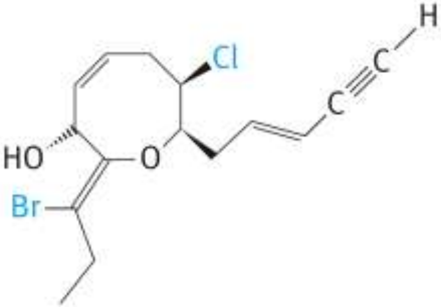
Chapter 6: Organic Halogen Compounds; Substitution and Elimination Reactions



Nucleophilic Substitution

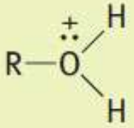
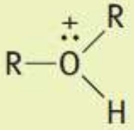
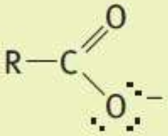
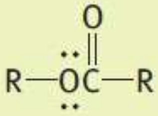
Examples of nucleophilic substitution reactions

Nucleophile

Substrate

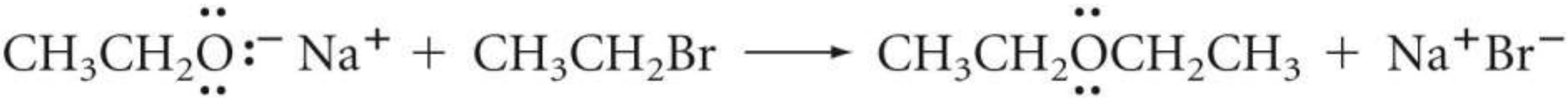
Leaving group

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. $\mathrm{H}\underset{\cdot\cdot}{\ddot{\mathrm{O}}}:^-$	hydroxide	$\mathrm{R}{-}\underset{\cdot\cdot}{\ddot{\mathrm{O}}}\mathrm{H}$	alcohol	
2. $\mathrm{R}\underset{\cdot\cdot}{\ddot{\mathrm{O}}}:^-$	alkoxide	$\mathrm{R}{-}\underset{\cdot\cdot}{\ddot{\mathrm{O}}}\mathrm{R}$	ether	
3. $\mathrm{H}\underset{\cdot\cdot}{\ddot{\mathrm{O}}}\mathrm{H}$	water		alkyloxonium ion	These ions lose a proton and the products are alcohols and ethers. $\xrightarrow{-\mathrm{H}^+}$ $\mathrm{R}\underset{\cdot\cdot}{\ddot{\mathrm{O}}}\mathrm{H}$ (alcohol) $\xrightarrow{-\mathrm{H}^+}$ $\mathrm{R}\underset{\cdot\cdot}{\ddot{\mathrm{O}}}\mathrm{R}$ (ether)
4. $\mathrm{R}\underset{\cdot\cdot}{\ddot{\mathrm{O}}}\mathrm{H}$	alcohol		dialkyloxonium ion	
5. 	carboxylate	 $\mathrm{R}{-}\underset{\cdot\cdot}{\ddot{\mathrm{O}}}\overset{\mathrm{O}}{\overset{\Vert}{\mathrm{C}}}{-}\mathrm{R}$	ester	
Nitrogen nucleophiles				
6. $\ddot{\mathrm{N}}\mathrm{H}_3$	ammonia	$\mathrm{R}{-}\overset{+}{\mathrm{N}}\mathrm{H}_3$	alkylammonium ion	With a base, these ions readily lose a proton to give amines. $\xrightarrow{-\mathrm{H}^+}$ $\mathrm{R}\ddot{\mathrm{N}}\mathrm{H}_2$ $\xrightarrow{-\mathrm{H}^+}$ $\mathrm{R}_2\ddot{\mathrm{N}}\mathrm{H}$ $\xrightarrow{-\mathrm{H}^+}$ $\mathrm{R}_3\mathrm{N}:$
7. $\mathrm{R}\ddot{\mathrm{N}}\mathrm{H}_2$	primary amine	$\mathrm{R}{-}\overset{+}{\mathrm{N}}\mathrm{H}_2\mathrm{R}$	dialkylammonium ion	
8. $\mathrm{R}_2\ddot{\mathrm{N}}\mathrm{H}$	secondary amine	$\mathrm{R}{-}\overset{+}{\mathrm{N}}\mathrm{HR}_2$	trialkylammonium ion	
9. $\mathrm{R}_3\ddot{\mathrm{N}}$	tertiary amine	$\mathrm{R}{-}\overset{+}{\mathrm{N}}\mathrm{R}_3$	tetraalkylammonium ion	

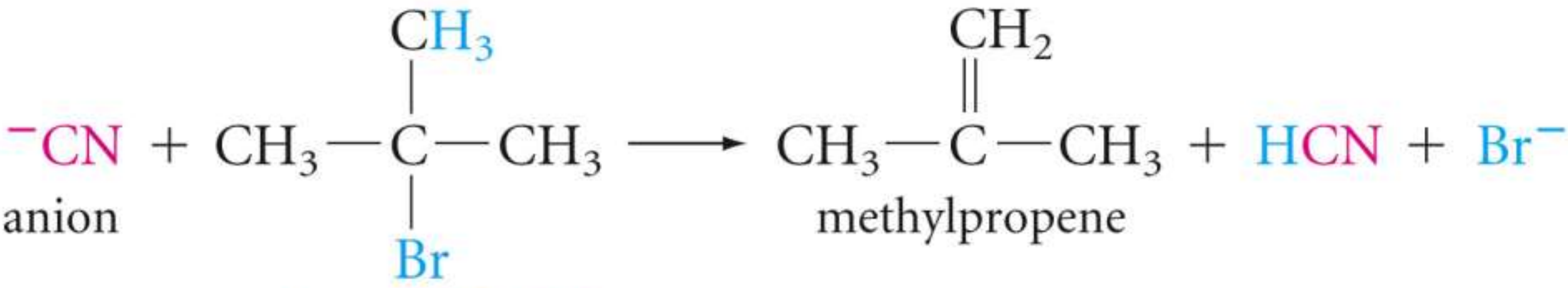
Sulfur nucleophiles				
10. $\mathrm{H}\underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{S}}}:^-$	hydrosulfide	$\mathrm{R{-}}\underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{S}}}\mathrm{H}$	thiol	
11. $\mathrm{R}\underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{S}}}:^-$	mercaptide	$\mathrm{R{-}}\underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{S}}}\mathrm{R}$	thioether (sulfide)	
12. $\mathrm{R_2}\overset{\cdot\cdot}{\mathrm{S}}:$	thioether	$\mathrm{R{-}}\underset{\cdot\cdot}{\overset{+}{\mathrm{S}}}\mathrm{R_2}$	trialkylsulfonium ion	
Halogen nucleophiles				
13. $:\underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{I}}}:^-$	iodide	$\mathrm{R{-}}\underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{I}}}:$	alkyl iodide	The usual solvent is acetone. Sodium iodide is soluble in acetone, but sodium bromide and sodium chloride are not.
Carbon nucleophiles				
14. $^-:\mathrm{C{\equiv}N}:$	cyanide	$\mathrm{R{-}C{\equiv}N}:$	alkyl cyanide (nitrile)	Sometimes the isonitrile, $\mathrm{R{-}}\overset{+}{\mathrm{N}}{\equiv}\overset{-}{\mathrm{C}}:$, is formed.
15. $^-:\mathrm{C{\equiv}CR}$	acetylide	$\mathrm{R{-}C{\equiv}CR}$	alkyne	

Reaction of sodium ethoxide with bromoethane



$$CH_3CH_2\ddot{\underset{\cdot\cdot}{O}}:^{-}\ Na^{+} + CH_3CH_2Br \longrightarrow CH_3CH_2\ddot{\underset{\cdot\cdot}{O}}CH_2CH_3 + Na^{+}Br^{-}$$

sodium ethoxide   bromoethane   diethyl ether

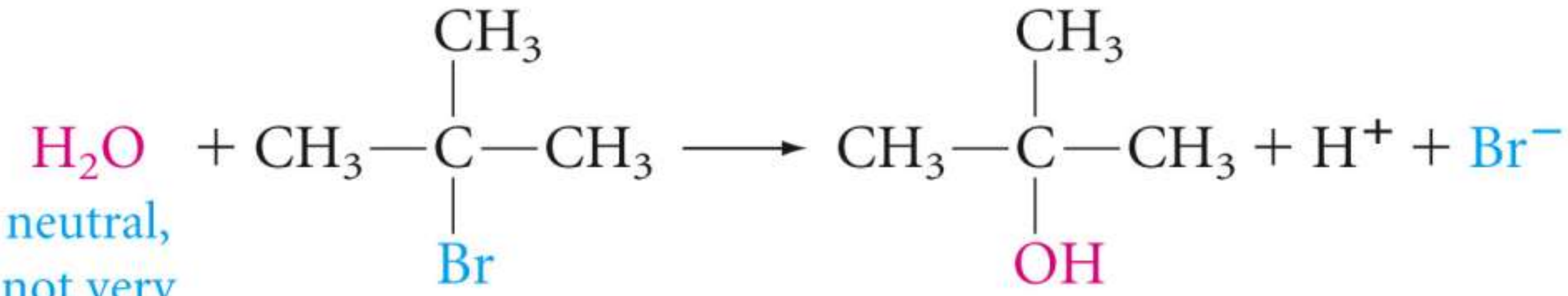


$$^{-}CN + CH_3-\underset{\underset{Br}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_3 \longrightarrow CH_3-\overset{\overset{CH_2}{\|}}{C}-CH_3 + HCN + Br^{-}$$

anion

tertiary alkyl halide

methylpropene

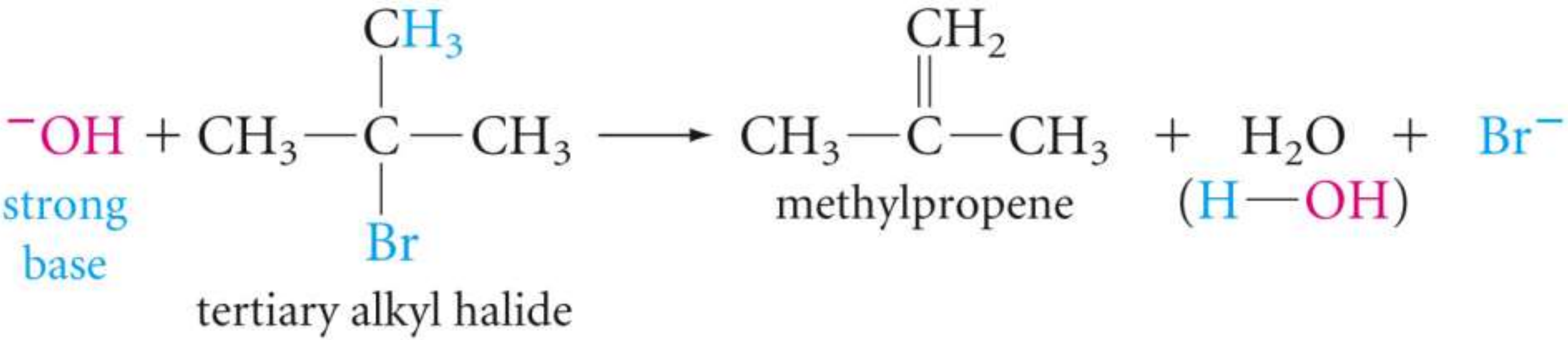


$$H_2O + (CH_3)_3CBr \longrightarrow (CH_3)_3COH + H^+ + Br^-$$

neutral, not very basic

tertiary alkyl halide

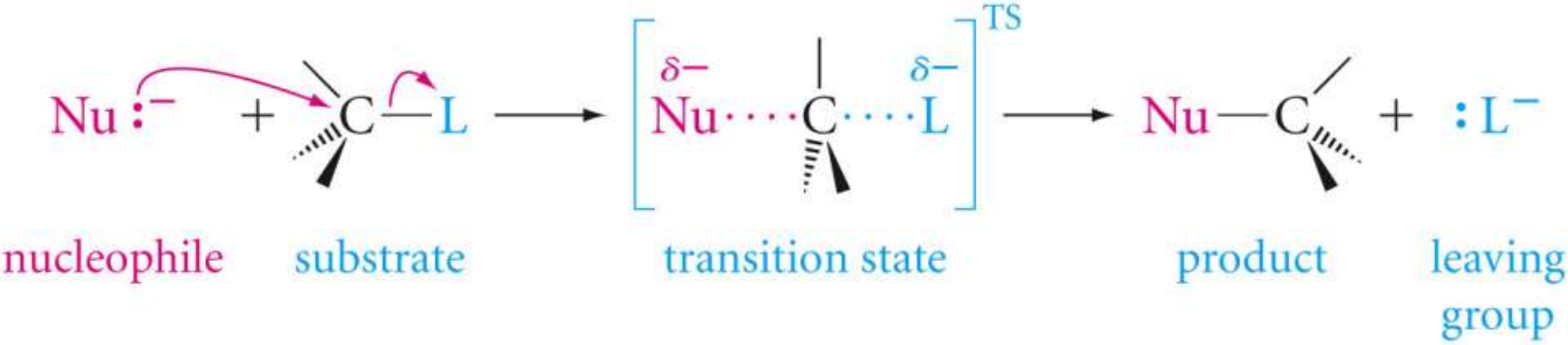
(about 80%; some methylpropene is also formed)

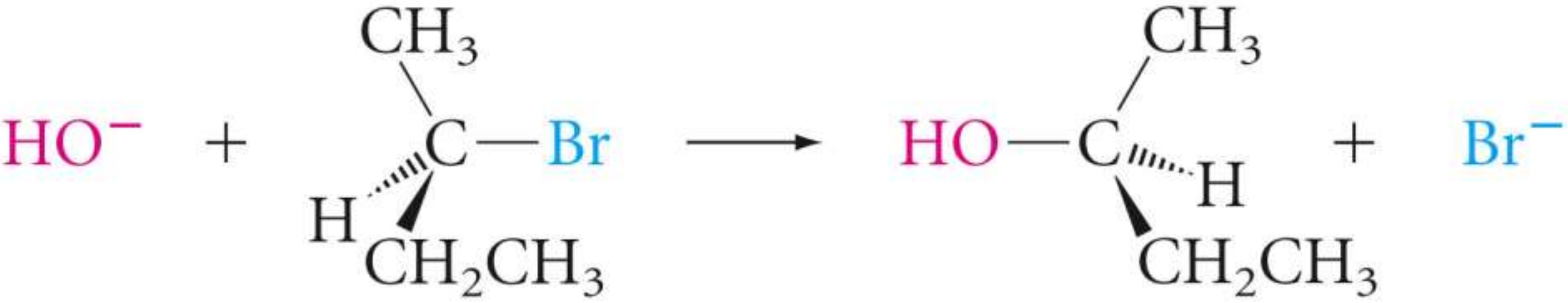


$$^{-}OH + CH_3-\underset{\underset{Br}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_3 \longrightarrow CH_3-\overset{\overset{CH_2}{\|}}{C}-CH_3 + \underset{(H-OH)}{H_2O} + Br^{-}$$

Nucleophilic Substitution Mechanism

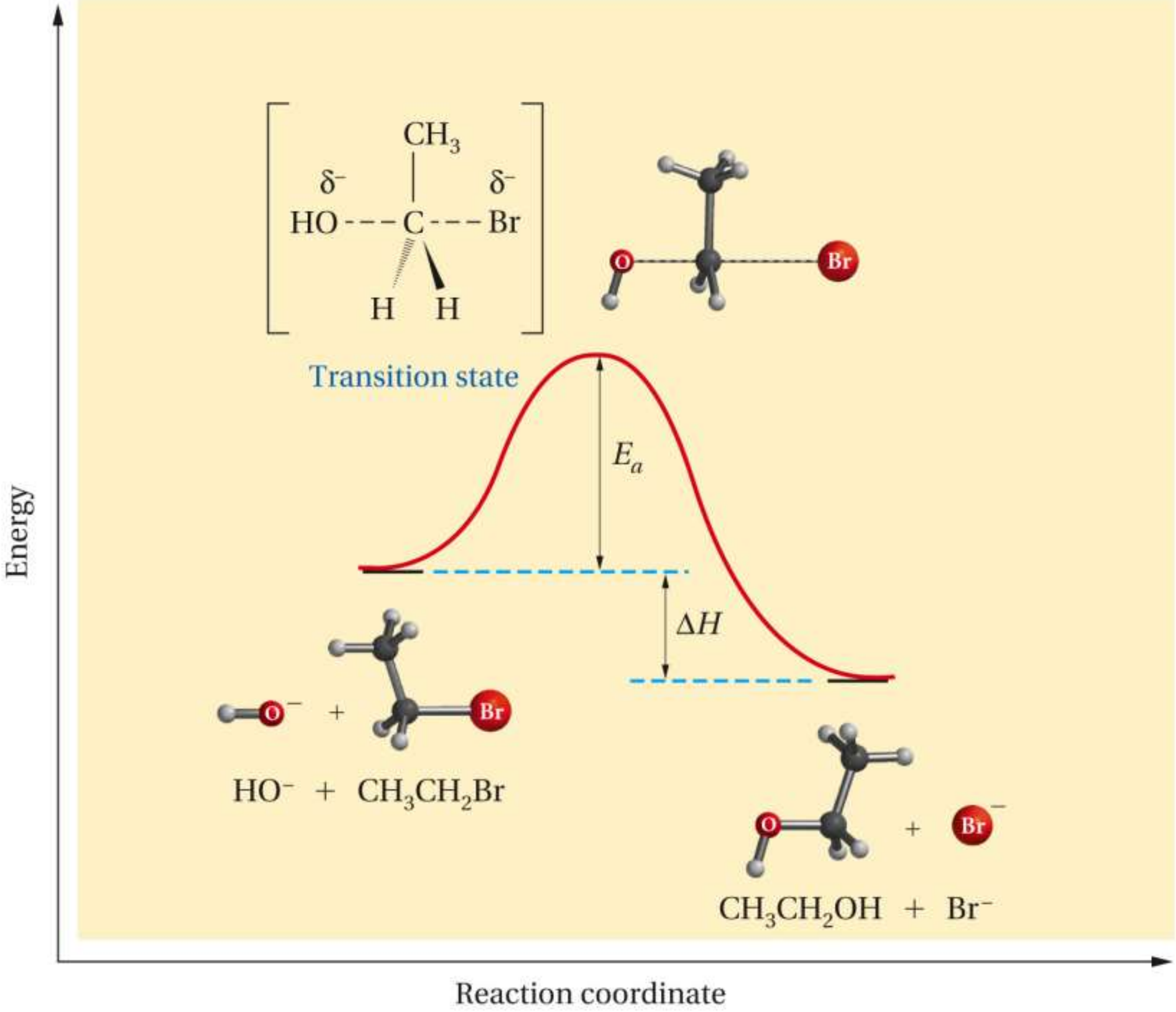
S_N2 Mechanism

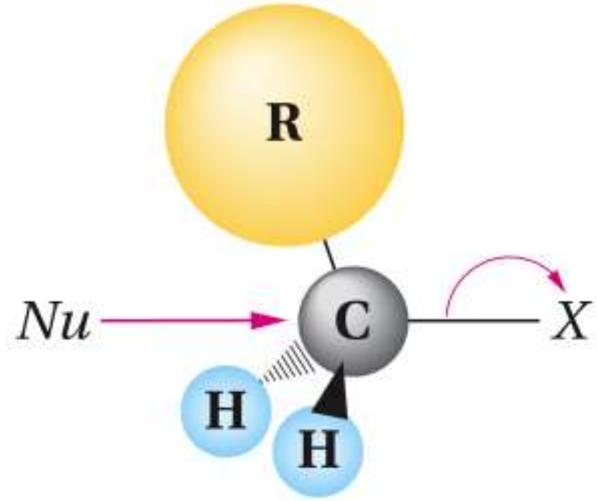




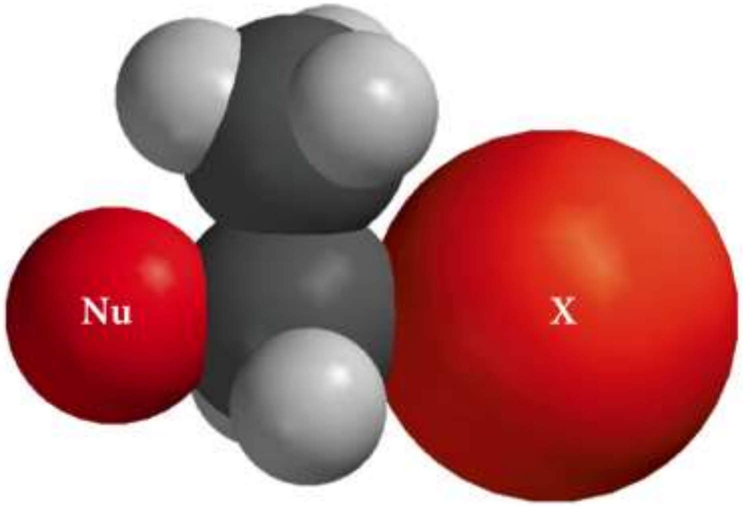
(*R*)-2-bromobutane (*S*)-2-butanol

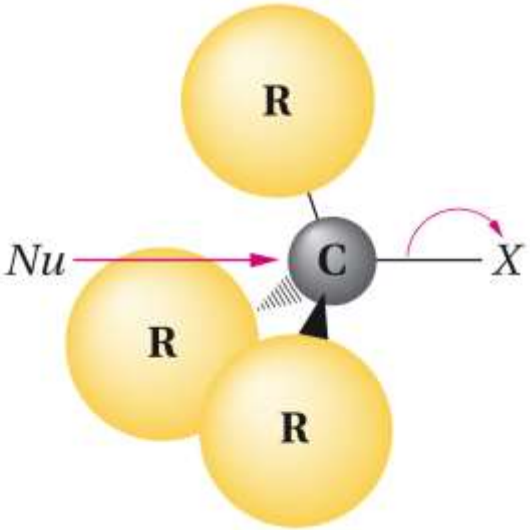
S_N2 displacement reactions occure with inversion of configuration. For example, if we treat (R)-2-bromobutane with sodium hydroxide, we obtain (S)-2-butanol

CH_3
δ⁻
δ⁻
HO - - - C - - - Br
H H
O
Br
Transition state
E_a
Energy
ΔH
O⁻
+
Br
$HO^- + CH_3CH_2Br$
O
+
Br⁻
$CH_3CH_2OH + Br^-$
Reaction coordinate

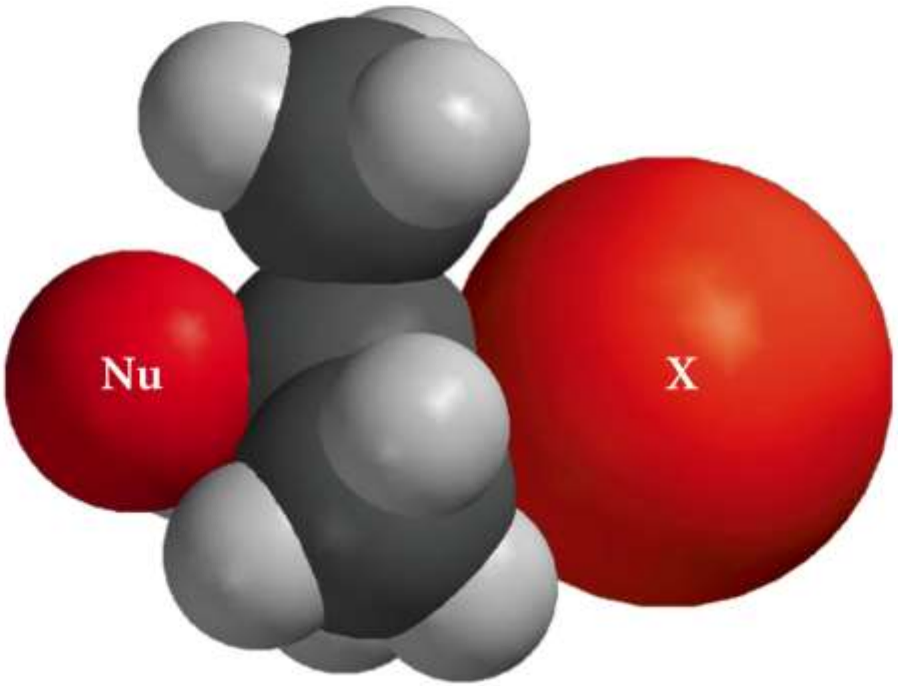


primary alkyl halide
(rear side not crowded; S_N2 fast)



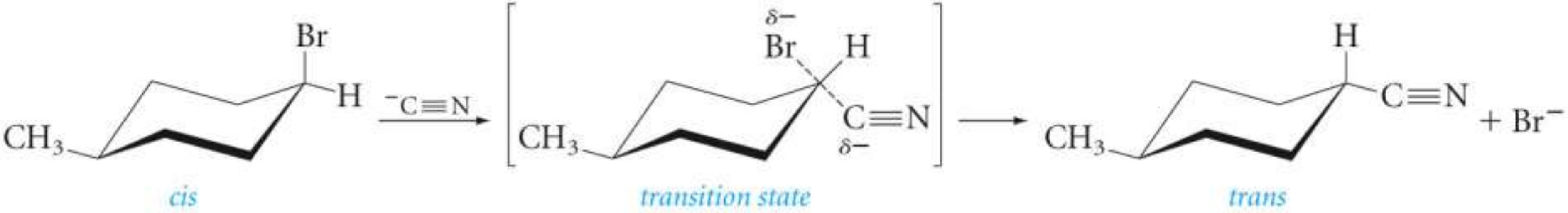


tertiary alkyl halide
(rear side crowded; S_N2 slow or impossible)

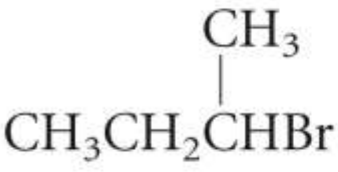


Example;

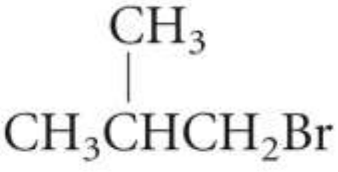
Predict the product of the S_N2 reaction of *cis*-4-methylcyclohexyl bromide with cyanide ion



Arrange the following compounds in order of decreasing S_N2 reactivity toward sodium ethoxide



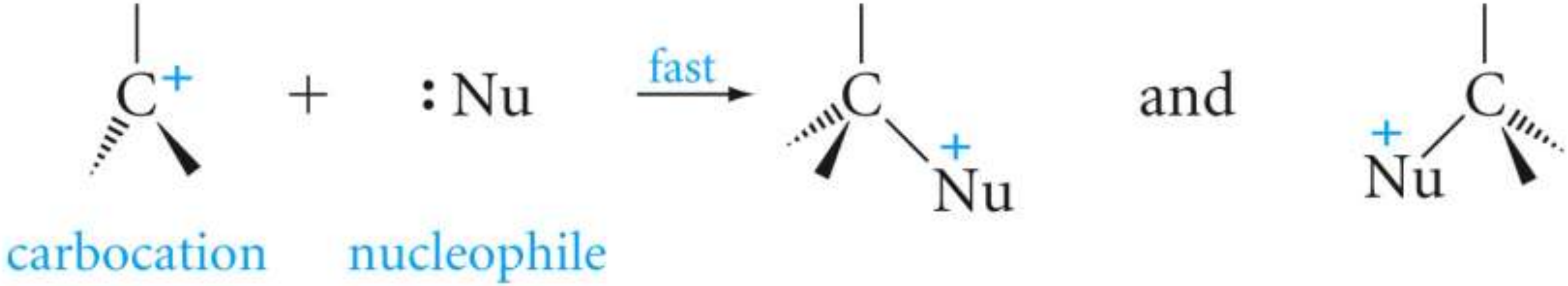
$\mathrm{CH_3CH_2\overset{\overset{CH_3}{|}}{C}HBr}$

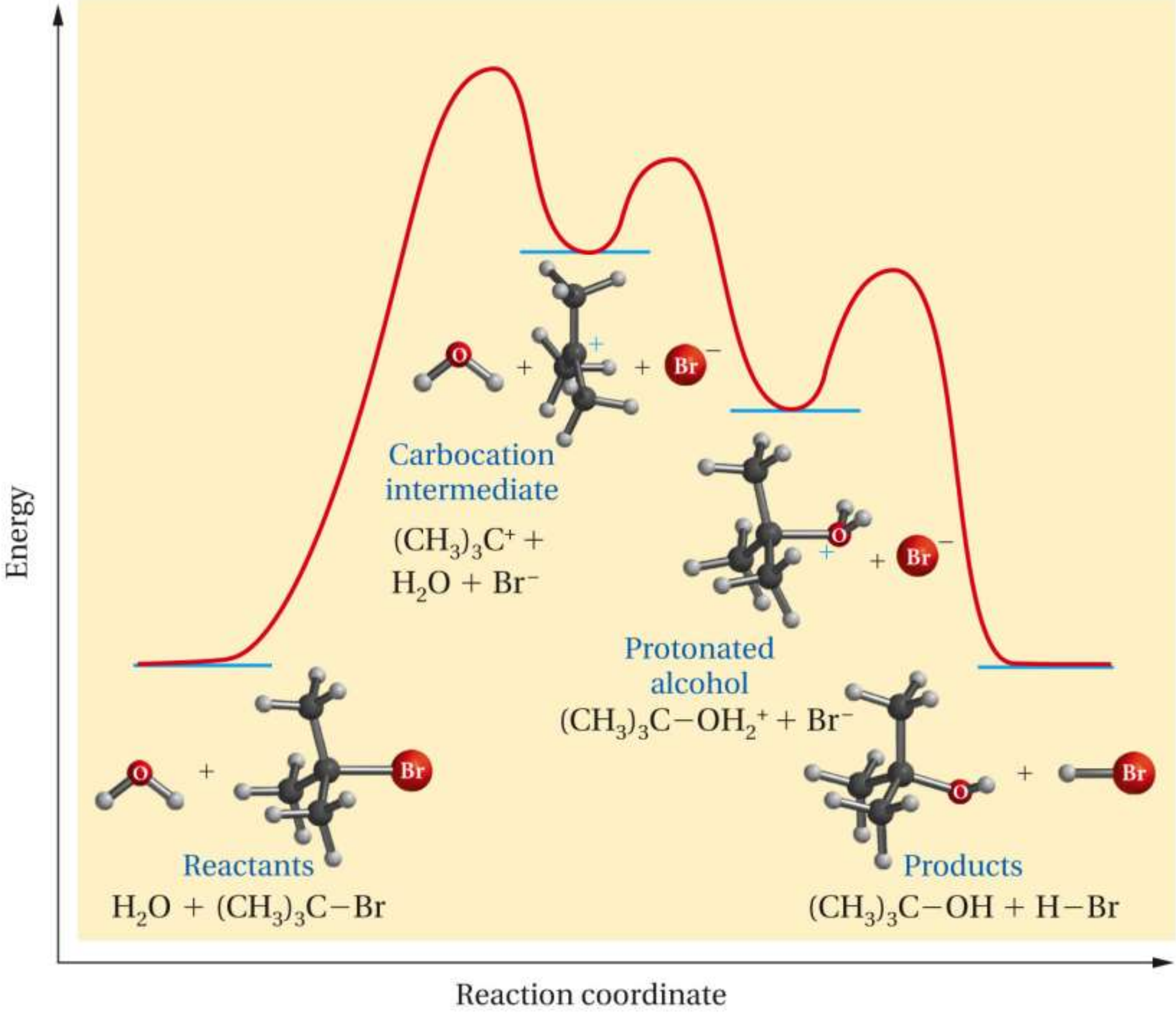


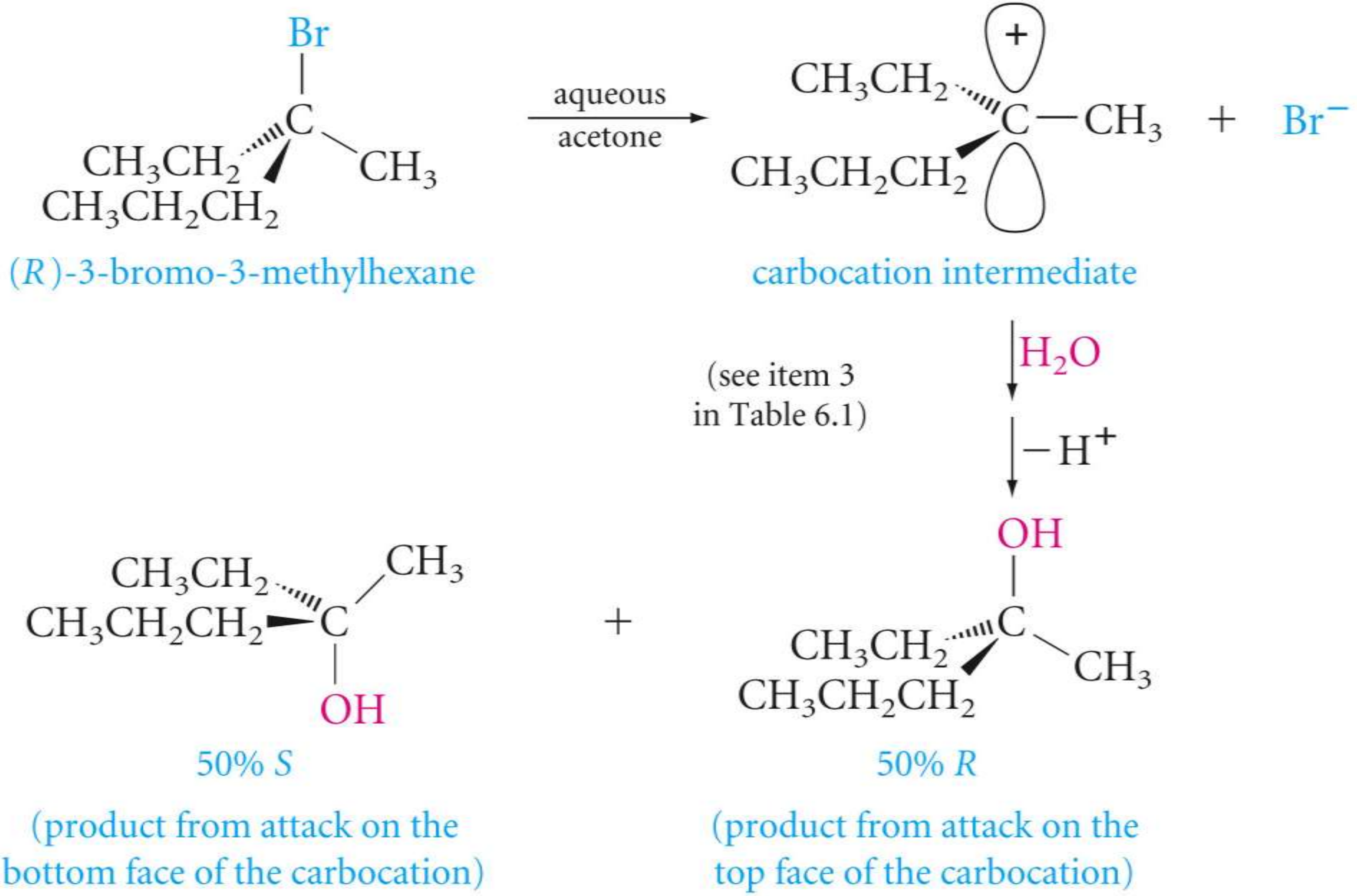
$\mathrm{CH_3\overset{\overset{CH_3}{|}}{C}HCH_2Br}$

$\mathrm{CH_3CH_2CH_2CH_2Br}$

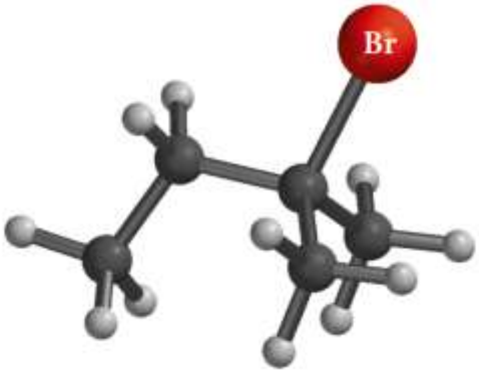
The S_N1 Mechanism




Energy
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
$(CH_3)_3C{-}OH$ + $H{-}Br$
O
Br
+
−


Br
CH_3CH_2
C
CH_3
$CH_3CH_2CH_2$
(R)-3-bromo-3-methylhexane
aqueous
acetone
+
CH_3CH_2
C
CH_3
$CH_3CH_2CH_2$
+ Br^-
carbocation intermediate
H_2O
(see item 3
in Table 6.1)
$-H^+$
OH
CH_3CH_2
C
CH_3
$CH_3CH_2CH_2$
CH_3
CH_3CH_2
$CH_3CH_2CH_2$
C
OH
+
50% S
(product from attack on the
bottom face of the carbocation)
50% R
(product from attack on the
top face of the carbocation)

Which of the following bromides will react faster with methanol (via S_N1 reaction)? and what are the reaction products in each case.



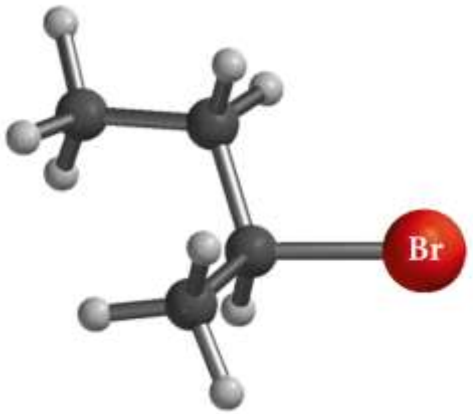
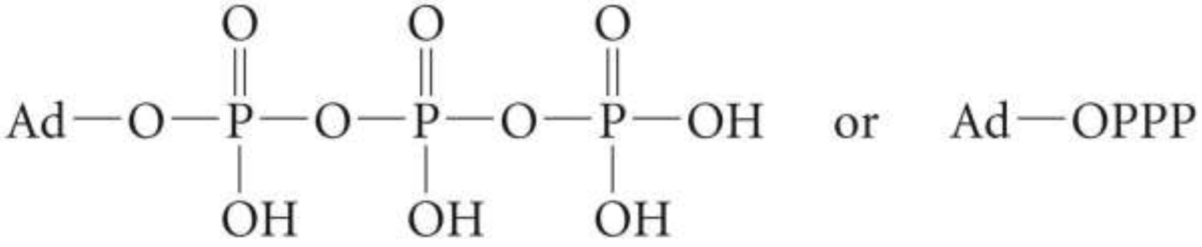


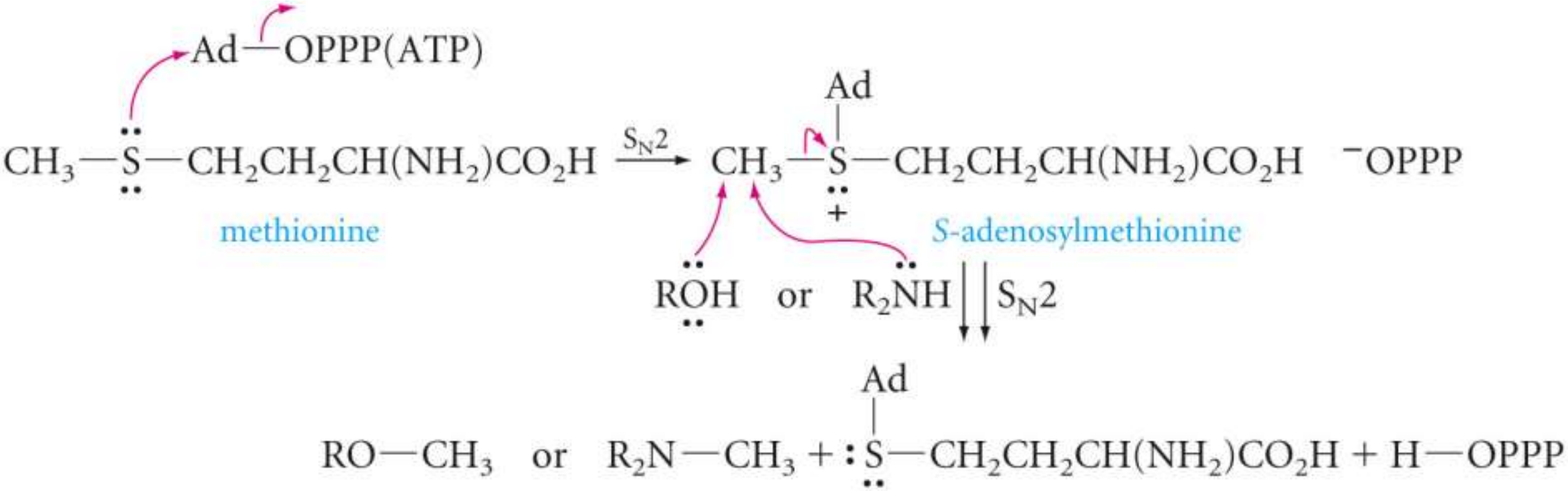
Table 6.2 Comparison of S_N2 and S_N1 Substitutions

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).

S_N2 reactions in Nature: Biological Methylations





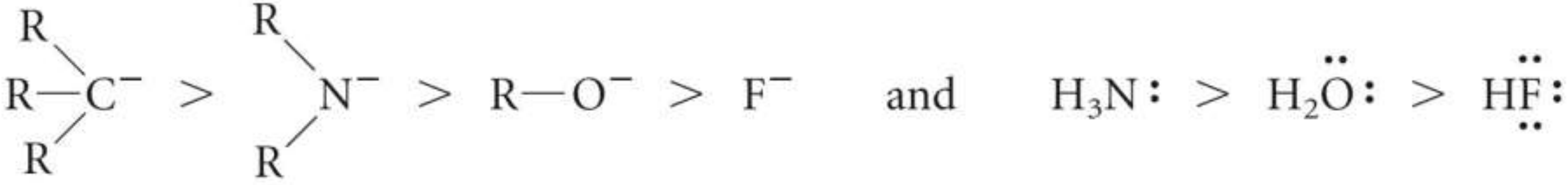
1. Negative ions are more nucleophilic, or better suppliers, than the corresponding neutral molecules.

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

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

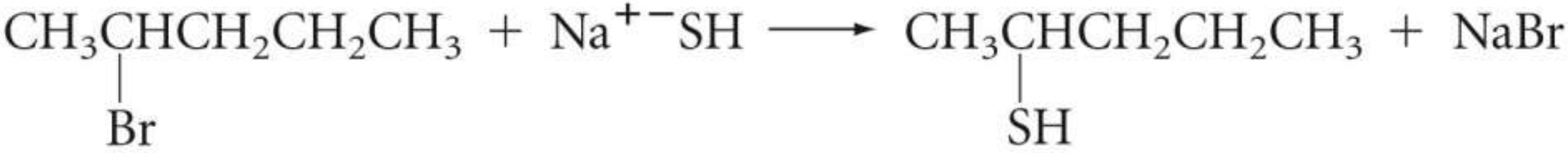
$HS^- > HO^-$ $I^- > Br^- > Cl^- > F^-$

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

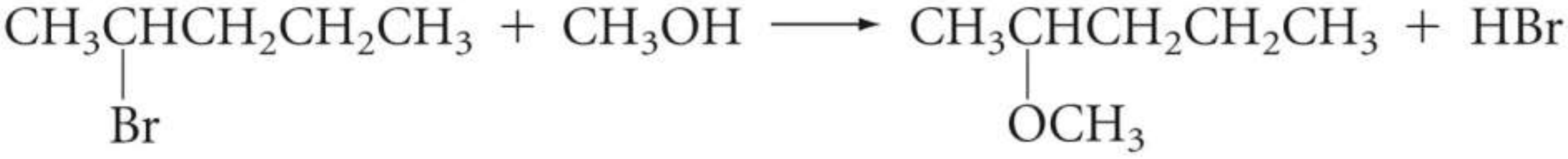


$R_3C^- > R_2N^- > R{-}O^- > F^-$ and $H_3N\!: > H_2\ddot{O}\!: > H\ddot{\underset{..}{F}}\!:$

Which mechanism, S_N1 or S_N2, would you predict for each of the following reactions?

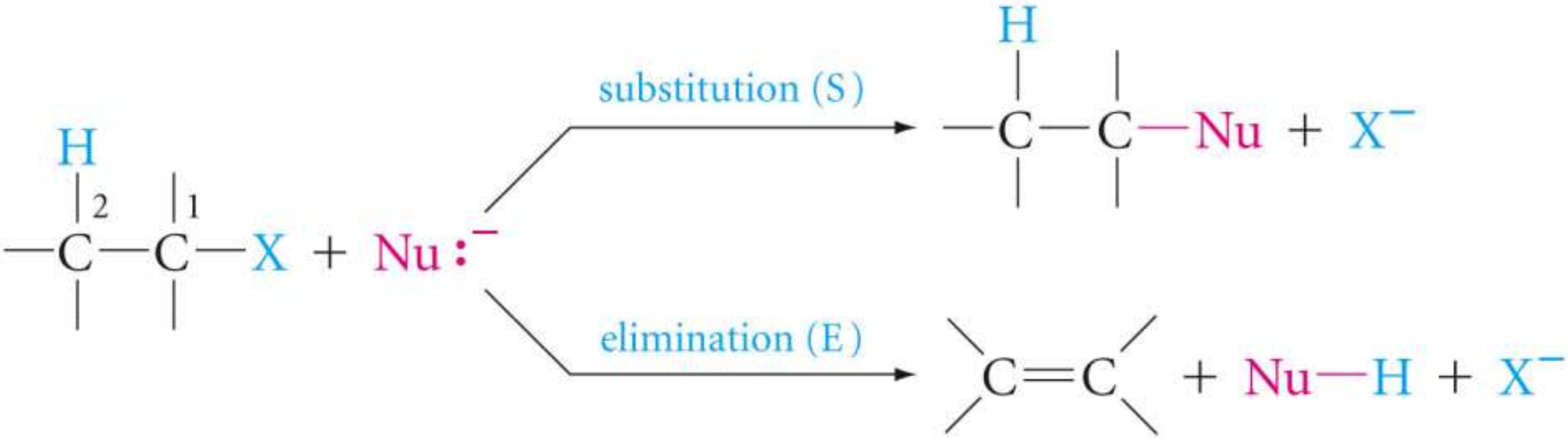


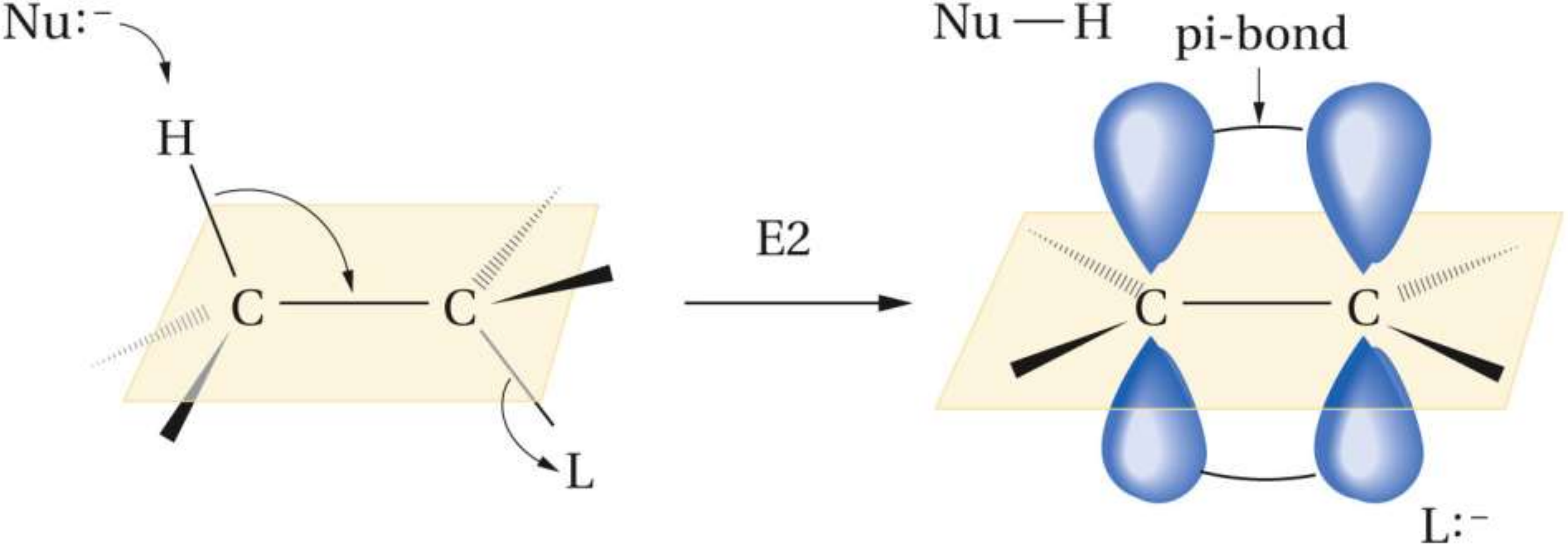
$$\mathrm{CH_3\underset{\underset{Br}{|}}{C}HCH_2CH_2CH_3 + Na^{+}\,{}^{-}SH \longrightarrow CH_3\underset{\underset{SH}{|}}{C}HCH_2CH_2CH_3 + NaBr}$$



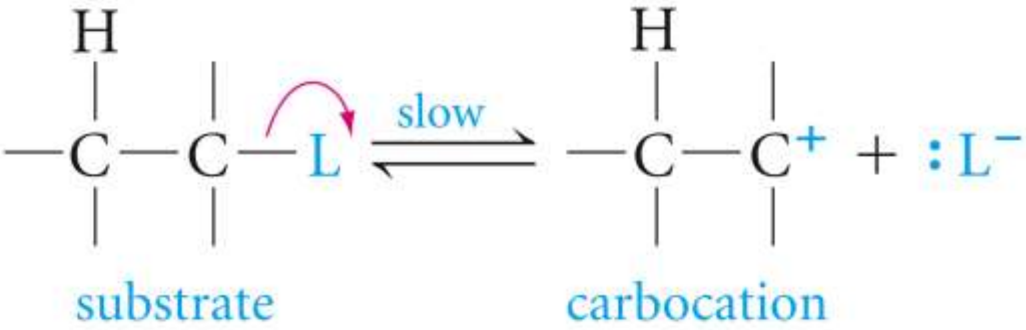
$$\mathrm{CH_3\underset{\underset{Br}{|}}{C}HCH_2CH_2CH_3 + CH_3OH \longrightarrow CH_3\underset{\underset{OCH_3}{|}}{C}HCH_2CH_2CH_3 + HBr}$$

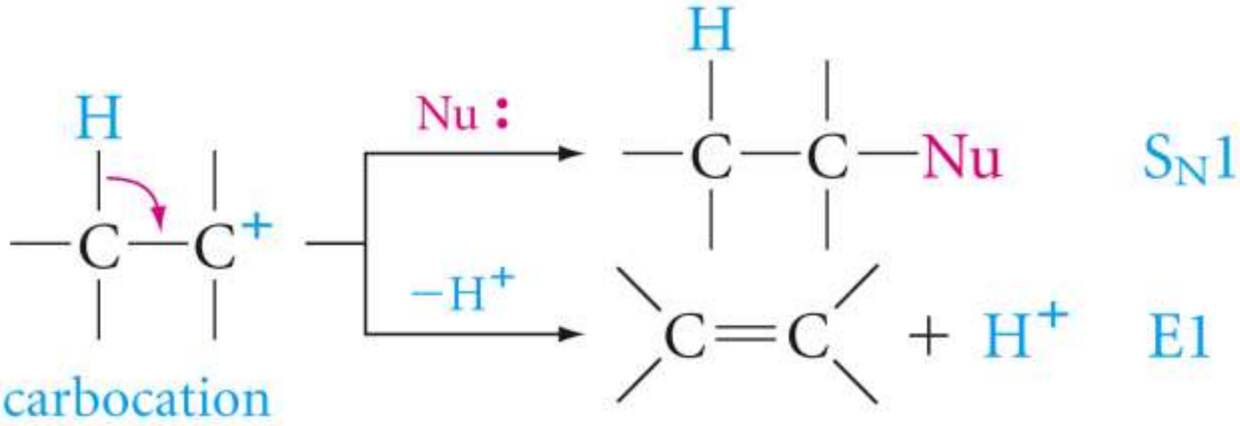
Dehydrohalogenation, and Elimination Reaction; The E2 and E1 Mechanisms




Nu:⁻
H
C
C
L
E2
Nu — H
pi-bond
C
C
L:⁻

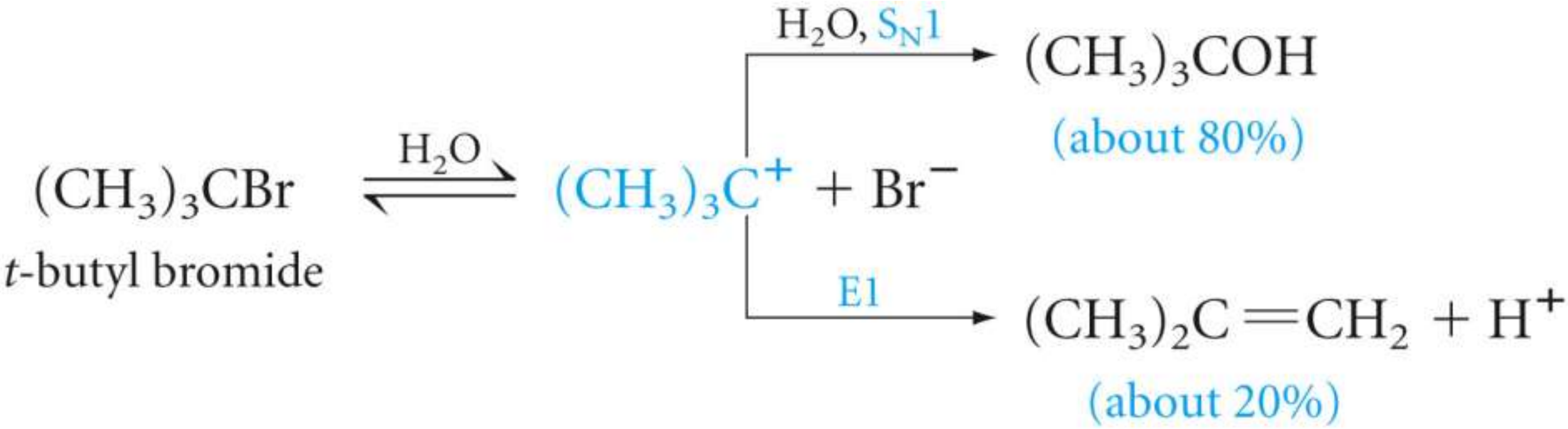
E1 mechanism

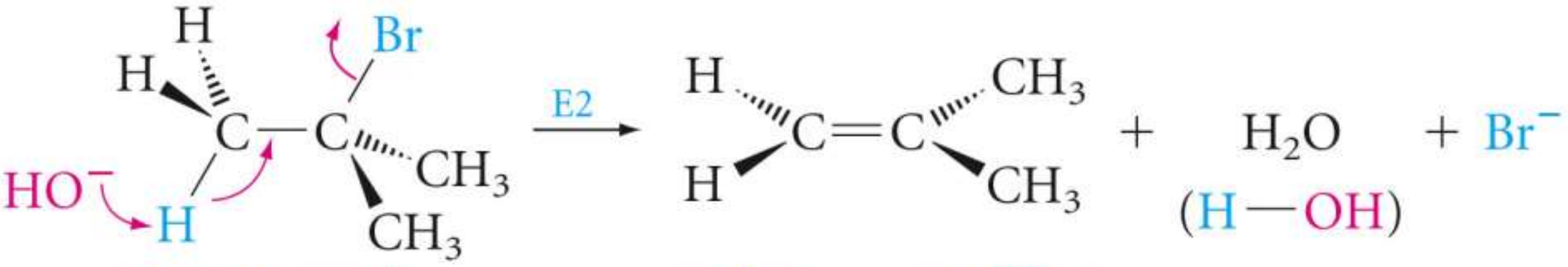




Substitution and Elimination in Competition

Tertiary Halides

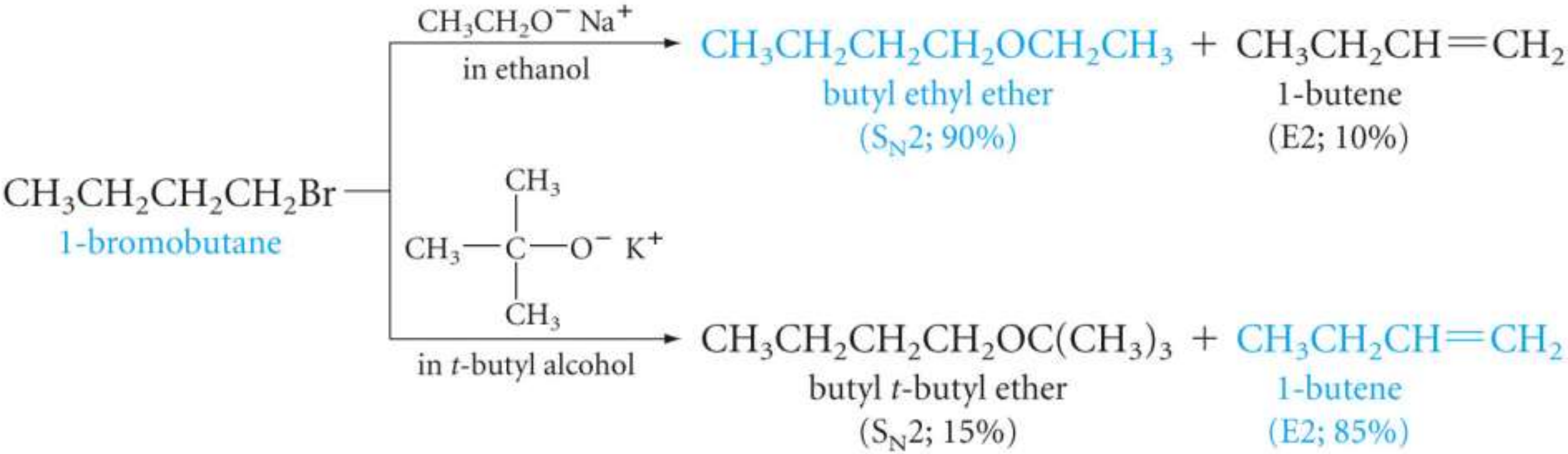


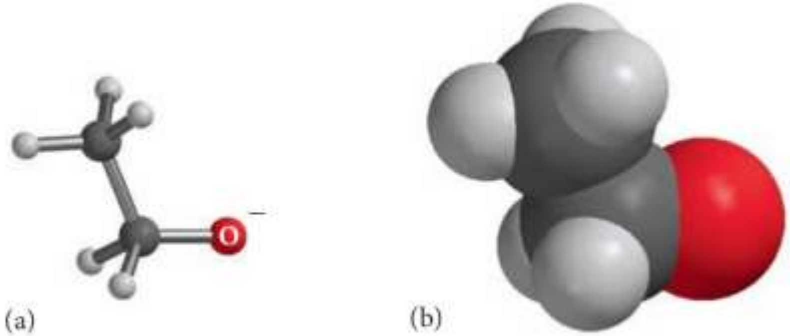


t-butyl bromide

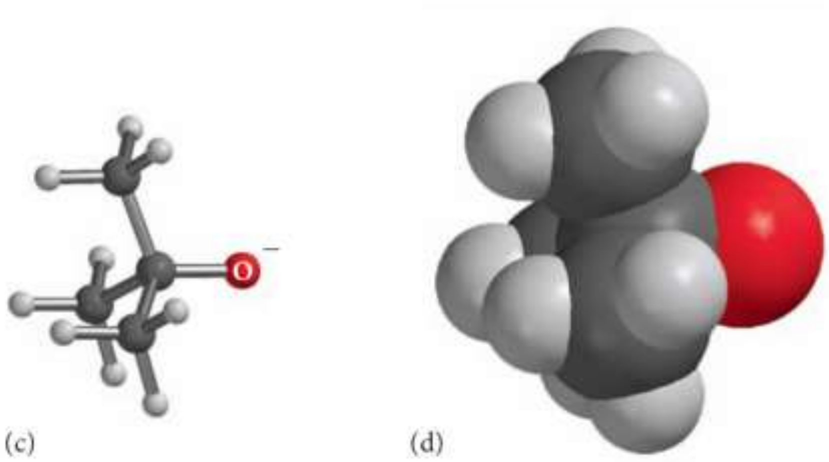
methylpropene (100%)

Primary Halides





Ethoxide



t-butoxide

Secondary Halides