



Chapter 6

Organic Halogen Compounds

Substitution and Elimination Reactions

Organic Halogen Compounds:

1- Alkyl Halides : R-X

primary R-CH₂-X

secondary $\begin{array}{c} \text{R} \\ | \\ \text{R}-\text{CH}-\text{X} \end{array}$

tertiary $\begin{array}{c} \text{R} \\ | \\ \text{R}-\text{C}-\text{X} \\ | \\ \text{R} \end{array}$

vinyl R-CH=CH-X

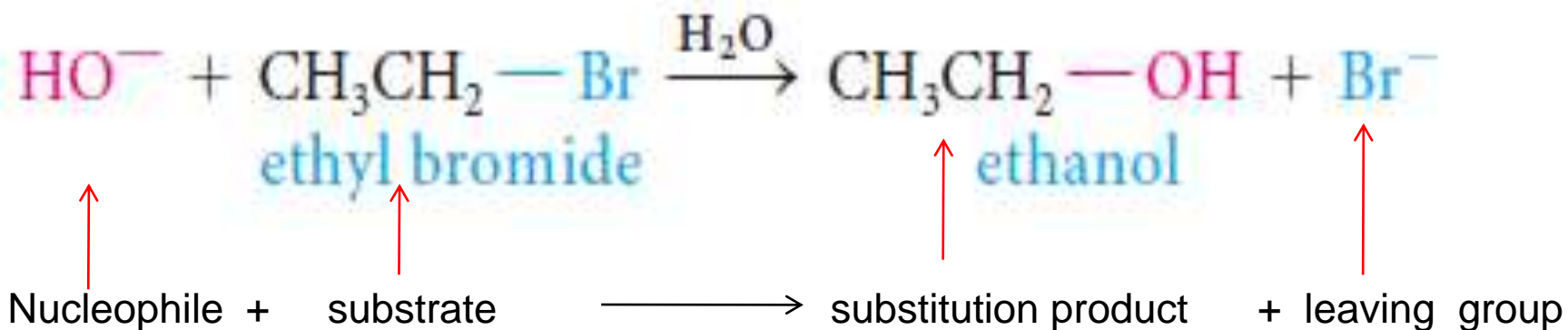
2- Aryl Halides : Ar-X

6.1 Nucleophilic Substitution :

Alkyl halides undergo **Nucleophilic Substitution reactions** (S_N1 , S_N2).

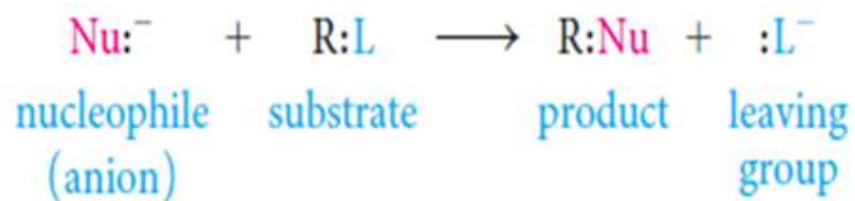
The Nucleophile (**Nu**) displaces the halide ion (X^- , **Leaving Group**) from the alkyl halide (**R-X**, **Substrate**)

Example:

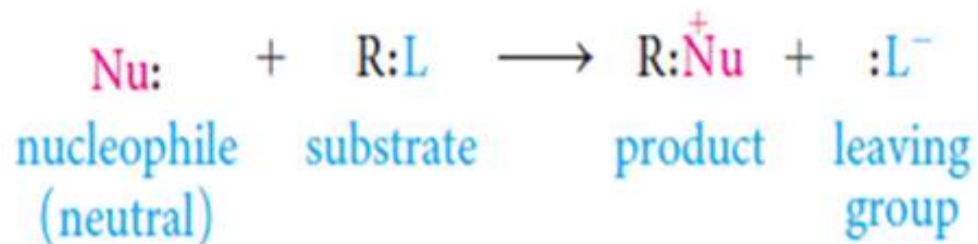


Nucleophiles may be : **1)** neutral (with lone pairs)
or **2)** negatively charged

1- Reaction with negatively charged nucleophiles:



2- Reaction with neutral nucleophiles:



6.2 Examples of Nucleophilic Substitution :

Types of Nucleophiles: (according to nucleophilic atom) :

oxygen nucleophiles : HO^- , CH_3O^- , H_2O , CH_3OH

nitrogen nucleophiles : NH_3 , RNH_2 , R_2NH , R_3N

sulfur nucleophiles : HS^- , RS^- , H_2S , RSH

halogen nucleophiles : Br^- , I^-

carbon nucleophiles : CN^- , R^-

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

Nu		R—Nu		Comments
Formula	Name	Formula	Name	
Oxygen nucleophiles				
1. HO^-	hydroxide	$\text{R}-\text{OH}$	alcohol	These ions lose a proton and the products are alcohols and ethers. $\xrightarrow{-\text{H}^+} \text{ROH}$ (alcohol) $\xrightarrow{-\text{H}^+} \text{ROR}$ (ether)
2. RO^-	alkoxide	$\text{R}-\text{OR}$	ether	
3. HOH	water	$\text{R}-\overset{+}{\text{O}}\text{H}_2$	alkyloxonium ion	
4. ROH	alcohol	$\text{R}-\overset{+}{\text{O}}\text{R}_2$	dialkyloxonium ion	
5. $\text{R}-\text{C}(=\text{O})\text{O}^-$	carboxylate	$\text{R}-\overset{+}{\text{O}}\text{C}(=\text{O})\text{R}$	ester	
Nitrogen nucleophiles				With a base, these ions readily lose a proton to give amines. $\xrightarrow{-\text{H}^+} \text{RNH}_2$ $\xrightarrow{-\text{H}^+} \text{R}_2\text{NH}$ $\xrightarrow{-\text{H}^+} \text{R}_3\text{N}$
6. NH_3	ammonia	$\text{R}-\overset{+}{\text{N}}\text{H}_3$	alkylammonium ion	
7. RNH_2	primary amine	$\text{R}-\overset{+}{\text{N}}\text{H}_2\text{R}$	dialkylammonium ion	
8. R_2NH	secondary amine	$\text{R}-\overset{+}{\text{N}}\text{HR}_2$	trialkylammonium ion	
9. R_3N	tertiary amine	$\text{R}-\overset{+}{\text{N}}\text{R}_3$	tetraalkylammonium ion	

Sulfur nucleophiles

10. $\text{H}\ddot{\text{S}}:^-$	hydrosulfide	$\text{R}-\ddot{\text{S}}\text{H}$	thiol
11. $\text{R}\ddot{\text{S}}:^-$	mercaptide	$\text{R}-\ddot{\text{S}}\text{R}$	thioether (sulfide)
12. $\text{R}_2\ddot{\text{S}}:$	thioether	$\text{R}-\overset{+}{\text{S}}\text{R}_2$	trialkylsulfonium ion

Halogen nucleophiles

13. $:\ddot{\text{I}}:^-$	iodide	$\text{R}-\ddot{\text{I}}:$	alkyl iodide
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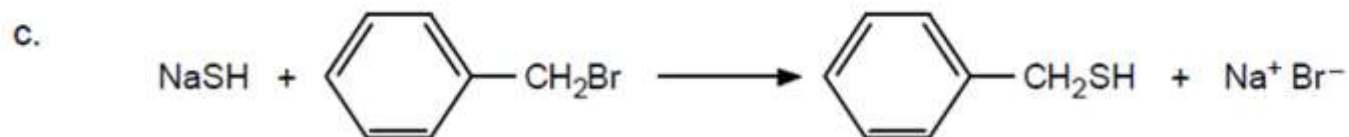
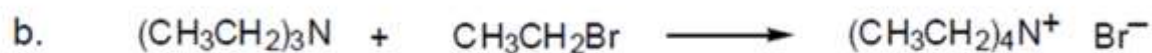
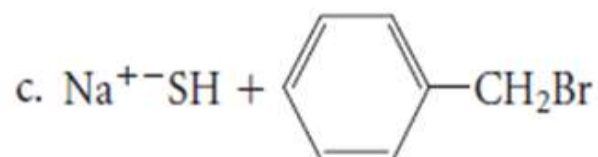
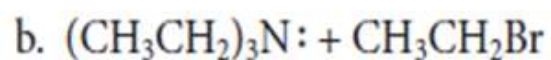
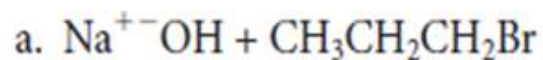
The usual solvent is acetone. Sodium iodide is soluble in acetone, but sodium bromide and sodium chloride are not.

Carbon nucleophiles

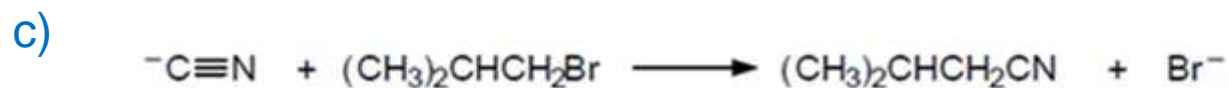
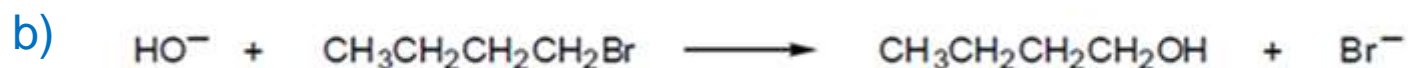
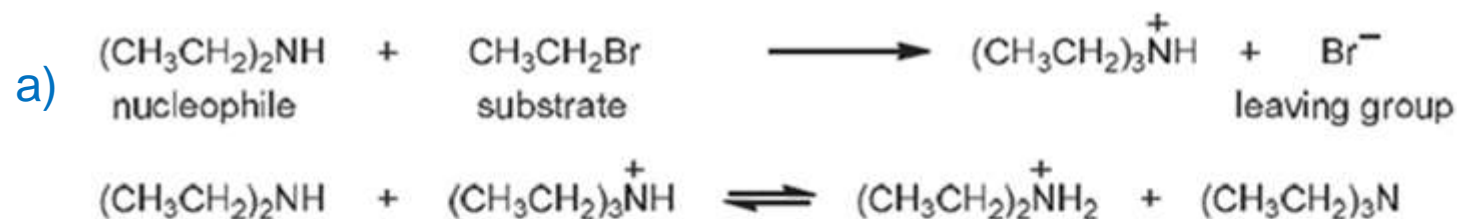
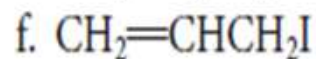
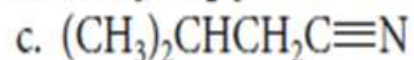
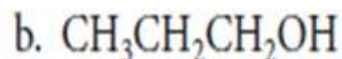
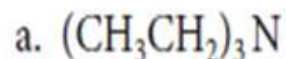
14. $^-:\text{C}\equiv\text{N}:$	cyanide	$\text{R}-\text{C}\equiv\text{N}:$	alkyl cyanide (nitrile)
15. $^-:\text{C}\equiv\text{CR}$	acetylide	$\text{R}-\text{C}\equiv\text{CR}$	alkyne

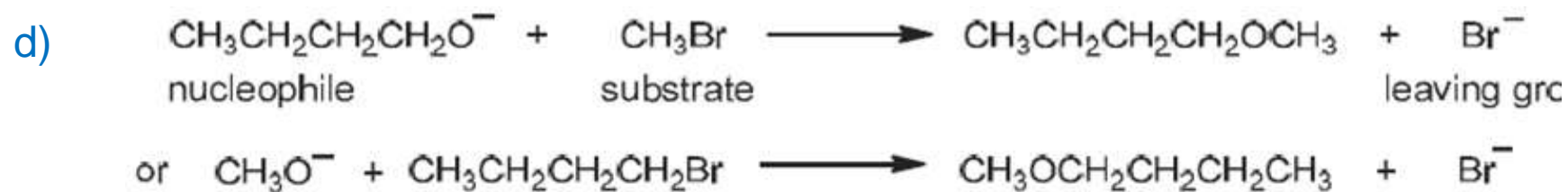
Sometimes the isonitrile, $\text{R}-\overset{+}{\text{N}}\equiv\bar{\text{C}}:$, is formed.

PROBLEM 6.1 Using Table 6.1, write complete equations for the following nucleophilic substitution reactions:



PROBLEM 6.2 Write an equation for the preparation of each of the following compounds, using a nucleophilic substitution reaction. In each case, label the nucleophile, the substrate, and the leaving group.

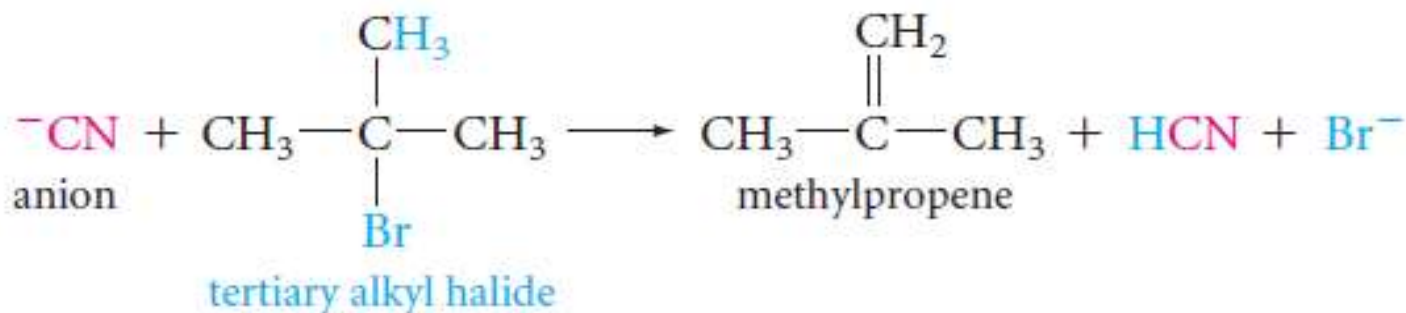


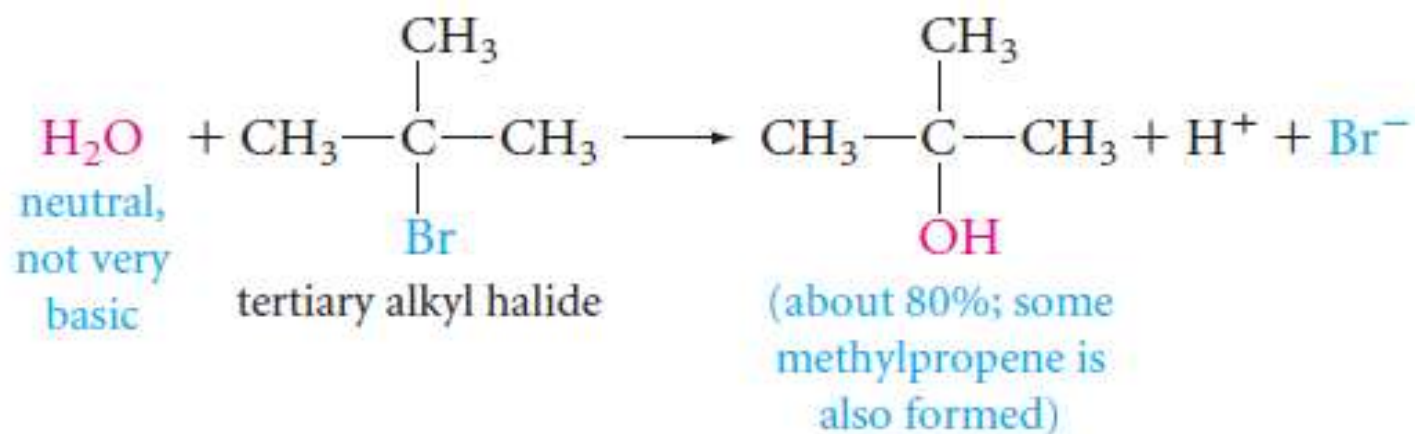


- Elimination occurs when the nucleophilic reagent is basic.



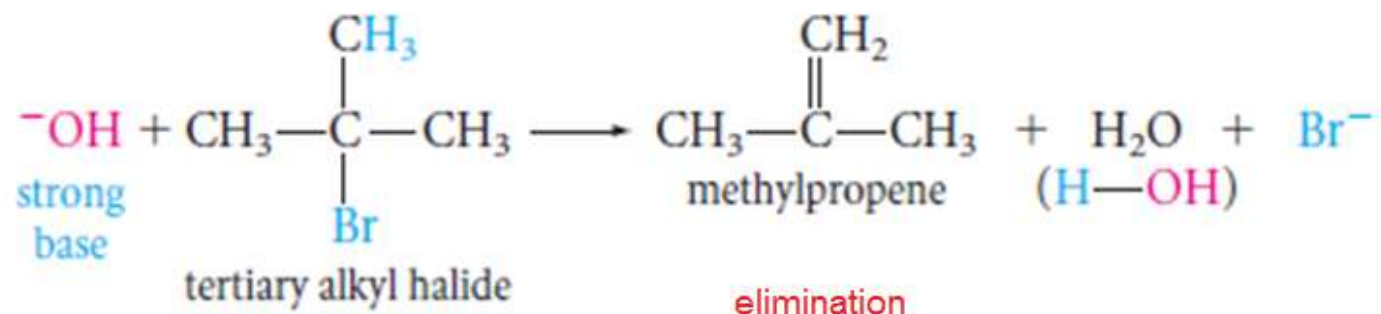
- Elimination occurs when the nucleophilic reagent is basic.





Neutral, not basic
Nucleophile :
Substitution

but

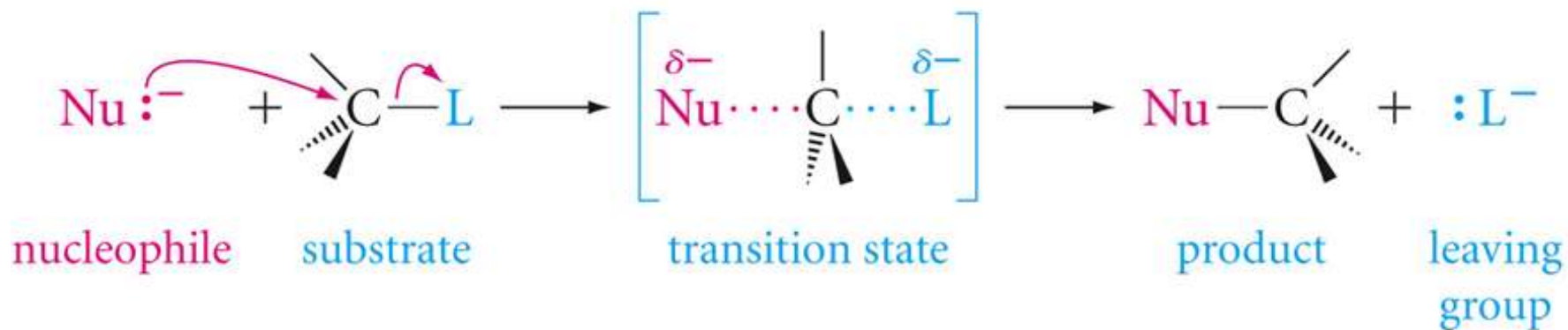


Basic Nucleophile :
Elimination

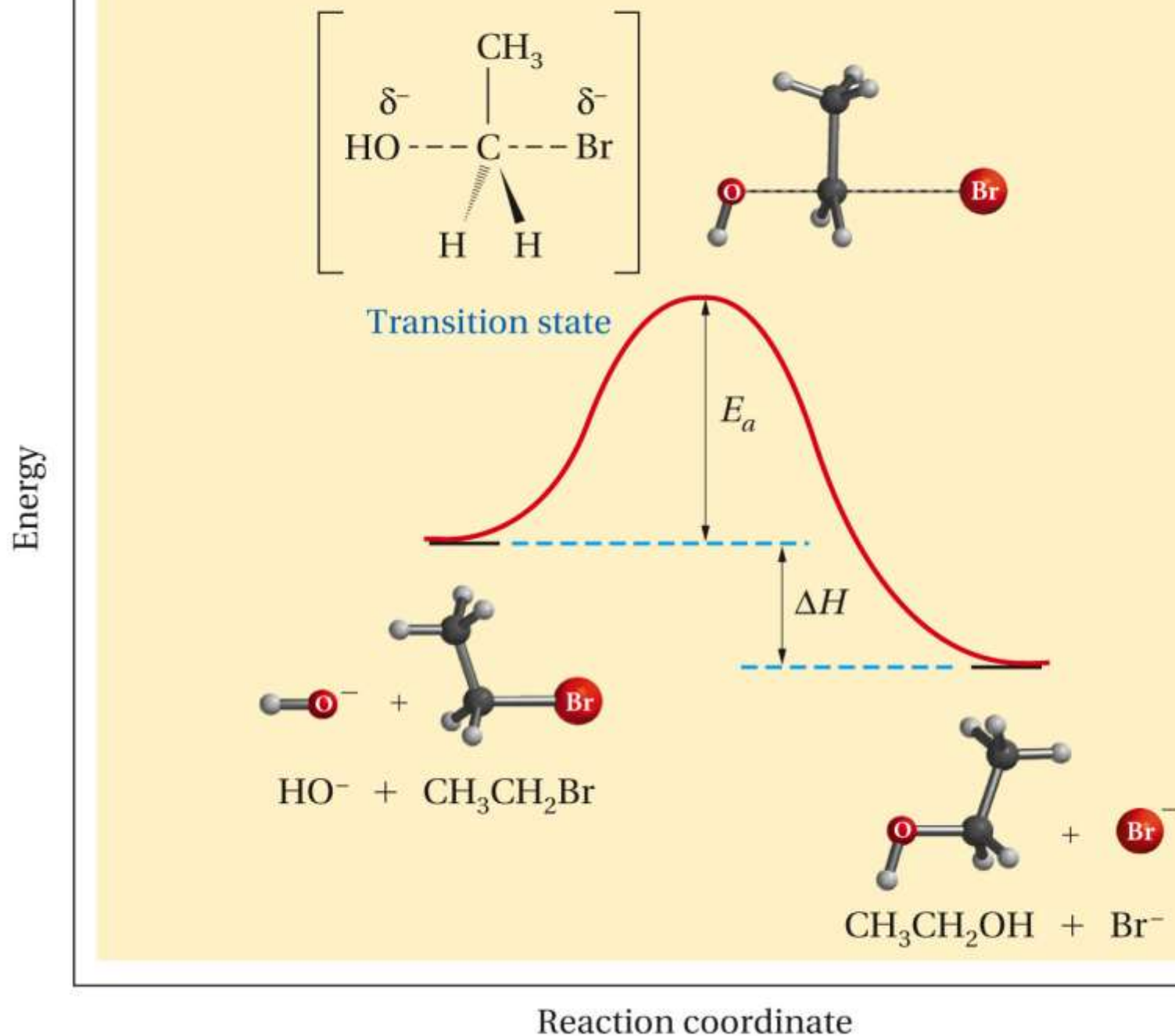
6.3 Nucleophilic Substitution Mechanisms : (S_N1 , S_N2)

S_N2 Mechanism :

One-step process: Bond to the leaving group is breaking at the same time the bond to the nucleophile is starting to form



One-step; one TransitionState; no intermediates;
bond breaking and formation at the same time



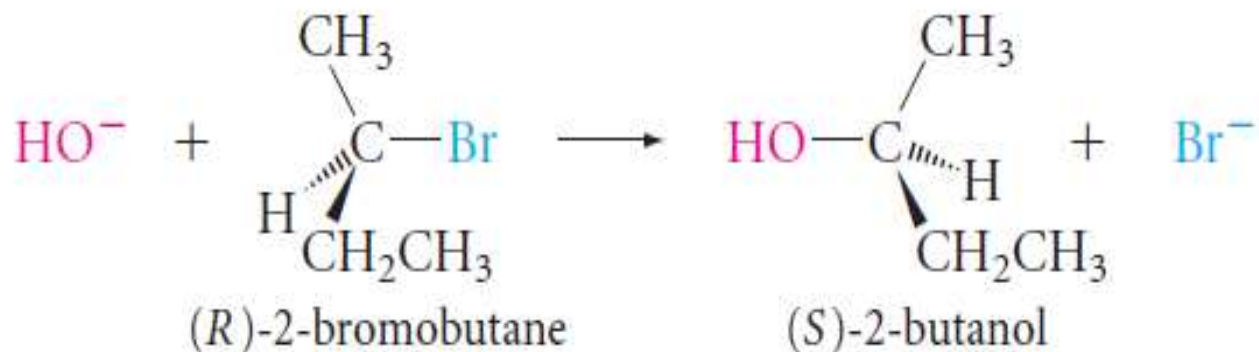
Characteristics of S_N2 reactions:

1. **Rate** : depends on concentration of both (**nucleophile + substrate**):

if concentration of RX is doubled, rate is doubled

if concentration of RX is doubled, rate is doubled

2. **Stereochemistry**: S_N2 reactions occur with **inversion** of configuration:

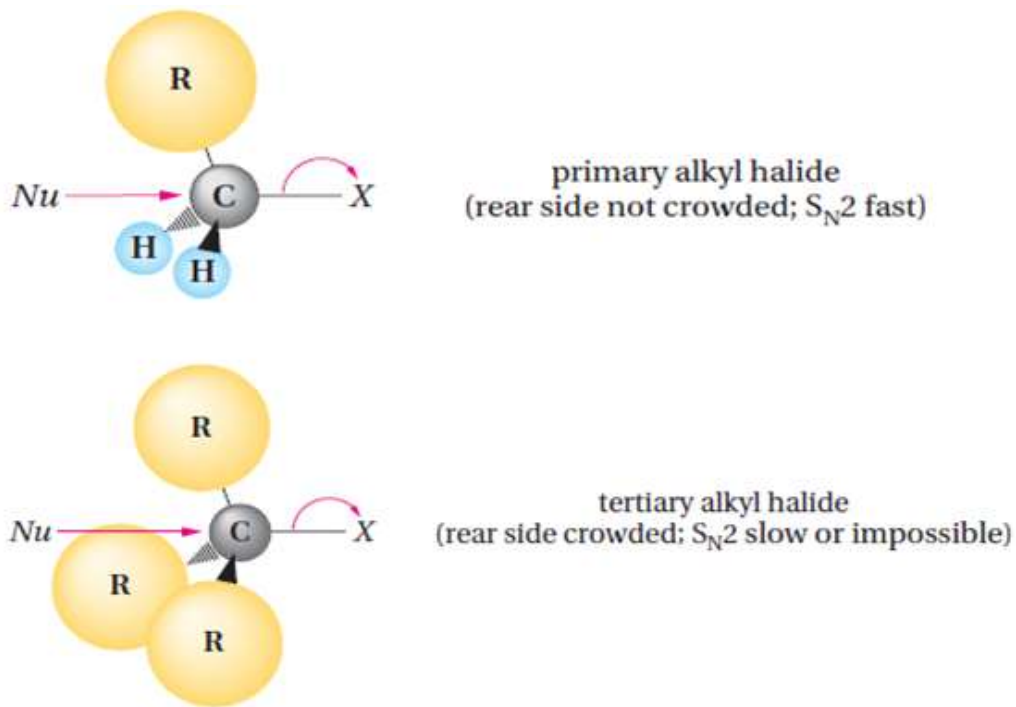


3. S_N2 reaction rates : (determined by **steric** factor – crowding)

methyl halides > primary > secondary >> tertiary

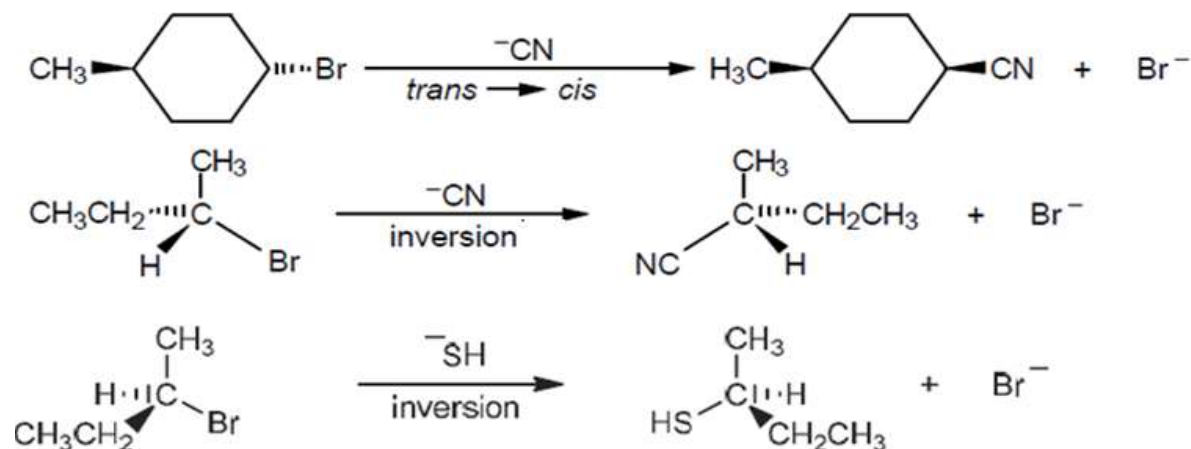
less crowded $\xrightarrow{\text{rate decreases}}$ most crowded

(**vinyl** and **aryl** : no reaction - leaving group at sp^2 C)

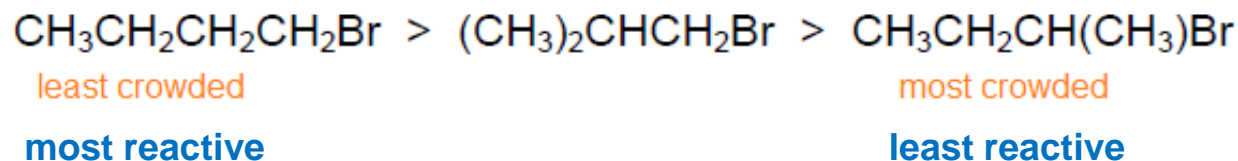
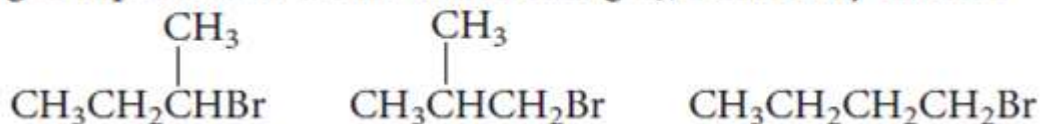


PROBLEM 6.4 Predict the product from the S_N2 reaction of

- trans*-4-methylcyclohexyl bromide with cyanide ion.
- (*S*)-2-bromopentane with cyanide ion.
- (*R*)-2-chlorobutane with NaSH.



PROBLEM 6.5 Arrange the following compounds in order of *decreasing* S_N2 reactivity toward sodium ethoxide:



Summary of S_N2 reactions :

- 1- S_N2 is one step (2nd order reaction, **bi-molecular**)
- 2- favored for : **a)** methyl + primary halides
b) needs strong nucleophile
- 3- slower with secondary and **not at all** with tertiary halides.
- 4- occur with **inversion** of configuration.
- 5- rate depends on conc. of nucleophile + substrate (R-X).
- 6- rate : methyl halides > primary > secondary >> tertiary
rate depends on **steric hindrance** (crowding)

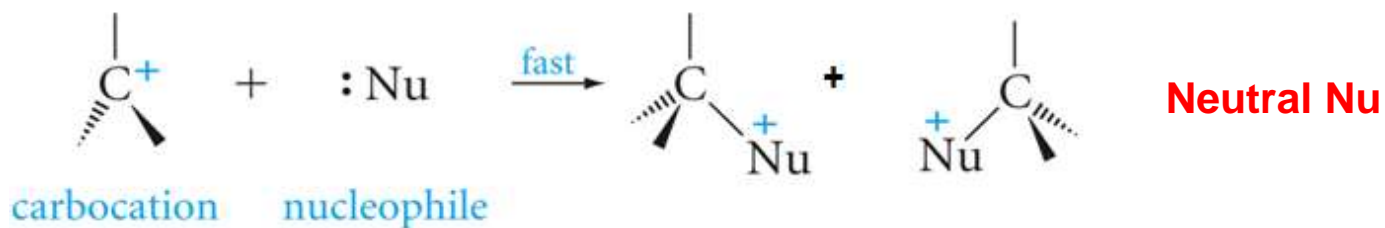
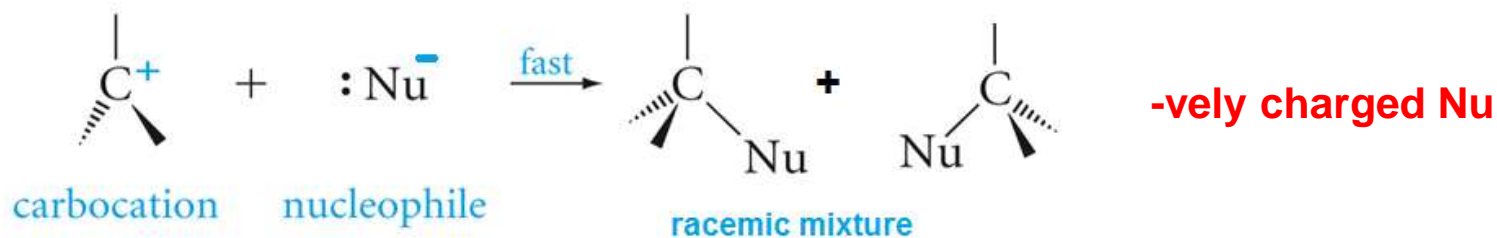


6.5 S_N1 Mechanism : two step process:

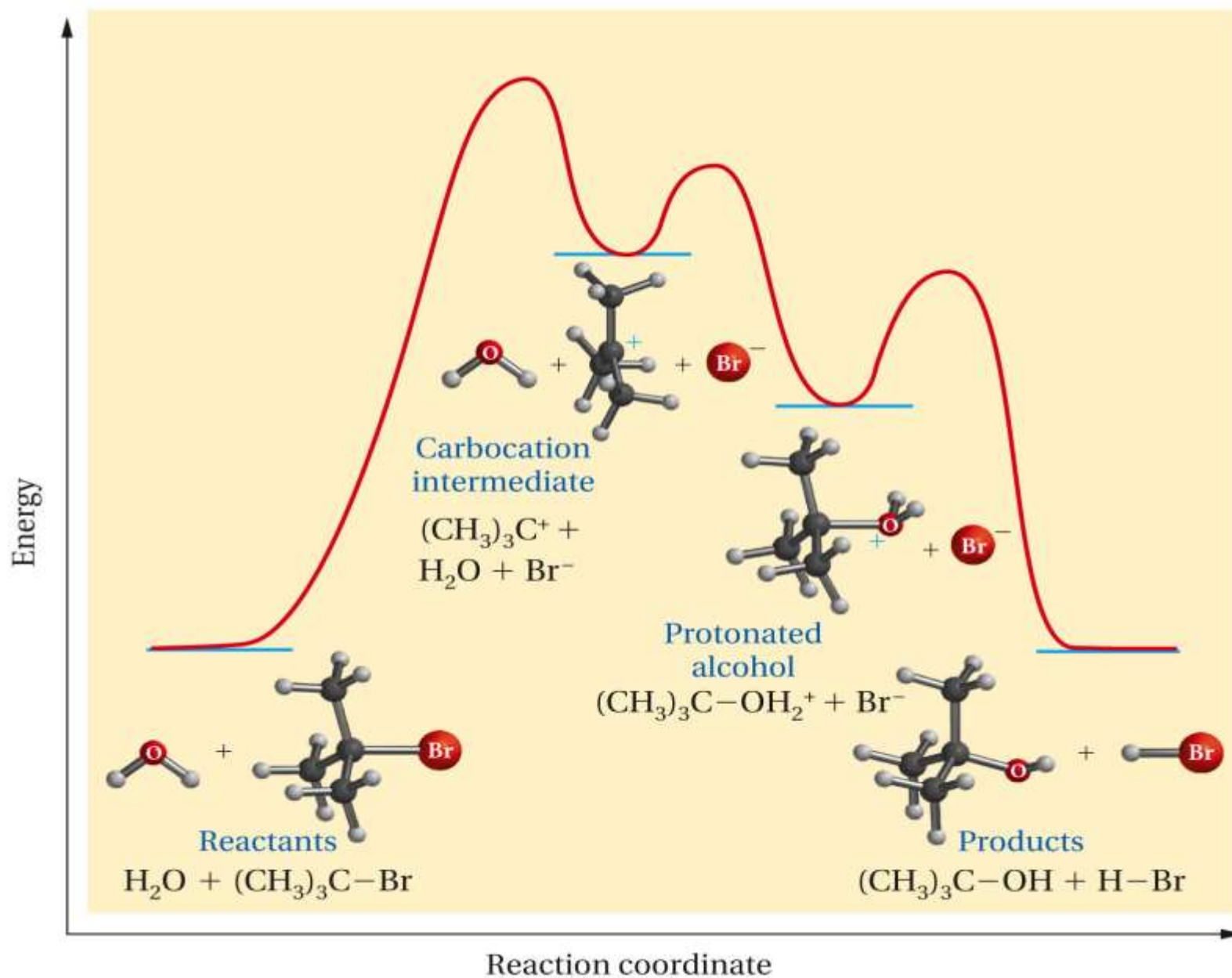
1- Step 1 : Leaving group leaves to form a carbocation intermediate

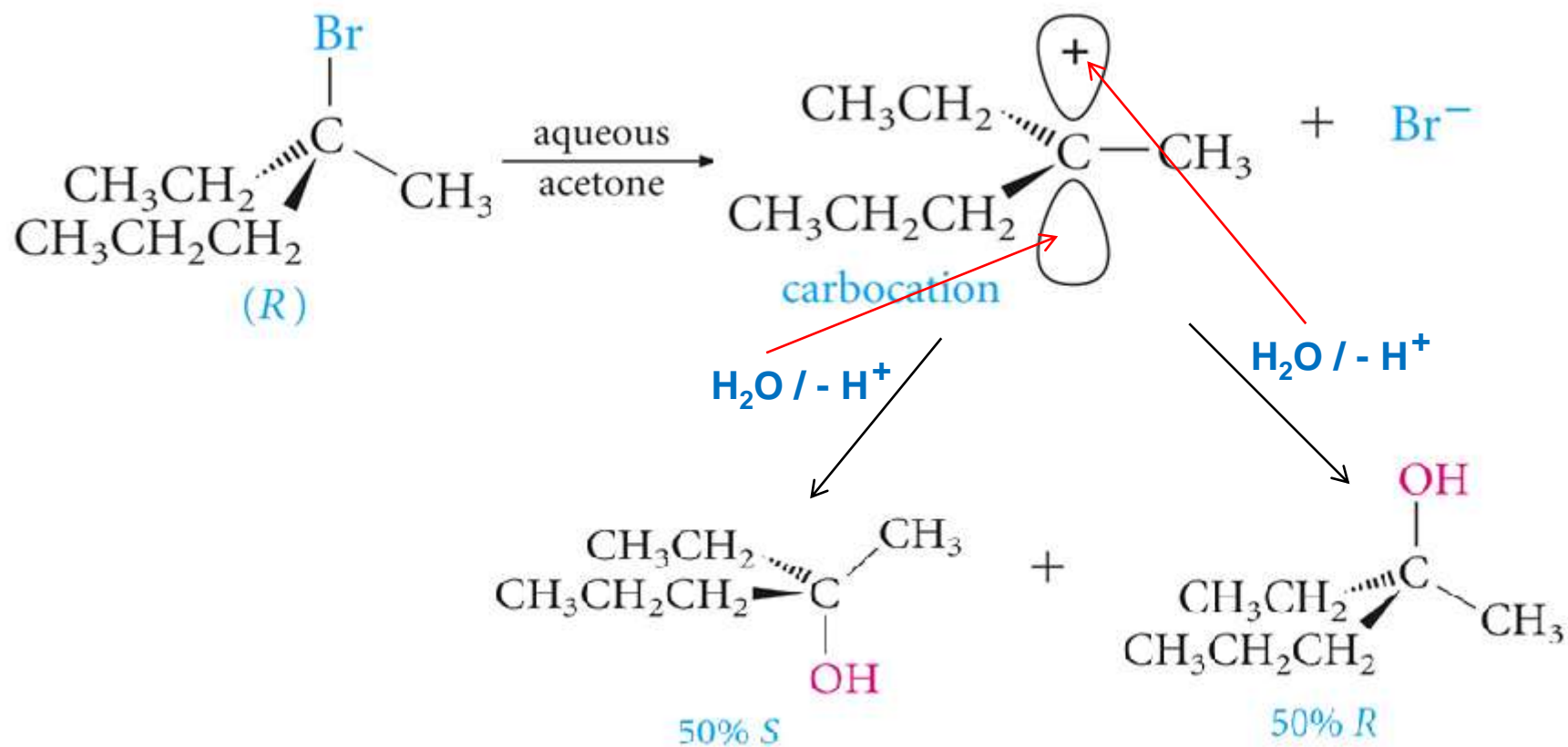


2- Step 2 : Carbocation then combines with nucleophile.




Two steps; one TransitionStates; one intermediate;
bond breaking first then bond formation





Summary of S_N1 reactions

- 1- S_N1 is a two-step process (**1st order reaction, uni-molecular**)
- 2- requires **polar protic** solvent.
- 3- favored for **a)** tertiary halides, **b) weak** nucleophiles (neutral).
- 4- slow with secondary, not at all with primary and methyl
- 5- S_N1 occur with **racemization** of configuration.
- 6- rate depends **only** on the concentration of **substrate** (alkyl halide), and **NOT on Nu** (its concentration or strength).
- 7- rate: tertiary halides > secondary >> primary >> methyl
(No reaction with vinyl and aryl halides)
- 8- depends on **Carbocation Stability**: **3° > 2° > 1° > methyl**

Table 6.2  **Comparison of S_N2 and S_N1 Substitutions**

Variables	S _N 2	S _N 1
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).

Nucleophilicity :

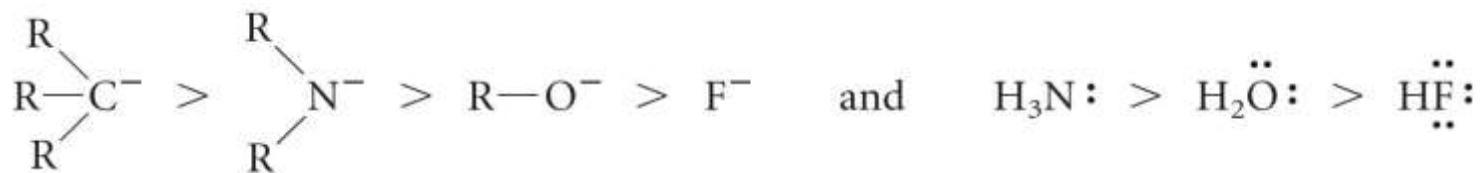
1. Negative ions are stronger than the corresponding neutral ones.



2. Elements low in the periodic table stronger than elements above
(Nu increases going down a group)



3. Across a row (period): the more electronegative the less nucleophilic.
(Nu decreasing from left to right)

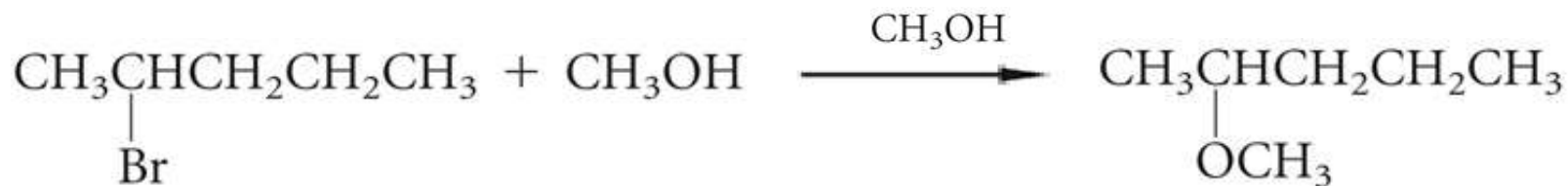
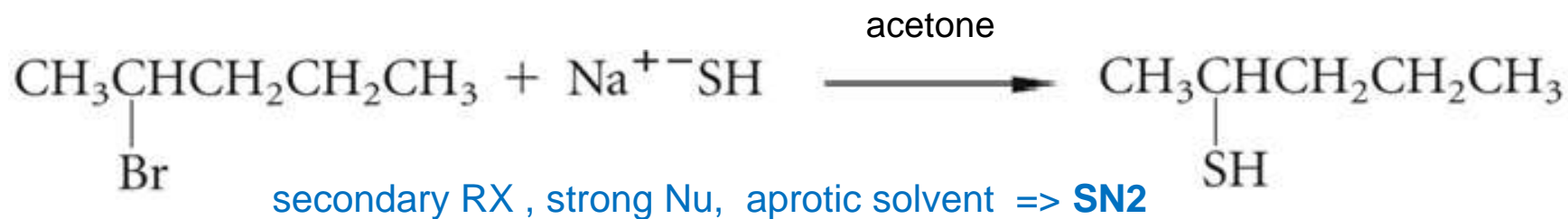


Effect of solvent:

S_N1 require polar **protic** solvent (H_2O , CH_3OH , C_2H_5OH)

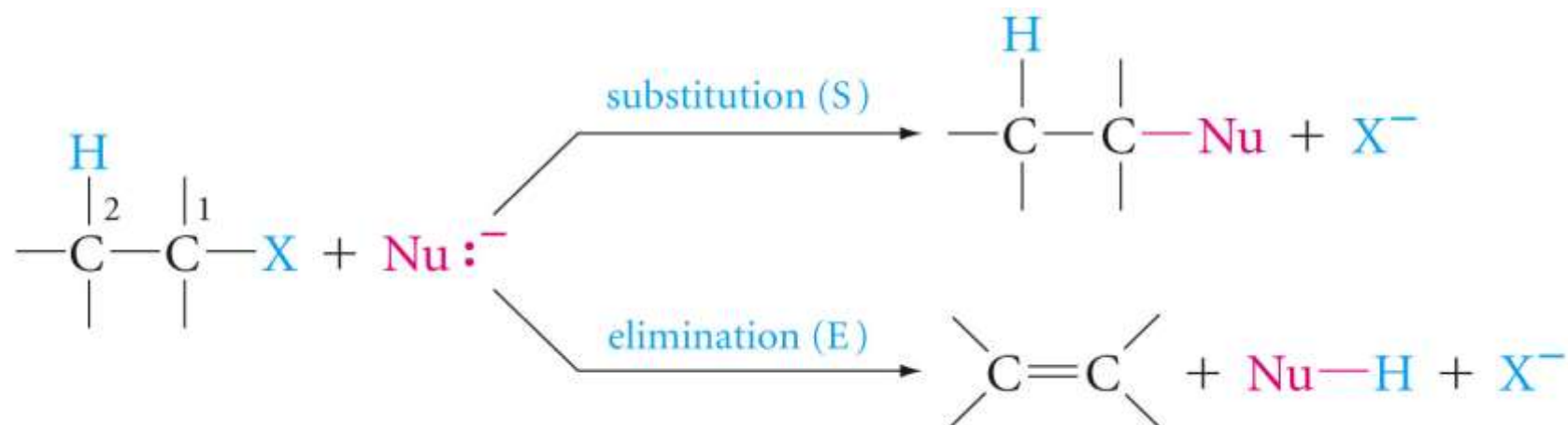
S_N2 prefer **aprotic** solvents (acetone, DMF, DMSO)

Question : Which mechanism do you predict for the following reactions?

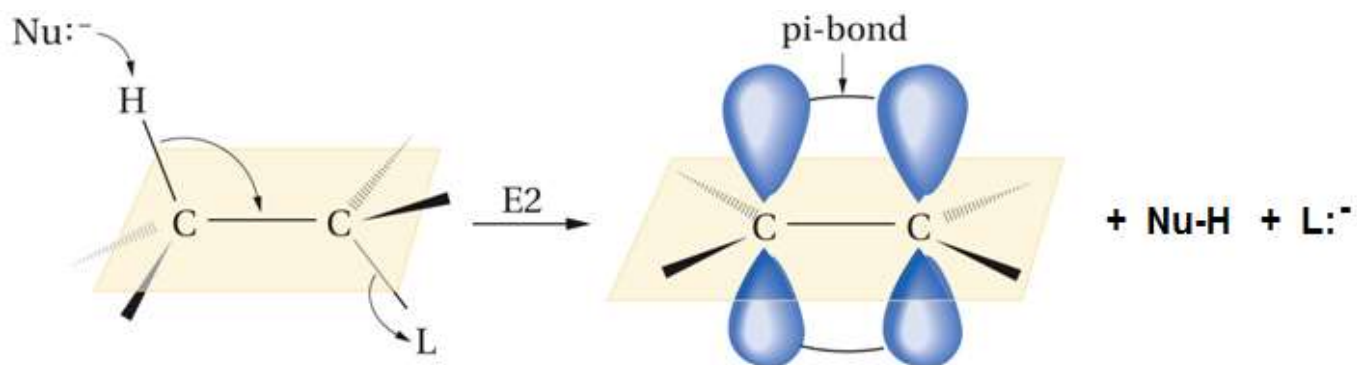


secondary RX , weak Nu, protic solvent => **SN1**

6.7 Elimination (Dehydrohalogenation) : (E1, E2)

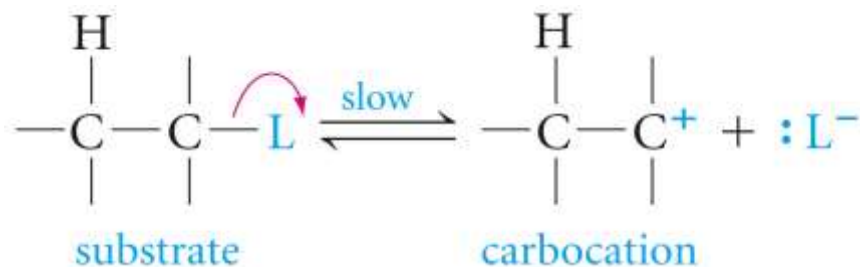


E2 mechanism : one step process (like $\text{S}_{\text{N}}2$) :
(**H**-C-C-**L**) in one plane, **H** and **L** **anti** (opposite)

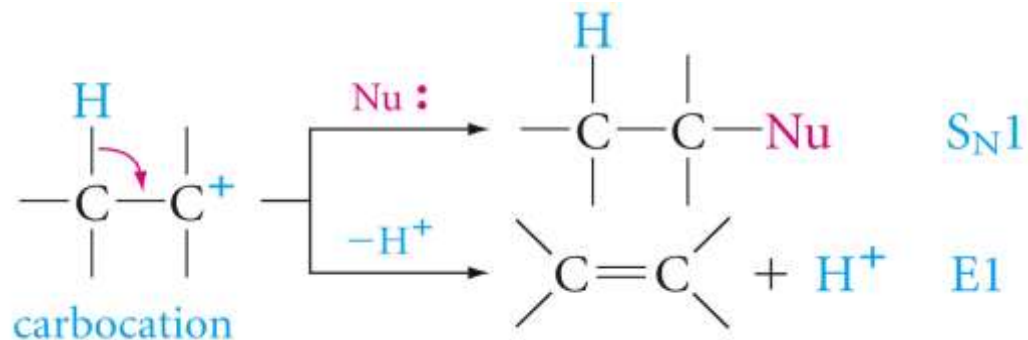


E1 mechanism : two-step (like S_N1) :

Step 1: loss of leaving group to form carbocation :



Step 2: loss of proton to form a pi-bond :

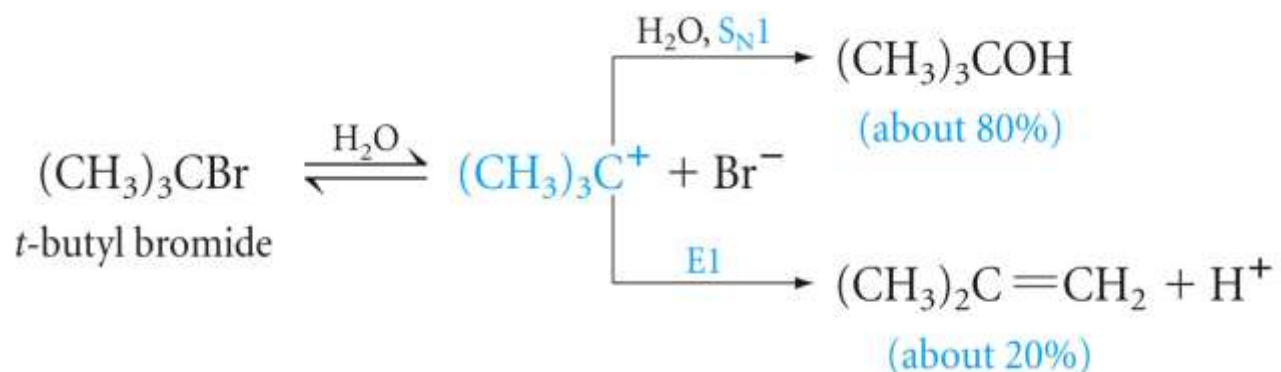


6.8 Substitution and Elimination in Competition :

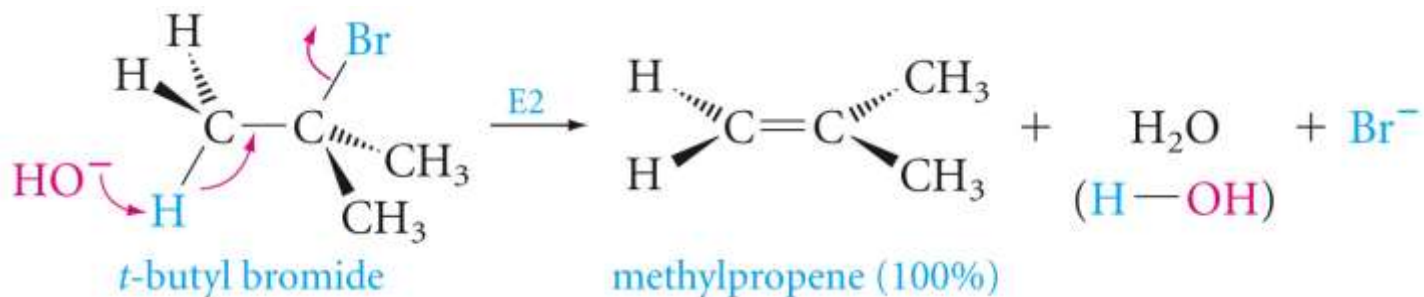
a) Tertiary Halides :

Substitution : only S_N1. Elimination : E1 or E2.

1) Weak nucleophile and polar solvent : S_N1 and E1 compete



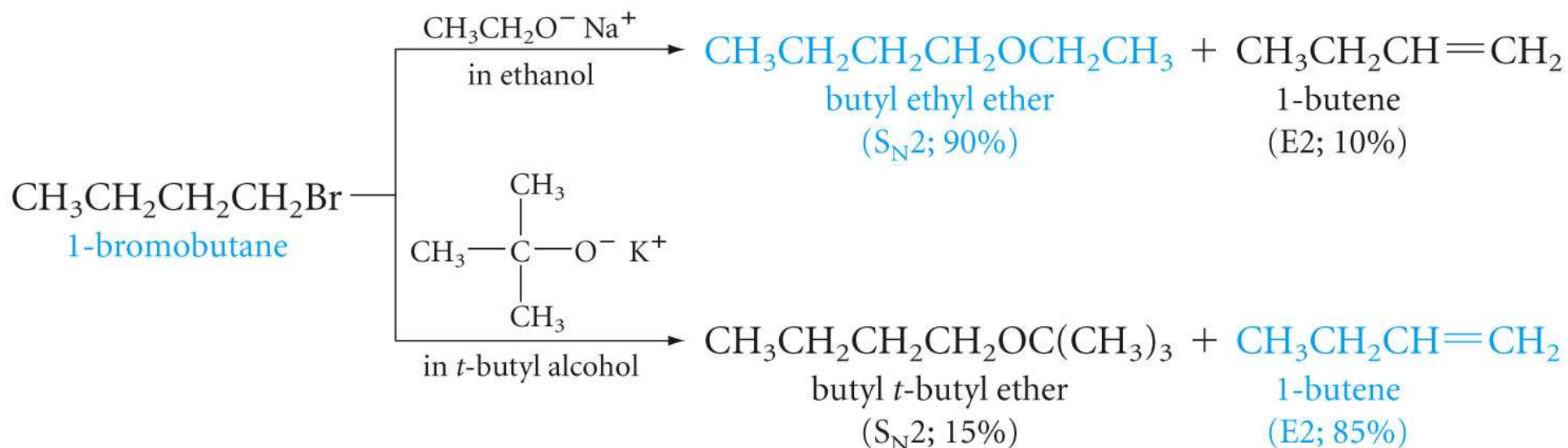
2) Basic nucleophiles : only elimination (CH₃O⁻, HO⁻, CN⁻)



b) Primary Halides :

Substitution : only S_N2 .

Elimination : only E2 (require bulky strong base like $t\text{-BuO}^-$)



c) Secondary Halides :

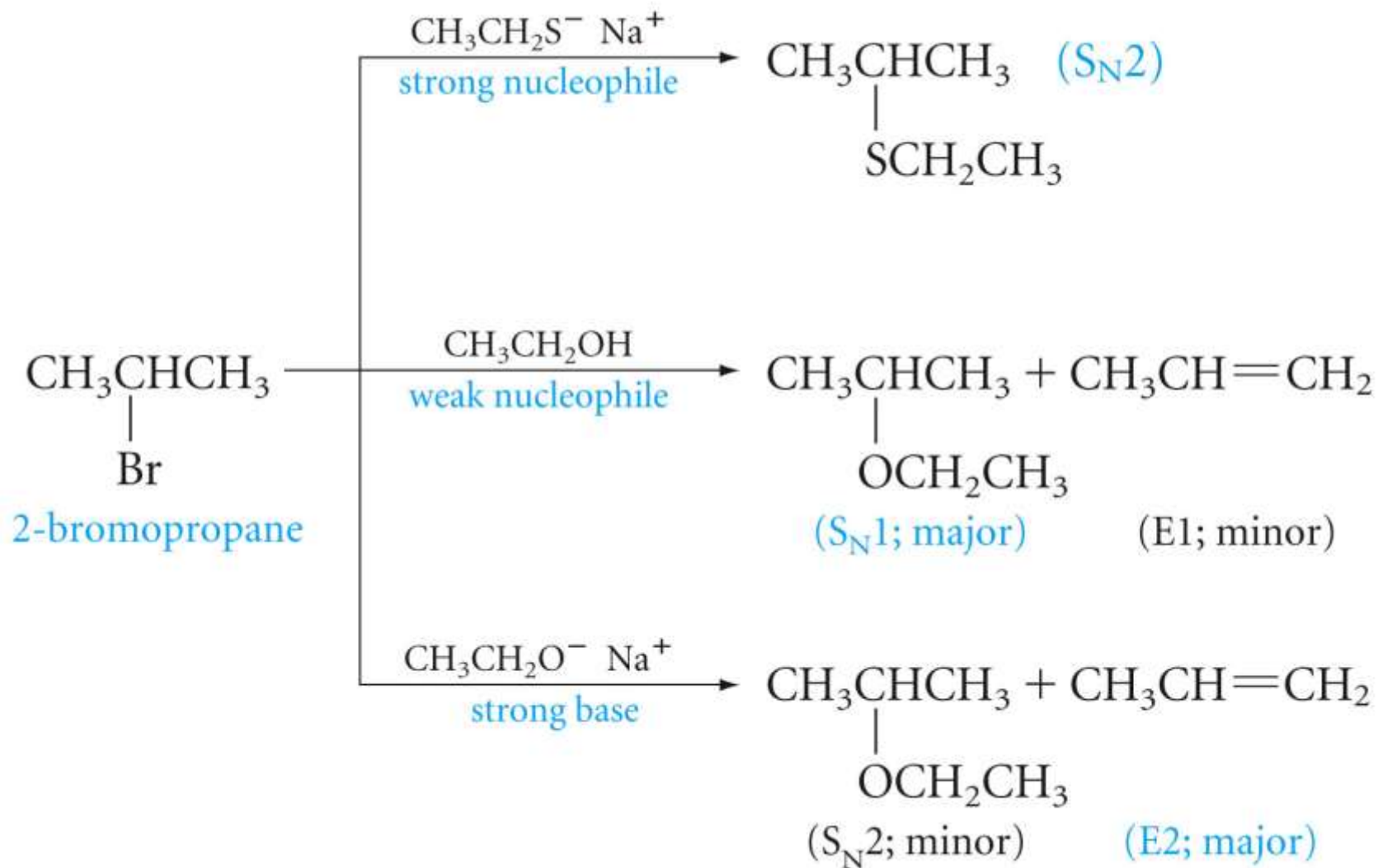
S_N2 / S_N1 ; $E1 / E2$: all possible.

depends on **1)** nucleophile (strength and basicity)
2) solvent (protic, aprotic)

strong Nu (not basic) : **S_N2** (with –ve charge)

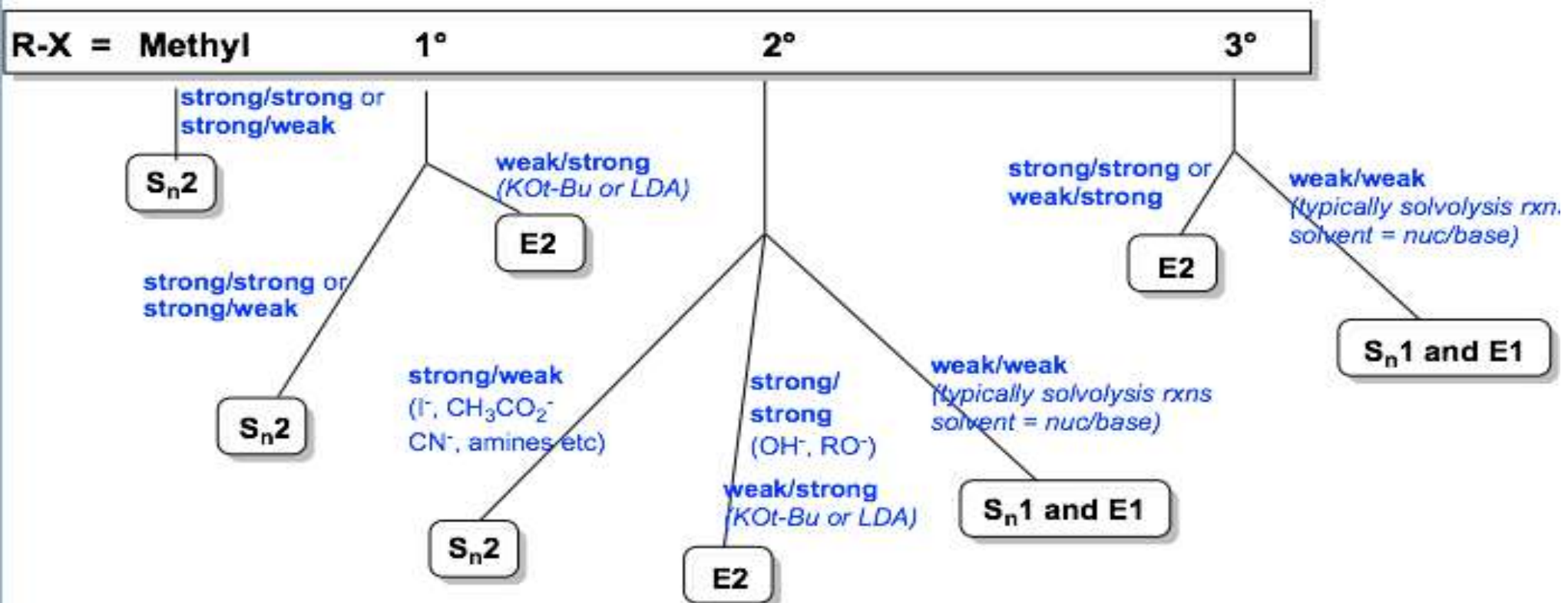
weak Nu (+ polar protic solvent) : **S_N1** (neutral)

strong base (NaOH, NaOCH₃) : **$E2$**



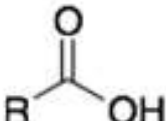
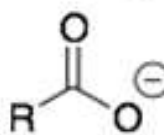
A Summary of Substitution and Elimination Reactions

Halide type	S_N1	S_N2	E1	E2
RCH_2X (primary)	Does not occur	Highly favored	Does not occur	Occurs when strong bases are used
R_2CHX (secondary)	Can occur with benzylic and allylic halides	Occurs in competition with E2 reaction	Can occur with benzylic and allylic halides	Favored when strong bases are used
R_3CX (tertiary)	Favored in hydroxylic solvents	Does not occur	Occurs in competition with S_N1 reaction	Favored when bases are used



R-X =

Nuc/Base Strength	methyl	1°	2°	3°
strong/strong	<i>SN2</i>	<i>SN2</i>	<i>E2</i>	<i>E2</i>
strong/weak	<i>SN2</i>	<i>SN2</i>	<i>SN2</i>	<i>no reaction</i>
weak/strong	<i>no reaction</i>	<i>E2</i>	<i>E2</i>	<i>E2</i>
weak/weak	<i>no reaction</i>	<i>no reaction</i>	<i>SN1/E1</i>	<i>SN1/E1</i>

strong/strong	weak/strong	strong/weak	weak/weak
OH ⁻		R-NH ₂ (amines)	H ₂ O
R-O ⁻		R-S ⁻	R-OH (alcohols)
(deprotonated alcohols not bulky)	KOt-Bu	CN ⁻ , N ₃ ⁻ , I ⁻	 (carboxylic acids)
R ₂ N ⁻	LDA		
(deprotonated amines not bulky)		H ₂ S, R-SH	

Nucleophiles / Bases :

(1) Strong base / strong nucleophile : strong bases are strong nucleophiles.

(-vely charged oxygen and nitrogen)

(2) Weak base / weak nucleophile : weak bases are weak nucleophiles.

(neutral oxygen Nu : HOH, ROH)

(3) Strong base / weak nucleophile : bulky (large) strong base (t-BuO^-)

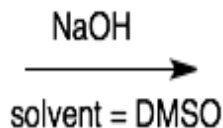
(4) Strong nucleophile / weak base :

a) neutral electronegative :

(nitrogen, sulfur : amines, thiols)

b) -vely charged with delocalized –ve charge: (acetate)

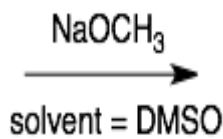
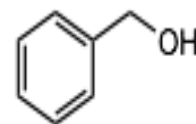
or –ve charge on a large atom: (sulfide, iodide ions)



$R-X = 1^\circ$ OH^- = strong nuc
strong base



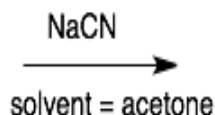
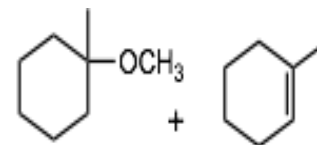
**SN2
product**



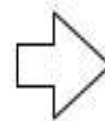
R-X = 3° CH₃OH = weak nuc
 weak base



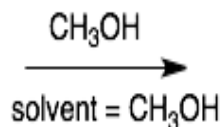
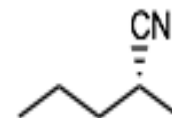
**SN1 + E1
product**



$R-X = 2^\circ$ $\cdot CN =$ strong nuc
weak base



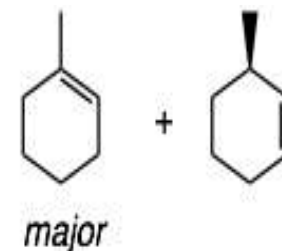
**SN2
product**



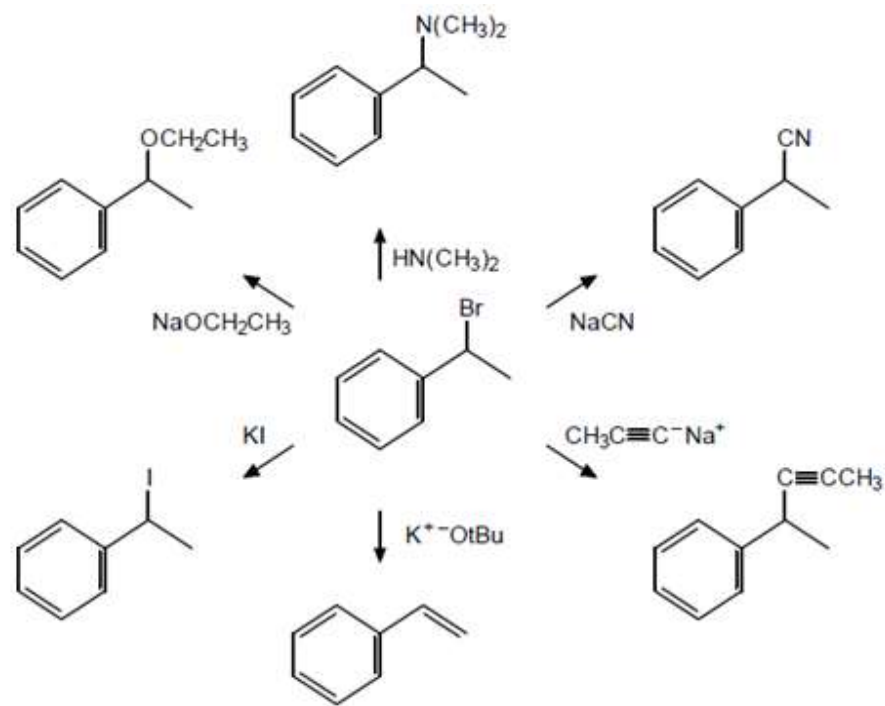
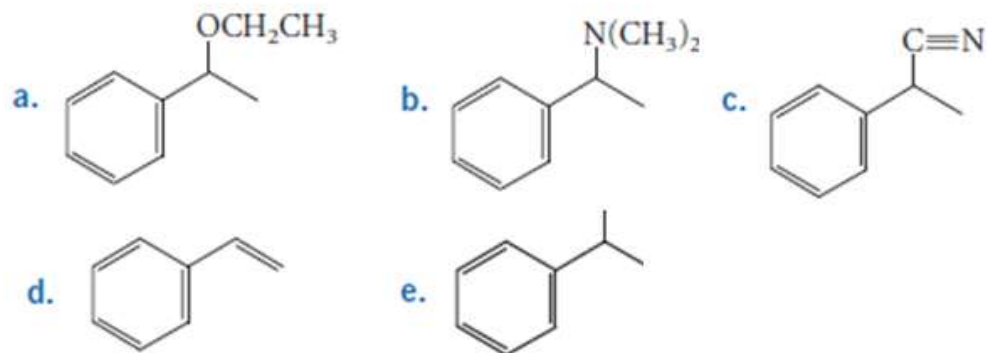
$R-X = 2^\circ$ $^-OCH_3$ = strong nuc
strong base



**E2
products**

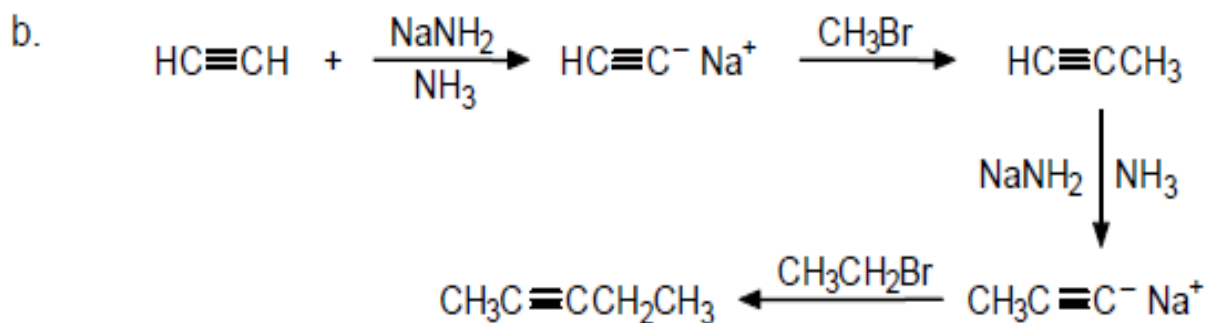
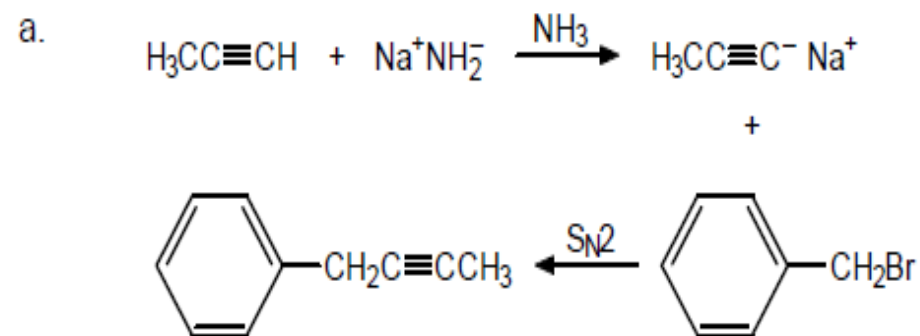


6.25 Provide equations for the synthesis of the following compounds from 1-bromo-1-phenylethane.



6.28 Combine the reaction in eq. 3.53 with a nucleophilic substitution to devise

- a. a two-step synthesis of $\text{CH}_3\text{C}\equiv\text{C}-\text{CH}_2-\text{C}_6\text{H}_5$ from $\text{C}_6\text{H}_5\text{CH}_2\text{Br}$.
- b. a four-step synthesis of $\text{CH}_3\text{C}\equiv\text{CCH}_2\text{CH}_3$ from acetylene and appropriate alkyl halides.



The order in which the alkyl halides were used could be reversed, with the same overall result.

6.29 Combine a nucleophilic substitution with a catalytic hydrogenation to synthesize

a. *cis*-3-heptene from butyne and bromopropane.

b. $\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}$ from $\text{CH}_2=\text{CHCH}_2\text{Br}$.

