Chapter 6

Nucleophilic Substitution and Elimination Reactions of Alkyl Halides

Created by
**Professor William Tam & Dr. Phillis Chang**

About The Authors

These PowerPoint Lecture Slides were created and prepared by Professor William Tam and his wife, Dr. Phillis Chang.

Professor William Tam received his B.Sc. at the University of Hong Kong in 1990 and his Ph.D. at the University of Toronto (Canada) in 1995. He was an NSERC postdoctoral fellow at the Imperial College (UK) and at Harvard University (USA). He joined the Department of Chemistry at the University of Guelph (Ontario, Canada) in 1998 and is currently a Full Professor and Associate Chair in the department. Professor Tam has received several awards in research and teaching, and according to *Essential Science Indicators*, he is currently ranked as the Top 1% most cited Chemists worldwide. He has published four books and over 80 scientific papers in top international journals such as *J. Am. Chem. Soc., Angew. Chem., Org. Lett.,* and *J. Org. Chem.*

Dr. Phillis Chang received her B.Sc. at New York University (USA) in 1994, her M.Sc. and Ph.D. in 1997 and 2001 at the University of Guelph (Canada). She lives in Guelph with her husband, William, and their son, Matthew.
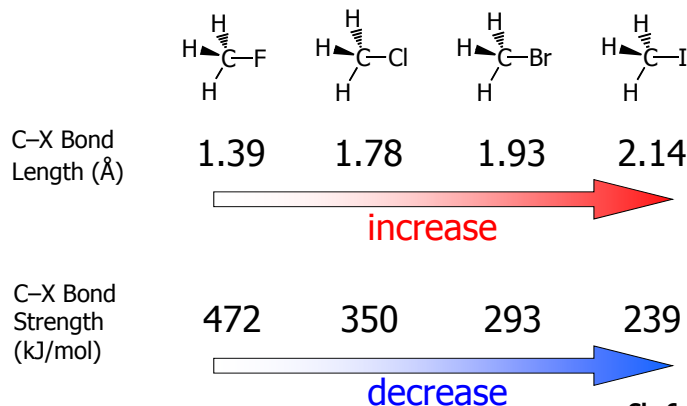
1. Organic Halides

X = Cl, Br, I
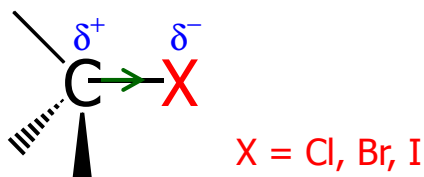
❖ Halogens are more electronegative than carbon

Carbon-Halogen Bond Lengths and Bond Strength

	F	Cl	Br	I
C–X Bond Length (Å)	1.39	1.78	1.93	2.14

increase

	F	Cl	Br	I
C–X Bond Strength (kJ/mol)	472	350	293	239

decrease

1A. Physical Properties of Organic Halides: Boiling Point (bp/°C)

Group	Fluoride	Chloride	Bromide	Iodide
Me	-78.4	-23.8	3.6	42.5
Et	-37.7	13.1	38.4	72
Bu	32	78.4	101	130
sBu	-	68	91.2	120
iBu	-	69	91	119
tBu	12	51	73.3	100(dec)

Physical Properties of Organic Halides: Density (ρ)

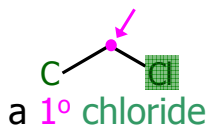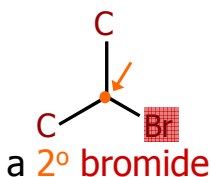| Group	Fluoride	Chloride	Bromide	Iodide
Me	0.84(-60)	0.92	1.73(0)	2.28
Et	0.72	0.91(15)	1.46	1.95
Bu	0.78	0.89	1.27	1.61
sBu	-	0.87	1.26	1.60
iBu	-	0.87	1.26	1.60
tBu	0.75(12)	0.84	1.22	1.57(0)

Different Types of Organic Halides

❖ Alkyl halides (haloalkanes)

sp^3
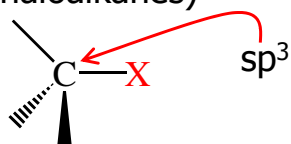
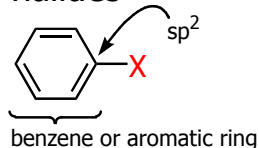| Attached to 1 carbon atom	Attached to 2 carbon atoms	Attached to 3 carbon atoms

a 1° chloride   a 2° bromide   a 3° iodide
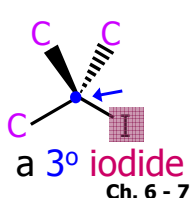
❖ Vinyl halides (Alkenyl halides)
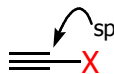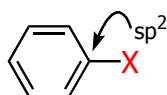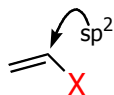
sp^2

❖ Aryl halides

sp^2

benzene or aromatic ring
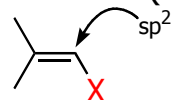
❖ Acetylenic halides (Alkynyl halides)

sp
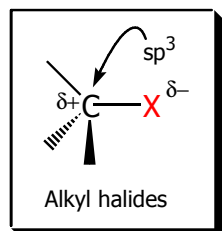
❖ Prone to undergo Nucleophilic Substitutions (S_N) and Elimination Reactions (E) (the focus of this Chapter)

sp^3

$\delta+$ X $\delta-$

Alkyl halides

sp^2 sp^2 sp

X   X   X

❖ Different reactivity than alkyl halides, and do not undergo S_N or E reactions

2. Nucleophilic Substitution Reactions

:Ñu $^\ominus$ + $\delta+$ $\delta-$ C—X   →   Nu—C   +   X $^\ominus$

(nucleophile)   (substrate)   (product)   (leaving group)
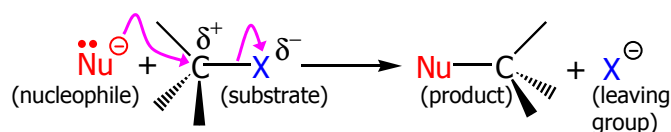
The Nu$^\ominus$ donates an e$^\ominus$ pair to the substrate

The bond between C and LG breaks, giving both e$^\ominus$ from the bond to LG

The Nu$^\ominus$ uses its e$^\ominus$ pair to form a new covalent bond with the substrate C
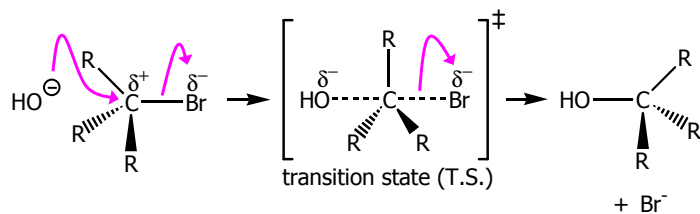
The LG gains the pair of e$^\ominus$ originally bonded in the substrate

Timing of The Bond Breaking & Bond Making Process
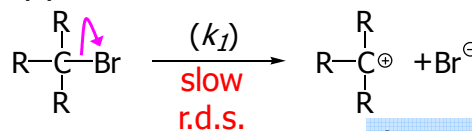
❖ Two types of mechanisms
- 1st type: S_N2 (concerted mechanism)

HO$^\ominus$ $\delta+$ $\delta-$ C—Br   →   [HO----C----Br]‡ →   HO—C

transition state (T.S.)

+ Br$^-$

- 2nd type: S_N1 (stepwise mechanism)

Step (1):

R—C—Br $\xrightarrow[\text{slow r.d.s.}]{(k_1)}$ R—C$\oplus$ + Br$^\ominus$

Step (2)

R—C$\oplus$ + H$_2$Ö: $\underset{\text{fast}}{\overset{(k_2)}{\rightleftharpoons}}$ R—C—O$\oplus$H$_2$

$k_1 << k_2$ and k_3

Step (3)

R—C—O$\oplus$H$_2$ + H$_2$Ö $\underset{\text{fast}}{\overset{(k_3)}{\rightleftharpoons}}$ R—C—OH + H$_3$O$^+$
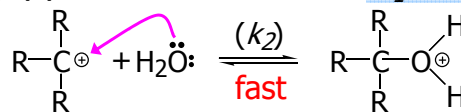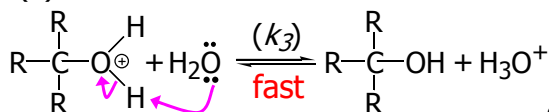
3. Nucleophiles

❖ A reagent that seeks a positive center
❖ Has an unshared pair of $e^{\ominus}$
   e.g.: $HO^{\ominus}$, $CH_3O^{\ominus}$, $H_2N^{\ominus}$ (negative charge)

   $H_2\ddot{O}$, $\ddot{N}H_3$ (neutral)

This is the positive center that the $Nu^{\ominus}$ seeks

$$\delta^+ \quad \delta^-$$
$$C—X$$

❖ Examples:

$$HO\ddot{:}^{\ominus} + CH_3\overset{H\ \ H}{\underset{Cl}{C}} \longrightarrow CH_3\overset{H\ \ H}{\underset{OH}{C}} + Cl^{\ominus}$$

($Nu^{\ominus}$) (substrate) (product) (L.G.)

$$H\overset{\ddot{O}}{\ }H + CH_3\overset{H\ \ H}{\underset{Cl}{C}} \longrightarrow CH_3\overset{H\ \ H}{\underset{\overset{\oplus}{O}H}{C}} + Cl^{\ominus}$$

($Nu^{\ominus}$) (substrate) H (L.G.)

(product) $CH_3\overset{H\ \ H}{\underset{OH}{C}} + H_3O^{\oplus}$
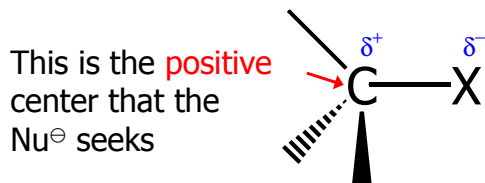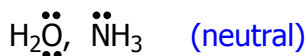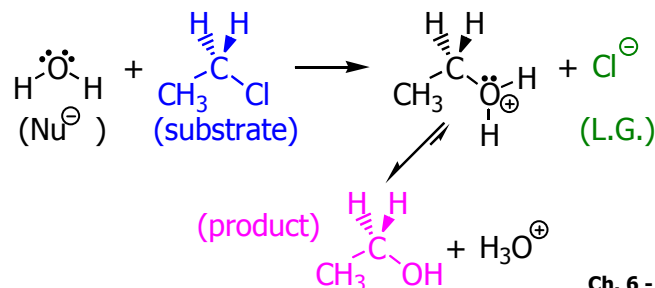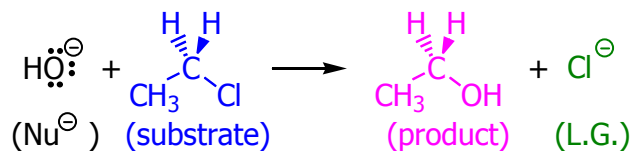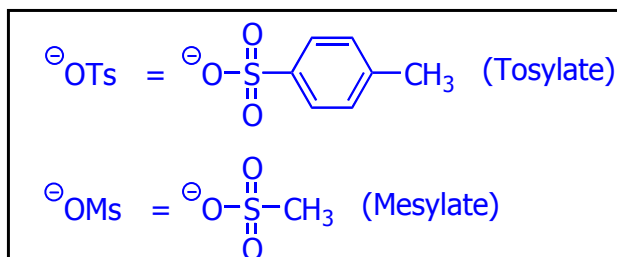
4. Leaving Groups

❖ To be a good leaving group, the substituent must be able to leave as a relatively stable, weakly basic molecule or ion
   e.g.: $I^{\ominus}$, $Br^{\ominus}$, $Cl^{\ominus}$, $TsO^{\ominus}$, $MsO^{\ominus}$, H_2O, NH_3

$$^{\ominus}OTs = ^{\ominus}O-\overset{O}{\underset{O}{S}}-\bigcirc-CH_3 \quad \text{(Tosylate)}$$

$$^{\ominus}OMs = ^{\ominus}O-\overset{O}{\underset{O}{S}}-CH_3 \quad \text{(Mesylate)}$$

5. Kinetics of a Nucleophilic Substitution Reaction: An S_N2 Reaction
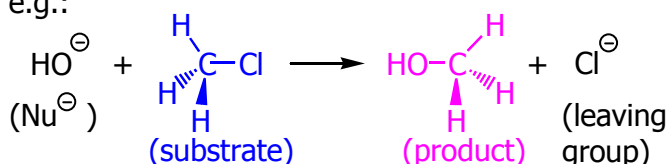
$$HO^{\ominus} + CH_3-Br \longrightarrow HO-CH_3 + Br^{\ominus}$$

$$\text{Rate} = k[CH_3Br][OH^-]$$

❖ The rate of the substitution reaction is linearly dependent on the concentration of $OH^{\ominus}$ and CH_3Br
❖ Overall, a *second-order* reaction $\Rightarrow$ bimolecular

5A. How Do We Measure the Rate of This Reaction?

e.g.:

$$HO^{\ominus} + \overset{H}{\underset{H}{\overset{|}{C}}}-Cl \longrightarrow HO-\overset{H}{\underset{H}{C}} + Cl^{\ominus}$$

($Nu^{\ominus}$) (substrate) (product) (leaving group)
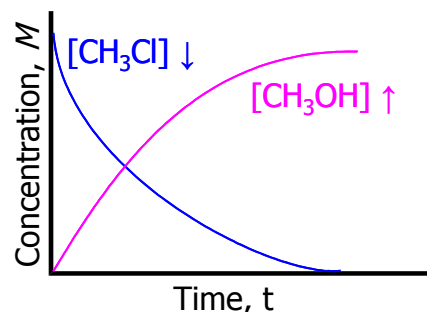
❖ The rate of reaction can be measured by
  ● The consumption of the reactants ($HO^{\ominus}$ or CH_3Cl) or
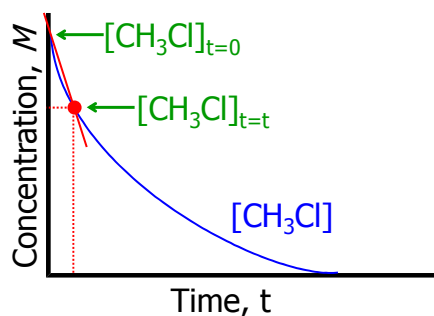 ● The appearance of the products (CH_3OH or $Cl^{\ominus}$) over time

Graphically...

Concentration, M — $[CH_3Cl]\downarrow$ — $[CH_3OH]\uparrow$

Time, t

$$\text{Rate} = \frac{\Delta[CH_3Cl]}{\Delta t} = -\left\{\frac{[CH_3Cl]_{t=t} - [CH_3Cl]_{t=0}}{\text{Time in seconds}}\right\}$$

Initial Rate

Initial Rate
(from slope) $= -\left\{\dfrac{[CH_3Cl]_{t=t} - [CH_3Cl]_{t=0}}{\Delta t}\right\}$

Ch. 6 - 19

❖ Example:

$$HO^{\ominus} + Cl-CH_3 \xrightarrow[H_2O]{60^oC} HO-CH_3 + Cl^{\ominus}$$
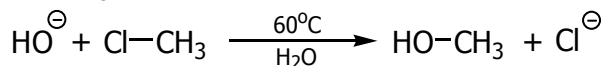
$[OH^{\ominus}]_{t=0}$	$[CH_3Cl]_{t=0}$	Initial rate mole L^{-1}, s^{-1}	Result
1.0 M	0.0010 M	4.9×10^{-7}	
1.0 M	0.0020 M	9.8×10^{-7}	Doubled
2.0 M	0.0010 M	9.8×10^{-7}	Doubled
2.0 M	0.0020 M	19.6×10^{-7}	Quadrupled

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❖ Conclusion:

$$HO^{\ominus} + Cl-CH_3 \xrightarrow[H_2O]{60^oC} HO-CH_3 + Cl^{\ominus}$$
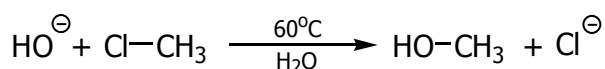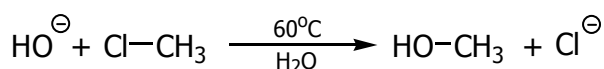
- The rate of reaction is directly proportional to the concentration of either reactant.

- When the concentration of either reactant is doubled, the rate of reaction doubles.
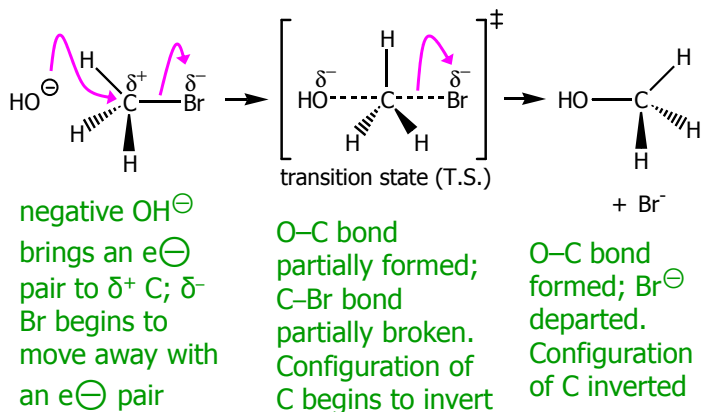
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The Kinetic Rate Expression

$$HO^{\ominus} + Cl-CH_3 \xrightarrow[H_2O]{60^oC} HO-CH_3 + Cl^{\ominus}$$

Rate α $[OH^{\ominus}][CH_3Cl]$

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

$k = \dfrac{\text{Initial Rate}}{[OH^{\ominus}][CH_3Cl]}$

$= 4.9 \times 10^{-7}$ L mol^{-1} s^{-1}

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6. A Mechanism for the S$_N$2 Reaction

negative OH$^{\ominus}$ brings an e$^{\ominus}$ pair to δ$^+$ C; δ$^-$ Br begins to move away with an e$^{\ominus}$ pair

O–C bond partially formed; C–Br bond partially broken. Configuration of C begins to invert

O–C bond formed; Br$^{\ominus}$ departed. Configuration of C inverted

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7. Transition State Theory: Free Energy Diagrams

❖ A reaction that proceeds with a negative free-energy change (releases energy to its surroundings) is said to be **exergonic**

❖ A reaction that proceeds with a positive free-energy change (absorbs energy from its surroundings) is said to be **endergonic**

Ch. 6 - 24

❖ At 60°C (333 K)

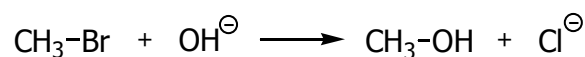$$CH_3-Br + OH^{\ominus} \longrightarrow CH_3-OH + Cl^{\ominus}$$
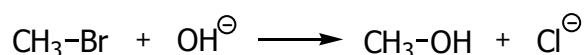
$$\Delta G^o = -100 \text{ kJ/mol}$$

● This reaction is highly **exergonic**

$$\Delta H^o = -75 \text{ kJ/mol}$$

● This reaction is **exothermic**

$$CH_3-Br + OH^{\ominus} \longrightarrow CH_3-OH + Cl^{\ominus}$$

● Its equilibrium constant (K_{eq}) is

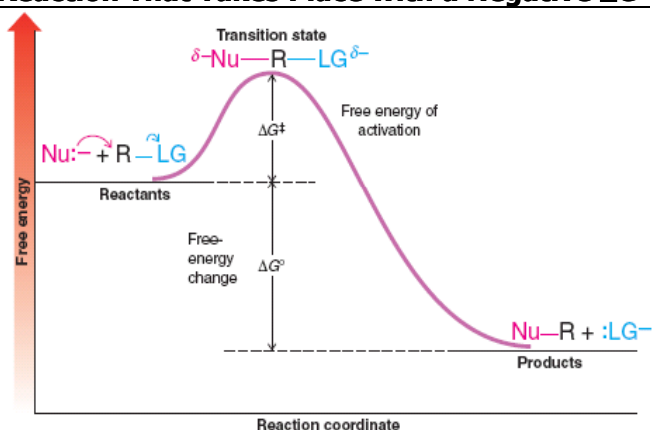$$\Delta G^o = -RT \ln K_{eq}$$

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

$$= \frac{-(-100 \text{ kJ/mol})}{(0.00831 \text{ kJ K}^{-1} \text{ mol}^{-1})(333 \text{ K})}$$

$$= 36.1$$

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

A Free Energy Diagram for a Hypothetical S$_N$2 Reaction That Takes Place with a Negative ΔG^o

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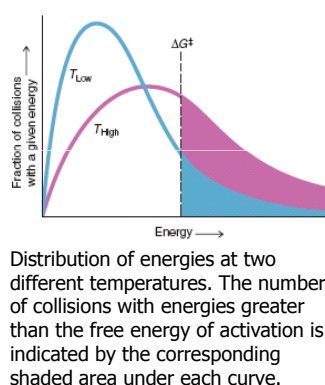
❖ The **reaction coordinate** indicates the progress of the reaction, in terms of the conversion of reactants to products

❖ The top of the energy curve corresponds to the **transition state** for the reaction

❖ The **free energy of activation** (ΔG‡) for the reaction is the difference in energy between the reactants and the transition state

❖ The **free energy change for the reaction** (ΔG^o) is the difference in energy between the reactants and the products

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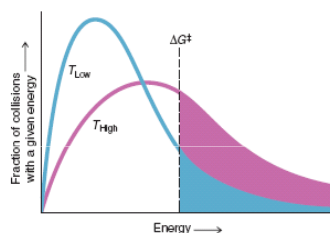**A Free Energy Diagram for a Hypothetical Reaction with a Positive Free-Energy Change**
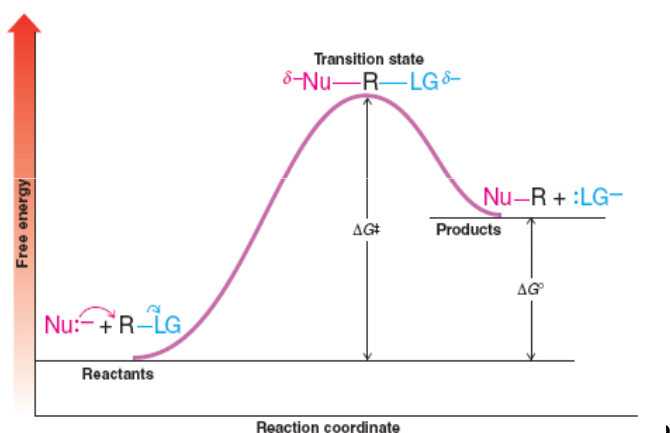
7A. Temperature, Reaction Rate, and the Equilibrium Constant

Distribution of energies at two different temperatures. The number of collisions with energies greater than the free energy of activation is indicated by the corresponding shaded area under each curve.

❖ A 10°C increase in temperature will cause the reaction rate to double for many reactions taking place near room temperature

❖ The relationship between the rate constant (k) and $\Delta G^{\ddagger}$ is *exponential* :

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

e = 2.718, the base of natural logarithms

k_0 = absolute rate constant, which equals the rate at which all transition states proceed to products (At 25°C, $k_0 = 6.2 \times 10^{12}\ s^{-1}$)

Distribution of energies at two different temperatures. The number of collisions with energies greater than the free energy of activation is indicated by the corresponding shaded area under each curve.
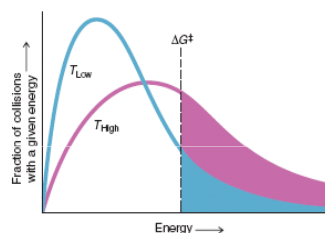

❖ A reaction with a lower free energy of activation ($\Delta G^{\ddagger}$) will occur exponentially faster than a reaction with a higher $\Delta G^{\ddagger}$, as dictated by
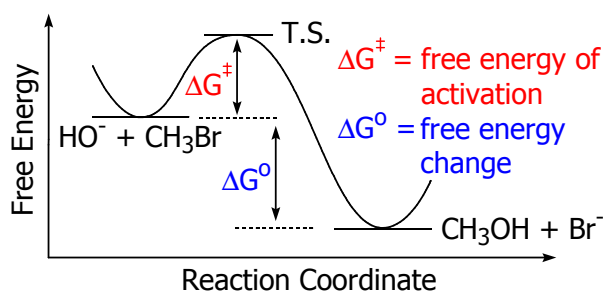
$$k = k_0\, e^{-\Delta G^{\ddagger}/RT}$$

Distribution of energies at two different temperatures. The number of collisions with energies greater than the free energy of activation is indicated by the corresponding shaded area under each curve.

Free Energy Diagram of S$_N$2 Reactions

T.S.

$\Delta G^{\ddagger}$ = free energy of activation

ΔG^{o} = free energy change

HO⁻ + CH₃Br

$\Delta G^{\ddagger}$

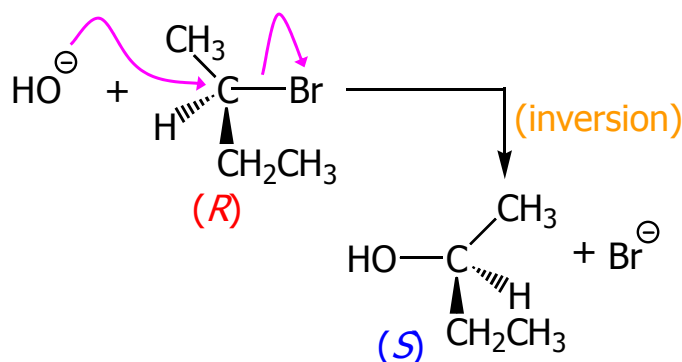ΔG^{o}

CH₃OH + Br⁻

Reaction Coordinate

Free Energy

❖ Exothermic (ΔG^o is negative)
❖ Thermodynamically favorable process

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8. The Stereochemistry of S$_N$2 Reactions

❖ Inversion of configuration
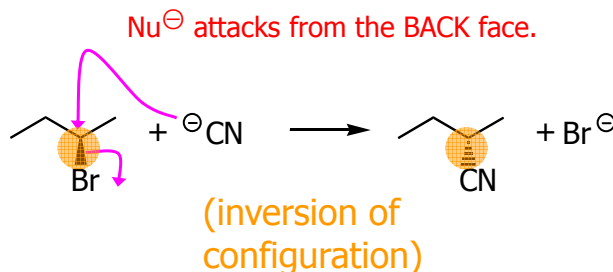

$HO^{\ominus}$ + ... C—Br → (inversion)

CH₃

H

CH₂CH₃

(*R*)

HO—C

CH₃

H

CH₂CH₃

+ $Br^{\ominus}$

(*S*)

❖ Example:

Nu$^{\ominus}$ attacks from the TOP face.

CH₃ ... I + $^{\ominus}OCH_3$

(inversion of configuration)

CH₃ ... OCH₃ + I$^{\ominus}$

❖ Example:

Nu$^{\ominus}$ attacks from the BACK face.

+ $^{\ominus}CN$ → + $Br^{\ominus}$

Br

CN

(inversion of configuration)
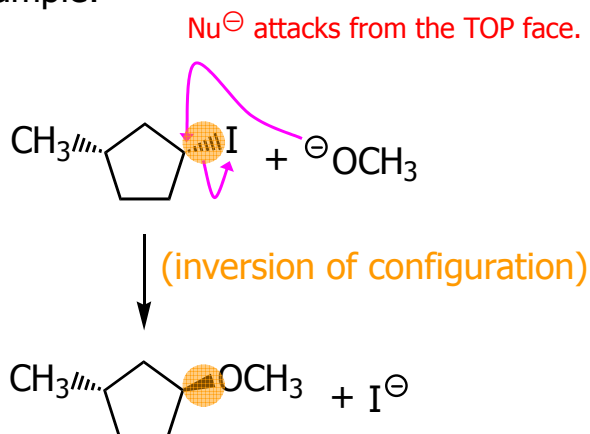
9. The Reaction of tert-Butyl Chloride with Hydroxide Ion: An S_N1 Reaction

$$CH_3-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-Br + H_2\ddot{O} \longrightarrow CH_3-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-OH + HBr$$
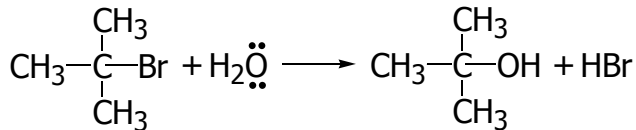
- The rate of S_N1 reactions depends only on concentration of the alkyl halide and is independent on concentration of the $Nu^{\ominus}$
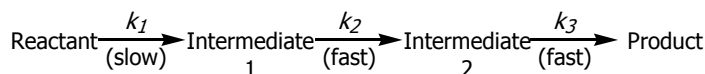
  Rate = k[RX]

  In other words, it is a *first-order* reaction
  $\Rightarrow$ unimolecular nucleophilic substitution
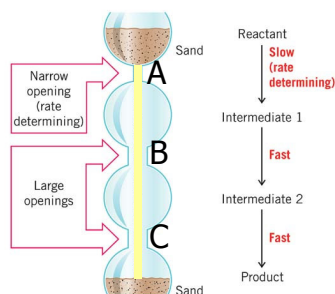
9A. Multistep Reactions & the Rate-Determining Step

- In a multistep reaction, the rate of the overall reaction is the same as the rate of the **SLOWEST** step, known as the rate-determining step (r.d.s)

- For example:

$$Reactant \xrightarrow[(slow)]{k_1} Intermediate\ 1 \xrightarrow[(fast)]{k_2} Intermediate\ 2 \xrightarrow[(fast)]{k_3} Product$$
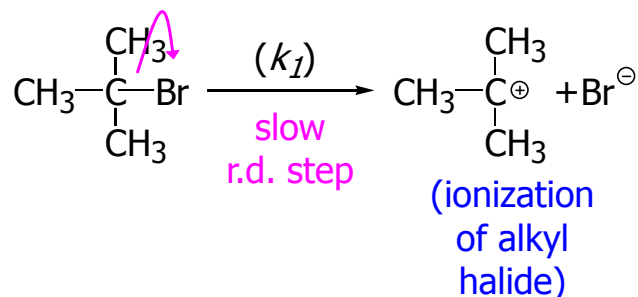
$$k_1 << k_2\ or\ k_3$$

- ❖ The opening A is much smaller than openings B and C
- ❖ The overall rate at which sand reaches to the bottom of the hourglass is limited by the rate at which sand falls through opening A
- ❖ Opening A is analogous to the rate-determining step of a multistep reaction
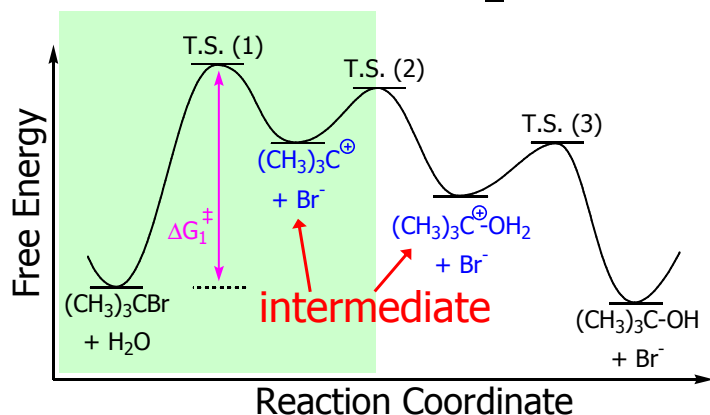
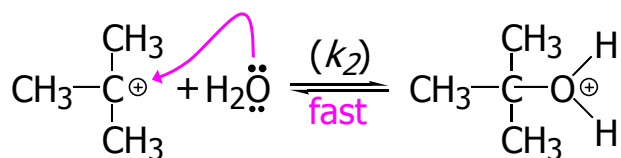## 10. A Mechanism for the S_N1 Reaction

- ❖ A multistep process

Step (1):

$$CH_3-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-Br \xrightarrow[\substack{slow \\ r.d.\ step}]{(k_1)} CH_3-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}^{\oplus} + Br^{\ominus}$$

(ionization of alkyl halide)

Free Energy Diagram of S_N1 Reactions

intermediate

Step (2)

$$CH_3-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}^{\oplus} + H_2\ddot{O} \underset{fast}{\overset{(k_2)}{\rightleftharpoons}} CH_3-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-\overset{\oplus}{\underset{H}{\overset{H}{O}}}$$

Free Energy Diagram of S$_N$1 Reactions

Free Energy vs. Reaction Coordinate

T.S. (1), T.S. (2), T.S. (3)

$\Delta G_1^{\ddagger}$

$(CH_3)_3CBr + H_2O$

$(CH_3)_3C^{\oplus} + Br^-$

$(CH_3)_3C^{\oplus}-OH_2 + Br^-$

$(CH_3)_3C-OH + Br^-$

intermediate

Ch. 6 - 43

Step (2)

$$CH_3-\overset{CH_3}{\underset{CH_3}{C}}{}^{\oplus} + H_2\ddot{O} \underset{fast}{\overset{(k_2)}{\rightleftharpoons}} CH_3-\overset{CH_3}{\underset{CH_3}{C}}-\overset{H}{\underset{H}{O}}{}^{\oplus}$$

Step (3)

$$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-\overset{H}{\underset{H}{O}}{}^{\oplus} + H_2\ddot{O} \underset{fast}{\overset{(k_3)}{\rightleftharpoons}} CH_3-\overset{CH_3}{\underset{CH_3}{C}}-OH + H_3O^+$$

Ch. 6 - 44

Free Energy Diagram of S$_N$1 Reactions

Free Energy vs. Reaction Coordinate

T.S. (1), T.S. (2), T.S. (3)

$\Delta G_1^{\ddagger}$

$(CH_3)_3CBr + H_2O$

$(CH_3)_3C^{\oplus} + Br^-$

$(CH_3)_3C^{\oplus}OH_2 + Br^-$

$(CH_3)_3C-OH + Br^-$

intermediate

Ch. 6 - 45

Step (2)

$$CH_3-\overset{CH_3}{\underset{CH_3}{C}}{}^{\oplus} + H_2\ddot{O} \underset{fast}{\overset{(k_2)}{\rightleftharpoons}} CH_3-\overset{CH_3}{\underset{CH_3}{C}}-\overset{H}{\underset{H}{O}}{}^{\oplus}$$

Step (3)

$k_1 \ll k_2$ and k_3

$$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-\overset{H}{\underset{H}{O}}{}^{\oplus} + H_2\ddot{O} \underset{fast}{\overset{(k_3)}{\rightleftharpoons}} CH_3-\overset{CH_3}{\underset{CH_3}{C}}-OH + H_3O^+$$

Ch. 6 - 46
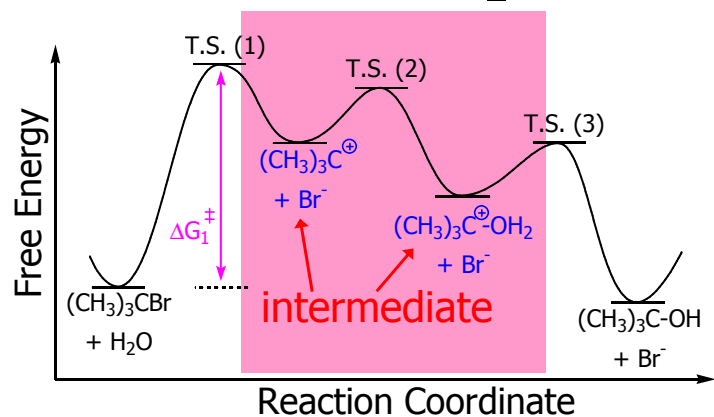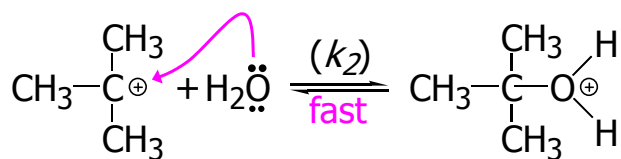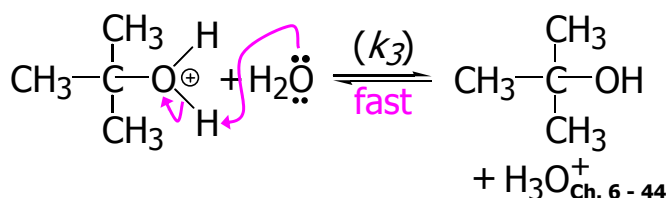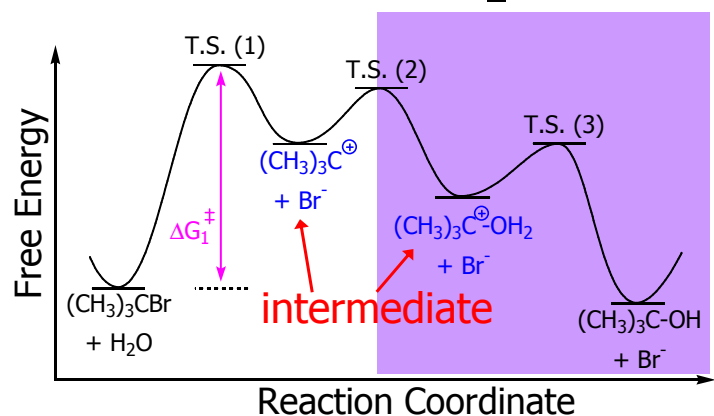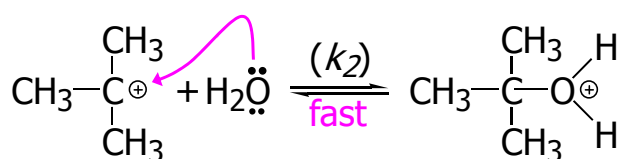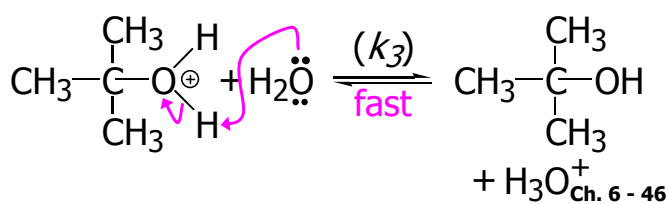
❖ 2 intermediates and 3 transition states (T.S.)

❖ The most important T.S. for S$_N$1 reactions is T.S. (1) of the rate-determining step (r.d.s.)

$$\left[CH_3-\overset{CH_3}{\underset{CH_3}{\overset{\delta^+}{C}}}\cdots\overset{\delta^-}{Br} \right]^{\ddagger}$$
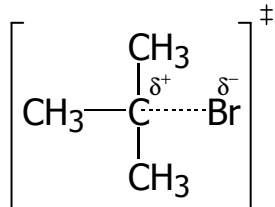
Ch. 6 - 47

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11. Carbocations

11A. The Structure of Carbocations

sp^2-sp^3 π bond
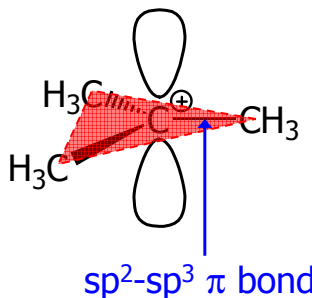
❖ Carbocations are trigonal planar
❖ The central carbon atom in a carbocation is electron deficient; it has only six e$^{\ominus}$ in its valence shell
❖ The *p* orbital of a carbocation contains no electrons, but it can accept an electron pair when the carbocation undergoes further reaction
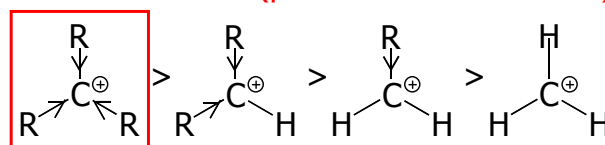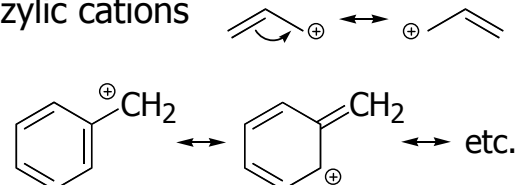
Ch. 6 - 48

11B. The Relative Stabilities of Carbocations

❖ General order of reactivity (towards S_N1 reaction)
  ● $3^o > 2^o >> 1^o >$ methyl

❖ The more stable the carbocation formed, the faster the S_N1 reaction

❖ Stability of cations

most stable (positive inductive effect)

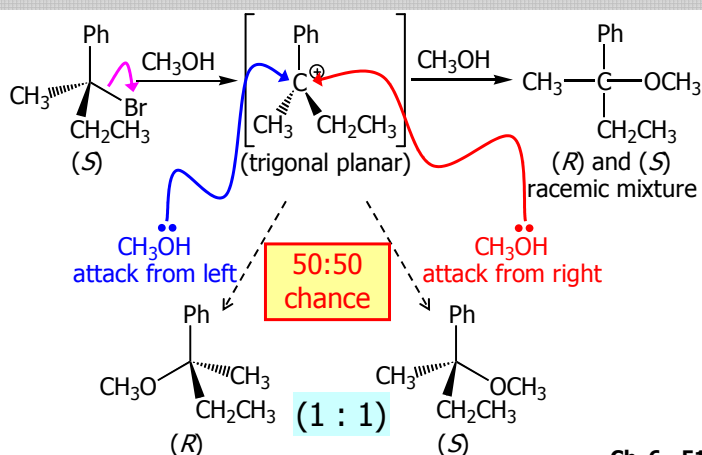❖ Resonance stabilization of allylic and benzylic cations

etc.
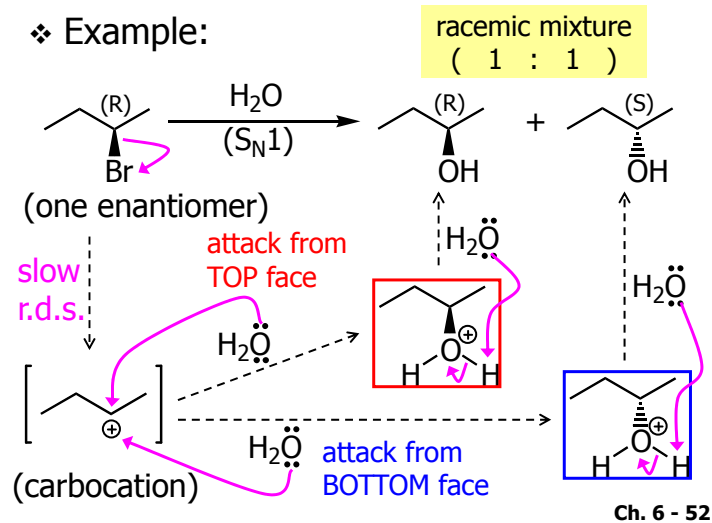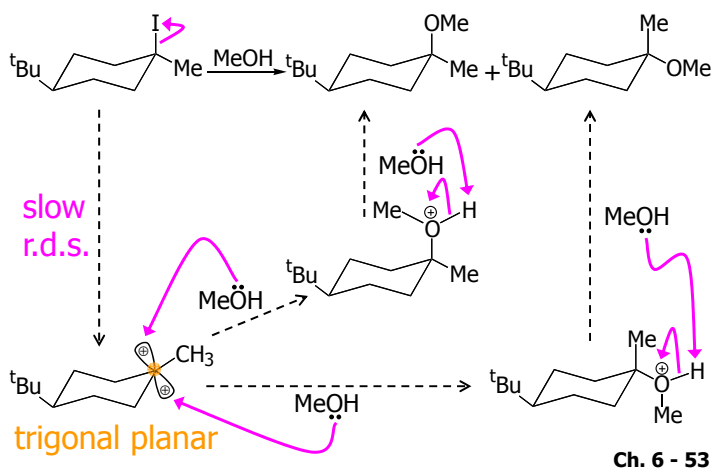
12. The Stereochemistry of S_N1 Reactions

50:50 chance

(1 : 1)

❖ Example:

racemic mixture (1 : 1)

(one enantiomer)

slow r.d.s.

attack from TOP face

(carbocation)

$H_2\ddot{O}$ attack from BOTTOM face

❖ Example:

slow r.d.s.

trigonal planar

13. Factors Affecting the Rates of S_N1 and S_N2 Reactions

❖ The structure of the substrate

❖ The concentration and reactivity of the nucleophile (for S_N2 reactions only)

❖ The effect of the solvent

❖ The nature of the leaving group

13A. The Effect of the Structure of the Substrate

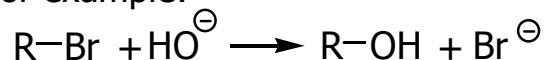❖ General order of reactivity (towards S_N2 reaction)

- Methyl > 1° > 2° >> 3° > vinyl or aryl

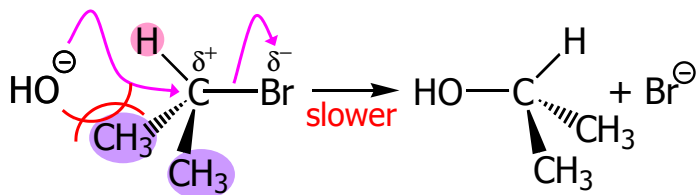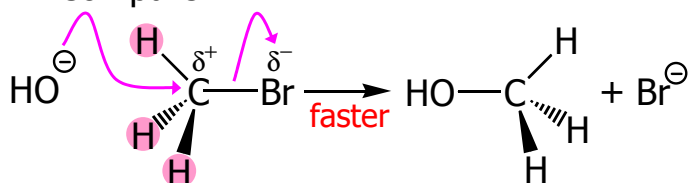**DO NOT undergo S_N2 reactions**

Ch. 6 - 55

❖ For example:

$$R-Br + HO^{\ominus} \longrightarrow R-OH + Br^{\ominus}$$

Relative Rate (towards S_N2)				
CH_3-Br	CH_3CH_2-Br	$CH_3\overset{\underset{\textstyle CH_3}{\vert}}{CH}-Br$	$CH_3-\overset{\underset{\textstyle CH_3}{\vert}}{\overset{\overset{\textstyle CH_3}{\vert}}{C}}-CH_2Br$	$CH_3-\overset{\underset{\textstyle CH_3}{\vert}}{\overset{\overset{\textstyle CH_3}{\vert}}{C}}-Br$
methyl	1°	2°	neopentyl	3°
2×10^6	4×10^4	500	1	< 1
Most reactive	⬅			Least reactive

Ch. 6 - 56

❖ Compare

faster

slower

Ch. 6 - 57

very slow

extremely slow
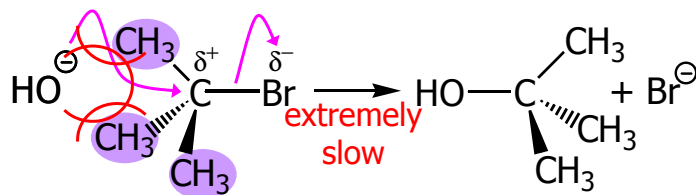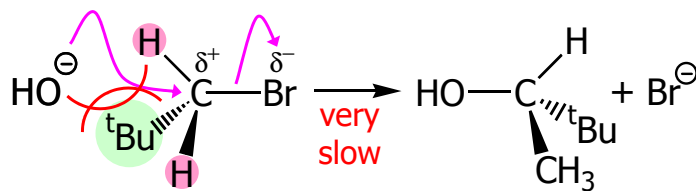
Ch. 6 - 58

❖ Note **NO** S_N2 reaction on sp^2 or sp carbons

e.g.

sp^2 + $Nu^{\ominus}$ ⟶✗ No reaction

sp^2 + $Nu^{\ominus}$ ⟶✗ No reaction

sp + $Nu^{\ominus}$ ⟶✗ No reaction
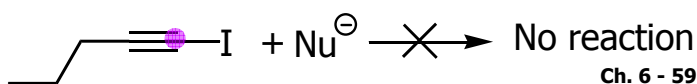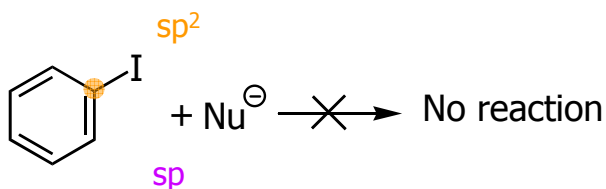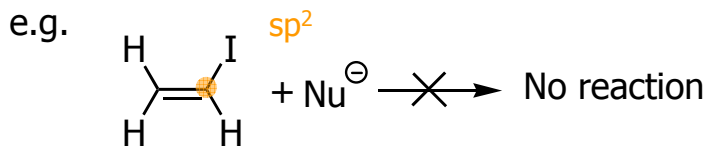
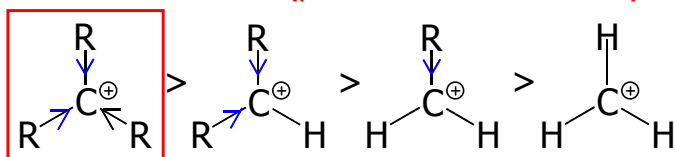Ch. 6 - 59

Reactivity of the Substrate in S_N1 Reactions

❖ General order of reactivity (towards S_N1 reaction)
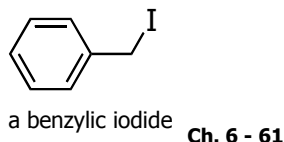- 3° > 2° >> 1° > methyl

❖ The more stable the carbocation formed, the faster the S_N1 reaction

Ch. 6 - 60

❖ Stability of cations
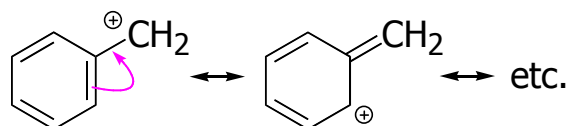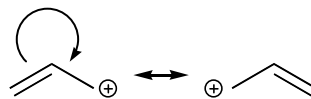
most stable (positive inductive effect)

❖ Allylic halides and benzylic halides also undergo S_N1 reactions at reasonable rates

an allylic bromide   a benzylic iodide

❖ Resonance stabilization for allylic and benzylic cations

etc.

13B. The Effect of the Concentration & Strength of the Nucleophile

❖ For S_N1 reaction
Recall: **Rate = k[RX]**
- The $Nu^\ominus$ does **NOT** participate in the r.d.s.
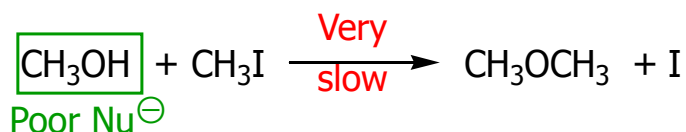- Rate of S_N1 reactions are **NOT** affected by either the **concentration** or the **identity** of the $Nu^\ominus$

❖ For S_N2 reaction
Recall: **Rate = k[RX][RX]**
- The rate of S_N2 reactions depends on both the **concentration** and the **identity** of the attacking $Nu^\ominus$

❖ **Identity** of the $Nu^\ominus$
- The relative strength of a $Nu^\ominus$ (its *nucleophilicity*) is measured in terms of the relative rate of its S_N2 reaction with a given substrate

$CH_3O^\ominus$ + CH_3I $\xrightarrow{\text{rapid}}$ CH_3OCH_3 + I
Good $Nu^\ominus$

CH_3OH + CH_3I $\xrightarrow[\text{slow}]{\text{Very}}$ CH_3OCH_3 + I
Poor $Nu^\ominus$

❖ The relative strength of a $Nu^\ominus$ can be correlated with 3 structural features
- A negatively charged $Nu^\ominus$ is always a more reactive $Nu^\ominus$ than its conjugated acid
  - e.g. $HO^\ominus$ is a better $Nu^\ominus$ than H_2O and $RO^\ominus$ is better than ROH
- In a group of $Nu^\ominus$s in which the nucleophilic atom is the same, nucleophilicities parallel basicities
  - e.g. for O compounds,
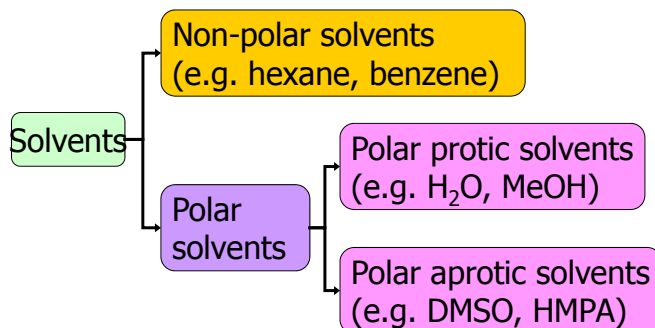 $RO^\ominus > HO^\ominus >> RCO_2^\ominus > ROH > H_2O$

- When the nucleophilic atoms are different, then nucleophilicities may not parallel basicities
  - e.g. in protic solvents $HS^{\ominus}$, $CN^{\ominus}$, and $I^{\ominus}$ are all weaker bases than $HO^{\ominus}$, yet they are stronger $Nu^{\ominus}$s than $HO^{\ominus}$

$$HS^{\ominus} > CN^{\ominus} > I^{\ominus} > HO^{\ominus}$$

13C. Solvent Effects on S_N2 Reactions: Polar Protic & Aprotic Solvents

❖ Classification of solvents

Solvents → Non-polar solvents (e.g. hexane, benzene)

Solvents → Polar solvents → Polar protic solvents (e.g. H_2O, MeOH)

Polar solvents → Polar aprotic solvents (e.g. DMSO, HMPA)
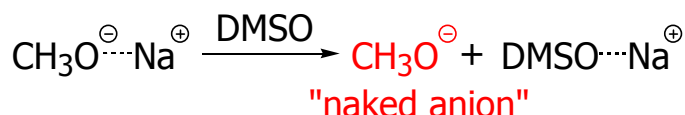
❖ S_N2 Reactions in Polar Aprotic Solvents
  - The best solvents for S_N2 reactions are
    - Polar aprotic solvents, which have strong dipoles but do not have OH or NH groups
    - Examples

(DMSO)   (DMF)   (HMPA)   (Acetonitrile)
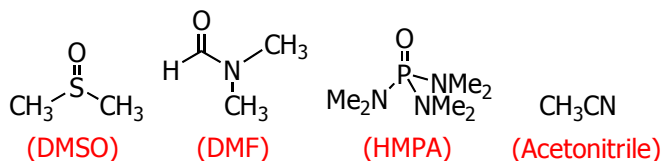
  - Polar aprotic solvents tend to solvate metal cations rather than nucleophilic anions, and this results in "naked" anions of the $Nu^{\ominus}$ and makes the $e^{\ominus}$ pair of the $Nu^{\ominus}$ more available

$$CH_3O^{\ominus}\cdots Na^{\oplus} \xrightarrow{DMSO} CH_3O^{\ominus} + DMSO\cdots Na^{\oplus}$$
"naked anion"

  - Tremendous acceleration in S_N2 reactions with polar aprotic solvent

$$CH_3Br + NaI \longrightarrow CH_3I + NaBr$$

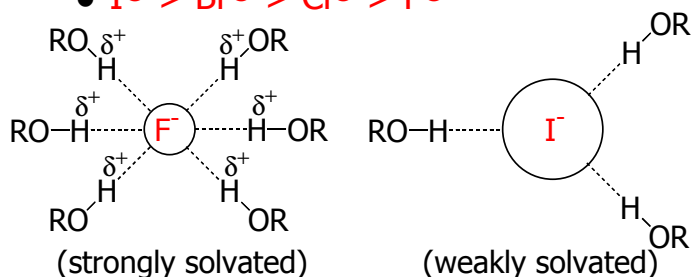| Solvent	Relative Rate
MeOH	1
DMF	10^6

❖ S_N2 Reactions in Polar Protic Solvents
  - In polar protic solvents, the $Nu^{\ominus}$ anion is solvated by the surrounding protic solvent which makes the $e^{\ominus}$ pair of the $Nu^{\ominus}$ less available and thus less reactive in S_N2 reactions
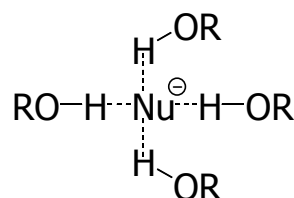
❖ Halide Nucleophilicity in Protic Solvents
  ● $I^{\ominus} > Br^{\ominus} > Cl^{\ominus} > F^{\ominus}$

(strongly solvated)   (weakly solvated)

☞ Thus, $I^{\ominus}$ is a stronger $Nu^{\ominus}$ in protic solvents, as its $e^{\ominus}$ pair is more available to attack the substrate in the S_N2 reaction.

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❖ Halide Nucleophilicity in Polar Aprotic Solvents (e.g. in DMSO)
  ● $F^{\ominus} > Cl^{\ominus} > Br^{\ominus} > I^{\ominus}$

  ♦ Polar aprotic solvents do not solvate anions but solvate the cations

  ♦ The "naked" anions act as the $Nu^{\ominus}$

  ♦ Since $F^{\ominus}$ is smaller in size and the charge per surface area is larger than $I^{\ominus}$, the nucleophilicity of $F^{\ominus}$ in this environment is greater than $I^{\ominus}$

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13D. Solvent Effects on S_N1 Reactions: The Ionizing Ability of the Solvent

❖ Solvent plays an important role in S_N1 reactions but the reasons are different from those in S_N2 reactions

❖ Solvent effects in S_N1 reactions are due largely to stabilization or destabilization of the transition state

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❖ Polar protic solvents stabilize the development of the polar transition state and thus accelerate this rate-determining step (r.d.s.):
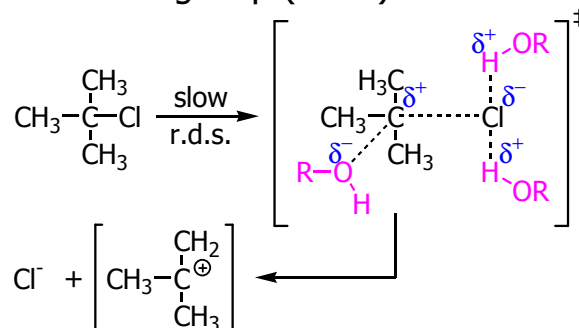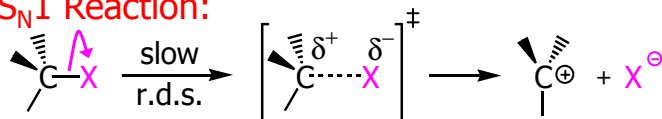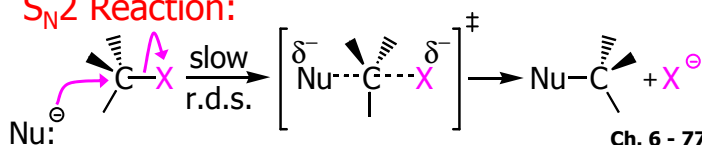

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13E. The Nature of the Leaving Group

❖ The better a species can stabilize a negative charge, the better the LG in an S_N2 reaction
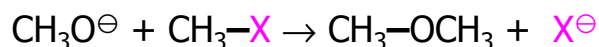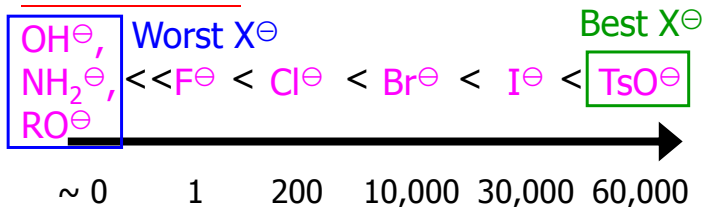
S_N1 Reaction:

S_N2 Reaction:
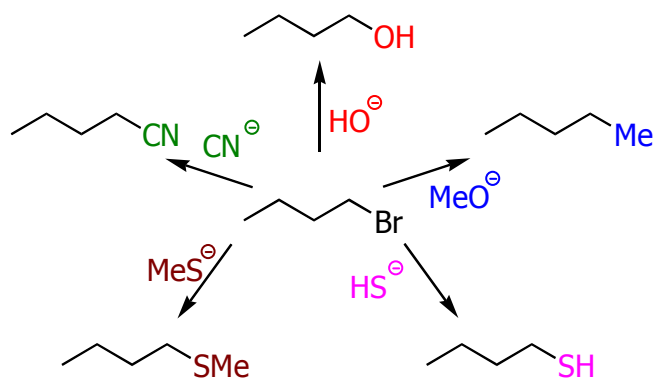
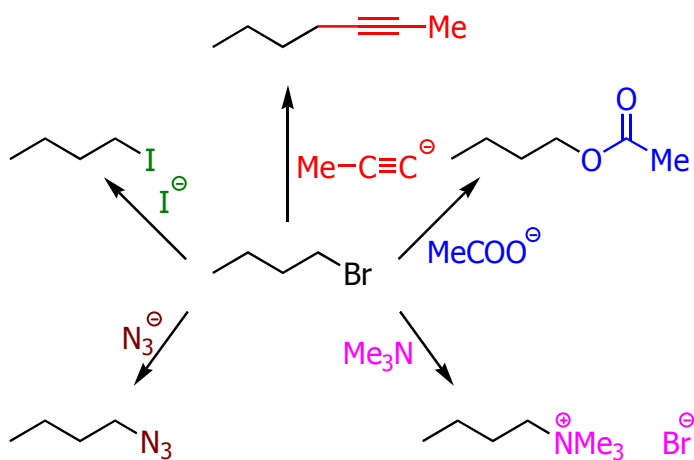

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❖ Examples of the reactivity of some $X^{\ominus}$:
  $CH_3O^{\ominus} + CH_3{-}X \rightarrow CH_3{-}OCH_3 + X^{\ominus}$

Relative Rate:

$OH^{\ominus}$, Worst $X^{\ominus}$ Best $X^{\ominus}$
$NH_2^{\ominus}$, $<< F^{\ominus} < Cl^{\ominus} < Br^{\ominus} < I^{\ominus} < TsO^{\ominus}$
$RO^{\ominus}$

  ~ 0   1   200   10,000 30,000 60,000

☞ Note: Normally R–F, R–OH, R–NH₂, R–OR' do not undergo S_N2 reactions.

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R—OH $\xrightarrow{\text{Nu}^\ominus}$ R—Nu + OH$^\ominus$

a poor leaving group

a strong basic anion

H$^\oplus$

R—O$^\oplus$H H $\xrightarrow{\text{Nu}^\ominus}$ R—Nu + H$_2$O

a good leaving group

weak base

---

14. Organic Synthesis: Functional Group Transformation Using S$_N$2 Reactions

CN CN$^\ominus$

HO$^\ominus$ → OH

MeO$^\ominus$ → Me

Br

MeS$^\ominus$

HS$^\ominus$ → SH

SMe

≡—Me

Me—C≡C$^\ominus$

I I$^\ominus$

MeCOO$^\ominus$ → O–C(=O)–Me

Br

N$_3^\ominus$ → N$_3$

Me$_3$N → $\overset{\oplus}{N}$Me$_3$ Br$^\ominus$

❖ Examples:

Br $\xrightarrow{\text{NaOEt, DMSO}}$ O

I $\xrightarrow{\text{NaSMe, DMSO}}$ SMe

❖ Examples:

I (optically active, chiral) $\xrightarrow{??}$ CN (optically active, chiral)
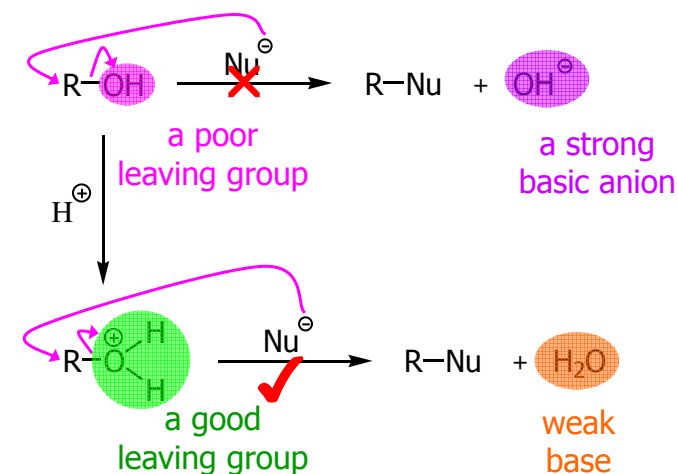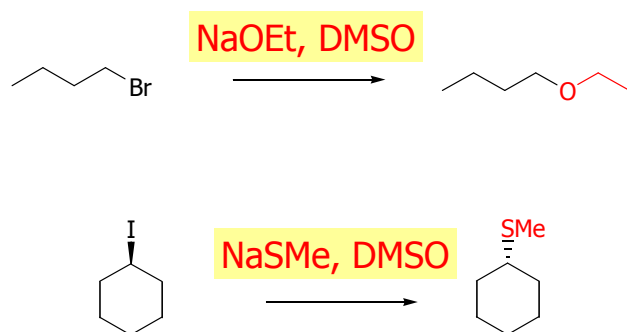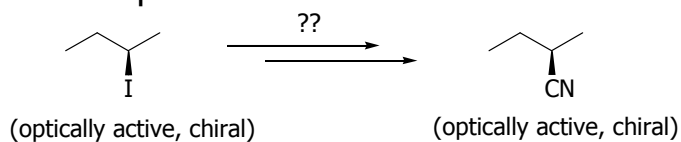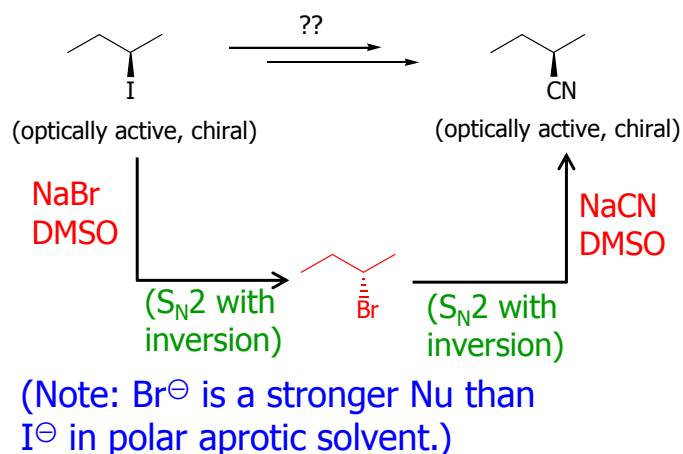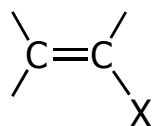
- Need S$_N$2 reactions to control stereochemistry
- But S$_N$2 reactions give the inversion of configurations, so how do you get the "retention" of configuration here??
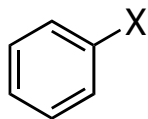- Solution:
  "double inversion" ⇒ "retention"

I (optically active, chiral) $\xrightarrow{??}$ CN (optically active, chiral)

NaBr DMSO

(S$_N$2 with inversion)

Br

NaCN DMSO

(S$_N$2 with inversion)

(Note: Br$^\ominus$ is a stronger Nu than I$^\ominus$ in polar aprotic solvent.)

14A. The Unreactivity of Vinylic and Phenyl Halides

vinylic halide   phenyl halide

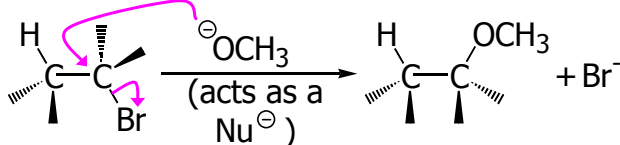❖ Vinylic and phenyl halides are generally unreactive in S_N1 or S_N2 reactions
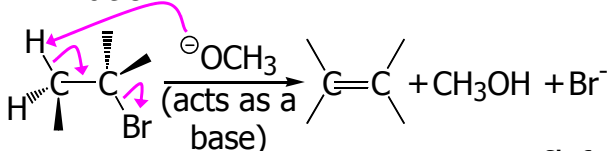

❖ Examples

$$\text{CH}_2=\text{CHBr} \xrightarrow[\text{DMSO}]{\text{NaCN}} \text{No Reaction}$$

$$\text{Ph-I} \xrightarrow[\text{HMPA}]{\text{NaSMe}} \text{No Reaction}$$

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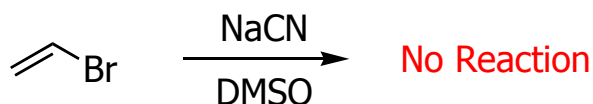
15. Elimination Reactions of Alkyl Halides

❖ Substitution

$$\xrightarrow[\substack{\text{(acts as a} \\ \text{Nu}^{\ominus})}]{^{\ominus}\text{OCH}_3} + \text{Br}^-$$

❖ Elimination

$$\xrightarrow[\substack{\text{(acts as a} \\ \text{base)}}]{^{\ominus}\text{OCH}_3} \quad \text{C}=\text{C} + \text{CH}_3\text{OH} + \text{Br}^-$$

❖ Substitution reaction (S_N) and elimination reaction (E) are processes in competition with each other

e.g.

$$\xrightarrow[^t\text{BuOH}]{^t\text{BuOK}} \quad \text{O}^t\text{Bu} \quad + $$

S_N2: 15%   E2: 85%

15A. Dehydrohalogenation

β hydrogen   α carbon
β carbon   halide as LG

$$\xrightarrow[^t\text{BuOH}, 60^o\text{C}]{^t\text{BuOK}} \quad + \text{ KBr } + \text{ }^t\text{BuOH}$$
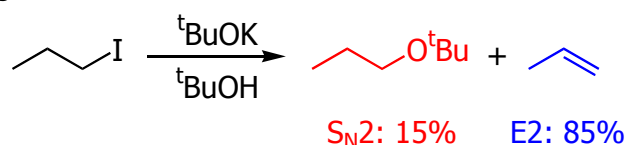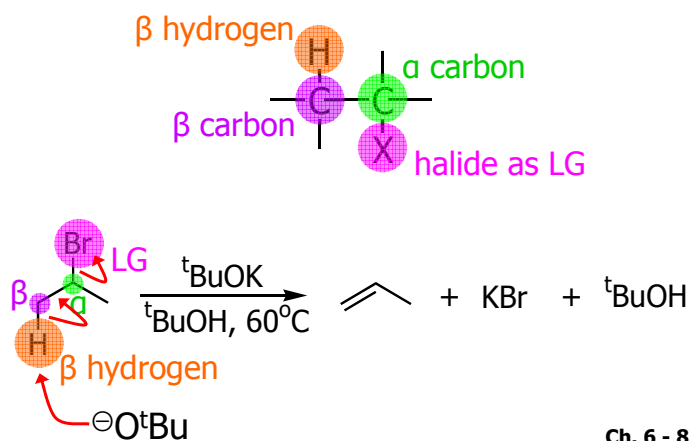
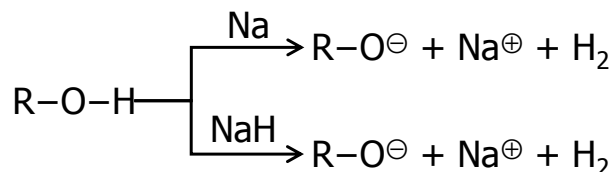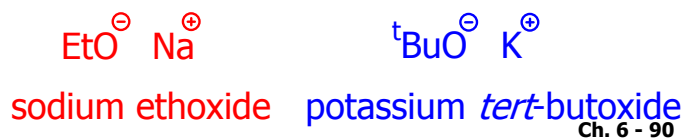
15B. Bases Used in Dehydrohalogenation

❖ Conjugate base of alcohols is often used as the base in dehydrohalogenations

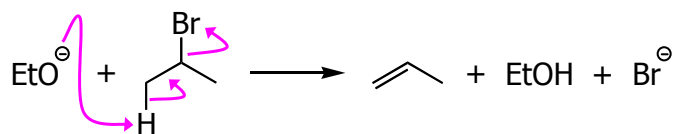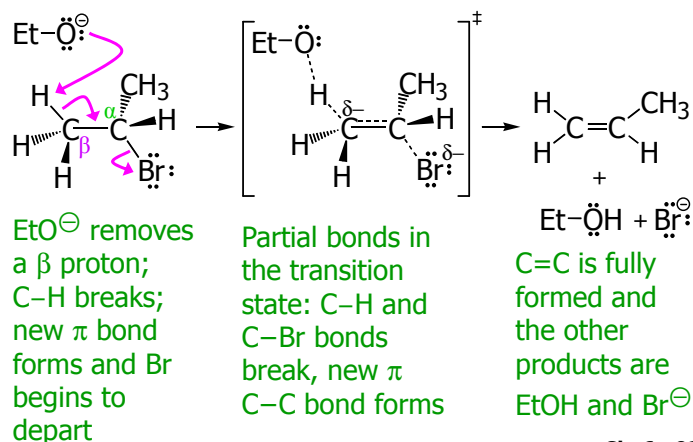$$\text{R-O-H} \begin{cases} \xrightarrow{\text{Na}} \text{R-O}^{\ominus} + \text{Na}^{\oplus} + \text{H}_2 \\ \xrightarrow{\text{NaH}} \text{R-O}^{\ominus} + \text{Na}^{\oplus} + \text{H}_2 \end{cases}$$

e.g.

EtO$^{\ominus}$ Na$^{\oplus}$ ^{t}BuO$^{\ominus}$ K$^{\oplus}$

sodium ethoxide   potassium *tert*-butoxide

16. The E2 Reaction

EtO⁻ + (CH₃CHBrCH₃) → CH₂=CHCH₃ + EtOH + Br⁻

❖ Rate = k[CH$_3$CHBrCH$_3$][EtO$^\ominus$]

❖ Rate determining step involves both the alkyl halide and the alkoxide anion

❖ A **bimolecular** reaction

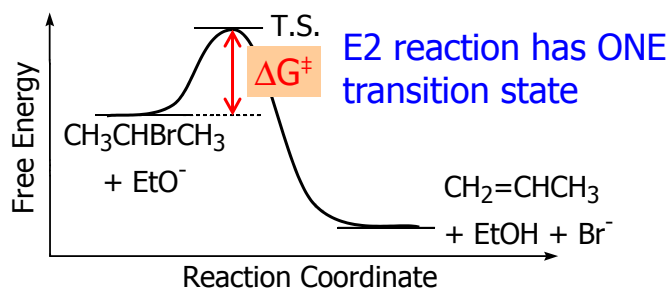## Mechanism for an E2 Reaction

EtO$^\ominus$ removes a β proton; C–H breaks; new π bond forms and Br begins to depart

Partial bonds in the transition state: C–H and C–Br bonds break, new π C–C bond forms

C=C is fully formed and the other products are EtOH and Br$^\ominus$

Free Energy Diagram of E2 Reaction

E2 reaction has ONE transition state

Rate = k[CH$_3$CHBrCH$_3$][EtO$^\ominus$]

❖ *Second-order* overall ⇒ bimolecular

17. The E1 Reaction

❖ E1: Unimolecular elimination

slow r.d.s.

(major (S$_N$1)) (minor (E1))

H₂O as nucleophile   H₂O as base
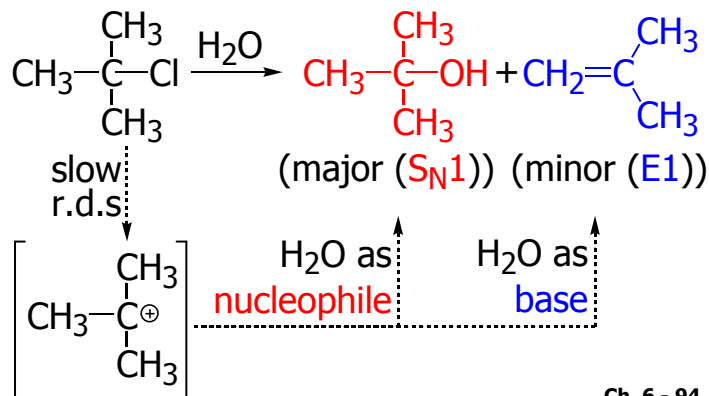
Mechanism of an E1 Reaction

β hydrogen   α carbon

slow r.d.s.

fast

(E1 product)

fast H₂O:

(S$_N$1 product)

Free Energy Diagram of E1 Reaction

T.S. (1)   T.S. (2)

(CH₃)₃C$^\oplus$ + Cl⁻

(CH₃)₃CCl + H₂O

$\Delta G_1^{\ddagger}$

(CH₃)₂C=CH₂ + H₃O$^\oplus$ + Cl⁻

Reaction Coordinate

Step (1):

$$CH_3 \overset{CH_3}{\underset{CH_3}{-}} \overset{\displaystyle |}{C} - Cl \xrightarrow[\substack{slow \\ r.d.\ step}]{\substack{H_2\ddot{O} \\ (k_1)}} CH_3 \overset{CH_3}{\underset{CH_3}{-}} \overset{\displaystyle |}{C}{}^{\oplus} + Cl^{\ominus}$$

Aided by the polar solvent, a chlorine departs with the e$^{\ominus}$ pair that bonded it to the carbon

Produces relatively stable 3° carbocation and a Cl$\ominus$. The ions are solvated (and stabilized) by surrounding H$_2$O molecules

Free Energy Diagram of E1 Reaction

Step (2)

H$_2$O molecule removes one of the β hydrogens which are acidic due to the adjacent positive charge. An e$^{\ominus}$ pair moves in to form a double bond between the β and α carbon atoms
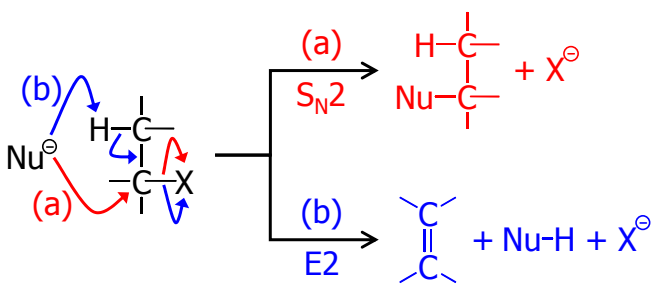
Produces alkene and hydronium ion

18. How To Determine Whether Substitution or Elimination Is Favoured

❖ All nucleophiles are potential bases and all bases are potential nucleophiles

❖ Substitution reactions are always in competition with elimination reactions

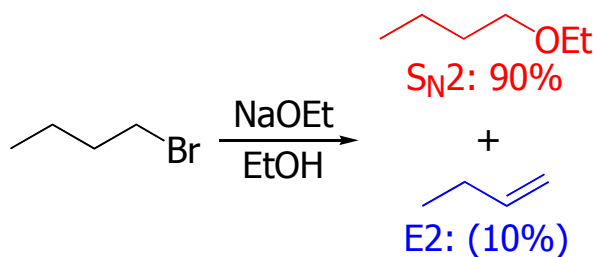❖ Different factors can affect which type of reaction is favoured

18A. S$_N$2 vs. E2

Primary Substrate

❖ With a strong base, e.g. EtO$^{\ominus}$
  • Favor S$_N$2

S$_N$2: 90%

+

E2: (10%)

Secondary Substrate

❖ With a strong base, e.g. $EtO^{\ominus}$
- ● Favor E2

E2: 80%

S_N2: 20%
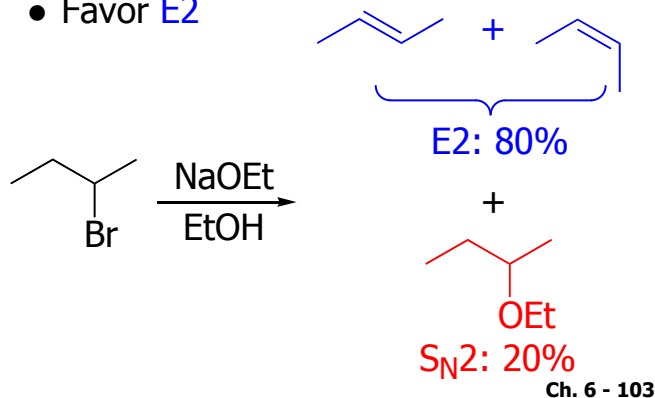
Tertiary Substrate

❖ With a strong base, e.g. $EtO^{\ominus}$
- ● E2 is highly favored

E2: 91% S_N1: 9%
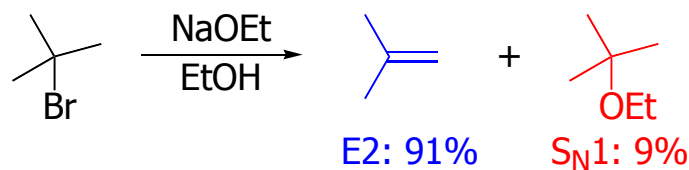
Base/Nu$^{\ominus}$: Small vs. Bulky

❖ Unhindered "small" base/Nu$^{\ominus}$

S_N2: 99%   E2: 1%
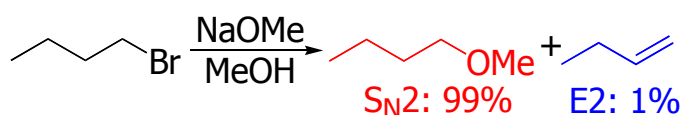
❖ Hindered "bulky" base/Nu$^{\ominus}$

S_N2: 15%   E2: 85%
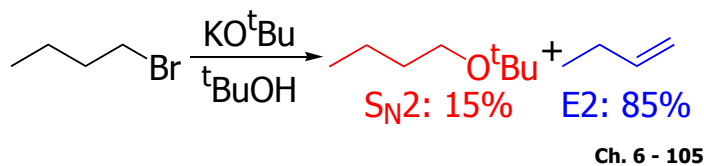
Basicity vs. Polarizability

(weak base) S_N2: 100%   E2: 0%

$EtO^{\ominus}$ (strong base) S_N2: 20%   E2: 80%
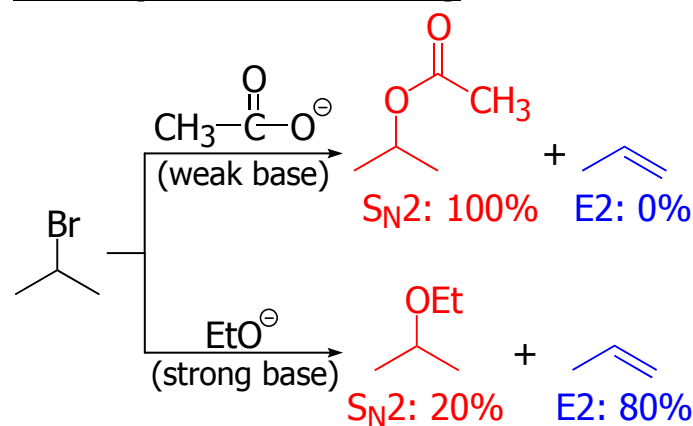
Tertiary Halides: S_N1 vs. E1 & E2

$EtO^{\ominus}$ (strong base)   E2: 100% S_N1: 0%

EtOH heat   E1 + E2: 20% S_N1: 80%
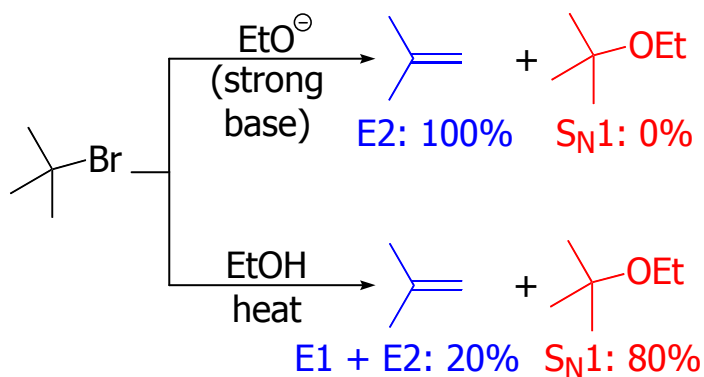
19. Overall Summary

	S_N1	S_N2	E1	E2
CH_3X	–	Very fast	–	–
RCH_2X	–	Mostly	–	Hindered bases give mostly alkenes; e.g. with $^tBuO^{\ominus}$
R' RCHX	Very little; Solvolysis possible; e.g. with H_2O; MeOH	Mostly S_N2 with weak bases; e.g. with $CH_3COO^{\ominus}$	Very little	Strong bases promote E2; e.g. with $RO^{\ominus}$, $HO^{\ominus}$
R' RCX R"	Very favorable with weak bases; e.g. with H_2O; MeOH	–	Always competes with S_N1	Strong bases promote E2; e.g. with $RO^{\ominus}$, $HO^{\ominus}$

Review Problems

(1)

S_N2 with inversion

(2)

Intramolecular S_N2

(3)

(50 : 50)

$Cl^{\ominus}$ attacks from top face

$Cl^{\ominus}$ attacks from bottom face

S_N1 with racemization

sp^2 hybridized carbocation

♫ END OF CHAPTER 6 ♫