

Nucleophilic substitution Reactions

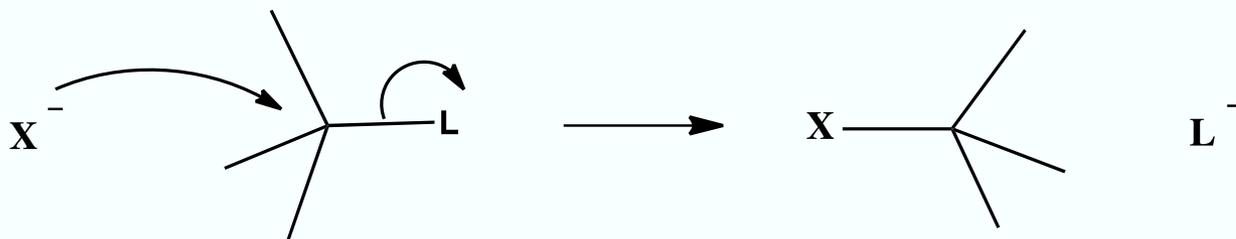
Key words: nucleophilic substitution reaction, carbocation intermediate, solvent effects, rate of reaction, inversion of configuration

Introduction

In this module, details of different types of nucleophilic substitution reactions are described. These reactions are an useful class of reactions for carbon-carbon and carbon-heteroatom bond formation reactions. The approach is also widely used for synthetic transformations (e.g., leaving groups such as tosylates). Depending on the nature of the nucleophiles and reaction conditions, different mechanisms are possible. These reactions typically occur on a saturated carbon atom, attached to a leaving group. You will find terminologies such as intermediates, transition states etc., in this module.

I. Nucleophilic substitution reactions bimolecular (S_N2)

- The notation S_N2 represents *Substitution Nucleophilic Bimolecular*.
- This mechanism is a concerted process in which the bond forming and bond breaking occur simultaneously.



- Energy required to break the bond is compensated by bond formation.

Kinetics

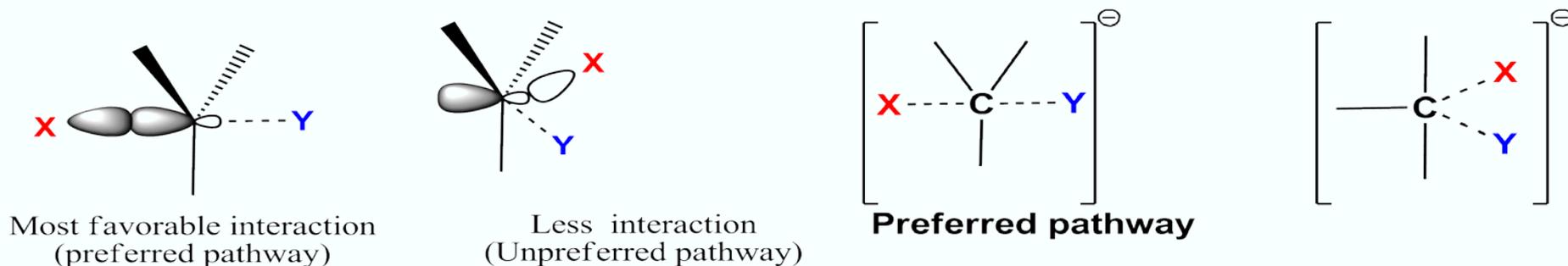
- The rate of the reaction is found vary linearly with non zero slope with respect to electrophile as well as nucleophile .

$$\text{rate} \propto [\text{elec}][\text{nucl}]$$

- 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”.

Mechanism

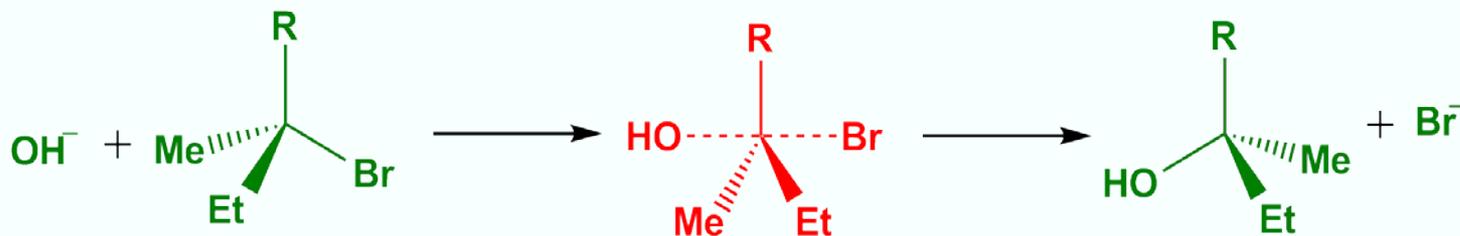
- During S_N2 reaction nucleophile first approaches the anti-bonding molecular orbital of the C-L bond.
- The attractive interaction between the donor orbital (filled electrons) and the acceptor orbital (unfilled) results in a new bonding between incoming group and the carbon atom. Simultaneously the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



- 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° away from the leaving group.

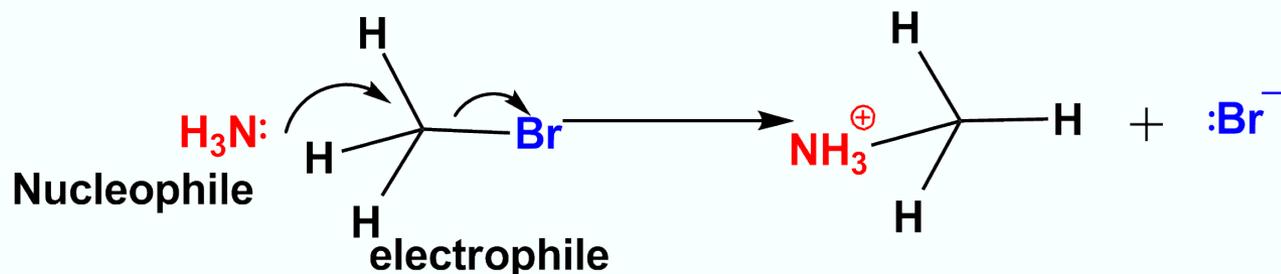
Walden Inversion

- 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.

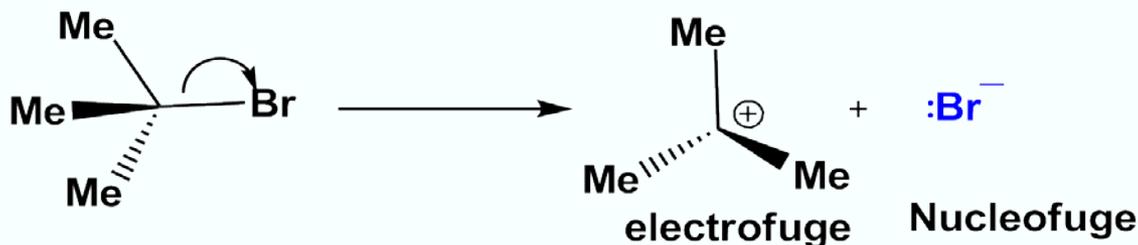


Additional terminologies: Nucleophile and Nucleofuge

- Nucleophile is a species that would combine with a positive charge (nucleus) to which it can donate its electron.
- Usually nucleophiles are electron rich species.
- They have higher energy HOMO



- A Nucleofuge is nucleophile that departs from a molecule (leaving group)



- The terms Nucleophile and Nucleofuge are generally used in the discussion of reactivity and kinetics.

Effect of Solvent

- Solvent may play a vital role in the rate of S_N2 reaction as it involves either creation or dispersion of charge (particularly in the transition state).
- Charged species are more stabilized in polar solvent than non-polar solvent.
- Difference between the solvation capacity of reactant and transition state in various solvent lead to the solvent effect in a reaction.

Reactants	Transition State	Charge Creation/Dispersion	Effect of Increasing the Polarity of Solvent
$\text{Nuc}^- + \text{R-LG}$	$\overset{\delta^+}{\text{Nuc}} \cdots \text{R} \cdots \overset{\delta^-}{\text{LG}}$	Charge dispersion	Retard the reaction
$\text{Nuc} + \text{R-LG}$	$\overset{\delta^-}{\text{Nuc}} \cdots \text{R} \cdots \overset{\delta^+}{\text{LG}}$	Charge creation	speed the reaction
$\text{Nuc}^- + \text{R-LG}^+$	$\overset{\delta^-}{\text{Nuc}} \cdots \text{R} \cdots \overset{\delta^-}{\text{LG}}$	Charge dispersion	Retard the reaction
$\text{Nuc}^+ + \text{R-LG}$	$\overset{\delta^+}{\text{Nuc}} \cdots \text{R} \cdots \overset{\delta^+}{\text{LG}}$	Charge dispersion	Retard the reaction

- In the case of a negatively charged nucleophile, a remarkable change in the rate of S_N2 reaction is observed while changing the solvent from polar protic to polar non-protic solvent.
- In polar aprotic solvents, negatively charged nucleophile are generally less soluble but solvent are polar enough to solubilize the nucleophile making them highly reactive.
- Solubility of nucleophile is a major problem in substitution reactions, particularly in less polar aprotic solvents.
- Crown ether is added to solvate the counter-cation which induce the solubility of corresponding anionic nucleophile.

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: $\text{NH}_2^- > \text{NH}_3$, $\text{OH}^- > \text{H}_2\text{O}$,

2. Nucleophilicity generally follows similar order as basicity

Example: $\text{R}_3\text{C}^- > \text{R}_2\text{N}^- > \text{RO}^- > \text{F}^-$

$\text{NH}_2^- > \text{RO}^- > \text{R}_2\text{NH}^- > \text{ArO}^- > \text{NH}_3 > \text{Pyridine} > \text{F}^- > \text{H}_2\text{O} > \text{ClO}_4^-$

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

Example: $\text{I}^- > \text{Br}^- > \text{Cl}^- > \text{F}^-$ (less solvation, Higher polarization)

$\text{S}^- > \text{O}^-$

Structure Function Correlation with Nucleophile

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: $\text{NaOH}_{\text{DMSO}} > \text{NaOH}_{\text{water}}$ (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

- Negative charge develops on the leaving group during the rate determining step. Thus, reaction proceed faster with a leaving group which stabilize the negative charge better.
- Better leaving groups are mostly weak bases which stabilize the negative charges.

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

- In the presence of better leaving group, $\text{S}_{\text{N}}1$ reaction do not require strong base, but for $\text{S}_{\text{N}}2$ reaction it is required.

Example:

1. XH is always a weaker base than X^- . Thus XH is a better leaving group which facilitates $\text{S}_{\text{N}}2$ reaction.

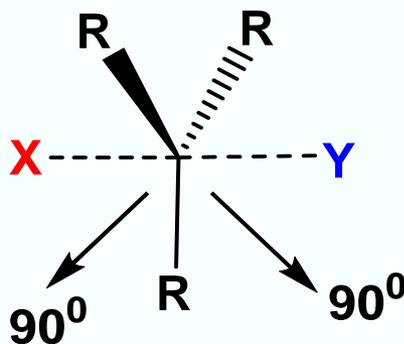


2. Acidic medium also protonate the base making them weaker.

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

Structure Function Correlation With R Group

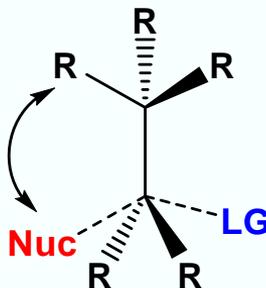
- R group plays vital role on the rate of reaction
- R group may have steric, electronic and neighboring group effect.
- Steric hindrance may slow the rate of reaction, as nucleophile adds to the carbon centre in the rate determining step.
- In the transition state, the incoming nucleophile(Nuc) and leaving group(LG) are 90° to the R group. Larger R groups can result in increased strain leading to slower reaction rates.



Bulkier R group increase steric hindrance

Structure Function Correlation With R Group

➤ 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.

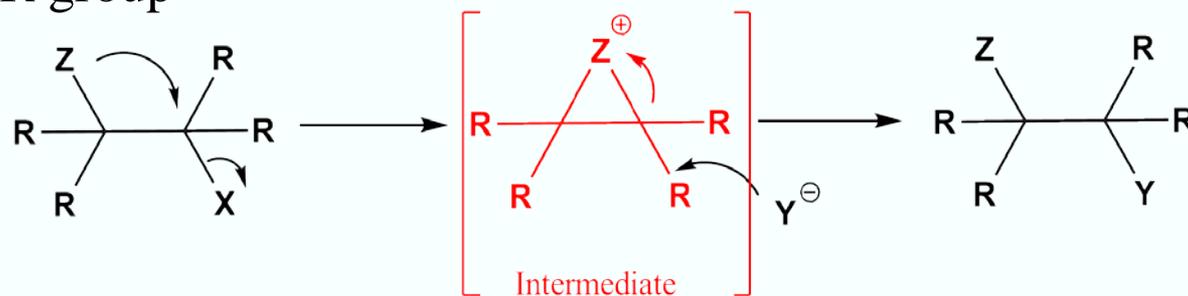
Example:

Higher rate for nucleophilic substitution at allyl and benzyl system.

Neighboring Group Participation (NGP)

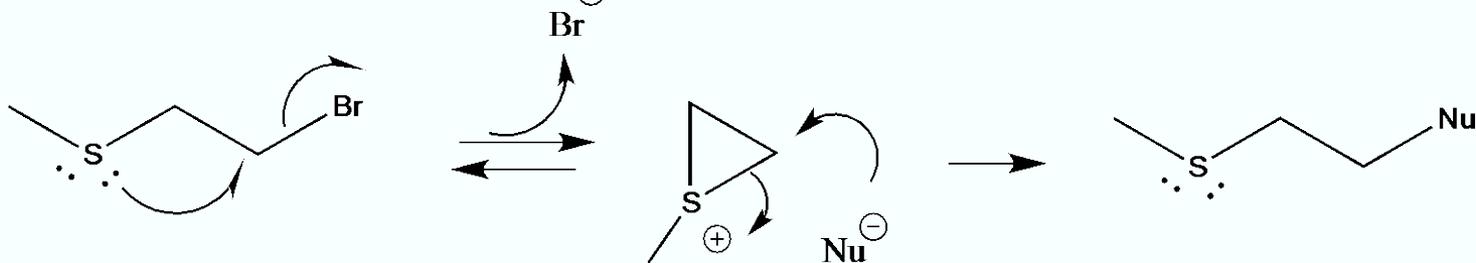
➤ In the presence of an electron donating neighboring group, the reaction proceeds faster than expected. In addition, either inversion nor racemisation is observed in such cases.

➤ 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)



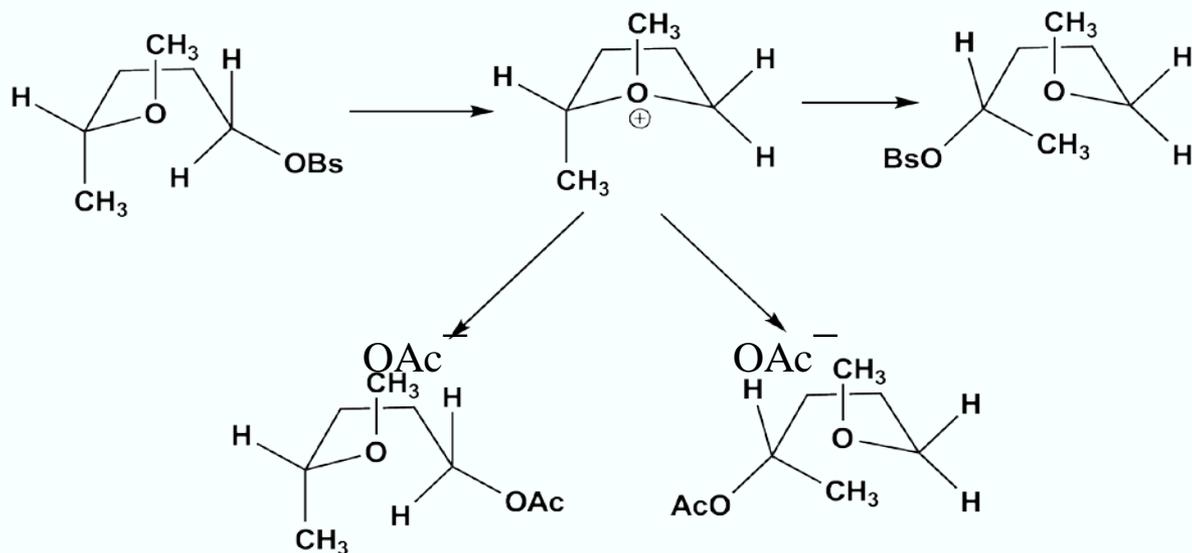
➤ Two consecutive S_N2 substitution, leads to retention of configuration.

Example 1



Neighboring Group Participation

Example 2

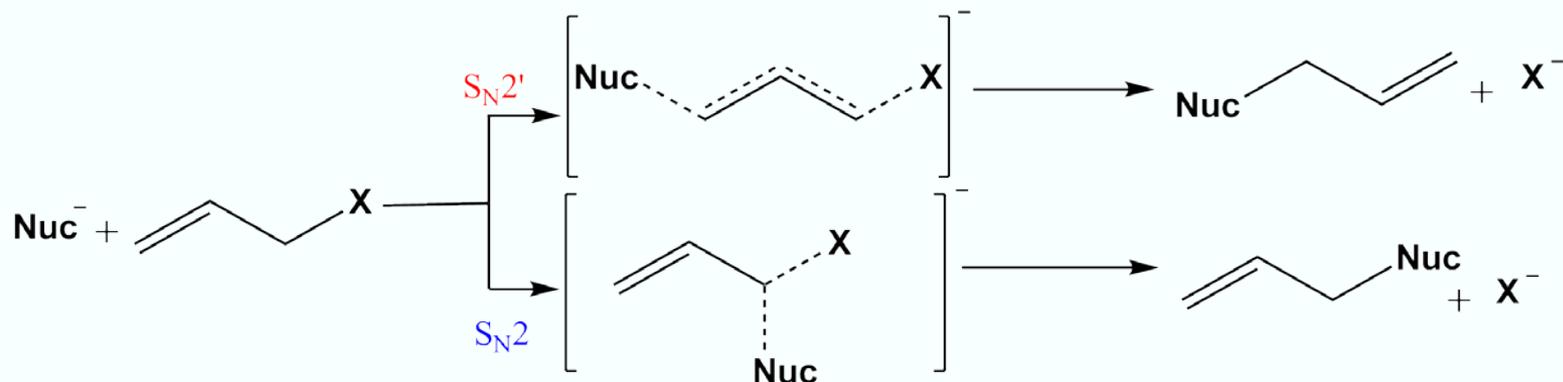


- The most likely neighboring group participation leads to three, five, six membered rings
- Four membered ring neighboring group participation is higher in case of alkyl substitution on α or β carbon.
- The effect of halogen increase as going down the group (**I** > **Br** > **Cl**).

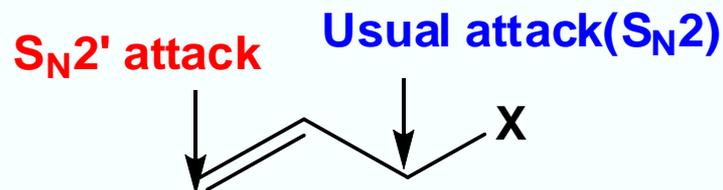
Some of the neighboring groups are COO^- , COOR , COAr , OCOR , OR , OH , O^- , NH_2 , NHR , NHCOR , SH , SR , I , Br , S^-

S_N2' Reaction*

➤ allylic rearrangement under S_N2 conditions are known as S_N2' 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'

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

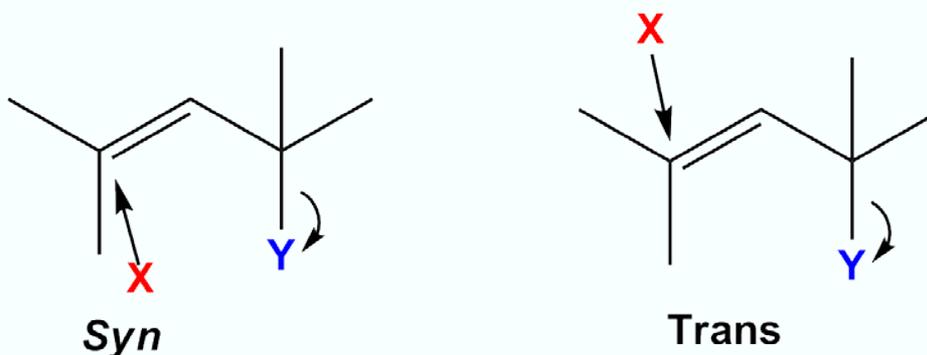
S_N2 Reaction*

➤ 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

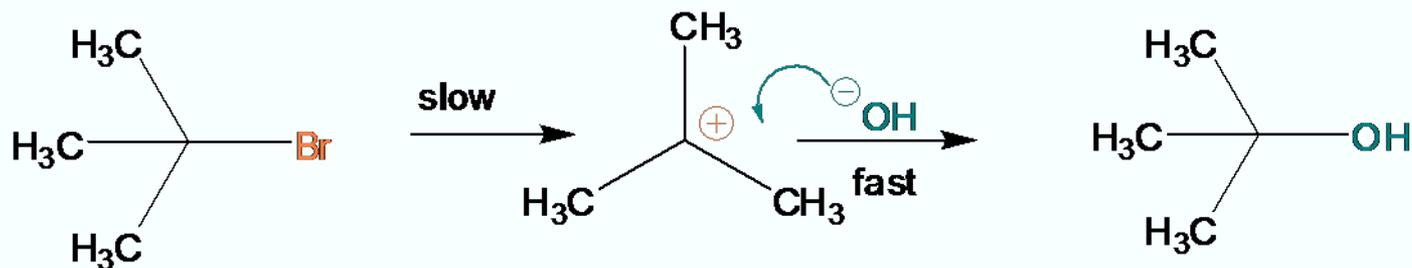
in S_N2 reaction, still *syn*-substitution is preferred over *anti*.



II. Nucleophilic substitution unimolecular (S_N1) Reaction

Introduction

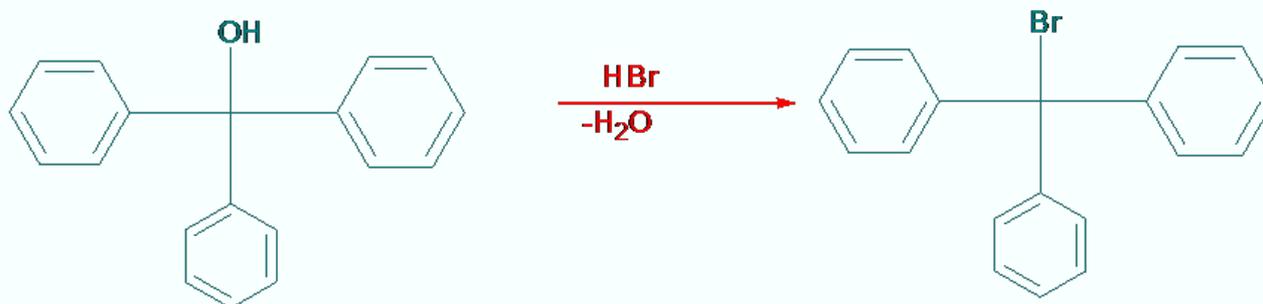
- S_N1 corresponds to Substitution Nucleophilic Unimolecular
- The rate depends on the concentration of only 1 reactant, i.e., **the substrate** and not the nucleophile
- Highly substituted reactants undergo S_N1 reactions. Increase in substitution at carbon favors S_N1 pathway.



In this example, heterolytic bond cleavage of C-Br bond leads to a tertiary carbocation, which is subsequently attacked by the nucleophile (hydroxide here). The speed of the reaction is decided by how fast the carbocation can be generated

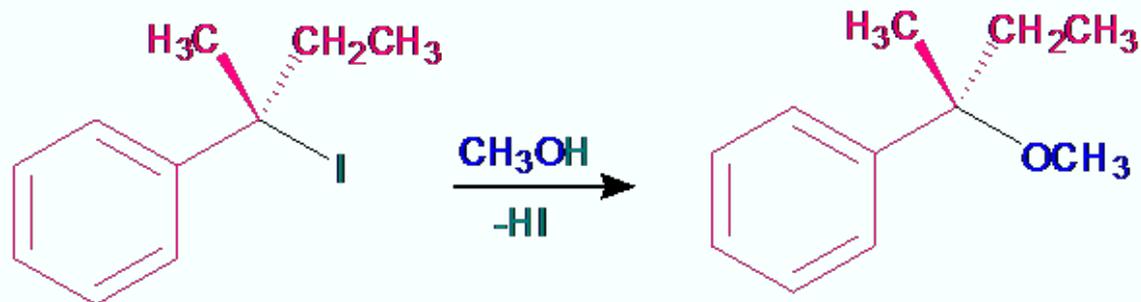
Introduction

Example 1



In the above example, protonation of the OH group will convert it into a very good leaving group (H₂O), 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



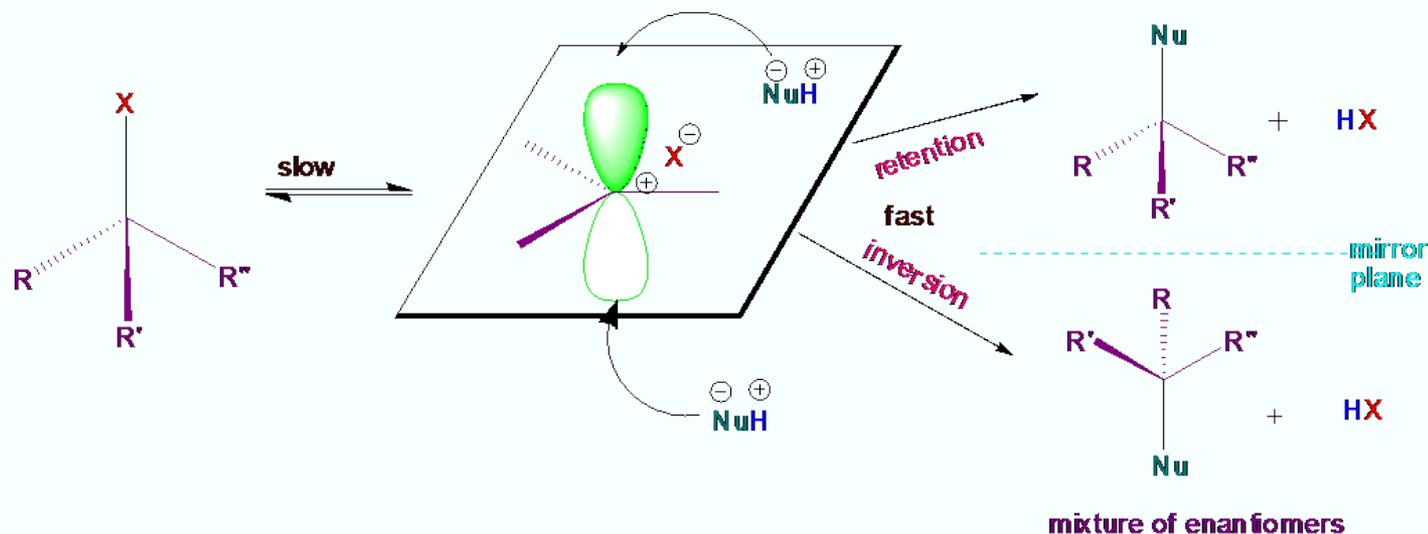
Kinetics

- The kinetics of S_N1 follow first order kinetics.
rate \propto [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.

Mechanism

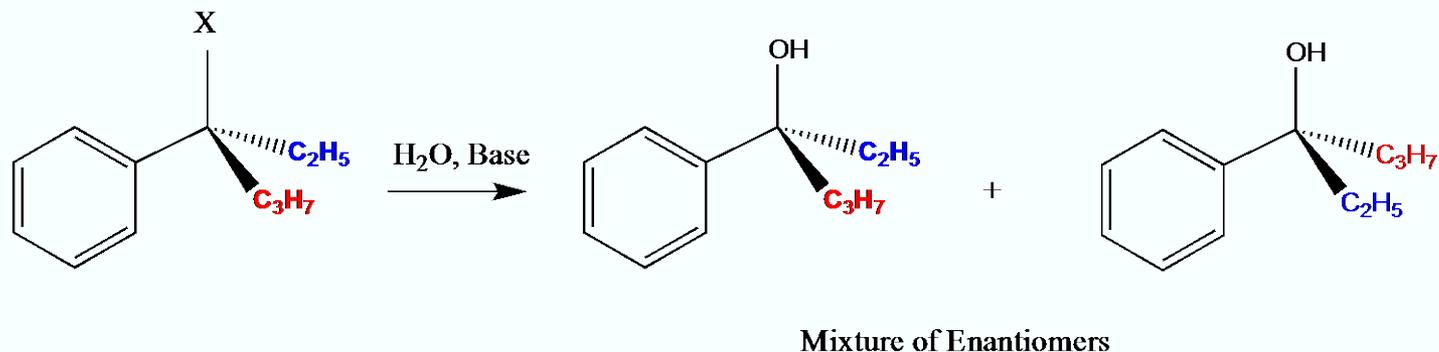
- The first step of the reaction involves the formation of a carbocation. This is a slow process due to higher activation energy for bond breaking
- Carbocation can be stabilized by the substituents through two important effects (i) hyperconjugation if the carbon is highly substituted or (i) by resonance
- The second step proceeds fast as it involves combination of two ionic substrate and the incoming nucleophile.

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:



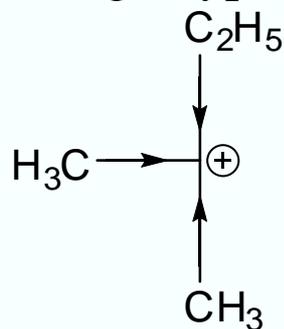
Attention: the position of the R groups are not identical in the two enantiomeric products given

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 or bottom of the plane, leading to racemization.

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

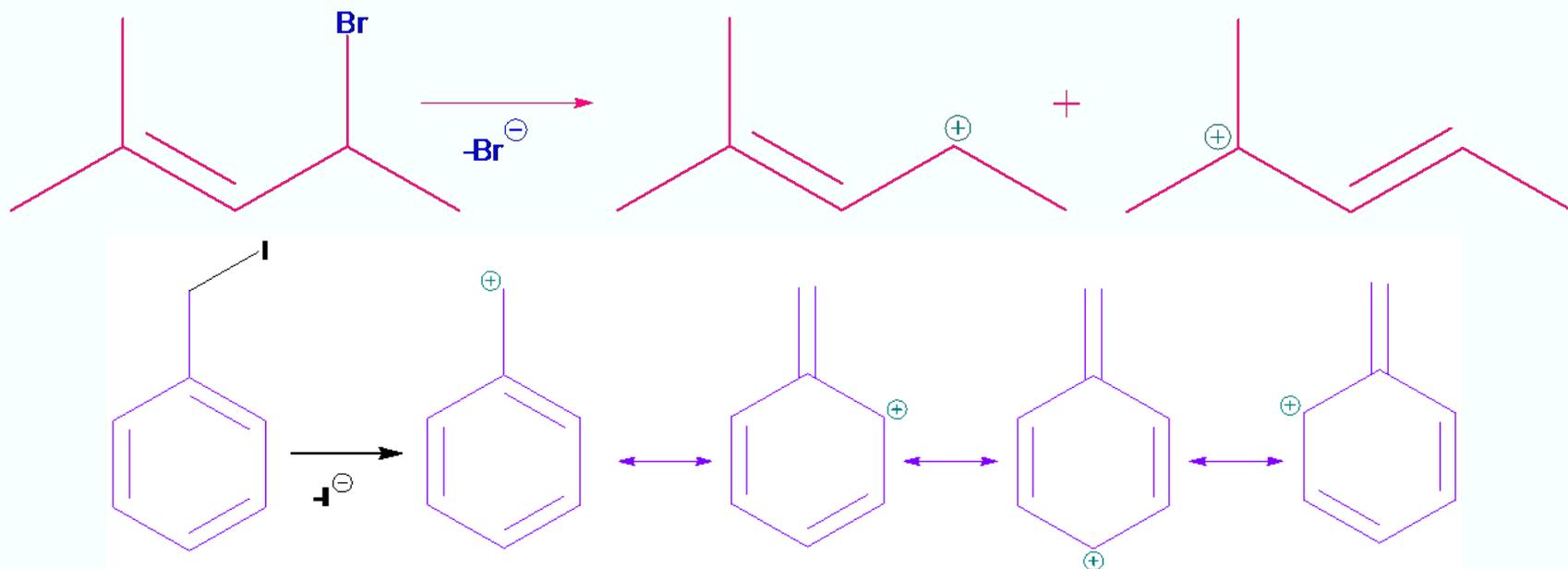
Stability of carbocation

- 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° allylic \approx 3° benzylic $>$ 2° allylic \approx 2° benzylic $>$ 1° allylic \approx 1° benzylic.
- 3° alkyl $>$ 2° alkyl $>$ 1° allylic \approx 1° benzylic .
- The lesser the size of substituent present on carbocation, lower is the chances of it favoring $\text{S}_{\text{N}}1$ pathway.

Leaving group

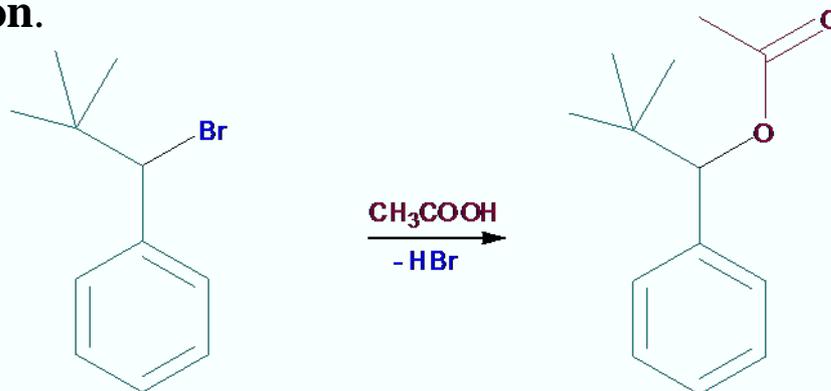
- Leaving group has significant contribution to the rate of reaction, easier the departure of a leaving group, faster will be the rate of reaction.
- Larger anions which can stabilize the negative charge are good leaving groups. (e.g., a tosyl group)

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 rate.

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

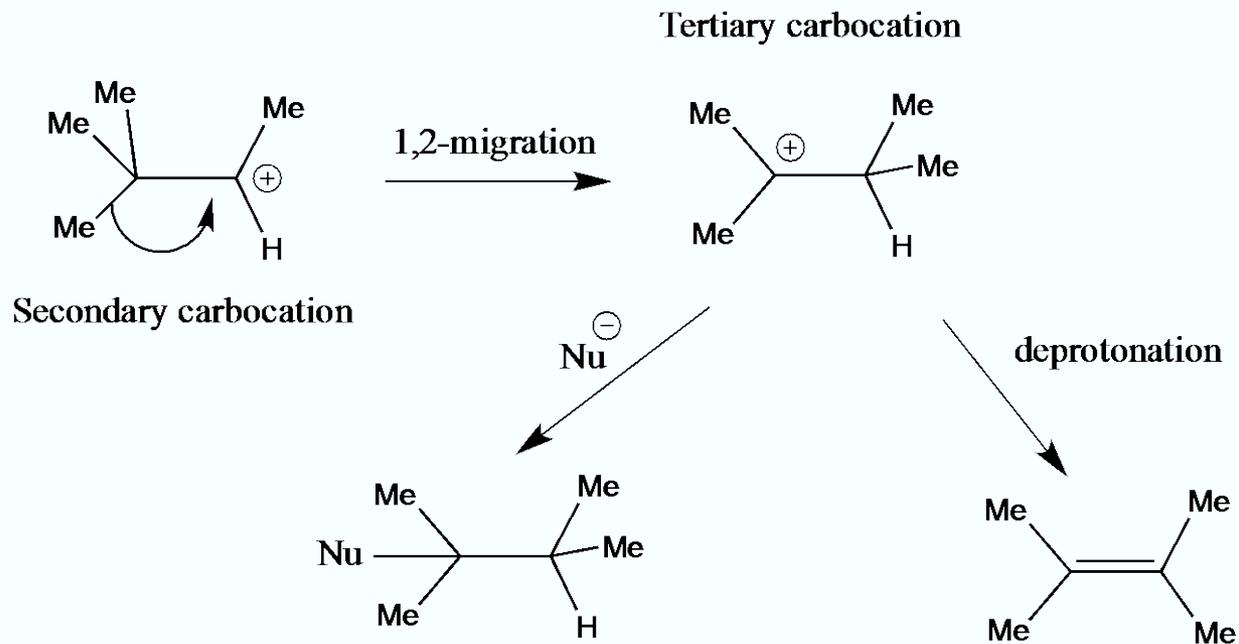
- Reactions in which polar solvent molecules get added to the carbocation are called **solvolysis reaction**.



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

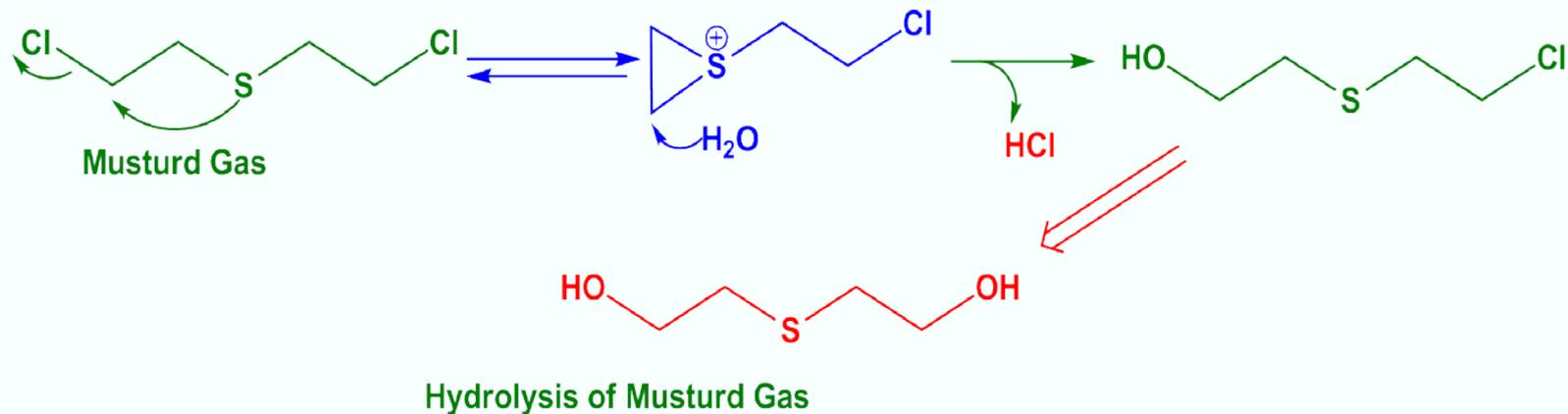


The ability of certain type of carbocation intermediates formed in S_N1 reaction can rearrange to form another (usually lower energy intermediate) before the attack of the nucleophile.

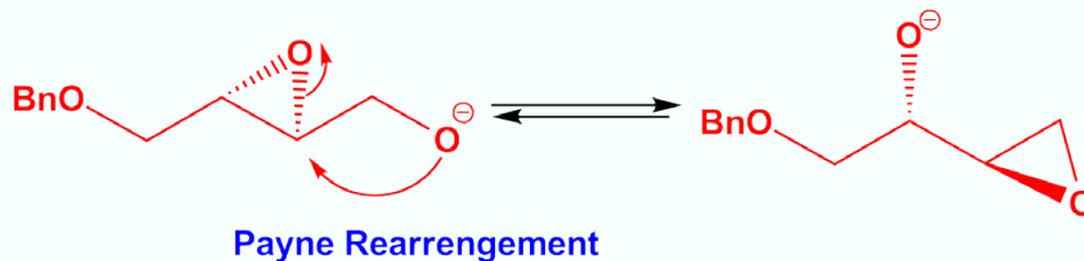
It should be noted that the intramolecular rearrangements can be quite fast as it doesn't require collision by another species (such as a nucleophile).

Additional/Practice problems with solution

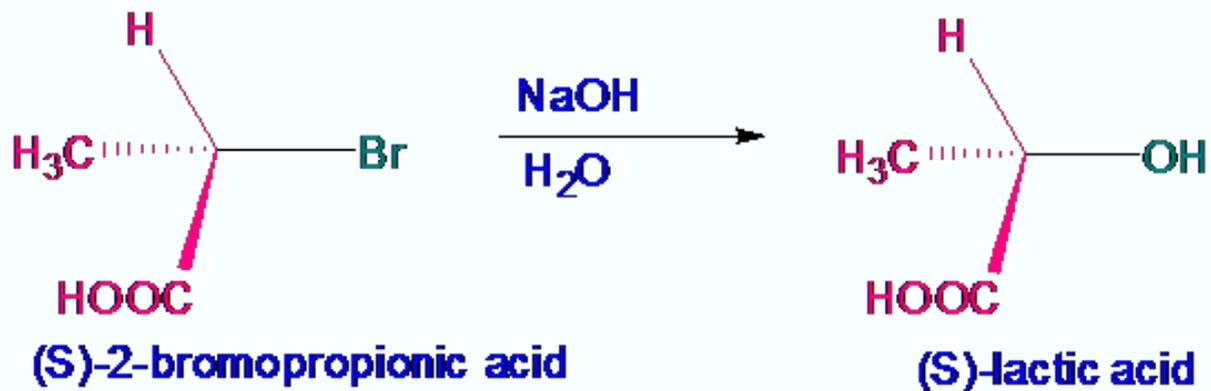
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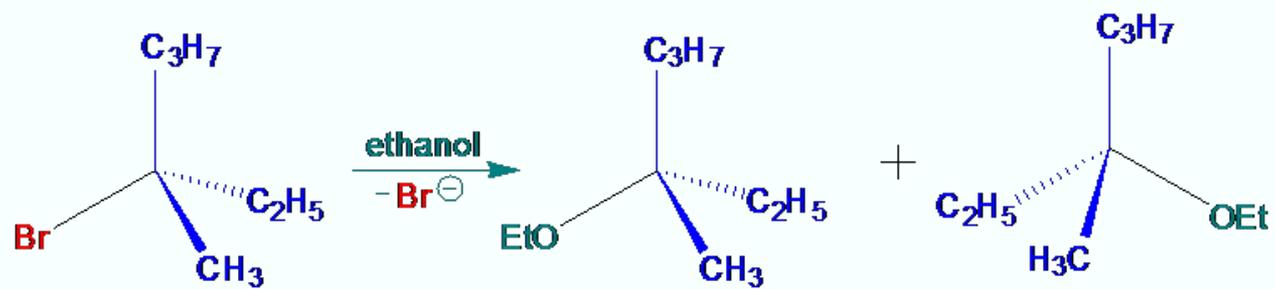
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