CHAPTER

5

Reaction Mechanism

5.1. Nucleophilic substitution:

Types of Nucleophilic Substitution reactions:

(i) The S_N2 Mechanism:

The reaction is preceded by a common single-step mechanism of second order reaction. The features of the S_N2 mechanism are inversion at the alpha-carbon, increases reactivity with increasing nucleophilicity of the nucleophilic reagent.

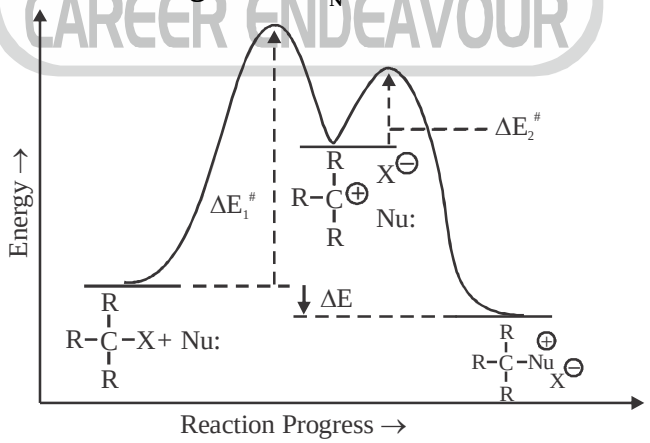
$$CH_3CH_2 - Cl + KOH \xrightarrow{\text{alcohol}} CH_3CH_2OH + KCl$$

(ii) The S_N1 Mechanism:

It not only shows first order kinetics, but the chiral 3°-alkyl bromide reactant undergoes substitution by the modest nucleophile water with extensive racemization.

$$(CH_3)_3C - Br + H_2O \longrightarrow (CH_3)_3C - \overset{\oplus}{O}H_2 + Br^- \xrightarrow{-H^+} (CH_3)_3C - OH + HBr$$

PES diagram for S_N1 reaction



The first order kinetics of these reactions suggest a two-step mechanism in which the rate-determining step consists of the ionization of the alkyl halide. In this mechanism, a carbocation is formed as a high-energy intermediate, and this form bonds immediately to nearby nucleophiles.

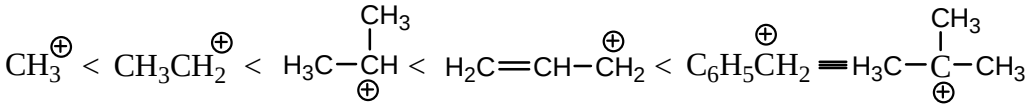
Various features for S_N1:

(i) The reactant having the tendency to form stable carbon cation, we expect the S_N1 mechanism.

(ii) Since nucleophiles only participate in the fast second step, recombination of the halide anion with the carbocation intermediate simply reforms the starting compound.

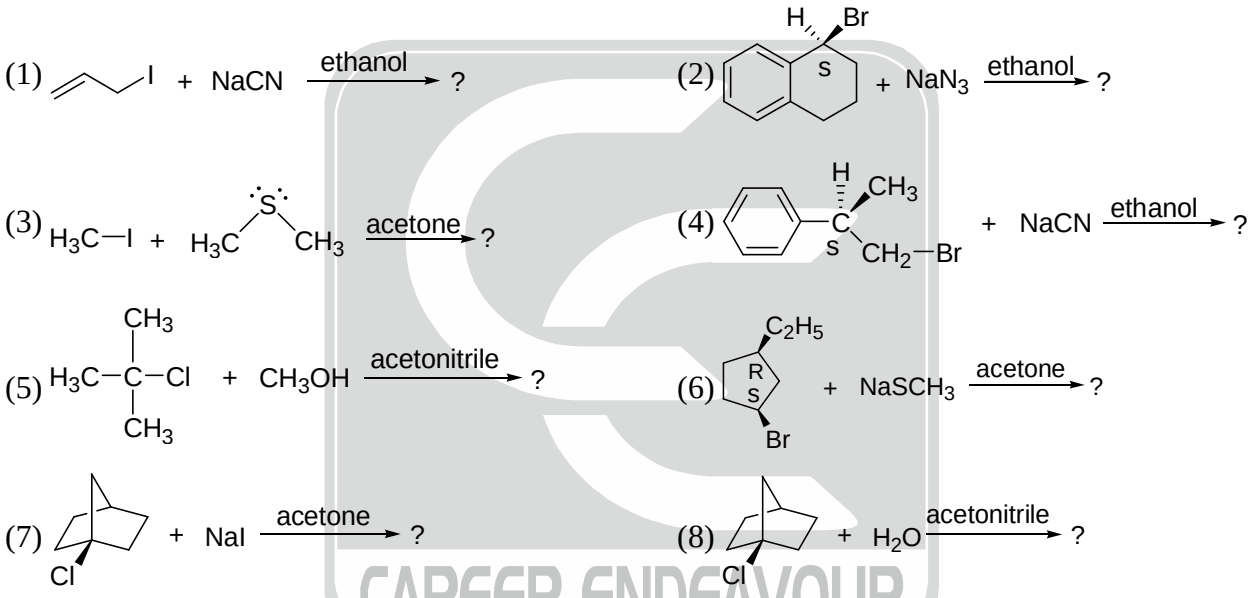
(iii) The Hammond postulate suggests that the activation energy of the rate-determining first step will be inversely proportional to the stability of the carbocation intermediate.

Carbocation Stability:



(iv) The stereospecificity of these reactions may vary. The positively-charged carbon atom of a carbocation has a trigonal (flat) configuration (it prefers to be sp^2 hybridized), and can bond to a nucleophile equally well from either face.

Problem: Predict which of the following reaction is occured by S_N1, S_N2 and neither S_N1 nor S_N2 mechanism.



Activation by electrophilic cations:

Heterolytic cleavage of the carbon-halogen bond of alkyl halides may be facilitated by the presence of certain metal cations. In the extreme, carbocations may be generated as shown in the following equation, where R is alkyl or hydrogen, and M = Al (n=3) or Fe (n=3) or Sn (n=4) or Zn (n=2).

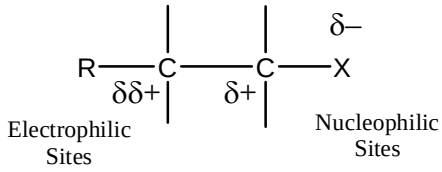
$$R_3C-X+MX_n \text{ (reactivity = Al > Fe > Sn > Zn)} \longrightarrow R_3C^{\oplus} + MX_n - X^-$$

In aqueous or alcoholic solution it promotes ionization of the alkyl halide and the formation of S_N1 products. When silver nitrate is used with 1° or 2°-alkyl halides, rearrangement may occur before the product formation stage. For example:

$$(CH_3)_3CCH_2-Br+H_2O+AgNO_3 \longrightarrow (CH_3)_2C(OH)CH_2CH_3+AgBr+HNO_3$$

5.2. Elimination versus Substitution:

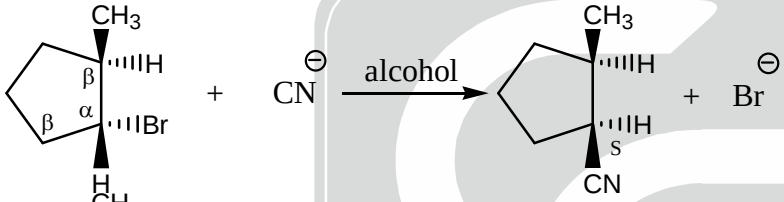
For many combinations of alkyl halides and nucleophiles, elimination reactions may compete with substitution,

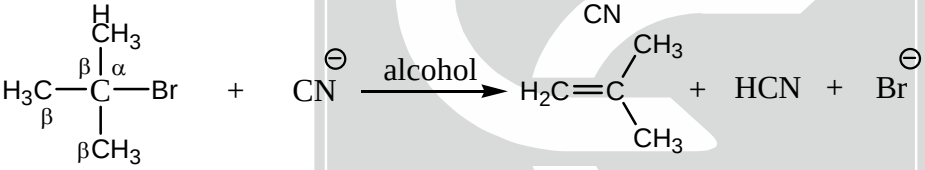


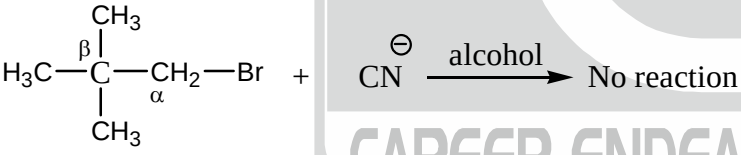
In describing these, it is useful to designate the halogen-bearing carbon as **alpha** and the carbon atom adjacent to it as **beta**, as noted in the first four equations shown below. Replacement or substitution of the halogen on the α-carbon by a nucleophilic reagent is a commonly observed reaction, as shown in equations **1, 2, 5, 6 & 7** below. Also, since the electrophilic character introduced by the halogen extends to the β-carbons, and since nucleophiles are also bases, the possibility of base induced H-X elimination must also be considered, as illustrated by equation **3**.

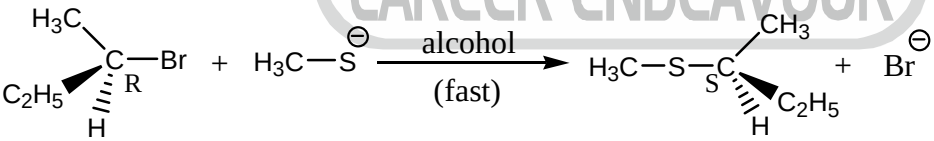
- Nucleophiles having basic characater give elimination reaction.
- Nucleophiles having non-basic character give substitution reaction.

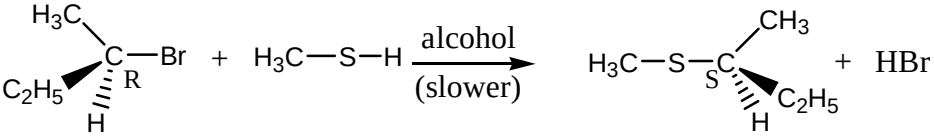
1. $CH_3\underset{\beta}{C}H_2\underset{\alpha}{C}H_2CH_2Br + CN^{\ominus} \xrightarrow[\text{(fast)}]{\text{alcohol}} CH_3CH_2CH_2CH_2CN + Br^{\ominus}$

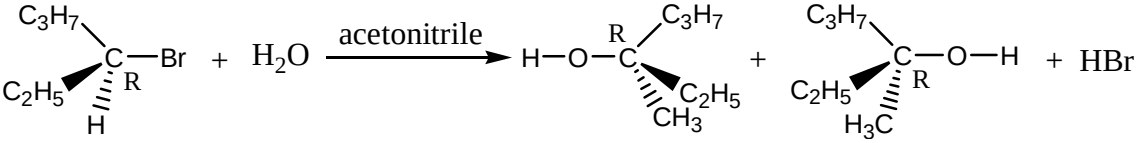
2. 

3. 

4. 

5. 

6. 

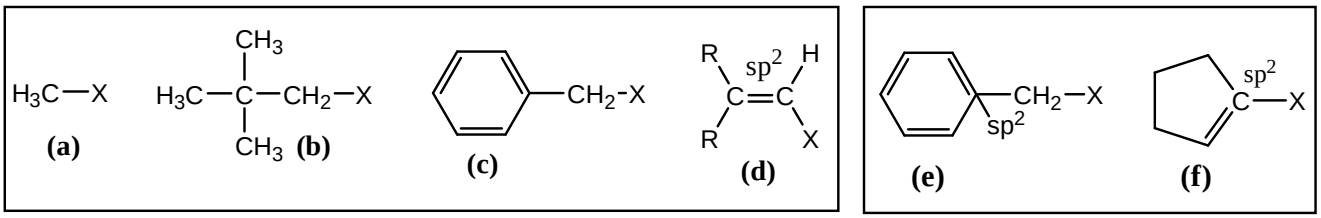
7. 

R = alkyl group

$R - X + Nu: \xrightarrow{\text{Solvent}} \text{Product}$ X = Cl, Br or I

Nu := nucleophile

One conclusion, relating the structure of the R-group to possible products, should be immediately obvious. **If R- has no beta-hydrogens an elimination reaction is not possible**, unless a structural rearrangement occurs first. The first four halides shown below (a, b, c, d) do not give elimination reactions on treatment with base, because they have no β-hydrogens. The two halides on the right (e, f) do not normally undergo such reactions because the potential elimination products have highly strained double or triple bonds.



no β-hydrogents strained elimination product

Using the general reaction shown above as our reference, we can identify the following variables and observables.

Variables	**R** change α-carbon from 1º to 2º to 3º if the α-carbon is a chiral center, set as (*R*) or (*S*) **X** change from Cl to Br to I (F is relatively unreactive) **Nu:** change from anion to neutral; change basicity; change polarizability **Solvent** polar vs. non-polar; protic vs. non-protic
Observables	**Products** substitution, elimination, no reaction. **Stereospecificity** if the α-carbon is a chiral center what happens to its configuration? **Reaction Rate** measure as a function of reactant concentration.

1. Nucleophilicity:

Nucleophilicity is thereby related to the relative rate of substitution reactions at the halogen-bearing carbon atom of the reference alkyl halide.

Nucleophilicity: $CH_3CO_2^- < Cl^- < Br^- < N_3^- < CH_3O^- < CN^- < SCN^- < I^- < CH_3S^-$

Increasing Nucleophile Strength:

The cumulative results of studies of this kind has led to useful empirical rules pertaining to nucleophilicity:

(i) For a given element, negatively charged species are more nucleophilic (and basic) than equivalent neutral species.

(ii) For a given period of the periodic table, nucleophilicity (and basicity) decreases on moving from left to right.

(iii) For a given group of the periodic table, nucleophilicity increases from top to bottom (*i.e.* with increasing size), although there is a solvent dependence due to hydrogen bonding. Basicity varies in the opposite manner.

2. Solvent effects:

Solvation of nucleophilic anions markedly influences their reactivity. Polar, aprotic solvents such as DMSO (dimethyl sulfoxide), DMF (dimethylformamide) and acetonitrile do not solvate anions nearly as well as methanol, but provide good solvation of the accompanying cations. Consequently, most of the nucleophiles discussed here react more rapidly in solutions prepared from these solvents. These solvent effects are more pronounced for small basic anions than for large weakly basic anions. Thus, for reaction in DMSO solution we observe the following reactivity order :

Nucleophilicity:

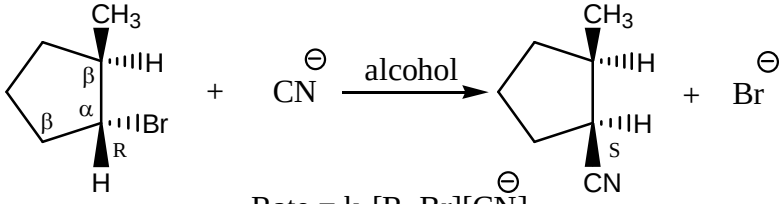
$$I^- < SCN^- < Br^- < Cl^- < N_3^- < CH_3CO_2^- < CN^- < CH_3O^- < CH_3S^-$$

3. The Alkyl Moiety:

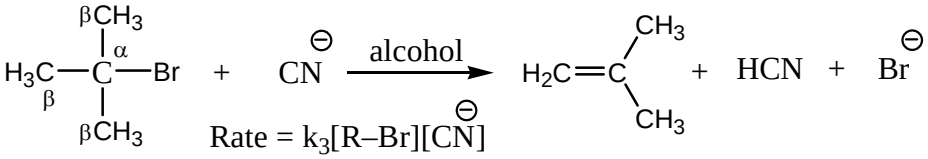
- Crowded alkyl moiety gives elimination reaction.
- Less crowded alkyl moiety gives substitution reaction.

1. $CH_3\underset{\beta}{CH_2}\underset{\alpha}{CH_2}CH_2Br + \overset{\ominus}{C}N \xrightarrow[\text{(fast)}]{\text{alcohol}} CH_3CH_2CH_2CH_2CN + \overset{\ominus}{B}r$

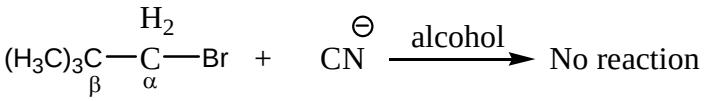
1º-bromide $\quad Rate = k_1[R–Br][\overset{\ominus}{C}N]$

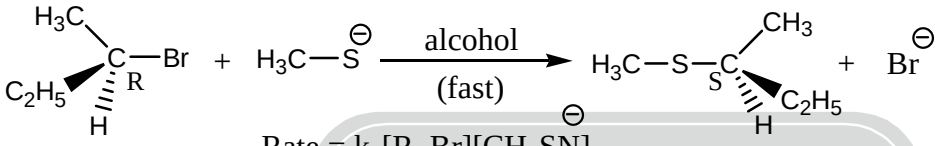
2. 

2°-bromide Rate = $k_2[R–Br][CN^-]$

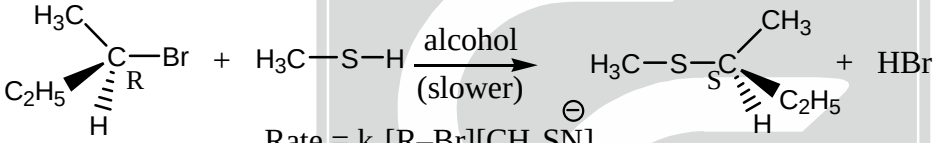
3. 

Rate = $k_3[R–Br][CN^-]$

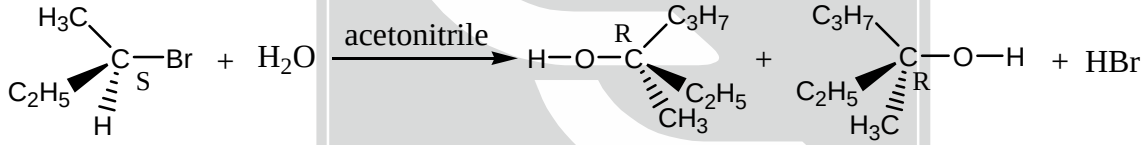
4. 

5. 

(R)-2-bromobutane Rate = $k_5[R–Br][CH_3SN^-]$ (S)-2-(methylthio)butane

6. 

Rate = $k_6[R–Br][CH_3SN^-]$ (S)-2-(methylthio)butane

7. 

(S)-3-bromo-3-methylhexane racemic 3-methyl--hexanol

Rate = $k_7[R–Br]$

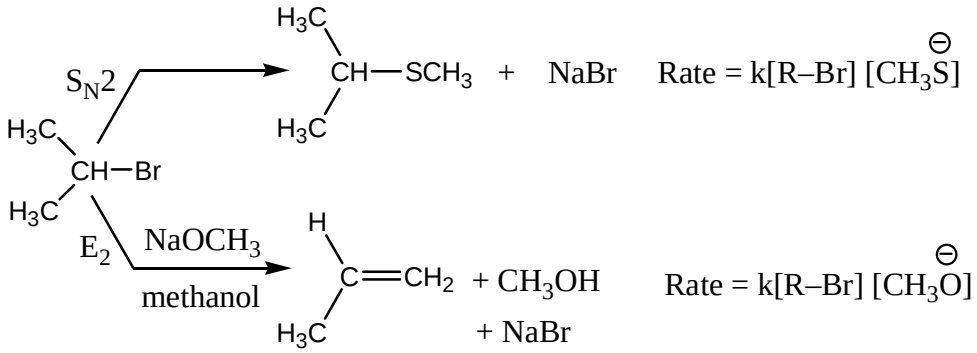
5.3. Elimination reaction:

Types of Elimination reaction:

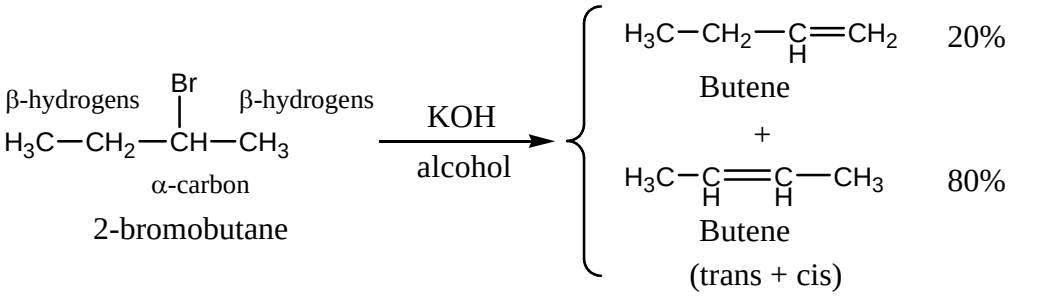
(1) The E_2 Reaction: We have not yet considered the factors that influence elimination reactions, such as example 3 in the group presented at the beginning of this section. Elimination of second order is called E_2 reaction.

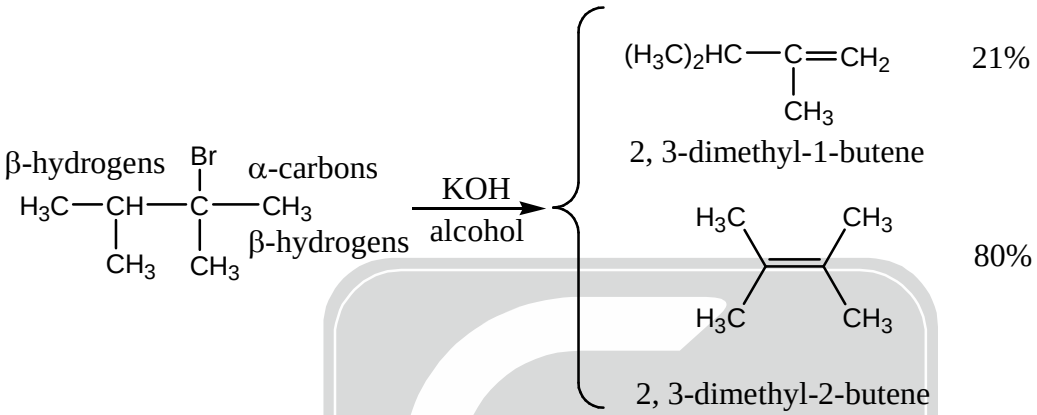
$$(CH_3)_3C-Br + CN^- \longrightarrow (CH_3)_2C=CH_2 + Br^- + HCN$$

For E_2 reaction, there is no formation of intimate ion pair that is carbocation (if formed) is not stable.



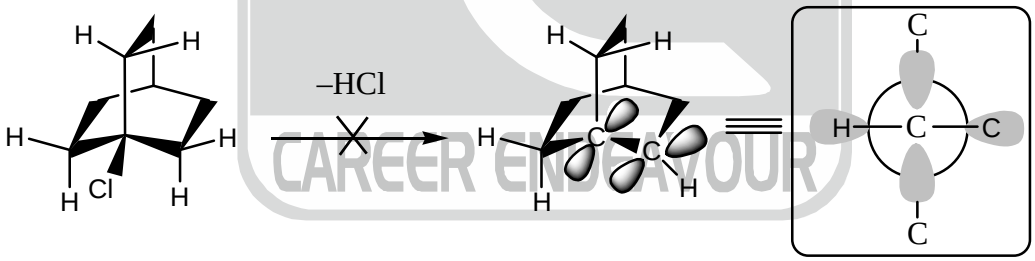
If two or more structurally distinct groups of beta-hydrogens are present in a given reactant, then several constitutionally isomeric alkenes may be formed by an E_2 elimination. This situation is illustrated by the 2-bromobutane and 2-bromo-2,3-dimethylbutane elimination examples given below.

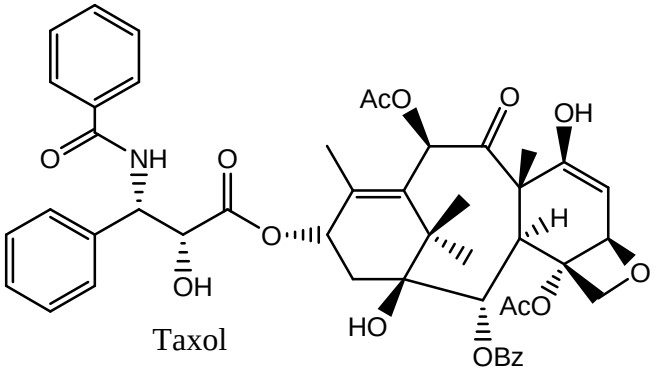




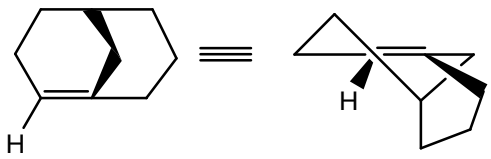
These results point to a strong regioselectivity favoring the more substituted double bond, an empirical statement generally called the **Zaitsev's Rule**.

Bredt's Rule: **Double bond can never be formed to bridge head carbons in bicyclic system due to impossibility of formation of planarity at bridge head carbon.**





Taxol

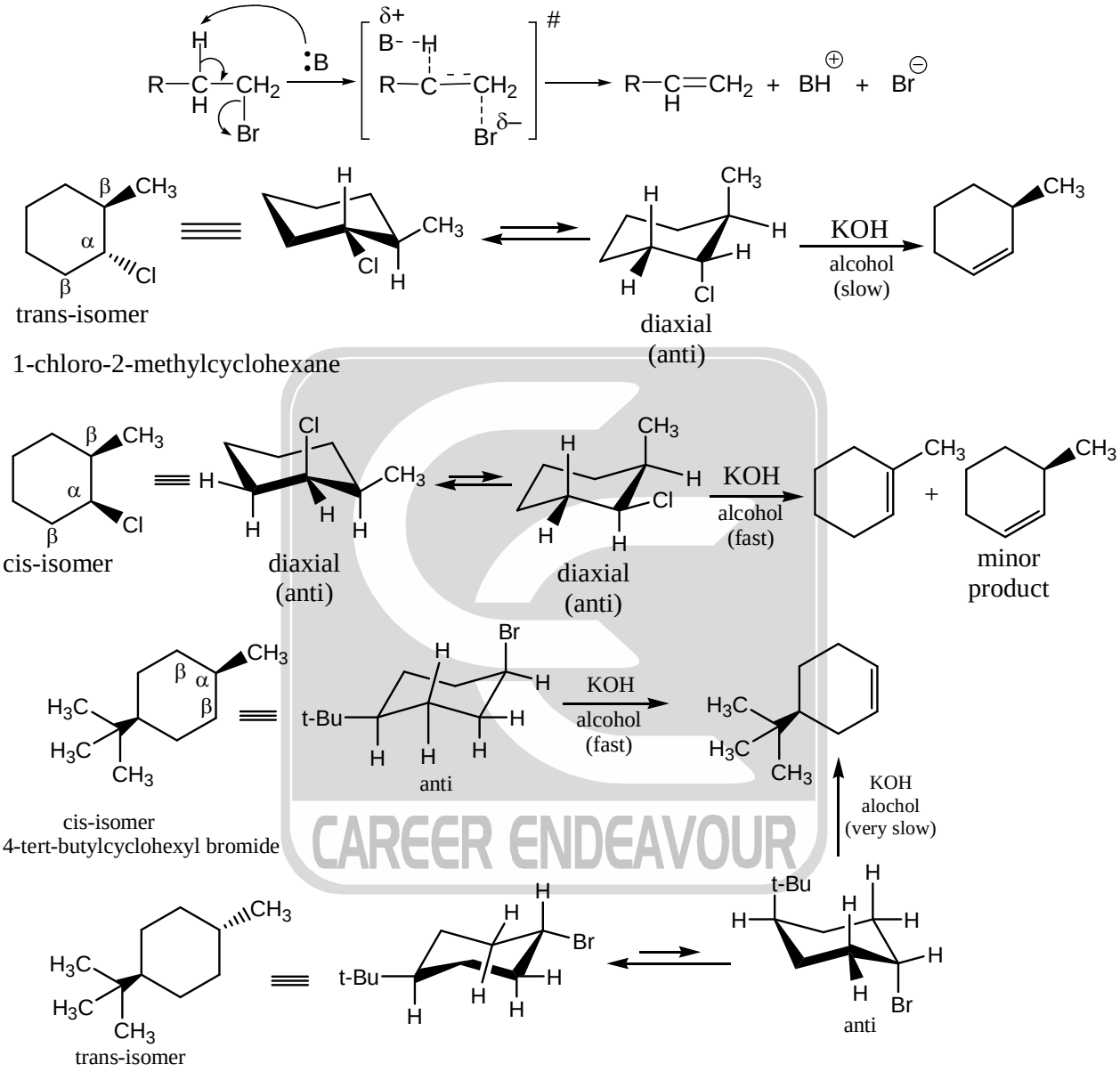


A brigehead double bond
in 1-bicyclo[3, 3, 1]octene

2. Stereochemistry of the E_2 Reaction:

E_2 elimination reactions of certain isomeric cycloalkyl halides show unusual rates and regioselectivity that are not explained by the principles thus far discussed. For example, trans-2-methyl-1-chlorocyclohexane reacts with alcoholic KOH at a much slower rate than does its cis-isomer. Furthermore, the product from elimination of the trans-isomer is 3-methylcyclohexene (not predicted by the Zaitsev rule), whereas the cis-isomer gives the predicted 1-methylcyclohexene as the chief product.

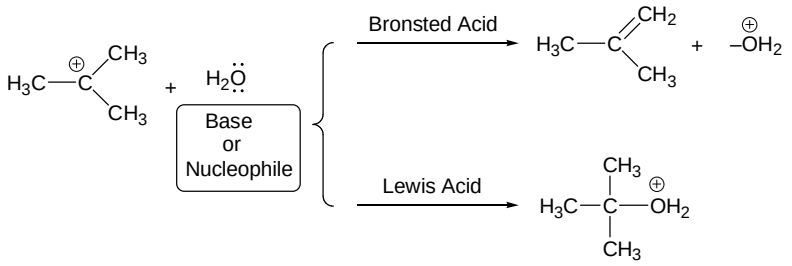
Unlike open chain structures, cyclic compounds generally restrict the spatial orientation of ring substituents to relatively few arrangements.



Note: Both eleminating group must be antiperiplanar to each other.

3. The E_1 Reaction:

Just as there were two mechanisms for nucleophilic substitution, there are two elimination mechanisms. The E_1 mechanism is nearly identical to the S_N1 mechanism, differing only in the course of reaction taken by the carbocation intermediate. As shown by the following equations, a carbocation bearing beta-hydrogens may function either as a Lewis acid (electrophile), as it does in the S_N1 reaction, or a Brønsted acid, as in the E_1 reaction.



$$(CH_3)_3C-Cl + H_2O \longrightarrow [(CH_3)_3C^+)] + Cl^- + H_2O \longrightarrow (CH_3)_3C-OH + (CH_3)_2C=CH_2 + HCl + H_2O$$

To summarize, when carbocation intermediates are formed one can expect them to react further by one or more of the following modes:

1. The cation may bond to a nucleophile to give a substitution product.
2. The cation may transfer a beta-proton to a base, giving an alkene product.
3. The cation may rearrange to a more stable carbocation, and then react by mode E_1 or E_2.
Since the S_N1 and E_1 reactions proceed via the same carbocation intermediate.
The most important being the structure of the alkyl group and the nature of the nucleophilic reactant.

Note that halogens bonded to sp^2 or sp hybridized carbon atoms do not normally undergo substitution or elimination reactions with nucleophilic reagents.

Nucleophile	Non-Basic Anionic Nucleophile	Basic Anionic Nucleophile	Neutral Nucleophile
Alkyl Group	(Weak Bases: I^-, Br^-, SCN^-, N_3^- ,$CH_3CO_2^-$, RS^-, CN^- etc.) pKa's from -9 to 10 (left to right)	(Strong Bases: HO^-, RO^-) pKa's > 15	(H_2O, ROH, RSH, R_3N) pKa's ranging from -2 to 11
Primary RCH_2^-	Rapid S_N2 substitution. The rate may be reduced by substitution of β-carbons, as in the case of neopentyl.	Rapid S_N2 substitution. E_2 elimination may also occur. *e.g.* $ClCH_2CH_2Cl + KOH \rightarrow CH_2=CHCl$	S_N2 substitution. ($SH^- > NH_2^- > OH^-$)
Secondary R_2CH^-	S_N2 substitution and / or E_2 elimination (depending on the basicity of the nucleophile). Bases weaker than acetate (pKa = 4.8) give less elimination. The rate of substitution may be reduced by branching at the β carbons, and this will increase elimination.	E_2 elimination will dominate.	S_N2 substitution. ($SH^- > NH_2^- > OH^-$) In high dielectric ionizing solvents, such as water, dimethyl sulfoxide & acetonitrile, S_N1 and E_1 products may be formed slowly.
Tertiary R_3C^-	E_2 elimination will dominate with most nucleophiles (even if they are weak bases). No S_N2 substitution due to steric hindrance. In high dielectric ionizing solvents, such as water, dimethyl sulfoxide & acetonitrile, S_N1 and E_1 products may be expected.	E_2 elimination will dominate. No S_N2 substitution will occur. In high dielectric ionizing solvents S_N1 and E_1 products may be formed.	E_2 elimination with nitrogen nucleophiles (they are bases). No S_N2 substitution. In high dielectric ionizing solvents S_N1 and E_1 products may be formed.
Allyl $H_2C=CH-CH_2$	Rapid S_N2 substitution for 1° and 2° -halides. For 3° -halides a very slow S_N2 substitution or, if the nucleophile is moderately basic, E_2 elimination. In high dielectric ionizing solvents, such as water, dimethyl sulfoxide and acetonitrile, S_N1 and E_1 products may be observed.	Rapid S_N2 substitution for 1° halides. E_2 elimination will compete with substitution in 2° - halides, and dominate in the case of 3°-halides. In high dielectric ionizing solvents S_N1 and E_1 products may be formed.	Nitrogen and sulfur nucleophiles will give S_N2 substitution in the case of 1° and 2° -halides. 3°-halides will probably give E_2 elimination with nitrogen nucleophiles (they are bases). In high dielectric ionizing solvents S_N1 and E_1 products may be formed. Water hydrolysis will be favorable for 2° & 3°-halides.
Benzyl $C_6H_5CH_2^-$	Rapid S_N2 substitution for 1° and 2° -halides. For 3° -halides a very slow S_N2 substitution or, if the nucleophile is moderately basic, E_2 elimination. In high dielectric ionizing solvents, such as water, dimethyl sulfoxide & acetonitrile, S_N1 and E_1 products may be observed.	Rapid S_N2 substitution for 1° halides (note there are no β hydrogens). E_2 elimination will compete with substitution in 2°-halides, and dominate in the case of 3°-halides. In high dielectric ionizing solvents S_N1 and E_1 products may be formed.	Nitrogen and sulfur nucleophiles will give S_N2 substitution in the case of 1° and 2°-halides. 3°-halides will probably give E_2 elimination with nitrogen nucleophiles (they are bases). In high dielectric ionizing solvents S_N1 and E_1 products may be formed. Water hydrolysis will be favorable for 2° and 3° halides.

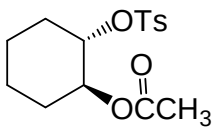
5.4. Neighbouring Group Participation:

The presence of nucleophilic groups in molecule undergoing nucleophilic substitution affects the kinetics and stereochemistry of reaction. The involvement of nearby nucleophilic substitutents such as lone pair electrons of group, in a substitution process is called neighbouring group participation.

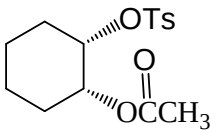
The leaving group and participating group are in the trans-position.

1. Acetoxy $\left(CH_3-\overset{\overset{O}{\|}}{C}-O\right)$ group:

The rate of solvolysis of the cis and trans isomers of 2-acetoxy cyclohexyl p- toluene sulfonate differs by a factor of about 670, trans isomers being more reactive one and the products obtained are also different.

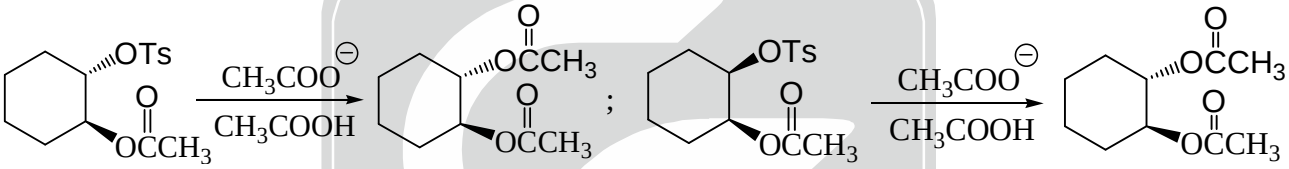


$K = 1.9 \times 10^{-4} S^{-1} (100^oC)$



$K = 2.9 \times 10^{-7} S^{-1} (100^oC)$

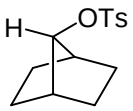
The diacetate obtained from the cis isomer is the trans-isomer (inverted stereochemistry) whereas retention of configuration is observed for the trans isomer.



The results can be explained by the participation of the trans acetoxy group in the ionisation process. The assistance provided by the acetoxy carbonyl group facilitates the ionisation of the tosylate group, accounting for the rate enhancement. This kind of backside participation by adjacent acetoxy group is both sterically and energetically favorable. The cation which is formed by participation is stabilised by two oxygen atoms and is for more stable than a secondary carbocation. The acetoxonium ion is subsequently opened by nucleophilic attack with inversion at one of the two equivalent carbons leading to the observed trans product. Whereas in case of cis isomer, simple S_N2 mechanism is involved.

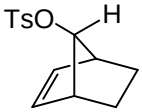
2. The electron of C=C bond:

C=C bond are also envolved in neighbouring group participation reaction e.g. the anti tosylate isomer in norbornyl systems are found to be more reactive toward acetolysis than that of saturated isomer by a factor of about 10^{11}. The product is also retention in configuration. This is due to being participation of π-electron of C=C bond to give ion which is more stabilised by delocalisation of the positive charge.



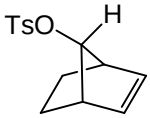
$K_{rel} = 1$

Norbornyl Tosylate



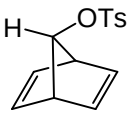
$\approx 10^4$

Norbornenyl Tosylate (syn)



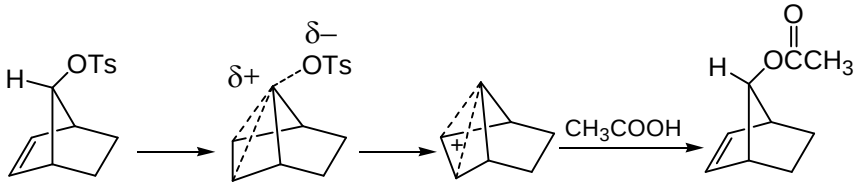
$\approx 10^{11}$

Norbornenyl Tosylate (anti)

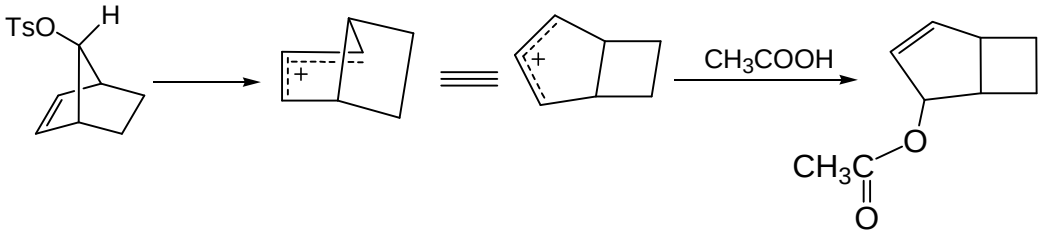


$\approx 10^{14}$

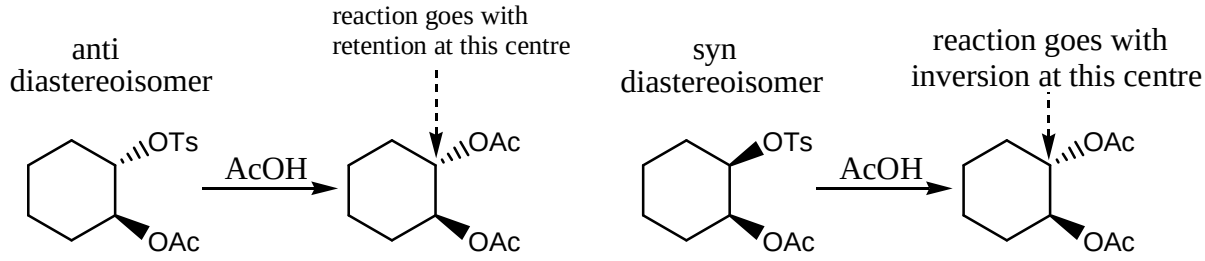
Norbornadienyl Tosylate



In contrast, syn isomers in which the double bond is not in the position to participate in the ionisation step therefore it reacts 10^7 times slower than that of anti isomer. The reaction product is derived from a rearranged carbocation ion that is stabilised by virtue of being allylic

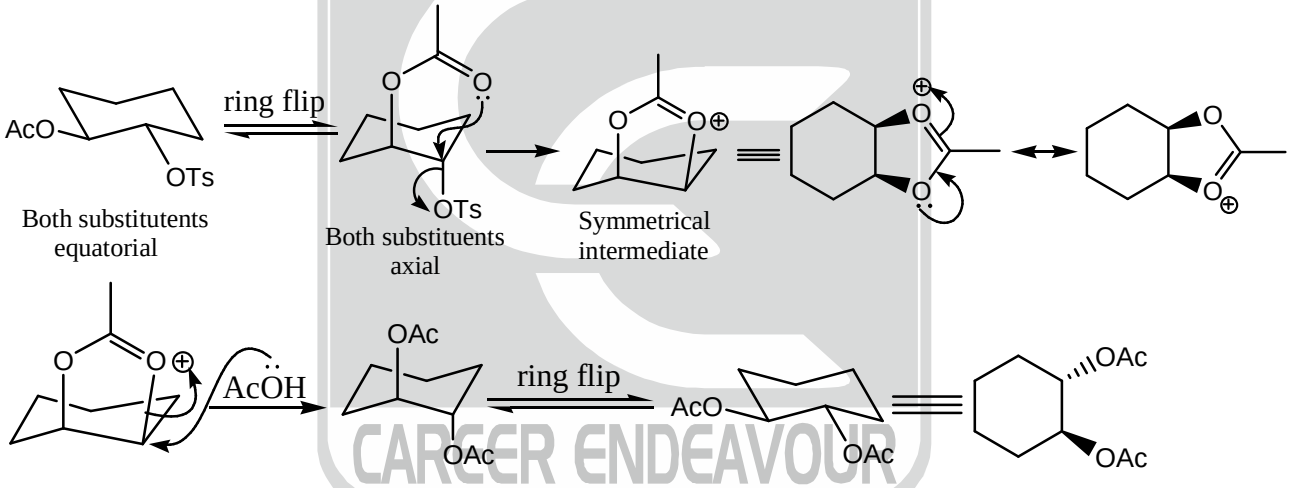


***Stereochemistry can indicate neighbouring group participation*:**



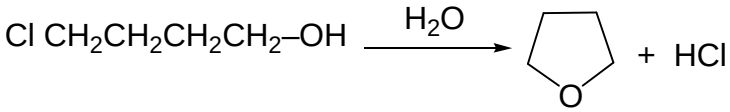
To explain this, we should first draw the six-membered rings in their real conformation. For the anti compound, both substituents can be equatorial.

However, not much can happen in this conformation–but, if we allow the ring to flip, you can see immediately that the acetate substituent is ideally placed to participate in the departure of the tosylate group.

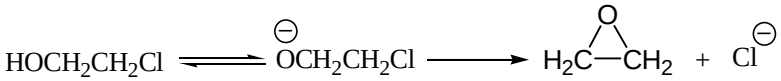


3. Hydroxy group (–OH) and oxygen atom :

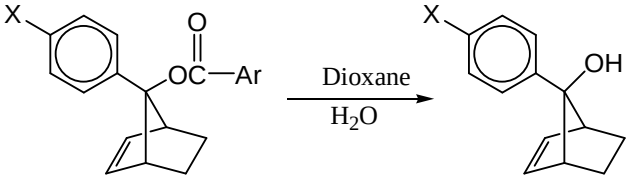
The hydroxy group acts as an intramolecular nucleophile i.e.; solvolysis of 4- chloro butanol in water gives a product i.e; tetrahydrofuran. The reaction is much faster than solvolysis of 3-chloro prapanol under similar condition



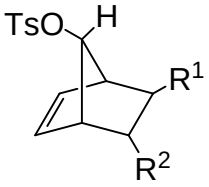
In basic solution, the alkoxide ions formed by deprotonation are even more effective nucleophile. In ethanol containing sodium ethoxide, 2-chloro-ethanol reacts about 5000 times faster than ethyl chloride. The product is ethylene oxide confirming the involvement of oxygen atom as a nucleophile.



Evidently, the extent of participation is a function of the stability of potential carbocation when an aryl group is present at C–7 position, the resulting benzyl - typed stabilisation decreases the relative importance of participation by double bond.



The factors which can affect C = C bond π-electron cloud, may also affect on the relative rate.



Relative rate

$R^1 = R^2 = H \longrightarrow 1.4 \times 10^{12}$

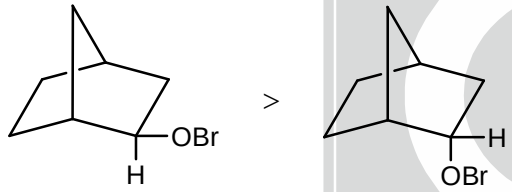
$R^1 = H\ R^2 = CF_3 \longrightarrow 15 \times 10^6$

$R^1 = R^2 = CF_3 \longrightarrow 1$

4. C-C bond or bonds as Neighbouring Group Participation:

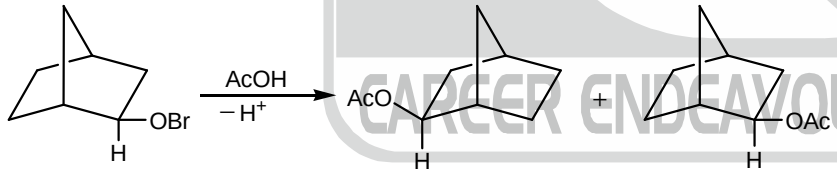
Winstein and Trifan found that solvolysis in acetic acid of optically active exo - 2 - norbornyl brosylate gave a racemic mixture of two exo - acelate.

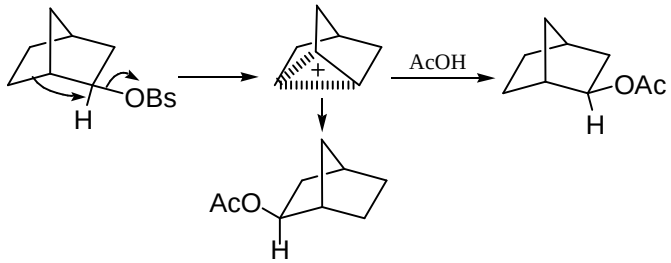
Exo - isomer solvolysed about 350 time faster than that of endo isomer.



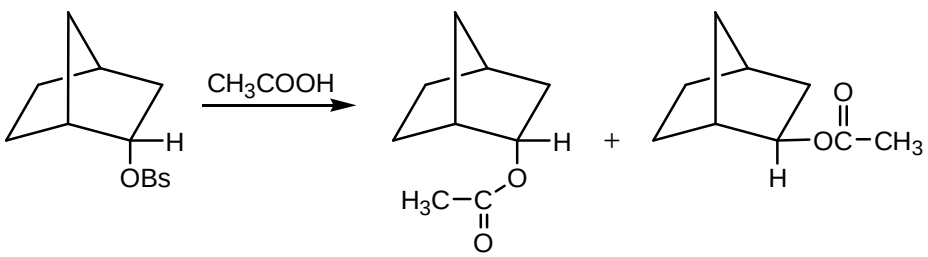
Exo-isomer Endo-isomer

This is due to that 1, 6 bond assist in departure of the leaving group (OBs-p-bromo benzene sulphonate) and forming non-classical intermediate (carbocation) in Exo-isomer.

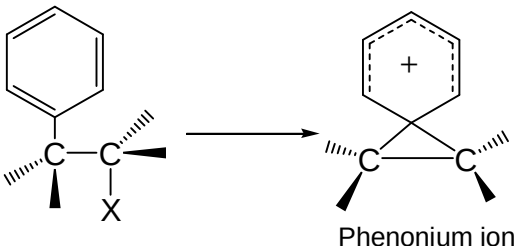




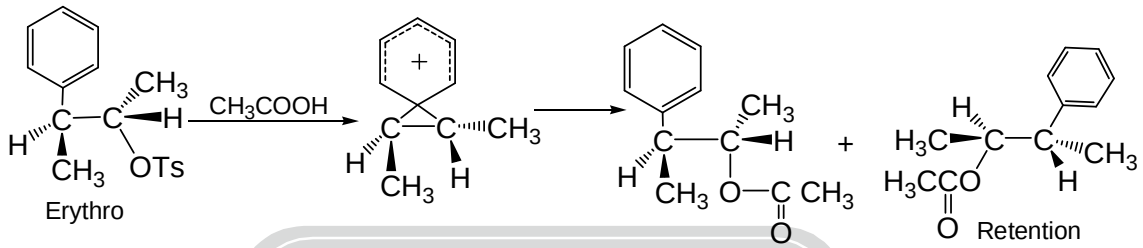
Whereas in case of endo isomer. The position is not favorable therefore it does not involve neighbouring group participation but it reacts normally

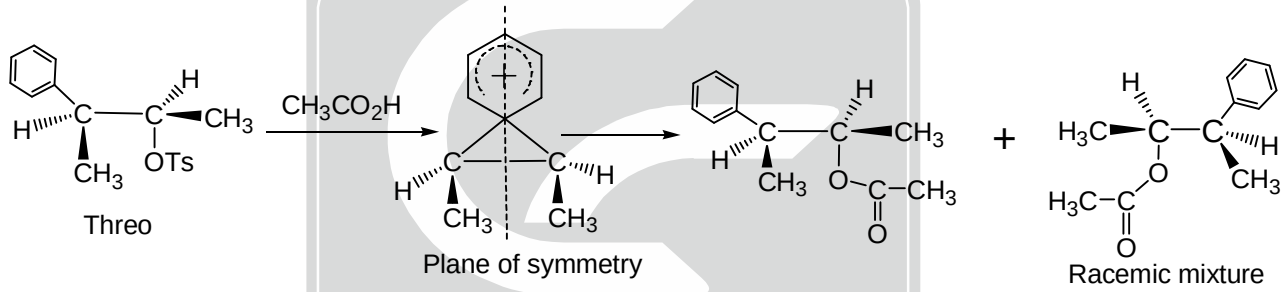


5. Aromatic π-electron participation :



The erythro isomer gives largely retention of configuration in the product. The result can be explained by/via the bridged ion intermediate. Threo isomer where participation leads to an achiral intermediate which gives racemic threo products.

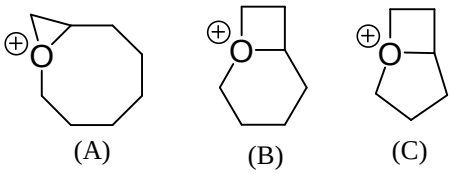




6. Trans annular ether oxygen as Neighbouring Group Participation:

The relative rate for molecules show that three is a large acceleration in the case of replacement of 5-CH_2 group by an ether oxygen.

The huge difference in rate that results from the alternative placement of oxygen in eight membered rings reflects the relative stability of various oxonium ions that results from participation. *B* ion is much more favorable than A and the rate retardation in first two case can be attributed to an unfavorable polar effect of the C-O bond.



Acetolysis of both 4-methoxy - 1-pentyl brosylate and 5- methoxy-2- pentyl brosylate give the same mixture of product is evidence of participation by ether oxygen in neighbouring group participation reaction