Sarika. V (13 copy)

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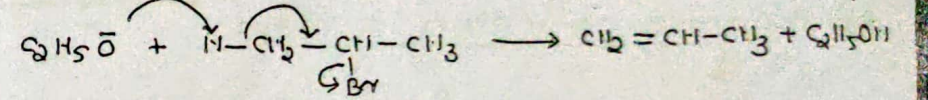
Unit - 4

CONFORMATIONAL ANALYSIS - II

(1) Debromination of dl and meso 2,3-dibromo butane — Kalsi + Finar + Jagadamba Singh

This rexn is an example for bimolecular elimination [E_2 elimination]. Both the substrate and the nucleophile participate in single step. So the rate of the rexn in E2 elimination

$$\text{Rate} = k\,[\text{substrate}]\,[\text{nucleophile}].$$



$$\text{Rate} = k_2\,[(CH_3)_2CHBr]\,[C_2H_5O^-]$$

→ in tertiary alkyl halides SN_2 rexn. will not take place but E2 rexn favours with strong base

Anti elimination is preferred in E2 rexn's.

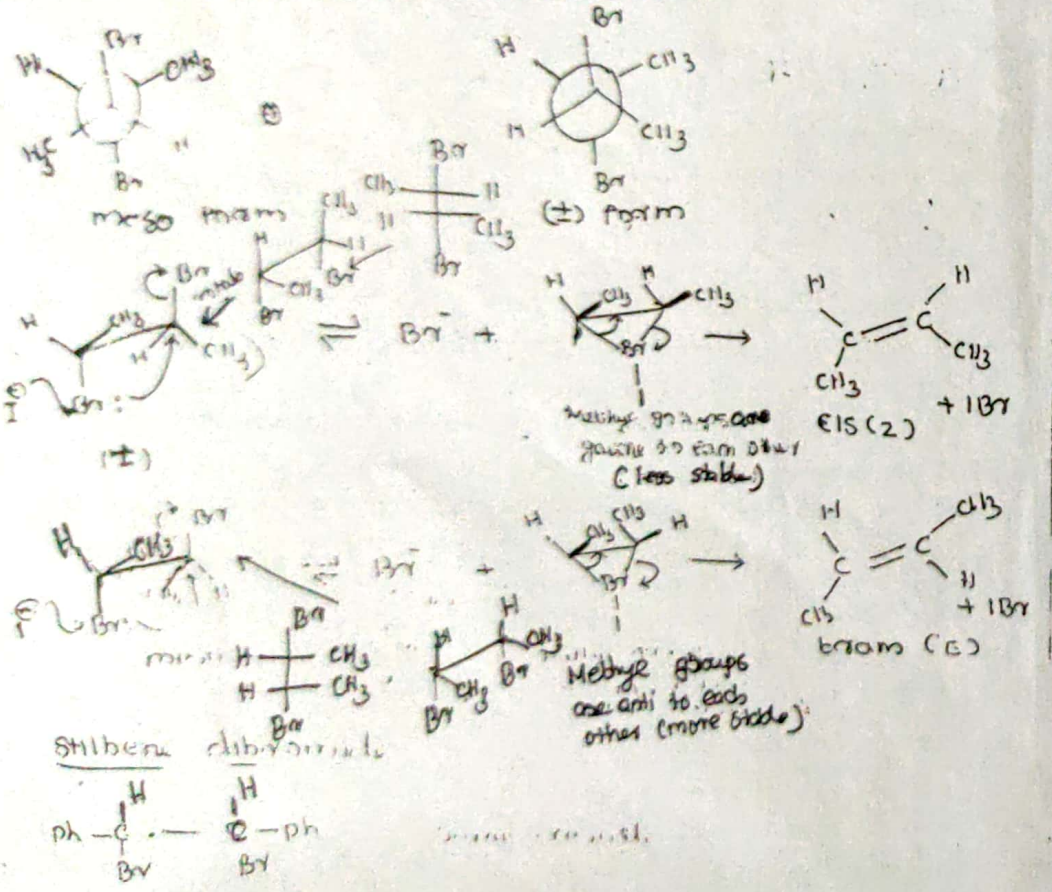
→ The anti coplanar arrangement is more stable (dihedral angle b/wn eliminating groups is 180°) bec² it is staggard (elimination of the groups from the opposit side of the molecule (anti coplanar) is called anti elimination.)

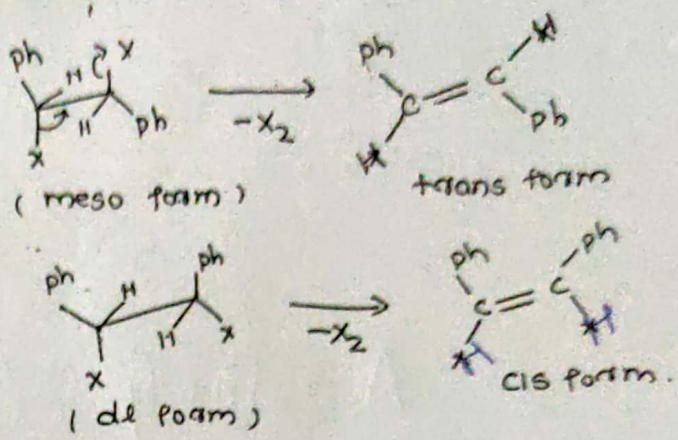
→ Elimination of the groups from the same side of the molecule (syn coplanar) is termed as syn-elimination. Syn elimination is difficult because it is an eclipsed conformation.

① Debromination of 2,3-dibromobutane is E_2 elimination rexn

The debromination of 2,3-dibromo butane by KI in acetone solution or with a metal such as Zn is an example for E2 elimination rexn. E2 elimination can occur only through a conformation of the starting compd which places the two eliminating groups (bromine atoms) in an anti-

periplanar arrangement, regardless the fact if or not this is the most stable conformation. Meso 2,3-dibromobutane can eliminate bromine more easily to give trans-2-butene; whereas (±) 2,3-dibromo butane undergo elimination to less extent to give cis-2-butene. The reaction of the (±) isomer involves less stable transition state (two methyl groups are gauche to each other) compared to the meso isomer (the two methyl groups are anti to each other). Thus the elimination with iodide is 2 times faster for the meso isomer than ± isomer.





(2) Dehydrohalogenation of 1-bromo-1,2-diphenylpropane

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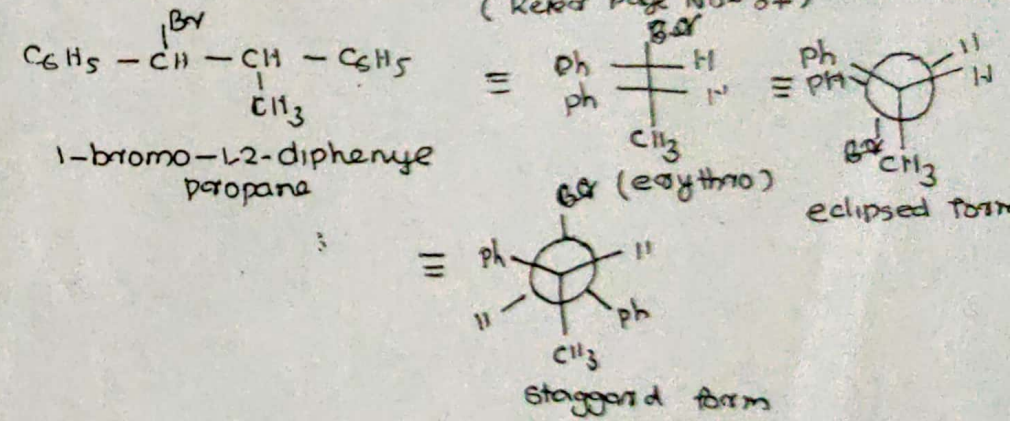
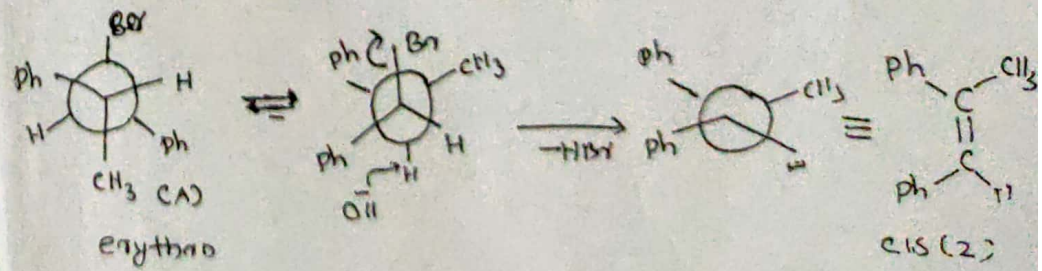
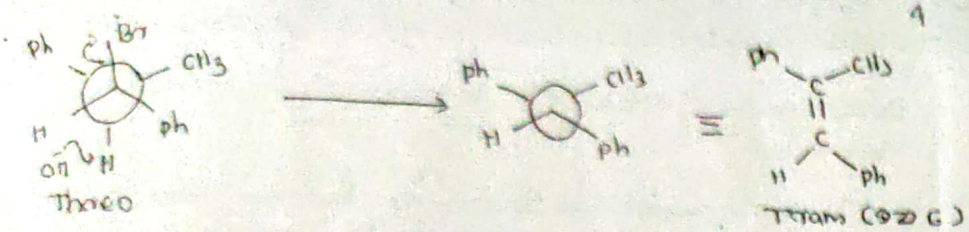


→ this compound has two stereogenic carbons (stereo centres), thus it could exist as four stereoisomeric forms. (pair of enantiomers).

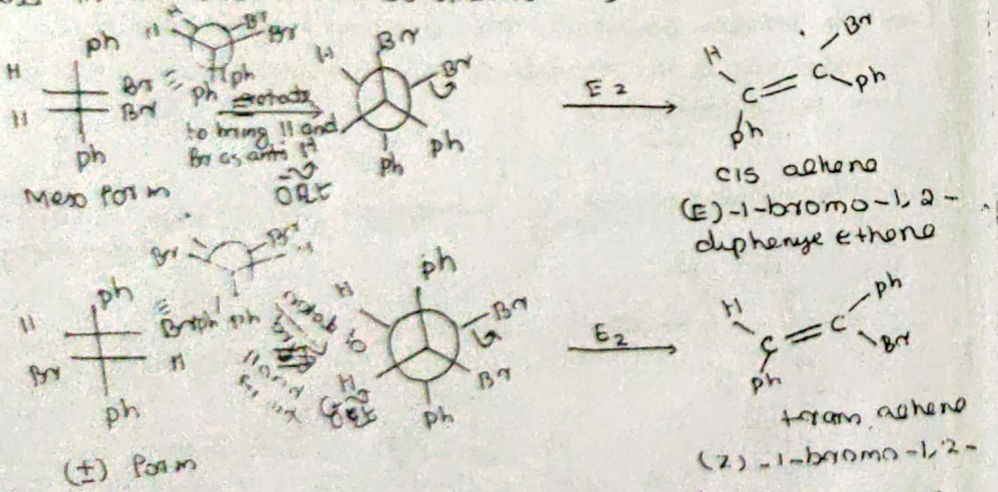




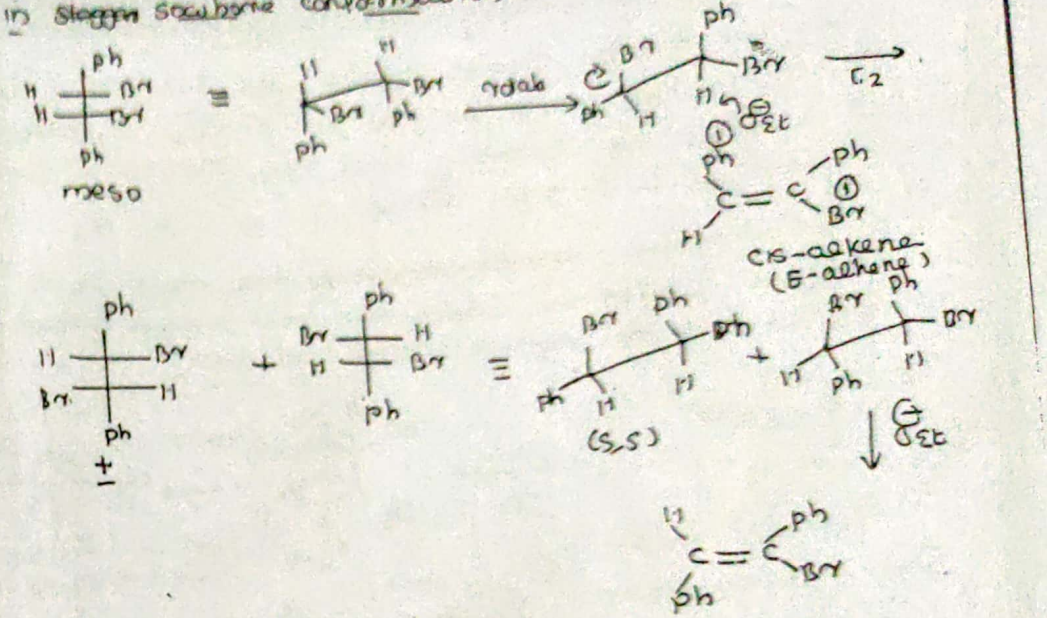
The erythro and threo isomers under E_2 elimination by anti elimination pathway with NaOEt/EtOH. erythro will give Z-alkene, threo will give E-alkene.

) Dehydrohalogenation of 1,2-dibromo-1,2-diphenyle ethane (Stilbene dibromide)

The compd exist in two enantiomeric and in a meso form. (3 stereomers).



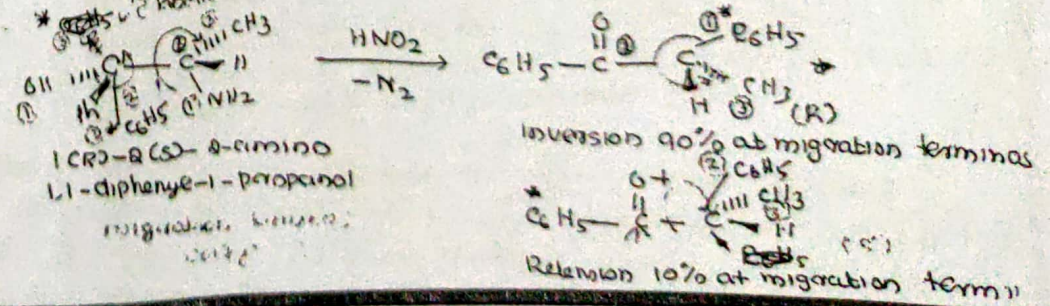
In staggered conformation



meso stereomer gives (E) alkene having the phenye groups cis, while racemic dibromide give only Z-alkene

Pinacolic deamination — Kalsi

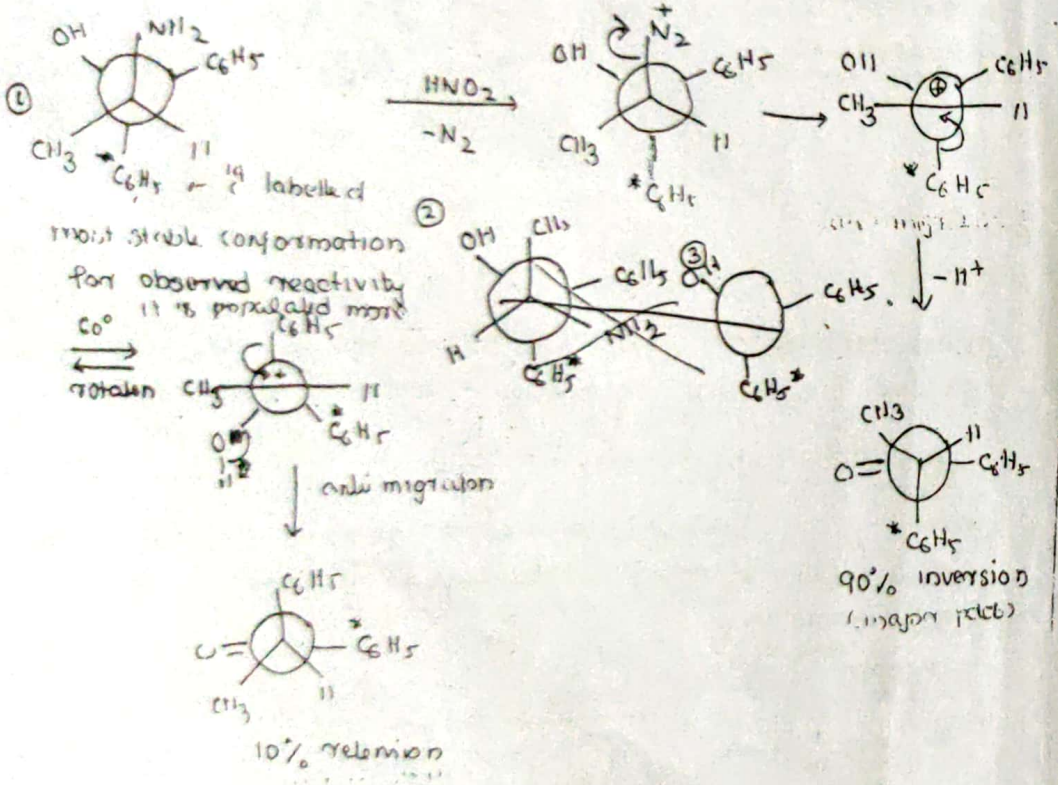
Deaminative rearrangement of one optically active isomer 2-amino 1,1-diphenye 1-propanol proceed with 90% inversion



(R)-2-amino-1,1-diphenye-1-propanol

when one specific phenyl group was labelled with ^{14}C the labelled group to give the product of inversion at the migration terminus and the unlabelled group migrated so as to give retension.

→ the reaction proceeds involving the most stable staggered conformer, where the two phenyl groups are adjacent to the smallest atom hydrogen



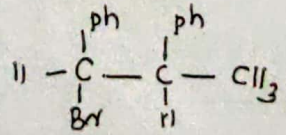
pinacolic deamination involves the most stable conform. the two Ph groups adjacent to NH2 atom. The labelled Ph* (being suitably located) migrates to the carbocation to give 90% inversion. A rotation of the carbocation (60°) then initiates ph migration with retension.

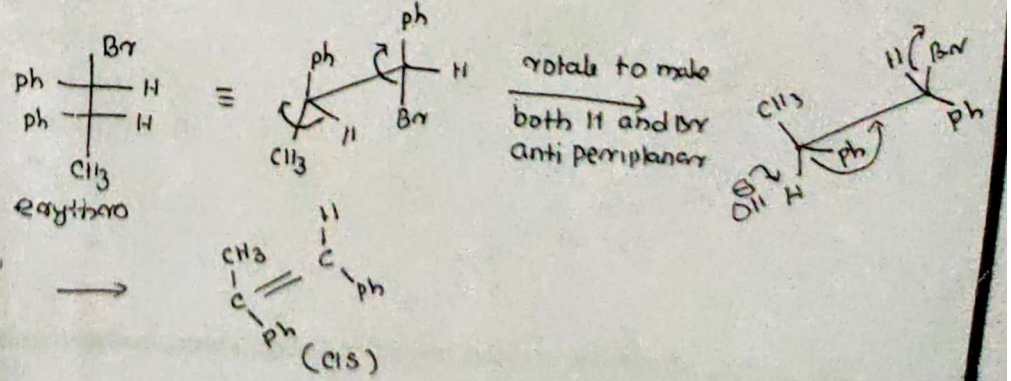
→ The carbocation is produced by the loss of nitrogen gas in the compound with ^{14}C labelled phenyl. the migration of labelled phenyl group gives the major product of inversion (the labelled phenyl group is suitably located in the plane of vaccat p orbital of the carbocation)

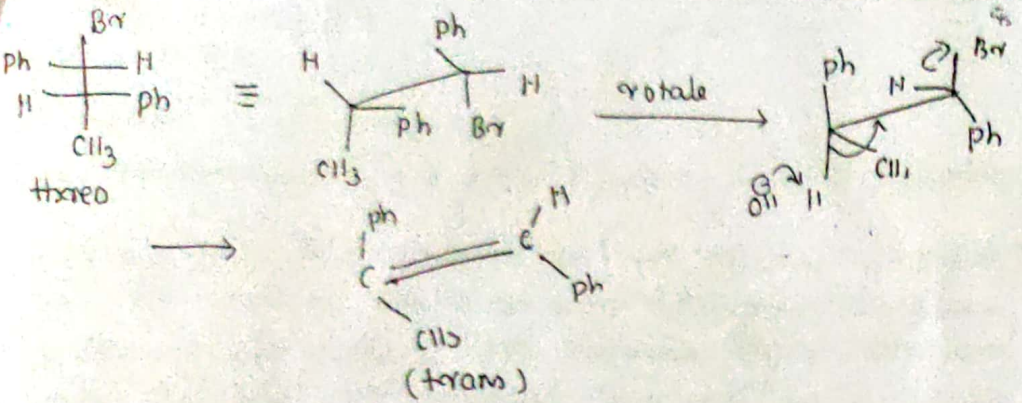
→ If the intermediate carbocation rotates by an angle of 60° a conformation is attained, in which now the unlabelled phenyl migration gives the product of retension of config.

→ The results support the assumption that the observed reactivity is the result of one predominant conformation of the substrate.

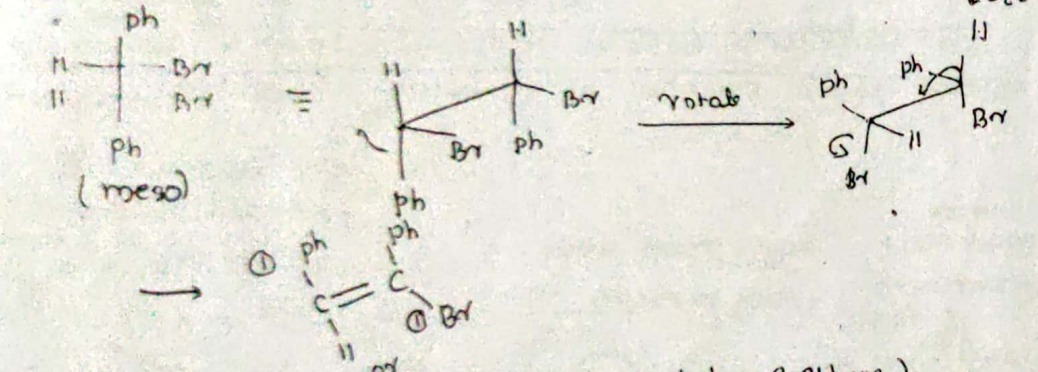
Dehydrohalogenation of 1-bromo-1,2-diphenyl propane (Repeating one)

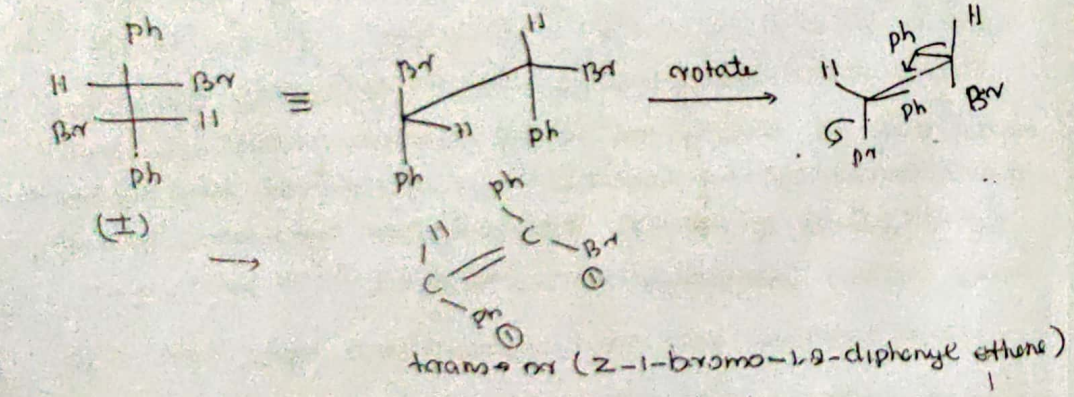




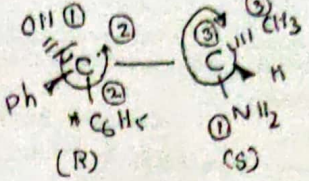


Dehydrohalogenation of Stilbene dibromide

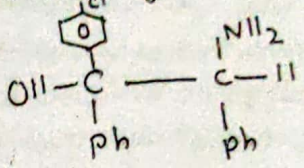


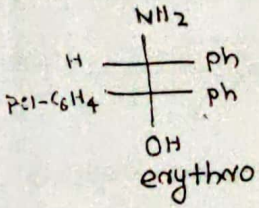


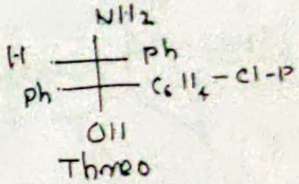
→ 1(R) - 2(S) - 2-amino -1,1- diphenyl-1-propanol



→ 1,2- diphenyl -1(-p-chlorophenyl) - 2-amino ethanol



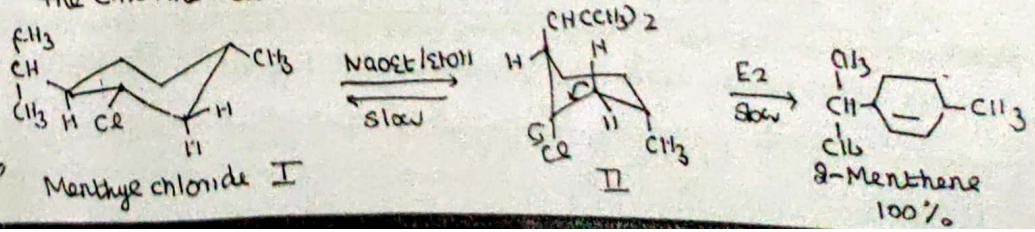




E-2 elimination from menthyl and Neomenthyl chloride —kalsi

Menthyl and neomenthyl chlorides are substituted cyclohexyl chlorides and are diastereomers, which differ only in the config of the chlorine substituent.

→ In menthyl chloride all the substituents are equatorial when it is treated with sodium ethoxide in ethanol elimination occurs very slowly to produce alkene - 2-menthene as the only product. Thus in menthyl chloride the chlorine atom must be equatorial.



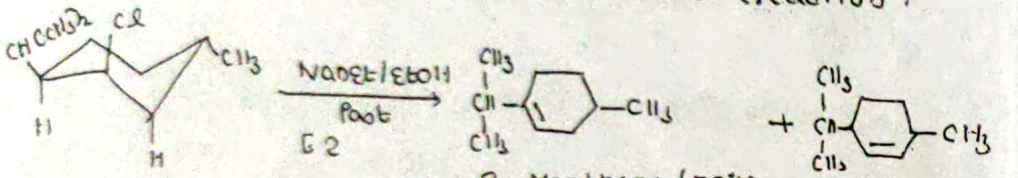
Menthyl chloride I

II

I = more stable conformation but no H is anti to Cl.

II = less stable conformation but one H anti to Cl

E2 elimination therefore occurs from a less favourable conformation obtained by ring flip. At any one time only a small percentage of the molecule will have this conformation. A low population of this reactive conformation leads to a slow elimination reaction.



Neomenthyl chloride
Cl has anti periplanar
β H's on both sides

→ when neomenthyl chloride is reacted under similar condition it reacts rapidly to give a mixture of two alkenes 2 and 3-menthene.

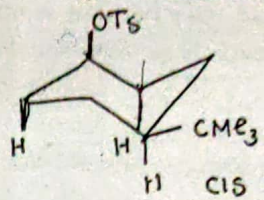
→ The elimination must occur from a conformation where hydrogen and chlorine are anticoplanar, thus in neomenthyl chloride, the chlorine substituents must be axial. Loss of either of two different anti periplanar β-hydrogen atom gives the mixture of alkenes

Elimination from cis and trans 4-t-butyl cyclohexyl tosylate

Trans diaxial. Syn

cis - a, e
trans - ee or aa

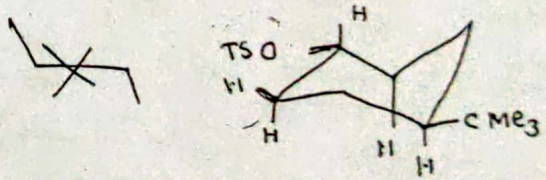
Cis isomer of 4-t-butyl cyclohexyl tosylate undergoes elimination in the presence of sodium ethoxide in ethanol at 70°C 100 times faster than that of its trans isomer.



(a,e)

This is because in the cis isomer the tosylate (OTs) group is axial and hydrogens on the adjacent carbons are anti to OTs group.

The trans isomer (ee) has an equatorial OTs which is not anti to the hydrogen on either of the adjacent carbons. So it will not undergo E2 elimination.



However the other trans isomer (a,a) having OTs and t-butyl groups in axial position would be more favourable for the elimination, but t-butyl is an anchoring group the population of this conformer will be very very low to produce the result.

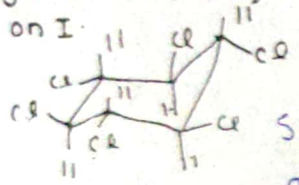
* For E2 elimination the eliminating groups must be at axial position

Cyclohexane

Elimination of ~~Benzene~~ hexachloride - Jerry March

In open chain compounds the molecule can usually adopt the conformation in which H and X are anti periplanar. However in cyclic system this is not always

the one. There are nine stereoisomers of 1,2,3,4,5,6-hexa chlorocyclohexane seven meso form and a dl pair. Four of the meso compounds and the dl pair were subjected to elimination of HCl. Only one of these (I) has no Cl trans to an H. Of the other isomers, the fastest elimination rate was about three times as fast as the slowest but for I was 7000 times slower than that of the slowest of the other isomers. This results demonstrates that with these compds anti elimination is greatly favored over syn elimination however syn elimination is taking place on I.

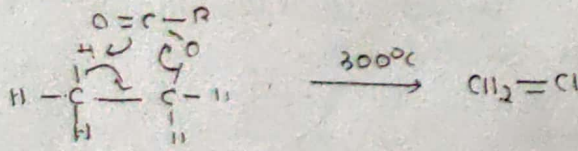


I

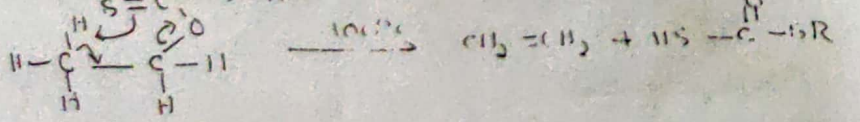
Syn periplanar arrangement

Pyrolytic elimination of esters (cis elimination) – Kalsi

Pyrolitic elimination reactions of acetates, benzoates and xanthates take place through cyclic 6 membered transition states which require a syn (cis) arrangement and proceed by concerted pathway. The order of decomposition is xanthate > benzoate > acetate.



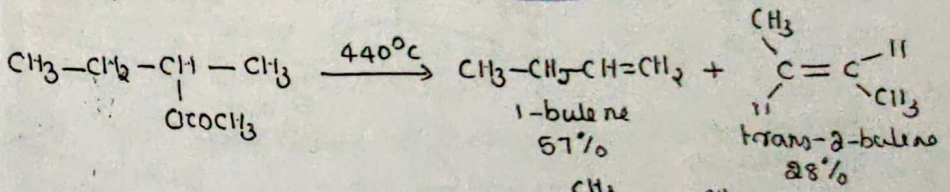
Ester pyrolysis

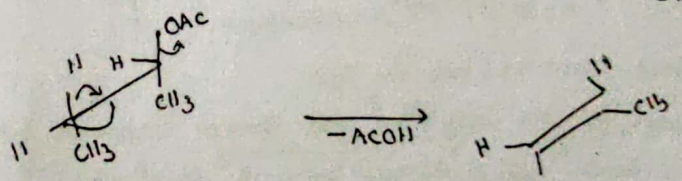


Xanthate pyrolysis

(1) Acyclic Systems

The pyrolytic reactions requires that the groups to be eliminated depart from the same side of the molecule (syn stereochemistry) in the transition state even if they are not eclipsed in the starting material. If two or more syn periplanar arrangements are available the one with least crowding is preferred, generally leading to the product in which the bulky groups are trans.

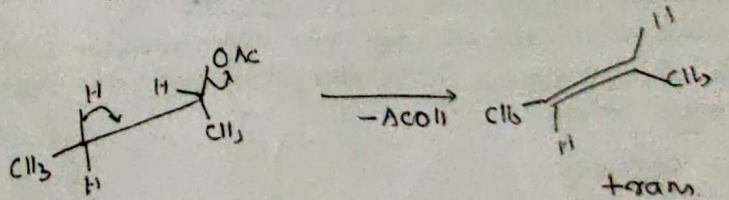




(cis-2-butene).

CH_3/CH_3 $\theta = 0°$
More hindered
Syn periplanar relationship

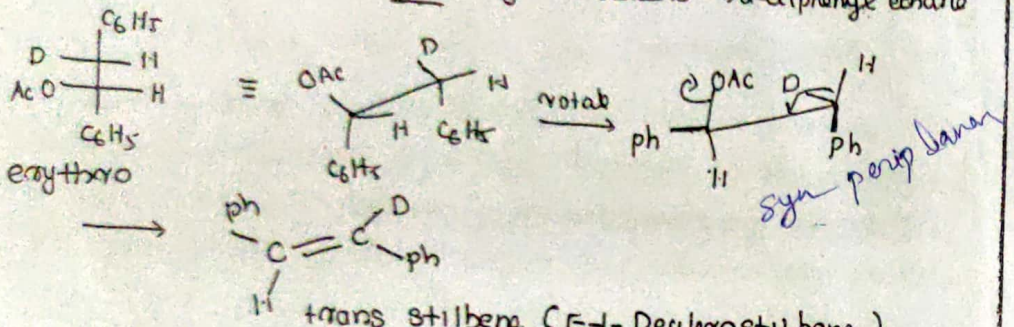
cis

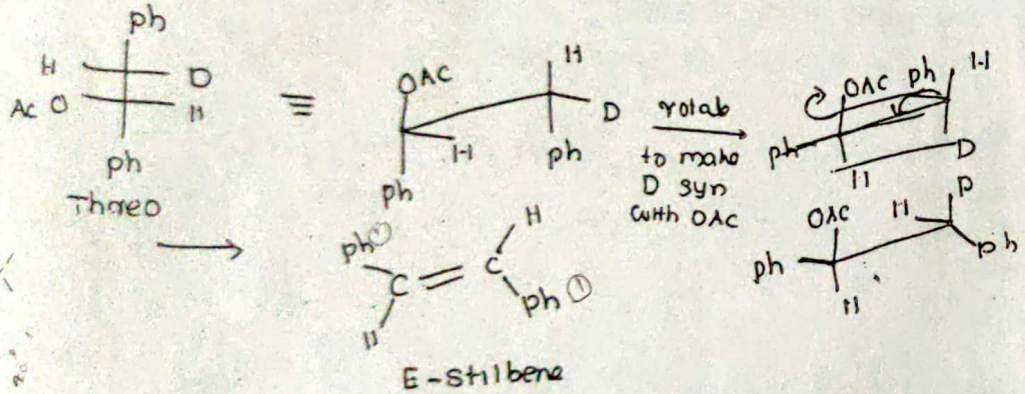


CH_3/CH_3 $\theta = 120°$
Less hindered
Syn periplanar relationship

trans (major)

Pyrolytic elimination of 1-acetoxy-2-deutero-1,2-diphenyle ethane





→ the pyrolitic elimination is syn

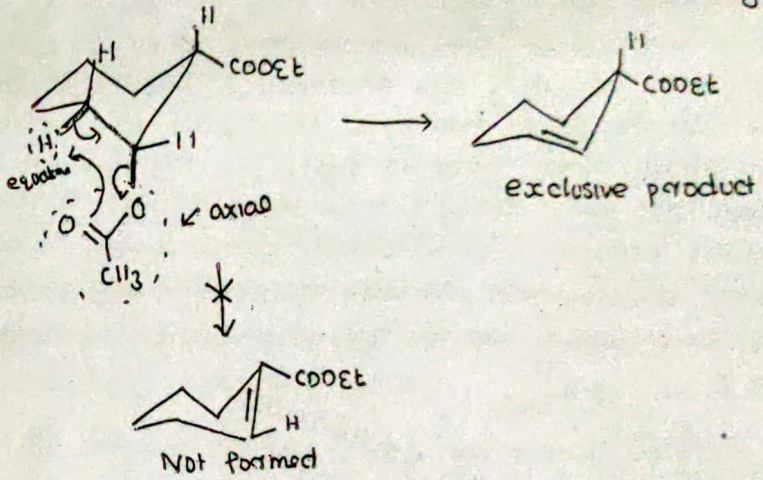
→ The pyrolysis of the erythro and threo isomers of 1-acetoxy-2-deutero-1,2-diphenyle ethane will give trans stilbene in each case.

→ Stilbene from erythro compd ~~do not~~ retained the deuterium, while the threo compd lost H

→ Preferred conformations for syn elimination are those in which phenyle groups are far removed as possible from each other.

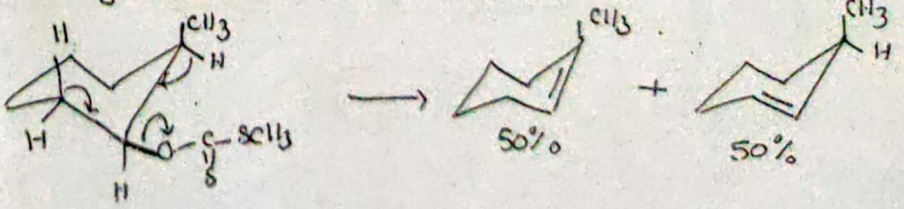
(ii) Alicyclic systems

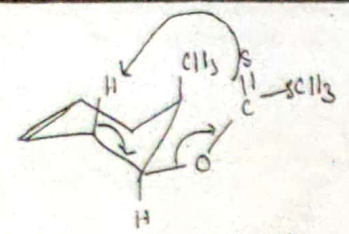
→ In a cyclohexane system if the leaving group is axial then hydrogen on the adjacent carbon must be equatorial (1,2-ae-cis) ie cis relationship btwn leaving groups



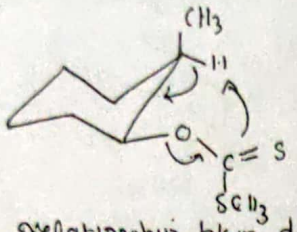
The double bond in the direction of carbethoxye group does not form even though it would be conjugated, since there is no equatorial hydrogen on that side. thus if the leaving group is axial, it cannot attain a transition state with an axial neighbouring H

→ In case the leaving group is equatorial, it can still form a transition state with a H atom on adjacent carbon that is either axial (cis relationship) or equatorial (trans relationship). thus an equatorial leaving group can equally well eliminate a neighboring equatorial and axial H.

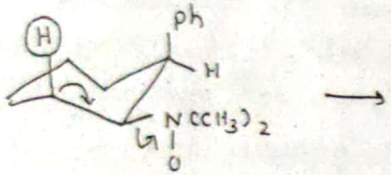




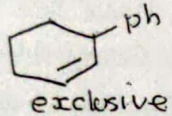
Transition state with required cis-relationship b/wn departing groups



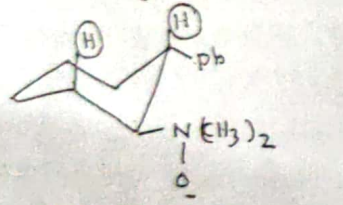
relationship b/wn departing group is trans, however the transition state is stable trans-decalin type



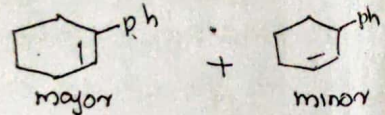
cis relationship only one axial H



exclusive



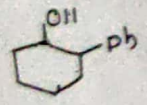
cis relationship two axial H



major (conjugated one) + minor

× Elimination of 2-phenylcyclohexanols

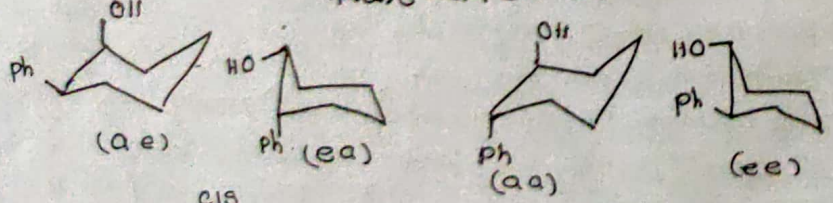
Krasimsirs Note (Not needed) ×



1,2-isomer

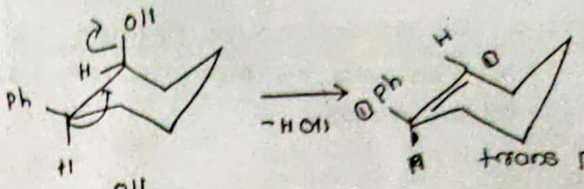
cis – a,e or e a

trans – aa or ee

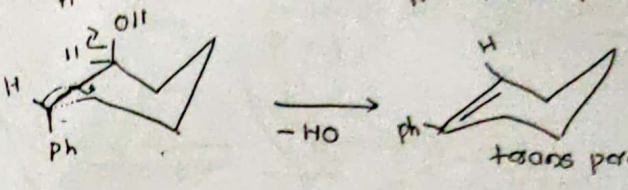


(a e) (e a) cis

(a a) (e e) trans



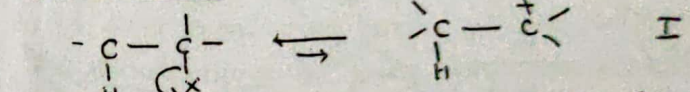
trans product



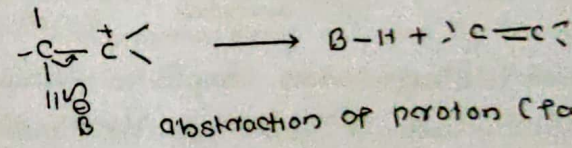
trans product

Cis and trans form on elimination gives trans products.

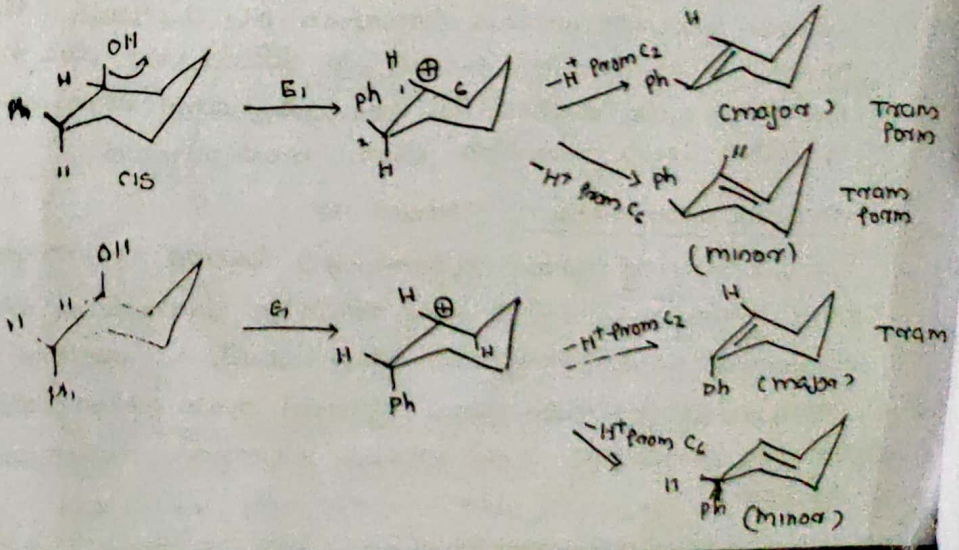
E1 elimination



elimination of leaving group (rate determining step)



abstraction of proton (fast step)



(major) Trans form

(minor) Trans form

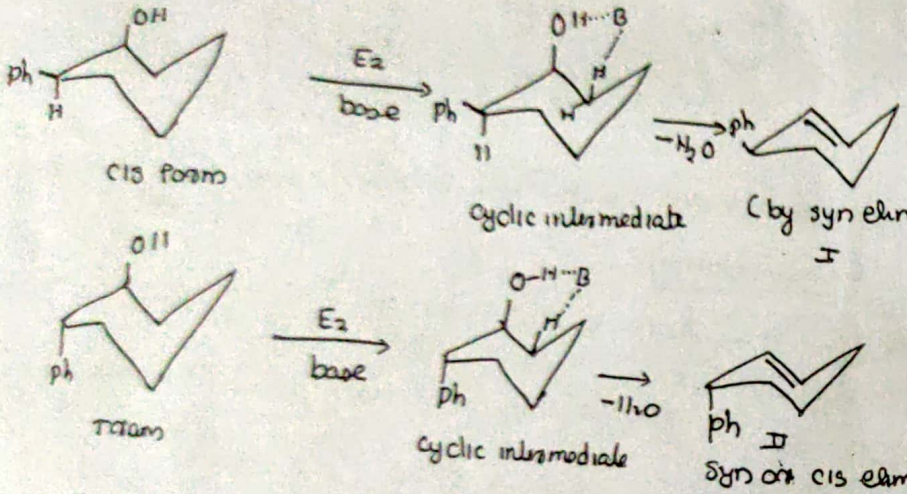
Trans

(major)

(minor)

In E1 elimination a carbonium ion is formed at C_1 in both cis and trans followed by elimination (anti) of an H^+ from C_2 or C_6 atoms.

E2 elimination

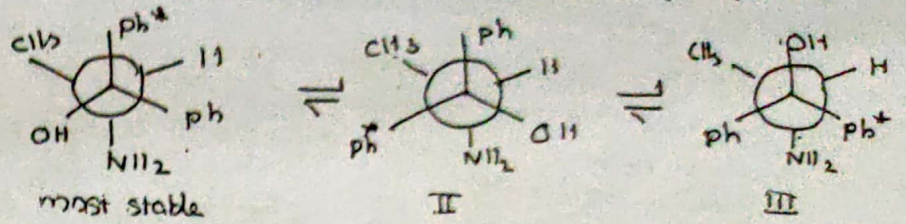


In E_2 elimination an activation complex is formed ~~is formed~~ by the interaction of H^+ from C_2 or C_6 atoms. In the 1st case Anti-anti cyclic intermediate formation is difficult. then syn or cis elimination favours. In second case due to the lack of of cyclic intermediate formation, anti elimination is blocked again gives syn elimination product

Pinacolic deamination — Nasisxisi

If the leaving group is removed before the migration starts giving rise to a very reactive carbocation, the migrating group migrates from which the position it occupies in the most stable ground state conformation of the substrate and result inversion, retension or both.

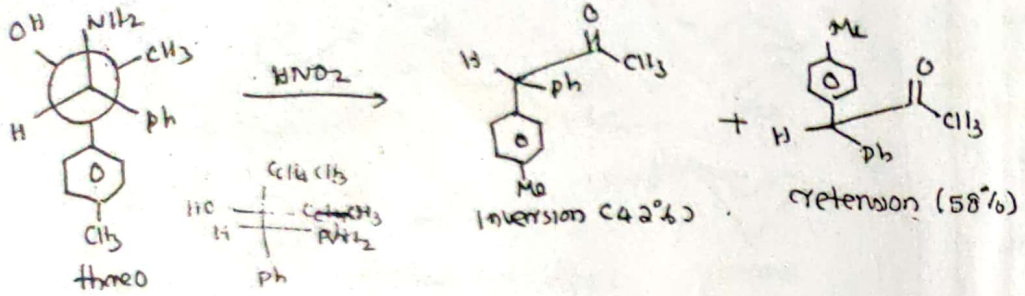
eg: 1-phenyl-1-phenyl-C^{14}-2-amino-1-propanol



Ground state of the molecule is almost entirely populated by the conformer (I) in which the two bulky ph groups have an H atom in btwn. The other two conformers (II and III) have Me and NH_2 respectively separating the two ph groups. The intermediate nitronium ion undergoes a rapid elimination of N_2 and the reactive carbocation so formed immediately collapses with concominant anti migration of ph* and syn migration of ph, the former being preferred

In the other case, if the carbocation so formed is very stable through resonance there would be enough time for the C_2-C_3 bond to rotate and to form more than one transition state, the relative stabilities of which would determin the stereochemistry of the migration terminus.

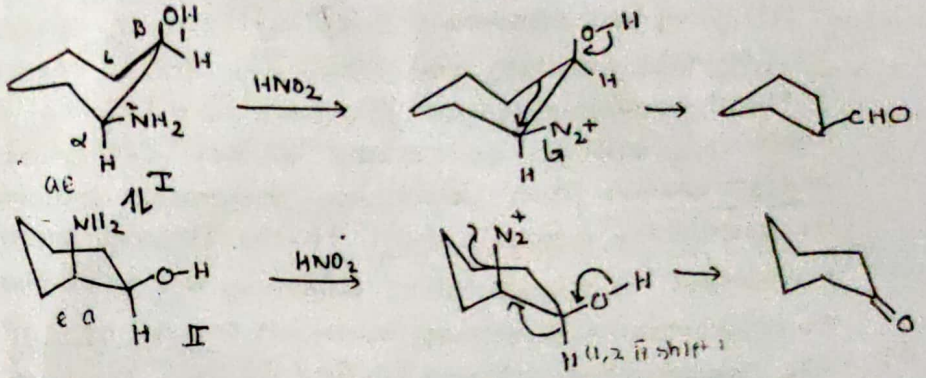
eg: Threo-1-amino-1-phenyl-2-(4-methylphenyl)-2-propanol. Two intermediates could be written involving tolyl participation. One with ph and Me trans and the other with ph and Me cis. The former is pretenned and leads to retension of config, while the latter is unfavoured and gives inversion



Deamination of β-aminocyclohexanol — Nasipuri

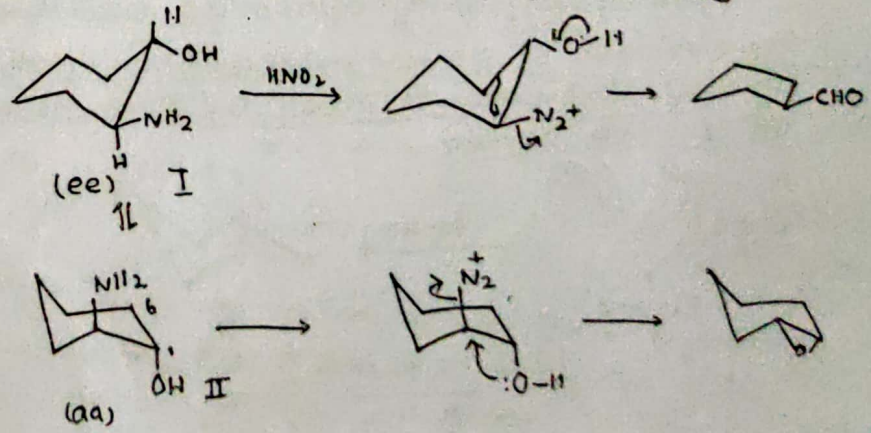
Deamination reaction in β-aminocyclohexanol is a type of molecular rearrangement and lead to ring contraction or ring expansion. This requirment are the presence of a carbon atom (C_α) with a leaving group (migration terminus) a migrating group (part of the ring or group) at C_β (migration origin) and preferably an $\bar{E}$ donating substituent at C_β eg O-H which would help to detach the migrating group. If C_α is outside the ring, a ring expansion occurs, if it is inside, the ring contraction occurs and if C_α and C_β belong to two rings both a ring contraction and expansion occur. The process may be concerted or non concerted. the carbocation at C_α is first formed followed by 1,2-shift of the migrating group. The migrating group, if chiral retains its config, the migration terminus undergoes inversion (SN2 process) and the migration origin if it remains tetrahedral undergoes inversion. The migrating group and the leaving group must be anti periplanar (or approximately so)

1. Deamination of cis-β-aminocyclohexanols



cis β-aminocyclohexanols exist in two conformations (ae, ee) in the first equatorial NH_2 is anti to an endocyclic bond (1-6) and its deamination gives cyclopentanecarboxaldehyde (ring contraction). The second conformer has the NH_2 group antiperiplanar to the carbinol H which undergoes 1,2-hydride shift, the process being assisted by the concomitant movement of the O-H σ $\bar{e}$ pair resulting cyclohexanone

2. Deamination of trans-β-aminocyclohexanols



In the trans isomer (ee) I has the NH_2 group anti to the 1,6 bond and so ring contraction results. The diaxial conformer will not have much population than formation of possible epoxide from this is less.

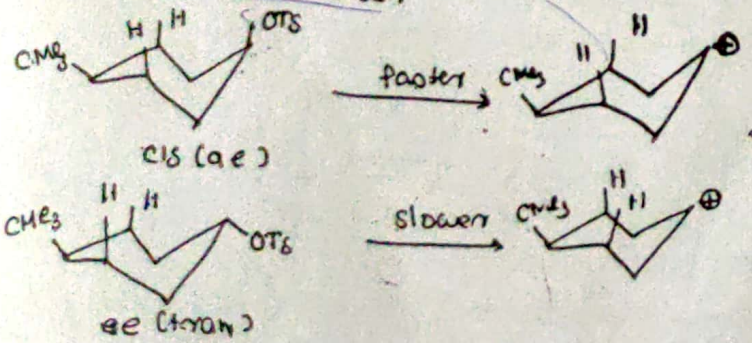
Nucleophilic substitution rexn (SN1 and SN2)

Stereochemistry of various rexns

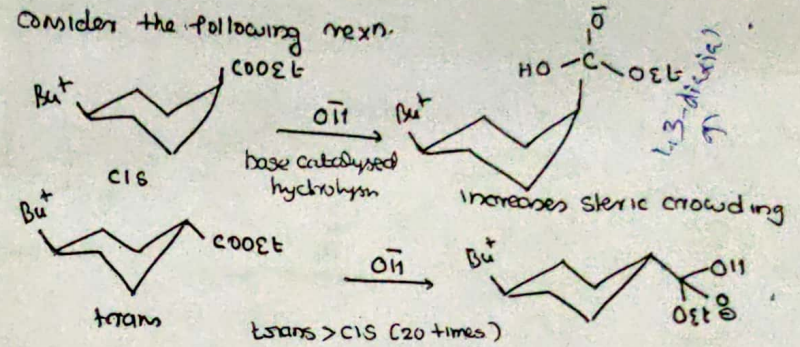
① In SN2 reactions the incoming nucleophile, the centre undergoing substitution and the leaving group must be collinear. ② In E2 reactions, the pairs reacting centres involved must be coplanar with the two leaving groups preferably anti to each other across C–C bond (ie antiperiplanar). ③ In migrating molecular rearrangements the migrating group is anti to the leaving group. ④ In a nucleophilic addition to a carbonyl grp the nucleophile approaches with an angle of 110° to the carbonyl plane etc are the various common conditions

SN1 reaction

SN1 reaction proceeds through the formation of carbocation, which relieves the steric strain of the axial isomer due to 1,3-diaxial interaction. Thus the SN1 reaction is sterically assisted for an axial substituents, such type of steric acceleration will not occur with the corresponding equatorial substituent. eg: the acetolysis of cis-4-t-butyl cyclohexyl tosylate, with an axial tosyl group is about 3·4 times faster than that of the trans isomer



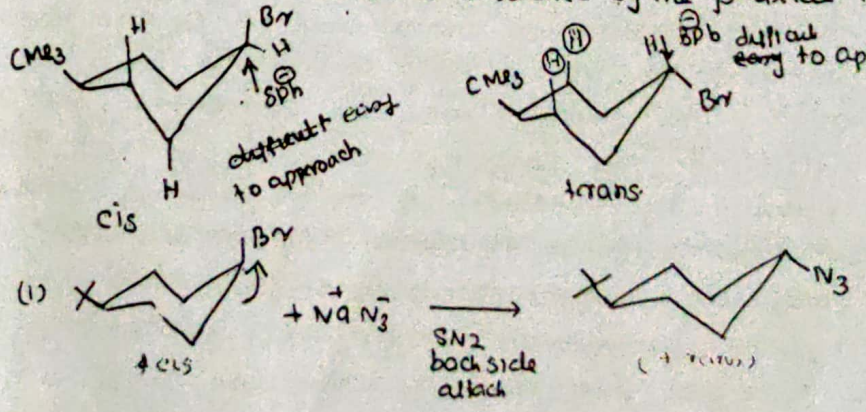
Consider the following rexn.



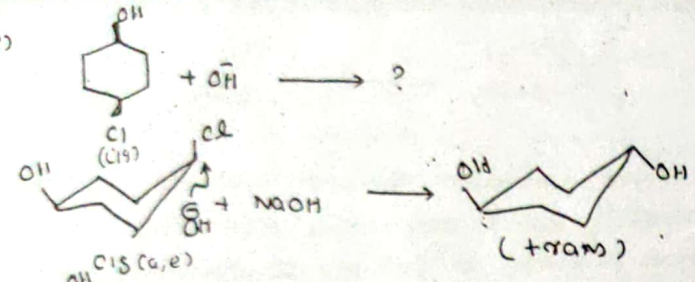
here base catalysed hydrolysis of trans isomer take place fastest (about 20 times) than cis, bec² in cis isomer addition OH^- ion further increases molecular crowding with axial hydrogens. but not in trans isomer.

SN2 reaction

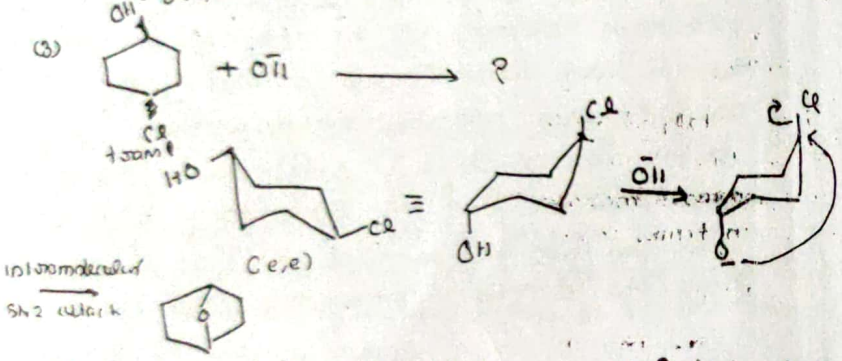
SN2 reactions take place more readily with axial substituent than equatorial. For example SN2 rexn of thiophenoxide ion with 4-t-butyl cyclohexyl bromide having an axial Br take place about 60 times faster as compared to the equatorial isomer; bec the attack of SPh^- ion on the equatorial isomer is hindered by the β-axial hydrogens.



(2)

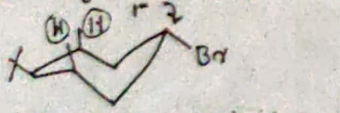


(3)

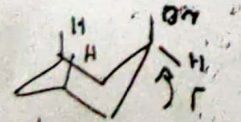


The bicyclic product is formed from an intramolecular (SN2) backside attack of the deprotonated axial OH group on axial Cl. Only trans isomer can adopt a diaxial relationship needed for the process.

→ halogenation of haloacyclohexane by SN2 mech is little difficult



approach of I⁻ hindered by axial Hs

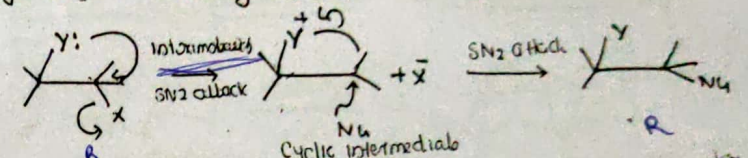


departure of bromide is now hindered by axial hydrogens

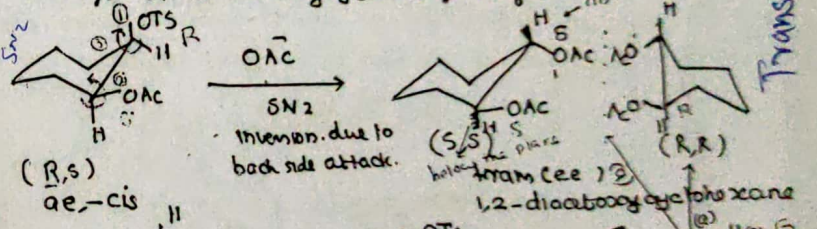
[Refer more from Kalsi]

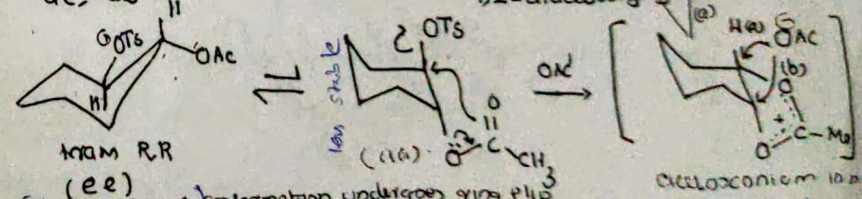
✓ Neighbouring group participation – Nasipuri

If a substrate of an SN mech happens to contain a nucleophilic group appropriately positioned. It often participates in the mech by removing the leaving group through an intramolecular SN2 mechanism and giving a cyclic intermediate. The latter then reacts with the external nucleophile or solvent by another SN2 process and the internal nucleophile returns its original position. This is called neighbouring group participation which is associated with ① enhancement of rate ② retention of config at the reacting centre.



eg: acetolysis of 2-acetoxycyclohexyl tosylate



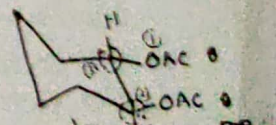


The diequatorial conformation undergoes ring flip so as to bring an anti relationship bwn nucleophile and leaving group ⊥ T]

[For R,S config take axial H-above / axial H-below

Refer more ?

neighbouring gp SN2 ?



Both cis and trans isomers give trans-1,2-diacetoxycyclohexane the former by direct SN2 mech and the latter through NGP. In the diaxial conformer of the trans isomer the acetoxy group is suitably disposed to remove the tosyl group by an intramolecular SN2 mech to give an intermediate acetoxonium ion with cis fused 6,5 ring

Retention of configuration / Rate much higher

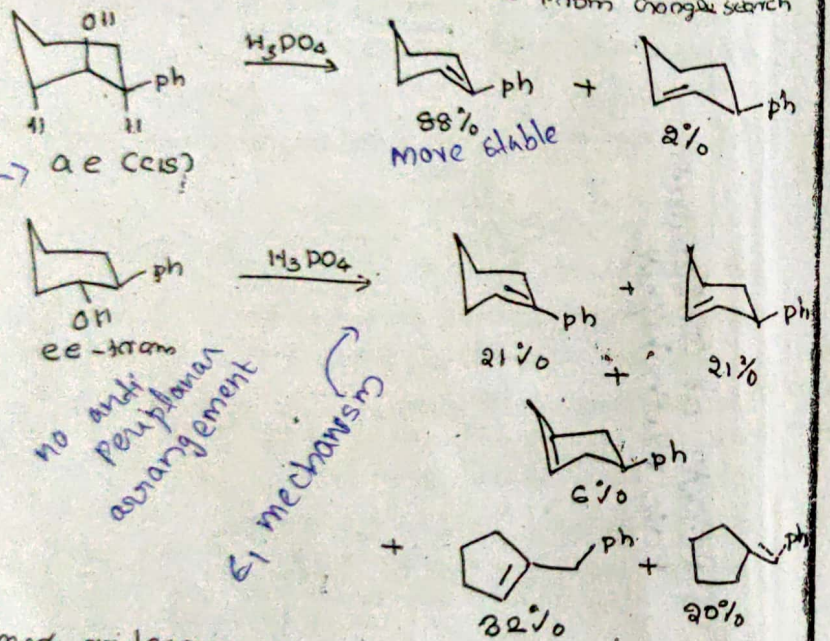
Trans rate higher

Intramolecular S_N2 reaction

The nucleophilic attack by acetate ion at either ring junction gives the trans diacetate. The reactivity of the trans isomer is almost 700 times greater than that of the cis isomer. Despite the very low concn of the reactive conformer in the former.

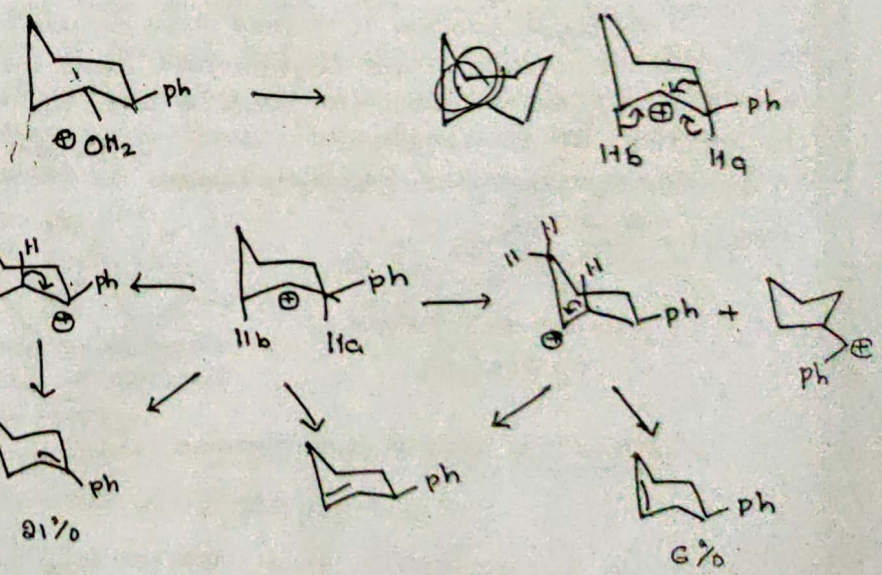
Acid-catalysed dehydration of 2-phenyl cyclohexanol

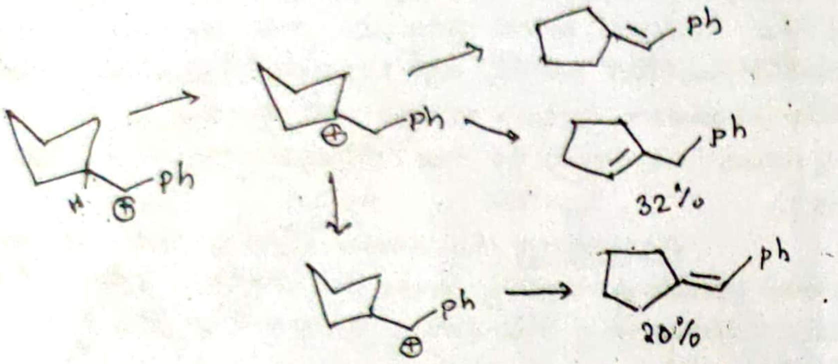
– From Chemsketch



cis-isomer undergoes E2 elimination through the anti-periplanar conformation of the starting material. Two different ~~product~~ protons can be eliminated giving rise to two different alkenes. The one on the left is the major product bec² conjugation with the phenyl group stabilizes its double bond.

Trans-isomer cannot achieve the anti-periplanar arrangement required for the E2 elimination and instead a cation is formed and the reaction proceeds according to E1 mechanism. The original cation can deprotonate directly or undergo one of three possible arrangements (hydride shifts, alkyl shift). Additional rearrangement are possible for the secondary benzylic cation. Any one of these cation can deprotonate to give the different products observed.





axial alcohols oxidise faster to ketones.

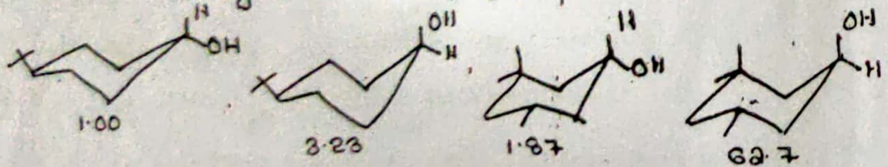
Chromic acid oxidation of cyclohexanols — Nasipuri + Jagadamini Singh

The chromic acid oxidation of a secondary alcohol to a ketone is believed to go in two steps (1) the rapid formation of a chromate ester followed by its (2) rate determining decomposition in to the ketone, chromite ion and a proton

$$R_2-CH-OH + HCrO_4^- + H^+ \rightleftharpoons R_2CH-O-CrO_2-OH + H_2O$$ (chromate ester)

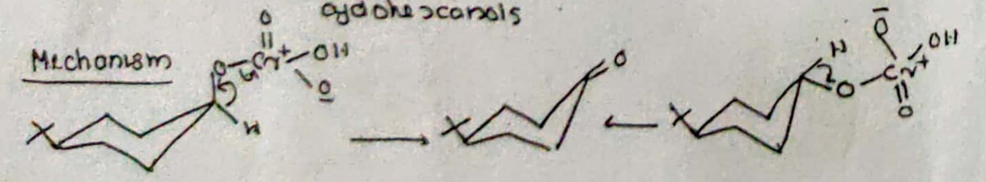
$$R_2CH\,O\,CrO_2-OH \xrightarrow{\text{rate determining step}} R_2-C{=}O + HCrO_3^- + H^+$$ (ketone)

In substituted cyclohexanol and in steroidal alcohols, the axial alcohols are oxidised at a faster rate than the equatorial one by a factor of 3 to 6.

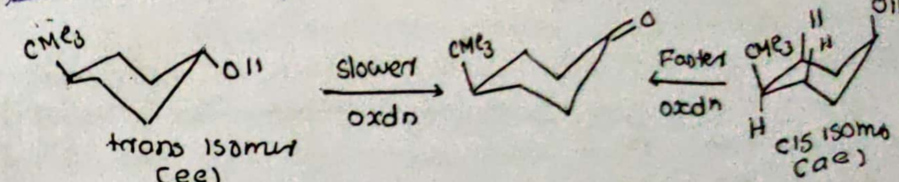


Relative rates of chromic acid oxidation of cyclohexanols

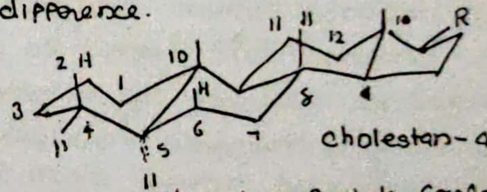
Mechanism



eg: Oxidation of cis and trans 4-t-butylcyclohexanols with chromic acid gives ketone, but the rexn is 3 times faster in cis isomer than trans isomer. In the preferred conformation the cis isomer has an axial hydroxyl group which is removed in the oxidation to allow relief from 1,3-diaxial interactions.



Thus the relief of steric strain in the transition state in going from the chromate ester to the ketone is responsible for the rate difference.

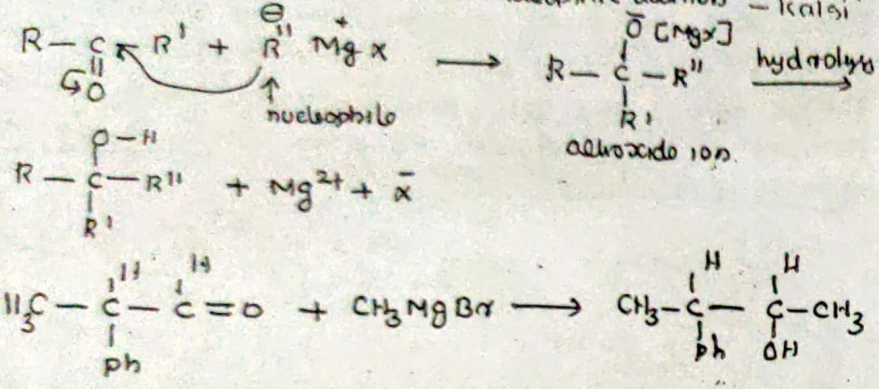


Steroidal alcohols (relative rate)

Position of OH (e/a)	Relative rate
3β-ol (e)	1.0
3α-ol (a)	3.0
6α-ol (e)	2.0
6β-ol (a)	36.0
11α-ol (e)	14.0
11β-ol (a)	>900

Cholestan 4α-ol in which 4β-H suffers from synaxial interaction with 10-Me is oxidised twice as fast as cholestan-3β-ol

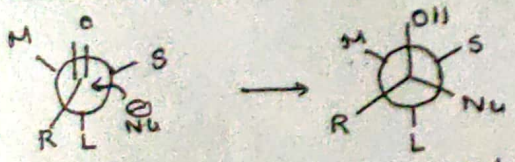
Action of methyl magnesium bromide on 2-phenyl propanal
– Nucleophilic addition – Kalasi



A carbonyl carbon when bonded to two different substituents is a prochiral carbon and such carbonyl compounds will have enantiotopic faces Re and Si. The addition of grignard reagent to either face is equally possible to get racemic mixture. However the two faces of a carbonyl group close to a stereocentre are diastereotopic and then on addition of a grignard reagent one of the two possible diastereomers will predominate in the product.

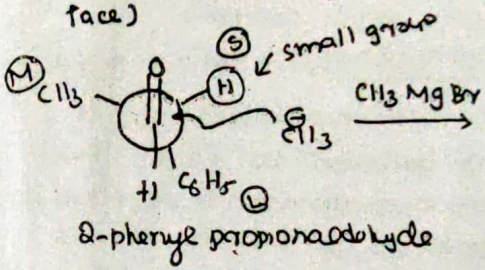
The reaction of 2-phenyl propionaldehyde with CH_3MgBr gives erythro compound as the major product. Cram's rule and Felkin-Ahn model is used to predict the stereochemistry of the product.

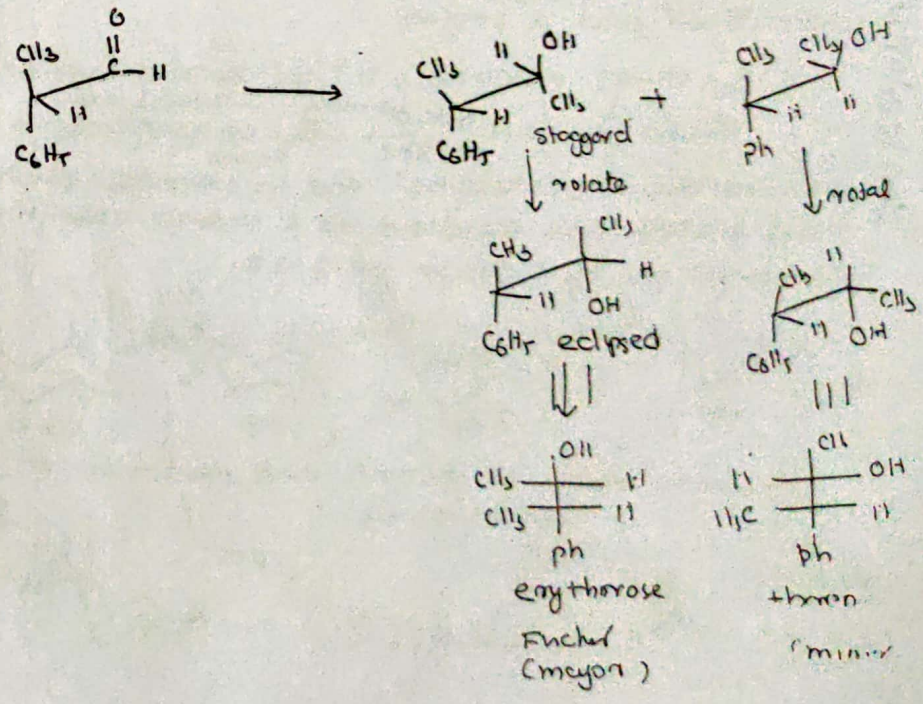
Cram's rule



The oxygen of the carbonyl grp orient b/w the small and the medium sized groups. The largest group is oriented as far away as possible from the carbonyl group, however L will eclipse the group R. So the 4 groups attached to the stereocentre are CO, R, S, M and L.

According to cram's rule the incoming group preferencially attack on the side of the plane containing the small group-C ie less hindered face)





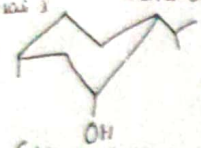
Rate of esterification — Finar — Google search

2-Isopropyl-5-methylcyclohexanol — Menthols

menthol
(All substituents are equatorial)
(most stable)

isomenthol
(One substituent is axial)

neomenthol
(OH is axial)



(least stable)

or

(OH is equatorial and bulky group is axial)

neoisomenthol

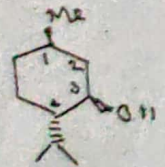
Ehel (1955) applied the principle that the esterification of an axial hydroxyl group less readily than with an equatorial one. Furthermore, Ehel postulated that the oxid proceeds via the conformation of the molecule in which the reactive hydroxyl group is equatorial and that the rate difference should be attributed to that energy necessary to place the other substituents, if necessary in to the axial conformation on this basis, the rates of esterification of the isomeric menthol will be

menthol > iso > neoiso > neo

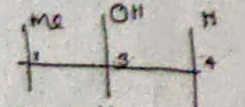
(−) menthol — 16·5, (+) isomenthol — 12·3

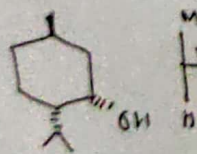
(+) neoisomenthol — 3·1 (−) neomenthol — 1·0

→ menthol $C_{10}H_{20}O$ is an optically active compd only the (−) form occurs naturally.

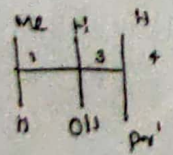


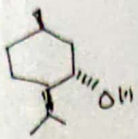
menthol



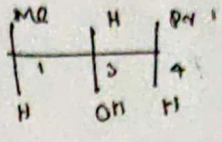


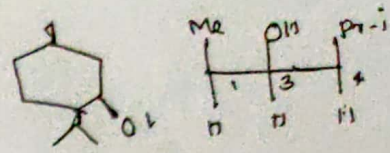
neomenthol





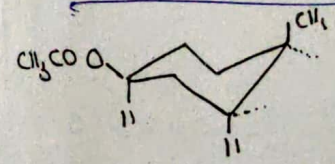
isomenthol





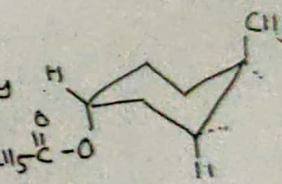
Karlsbarns Advanced org. chem. vol. — 1 (Google search)

Esterification and hydrolysis — Equatorial and axial conformational isomers normally react at different rates due to the hindered character of an axial group (1,3-diaxial interaction) esterification and hydrolysis occurs more readily with the equatorial conformation. For example cholestanyl acetate (having acetate in equatorial position) saponifies more rapidly than epicholestanyl acetate (having acetate in axial position)



Cholestanyl acetate
(equatorial ester)

saponifies rapidly than



Epicholestanyl acetate
(axial ester)

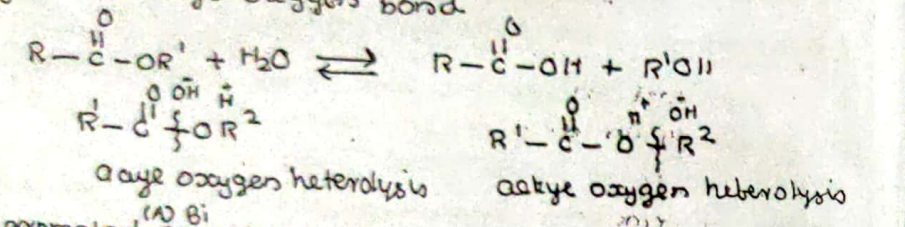
→ axial bonds experience non bonded interaction with other axial bond at 3 and 5 position whereas the equatorial bonds are free from such steric interaction. Thus the equatorially bound groups in cyclohexane derivatives are more active than the axially bound so equatorially bound hydroxyl groups are more easily esterified than the axial ones. Similarly the equatorial acetoxy group undergoes hydrolysis faster than axial groups. The same is true for esterification of the carboxyl and the hydrolysis of esters. (S.M. Mukherji)

Rate of ester hydrolysis is lower in axial substituted acidalcohol

Nasipuri + Finar + Kalsi + Raghavan

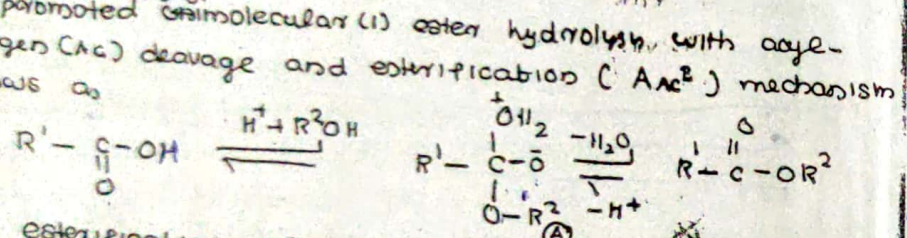
Ester hydrolysis and esterification

The conversion of an ester into an acid and alcohol moieties is termed as ester hydrolysis. This hydrolysis can involve cleavage either at the acyl oxygen or alkyl oxygen bond.



acyl oxygen heterolysis — alkyl oxygen heterolysis

Acid promoted (A) Bi (bimolecular) (1) ester hydrolysis with acyl-oxygen (A_{Ac}) cleavage and esterification ($A_{Ac}2$) mechanism follows as



In the esterification of cyclohexanol ($R^2 = C_6H_{11}$, $R^1 = R$) the ex^n proceeds the intermediate (A). Replacement of the hydroxylic hydrogen in R^2OH by the large group (shown in the intermediate) very much increases the non bonded interactions in R^2O. This interactions will be far greater for an axial OH than an equatorial OH. Hence the rate of esterification of ~~ester~~ and hydrolysis will be ~~greater for equatorial one than axial~~. Since hydrolysis by the $A_{Ac}2$ mechanism is the reverse of esterification hydrolysis also proceeds through the intermediate (A)

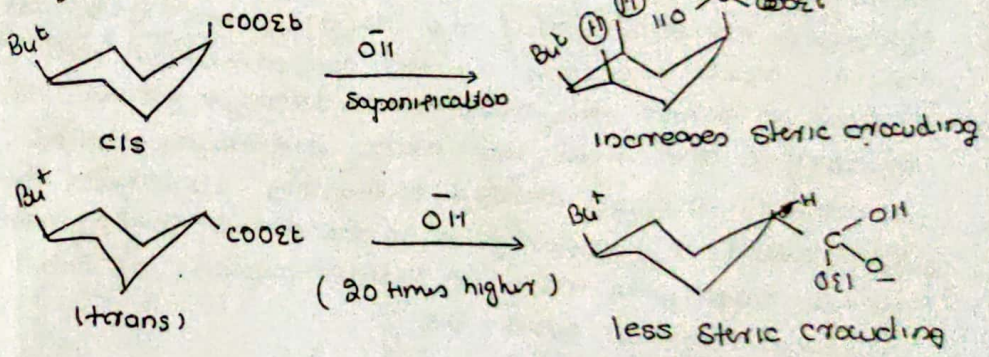
In hydrolysis case ester already has the large group R^1CO attached to the oxygen atom of R^2O, but in the formation of (A) hybridisation of the carbonyl carbon atom has changed from (sp^2) → planar to sp^3-tetrahedral. Thus the volume of the group has

Rate of esterification is faster for equi. substituted

increased in (A) and consequently non bonded interactions are increased. Hence the axial ester would be expected to undergo hydrolysis more slowly than the equatorial ester

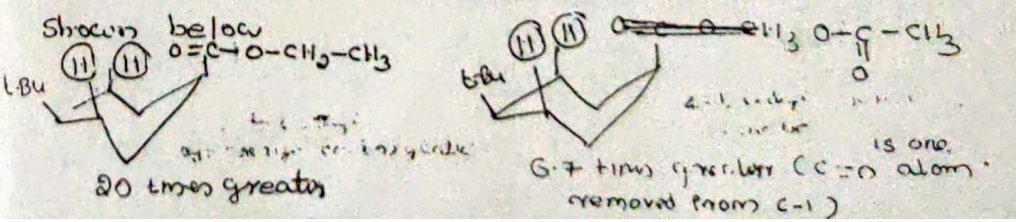
→ Similar arguments can be applied to the hydrolysis by $B_{Ac}2$ (base promoted bimolecular hydrolysis with acyl-oxygen cleavage. (saponification)

→ esterification of cyclohexane carboxylic acid ($R^1 = C_6H_{11}$, $R^2 = R$) and the hydrolysis of its esters, both proceed through the intermediate (A) and using the same concept axial conformer would be expected to undergo esterification and hydrolysis more slowly than the equatorial conformer.

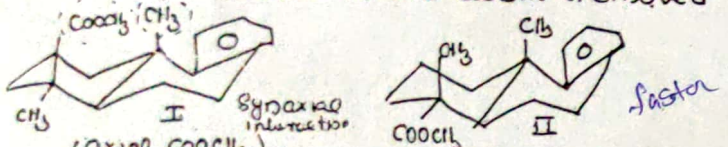


In base catalysed hydrolysis of trans isomer take place faster (about 20 times) than cis, beca in cis isomer addition of $\bar{O}H$ ion further increases molecular crowding but not in trans.

→ This difference k_{trans}/k_{cis} for saponification is as shown below

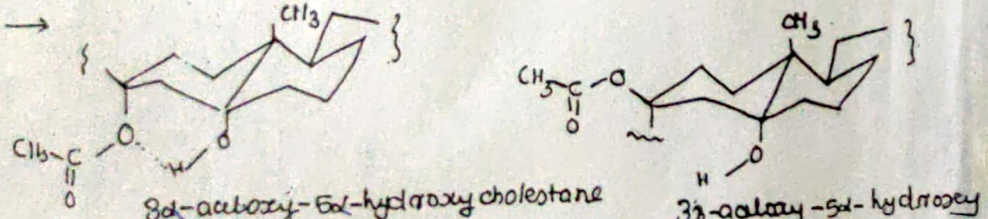


The difference in the rates of a reaction for an equatorial and an axial isomer is diminished as the site of crowding moves away from the ring. Thus k_{ax}/k_{eq} for the saponification of 4-t-butylcyclohexane carboxylate and 4-t-butylcyclohexyl acetate is 20 and 6.7 respectively (in the latter C=O is one atom removed from C-1)



diterpenes

The hydrolysis rate of axial carboxymethyl group is further reduced by the syn axial interaction of the angular methyl group. Thus the two esters can be easily identified and even can be separated from each other by preferential hydrolysis. Thus the relative rates of esterification and saponification is used to assign the config of a carboxyl or hydroxyl group in many natural products.



(axial will hydrolyse faster than equatorial)

In 3α-acyloxy-5α-hydroxy cholestane, the acyloxy group is syn axial to the hydroxyl group permitting the formation of an intramolecular H bond. The H bond would be much stronger in the transition state where the other oxygen develop partial negative charge during hydrolysis. As a result, the free energy of activation is considerably decreased for 3α-acyloxy than for 3β-acyloxy derivative and the axial one hydrolyses faster.

→ Substituents at the adjacent positions in the ring also affect relative rates. For example the saponification of an e-Me retards the rate of an adjacent e-$COOCH_3$ much more than that of an a-$COOCH_3$.

≡ 2 elimination from 1-~~chloro~~ Bromo 1,2-diphenyl propane

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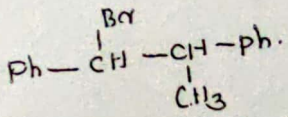
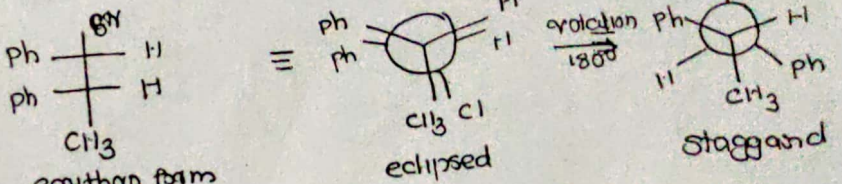
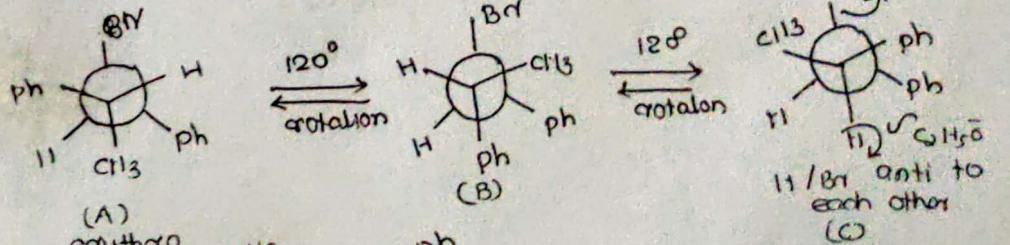
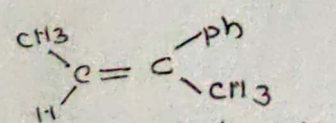


1-bromo-1,2-diphenyl propane



This compound has two stereogenic carbons, thus it would exist in four stereoisomeric forms



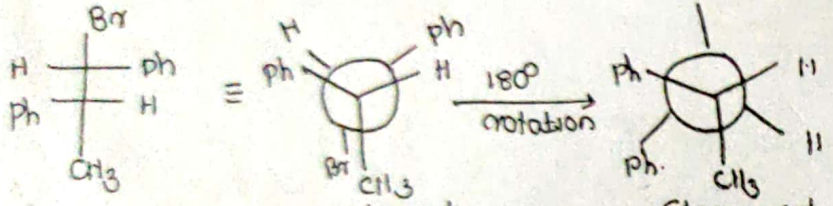


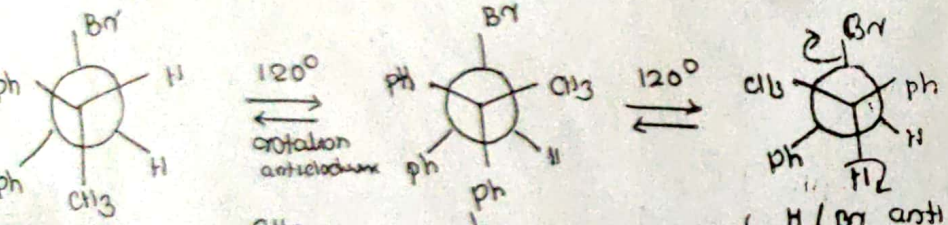
Z-1,2-diphenyl propane

In conformer (A) the eliminating groups are not suitable for anti elimination, so the conformer is rotated

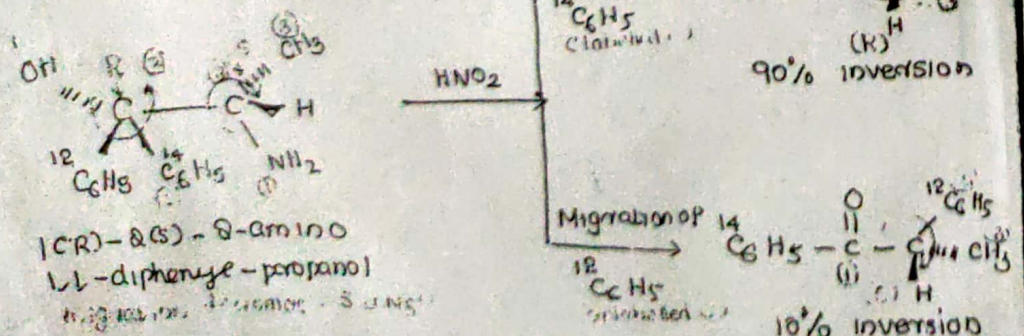
Further appropriately so as to bring H and Br in anti periplanar relationship. This undergoes E2 elimination (CNaOEt / EtOH) to give Z-alkene. Thus out of three possible staggard rotamers of erythro diastereomer, only rotamer (c) is suitable for anti elimination and which only give Z-alkene

→ similarly in the threo diastereomer the rotamer gives E-alkene





Pinacolic deamination



(1R)-2(S)-2-amino
1,1-diphenyle-propanol