Nucleophilic Substitution and Elimination Reactions

Self-Study Material

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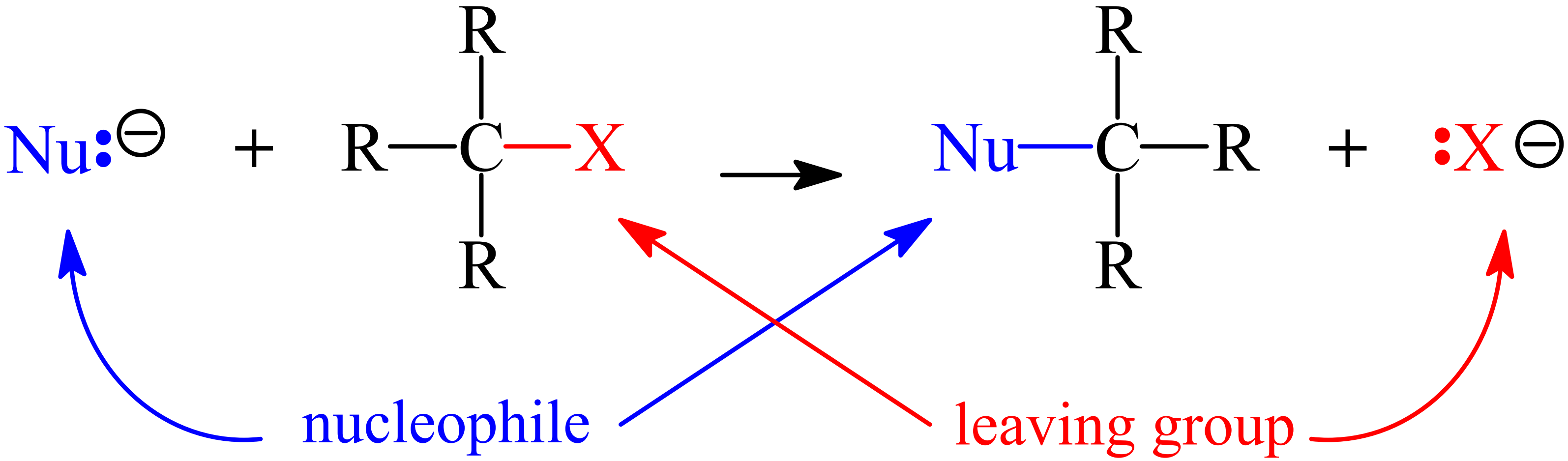
by Daniel Berger

Bluffton College
The Truth Makes Free

Nucleophilic Aliphatic Substitution

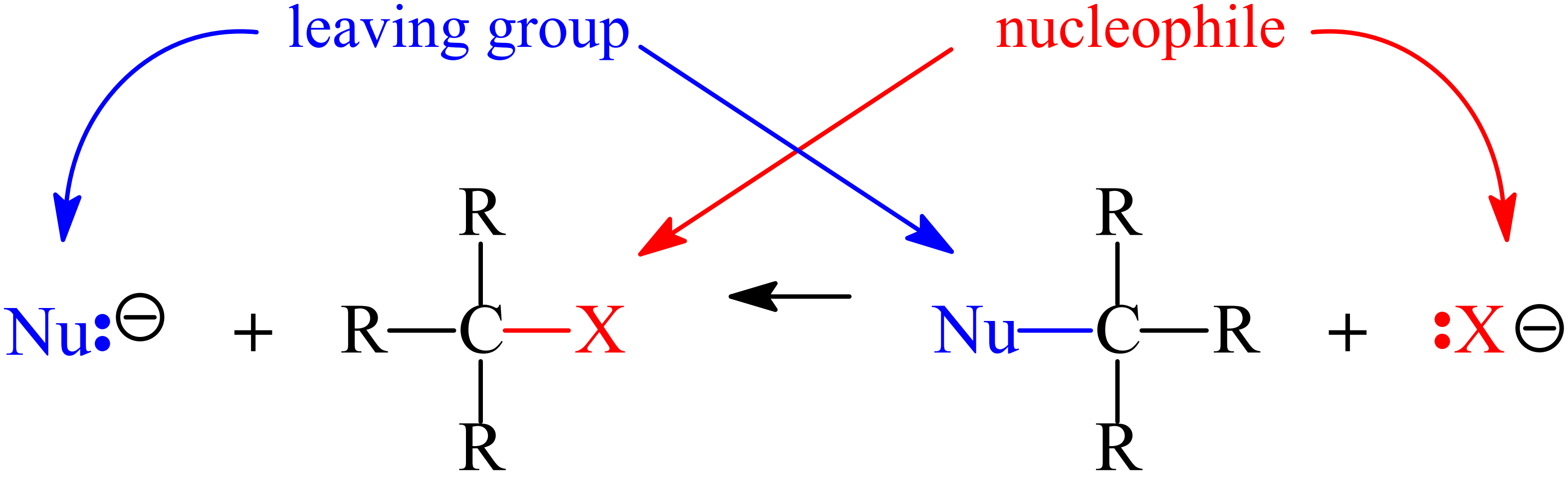


$$\mathrm{Nu}:^{\ominus} + R-\overset{R}{\underset{R}{\mathrm{C}}}-X \longrightarrow \mathrm{Nu}-\overset{R}{\underset{R}{\mathrm{C}}}-R + :X^{\ominus}$$

nucleophile

leaving group

Nucleophilic Aliphatic Substitution



leaving group

nucleophile

$$\mathrm{Nu}{:}^{\ominus} + \mathrm{R{-}\overset{R}{\underset{R}{C}}{-}X} \longleftarrow \mathrm{Nu{-}\overset{R}{\underset{R}{C}}{-}R} + {:}\mathrm{X}^{\ominus}$$

in reverse

Nucleophilic Substitution in Synthesis

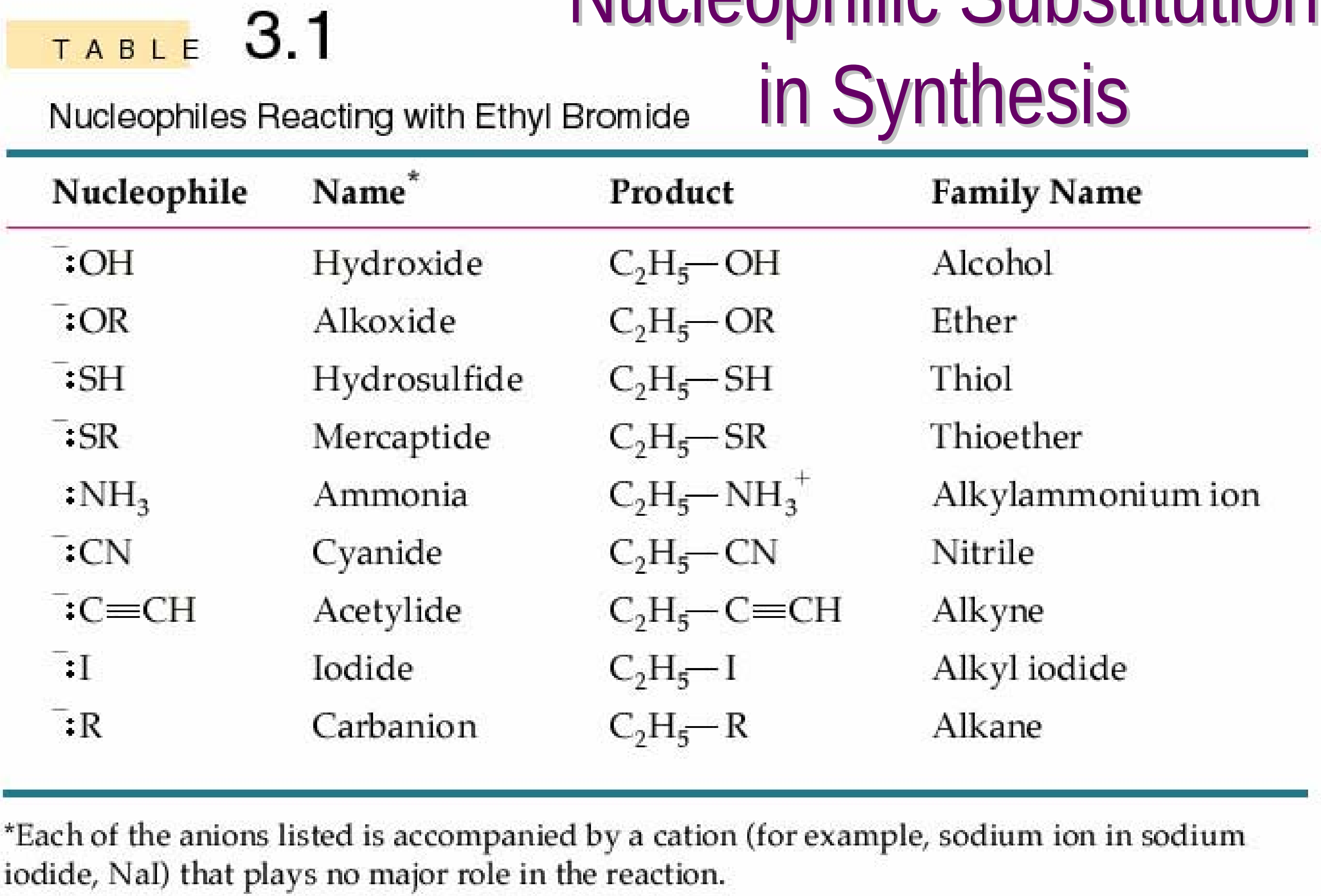


TABLE 3.1

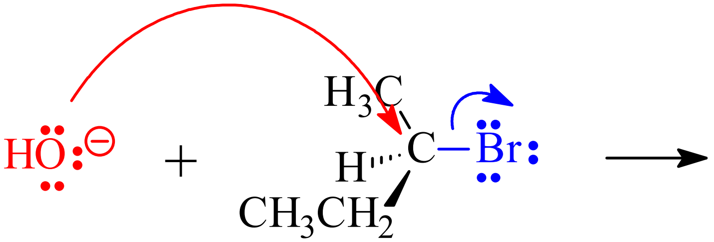
Nucleophiles Reacting with Ethyl Bromide

Nucleophile	Name*	Product	Family Name
$^{-}{:}OH$	Hydroxide	$C_2H_5{-}OH$	Alcohol
$^{-}{:}OR$	Alkoxide	$C_2H_5{-}OR$	Ether
$^{-}{:}SH$	Hydrosulfide	$C_2H_5{-}SH$	Thiol
$^{-}{:}SR$	Mercaptide	$C_2H_5{-}SR$	Thioether
${:}NH_3$	Ammonia	$C_2H_5{-}NH_3^{+}$	Alkylammonium ion
$^{-}{:}CN$	Cyanide	$C_2H_5{-}CN$	Nitrile
$^{-}{:}C{\equiv}CH$	Acetylide	$C_2H_5{-}C{\equiv}CH$	Alkyne
$^{-}{:}I$	Iodide	$C_2H_5{-}I$	Alkyl iodide
$^{-}{:}R$	Carbanion	$C_2H_5{-}R$	Alkane

*Each of the anions listed is accompanied by a cation (for example, sodium ion in sodium iodide, NaI) that plays no major role in the reaction.

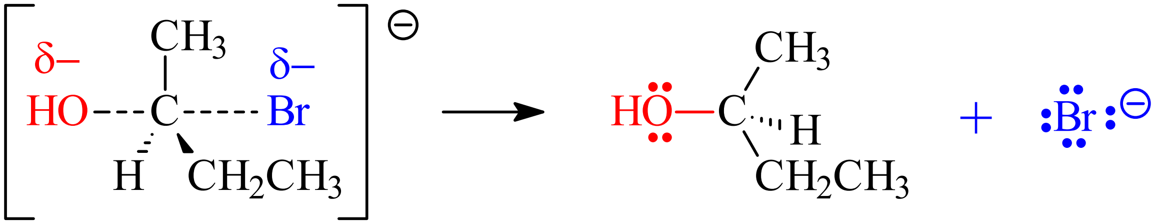
The nucleophile
attacks the alkyl
halide 180° away
from the halogen

The S_N2 Mechanism



(R)-2-bromobutane

The configuration
at carbon is inverted



Transition state with
simultaneous bond breaking
and bond forming

(S)-2-butanol

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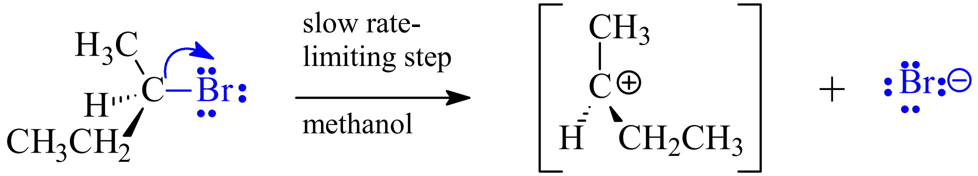
The S_N1 Mechanism

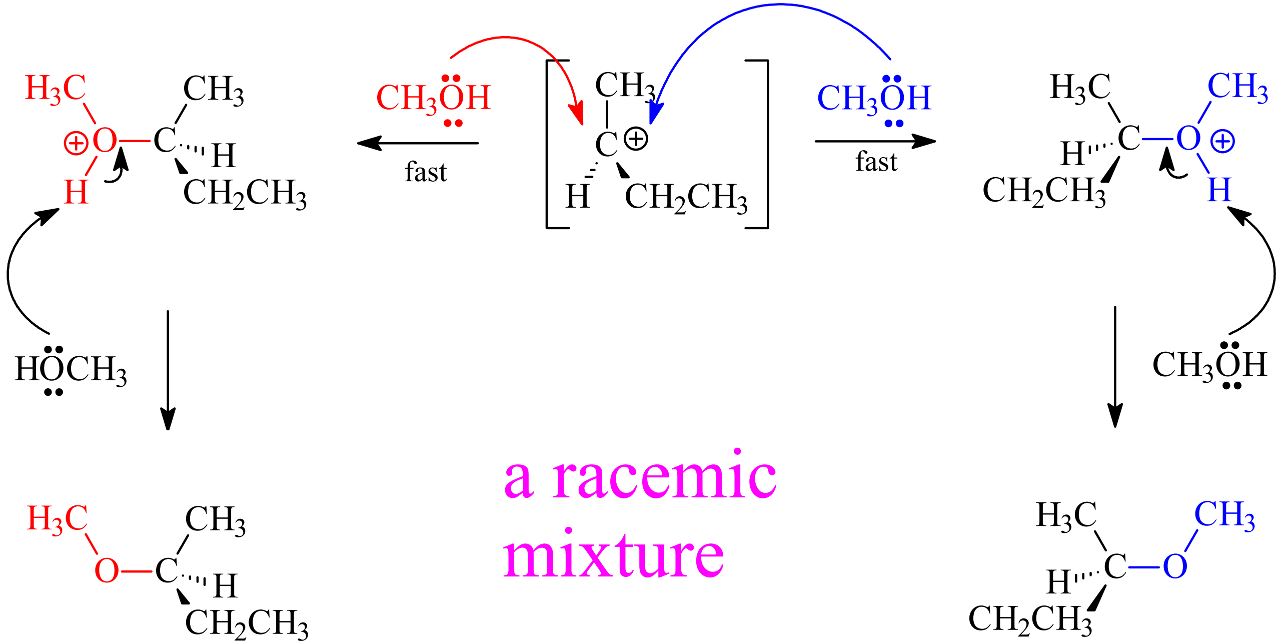
1.



A **planar** carbocation

2.

3.



a racemic mixture

(S)-2-methoxybutane

(R)-2-methoxybutane

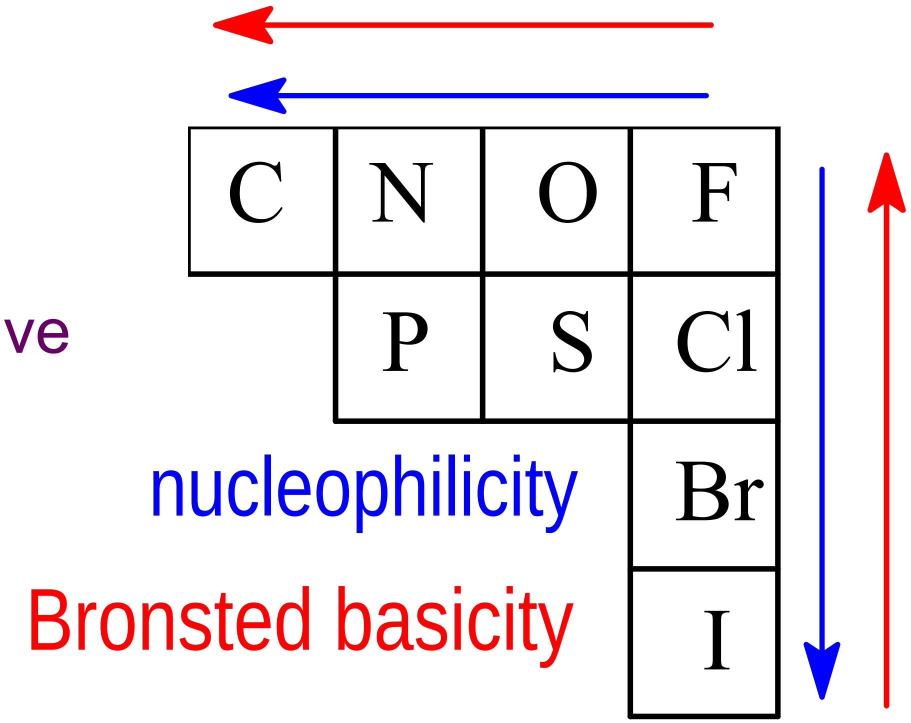
On the web

Whether a reaction is S_N1 or S_N2

1. Structure of nucleophile
   - Also affects side reactions
2. Structure of alkyl halide substrate
3. Structure of leaving group

What makes a good nucleophile

- Negative charge
  - $OH^- > H_2O$
- Polarizability
  - Less electronegative
  - Larger
- Basicity
  - Brønsted
  - Lewis

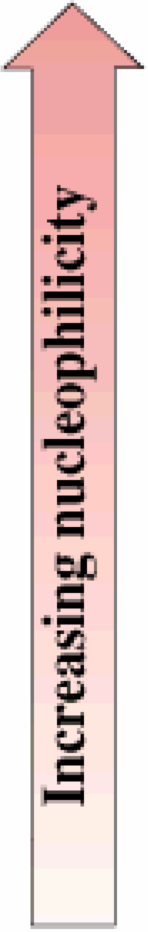


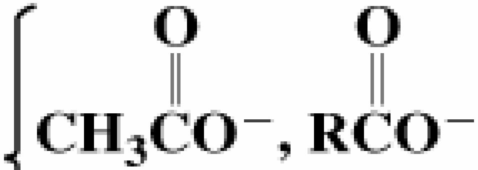
C	N	O	F
	P	S	Cl
			Br
			I

nucleophilicity

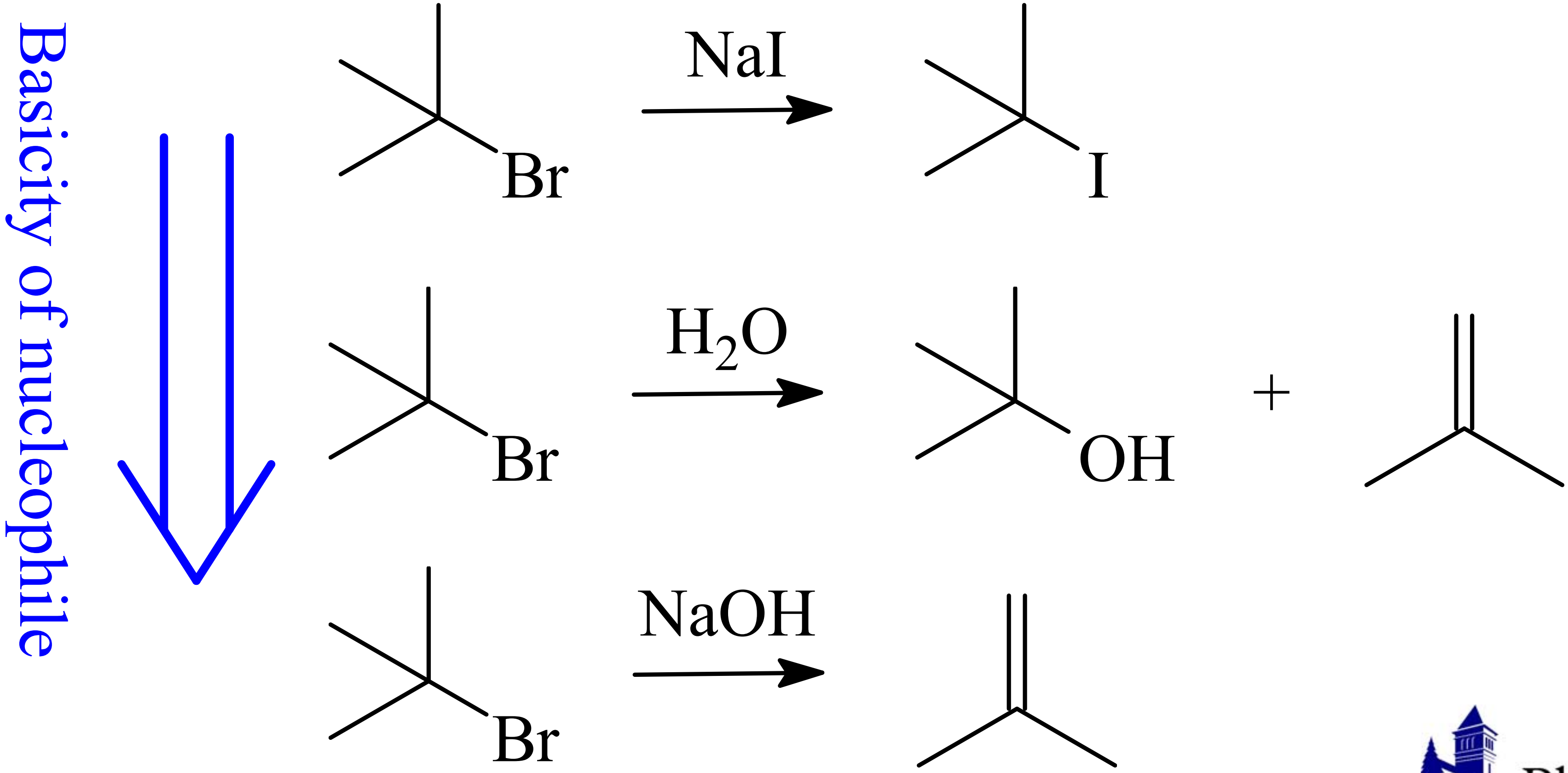
Bronsted basicity

Common nucleophiles and their relative nucleophilicities



Effectiveness as a nucleophile	Nucleophile
strong	Br^-, I^- HO^-, CH_3O^-, RO^- CN^-, N_3^- CH_3S^-, RS^-
moderate	 $CH_3\overset{O}{\overset{\|}{C}}O^-$, $R\overset{O}{\overset{\|}{C}}O^-$ CH_3SH, RSH, R_2S NH_3, RNH_2, R_2NH, R_3N
weak	H_2O CH_3OH, ROH  $CH_3\overset{O}{\overset{\|}{C}}OH$, $R\overset{O}{\overset{\|}{C}}OH$

Side reactions in the SN1 mechanism

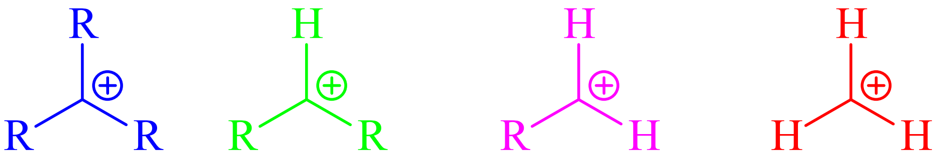


Whether a reaction is S_N1 or S_N2

1. Structure of nucleophile
    - Also affects side reactions
2. Structure of alkyl halide substrate
3. Structure of leaving group

Structure of Alkyl Halide

Governed by electronic factors



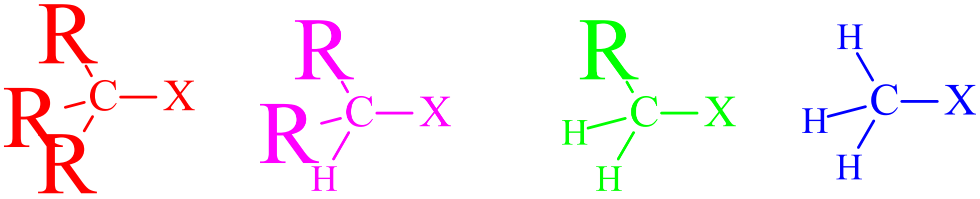
S_N1

Increasing stability of carbocation intermediate

R_3CX (tertiary) R_2CHX (secondary) RCH_2X (primary) CH_3X (methyl)

Increasing ease of access to site of reaction

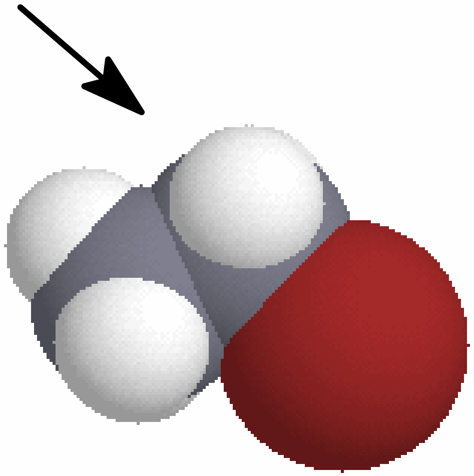
S_N2



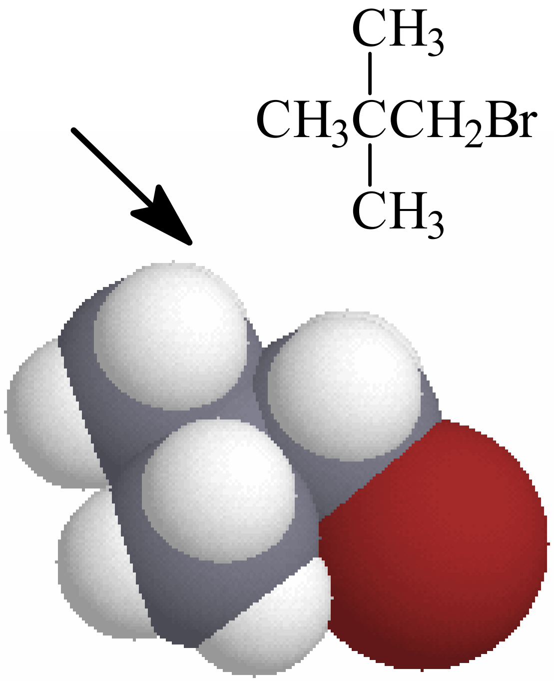
Governed by steric factors

Steric Hindrance of S_N2

CH_3CH_2Br



Rate = 1



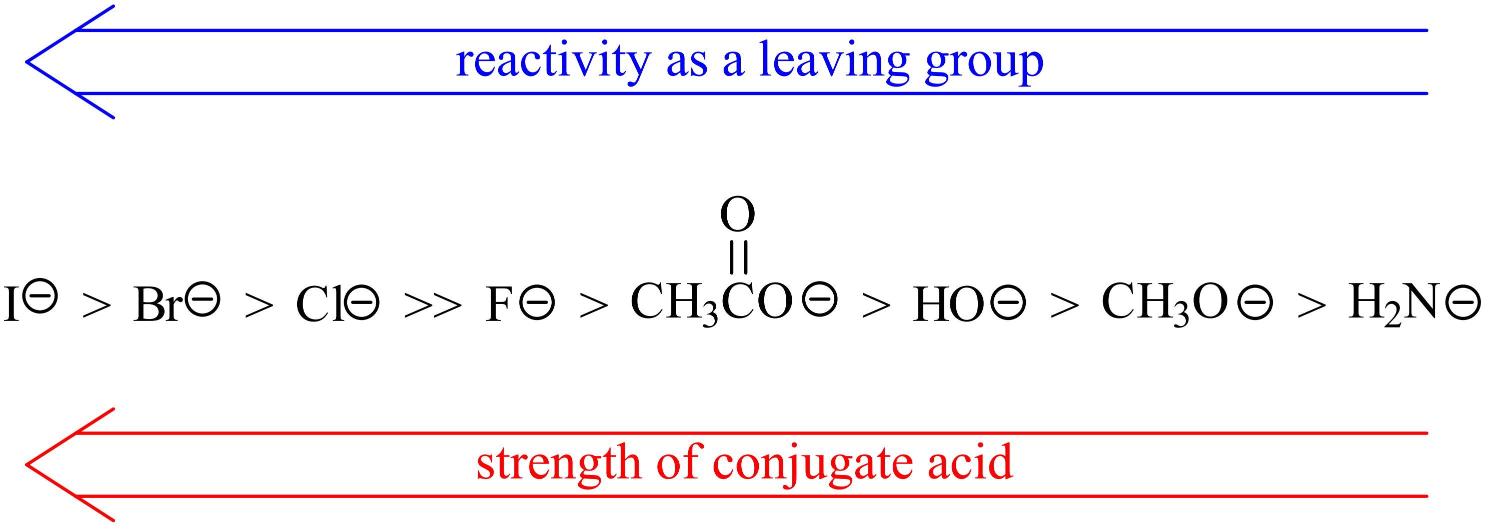
$$\begin{array}{c} CH_3 \\ | \\ CH_3CCH_2Br \\ | \\ CH_3 \end{array}$$

Rate = 10^{-30}

Whether a reaction is S_N1 or S_N2

1. Structure of nucleophile
   - Also affects side reactions
2. Structure of alkyl halide substrate
3. Structure of leaving group

Leaving Group Ability Correlates with Acid Strength



reactivity as a leaving group

$$\mathrm{I}^{\ominus} > \mathrm{Br}^{\ominus} > \mathrm{Cl}^{\ominus} >> \mathrm{F}^{\ominus} > \mathrm{CH_3}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{O}^{\ominus} > \mathrm{HO}^{\ominus} > \mathrm{CH_3O}^{\ominus} > \mathrm{H_2N}^{\ominus}$$

strength of conjugate acid

Protonated leaving groups are good, because the conjugate acids of neutral molecules are more acidic.

(In other words, the leaving groups are less basic.)

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Nucleophilic substitution will not occur with a poor leaving group!

good leaving groups	**poor leaving groups**
$TsO^- \geq X^- \approx RS^- > HOR \approx HNR_2$	$CN^- > OR^- > NR_2^-$

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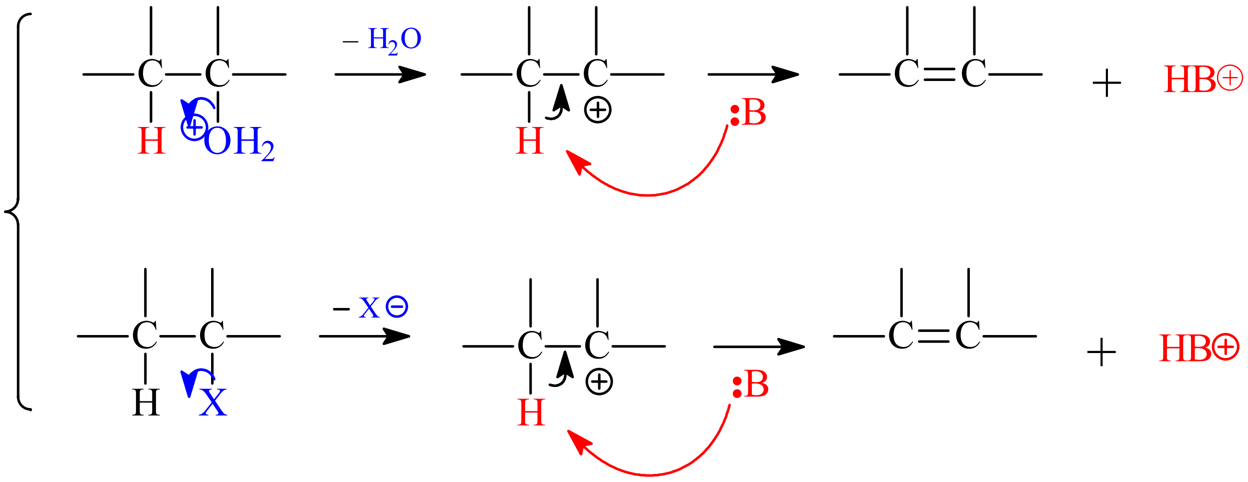
Summary: S_N1 vs. S_N2 Reactions

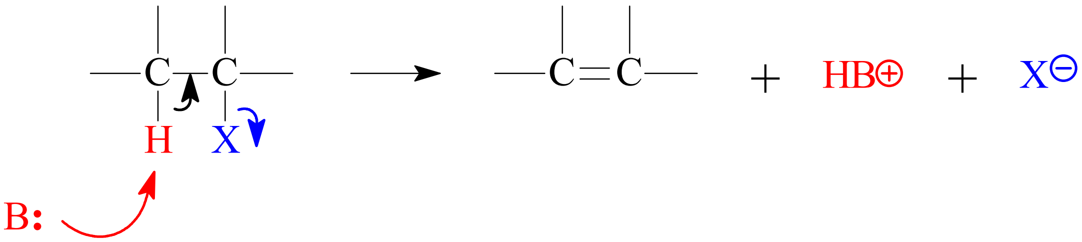
Type of Alkyl Halide	**S_N2**	**S_N1**
methyl CH_3X	**Favored.**	Does not occur because of cation instability.
primary RCH_2X	**Favored.**	Rarely occurs because of cation instability.
secondary R_2CHX	**Favored** in aprotic solvents with good nucleophiles	**Favored** in protic solvents with poor nucleophiles
tertiary R_3CX	Does not occur because of sterics.	**Favored** because of cation stability.
stereocenter	**Inversion**	**Racemization**

β-Elimination

E1



E2



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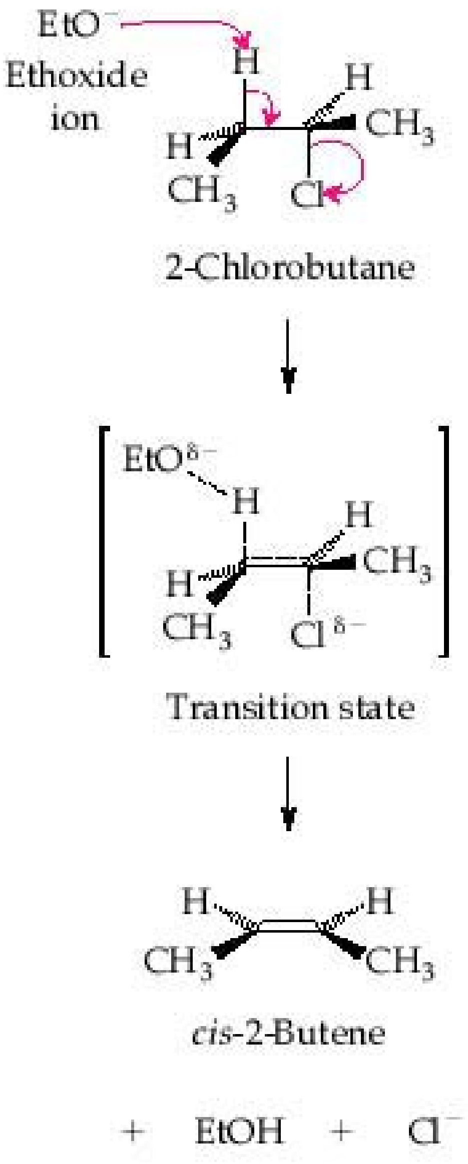
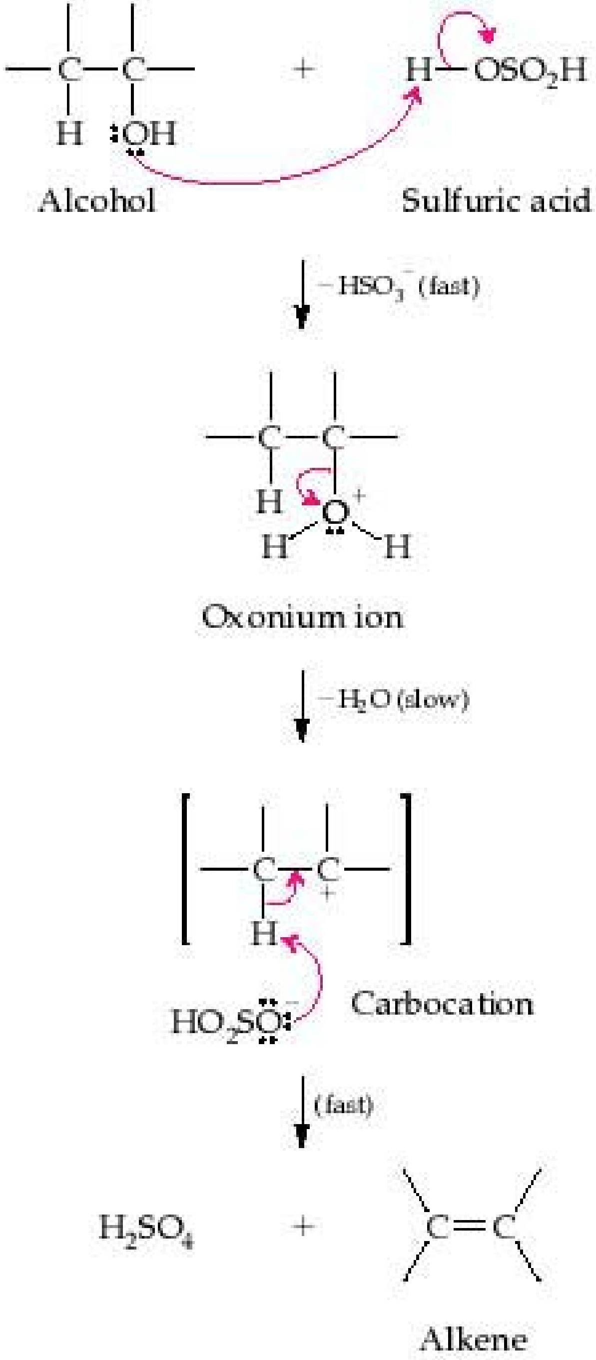
E2 Mechanism



The base attacks a hydrogen on a carbon adjacent to the leaving group (chlorine). The reaction is a single-step reaction, all of the electron shifts portrayed take place approximately simultaneously. Thus, it is often called a *concerted reaction*. The transition state for the reaction has the base, the hydrogen, the two carbons, and the chlorine all lying in a single plane (in this case, the plane of the page). The transition state is depicted with dashed lines representing the bonds that are partially formed or partially broken at that point in the reaction. The ethoxide ion is losing its charge as those electrons are used to form the bond with hydrogen, and the chlorine is acquiring charge as its bond to carbon is being broken.

E1 Mechanism



The alcohol is protonated by a strong acid—in this case, sulfuric acid—to form an oxonium ion. Such protonations are very rapid.

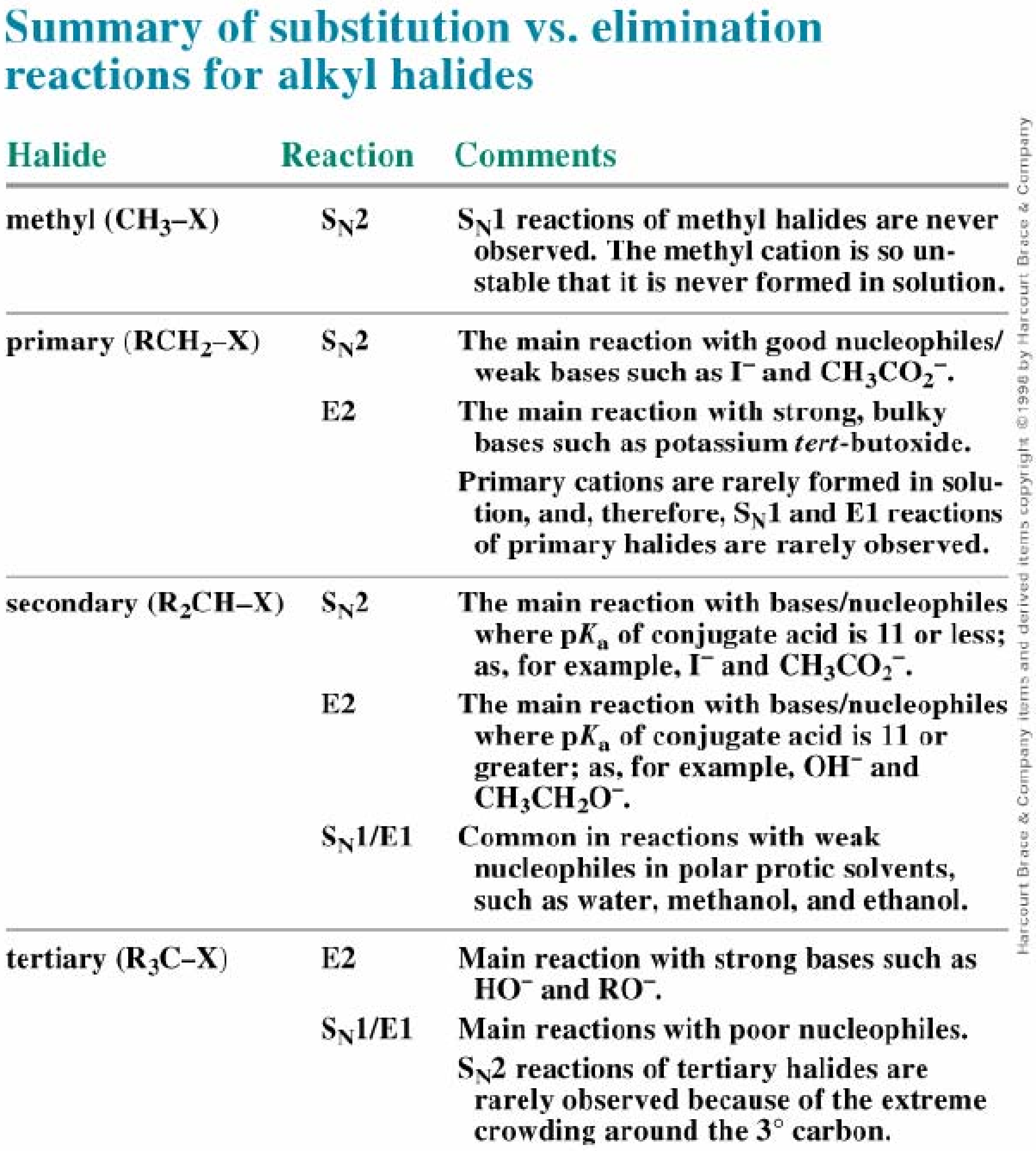
Water is a good leaving group, taking the carbon-oxygen bonding electrons with it and leaving behind a carbocation. Because of the relative instability of a carbocation, this is the slowest step (it requires the most energy).

The positively charged carbon of the carbocation can return to a tetravalent form by acquiring a shared pair of electrons through one of two possible steps: by reacting with a nucleophile (an S_N1 reaction) or by sharing a pair of electrons with the adjacent carbon atom, which obtains the necessary electrons through loss of a proton to bisulfate anion (an E1 reaction, leading to formation of an alkene).

TABLE 6.1

Substitution (S_N2) versus Elimination (E2) Reactions of Alkyl Halides

Reaction	**Favoring Conditions**
Substitution (S_N2)	1. Low reaction temperatures 2. Modest bases/nucleophiles 3. Sterically small bases 4. Relative reactivity of alkyl groups: 1° > 2° > 3°
Elimination (E2)	1. Higher reaction temperatures 2. Strong bases (for example, ethoxide) 3. Bulkier bases (reserve *t*-butoxide for reversing Zaitzev's rule) 4. Relative reactivity of alkyl groups: 3° > 2° > 1°



Summary of substitution vs. elimination reactions for alkyl halides

Halide	Reaction	Comments
methyl ($CH_3{-}X$)	S_N2	S_N1 reactions of methyl halides are never observed. The methyl cation is so unstable that it is never formed in solution.
primary ($RCH_2{-}X$)	S_N2	The main reaction with good nucleophiles/weak bases such as I^- and $CH_3CO_2^-$.
	E2	The main reaction with strong, bulky bases such as potassium *tert*-butoxide.
		Primary cations are rarely formed in solution, and, therefore, S_N1 and E1 reactions of primary halides are rarely observed.
secondary ($R_2CH{-}X$)	S_N2	The main reaction with bases/nucleophiles where pK_a of conjugate acid is 11 or less; as, for example, I^- and $CH_3CO_2^-$.
	E2	The main reaction with bases/nucleophiles where pK_a of conjugate acid is 11 or greater; as, for example, 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 ($R_3C{-}X$)	E2	Main reaction with strong bases such as HO^- and RO^-.
	S_N1/E1	Main reactions with poor nucleophiles.
		S_N2 reactions of tertiary halides are rarely observed because of the extreme crowding around the 3° carbon.