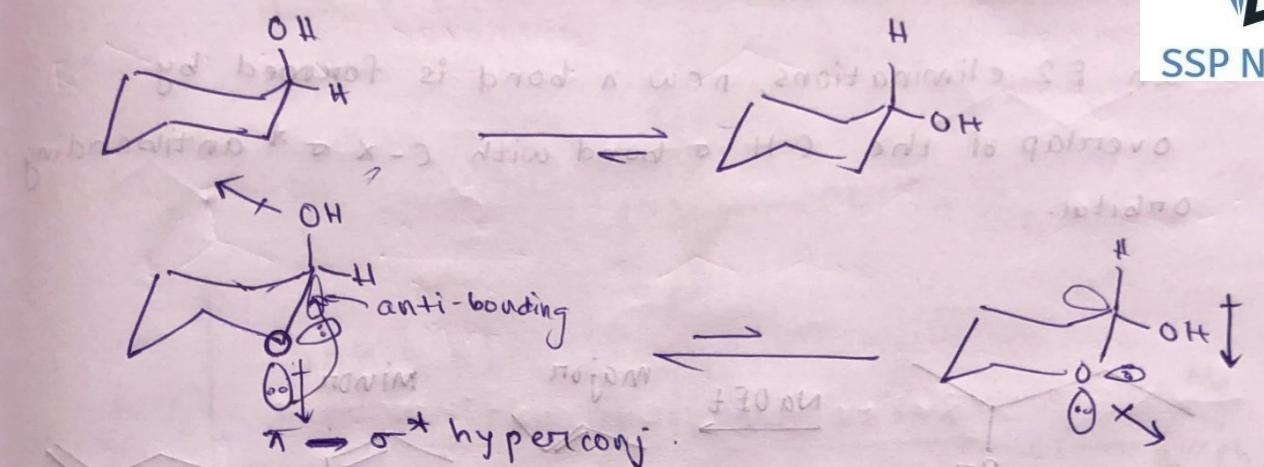
b)



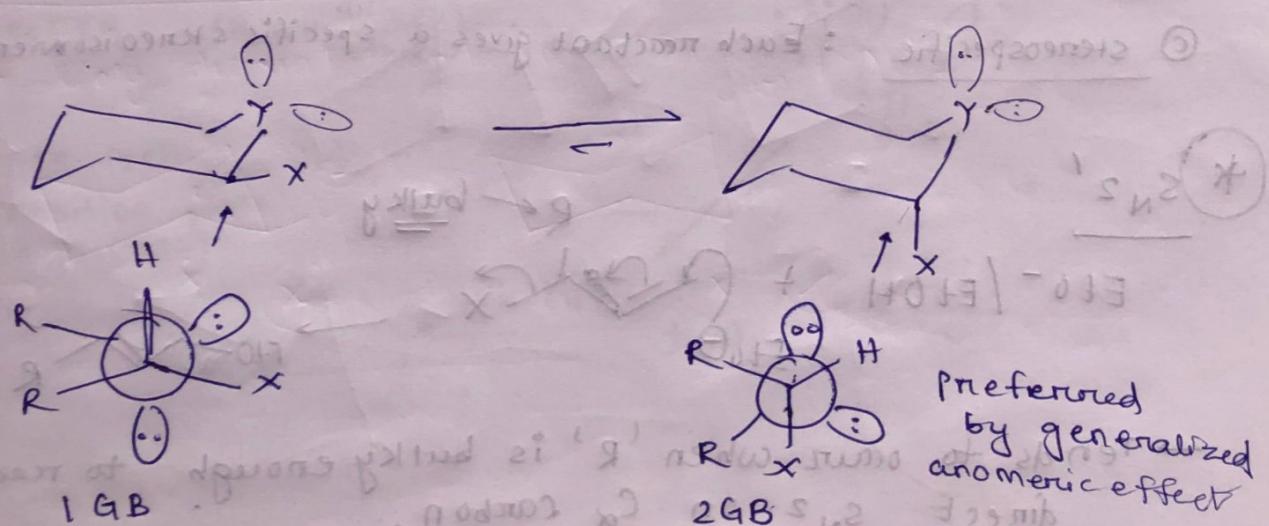
## \* Anomeric Effect



SSP Notes

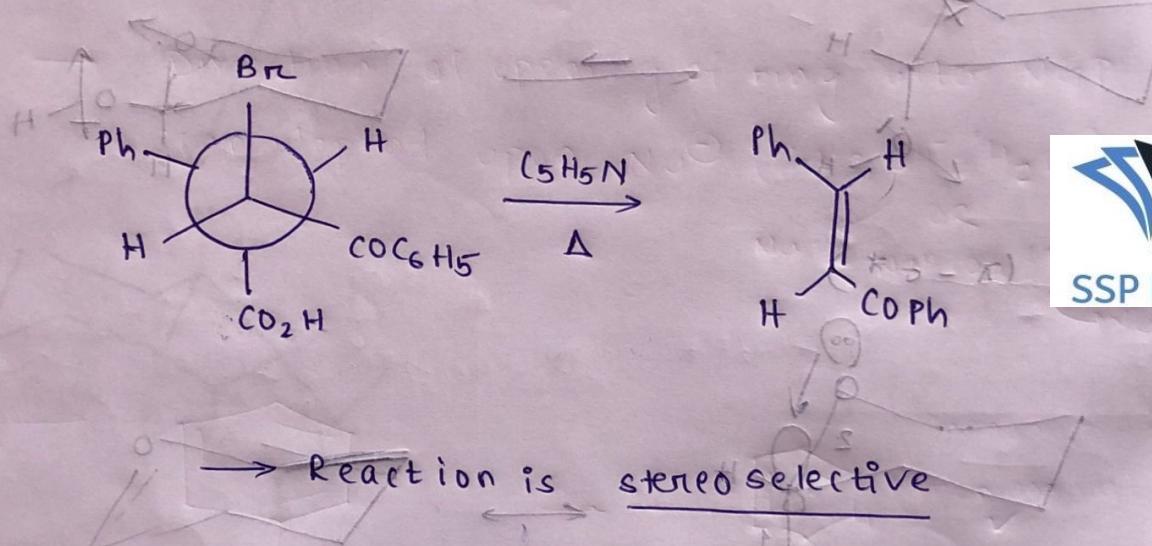
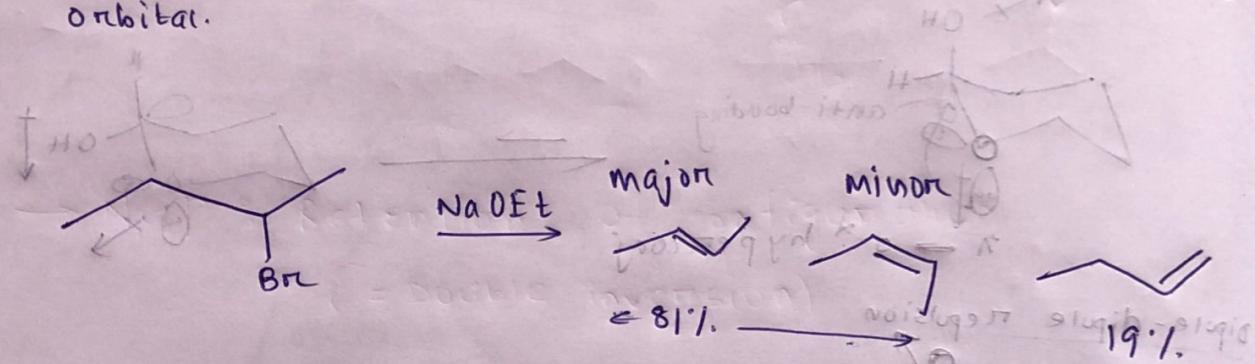


### Electrostatic repulsion factor



\* E-2 eliminations have anti-periplanar transition states

→ In E2 eliminations, new  $\pi$  bond is formed by overlap of the C-H  $\sigma$  bond with C-X  $\sigma^*$  antibonding orbital.

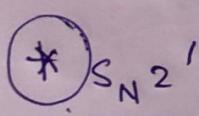


→ Reaction is stereo-selective

(a) Regioselective : Reactant gives two/more structural isomers — one of them is major

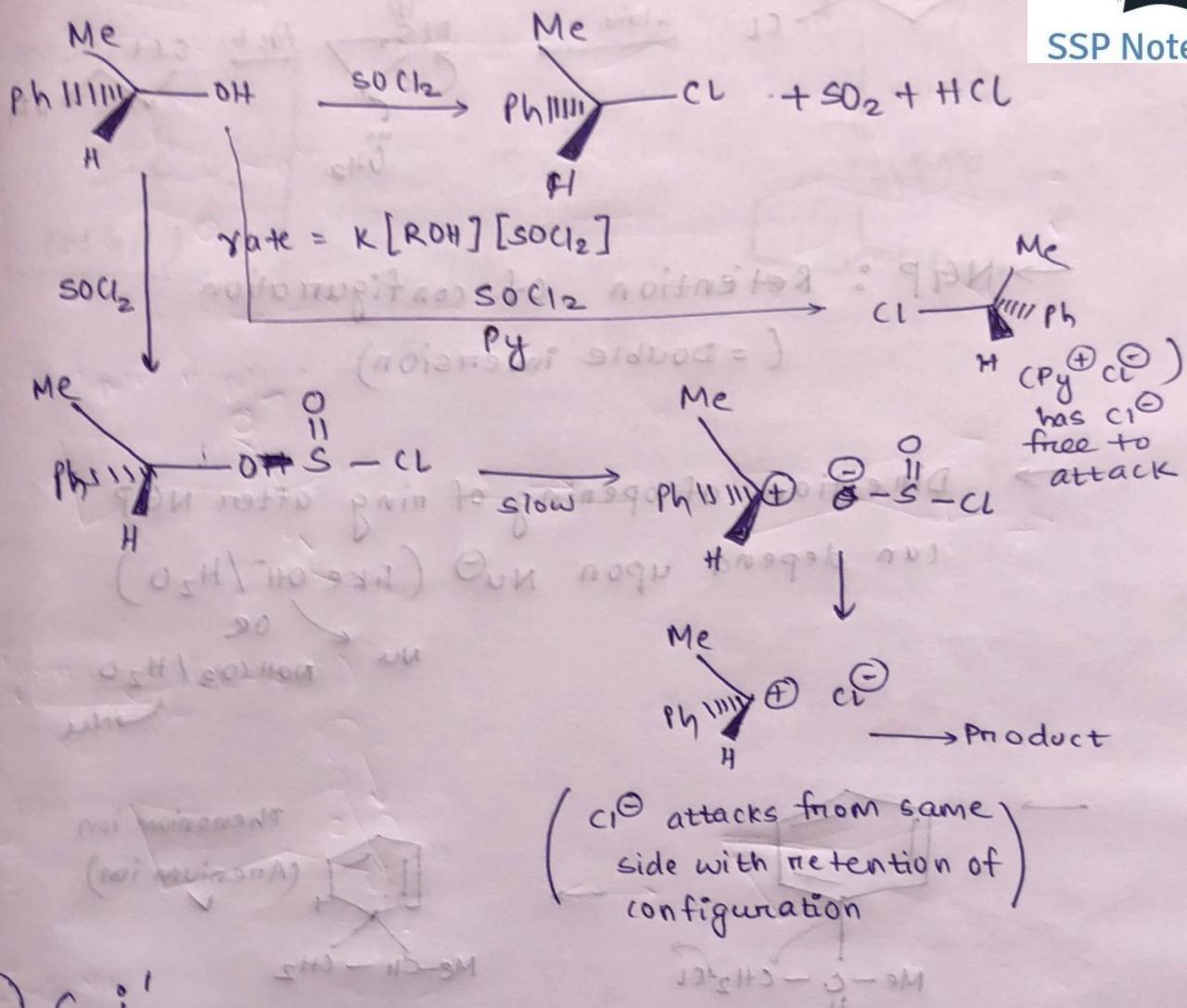
(b) Stereo-selective : Reactant gives two/more stereoisomers — one of them is major

(c) stereospecific : Each reactant gives a specific stereoisomer.

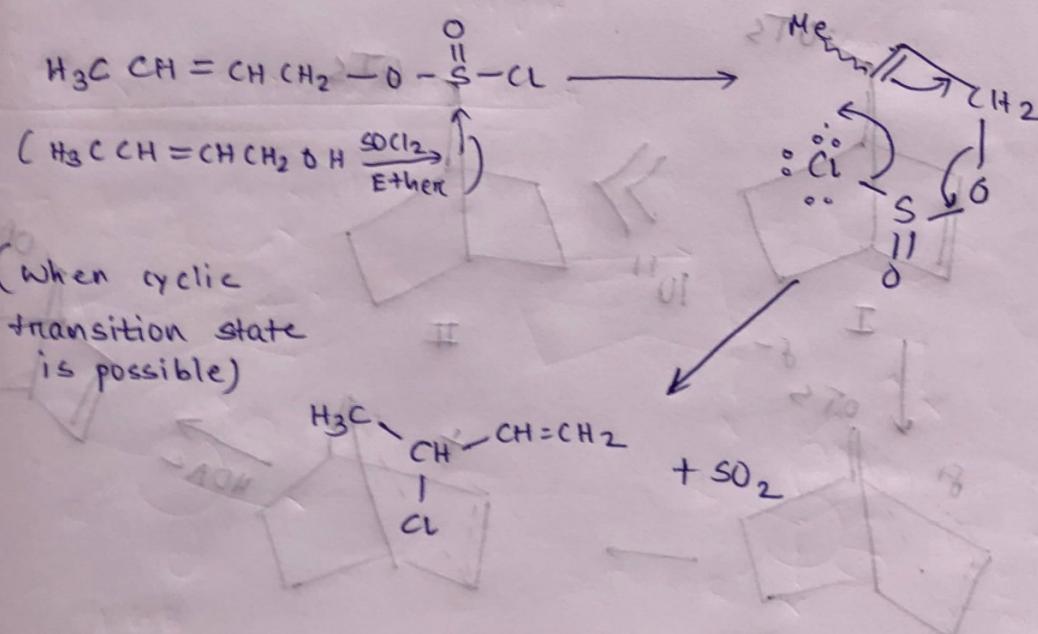


→ Tends to occur when 'R' is bulky enough to reduce direct  $\text{S}_{\text{N}}^{\text{2}}$  on  $\text{C}_\alpha$  carbon.

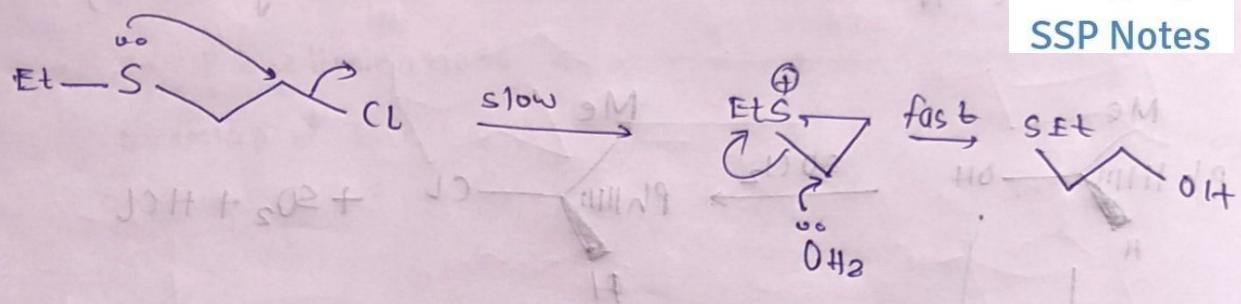
\*  $S_N^i$  (Substitution Nucleophilic internal)  
 ( $S_N^2$  with retention of configuration)



\*  $S_N^{i'}$



# \* Anchimeric Assistance (NGP)



→ NGP : Retention of configuration  
(= Double inversion)

→ Direction of opening of ring after NGP

can depend upon  $\text{Nu}^-$  (like  $\text{OH}^-/\text{H}_2\text{O}$ )

$\text{Nu}^-$  OR  $\text{NaHCO}_3/\text{H}_2\text{O}$

