General principles of reaction mechanisms

- Energy consideration

for a reaction to take place free energy change has to be negative . A negative value of free energy change tells us that thermodynamics is favourable for the reaction.

Change in gibbs free energy = enthalpy(H) change – temprature(T) * entropy(S) change

kinetics

- As thermodynamics only predicts the position of equilibrium kinetics deals with rates of reactions
- So a reaction having negative free energy does not surely mean that the transformation will take place

  for ex: degradation of diamond to graphite is thermodynamically feasible but not kinetically due to very slow rate
- theories for reactivity and rate of reaction

  1. Collision Theory
  2. Transition State theory

Collision theory

- Molecules react only when they collide.
- Collision between molecules will be successful only when they contain at least a minimum amount of energy (Ea = activation energy). Reactants have to pass through highest energy state , called an activated complex.
- Colliding activated molecules must be effectively oriented with respect to each other for a successful combination

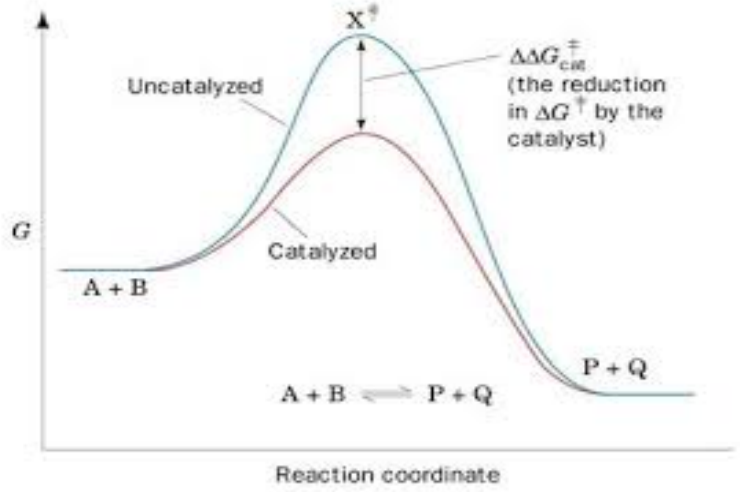
  rate = P Z exp[-Ea/RT]

  P= probability factor , Z = no. of collisions per uni time

Transition state theory

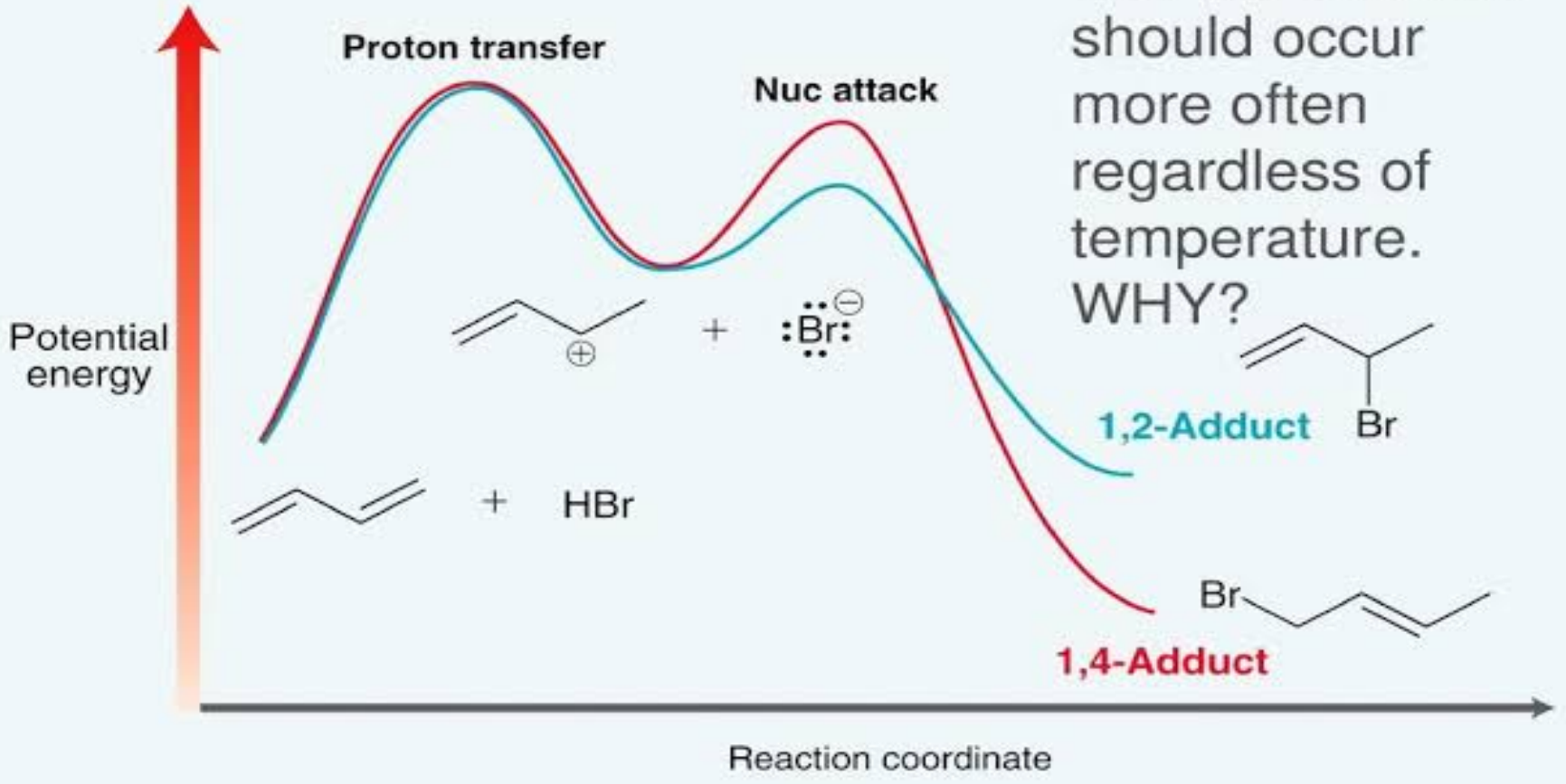
- The rate of reaction depends on the rate at which the reactants reach the transition state instead of frequency of collisions.
- The transition state is the state of highest potential energy acquired by the reactant during the transformation.
- The transition state species is in equilibrium with reactants. Equilibrium constant(K++) is related to enthaply and entropy of activation

Reaction Coordinate Diagram



The course of a reaction can be illustrated by means of a reaction coordinate diagram. The **Transition State** is the point of highest energy along the minimum energy trajectory (i.e., the reaction coordinate) of a reaction. The **Energy of Activation** is defined as the energy required to attain the Transition State.

Thermodynamic Control vs. Kinetic Control



- The 1,2 addition should occur more often regardless of temperature. WHY?

Reaction mechanism is a step by step description of a sequence of elementary reactions through which the overall chemical change occurs.

Which bonds are broken, which are formed, in what sequence/order, how many steps are involved and relative rates of each such steps are the details one can obtain through the study of reaction mechanism.

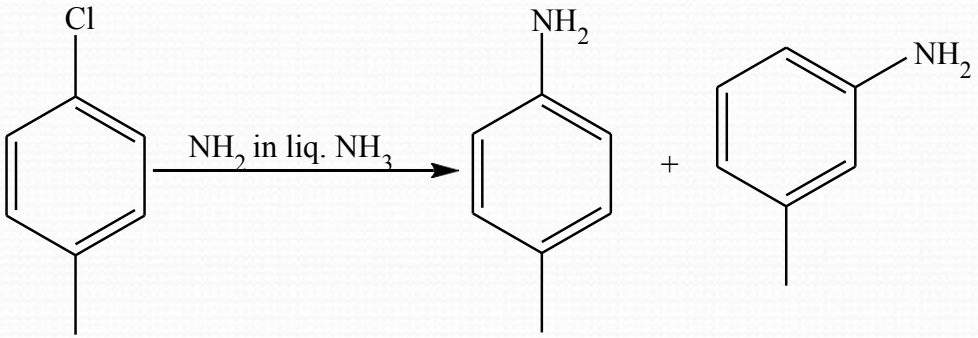
Course of reaction i.e. mechanism of reaction can be determined by various methods available.

- **Nature of products :**

Of all available ones, most useful information can be obtained by, study of products obtained, in course of a chemical reaction.

In organic reactions, more than one product can be obtained. So, in order to determine the mechanism of reaction, one should know the relative amount of products formed. This can be done by various methods available like chromatography, spectroscopy etc.

e.g. in reaction of p-chlorotoluene with amide in liquid ammonia, m-toluidine is also obtained, along with expected p-toluidine and in fact major product



p-toluidine + m-touidine

Later can not be obtained by simple substitution of chloro by amino group. And if both products are obtained through same intermediates then, the former also, can not be obtained by direct substitution. And some different mechanism is taking place, in which, symmetrical intermediate is formed, which later proved to be benzyne intermediate.

Kinetic studies :

Determining reaction mechanism from kinetic data is one of the most widely used techniques. This technique is based on the study of change in concentration of either the reactant or product.

The choice of method depends on its applicability to the reaction being studied. Some common methods include

Monitoring through periodic or continuous measurements (using spectroscopy, polarimetry), quenching and analyzing the reaction mixture at regular intervals by taking out aliquots etc.,

In a chemical reaction, a reacting species may be or usually different from what is been introduced into the reaction mixture. The relation between these two may be quite complex too.

In an aromatic nitration reaction, the effective attacking species is, NO_2^+, but changing concentration of HNO_3 is what one would typically measure.

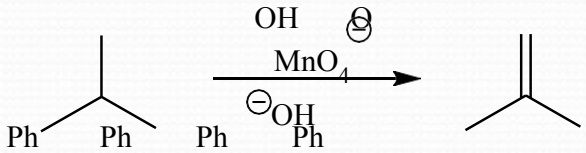
Also, merely by observing the rates of chemical reaction, its mechanism can not be deduced.

Use of isotopes :

Whether, a particular bond is broken or not, in the rate determining step of a reaction under also provides useful information. Simple kinetic studies can not explicitly provide this information. But, can be obtained by **using isotopically labeled compounds.**

For example, whether C-H bond is being broken or not in the rate determining step can be confirmed by replacing the C-H bond of interest with a C-D bond and measuring the relative rates between modified and unmodified substrates .

Two bond dissociation energies will be different as the two atoms have different masses. This will influence the rate of reaction. E.g., The rate of oxidation of Ph_2CHOH is 6.7 times faster than Ph_2CDOH.



This clearly indicates that C-H bond is involved in the rate determining step.

It is known as **Primary kinetic isotope effect**

The change in reaction rate that occurs upon isotope substitution is known as kinetic isotope effect.

An isotopic substitution will have a pronounced effect on the reaction rate when the isotopic substitution (i.e. D for H) is part of a chemical bond that is broken, formed or modified in the rate determining step. The magnitude of the effect is dependent on whether the bond with the isotopic substitution is being broken or formed (primary KIE) or if the hybridization of the atom to which isotope is attached is changing (secondary KIE).

In summary, primary kinetic isotope effect is a change in rate due to isotopic substitution at a site of bond breaking or bond making in the rate determining step of a mechanism.

Kinetic isotope effect can also be observed with other pair of isotopes such as H & T; ^{12}C & ^{13}C or ^{14}C; ^{16}O & ^{18}O; ^{35}Cl & ^{37}Cl etc.,

Kinetic isotope effects are expressed as the ratio of the reaction rates in the presence of the reactants when containing one isotope as compared to the other.

It is observed experimentally and its values are intermediate between unity i.e. no isotope effect and maximum as large as ~7 (at 25^0C) in case of H & D.

For other elements, these values are low because relative mass difference is small.

Secondary kinetic isotope effect, on the other hand, is the change in rate due to isotopic substitution at site(s) than that of bond breaking or bond making in the rate determining step of a mechanism.

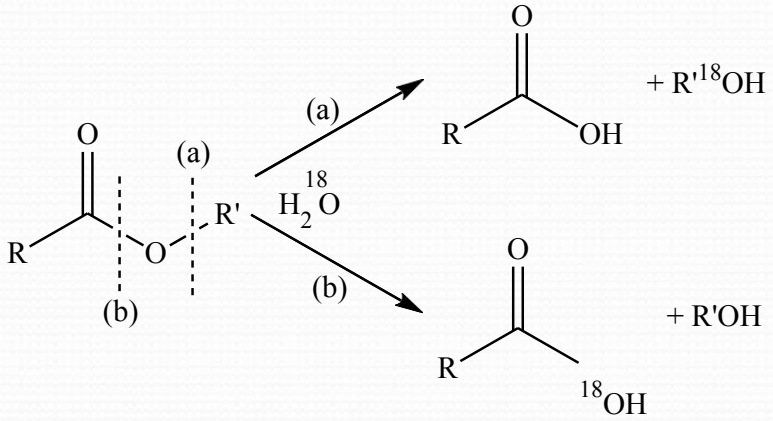
Primary Kinetic Isotope Effect: Typical Values

Nuclide	k_{light} / k_{heavy} (at 25° C)
C-H/C-D	6 - 8
C-H/C-T	15 - 16
$^{12}C / ^{13}C$	1.0 4
$^{12}C / ^{14}C$	1.0 7
$^{14}N / ^{15}N$	1.0 3
$^{16}O / ^{18}O$	1.0 2
$^{32}S / ^{34}S$	1.0 1
$^{35}Cl / ^{37}Cl$	1.0 1

Isotope can also be used in studying mechanistic problems that are non-kinetic and useful information can be obtain by isotopic labeling.

aqueous hydrolysis of esters to yield acid and alcohol can, in principle, proceed through alkyl or acyl oxygen fission.

If the reaction is carried out in labeled water containing ^{18}O, *path-a* will give alcohol with ^{18}O and *path-b* will give acid with ^{18}O (shown below)

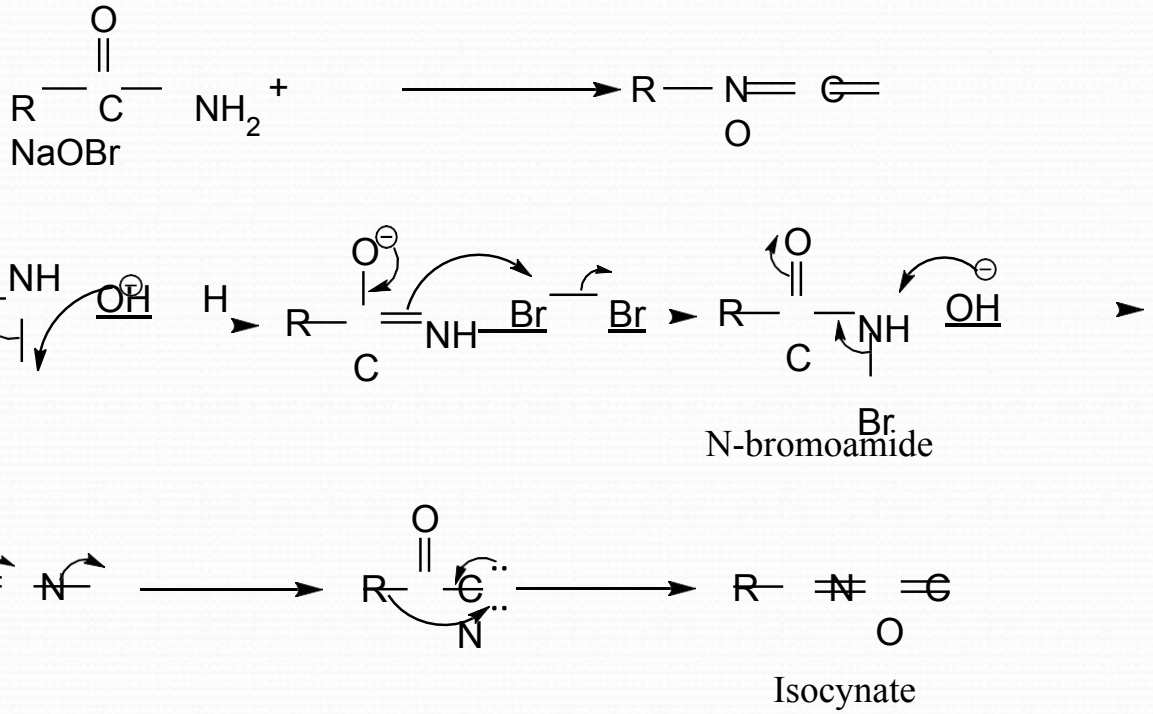


Most simple esters are found to yield ^{18}O enriched acid, indicating path (b) i.e., acyl oxygen fission.

Study of intermediates :

Among all these methods, most concrete evidence is obtained by, actual isolation of intermediate involved in the reaction.

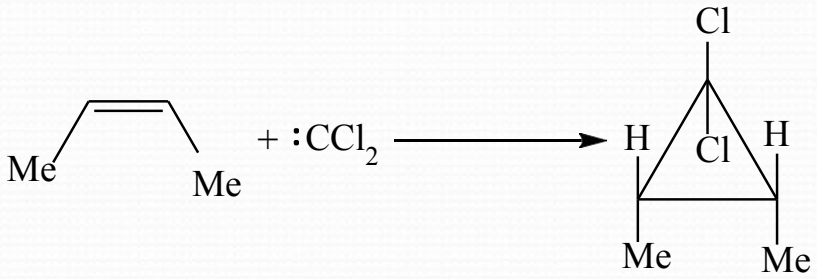
In Hofmann rearrangement, thus, if carefully isolated, all intermediates can be obtained. These are N-bromoamide, its anion and an isocynate. This clearly gives insight of the mechanism of reaction.



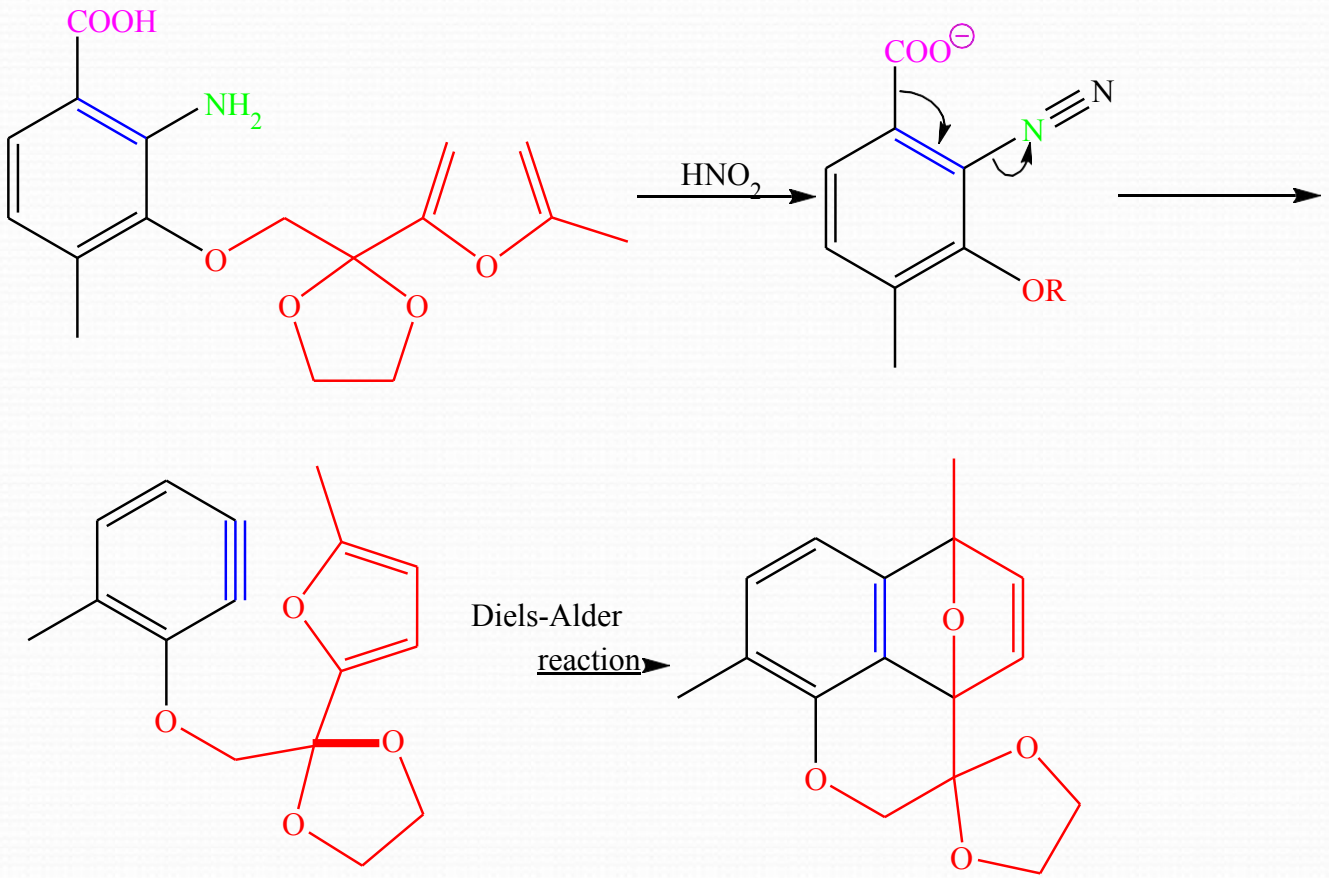
The isolated intermediate should be distinguishable from the final product or other side products. The species isolated should also be a true intermediate or should be in equilibrium with a true intermediate (toward establishing the mechanism convincingly)

Some intermediates are very **labile** to be isolated by regular techniques. Such species can be detected by physical techniques (spectroscopic methods such as ESR, NMR, IR), or by trapping with other species so as to divert it from forming the final product.

Presence of one such species, carbene can be confirmed by its reaction with cis-2-butene. It gives stable cyclopropane derivative.



Another example for the existence of of intermediate such as benzyne can be proven by trapping through a Diels-Alder reaction as shown below.



Application of Raman spectroscopic methods have helped in the detection of NO_2^+ species in nitration of benzene

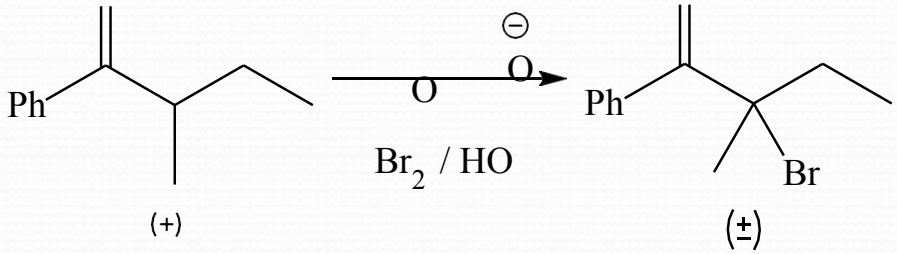
To be convincing, evidence for an intermediate should include:

- detection of intermediate in the reaction mixture, perhaps by trapping reaction
- demonstration that intermediate gives product when added to the reaction mixture i.e. it can be prepared as reasonably stable compound
- kinetic evidence that the rate of formation and rate of disappearance are adequate

Stereochemical criteria :

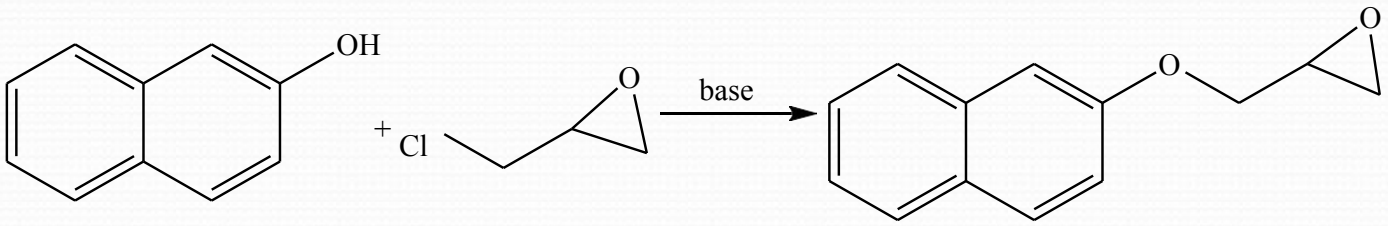
Study of stereochemistry of product can also provide some useful insight on the course of reaction.

Optically active stereoisomer of a ketone (shown below), on base catalyzed bromination, gives an optically inactive racemic product. This indicates the involvement of a planar transition state or intermediate, which can be attacked by the incoming nucleophile from both sides to give equal amount of both stereoisomers.



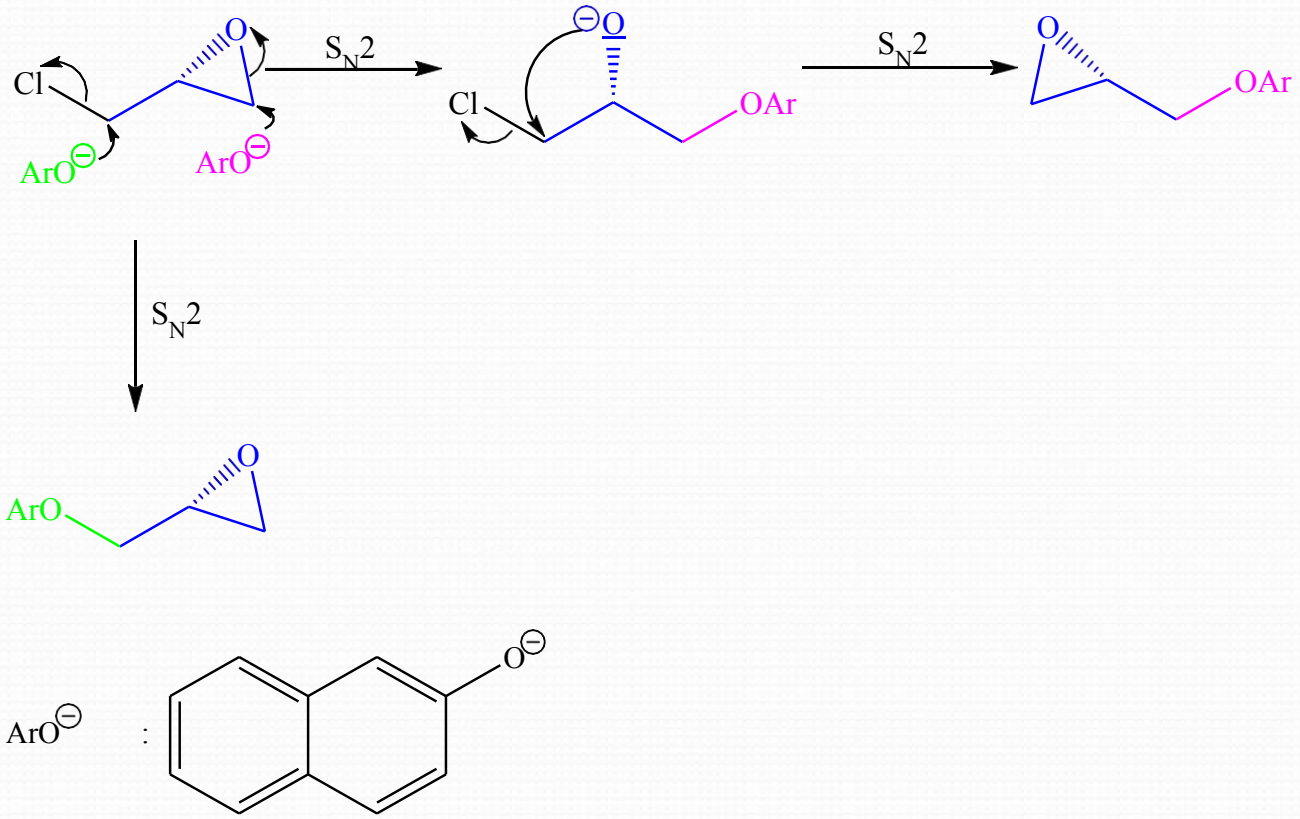
This implies that reaction must be taking place in two steps.

Another useful reaction is nucleophilic substitution of epichlorohydrin by naphthyloxide anion.



Investigation of product formed in the reaction, when enantiomerically pure epichlorohydrin is used, suggests that, reaction can not be taking place by simple S_N2 pathway. As it would give the product with opposite stereochemistry, than is obtained in the reaction.

Formation of the product other than expected can be accounted by taking into consideration, the other way of nucleophilic substitution.



In fact the reaction goes through this mechanism where naphthyloxide anion attacks other side of epoxide ring, resulting in ring opening and then followed by ring closure other way round.

Kinetic evidence

- Hydrolysis of alkyl halides:

  the rate expression for reaction of methyl bromide with hydroxide ion is

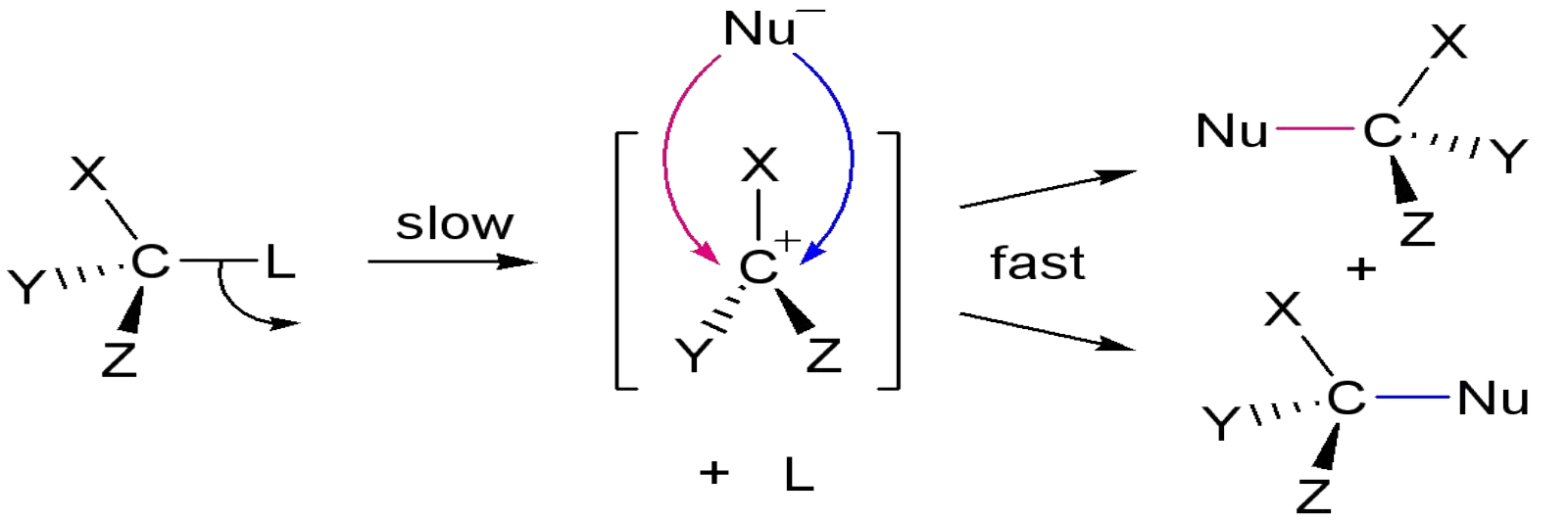
  $-d[CH_3Br]/dt = k[CH_3Br][^-OH]$

- for the reaction of t-butyl bromide with hydroxide ion is

  $-d[(CH_3)_3CBr]/dt = k[(CH_3)_3CBr]$

- In conjucation with stereochemical evidence , has led to the formulation of two different mechanistic paths (SN1 and SN2)

The S_N1 Reaction



Substrate

Carbocation Intermediate

Products

The S_N1 Reaction

SN1 reactions are nucleophilic substitutions, involving a nucleophile replacing a leaving group (just like SN2).

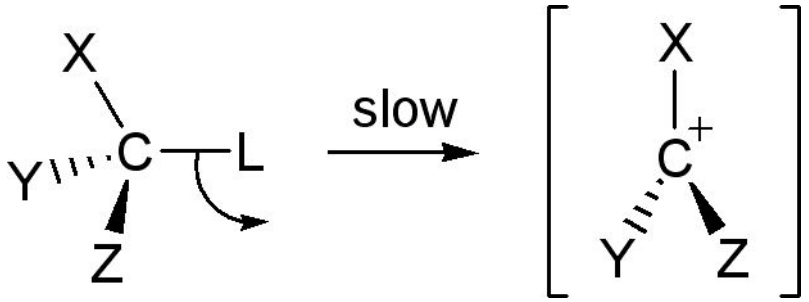
However: SN1 reactions are **unimolecular:** the rate of this reaction depends only on the concentration of *one reactant.*

- SN1 reactions happen in two steps:

1. The leaving group leaves, and the substrate forms a *carbocation intermediate*.
2. The nucleophile attacks the carbocation, forming the product.

The S_N1 Reaction

1. The Slow Step:



First step of the SN1 reaction:

The leaving group leaves, and the substrate carbon now only has thre

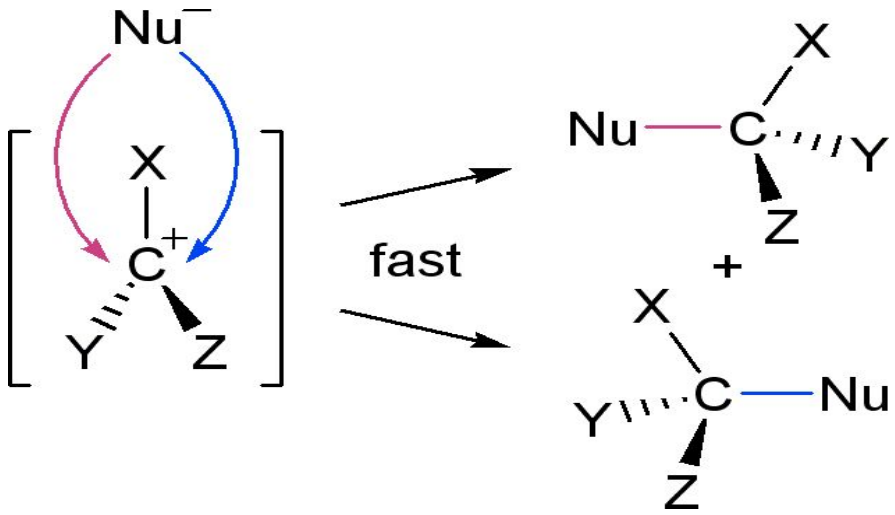
- Carbocations are most stable when there are more atoms to distribute
- Carbocation stability:

$$3^o > 2^o >> 1^o$$

- Tip: study the difference between reaction intermediates and

The S_N1 Reaction

2. The Fast Step:

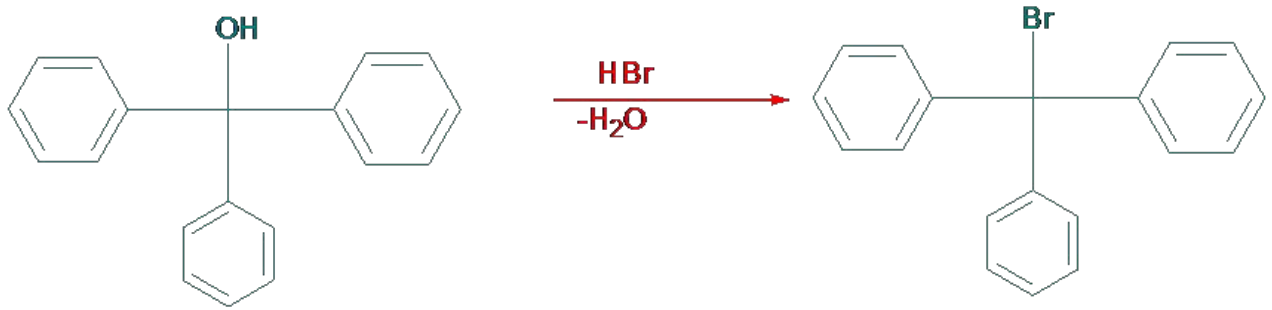


Second step of the SN1 reaction:

The nucleophile attacks the carbocation intermediate, bringing its ele

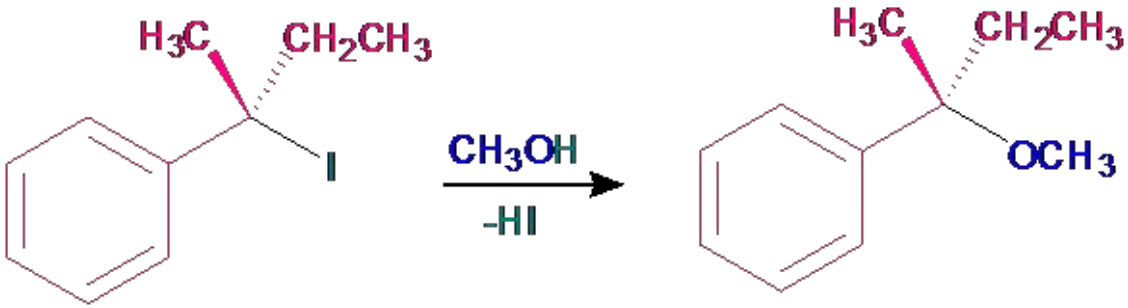
- The substrate loses any stereospecificity during the carbocation inter

Example 1



In the above example, protonation of the OH group will convert it into a very good leaving group (H_2O), resulting in the formation of a carbocation. Note that this is a stabilized carbocation due to extended delocalization of the positive charge by the three phenyl groups. Subsequently, this will be attacked by the bromide ion to form the final product

Example 2



Kinetics

- The kinetics of S_N1 follow first order kinetics.

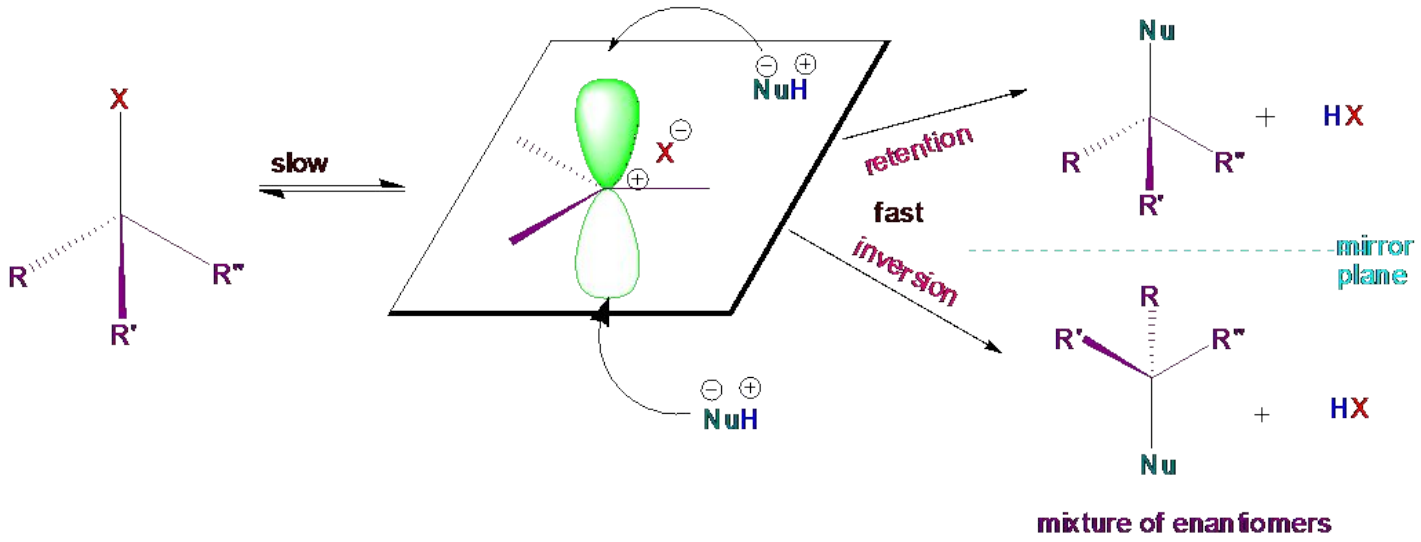
  rate α [reactant]

- The rate constant is dependent on how fast the leaving group can depart. It is independent of the incoming nucleophile

- On what will the rate depend ?

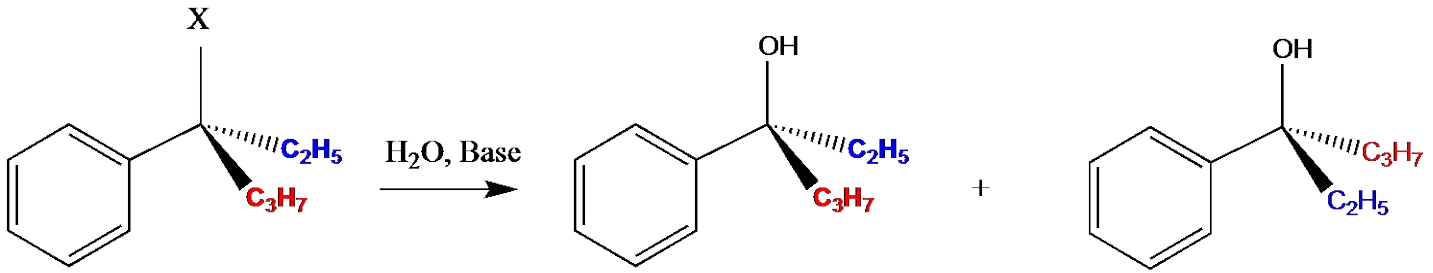
1. The nature of the substrate.
2. The rate of leaving group departure.
3. The nature of the solvent.

Stereochemistry



- The nucleophile can approach the planar carbocation intermediate from either of the faces (as shown above), resulting in a racemic mixture with equal quantity of both enantiomers (provided the R groups on the central carbon are not identical).

Example:



Mixture of Enantiomers

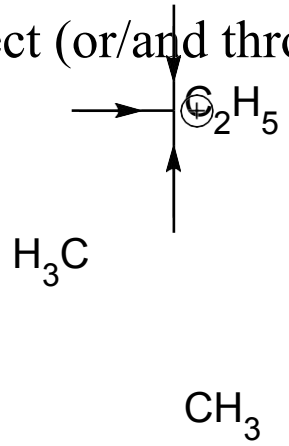
Attention: the position of the R groups are not identical in the two enantiomeric products given

Note: The starting compound has a chiral carbon atom here. Upon generation of a planar carbocationic intermediate, the incoming nucleophile (water in the present case) can either attack from the top of bottom of the plane, leading to racemization.

In the next section, factors that influence the unimolecular substitution reaction are described in detail.

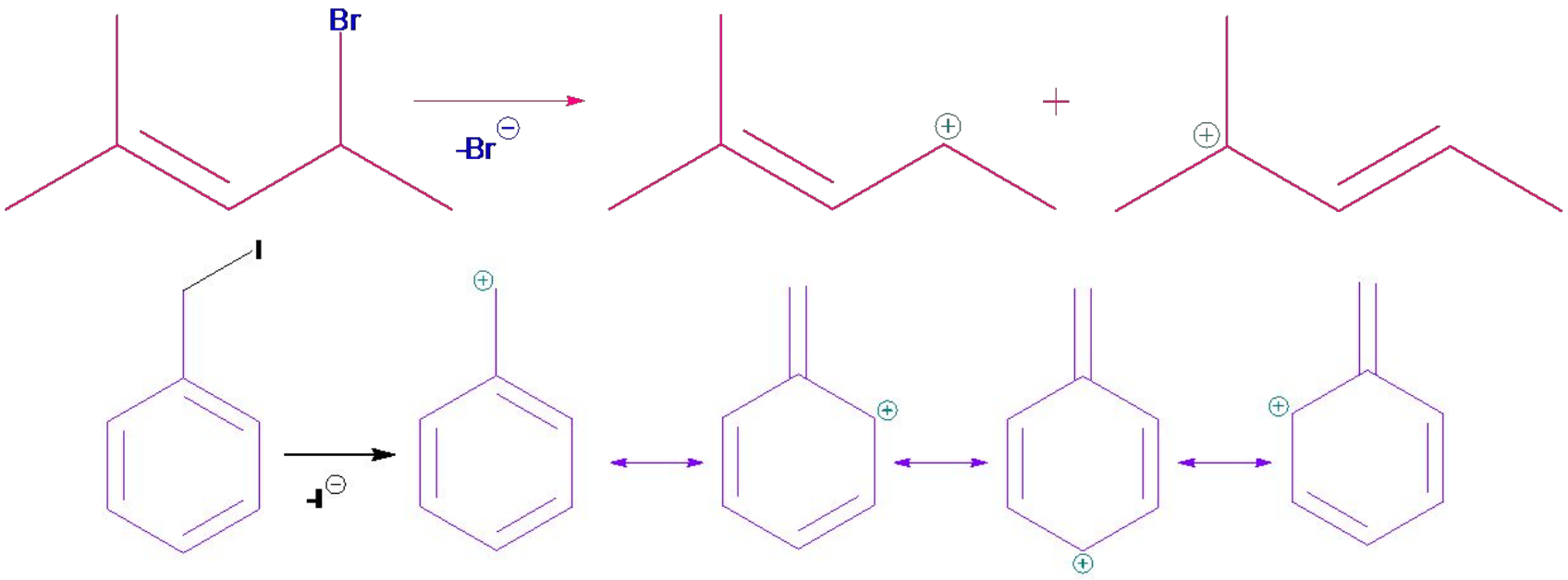
Stability of carbocation

- The rate of S_N1 reaction depends on how readily a carbocation is formed and the effect of such stabilizations in the developing carbocation in the transition state.
- This will in turn depend on the substituents attached (and the pi bond electron density in case of allylic and benzylic carbocation).
- The presence of more alkyl groups stabilizes the carbocation by inductive effect (or/and through hyperconjugation).



- When the stabilization is assisted by π bonded electron it is called *resonance stabilization*. Benzylic and allylic systems provide resonance stabilization.

- Resonance stabilization in allylic and benzylic carbocation.



- Relative stabilization comparison of carbocation :-
- 3^0allylic ≈ 3^0 benzylic > 2^0 allylic ≈ 2^0 benzylic > 1^0 allylic ≈ 1^0 benzylic.
- 3^0 alkyl > 2^0 alkyl > 1^0 allylic ≈ 1^0 benzylic .
- The lesser the size of substituent present on carbocation, lower is the chances of it favoring S_N1 pathway.

Leaving group

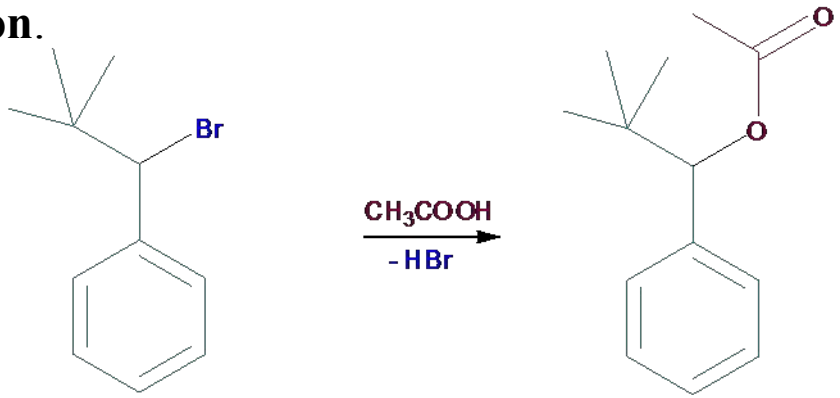
- Leaving group has significant contribution to the rate of reaction, easier the departure of a leaving group, faster will be the rate of reaction.
- Larger anions which can stabilize the negative charge are good leaving groups. (e.g., a tosyl group)

Effect of solvent

- Factors that stabilize the developing carbocation in the transition state will increase the rate of an S_N1 transformation.
- Polar solvents can stabilize the carbocation intermediate hence lower the activation energy, leading to an increase in the rate of reaction.
- Polar protic solvents have high dipole moment which stabilize the T.S.
- Higher the dielectric constant of the solvent, faster is the rate.
- The rate-determining step of an S_N1 reaction is the ionization of the leaving group-carbon bond, polar solvent can best ionise the leaving group.
- Conversion of t-butylbromide to t-butylalcohol or t-butylester taking ethanol as the reference solvent, conveys that smaller molecule has faster rat

Solvent	Rate of reaction
Pure Ethanol	1
Ethanol with 20% water	10
Equal quantity of both solvent	60
100% water	1200

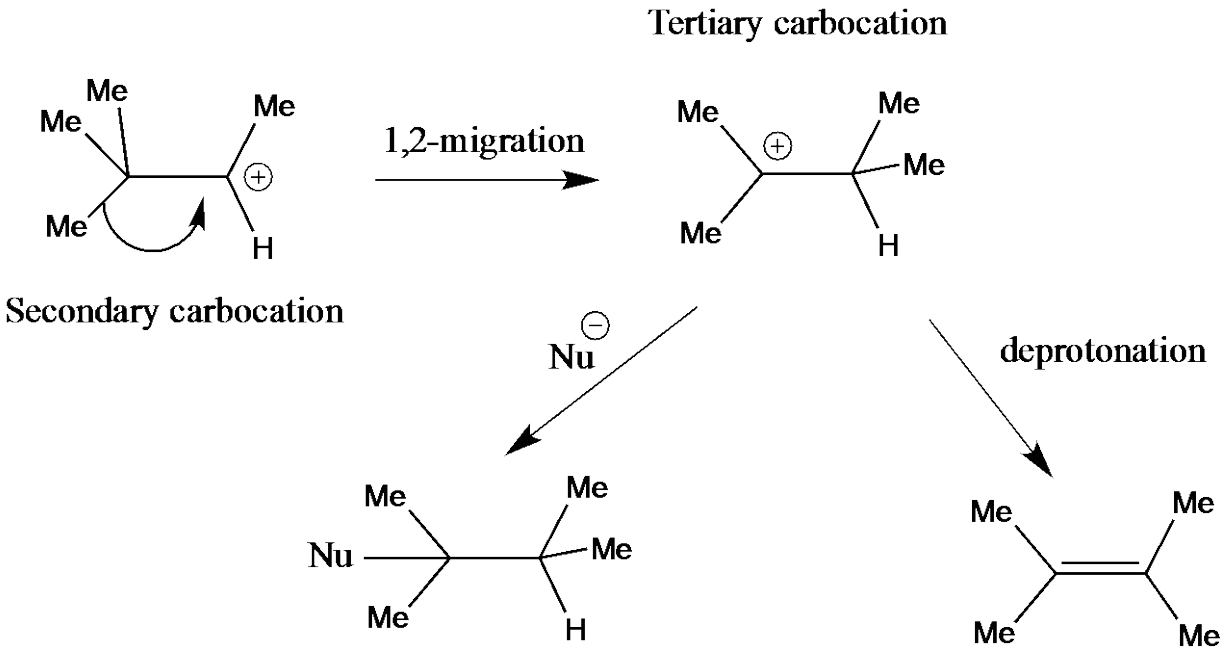
- Reactions in which polar solvent molecules get added to the carbocation are called **solvolysis reaction**.



Note: In the above example, acetic acid acts as the solvent which combines with stabilized carbocation generated by the heterolytic cleavage of C-Br bond. This can also be termed as a acetolysis reaction

- As per Huges-Ingold predictions an increase in solvent polarity accelerates the rates of reactions where a charge is developed in the activated complex from a neutral or a slightly charged reactant.
- The presence of proton will neutralize the nucleophile, but S_N1 reaction rate is independent of the nucleophile.
- Non- polar solvent provide no assistance to the carbocation stabilization, hence slow down the rate.

- Some general Issues with S_N1 reaction

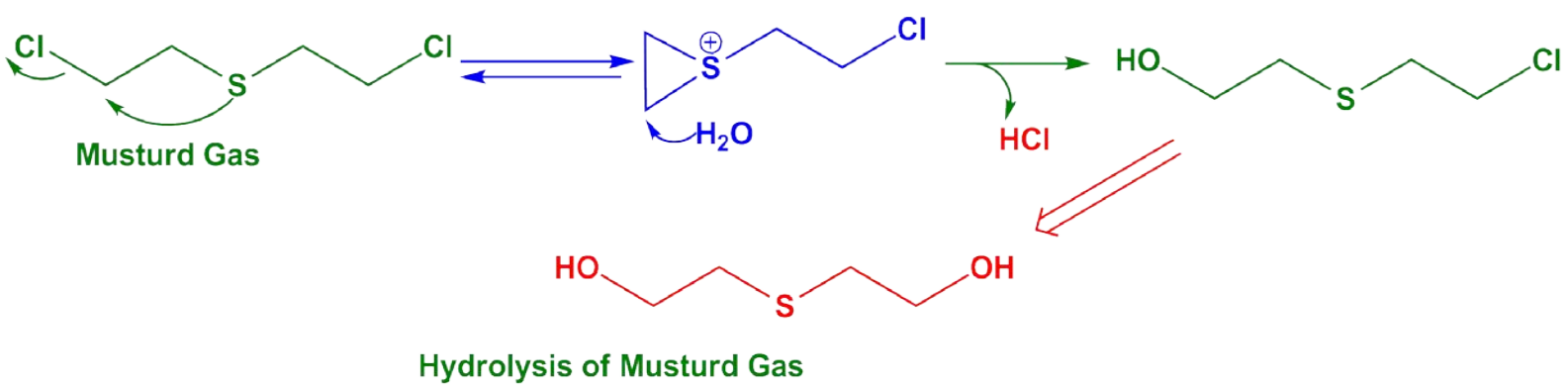


The ability of certain type of carbocation intermediates formed in S_N1 reaction can rearrange to form another (usually lower energy intermediate) before the attack of the nucleophile.

It should be noted that the intramolecular rerrangements can be quite fast as it doesn't require collision by another species (such as a nucleophile).

Additional/Practice problems with solution

(1)



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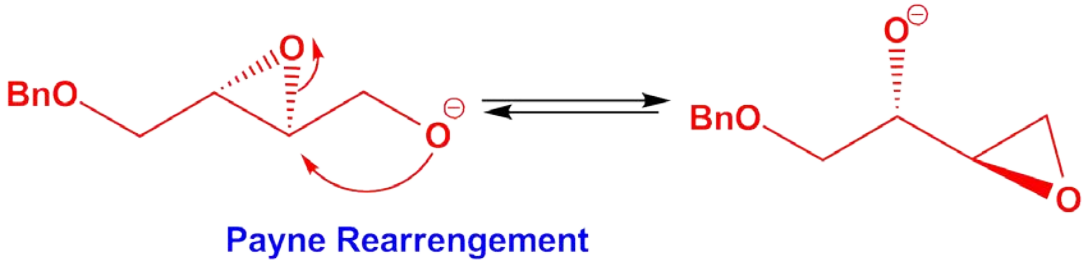

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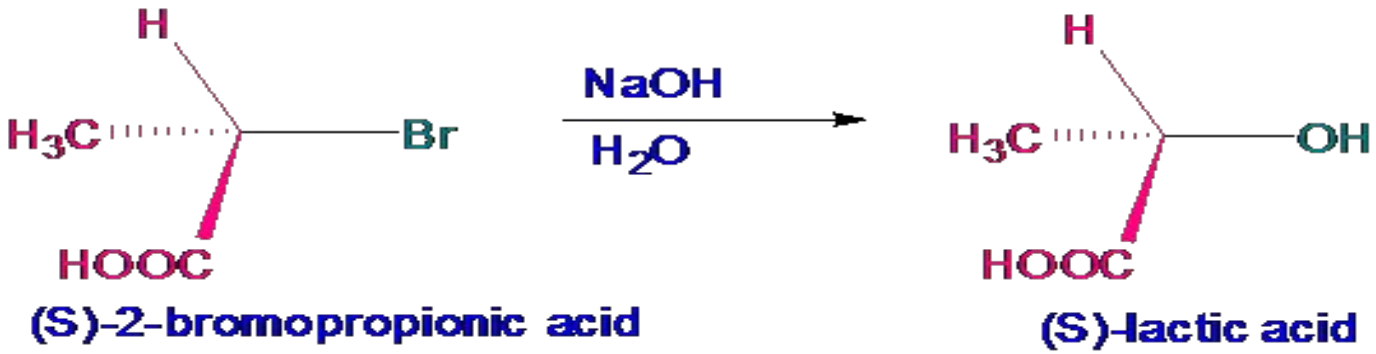

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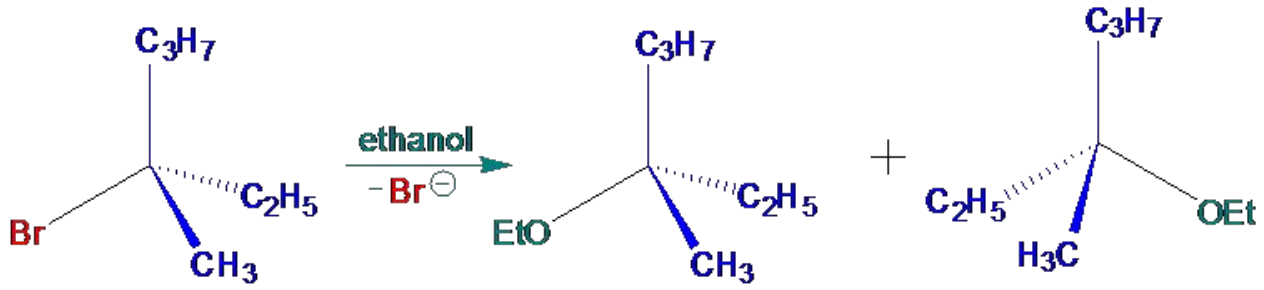
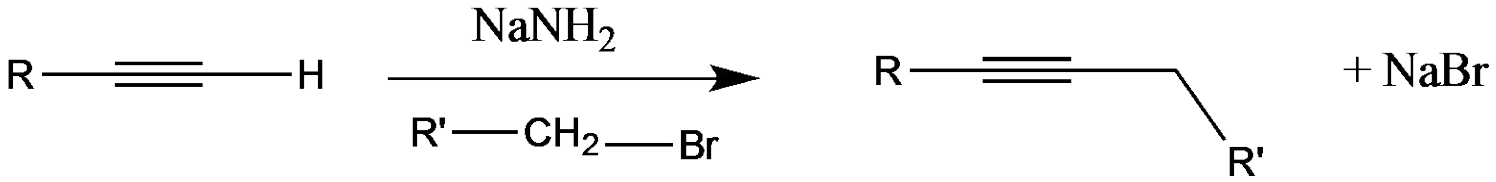
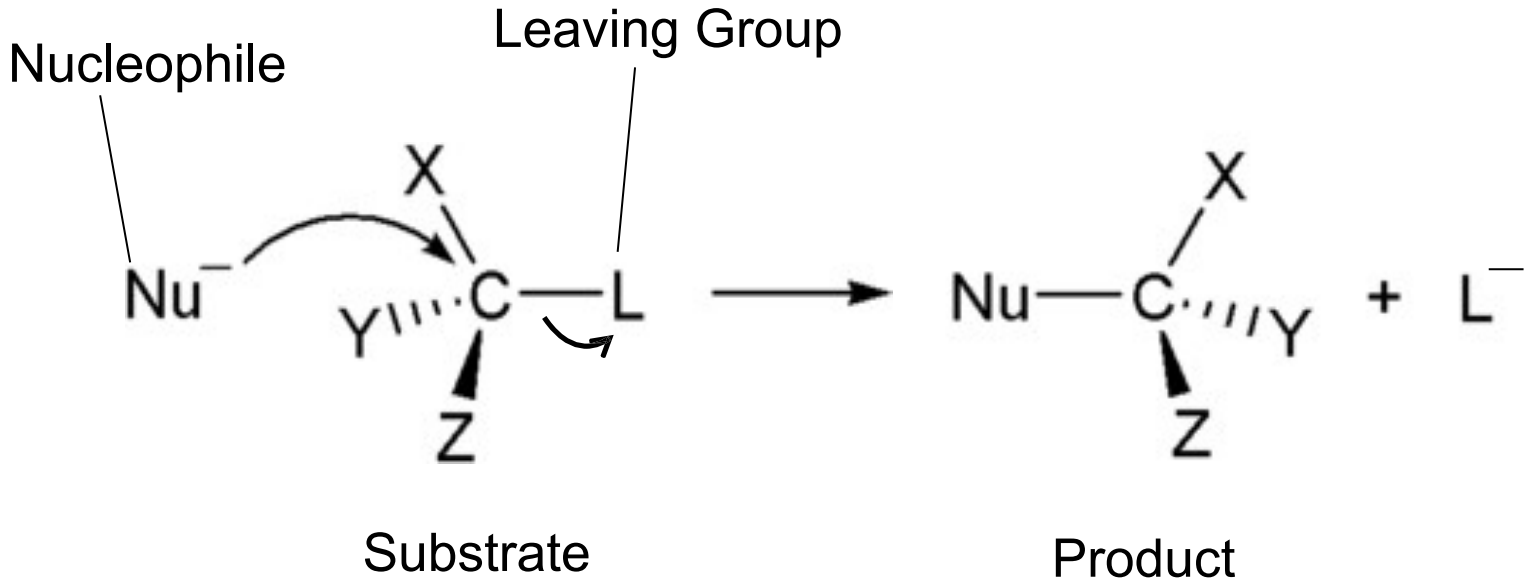

C3H7
C2H5
Br
CH3
ethanol
−Br⊖
C3H7
C2H5
EtO
CH3
+
C3H7
C2H5
OEt
H3C

(5)


R
H
NaNH2
R'—CH2—Br
R
R'
+ NaBr

The S_N2 Reaction



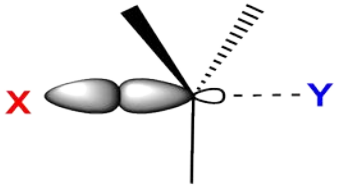
The S_N2 Reaction

Bimolecular: A *bi*molecular reaction is one whose rate depends on the concentrations of *two* of its reactants.

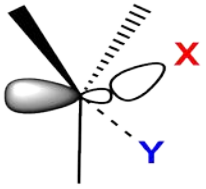
- SN2 reactions happen in one step – the nucleophile attacks the substrate as the leaving group leaves the substrate.
- Tip: Recall that the rate of a reaction depends on the slowest step. In bimolecular reactions, therefore, the slow step involves two reactants. For SN2 reactions, there are only two reactants; this means that the slow step is the *only* step.

Mechanism

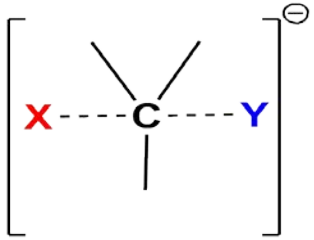
- During S_N2 reaction nucleophile first approaches the anti-bonding molecular orbital of the C-L bond.
- The attractive interaction between the donor orbital (filled electrons) and the acceptor orbital (unfilled) results in a new bonding between incoming group and the carbon atom. Simultaneously the leaving group begin to depart away from the carbon center.



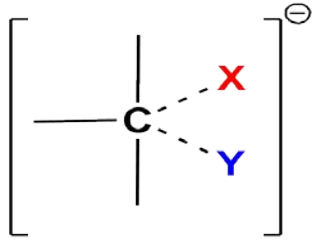
Most favorable interaction
(preferred pathway)



Less interaction
(Unpreferred pathway)

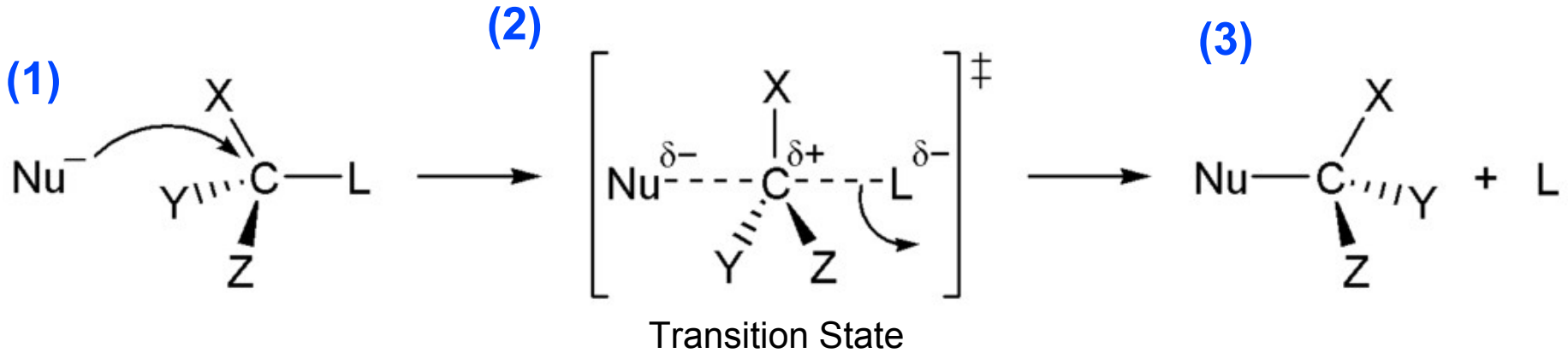


Preferred pathway



- Substitution may be possible either via front side or backside attack of nucleophile.
- In S_N2 substitution backside attack is preferred in which approach of the nucleophile is 180^0 away from the leaving group.

The S_N2 Reaction



Transition State

SN2 summary:

(1) Nucleophile back-side attacks the δ+ carbon center.

(2) Transition state forms in which nucleophile is forming bo

(3) The leaving group leaves, forming the final product.

The S_N2 Reaction

Notes:

- In the SN2 reaction, the nucleophile attacks from the most δ+ region
- This back-side attack causes an *inversion* (study the previous slide):
- The nucleophile must be able to reach the δ+ carbon center that it is

Kinetics

- The rate of the reaction is found vary linearly with non zero slope with respect to electrophile as well as nucleophile .

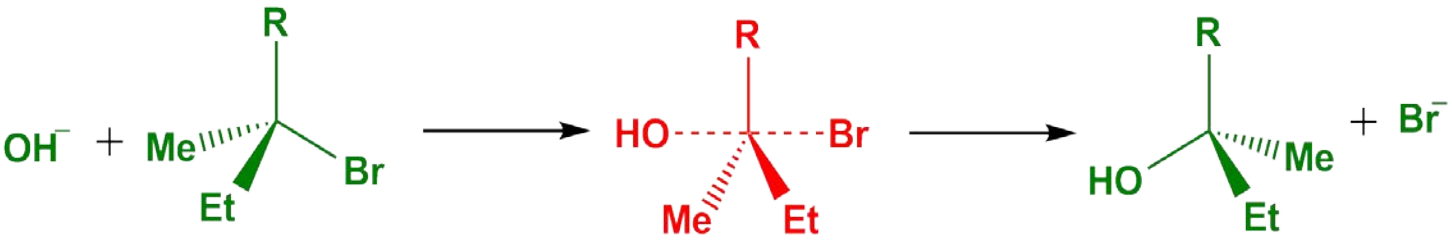
rate α [elec][nucl]

- In the presence of large excess of nucleophile, the kinetics tends to follow first order even though the mechanism is bimolecular.

- Nucleophile affects the rate even being in large excess but concentration does not vary significantly and rate is found to be determined alone by the electrophile. Such a situation is known as "Pseudo first order reaction".

Walden Inversion

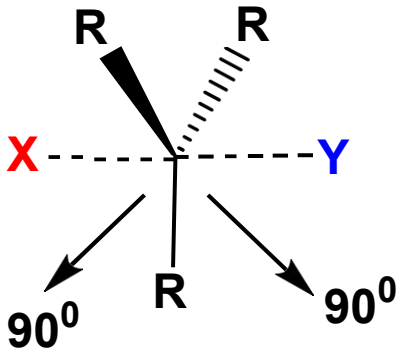
- Complete inversion in stereochemistry is observed during aliphatic nucleophilic substitution via S_N2 pathway, confirming that backside attack is preferred over the front side attack.
- Stereochemical outcome of the S_N2 reaction is termed as Walden inversion in honor of his discovery.



Structure Function Correlation With R Group

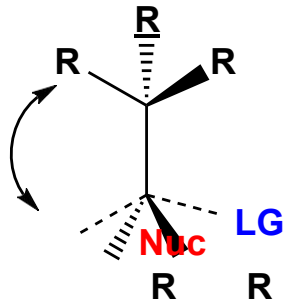
- R group plays vital role on the rate of reaction
- R group may have steric, electronic and neighboring group effect.
- Steric hindrance may slow the rate of reaction, as nucleophile adds to the carbon centre in the rate determining step.

- In the transition state, the incoming nucleophile(Nuc) and leaving group(LG) are 90^0 to the R group. Larger R groups can result in increased strain leading to slower reaction rates.



Bulkier R group increase steric hindrance

- A bulkier adjacent group may deflect the trajectory of the nucleophile away from the linear approach.



Strained transition state due to adjacent group steric effect

- electron withdrawing nature of groups having sp^2 carbon(vinyl and phenyl) makes the adjacent carbon more electrophilic and hence reactivity towards nucleophile increases.

Example:

Higher rate for nucleophilic substitution at allyl and benzyl system.

Structure Function Correlation with Nucleophile

- In S_N2 reaction stronger the nucleophile faster would be the reaction.
- Strength of a nucleophile can be determined by the following general guidelines-

1. A nucleophile with negative charge is more powerful than its conjugate acid.

Example: $NH_2^- > NH_3$, $OH^- > H_2O$,

2. Nucleophilicity generally follows similar order as basicity

Example: $R_3C^- > R_2N^- > RO^- > F^-$

$NH_2^- > RO^- > R_2NH^- > ArO^- > NH_3 > Pyridine > F^- > H_2O > ClO_4^-$

3. Going down in a group, nucleophilicity increase while basicity decrease.

Example: $I^- > Br^- > Cl^- > F^-$ (less solvation, Higher polarization) $S^- > O^-$

4. More free nucleophile, more nucleophilicity.

Example 1: Rate of reaction using NaOH can be largely enhanced by specifically solvating cation Na^+. (use of crown ether).

Example 2: $NaOH_{DMSO} > NaOH_{water}$ (basicity)

In water Na^+ and HO^- both are solvated while in DMSO Na^+ is solvated preferably than HO^- leaving HO^- as free nucleophile.

Structure function correlation with leaving group

- Better leaving groups are mostly weak bases which stabilize the negative charges.

  Example: TsO^-, MsO^-, TfO^-

- In the presence of better leaving group, S_N1 reaction do not require strong base, but for SN2 reaction it is required.

Example:

1. XH is always a weaker base than X^-. Thus XH is a better leaving group which facilitates S_N2 reaction.

   $HS^- > H_2S$, $HO^- > H_2O$, $I^- > HI$, $NH_2^- > NH_3$

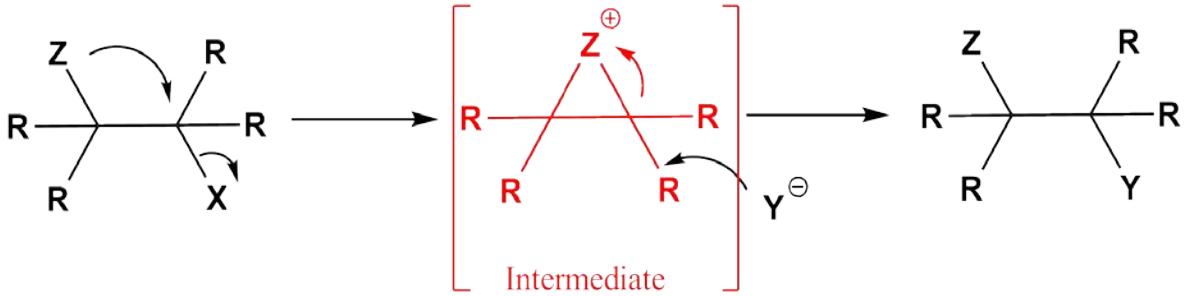
2. Acidic medium also protonate the base making them weaker.

   ROH is converted to ROH_2^+ in acid medium which is a better leaving group.

Neighboring Group Participation

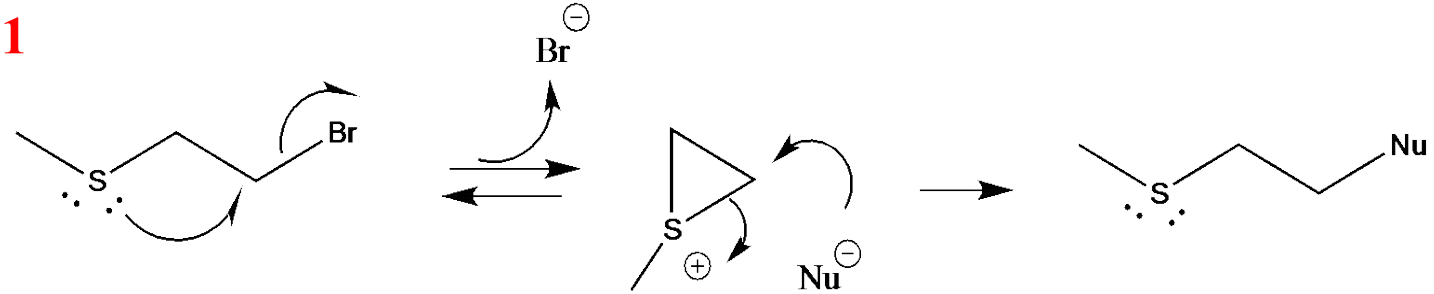
- In the presence of an electron donating neighboring group, the reaction proceeds faster than expected. In addition, either inversion nor racemisation is observed in such cases.

- In the following generalized representation, a neighboring group participation is illustrated. The lone-pair bearing atom/group such as Z would help in the removal of the leaving group by the mechanism shown below. (please note that the incoming nucleophile "Y" attacks the carbon atom of the three membered ring, not on the R group

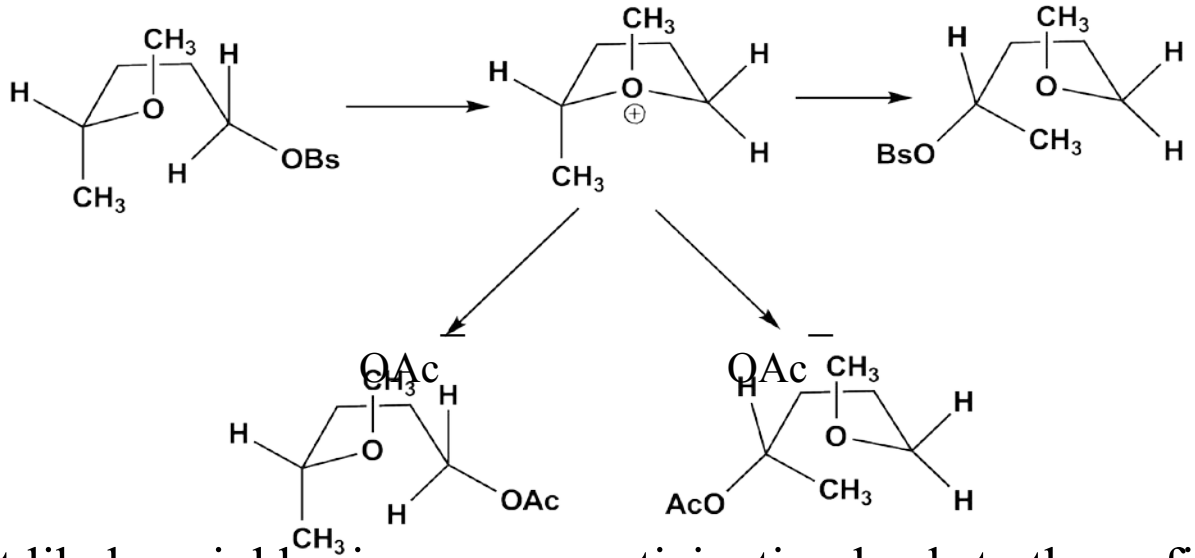


- Two consecutive S_N2 substitution, leads to retention of configuration.

Example 1



Example 2

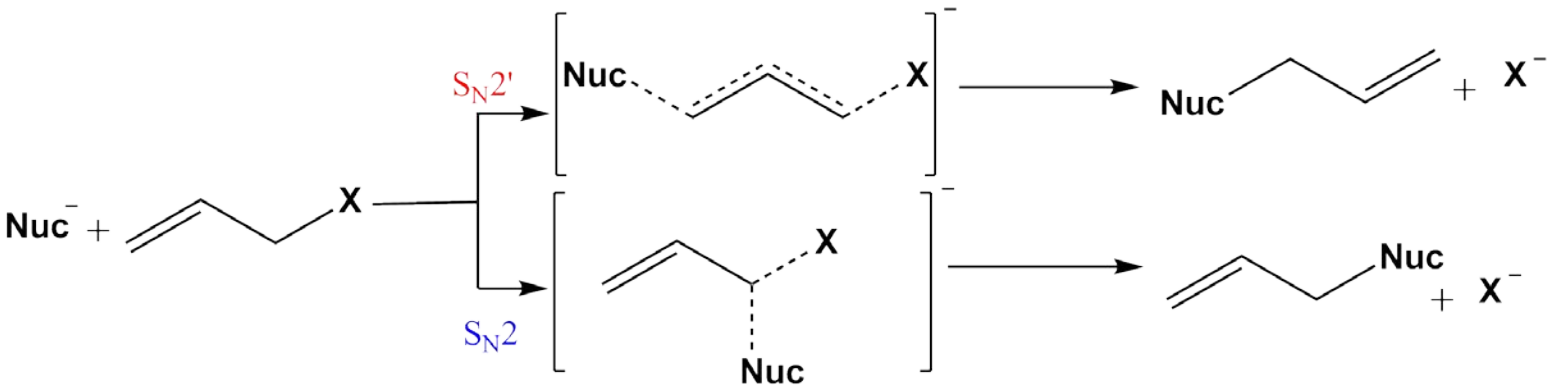


- The most likely neighboring group participation leads to three, five, six membered rings
- Four membered ring neighboring group participation is higher in case of alkyl substitution on α or β carbon.
- The effect of halogen increase as going down the group (**I> Br> Cl**).

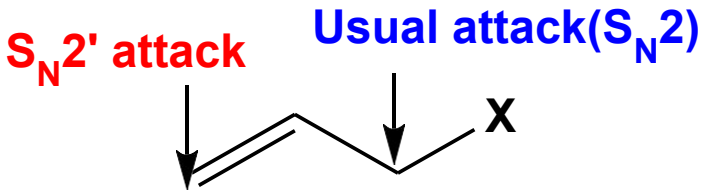
Some of the neighboring groups are COO^-, COOR, COAr, OCOR, OR, OH, O^-, NH_2 , NHR , NHCOR, SH, SR, I, Br, S^-

$S_N2\square$ Reaction*

- allylic rearrangement under S_N2 conditions are known as $S_N2\square$ reaction



- Simultaneous movement of three electron pair in the transition state



Attack at γ carbon under S_N2 reaction condition is termed as $S_N2\square$

Note: The attack of the nucleophile is not on the same carbon atom as that of the leaving group. But the final product resembles that of an S_N2 product.

* Read as S_N2 prime

S_N2□ Reaction*

- Increasing the size of the nucleophile as well as steric hindrance at the α-carbon increases the extent of S_N2□product

- Leaving group also an affect in deciding the extent of reaction in certain cases. Stereochemistry depends on the nature of the incoming and leaving groups in S_N2□ reaction, still *syn*-substitution is preferred over *anti*.