

S_N^2 and S_N^1
3 - Factors Affecting
Substitution Reactions

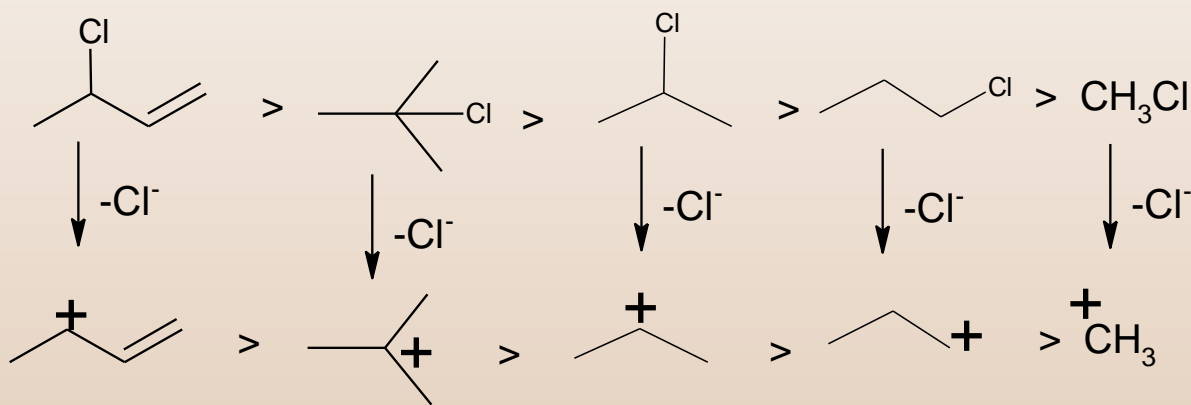
Dr. Sapna Gupta

Factors Affecting S_N2 and S_N1 Reactions

1. Nature of the Substrate (Subs)
2. Strength of the Nucleophile (Nu^-)
3. Leaving group ability (LG)
4. Solvent type

1) Nature of Substrate

Substrate can be 1°, 2°, 3° or allylic halide, to give the respective carbocation.

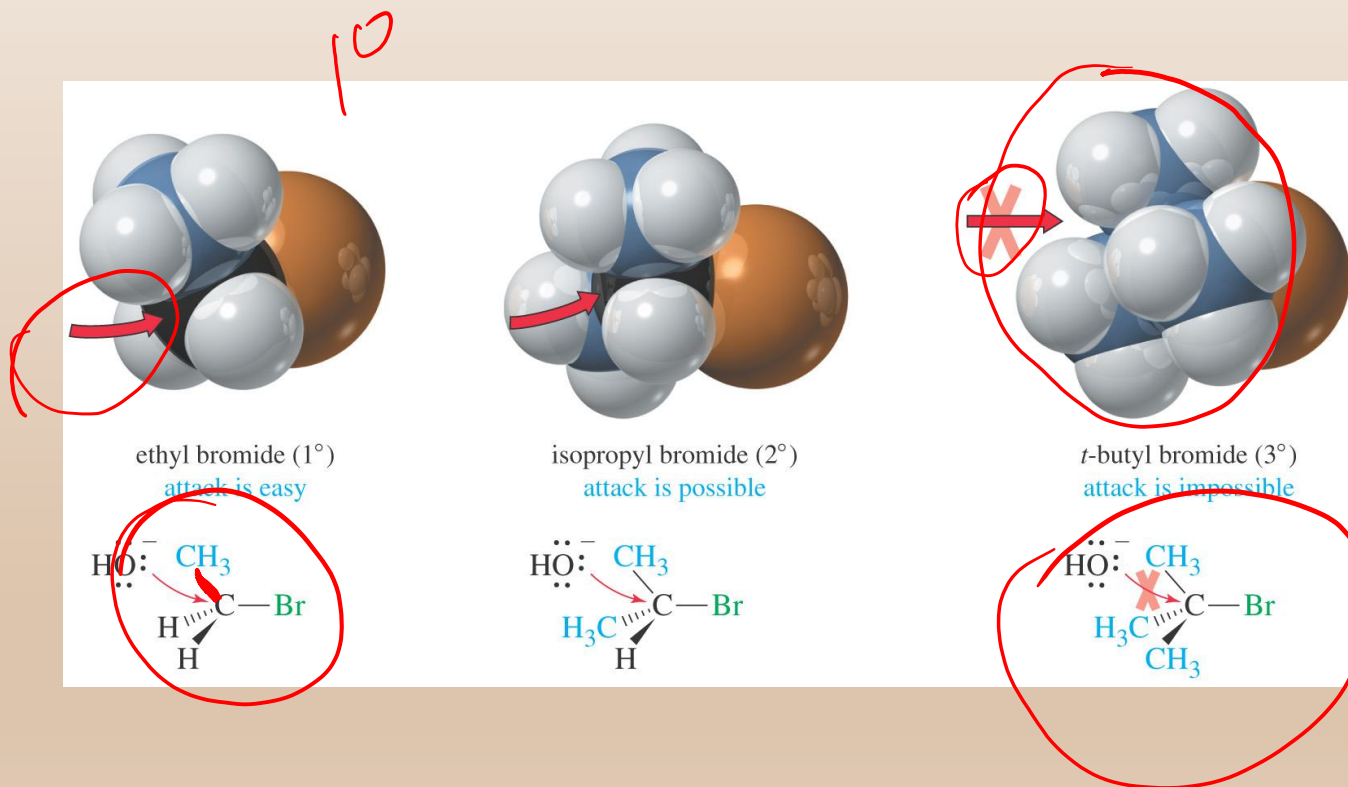


SN2	SN1
Mechanism involves back side attack, so it is important for a-carbon to be accessible.	Mechanism involves forming carbocation, so carbocation must be stable.
Steric hinderance: A carbon cannot be hindered (sterically hindered)	Steric hinderance is not a problem. Carbocation forms a trigonal planar shape hence accessibility is not a problem.
Stability of carbocation: $\text{CH}_3\text{X} \gg 1^\circ > 2^\circ > 3^\circ$	Stability of carbocation: $\text{C}=\text{C}-\text{C}^+ > 3^\circ > 2^\circ > 1^\circ \gg \text{CH}_3\text{X}$

1) Substrate..contd Steric Hindrance - 1

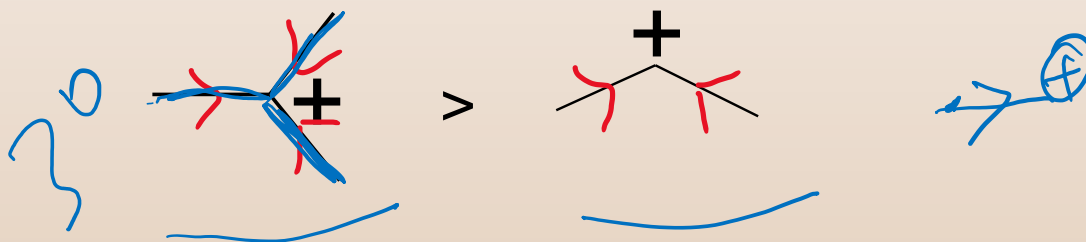
- Nucleophile approaches from the back side hence the electrophilic carbon should not be hindered.
- Best substrates for S_N2 are primary halides.

$1^\circ > 2^\circ > 3^\circ$

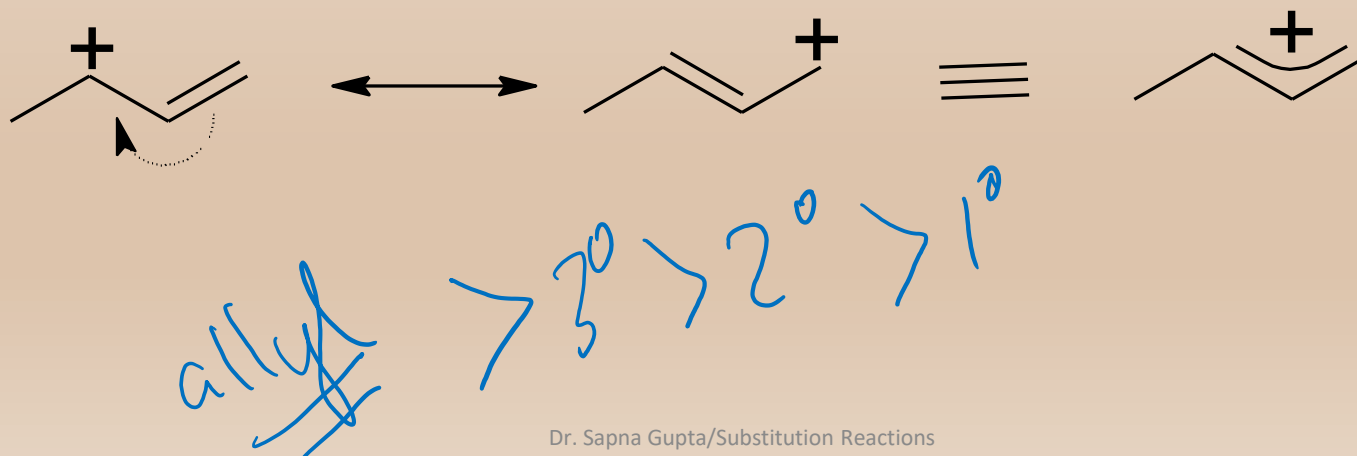


1) Substrate...contd – Stability - 2

- Stability of tertiary carbocation is highest due to electron donation, inductive effect, of alkyl groups. More alkyl groups stabilize the carbocation more.



- Why is allyl cation more stable? Because of resonance. The hybrid shows the delocalization of the cation.



2) Nucleophilic Strength

- Nucleophile should be a stronger base/nucleophile than the leaving group.
- Strong bases are strong nucleophiles, but not all strong nucleophiles are basic*.
- Strength of Nu is based on:
 - Charge: In a conjugate acid-base pair, the base (anion) is stronger:
 $\text{OH}^- > \text{H}_2\text{O}$, $\text{NH}_2^- > \text{NH}_3$
 - Periodicity: Decreases left to right on the Periodic Table. More electronegative atoms less likely to form new bond:
 $\text{OH}^- > \text{F}^-$, $\text{NH}_3 > \text{H}_2\text{O}$
 - Size: Increases down Periodic Table, as size and polarizability increase: $\text{I}^- > \text{Br}^- > \text{Cl}^-$
 - Size and Inductive effect: E.g. EtO^- better than MeO^- due to higher electron density and inductive effect.



* Bases are characterised by their ability to abstract a proton while nucleophiles reacts with electrophiles.

2) Nucleophiles...contd – S_N¹ vs S_N²

- **Size:** Larger nucleophiles are not good for S_N² because of steric hinderance. They will not be able to access the electrophilic carbon. E.g. EtO⁻ better than tBuO⁻ even though tBuO⁻ is a stronger base.
- **Strength:** For stronger Nu⁻ than LG is favorable for reaction. For S_N¹ – strength of Nu⁻ does not matter, as it is not part of the rate determining step.

Some examples

strong nucleophiles	$(\text{CH}_3\text{CH}_2)_3\text{P}:$ $-\ddot{\text{S}}-\text{H}$ $:\ddot{\text{I}}:-$ $(\text{CH}_3\text{CH}_2)_2\ddot{\text{N}}\text{H}$ $-\text{:C}\equiv\text{N}$ $(\text{CH}_3\text{CH}_2)_3\text{N}:$ $\text{H}-\ddot{\text{O}}:-$ $\text{CH}_3-\ddot{\text{O}}:-$	moderate nucleophiles	$:\ddot{\text{Br}}:-$ $:\text{NH}_3$ $\text{CH}_3-\ddot{\text{S}}-\text{CH}_3$ $:\ddot{\text{Cl}}:-$ O \parallel $\text{CH}_3\text{C}-\ddot{\text{O}}:-$
		weak nucleophiles	$:\ddot{\text{F}}:-$ $\text{H}-\ddot{\text{O}}-\text{H}$ $\text{CH}_3-\ddot{\text{O}}-\text{H}$

2) Nucleophile, contd...Making them

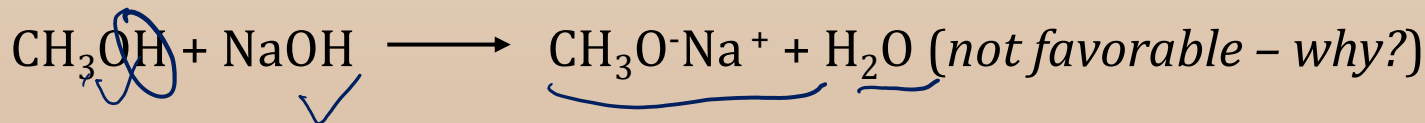
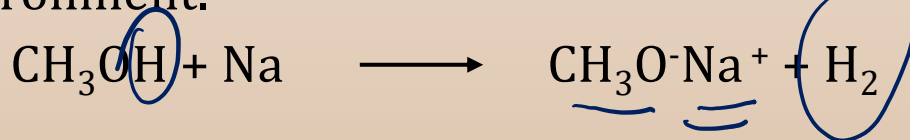
Using Salts for Nu⁻

In case of simple Nu, like, I⁻ (NaI), SH⁻ (NaSH), CN⁻ (KCN), OH⁻ (NaOH) the ionic salts can be used.

Using Alkoxides

alk oxide RO^-

CH₃O⁻Na⁺, CH₃CH₂O⁻K⁺ - alkoxides are synthesized as salts – potassium or sodium. They are synthesized by dissolving solid sodium or potassium in the respective alcohol in a moisture and oxygen free environment.




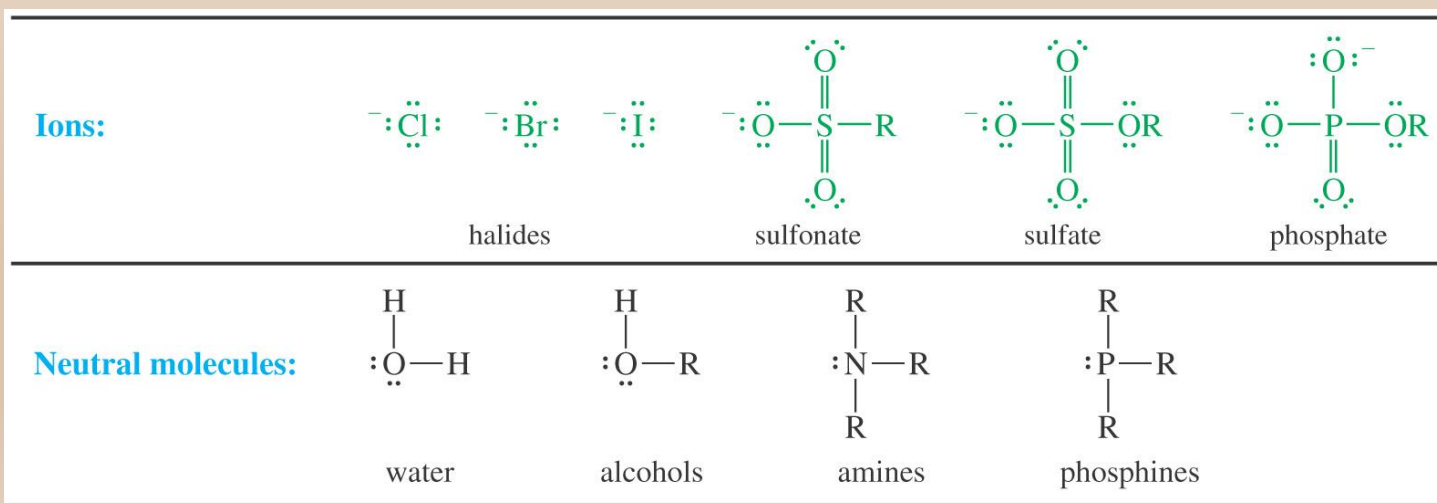
- Nomenclature: CH₃O⁻Na⁺, sodium methoxide, CH₃CH₂O⁻K⁺ potassium ethoxide, (CH₃)₃CO⁻Na⁺ sodium t-butoxide

3) Leaving Group

- LG should be electron-withdrawing to provide an electrophilic carbon.
- It should be stable once it has left (a weak base not a strong base).
- Weaker base cannot displace stronger base (LG) in a S_N2 reaction.
- Usually, halides are good LG.

Relative reactivity	$\underbrace{\text{OH}^-, \text{NH}_2^-, \text{OR}^-}_{\ll 1}$	F^-	Cl^-	Br^-	I^-	TosO^-
		1	200	10,000	30,000	60,000

Leaving group reactivity 

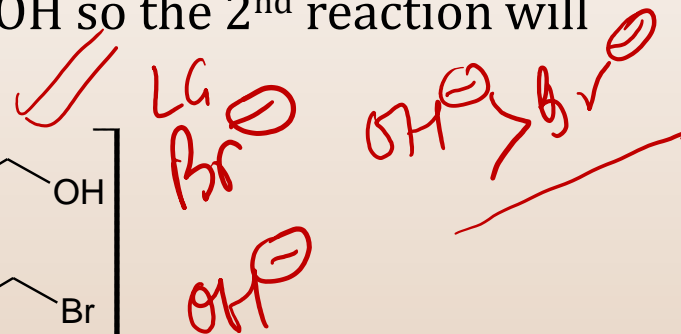
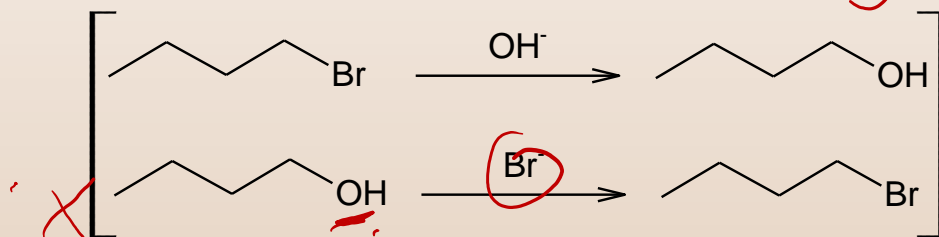


Examples of leaving groups

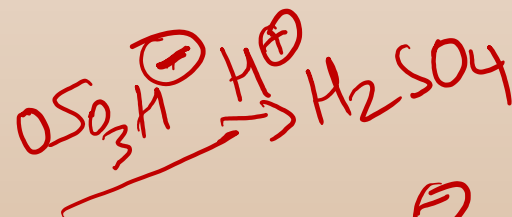
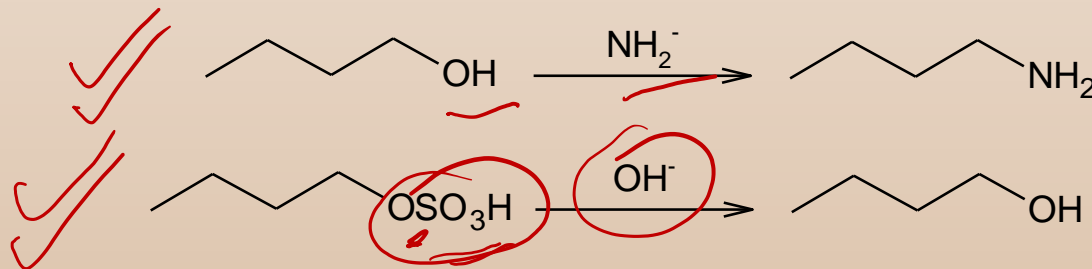
3) Leaving Group...contd Reaction Examples

Examples:

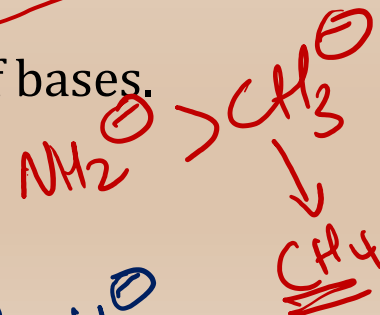
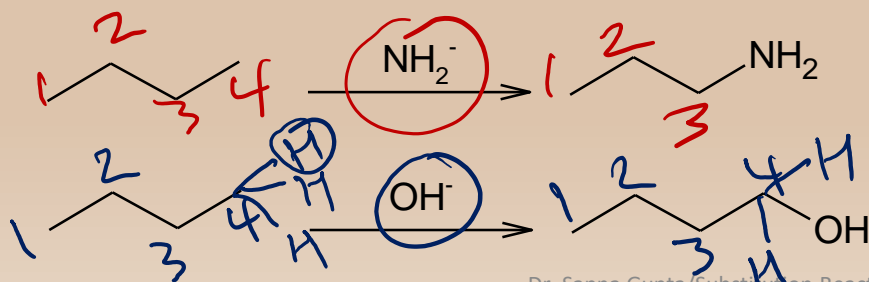
- OH⁻ can displace Br but Br cannot displace OH so the 2nd reaction will not occur as written.



- Both these reactions can occur as LG is weaker base than Nu⁻



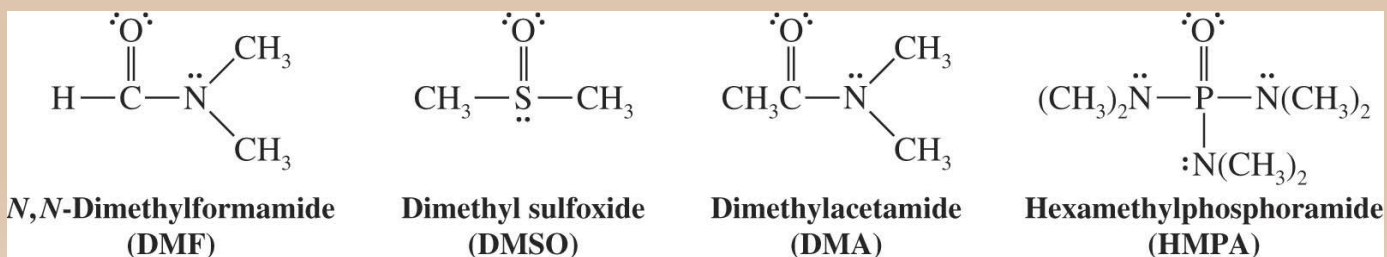
- Some reactions will NOT occur as the LG is most strong of bases.



4) Solvents

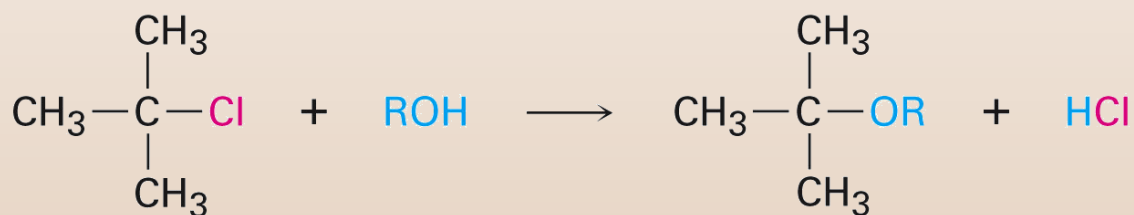
There are 3 kinds of solvents: polar protic, polar aprotic and non polar

Solvent	Polar protic	polar aprotic	non polar
	Have an acidic proton	Polar solvent, no acidic proton	Non polar solvents
Examples	H ₂ O CH ₃ OH, CH ₃ CH ₂ OH	DMF (dimethyl formamide), DMSO (dimethyl sulfoxide) <i>Shown below.</i>	Hexane Toluene Diethyl ether Dichloromethane
Comments	Will form H-bonds with Nu and are good for S _N ¹ since they will	Does not form H-bond with Nu but still helps to solvate ions hence the best kind for S _N 2	Not good for S _N ² since they will not stabilize the ions formed.



4) Solvent...contd

Polar solvents help with ionization and stability of the carbocation.



	Ethanol	40% Water/ 60% Ethanol	80% Water/ 20% Ethanol	Water
Relative reactivity	1	100	14,000	100,000

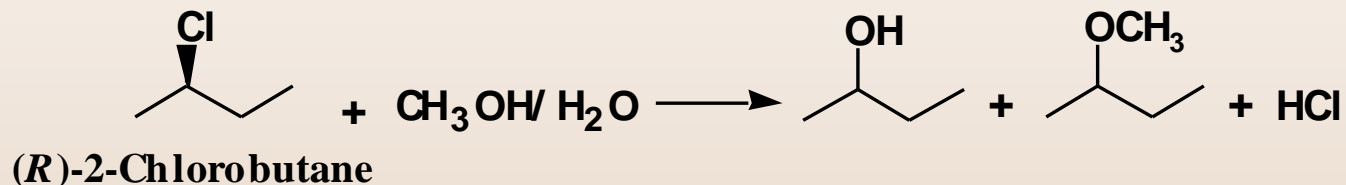
Solvent reactivity 

S_N2 or S_N1 ?

	S_N2	S_N1
Substrate	Primary or methyl	Tertiary
Nucleophile	Strong nucleophile	Weak nucleophile (may also be solvent)
Solvent	Polar aprotic solvent	Polar protic solvent, silver salts
Kinetics	$[\text{substrate}][\text{Nu}]$	$[\text{substrate}]$
Stereochemistry	Inversion	Racemic mixture
Rearrangement	No	Yes

Solved Problems

- Predict mechanism and stereochemistry of each product



- Predict mechanism of the following reaction



- Predict mechanism and stereochemistry of each product



Key Words/Concepts

- Substitution Reaction
- Nucleophile
- Electrophile
- Leaving group
- 1st order reaction (unimolecular)
- 2nd order reaction (bimolecular)
- Transition state
- Rate determining step
- Carbocation
- Polar protic solvent
- Polar aprotic solvent
- Non polar solvent