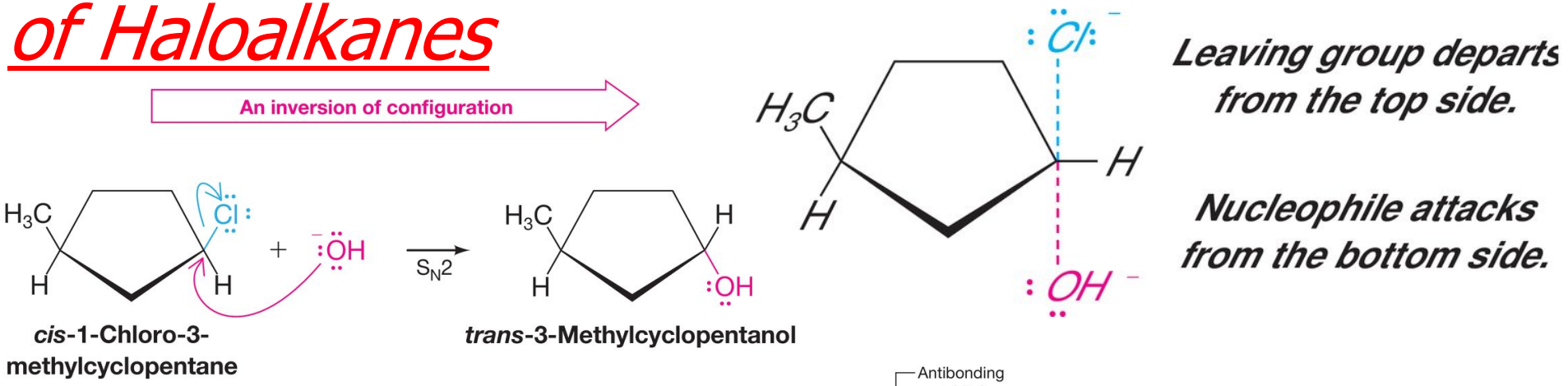
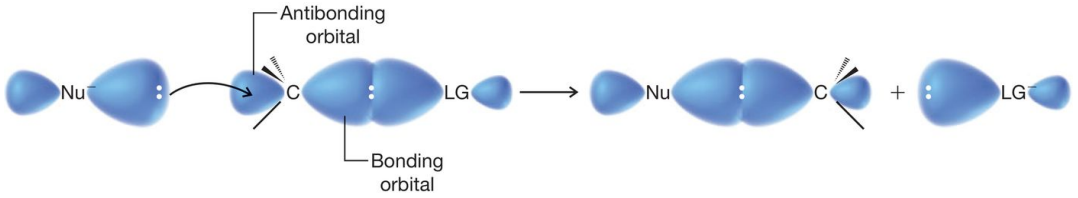
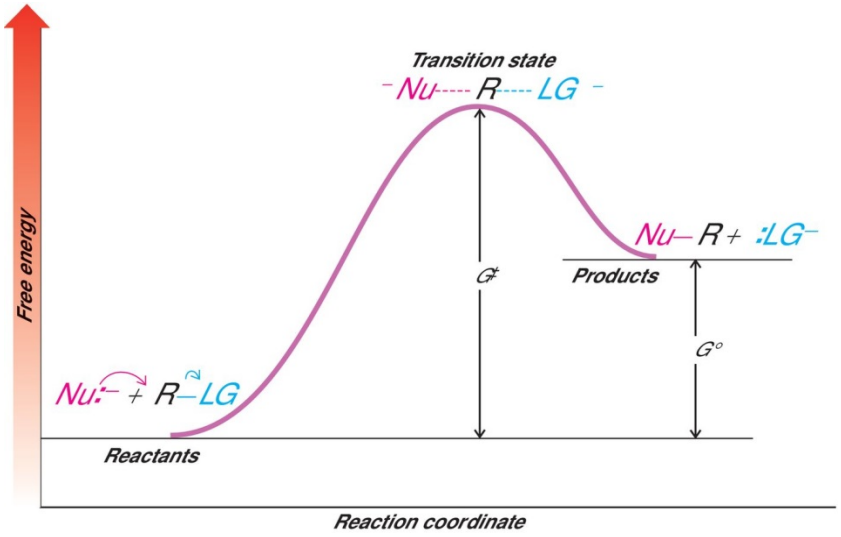
Chapter 7, Haloalkanes,

Properties and Substitution Reactions of Haloalkanes







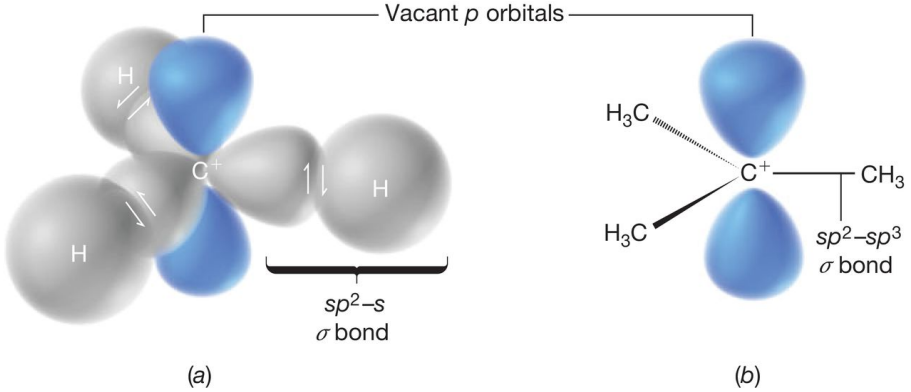


Table of Contents

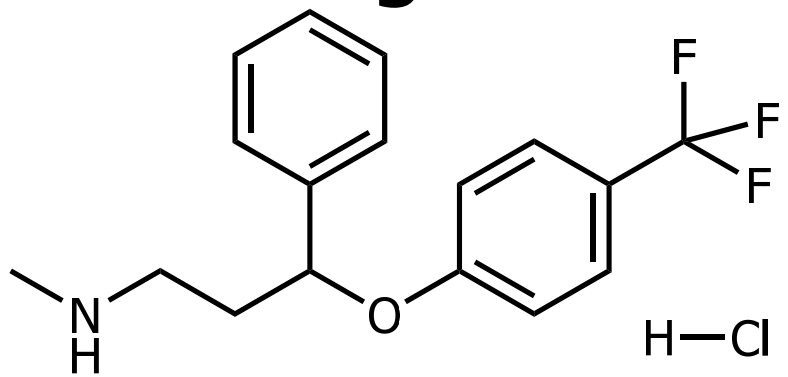
In this chapter we will consider:

- What groups can be *replaced* (i.e., substituted) or eliminated
- The various *mechanisms* by which such processes occur
- The *conditions* that can promote such reactions

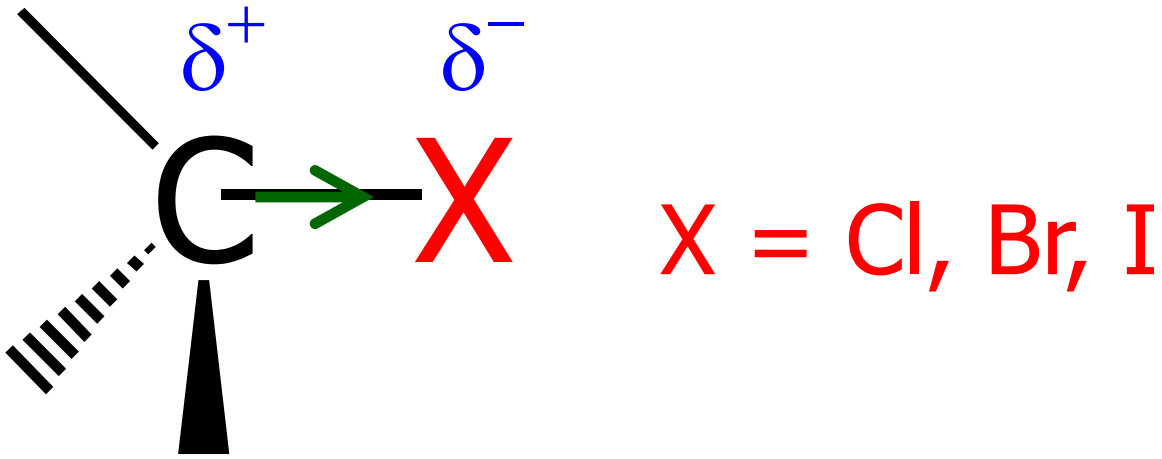
Alkyl Halides (Haloalkane)

- An alkyl halide has a halogen atom bonded to an sp^3-hybridized (tetrahedral) carbon atom

- The carbon–chlorine and carbon–bromine bonds are polarized because the halogen is more electronegative than carbon

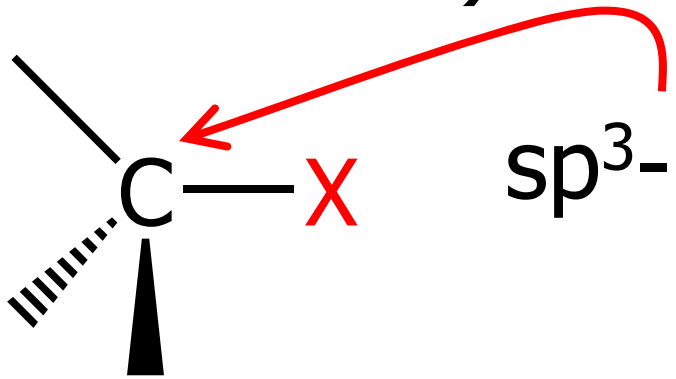


- The carbon-iodine bond do not have a permanent dipole, the bond is easily *polarizable*
- Iodine is a good *leaving group* due to its polarizability, i.e. its ability to stabilize a charge due to its large atomic size
- Generally, a carbon-halogen bond is polar with a partial positive ($\delta+$) charge on the carbon and partial negative ($\delta-$) charge on the halogen



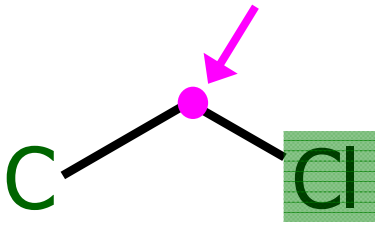
Different Types of Organic Halides

- Alkyl halides (haloalkanes)



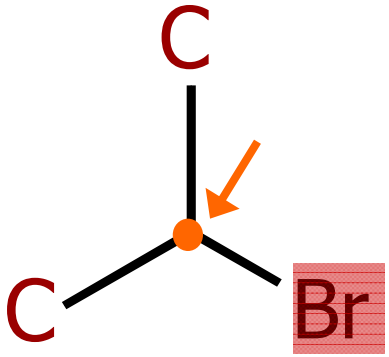
sp^3-hybridized

Attached to
1 carbon atom



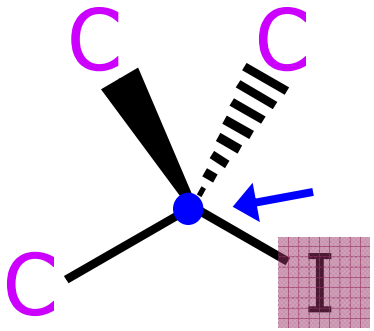
a 1° chloride

Attached to
2 carbon atoms



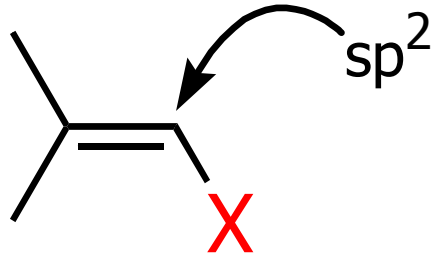
a 2° bromide

Attached to
3 carbon atoms

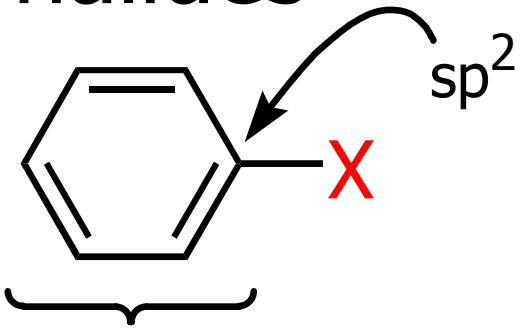


a 3° iodide

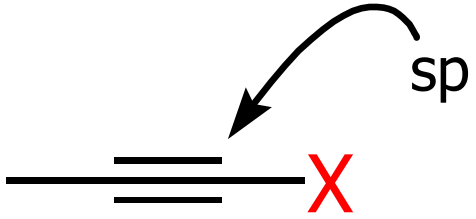
- Vinyl halides (Alkenyl halides)

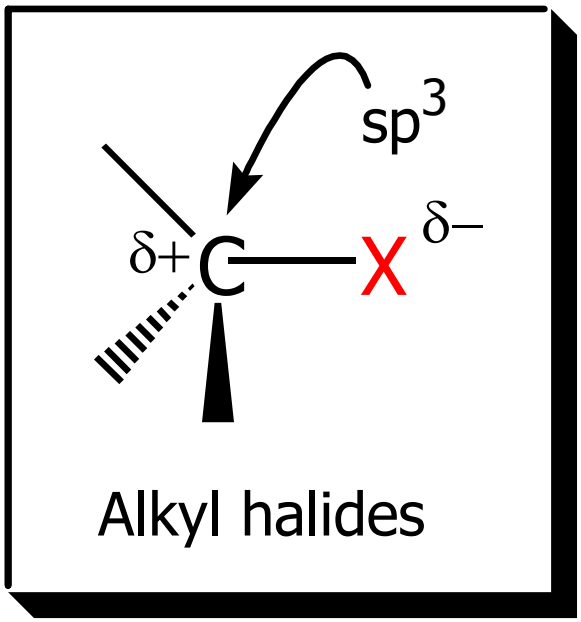


- Aryl halides

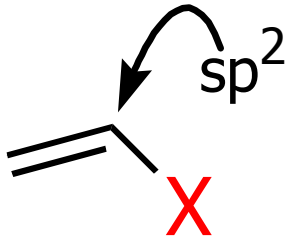


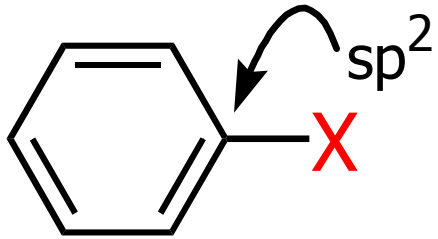
- Acetylenic halides (Alkynyl halides)

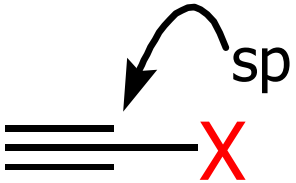




- Alkyl halides are prone to undergo Nucleophilic Substitutions (S_N) and Elimination Reactions (E)



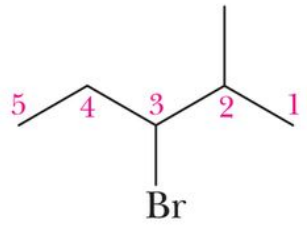




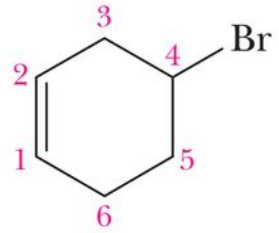
- Alkenyl halides, aryl (phenyl) halides, and alkynyl halides have different reactivity than alkyl halides, and do not generally undergo S_N or E reactions

Nomenclature - IUPAC

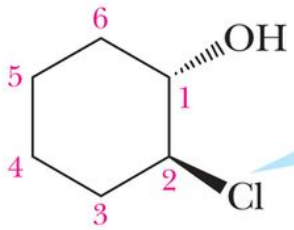
- Locate the parent alkane.
- Number the parent chain to give the substituent encountered first the lower number.
- Show halogen substituents by the prefixes fluoro-, chloro-, bromo-, and iodo- and list them in alphabetical order with other substituents.
- Locate each halogen on the parent chain.



3-Bromo-2-methylpentane



4-Bromocyclohexene



(1*S*,2*S*)-2-Chlorocyclohexanol
or
trans-2-Chlorocyclohexanol

haloalkanes are named by treating the halogen as substituents in the IUPAC system of nomenclature

Nomenclature

- Several polyhaloalkanes are common solvents and are generally referred to by their common or trivial names.

CH_2Cl_2	$CHCl_3$	CH_3CCl_3	$Cl_2C=CCl_2$
Dichloromethane	Trichloromethane	1,1,1-Trichloroethane	Tetrachloroethene
(Methylene chloride)	(Chloroform)	(Methyl chloroform)	(Tetrachloroethylene)

Freons & Their Alternatives

- The Freons are **chlorofluorocarbons (CFCs)**
  - Among the most widely used were:
  - Much lower ozone-depleting alternatives are the hydro-fluorocarbons (HFCs) and the hydrochlorofluorocarbons (HCFCs), including:

CCl_3F

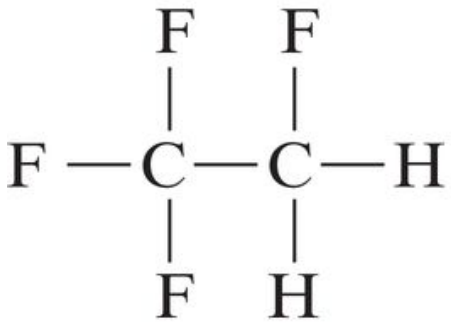
Trichlorofluoromethane

(Freon-11)

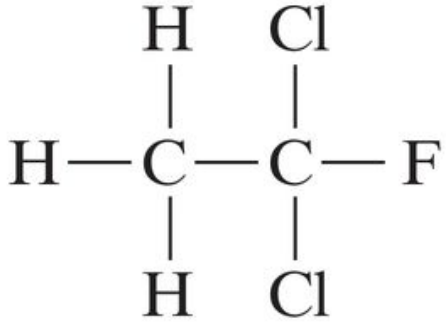
CCl_2F_2

Dichlorodifluoromethane

(Freon-12)



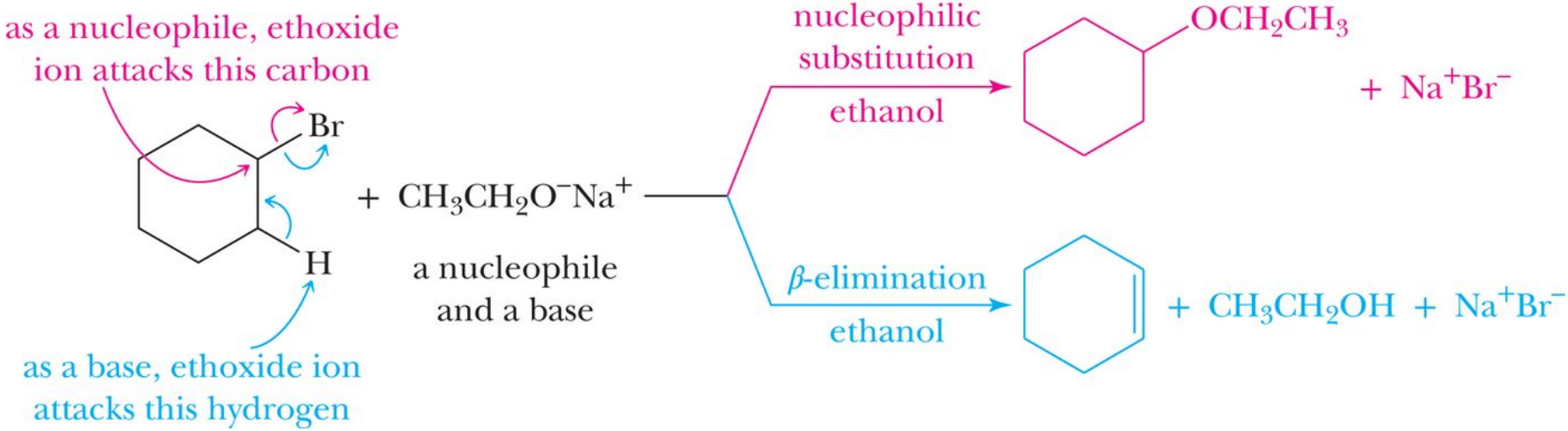
HFC-134a



HCFC-141b

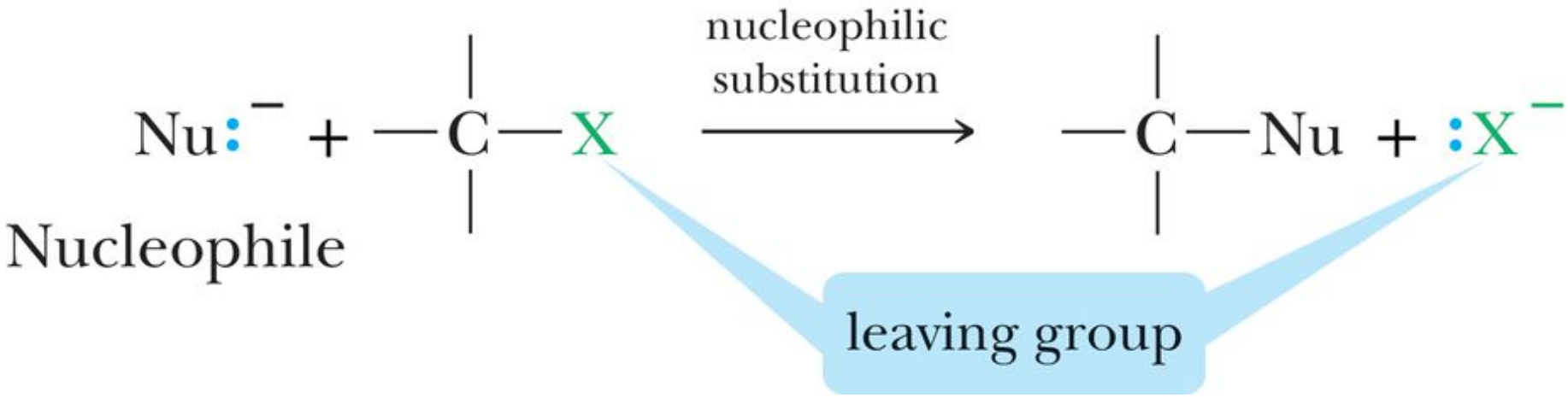
Substitution & Elimination

- In this chapter we, concentrate on two types of reactions:
  - nucleophilic substitution
  - β-elimination



Nucleophilic Substitution

- In the following general reaction, substitution takes place on an sp^3 hybridized (tetrahedral) carbon.



Nucleophilic Substitution

TABLE 7.1 Some Nucleophilic Substitution Reactions

Reaction: $Nu:^- + CH_3X \longrightarrow CH_3Nu + :X^-$

Nucleophile		Product	Class of Compound Formed
$HO:^-$	$\longrightarrow$	CH_3OH	An alcohol
$RO:^-$	$\longrightarrow$	CH_3OR	An ether
$HS:^-$	$\longrightarrow$	CH_3SH	A thiol (a mercaptan)
$RS:^-$	$\longrightarrow$	CH_3SR	A sulfide (a thioether)
$:I:^-$	$\longrightarrow$	$CH_3I:$	An alkyl iodide
$:NH_3$	$\longrightarrow$	$CH_3NH_3^+$	An alkylammonium ion
HOH	$\longrightarrow$	$CH_3\overset{+}{O}(H)H$	An alcohol (after proton transfer)
CH_3OH	$\longrightarrow$	$CH_3\overset{+}{O}(H)CH_3$	An ether (after proton transfer)

notice that a nucleophile does not need to be negatively charged

Mechanisms, S_N2 and S_N1

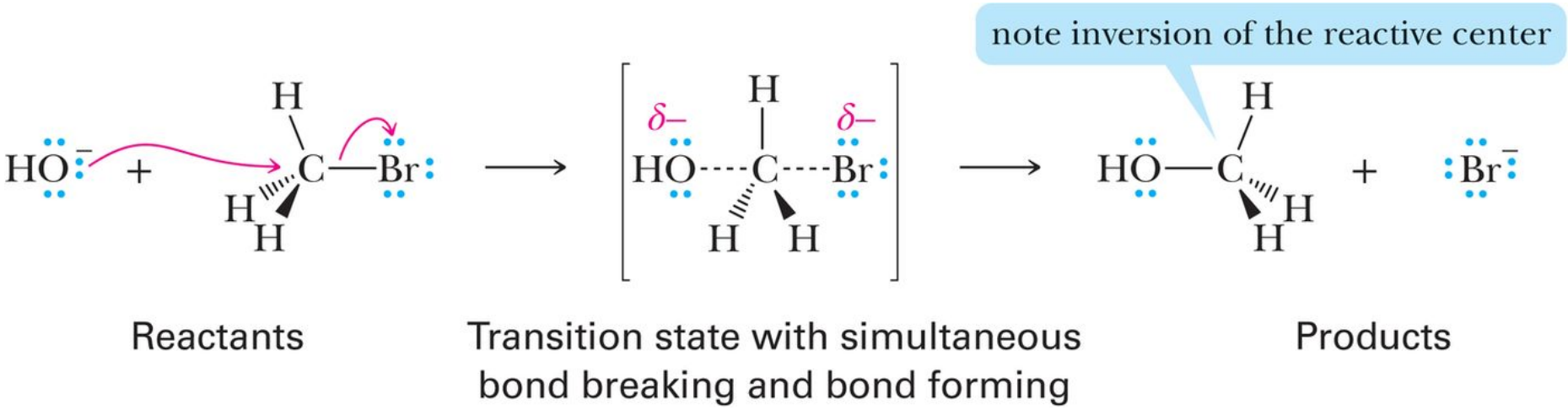
- There are two mechanisms for nucleophilic substitutions.
  - A fundamental difference between them is *the timing* of the bond-breaking and bond-forming steps.

- At one extreme, designated **S_N2**, the two processes take place simultaneously;
  S = substitution
  N = nucleophilic
  2 = bimolecular (two species are involved in the rate-determining step)
  rate = k[haloalkane][nucleophile]

S_N2

- Both reactants are involved in the transition state of the rate-determining step.

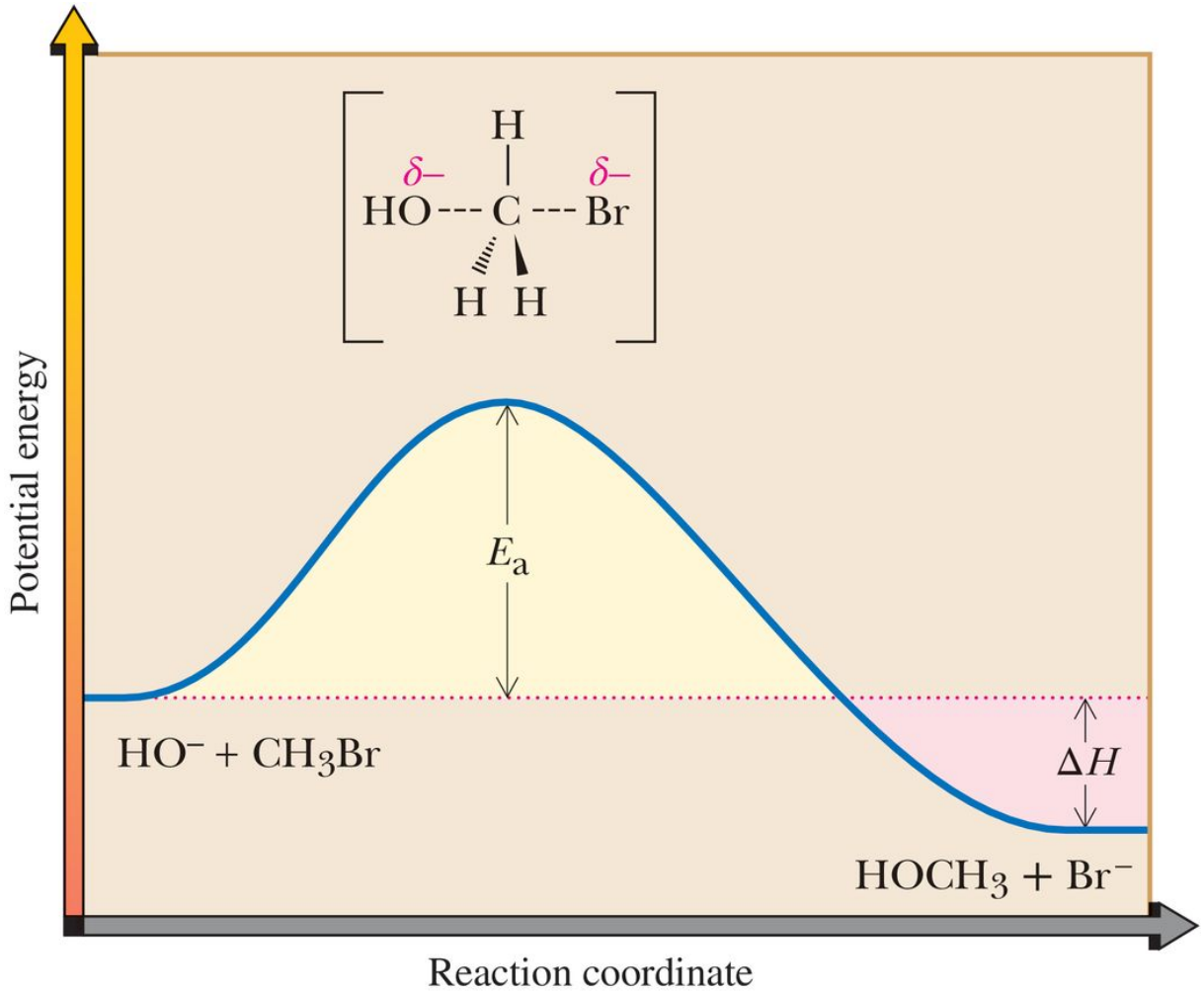
- The nucleophile attacks the reactive center from the side opposite the leaving group. The key step is **reaction of a nucleophile and an electrophile to form a new covalent bond**.



S_N2

Figure 7.1 An energy diagram for an S_N2 reaction.

- There is one transition state and no reactive intermediate.



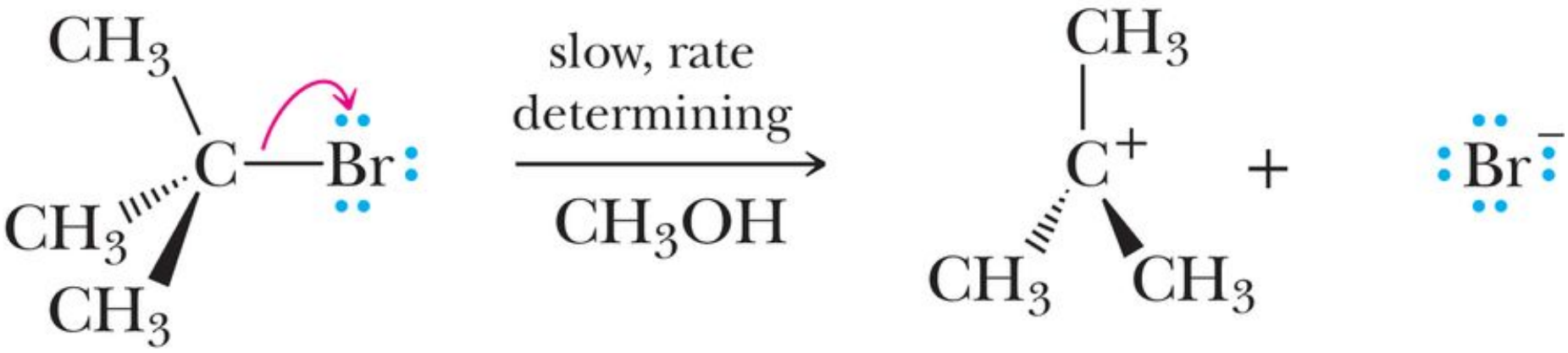
S_N1

- In the other limiting mechanism, bond breaking between carbon and the leaving group is entirely completed before bond forming with the nucleophile begins.

- This mechanism is designated S_N1 where
  S = substitution
  N = nucleophilic
  1 = unimolecular (only one species, RX is involved in the rate-determining step)
  rate = k[haloalkane]

S_N1

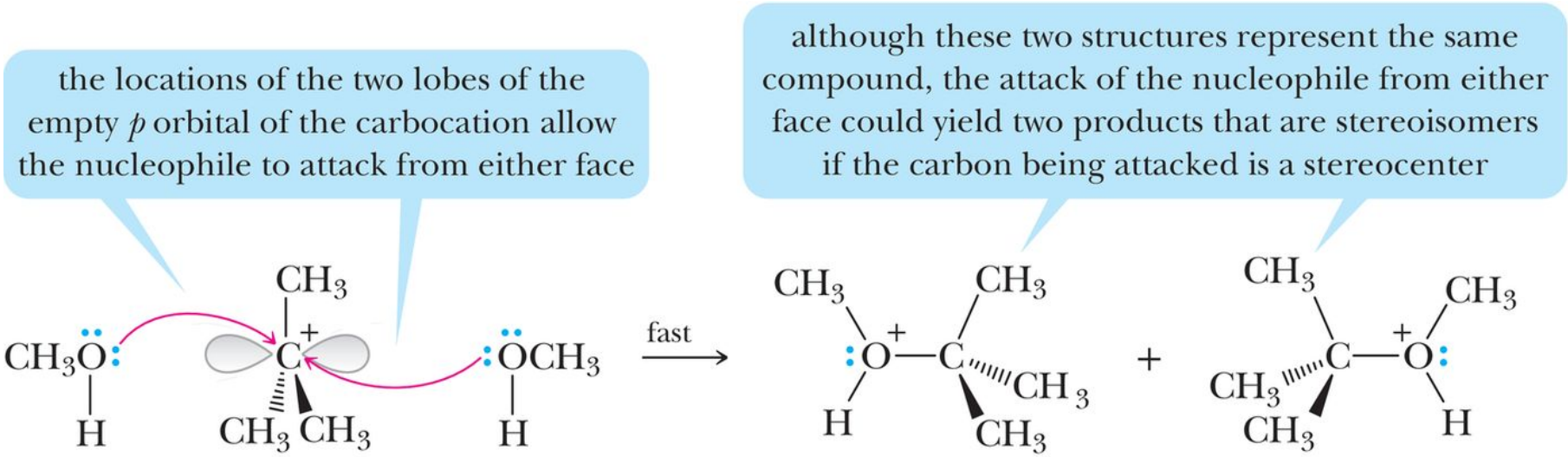
- S_N1 is illustrated by the solvolysis of *tert*-butyl bromide. Methanol is the solvent.
  - **Step 1: Break a bond to form a stable ion or molecule**. Ionization of the C-X bond gives a 3° *carbocation* intermediate and bromide ion.



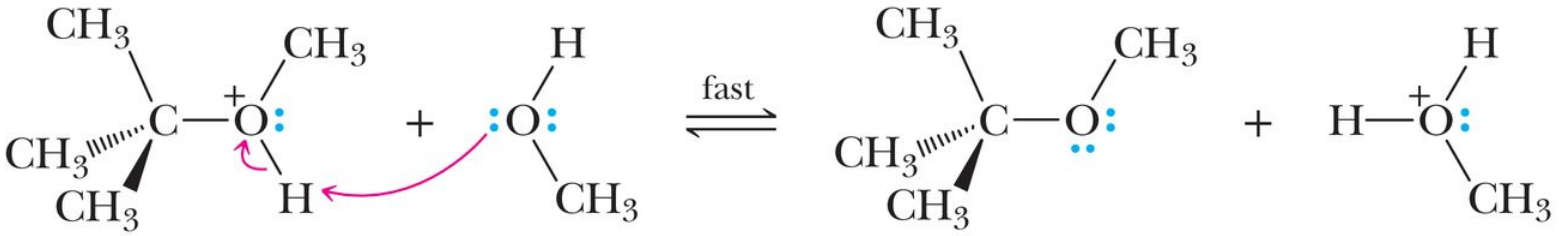
A carbocation intermediate;
carbon is trigonal planar

S_N1

- **Step 2: Reaction of a nucleophile and an electrophile to form a new covalent bond.**

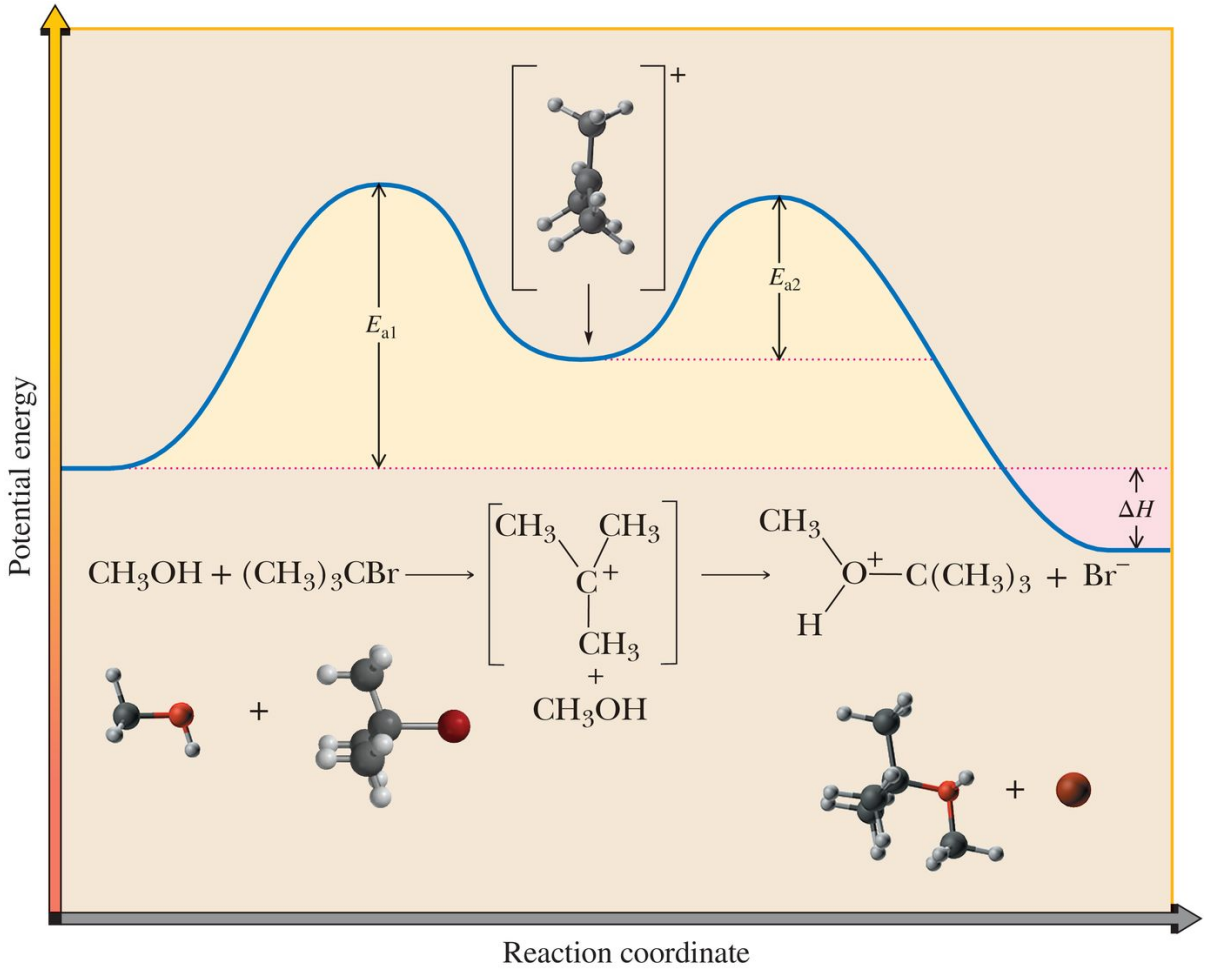


- **Step 3: Take a proton away.** Proton transfer to methanol completes the reaction.



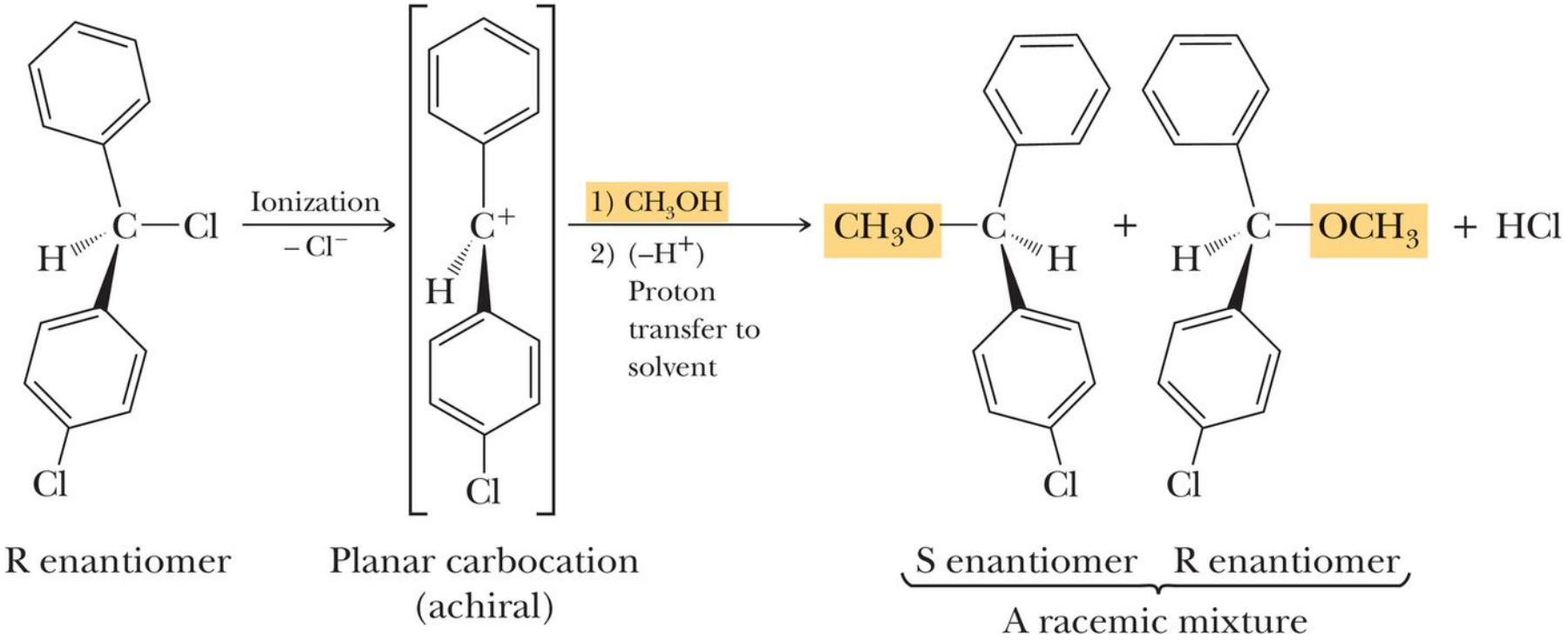
S_N1

Figure 7.2 An energy diagram for an S_N1 reaction. There are two transition states and one intermediate. The first step is rate-determining.



S_N1

- For an S_N1 reaction at a stereocenter, the product is a racemic mixture.



Evidence for S_N Reactions

- Let us examine some of the experimental evidence on which these two mechanisms are based and, as we do, consider the following questions.
  - What affect does the structure of the nucleophile have on the rate of reaction?
  - What effect does the structure of the haloalkane have on the rate of reaction?
  - What effect does the structure of the leaving group have on the rate of reaction?
  - What is the role of the solvent?

Nucleophilicity

- **Nucleophilicity**: a kinetic property measured by the rate at which a Nu: attacks a reference compound under a standard set of experimental conditions.
  - For example, the rate at which a set of nucleophiles displaces bromide ion from bromoethane in ethanol at 25 °C.

- Table 7.2 shows common nucleophiles and their relative nucleophilicities (next).

Relative Nucleophilicity

TABLE 7.2 Examples of Common Nucleophiles and Their Relative Effectiveness

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

Increasing nucleophilicity

the table shows that negatively charged species are better nucleophiles than neutral species

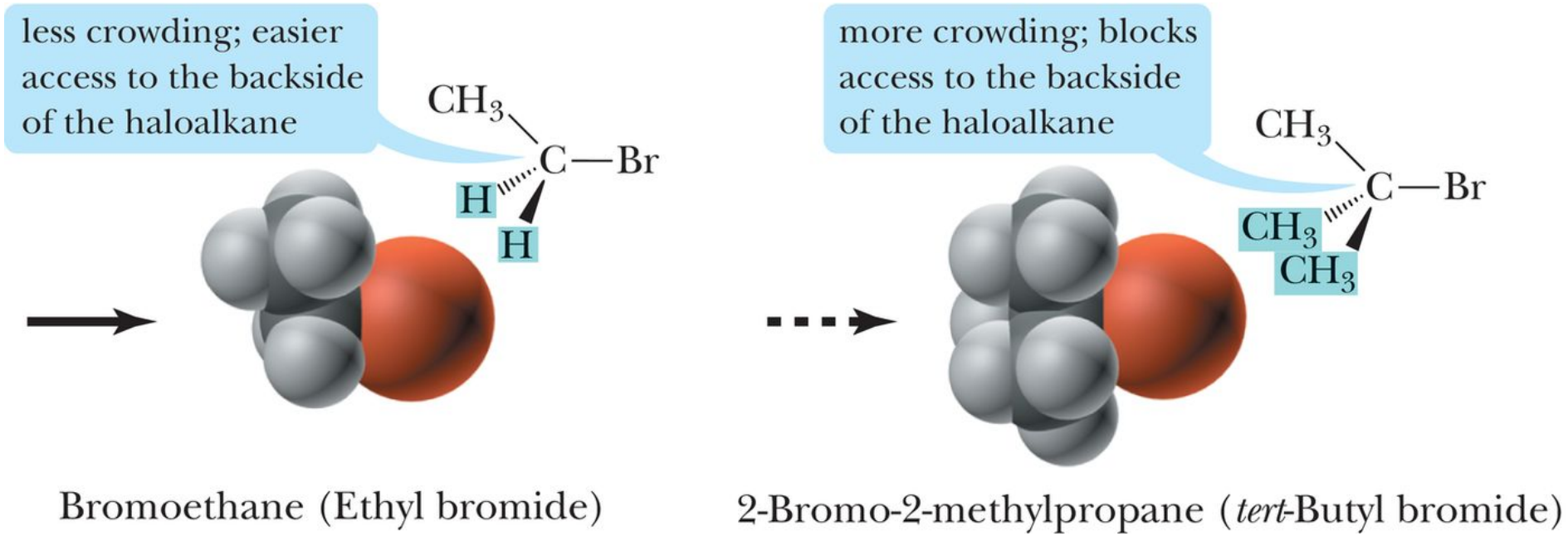
Structure of the Haloalkane

- S_N1 reactions
  - Governed by **electronic factors**, namely the relative stabilities of carbocation intermediates.
  - Relative rates: 3° > 2° > 1° > methyl

- S_N2 reactions
  - Governed by **steric factors**, namely the relative ease of approach of the nucleophile to the site of reaction.
  - Relative rates: methyl > 1° > 2° > 3°

Structure of the Haloalkane

- **Steric factors**
  - Compare access to the reaction center in bromoethane and 2-bromo-2-methylpropane (*tert*-butyl chloride).

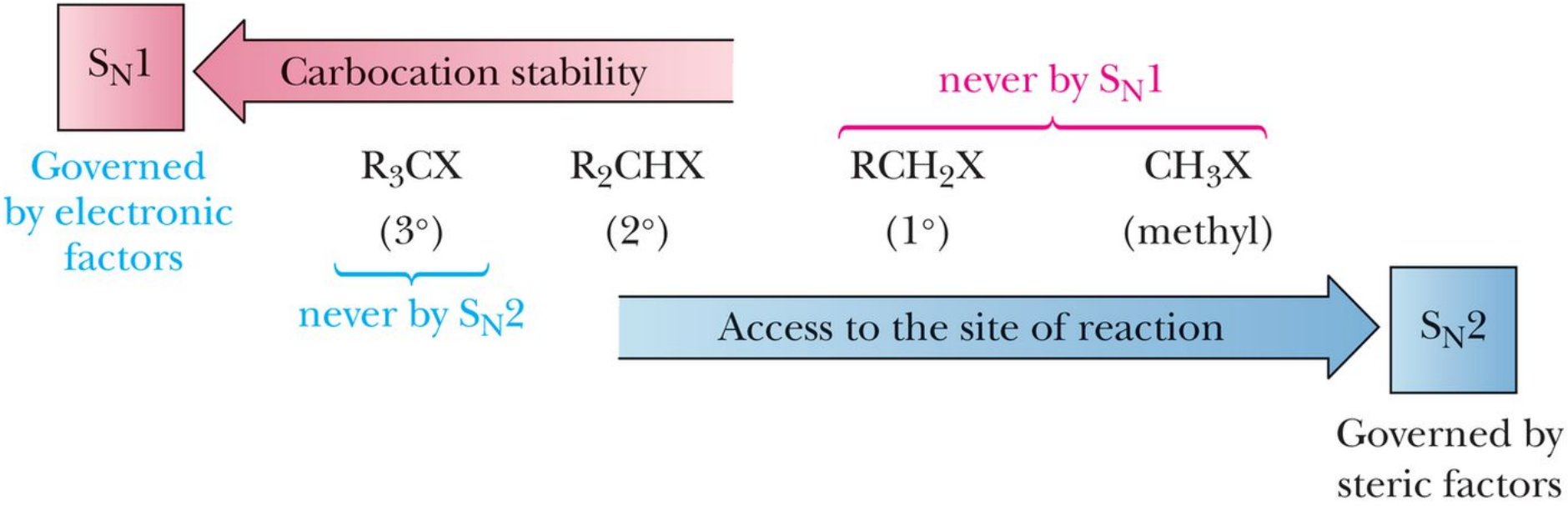


Bromoethane (Ethyl bromide)

2-Bromo-2-methylpropane (*tert*-Butyl bromide)

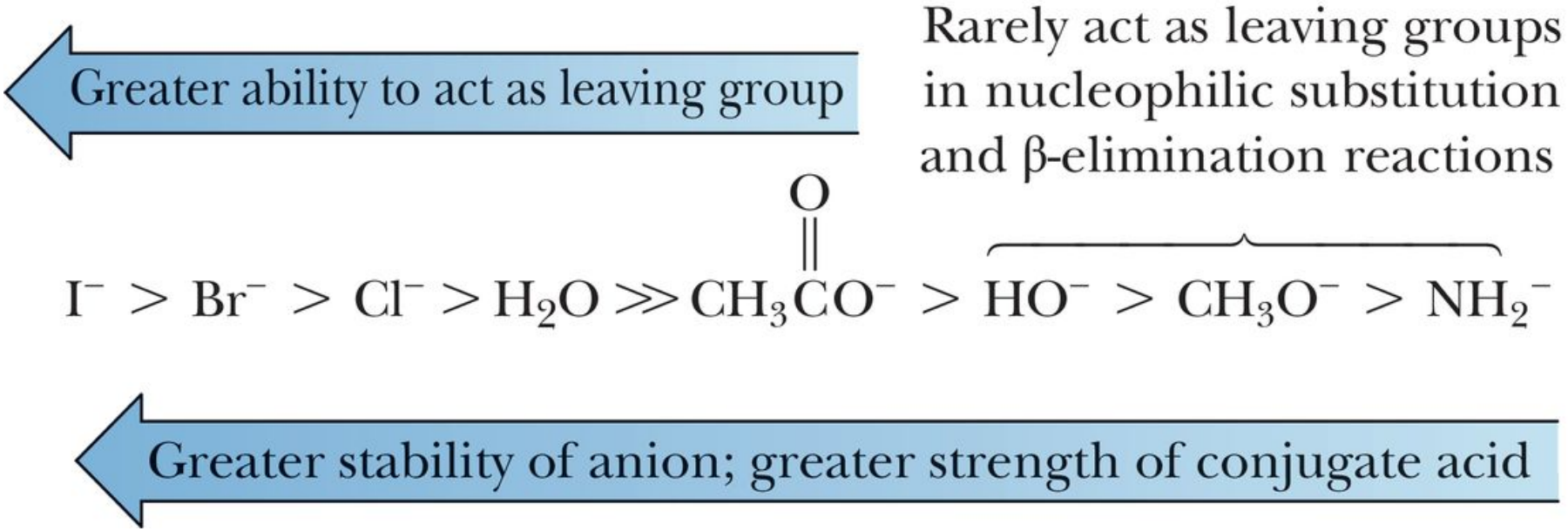
Structure of the Haloalkane

- **Figure 7.3** Effect of electronic and steric factors on competition between S_N1 and S_N2 reactions of haloalkanes.



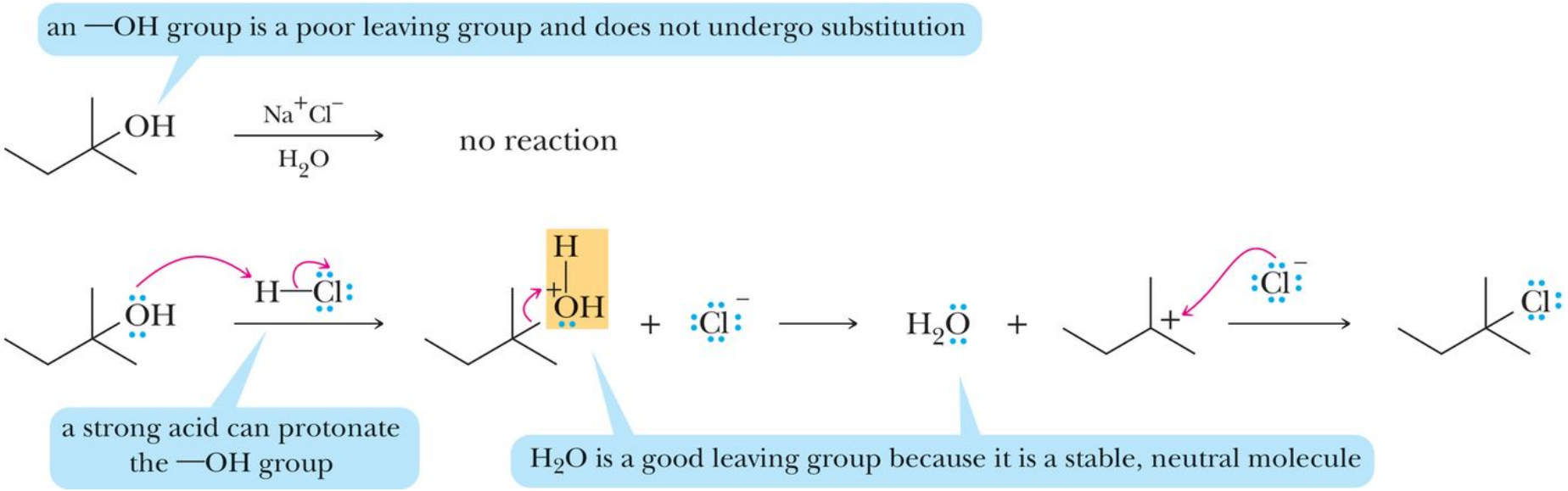
The Leaving Group

- The best leaving groups in this series are the halogens I^-, Br^-, and Cl^-.
- OH^-, RO^-, and NH_2^- are such poor leaving groups that they are rarely if ever displaced in nucleophilic substitution reactions.



The Leaving Group

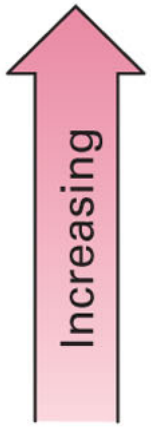
- Hydroxide ion, OH^-, is a poor leaving. However, the –OH group of an alcohol can act as a leaving group, H_2O, if the –OH group is first protonated by an acid to form —OH_2^+, a better leaving group.



The Solvent

- **Protic solvent**: a solvent that contains an –OH group and is a hydrogen bond donor.

TABLE 7.3 Common Protic Solvents

Protic Solvent	Structure	Polarity of Solvent	Notes
Water	H_2O		These solvents favor S_N1 reactions. The greater the polarity of the solvent, the easier it is to form carbocations in it because both the carbocation and the negatively charged leaving group can be solvated.
Formic acid	HCOOH		
Methanol	CH_3OH		
Ethanol	CH_3CH_2OH		
Acetic acid	CH_3COOH		

The Solvent

- **Aprotic solvent**: A solvent that does not contain an –OH group and is not a hydrogen bond donor.
  - Aprotic solvents favor S_N2 reactions. Although the solvents at the top of the table are polar, formation of carbocations in them is more difficult than in protic solvents.

TABLE 7.4 Common Aprotic Solvents

Aprotic Solvent	Structure	Polarity of Solvent	Notes
Dimethyl sulfoxide (DMSO)	$CH_3\overset{\overset{O}{\|}}{S}CH_3$	Increasing	These solvents favor S_N2 reactions. Although solvents at the top of this list are polar, the formation of carbocations in them is far more difficult than in protic solvents because the anionic leaving group cannot be solvated by these solvents.
Acetone	$CH_3\overset{\overset{O}{\|}}{C}CH_3$		
Dichloromethane	CH_2Cl_2		
Diethyl ether	$(CH_3CH_2)_2O$		

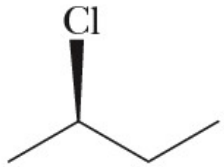
Summary of S_N1 and S_N2 Reactions of Haloalkanes

TABLE 7.5 Summary of S_N1 versus S_N2 Reactions of Haloalkanes

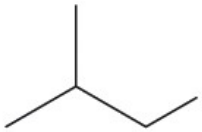
Type of Haloalkane	S_N2	S_N1
Methyl CH_3X	**S_N2 is favored.**	**S_N1 does not occur.** The methyl cation is so unstable that it is never observed in solution.
Primary RCH_2X	**S_N2 is favored.**	**S_N1 does not occur.** Primary carbocations are so unstable that they are not observed in solution.
Secondary R_2CHX	**S_N2 is favored** in aprotic solvents with good nucleophiles.	**S_N1 is favored** in protic solvents with poor nucleophiles.
Tertiary R_3CX	**S_N2 does not occur,** because of steric hindrance around the substitution center.	**S_N1 is favored** because of the ease of formation of tertiary carbocations.
Substitution at a stereocenter	**Inversion of configuration.** The nucleophile attacks the stereocenter from the side opposite the leaving group.	**Racemization.** The carbocation intermediate is planar, and attack by the nucleophile occurs with equal probability from either side.

Nucleophilic Substitution

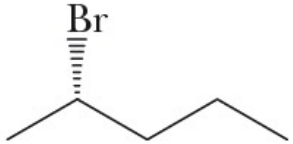
Example: Predict the product of each reaction, the reaction mechanism, and the stereochemistry of the product.

1. 

$+ \ CH_3OH \longrightarrow \underset{CH_3OH}{}$

2. 

$+ \ Na^+I^- \xrightarrow[DMSO]{}$

3. 

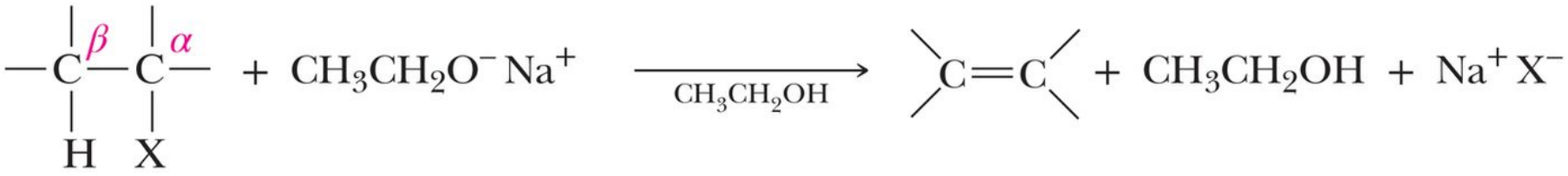
$+ \ CH_3S^-Na^+ \xrightarrow[acetone]{}$

4. 

$+ \ Na^+SH^- \xrightarrow[acetone]{}$

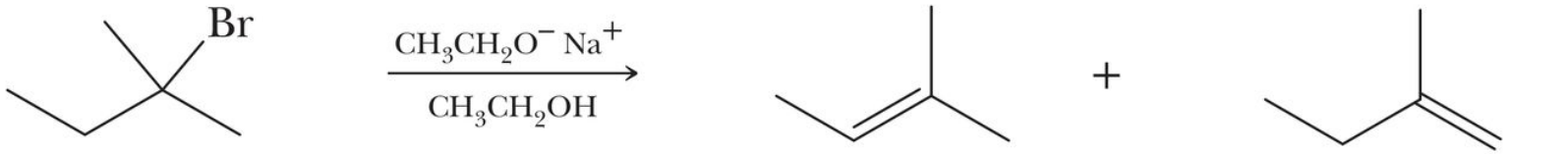
β-Elimination

- **β-Elimination**: Removal of atoms or groups of atoms from adjacent carbons to form a carbon-carbon double bond.
  - We study a type of β-elimination called **dehydrohalogenation** (the elimination of HX).



β-Elimination

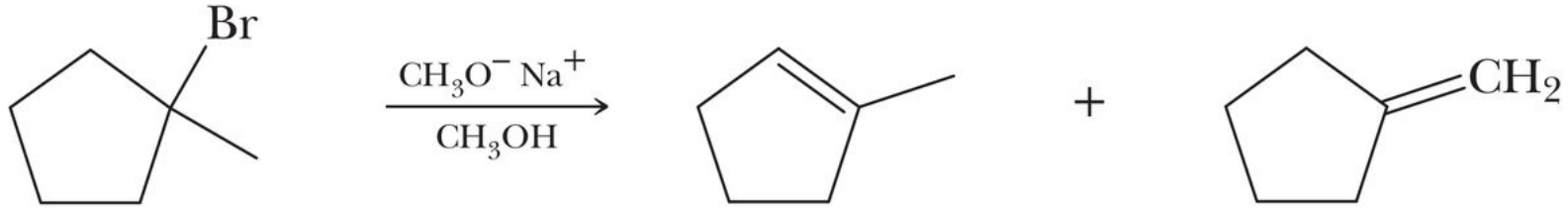
- **Zaitsev's rule**: The major product of a β-elimination is the more stable (the more highly substituted) alkene. When *cis-trans* isomerism is possible, the *trans* isomer is favored.



2-Bromo-2-methylbutane

2-Methyl-2-butene (major product)

2-Methyl-1-butene



1-Bromo-1-methylcyclopentane

1-Methylcyclopentene (major product)

Methylenecyclopentane

β-Elimination

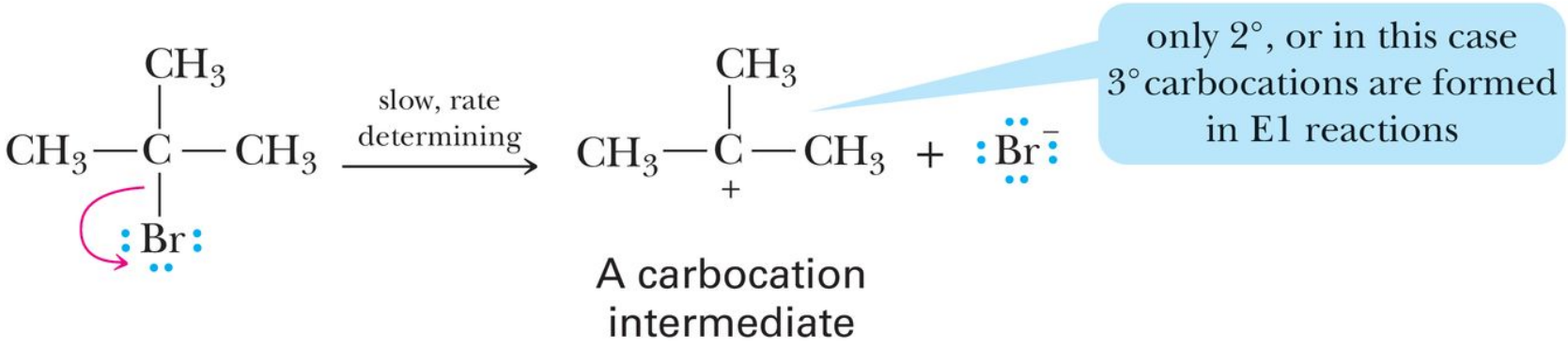
- There are two limiting mechanisms for β-elimination reactions.

- **E1 mechanism**: at one extreme, breaking of the C-X bond is complete before reaction with base breaks the C-H bond.
  - Only R-X is involved in the rate-determining step.

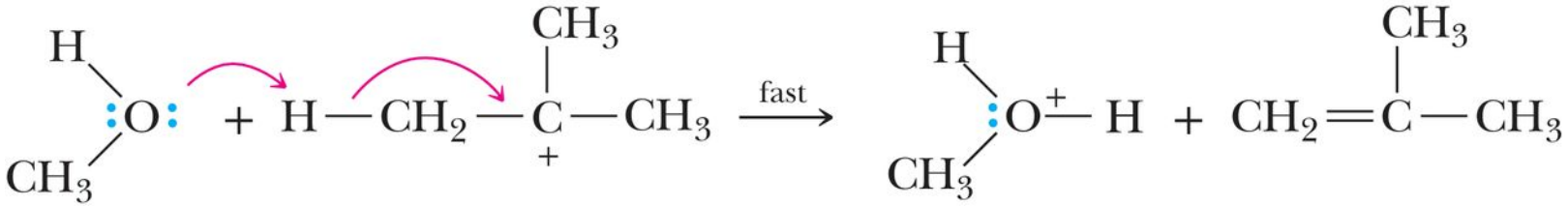
- **E2 mechanism**: at the other extreme, breaking of the C-X and C-H bonds is concerted.
  - Both R-X and base are involved in the rate-determining step.

E1 Mechanism

- **Step 1: Break a bond to give a stable molecule or ion.** Rate-determining ionization of C-X gives a carbocation intermediate and halide ion.

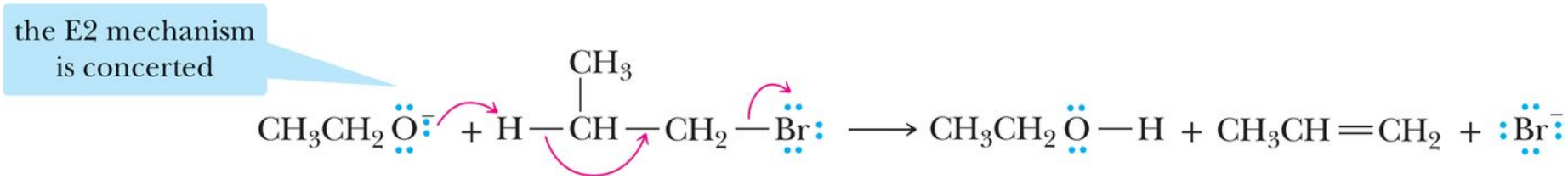


- **Step 2: Take a proton away.** Proton transfer from the carbocation to a base (in this case, the solvent) gives the alkene.



E2 Mechanism

- A one-step mechanism; all bond-breaking and bond-forming steps are concerted. Simultaneously (1) take a proton away and (2) break a bond to form a stable ion or molecule.



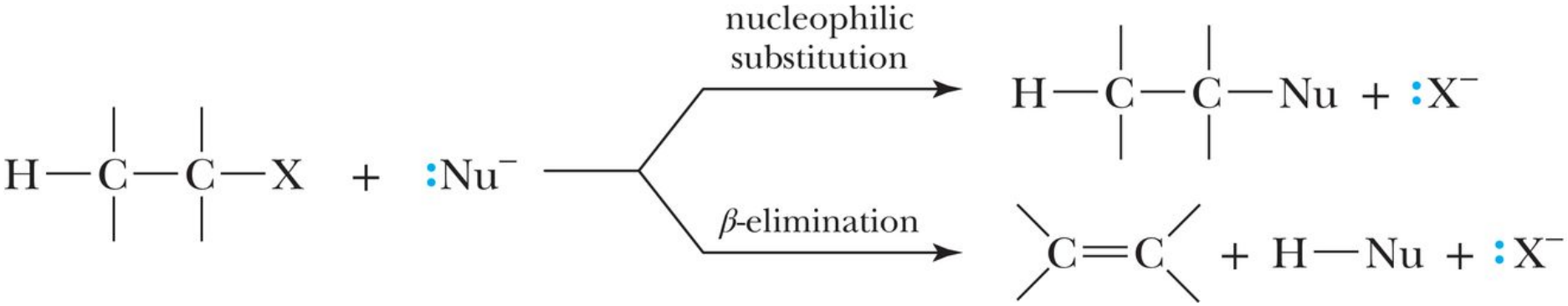
Elimination Reactions (β-Elimination)

TABLE 7.6 Summary of E1 versus E2 Reactions of Haloalkanes

Haloalkane	E1	E2
Primary RCH_2X	E1 does not occur. Primary carbocations are so unstable that they are never observed in solution.	E2 is favored.
Secondary R_2CHX	Main reaction with weak bases such as H_2O and ROH.	Main reaction with strong bases such as OH^- and OR^-.
Tertiary R_3CX	Main reaction with weak bases such as H_2O and ROH.	Main reaction with strong bases such as OH^- and OR^-.

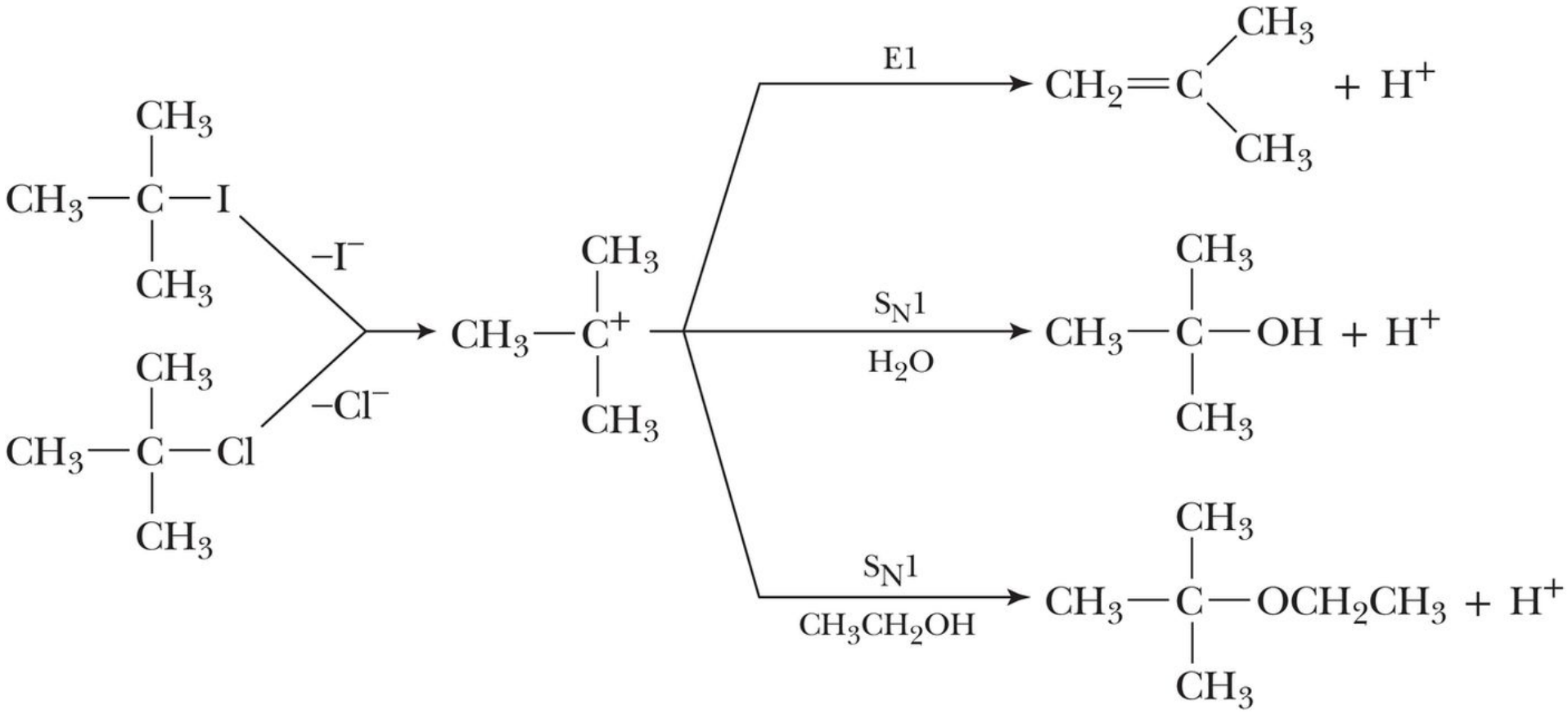
Substitution versus Elimination

- Because many nucleophiles are also strong bases (OH^- and RO^-), S_N and E reactions often compete.
  - The ratio of S_N/E products depends on the relative rates of the two reactions.



S_N1 versus E1

- Reactions of 2° and 3° haloalkanes in polar protic solvents give mixtures of substitution and elimination products. Product ratios are difficult to predict.

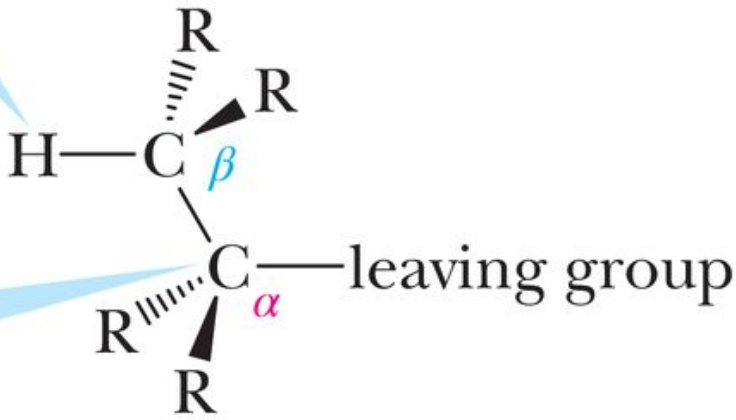


S_N2 versus E2

- It is considerably easier to predict the ratio of S_N2 to E2 products.

attack of a base on a β-hydrogen by E2 is only slightly affected by branching at the α-carbon; alkene formation is accelerated

S_N2 attack of a nucleophile is impeded by branching at the α- and β-carbons



Summary of S_N versus E for Haloalkanes

- For Methyl and Primary Haloalkanes

TABLE 7.7 Summary of Substitution versus Elimination Reactions of Haloalkanes

Halide	Reaction	Comments
Methyl CH_3X	S_N2	The only substitution reactions observed.
	~~S_N1~~	S_N1 reactions of methyl halides are never observed. The methyl cation is so unstable that it is never formed in solution.
Primary RCH_2X	S_N2	The main reaction with strong bases such as OH^- and EtO^-. Also, the main reaction with good nucleophiles/weak bases, such as I^- and CH_3COO^-.
	E2	The main reaction with strong, bulky bases, such as potassium *tert*-butoxide.
	~~S_N1/E1~~	Primary cations are never formed in solution; therefore, S_N1 and E1 reactions of primary halides are never observed.

Summary of S_N versus E for Haloalkanes

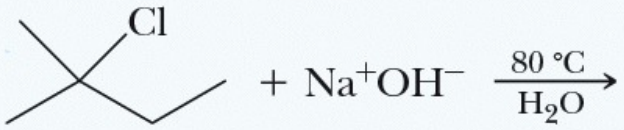
- For Secondary and Tertiary Halo-alkanes

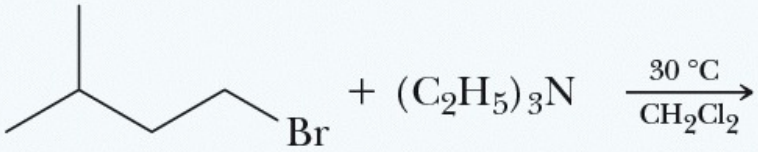
TABLE 7.7 Summary of Substitution versus Elimination Reactions of Haloalkanes

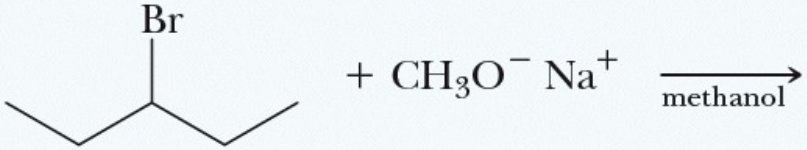
Halide	Reaction	Comments
Secondary R_2CHX	S_N2	The main reaction with weak bases/good nucleophiles, such as I^- and CH_3COO^-.
	E2	The main reaction with strong bases/good nucleophiles, such as OH^- and $CH_3CH_2O^-$.
	S_N1/E1	Common in reactions with weak nucleophiles in polar protic solvents, such as water, methanol, and ethanol.
Tertiary R_3CX	~~S_N2~~	S_N2 reactions of tertiary halides are never observed because of the extreme crowding around the 3° carbon.
	E2	Main reaction with strong bases, such as HO^- and RO^-.
	S_N1/E1	Main reactions with poor nucleophiles/weak bases.

Summary of S_N versus E for Haloalkanes

- **Examples**: Predict the major product and the mechanism for each reaction.

1. 

2. 

3. 

4.