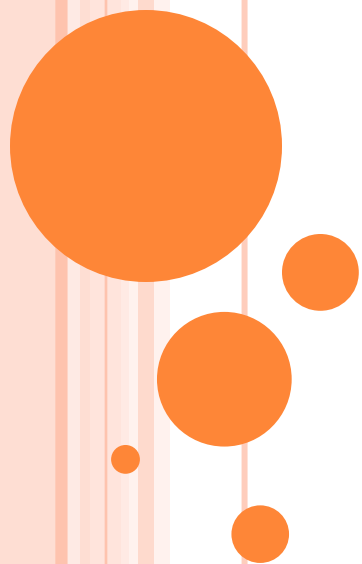
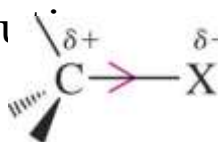


**ALKYL HALIDES :  
NUCLEOPHILIC SUBSTITUTION AND  
ELIMINATION REACTIONS**

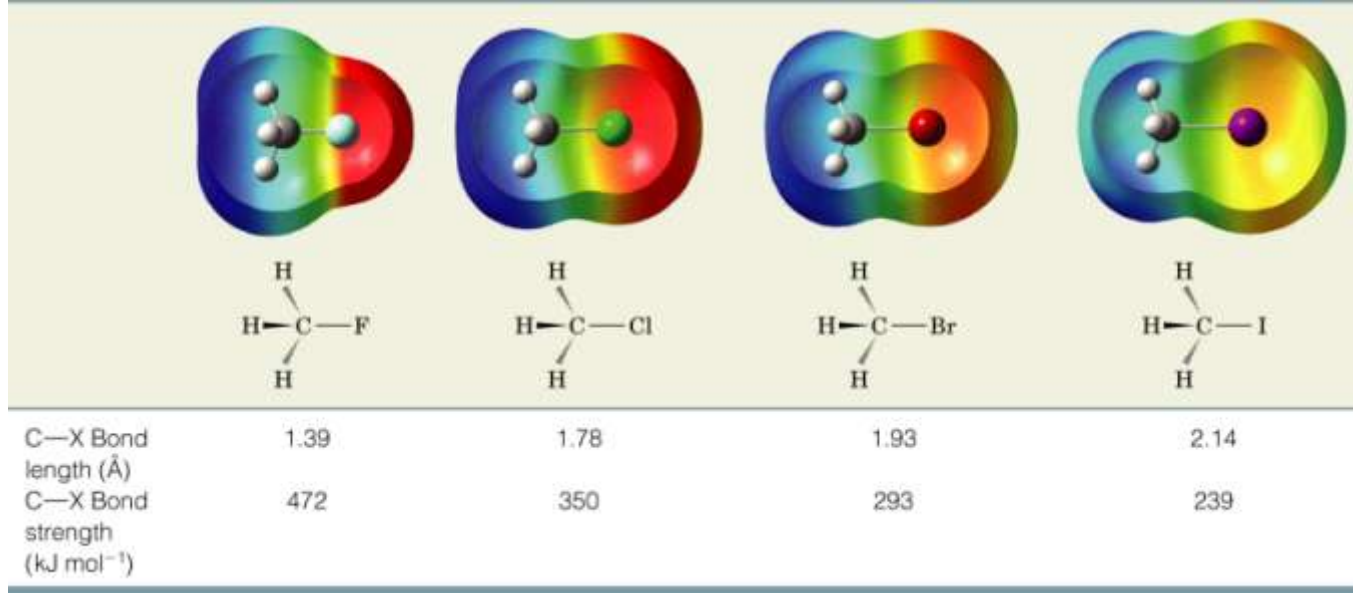


## ○ Introduction

- The polarity of a carbon-halogen bond leads to the carbon having a partial positive charge
  - In alkyl halides this polarity causes the carbon to become activated to substitution reactions with nucleophiles

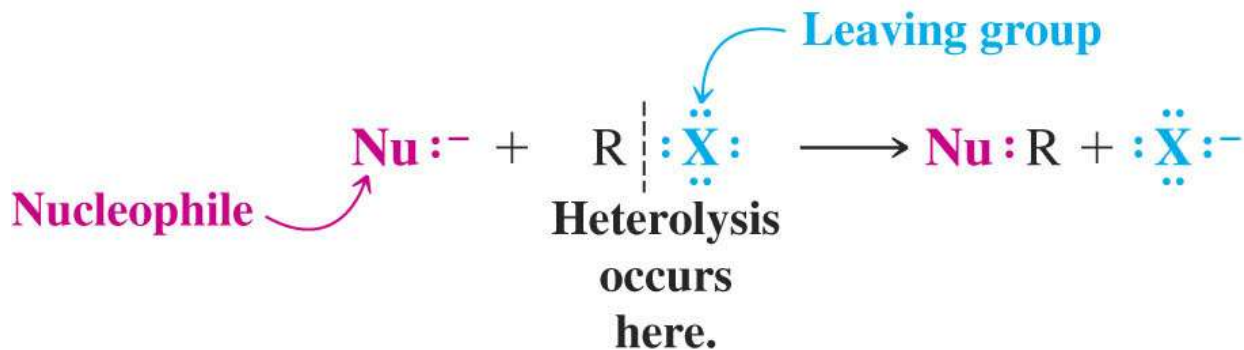


- Carbon-halogen bonds get less polar, longer and weaker in

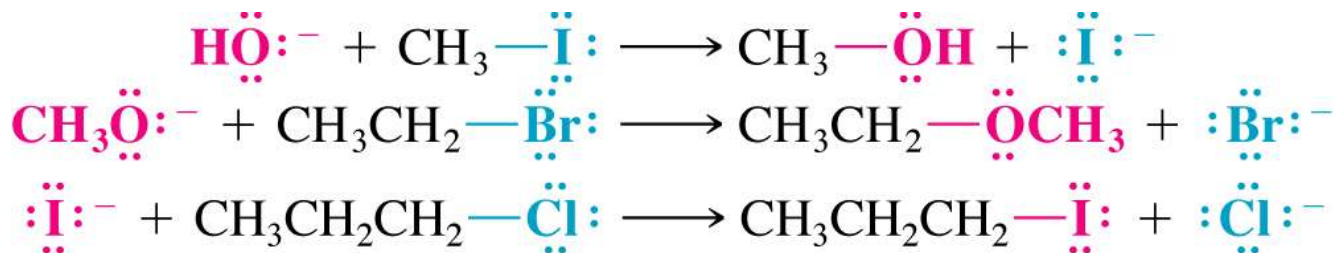


## ○ Nucleophilic Substitution Reactions

- In this reaction a nucleophile is a species with an unshared electron pair which reacts with an electron deficient carbon
- A leaving group is substituted by a nucleophile

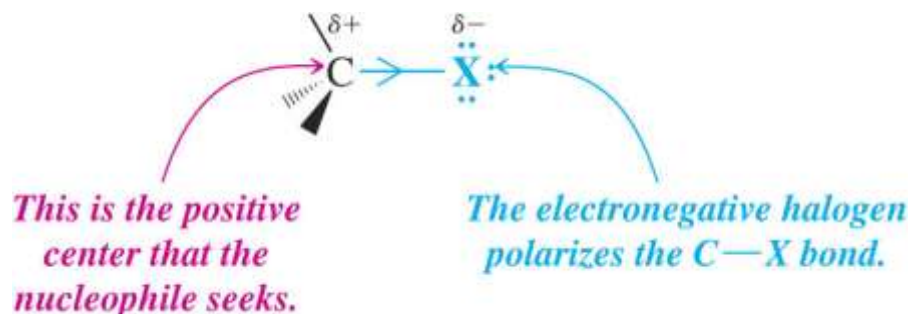


- Examples of nucleophilic substitution

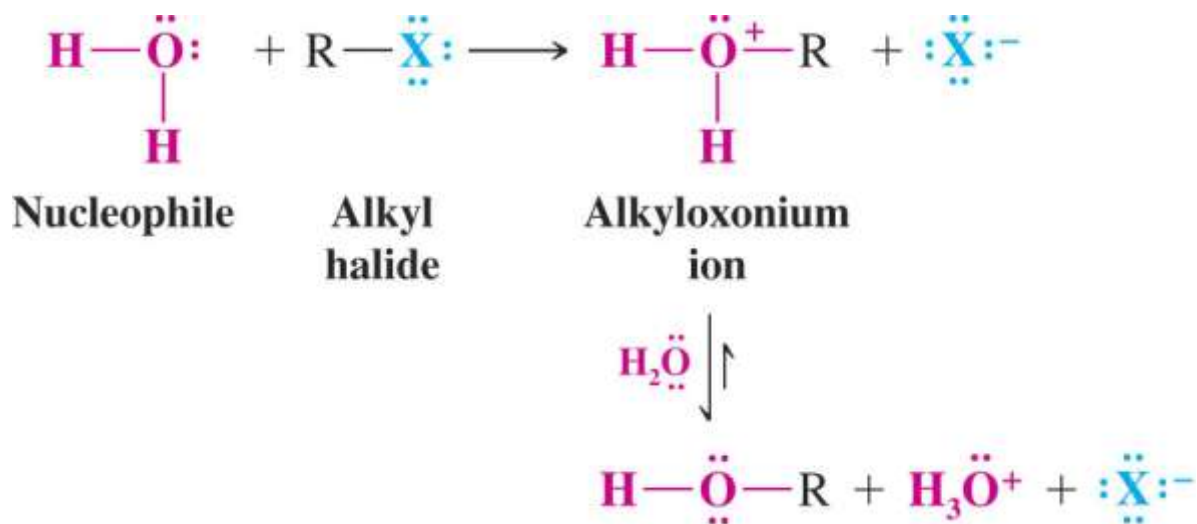


## ○ Nucleophile

- The nucleophile reacts at the electron deficient carbon

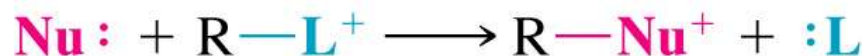
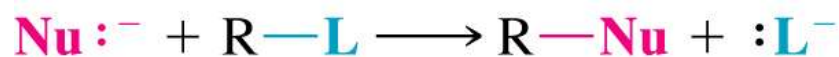


- A nucleophile may be any molecule with an unshared electron pair

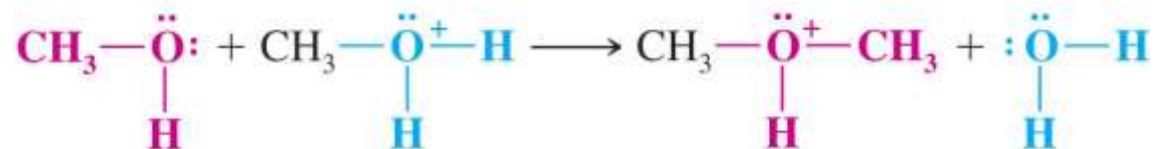


## ○ Leaving Group

- A leaving group is a substituent that can leave as a relatively stable entity
- It can leave as an anion or a neutral species

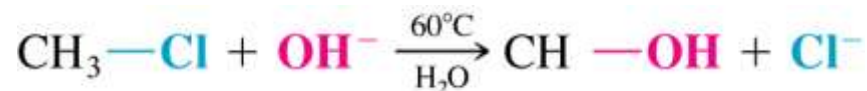


### *Specific Example*



## ○ Kinetics of a Nucleophilic Substitution Reaction: An S<sub>N</sub>2 Reaction

- The initial rate of the following reaction is measured



- The rate is directly proportional to the initial concentrations of both methyl chloride and hydroxide

Experiment Number	Initial [CH <sub>3</sub> Cl]	Initial [OH <sup>-</sup> ]	Initial Rate (mol L <sup>-1</sup> s <sup>-1</sup> )
1	0.0010	1.0	4.9 × 10 <sup>-7</sup>
2	0.0020	1.0	9.8 × 10 <sup>-7</sup>
3	0.0010	2.0	9.8 × 10 <sup>-7</sup>
4	0.0020	2.0	19.6 × 10 <sup>-7</sup>

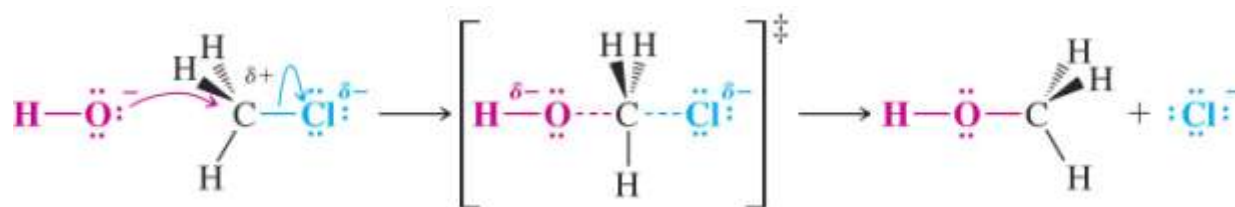
- The rate equation reflects this dependence

$$\text{Rate} = k[\text{CH}_3\text{Cl}][\text{OH}^-]$$

- S<sub>N</sub>2 reaction: substitution, nucleophilic, 2nd order (bimolecular)



## ○ A Mechanism for the S<sub>N</sub>2 Reaction



The negative hydroxide ion brings a pair of electrons to the partially positive carbon from the back side with respect to the leaving group. The chlorine begins to move away with the pair of electrons that bonded it to the carbon.

**Transition state**  
In the transition state, a bond between oxygen and carbon is partially formed and the bond between carbon and chlorine is partially broken. The configuration of the carbon atom begins to invert.

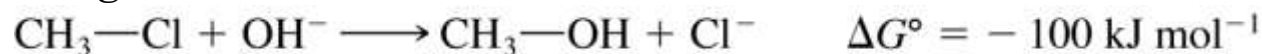
Now the bond between the oxygen and carbon has formed and the chloride ion has departed. The configuration of the carbon has inverted.

ion

- It is an unstable entity with a very brief existence (10<sup>-12</sup> s)
- In the transition state of this reaction bonds are partially formed and broken
  - Both chloromethane and hydroxide are involved in the transition state and this explains why the reaction is second order

## ○ Transition State Theory: Free-Energy Diagrams

- Exergonic reaction: negative  $\Delta G^\circ$  (products favored)
- Endergonic reaction: positive  $\Delta G^\circ$  (products not favored)
- The reaction of chloromethane with hydroxide is highly exergonic



- The equilibrium constant is very large

$$\Delta G^\circ = -RT \ln K_{\text{eq}}$$

$$\ln K_{\text{eq}} = \frac{-\Delta G^\circ}{RT}$$

$$\ln K_{\text{eq}} = \frac{-(-100 \text{ kJ mol}^{-1})}{0.00831 \text{ kJ K}^{-1} \text{ mol}^{-1} \times 333 \text{ K}}$$

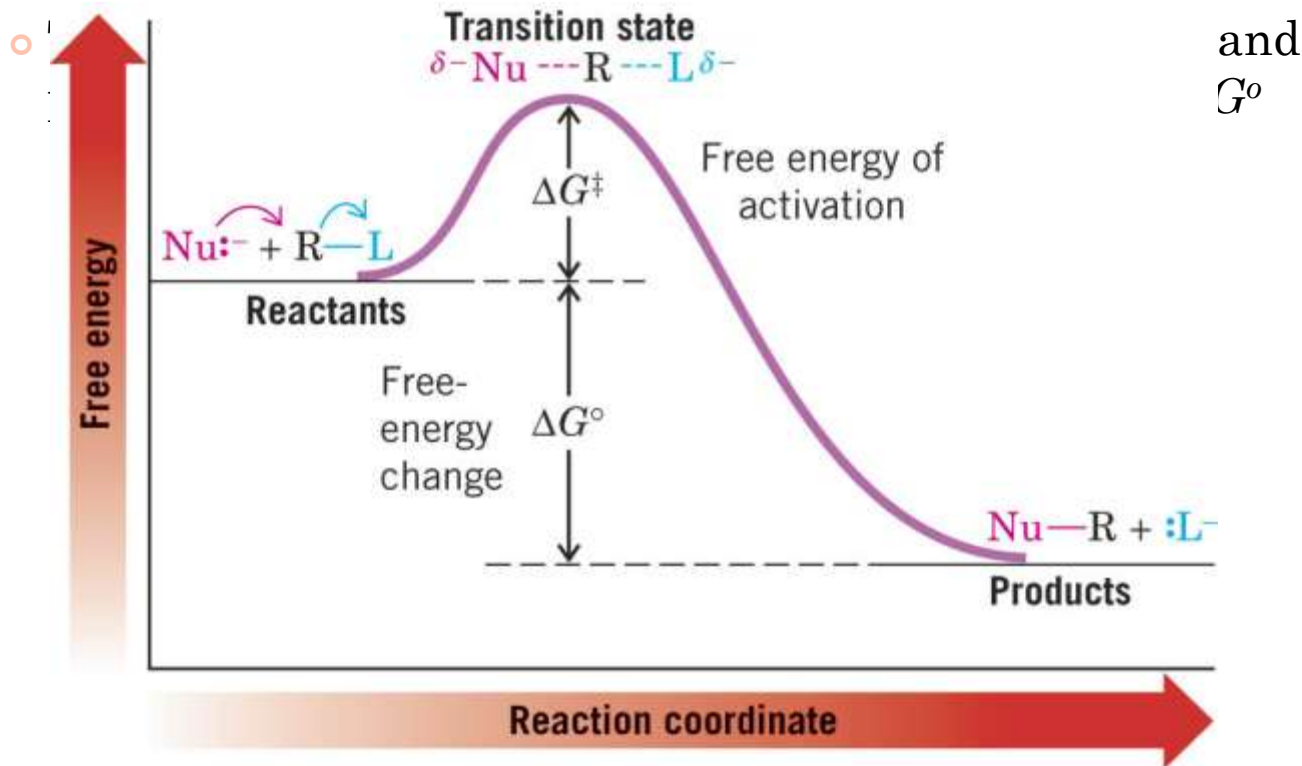
$$\ln K_{\text{eq}} = 36.1$$

$$K_{\text{eq}} = 5.0 \times 10^{15}$$

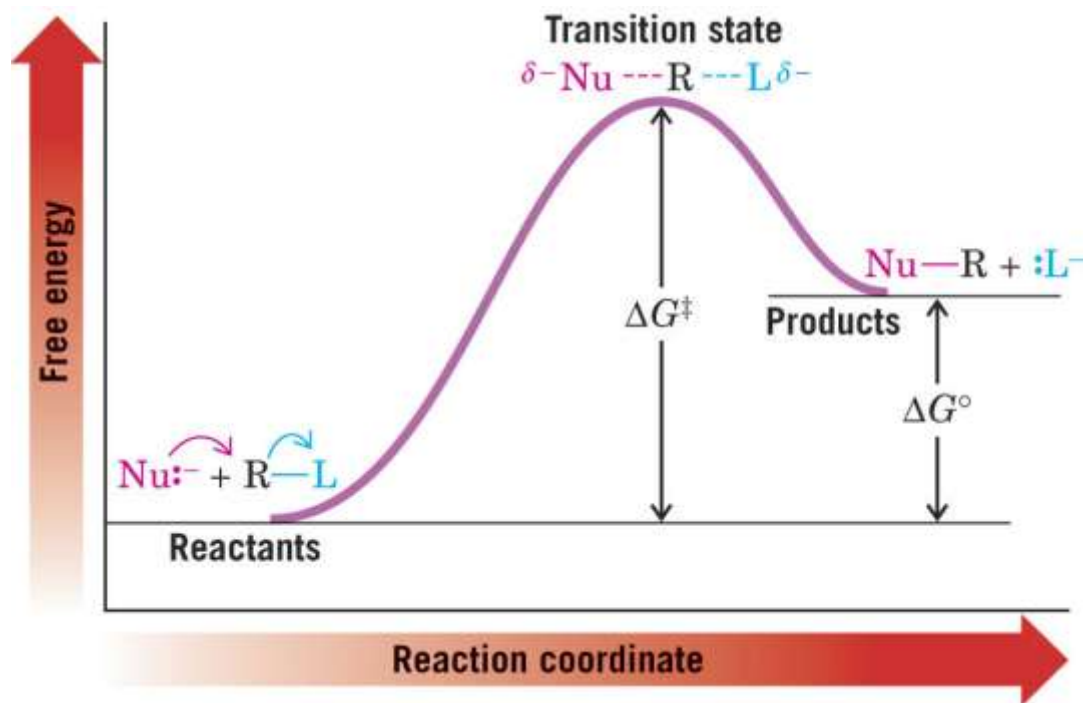




- An energy diagram of a typical  $S_N2$  reaction
  - An energy barrier is evident because a bond is being broken in going to the transition state (which is the top of the energy barrier)
  - The difference in energy between starting material and the transition state is the free energy of activation ( $\Delta G^\ddagger$ )



- In a highly endergonic reaction of the same type the energy barrier will be even higher ( $\Delta G^\ddagger$  is very large)



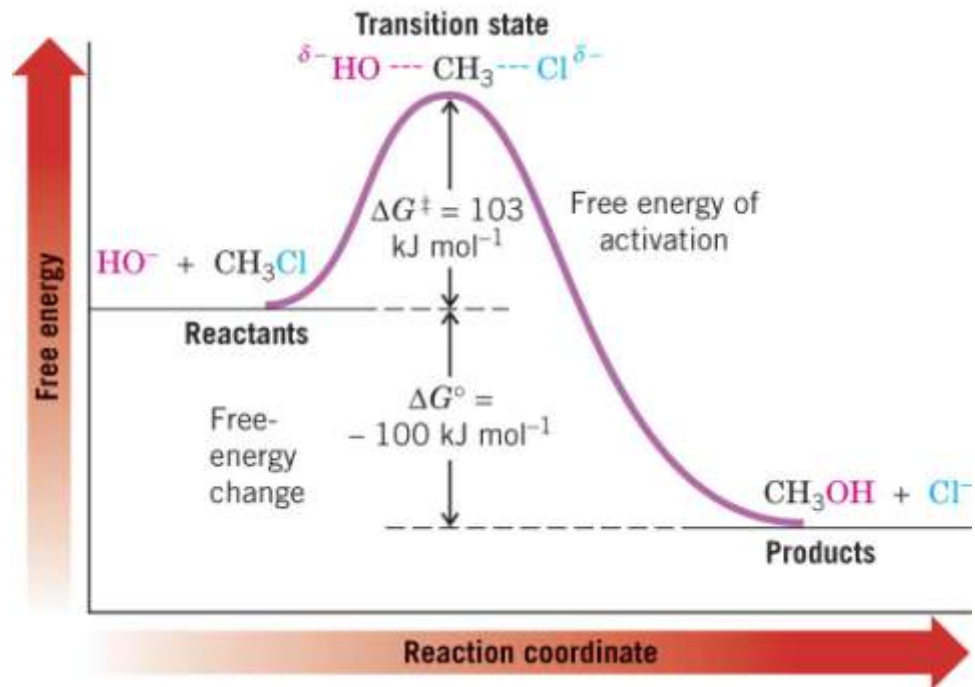
- There is a direct relationship between  $\Delta G^\ddagger$  and the temperature of a reaction
  - The higher the temperature, the faster the rate

$$k = k_0 e^{-\Delta G^\ddagger/RT}$$

- Near room temperature, a 10°C increase in temperature causes a doubling of rate
- Higher temperatures cause more molecules to collide with enough energy to reach the transition state and react



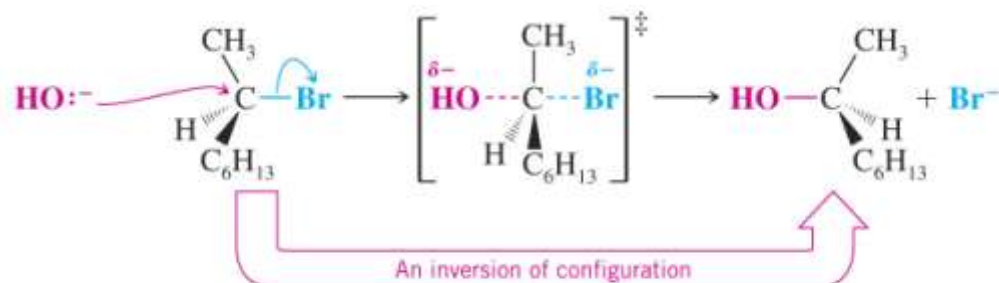
- The energy diagram for the reaction of chloromethane with hydroxide:



- A reaction with  $\Delta G^\ddagger$  above  $84 \text{ kJ mol}^{-1}$  will require heating to proceed at a reasonable rate
- This reaction has  $\Delta G^\ddagger = 103 \text{ kJ mol}^{-1}$  so it will require heating

## ○ The Stereochemistry of S<sub>N</sub>2 Reactions

- Backside attack of nucleophile results in an inversion of configuration



(*R*)-(-)-2-Bromooctane

$[\alpha]_D^{25} = -34.25^\circ$

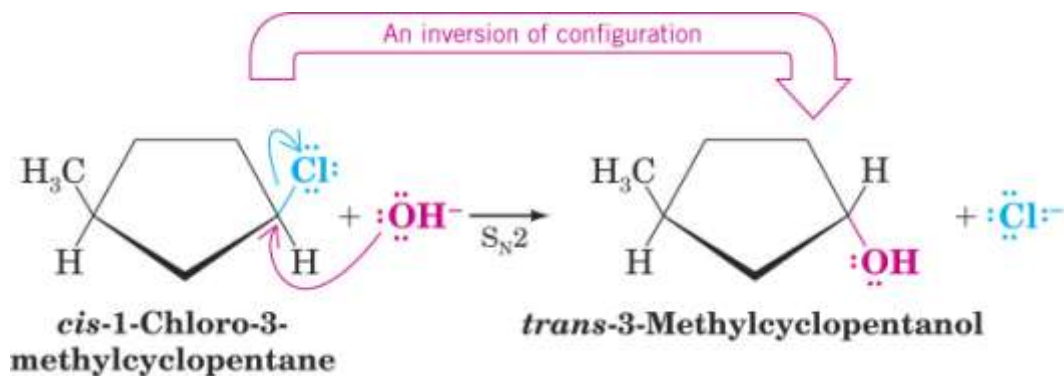
Enantiomeric purity = 100%

(*S*)-(+)-2-Octanol

$[\alpha]_D^{25} = +9.90^\circ$

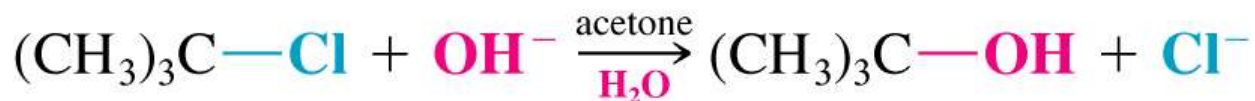
Enantiomeric purity = 100%

- In cyclic systems a *cis* compound can react and become *trans* product



## ○ The Reaction of *tert*-Butyl Chloride with Hydroxide Ion: An S<sub>N</sub>1 Reaction

- *tert*-Butyl chloride undergoes substitution with hydroxide
- The rate is independent of hydroxide concentration and depends only on concentration of *tert*-butyl chloride



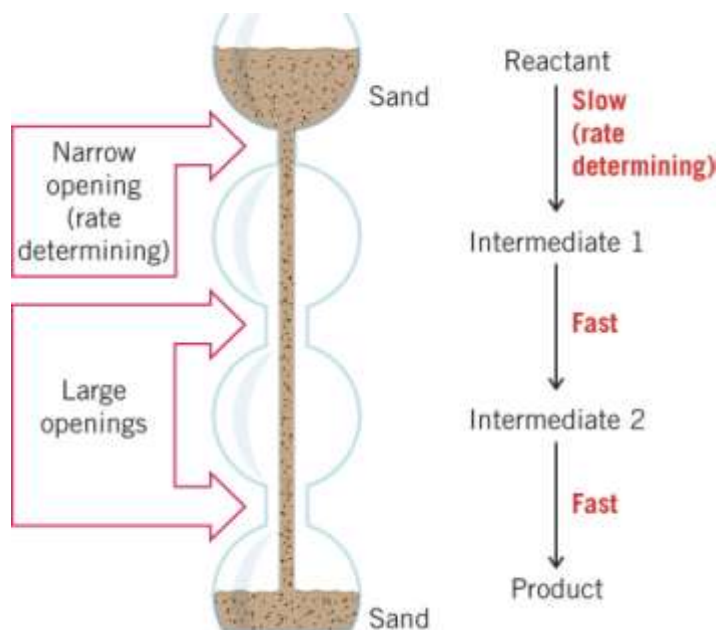
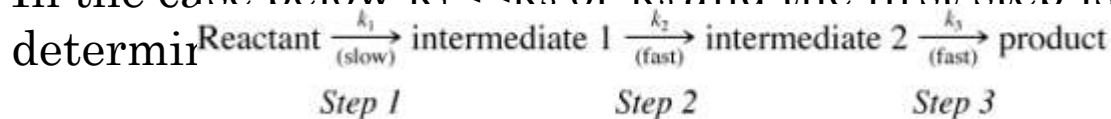
$$\text{Rate} \propto [(\text{CH}_3)_3\text{CCl}]$$

$$\text{Rate} = k[(\text{CH}_3)_3\text{CCl}]$$

- S<sub>N</sub>1 reaction: Substitution, nucleophilic, 1st order (unimolecular)
  - The rate depends only on the concentration of the alkyl halide
  - Only the alkyl halide (and not the nucleophile) is involved in the transition state of the step that controls the rate

# ○ Multistep Reactions and the Rate-Determining Step

- In multistep reactions, the rate of the slowest step will be the rate of the entire reaction
- This is called the rate determining step
- In the case below  $k_1 \ll k_2$  or  $k_3$  and the first step is rate determining

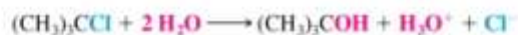


- A Mechanism for the  $S_N1$  Reaction (next slide)
  - Step 1 is rate determining (slow) because it requires the formation of unstable ionic products
  - In step 1 water molecules help stabilize the ionic products



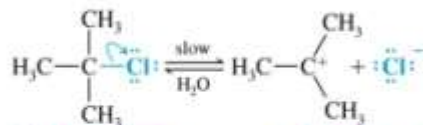


Reaction:



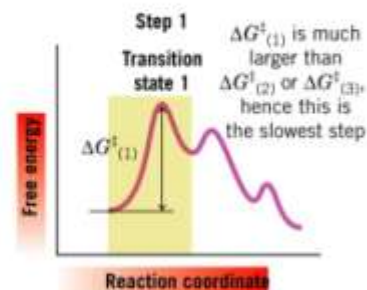
Mechanism:

Step 1

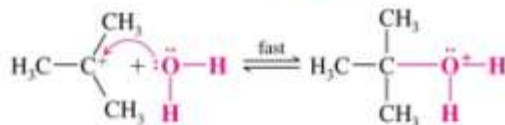


Aided by the polar solvent a chlorine departs with the electron pair that bonded it to the carbon.

This slow step produces the relatively stable  $3^\circ$  carbocation and a chloride ion. Although not shown here, the ions are solvated (and stabilized) by water molecules.

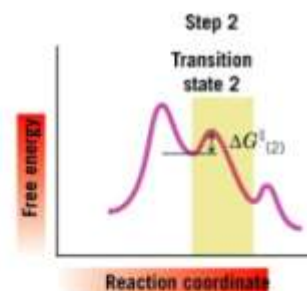


Step 2



A water molecule acting as a Lewis base donates an electron pair to the carbocation (a Lewis acid). This gives the cationic carbon eight electrons.

The product is a *tert*-butyloxonium ion (or protonated *tert*-butyl alcohol).

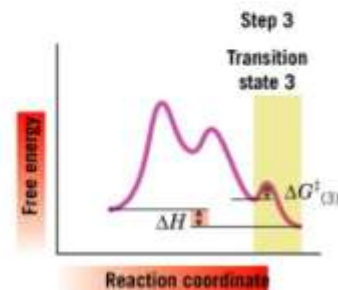


Step 3



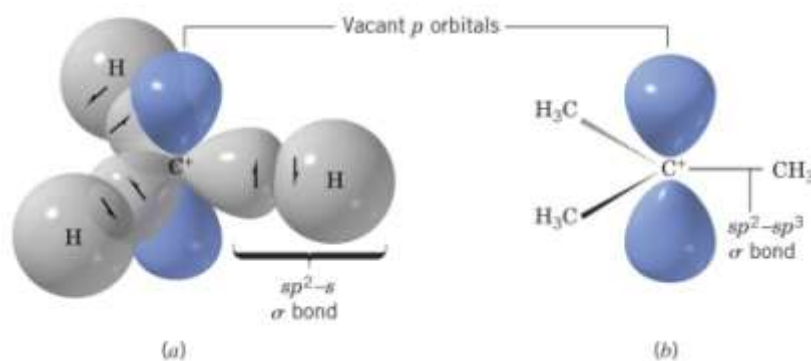
A water molecule acting as a Brønsted base accepts a proton from the *tert*-butyloxonium ion.

The products are *tert*-butyl alcohol and a hydronium ion.

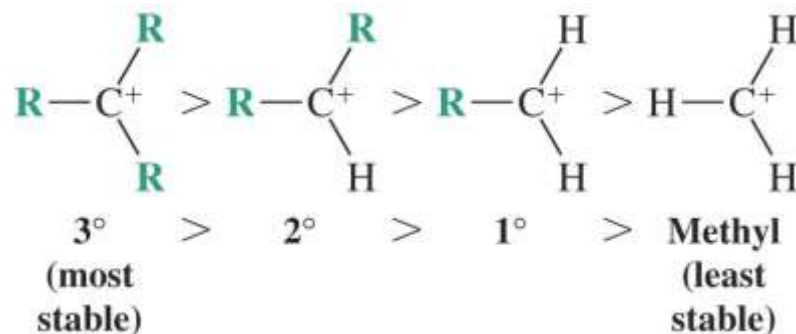


## Carbocations

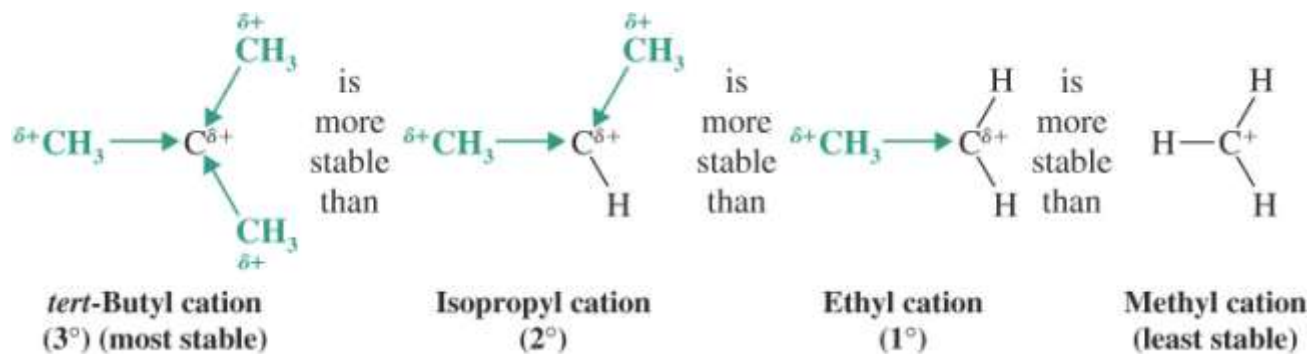
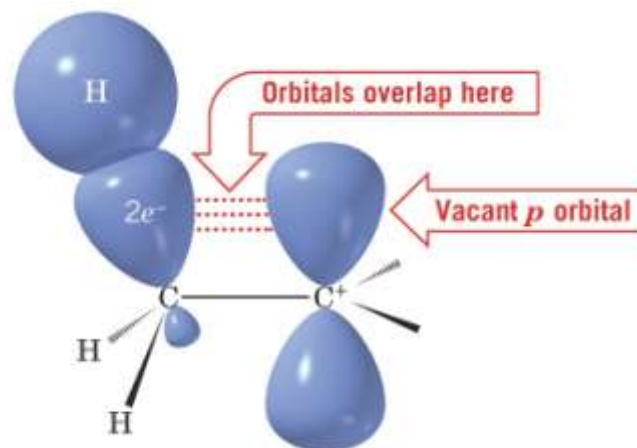
- A carbocation has only 6 electrons, is  $sp^2$  hybridized and has an empty  $p$  orbital



- The more highly substituted a carbocation is, the more stable it is
  - The more stable a carbocation is, the easier it is to form

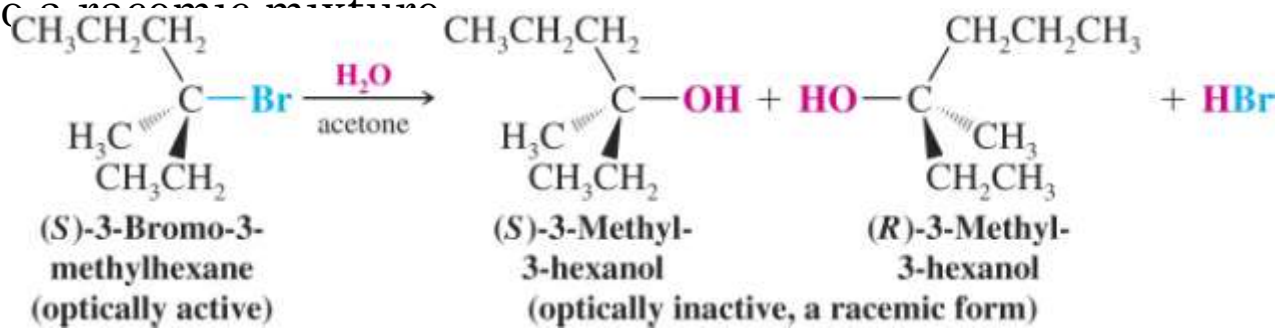


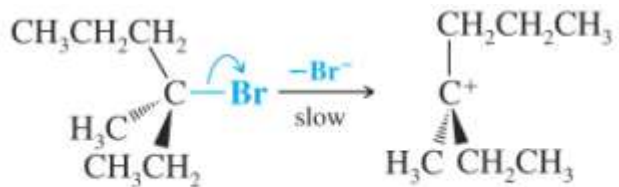
- Hyperconjugation stabilizes the carbocation by donation of electrons from an adjacent carbon-hydrogen or carbon-carbon  $\sigma$  bond into the empty  $p$  orbital
  - More substitution provides more opportunity for hyperconjugation



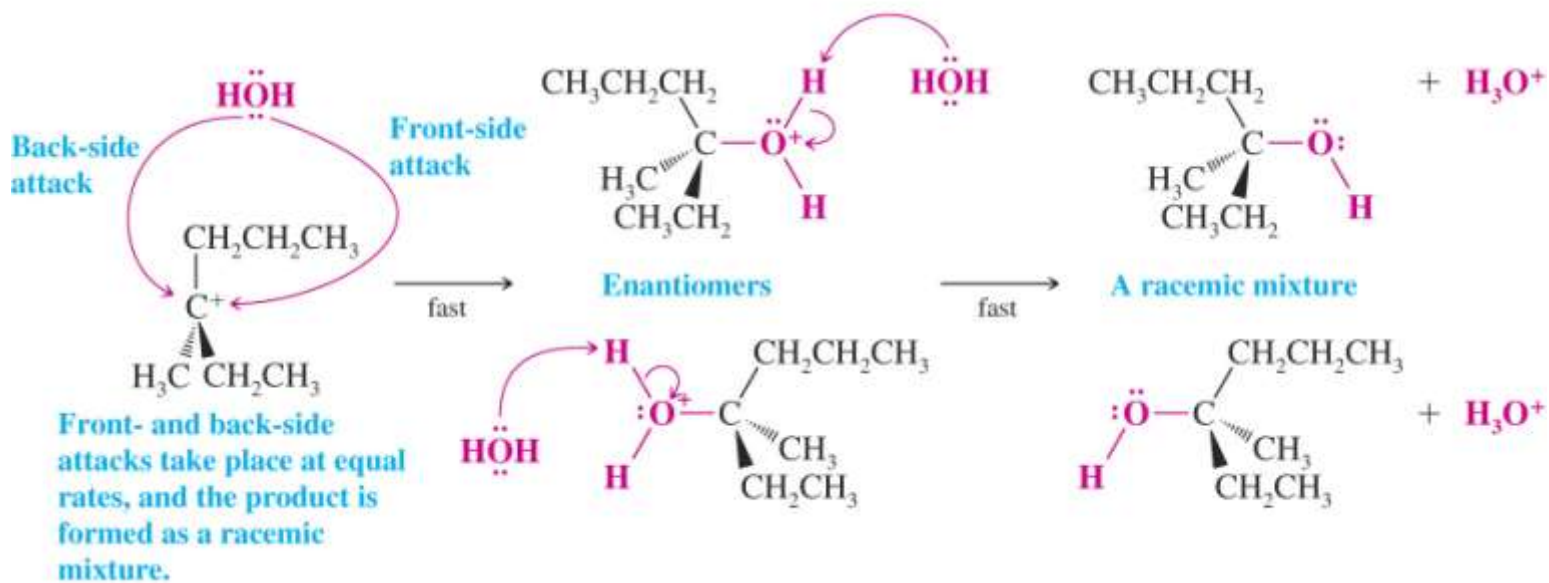
## ○ The Stereochemistry of S<sub>N</sub>1 Reactions

- When the leaving group leaves from a stereogenic center of an optically active compound in an S<sub>N</sub>1 reaction, racemization will occur
  - This is because an achiral carbocation intermediate is formed
- Racemization: transformation of an optically active compound to a racemic mixture



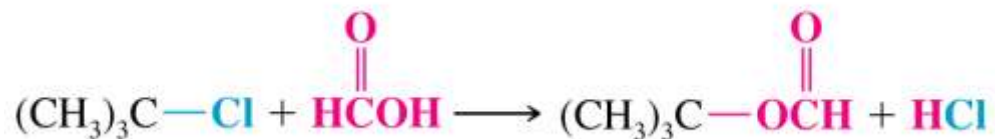


The carbocation has a trigonal planar structure and is achiral.



## ○ Solvolysis

- A molecule of the solvent is the nucleophile in a substitution reaction
  - If the solvent is water the reaction is a hydrolysis



# Factors Affecting the Rate of $S_N1$ and $S_N2$ Reactions

- The Effects of the Structure of the Substrate

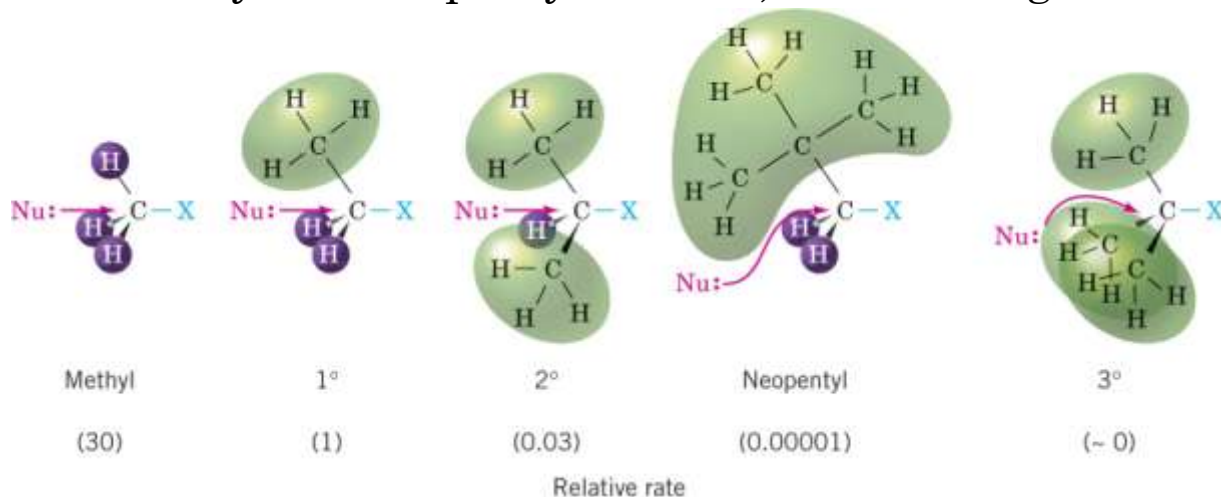
- $S_N2$  Reactions

- In  $S_N2$  reactions alkyl halides show the following general order of reactivity

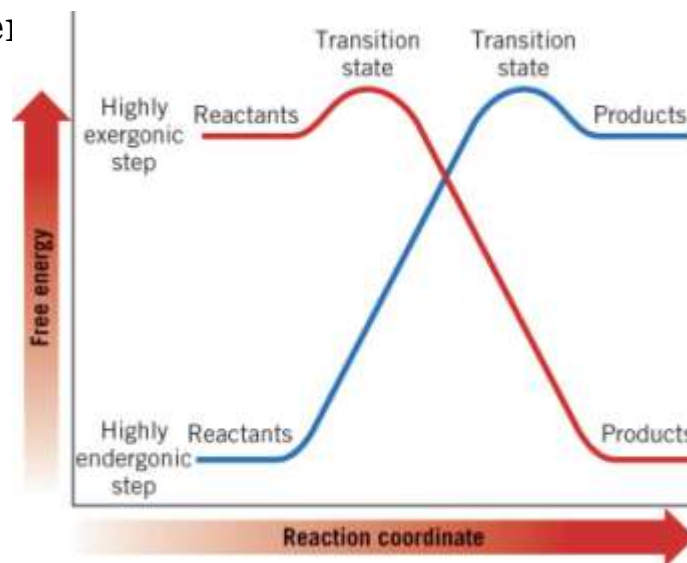
Methyl > primary > secondary >> (tertiary – unreactive)

- Steric hinderance: the spatial arrangement of the atoms or groups at or near a reacting site hinders or retards a reaction

- In tertiary and neopentyl halides, the reacting carbon is too



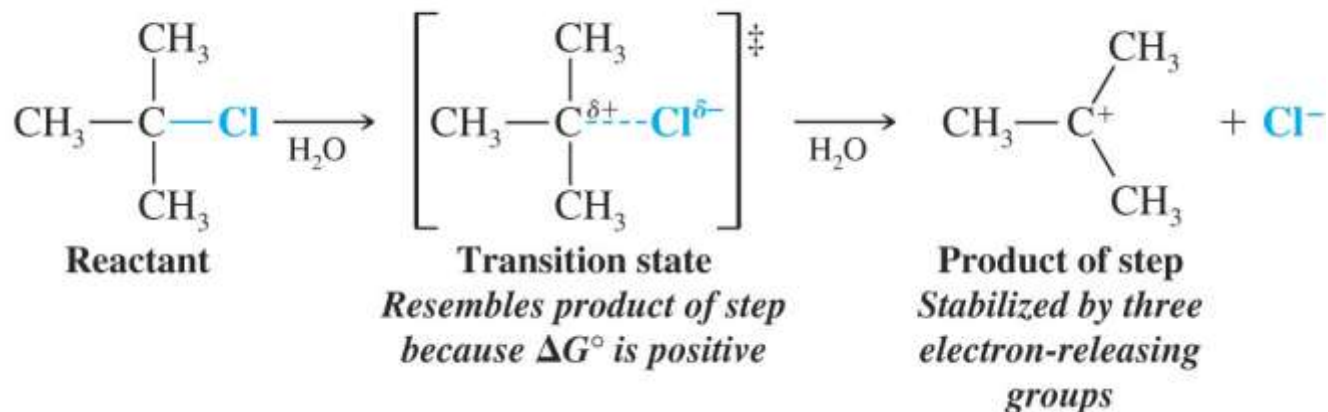
- $S_N1$  reactions
  - Generally only tertiary halides undergo  $S_N1$  reactions because only they can form relatively stabilized carbocations
- *The Hammond-Leffler Postulate*
  - The transition state for an exergonic reaction looks very much like starting material
  - The transition state for an endergonic reaction looks very much like product
  - Generally the transition state looks most like the species it is closest to in energy



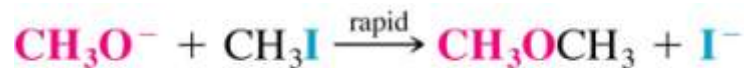


- In the first step of the S<sub>N</sub>1 reaction the transition state looks very much like carbocation
- The carbocation-like transition state is stabilized by all the factors that stabilize carbocations
- The transition state leading to tertiary carbocations is much more stable and lower in energy than transition states leading to other carbocations

*Ionization of the Leaving Group*



- The Effects of the Concentration and Strength of Nucleophile
- $S_N1$  Reaction
  - Rate does not depend on the identity or concentration of nucleophile
- $S_N2$  Reaction
  - Rate is directly proportional to the concentration of nucleophile
  - Stronger nucleophiles also react faster
    - A negatively charged nucleophile is always more reactive than its  $\text{RO}^- > \text{HO}^- \gg \text{RCO}_2^- > \text{ROH} > \text{H}_2\text{O}$
    - When comparing nucleophiles with the same nucleophilic atom, nucleophilicities parallel basicities



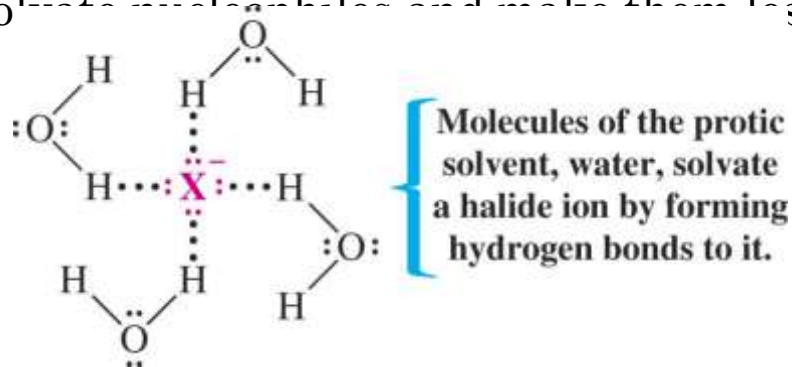
- Methoxide  $\text{CH}_3\text{OH} + \text{CH}_3\text{I} \xrightarrow{\text{very slow}} \text{CH}_3\overset{+}{\text{O}}\text{CH}_3 + \text{I}^-$  methanol

- Solvent Effects on S<sub>N</sub>2 Reactions: Polar Protic and Aprotic Solvents

- Polar Protic Solvents

- Polar solvents have a hydrogen atom attached to strongly electronegative atoms

- They solvate nucleophiles and make them less reactive



- Larger nucleophilic atoms are less solvated and therefore more reactive in polar protic solvents

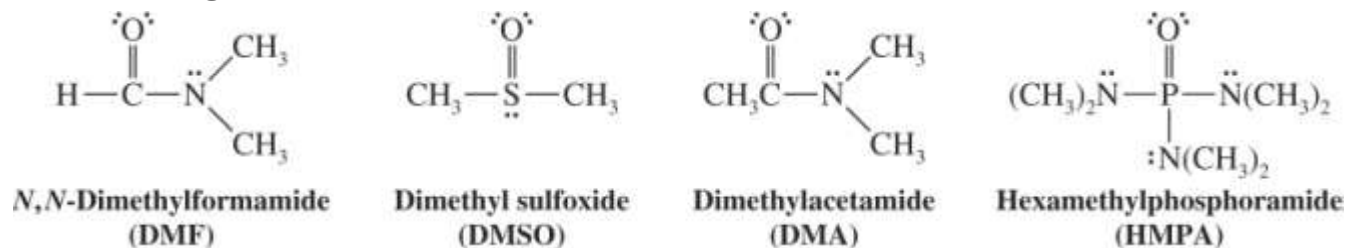


- Larger nucleophiles are also more polarizable and can donate more electron density

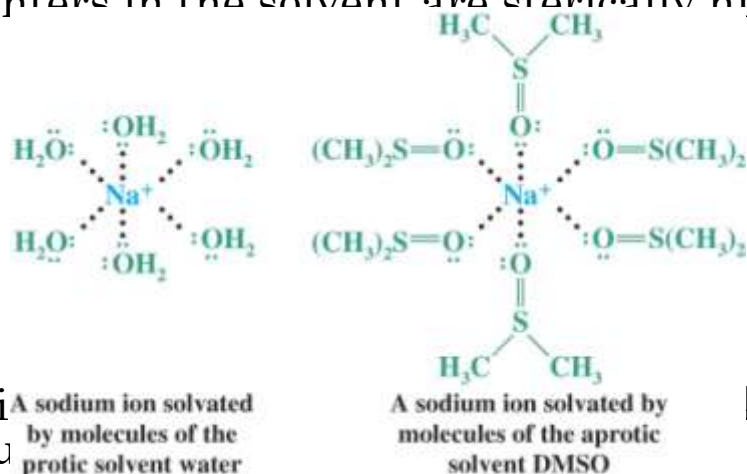


- Polar Aprotic Solvents

- Polar aprotic solvents do not have a hydrogen attached to an electronegative atom



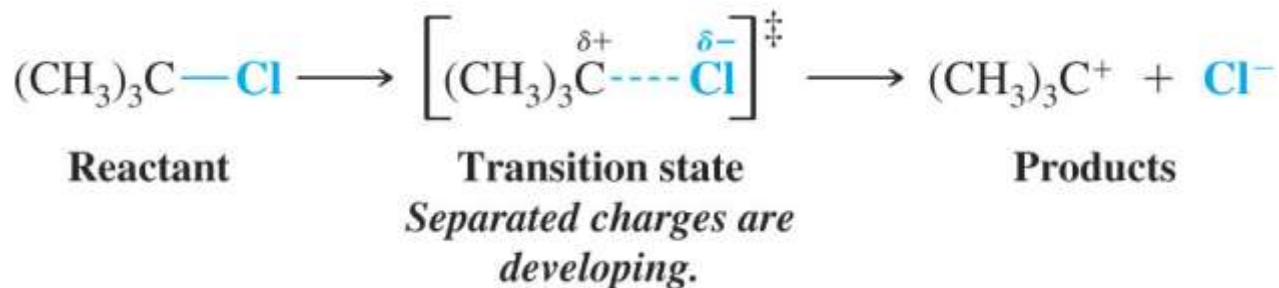
- They solvate cations well but leave anions unsolvated because positive centers in the solvent are sterically hindered



- Polar protic solvents are "hindered" and very reactive nucleophiles
- Trends for nucleophilicity are the same as for basicity
- They are excellent solvents for S<sub>N</sub>2 reactions



- Solvent Effects on S<sub>N</sub>1 Reactions: The Ionizing Ability of the Solvent
  - Polar protic solvents are excellent solvents for S<sub>N</sub>1 reactions
  - Polar protic solvents stabilize the carbocation-like transition state leading to the carbocation thus lowering ΔG<sup>‡</sup>
  - Water-ethanol and water-methanol mixtures are most common



- The Nature of the Leaving Group

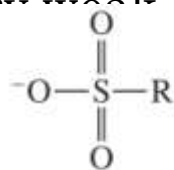
- The best leaving groups are weak bases which are relatively stable

- The leaving group can be an anion or a neutral molecule

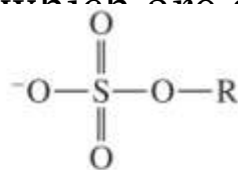
- Leaving group  $I^- > Br^- > Cl^- \gg F^-$

- This trend is opposite to basicity:  $F^- \gg Cl^- > Br^- > I^-$

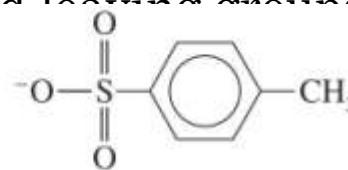
- Other very weak bases which are good leaving groups:



An alkanesulfonate ion

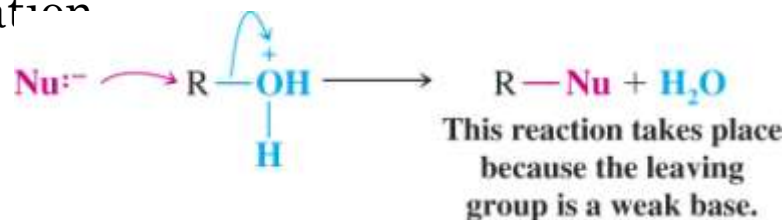
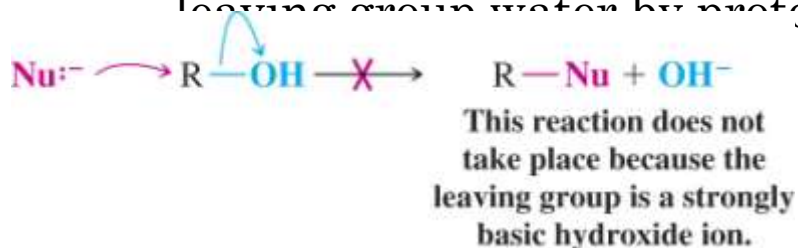


An alkyl sulfate ion



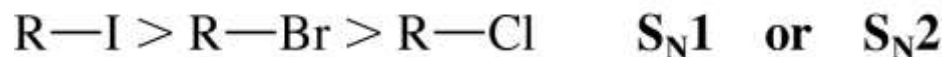
*p*-Toluenesulfonate ion

- The poor leaving group hydroxide can be changed into the good leaving group water by protonation



- Summary  $S_N1$  vs.  $S_N2$

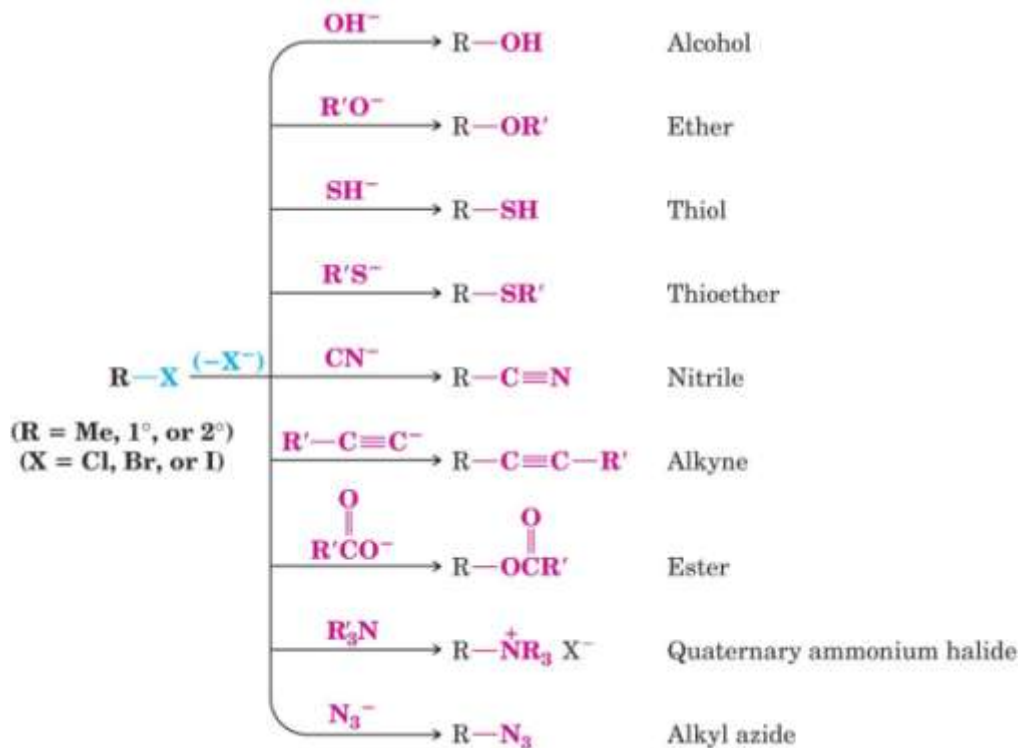
- In both types of reaction alkyl iodides react the fastest because of superior leaving group ability



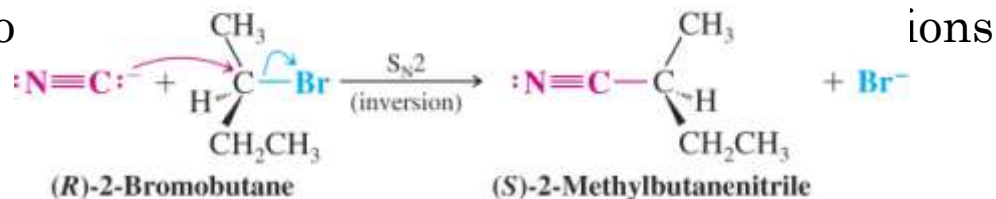
Factor	$S_N1$	$S_N2$
Substrate	3° (requires formation of a relatively stable carbocation)	Methyl > 1° > 2° (requires unhindered substrate)
Nucleophile	Weak Lewis base, neutral molecule, nucleophile may be the solvent (solvolysis)	Strong Lewis base, rate favored by high concentration of nucleophile
Solvent	Polar protic (e.g., alcohols, water)	Polar aprotic (e.g., DMF, DMSO)
Leaving group	I > Br > Cl > F for both $S_N1$ and $S_N2$ (the weaker the base after the group departs, the better the leaving group)	



# Organic Synthesis: Functional Group Transformations Using S<sub>N</sub>2 Reactions



## Stereo





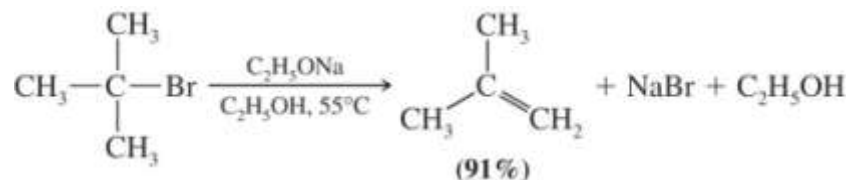
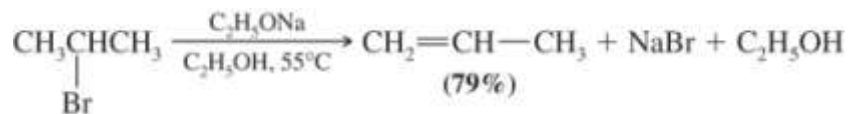
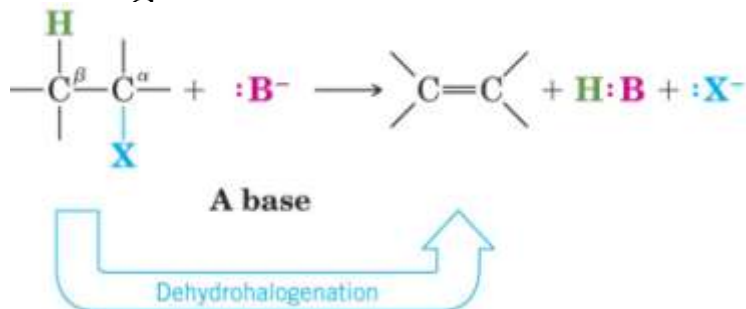
# Elimination Reactions of Alkyl Halides

- Dehydrohalogenation

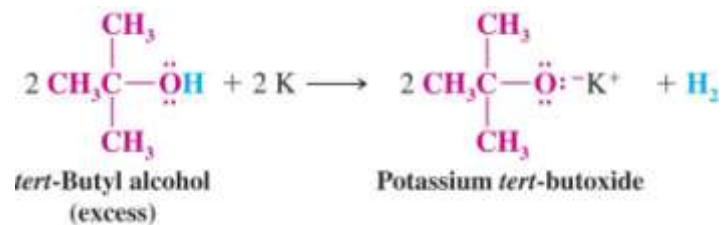
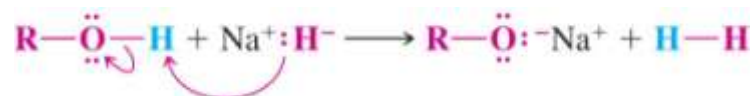
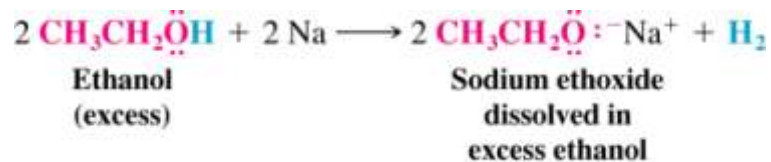
- Used for the synthesis of alkenes

- Elimination competes with substitution reaction

- Strong bases such as alkoxides favor elimination



- The alkoxide bases are made from the corresponding alcohols



## ○ The E2 Reaction

- E2 reaction involves concerted removal of the proton, formation of the double bond, and departure of the leaving group

- Both alkyl halide and base concentrations affect rate and therefore the  

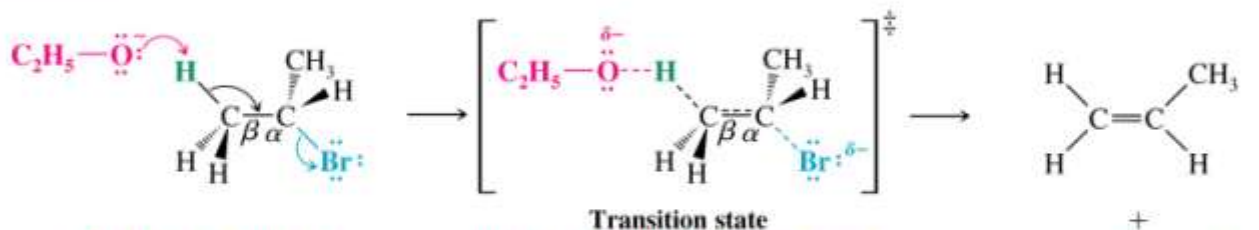
$$\text{Rate} \propto [\text{CH}_3\text{CHBrCH}_3][\text{C}_2\text{H}_5\text{O}^-]$$

$$\text{Rate} = k[\text{CH}_3\text{CHBrCH}_3][\text{C}_2\text{H}_5\text{O}^-]$$

Reaction:



Mechanism:



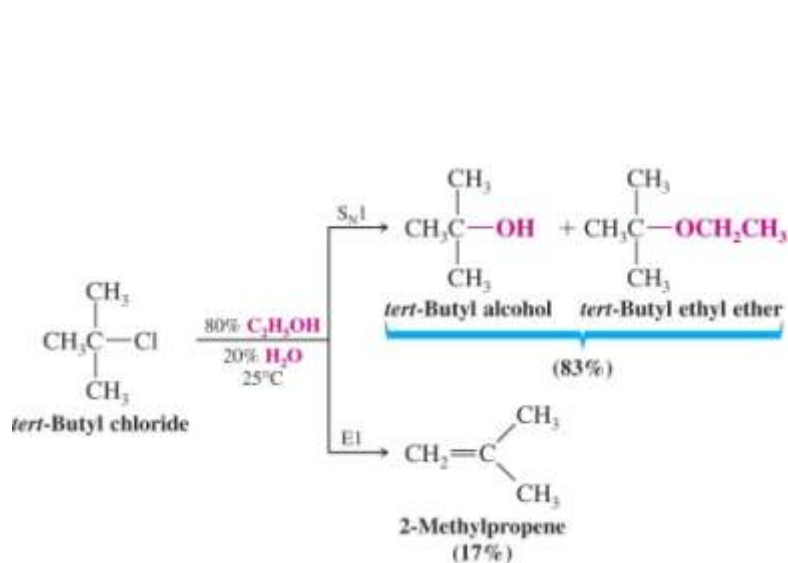
The basic ethoxide ion begins to remove a proton from the β carbon using its electron pair to form a bond to it. At the same time, the electron pair of the β C—H bond begins to move in to become the π bond of a double bond, and the bromine begins to depart with the electrons that bonded it to the α carbon

Partial bonds in the transition state extend from the oxygen atom that is removing the β hydrogen, through the carbon skeleton of the developing double bond, to the departing leaving group. The flow of electron density is from the base toward the leaving group as an electron pair fills the π bonding orbital of the alkene.

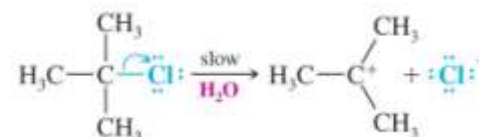
At completion of the reaction, the double bond is fully formed and the alkene has a trigonal planar geometry at each carbon atom. The other products are a molecule of ethanol and a bromide ion.

# ○ The E1 Reaction

- The E1 reaction competes with the S<sub>N</sub>1 reaction and likewise goes through a carbocation intermediate

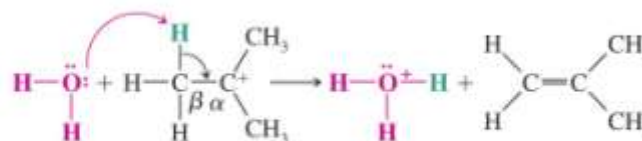


Step 1



Aided by the polar solvent, a chlorine departs with the electron pair that bonded it to the carbon.

This slow step produces the relatively stable 3° carbocation and a chloride ion. The ions are solvated (and stabilized) by surrounding water molecules.



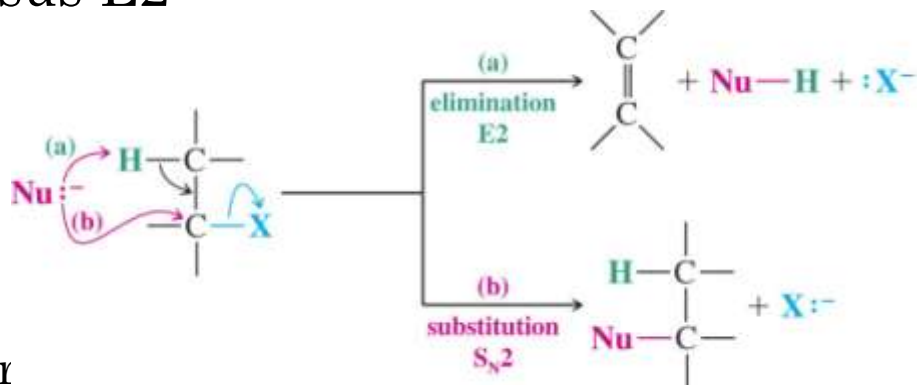
A molecule of water removes one of the hydrogens from the β carbon of the carbocation. These hydrogens are acidic due to the adjacent positive charge. At the same time an electron pair moves in to form a double bond between the α and β carbon atoms.

This step produces the alkene and a hydronium ion.



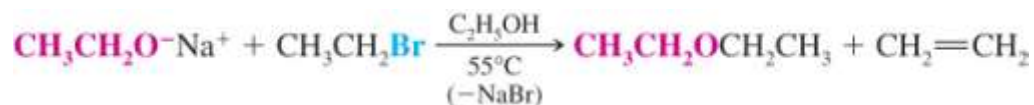
## ○ Substitution versus Elimination

- S<sub>N</sub>2 versus E2



### ○ Primary

- If the base is small, S<sub>N</sub>2 competes strongly because approach at carbon is unhindered

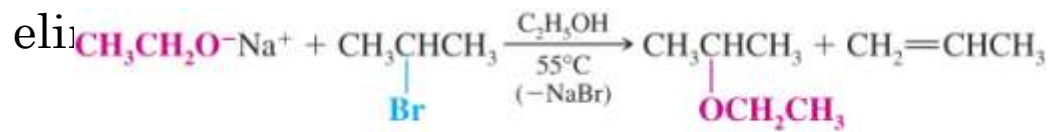


S<sub>N</sub>2  
(90%)

E2  
(10%)

### ○ Secondary substrate

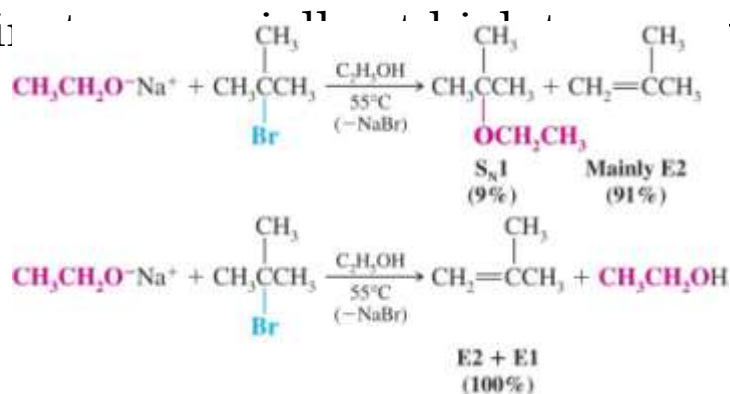
- Approach to carbon is sterically hindered and E2



S<sub>N</sub>2  
(21%)

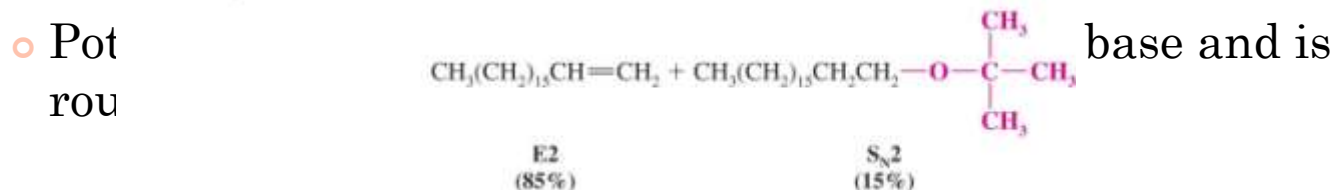
E2  
(79%)

- Tertiary substrate
  - Approach to carbon is extremely hindered and elimination predominates



- Temperature
  - Increasing temperature favors elimination over substitution
- Size of the Base/Nucleophile

- Large sterically hindered bases favor elimination because they are bulky enough to approach the carbon atom only from the backside



## Overall Summary

Factor	S <sub>N</sub> 1	S	N <sub>2</sub>
Substrate	3° (requires formation of a relatively stable carbocation)	Methyl > 1° > 2° (requires unhindered substrate)	
Nucleophile	Weak Lewis base, neutral molecule, nucleophile may be the solvent (solvolysis)	Strong Lewis base, rate favored by high concentration of nucleophile	
Solvent	Polar protic (e.g., alcohols, water)	Polar aprotic (e.g., DMF, DMSO)	
Leaving group	I > Br > Cl > F for both S <sub>N</sub> 1 and S <sub>N</sub> 2 (the weaker the base after the group departs, the better the leaving group)		

