Chapter 6
Ionic Reactions-Nucleophilic Substitution and Elimination Reactions of Alkyl Halides
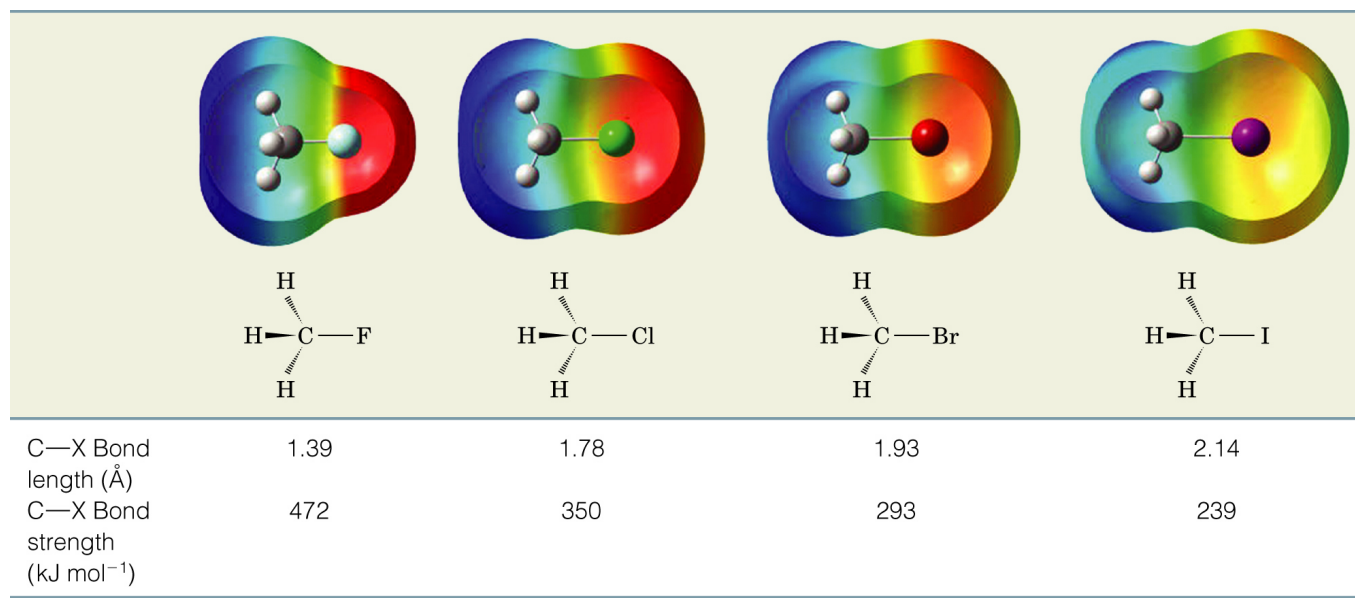
♦ Introduction

➡ 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 going from fluorine to iodine
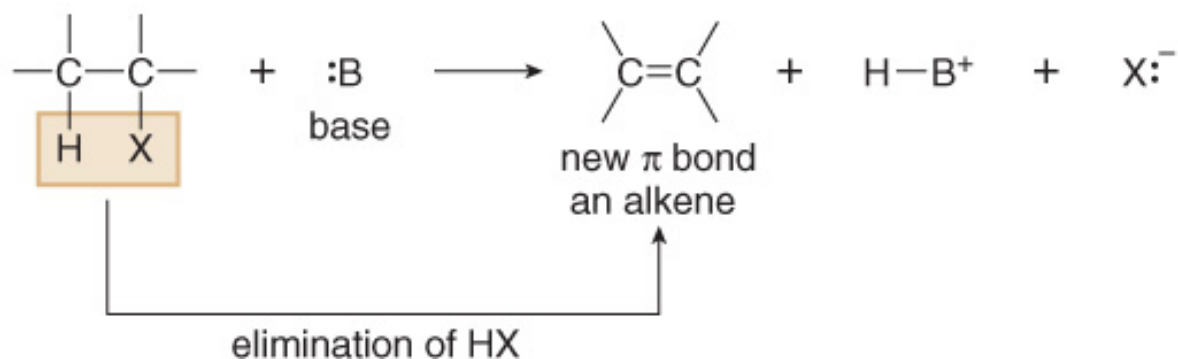

	H	H	H	H
	H—C—F	H—C—Cl	H—C—Br	H—C—I
	H	H	H	H
C—X Bond length (Å)	1.39	1.78	1.93	2.14
C—X Bond strength (kJ mol^{-1})	472	350	293	239

Alkyl Halides and Nucleophilic Substitution

The Polar Carbon-Halogen Bond

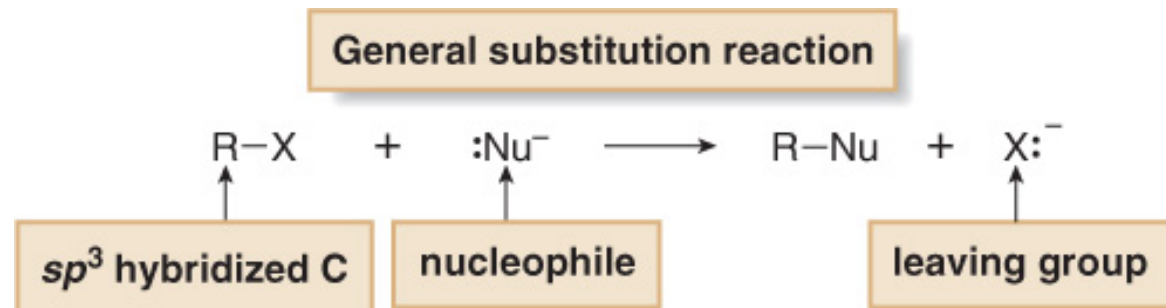◆ Alkyl halides undergo substitution reactions with nucleophiles.

$$R-X \ + \ :Nu^- \ \longrightarrow \ R-Nu \ + \ X:^-$$

nucleophile

substitution of X by Nu
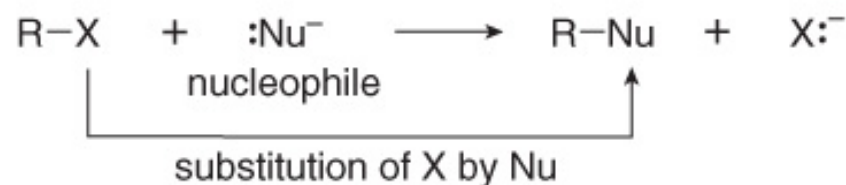
◆ Alkyl halides undergo elimination reactions with Brønsted–Lowry bases.

$$-\underset{H}{\overset{|}{C}}-\underset{X}{\overset{|}{C}}- \ + \ :B \ \longrightarrow \ \overset{\backslash}{\underset{/}{C}}=\overset{/}{\underset{\backslash}{C}} \ + \ H-B^+ \ + \ X:^-$$

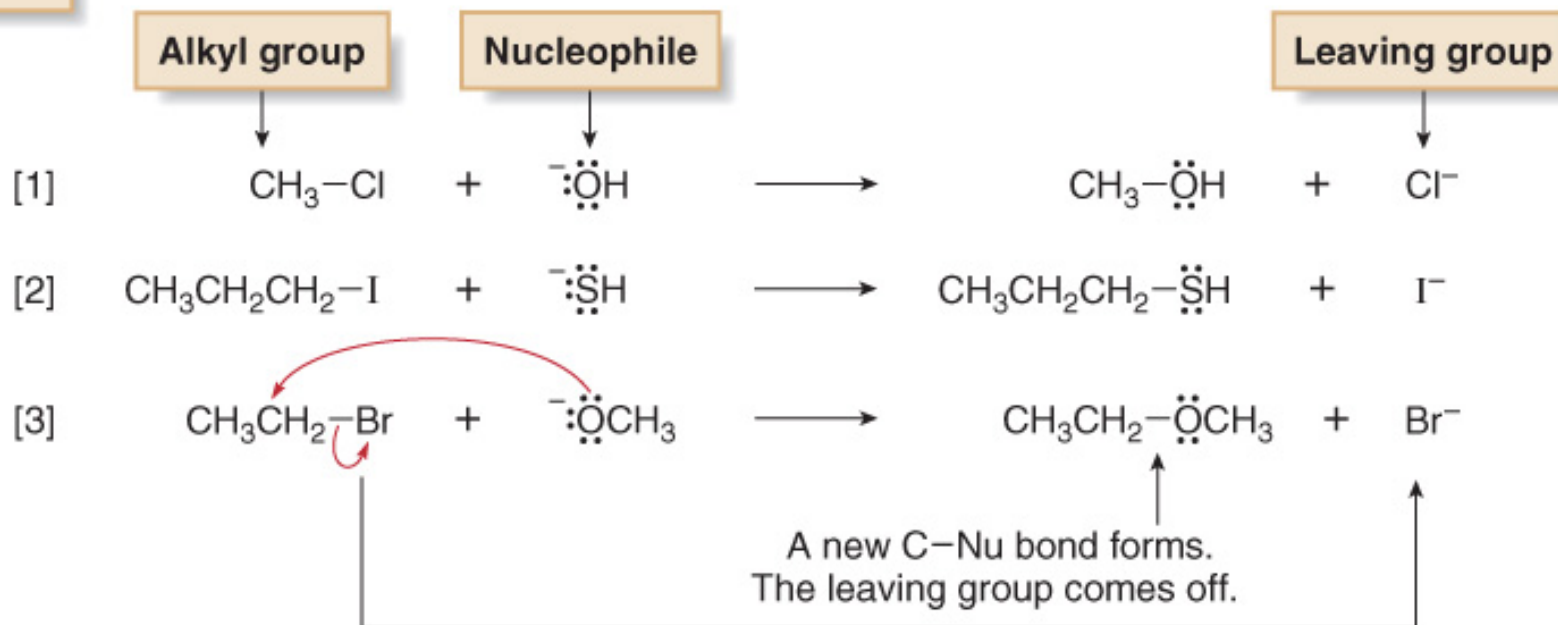base   new π bond   an alkene

elimination of HX

Alkyl Halides and Nucleophilic Substitution

General Features of Nucleophilic Substitution

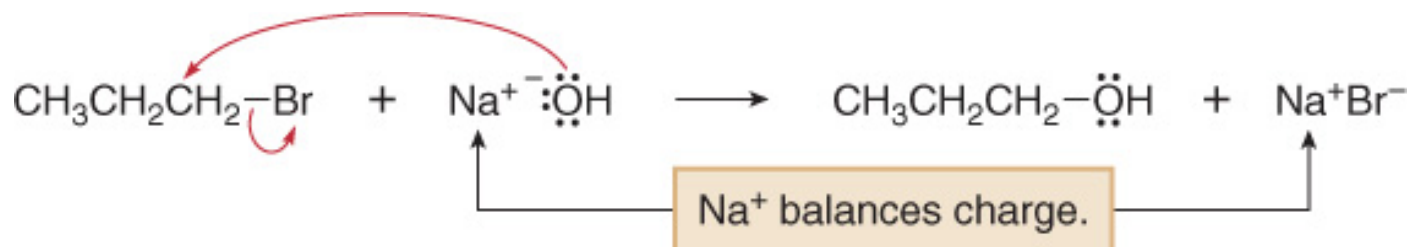- **Three components are necessary in any substitution reaction.**

General substitution reaction

$$R-X \quad + \quad :Nu^- \quad \longrightarrow \quad R-Nu \quad + \quad X:^-$$

sp^3 hybridized C | nucleophile | leaving group

Examples

	Alkyl group		Nucleophile			Leaving group
[1]	CH_3-Cl	+	$^-:\ddot{O}H$	$\longrightarrow$	$CH_3-\ddot{O}H$ +	Cl^-
[2]	$CH_3CH_2CH_2-I$	+	$^-:\ddot{S}H$	$\longrightarrow$	$CH_3CH_2CH_2-\ddot{S}H$ +	I^-
[3]	CH_3CH_2-Br	+	$^-:\ddot{O}CH_3$	$\longrightarrow$	$CH_3CH_2-\ddot{O}CH_3$ +	Br^-

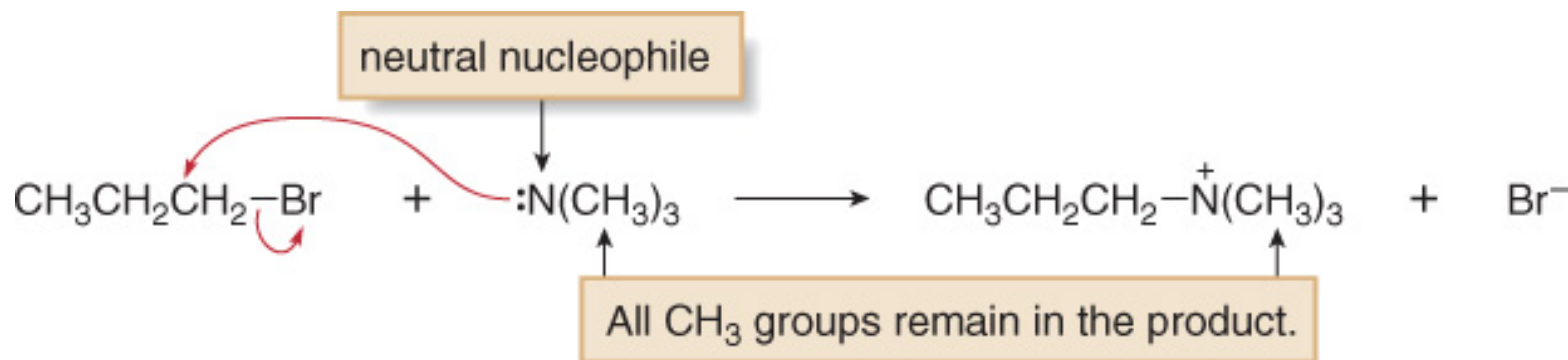A new C−Nu bond forms.
The leaving group comes off.

Alkyl Halides and Nucleophilic Substitution

General Features of Nucleophilic Substitution

- Negatively charged nucleophiles like HO⁻ and HS⁻ are used as salts with Li^+, Na^+, or K^+ counterions to balance the charge. Since the identity of the counterion is usually inconsequential, it is often omitted from the chemical equation.
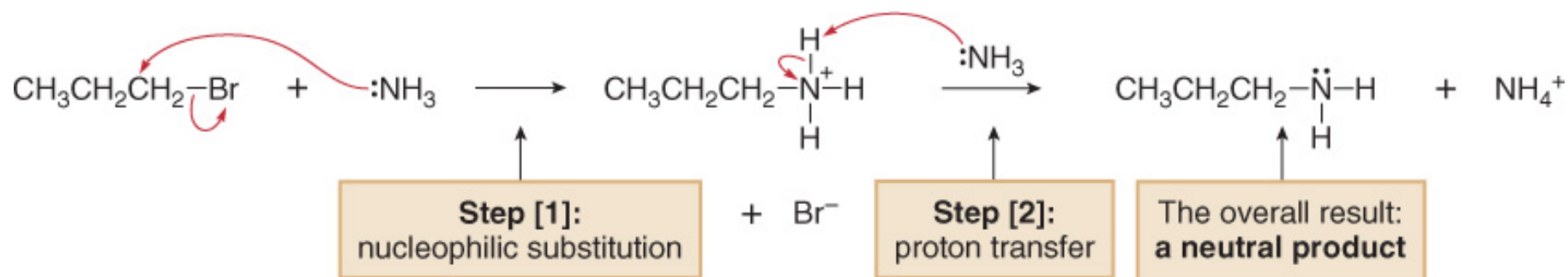
$$CH_3CH_2CH_2-Br \ + \ Na^+ \ :\overset{..}{\underset{..}{O}}H \longrightarrow CH_3CH_2CH_2-\overset{..}{\underset{..}{O}}H \ + \ Na^+Br^-$$

Na⁺ balances charge.

- When a neutral nucleophile is used, the substitution product bears a positive charge.

neutral nucleophile

$$CH_3CH_2CH_2-Br \ + \ :N(CH_3)_3 \longrightarrow CH_3CH_2CH_2-\overset{+}{N}(CH_3)_3 \ + \ Br^-$$

All CH₃ groups remain in the product.

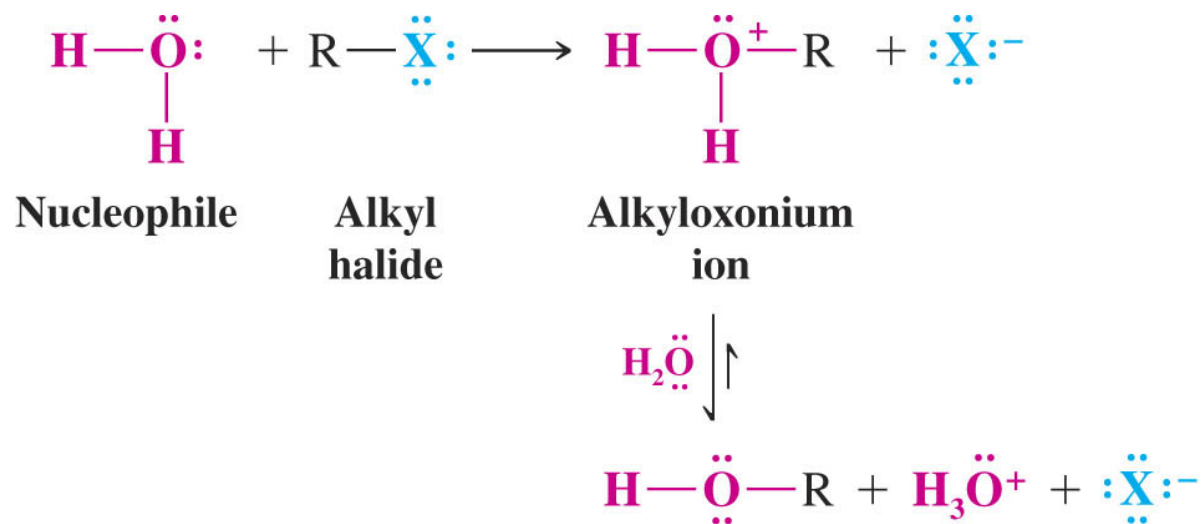# Alkyl Halides and Nucleophilic Substitution

General Features of Nucleophilic Substitution

- **Furthermore, when the substitution product bears a positive charge and also contains a proton bonded to O or N, the initially formed substitution product readily loses a proton in a Brønsted-Lowry acid-base reaction, forming a neutral product.**

$CH_3CH_2CH_2-Br$ + :NH_3 $\longrightarrow$ $CH_3CH_2CH_2-\overset{+}{N}H-H$ $\xrightarrow{\quad :NH_3 \quad}$ $CH_3CH_2CH_2-\ddot{N}-H$ + NH_4^+

| **Step [1]:** nucleophilic substitution | + Br⁻ | **Step [2]:** proton transfer | The overall result: **a neutral product** |

♦ The Nucleophile

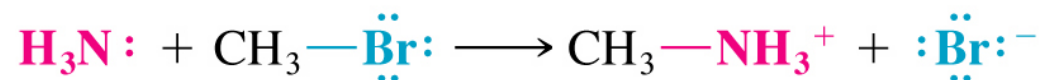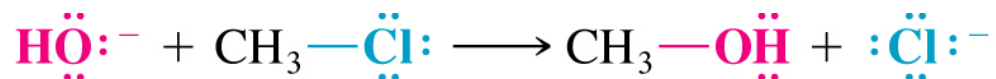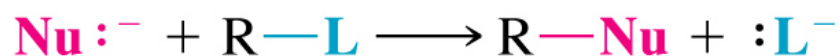**A nucleophile may be any molecule with an unshared electron pair**

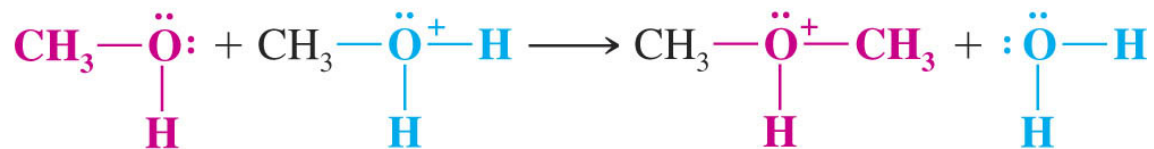We'll discuss later what makes a nucleophile
strong or weak (good or bad)

Leaving Groups

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

It can either leave as an anion….

$$Nu\!:^- + R\!-\!L \longrightarrow R\!-\!Nu + :L^-$$

$$H\ddot{O}\!:^- + CH_3\!-\!\ddot{\underset{\cdot\cdot}{C}l}\!: \longrightarrow CH_3\!-\!O\ddot{H} + :\ddot{\underset{\cdot\cdot}{C}l}\!:^-$$

$$H_3N\!: + CH_3\!-\!\ddot{\underset{\cdot\cdot}{B}r}\!: \longrightarrow CH_3\!-\!NH_3^+ + :\ddot{\underset{\cdot\cdot}{B}r}\!:^-$$

…or as a neutral molecule

$$Nu\!: + R\!-\!L^+ \longrightarrow R\!-\!Nu^+ + :L$$

$$CH_3\!-\!\ddot{O}\!: + CH_3\!-\!\overset{+}{\ddot{O}}\!-\!H \longrightarrow CH_3\!-\!\overset{+}{\ddot{O}}\!-\!CH_3 + :\ddot{O}\!-\!H$$

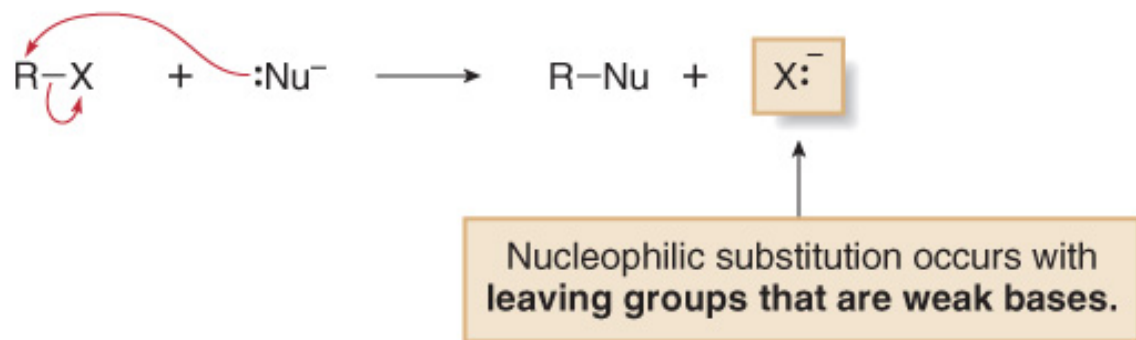(with H substituents below each oxygen)

Alkyl Halides and Nucleophilic Substitution

The Leaving Group

- **In a nucleophilic substitution reaction of R—X, the C—X bond is heterolytically cleaved, and the leaving group departs with the electron pair in that bond, forming X:¯. The more stable the leaving group X:¯, the better able it is to accept an electron pair.**

◆ In comparing two leaving groups, the better leaving group is the weaker base.

$$R\overset{\frown}{-}X \quad + \quad :Nu^- \longrightarrow \quad R-Nu \quad + \quad \boxed{X:^-}$$

Nucleophilic substitution occurs with **leaving groups that are weak bases.**

Alkyl Halides and Nucleophilic Substitution

The Leaving Group

| TABLE 7.2	Good Leaving Groups for Nucleophilic Substitution		
Starting material	Leaving group	Conjugate acid	pK_a
R—Cl	Cl^-	HCl	−7
R—Br	Br^-	HBr	−9
R—I	I^-	HI	−10
R—OH_2^+	H_2O	H_3O^+	−1.7

These molecules undergo nucleophilic substitution.

good leaving groups

Alkyl Halides and Nucleophilic Substitution

The Leaving Group

TABLE 7.3   Poor Leaving Groups for Nucleophilic Substitution

Starting material	Leaving group	Conjugate acid	pK_a
R—F	F^-	HF	3.2
R—OH	^-OH	H_2O	15.7
R—NH_2	$^-NH_2$	NH_3	38
R—H	H^-	H_2	35
R—R	R^-	RH	50

These molecules do *not* undergo nucleophilic substitution.

poor leaving groups

Neutral molecules as leaving groups

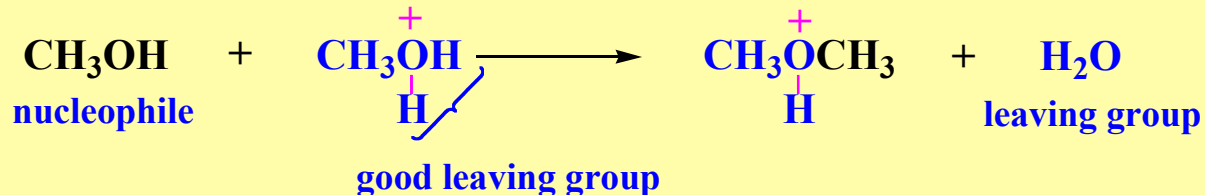Poor leaving groups can be turned into good leaving groups by **protonation.**

CH_3-OH
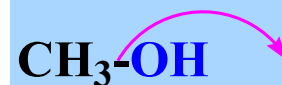
Hydroxide ion is a poor leaving group because it is the anion of a weak acid, H_2O.
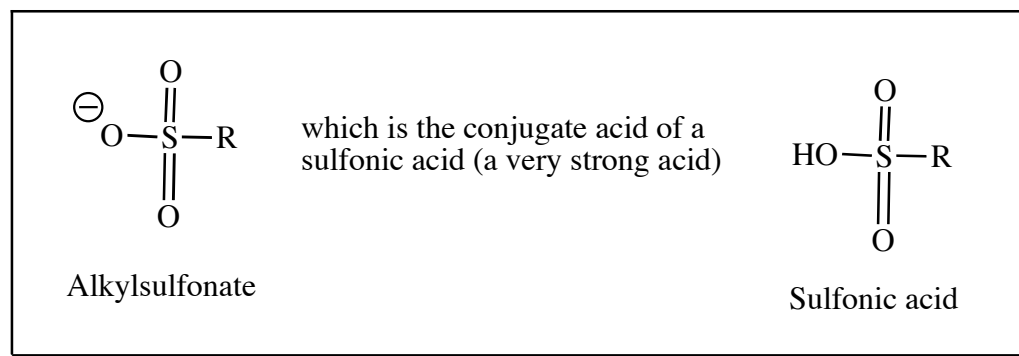
In the presence of a strong acid,

$$CH_3\ddot{O}H \quad + \quad H_2SO_4 \quad \rightleftharpoons \quad CH_3\overset{+}{O}H \quad + \quad HSO_4^{-}$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad H$$

a nucleophilic substitution reaction occurs:

$$CH_3OH \quad + \quad CH_3\overset{+}{O}H \longrightarrow CH_3\overset{+}{O}CH_3 \quad + \quad H_2O$$
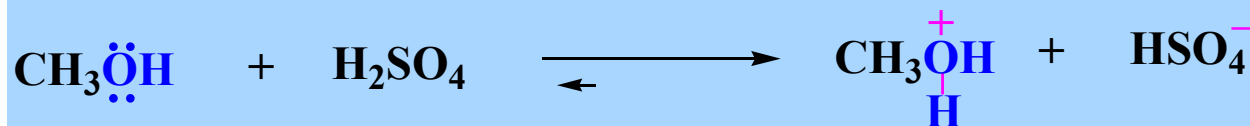
nucleophile $\qquad$ H $\qquad\qquad\qquad$ H $\qquad\qquad$ leaving group
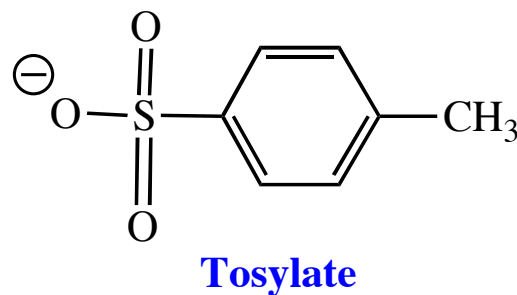
good leaving group

- **The Leaving Group**
  - ➡ **The best leaving groups are weak bases which are relatively stable**

   - ★ **Other very weak bases (besides halide ions) which are good leaving groups:**

$$\overset{\ominus}{O}-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}-R \qquad \text{which is the conjugate acid of a} \atop \text{sulfonic acid (a very strong acid)} \qquad HO-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}-R$$

Alkylsulfonate   Sulfonic acid

The most common
alkylsulfonate is:

$$\overset{\ominus}{O}-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}-\text{C}_6\text{H}_4-CH_3$$

Tosylate

◆ Kinetics of a Nucleophilic Substitution Reaction: An S_N2 Reaction

➡ **The initial rate of the following reaction is measured**

$$CH_3-Cl + OH^- \xrightarrow[H_2O]{60°C} CH-OH + Cl^-$$
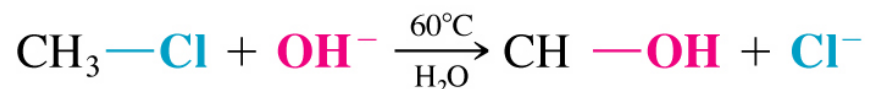
➡ **The rate is directly proportional to the initial concentrations of both methyl chloride and hydroxide**

Experiment Number	Initial [CH₃Cl]	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**

$$\text{Rate} = k[CH_3Cl][OH^-]$$

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

♦ A Mechanism for the S_N2 Reaction
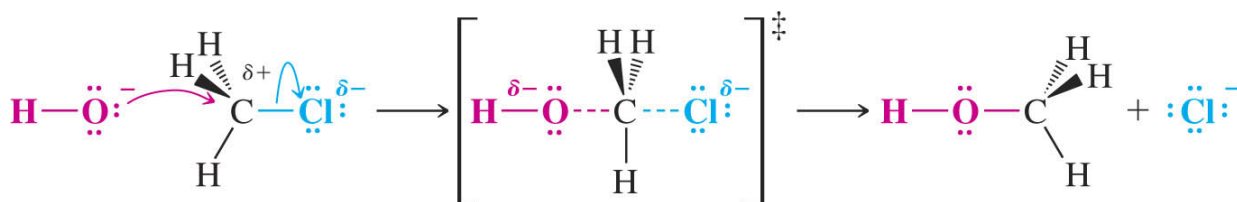
Transition state

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.

➡ **A *transition state* is the high energy state of the reaction**

　★ **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**
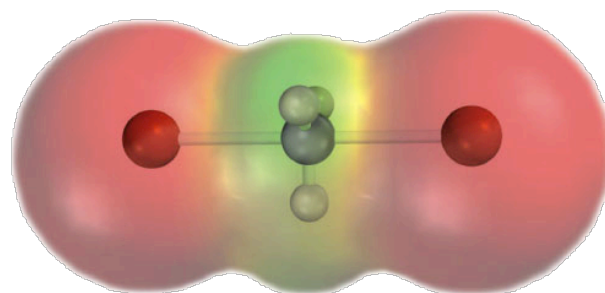
Chapter 6   15

The S$_N$2 Reaction

♦ **The S$_N$2 reaction occurs when an electron pair on the nucleophile Nu:⁻ forces out the group X:⁻, which takes with it the electron pair from the former C-X bond**
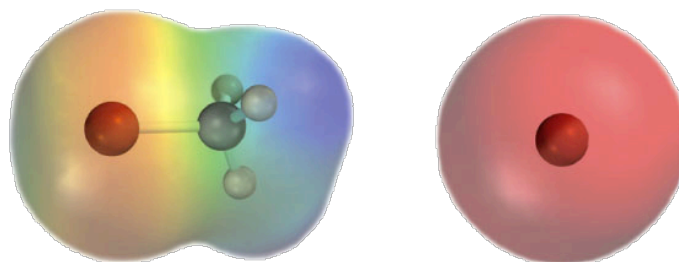
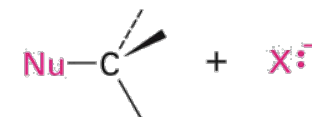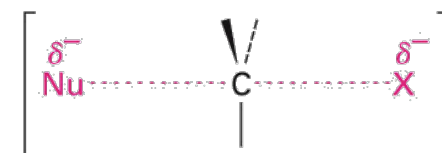   ● **The transition state of an S$_N$2 reaction has a planar arrangement of the carbon atom and the remaining three groups**
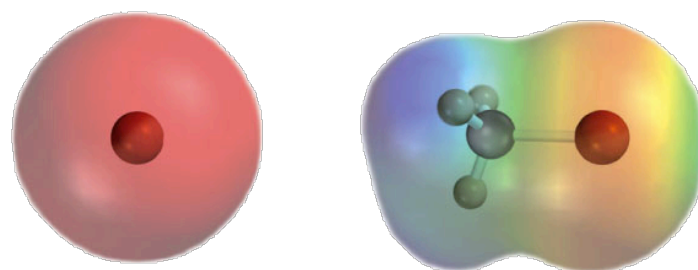
Tetrahedral

Planar

Tetrahedral

$$Nu{:}^- \; + \; \overset{}{\underset{}{C}}{-}X$$

$$\left[\; \overset{\delta^-}{Nu} \cdots\cdots \overset{}{C} \cdots\cdots \overset{\delta^-}{X} \; \right]$$
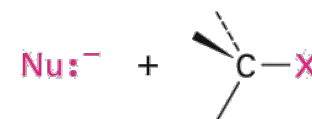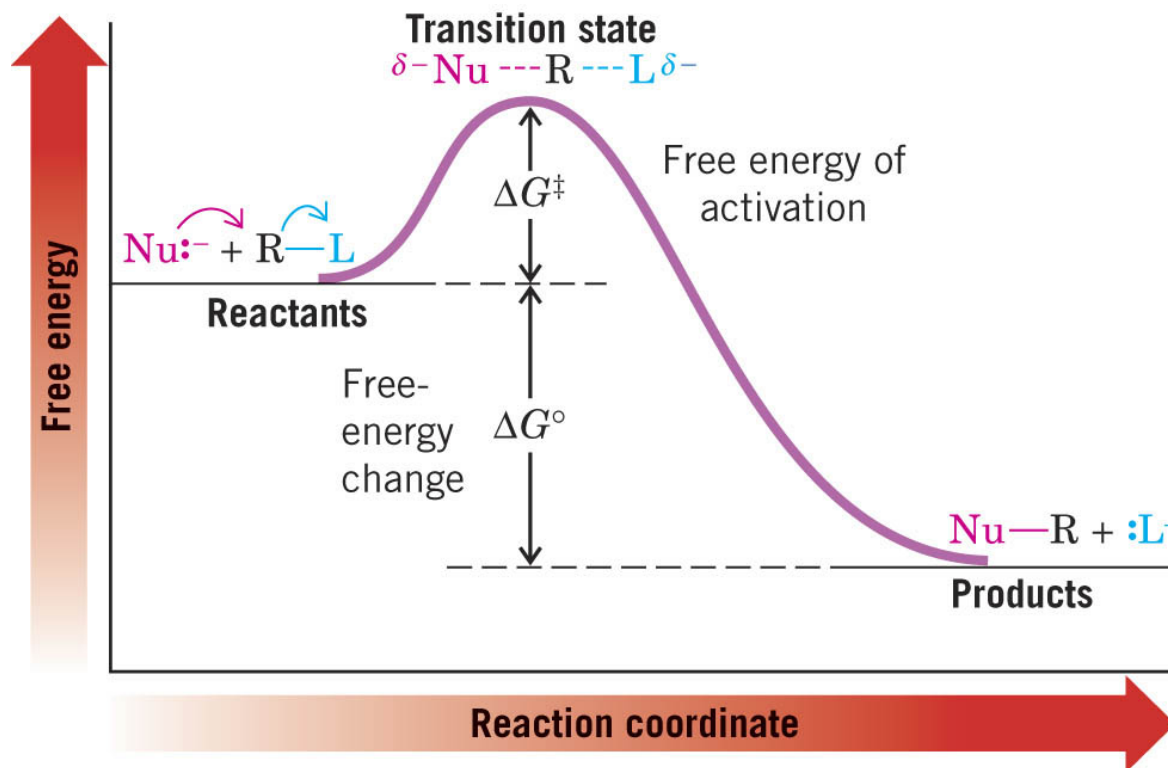
$$Nu{-}C \quad + \quad X{:}^-$$

➡ An energy diagram of a typical S$_N$2 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 ($\Delta G^{\ddagger}$)
- ★ The difference in energy between starting molecules and products is the free energy change of the reaction, ΔG^o

Transition state

δ^-Nu ---R ---Lδ^-

$\Delta G^{\ddagger}$

Free energy of activation

Nu:$^-$ + R—L

Reactants

Free-energy change

ΔG^o

Nu—R + :L$^-$

Products

Free energy

Reaction coordinate

Chapter 6   17

➡ **In a highly endergonic reaction of the same type the energy barrier will be even higher ($\Delta G^{\ddagger}$ is very large)**
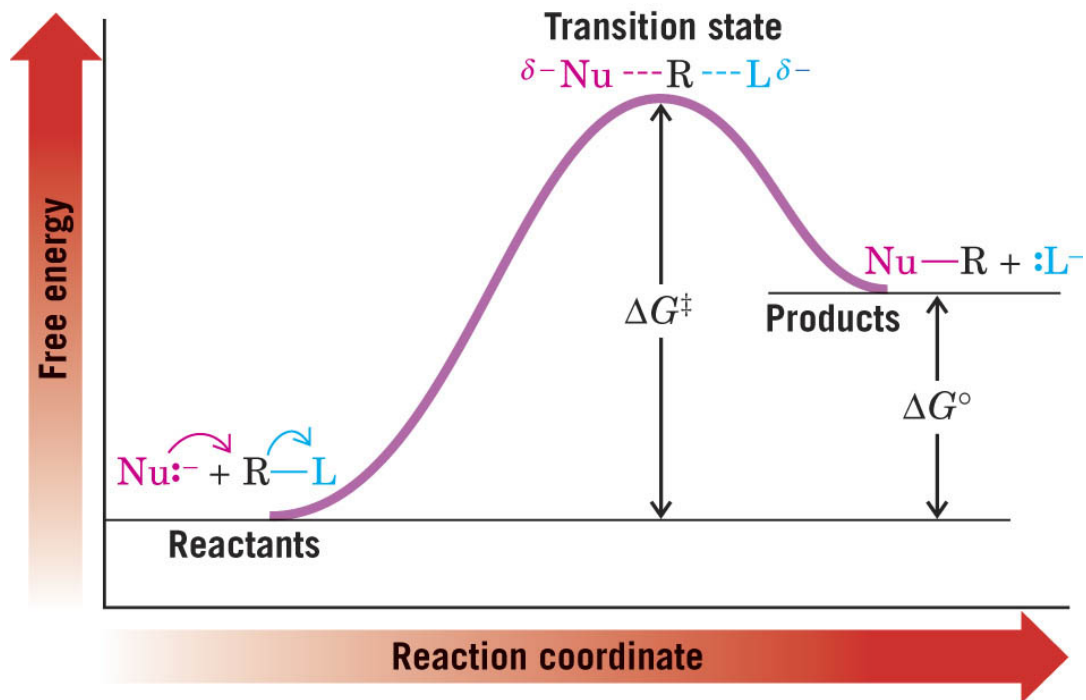
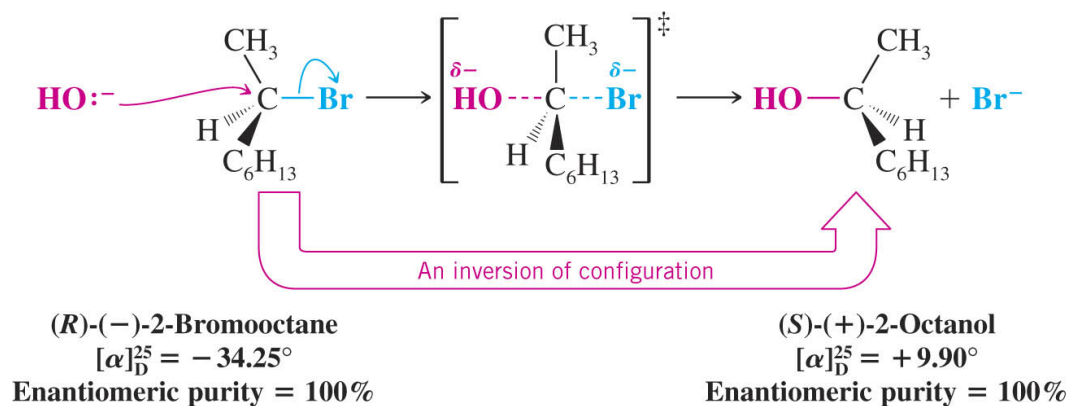➡ **There is a direct relationship between $\Delta G^{\ddagger}$ and the temperature of a reaction**

★ **The higher the temperature, the faster the rate**
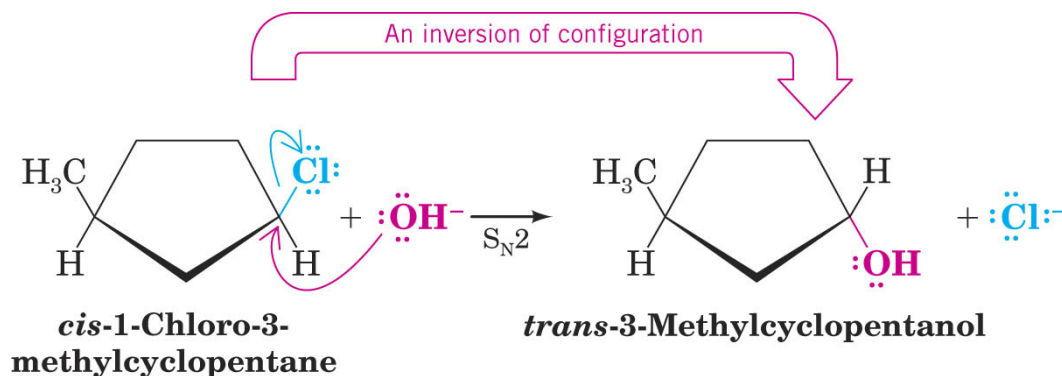
$$k = k_0 e^{-\Delta G^{\ddagger}/RT}$$

★ **Near room temperature, a 10ºC 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 Stereochemistry of S$_N$2 Reactions

➡ **Backside attack of nucleophile results in an inversion of configuration**

(R)-(−)-2-Bromooctane
$[\alpha]_D^{25} = -34.25°$
Enantiomeric purity = 100%

(S)-(+)-2-Octanol
$[\alpha]_D^{25} = +9.90°$
Enantiomeric purity = 100%

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

cis-1-Chloro-3-methylcyclopentane
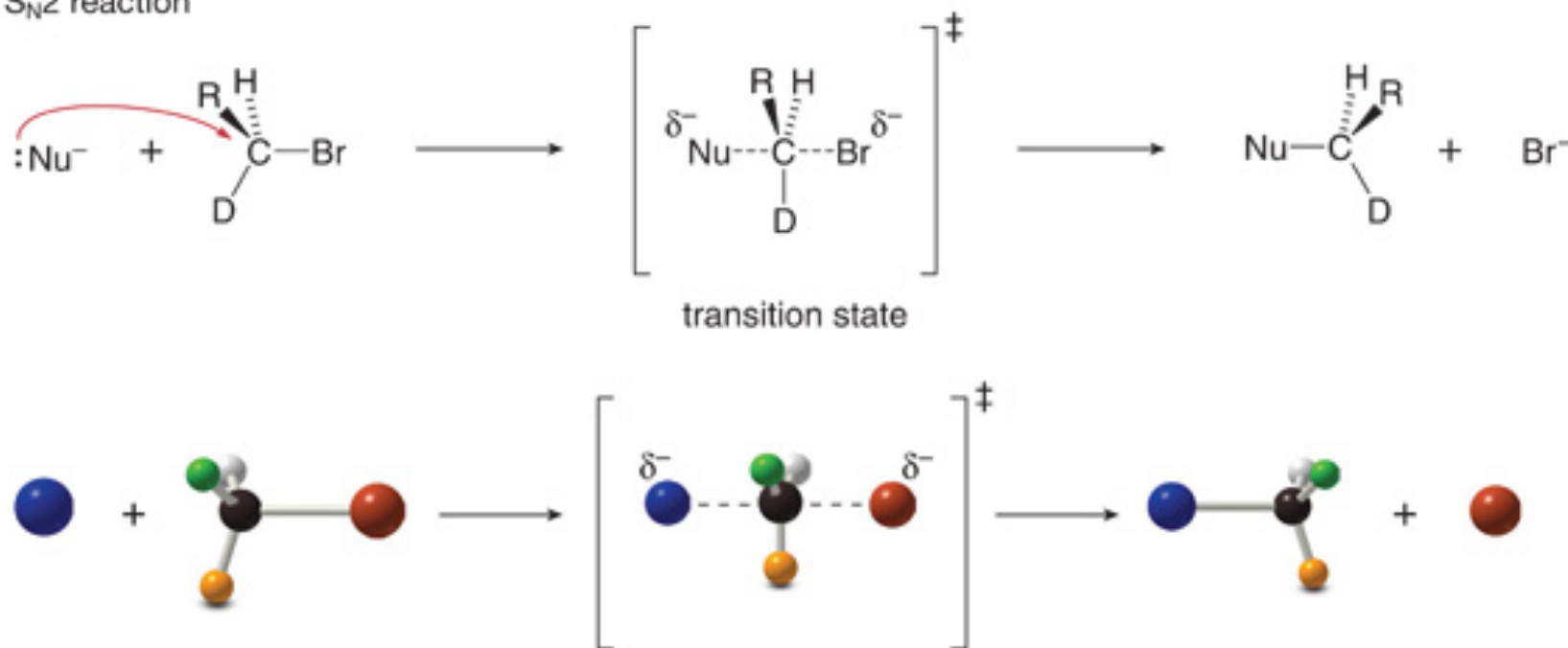
trans-3-Methylcyclopentanol

Alkyl Halides and Nucleophilic Substitution

Mechanisms of Nucleophilic Substitution

- All S_N2 reactions proceed with backside attack of the nucleophile, resulting in inversion of configuration at a stereogenic center.

**Figure 7.9** Stereochemistry of the S_N2 reaction

transition state

:Nu⁻ and Br⁻ are 180° away from each other, on either side of a plane containing R, H, and D.

Alkyl Halides and Nucleophilic Substitution

## Mechanisms of Nucleophilic Substitution

Figure 7.10 Two examples of inversion of configuration in the S_N2 reaction

- The bond to the nucleophile in the product is always on the **opposite side** relative to the bond to the leaving group in the starting material.
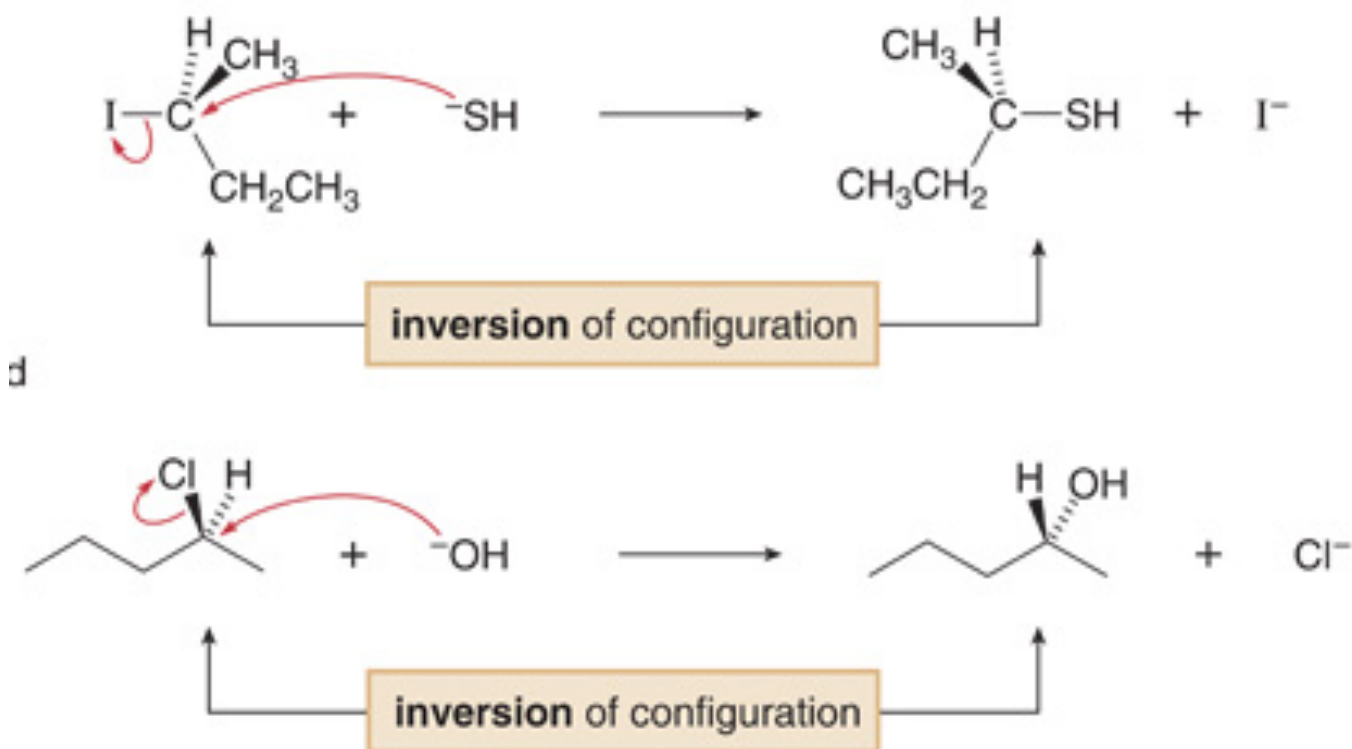
♦ The Reaction of *tert*-Butyl Chloride with Hydroxide Ion: An S_N1 Reaction

➡ *tert*-Butyl chloride undergoes substitution with hydroxide

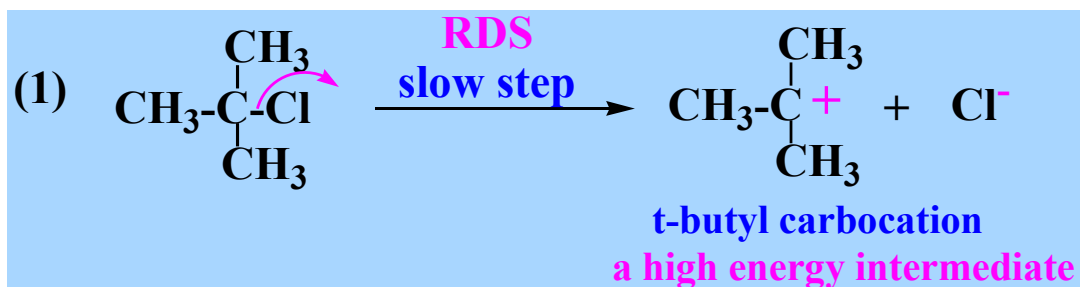➡ The rate is independent of hydroxide concentration and depends only on concentration of *tert*-butyl chloride

$$(CH_3)_3C\text{—}Cl + OH^- \xrightarrow[H_2O]{acetone} (CH_3)_3C\text{—}OH + Cl^-$$
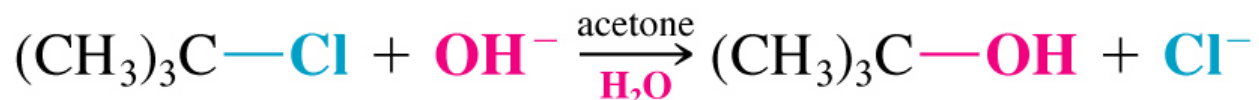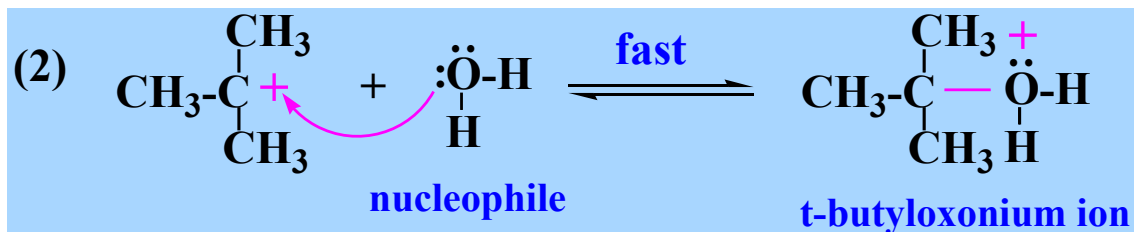
$$Rate \propto [(CH_3)_3CCl]$$

$$Rate = k[(CH_3)_3CCl]$$

➡ 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
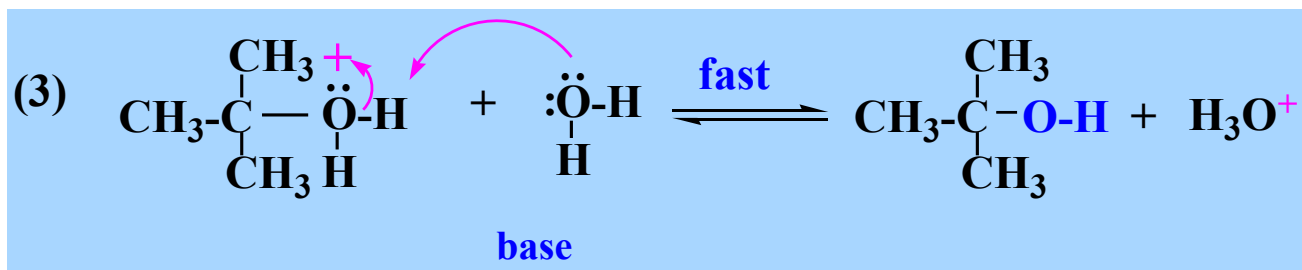
Mechanism of the S_N1 Reaction (Stepwise)

bond heterolysis:

(1) $CH_3-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-Cl$ $\xrightarrow[\text{slow step}]{\text{RDS}}$ $CH_3-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}+$ $+$ Cl^-

t-butyl carbocation
a high energy intermediate

nucleophilic addition:

(2) $CH_3-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}+$ $+$ $:\ddot{O}\text{-}H \ \underset{H}{|}$ $\underset{\text{fast}}{\rightleftharpoons}$ $CH_3-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-\overset{+}{\underset{\underset{H}{|}}{\ddot{O}}}\text{-}H$

nucleophile   t-butyloxonium ion

proton exchange:

(3) $CH_3-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-\overset{+}{\underset{\underset{H}{|}}{\ddot{O}}}\text{-}H$ $+$ $:\ddot{O}\text{-}H \ \underset{H}{|}$ $\underset{\text{fast}}{\rightleftharpoons}$ $CH_3-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-O\text{-}H$ $+$ H_3O^+
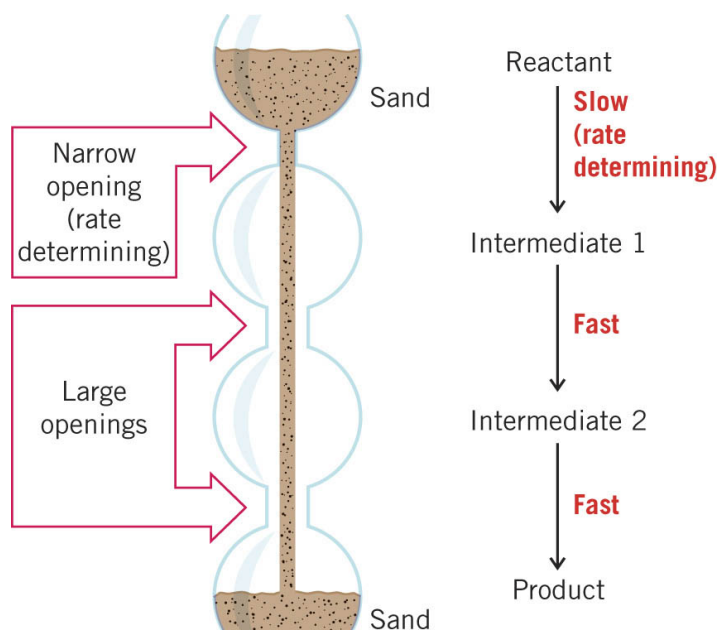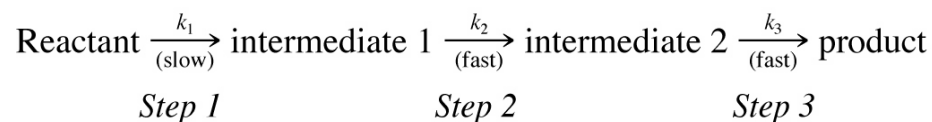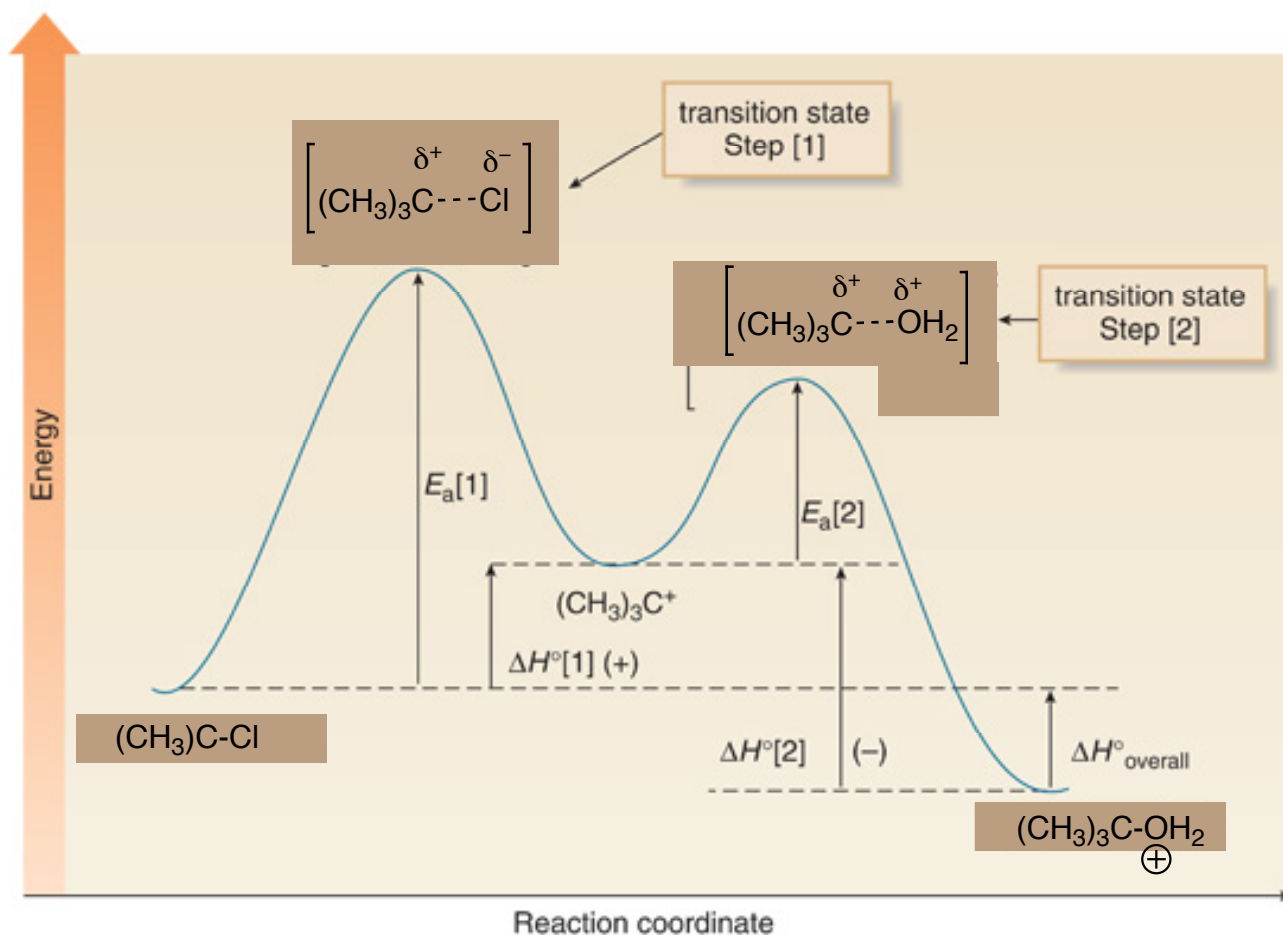
base

♦ 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 $k_1 << k_2$ or k_3 and the first step is rate determining**

$$\text{Reactant} \xrightarrow[\text{(slow)}]{k_1} \text{intermediate 1} \xrightarrow[\text{(fast)}]{k_2} \text{intermediate 2} \xrightarrow[\text{(fast)}]{k_3} \text{product}$$

Step 1   *Step 2*   *Step 3*

25

Mechanism of the S$_N$1 Reaction

Key features of the S$_N$1 mechanism are that it has two steps and involves a carbocation intermediate.

Reaction Energy Diagram: S_N1 Mechanism

transition state
Step [1]

$$\begin{bmatrix} \delta^+ & \delta^- \\ (CH_3)_3C\text{-}\text{-}\text{-}Cl \end{bmatrix}$$

$$\begin{bmatrix} \delta^+ & \delta^+ \\ (CH_3)_3C\text{-}\text{-}\text{-}OH_2 \end{bmatrix}$$

transition state
Step [2]

Energy

$E_a[1]$

$E_a[2]$

$(CH_3)_3C^+$

$\Delta H°[1]\ (+)$

$(CH_3)C\text{-}Cl$

$\Delta H°[2] \quad (-)$

$\Delta H°_{overall}$

$(CH_3)_3C\text{-}OH_2$
$\oplus$

Reaction coordinate

- Since the S_N1 mechanism has two steps, there are two energy barriers.
- Step [1] is rate-determining; $E_a[1] > E_a[2]$.
- In each step only one bond is broken or formed, so the transition state for each step has one partial bond.
- The reaction is drawn with $\Delta H°_{overall}$ as a negative value, since the products are lower in energy than the starting materials.

27

Alkyl Halides and Nucleophilic Substitution

Carbocation Stability

- **The effect of the type of alkyl halide on S_N1 reaction rates can be explained by considering carbocation stability.**

- **Carbocations are classified as primary (1^0), secondary (2^0), or tertiary (3^0), based on the number of R groups bonded to the charged carbon atom. As the number of R groups increases, carbocation stability increases.**
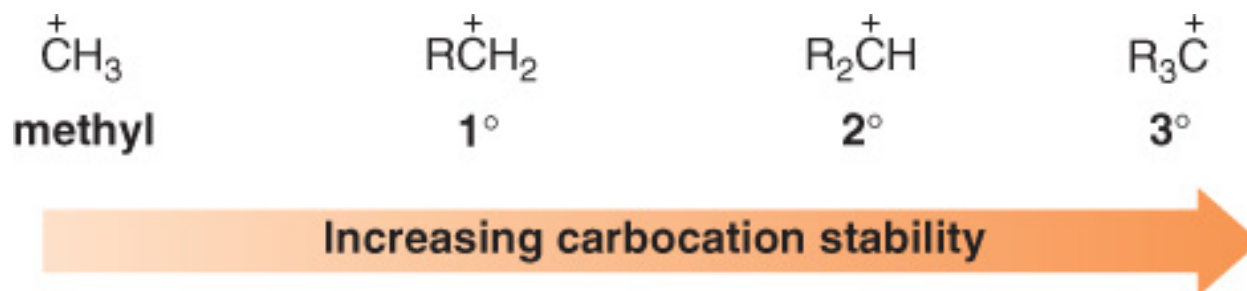
$$\overset{+}{C}H_3 \qquad R\overset{+}{C}H_2 \qquad R_2\overset{+}{C}H \qquad R_3\overset{+}{C}$$

methyl   1°   2°   3°

Increasing carbocation stability →

Alkyl Halides and Nucleophilic Substitution

Carbocation Stability

- **The order of carbocation stability can be rationalized through inductive effects and hyperconjugation.**

- **Inductive effects are electronic effects that occur through σ bonds. Specifically, the inductive effect is the pull of electron density through σ bonds caused by electronegativity differences between atoms.**

- **Alkyl groups are electron donating groups that stabilize a positive charge. Since an alkyl group has several σ bonds, each containing electron density, it is more polarizable than a hydrogen atom, and more able to donate electron density.**

- **In general, the greater the number of alkyl groups attached to a carbon with a positive charge, the more stable will be the cation.** Chapter 6

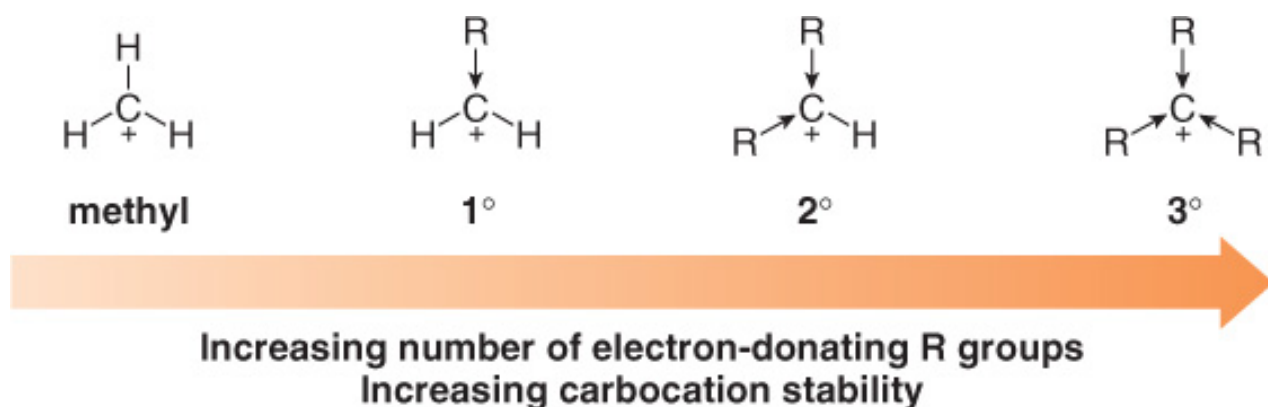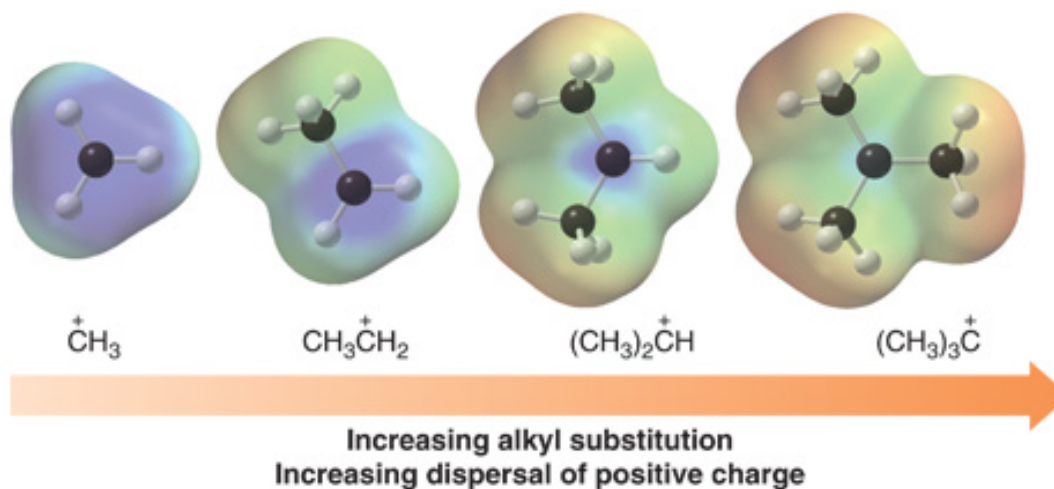# Alkyl Halides and Nucleophilic Substitution

Carbocation Stability

methyl   1°   2°   3°

Increasing number of electron-donating R groups
Increasing carbocation stability

Figure 7.17 Electrostatic potential maps for different carbocations

$\overset{+}{C}H_3$ $CH_3\overset{+}{C}H_2$ $(CH_3)_2\overset{+}{C}H$ $(CH_3)_3\overset{+}{C}$

Increasing alkyl substitution
Increasing dispersal of positive charge

- Dark blue areas in electrostatic potential plots indicate regions low in electron density. As alkyl substitution increases, the region of positive charge is less concentrated on carbon.
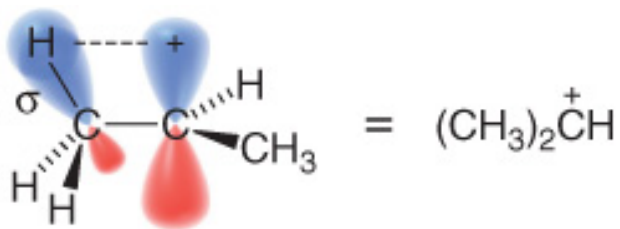
Alkyl Halides and Nucleophilic Substitution

Carbocation Stability

- **The order of carbocation stability is also a consequence of hyperconjugation.**

- **Hyperconjugation is the spreading out of charge by the overlap of an empty *p* orbital with an adjacent σ bond. This overlap (hyperconjugation) delocalizes the positive charge on the carbocation, spreading it over a large volume, and this stabilizes the carbocation.**

- **Example: CH_3^+ cannot be stabilized by hyperconjugation, but $(CH_3)_2CH^+$ can.**

$$\overset{+}{C}H_3 \quad = \quad H-\overset{+}{C}\overset{H}{\underset{H}{\,}}$$
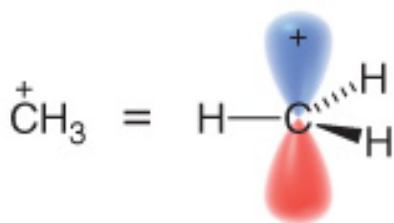
This carbocation has no opportunity for orbital overlap with the vacant *p* orbital.

$$\quad = \quad (CH_3)_2\overset{+}{C}H$$

Overlap of the C−H σ bond with the adjacent vacant *p* orbital stabilizes the carbocation.

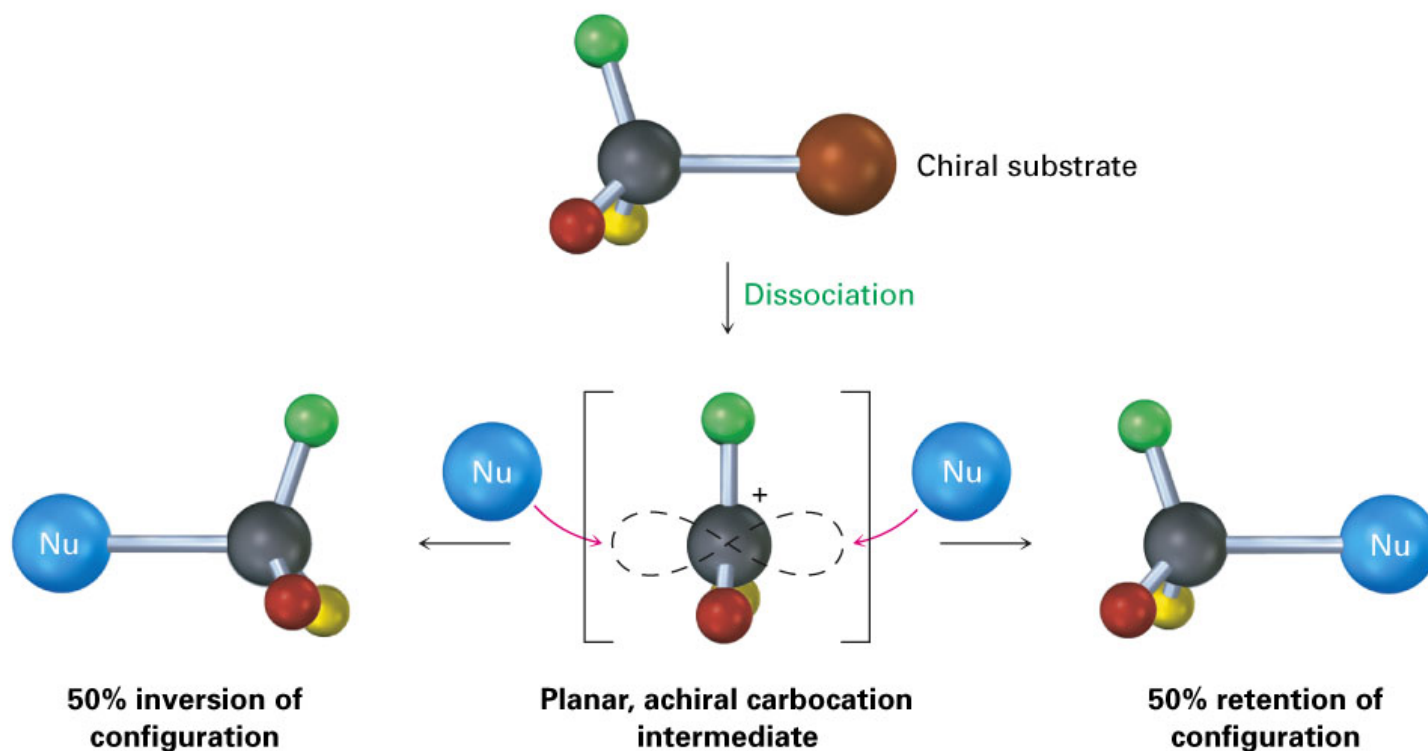# Alkyl Halides and Nucleophilic Substitution

Stereochemistry of the S$_N$1 Reaction:

- **Loss of the leaving group in Step [1] generates a planar carbocation that is achiral. Attack of the nucleophile in Step [2] can occur on either side to afford two products which are a pair of enantiomers.**

- **Because there is no preference for nucleophilic attack from either direction, an equal amount of the two enantiomers is formed—a racemic mixture. We say that racemization has occurred.**
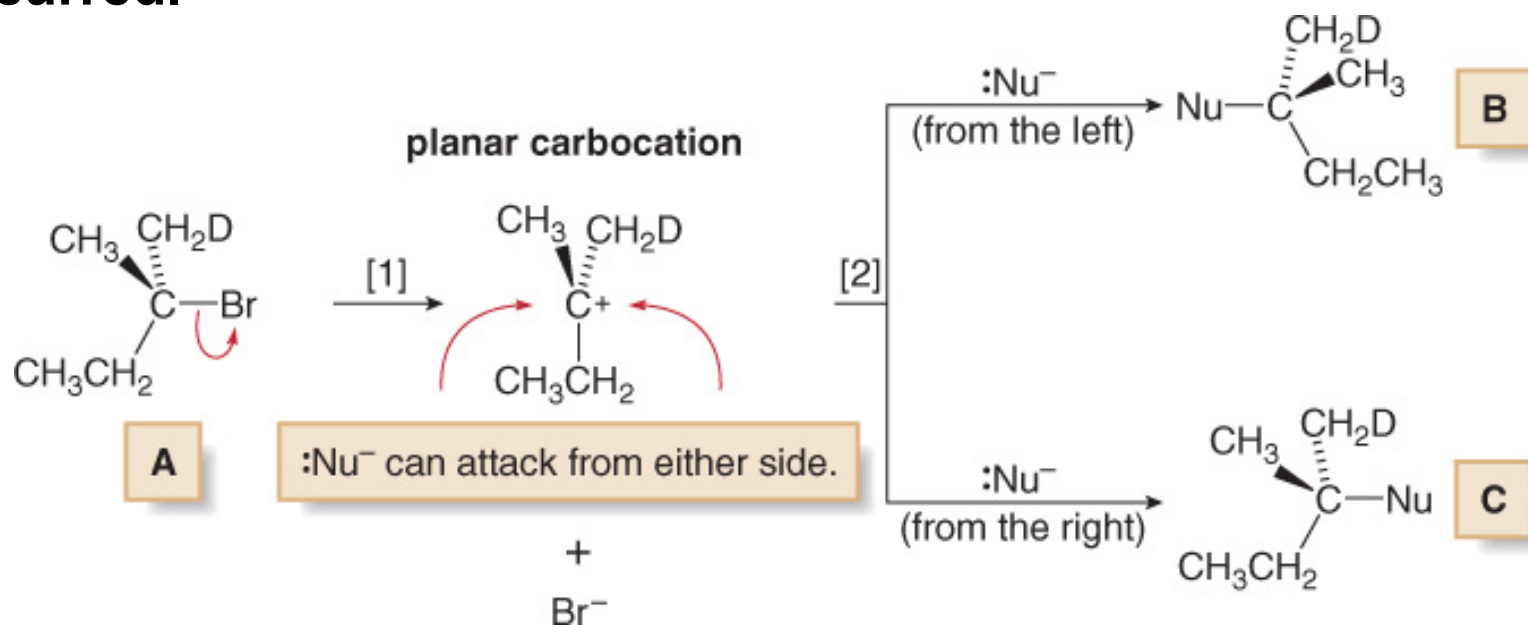
The S$_N$1 Reaction

♦ **If an S$_N$1 reaction is carried out on one enantiomer of a chiral reactant and proceeds through an achiral carbocation intermediate, the product will be optically inactive**

♦ **The symmetrical intermediate carbocation can react with a nucleophile equally well from either side, leading to a racemic 50 : 50 mixture of enantiomers**

Chiral substrate

Dissociation

Nu

Nu

+

Nu

Nu

50% inversion of configuration

Planar, achiral carbocation intermediate

50% retention of configuration

Alkyl Halides and Nucleophilic Substitution

Mechanisms for Nucleophilic Substitution

Figure 7.16 Two examples of racemization in the S_N1 reaction
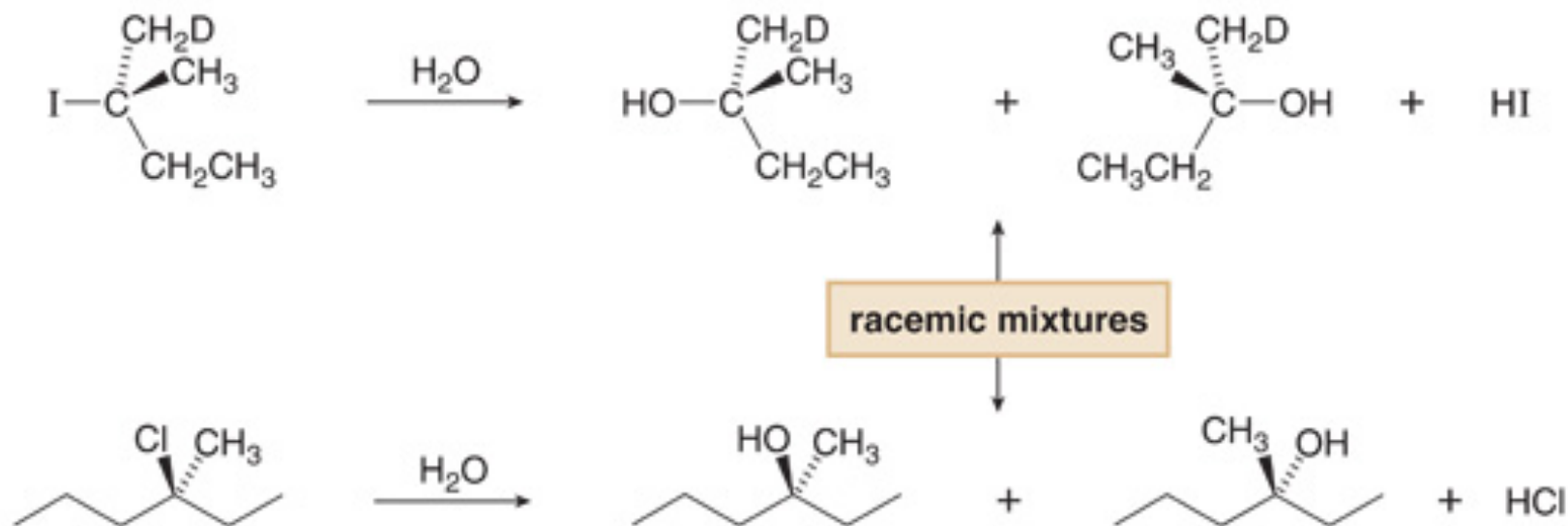
racemic mixtures

- Nucleophilic substitution of each starting material by an S_N1 mechanism forms a **racemic mixture** of two products.
- With H_2O, a neutral nucleophile, the initial product of nucleophilic substitution (ROH_2^+) loses a proton to form the final neutral product, ROH (Section 7.6).

♦ **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 sterically hindered to react**

Methyl	1°	2°	Neopentyl	3°
(30)	(1)	(0.03)	(0.00001)	(~ 0)
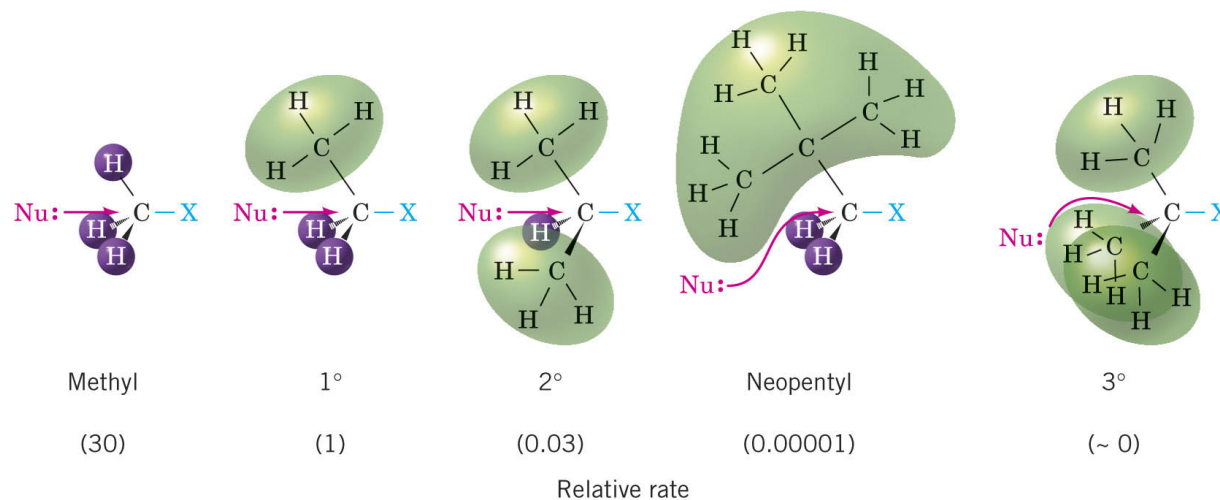
Relative rate

- ## *S$_N$1 reactions*

  ➡ **Generally only tertiary halides undergo S$_N$1 reactions because only they can form relatively stabile carbocations.**

  (Secondary substrates can be made to undergo S$_N$1 reactions by manipulating other factors which help stabilize the 2$^°$ carbocation.)

- ## *The Hammond-Leffler Postulate*

  SKIP THIS SECTION

- **The Effect of the Concentration of the 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**
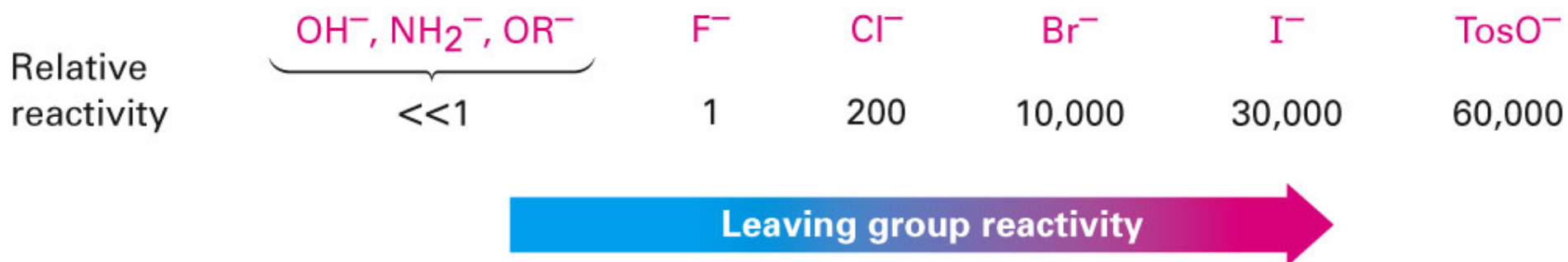
Characteristics of the S$_N$2 Reaction

♦ **Nucleophilicity usually increases going down a column of the periodic table**

- **HS⁻ is more nucleophilic than HO⁻**
- **Halide reactivity order is I⁻ > Br⁻ > Cl⁻**
- **Going down the periodic table, elements have their valence electrons in successively larger shells, where they are successively farther from the nucleus, less tightly held, and consequently more reactive**

♦ **Negatively charged nucleophiles are usually more reactive than neutral ones**

- **S$_N$2 reactions are often carried out under basic conditions rather than neutral or acidic conditions**

(in order to insure that the nucleophile has a charge)

Characteristics of the S$_N$2 Reaction
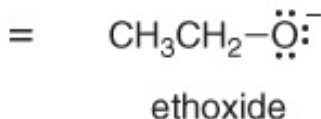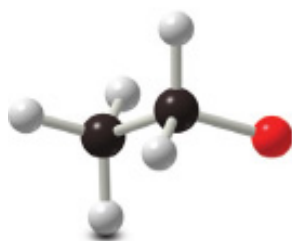
The Leaving Group

♦ **Best leaving groups are the most stable bases.**

● **Weak bases such as Cl$^-$ and tosylate ion make good leaving groups, while strong bases such as OH$^-$ and NH$_2^-$ make poor leaving groups**

	OH$^-$, NH$_2^-$, OR$^-$	F$^-$	Cl$^-$	Br$^-$	I$^-$	TosO$^-$
Relative reactivity	<<1	1	200	10,000	30,000	60,000

Leaving group reactivity →

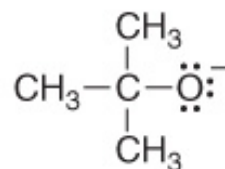# THE STRENGTH OF THE NUCLEOPHILE

However,

- **Nucleophilicity does not parallel basicity when steric hindrance becomes a factor.**

  - Steric hindrance **causes a decrease in nucleophile reactivity due to the presence of bulky groups as the site of a reaction.**

  - **Steric hindrance decreases nucleophilicity but not basicity.**

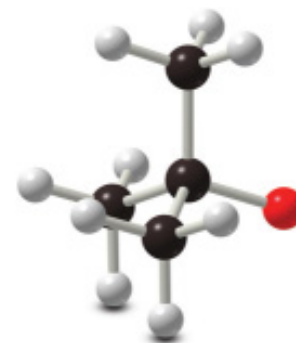 - **Sterically hindered bases that are poor nucleophiles are called nonnucleophilic bases.**

= $CH_3CH_2-\ddot{\underset{..}{O}}\,\overline{:}$

ethoxide

stronger nucleophile

$CH_3-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}-\ddot{\underset{..}{O}}\,\overline{:}$

tert-butoxide

stronger base

Three CH_3 groups sterically hinder the O atom, making it a **weaker nucleophile.**

THE STRENGTH OF THE NUCLEOPHILE

Also, remember that nucleophilicity <u>does not </u>parallel basicity in polar protic solvents (defined later):

That is, nucleophilicity increases down a column of the periodic table as the size of the anion increases. This opposite to basicity.

Down a column
of the periodic table

F^- Cl^- Br^- I^-

Increasing nucleophilicity
in polar protic solvents
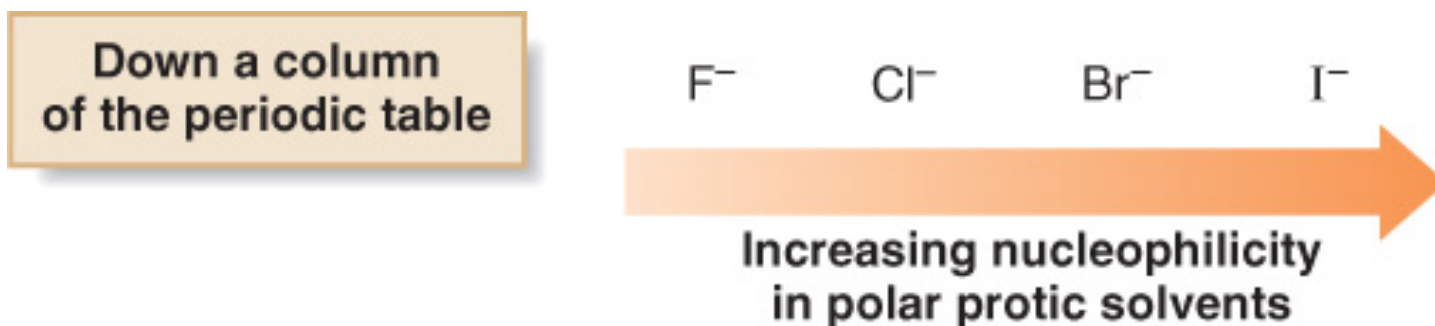
● Solvent Effects on S_N2 Reactions:

Polar Protic and Aprotic Solvents

➡ Polar Protic Solvents

★ Polar protic solvents have a hydrogen atom attached to strongly electronegative atoms. That is, they contain an –OH or –NH group

★ They solvate nucleophiles and therefore they slow down S_N2 reactions by forming a "cage" around the nucleophile.

Molecules of the protic solvent, water, solvate a halide ion by forming hydrogen bonds to it.
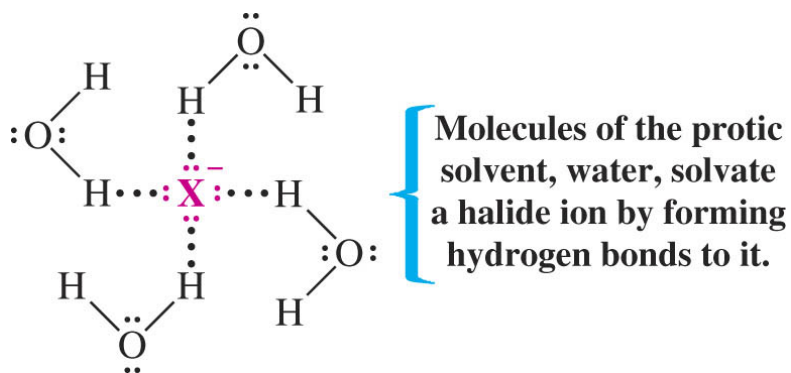
★ Larger nucleophilic atoms are less solvated and therefore more reactive in polar protic solvents $\quad I^- > Br^- > Cl^- > F^-$

★ Relative nucleophilicity in polar protic solvents:

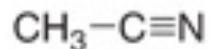$$SH^- > CN^- > I^- > OH^- > N_3^- > Br^- > CH_3CO_2^- > Cl^- > F^- > H_2O$$

Effects of Polar Protic and Polar Aprotic Solvents

- **Polar aprotic solvents** have no O—H or N—H bonds. Thus, they are incapable of hydrogen bonding. However, they are still very polar. They solvate the metal cations but not the nucleophilic anions.
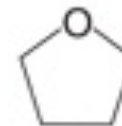
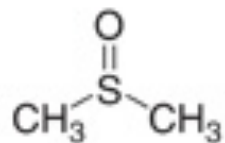**Figure 7.7**   Examples of polar aprotic solvents
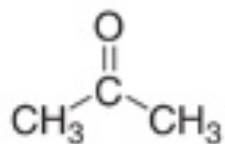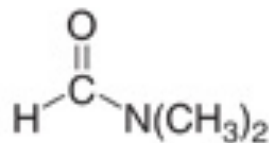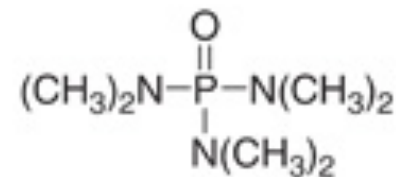

acetone

acetonitrile

tetrahydrofuran
THF

dimethyl sulfoxide
DMSO

dimethylformamide
DMF

hexamethylphosphoramide
HMPA

Nucleophiles in Polar Protic Solvents

Polar aprotic solvents solvate cations by ion—dipole interactions, BUT anions are not well solvated because the solvent cannot hydrogen bond to them. These anions are said to be "naked". These bare, unsolvated anions have greater nucleophilicity and S_N2 reactions occur at a faster rate.
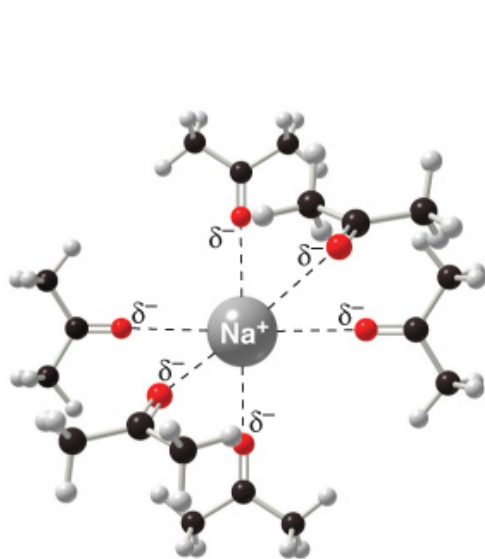
$(CH_3)_2C=O$ solvates Na^+ well by ion–dipole interactions.
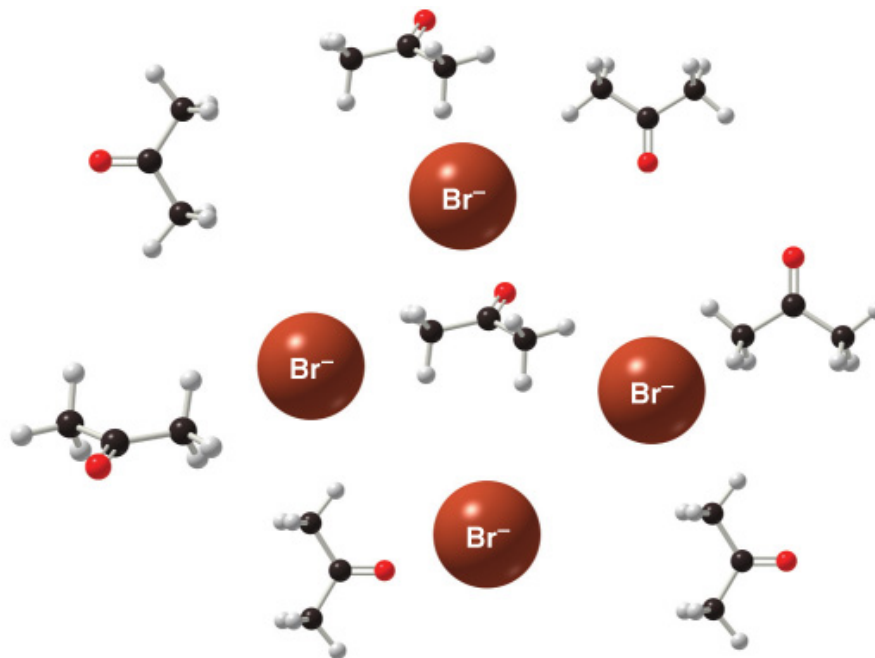
Br^- anions are surrounded by solvent but not well solvated by the $(CH_3)_2C=O$ molecules.

Effects of Polar Protic and Polar Aprotic Solvents
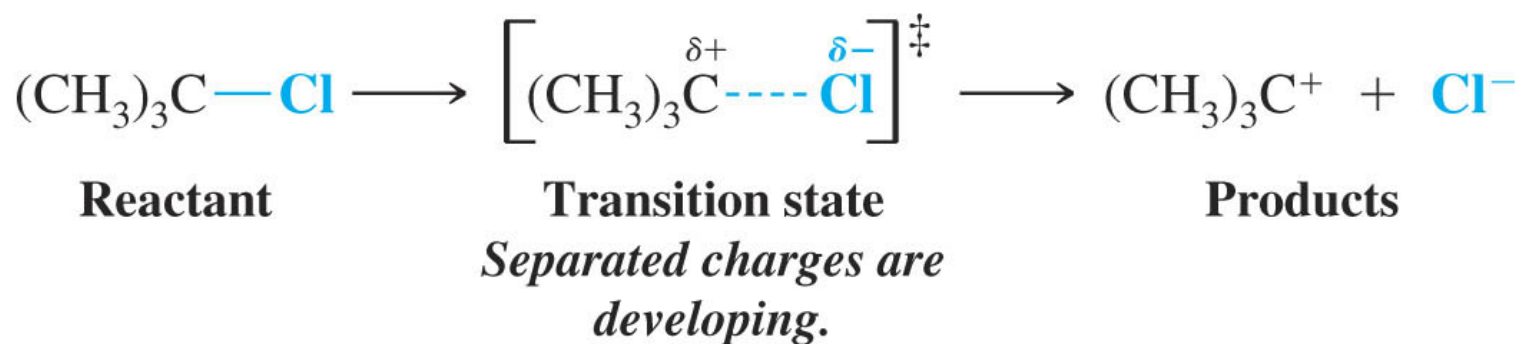
The result is that -

- in polar aprotic solvents, nucleophilicity <u>does</u> parallel basicity, and the stronger base is indeed the stronger nucleophile.

- Because basicity decreases with size down a column, nucleophilicity decreases as well.

Down a column
of the periodic table

F^- Cl^- Br^- I^-

Increasing nucleophilicity
in polar aprotic solvents

- **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 transition state leading to the carbocation thus lowering the activation energy.**
➡ **Water-ethanol and water-methanol mixtures are most common.**

$$(CH_3)_3C-Cl \longrightarrow \left[(CH_3)_3\overset{\delta+}{C}----\overset{\delta-}{Cl}\right]^{\ddagger} \longrightarrow (CH_3)_3C^+ + Cl^-$$

Reactant   Transition state   Products

Separated charges are developing.

● Summary S_N1 vs. S_N2

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

$$R—I > R—Br > R—Cl \qquad S_N1 \quad or \quad S_N2$$

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)	

Chapter 6

47

Alkyl Halides and Nucleophilic Substitution

Predicting the Likely Mechanism of a Substitution Reaction.

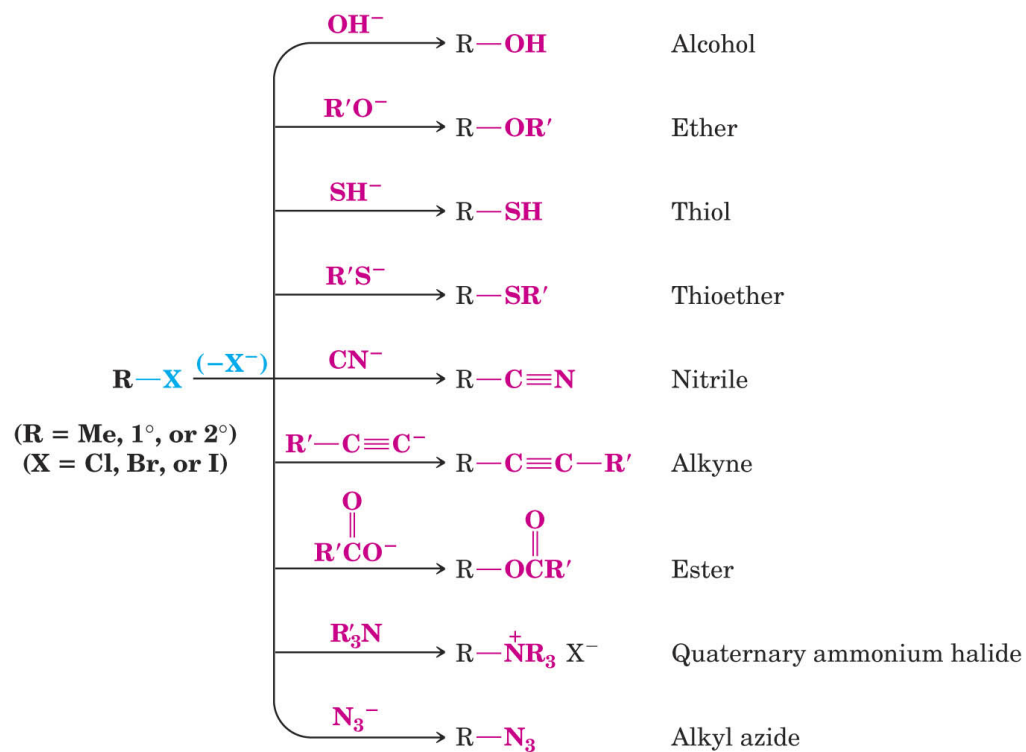**TABLE 7.7** Summary of Factors that Determine the S_N1 or S_N2 Mechanism

Alkyl halide	Mechanism	Other factors
CH_3X RCH_2X (1°)	S_N2	Favored by • **strong nucleophiles** (usually a net negative charge) • polar **aprotic** solvents
R_3CX (3°)	S_N1	Favored by • **weak nucleophiles** (usually neutral) • polar **protic** solvents
R_2CHX (2°)	S_N1 or S_N2	The mechanism depends on the conditions. • **Strong nucleophiles favor the S_N2 mechanism over the S_N1 mechanism.** For example, RO^- is a stronger nucleophile than ROH, so RO^- favors the S_N2 reaction and ROH favors the S_N1 reaction. • **Protic solvents favor the S_N1 mechanism and aprotic solvents favor the S_N2 mechanism.** For example, H_2O and CH_3OH are polar protic solvents that favor the S_N1 mechanism, whereas acetone [$(CH_3)_2C{=}O$] and DMSO [$(CH_3)_2S{=}O$] are polar aprotic solvents that favor the S_N2 mechanism.

Predicting the Mechanism of a Nucleophilic Substitution Reaction

S_N1 reactions are favored by tertiary substrates, by good leaving groups, by nonbasic (i.e., weak) nucleophiles, and by polar protic solvents.

S_N2 reactions are favored by primary substrates, by good leaving groups, by good nucleophiles, and by polar aprotic solvents

♦ Organic Synthesis: Functional Group Transformations Using S$_N$2 Reactions

OH^- → R—OH   Alcohol

$R'O^-$ → R—OR'   Ether

SH^- → R—SH   Thiol

$R'S^-$ → R—SR'   Thioether

$R—X \xrightarrow{(-X^-)}$

(R = Me, 1°, or 2°)
(X = Cl, Br, or I)

CN^- → R—C≡N   Nitrile

$R'—C≡C^-$ → R—C≡C—R'   Alkyne

$R'CO^-$ (with =O) → R—OCR' (with =O)   Ester

R'_3N → R—$\overset{+}{N}R_3$ X$^-$ Quaternary ammonium halide

N_3^- → R—N$_3$ Alkyl azide

Elimination Reactions

Remember, another major class of organic reactions is **elimination reactions**.

In an elimination reaction, groups X and Y are lost from a larger molecule

$$-\overset{|}{\underset{X}{C}}-\overset{|}{\underset{Y}{C}}- \xrightarrow{\text{(-XY)}} \overset{\diagdown}{\diagup}C=C\overset{\diagup}{\diagdown}$$
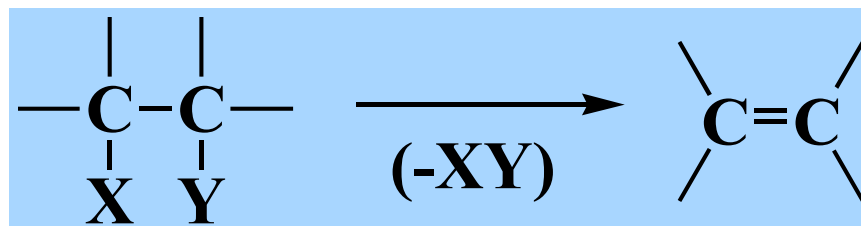
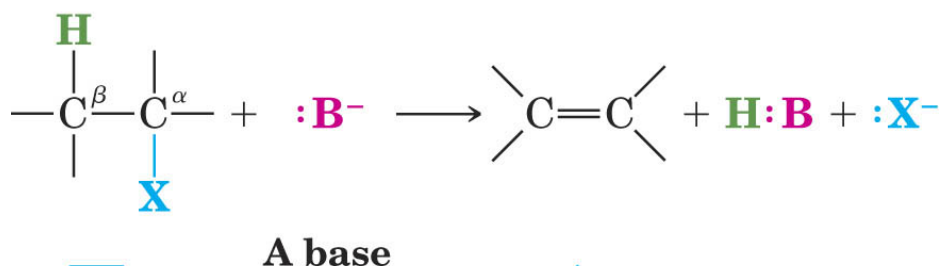When X and Y are on adjacent C's, this is called 1,2-elimination or beta-elimination

♦ **For example, loss of HX from an alkyl halide produces an alkene. This elimination reaction is called DEHYDROHALOGENATION**
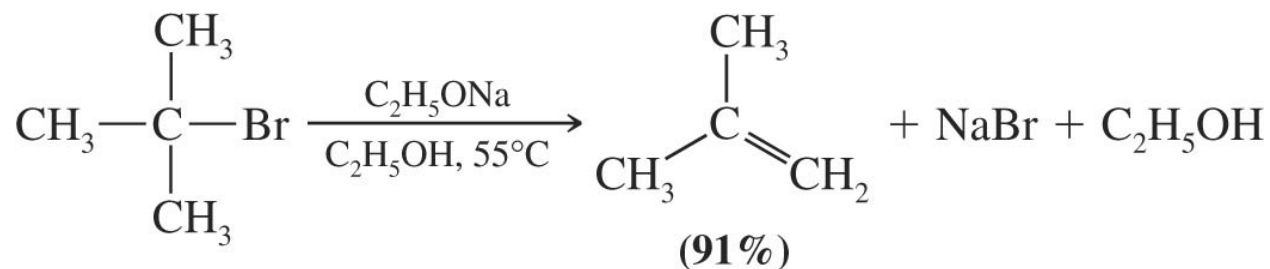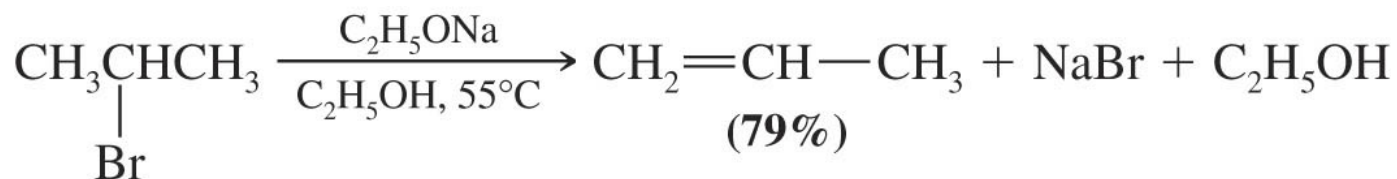
$$-\overset{H}{\underset{X}{\overset{|}{C}}}{}^{\beta}-\overset{|}{C}{}^{\alpha}- + \; :B^- \longrightarrow \overset{\diagdown}{\diagup}C=C\overset{\diagup}{\diagdown} + H:B + :X^-$$
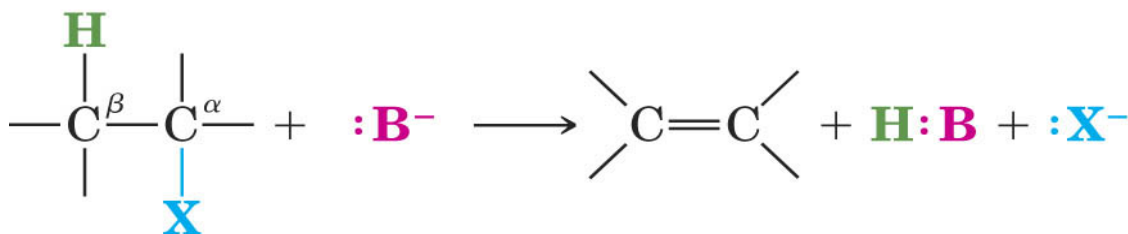
A base

Elimination Reactions of Alkyl Halides

A base

♦ **Useful for the synthesis of alkenes**

♦ **Strong bases such as alkoxides favor this elimination reaction**

$$CH_3CHCH_3 \ (Br) \xrightarrow[\text{C}_2\text{H}_5\text{OH, 55°C}]{\text{C}_2\text{H}_5\text{ONa}} CH_2{=}CH{-}CH_3 + NaBr + C_2H_5OH$$

(79%)

(91%)

Alkoxide bases are made from the corresponding alcohols

By adding metallic Na or K to carefully dried alcohol

$$2\ CH_3CH_2\ddot{O}H + 2\ Na \longrightarrow 2\ CH_3CH_2\ddot{O}:^-Na^+ + H_2$$

Ethanol
(excess)

Sodium ethoxide
dissolved in
excess ethanol

$$2\ CH_3\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}-\ddot{O}H + 2\ K \longrightarrow 2\ CH_3\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}-\ddot{O}:^-K^+ + H_2$$

tert-Butyl alcohol
(excess)

Potassium tert-butoxide
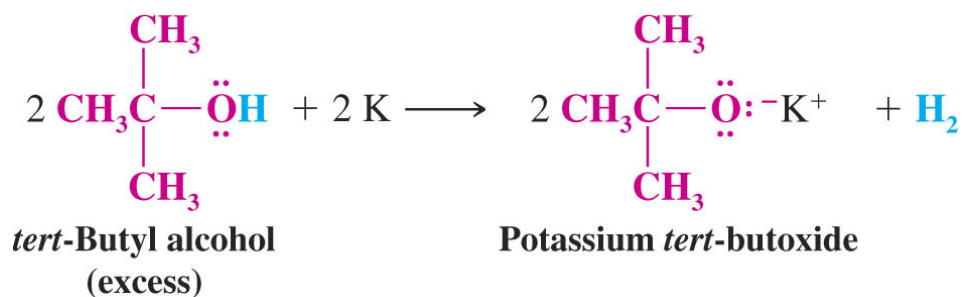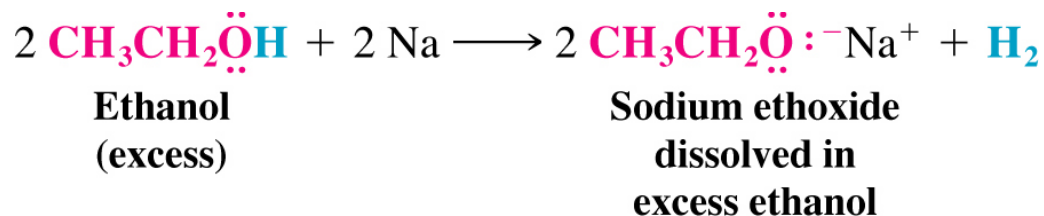
Or by using a stronger base like sodium hydride (NaH)

$$R-\ddot{O}-H + Na^+:H^- \longrightarrow R-\ddot{O}:^-Na^+ + H-H$$

$pK_a = 16$

$pK_a = 35$

Mechanism of Dehydrohalogenation: the E2 Reaction

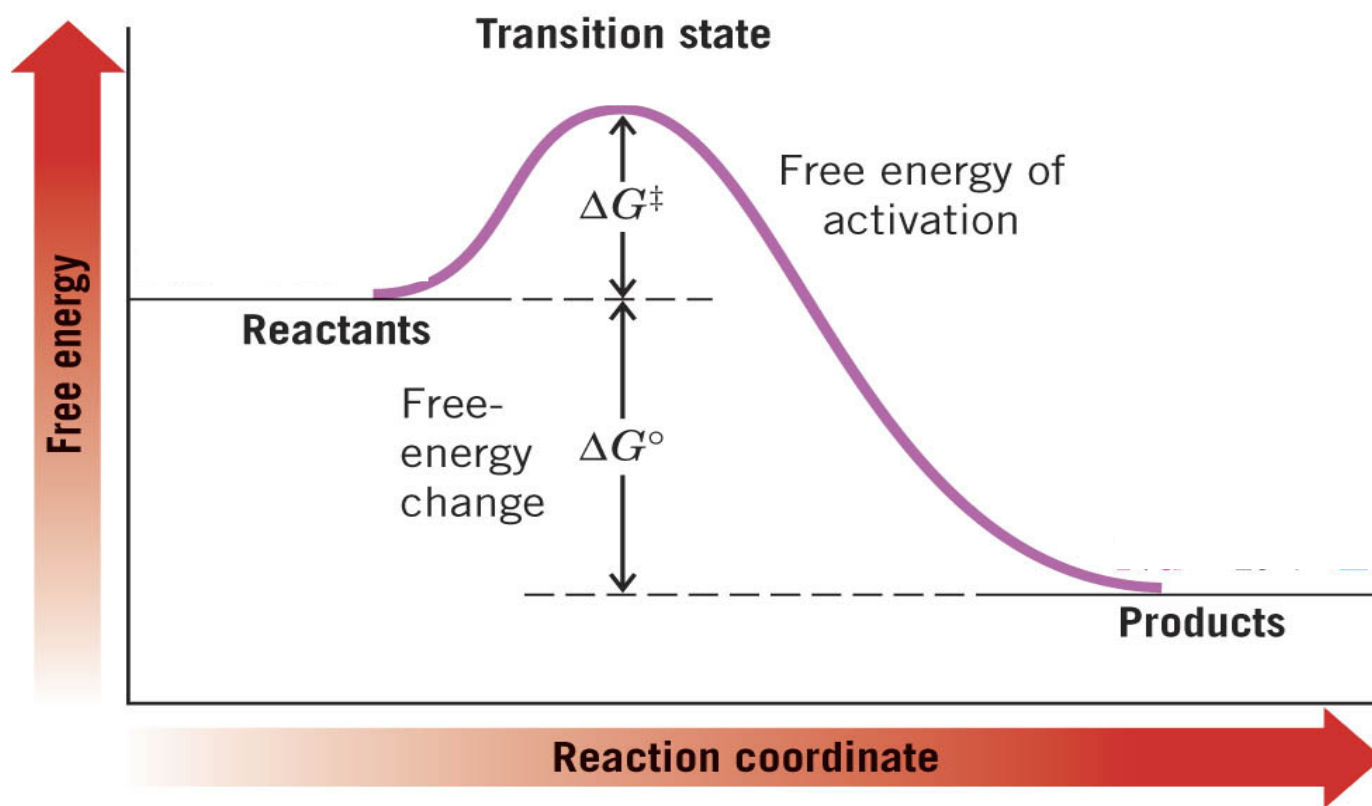**The reaction of isopropyl bromide with sodium ethoxide shows second order kinetics**
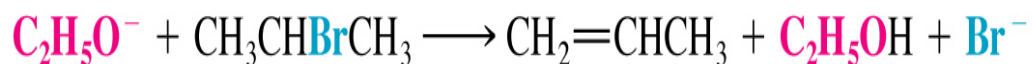
$$C_2H_5O^- + CH_3CHBrCH_3 \longrightarrow CH_2{=}CHCH_3 + C_2H_5OH + Br^-$$

$$\text{Rate} \propto [CH_3CHBrCH_3][C_2H_5O^-]$$
$$\text{Rate} = k[CH_3CHBrCH_3][C_2H_5O^-]$$

Mechanism:

Transition state
Partial bonds in the transition state
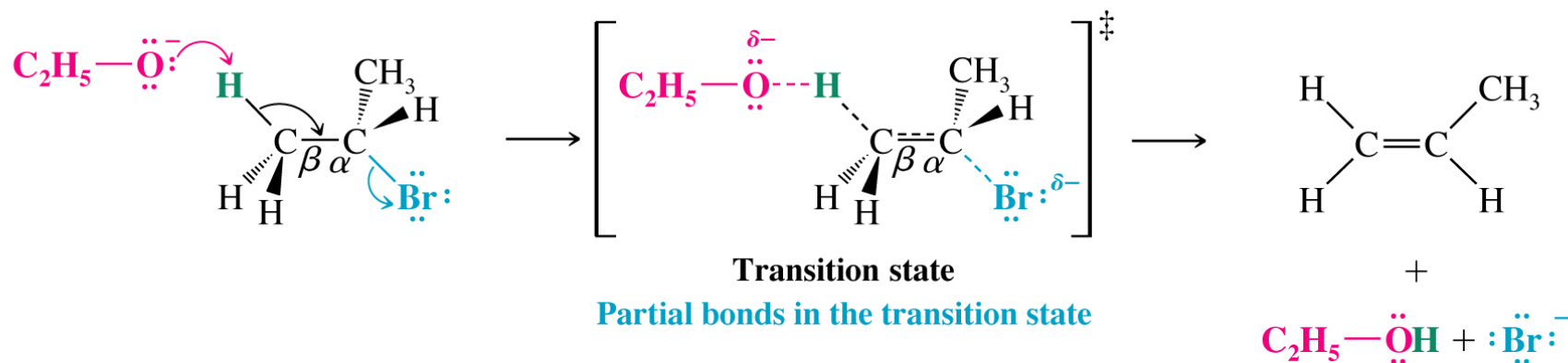
Energy diagram of the E2 reaction

$$C_2H_5O^- + CH_3CHBrCH_3 \longrightarrow CH_2{=}CHCH_3 + C_2H_5OH + Br^-$$

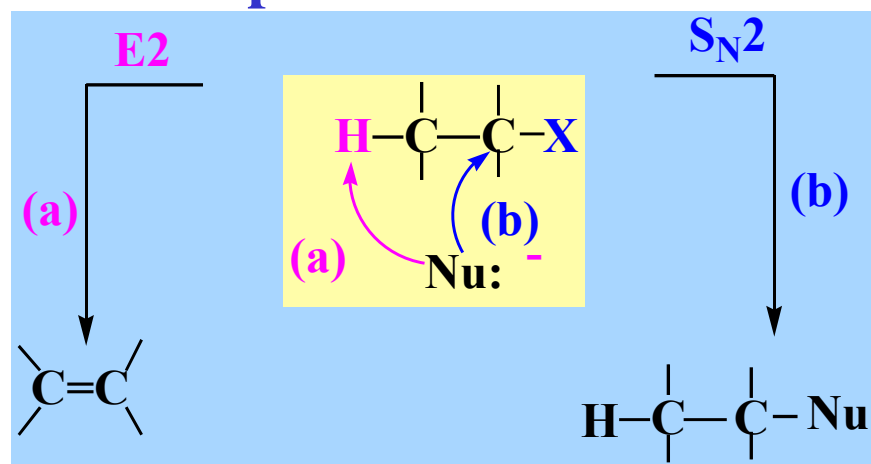**Concerted means a single step, with no intermediates – like S_N2**

Substitution versus Elimination

Every time an S_N2 reaction takes place, there will also be some E2 occurring as well.
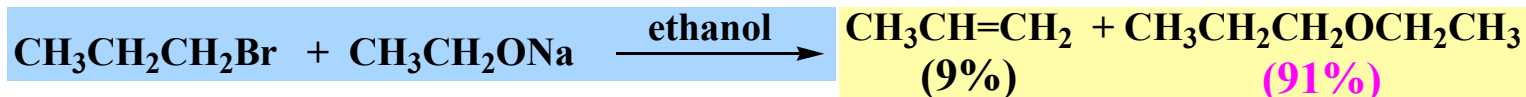
Why? **Because nucleophiles are also bases.**

$$\text{Rate} = k_{elim}\,[\text{RX}]\,[\text{Nu}^-] \qquad \text{Rate} = k_{sub}[\text{RX}][\text{Nu}^-]$$

However, this competition depends on the structure of RX and choice of base.

♦ Substitution versus Elimination

● S$_N$2 VERSUS E2

➡ PRIMARY SUBSTRATE

★ **If the base is small**, S$_N$2 is favored because approach at carbon is unhindered

$$CH_3CH_2CH_2Br + CH_3CH_2ONa \xrightarrow{\text{ethanol}} CH_3CH=CH_2 + CH_3CH_2CH_2OCH_2CH_3$$
$$(9\%) \qquad\qquad (91\%)$$

★ **If the base is bulky**, E2 is favored because approach at carbon is hindered

$$CH_3CH_2CH_2Br + CH_3\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}OK \xrightarrow{\text{t-butyl alcohol}} CH_3CH=CH_2 + CH_3CH_2CH_2OC(CH_3)_3$$
$$(85\%) \qquad\qquad (15\%)$$

potassium tert-butoxide
(a hindered base)
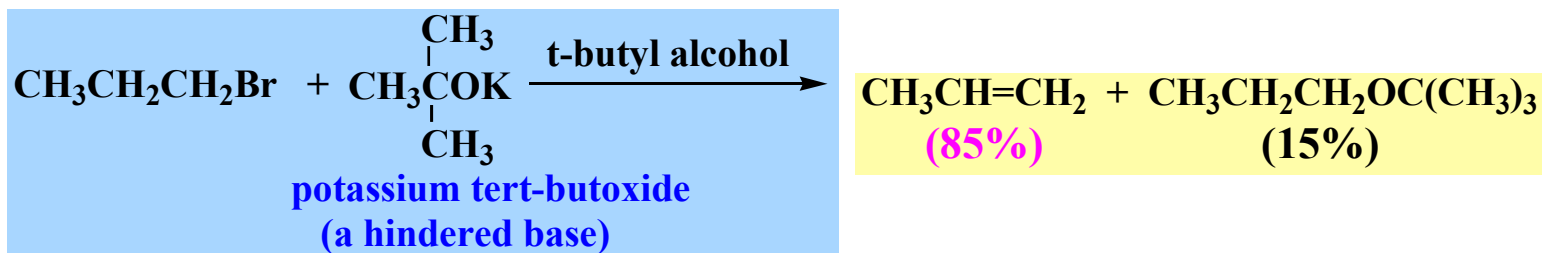
➡ SECONDARY SUBSTRATE

★**Approach to carbon is sterically hindered and E2 ELIMINATION IS FAVORED, especially if the base is strong.**

$$CH_3CH_2O^-Na^+ + CH_3\underset{\underset{Br}{|}}{CH}CH_3 \xrightarrow[\substack{55°C \\ (-NaBr)}]{C_2H_5OH} CH_3\underset{\underset{OCH_2CH_3}{|}}{CH}CH_3 + CH_2{=}CHCH_3$$
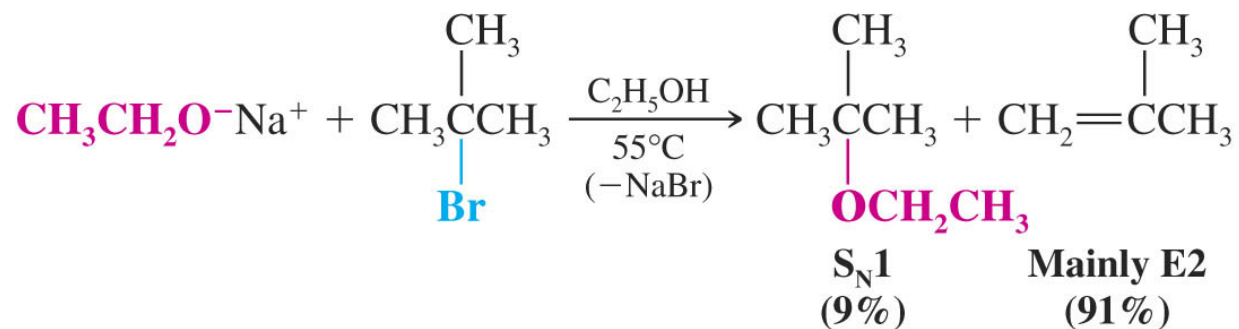
$$\underset{\substack{S_N2 \\ (21\%)}}{} \qquad \underset{\substack{E2 \\ (79\%)}}{}$$
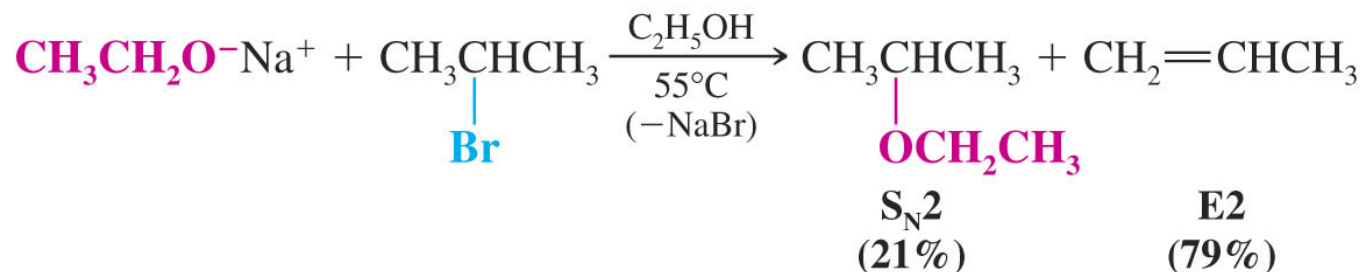
➡ TERTIARY SUBSTRATE

★**Approach to carbon is extremely hindered and ELIMINATION PREDOMINATES.**

$$CH_3CH_2O^-Na^+ + CH_3\underset{\underset{Br}{|}}{\overset{\overset{CH_3}{|}}{C}}CH_3 \xrightarrow[\substack{55°C \\ (-NaBr)}]{C_2H_5OH} CH_3\underset{\underset{OCH_2CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}CH_3 + CH_2{=}\overset{\overset{CH_3}{|}}{C}CH_3$$

$$\underset{\substack{S_N1 \\ (9\%)}}{} \qquad \underset{\substack{\text{Mainly E2} \\ (91\%)}}{}$$
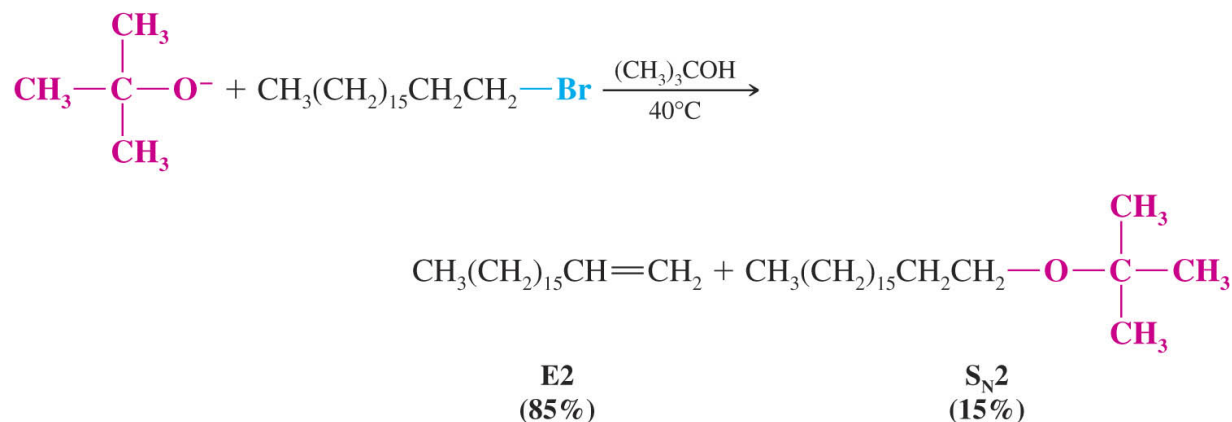
Chapter 6

➡ EFFECT OF TEMPERATURE

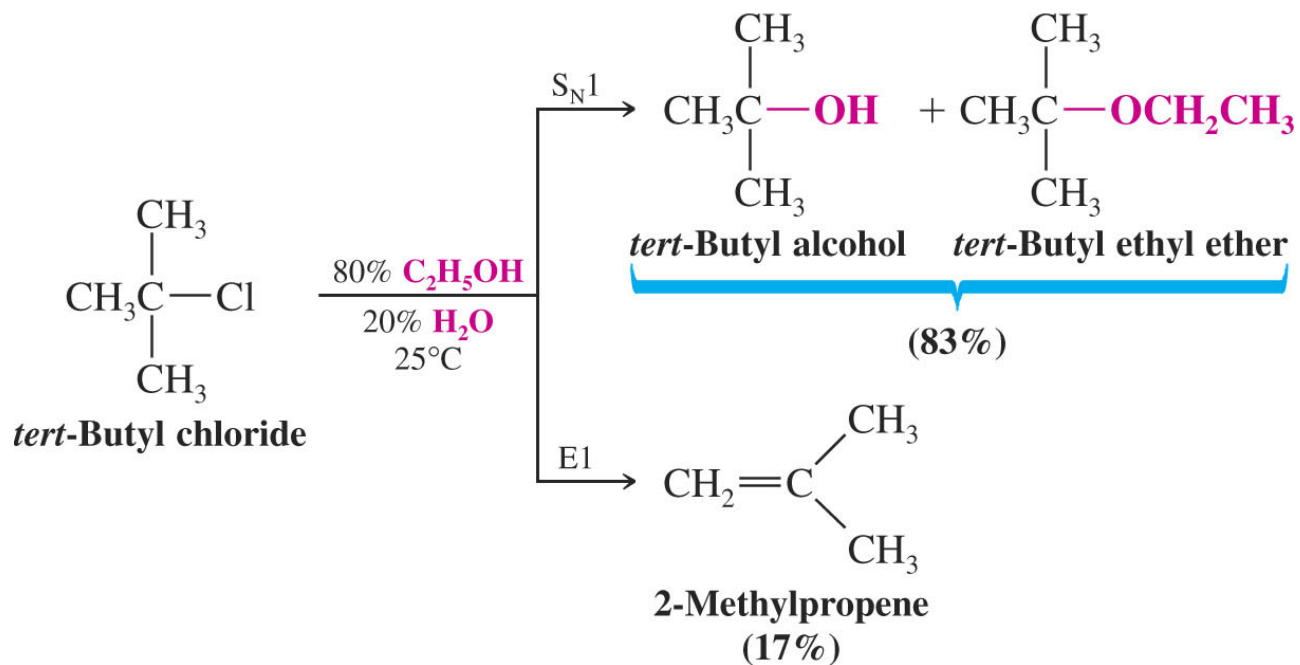★ **Increasing temperature favors elimination over substitution**

➡ EFFECT OF THE SIZE OF THE BASE/NUCLEOPHILE

★ **Large, sterically hindered bases favor elimination because they cannot directly approach the carbon closely enough to react in a substitution**

★ **Potassium *tert*-butoxide is an extremely bulky base and is routinely used to favor E2 reaction**

$$CH_3-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-O^- + CH_3(CH_2)_{15}CH_2CH_2-Br \xrightarrow[40°C]{(CH_3)_3COH}$$

$$CH_3(CH_2)_{15}CH=CH_2 + CH_3(CH_2)_{15}CH_2CH_2-O-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_3$$
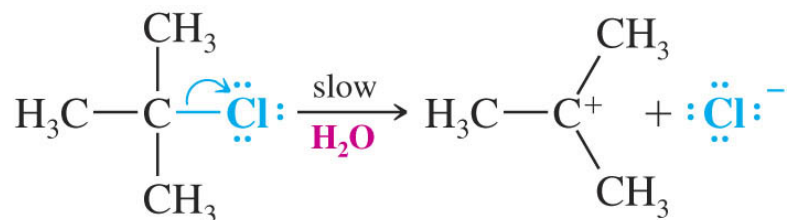
| E2 | S_N2 |
| (85%) | (15%) |

♦Elimination can also follow first order kinetics: the E1 REACTION

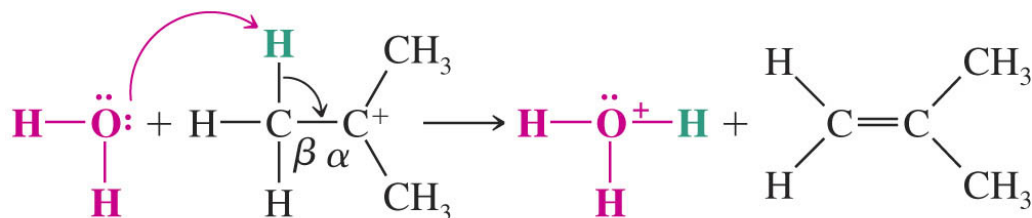**The E1 reaction competes with the S$_N$1 reaction and likewise goes through a carbocation intermediate**

tert-Butyl chloride → 80% C$_2$H$_5$OH, 20% H$_2$O, 25°C

S$_N$1 → tert-Butyl alcohol + tert-Butyl ethyl ether (83%)

E1 → 2-Methylpropene (17%)

Mechanism for E1

Step 1

Slow step is ionization of C-Cl bond, aided by solvent
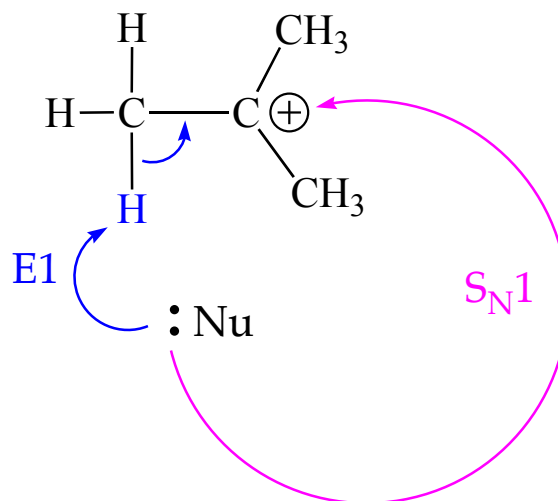
Step 2

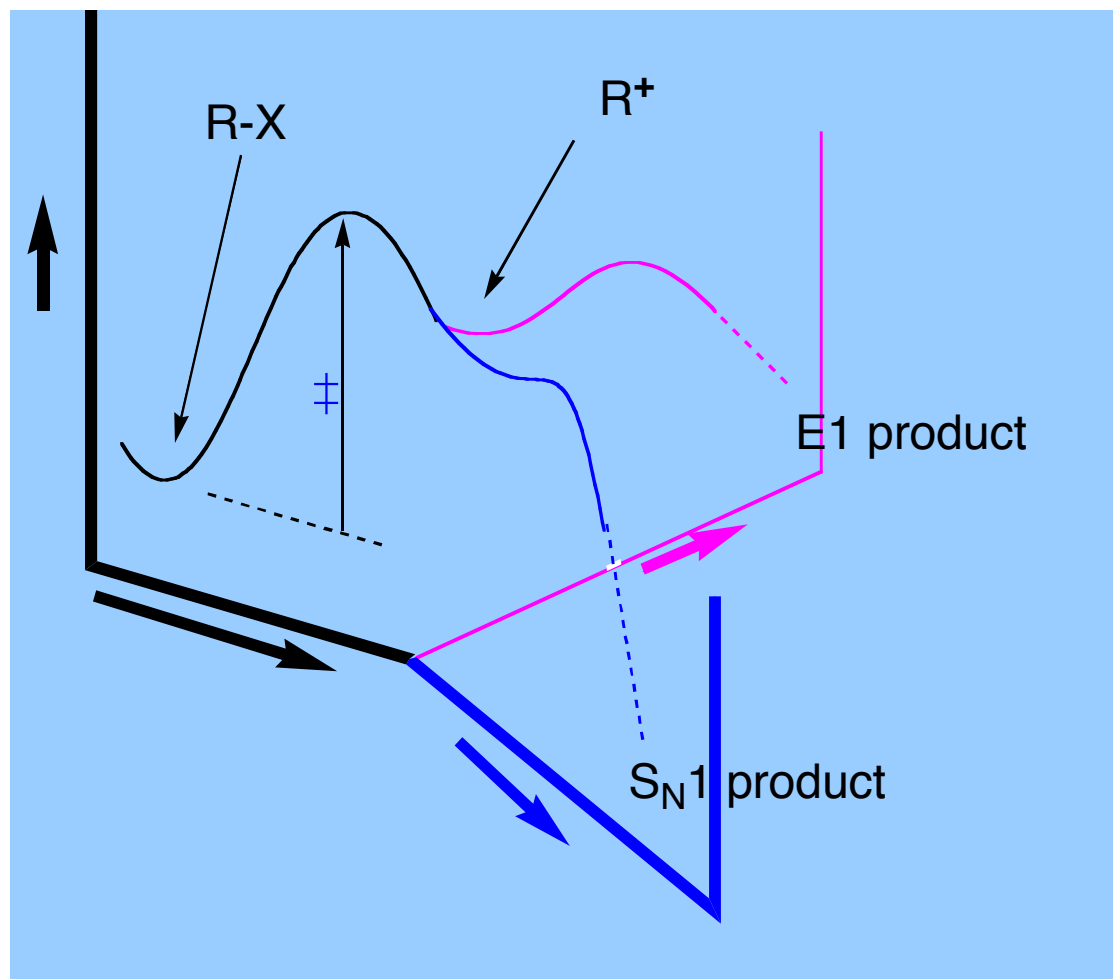**Water can act as nucleophile (S_N1) OR as base (E1)**

Mechanism for E1

In other words, there are two competing pathways that a carbocation can take:

1. The nucleophile bonds to the carbocation carbon giving the S_N1 product.

                            OR

2. The nucleophile acts as a base and removes the β proton giving the E1 product.

Free Energy Diagram for competing pathways

R-X

R$^+$

‡

E1 product

S$_N$1 product

Once the carbocation forms, it can go two different ways
to give the S$_N$1 product and the E1 product.

♦ Overall Summary

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)	

Overall Summary of Substitution/Elimination
Effect of Substrate Structure

	S_N1	S_N2	E1	E2
CH_3X	—	yes, very fast	—	—
RCH_2X	—	mostly	—	but hindered bases give mostly alkenes
$\overset{R'}{\underset{\mid}{R}CHX}$	very little	mostly S_N2 with weak bases	very little	strong bases promote E2
$\overset{R'}{\underset{R''}{R}CX}$	very favorable	none	always competes with S_N1	strong bases promote E2 path

Alkyl Halides and Nucleophilic Substitution

Predicting the Likely Mechanism of a Substitution Reaction.

TABLE 7.7	Summary of Factors that Determine the S_N1 or S_N2 Mechanism	
Alkyl halide	**Mechanism**	**Other factors**
CH_3X RCH$_2$X (1°)	S_N2	Favored by • **strong nucleophiles** (usually a net negative charge) • polar **aprotic** solvents
R_3CX (3°)	S_N1	Favored by • **weak nucleophiles** (usually neutral) • polar **protic** solvents
R_2CHX (2°)	S_N1 or S_N2	The mechanism depends on the conditions. • **Strong nucleophiles favor the S_N2 mechanism over the S_N1 mechanism.** For example, RO$^-$ is a stronger nucleophile than ROH, so RO$^-$ favors the S_N2 reaction and ROH favors the S_N1 reaction. • **Protic solvents favor the S_N1 mechanism and aprotic solvents favor the S_N2 mechanism.** For example, H_2O and CH_3OH are polar protic solvents that favor the S_N1 mechanism, whereas acetone [$(CH_3)_2C=O$] and DMSO [$(CH_3)_2S=O$] are polar aprotic solvents that favor the S_N2 mechanism.