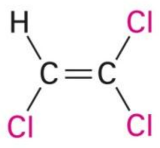
Organohalides: Nucleophilic Substitutions and Eliminations

McMurry,
'Fundamentals of Organic Chemistry', 7th Ed.

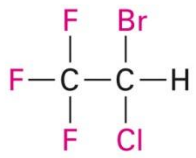
Chapter 7

What Is an Organohalides

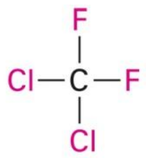
- An organic compound containing at least one carbon-halogen bond (C-X)
  - X (F, Cl, Br, I) replaces H
- Can contain many C-X bonds
- Properties and some uses
  - Fire-resistant solvents
  - Refrigerants
  - Pharmaceuticals and precursors



Trichloroethylene
(a solvent)



Halothane
(an inhaled anesthetic)



Dichlorodifluoromethane
(a refrigerant)

Bromomethane
(a fumigant)

Why this Chapter?

- Reactions involving organohalides are less frequently encountered than other organic compounds, but reactions such as nucleophilic substitutions/eliminations that they undergo will be encountered
- Alkyl halide chemistry is model for mechanistically similar but more complex
- Reactions will be examined closely to see:
  - How they occur
  - What their characteristics are
  - How they can be used

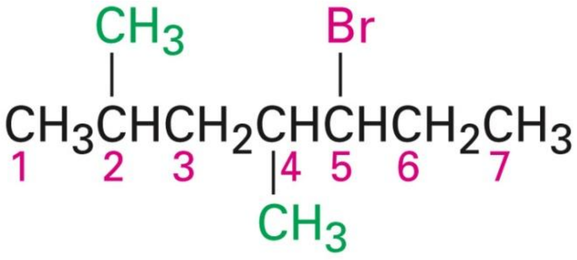
7.1 Naming Alkyl Halides

Step 1. Find longest chain, name it as parent chain

- Contains double or triple bond if present

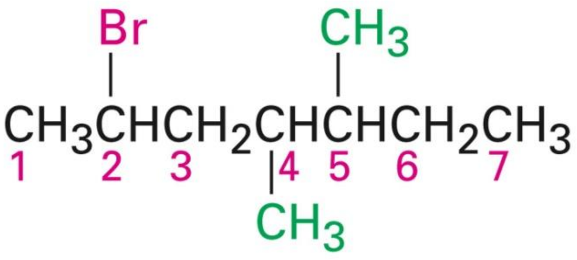
Step 2. Number from the end nearest any substituent (alkyl or halogen)

- Begin at the end nearer the substituent whose name comes first in the alphabet



$$CH_3\overset{CH_3}{\overset{|}{C}}HCH_2\underset{\underset{CH_3}{|}}{C}H\overset{Br}{\overset{|}{C}}HCH_2CH_3$$

5-Bromo-2,4-dimethylheptane

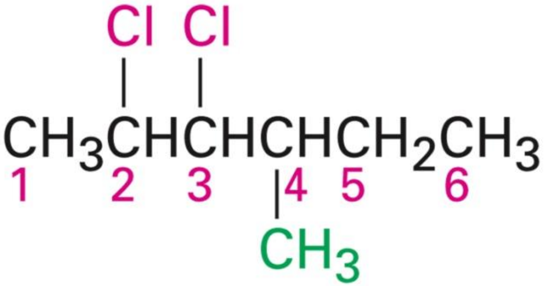


$$CH_3\overset{Br}{\overset{|}{C}}HCH_2\underset{\underset{CH_3}{|}}{C}H\overset{CH_3}{\overset{|}{C}}HCH_2CH_3$$

2-Bromo-4,5-dimethylheptane

Step 3. Write the name

- Use prefixes *di-*, *tri-*, and so forth if more than one of the same substituent is present



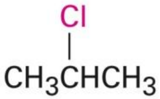
$$CH_3\overset{Cl}{C}H\overset{Cl}{C}H\underset{CH_3}{C}HCH_2CH_3$$

2,3-Dichloro-4-methylhexane

Common names

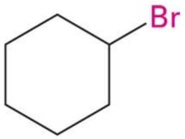
CH_3I

Iodomethane
(or methyl iodide)



$$CH_3\overset{Cl}{C}HCH_3$$

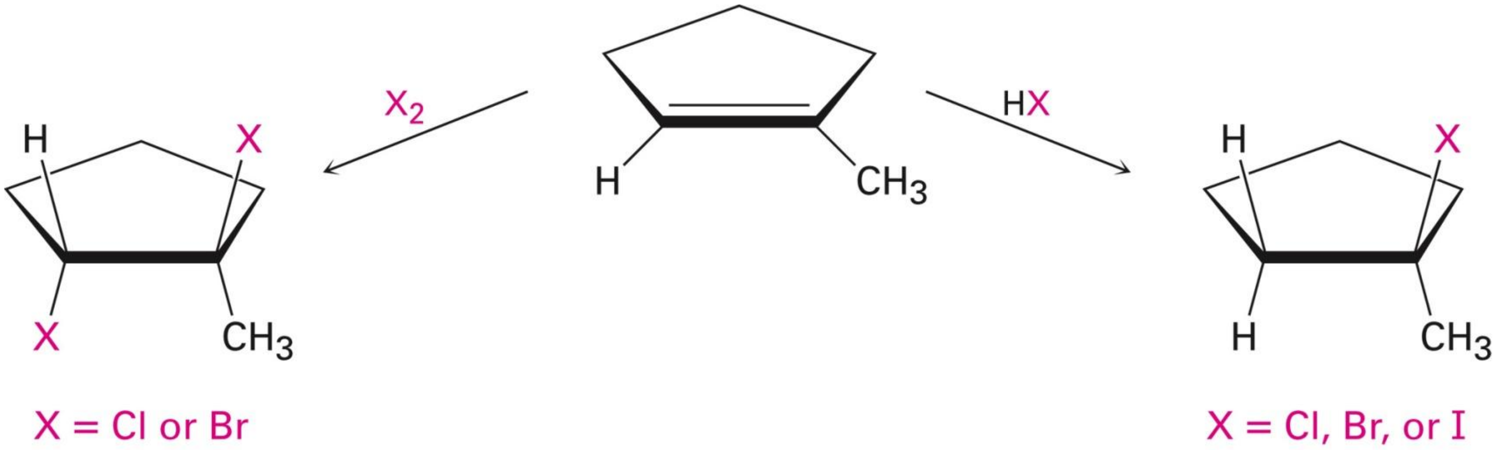
2-Chloropropane
(or isopropyl chloride)



Bromocyclohexane
(or cyclohexyl bromide)

7.2 Preparing Alkyl Halides

- **Alkyl halide from addition of HCl, HBr, HI to alkenes to give Markovnikov product (see Alkenes chapter)**
- **Alkyl dihalide from *anti* addition of bromine or chlorine**

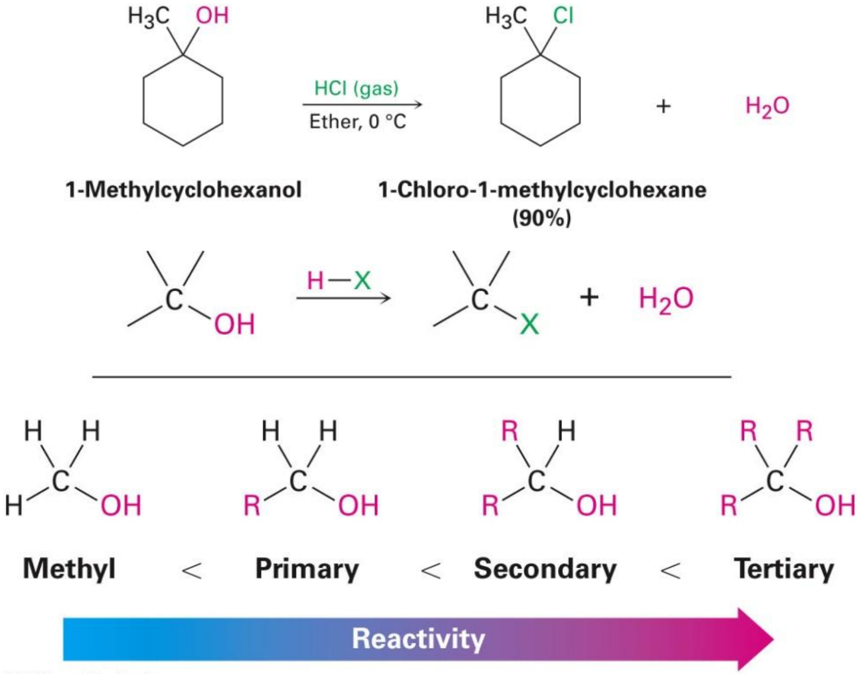


$$CH_4 + Cl_2 \xrightarrow{h\nu} CH_3Cl + HCl$$

Methane **Chloromethane**

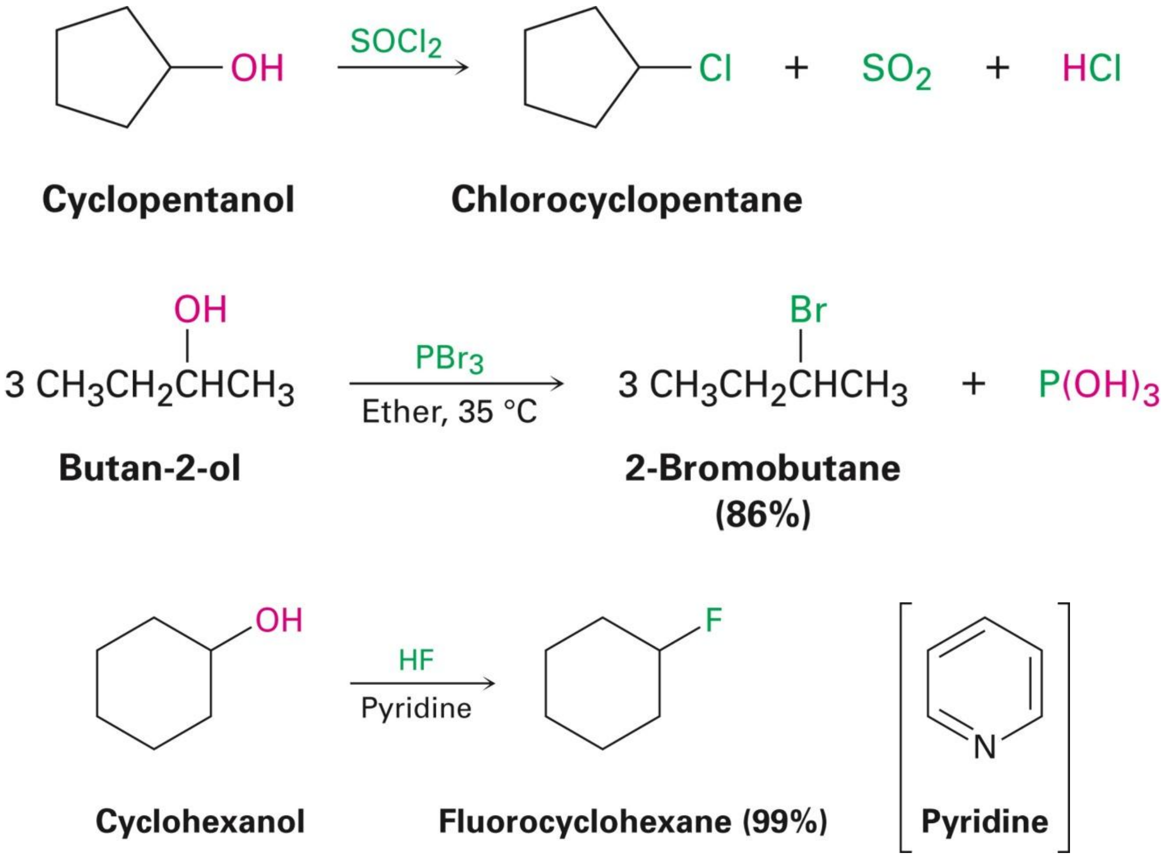
Preparing Alkyl Halides from Alcohols

- Reaction of tertiary C-OH with HX is fast and effective
  - Add HCl or HBr gas into ether solution of tertiary alcohol
- Primary and secondary alcohols react very slowly and often rearrange, so alternative methods are used



Other methods

- **Primary and secondary alcohols**



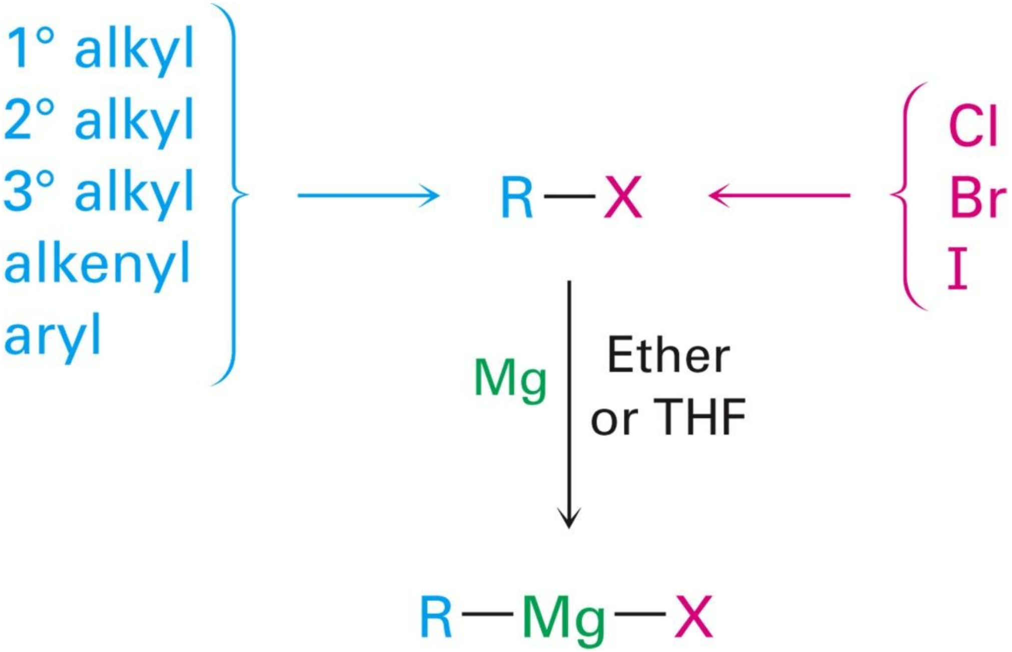
Cyclopentanol **Chlorocyclopentane**

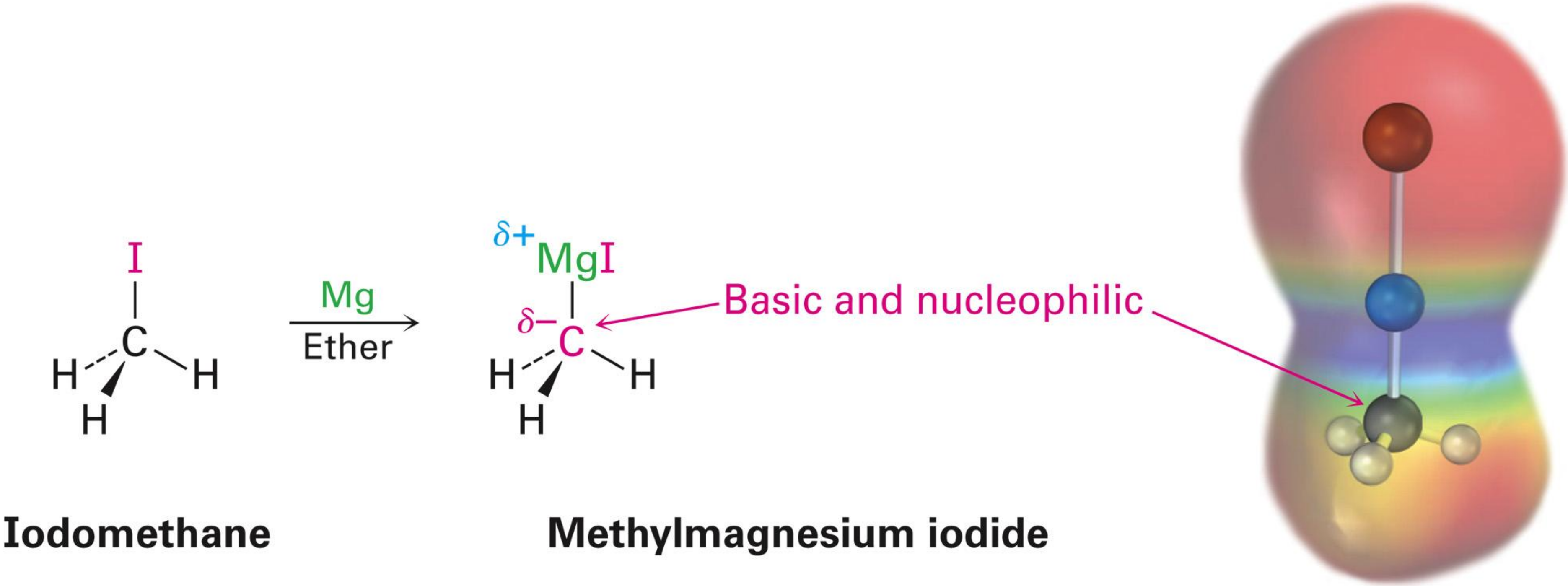
Butan-2-ol **2-Bromobutane (86%)**

Cyclohexanol **Fluorocyclohexane (99%)** **Pyridine**

7.3 Reactions of Alkyl Halides: Grignard Reagents

- Reaction of RX with Mg in ether or THF
- Product is RMgX – an ***organometallic*** compound (alkyl-metal bond)
  - R is alkyl 1°, 2°, 3°, aryl, alkenyl
  - X = Cl, Br, I

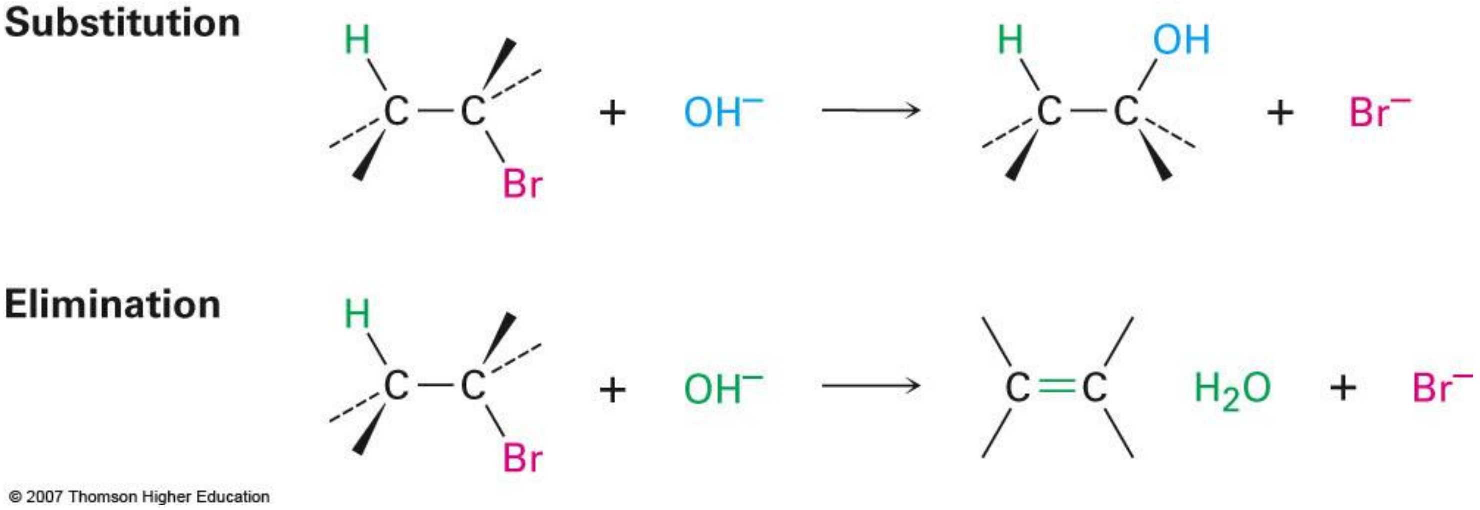




- **A Grignard reagent is formally the magnesium salt, $R_3C^{-+}MgX$ and is thus a carbon anion, or carbanion**

7.4 Nucleophilic Substitution Reactions

- Alkyl halides are polarized at the carbon-halide bond, making the carbon electrophilic
- Nucleophiles will replace the halide in C-X bonds of many alkyl halides (substitution)
- Nucleophiles that are Brønsted bases produce elimination



The Discovery of Nucleophilic Substitution Reactions

- In 1896, Walden showed that (-)-malic acid could be converted to (+)-malic acid by a series of chemical steps with achiral reagents
- This established that optical rotation was directly related to chirality and that it changes with chemical alteration
  - Reaction of (-)-malic acid with PCl_5 gives (+)-chlorosuccinic acid
  - Further reaction with wet silver oxide gives (+)-malic acid
  - The reaction series starting with (+)-malic acid gives (-) acid

Reactions of the Walden Inversion

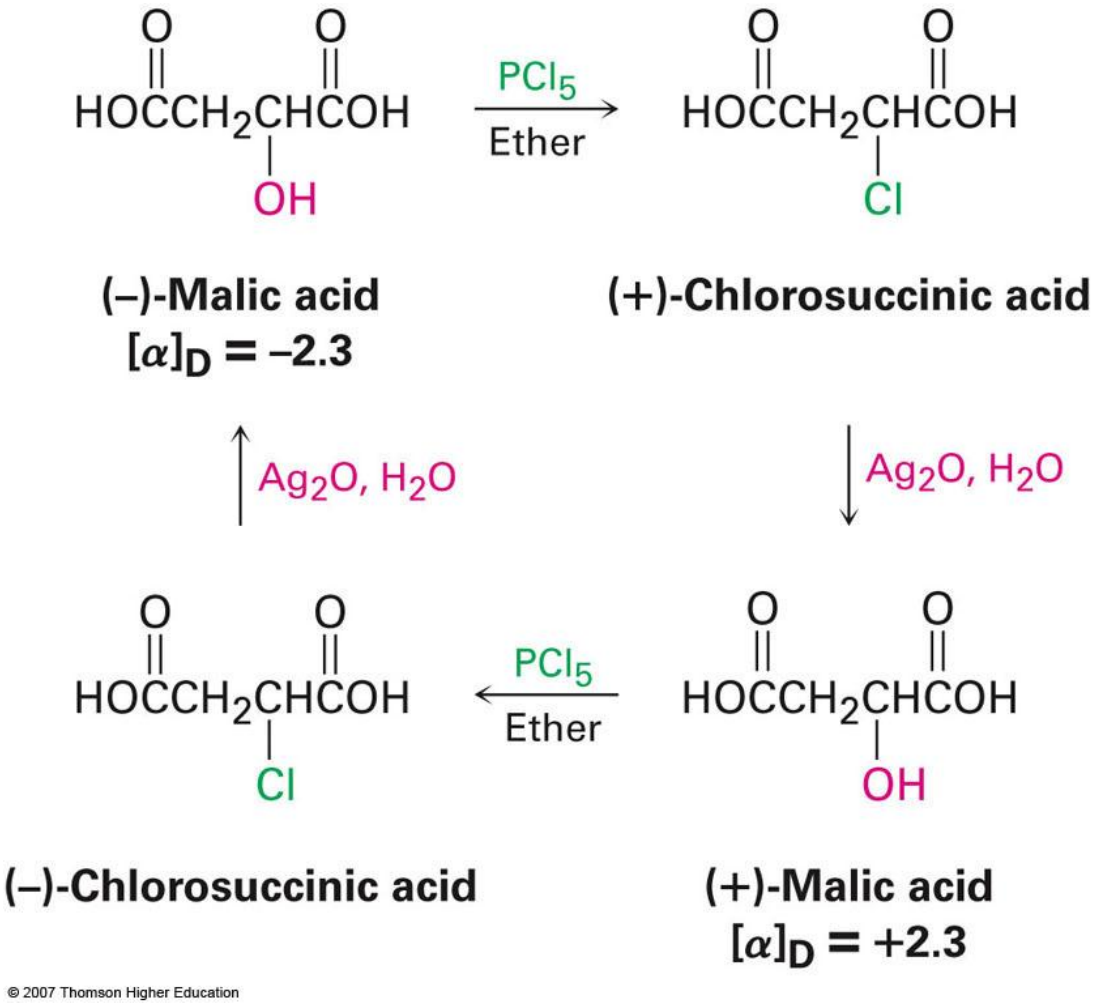


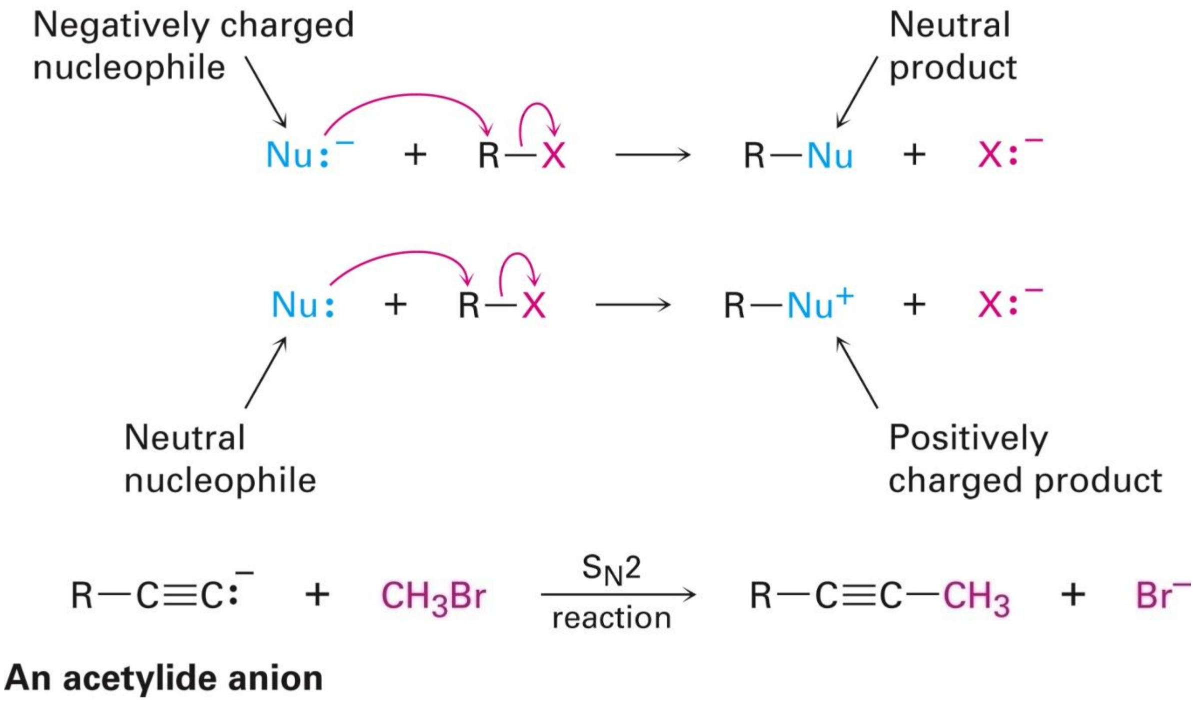
Figure 7.1 Walden’s cycle of reactions interconverting (+)- and (-)-malic acids.

Nucleophilic Substitution: S_N1 or S_N2 Reaction

S = substitution
N (subscript) = nucleophilic
1 or 2

- **Nucleophile and Leaving group**

$$\boxed{R{-}X \quad + \quad Nu{:}^- \quad \longrightarrow \quad R{-}Nu \quad + \quad X{:}^-}$$



An acetylide anion

Table 7.1 Some Nucleophilic Substitution Reactions with Bromomethane

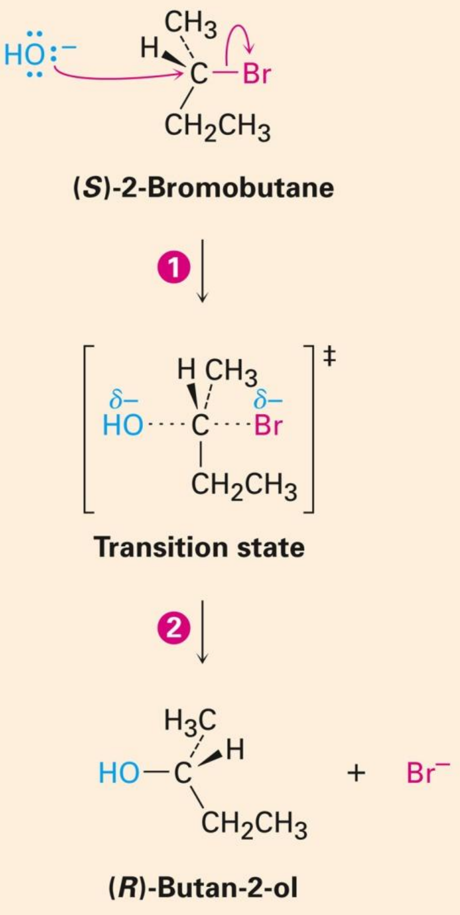
$$Nu:^- + CH_3Br \rightarrow CH_3Nu + Br^-$$

Nucleophile		Product	
Formula	**Name**	**Formula**	**Name**
H_2O	Water	$CH_3OH_2^+$	Methylhydronium ion
$CH_3CO_2^-$	Acetate	$CH_3CO_2CH_3$	Methyl acetate
NH_3	Ammonia	$CH_3NH_3^+$	Methylammonium ion
Cl^-	Chloride	CH_3Cl	Chloromethane
HO^-	Hydroxide	CH_3OH	Methanol
CH_3O^-	Methoxide	CH_3OCH_3	Dimethyl ether
I^-	Iodide	CH_3I	Iodomethane
^-CN	Cyanide	CH_3CN	Acetonitrile
HS^-	Hydrosulfide	CH_3SH	Methanethiol

7.5 Substitution: The S_N2 Reaction

- **Reaction takes place in a single step without intermediates**

Figure 7.2 The mechanism of the S_N2 reaction.

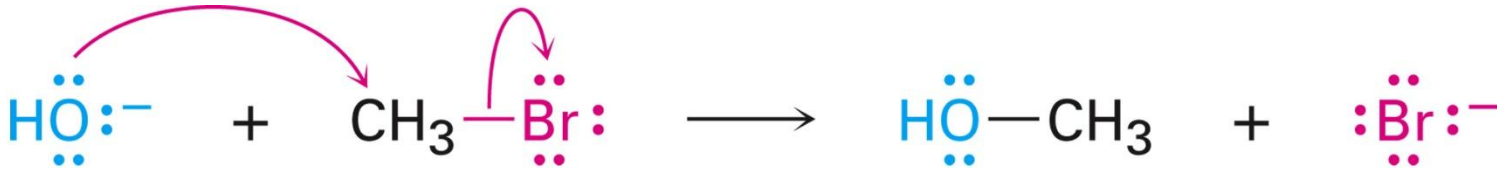


① The nucleophile ⁻OH uses its lone-pair electrons to attack the alkyl halide carbon 180° away from the departing halogen. This leads to a transition state with a partially formed C–OH bond and a partially broken C–Br bond.

② The stereochemistry at carbon is inverted as the C–OH bond forms fully and the bromide ion departs with the electron pair from the former C–Br bond.

Rates of S_N2 Reactions: Bimolecular

- **The rate of the reaction depends on the concentrations of alkyl halide and nucleophile**

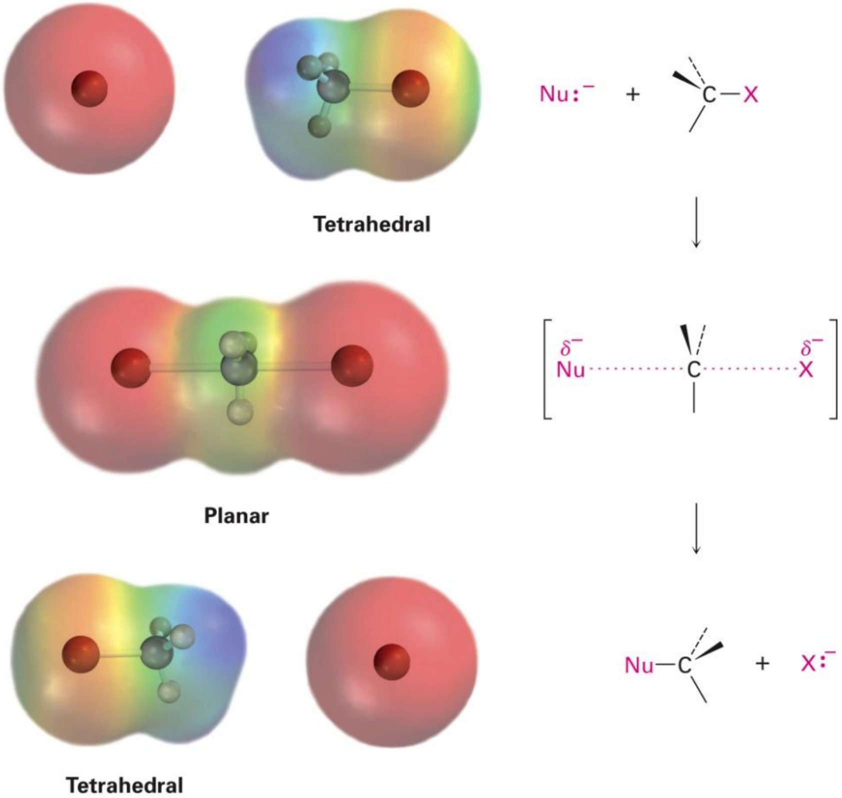


- **rate = k[RX][Nu$^-$]**

Stereochemistry of S_N2 Reactions

- **The transition state of an S_N2 reaction has a planar arrangement of the carbon atom and the remaining three groups**
- **Product with inversion configuration**

Figure 7.3 The transition state of the S_N2 reaction has a planar arrangement of the carbon atom and the remaining three group.



Steric Effects in S_N2 Reactions

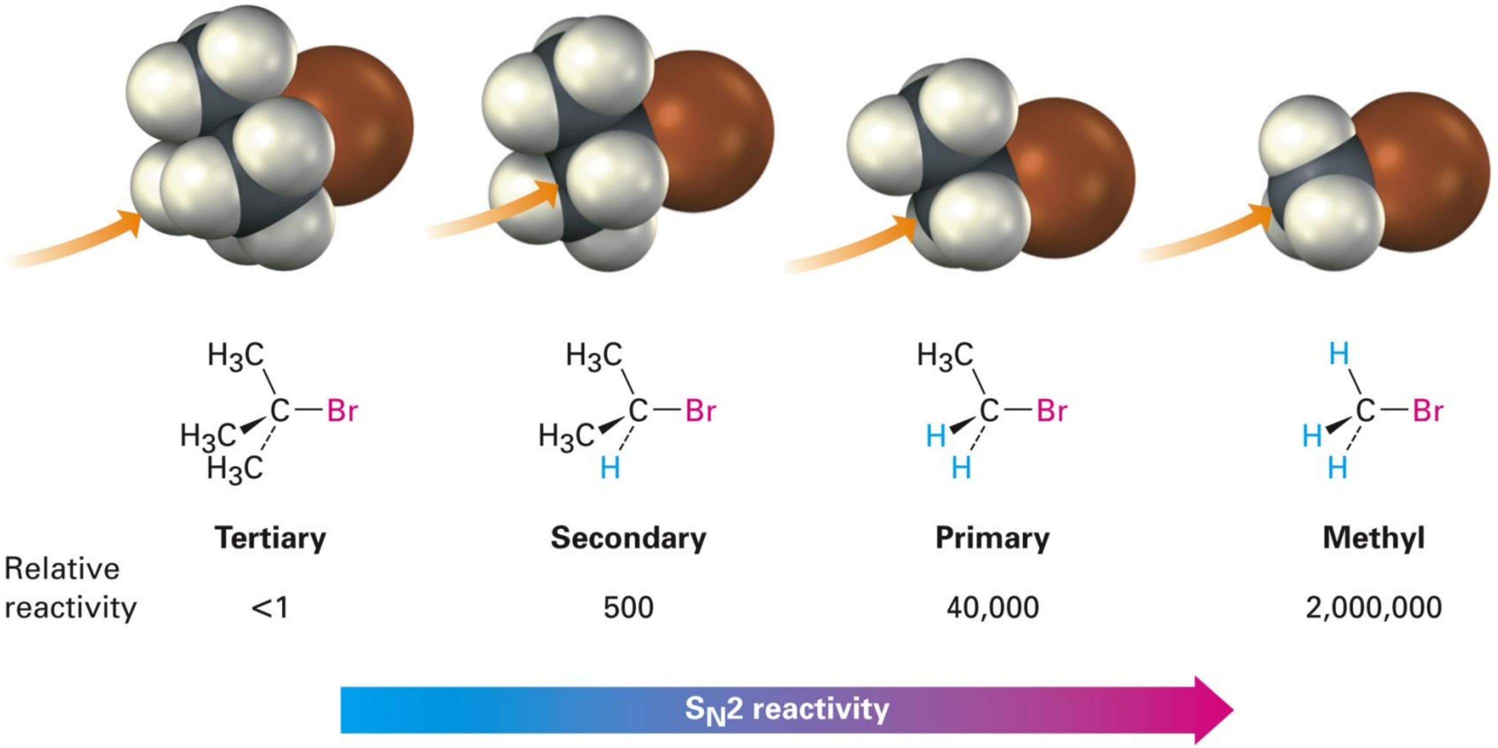


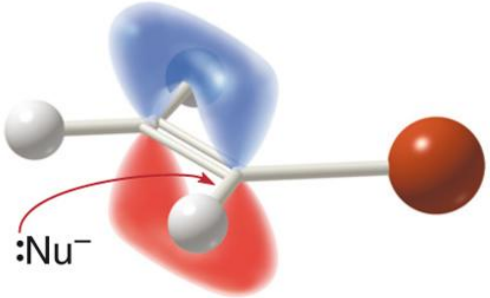
Figure 7.4 Steric hindrance to the S_N2 reaction.

The carbon atom in (a) bromomethane is readily accessible, resulting in a fast S_N2 reaction. The carbon atoms in (b) bromoethane (primary), (c) 2-bromopropane (secondary), and (d) 2-bromo-2-methylpropane (tertiary) are successively more hindered, resulting in successively slower S_N2 reactions.

Vinylic halide

Aryl halide

Vinyl halides and the S_N2 mechanism: Backside attack of the nucleophile is not possible.

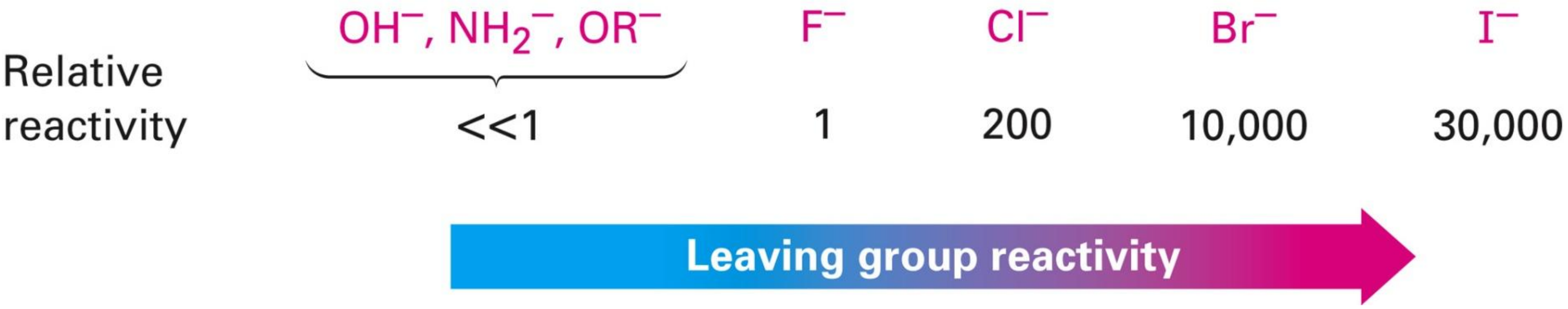


Steric hindrance

Backside attack would force the nucleophile to approach in the plane of the double bond.

The Leaving Group in S_N2 Reactions

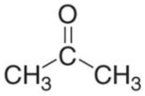
- A good leaving group reduces the barrier to a reaction
- Stable anions that are weak bases are usually excellent leaving groups and can delocalize charge



	OH^-, NH_2^-, OR^-	F^-	Cl^-	Br^-	I^-
Relative reactivity	<<1	1	200	10,000	30,000

Solvent in S_N2 Reactions

- ***Polar aprotic*** **solvents favor S_N2 reactions because nucleophiles are not well solvated, and therefore, are more nucleophilic**

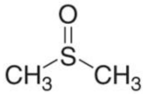


acetone

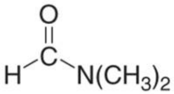
$CH_3-C\equiv N$

acetonitrile

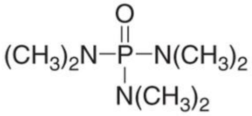
tetrahydrofuran
THF



dimethyl sulfoxide
DMSO

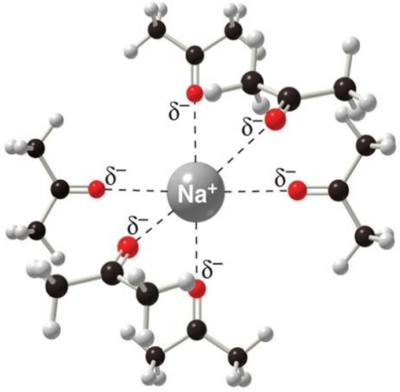


dimethylformamide
DMF

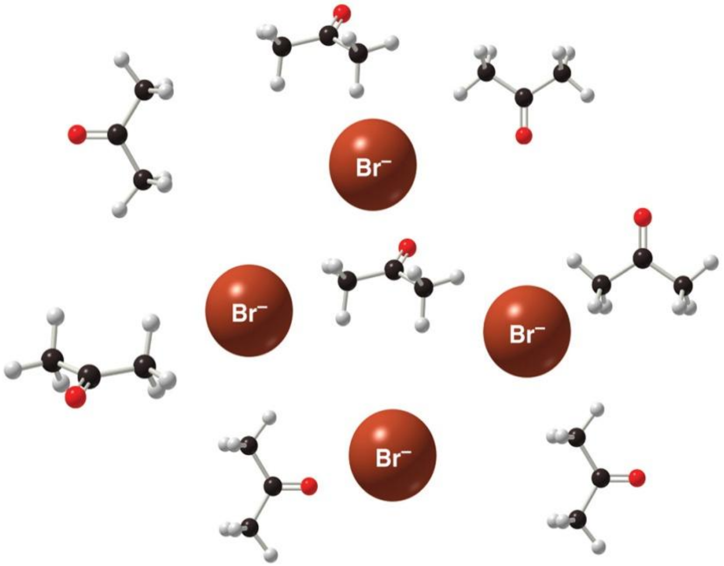


$$(CH_3)_2N-\underset{\displaystyle N(CH_3)_2}{\underset{|}{\overset{\overset{\displaystyle O}{\|}}{P}}}-N(CH_3)_2$$

hexamethylphosphoramide
HMPA



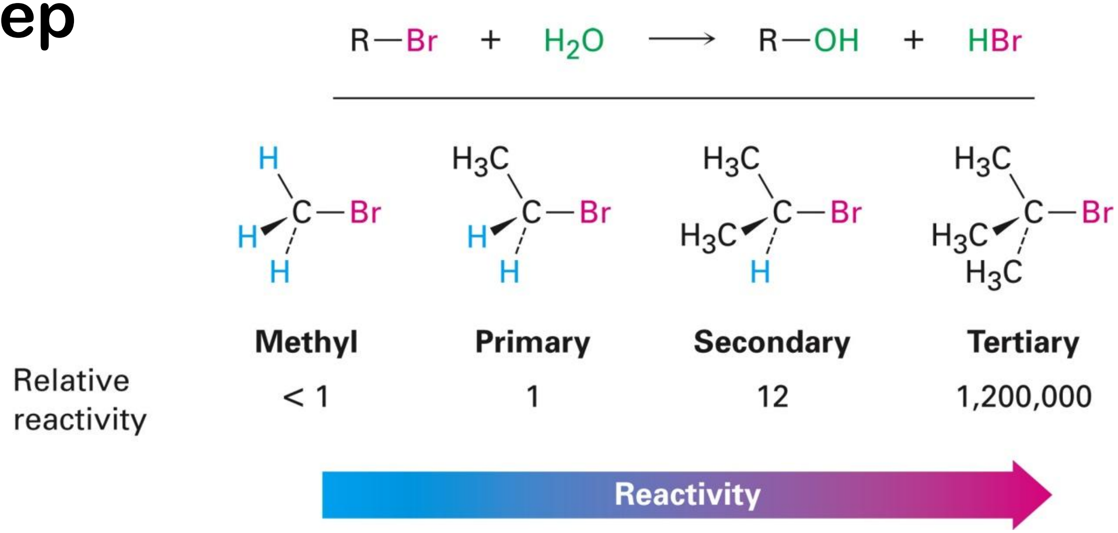
$(CH_3)_2C{=}O$ solvates Na^+ well by ion−dipole interactions.



Br^- anions are surrounded by solvent but not well solvated by the $(CH_3)_2C{=}O$ molecules.

7.6 Substitution: The S_N1 Reaction

- Tertiary alkyl halides react rapidly in protic solvents by a mechanism that involves departure of the leaving group prior to addition of the nucleophile
- Called an S_N1 reaction – occurs in two distinct steps while S_N2 occurs with both events in same step
- If nucleophile is present in reasonable concentration (or it is the solvent), then ionization is the slowest step

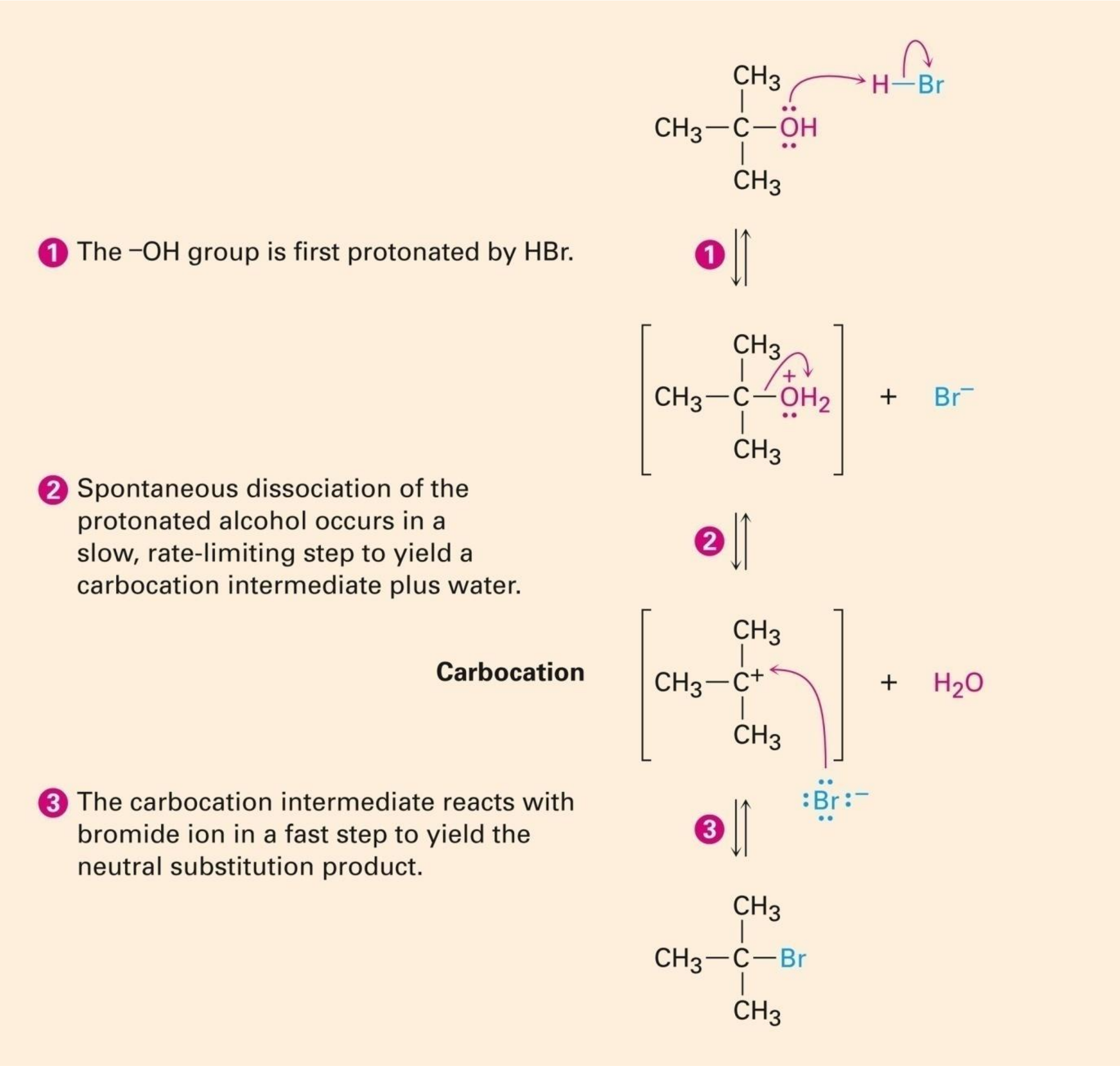


Rates of S_N1 Reactions: Unimolecular

- **Rate-determining step is formation of carbocation**

Figure 7.5 The mechanism of the S_N1 reaction of *tert*-butyl alcohol with HBr to yield an alkyl halide.

- **rate = *k*[RX]**



① The –OH group is first protonated by HBr.

② Spontaneous dissociation of the protonated alcohol occurs in a slow, rate-limiting step to yield a carbocation intermediate plus water.

Carbocation

③ The carbocation intermediate reacts with bromide ion in a fast step to yield the neutral substitution product.

Stereochemistry of S_N1 Reactions

- The planar intermediate leads to loss of chirality
  - A free carbocation is achiral
- Product is racemic mixture

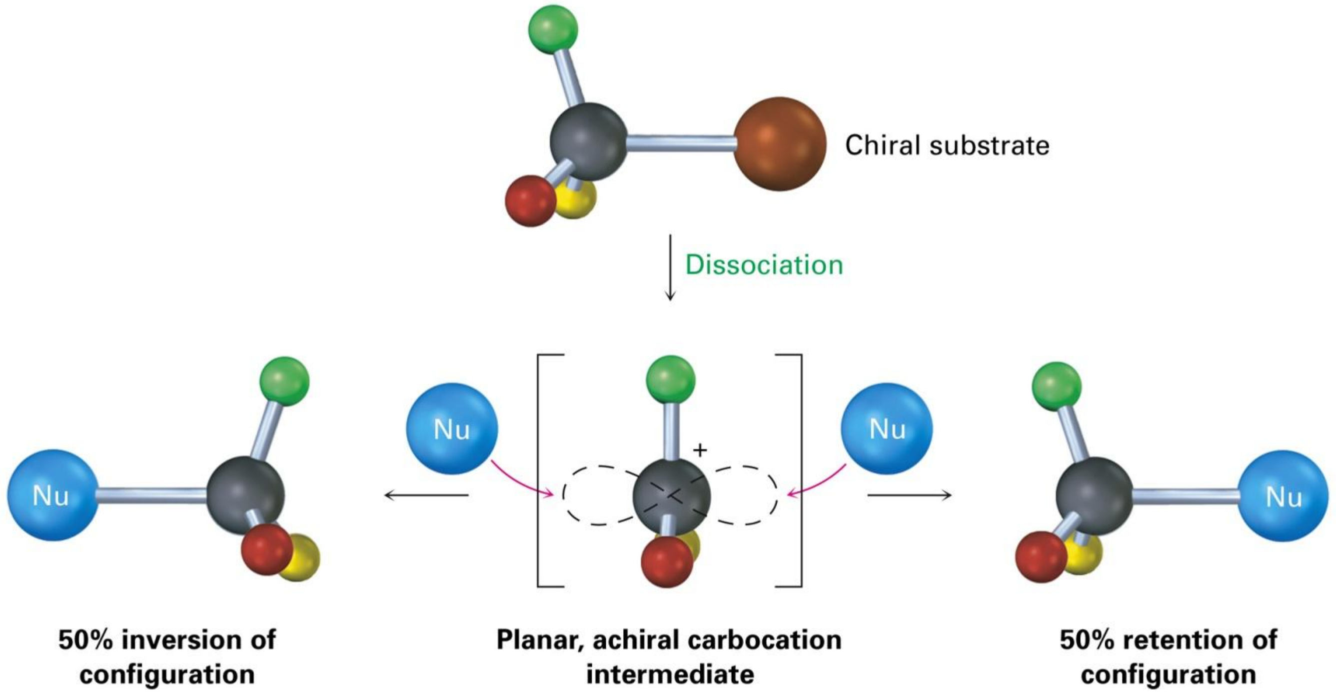
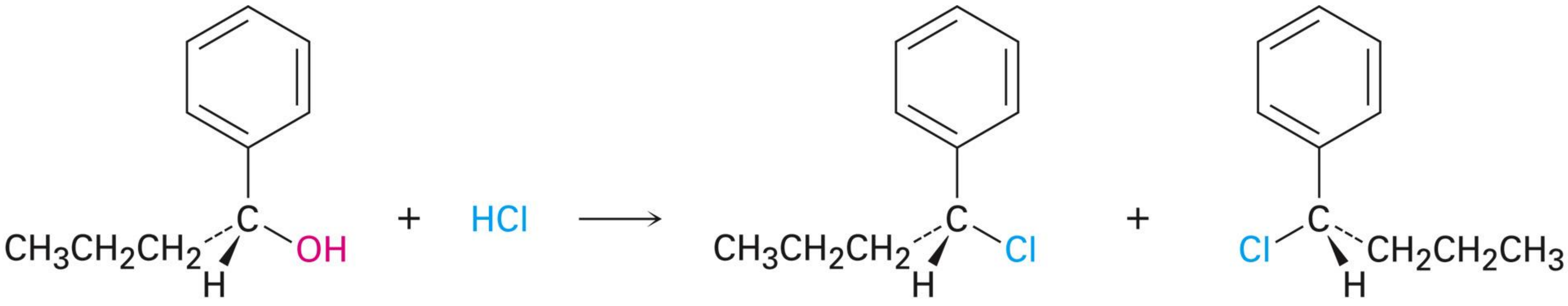


Figure 7.6 A stereochemistry of the S_N1 reaction.



(*R*)-Phenylbutan-1-ol

(*R*)-1-Phenyl-1-chlorobutane
(50%, retention)

(*S*)-1-Phenyl-1-chlorobutane
(50%, inversion)

The Leaving Group in S_N1 Reactions

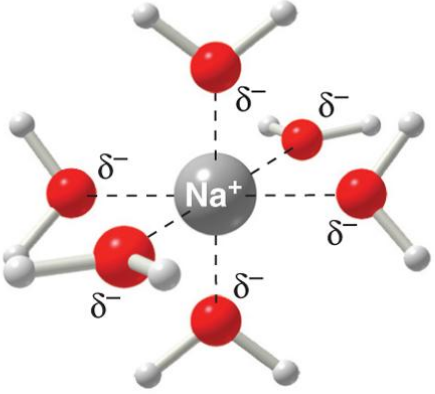
- Critically dependent on leaving group
  - Reactivity: the larger halides ions are better leaving groups
- In acid, OH of an alcohol is protonated and leaving group is H_2O, which is still less reactive than halide

$HO^- < Cl^- < Br^- < I^- \approx H_2O$

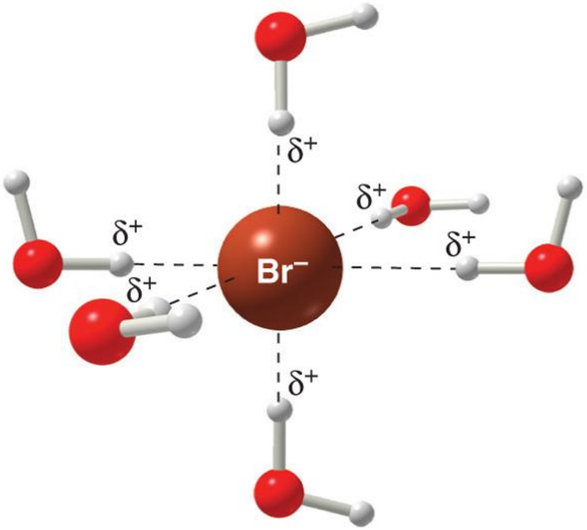
Solvent in S_N1 Reactions

- ***Polar protic*** **solvents like H_2O and ROH favor S_N1 reactions because the ionic intermediates (both cations and anions) are stabilized by solvation**

H_2O	CH_3OH	CH_3CH_2OH	$(CH_3)_3COH$	CH_3COOH
	methanol	ethanol	*tert*-butanol	acetic acid



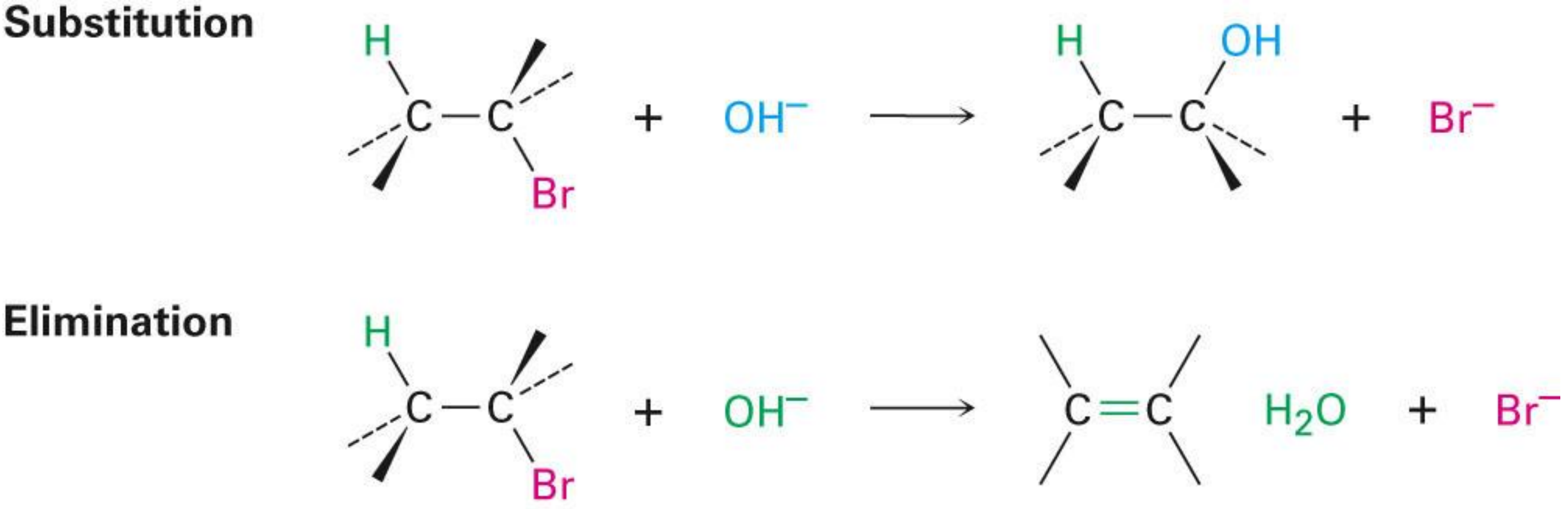
Na^+ is solvated by ion–dipole interactions with H_2O.



Br^- is solvated by hydrogen bonding with H_2O.

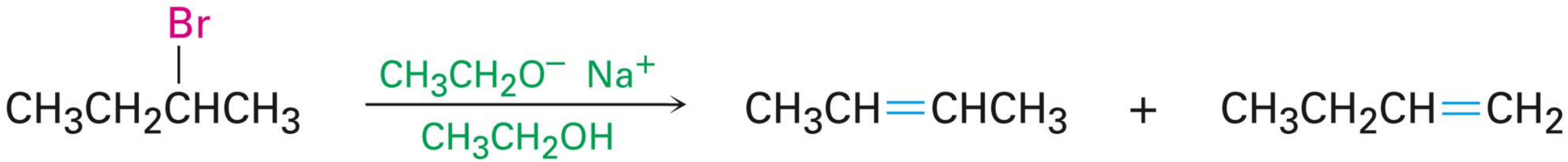
7.7 Eliminations: The E2 Reaction

- Elimination is an alternative pathway to substitution
- Opposite of addition
- Generates an alkene
- Can compete with substitution and decrease yield, especially for S_N1 processes



Zaitsev's Rule for Elimination Reactions

- In the elimination of HX from an alkyl halide, the more highly substituted alkene product predominates



$$CH_3CH_2\overset{\overset{Br}{|}}{C}HCH_3 \xrightarrow[CH_3CH_2OH]{CH_3CH_2O^- \ Na^+} CH_3CH{=}CHCH_3 + CH_3CH_2CH{=}CH_2$$

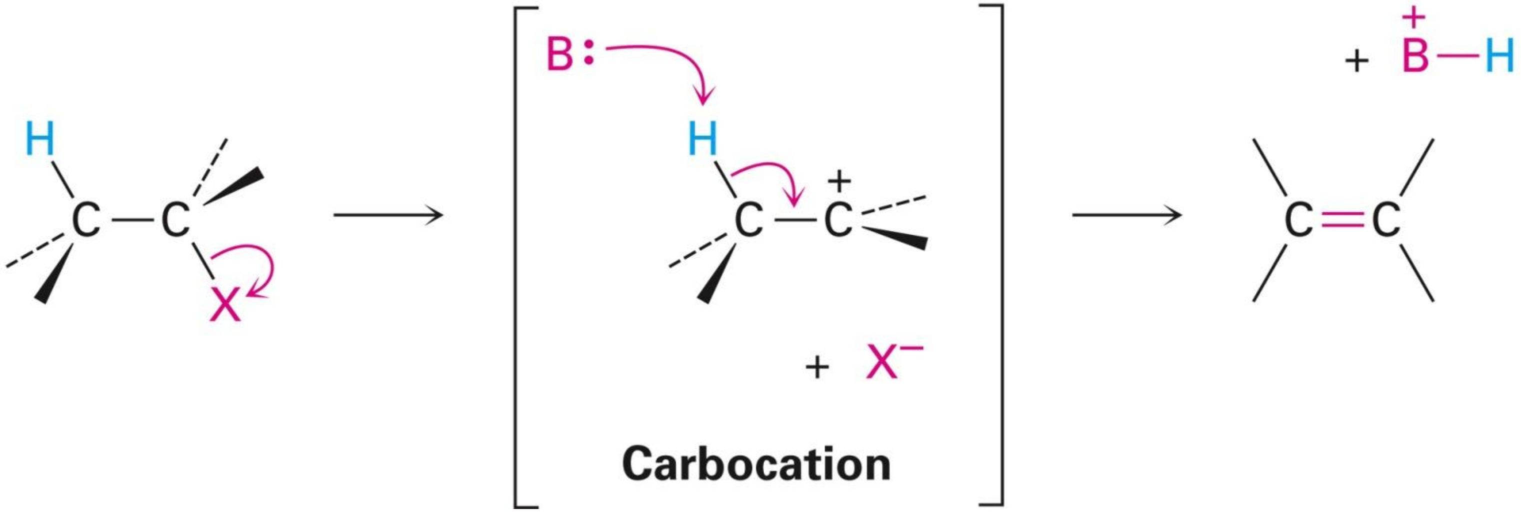
2-Bromobutane

But-2-ene
(81%)

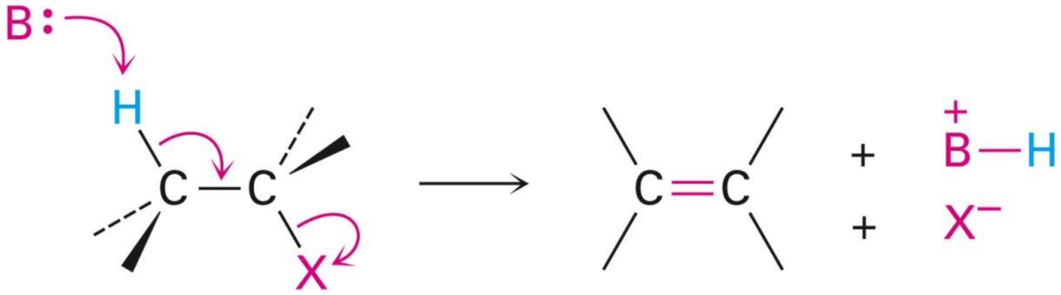
But-1-ene
(19%)

Mechanisms of Elimination Reactions

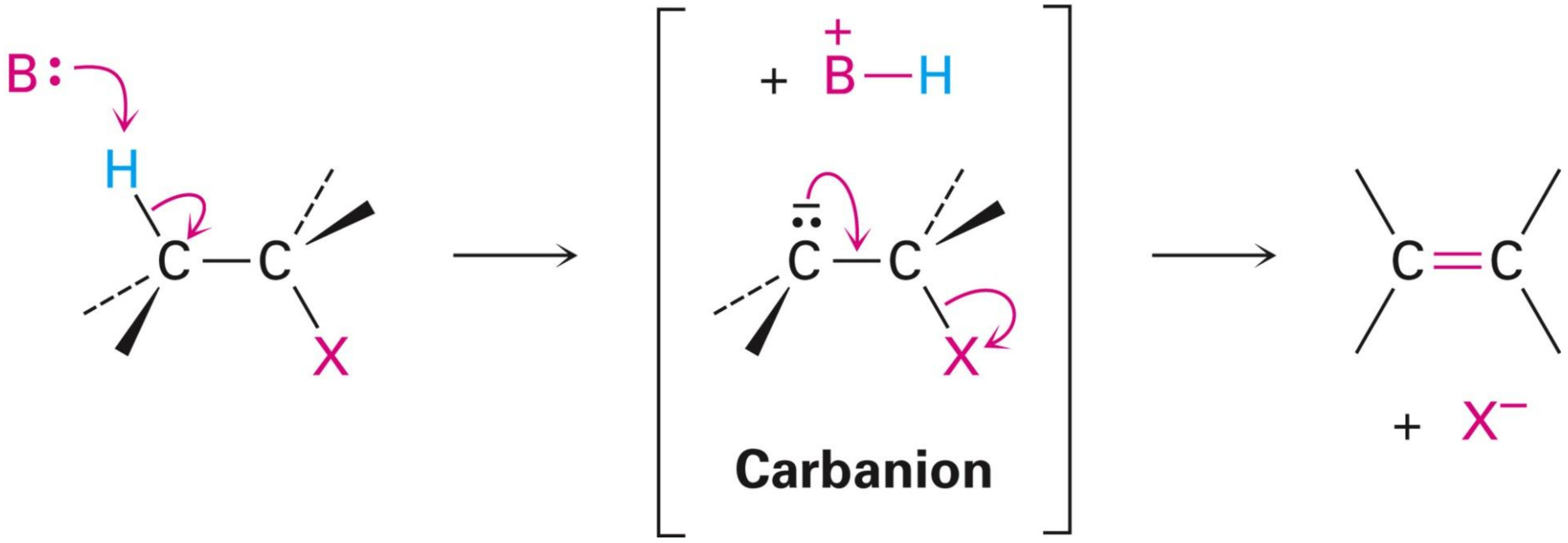
E1 Reaction: C–X bond breaks first to give a carbocation intermediate, followed by base removal of a proton to yield the alkene.



E2 Reaction: C–H and C–X bonds break simultaneously, giving the alkene in a single step without intermediates.



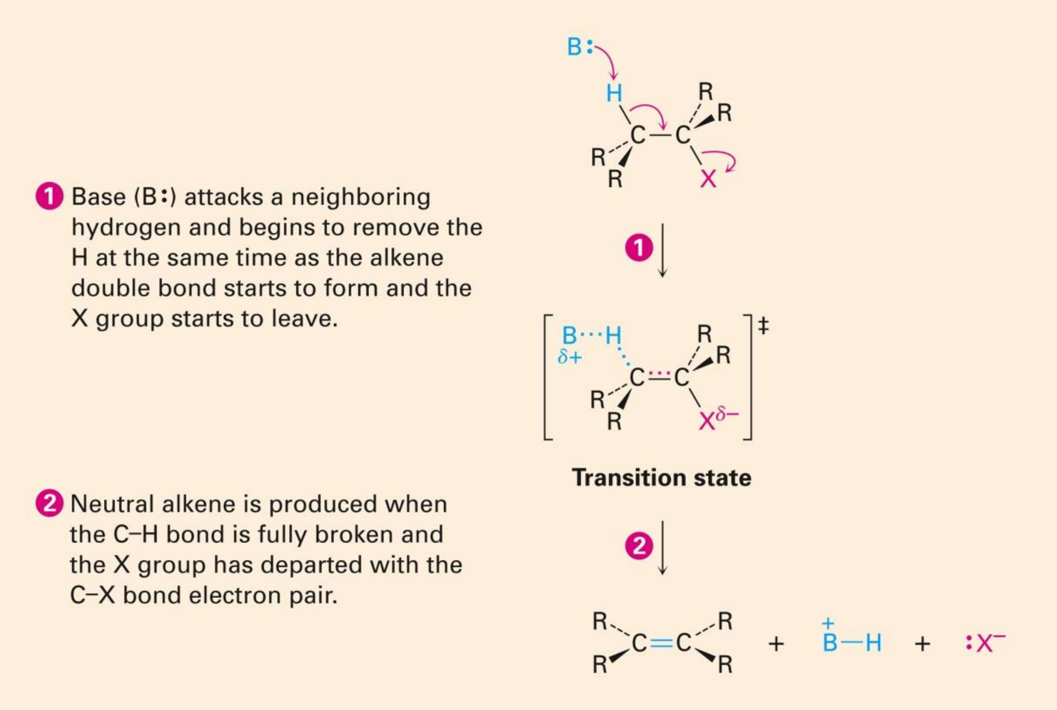
E1cB Reaction: C–H bond breaks first, giving a carbanion intermediate that loses X^- to form the alkene.



- **The E1cB mechanism predominates in biological pathway**

The E2 Reaction: Elimination, Bimolecular

- A proton is transferred to **strong base** as leaving group begins to depart
- Transition state combines leaving of X and transfer of H
- Product alkene forms stereospecifically



① Base (B:) attacks a neighboring hydrogen and begins to remove the H at the same time as the alkene double bond starts to form and the X group starts to leave.

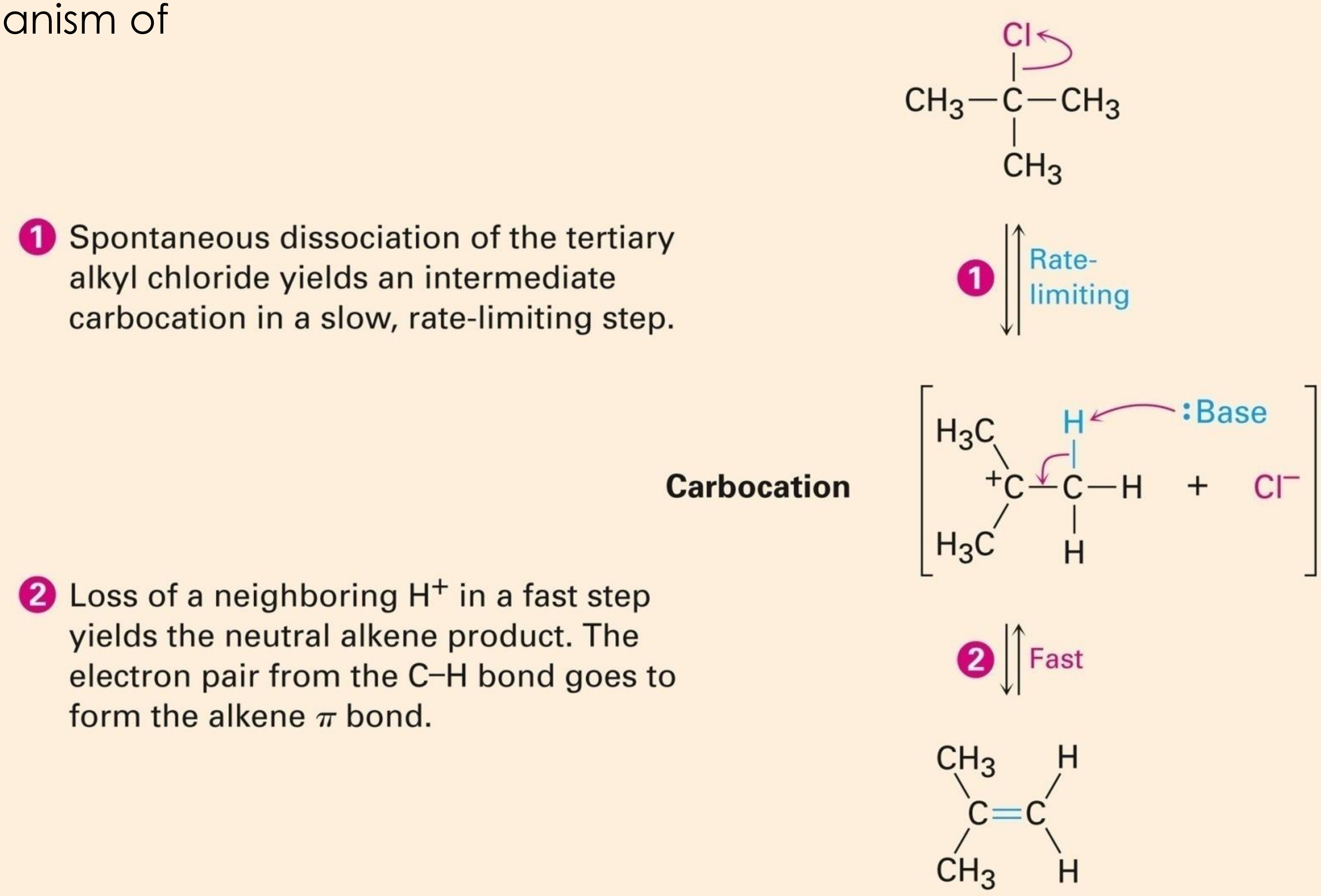
② Neutral alkene is produced when the C–H bond is fully broken and the X group has departed with the C–X bond electron pair.

Figure 7.7 Mechanism of the E2 reaction.

7.8 Eliminations: The E1and E1cB Reactions

E1 Reaction: Elimination, Unimolecular

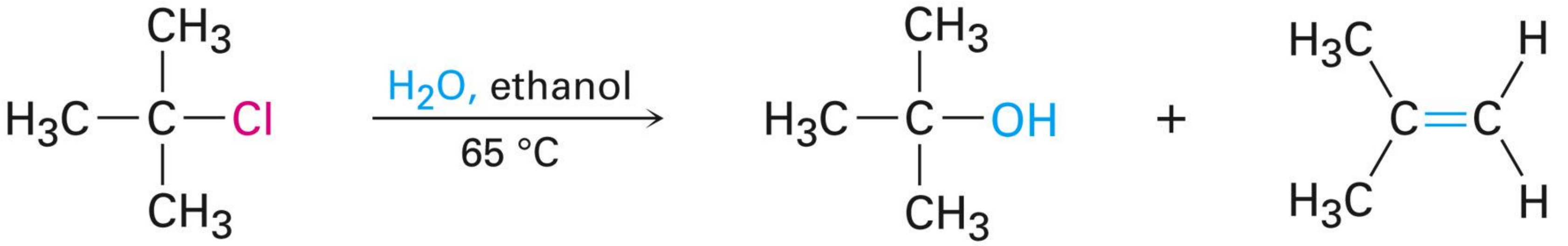
Figure 7.8 Mechanism of the E1 reaction.



① Spontaneous dissociation of the tertiary alkyl chloride yields an intermediate carbocation in a slow, rate-limiting step.

② Loss of a neighboring H^+ in a fast step yields the neutral alkene product. The electron pair from the C–H bond goes to form the alkene π bond.

- The E1 and S_N1 reactions normally occur in a hydroxylic solvent with a nonbasic nucleophile



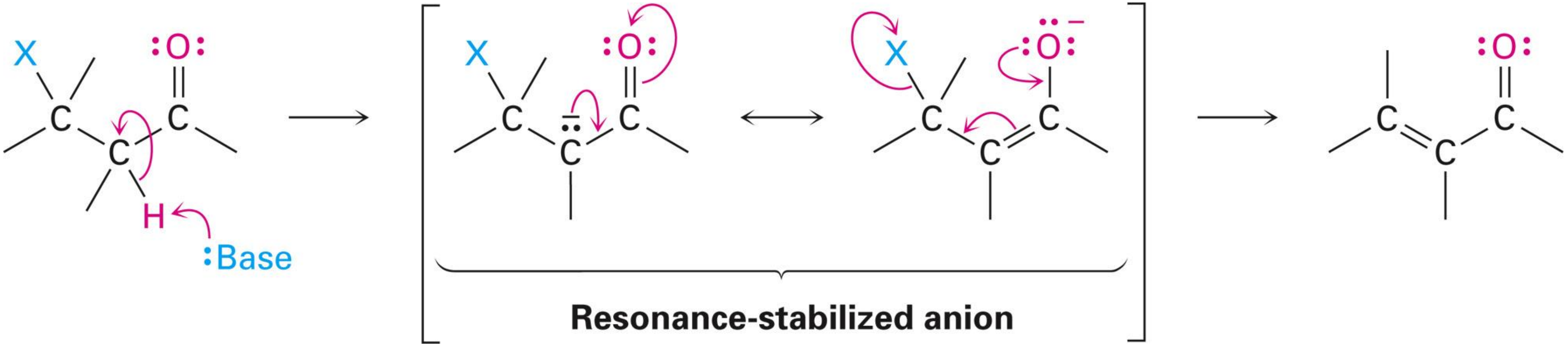
2-Chloro-2-methylpropane

2-Methylpropan-2-ol (64%)

2-Methylpropene (36%)

E1cB Reaction

- Takes place through a ***carbanion*** intermediate
- The reaction is particularly common in substrates that have a poor leaving group, such as –OH, two carbons removed from a carbonyl group, HO-C-CH-C=O



7.9 A Summary of Reactivity: S_N1, S_N2, E1,E1cB, E2

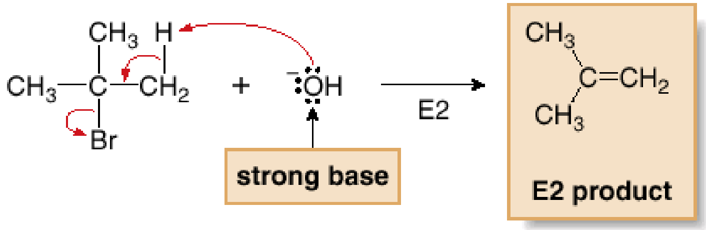
- Alkyl halides undergo different reactions in competition, depending on the reacting molecule and the conditions
- Based on patterns, we can predict likely outcomes
- Primary alkyl halide (RCH_2X): S_N2, E2 and E1cB
- Secondary alkyl hakide (R_2CHX): S_N2, E2 and E1cB
- Tertiary alkyl halide (R_3CX): E2, S_N1, E1 and E1cB
- **E1cB** elimination takes place if the leaving group is two carbons away from a carbonyl group, HO-C-CH-C=O

Determining whether an alkyl halide reacts by an S_N1, S_N2, E1, or E2 mechanism

[1] 3° Alkyl halides (R_3CX react by all mechanisms except S_N2.)

- With strong bases

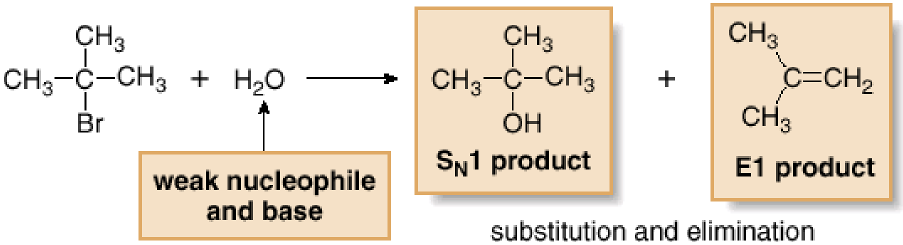
- **Elimination occurs by an E2 mechanism.**
- Rationale: A strong base or nucleophile favors an S_N2 or E2 mechanism, but 3° halides are too sterically hindered to undergo an S_N2 reaction, so only E2 elimination occurs.
- Example:



elimination only

- With weak nucleophiles or bases

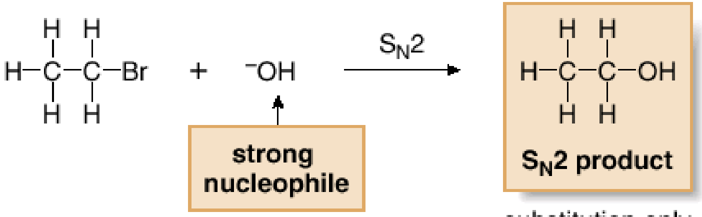
- **A mixture of S_N1 and E1 products results.**
- Rationale: A weak base or nucleophile favors S_N1 and E1 mechanisms, and both occur.
- Example:



substitution and elimination

[2] 1° Alkyl halides (RCH_2X react by S_N2 and E2 mechanisms.)

- With strong nucleophiles
  - **Substitution occurs by an S_N2 mechanism.**
  - Rationale: A strong base or nucleophile favors S_N2 or E2, but 1° halides are the least reactive halide type in elimination; therefore, only an S_N2 reaction occurs.
  - Example:

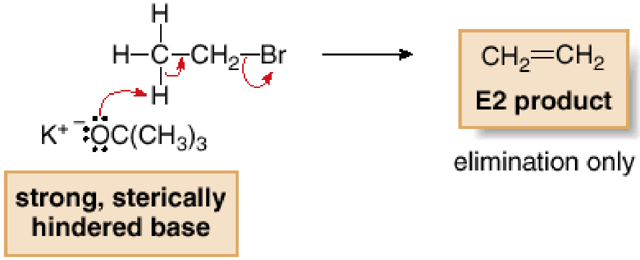


strong nucleophile

S_N2 product

substitution only

- With strong, sterically hindered bases
  - **Elimination occurs by an E2 mechanism.**
  - Rationale: A strong, sterically hindered base cannot act as a nucleophile, so elimination occurs and the mechanism is E2.
  - Example:



strong, sterically hindered base

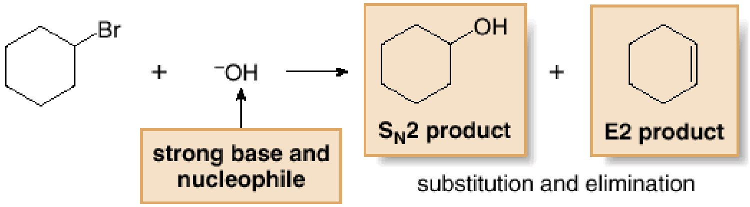
E2 product

elimination only

[3] 2° Alkyl halides (R_2CHX react by all mechanisms.)

- With strong bases and nucleophiles

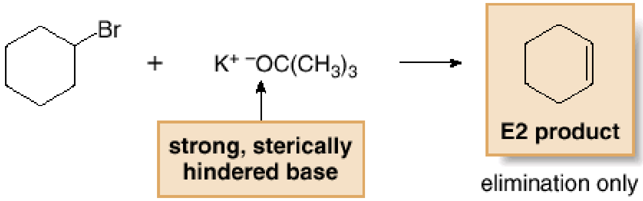
- **A mixture of S_N2 and E2 products results.**
- Rationale: A strong base that is also a strong nucleophile gives a mixture of S_N2 and E2 products.
- Example:



substitution and elimination

- With strong, sterically hindered bases

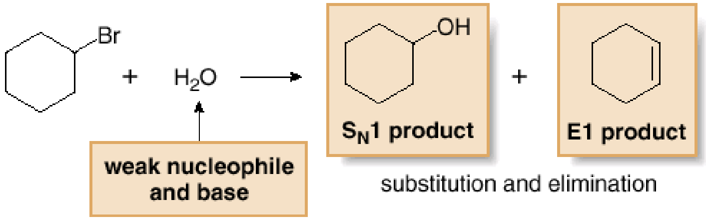
- **Elimination occurs by an E2 mechanism.**
- Rationale: A strong, sterically hindered base cannot act as a nucleophile, so elimination occurs and the mechanism is E2.
- Example:



elimination only

- With weak nucleophiles or bases

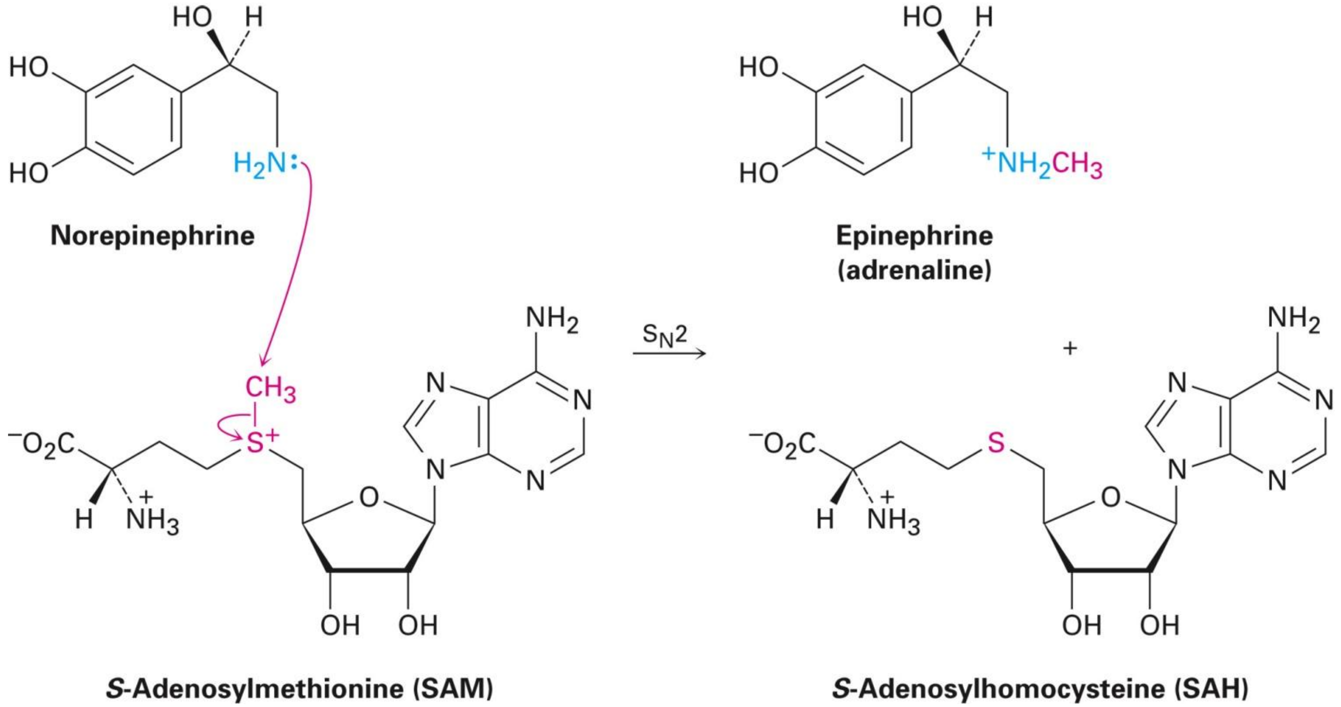
- **A mixture of S_N1 and E1 products results.**
- Rationale: A weak base or nucleophile favors S_N1 and E1 mechanisms, and both occur.
- Example:



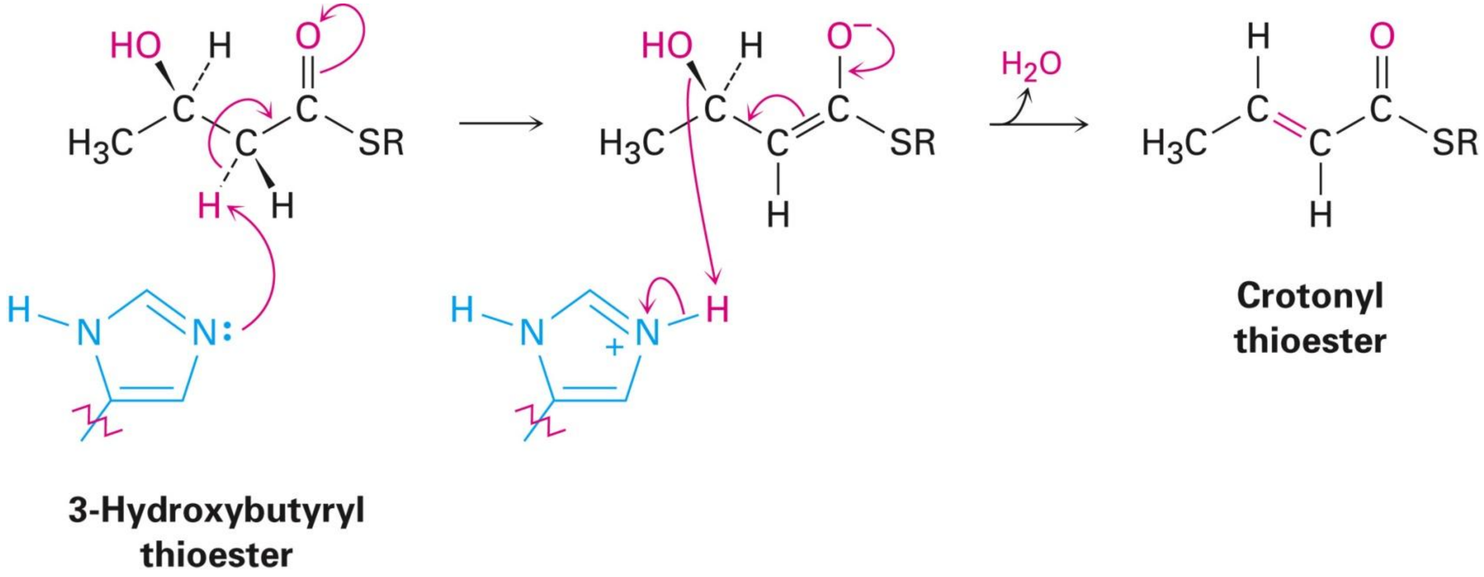
substitution and elimination

7.10 Substitution and Elimination Reactions in Living Organisms

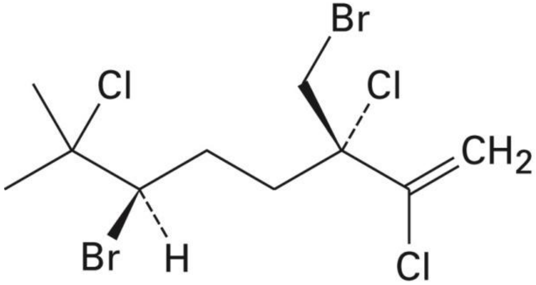
- S_N1 and S_N2 reactions are well known in biological chemistry



- **All three elimination reactions occur in biological pathways**
- **E1cB very common**
- **Typical example occurs during biosynthesis of fats when 3-hydroxybutyryl thioester is dehydrated to corresponding thioester**



Naturally Occurring Organohalides



Halomon