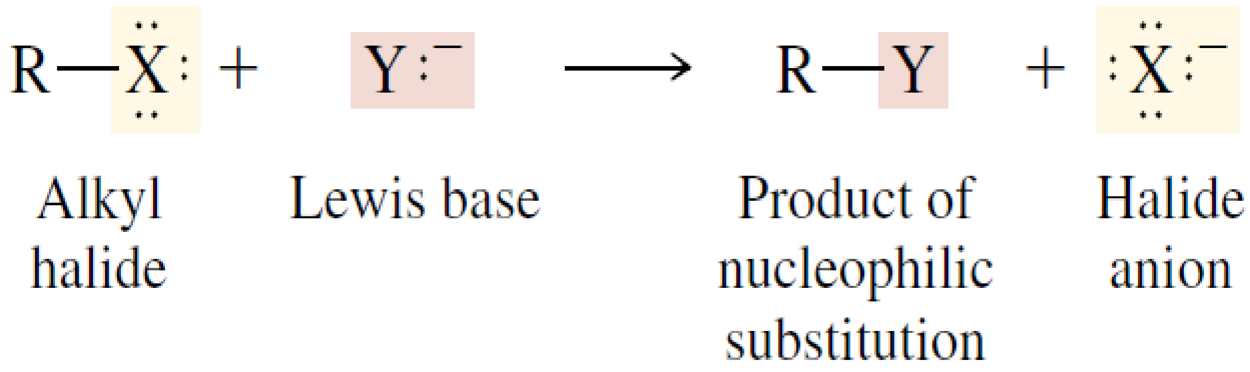
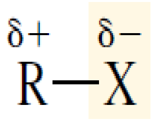
Nucleophilic substitution

Functional group transferation



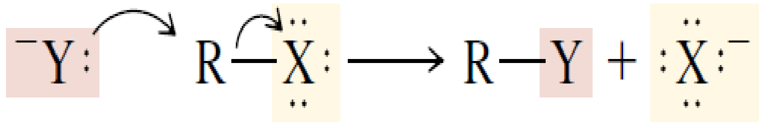
$$R-X + Y^{-} \longrightarrow R-Y + X^{-}$$

The carbon–halogen bond in an alkyl halide is polar



X = I, Br, Cl, F

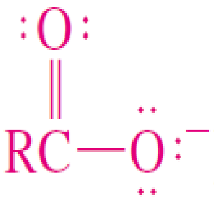
and is cleaved on attack by a nucleophile so that the two electrons in the bond are retained by the halogen



$$Y^{-} + R-X \longrightarrow R-Y + X^{-}$$

MOR (a metal *alkoxide*, a source of the nucleophilic anion $\mathrm{R\ddot{O}\!:^{-}}$)

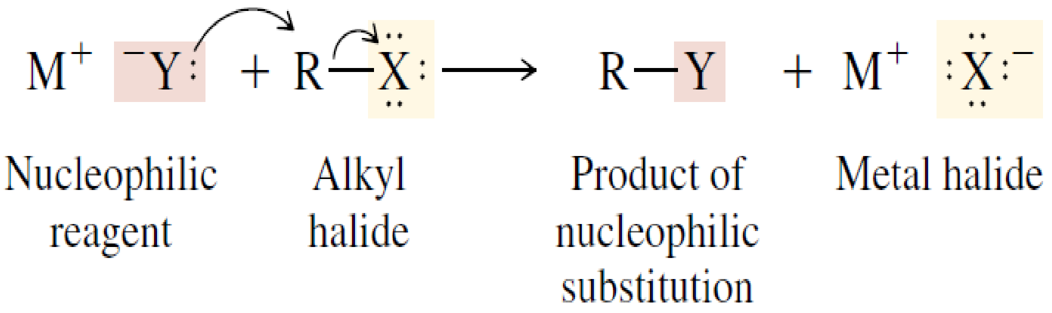
$\mathrm{M}\overset{\overset{\mathrm{O}}{\|}}{\mathrm{O}\mathrm{C}}\mathrm{R}$ (a metal *carboxylate*, a source of the nucleophilic anion $\mathrm{R}\overset{\overset{:\mathrm{O}:}{\|}}{\mathrm{C}}\mathrm{-}\ddot{\mathrm{O}}\!:^{-}$)



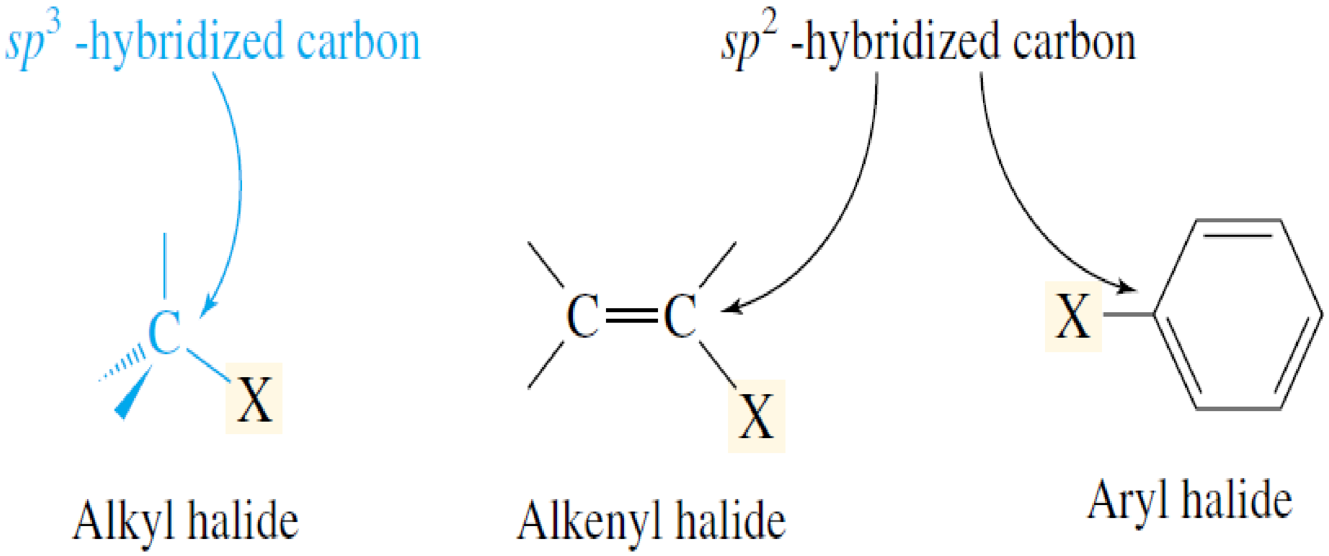
MSH (a metal *hydrogen sulfide*, a source of the nucleophilic anion $\mathrm{H\ddot{S}\!:^{-}}$)

MCN (a metal *cyanide*, a source of the nucleophilic anion $\mathrm{^{-}\!:C{\equiv}N\!:}$)

$\mathrm{MN_3}$ (a metal *azide*, a source of the nucleophilic anion $\mathrm{:\overset{-}{N}{=}\overset{+}{N}{=}\overset{-}{N}\!:}$)



Alkyl halides; Alkenyl halides; Aryl halides



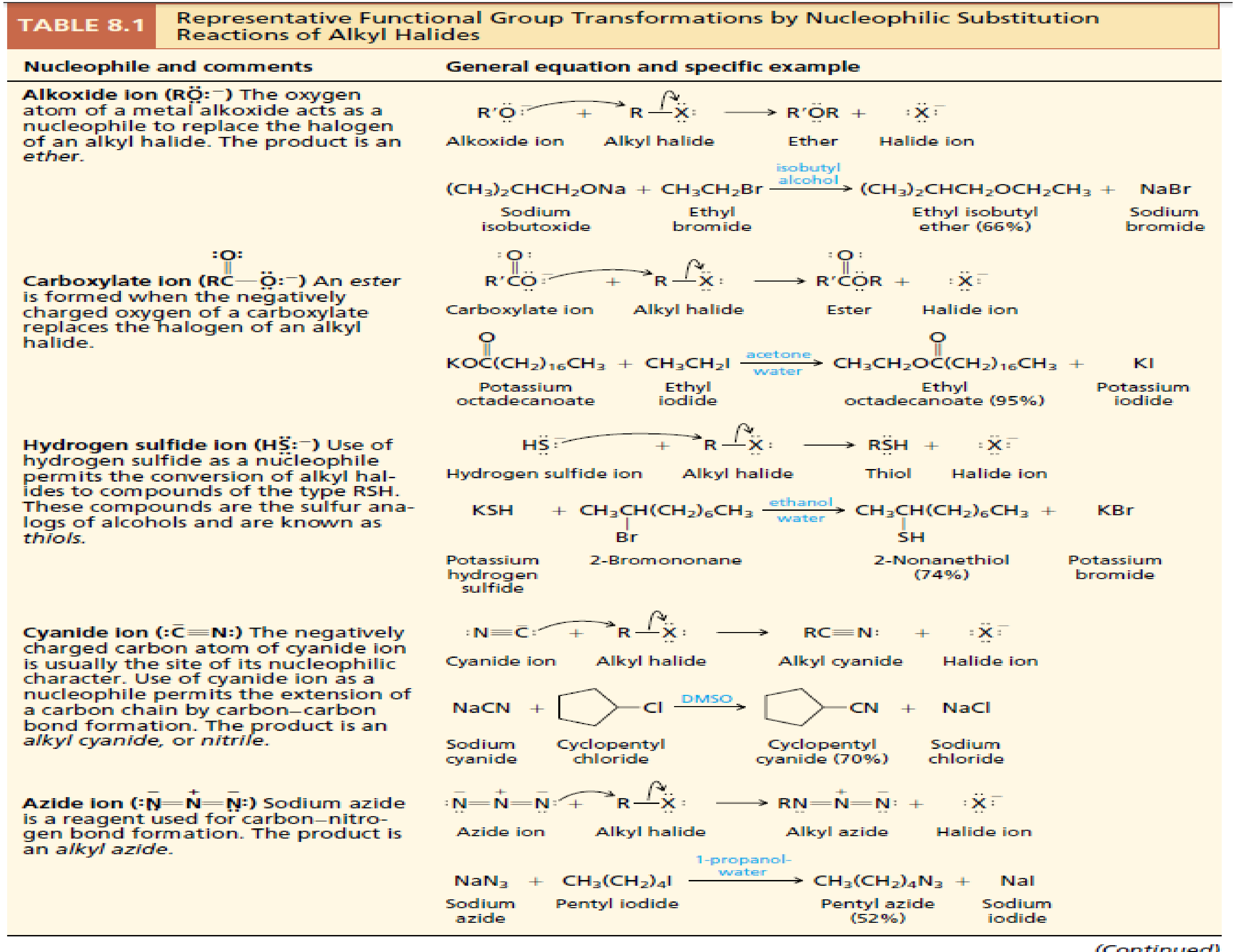


TABLE 8.1 Representative Functional Group Transformations by Nucleophilic Substitution Reactions of Alkyl Halides

Nucleophile and comments	General equation and specific example
Alkoxide ion ($R\ddot{O}:^-$) The oxygen atom of a metal alkoxide acts as a nucleophile to replace the halogen of an alkyl halide. The product is an *ether*.	$R'\ddot{O}:^- + R-\ddot{X}: \longrightarrow R'\ddot{O}R + :\ddot{X}:^-$ Alkoxide ion Alkyl halide Ether Halide ion $(CH_3)_2CHCH_2ONa + CH_3CH_2Br \xrightarrow{\text{isobutyl alcohol}} (CH_3)_2CHCH_2OCH_2CH_3 + NaBr$ Sodium isobutoxide Ethyl bromide Ethyl isobutyl ether (66%) Sodium bromide
Carboxylate ion ($R\overset{:O:}{\overset{\|}{C}}-\ddot{O}:^-$) An *ester* is formed when the negatively charged oxygen of a carboxylate replaces the halogen of an alkyl halide.	$R'\overset{:O:}{\overset{\|}{C}}\ddot{O}:^- + R-\ddot{X}: \longrightarrow R'\overset{:O:}{\overset{\|}{C}}\ddot{O}R + :\ddot{X}:^-$ Carboxylate ion Alkyl halide Ester Halide ion $K O\overset{O}{\overset{\|}{C}}(CH_2)_{16}CH_3 + CH_3CH_2I \xrightarrow[\text{water}]{\text{acetone}} CH_3CH_2O\overset{O}{\overset{\|}{C}}(CH_2)_{16}CH_3 + KI$ Potassium octadecanoate Ethyl iodide Ethyl octadecanoate (95%) Potassium iodide
Hydrogen sulfide ion ($H\ddot{S}:^-$) Use of hydrogen sulfide as a nucleophile permits the conversion of alkyl halides to compounds of the type RSH. These compounds are the sulfur analogs of alcohols and are known as *thiols*.	$H\ddot{S}:^- + R-\ddot{X}: \longrightarrow R\ddot{S}H + :\ddot{X}:^-$ Hydrogen sulfide ion Alkyl halide Thiol Halide ion $KSH + CH_3\underset{Br}{\underset{\|}{C}H}(CH_2)_6CH_3 \xrightarrow[\text{water}]{\text{ethanol}} CH_3\underset{SH}{\underset{\|}{C}H}(CH_2)_6CH_3 + KBr$ Potassium hydrogen sulfide 2-Bromononane 2-Nonanethiol (74%) Potassium bromide
Cyanide ion ($:\bar{C}{\equiv}N:$) The negatively charged carbon atom of cyanide ion is usually the site of its nucleophilic character. Use of cyanide ion as a nucleophile permits the extension of a carbon chain by carbon–carbon bond formation. The product is an *alkyl cyanide*, or *nitrile*.	$:N{\equiv}\bar{C}: + R-\ddot{X}: \longrightarrow RC{\equiv}N: + :\ddot{X}:^-$ Cyanide ion Alkyl cyanide Alkyl halide Halide ion NaCN + ⬠—Cl $\xrightarrow{\text{DMSO}}$ ⬠—CN + NaCl Sodium cyanide Cyclopentyl chloride Cyclopentyl cyanide (70%) Sodium chloride
Azide ion ($:\bar{N}{=}\overset{+}{N}{=}\bar{N}:$) Sodium azide is a reagent used for carbon–nitrogen bond formation. The product is an *alkyl azide*.	$:\bar{\ddot{N}}{=}\overset{+}{N}{=}\bar{\ddot{N}}: + R-\ddot{X}: \longrightarrow R\ddot{N}{=}\overset{+}{N}{=}\bar{\ddot{N}}: + :\ddot{X}:^-$ Azide ion Alkyl halide Alkyl azide Halide ion $NaN_3 + CH_3(CH_2)_4I \xrightarrow{\text{1-propanol-water}} CH_3(CH_2)_4N_3 + NaI$ Sodium azide Pentyl iodide Pentyl azide (52%) Sodium iodide

(Continued)

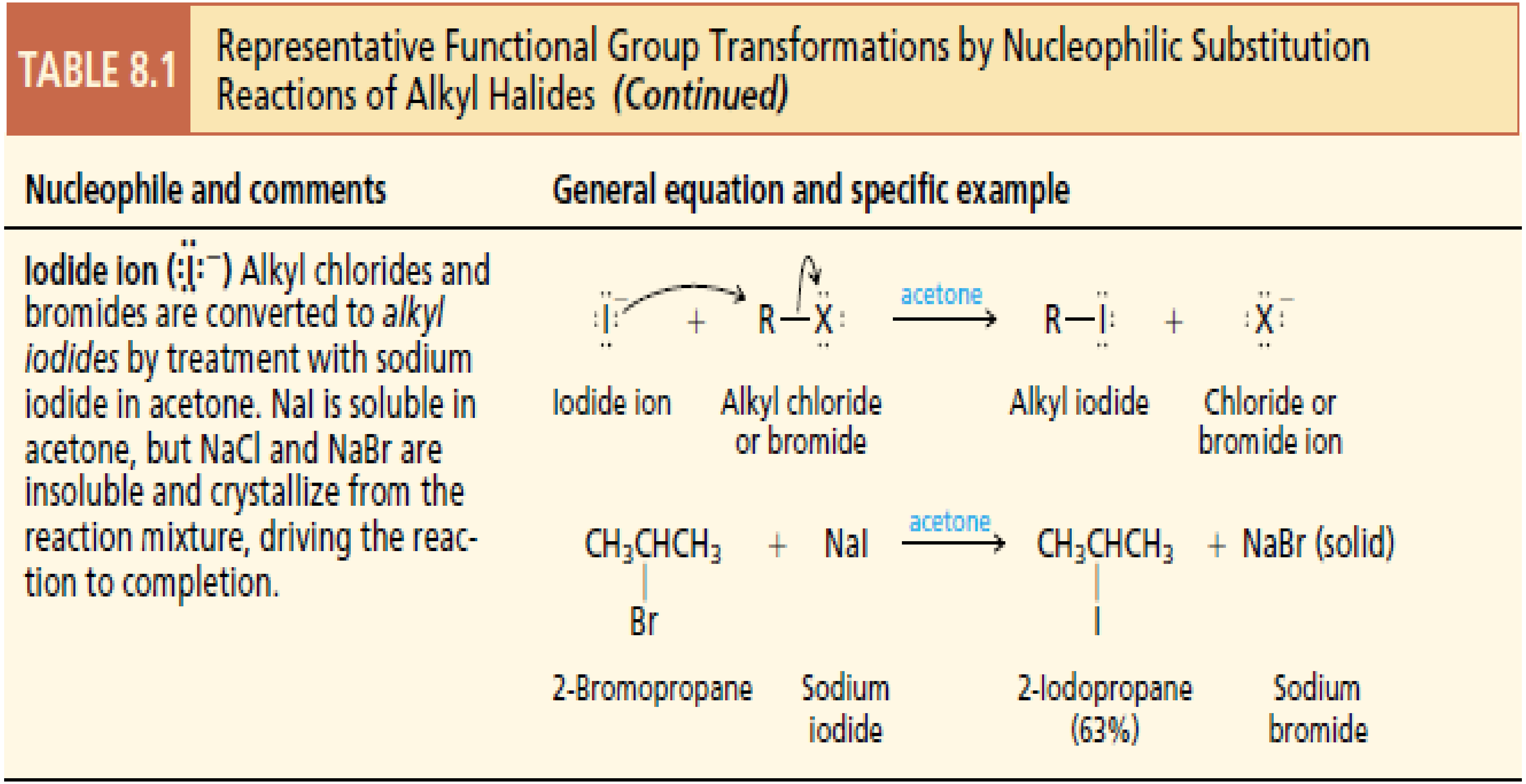


TABLE 8.1 Representative Functional Group Transformations by Nucleophilic Substitution Reactions of Alkyl Halides *(Continued)*

Nucleophile and comments	General equation and specific example
Iodide ion ($:\ddot{\underset{..}{I}}:^-$) Alkyl chlorides and bromides are converted to *alkyl iodides* by treatment with sodium iodide in acetone. NaI is soluble in acetone, but NaCl and NaBr are insoluble and crystallize from the reaction mixture, driving the reaction to completion.	$:\ddot{\underset{..}{I}}:^- + R-\ddot{\underset{..}{X}}: \xrightarrow{\text{acetone}} R-\ddot{\underset{..}{I}}: + :\ddot{\underset{..}{X}}:^-$ Iodide ion; Alkyl chloride or bromide; Alkyl iodide; Chloride or bromide ion $\underset{\text{Br}}{\underset{\mid}{\mathrm{CH_3CHCH_3}}} + \mathrm{NaI} \xrightarrow{\text{acetone}} \underset{\text{I}}{\underset{\mid}{\mathrm{CH_3CHCH_3}}} + \mathrm{NaBr}\ (\text{solid})$ 2-Bromopropane; Sodium iodide; 2-Iodopropane (63%); Sodium bromide

Relative reactivity of halides leaving groups

Increasing rate of substitution by nucleophiles

$RF \ll RCl < RBr < RI$

Least reactive

Most reactive

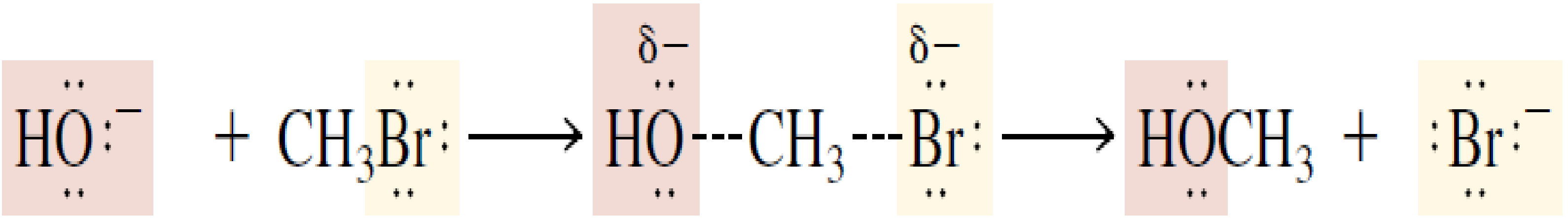
S_N2 Mechanism

$$\underset{\text{Methyl bromide}}{CH_3Br} \quad + \quad \underset{\text{Hydroxide ion}}{HO^-} \quad \longrightarrow \quad \underset{\text{Methyl alcohol}}{CH_3OH} \quad + \quad \underset{\text{Bromide ion}}{Br^-}$$

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

Substitution nucleophilic bimolecular

Direct displacement

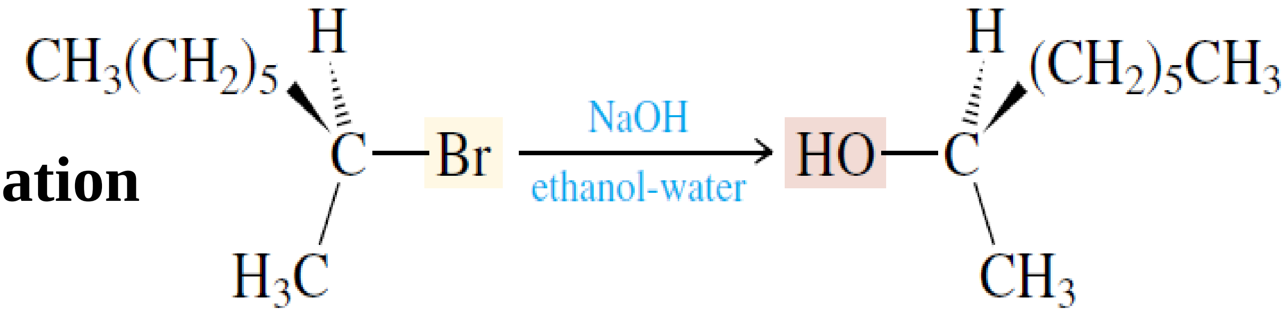


$HO^- + CH_3Br \longrightarrow HO \cdots CH_3 \cdots Br \longrightarrow HOCH_3 + Br^-$

Hydroxide ion | Methyl bromide | Transition state | Methyl alcohol | Bromide ion

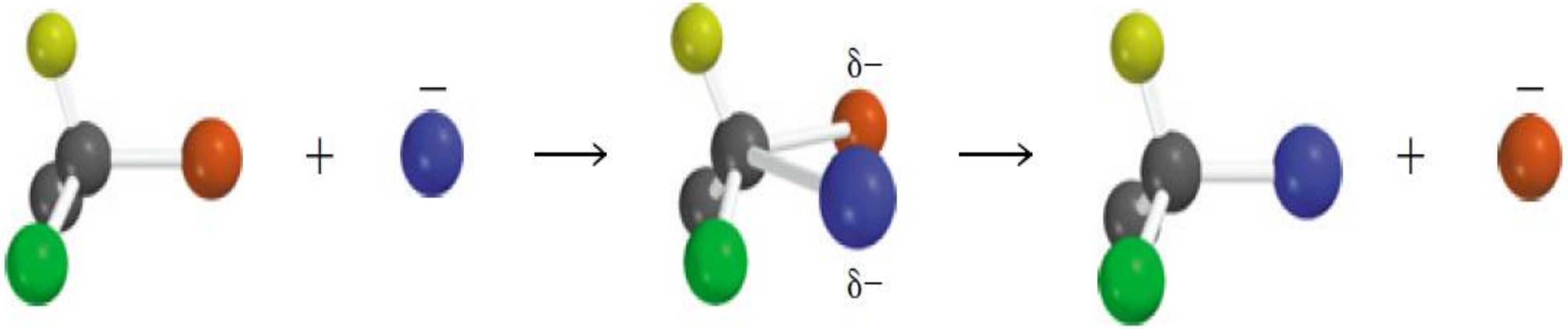
Stereochemistry of S_N2 reaction

Inversion of configuration

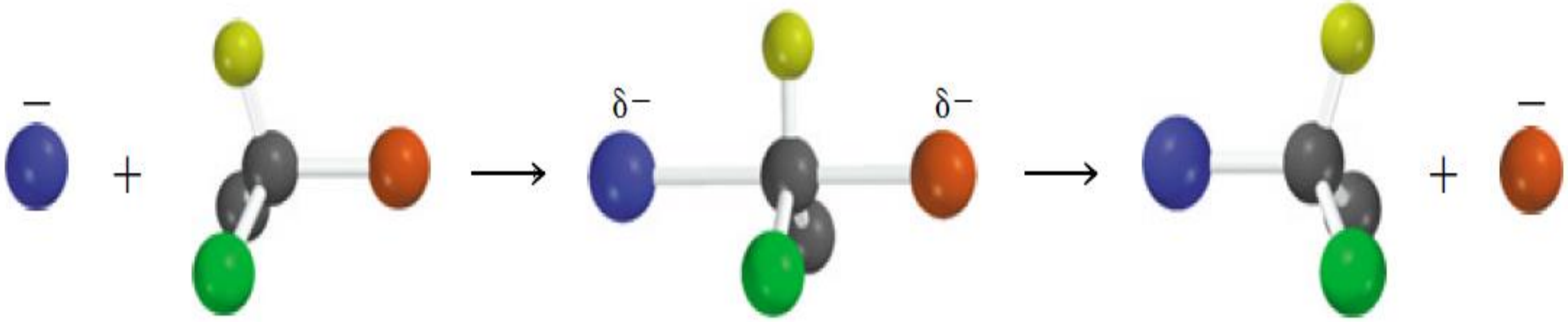


(*S*)-(+)-2-Bromooctane

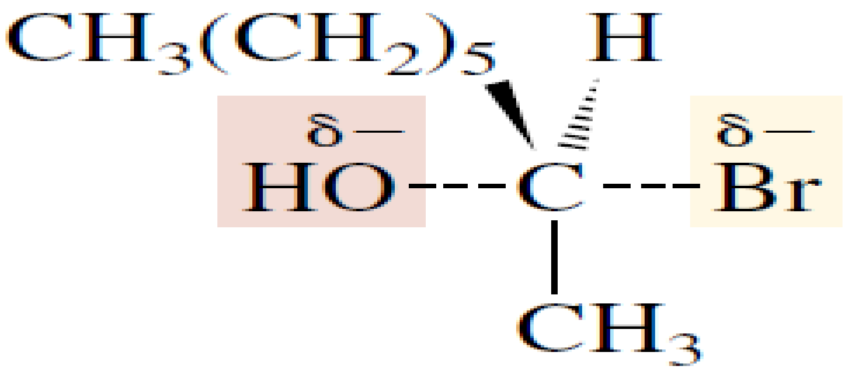
(*R*)-(−)-2-Octanol



(*a*) Nucleophilic substitution with retention of configuration

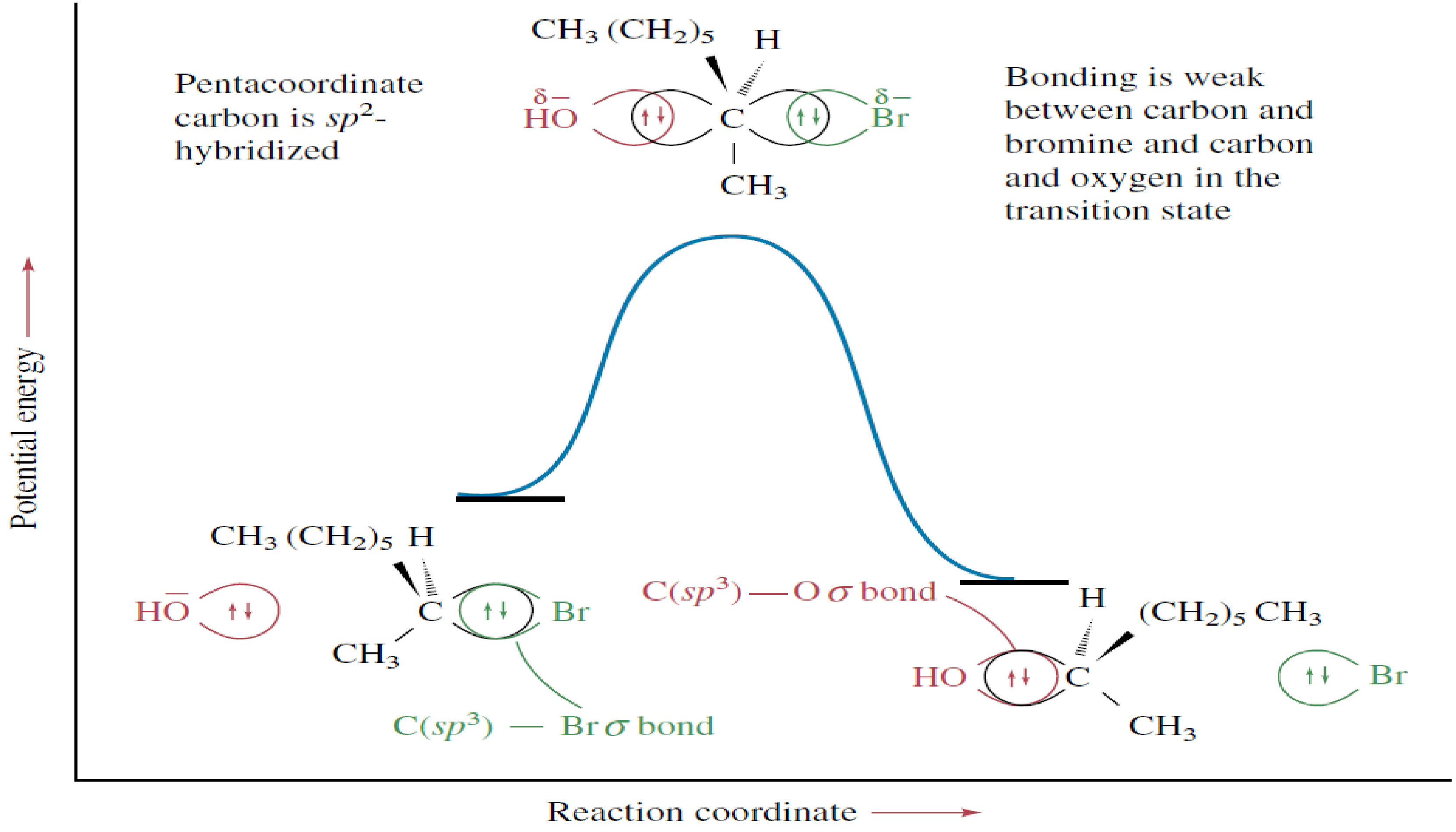


(*b*) Nucleophilic substitution with inversion of configuration

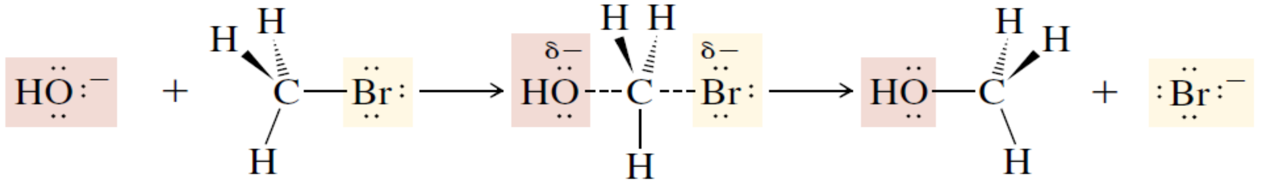


figuration at the carbon that bears the leaving group. *There is a stereoelectronic requirement for the nucleophile to approach carbon from the side opposite the bond to the leaving group*. Organic chemists often speak of this as a **Walden inversion,** after the German

How S_N2 reaction occur



Steric effects in S_N2 reactions



Hydroxide ion
Methyl bromide
Transition state
Methyl alcohol
Bromide ion

$$RBr + LiI \xrightarrow{acetone} RI + LiBr$$

Alkyl bromide
Lithium iodide
Alkyl iodide
Lithium bromide

Increasing rate of substitution by the S_N2 mechanism

R_3CX	<	R_2CHX	<	RCH_2X	<	CH_3X
Tertiary Least reactive, most crowded		Secondary		Primary		Methyl Most reactive, least crowded

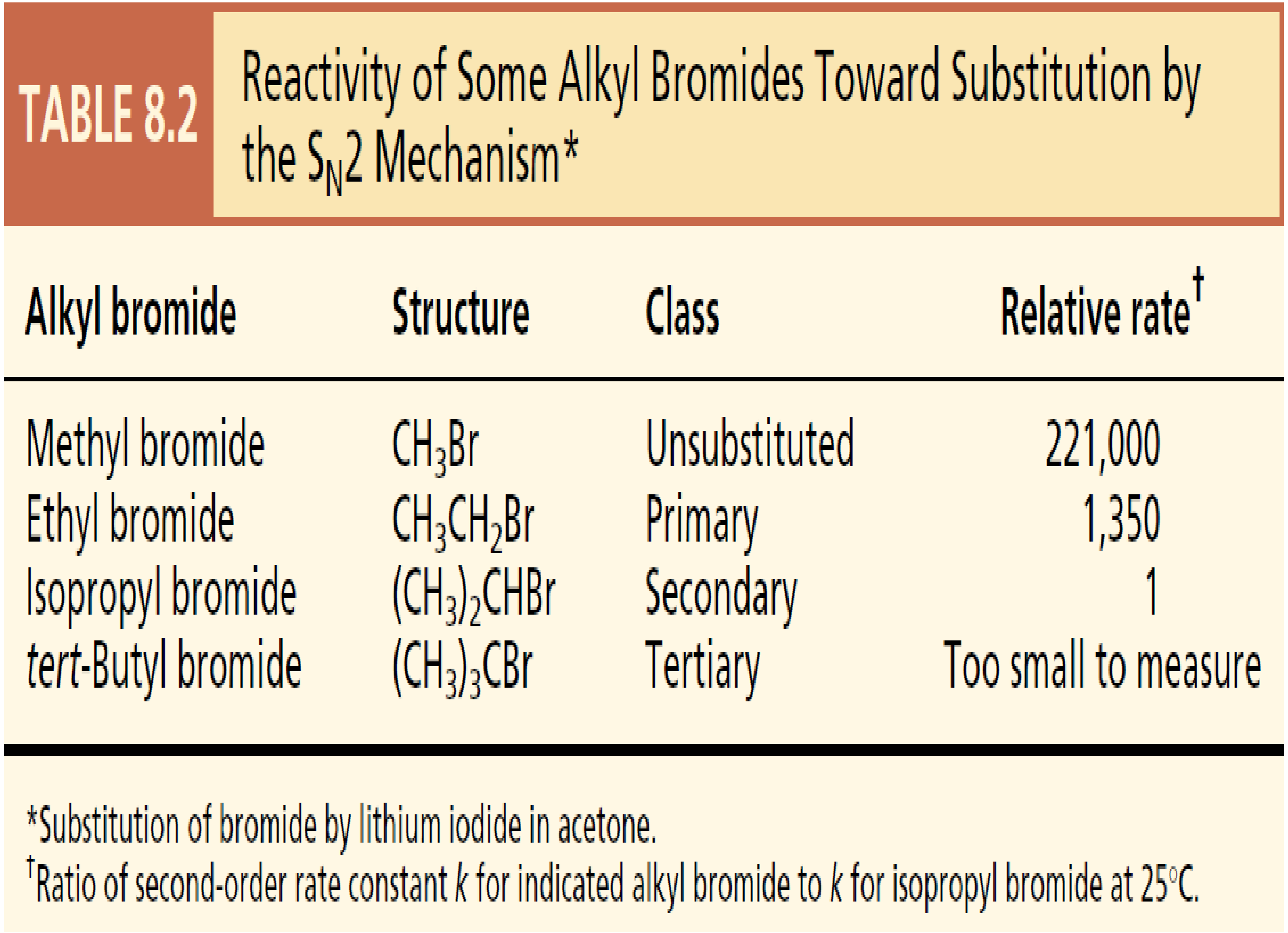


TABLE 8.2 Reactivity of Some Alkyl Bromides Toward Substitution by the S_N2 Mechanism*

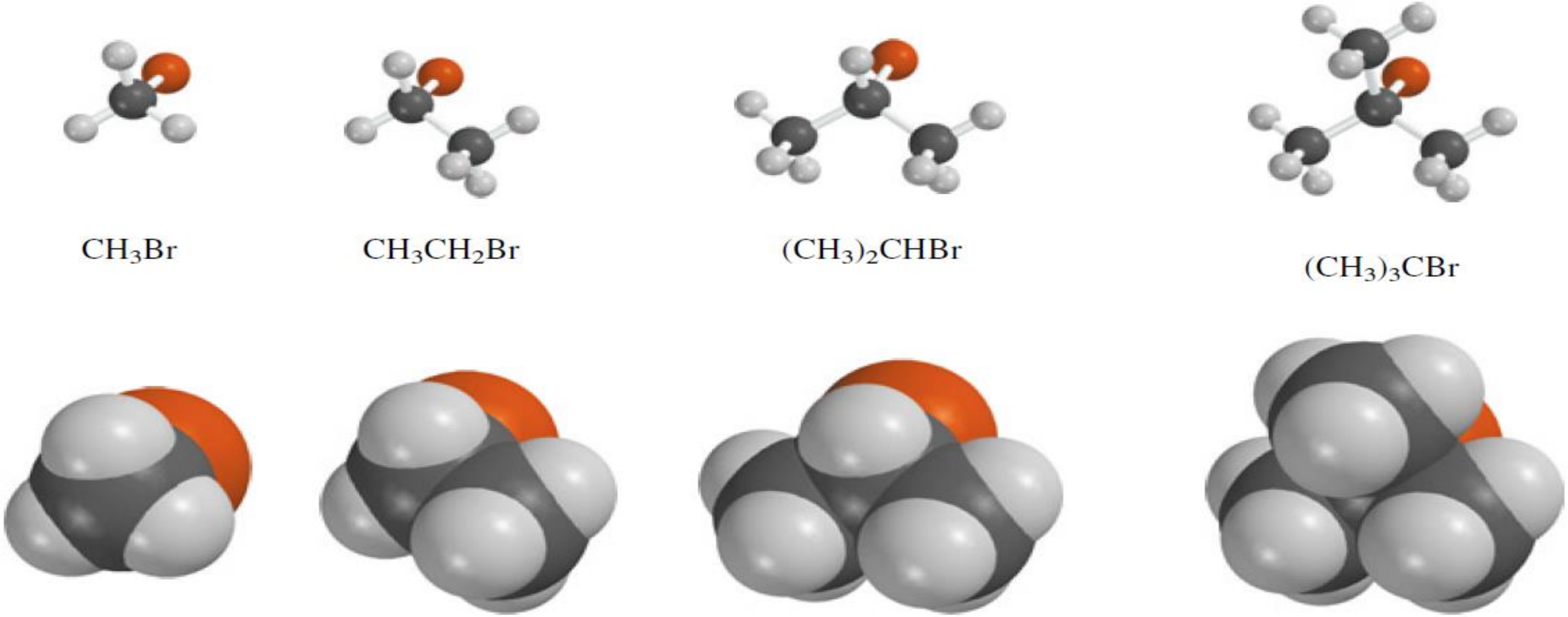
Alkyl bromide	Structure	Class	Relative rate†
Methyl bromide	CH_3Br	Unsubstituted	221,000
Ethyl bromide	CH_3CH_2Br	Primary	1,350
Isopropyl bromide	$(CH_3)_2CHBr$	Secondary	1
tert-Butyl bromide	$(CH_3)_3CBr$	Tertiary	Too small to measure

*Substitution of bromide by lithium iodide in acetone.

†Ratio of second-order rate constant *k* for indicated alkyl bromide to *k* for isopropyl bromide at 25°C.

Least crowded–
most reactive

Most crowded–
least reactive



CH_3Br

CH_3CH_2Br

$(CH_3)_2CHBr$

$(CH_3)_3CBr$

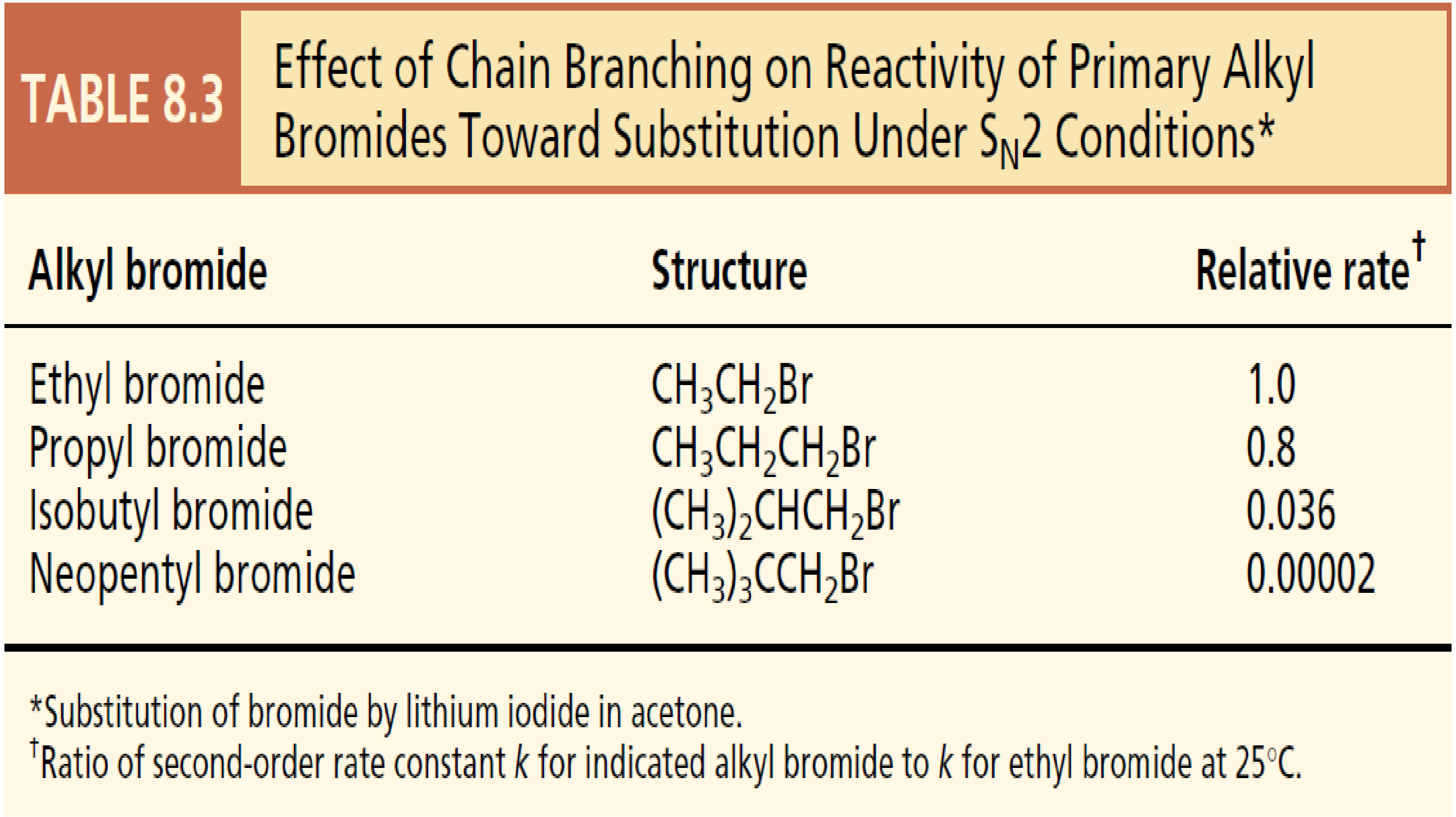


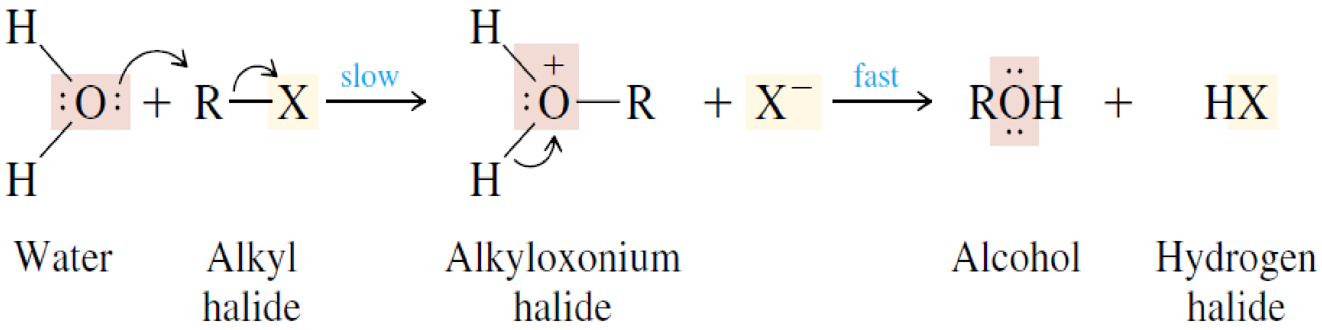
TABLE 8.3 Effect of Chain Branching on Reactivity of Primary Alkyl Bromides Toward Substitution Under S_N2 Conditions*

Alkyl bromide	Structure	Relative rate[†]
Ethyl bromide	CH_3CH_2Br	1.0
Propyl bromide	$CH_3CH_2CH_2Br$	0.8
Isobutyl bromide	$(CH_3)_2CHCH_2Br$	0.036
Neopentyl bromide	$(CH_3)_3CCH_2Br$	0.00002

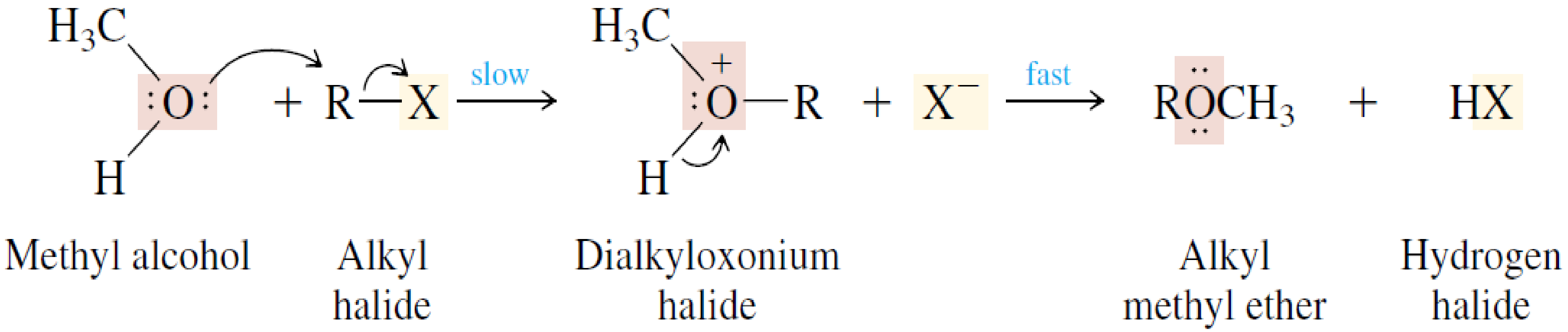
*Substitution of bromide by lithium iodide in acetone.

[†] Ratio of second-order rate constant *k* for indicated alkyl bromide to *k* for ethyl bromide at 25°C.

Nucleophile and nucleophilisity



Solvolysis in *methyl alcohol* converts an alkyl halide to an *alkyl methyl ether.*



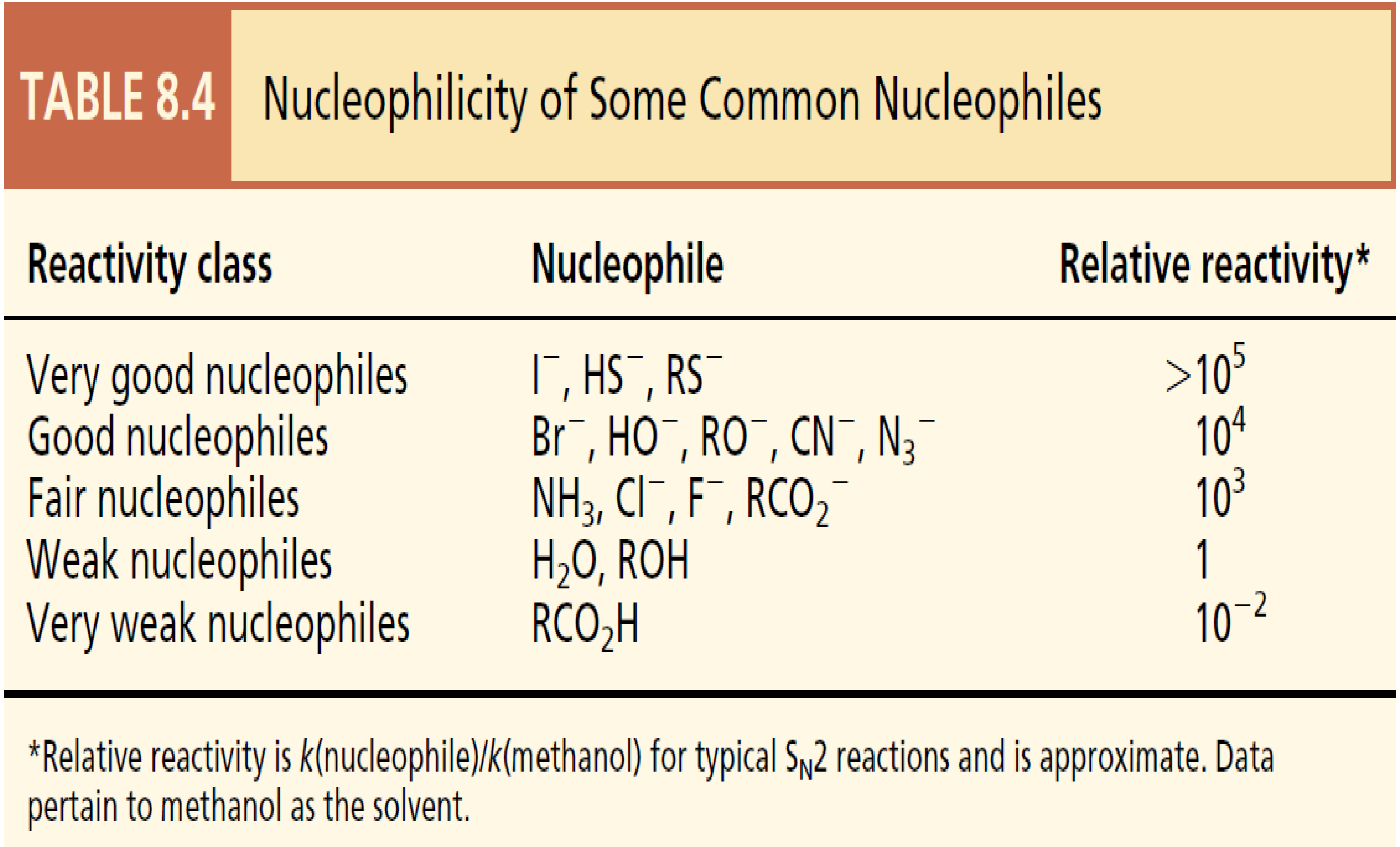


TABLE 8.4 Nucleophilicity of Some Common Nucleophiles

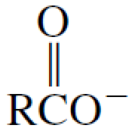
Reactivity class	Nucleophile	Relative reactivity*
Very good nucleophiles	I^-, HS^-, RS^-	$>10^5$
Good nucleophiles	Br^-, HO^-, RO^-, CN^-, N_3^-	10^4
Fair nucleophiles	NH_3, Cl^-, F^-, RCO_2^-	10^3
Weak nucleophiles	H_2O, ROH	1
Very weak nucleophiles	RCO_2H	10^{-2}

*Relative reactivity is *k*(nucleophile)/*k*(methanol) for typical S_N2 reactions and is approximate. Data pertain to methanol as the solvent.

RO^- is more nucleophilic than ROH

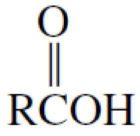
Alkoxide ion

Alcohol



$R\overset{\overset{O}{\|}}{C}O^-$

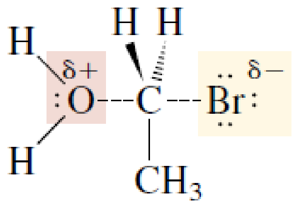
is more nucleophilic than



$R\overset{\overset{O}{\|}}{C}OH$

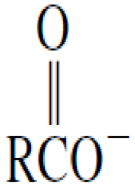
Carboxylate ion

Carboxylic acid



Bimolecular transition state
for hydrolysis of ethyl bromide

RO^- is more nucleophilic than



$R\overset{\overset{O}{\|}}{C}O^-$

Stronger base
Conjugate acid is ROH:
$K_a = 10^{-16}$ ($pK_a = 16$)

Weaker base
Conjugate acid is RCO_2H:
$K_a = 10^{-5}$ ($pK_a = 5$)

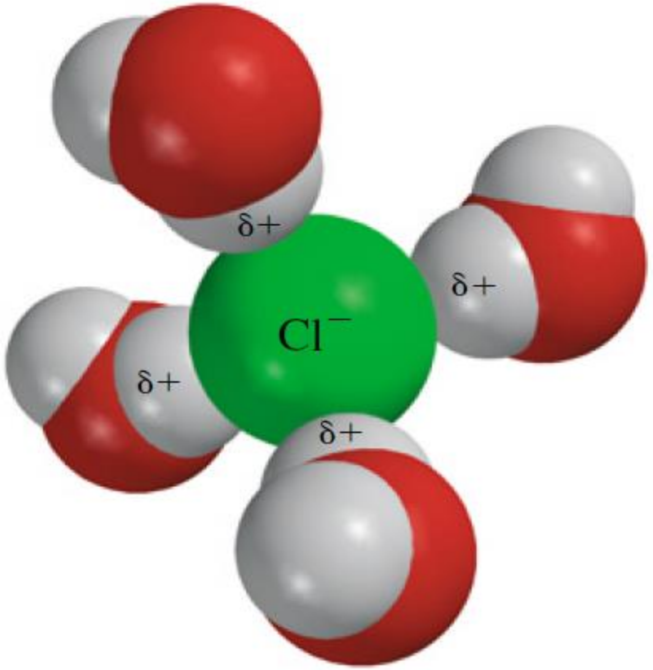


FIGURE 8.4 Solvation of a chloride by ion–dipole attractive forces with water. The negatively charged chloride ion interacts with the positively polarized hydrogens of water.

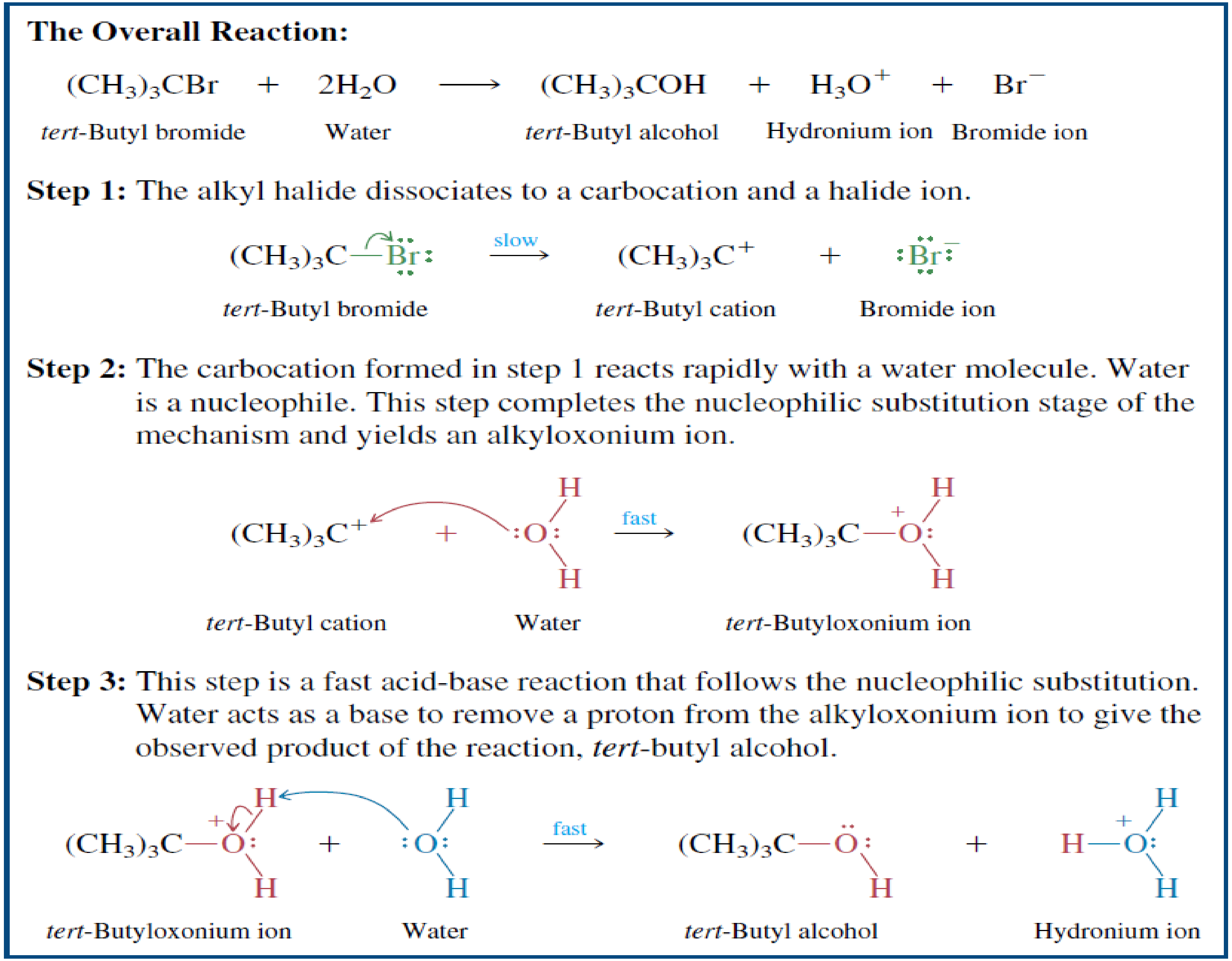
Substitution nucleophilic unimolecular

$$\underset{\textit{tert}\text{-Butyl bromide}}{(CH_3)_3CBr} + \underset{\text{Water}}{H_2O} \longrightarrow \underset{\textit{tert}\text{-Butyl alcohol}}{(CH_3)_3COH} + \underset{\text{Hydrogen bromide}}{HBr}$$

$$\text{Rate} = k[(CH_3)_3CBr]$$

$$\underset{\text{Alkyl halide}}{RX} + \underset{\text{Water}}{H_2O} \xrightarrow{\text{formic acid}} \underset{\text{Alcohol}}{ROH} + \underset{\text{Hydrogen halide}}{HX}$$

Mechanism of S_N1 reactions; Stability of carbonations



The Overall Reaction:

$$(CH_3)_3CBr + 2H_2O \longrightarrow (CH_3)_3COH + H_3O^+ + Br^-$$

tert-Butyl bromide, Water, *tert*-Butyl alcohol, Hydronium ion, Bromide ion

Step 1: The alkyl halide dissociates to a carbocation and a halide ion.

$$(CH_3)_3C{-}\ddot{\underset{\cdot\cdot}{Br}}{:} \xrightarrow{\text{slow}} (CH_3)_3C^+ + {:}\ddot{\underset{\cdot\cdot}{Br}}{:}^-$$

tert-Butyl bromide, *tert*-Butyl cation, Bromide ion

Step 2: The carbocation formed in step 1 reacts rapidly with a water molecule. Water is a nucleophile. This step completes the nucleophilic substitution stage of the mechanism and yields an alkyloxonium ion.

$$(CH_3)_3C^+ + {:}O{:}H_2 \xrightarrow{\text{fast}} (CH_3)_3C{-}\overset{+}{O}{:}H_2$$

tert-Butyl cation, Water, *tert*-Butyloxonium ion

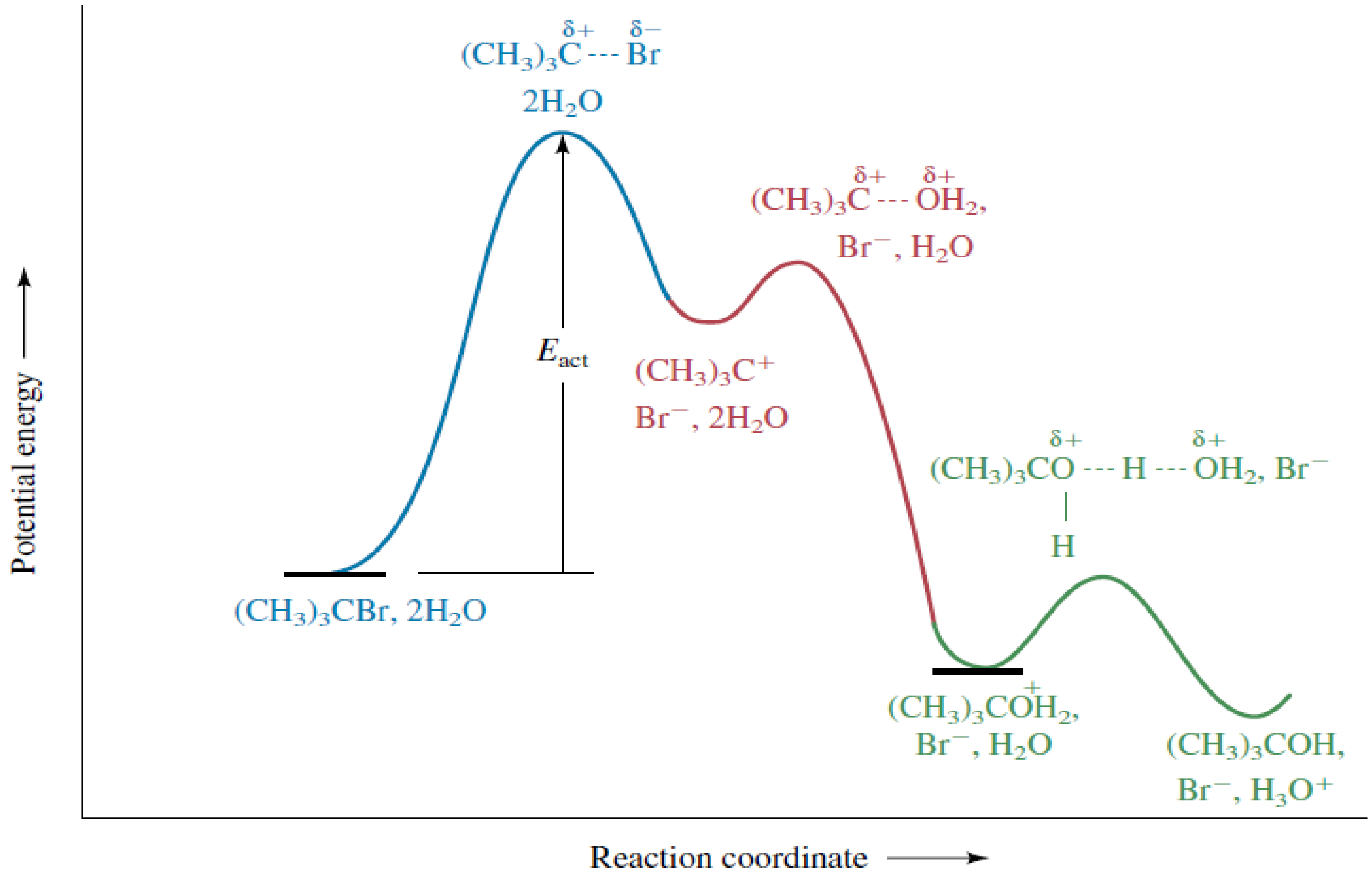
Step 3: This step is a fast acid-base reaction that follows the nucleophilic substitution. Water acts as a base to remove a proton from the alkyloxonium ion to give the observed product of the reaction, *tert*-butyl alcohol.

$$(CH_3)_3C{-}\overset{+}{O}{:}H_2 + {:}O{:}H_2 \xrightarrow{\text{fast}} (CH_3)_3C{-}\ddot{O}{:}H + H{-}\overset{+}{O}{:}H_2$$

tert-Butyloxonium ion, Water, *tert*-Butyl alcohol, Hydronium ion

S_N1 reactivity: methyl < primary < secondary < tertiary

S_N2 reactivity: tertiary < secondary < primary < methyl



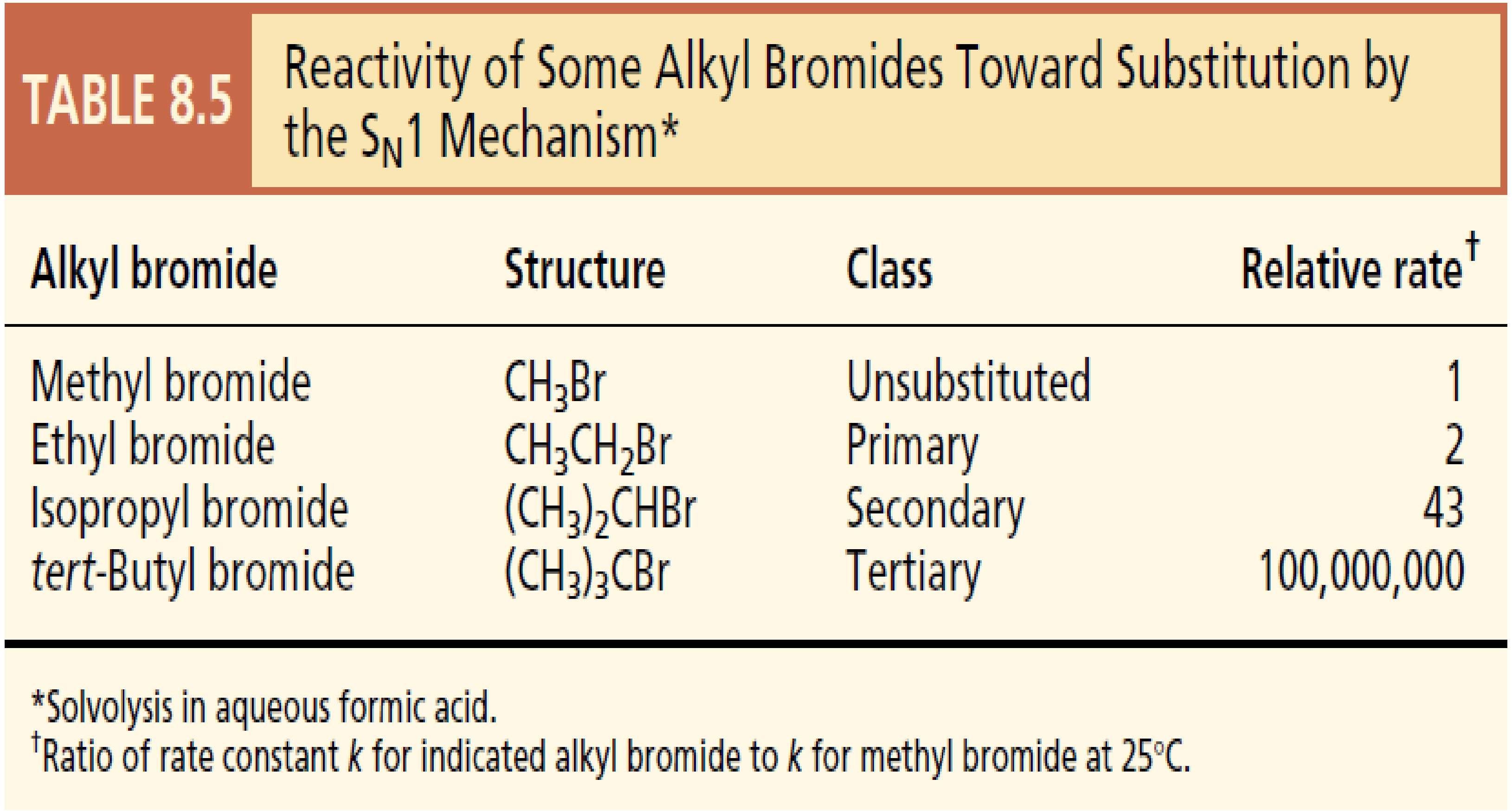


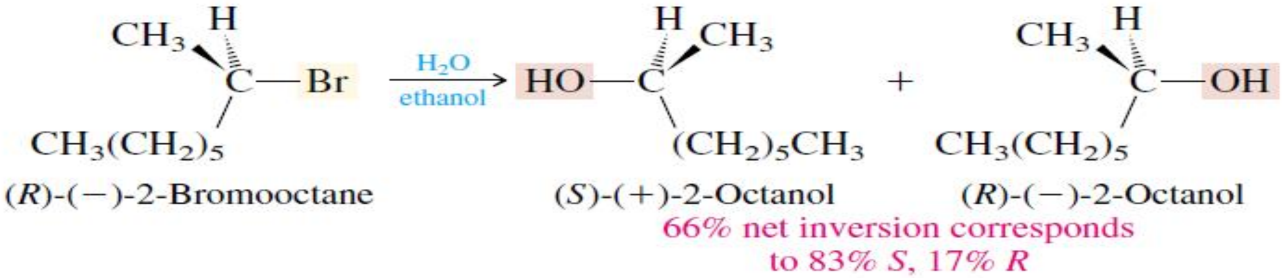
TABLE 8.5 Reactivity of Some Alkyl Bromides Toward Substitution by the S_N1 Mechanism*

Alkyl bromide	Structure	Class	Relative rate[†]
Methyl bromide	CH_3Br	Unsubstituted	1
Ethyl bromide	CH_3CH_2Br	Primary	2
Isopropyl bromide	$(CH_3)_2CHBr$	Secondary	43
tert-Butyl bromide	$(CH_3)_3CBr$	Tertiary	100,000,000

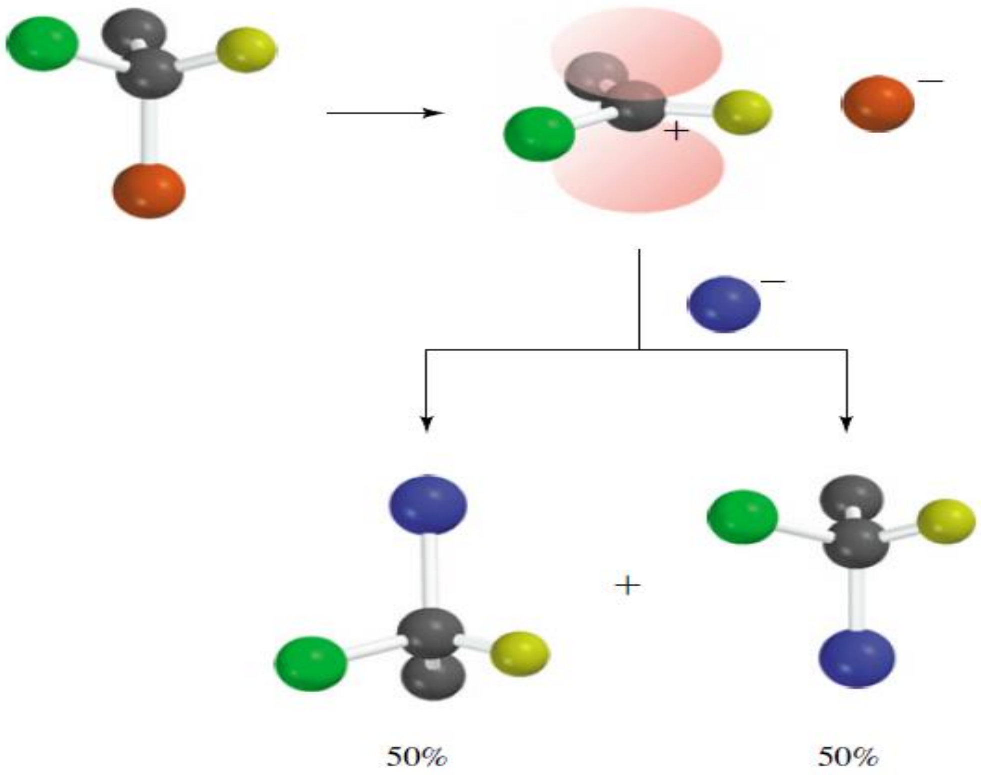
*Solvolysis in aqueous formic acid.

[†] Ratio of rate constant *k* for indicated alkyl bromide to *k* for methyl bromide at 25°C.

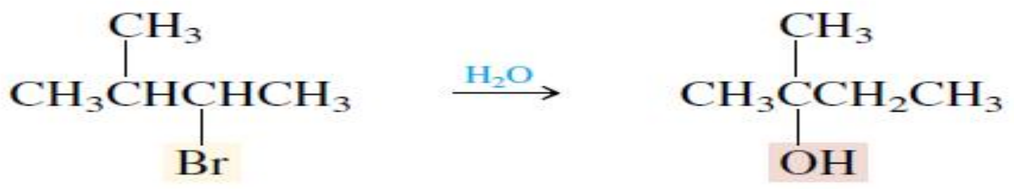
Stereochemistry of S_N1



66% net inversion corresponds to 83% S, 17% R



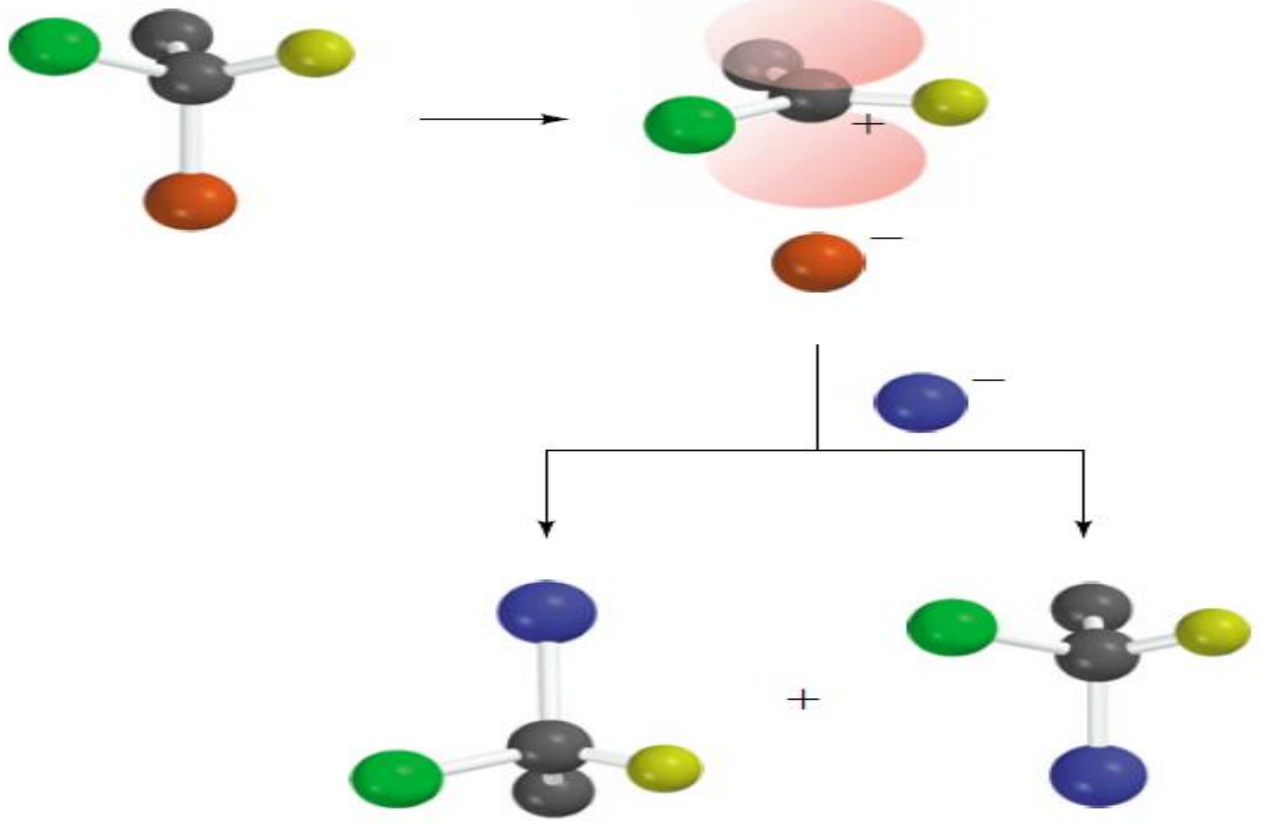
Carbocation stability



$$CH_3CH(CH_3)CH(Br)CH_3 \xrightarrow{H_2O} CH_3C(CH_3)(OH)CH_2CH_3$$

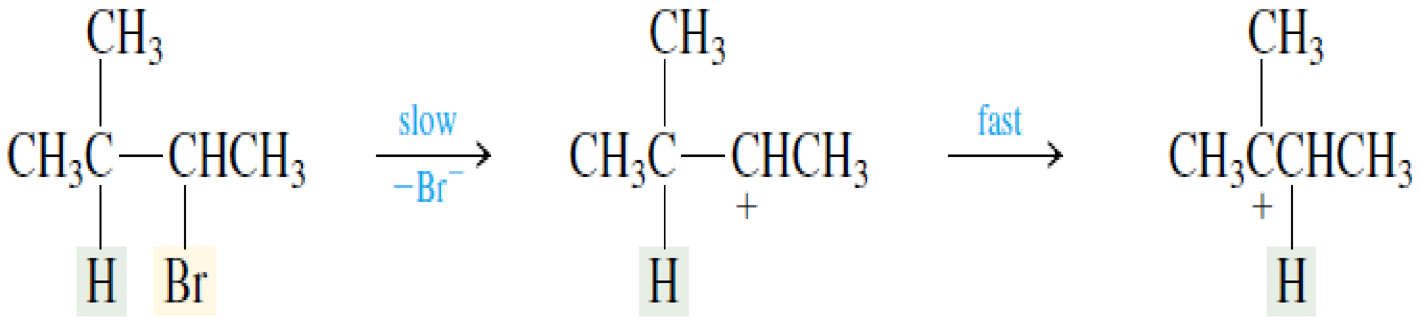
2-Bromo-3-methylbutane

2-Methyl-2-butanol (93%)



More than 50%

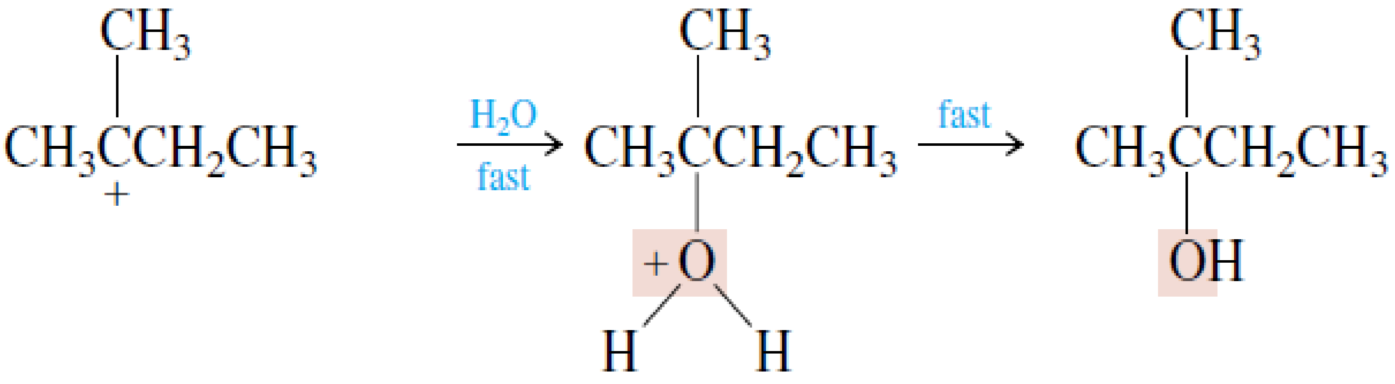
Less than 50%



2-Bromo-3-methylbutane

1,2-Dimethylpropyl cation
(a secondary carbocation)

1,1-Dimethylpropyl cation
(a tertiary carbocation)



1,1-Dimethylpropyl cation

2-Methyl-2-butanol

8.12 EFFECT OF SOLVENT ON THE RATE OF NUCLEOPHILIC SUBSTITUTION

The major effect of the solvent is on the *rate* of nucleophilic substitution, not on what the products are. Thus we need to consider two related questions:

1. What properties of the *solvent* influence the rate most?
2. How does the rate-determining step of the *mechanism* respond to this property of the solvent?

Because the S_N1 and S_N2 mechanisms are so different from each other, let's examine each one separately.

Solvent Effects on the Rate of Substitution by the S_N1 Mechanism. Table 8.6 lists the relative rate of solvolysis of *tert*-butyl chloride in several media in order of increasing **dielectric constant** (ϵ). Dielectric constant is a measure of the ability of a material, in this case the solvent, to moderate the force of attraction between oppositely charged particles compared with that of a standard. The standard dielectric is a vacuum, which is assigned a value ϵ of exactly 1. The higher the dielectric constant ϵ, the better the medium is able to support separated positively and negatively charged species. Solvents with high dielectric constants are classified as *polar solvents.* As Table 8.6 illustrates, the rate of solvolysis of *tert*-butyl chloride (which is equal to its rate of ionization) increases dramatically as the dielectric constant of the solvent increases.

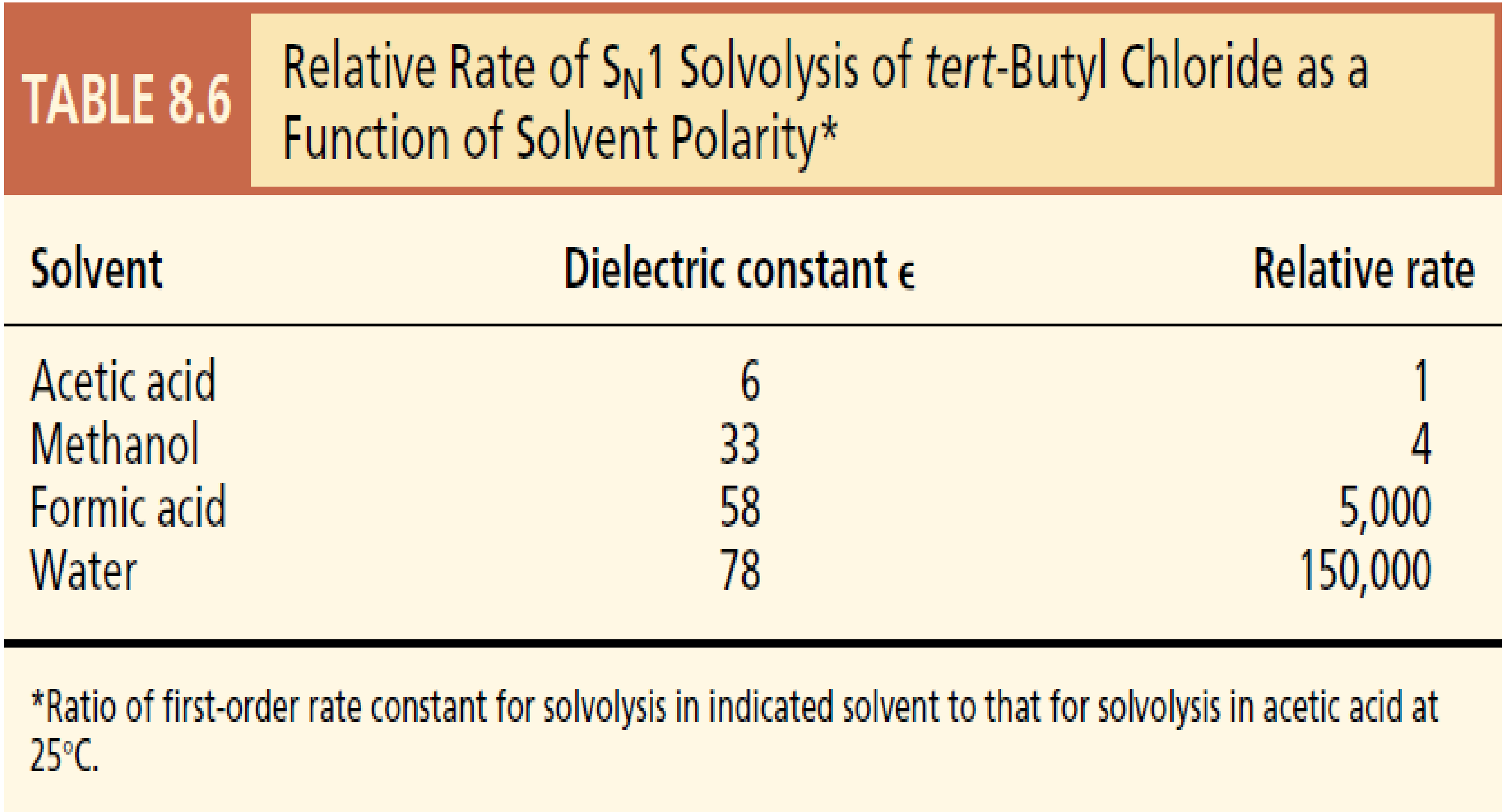
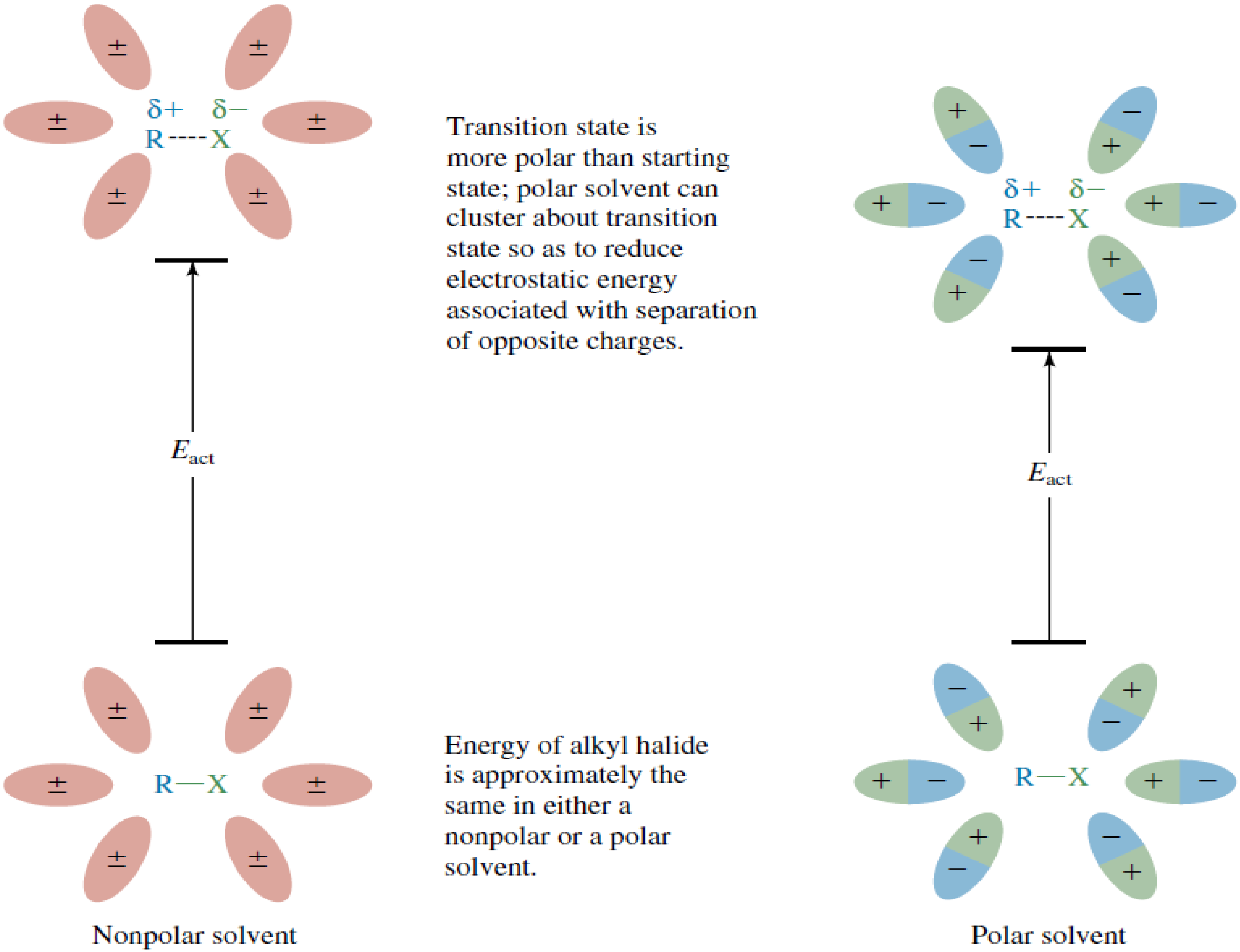


TABLE 8.6 Relative Rate of S_N1 Solvolysis of *tert*-Butyl Chloride as a Function of Solvent Polarity*

Solvent	Dielectric constant ϵ	Relative rate
Acetic acid	6	1
Methanol	33	4
Formic acid	58	5,000
Water	78	150,000

*Ratio of first-order rate constant for solvolysis in indicated solvent to that for solvolysis in acetic acid at 25°C.



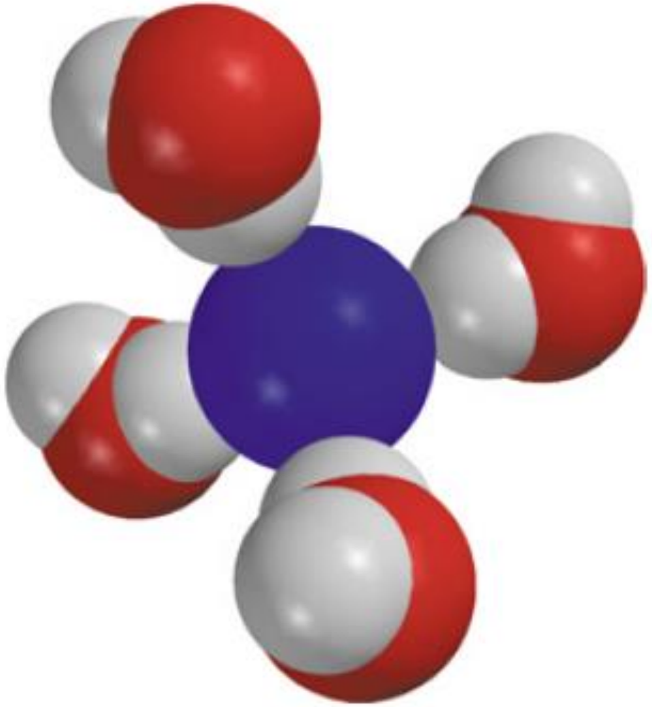
Transition state is more polar than starting state; polar solvent can cluster about transition state so as to reduce electrostatic energy associated with separation of opposite charges.

Energy of alkyl halide is approximately the same in either a nonpolar or a polar solvent.

Solvent Effects on the Rate of Substitution by the S_N2 Mechanism. Polar solvents are required in typical bimolecular substitutions because ionic substances, such as the sodium and potassium salts cited earlier in Table 8.1, are not sufficiently soluble in nonpolar solvents to give a high enough concentration of the nucleophile to allow the reaction to occur at a rapid rate. Other than the requirement that the solvent be polar enough to dissolve ionic compounds, however, the effect of solvent polarity on the rate of S_N2 reactions is small. What is most important is whether or not the polar solvent is **protic** or **aprotic.**

Water (HOH), alcohols (ROH), and carboxylic acids (RCO_2H) are classified as *polar protic solvents;* they all have OH groups that allow them to form hydrogen bonds to anionic nucleophiles as shown in Figure 8.10. Solvation forces such as these stabilize the anion and suppress its nucleophilicity. *Aprotic solvents,* on the other hand, lack OH groups and do not solvate anions very strongly, leaving them much more able to express their nucleophilic character. Table 8.7 compares the second-order rate constants k for S_N2 substitution of 1-bromobutane by azide ion (a good nucleophile) in some common polar aprotic solvents with the corresponding k's for the much slower reactions observed in the polar protic solvents methanol and water.

$$\underset{\text{1-Bromobutane}}{CH_3CH_2CH_2CH_2Br} + \underset{\text{Azide ion}}{N_3^-} \longrightarrow \underset{\text{1-Azidobutane}}{CH_3CH_2CH_2CH_2N_3} + \underset{\text{Bromide ion}}{Br^-}$$



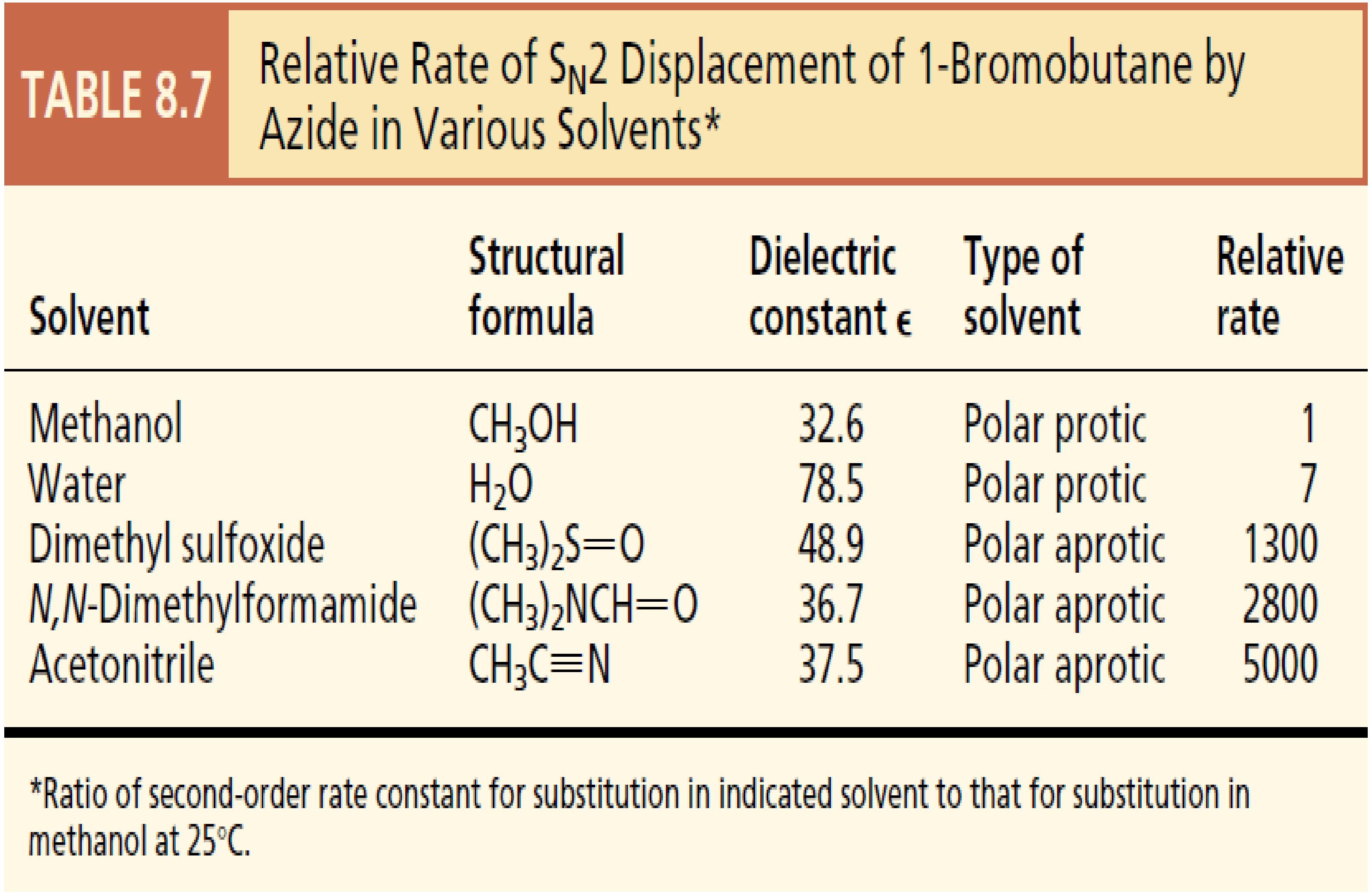


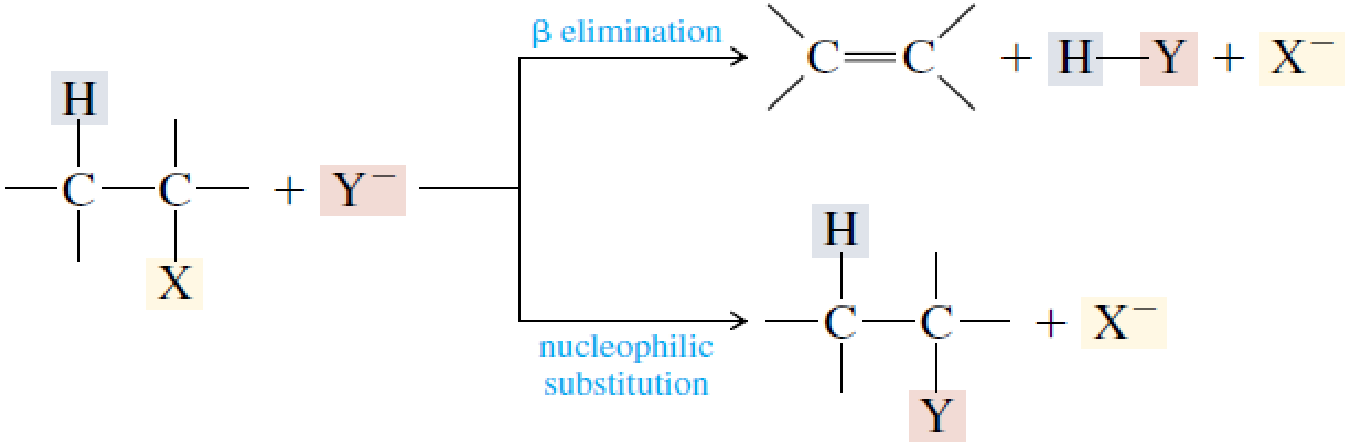
TABLE 8.7 Relative Rate of S_N2 Displacement of 1-Bromobutane by Azide in Various Solvents*

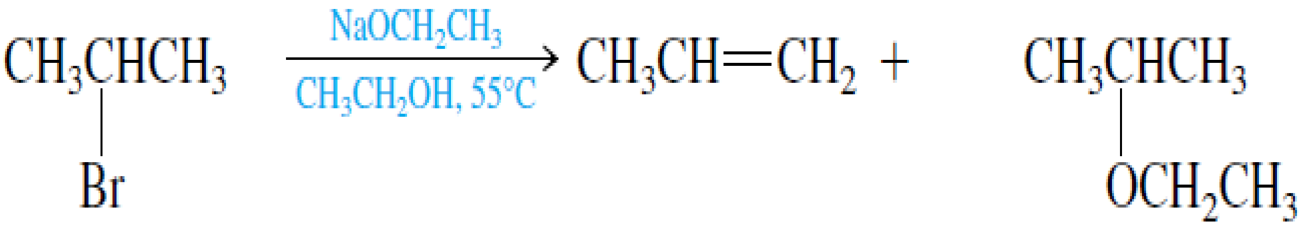
Solvent	Structural formula	Dielectric constant ϵ	Type of solvent	Relative rate
Methanol	CH_3OH	32.6	Polar protic	1
Water	H_2O	78.5	Polar protic	7
Dimethyl sulfoxide	$(CH_3)_2S{=}O$	48.9	Polar aprotic	1300
N,*N*-Dimethylformamide	$(CH_3)_2NCH{=}O$	36.7	Polar aprotic	2800
Acetonitrile	$CH_3C{\equiv}N$	37.5	Polar aprotic	5000

*Ratio of second-order rate constant for substitution in indicated solvent to that for substitution in methanol at 25°C.

$$CH_3(CH_2)_4CH_2X + NaCN \longrightarrow CH_3(CH_2)_4CH_2CN + NaX$$

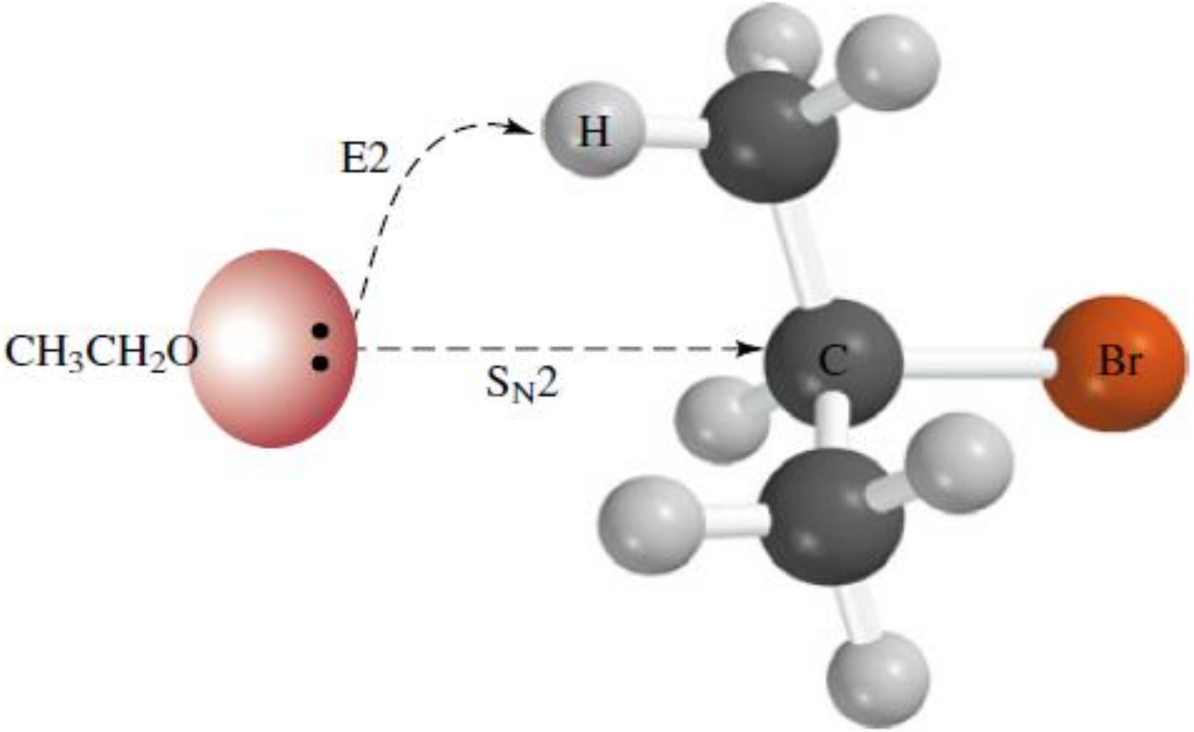
Hexyl halide Sodium cyanide Hexyl cyanide Sodium halide





$$\underset{\displaystyle Br}{CH_3CHCH_3} \xrightarrow[CH_3CH_2OH,\ 55°C]{NaOCH_2CH_3} CH_3CH{=}CH_2 + \underset{\displaystyle OCH_2CH_3}{CH_3CHCH_3}$$

Isopropyl bromide Propene (87%) Ethyl isopropyl ether (13%)


E2
H
CH$_3$CH$_2$O
C
Br
S$_N$2

$$CH_3CH_2CH_2Br \xrightarrow[CH_3CH_2OH,\ 55°C]{NaOCH_2CH_3} CH_3CH{=}CH_2 + CH_3CH_2CH_2OCH_2CH_3$$

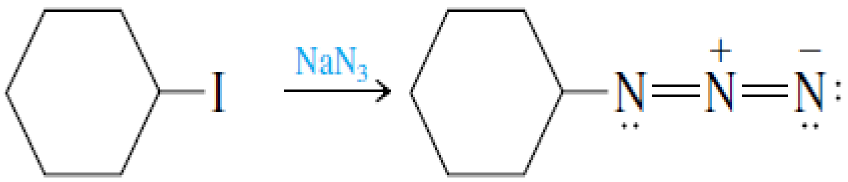
Propyl bromide   Propene (9%)   Ethyl propyl ether (91%)

$$CH_3(CH_2)_{15}CH_2CH_2Br \xrightarrow[(CH_3)_3COH,\ 40°C]{KOC(CH_3)_3} CH_3(CH_2)_{15}CH{=}CH_2 + CH_3(CH_2)_{15}CH_2CH_2OC(CH_3)_3$$

1-Bromooctadecane   1-Octadecene (87%)   *tert*-Butyl octadecyl ether (13%)

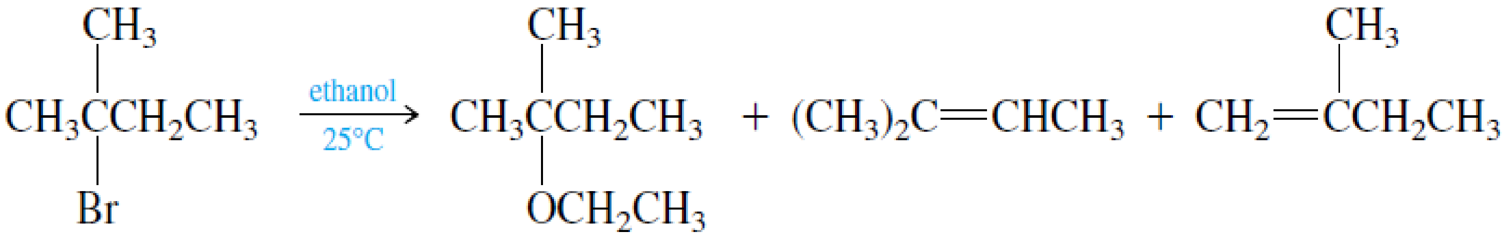
$$\underset{\displaystyle Cl}{CH_3\underset{|}{C}H}(CH_2)_5CH_3 \xrightarrow[DMSO]{KCN} \underset{\displaystyle CN}{CH_3\underset{|}{C}H}(CH_2)_5CH_3$$

2-Chlorooctane   2-Cyanooctane (70%)



Cyclohexyl iodide

Cyclohexyl azide (75%)



$$CH_3\underset{\displaystyle Br}{\overset{\displaystyle CH_3}{C}}CH_2CH_3 \xrightarrow[25^\circ\text{C}]{\text{ethanol}} CH_3\underset{\displaystyle OCH_2CH_3}{\overset{\displaystyle CH_3}{C}}CH_2CH_3 + (CH_3)_2C{=}CHCH_3 + CH_2{=}\overset{\displaystyle CH_3}{C}CH_2CH_3$$

2-Bromo-2-methyl-butane

2-Ethoxy-2-methylbutane

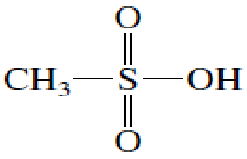
(Major product in absence of sodium ethoxide)

2-Methyl-2-butene

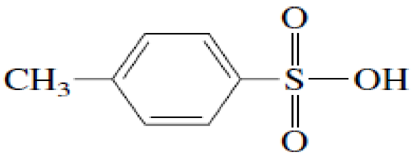
2-Methyl-1-butene

(Alkene mixture is major product in presence of sodium ethoxide)

8.14 SULFONATE ESTERS AS SUBSTRATES IN NUCLEOPHILIC SUBSTITUTION

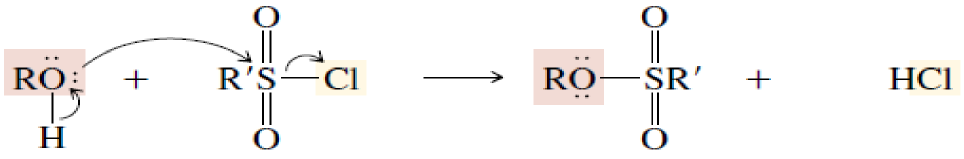


Methanesulfonic acid



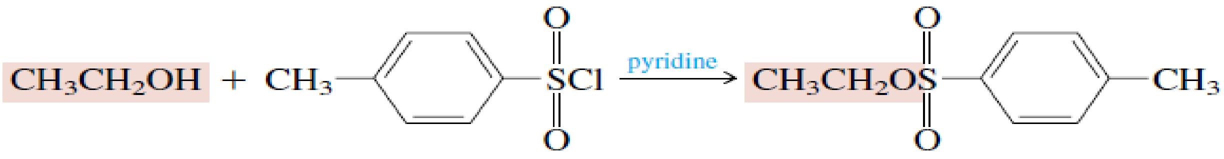
p-Toluenesulfonic acid

Alkyl sulfonates are derivatives of sulfonic acids in which the proton of the hydroxyl group is replaced by an alkyl group. They are prepared by treating an alcohol with the appropriate sulfonyl chloride.



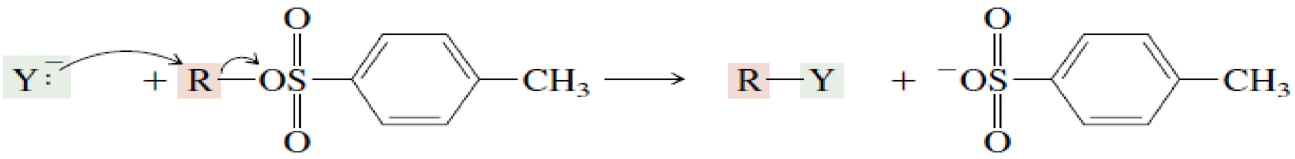
Alcohol Sulfonyl chloride Sulfonate ester Hydrogen chloride

These reactions are usually carried out in the presence of pyridine.



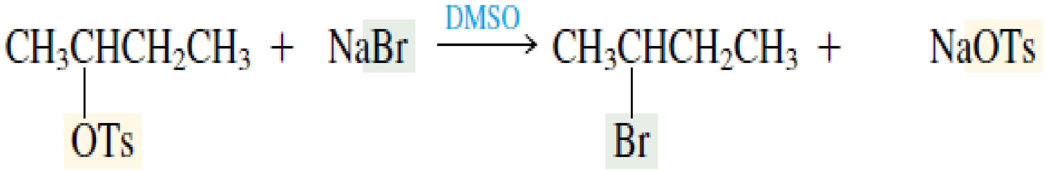
Ethanol *p*-Toluenesulfonyl chloride Ethyl *p*-toluenesulfonate (72%)

Alkyl sulfonate esters resemble alkyl halides in their ability to undergo elimination and nucleophilic substitution.



(3-Cyclopentenyl)methyl
p-toluenesulfonate

4-(Cyanomethyl)cyclo-pentene (86%)



$$\mathrm{CH_3\underset{\underset{OTs}{|}}{C}HCH_2CH_3} + \mathrm{NaBr} \xrightarrow{\mathrm{DMSO}} \mathrm{CH_3\underset{\underset{Br}{|}}{C}HCH_2CH_3} + \mathrm{NaOTs}$$

sec-Butyl
p-toluenesulfonate

Sodium
bromide

sec-Butyl
bromide (82%)

Sodium
p-toluenesulfonate

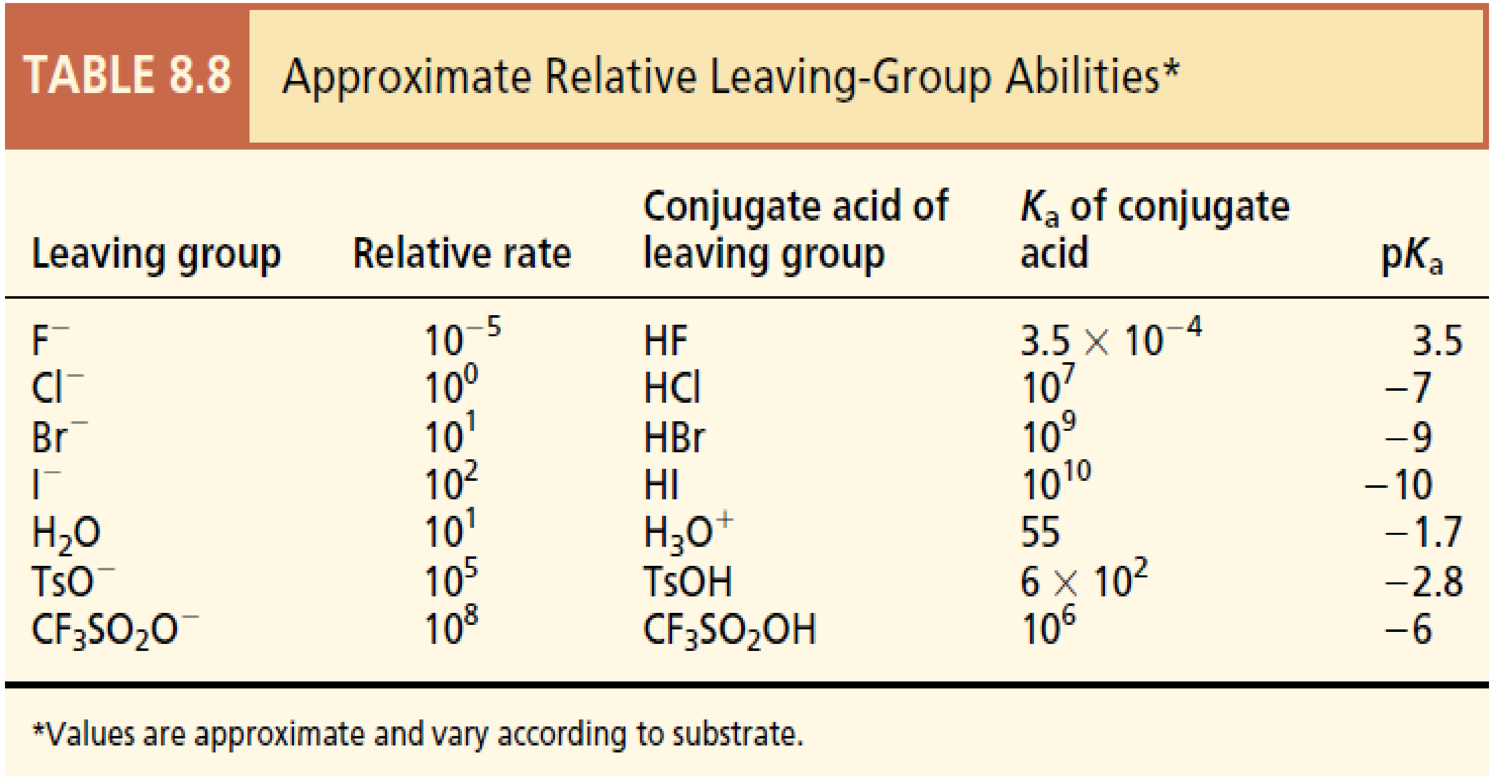
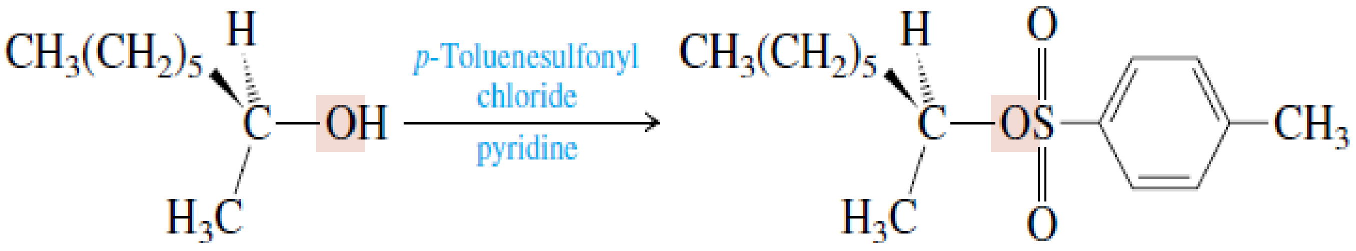


TABLE 8.8 Approximate Relative Leaving-Group Abilities*

Leaving group	Relative rate	Conjugate acid of leaving group	K_a of conjugate acid	pK_a
F^-	10^{-5}	HF	3.5×10^{-4}	3.5
Cl^-	10^{0}	HCl	10^{7}	−7
Br^-	10^{1}	HBr	10^{9}	−9
I^-	10^{2}	HI	10^{10}	−10
H_2O	10^{1}	H_3O^+	55	−1.7
TsO^-	10^{5}	TsOH	6×10^{2}	−2.8
$CF_3SO_2O^-$	10^{8}	CF_3SO_2OH	10^{6}	−6

*Values are approximate and vary according to substrate.



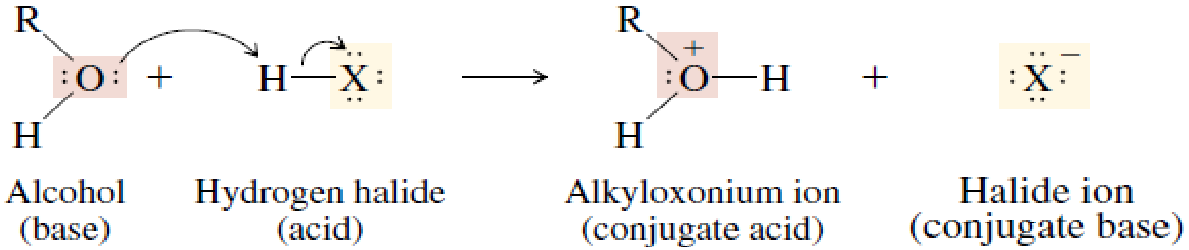
(*S*)-(+)-2-Octanol
$[\alpha]_D^{25}$ +9.9°
(optically pure)

(*S*)-(+)-1-Methylheptyl p-toluenesulfonate
$[\alpha]_D^{25}$ +7.9°
(optically pure)

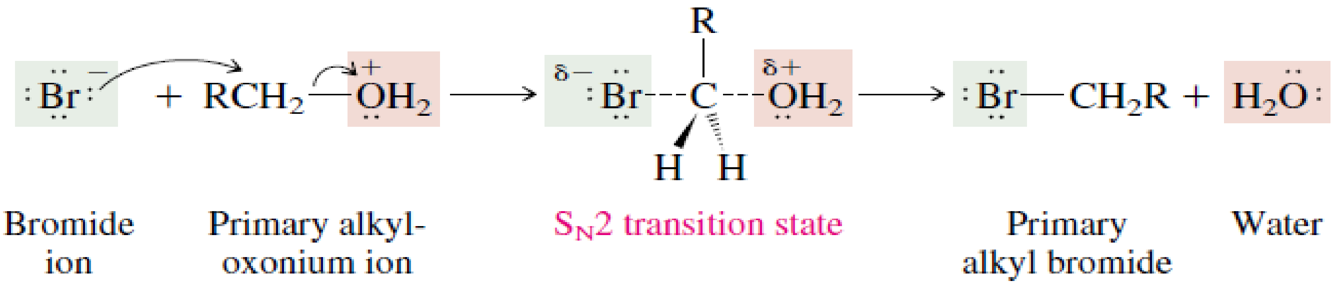
8.15 LOOKING BACK: REACTIONS OF ALCOHOLS WITH HYDROGEN HALIDES

The principles developed in this chapter can be applied to a more detailed examination of the reaction of alcohols with hydrogen halides than was possible when this reaction was first introduced in Chapter 4.

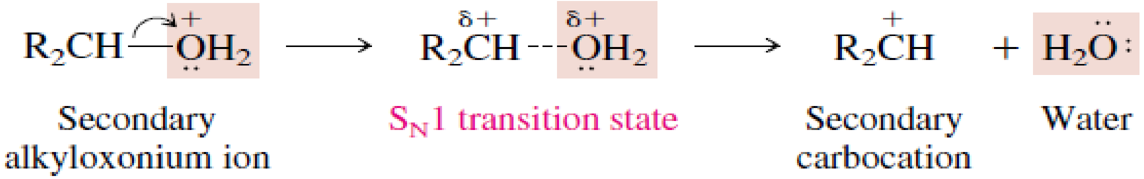
$$\underset{\text{Alcohol}}{\mathrm{ROH}} + \underset{\text{Hydrogen halide}}{\mathrm{HX}} \longrightarrow \underset{\text{Alkyl halide}}{\mathrm{RX}} + \underset{\text{Water}}{\mathrm{H_2O}}$$



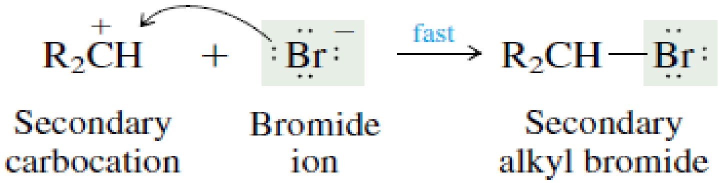
With primary alcohols, the next stage is an S_N2 reaction in which the halide ion, bromide, for example, displaces a molecule of water from the alkyloxonium ion.

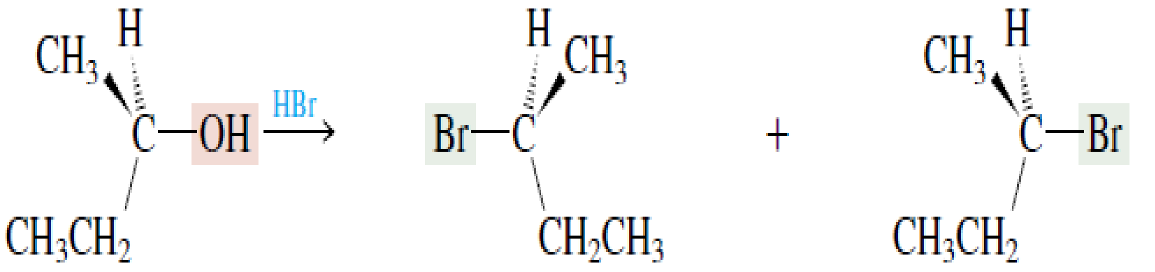


With secondary and tertiary alcohols, this stage is an S_N1 reaction in which the alkyloxonium ion dissociates to a carbocation and water.

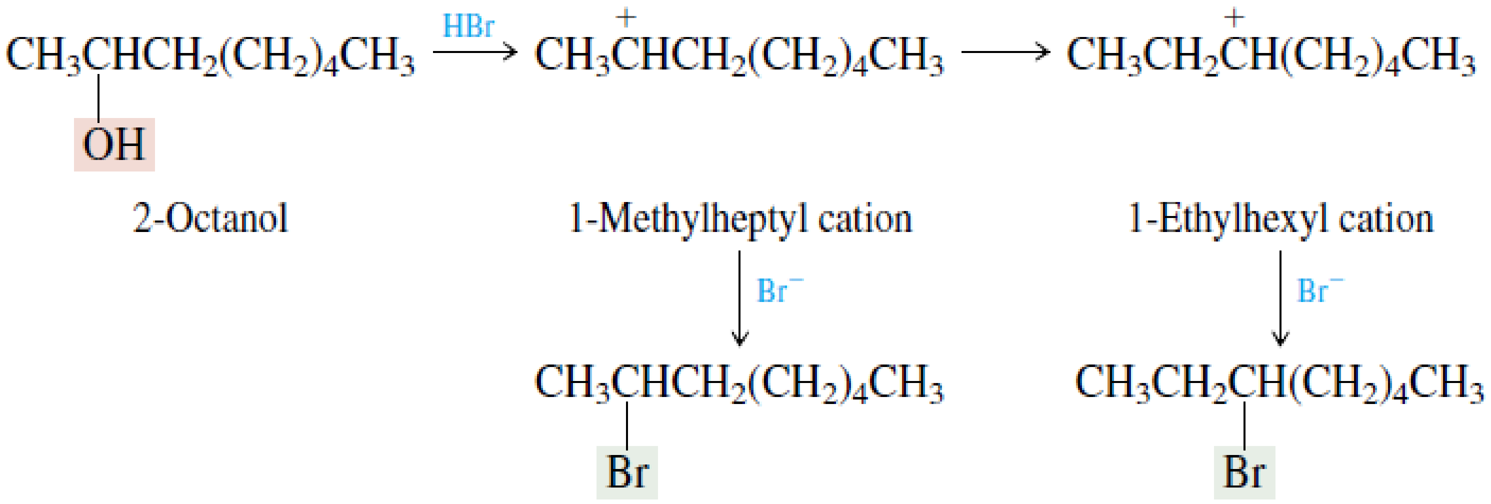


Following its formation, the carbocation is captured by halide.





(*R*)-(−)-2-Butanol (*S*)-(+)-2-Bromobutane (87%) (*R*)-(−)-2-Bromobutane (13%)



2-Octanol

1-Methylheptyl cation

1-Ethylhexyl cation

2-Bromooctane (93%)

3-Bromooctane (7%)

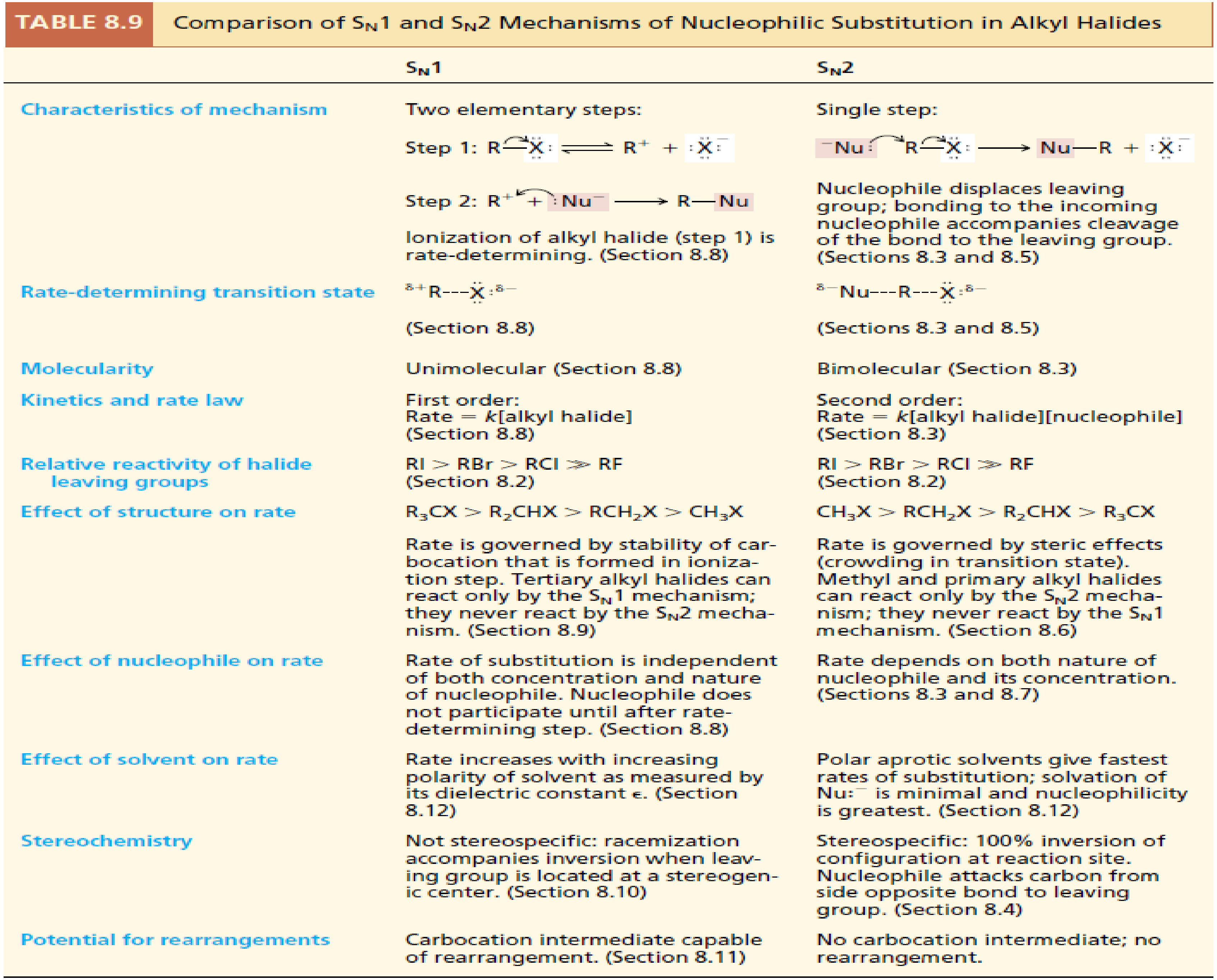


TABLE 8.9 Comparison of S_N1 and S_N2 Mechanisms of Nucleophilic Substitution in Alkyl Halides

	S_N1	S_N2
Characteristics of mechanism	Two elementary steps: Step 1: $R-\ddot{X}: \rightleftharpoons R^+ + :\ddot{X}:^-$ Step 2: $R^+ + :Nu^- \longrightarrow R-Nu$ Ionization of alkyl halide (step 1) is rate-determining. (Section 8.8)	Single step: $^-Nu: \;\; R-\ddot{X}: \longrightarrow Nu-R + :\ddot{X}:^-$ Nucleophile displaces leaving group; bonding to the incoming nucleophile accompanies cleavage of the bond to the leaving group. (Sections 8.3 and 8.5)
Rate-determining transition state	$^{\delta+}R---\ddot{X}:^{\delta-}$ (Section 8.8)	$^{\delta-}Nu---R---\ddot{X}:^{\delta-}$ (Sections 8.3 and 8.5)
Molecularity	Unimolecular (Section 8.8)	Bimolecular (Section 8.3)
Kinetics and rate law	First order: Rate $= k$[alkyl halide] (Section 8.8)	Second order: Rate $= k$[alkyl halide][nucleophile] (Section 8.3)
Relative reactivity of halide leaving groups	$RI > RBr > RCl \gg RF$ (Section 8.2)	$RI > RBr > RCl \gg RF$ (Section 8.2)
Effect of structure on rate	$R_3CX > R_2CHX > RCH_2X > CH_3X$ Rate is governed by stability of carbocation that is formed in ionization step. Tertiary alkyl halides can react only by the S_N1 mechanism; they never react by the S_N2 mechanism. (Section 8.9)	$CH_3X > RCH_2X > R_2CHX > R_3CX$ Rate is governed by steric effects (crowding in transition state). Methyl and primary alkyl halides can react only by the S_N2 mechanism; they never react by the S_N1 mechanism. (Section 8.6)
Effect of nucleophile on rate	Rate of substitution is independent of both concentration and nature of nucleophile. Nucleophile does not participate until after rate-determining step. (Section 8.8)	Rate depends on both nature of nucleophile and its concentration. (Sections 8.3 and 8.7)
Effect of solvent on rate	Rate increases with increasing polarity of solvent as measured by its dielectric constant ϵ. (Section 8.12)	Polar aprotic solvents give fastest rates of substitution; solvation of $Nu:^-$ is minimal and nucleophilicity is greatest. (Section 8.12)
Stereochemistry	Not stereospecific: racemization accompanies inversion when leaving group is located at a stereogenic center. (Section 8.10)	Stereospecific: 100% inversion of configuration at reaction site. Nucleophile attacks carbon from side opposite bond to leaving group. (Section 8.4)
Potential for rearrangements	Carbocation intermediate capable of rearrangement. (Section 8.11)	No carbocation intermediate; no rearrangement.