

Chapter 5

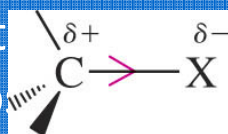
- Nucleophilic aliphatic substitution mechanism

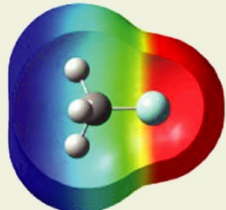
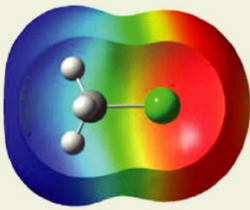
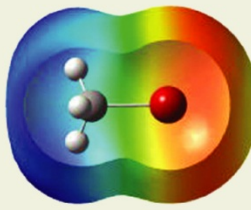
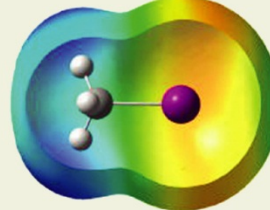
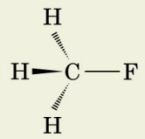
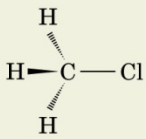
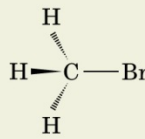
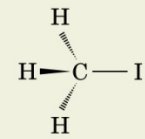
by
G.DEEPA

• Introduction

- The polarity of a carbon-halogen bond leads to the carbon having a partial positive charge

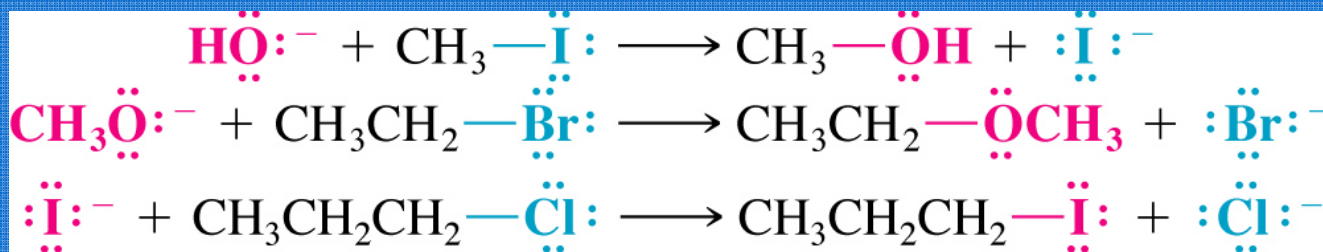
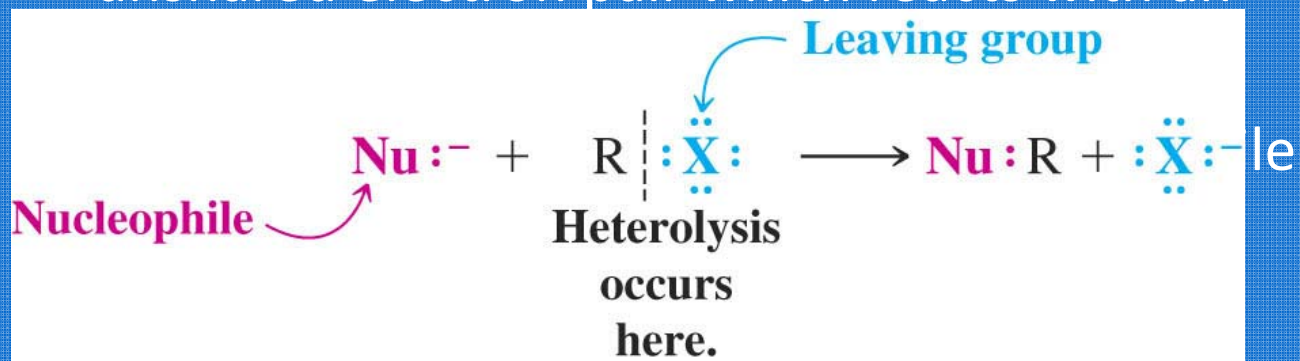
– In alkyl halides the δ^+ on C and δ^- on X causes the carbon to become activated to substitution reactions with nucleophiles



				
				
C—X Bond length (Å)	1.39	1.78	1.93	2.14
C—X Bond strength (kJ mol ⁻¹)	472	350	293	239

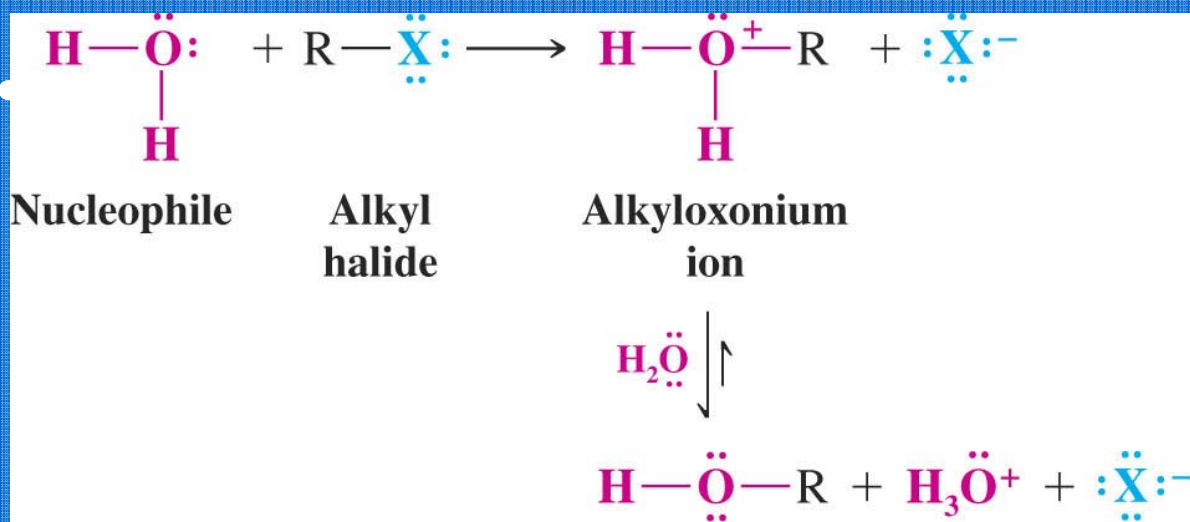
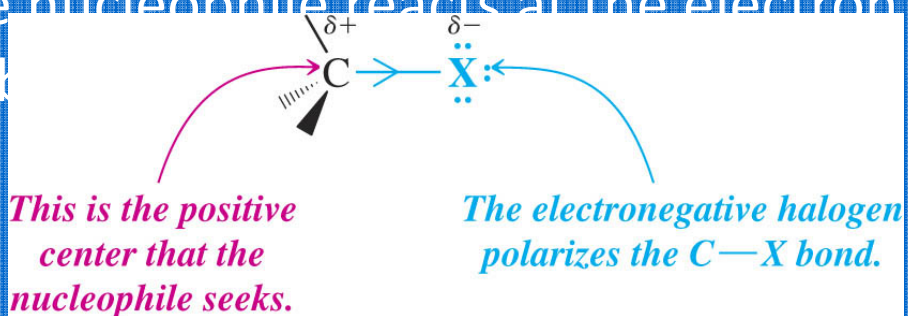
• Nucleophilic Substitution Reactions

- In this reaction a nucleophile is a species with an unshared electron pair which reacts with an



• Nucleophile

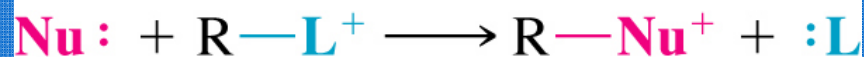
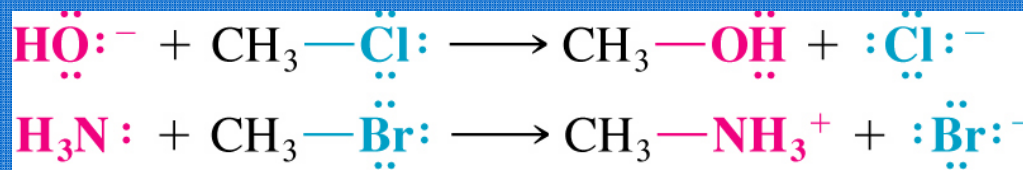
- The nucleophile reacts at the electron deficient carb



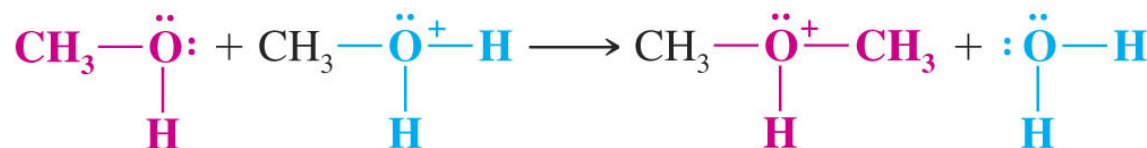
• Leaving Group

- A leaving group is a substituent that can leave as a relatively stable entity

- It can be defined as $\text{Nu}^- + \text{R}-\text{L} \longrightarrow \text{R}-\text{Nu} + \text{:L}^-$ species

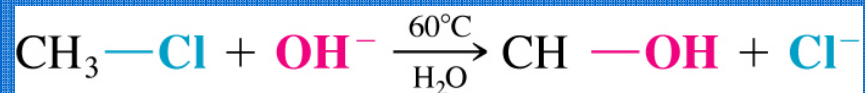


Specific Example



- Kinetics of a Nucleophilic Substitution Reaction: An S_N2 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

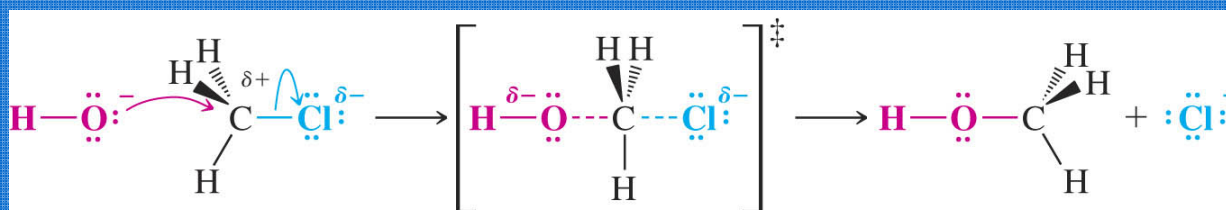
Experiment Number	Initial [CH ₃ Cl]	Initial [OH ⁻]	Initial Rate (mol L ⁻¹ s ⁻¹)
1	0.0010	1.0	4.9 × 10 ⁻⁷
2	0.0020	1.0	9.8 × 10 ⁻⁷
3	0.0010	2.0	9.8 × 10 ⁻⁷
4	0.0020	2.0	19.6 × 10 ⁻⁷

- The rate equation reflects this dependence

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

- S_N2 reaction: substitution, nucleophilic, 2nd order (bimolecular)

- A Mechanism for the S_N2 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.

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.

- It is an unstable entity with a very brief existence (10⁻¹² 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 ΔG° (products favored)



- The reaction of chloromethane with hydroxide is highly exergonic

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

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

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

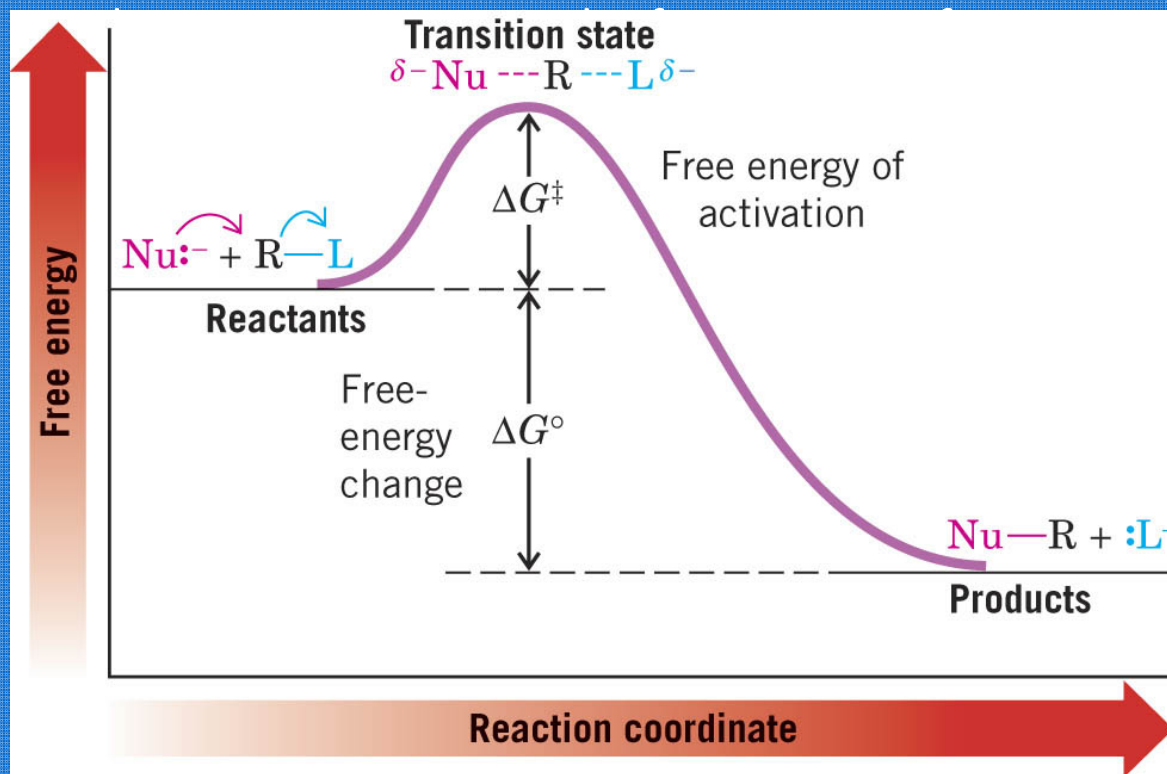
$$\ln K_{\text{eq}} = 36.1$$

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

- The equilibrium

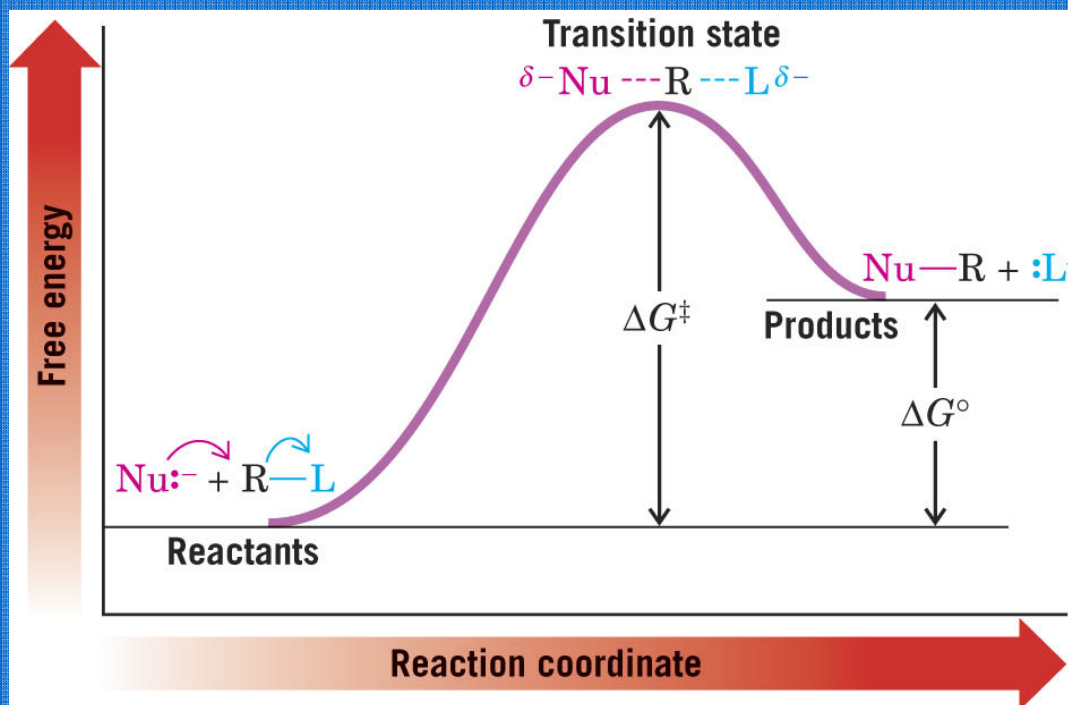
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- An energy diagram of a typical S_N2 reaction
 - An energy barrier is evident because a bond is being broken in going to the transition state (which is the top of the energy barrier)
 - The difference in energy between starting material and



(ΔG^\ddagger)
es and
, ΔG°

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

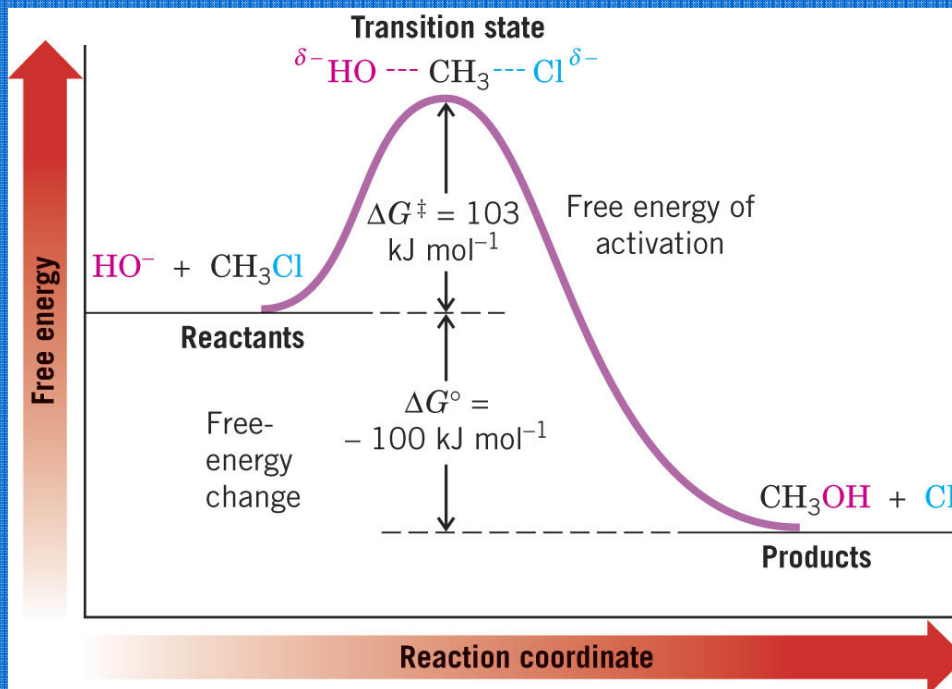


- There is a direct relationship between ΔG^\ddagger and the temperature of a reaction
 - The higher the temperature, the faster the rate

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

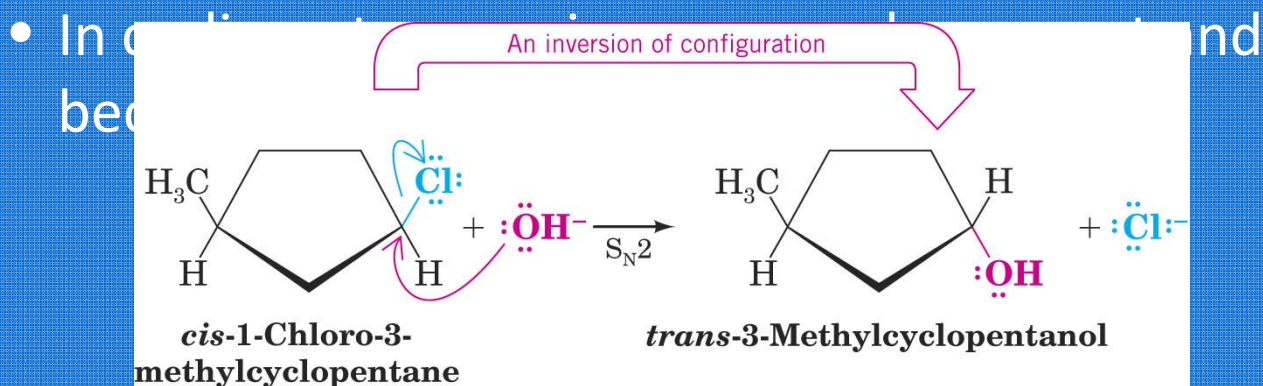
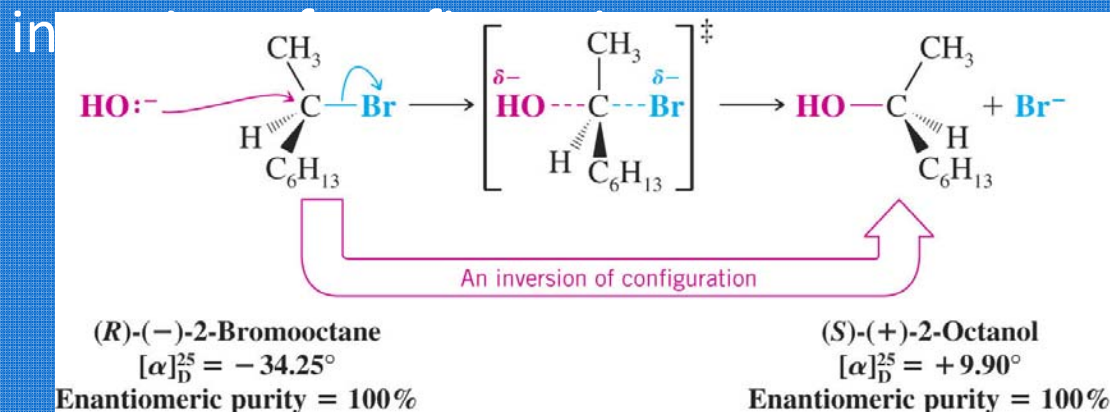
- Near room temperature, a 10°C increase in temperature causes a doubling of rate
- Higher temperatures cause more molecules to collide with enough energy to reach the transition state and react

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



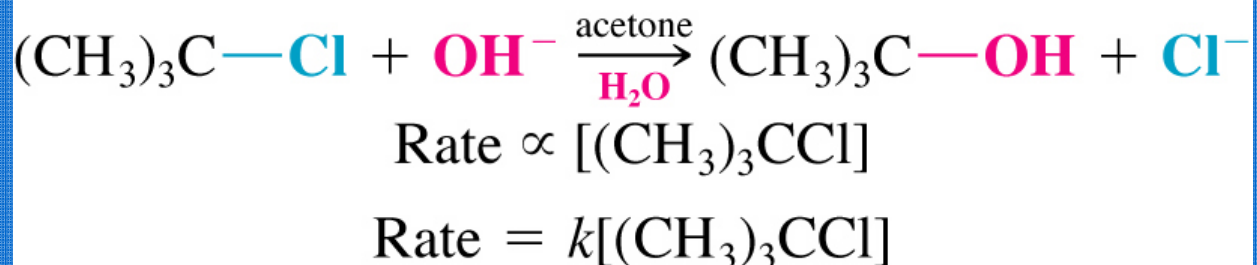
- A reaction with ΔG^\ddagger above 84 kJ mol^{-1} will require heating to proceed at a reasonable rate
- This reaction has $\Delta G^\ddagger = 103 \text{ kJ mol}^{-1}$ so it will require heating

- The Stereochemistry of S_N2 Reactions
 - Backside attack of nucleophile results in an



- The Reaction of *tert*-Butyl Chloride with Hydroxide Ion: An S_N1 Reaction

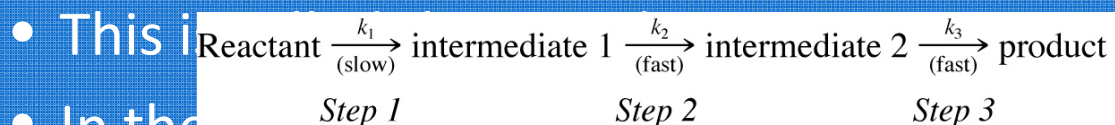
- *tert*-Butyl chloride undergoes substitution with hydroxide
- The rate is independent of hydroxide concentration and depends only on concentration of *tert*-butyl chloride



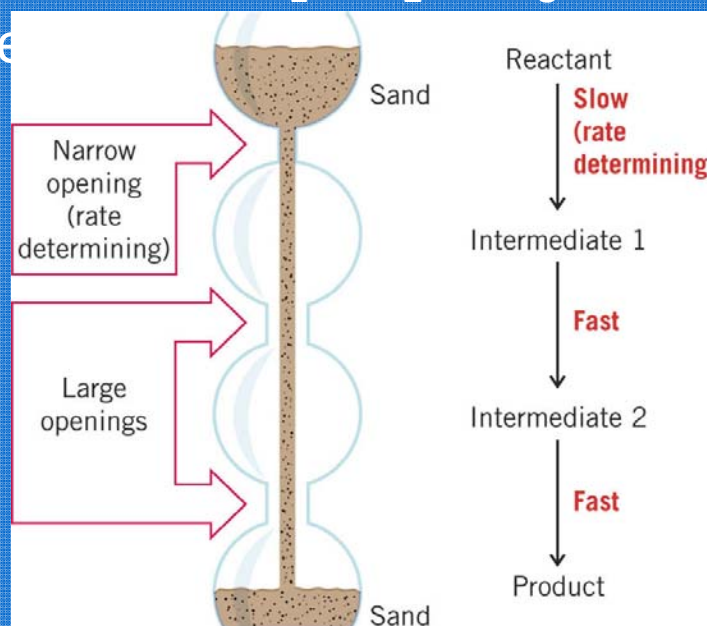
- S_N1 reaction: Substitution, nucleophilic, 1st order (unimolecular)
 - The rate depends only on the concentration of the alkyl halide
 - Only the alkyl halide (and not the nucleophile) is involved in the transition state of the step that controls the rate

Multistep Reactions and the Rate-Determining Step

- In multistep reactions, the rate of the slowest step will be the rate of the entire reaction

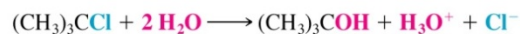


- In the case below $k_1 < k_2$ or k_3 and the first step is rate determining



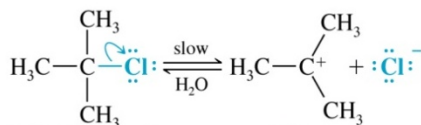
- A Mechanism for the S_N1 Reaction (next slide)
 - Step 1 is rate determining (slow) because it requires the formation of unstable ionic products
 - In step 1 water molecules help stabilize the ionic products

Reaction:



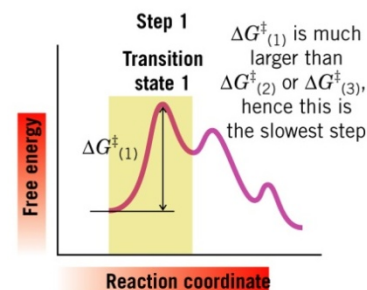
Mechanism:

Step 1

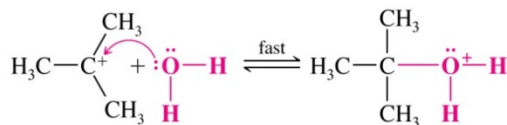


Aided by the polar solvent a chlorine departs with the electron pair that bonded it to the carbon.

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

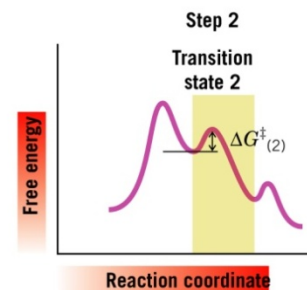


Step 2

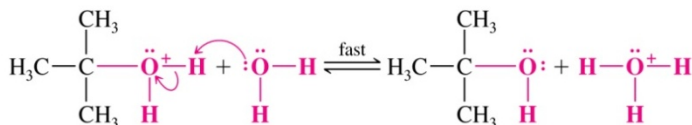


A water molecule acting as a Lewis base donates an electron pair to the carbocation (a Lewis acid). This gives the cationic carbon eight electrons.

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

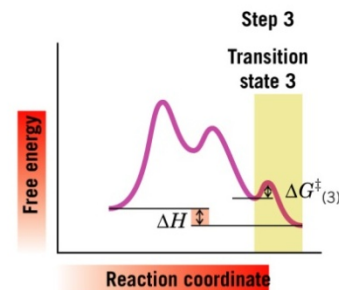


Step 3



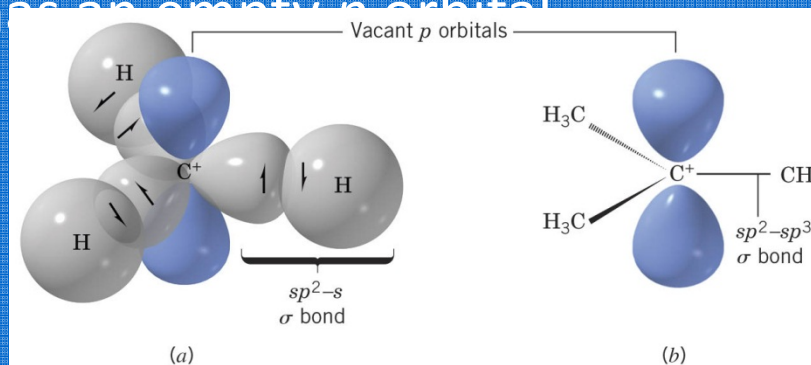
A water molecule acting as a Brønsted base accepts a proton from the *tert*-butyloxonium ion.

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



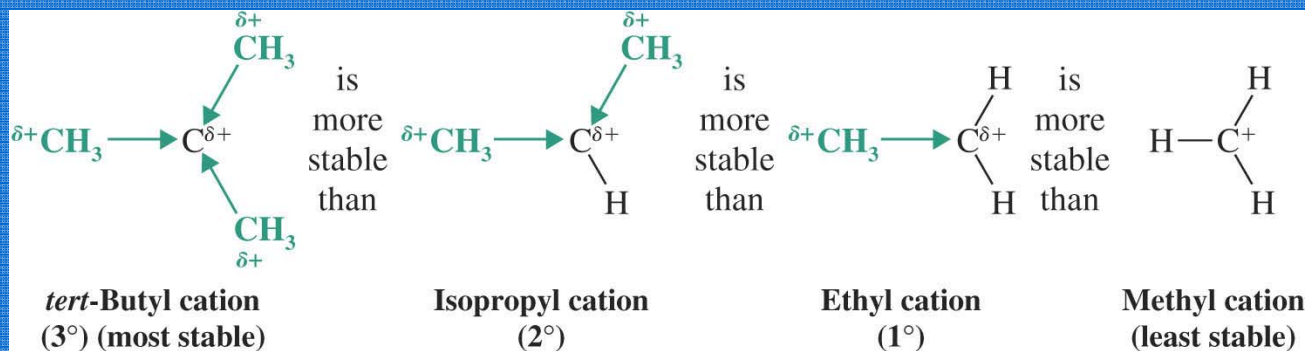
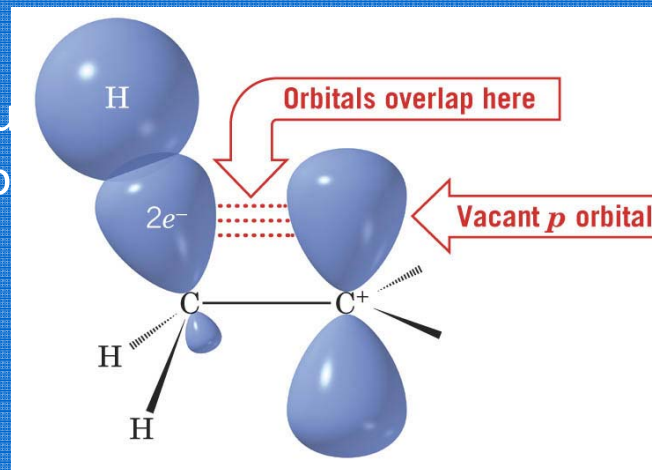
- The more alkyl groups attached to the carbocation is, the more stable it is.
 - The order of stability is:

$\text{R}-\text{C}^+$	$\text{R}-\text{C}^+$	$\text{R}-\text{C}^+$	$\text{H}-\text{C}^+$
/ \	/ \	/ \	/ \
R R	R H	H H	H H
3°	2°	1°	Methyl
(most stable)			(least stable)

- Hyperconjugation stabilizes the carbocation by donation of electrons from an adjacent carbon-hydrogen or carbon-carbon σ bond into the empty p orbital

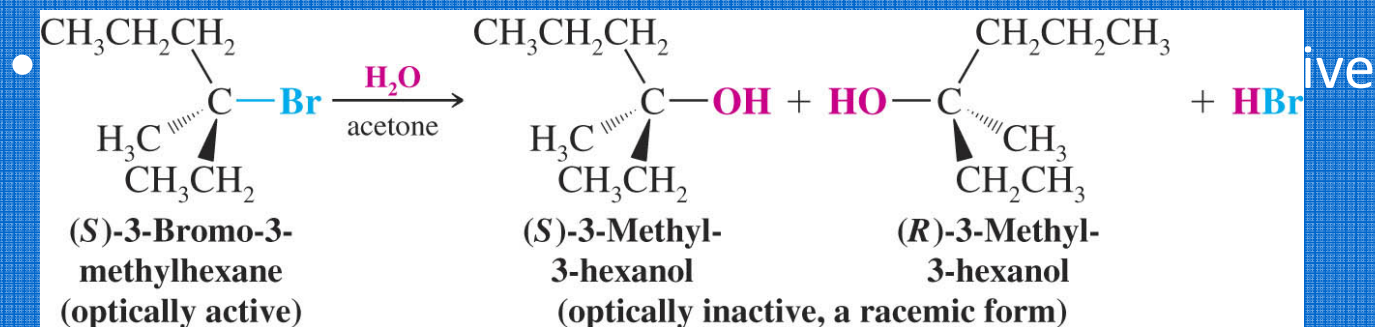
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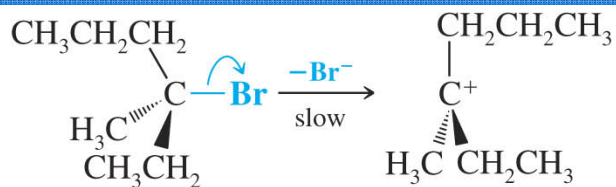
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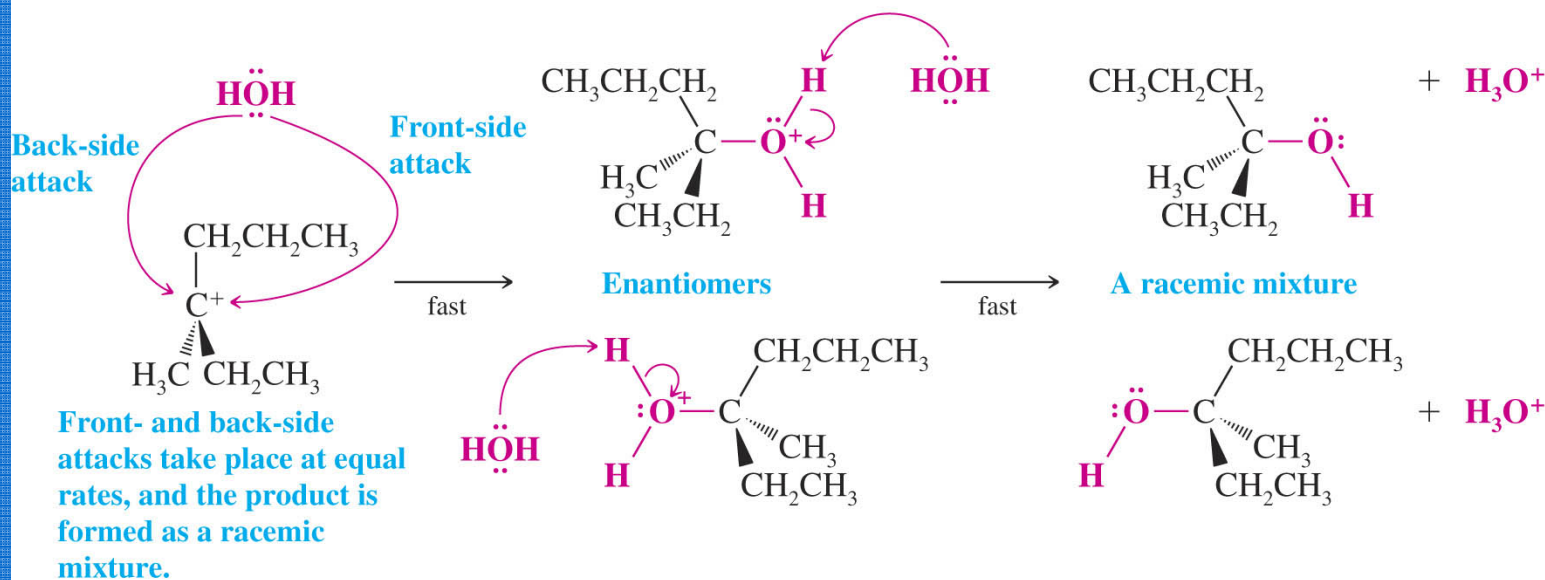
• The Stereochemistry of S_N1 Reactions

- When the leaving group leaves from a stereogenic center of an optically active compound in an S_N1 reaction, racemization will occur
 - This is because an achiral carbocation intermediate is formed





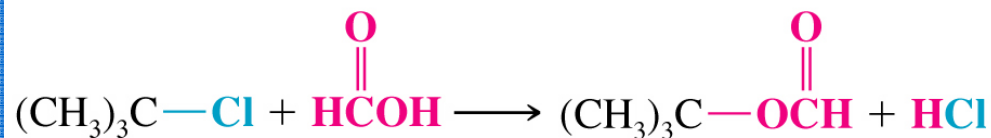
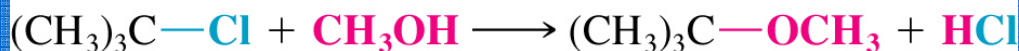
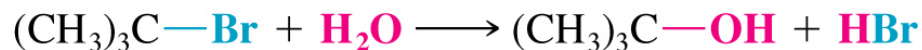
The carbocation has a trigonal planar structure and is achiral.



- Solvolysis

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

– If the solvent is water the reaction is a hydrolysis

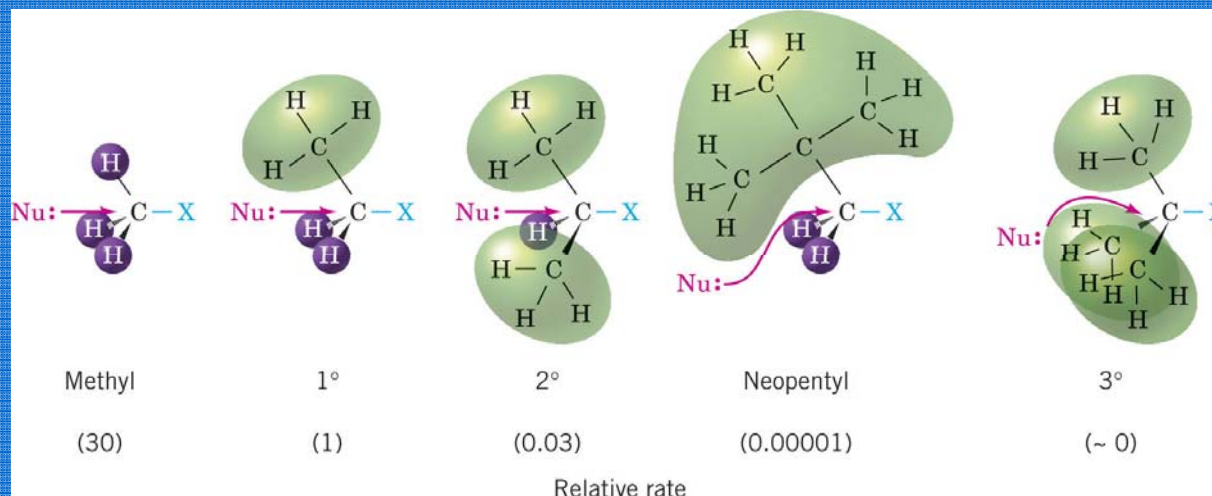


Factors Affecting the Rate of S_N1 and S_N2 Reactions

– The Effects of the Structure of the Substrate

– S_N2 Reactions

- **Methyl > primary > secondary >> (tertiary – unreactive)**
- In S_N2 reactions alkyl halides show the following general order of reactivity



– S_N1 reactions

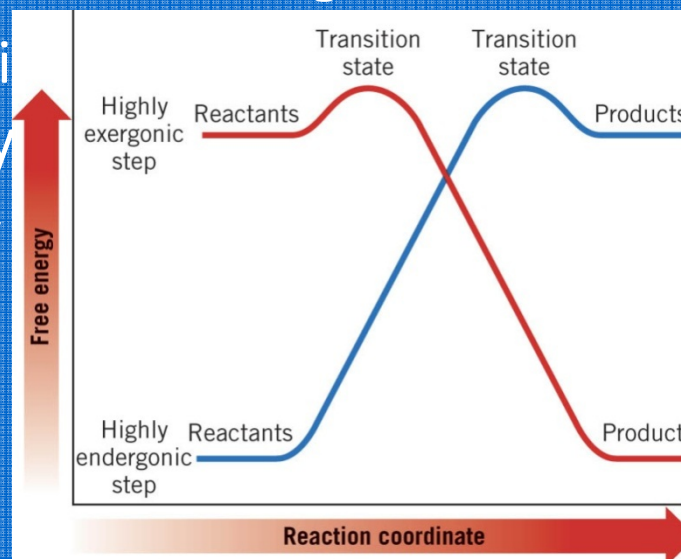
- Generally only tertiary halides undergo S_N1 reactions because only they can form relatively stabilized carbocations

– *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 the products

- Generally, the more exergonic a reaction is, the more reactant-like the transition state is

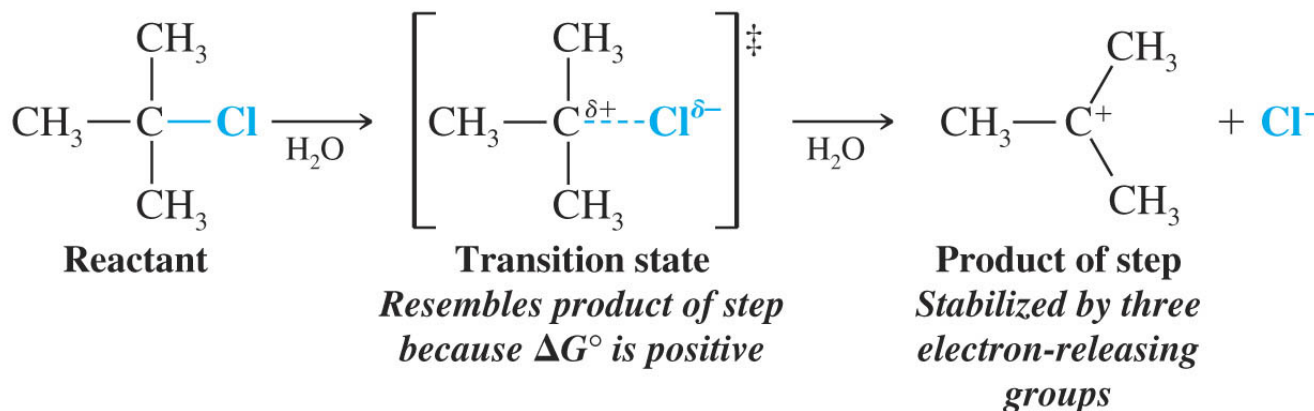


ic reaction

most like the

- In the first step of the S_N1 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

Ionization of the Leaving Group



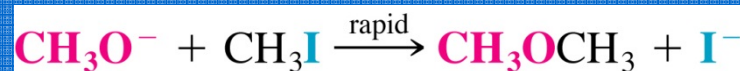
– The Effects of the Concentration and Strength of Nucleophile

– S_N1 Reaction

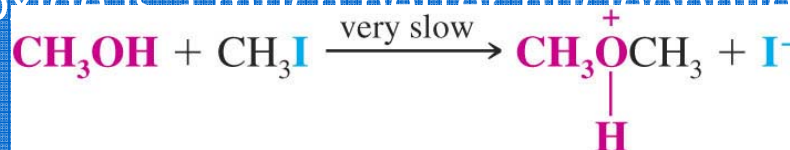
- Rate does not depend on the identity or concentration of nucleophile

– 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 neutral conjugate acid
 - When comparing nucleophiles with the same nucleophilic atom, nucleophilicities parallel basicities



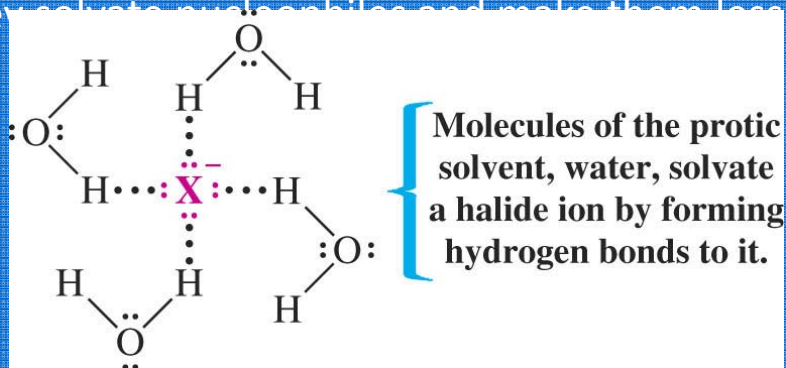
- Methoxide is a much better nucleophile than methanol



– Solvent Effects on S_N2 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

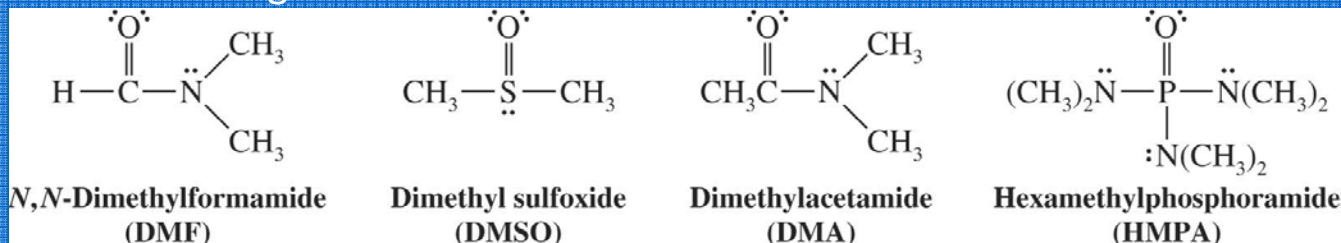


- Larger nucleophiles are also more polarizable and can donate more electron density
- Relative nucleophilicity in polar solvents:

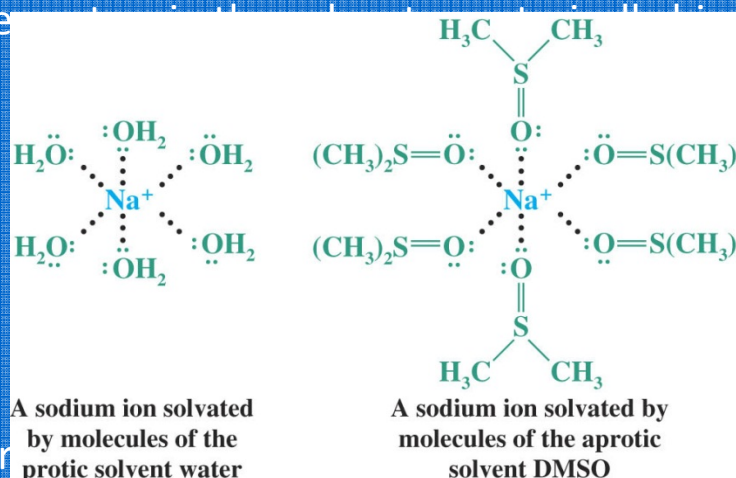


- Polar Aprotic Solvents

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



- They solvate cations well but leave anions unsolvated because positive

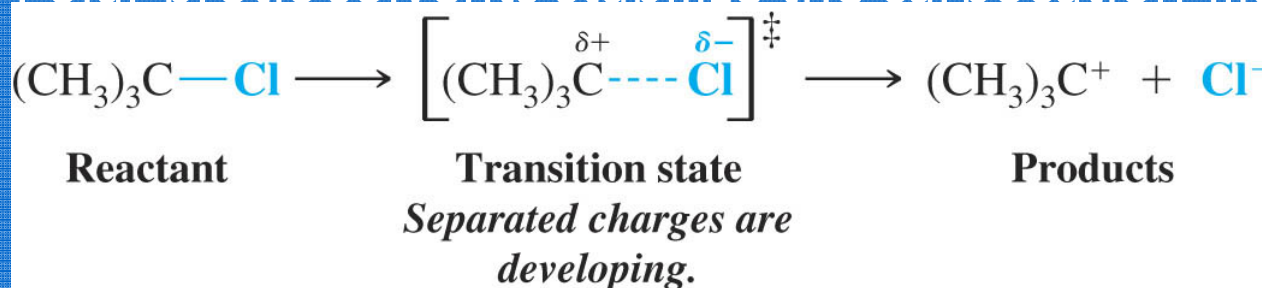


- Polar protic solvents are “hydrogen bonded” and very reactive nucleophiles
- Trends for nucleophilicity are the same as for basicity
- They are excellent solvents for S_N2 reactions



– Solvent Effects on S_N1 Reactions: The Ionizing Ability of the Solvent

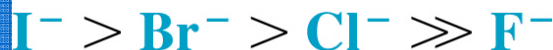
- Polar protic solvents are excellent solvents for S_N1 reactions
- Polar protic solvents stabilize the carbocation-like



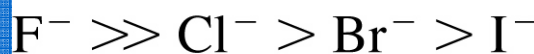
- most common

– 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

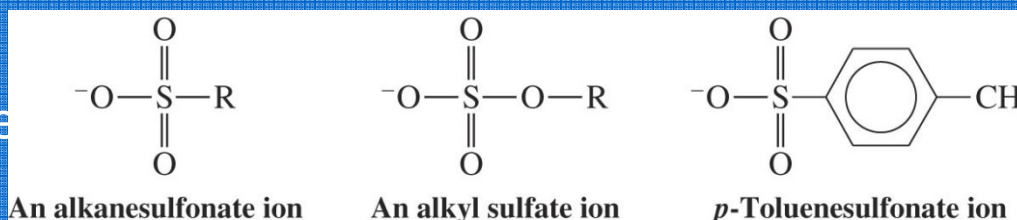


- Leaving group ability of halides:

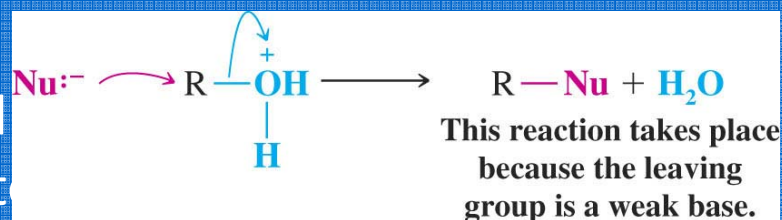
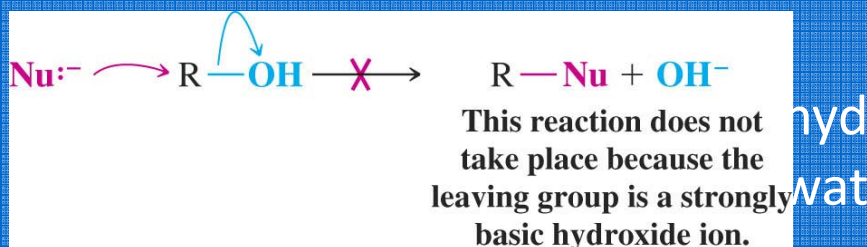


- This trend is opposite to basicity:

- Other



groups:

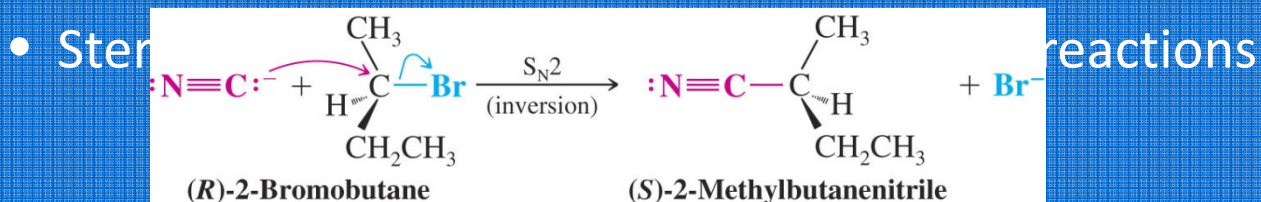
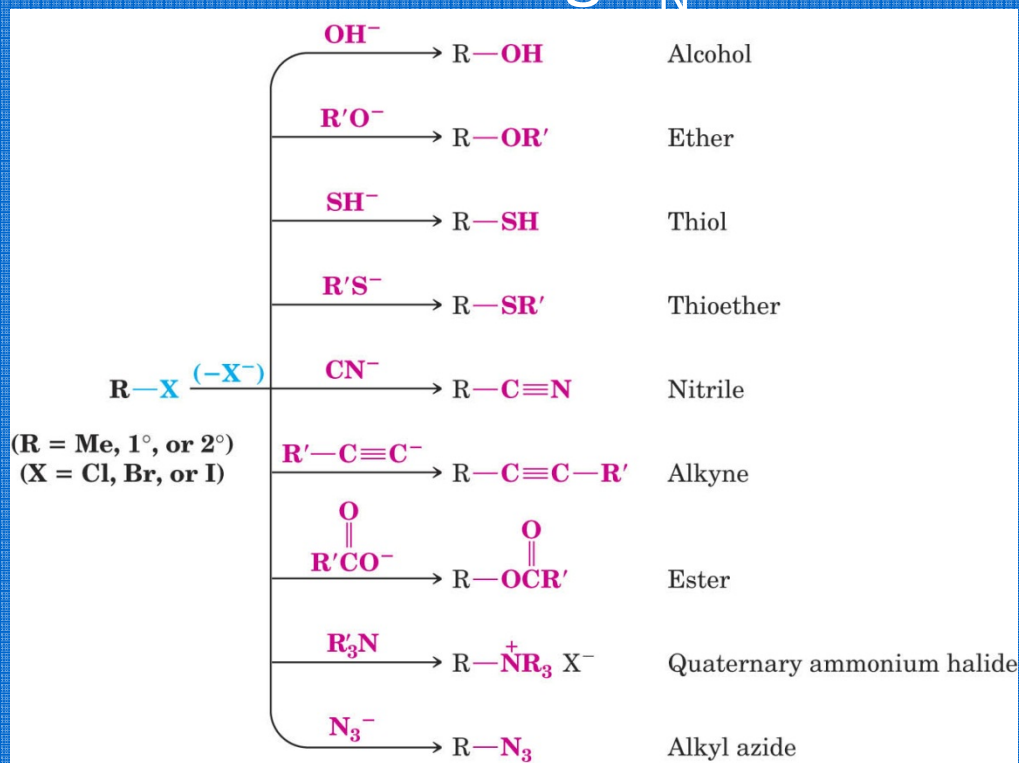


– Summary S_N1 vs. S_N2

- In both types of reaction alkyl iodides react the fastest because of superior leaving group ability
 $R-I > R-Br > R-Cl$ S_N1 or S_N2

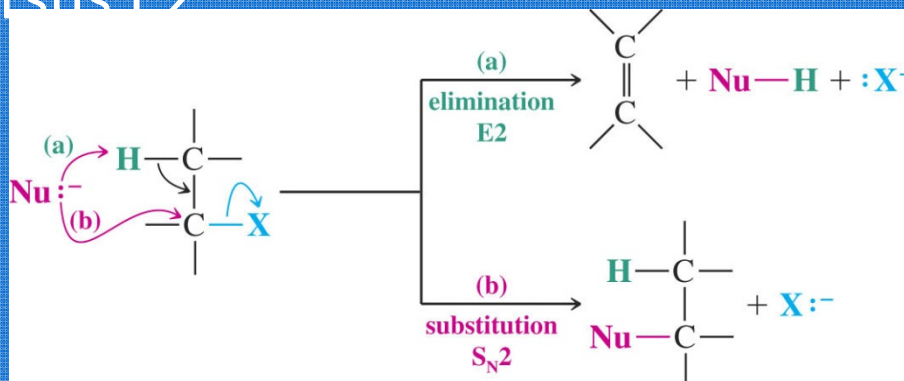
Factor	S_N1	S_N2
Substrate	3° (requires formation of a relatively stable carbocation)	Methyl $>$ 1° $>$ 2° (requires unhindered substrate)
Nucleophile	Weak Lewis base, neutral molecule, nucleophile may be the solvent (solvolysis)	Strong Lewis base, rate favored by high concentration of nucleophile
Solvent	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_N2 Reactions



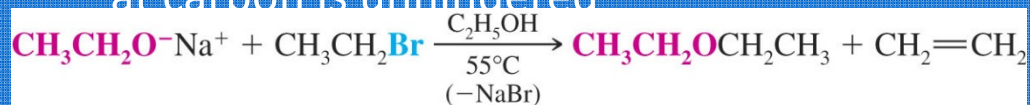
• Substitution versus Elimination

– S_N2 versus E2



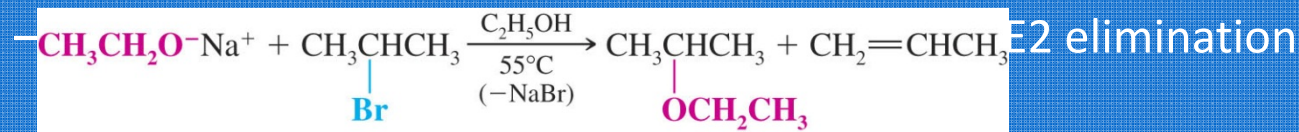
• Primary substrate

- If the base is small, S_N2 competes strongly because approach at carbon is unhindered



S _N 2	E2
(90%)	(10%)

• Secondary substrate



S _N 2	E2
(21%)	(79%)

- Overall Summary

Factor	S _N 1	S	N ₂
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 _N 1 and S _N 2 (the weaker the base after the group departs, the better the leaving group)		

THANK YOU