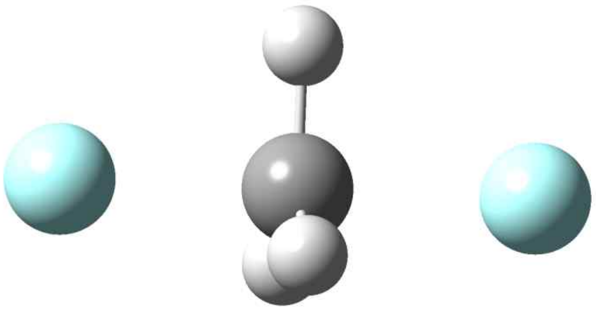
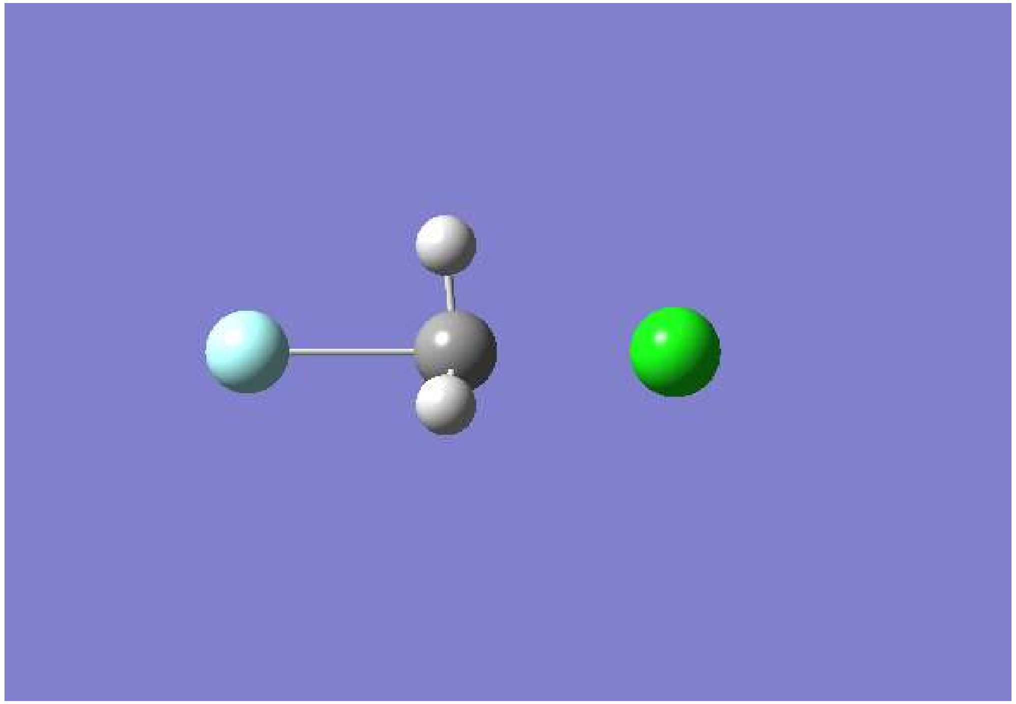
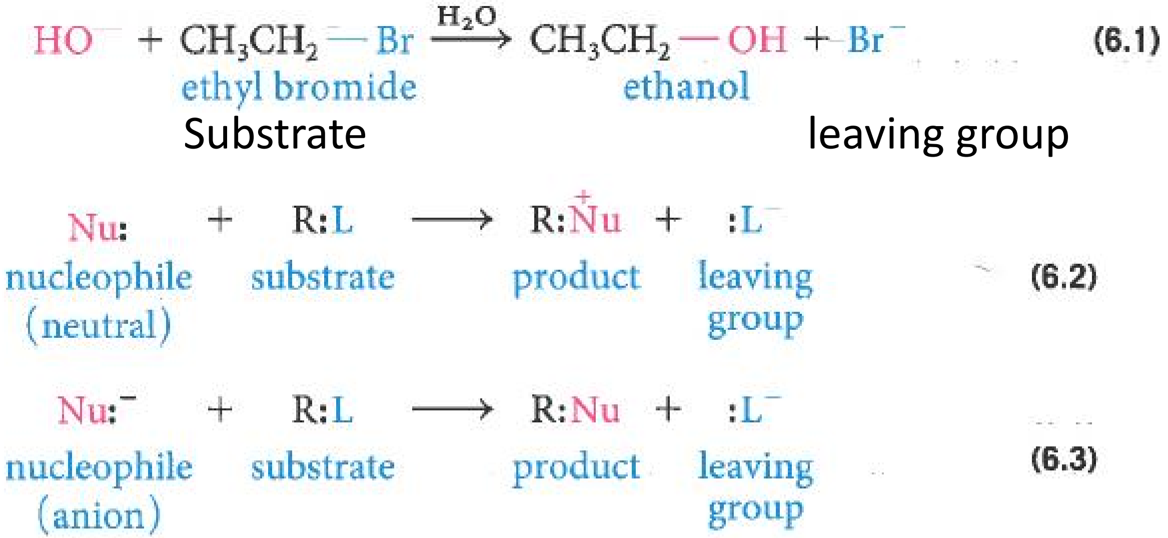


Chapter 6: Nucleophilic Substitution and Elimination Reactions



Nucleophilic Substitution

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



$$HO^- + CH_3CH_2{-}Br \xrightarrow{H_2O} CH_3CH_2{-}OH + Br^- \quad (6.1)$$

ethyl bromide — ethanol

Substrate — leaving group

$$Nu: + R:L \longrightarrow R:\overset{+}{Nu} + :L^- \quad (6.2)$$

nucleophile (neutral) — substrate — product — leaving group

$$Nu:^- + R:L \longrightarrow R:Nu + :L^- \quad (6.3)$$

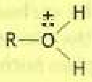
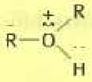
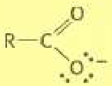
nucleophile (anion) — substrate — product — leaving group

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”.

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

Nu Formula	Name	R—Nu Formula	Name	Comments
Oxygen nucleophiles				
1. $H\ddot{\underset{..}{O}}:^-$	hydroxide	$R-\ddot{\underset{..}{O}}H$	alcohol	
2. $R\ddot{\underset{..}{O}}:^-$	alkoxide	$R-\ddot{\underset{..}{O}}R$	ether	
3. $H\ddot{\underset{..}{O}}H$	water		alkyloxonium ion	These ions lose a proton and the products are alcohols and ethers. $\xrightarrow{-H^+} R\ddot{\underset{..}{O}}H$ (alcohol) $\xrightarrow{-H^+} R\ddot{\underset{..}{O}}R$ (ether)
4. $R\ddot{\underset{..}{O}}H$	alcohol		dialkyloxonium ion	
5. 	carboxylate	 $R-\ddot{\underset{..}{O}}\overset{O}{\overset{\|}{C}}-R$	ester	
Nitrogen nucleophiles				
6. $\ddot{N}H_3$	ammonia	$R-\overset{+}{N}H_3$	alkylammonium ion	With a base, these ions readily lose a proton to give amines. $\xrightarrow{-H^+} R\ddot{N}H_2$ $\xrightarrow{-H^+} R_2\ddot{N}H$ $\xrightarrow{-H^+} R_3N:$
7. $R\ddot{N}H_2$	primary amine	$R-\overset{+}{N}H_2R$	dialkylammonium ion	
8. $R_2\ddot{N}H$	secondary amine	$R-\overset{+}{N}HR_2$	trialkylammonium ion	
9. $R_3\ddot{N}$	tertiary amine	$R-\overset{+}{N}R_3$	tetraalkylammonium ion	
Sulfur nucleophiles				
10. $H\ddot{\underset{..}{S}}:^-$	hydrosulfide	$R-\ddot{\underset{..}{S}}H$	thiol	
11. $R\ddot{\underset{..}{S}}:^-$	mercaptide	$R-\ddot{\underset{..}{S}}R$	thioether (sulfide)	
12. $R_2\ddot{S}:$	thioether	$R-\overset{+}{\underset{..}{S}}R_2$	trialkylsulfonium ion	
Halogen nucleophiles				
13. $:\ddot{\underset{..}{I}}:^-$	iodide	$R-\ddot{\underset{..}{I}}:$	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	

EXAMPLE 6.1

Use Table 6.1 to write an equation for the reaction of sodium ethoxide with bromoethane.

Solution

$$\underset{\text{sodium ethoxide}}{CH_3CH_2\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}:^{-}\,Na^{+}} + \underset{\text{bromoethane}}{CH_3CH_2Br} \longrightarrow \underset{\text{diethyl ether}}{CH_3CH_2\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}CH_2CH_3} + Na^{+}Br^{-}$$

Ethoxide is the nucleophile (entry 2 in Table 6.1), bromoethane is the substrate, and bromide ion is the leaving group. The product is diethyl ether, which is used as an anesthetic. Notice that the counterion of the nucleophile, Na^+, is merely a spectator during the reaction. It is present at the beginning and end of the reaction.

EXAMPLE 6.2

Devise a synthesis for propyl cyanide in which a nucleophilic substitution reaction is used.

Solution First, write the structure of the desired product.

$$\underset{\text{propyl cyanide}}{CH_3CH_2CH_2{-}C{\equiv}N:}$$

If we use cyanide ion as the nucleophile (entry 14 in Table 6.1), the alkyl halide must have the halogen (Cl, Br, or I) attached to a propyl group. The equation is

$$^{-}:C{\equiv}N: + CH_3CH_2CH_2Br \longrightarrow CH_3CH_2CH_2C{\equiv}N: + Br^{-}$$

Sodium cyanide or potassium cyanide can be used to supply the nucleophile.

EXAMPLE 6.3

Show how 1-butyne could be converted to 3-hexyne using a nucleophilic substitution reaction.

Solution Compare the starting material with the product.

$CH_3CH_2C{\equiv}CH$	$CH_3CH_2C{\equiv}CCH_2CH_3$
1-butyne	3-hexyne

From Table 6.1, entry 15, we see that acetylides react with alkyl halides to give acetylenes. We therefore need to convert 1-butyne to an acetylide (review eq. 3.53), then treat it with a 2-carbon alkyl halide.

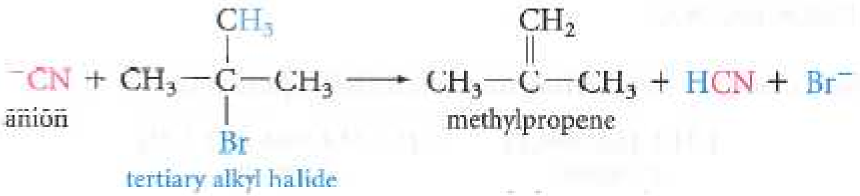
$$CH_3CH_2C{\equiv}CH + NaNH_2 \xrightarrow{NH_3} CH_3CH_2C{\equiv}C:^- \; Na^+$$

$$CH_3CH_2C{\equiv}C:^- \; Na^+ + CH_3CH_2Br \longrightarrow CH_3CH_2C{\equiv}CCH_2CH_3 + Na^+Br^-$$

SN rxn (O) ; alkyl halides (H bonded to sp3-hybridized carbon)
SN (X) ; aryl halide and vinyl halides (H is bonded to sp2-hybridized carbon)
Also, depending on nucleophile type (ex ; anion or base or both)

$$\underset{\text{anion}}{^{-}CN} + \underset{\text{primary alkyl halide}}{CH_3CH_2CH_2CH_2Br} \longrightarrow CH_3CH_2CH_2CH_2CN + Br^{-} \qquad \textbf{(6.4)}$$

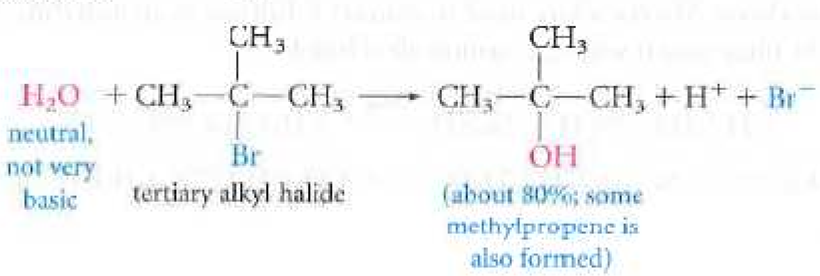
but



$$^{-}CN + CH_3-\underset{Br}{\overset{CH_3}{C}}-CH_3 \longrightarrow CH_3-\overset{CH_2}{\overset{\|}{C}}-CH_3 + HCN + Br^{-}$$

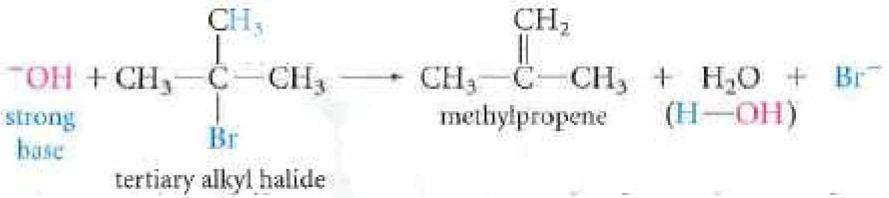
(6.5)

Another example is



$$H_2O + CH_3-\underset{Br}{\overset{CH_3}{C}}-CH_3 \longrightarrow CH_3-\underset{OH}{\overset{CH_3}{C}}-CH_3 + H^{+} + Br^{-}$$

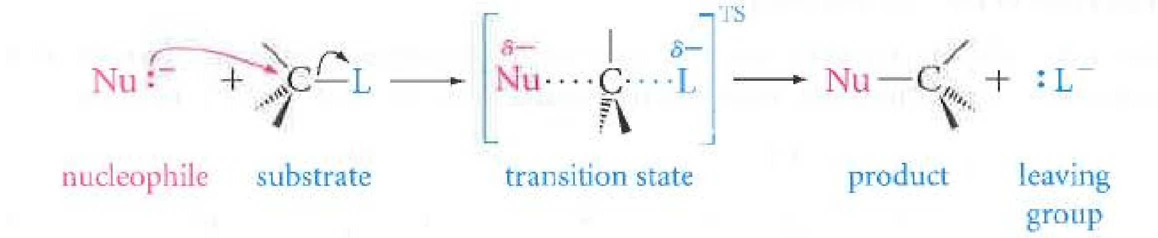
(6.6)



$$^{-}OH + CH_3-\underset{Br}{\overset{CH_3}{C}}-CH_3 \longrightarrow CH_3-\overset{CH_2}{\overset{\|}{C}}-CH_3 + H_2O + Br^{-}$$

(6.7)

The S_N2 mechanism

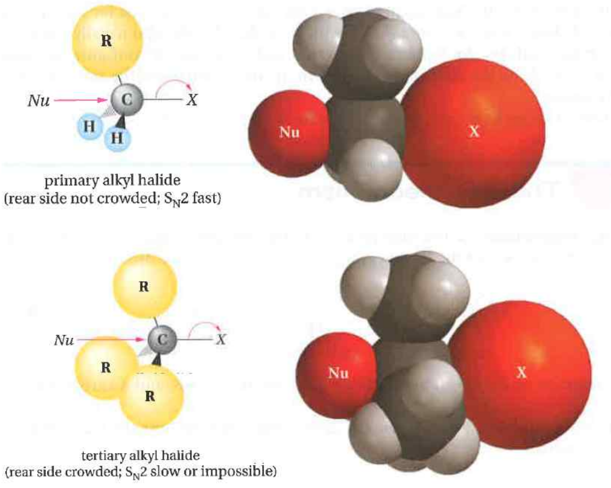


One step process in which the bond to the leaving group begin to break as the bond to the nucleophile begins to form

1. The rate of the rxn depends on both the Nu and the substrate concentration

2. Every Sn2 displacement occurs with inversion of configuration

(R)-2-bromobutane (S)-2-butanol



primary alkyl halide (rear side not crowded; S_N2 fast)

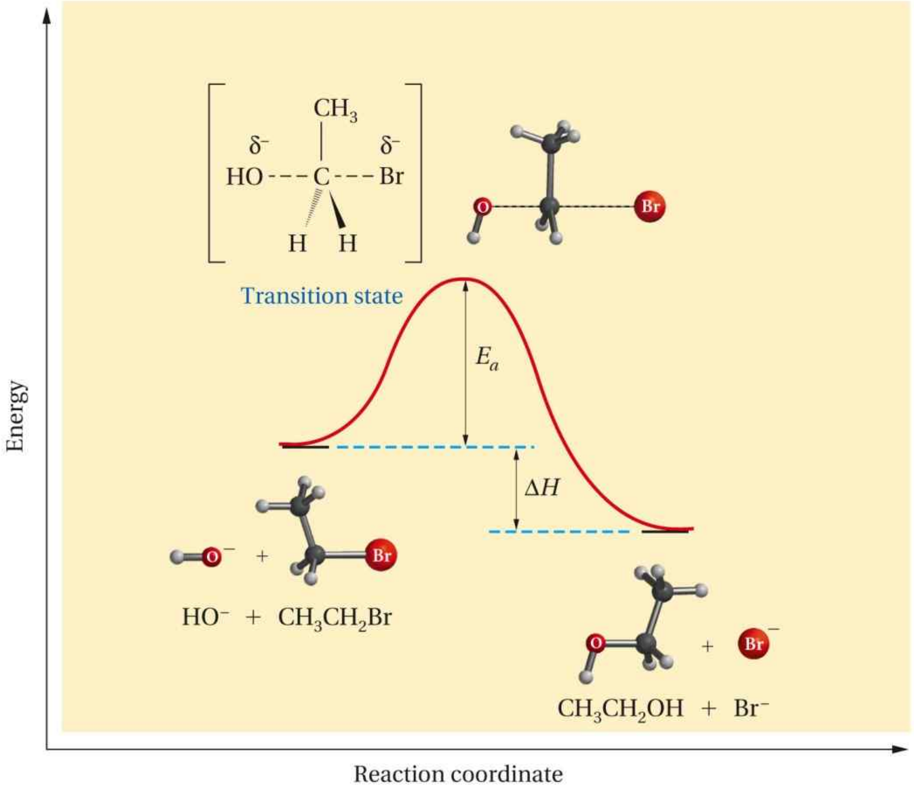
tertiary alkyl halide (rear side crowded; S_N2 slow or impossible)

3. When alkyl group of substrate is methyl or 1° is the fastest, and slowest when it is 3° Alkyl halide react at the intermediate rate.

Substitution Reactions: S_N2

The reaction coordinate diagram right indicate this one step mechanism.

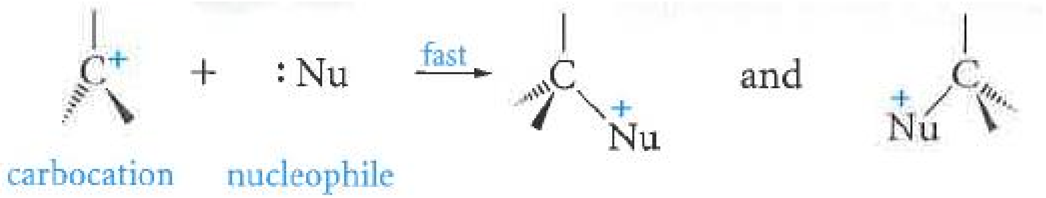
- Rate = [substrate] & [nu]
- S_N2 results in an inversion of configuration if it occurs at a chiral center. (Back-side attack of the Nu)
- Fastest for 1°, slowest for 3°



The S_N1 mechanism (two step)

The first step is slow. The bond between the C and the leaving group break

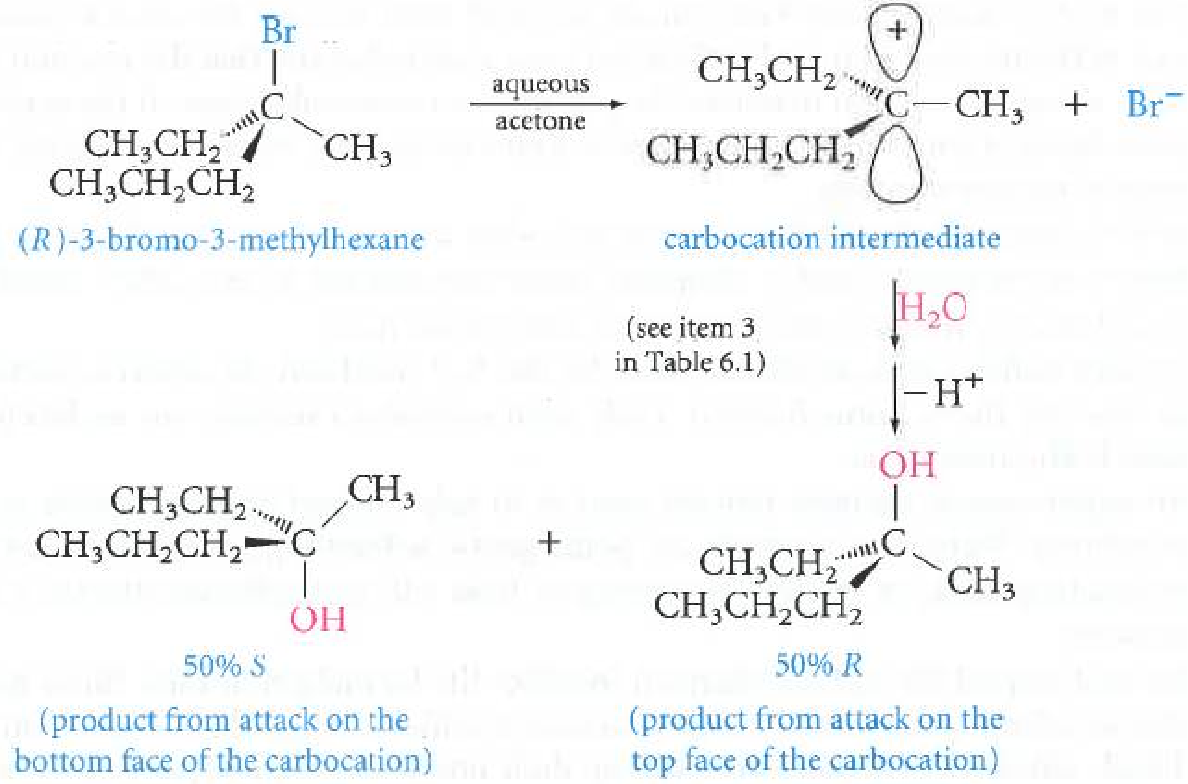
Second step is fast. The carbocation combines with the nucleophile to give product



When the Nu is a neutral molecule (eg water or alcohol), loss of proton from nuclephilic oxygen, in a third step gives the final product.

1. The rate of rxn does not depend on the concentration of Nu.

2. If the carbon bearing the leaving group is sterogenic, the reaction occurs mainly with loss of optical activity (racemization)

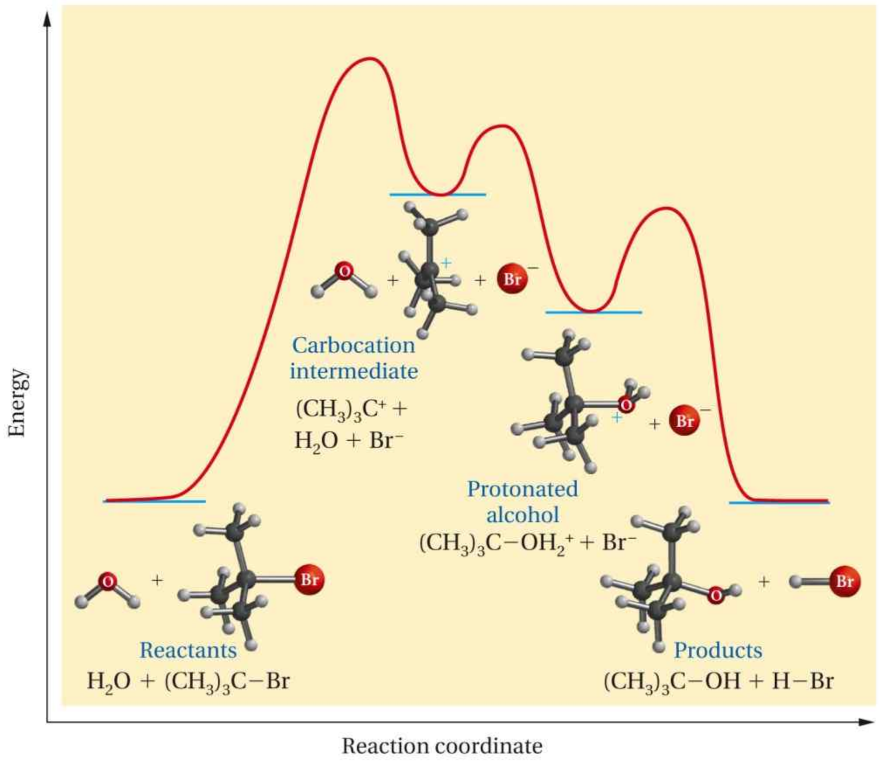


3. Rxn is the fastest in the order of $3^o > 2^o > 1^o$

Substitution Reactions: S_N1

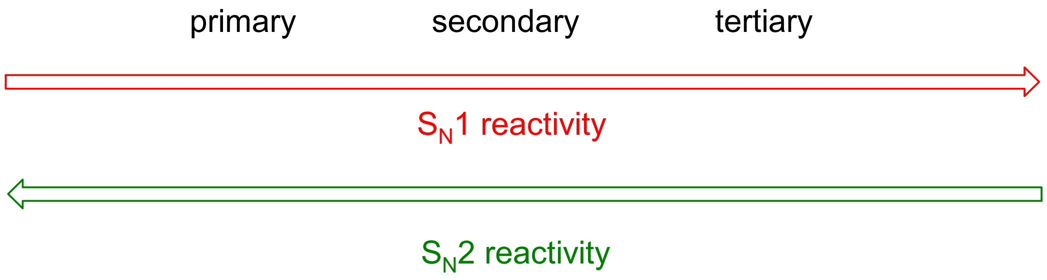
The reaction coordinate diagram right indicate this multi-step mechanism.

- Rate = [substrate]
- Generate intermediate carbocation
- S_N1 results in racemization of configuration if it occurs at a chiral center.
- Fastest for 3° (allylic), slowest for 1° (parallels C^+ stability)



S_N1 vs. S_N2: Nature of Substrate

The substrate itself has an effect on the mechanism. S_N1 requires an intermediate carbocation, while S_N2 requires a backside attack of the nucleophile (steric effects), i.e.



primary secondary tertiary

S_N1 reactivity

S_N2 reactivity

Table 6.2 ■ Comparison of S_N2 and S_N1 Substitutions

Variables	**S_N2**	**S_N1**
Halide structure		
Primary or CH_3	Common	Rarely*
Secondary	Sometimes	Sometimes
Tertiary	Rarely	Common
Stereochemistry	Inversion	Racemization
Solvent	Rate is retarded by polar protic solvents and increased by polar aprotic solvents	Because the intermediates are ions, the rate is increased by polar solvents
Nucleophile	Rate depends on nucleophile concentration; mechanism is favored when the nucleophile is an anion	Rate is independent of nucleophile concentration; mechanism is more likely with neutral nucleophiles

*Allyl and benzyl substrates are the common exceptions (see Problem 6.7b).

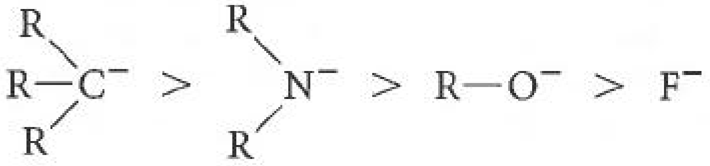
1. *Negative ions are more nucleophilic, or better electron suppliers, than the corresponding neutral molecules.* Thus,

$$HO^- > HOH \qquad RS^- > RSH \qquad RO^- > ROH$$

2. *Elements low in the periodic table tend to be more nucleophilic than elements above them in the same column.* Thus,

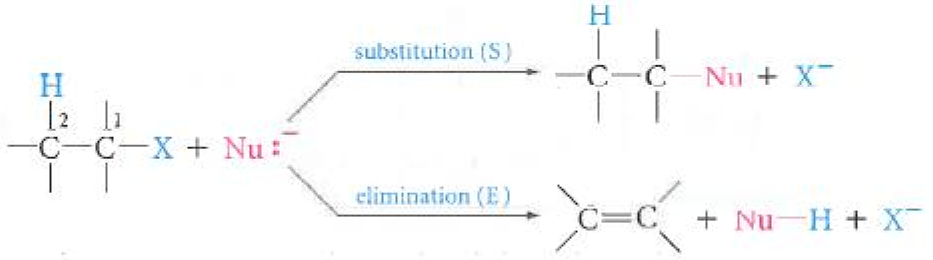
$$HS^- > HO^- \qquad I^- > Br^- > Cl^- > F^- \qquad \text{(in protic solvents)}$$

3. *Across a row in the periodic table, more electronegative elements (that is, the more tightly an element holds electrons to itself) tend to be less nucleophilic.* Thus,



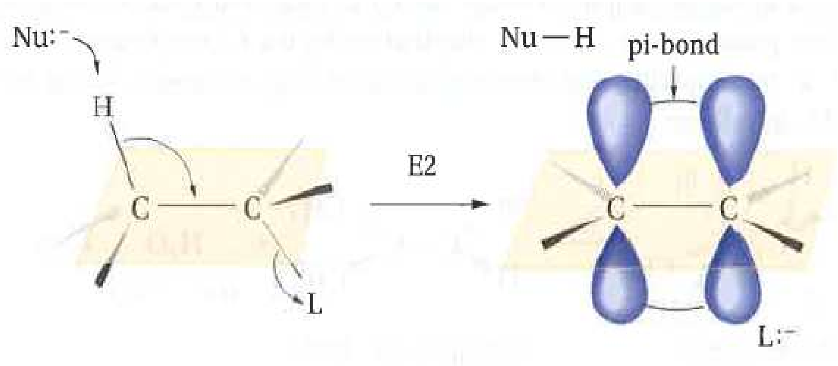
and $H_3N\!: > H_2\ddot{O}\!: > H\underset{\cdot\cdot}{\ddot{F}}\!:$

Elimination(dehygrohalogenation) Reactions

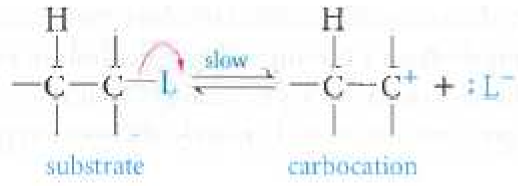


Elimination ; Halogen atom from adjacent carbons are eliminated and a C-C double bond is formed.

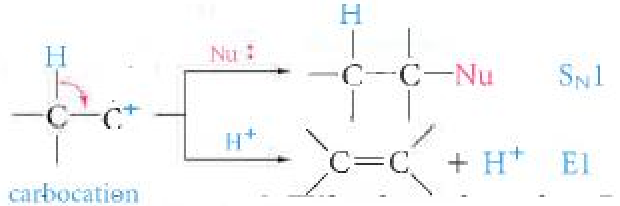
E2 mechanism ; one step process



E1 mechanism ; two step process

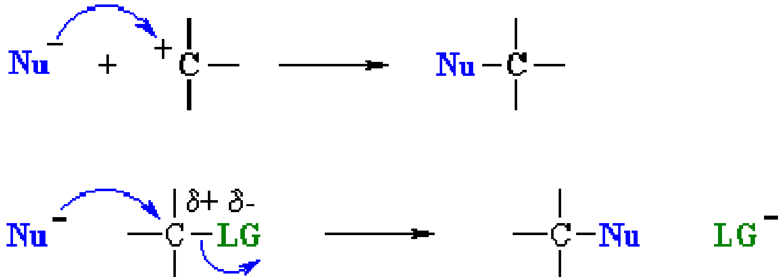


(6.18)



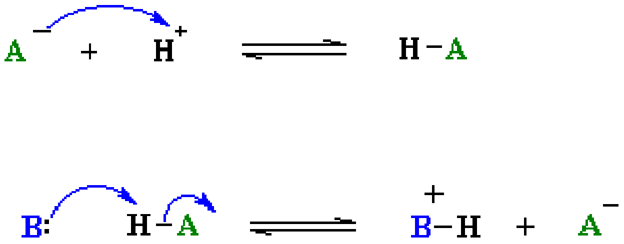
(6.19)

Nucleophilicity ; nucleophile attack any other atom than hydrogen



Both these reactions depict a nucleophile reacting with an electrophilic C atom

Basicity ; nucleophile attack hydrogen



Both these reactions depict a base reacting with an electrophilic H atom, a proton

Strong Bases, strong Nucleophile–

· Usually anions with a full negative charge (easily recognizable by the presence of sodium, lithium or potassium counterions)

· Participate in SN2 and E2-type eliminations

· May overlap with strong nucleophile list

(causing mixtures of both substitutions and eliminations to be produced)

Examples: OH^-, $R\text{-}O^-$, R_2N^- (deprotonated amines but bulky)

Weak Nucleophile, Weak base

H2O, R-OH, RCOOH etc

Strong Base, weak Nucleophile

· Usually anions that are very sterically hindered

· Participate in E2 ONLY

Examples:

Tert-butyl Lithium : tBuLi (also written as (CH3)3CLi)

PotassiumTert-butoxide : KOtBu (also written as (KOC(CH3)3)

Lithium Diisopropylamide : LDA (acronym) (also written as LiN(CH(CH3)2)2)

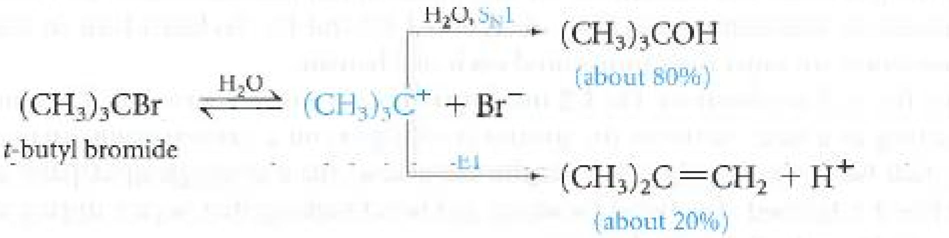
Strong Nucleophile, weak base

$R\text{-}NH_2$ (amine), $R\text{-}S^-$, CN^-, N_3^-, I^-, ROO^-, H_2S, R-SH etc

Substitution and Elimination in Competition

O Tertiary halide

Weak nucleophile and polar solvent ; SN 1 and E1 compete

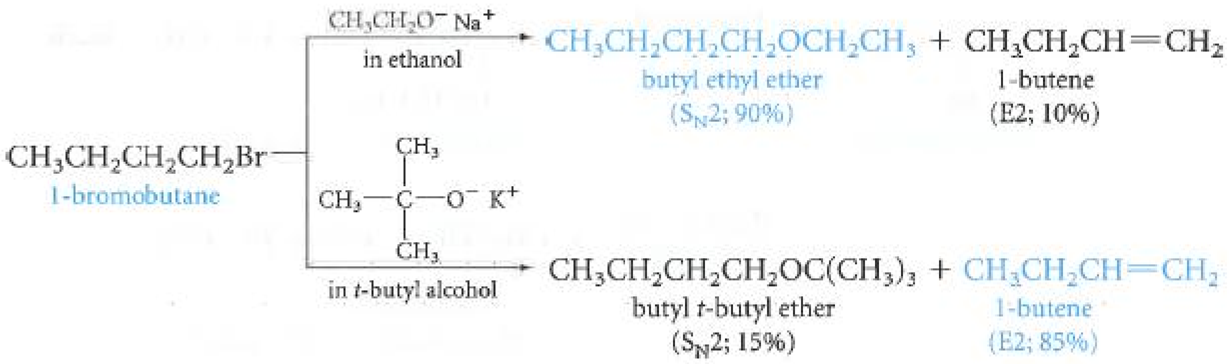


(6.20)

Strong Base and less solvent ; E2 only

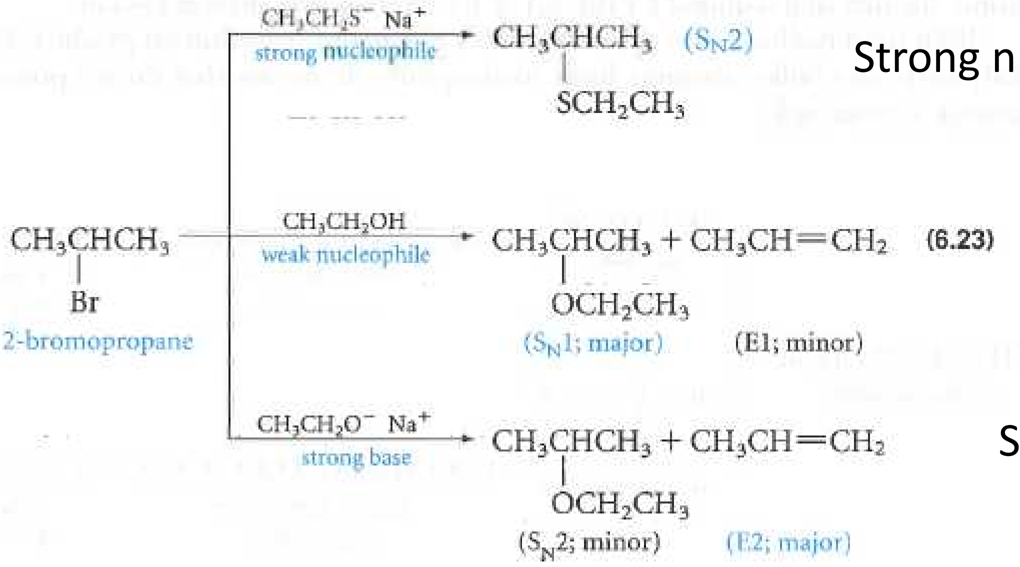
(6.21)

O Primary halide ; SN2 and E2 are possible



Dominant E2 when bulky and strong base

Secondary Halide ; Four reactions are possible
depending on nucleophile and reaction condition



Strong nucleophile (but not base)

Weak nucleophile in polar solvent

Strong base