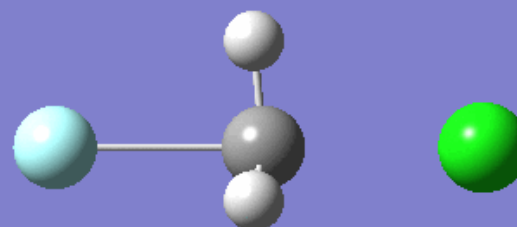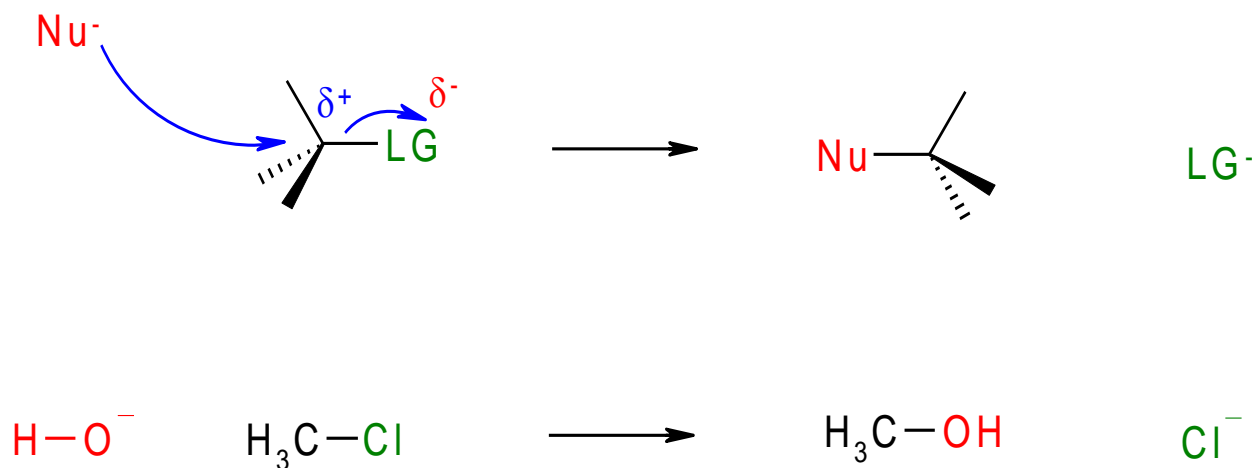# *Chapter 6: Nucleophilic Substitution and Elimination Reactions*

Nucleophilic Substitution

A *nucleophilic substitution* reaction involves the replacement of a *leaving group* with a *nucleophile*, i.e.

Note: this reaction is an equilibrium since the leaving group can, in principle, act as a nucleophile.

Nucleophiles

Nucleophiles (Nu) are electron rich (i.e. have lone pair(s) of electrons) and are attracted to the positive nuclear charge of an e^- poor species, the *electrophile* (E).

Nucleophilicity refers to the ability of the nucleophile to react this way, i.e. how available are the e^- in the nucleophile. The more available the e^- the more reactive the Nu. These may be lone pair e^- but π bonding e^- are also "available".

Nucleophiles

Common nucleophiles include:

Nucleophile	Neutral	Anionic
Halide		I^-, Br^-, Cl^-
Oxygen	H_2O, ROH	OH^-, RO^-, RCO_2^-
Nitrogen	NH_3, RNH_2, R_2NH, R_3N	N_3^-
Sulfur	RSH, R_2S	SH^-, RS^-
carbon		$N{\equiv}C^-$, $R\text{-}C{\equiv}C^-$

Nucleophiles

Nucleophilicity trends (compared with basicity):

1) Across a row in the periodic table nucleophilicity (lone pair donation) C^- > N^- > O^- > F^- since increasing electronegativity decreases the lone pair availability. This is the **same order** as for basicity.

2) For the same central atom, higher electron density will increase the nucleophilicity, *i.e.* an anion will be a better Nu (lone pair donor) than a neutral atom (*i.e.* HO^- > H_2O). This is the **same order** as for basicity.

3) Within a group in the periodic table, increasing **polarization** of the nucleophile as you go down a group enhances the ability to form the new C-X bond and increases the nucleophilicity, so I^- > Br^- > Cl^- > F^-. The electron density of larger atoms is more readily distorted *i.e.* polarized, since the electrons are further from the nucleus.
Note: this is the **opposite order** to basicity (acidity increases down a group) where polarizability is much less important for bond formation to the very small proton.

Nucleophiles

The following tables ranks the strength of common nucleophiles (as compared in methanol CH_3OH):

Strength	Nucleophile
Very Good	I^-, HS^-, RS^-
Good	Br^-, OH^-, RO^-, $N\equiv C^-$, N_3^-
Fair (moderate)	NH_3, Cl^-, RCO_2^-
Weak	H_2O, ROH
Very weak	RCO_2H

Leaving Groups

- A *leaving group* , LG, is an atom (or a group of atoms) that is displaced as a stable species taking with it the bonding electrons. Typically the LG is an anion (*i.e.* Cl^-) or a neutral molecule (*i.e.* H_2O). The better the LG, the more likely it is to depart.

- A "good" LG can be recognized as being the <u>conjugate base of a strong acid</u>.

- What do we mean by this? First we should write the chemical equations for the two processes:

$$H - A \rightleftharpoons H^+ + A^- \quad \text{compare with} \quad \overset{|}{\underset{|}{-C-}} LG \longrightarrow \overset{|}{\underset{|}{-C}}{}^+ + LG^-$$
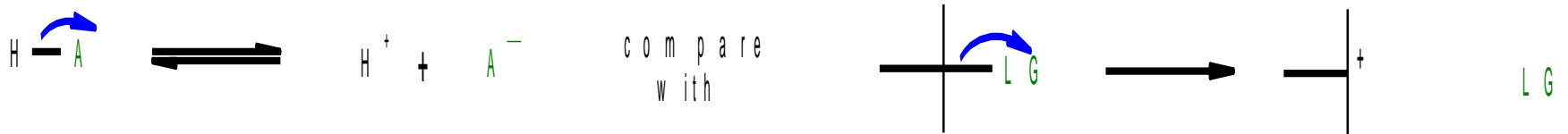
Leaving Groups

Note the similarity of the two equations: both show heterolytic cleavage of a σ bond to create an anion and a cation.

- For acidity, the more stable A^- is, then the more the equilibrium will favor dissociation, and release of protons meaning that HA is more acidic.

- For the leaving group, the more stable LG^- is, the more it favors "leaving".

- Hence factors that stabilize A^- also apply to the stabilization of a LG^-.

Leaving Groups

The following tables lists some of the common leaving groups.

| Strength	Leaving Group
Excellent	NH_3
Very Good	I^-, H_2O
Good	Br^-
Fair	Cl^-
Poor	F^-
Very poor	OH^-, RO^-, NH_2^-

Mechanism of Substitution Reactions

Experimentally if you measure the rate of substitution for the following reactions you will find the following rate laws:
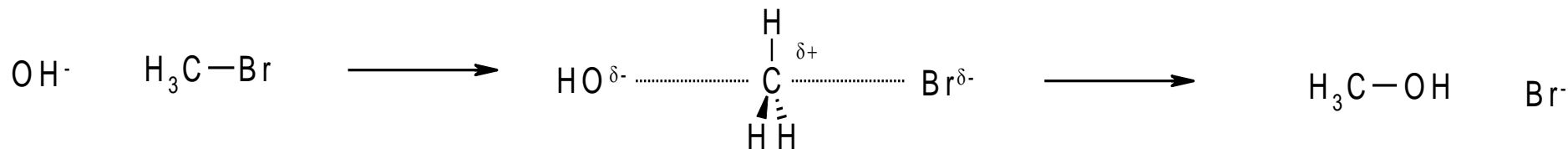
OH^- H_3C-Br ⟶ H_3C-OH Br^- rate = $k[CH_3Br][OH^-]$

OH^- $(CH_3)_3C-Br$ ⟶ $(CH_3)_3C-OH$ Br^- rate = $k[(CH_3)_3CBr]$
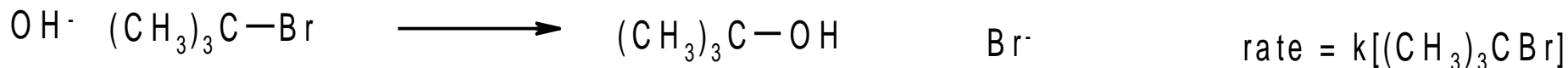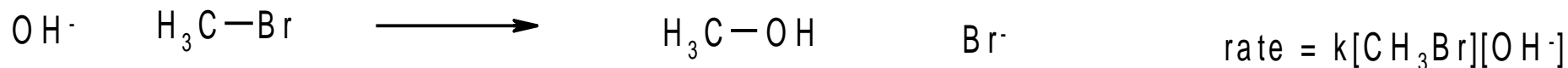
Why the difference?

Substitution Reactions: S$_N$2

The first reaction is dependent on the concentrations of both the substrate and nucleophile, i.e.

$$OH^- \quad H_3C-Br \quad \longrightarrow \quad H_3C-OH \quad Br^- \qquad rate = k[CH_3Br][OH^-]$$
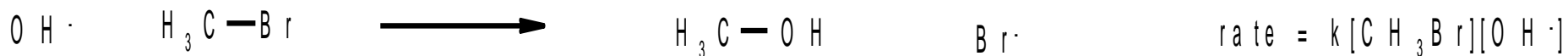
This implies it is a bimolecular reaction that occurs in one step.

There is a single TS in which the new bond to the Nu is forming while the old bond to the LG is breaking, i.e.

$$OH^- \quad H_3C-Br \quad \longrightarrow \quad HO^{\delta-}\cdots\underset{H\ \ H}{\overset{\overset{\displaystyle H}{|}}{C}}^{\delta+}\cdots Br^{\delta-} \quad \longrightarrow \quad H_3C-OH \quad Br^-$$

Substitution Reactions: S$_N$2

The reaction coordinate diagram right indicate this one step mechanism.

- Rate = [substrate] & [nu]

- S$_N$2 results in an inversion of configuration if it occurs at a chiral center. (Back-side attack of the Nu)

- Fastest for 1°, slowest for 3°
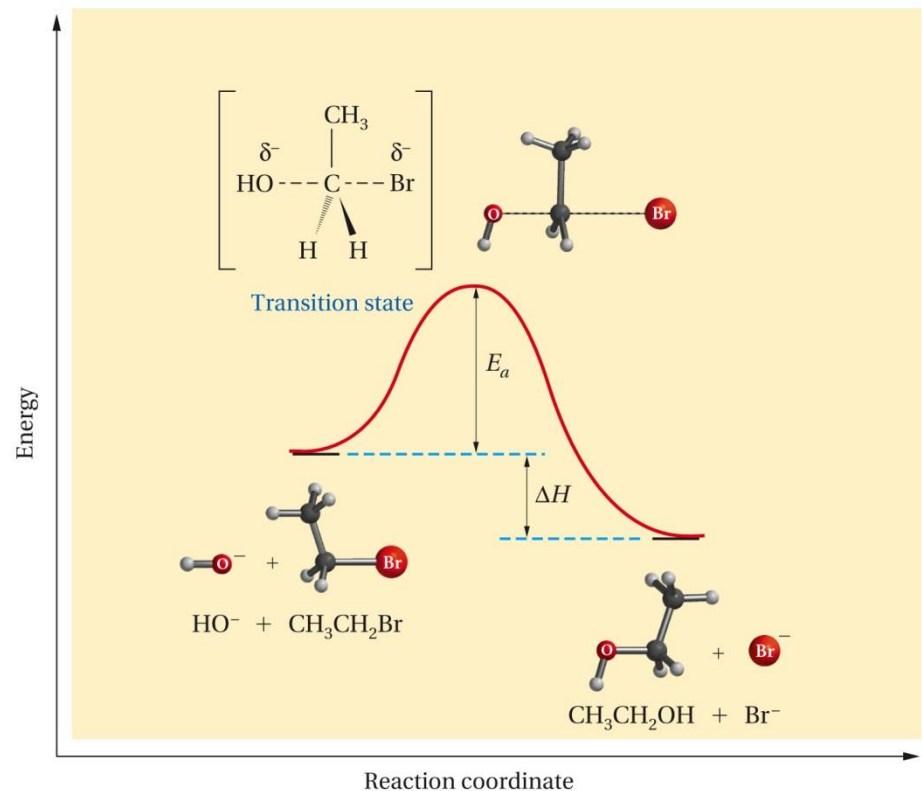
Substitution Reactions: S$_N$1

The second reaction is dependent only on the concentration of the substrate, i.e.

This implies it is a unimolecular reaction that occurs in several steps. The reaction involves the loss of the LG to generate an intermediate carbocation, i.e.

S$_N$1 Mechanism

- S$_N$1 is illustrated by the solvolysis of *tert*-butyl bromide.

  - **Step 1: Break a bond to form a stable ion or molecule**. Ionization of the C-X bond gives a *carbocation*.
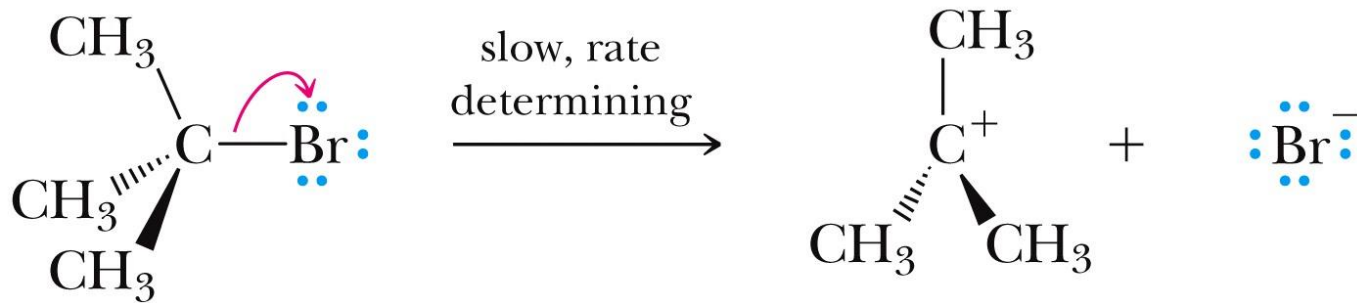
A carbocation intermediate; carbon is trigonal planar

– **Step 2: Reaction of a nucleophile and an electrophile to form a new covalent bond.**
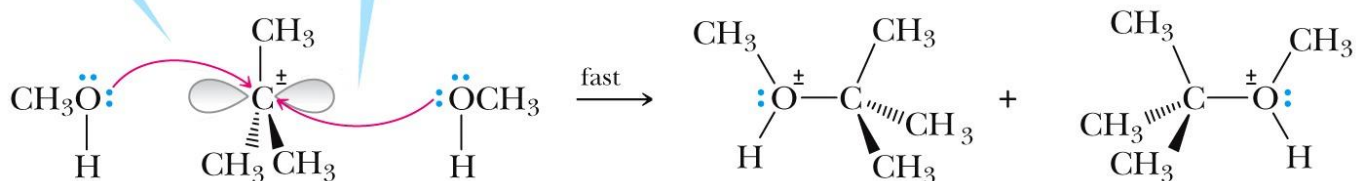
– **Step 3: Take a proton away.** Proton transfer to methanol completes the reaction.
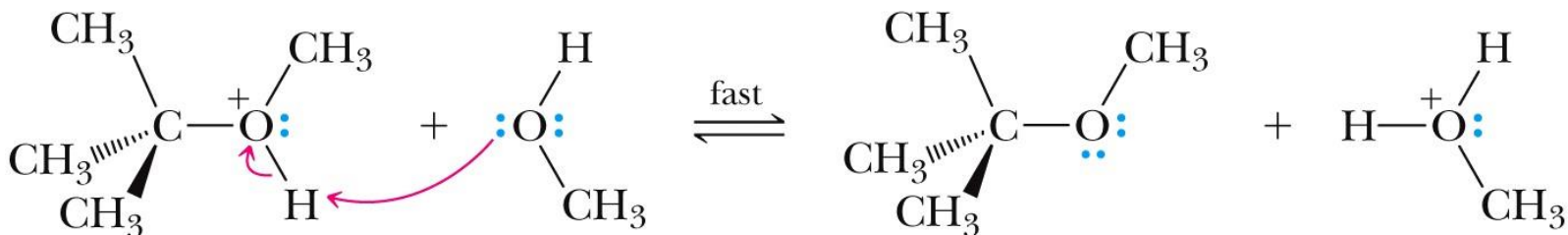
Substitution Reactions: S_N1

The reaction coordinate diagram right indicate this multi-step mechanism.

- Rate = [substrate]

- Generate intermediate carbocation

- S_N1 results in racemization of configuration if it occurs at a chiral center.
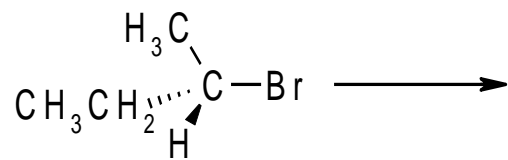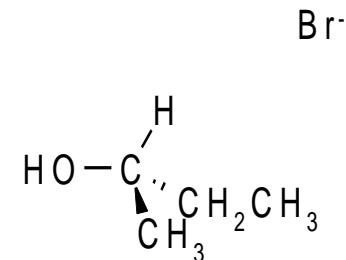
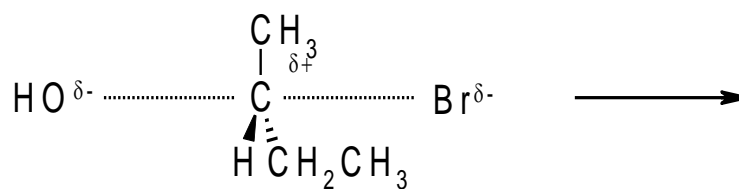- Fastest for 3°, slowest for 1° (parallels C^+ stability)

Energy vs. Reaction coordinate

Carbocation intermediate
$(CH_3)_3C^+ +$
$H_2O + Br^-$

Protonated alcohol
$(CH_3)_3C-OH_2^+ + Br^-$

Reactants
$H_2O + (CH_3)_3C-Br$

Products
$(CH_3)_3C-OH + H-Br$
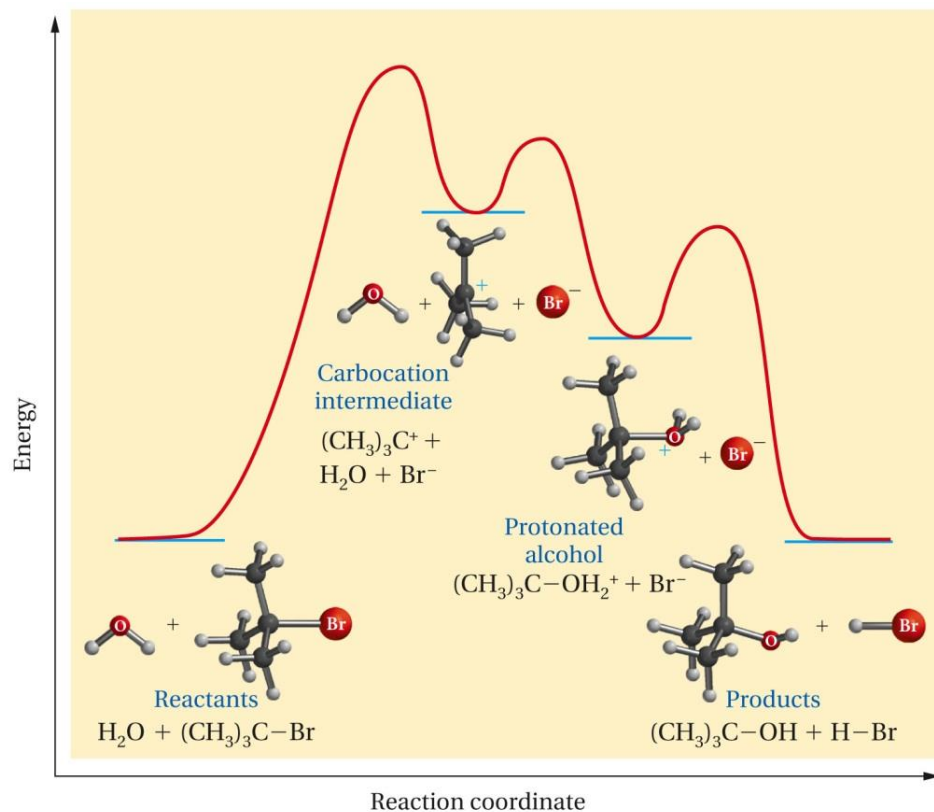
S$_N$2: Stereochemistry

Inversion of configuration for chiral atoms, i.e.

OH$^-$

Br$^-$

H$_3$C

CH$_3$CH$_2$

C—Br

H

HO $^{\delta-}$ ·········· C $^{\delta+}$ ·········· Br$^{\delta-}$
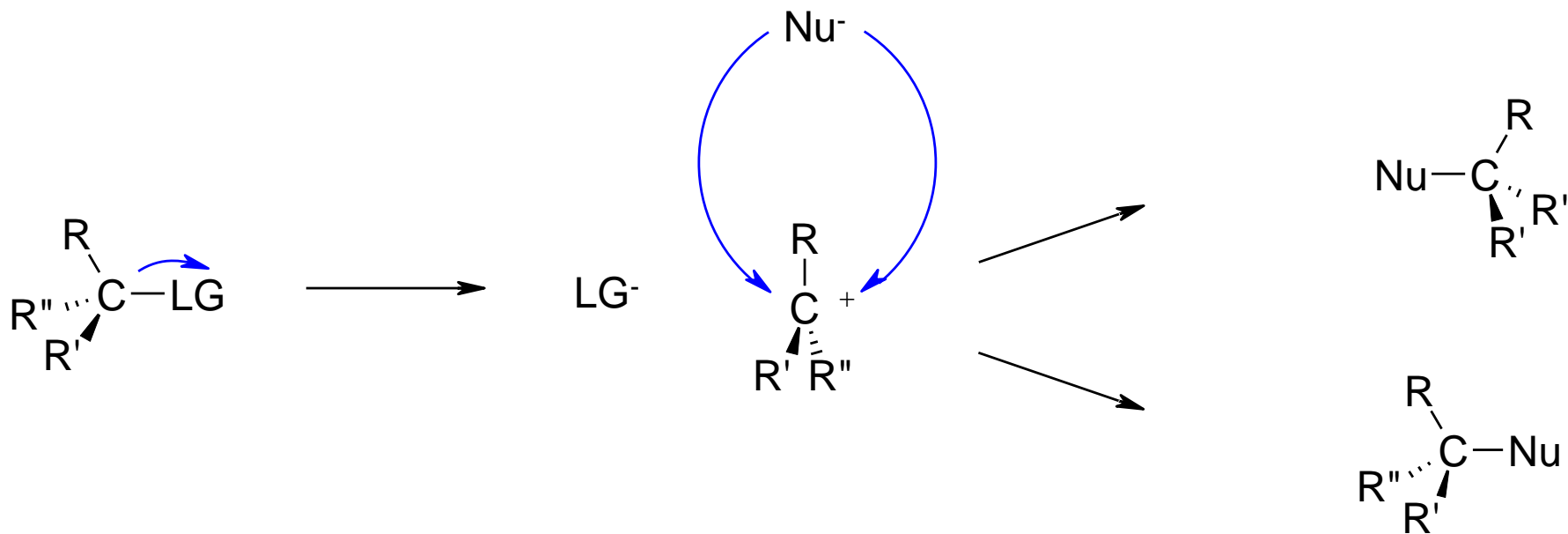
CH$_3$

H CH$_2$CH$_3$

HO—C
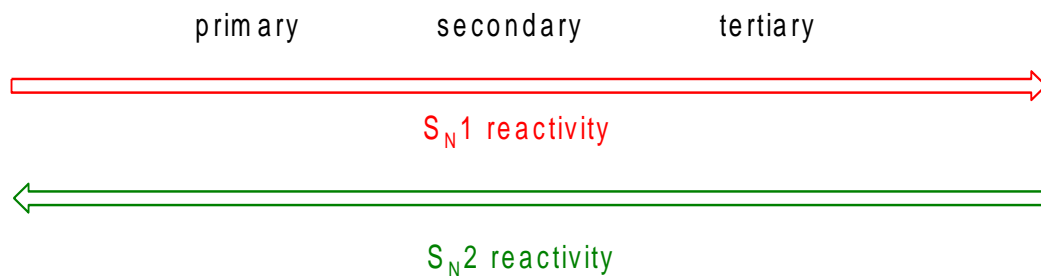
H

CH$_2$CH$_3$

CH$_3$

S-2-bromobutane

R-butan-2-ol

S$_N$1: Stereochemistry

Racemization of chiral atoms, i.e.

S$_N$1 vs. S$_N$2: Nature of Substrate

The substrate itself has an effect on the mechanism. S$_N$1 requires an intermediate carbocation, while S$_N$2 requires a backside attack of the nucleophile (steric effects), i.e.
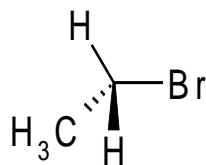
primary   secondary   tertiary
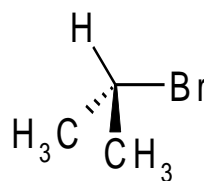
S$_N$1 reactivity

S$_N$2 reactivity

S_N1 vs. S_N2: Nature of Substrate
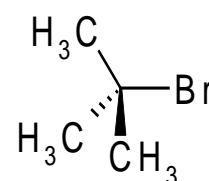
Reactivity of Alkyl bromide to S_N1 mechanism:
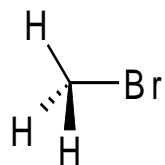
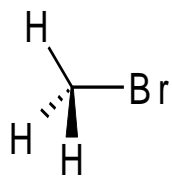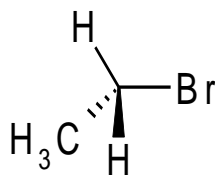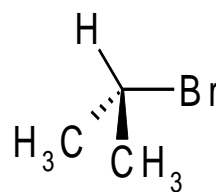| 1 | 2 | 43 | 100,000,000 |

Reactivity of Alkyl bromide to S_N2 mechanism:

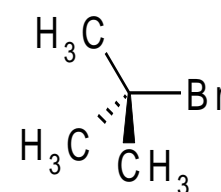| 220,000 | 1350 | 1 | too small to measure |

S$_N$1 vs. S$_N$2: Solvent Effects

The solvent can effect the rate of formation and stability of charged species. In general two types of solvents are used:

- Polar protic solvents: a solvent that contains an
  –OH group, they are good for dissolving anions and cations. This increases the rate of S$_N$1 but decreases S$_N$2 by solvating the Nu. (water, alcohols, acids)

- Polar aprotic solvents: only solvate cations well therefore good for S$_N$2 as the Nu is very reactive in these conditions. (acetone, DMSO, DMF, acetonitrile)
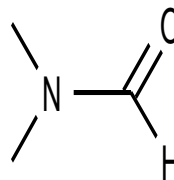
S$_N$1 vs. S$_N$2: Solvent Effects

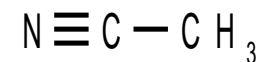Effects of polar protic/aprotic solvent polarity on S$_N$2 mechanism

Protic /aprotic Solvent	Relative Rate
CH$_3$OH	1
H$_2$O	7
(CH$_3$)$_2$SO (DMSO)	1,300
(CH$_3$)$_2$NCHO (DMF)	2,800
CH$_3$C≡N	5,000
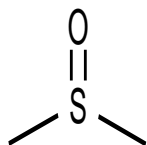
dimethylsulfoxide

dimethylformamide

acetonitrile

S$_N$1 vs. S$_N$2: Nucleophile

1) Anions are stronger nucleophiles than neutral molecules, i.e. HO$^-$ vs. H$_2$O (but more basic).

2) Nucleophilic strength increases down a column in the Periodic Table (polarizability).

3) Across a row in the periodic table nucleophilicity (lone pair donation) C$^-$ > N$^-$ > O$^-$ > F$^-$ since increasing electronegativity decreases the lone pair availability.

S$_N$1 vs. S$_N$2: Summary

Summary of S$_N$1 & S$_N$2 reactions:

Variable	S$_N$1	S$_N$2
Halide: 1°	NO	YES
2°	Yes	Yes
3°	YES	NO
Stereochemistry	Racemization	Inversion
nucleophile	Neutral ok as rate doesn't depend on [Nu]	Best when anionic
Solvent	Polar protic	Polar aprotic best, Polar protic slow

S_N1 vs. S_N2: Summary

Summary of S_N1 & S_N2 reactions:

- 1 ° - react S_N2! Can't make stable carbocation
- 3 ° - react S_N1! Too sterically crowded for S_N2
- 2 ° - reacts either S_N1 or S_N2, this is the one you have to use nucleophilic strength and solvent conditions to control the mechanism if needed.

Table 6.1 ■ Reactions of Common Nucleophiles with Alkyl Halides (Eqs. 6.2 and 6.3)

| Nu		R—Nu		
Formula	Name	Formula	Name	Comments
Oxygen nucleophiles				
1. $HO:^-$	hydroxide	$R—OH$	alcohol	
2. $RO:^-$	alkoxide	$R—OR$	ether	
3. HOH	water	$R—\overset{+}{O}\overset{H}{\diagdown_H}$	alkyloxonium ion	These ions lose a proton and the products are alcohols and ethers. $\xrightarrow{-H^+}$ ROH (alcohol); $\xrightarrow{-H^+}$ ROR (ether)
4. ROH	alcohol	$R—\overset{+}{O}\overset{R}{\diagdown_H}$	dialkyloxonium ion	
5. $R—C\overset{O}{\underset{O:^-}{\diagdown\!\!\diagup}}$	carboxylate	$R—O\overset{O}{\overset{\|}{C}}—R$	ester	
Nitrogen nucleophiles				
6. NH_3	ammonia	$R—\overset{+}{N}H_3$	alkylammonium ion	With a base, these ions readily lose a proton to give amines. $\xrightarrow{-H^+}$ RNH_2; $\xrightarrow{-H^+}$ R_2NH; $\xrightarrow{-H^+}$ $R_3N:$
7. RNH_2	primary amine	$R—\overset{+}{N}H_2R$	dialkylammonium ion	
8. R_2NH	secondary amine	$R—\overset{+}{N}HR_2$	trialkylammonium ion	
9. R_3N	tertiary amine	$R—\overset{+}{N}R_3$	tetraalkylammonium ion	
Sulfur nucleophiles				
10. $HS:^-$	hydrosulfide	$R—SH$	thiol	
11. $RS:^-$	mercaptide	$R—SR$	thioether (sulfide)	
12. $R_2S:$	thioether	$R—\overset{+}{S}R_2$	trialkylsulfonium ion	
Halogen nucleophiles				
13. $:\ddot{I}:^-$	iodide	$R—I:$	alkyl iodide	The usual solvent is acetone. Sodium iodide is soluble in acetone, but sodium bromide and sodium chloride are not.
Carbon nucleophiles				
14. $^-:C\equiv N:$	cyanide	$R—C\equiv N:$	alkyl cyanide (nitrile)	Sometimes the isonitrile, $R—\overset{+}{N}\equiv\overset{-}{C}:$, is formed.
15. $^-:C\equiv CR$	acetylide	$R—C\equiv CR$	alkyne	

Elimination Reactions

A problem arises in nucleophilic substitution reactions in that nucleophiles are also bases. This is especially true for anionic nucleophiles, i.e.

$$Nu:^- \;+\; H^+ \;\rightarrow\; Nu:H \;(Nu\text{-}H)$$

This can occur by the Nu abstracting a proton (i.e. acting as a base) from the substrate giving an elimination reaction.

Dehydrohalogenation Reactions

A dehydrohalogenation is an elimination reaction of alkyl halides. It will compete with a substitution to some degree, i.e.
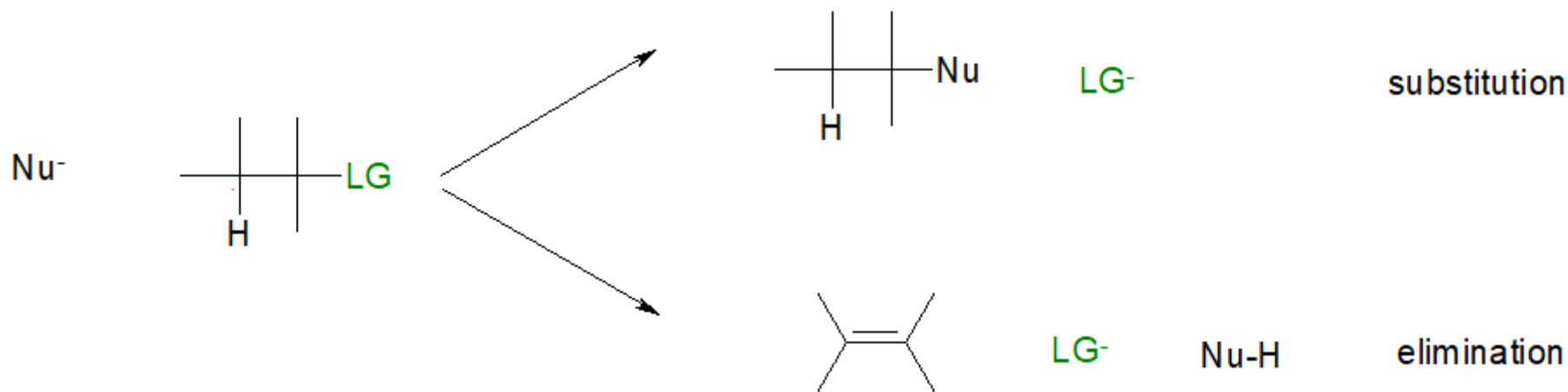
It is used to produce alkenes from alkyl halides

E Mechanisms

Like substitution there are several possible mechanisms for elimination reactions. We will examine two of them: E1 and E2

E2 Mechanism

- Rate = k[alkyl halide][base] (bimolecular)
- Stereochemical requirement: anti-periplanar arrangement of the H atom and LG is required
  - This results from an orbital interaction that allows the π bond to form.
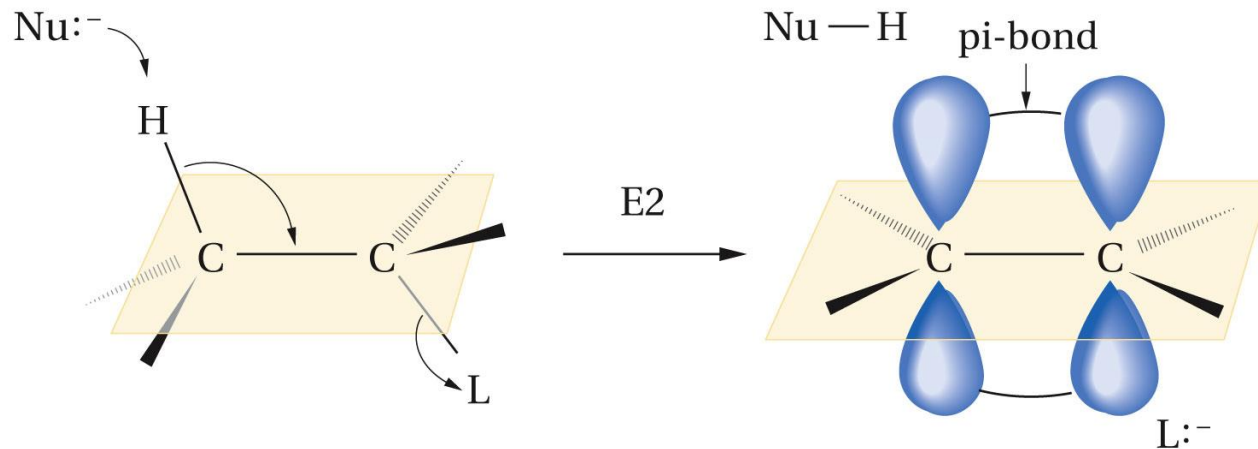
E2 Mechanism

Regioselectivity: where does the double bond form: *Zaitsev's rule*: most highly substituted alkene (watch for sterically hindered bases)

Stereoisomers: trans > cis

CH₃CH₂O⁻ / CH₃CH₂OH

20%   60%   20%
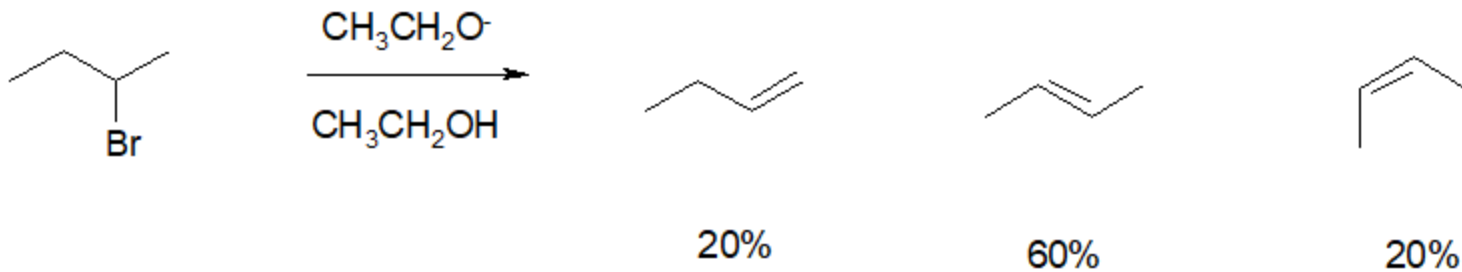
E1 Mechanism

- Rate = k[alkyl halide] (unimolecular)
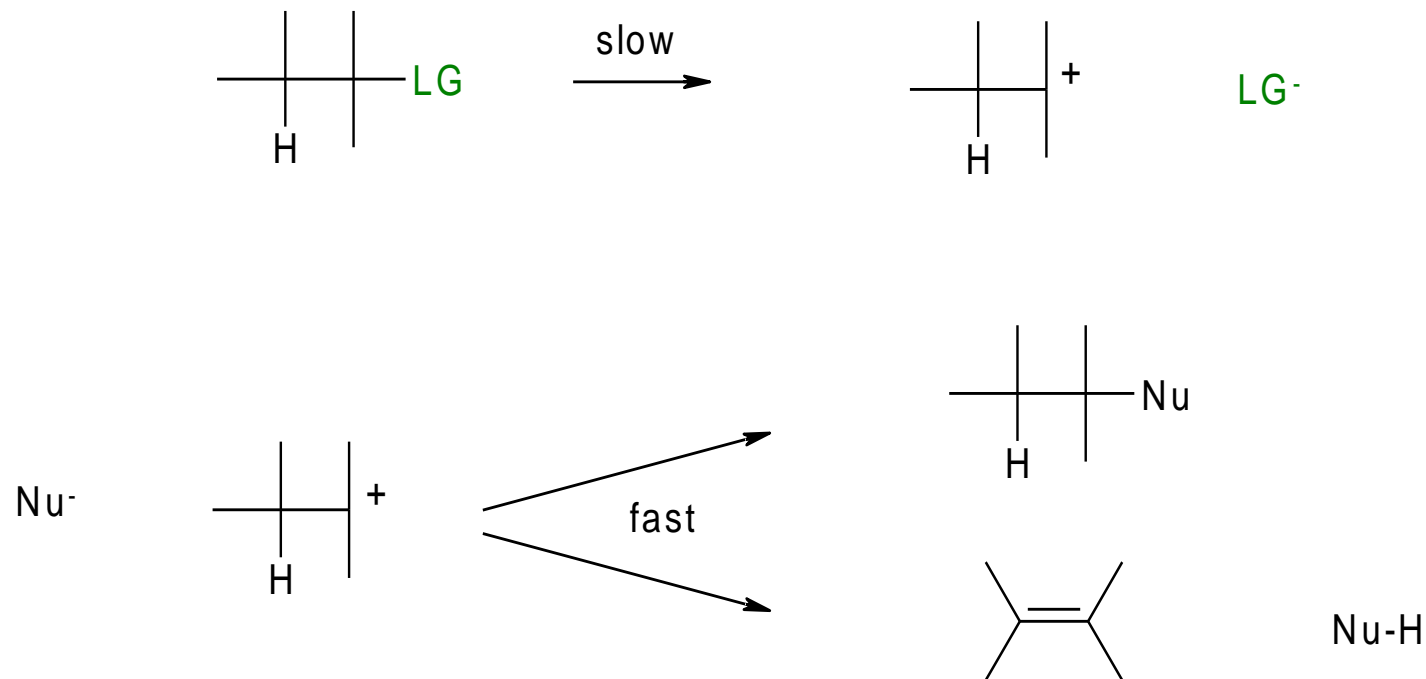
E1 Mechanism

Base strength and competing mechanisms:

S_N1 64%

30%

E1

6%

S_N1 7%

93%

E2
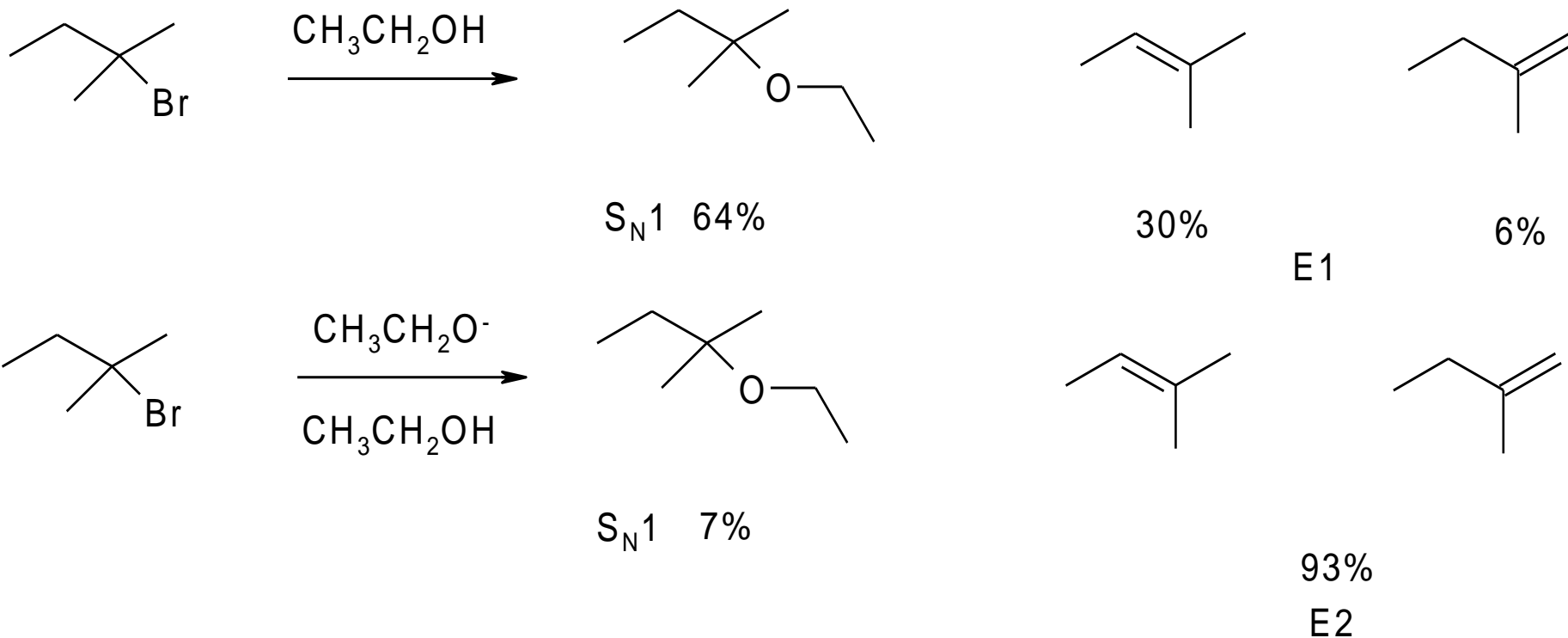
Substitution vs. Elimination

3° alkyl halides: only S_N1 but either (E1 or E2)
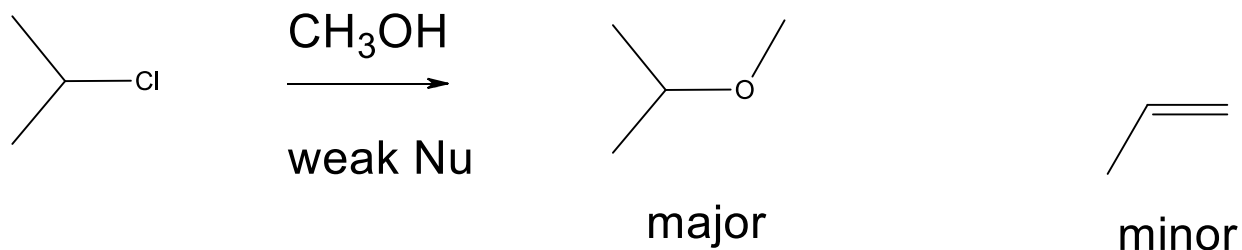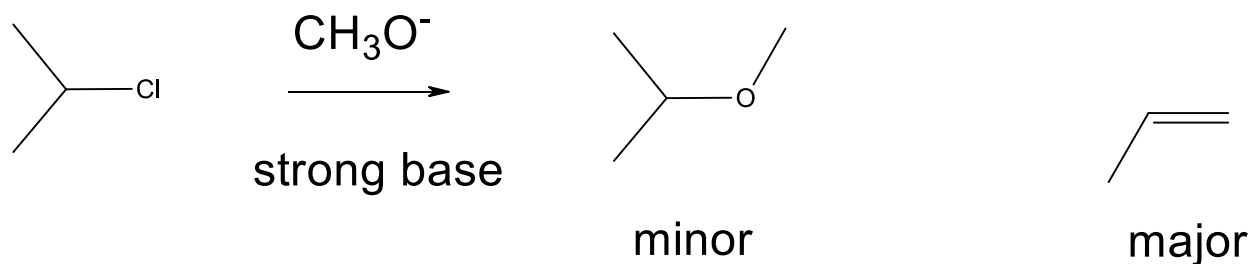- Weak Nu and polar solvent: S_N1 and E1 compete

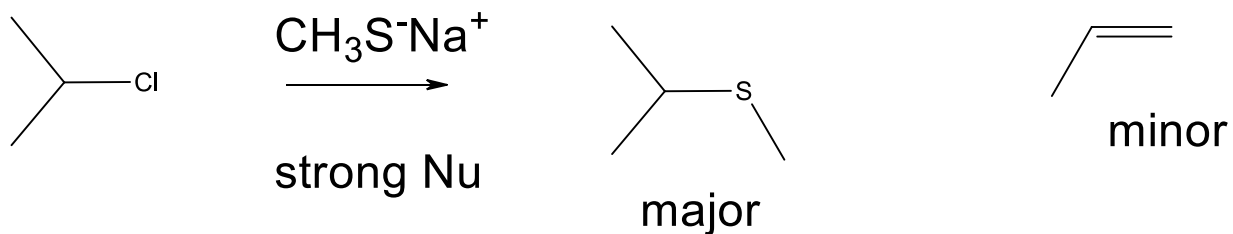H_2O

~80%   ~20%

OH^-

~0%   ~100%
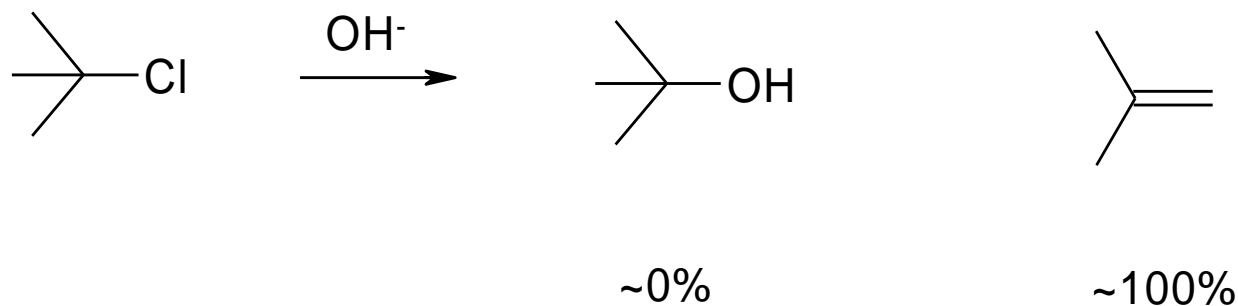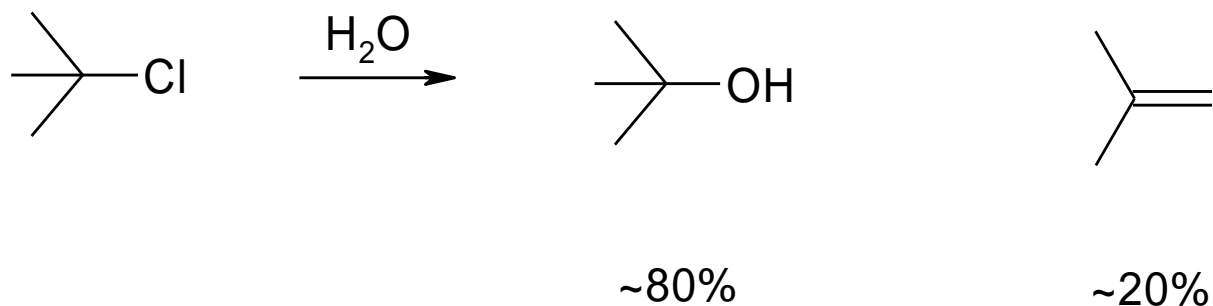
Substitution vs. Elimination

2° alkyl halides: S_N1, S_N2, E1 or E2 are all possible.

– Weak Nu ➔ substitution

– Strong base ➔ elimination

– Can use solvent to control S_N1 vs. S_N2
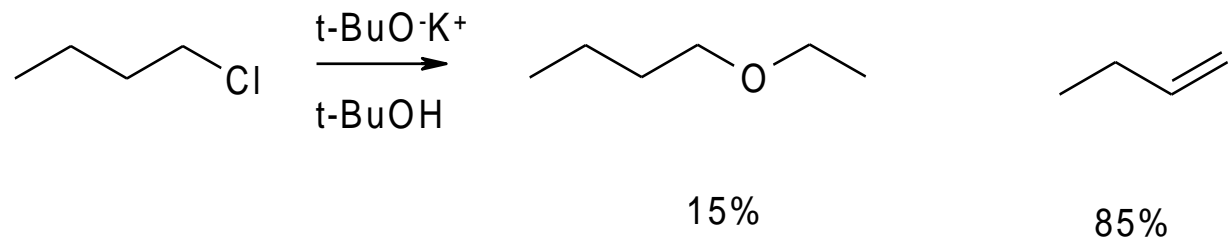
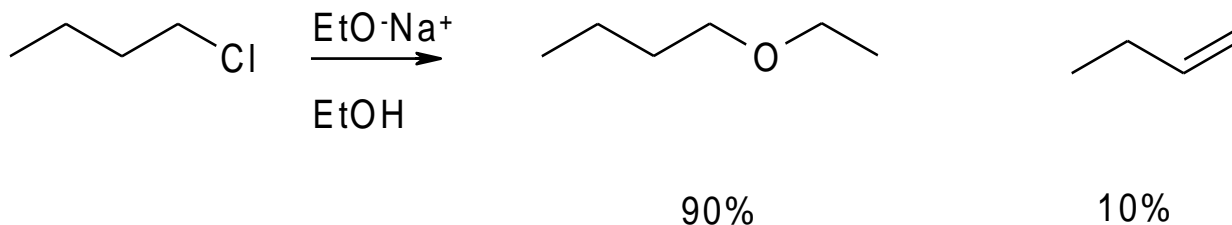# Substitution vs. Elimination

2° alkyl halides: i.e.

Substitution vs. Elimination

1° alkyl halides:

– Only S_N2 and E2 are possible (no carbocations)

– Substitution dominates unless you use a sterically hindered base like $(CH_3)_3CO^-K^+$

EtO⁻Na⁺ / EtOH

90%   10%

t-BuO⁻K⁺ / t-BuOH

15%   85%

Summary of S_N versus E for Haloalkanes

– For Methyl and Primary Haloalkanes

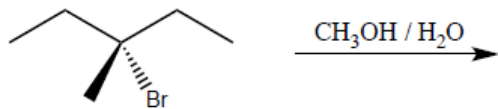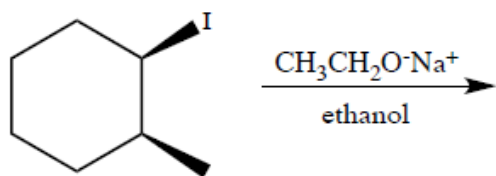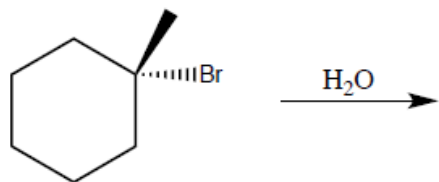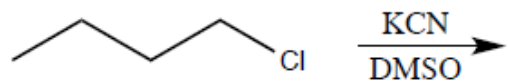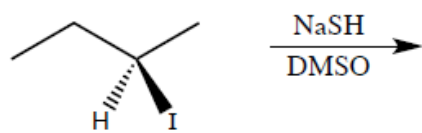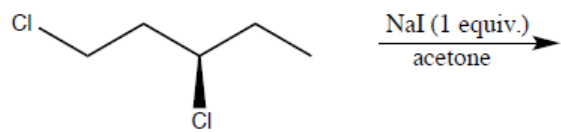| TABLE 7.7	Summary of Substitution versus Elimination Reactions of Haloalkanes	
Halide	Reaction	Comments
Methyl CH₃X	S_N2	The only substitution reactions observed.
	~~S_N1~~	S_N1 reactions of methyl halides are never observed. The methyl cation is so unstable that it is never formed in solution.
Primary RCH₂X	S_N2	The main reaction with strong bases such as OH⁻ and EtO⁻. Also, the main reaction with good nucleophiles/weak bases, such as I⁻ and CH₃COO⁻.
	E2	The main reaction with strong, bulky bases, such as potassium *tert*-butoxide.
	~~$S_N1/E1$~~	Primary cations are never formed in solution; therefore, S_N1 and E1 reactions of primary halides are never observed.

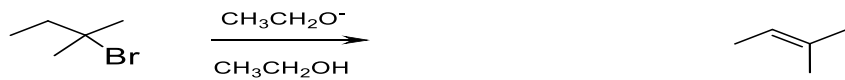# Summary of S_N versus E for Haloalkanes
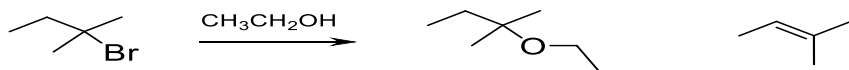## – For Secondary and Tertiary Haloalkanes

TABLE 7.7   Summary of Substitution versus Elimination Reactions of Haloalkanes

Halide	Reaction	Comments
Secondary R_2CHX	S_N2	The main reaction with weak bases/good nucleophiles, such as I^- and CH_3COO^-.
	E2	The main reaction with strong bases/good nucleophiles, such as OH^- and $CH_3CH_2O^-$.
	$S_N1/E1$	Common in reactions with weak nucleophiles in polar protic solvents, such as water, methanol, and ethanol.
Tertiary R_3CX	~~S_N2~~	S_N2 reactions of tertiary halides are never observed because of the extreme crowding around the 3° carbon.
	E2	Main reaction with strong bases, such as HO^- and RO^-.
	$S_N1/E1$	Main reactions with poor nucleophiles/weak bases.

Reaction 1:

(butyl chloride structure, CH$_3$CH$_2$CH$_2$CH$_2$—Cl)

$$\xrightarrow[\text{DMSO}]{\text{KCN}}$$

Reaction 2:

(1-methyl-1-bromocyclohexane, with CH$_3$ wedge up and Br dashed)

$$\xrightarrow{\text{H}_2\text{O}}$$

Reaction 3:

(trans-1-iodo-2-methylcyclohexane, I wedge and CH$_3$ wedge)

$$\xrightarrow[\text{ethanol}]{\text{CH}_3\text{CH}_2\text{O}^-\text{Na}^+}$$

Reaction 4:

(3-bromo-3-methylpentane type structure with Br dashed and CH$_3$ wedge)

$$\xrightarrow{\text{CH}_3\text{OH} / \text{H}_2\text{O}}$$

Cl—CH₂CH₂—CH(Cl)—CH₂CH₃

$$\xrightarrow[\text{acetone}]{\text{NaI (1 equiv.)}}$$

$$\xrightarrow[\text{DMSO}]{\text{NaSH}}$$

CH$_3$S$^-$

SCH$_3$

(CH$_3$)$_3$O$^-$

(CH$_3$)$_3$OH

NaI

Acetone

CH$_3$OH

OCH$_3$ OCH$_3$

+   +

CH$_3$CH$_2$OH

O

CH$_3$CH$_2$O$^-$

CH$_3$CH$_2$OH

93%
E2

CH₃S⁻Na⁺ — $CH_3S^-Na^+$
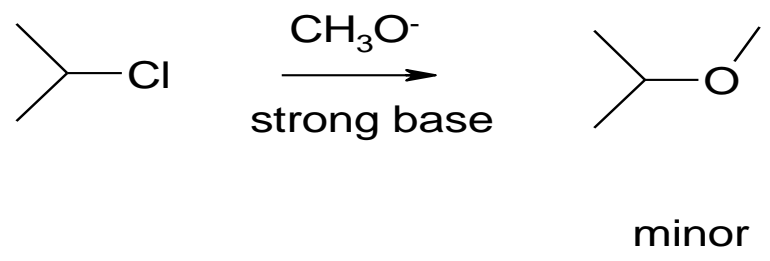strong Nu

CH₃OH — CH_3OH
weak Nu

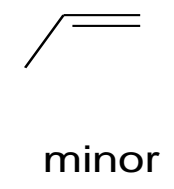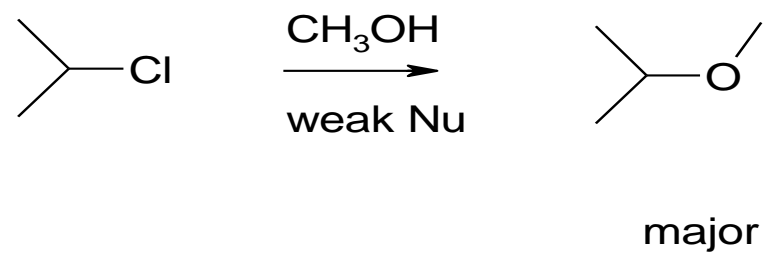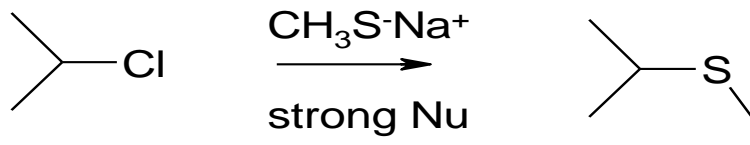major   minor

CH₃O⁻ — CH_3O^-
strong base

minor   major

Summary of S_N versus E for Haloalkanes

– **Examples**: Predict the **major** product and the **mechanism** for each reaction.

1.

$$+ \ Na^+OH^- \quad \xrightarrow[H_2O]{80\ °C}$$

2.

$$+ \ (C_2H_5)_3N \quad \xrightarrow[CH_2Cl_2]{30\ °C}$$

3.

$$+ \ CH_3O^- \ Na^+ \quad \xrightarrow[methanol]{}$$

4.

$$+ \ Na^+ OH^- \quad \xrightarrow[acetone]{}$$