Chapter 4
Alcohols and Alkyl Halides

Overview of Chapter

- Chapter 4 introduces chemical reactions and their mechanisms by focusing on two reactions that yield alkyl halides.

(1) alcohol + hydrogen halide

$$ROH + HX \rightarrow RX + H_2O$$

(2) alkane + halogen

$$RH + X_2 \rightarrow RX + HX$$

Both are substitution reactions.

4.1. Functional Group

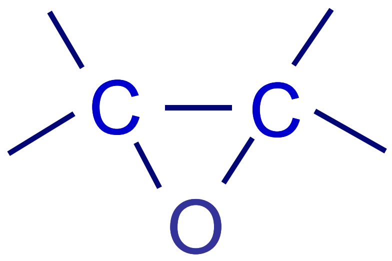
- A structural unit in a molecule responsible for its characteristic behavior under a particular set of reaction conditions.

Families of organic compounds and their functional groups

Alcohol	ROH
Alkyl halide RX	(X = F, Cl, Br, I)
Amine	primary amine: RNH_2 secondary amine: R_2NH tertiary amine: R_3N

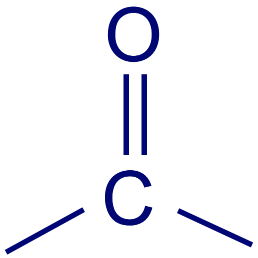
Families of organic compounds and their functional groups

Epoxide

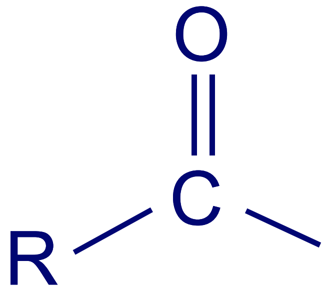


Ether	ROR'
Nitrile	RCN
Nitroalkane	RNO_2
Sulfide	RSR'
Thiol	RSH

Many classes of organic compounds contain a carbonyl group

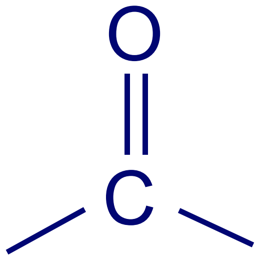


Carbonyl group

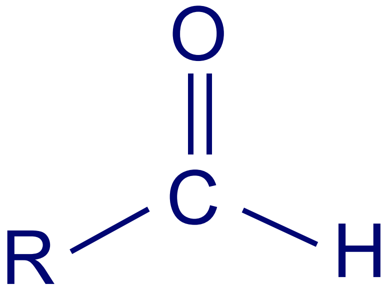


Acyl group

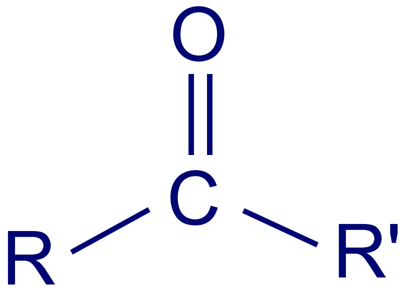
Many classes of organic compounds contain a carbonyl group



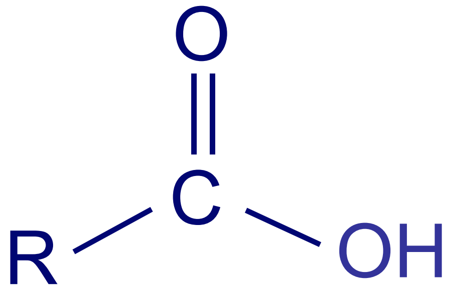
Carbonyl group



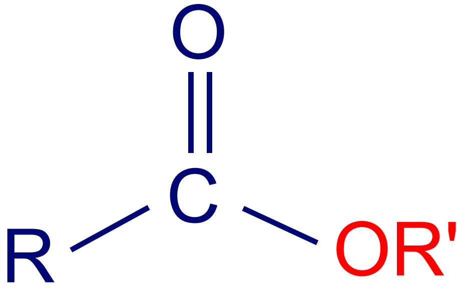
Aldehyde



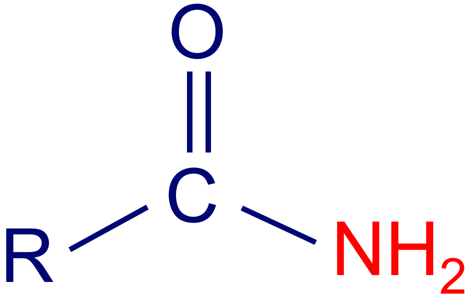
Ketone



Carboxylic acid



Ester



Amide

4.2. IUPAC Nomenclature of Alkyl Halides

- There are several kinds of IUPAC nomenclature.

- The two that are most widely used are:
    1. Functional class nomenclature
    2. Substitutive nomenclature

Both types can be applied to alcohols and alkyl halides.

Functional Class Nomenclature of Alkyl Halides

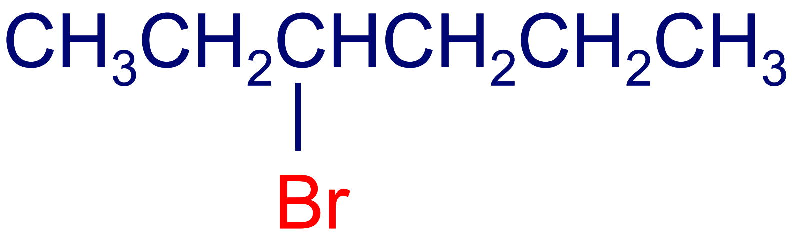
➢ Name the alkyl group and the halogen as separate words (*alkyl* + *halide*).

CH_3F

Methyl fluoride

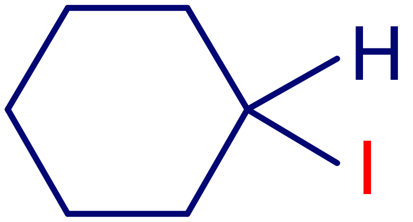
$CH_3CH_2CH_2CH_2CH_2Cl$

Pentyl chloride



$$\underset{\displaystyle Br}{CH_3CH_2\underset{|}{C}HCH_2CH_2CH_3}$$

1-Ethylbutyl bromide



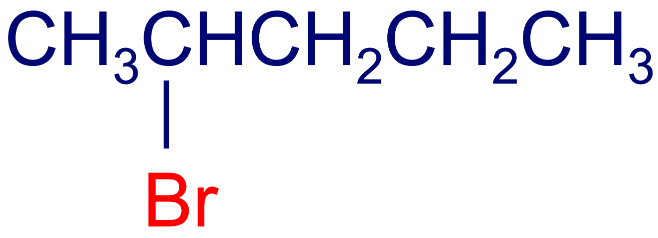
Cyclohexyl iodide

Substitutive Nomenclature of Alkyl Halides

- ➢ Name as halo-substituted alkanes.
- ➢ Number the longest chain containing the halogen in the direction that gives the lowest number to the substituted carbon.

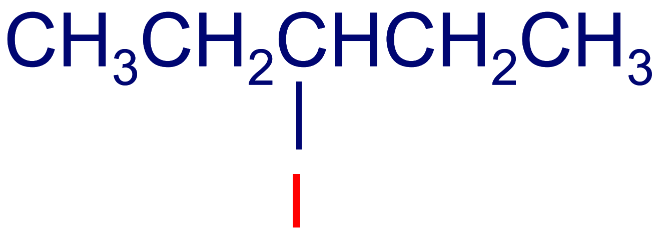
$CH_3CH_2CH_2CH_2CH_2F$

1-Fluoropentane



$CH_3\underset{\underset{\displaystyle Br}{|}}{CH}CH_2CH_2CH_3$

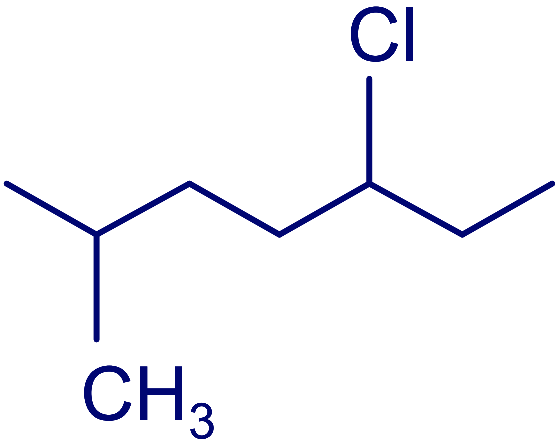
2-Bromopentane



$CH_3CH_2\underset{\underset{\displaystyle I}{|}}{CH}CH_2CH_3$

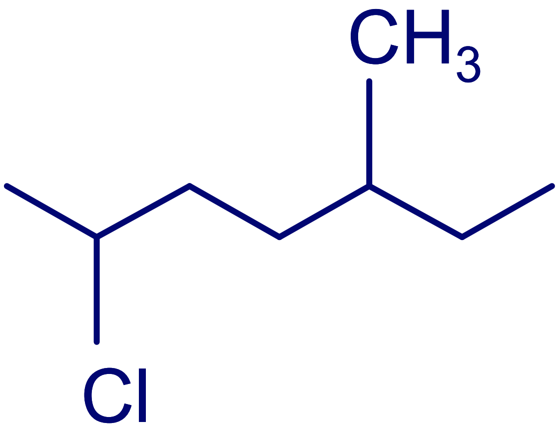
3-Iodopentane

Substitutive Nomenclature of Alkyl Halides



5-Chloro-2-methylheptane

- ➢ Halogen and alkyl groups are of equal rank when it comes to numbering the chain.



2-Chloro-5-methylheptane

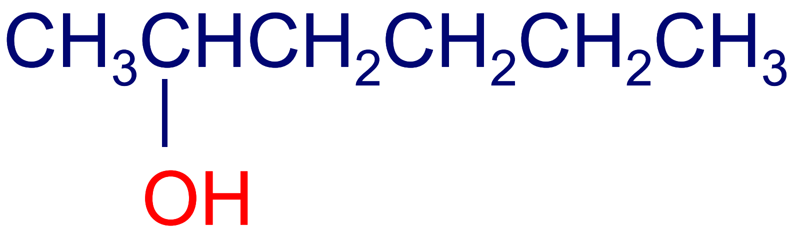
- ➢ Number the chain in the direction that gives the lowest number to the group (halogen or alkyl) that appears first.

4.3. IUPAC Nomenclature of Alcohols

- Name the alkyl group and add "alcohol" as a separate word.

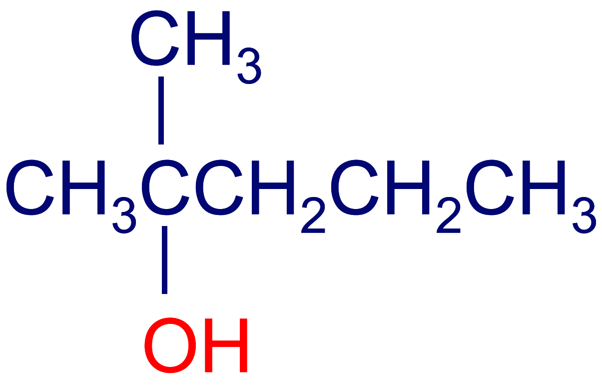
CH_3CH_2OH

Ethyl alcohol



$$CH_3\underset{\underset{OH}{|}}{C}HCH_2CH_2CH_2CH_3$$

1-Methylpentyl alcohol



$$CH_3\overset{\overset{CH_3}{|}}{\underset{\underset{OH}{|}}{C}}CH_2CH_2CH_3$$

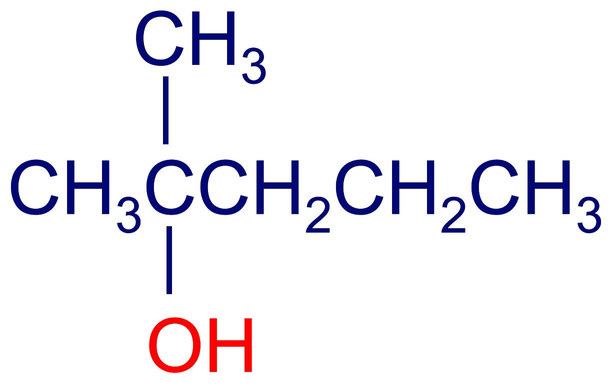
1,1-Dimethylbutyl alcohol

Substitutive Nomenclature of Alcohols

- Name as "alkanols." Replace -e ending of alkane name by -ol.
- Number chain in direction that gives lowest number to the carbon that bears the —OH group.

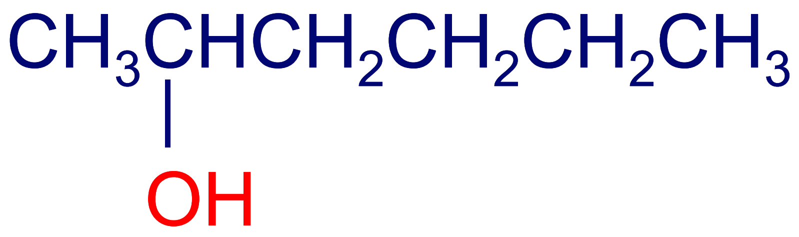
$\mathrm{CH_3CH_2OH}$

Ethanol



$$\mathrm{CH_3\overset{\overset{CH_3}{|}}{\underset{\underset{OH}{|}}{C}}CH_2CH_2CH_3}$$

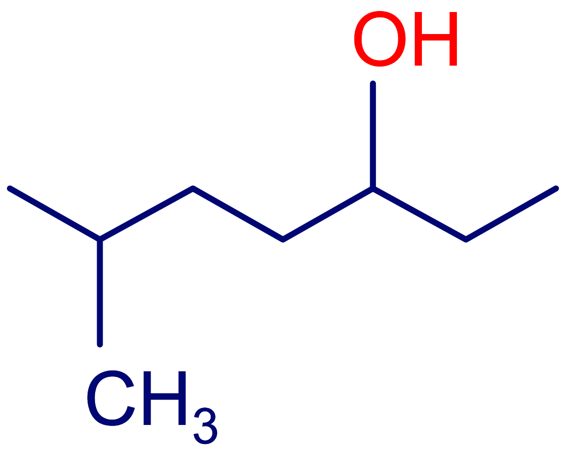
2-Methyl-2-pentanol



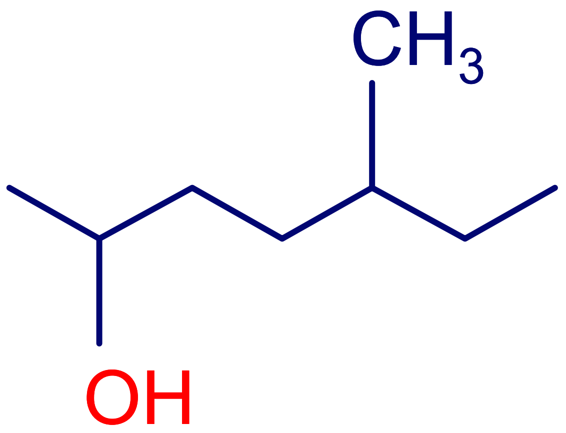
$$\mathrm{CH_3\underset{\underset{OH}{|}}{C}HCH_2CH_2CH_2CH_3}$$

2-Hexanol

Substitutive Nomenclature of Alcohols



6-Methyl-3-heptanol



5-Methyl-2-heptanol

- Hydroxyl groups outrank alkyl groups when it comes to numbering the chain.
- Number the chain in the direction that gives the lowest number to the carbon that bears the OH group.

4.4. Classes of Alcohols and Alkyl Halides

- Alcohols and alkyl halides are classified as
  - primary
  - secondary
  - tertiary

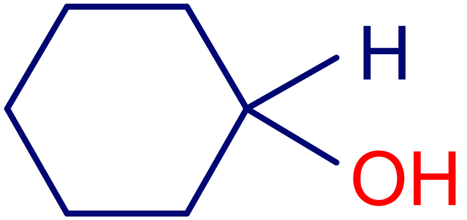
according to their "degree of substitution”.

- Degree of substitution is determined by counting the number of carbon atoms directly attached to the carbon that bears the halogen or hydroxyl group.

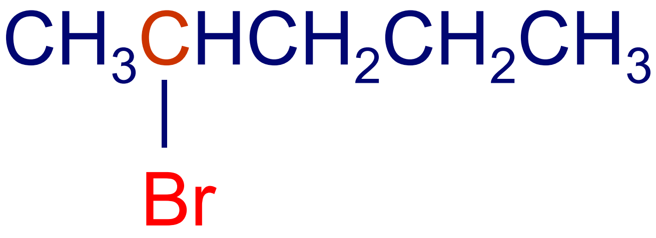
Classification

$CH_3CH_2CH_2CH_2CH_2F$

primary alkyl halide

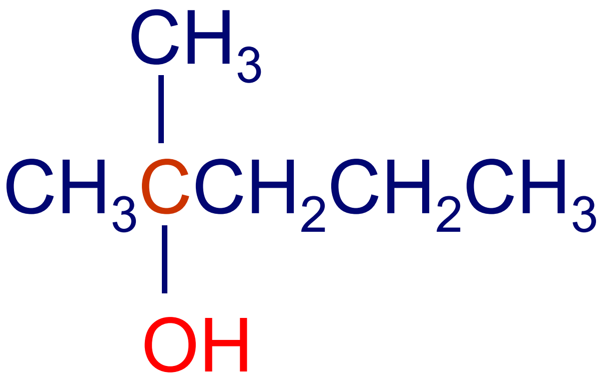


secondary alcohol



$$CH_3\underset{\displaystyle Br}{\underset{|}{C}}HCH_2CH_2CH_3$$

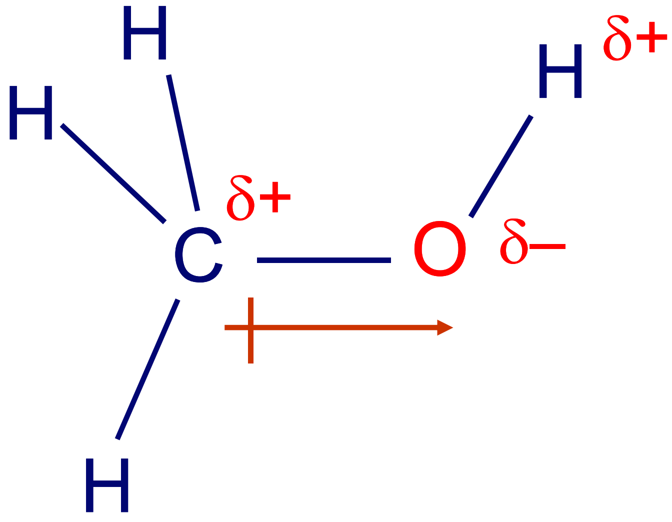
secondary alkyl halide



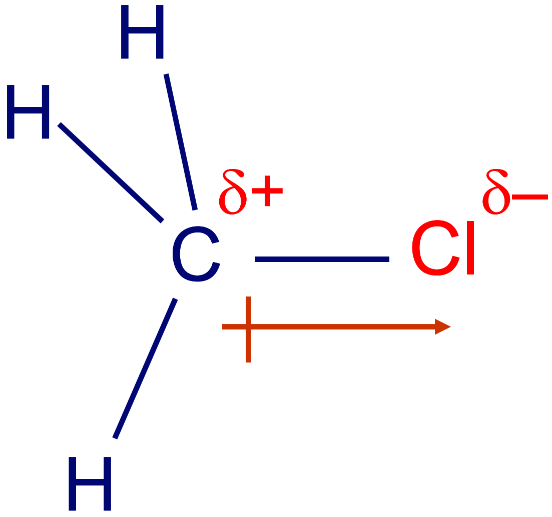
$$CH_3\underset{\displaystyle OH}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}CH_2CH_2CH_3$$

tertiary alcohol

4.5. Bonding in Alcohols and Alkyl Halides



μ = 1.7 D

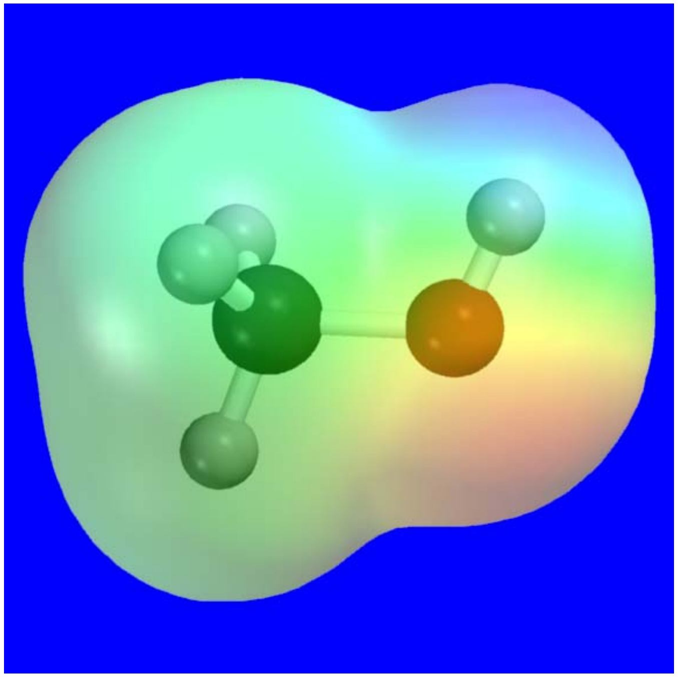


μ = 1.9 D

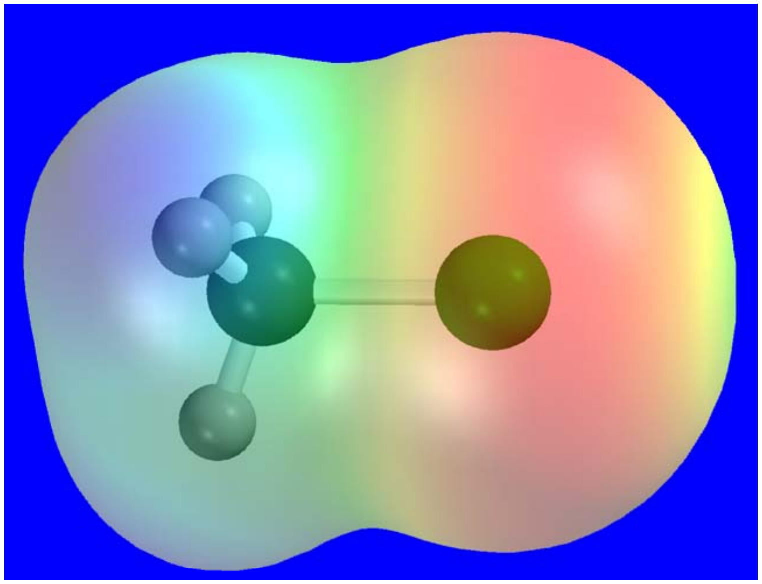
- Alcohols and alkyl halides are polar.

Dipole Moments

- Alcohols and alkyl halides are polar



$\mu = 1.7$ D



$\mu = 1.9$ D

Electrostatic potential maps of CH_3OH & CH_3Cl

4.6

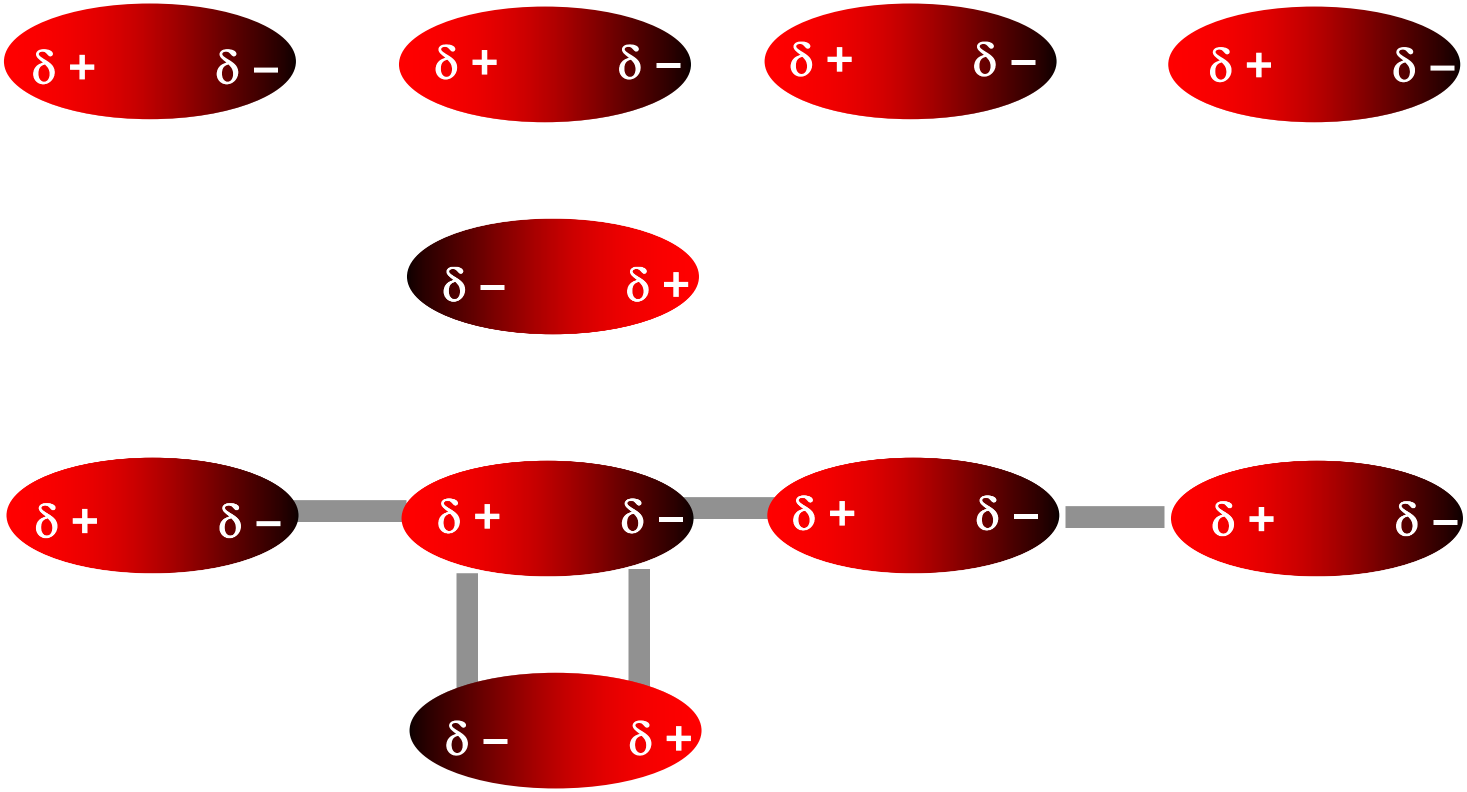
Physical Properties of Alcohols and Alkyl Halides: Intermolecular Forces

Boiling point

Solubility in water

Density

Dipole-Dipole Attractive Forces



- Two molecules of a polar substance associate so that the positively polarized region of and the negatively polarized region of the other attract each other.

Effect of Structure on Boiling Point

	$CH_3CH_2CH_3$	CH_3CH_2F	CH_3CH_2OH
Molecular weight	44	48	46
Boiling point, °C	-42	-32	+78
Dipole moment, D	0	1.9	1.7

Effect of Structure on Boiling Point

	$CH_3CH_2CH_3$
Molecular weight	44
Boiling point, °C	-42
Dipole moment, D	0

- Intermolecular forces are weak.
- Only intermolecular forces are induced dipole-induced dipole attractions.

Effect of Structure on Boiling Point

	CH_3CH_2F
Molecular weight	48
Boiling point, °C	-32
Dipole moment, D	1.9

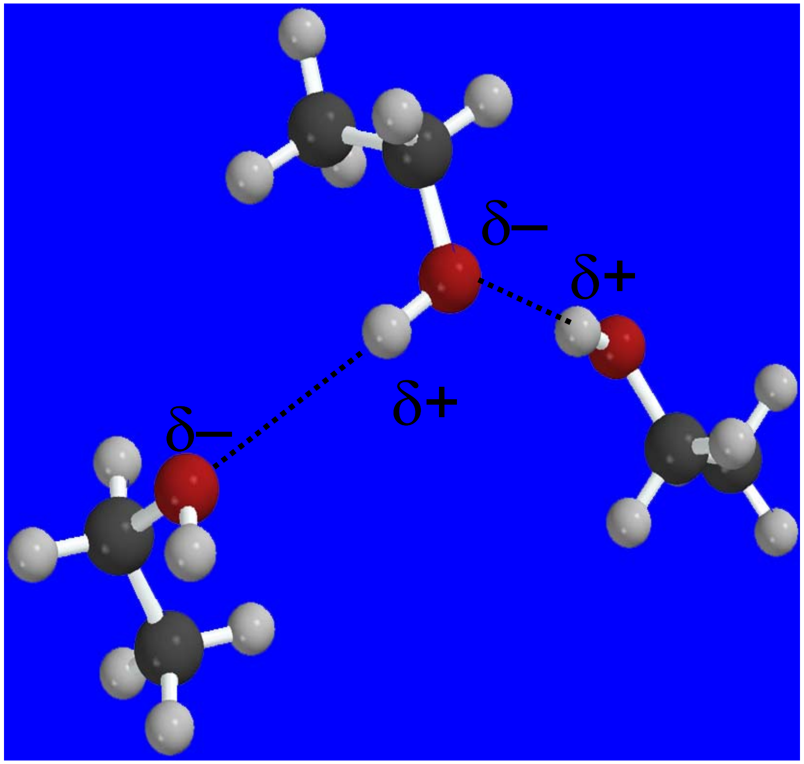
- A polar molecule; therefore dipole-dipole and dipole-induced dipole forces contribute to intermolecular attractions.

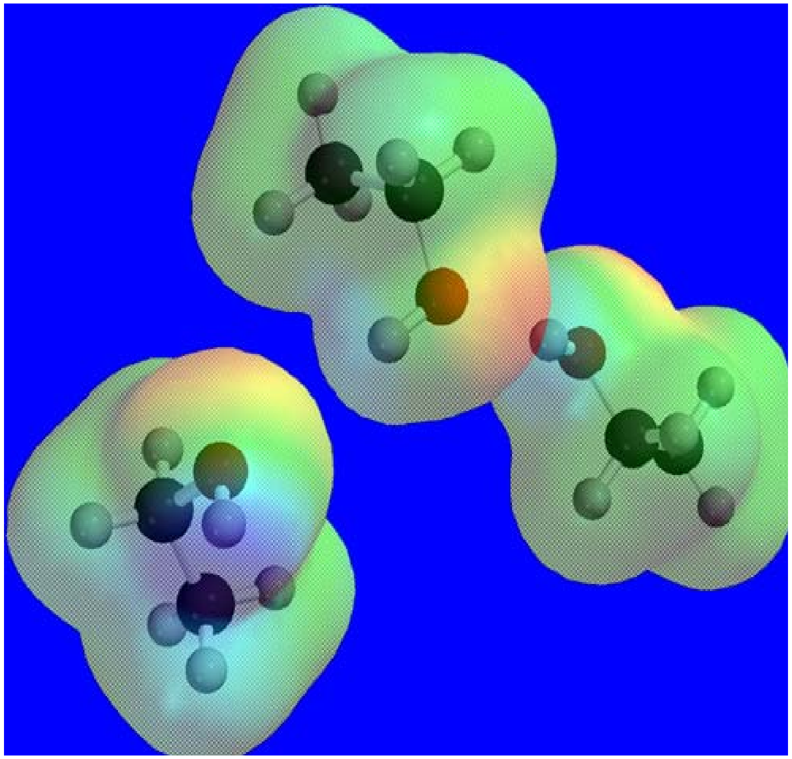
Effect of Structure on Boiling Point

	CH_3CH_2OH
Molecular weight	46
Boiling point, °C	+78
Dipole moment, D	1.7

- Highest boiling point; strongest intermolecular attractive forces.
- Hydrogen bonding is stronger than other dipole-dipole attractions.

Figure 4.4. Hydrogen bonding in ethanol





Boiling point increases with increasing number of halogens

Compound	Boiling Point
CH_3Cl	-24°C
CH_2Cl_2	40°C
$CHCl_3$	61°C
CCl_4	77°C

- Even though CCl_4 is the only compound in this list without a dipole moment, it has the highest boiling point.

- Induced dipole-induced dipole forces are greatest in CCl_4 because it has the greatest number of Cl atoms. Cl is more polarizable than H.

But trend is not followed when halogen is fluorine

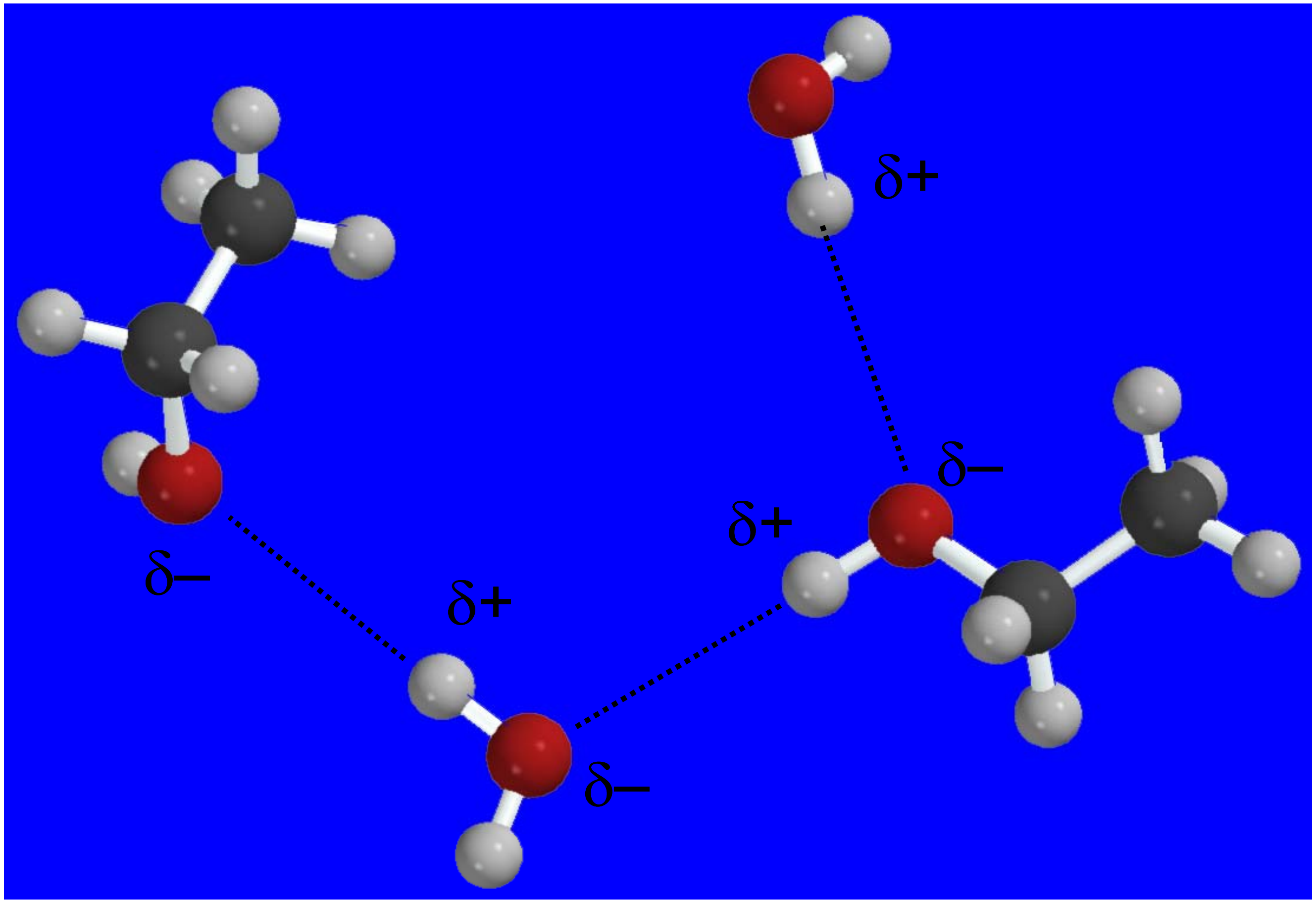
Compound	Boiling Point
CH_3CH_2F	-32°C
CH_3CHF_2	-25°C
CH_3CF_3	-47°C
CF_3CF_3	-78°C

- Fluorine is not very polarizable and induced dipole-induced dipole forces decrease with increasing fluorine substitution.

Solubility in water

- Alkyl halides are insoluble in water.
- Methanol, ethanol, isopropyl alcohol are completely miscible with water.
- The solubility of an alcohol in water decreases with increasing number of carbons (compound becomes more hydrocarbon-like).

Figure 4.5. Hydrogen Bonding Between Ethanol and Water



Density

- Alkyl fluorides and alkyl chlorides are less dense than water. However, $CHCl_3$, CH_2Cl_2, CCl_4 are more dense than water.
- Alkyl bromides and alkyl iodides are more dense than water.
- All liquid alcohols have densities of about 0.8 g/mL.

4.7. Preparation of Alkyl Halides from Alcohols and Hydrogen Halides

$$\mathrm{ROH} + \mathrm{HX} \rightarrow \mathrm{RX} + \mathrm{H_2O}$$

Reaction of Alcohols with Hydrogen Halides

$$ROH + HX \rightarrow RX + HOH$$

Hydrogen halide reactivity

HF HCl HBr HI

least reactive most reactive

Reaction of Alcohols with Hydrogen Halides

$$ROH + HX \rightarrow RX + HOH$$

Alcohol reactivity

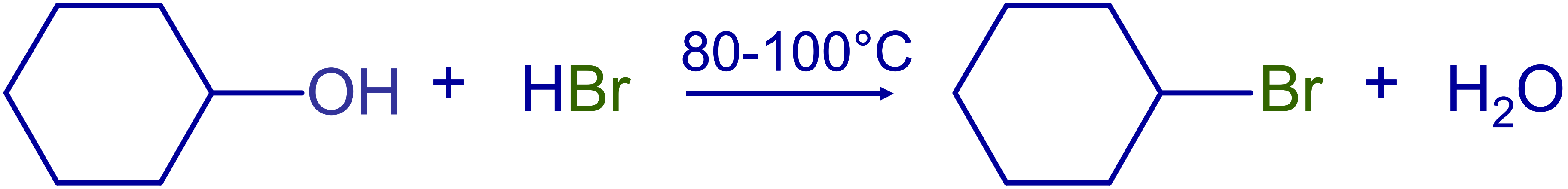
CH_3OH	RCH_2OH	R_2CHOH	R_3COH
Methanol	Primary	Secondary	Tertiary

least reactive → most reactive

Preparation of Alkyl Halides

$$(CH_3)_3COH + HCl \xrightarrow{25°C} (CH_3)_3CCl + H_2O$$

78-88%



73%

$$CH_3(CH_2)_5CH_2OH \;+\; HBr \xrightarrow{120°C}$$

$$CH_3(CH_2)_5CH_2Br \;+\; H_2O$$

87-90%

Preparation of Alkyl Halides

A mixture of sodium bromide and sulfuric acid may be used in place of HBr.

$$CH_3CH_2CH_2CH_2OH \xrightarrow[\text{heat}]{\substack{NaBr \\ H_2SO_4}} CH_3CH_2CH_2CH_2Br$$

70-83%

4.8. Mechanism of the Reaction of Alcohols with Hydrogen Halides: Hammond's Postulate

About mechanisms

- A mechanism describes how reactants are converted to products.
- Mechanisms are often written as a series of chemical equations showing the *elementary steps.*
- An elementary step is a reaction that proceeds by way of a single transition state.
- Mechanisms can be shown *likely* to be correct, but cannot be *proven* correct.

About Mechanisms

For the reaction:

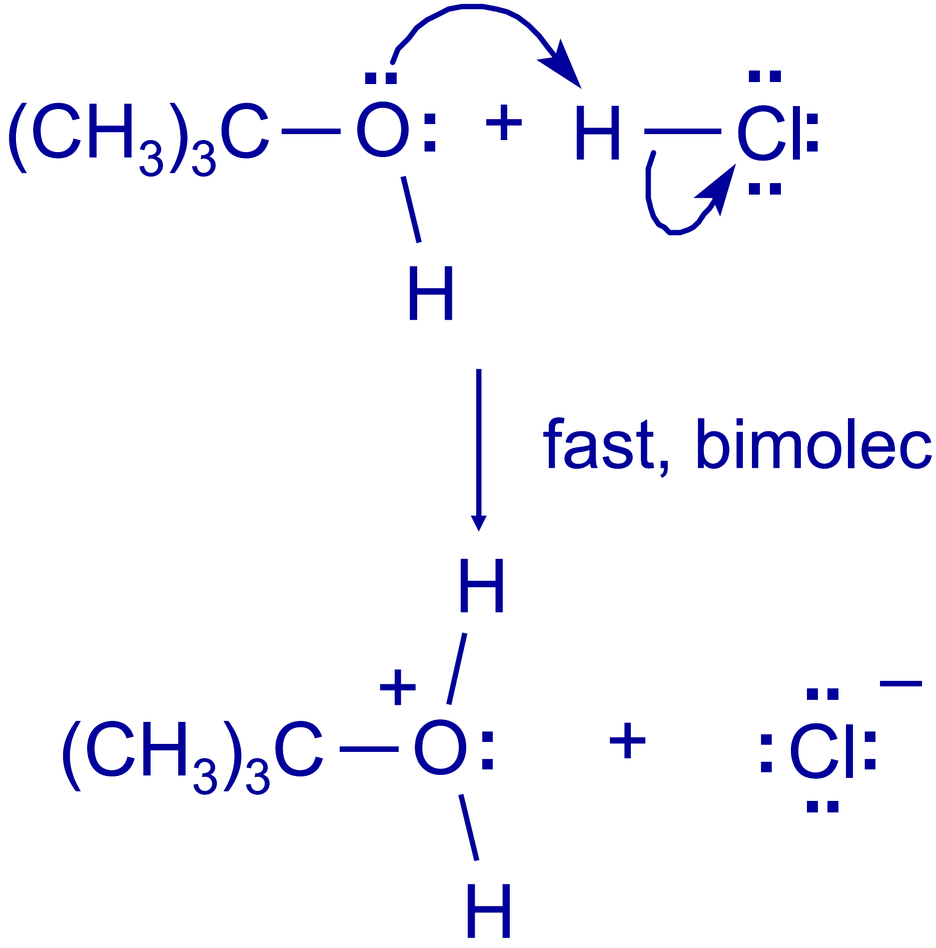
$$(CH_3)_3COH + HCl \xrightarrow{25°C} (CH_3)_3CCl + H_2O$$

tert-Butyl alcohol

tert-Butyl chloride

- The generally accepted mechanism involves three elementary steps.
- Step 1 is a Brønsted acid-base reaction.

Step 1: Proton transfer



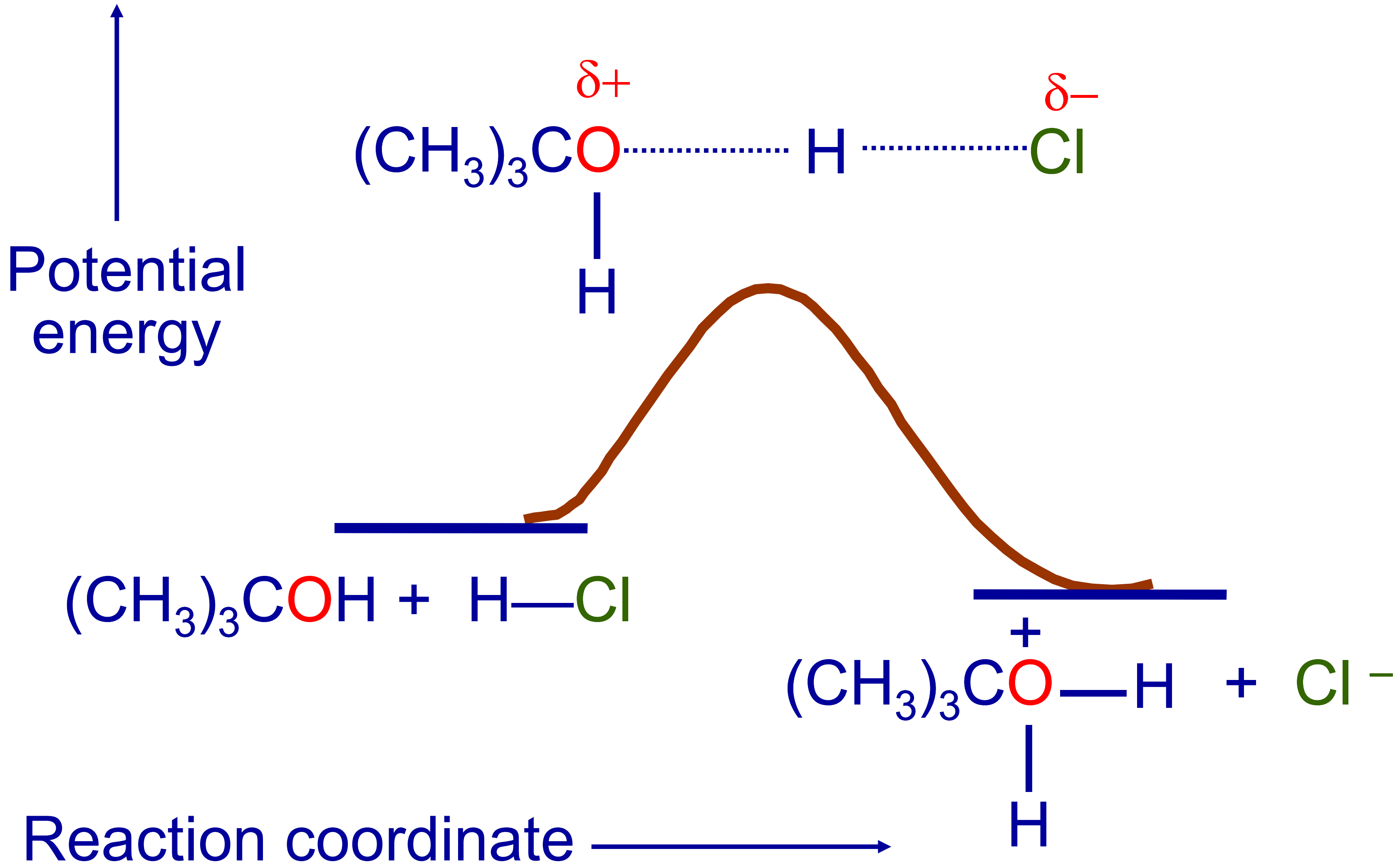
$$(CH_3)_3C-\ddot{O}H: + H-Cl: \xrightarrow{\text{fast, bimolecular}} (CH_3)_3C-\overset{+}{O}H_2 + :Cl:^-$$

- ➢ Like proton transfer from a strong acid to water, proton transfer from a strong acid to an alcohol is normally very *fast*.

- ➢ Two molecules react in this elementary step; therefore, it is *bimolecular*.

tert-Butyloxonium ion: an *intermediate* in the overall reaction.

Potential energy diagram for Step 1



$(CH_3)_3C\underset{\displaystyle H}{\overset{\delta+}{O}}\cdots\cdots H\cdots\cdots\overset{\delta-}{Cl}$

Potential energy

$(CH_3)_3COH + H—Cl$

$(CH_3)_3C\underset{\displaystyle H}{\overset{+}{O}}—H + Cl^-$

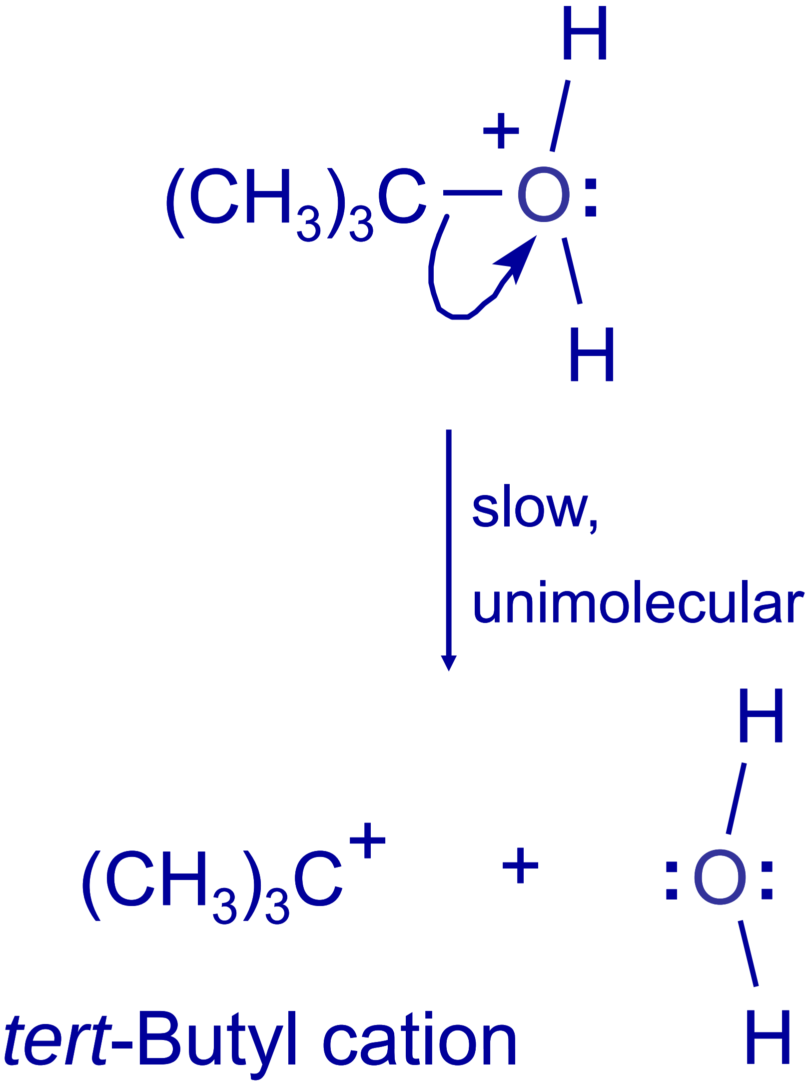
Reaction coordinate

Step 2: Carbocation formation

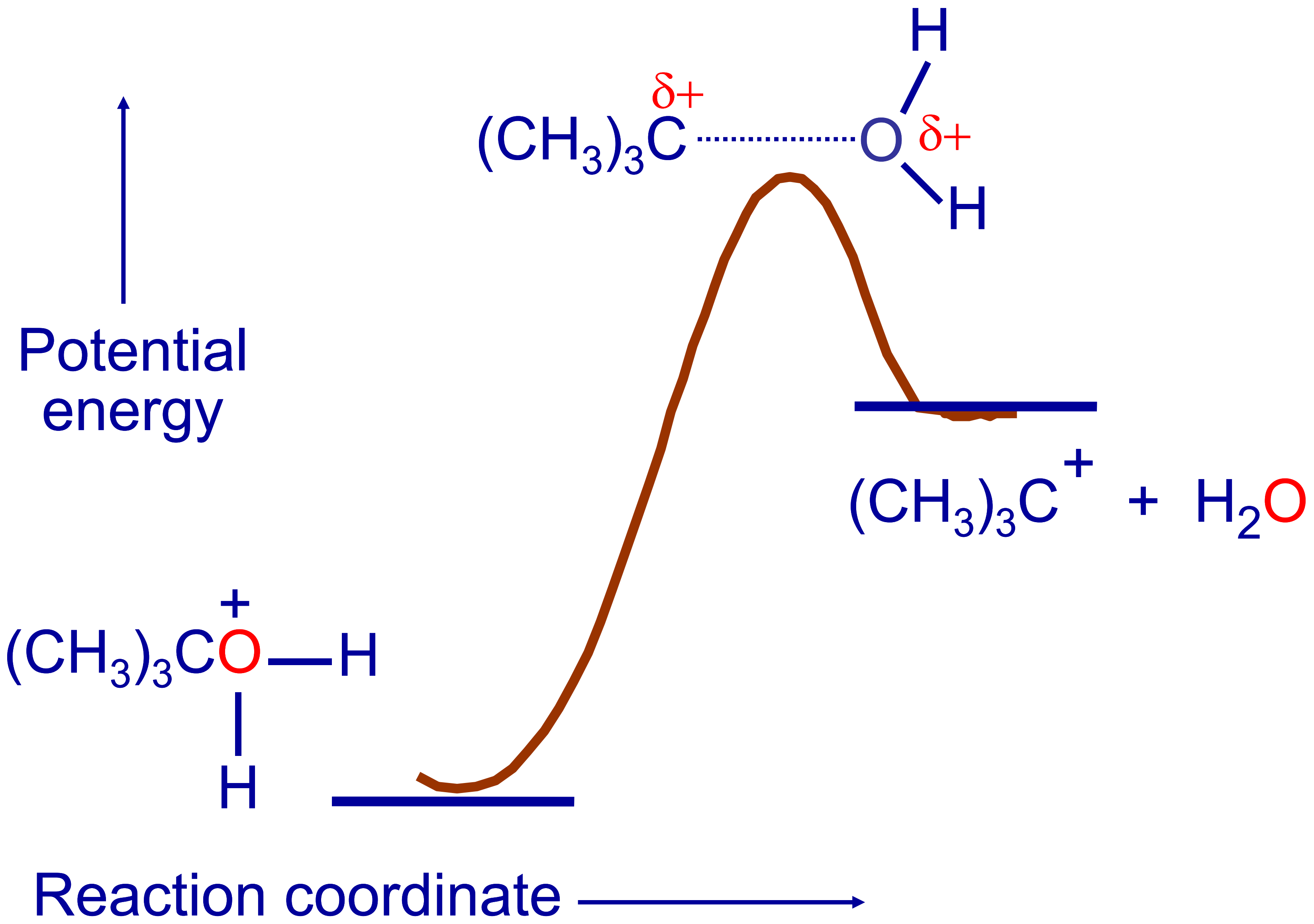
- Dissociation of the alkyloxonium ion involves bond-breaking, without any bond-making to compensate for it. It has a high activation energy and is *slow*.

- A single molecule reacts in this step; therefore, it is *unimolecular*.

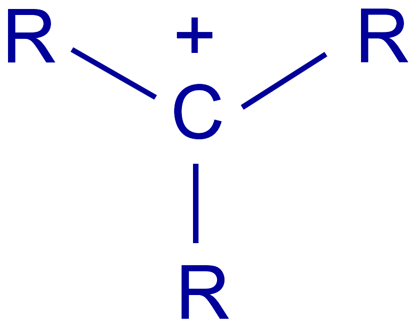
- The product of this step is a carbocation. It is an *intermediate* in the overall process.



Potential energy diagram for Step 2



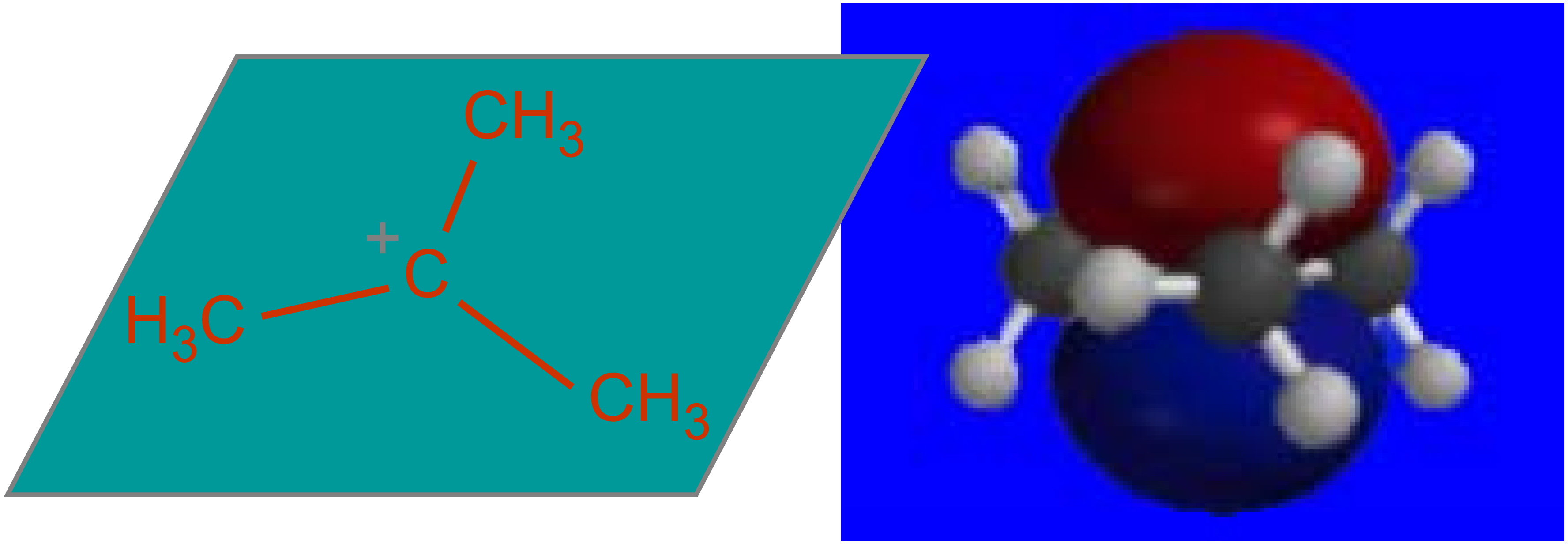
Carbocation



- The key intermediate in reaction of secondary and tertiary alcohols with hydrogen halides is a carbocation.

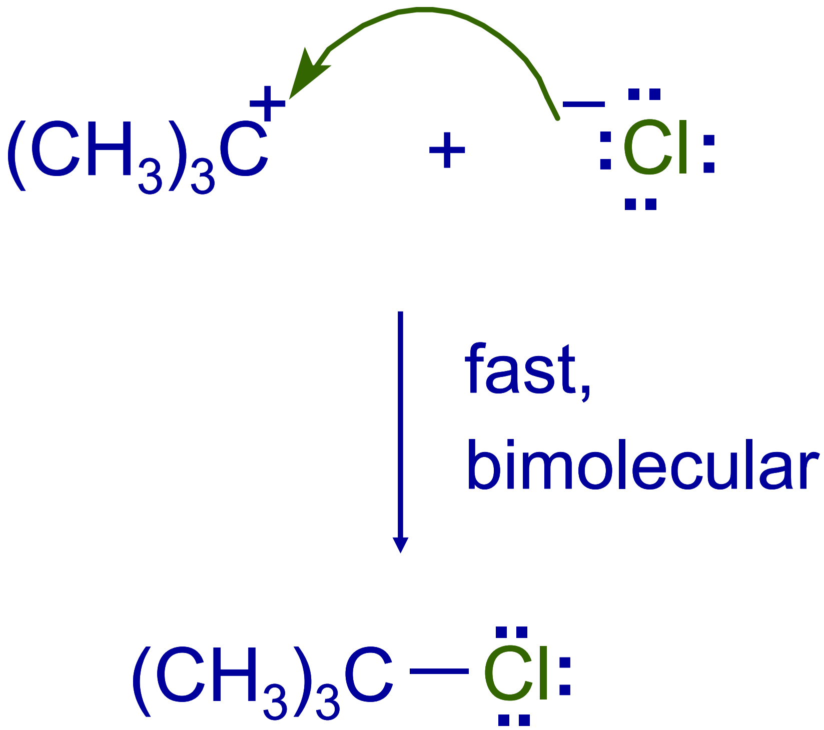
- A carbocation is a cation in which carbon has 6 valence electrons and a positive charge.

Figure 4.8. Structure of tert-Butyl Cation



- Positively charged carbon is *sp*^{2} hybridized.
- All four carbons lie in same plane.
- Unhybridized *p* orbital is perpendicular to plane of four carbons.

Step 3: Carbocation capture

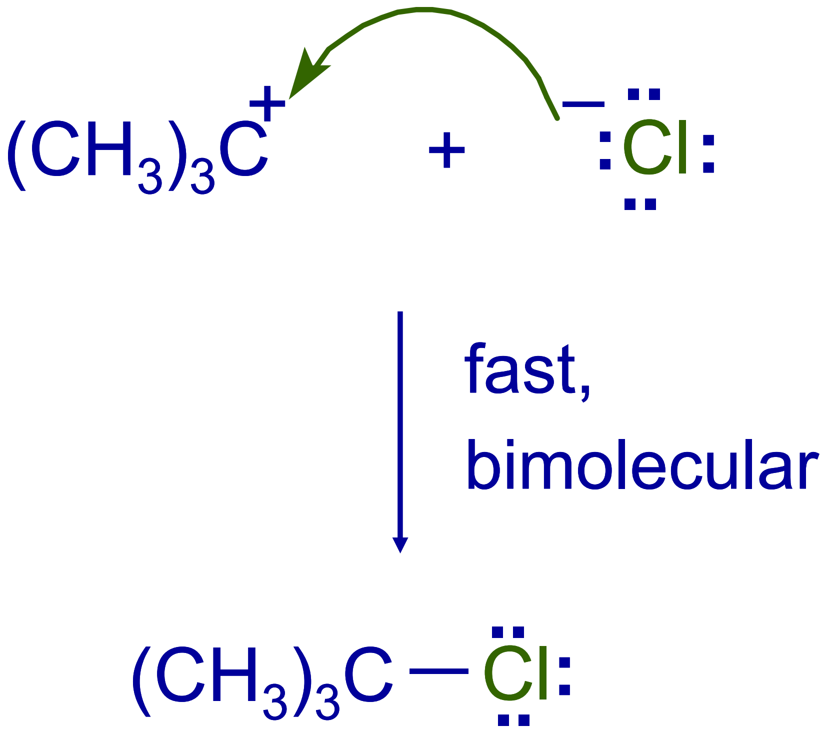


tert-Butyl chloride

- Bond formation between the positively charged carbocation and the negatively charged chloride ion is *fast*.

- Two species are involved in this step. Therefore, this step is *bimolecular*.

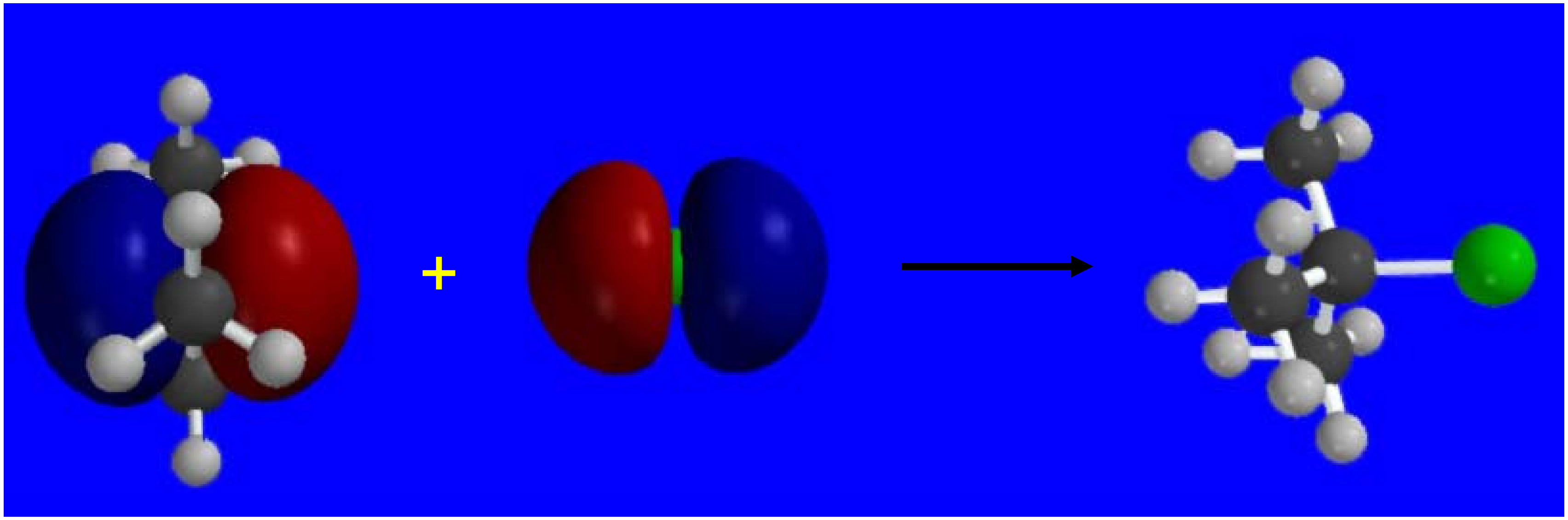
Step 3: Carbocation capture



tert-Butyl chloride

- This is a Lewis acid-Lewis base reaction. The carbocation is the Lewis acid; chloride ion is the Lewis base.
- The carbocation is an *electrophile*. Chloride ion is a *nucleophile.*

Step 3: Carbocation capture

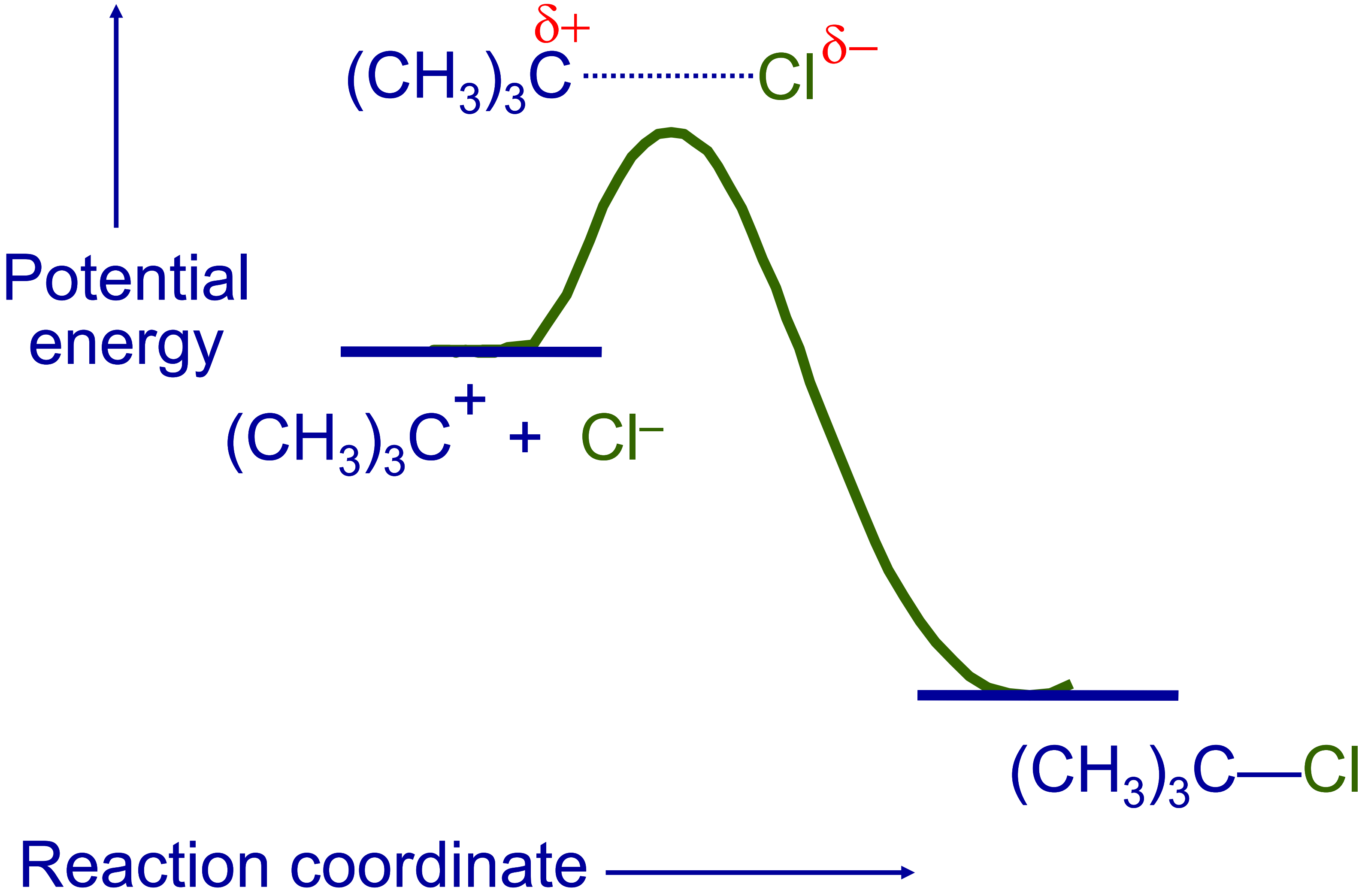


$(CH_3)_3C^+$ Cl $^-$ $(CH_3)_3CCl$

Lewis acid Lewis base

Electrophile Nucleophile

Potential energy diagram for Step 3



$(CH_3)_3\overset{\delta+}{C}\cdots\cdots Cl^{\delta-}$

Potential energy

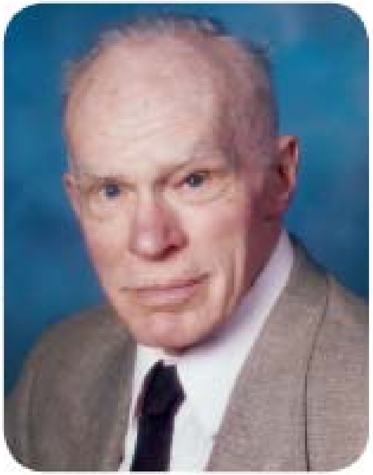
$(CH_3)_3C^+ + Cl^-$

$(CH_3)_3C—Cl$

Reaction coordinate

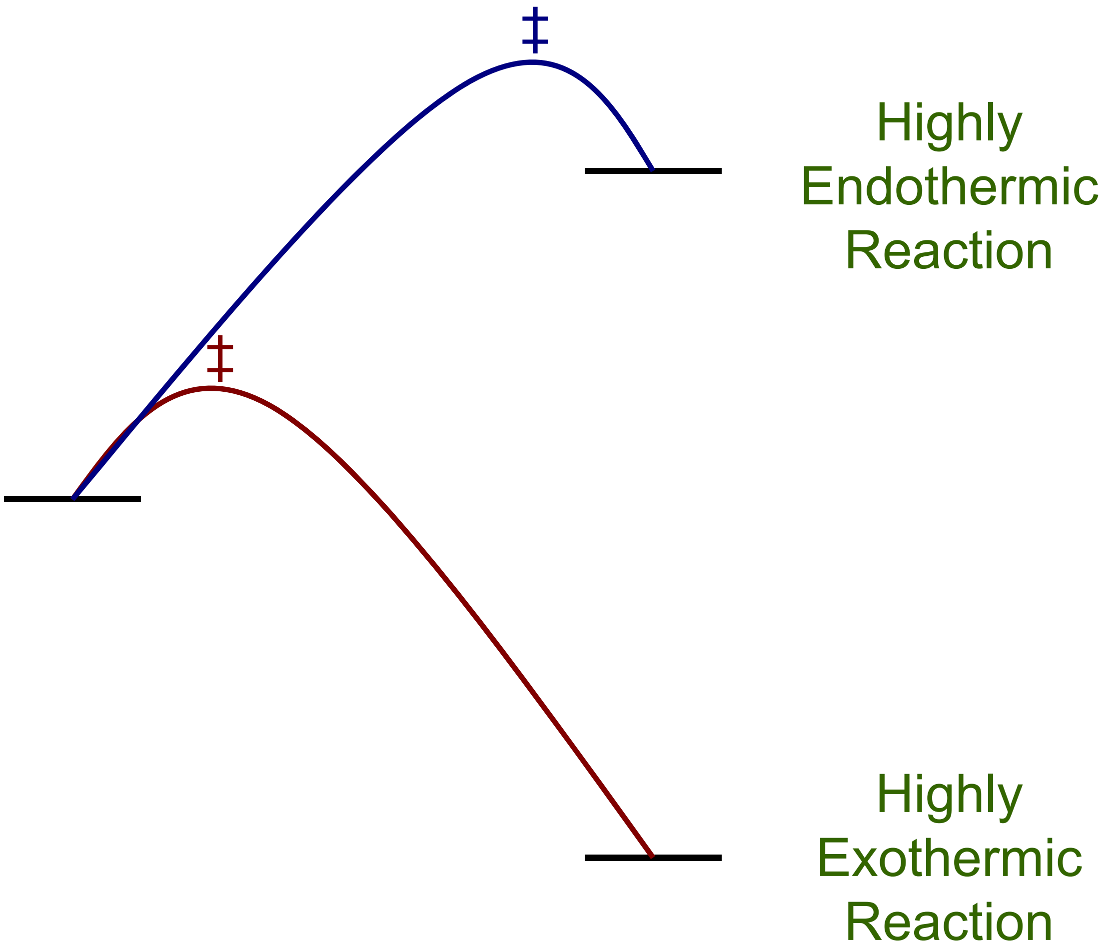
Hammond's postulate

- If two states are similar in energy, they are similar in structure.



Courtesy of BGSU

"Father of Organic Photochemistry"



Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334.

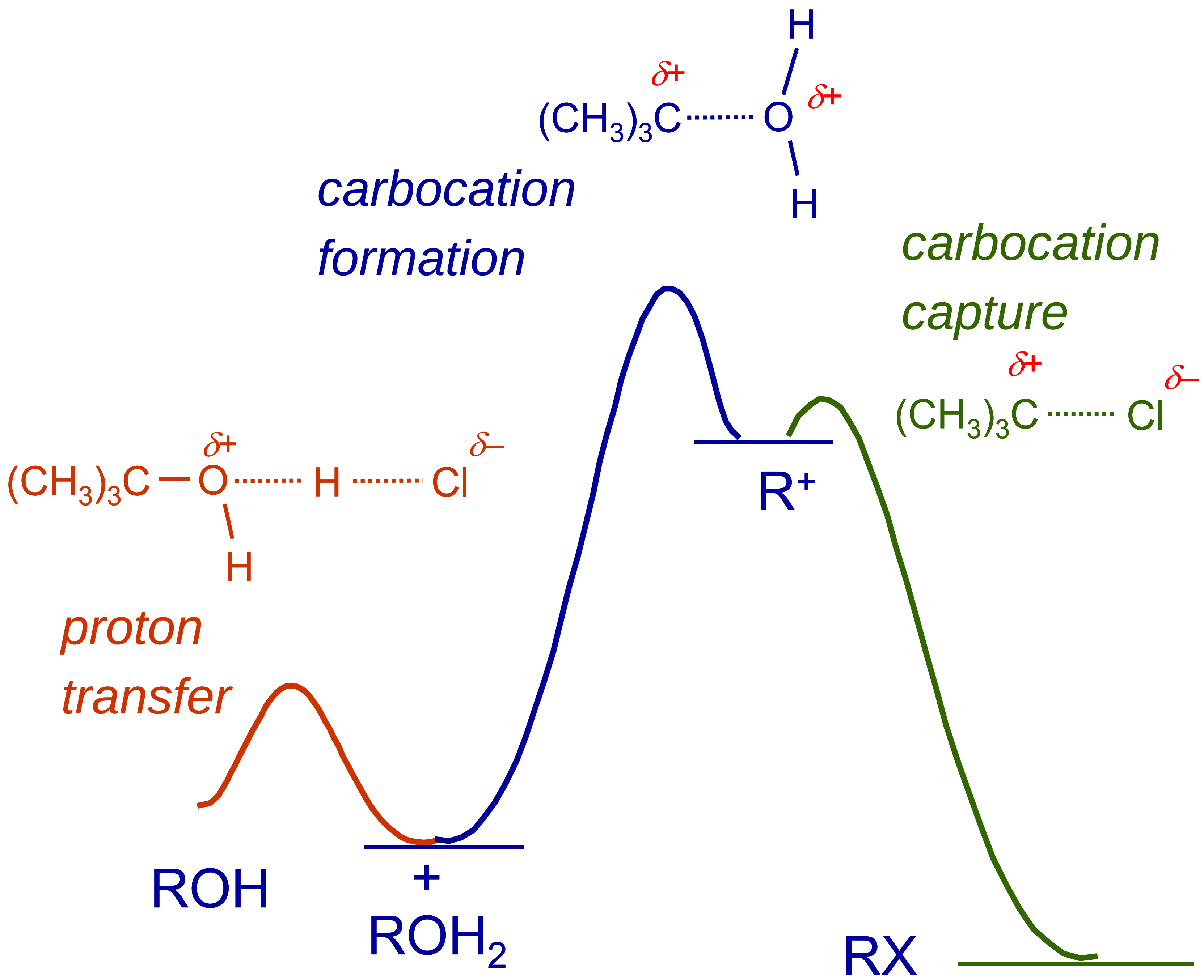
Total # of citations to date (March 2011): 1161 citations!

4.9. Potential Energy Diagrams for Multistep Reactions: The S_N1 Mechanism

- The potential energy diagram for a multistep mechanism is simply a collection of the potential energy diagrams for the individual steps.

- Consider the three-step mechanism for the reaction of *tert*-butyl alcohol with HCl.

$$(CH_3)_3COH + HCl \xrightarrow{25°C} (CH_3)_3CCl + H_2O$$



proton transfer

$$(CH_3)_3C-\overset{\delta+}{\underset{\displaystyle \backslash\, H}{O}}\cdots\cdots H\cdots\cdots\overset{\delta-}{Cl}$$

carbocation formation

$$\overset{\delta+}{(CH_3)_3C}\cdots\cdots\overset{\delta+}{\underset{\displaystyle H}{\overset{\displaystyle H}{O}}}$$

carbocation capture

$$\overset{\delta+}{(CH_3)_3C}\cdots\cdots\overset{\delta-}{Cl}$$

ROH

$R\overset{+}{O}H_2$

R^+

RX

Mechanistic Notation

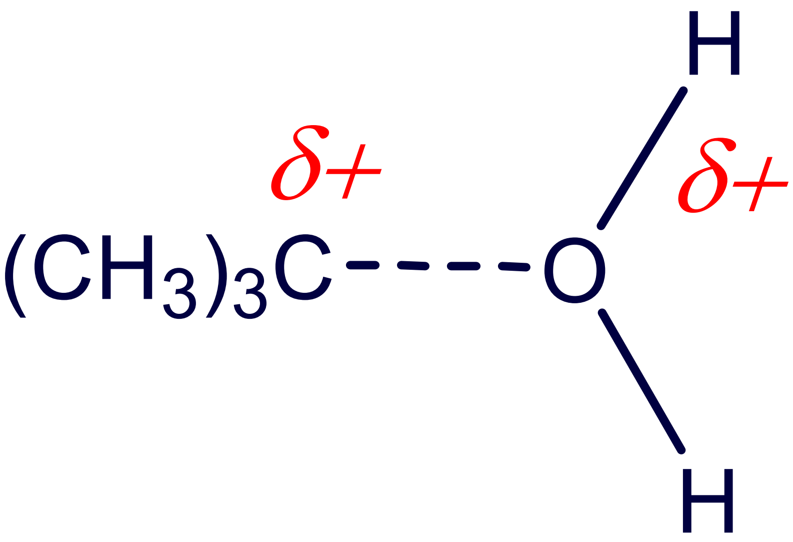
- The mechanism just described is an example of an S_N1 process.

- S_N1 stands for substitution-nucleophilic unimolecular.

- The molecularity of the rate-determining step defines the molecularity of the overall reaction.

Mechanistic notation

- The molecularity of the rate-determining step defines the molecularity of the overall reaction.

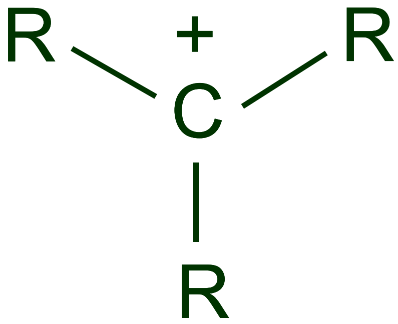


- Rate-determining step is unimolecular dissociation of alkyloxonium ion.

4.10

Structure, Bonding, and Stability of Carbocations

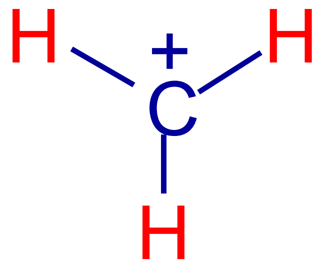
Carbocations



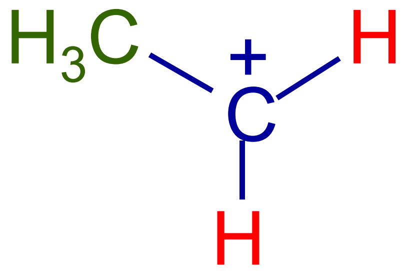
- Most carbocations are too unstable to be isolated, but occur as reactive intermediates in a number of reactions.

- When R is an alkyl group, the carbocation is stabilized compared to R = H.

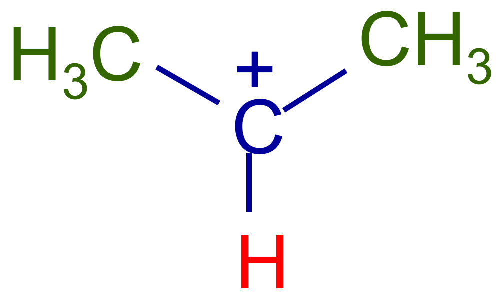
Carbocations



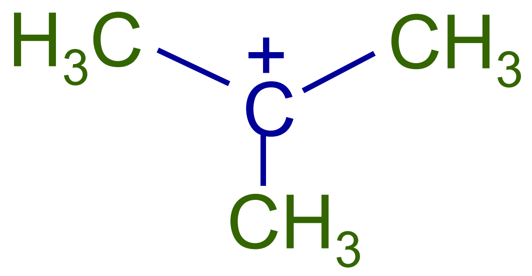
Methyl cation
least stable



Ethyl cation
(a primary carbocation)
is more stable than CH_3^+

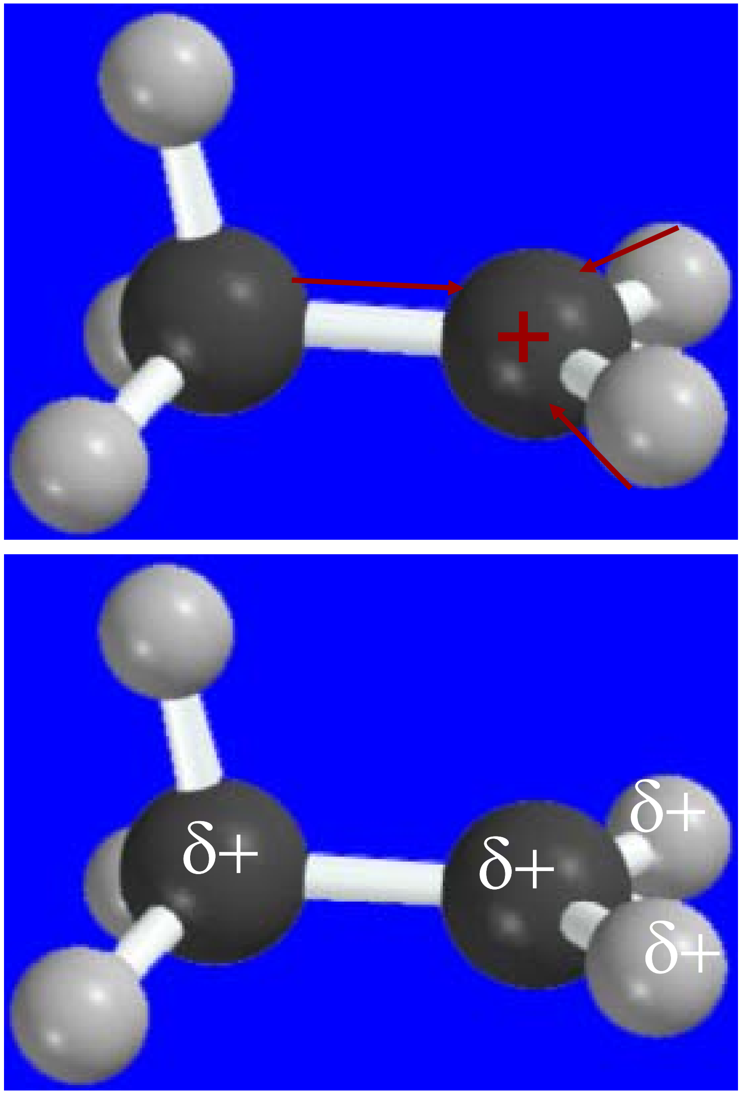


Isopropyl cation
(a secondary carbocation)
is more stable than $CH_3CH_2^+$



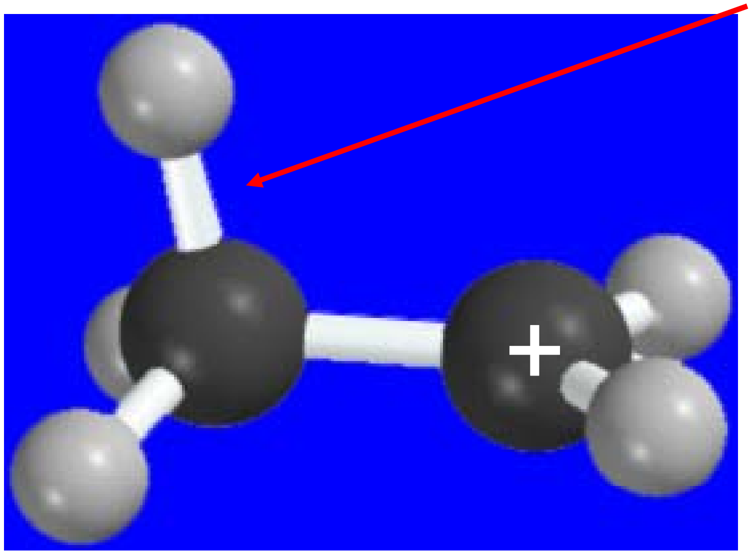
tert-Butyl cation
(a tertiary carbocation)
is more stable than $(CH_3)_2CH^+$

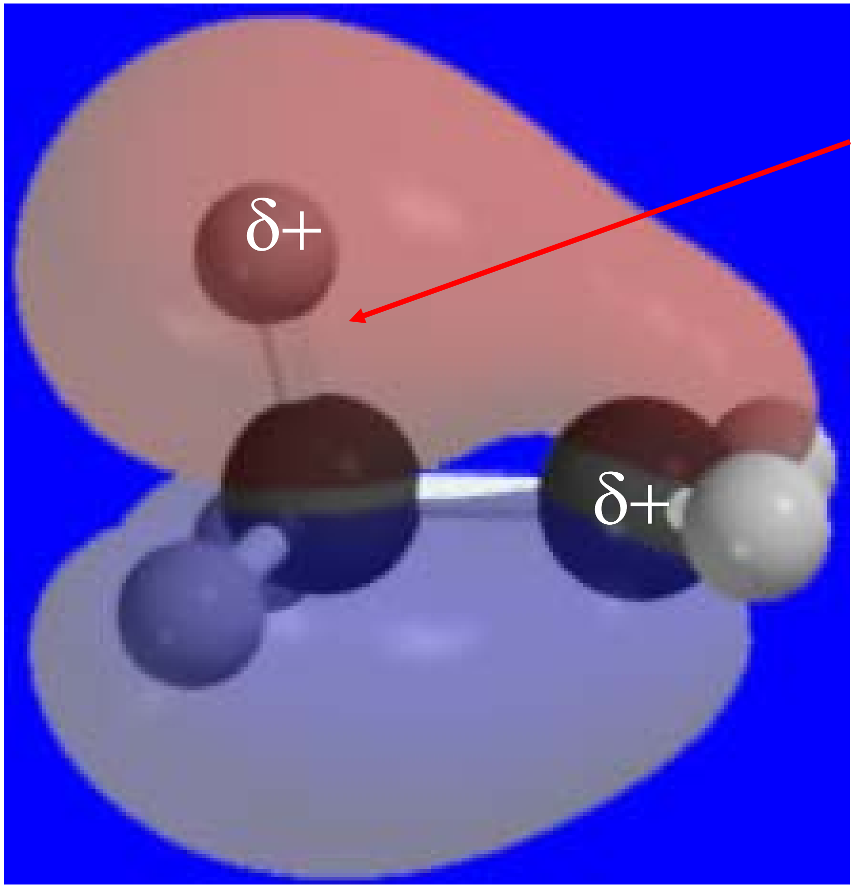
Figure 4.14. Stabilization of carbocations via the inductive effect



- Positively charged carbon pulls electrons in σ bonds closer to itself.
- Positive charge is "dispersed ", i.e., shared by carbon and the three atoms attached to it.
- Electrons in C—C bonds are more polarizable than those in C—H bonds; therefore, alkyl groups stabilize carbocations better than H.
- Electronic effects transmitted through σ bonds are called "inductive effects."

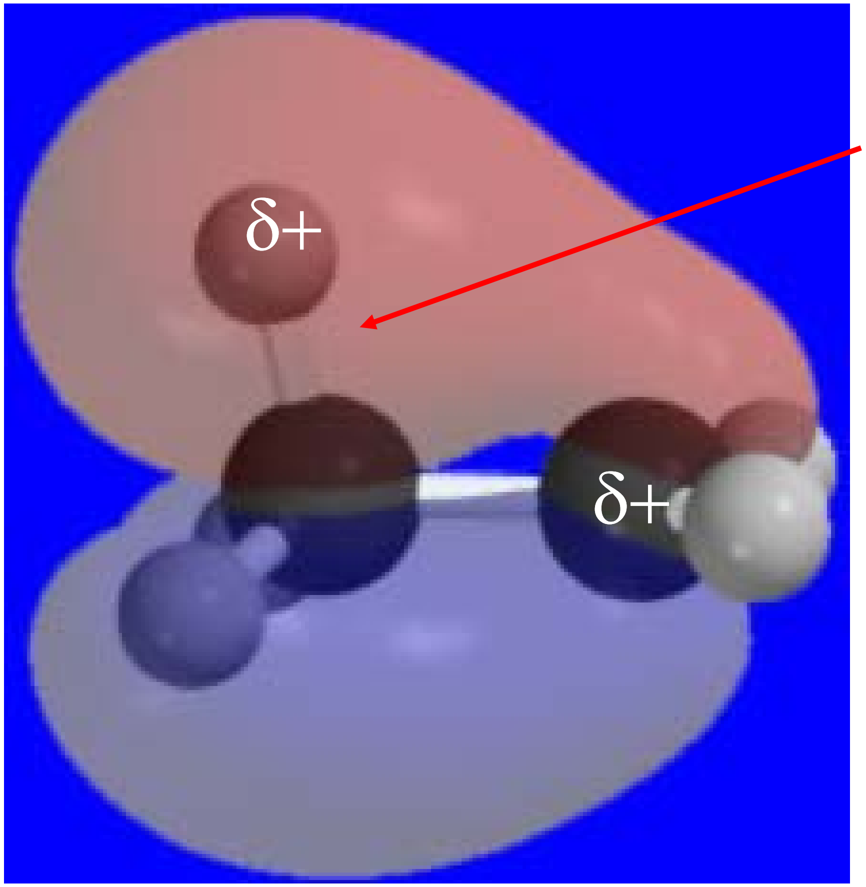
Figure 4.15. Stabilization of carbocations via hyperconjugation





- Electrons in this σ bond can be shared by positively charged carbon because they can overlap with the empty 2p orbital of positively charged carbon.

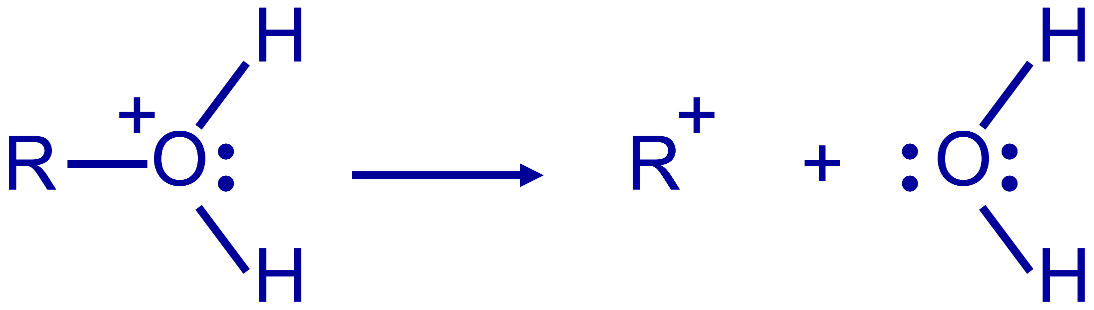
Figure 4.15. Stabilization of carbocations via hyperconjugation



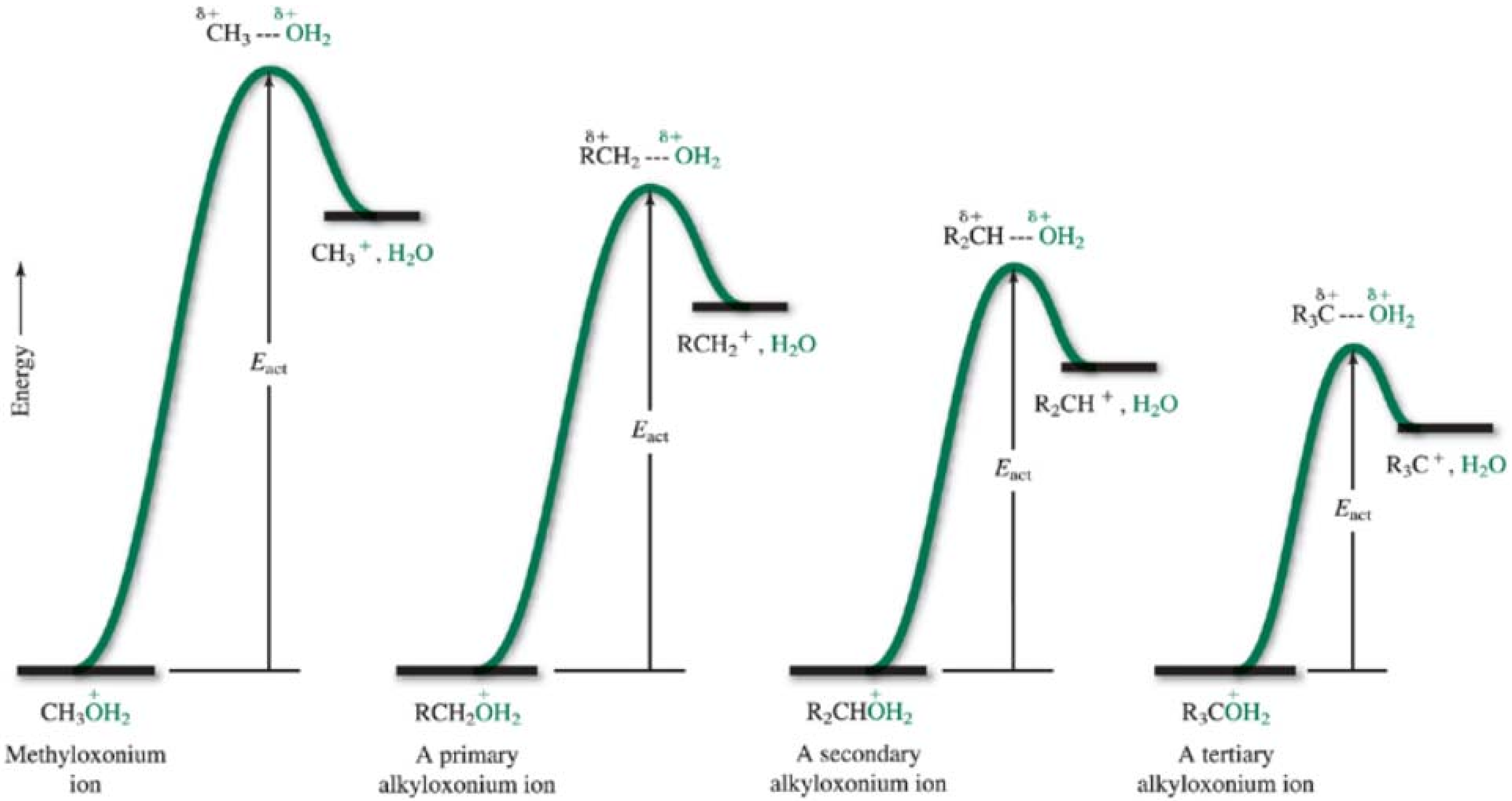
- Notice that an occupied orbital of this type is available when *sp*^{3} hybridized carbon is attached to C$^+$, but is not available when H is attached to C$^+$. Therefore, alkyl groups stabilize carbocations better than H does.

4.11
Effect of Alcohol Structure on Reaction Rate

Slow step is:



- The more stable the carbocation, the faster it is formed.
- Tertiary carbocations are more stable than secondary, which are more stable than primary, which are more stable than methyl.
- Tertiary alcohols react faster than secondary, which react faster than primary, which react faster than methanol.


Energy
$\overset{\delta+}{CH_3}$ --- $\overset{\delta+}{OH_2}$
E_{act}
CH_3^+, H_2O
$CH_3\overset{+}{O}H_2$
Methyloxonium ion
$\overset{\delta+}{RCH_2}$ --- $\overset{\delta+}{OH_2}$
E_{act}
RCH_2^+, H_2O
$RCH_2\overset{+}{O}H_2$
A primary alkyloxonium ion
$\overset{\delta+}{R_2CH}$ --- $\overset{\delta+}{OH_2}$
E_{act}
R_2CH^+, H_2O
$R_2CH\overset{+}{O}H_2$
A secondary alkyloxonium ion
$\overset{\delta+}{R_3C}$ --- $\overset{\delta+}{OH_2}$
E_{act}
R_3C^+, H_2O
$R_3C\overset{+}{O}H_2$
A tertiary alkyloxonium ion

4.12

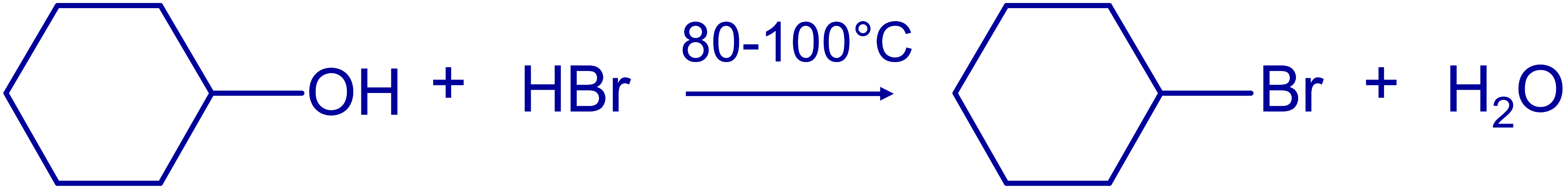
Reaction of Primary Alcohols with Hydrogen Halides.

The S_N2 Mechanism

Preparation of Alkyl Halides

$$(CH_3)_3COH + HCl \xrightarrow{25°C} (CH_3)_3CCl + H_2O$$

78-88%



73%

$$CH_3(CH_2)_5CH_2OH + HBr \xrightarrow{120°C} CH_3(CH_2)_5CH_2Br + H_2O$$

87-90%

Preparation of Alkyl Halides

- Primary carbocations are too high in energy to allow S_N1 mechanism. Yet, primary alcohols are converted to alkyl halides.

- Primary alcohols react by a mechanism called S_N2 (substitution-nucleophilic-bimolecular).

$$CH_3(CH_2)_5CH_2OH + HBr \xrightarrow{120°C} CH_3(CH_2)_5CH_2Br + H_2O$$

87-90%

The S_N2 Mechanism

➢ Two-step mechanism for conversion of alcohols to alkyl halides:

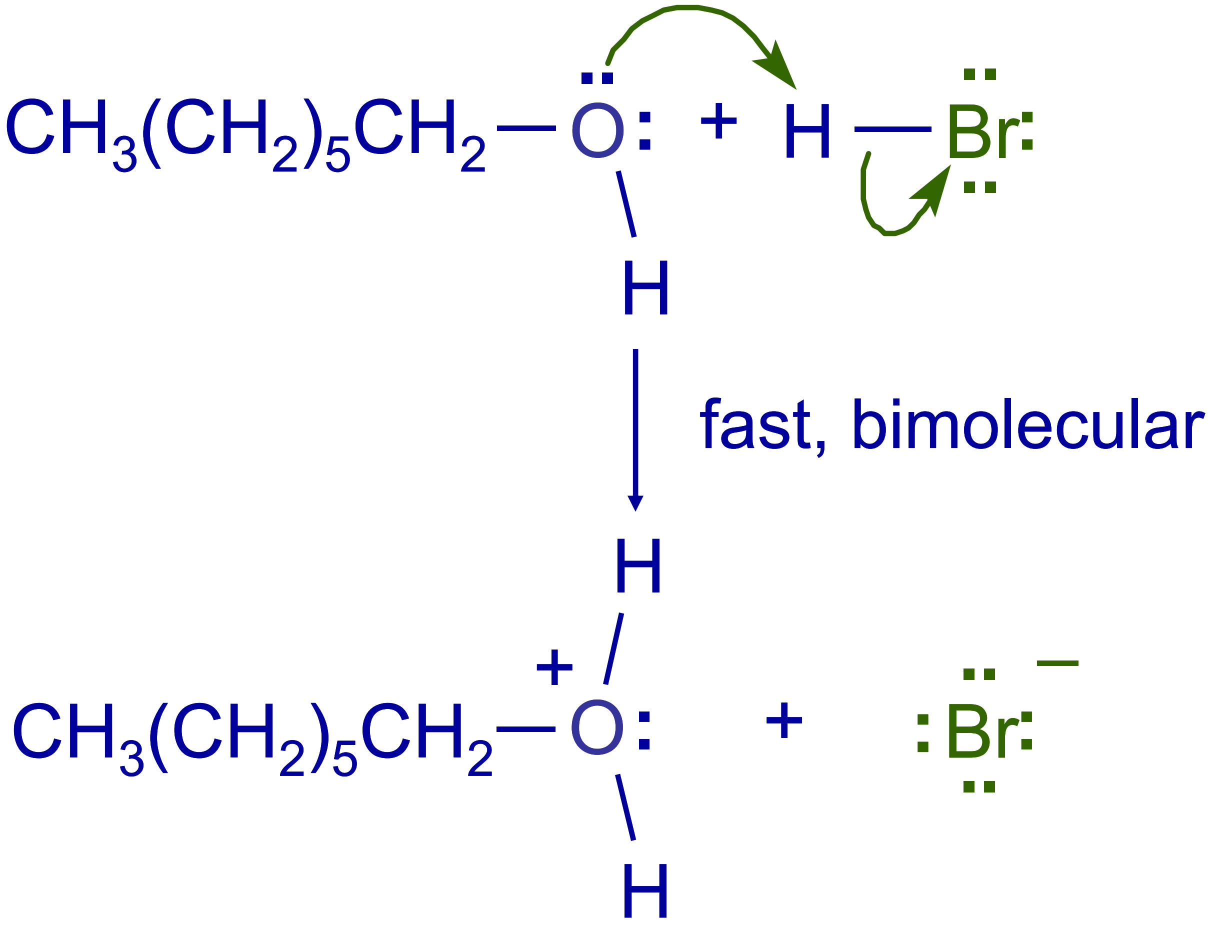
1. Proton transfer to alcohol to form alkyloxonium ion.
2. Bimolecular displacement of water from alkyloxonium ion by halide.

Example

$$CH_3(CH_2)_5CH_2OH + HBr \xrightarrow{120°C} CH_3(CH_2)_5CH_2Br + H_2O$$

Mechanism

Step 1: Proton transfer from HBr to 1-heptanol

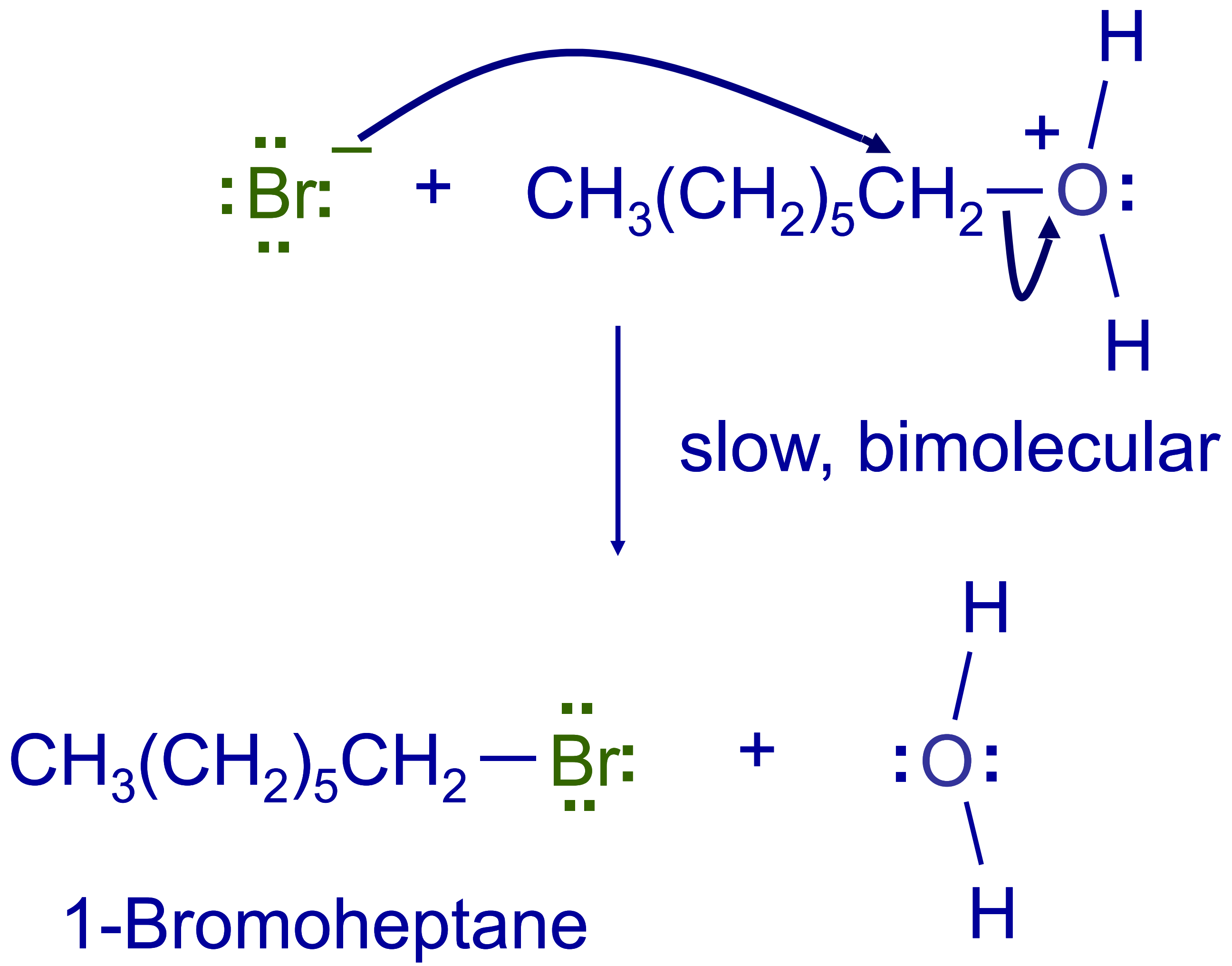


$$CH_3(CH_2)_5CH_2OH + HBr \xrightarrow{\text{fast, bimolecular}} CH_3(CH_2)_5CH_2\overset{+}{O}H_2 + Br^-$$

Heptyloxonium ion

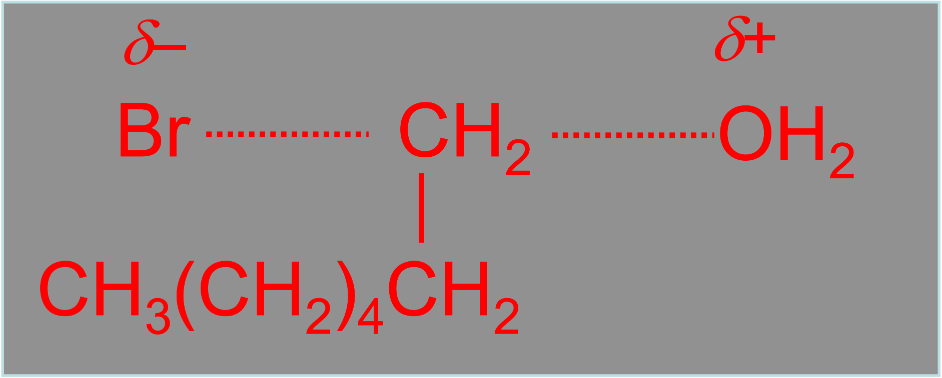
Mechanism

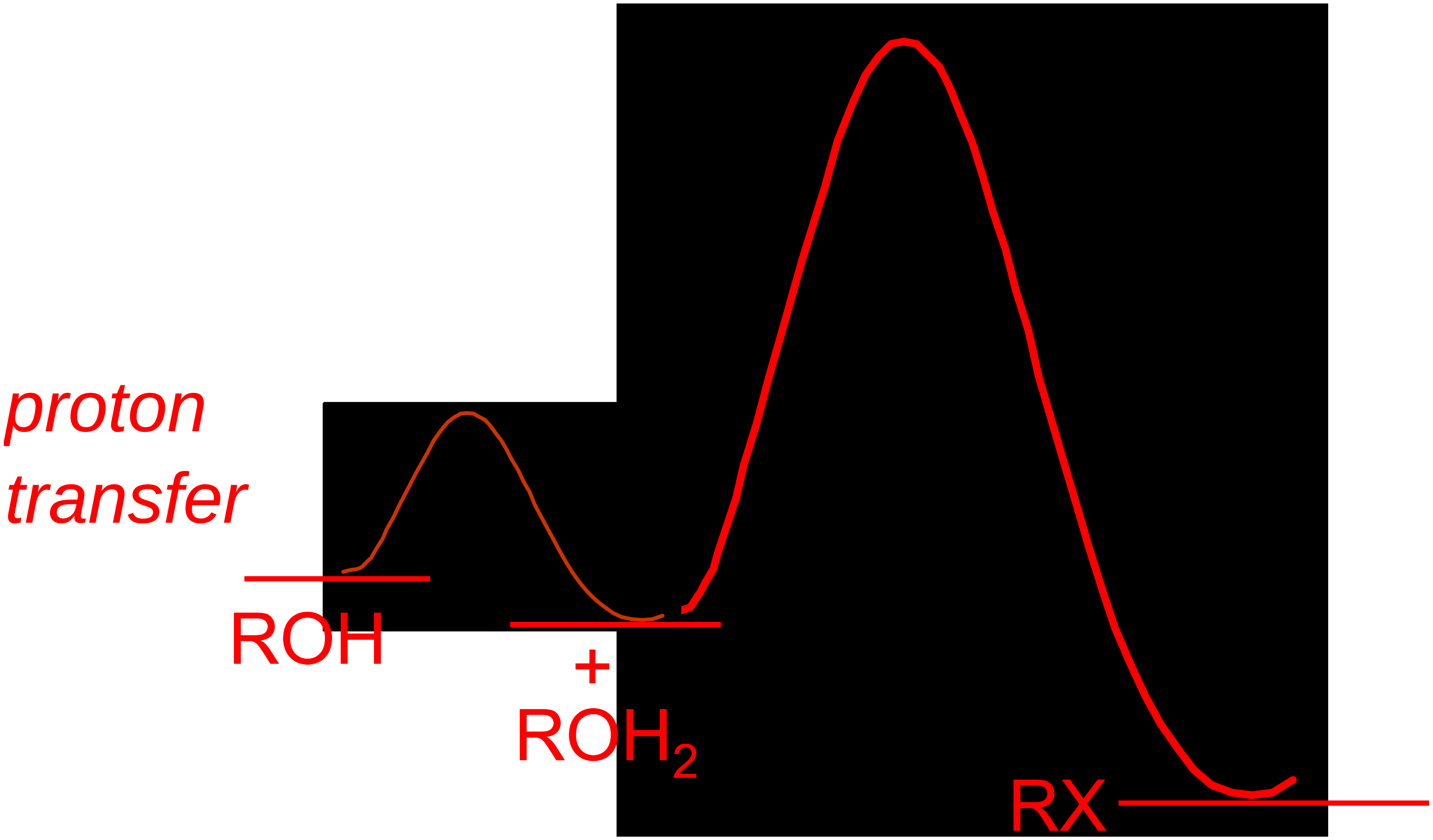
Step 2: Reaction of alkyloxonium ion with bromide ion.



$$:\ddot{\underset{\cdot\cdot}{Br}}:^{-} + CH_3(CH_2)_5CH_2-\overset{+}{O}H_2 \longrightarrow CH_3(CH_2)_5CH_2-\ddot{\underset{\cdot\cdot}{Br}}: + H_2\ddot{O}:$$

1-Bromoheptane


δ−
δ+
Br
CH_2
OH_2
$CH_3(CH_2)_4CH_2$


proton transfer
ROH
$\overset{+}{ROH_2}$
RX

Chapter 8

8.1. Functional Group Transformation By Nucleophilic Substitution

Nucleophilic Substitution

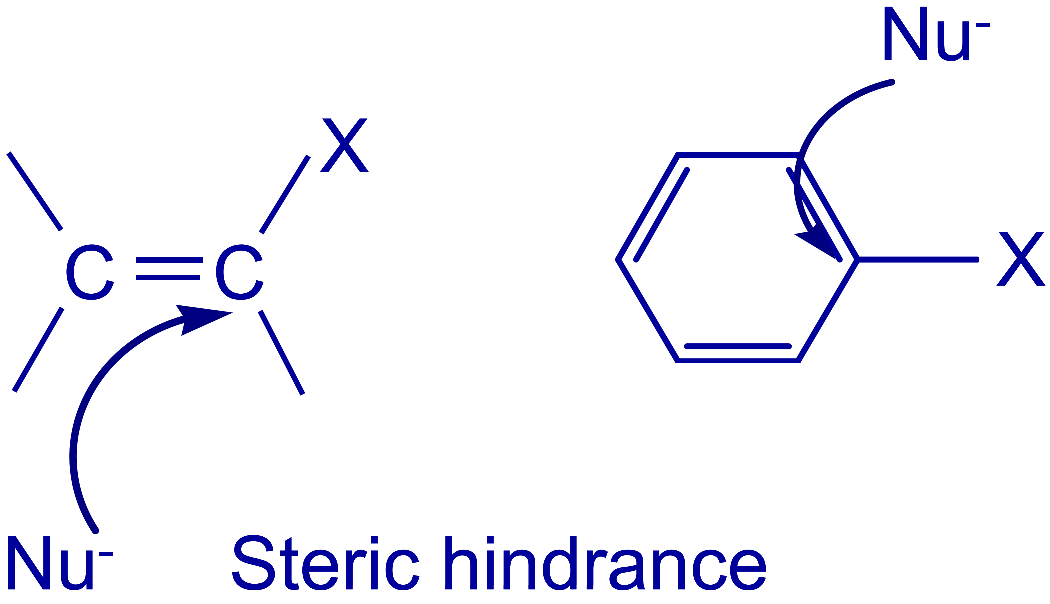
$$:Y^{-} + R-X \longrightarrow Y-R + :X^{-}$$

- Nucleophile is a Lewis base (electron-pair donor). Often negatively charged and used as Na^{+} or K^{+} salt.

- Substrate is usually an alkyl halide.

Nucleophilic Substitution

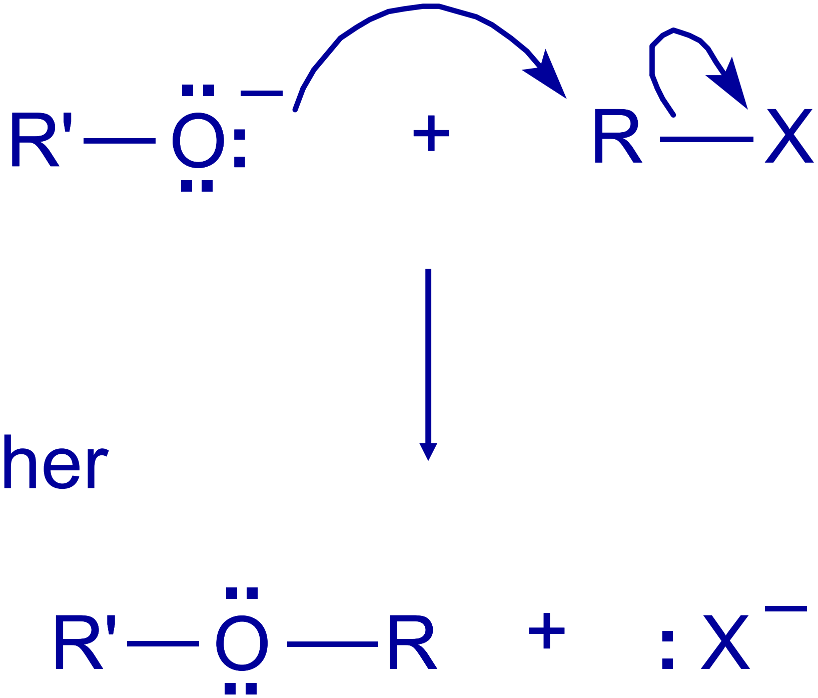
- Substrate cannot be a vinylic halide or an aryl halide, except under certain conditions to be discussed in Chapter 12.



Steric hindrance

Table 8.1. Examples of Nucleophilic Substitution

Alkoxide ion as the nucleophile:



gives an ether

Example

$$(CH_3)_2CHCH_2ONa \quad + \quad CH_3CH_2Br$$

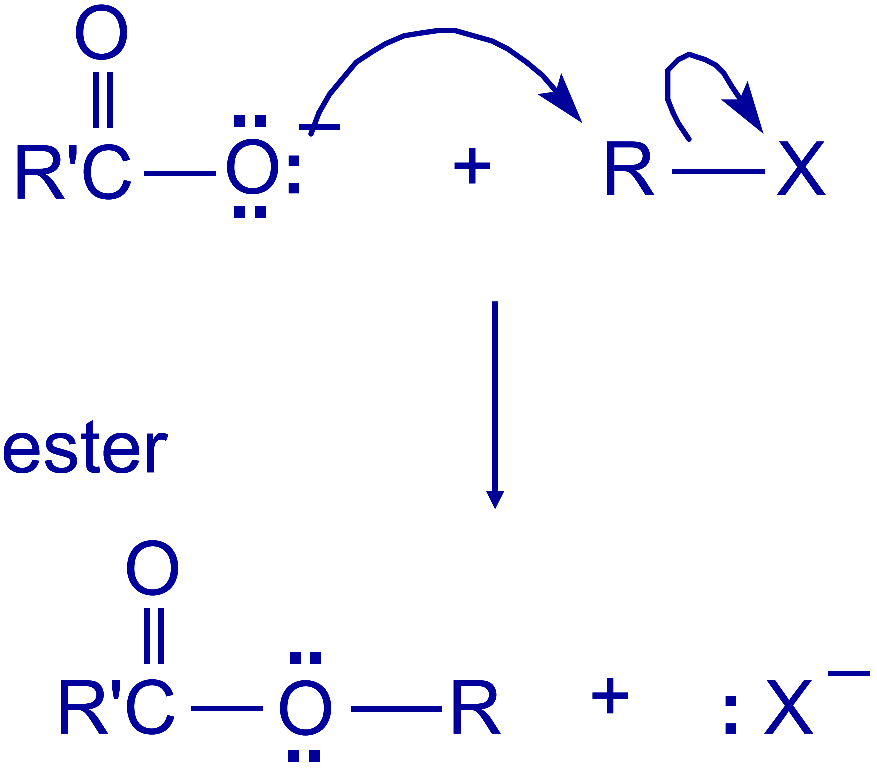
$$\Big\downarrow \text{ Isobutyl alcohol}$$

$$(CH_3)_2CHCH_2OCH_2CH_3 \quad + \quad NaBr$$

Ethyl isobutyl ether (66%)

Table 8.1. Examples of Nucleophilic Substitution

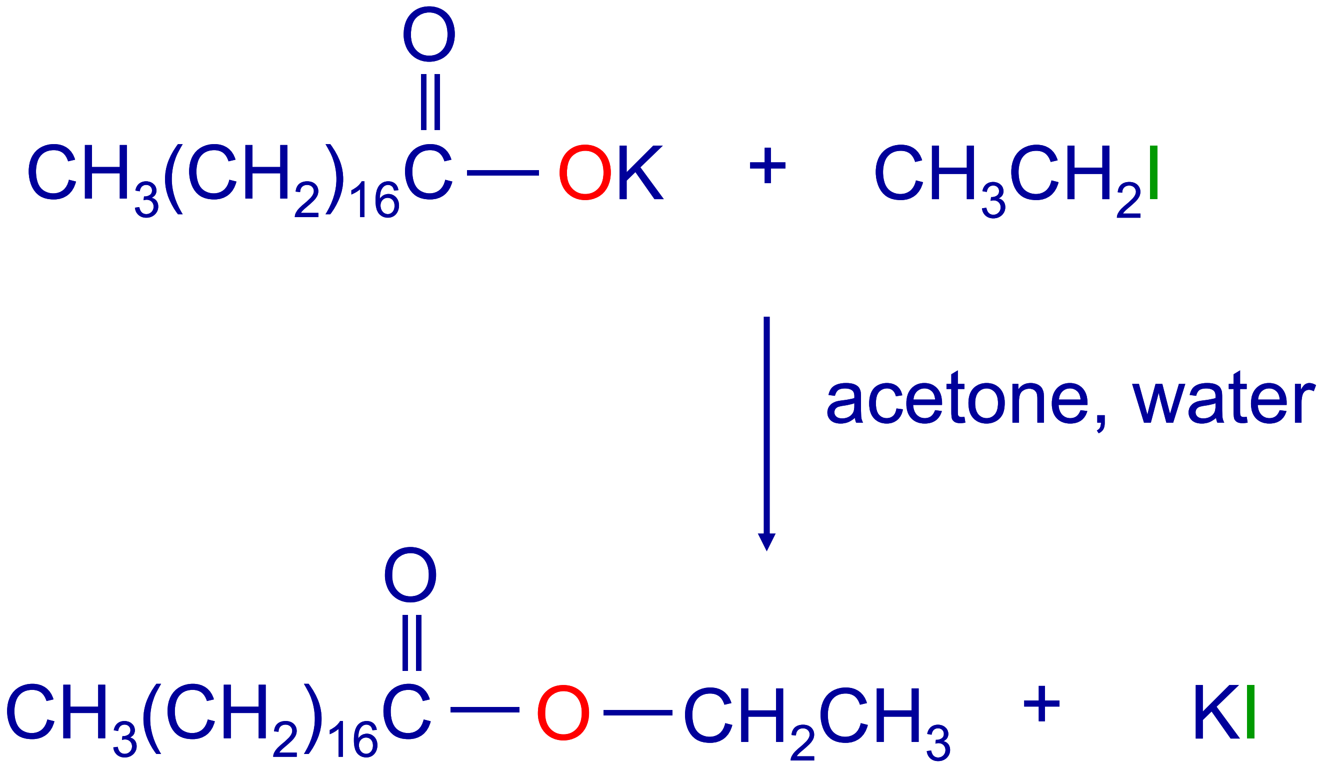
Carboxylate ion as the nucleophile:



$$R'\overset{\overset{\displaystyle O}{\|}}{C}-\ddot{\underset{\cdot\cdot}{O}}{:}^{-} + R-X \longrightarrow R'\overset{\overset{\displaystyle O}{\|}}{C}-\ddot{\underset{\cdot\cdot}{O}}-R + {:}X^{-}$$

gives an ester

Example

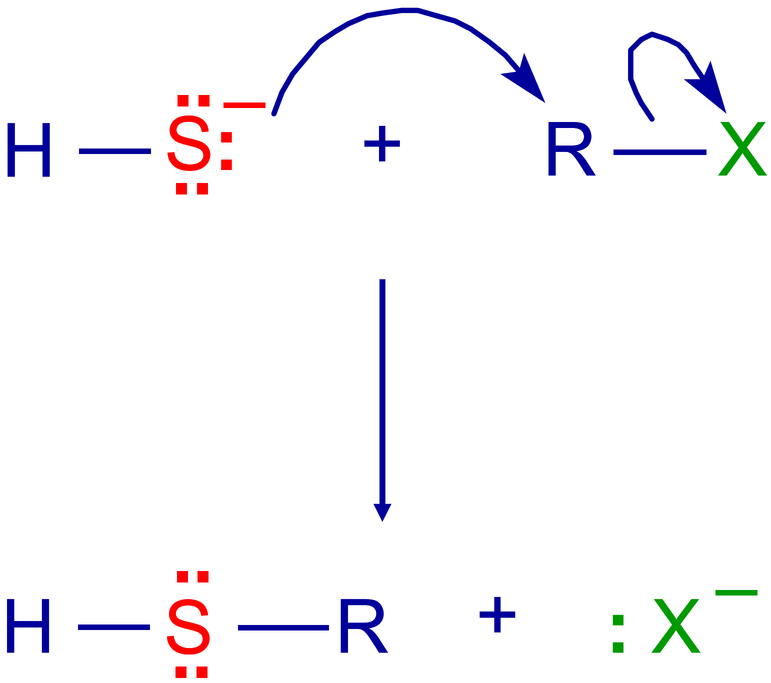


$$CH_3(CH_2)_{16}\overset{O}{\overset{\|}{C}}-OK + CH_3CH_2I \xrightarrow{\text{acetone, water}} CH_3(CH_2)_{16}\overset{O}{\overset{\|}{C}}-O-CH_2CH_3 + KI$$

Ethyl octadecanoate (95%)

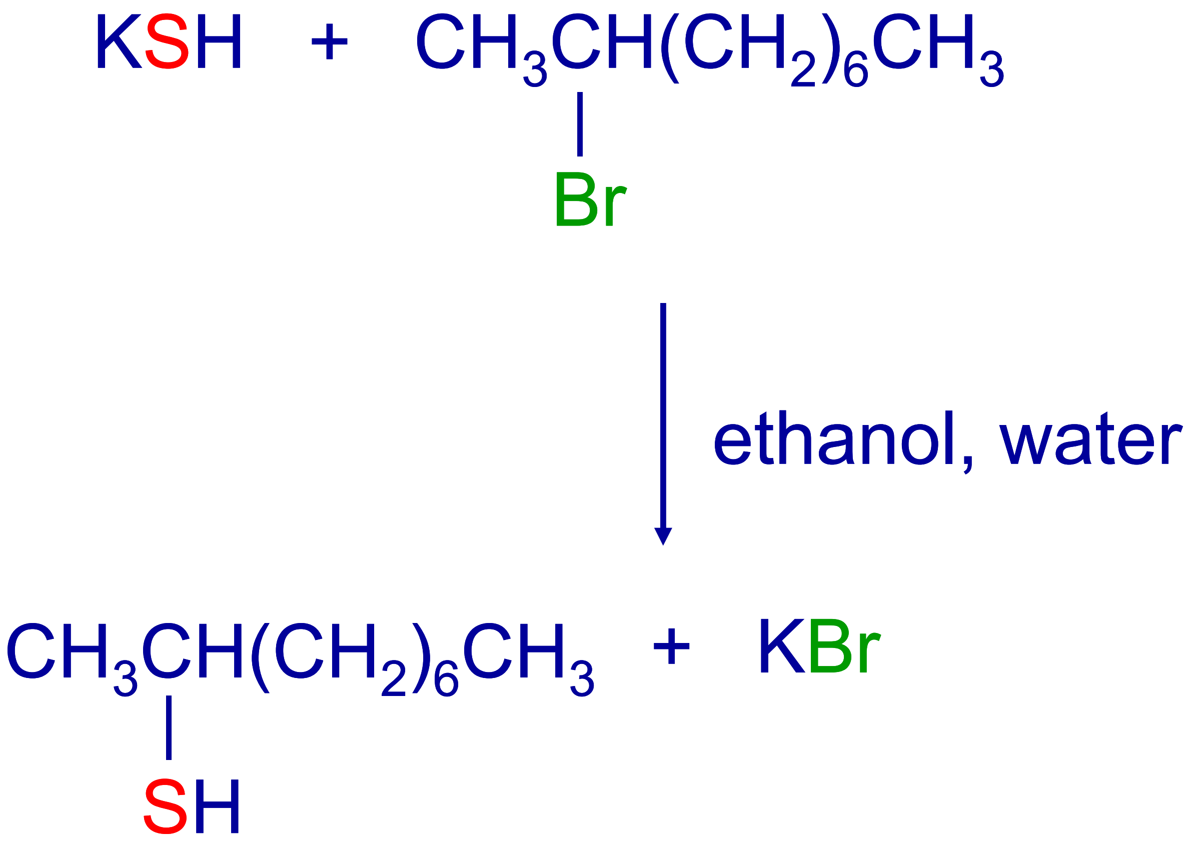
Table 8.1. Examples of Nucleophilic Substitution

Hydrogen sulfide ion as the nucleophile:



gives a thiol

Example

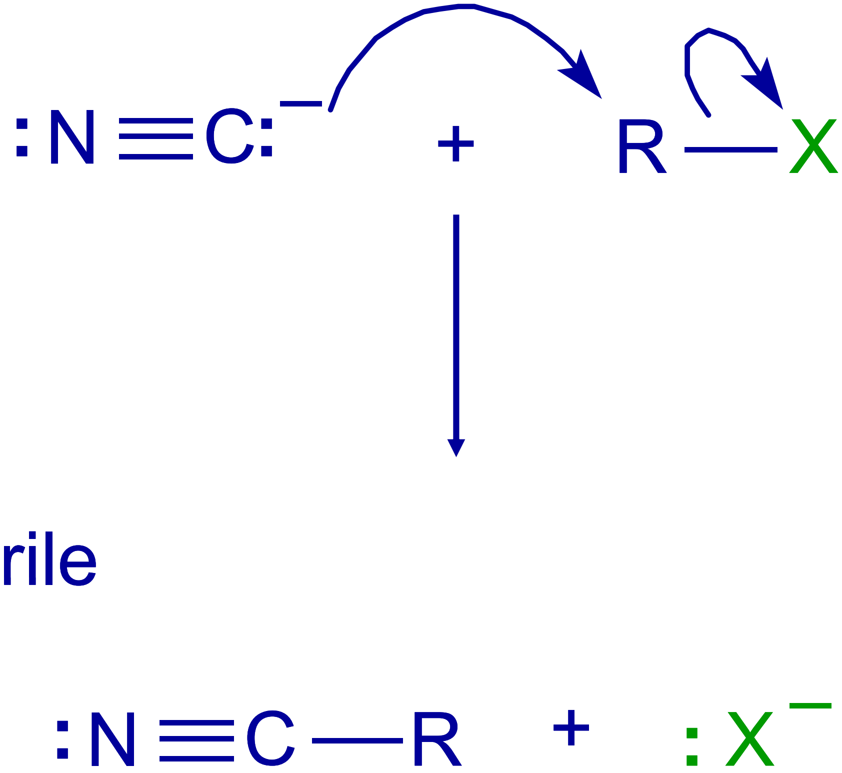


$$KSH + \underset{\displaystyle Br}{\underset{|}{CH_3CH}}(CH_2)_6CH_3 \xrightarrow{\text{ethanol, water}} \underset{\displaystyle SH}{\underset{|}{CH_3CH}}(CH_2)_6CH_3 + KBr$$

2-Nonanethiol (74%)

Table 8.1. Examples of Nucleophilic Substitution

Cyanide ion as the nucleophile:

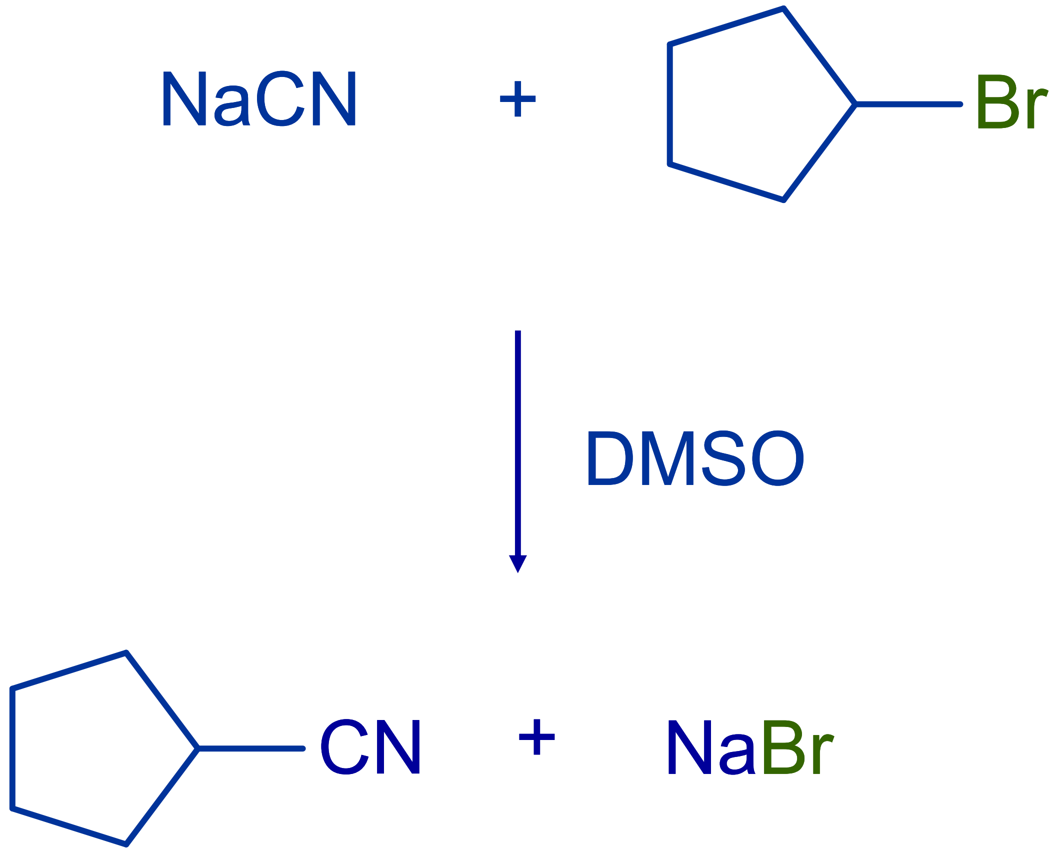


$$:N\equiv C:^{-} \quad + \quad R-X$$

gives a nitrile

$$:N\equiv C-R \quad + \quad :X^{-}$$

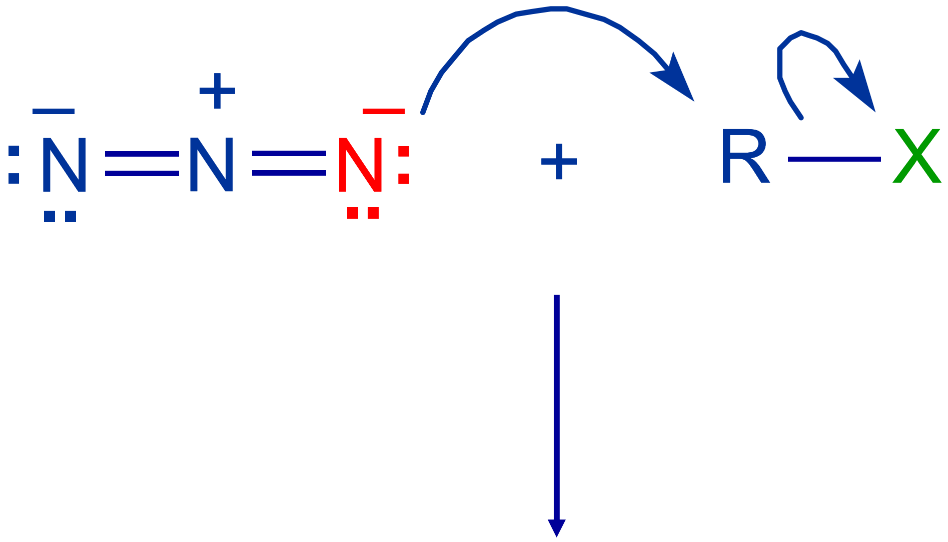
Example



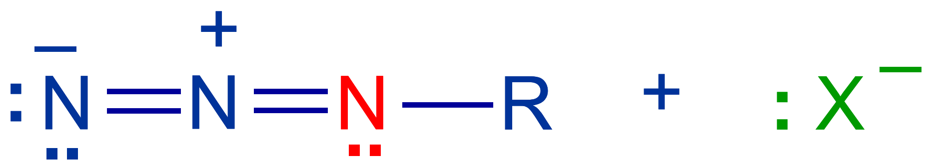
Cyclopentyl cyanide (70%)

Table 8.1. Examples of Nucleophilic Substitution

Azide ion as the nucleophile:



gives an alkyl azide



Example

$$NaN_3 \quad + \quad CH_3CH_2CH_2CH_2CH_2I$$

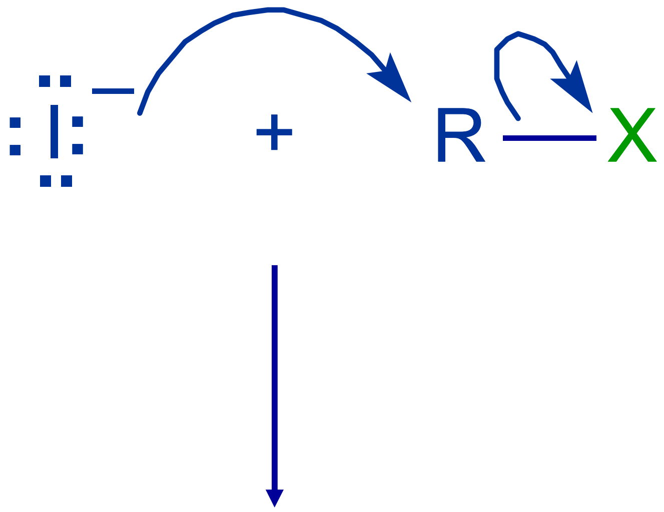
$$\Big\downarrow \text{ 2-Propanol-water}$$

$$CH_3CH_2CH_2CH_2CH_2N_3 \quad + \quad NaI$$

Pentyl azide (52%)

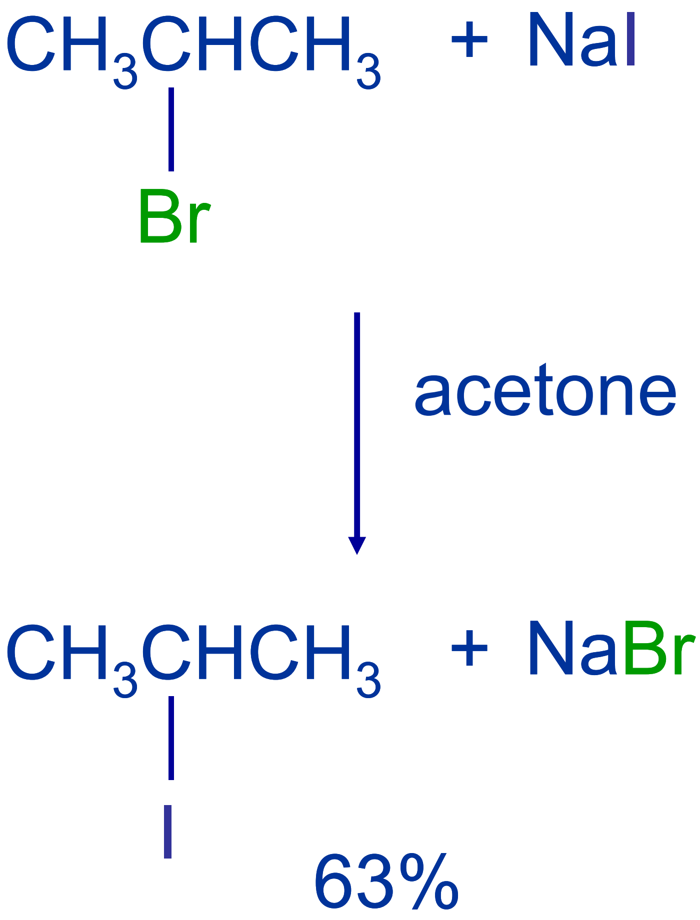
Table 8.1. Examples of Nucleophilic Substitution

Iodide ion as the nucleophile:



gives an alkyl iodide

Example



$$CH_3\underset{\underset{\displaystyle Br}{|}}{C}HCH_3 + NaI \xrightarrow{\text{acetone}} CH_3\underset{\underset{\displaystyle I}{|}}{C}HCH_3 + NaBr$$

63%

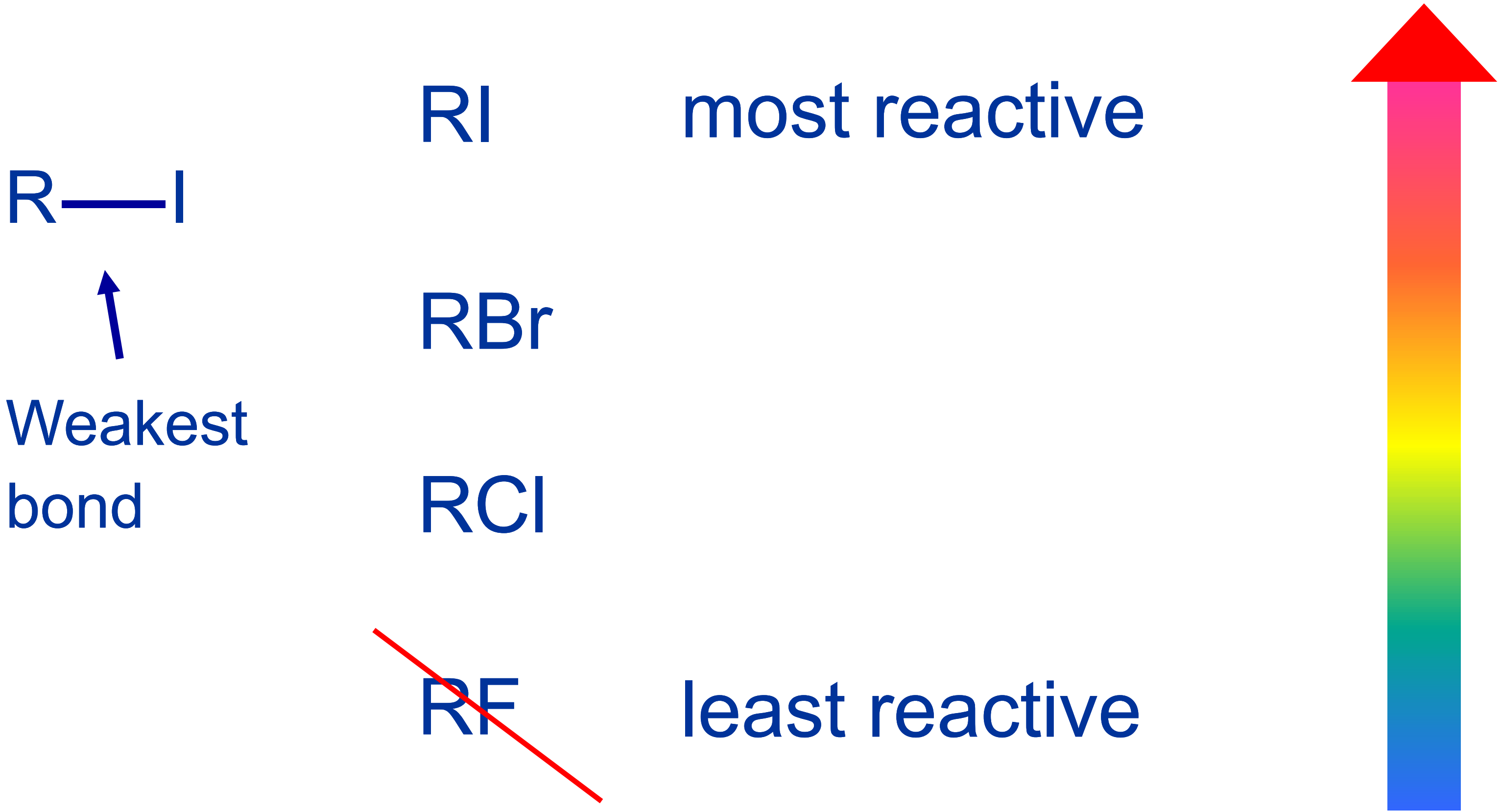
Finkelstein Rxn

NaI is soluble in acetone; NaCl and NaBr are not soluble in acetone.

8.2. Relative Reactivity of Halide Leaving Groups

Generalization

- Reactivity of halide leaving groups in nucleophilic substitution is the same as for elimination.



R—I

Weakest bond

RI most reactive

RBr

RCl

~~RF~~ least reactive

Problem 8.2

- A single organic product was obtained when 1-bromo-3-chloropropane was allowed to react with one molar equivalent of sodium cyanide in aqueous ethanol. What was this product?

$$\mathrm{BrCH_2CH_2CH_2Cl} \; + \; \mathrm{NaCN}$$

$$\downarrow$$

Br is a better leaving group than Cl

$$:\mathrm{N{\equiv}C{-}CH_2CH_2CH_2Cl} \; + \; \mathrm{NaBr}$$

8.3. The S_N2 Mechanism of Nucleophilic Substitution

Kinetics

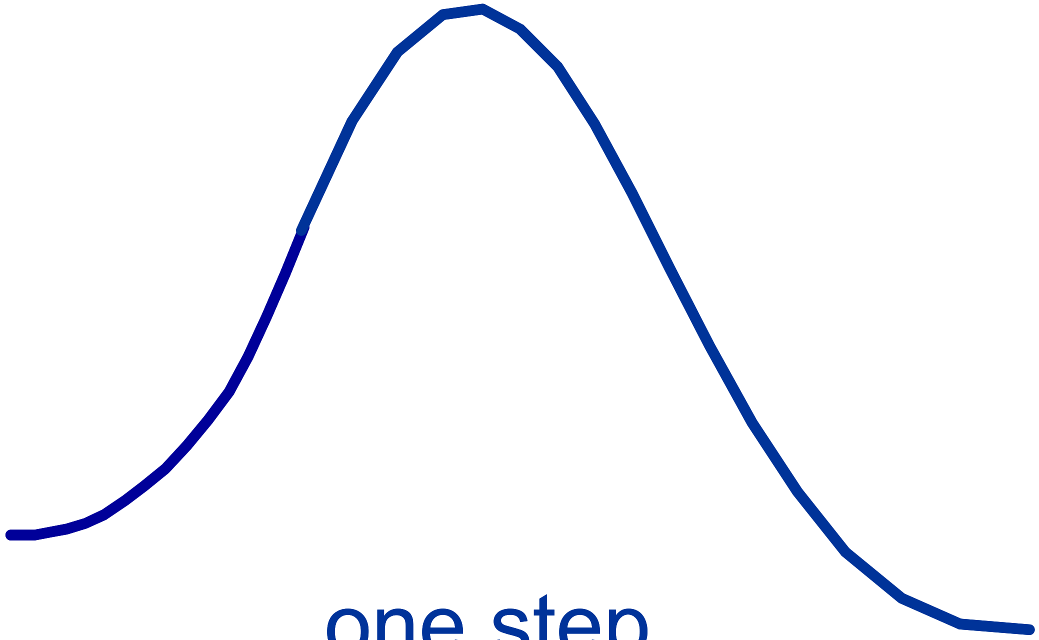
- Many nucleophilic substitutions follow a second-order rate law.

$$CH_3Br + HO^- \rightarrow CH_3OH + Br^-$$

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

- Inference: rate-determining step is bimolecular.

Bimolecular mechanism



$$\overset{\delta-}{\text{HO}}\text{------}\text{CH}_3\text{------}\overset{\delta-}{\text{Br}}$$

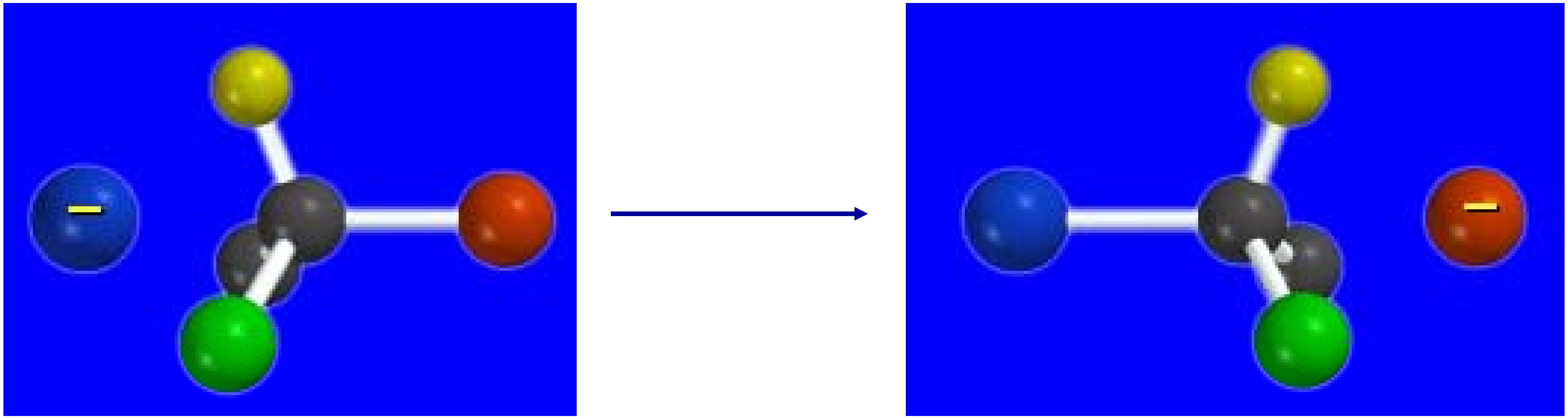
transition state

$$\text{HO}^- + \text{CH}_3\text{Br} \xrightarrow{\text{one step}} \text{HOCH}_3 + \text{Br}^-$$

Stereochemistry of S_N2 Reactions

- *Nucleophilic substitutions that exhibit second-order kinetic behavior are stereospecific and proceed with inversion of configuration.*

Inversion of Configuration



Nucleophile attacks carbon from side opposite bond to the leaving group.

Three-dimensional arrangement of bonds in product is opposite to that of reactant.

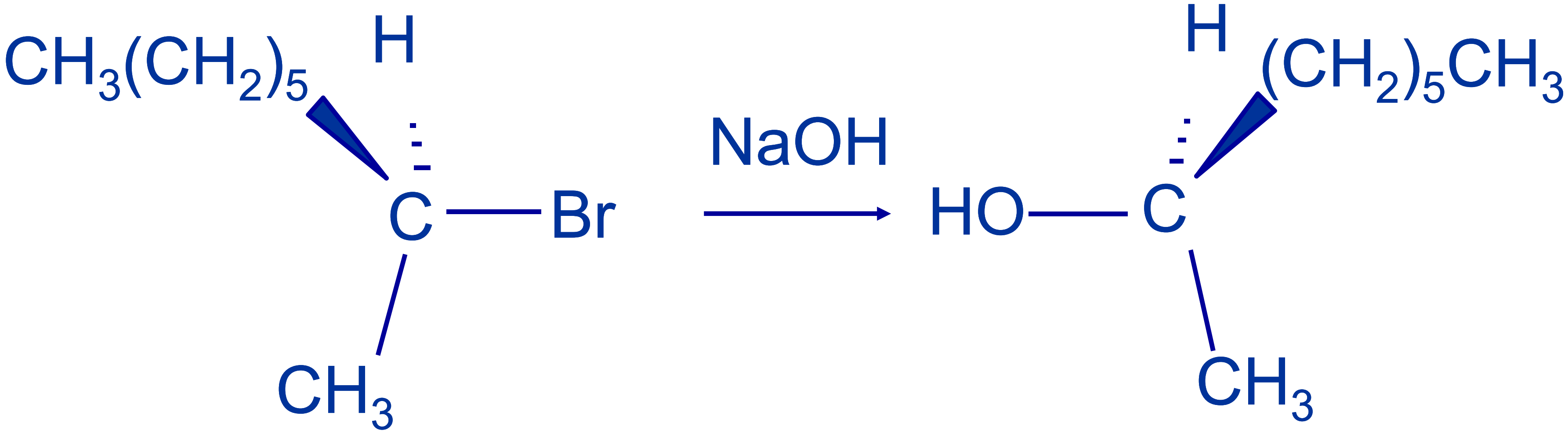
Stereospecific Reaction

- A stereospecific reaction is one in which stereoisomeric starting materials give stereoisomeric products.

- The reaction of 2-bromooctane with NaOH (in ethanol-water) is stereospecific.

(+)-2-Bromooctane → (–)-2-Octanol
(–)-2-Bromooctane → (+)-2-Octanol

Stereospecific Reaction

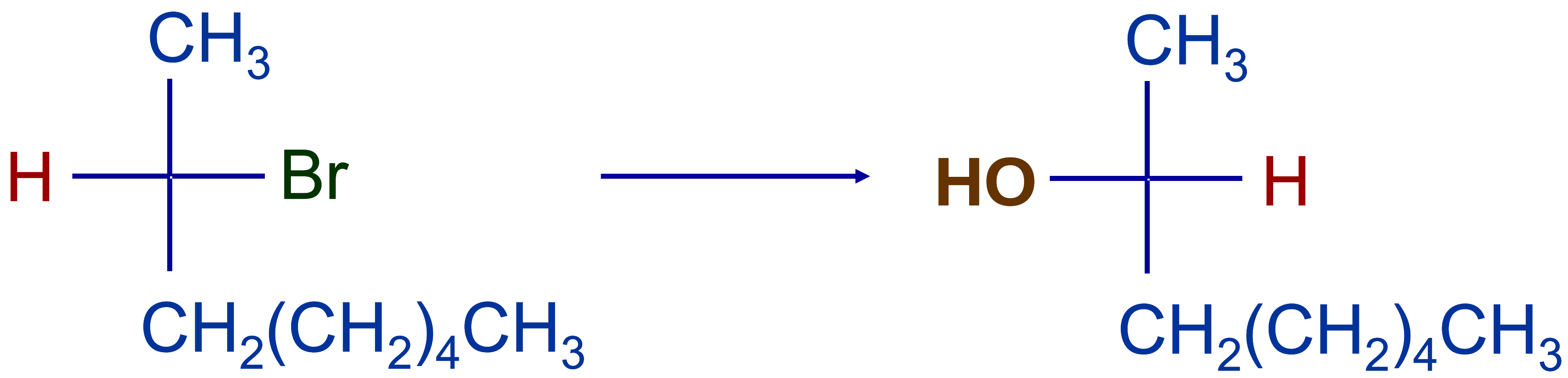


(*S*)-(+)-2-Bromooctane

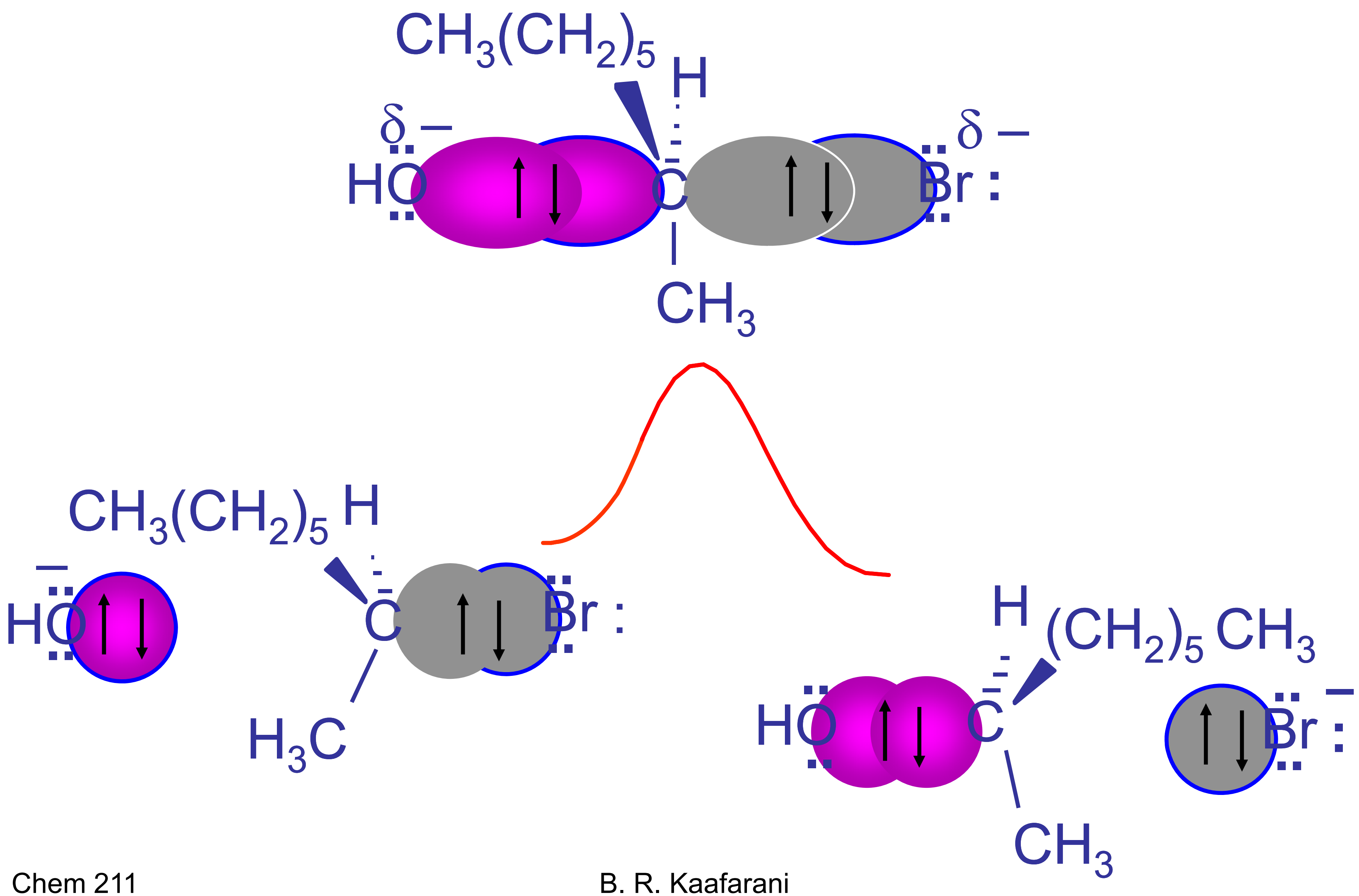
(*R*)-(–)-2-Octanol

Problem 8.5

- The Fischer projection formula for (+)-2-bromooctane is shown. Write the Fischer projection of the (–)-2-octanol formed from it by nucleophilic substitution with inversion of configuration.



How Do S_N2 Reactions Occur?



8.4. Steric Effects and S_N2 Reactions Rates

- The rate of nucleophilic substitution by the S_N2 mechanism is governed by steric effects.

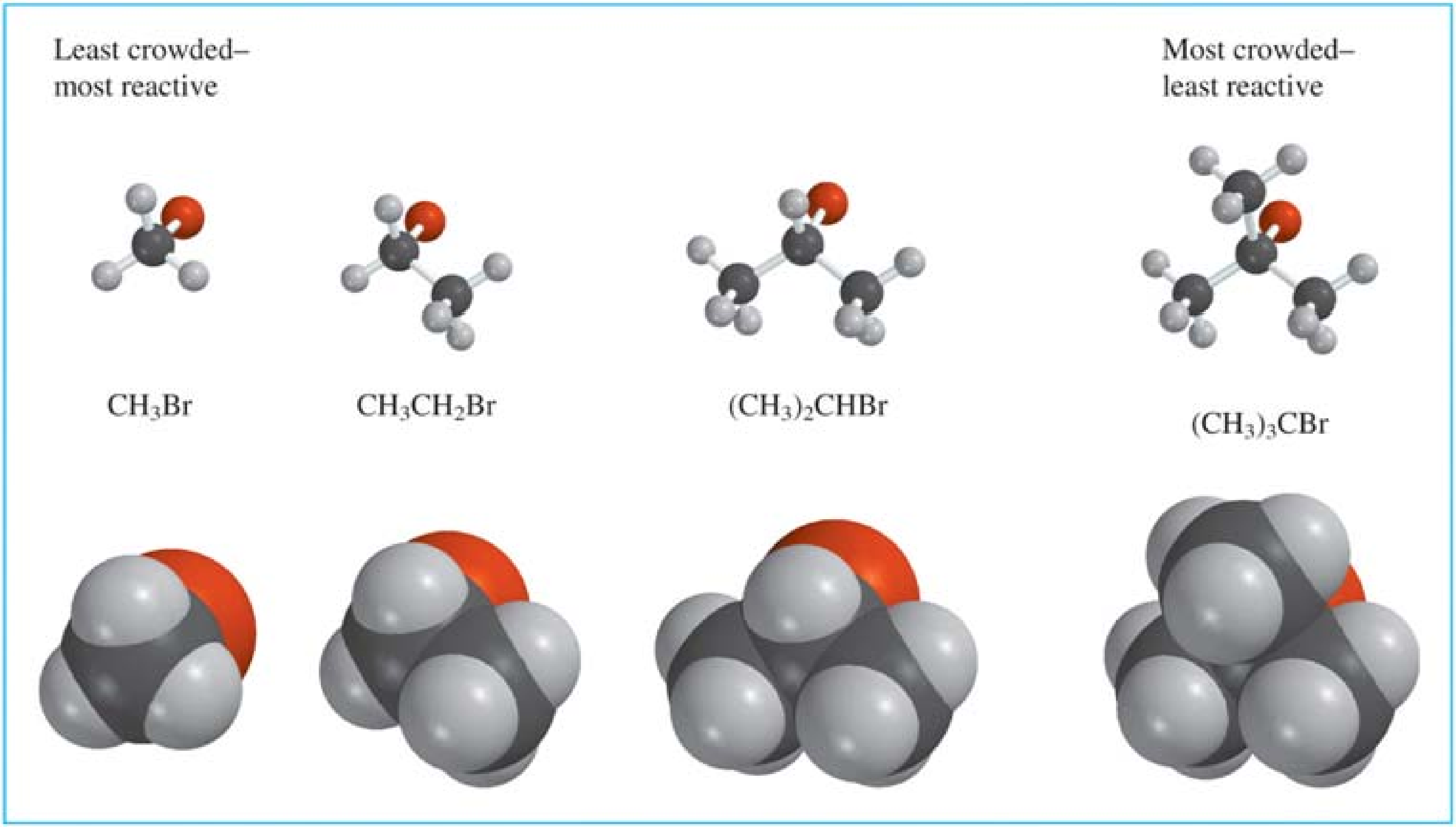
- Crowding at the carbon that bears the leaving group slows the rate of bimolecular nucleophilic substitution.

Table 8.2. Reactivity toward substitution by the S_N2 mechanism

$$RBr + LiI \rightarrow RI + LiBr$$

Alkyl bromide	Class	Relative rate
CH_3Br	Methyl	221,000
CH_3CH_2Br	Primary	1,350
$(CH_3)_2CHBr$	Secondary	1
$(CH_3)_3CBr$	Tertiary	too small to measure

Decreasing S_N2 Reactivity



Crowding Adjacent to the Reaction Site

- The rate of nucleophilic substitution by the S_N2 mechanism is governed by steric effects.

- Crowding at the carbon adjacent to the one that bears the leaving group also slows the rate of bimolecular nucleophilic substitution, but the effect is smaller.

Table 8.3. Effect of chain branching on rate of S_N2 substitution

$$RBr + LiI \rightarrow RI + LiBr$$

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

8.5. Nucleophiles and Nucleophilicity

- The nucleophiles described in Sections 8.1-8.4 have been anions.

$\mathrm{H\underset{\cdot\cdot}{\ddot{O}}\!:^{-}}$ $\mathrm{H\underset{\cdot\cdot}{\ddot{S}}\!:^{-}}$ $\mathrm{CH_3\underset{\cdot\cdot}{\ddot{O}}\!:^{-}}$ $\mathrm{:N{\equiv}\bar{C}\!:}$ etc.

- Not all nucleophiles are anions. Many are neutral.

$\mathrm{H\underset{\cdot\cdot}{\ddot{O}}H}$ $\mathrm{CH_3\underset{\cdot\cdot}{\ddot{O}}H}$ $\mathrm{:NH_3}$ for example

- All nucleophiles, however, are Lewis bases.

Nucleophiles

- Many of the solvents in which nucleophilic substitutions are carried out are themselves nucleophiles.

$H\underset{\cdot\cdot}{\ddot{O}}H$ $CH_3\underset{\cdot\cdot}{\ddot{O}}H$

for example

Solvolysis

- The term *solvolysis* refers to a nucleophilic substitution in which the nucleophile is the solvent. Substitution by an anionic nucleophile:

$$R—X + :Nu^{—} \longrightarrow R—Nu + :X^{—}$$

Solvolysis

$$R—X + :Nu—H \longrightarrow R—\overset{+}{Nu}—H + :X^{—}$$

Step in which nucleophilic substitution occurs

Solvolysis

- Substitution by an anionic nucleophile.

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

Solvolysis:

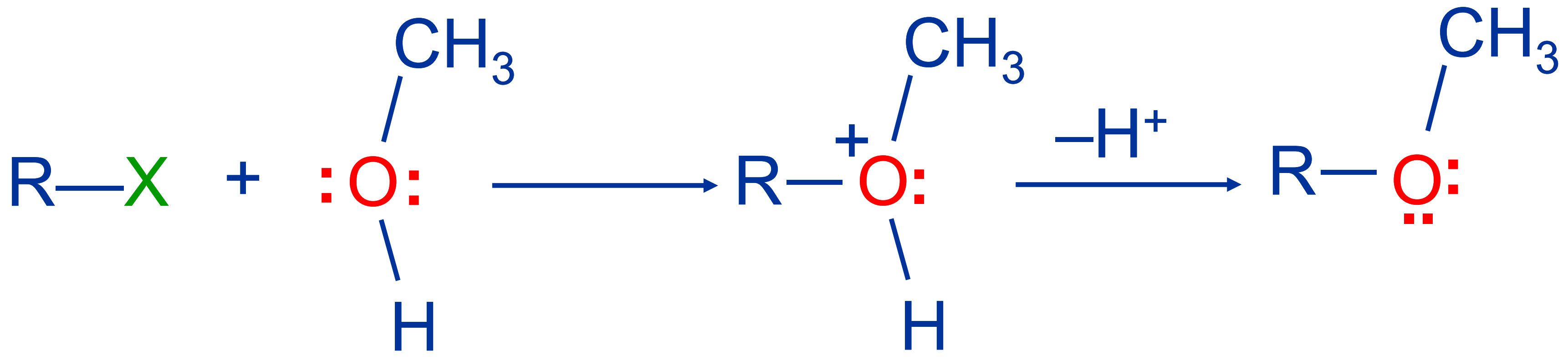
$$R{-}X + :Nu{-}H \longrightarrow R{-}\overset{+}{Nu}{-}H + :X^{-}$$

$$\downarrow$$

Products of overall reaction —— $R{-}Nu + HX$

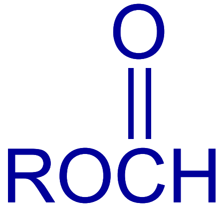
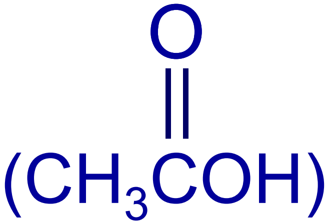
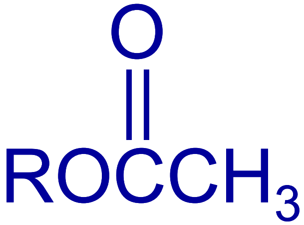
Example: Methanolysis

- Methanolysis is a nucleophilic substitution in which methanol acts as both the solvent and the nucleophile.



The product is a methyl ether.

Typical solvents in solvolysis

Solvent	Product from RX
Water (HOH)	ROH
Methanol (CH_3OH)	$ROCH_3$
Ethanol (CH_3CH_2OH)	$ROCH_2CH_3$
Formic acid  $(\mathrm{H}\overset{\overset{\mathrm{O}}{\Vert}}{\mathrm{C}}\mathrm{OH})$	 $\mathrm{RO}\overset{\overset{\mathrm{O}}{\Vert}}{\mathrm{C}}\mathrm{H}$
Acetic acid  $(\mathrm{CH_3}\overset{\overset{\mathrm{O}}{\Vert}}{\mathrm{C}}\mathrm{OH})$	 $\mathrm{RO}\overset{\overset{\mathrm{O}}{\Vert}}{\mathrm{C}}\mathrm{CH_3}$

Nucleophilicity is a measure of the reactivity of a nucleophile

- Table 8.4 compares the relative rates of nucleophilic substitution of a variety of nucleophiles toward methyl iodide as the substrate. The standard of comparison is methanol, which is assigned a relative rate of 1.0.

$$CH_3{-}I + :Nu^{-} \longrightarrow R{-}Nu + :X^{-}$$

Table 8.4. Nucleophilicity

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

Major factors that control nucleophilicity

- Basicity.
- Solvation.

  - Small negative ions are highly solvated in protic solvents.

  - Large negative ions are less solvated.

Table 8.4. Nucleophilicity

Rank	Nucleophile	Relative rate
Good	HO^-, RO^-	10^4
Fair	RCO_2^-	10^3
Weak	H_2O, ROH	1

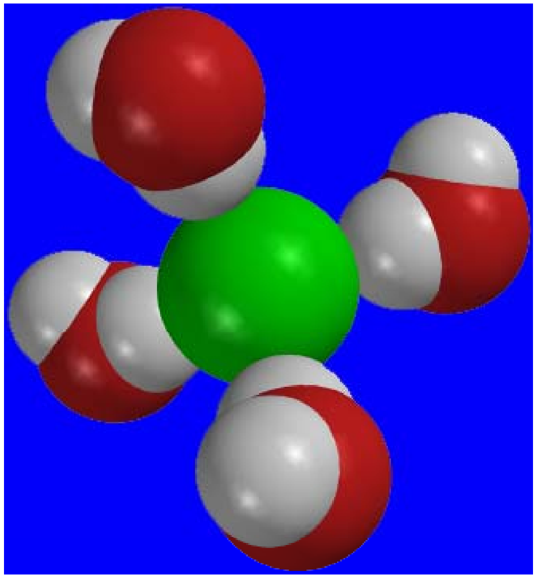
- When the attacking atom is the same (oxygen in this case), nucleophilicity increases with increasing basicity. Also, if the attacking atoms are of the same period, nucleophilicity increases with increasing basicity.

Table 8.4. Nucleophilicity

Rank	Nucleophile	Relative rate
Strong	I^-	$>10^5$
Good	Br^-	10^4
Fair	Cl^-, F^-	10^3

- A tight solvent shell around an ion makes it less reactive. Larger ions are less solvated than smaller ones and are more nucleophilic.

Figure 8.3

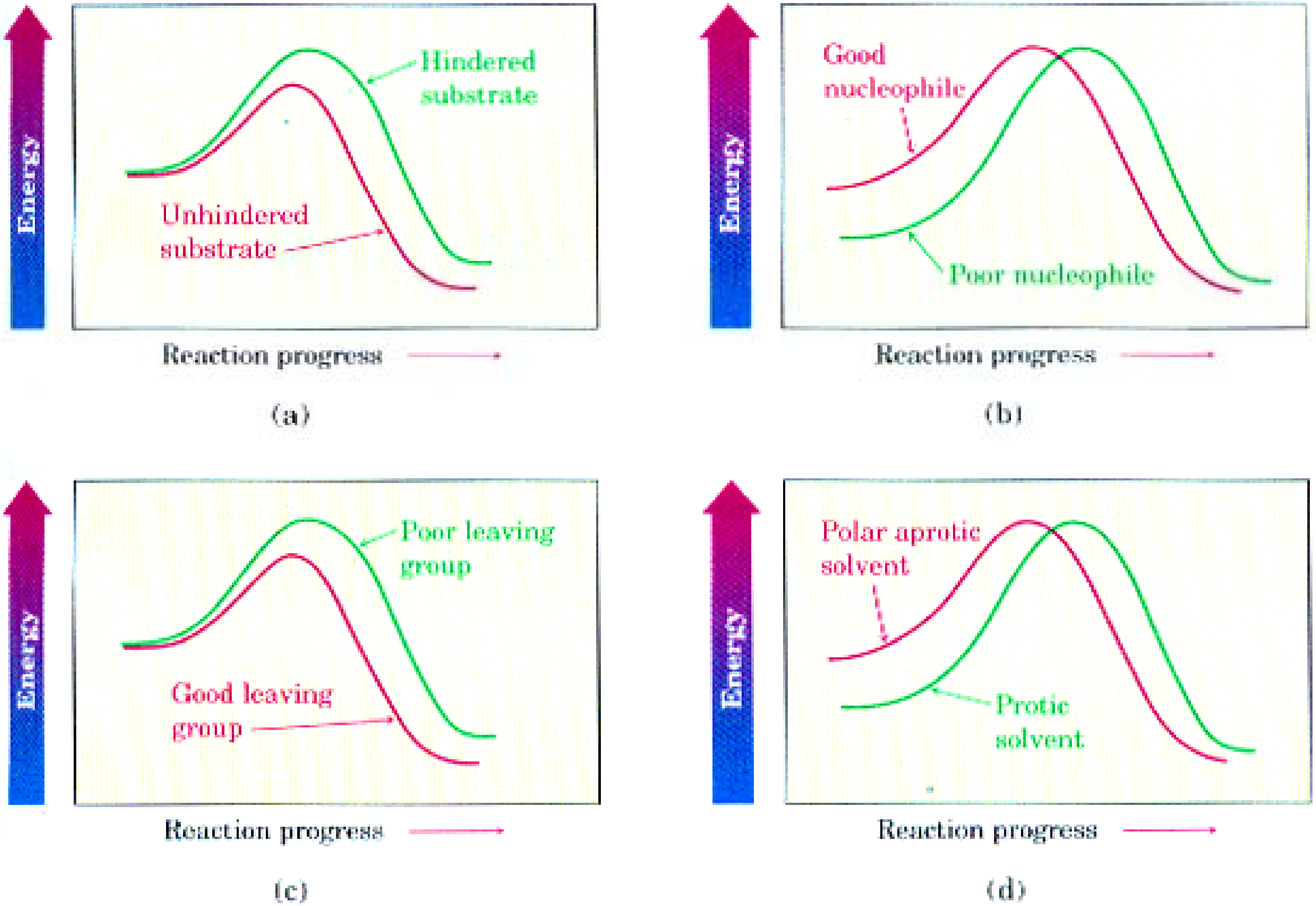


- Solvation of a chloride ion by ion-dipole attractive forces with water. The negatively charged chloride ion interacts with the positively polarized hydrogens of water.

S_N2 Reaction Characteristics

- The effect on S_N2 reactions of four variables:
  - Substrate structure
  - Nucleophile
  - Leaving group
  - Solvent

Reaction energy diagrams showing the effects of substrate, nucleophile, leaving group, and solvent



(a) (b) (c) (d)

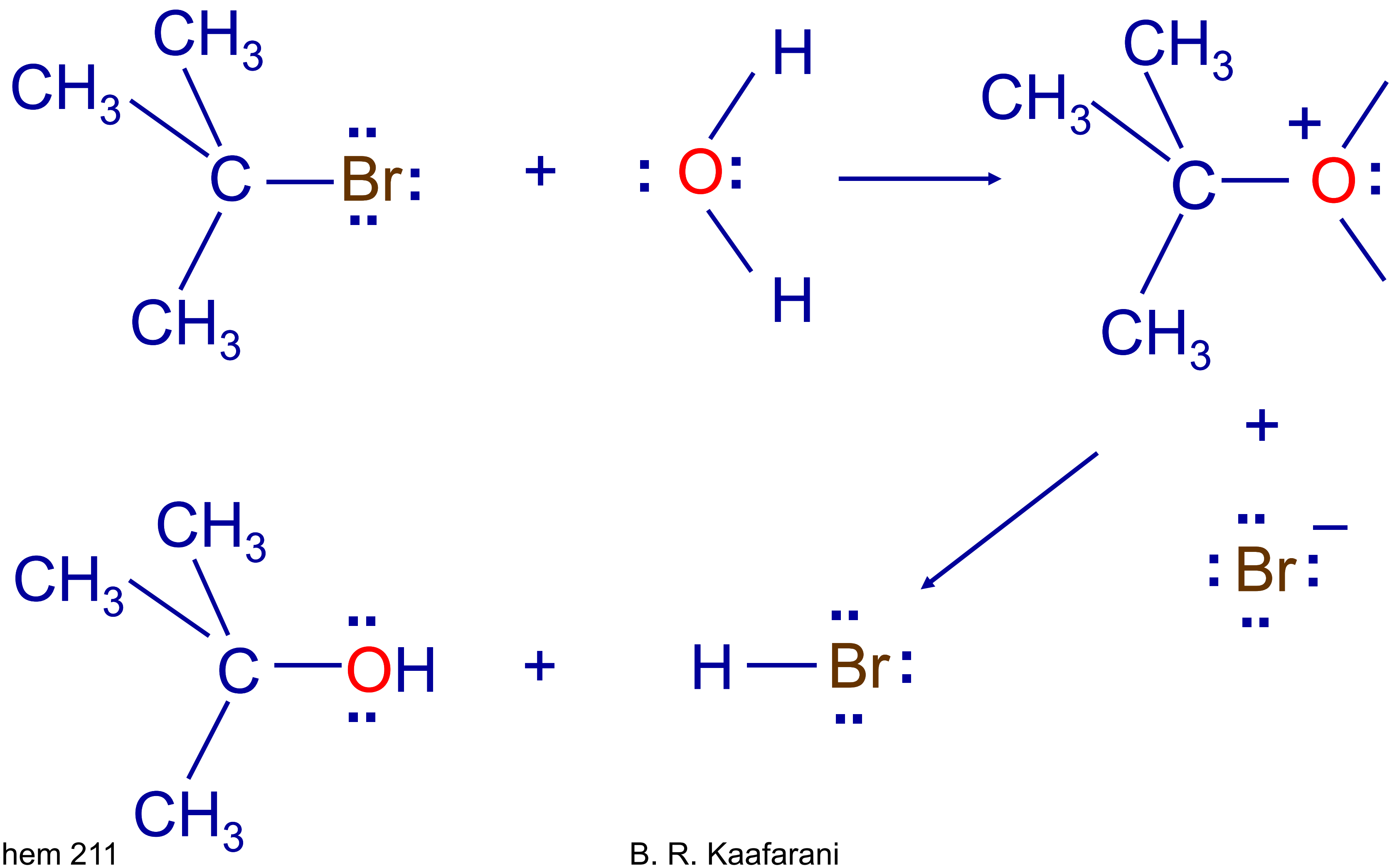
8.6. The S_N1 Mechanism of Nucleophilic Substitution

A Question...

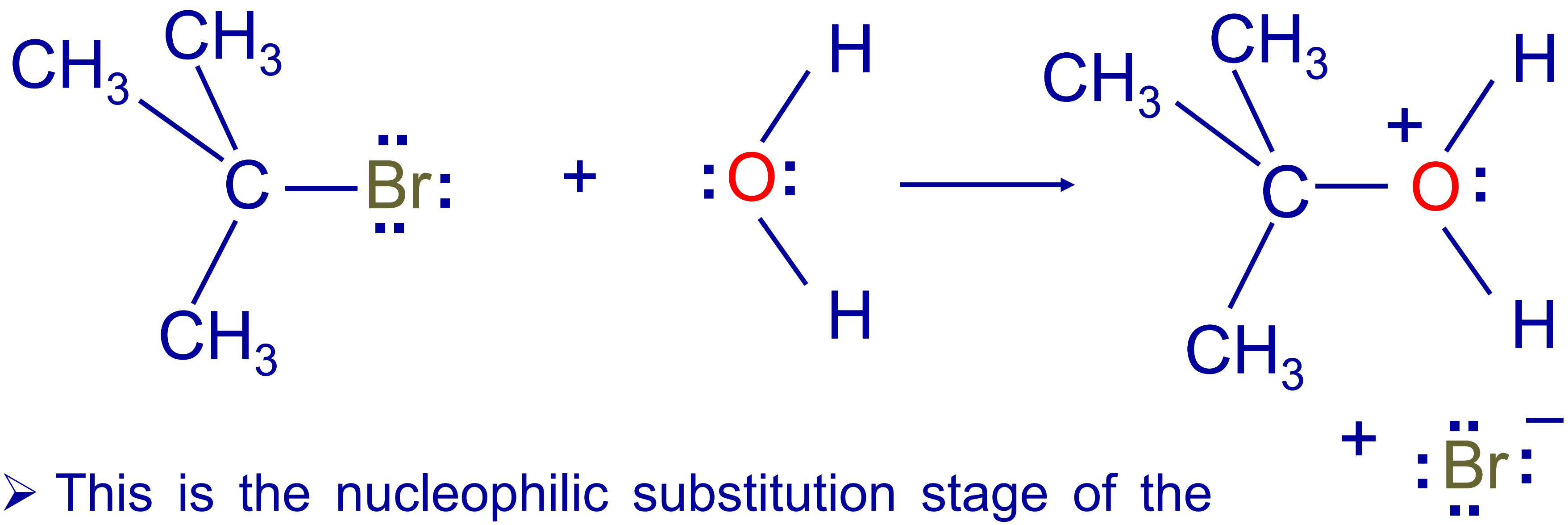
- Tertiary alkyl halides are very unreactive in substitutions that proceed by the S_N2 mechanism. Do they undergo nucleophilic substitution at all?

- Yes. But by a mechanism different from S_N2. The most common examples are seen in solvolysis reactions.

Example of a solvolysis.
Hydrolysis of *tert*-butyl bromide.

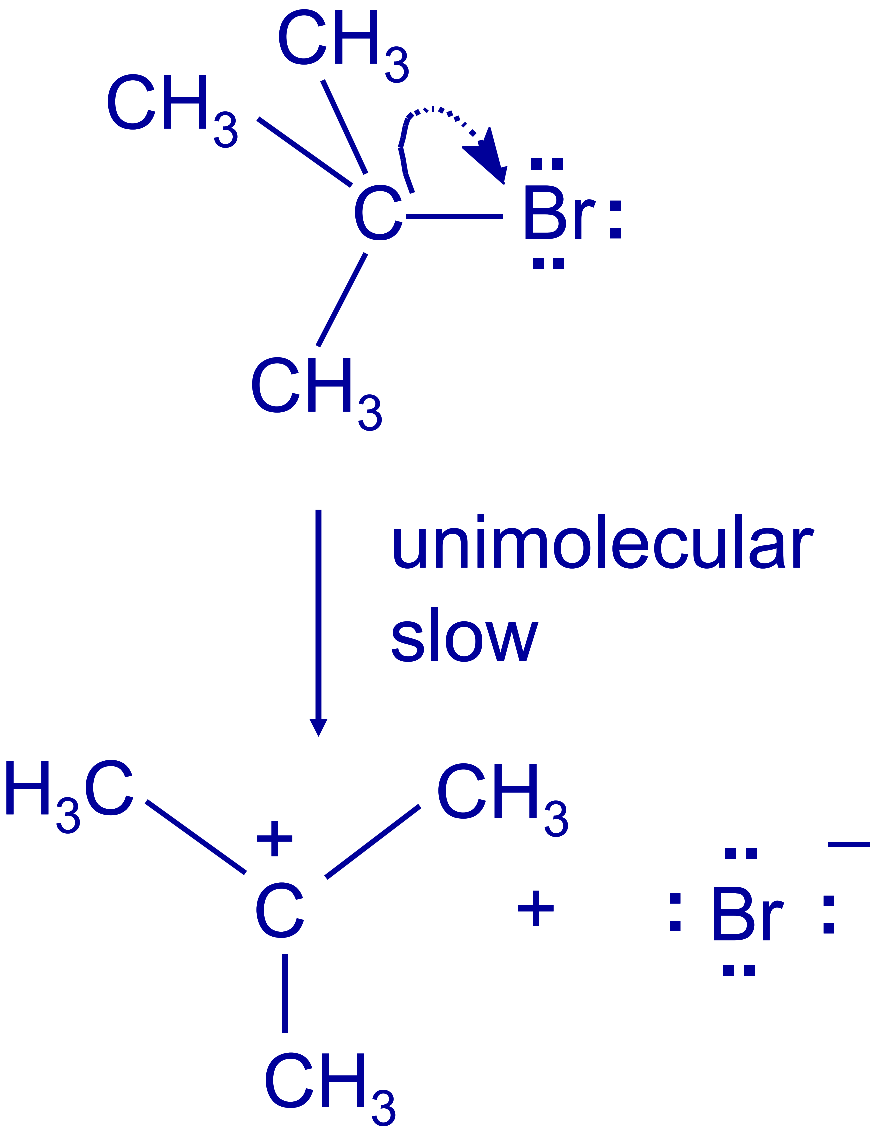


Example of a solvolysis. Hydrolysis of *tert*-butyl bromide



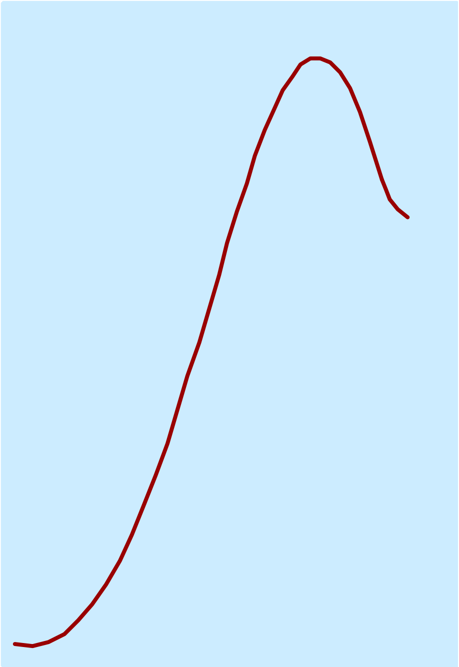
- This is the nucleophilic substitution stage of the reaction; the one with which we are concerned.
- The reaction rate is independent of the concentration of the nucleophile and follows a first-order rate law. Rate = $k[(CH_3)_3CBr]$
- The mechanism of this step is not S_N2. It is called S_N1 and begins with ionization of $(CH_3)_3CBr$.

Mechanism

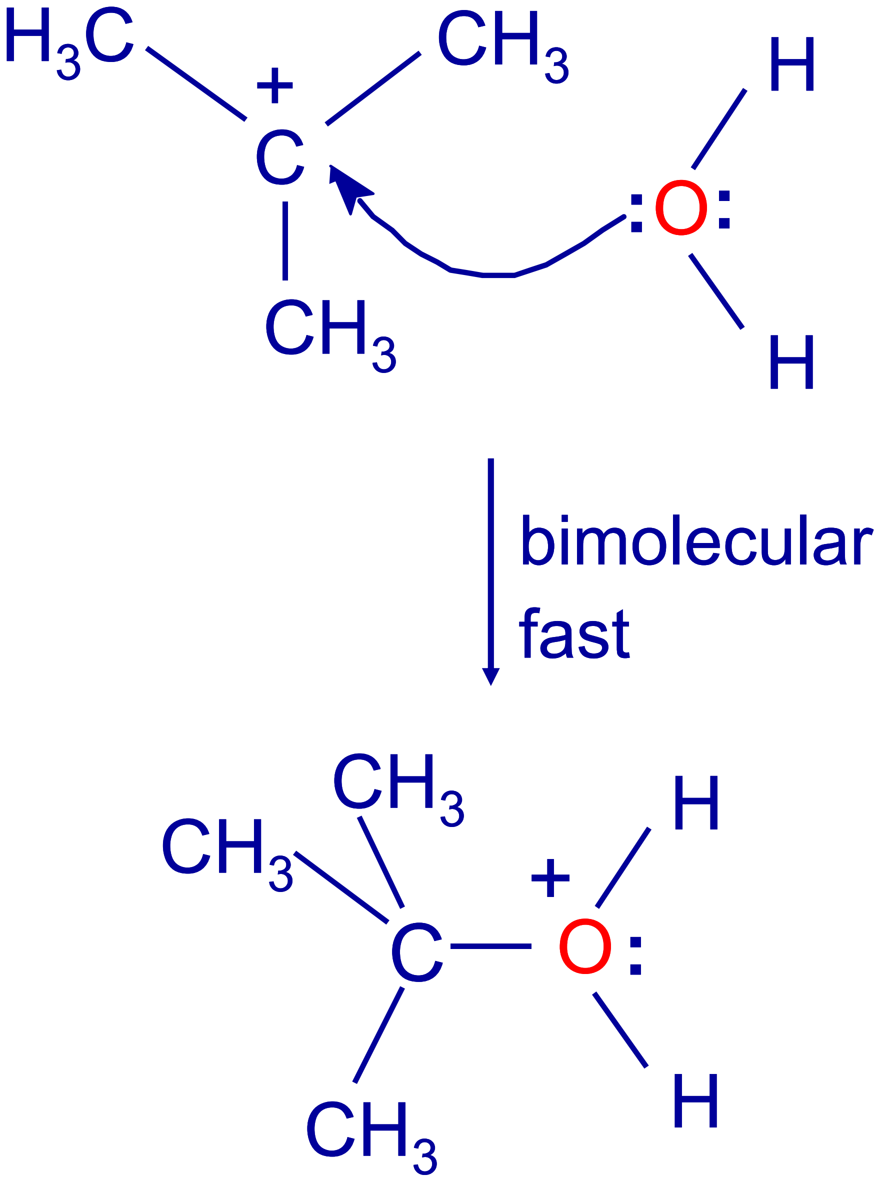


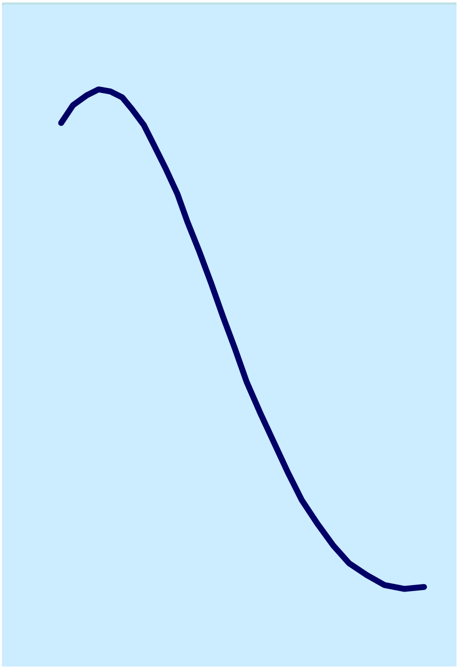
unimolecular

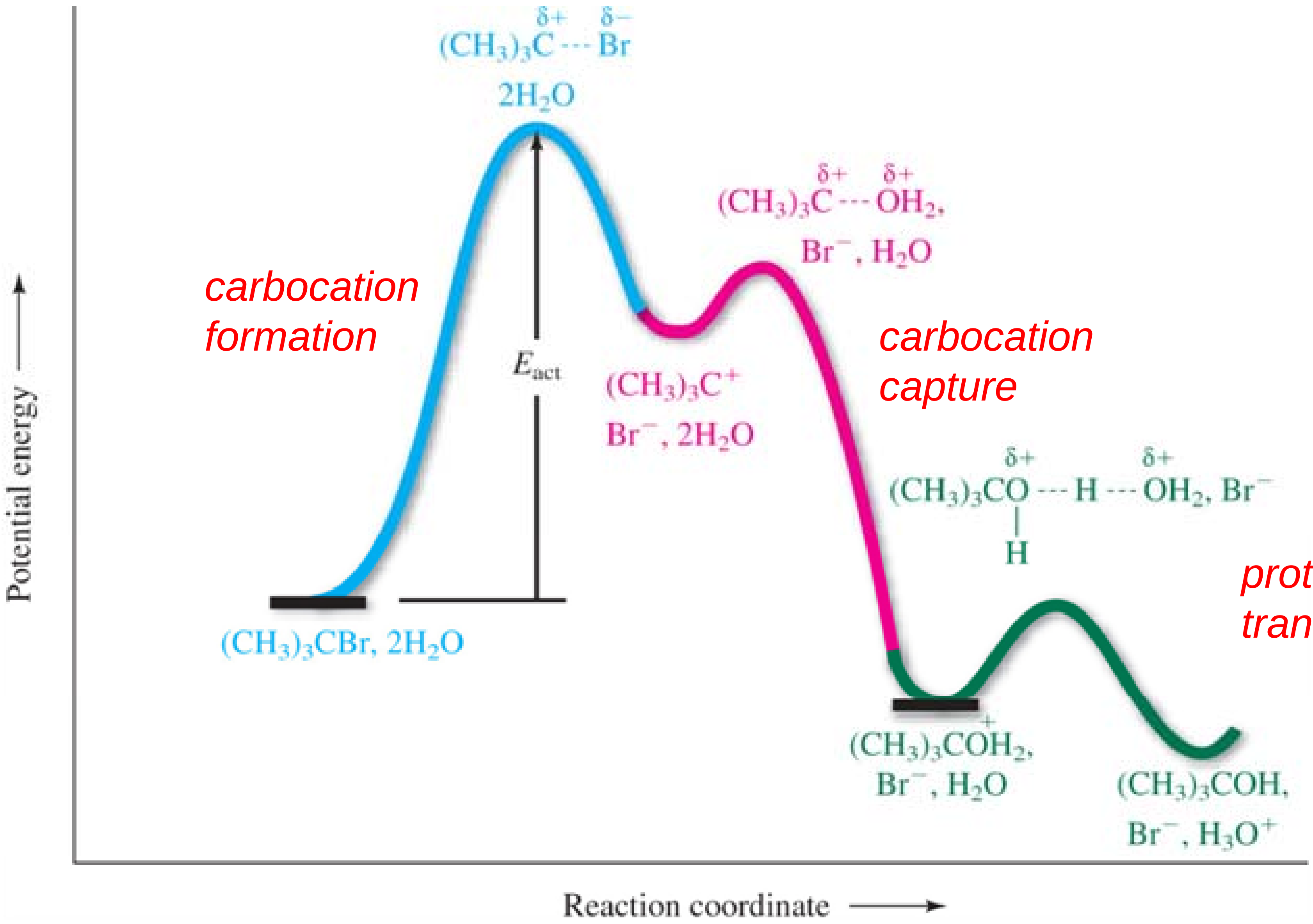
slow



Mechanism







carbocation formation

carbocation capture

proton transfer

Characteristics of the S_N1 mechanism

- First order kinetics: rate = k[RX]

  Unimolecular rate-determining step.

- Carbocation intermediate
  - Rate follows carbocation stability.
  - Rearrangements sometimes observed.

- Reaction is not stereospecific
  - Much racemization in reactions of optically active alkyl halides.

8.7. Carbocation Stability and S_N1 Reaction Rates

- The rate of nucleophilic substitution by the S_N1 mechanism is governed by electronic effects.

- Carbocation formation is rate-determining. The more stable the carbocation, the faster its rate of formation, and the greater the rate of unimolecular nucleophilic substitution.

Table 8.5. Reactivity toward substitution by the S_N1 mechanism

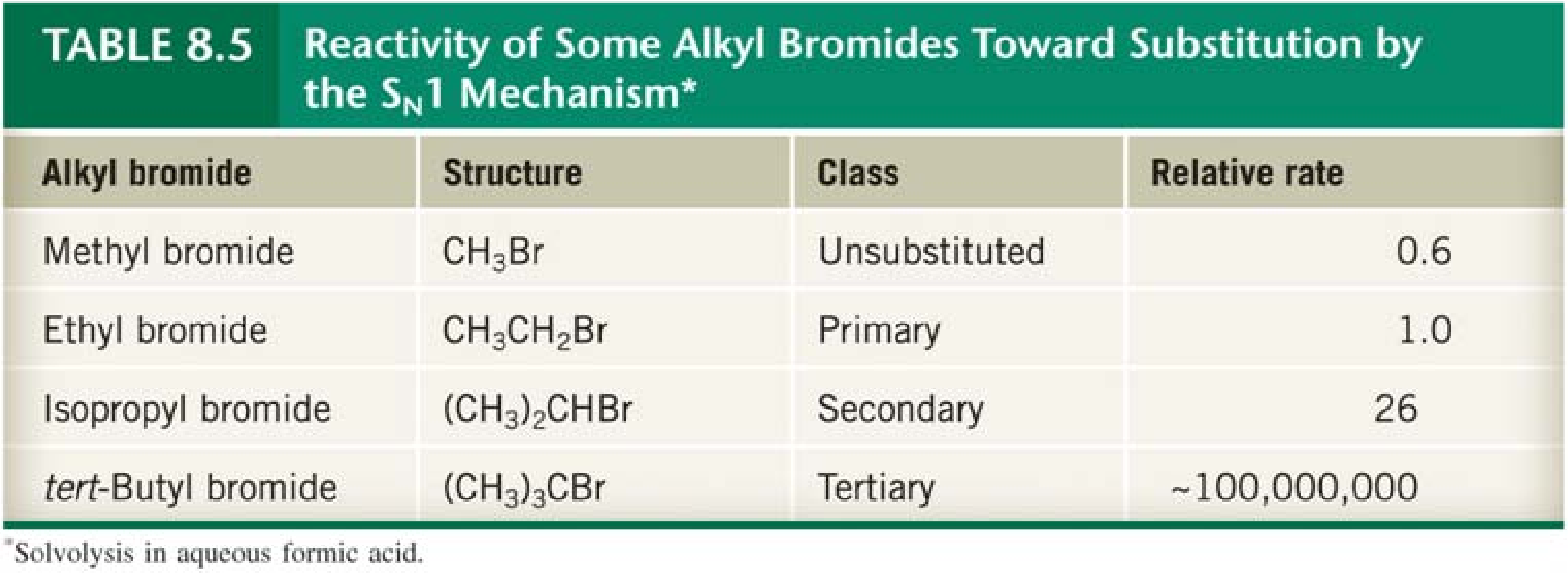
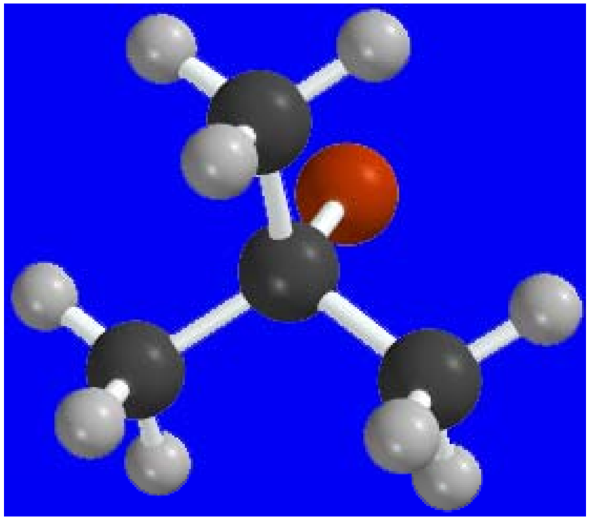


TABLE 8.5 **Reactivity of Some Alkyl Bromides Toward Substitution by the S_N1 Mechanism***

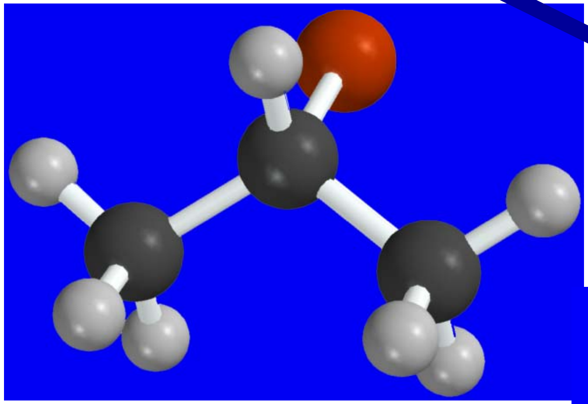
Alkyl bromide	Structure	Class	Relative rate
Methyl bromide	CH_3Br	Unsubstituted	0.6
Ethyl bromide	CH_3CH_2Br	Primary	1.0
Isopropyl bromide	$(CH_3)_2CHBr$	Secondary	26
tert-Butyl bromide	$(CH_3)_3CBr$	Tertiary	~100,000,000

*Solvolysis in aqueous formic acid.

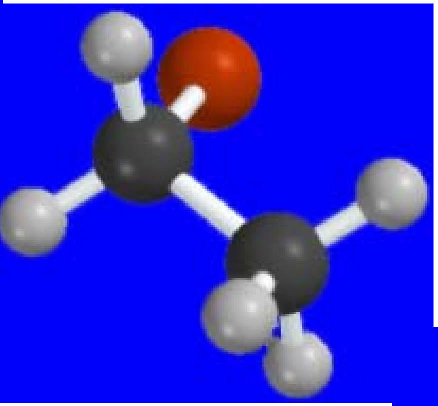
Decreasing S_N1 Reactivity



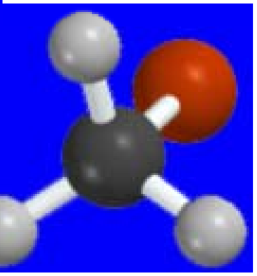
$(CH_3)_3CBr$



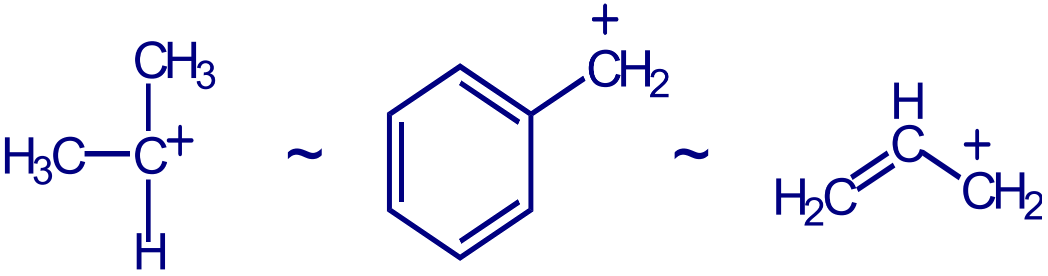
$(CH_3)_2CHBr$

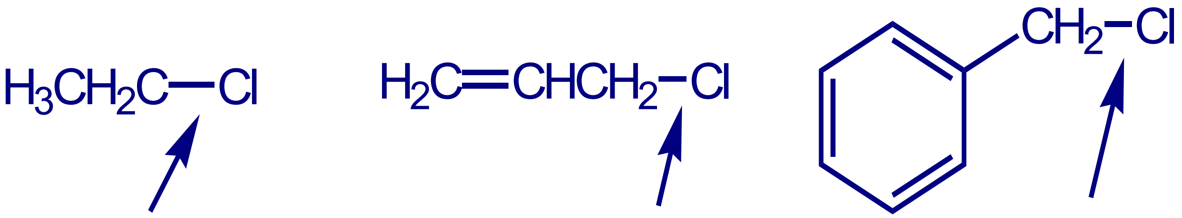


CH_3CH_2Br



CH_3Br

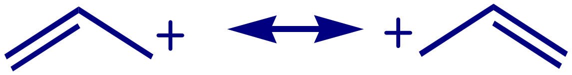


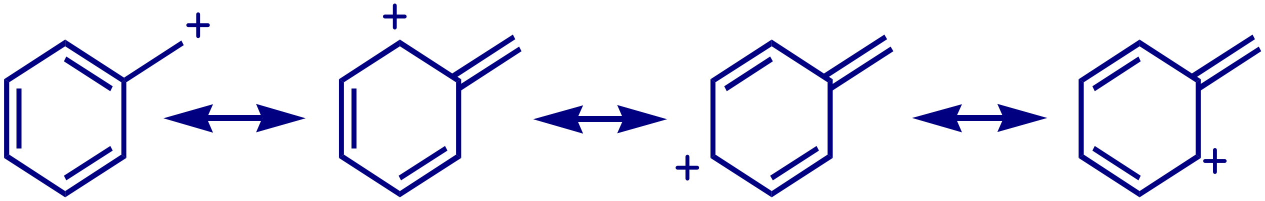


338 kJ/mol
(81 kcal/mol)

289 kJ/mol
(69 kcal/mol)

293 kJ/mol
(70 kcal/mol)



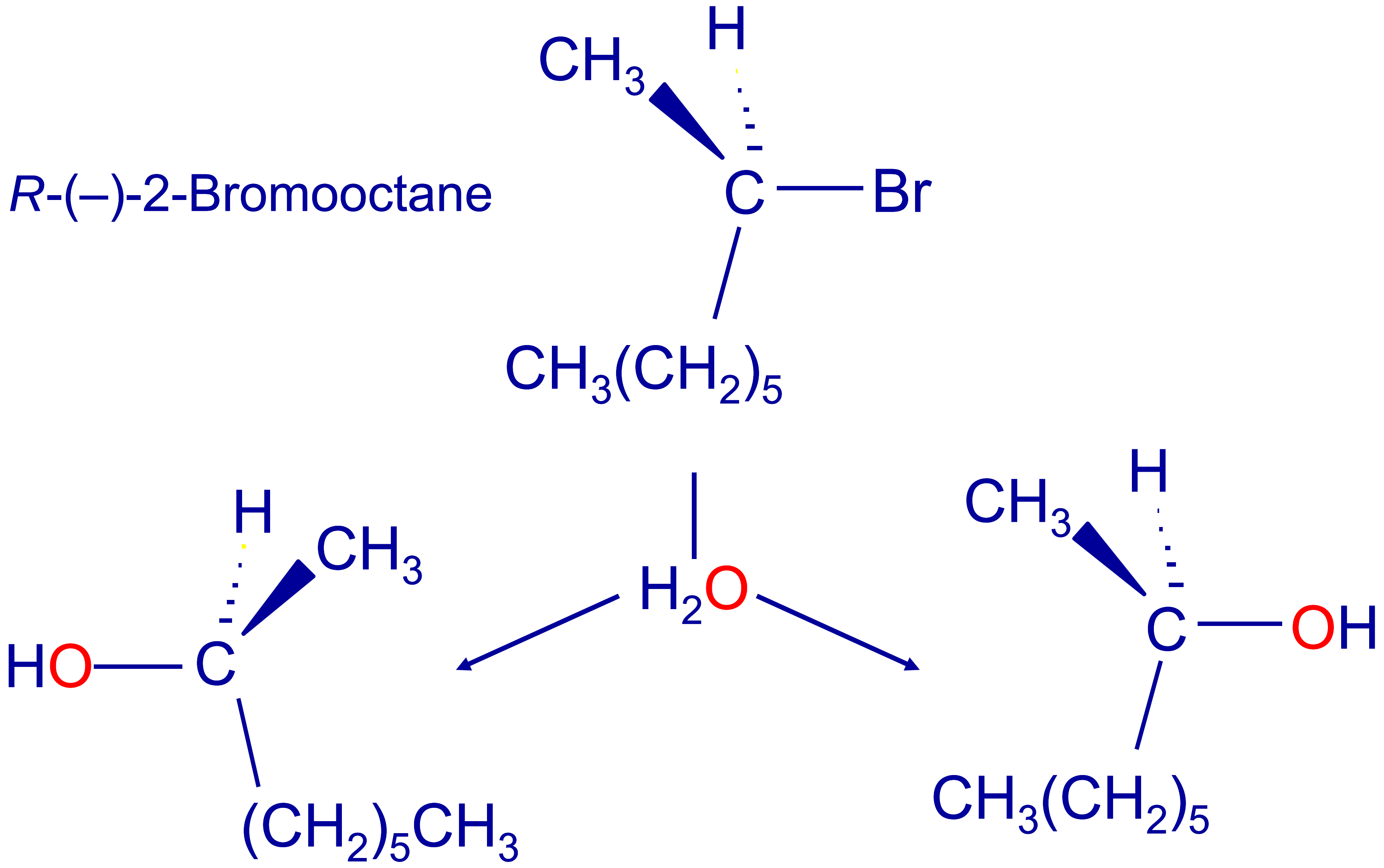


8.8. Stereochemistry of S_N1 Reactions

Generalization

Nucleophilic substitutions that exhibit first-order kinetic behavior are ***NOT*** stereospecific.

Stereochemistry of an S_N1 Reaction

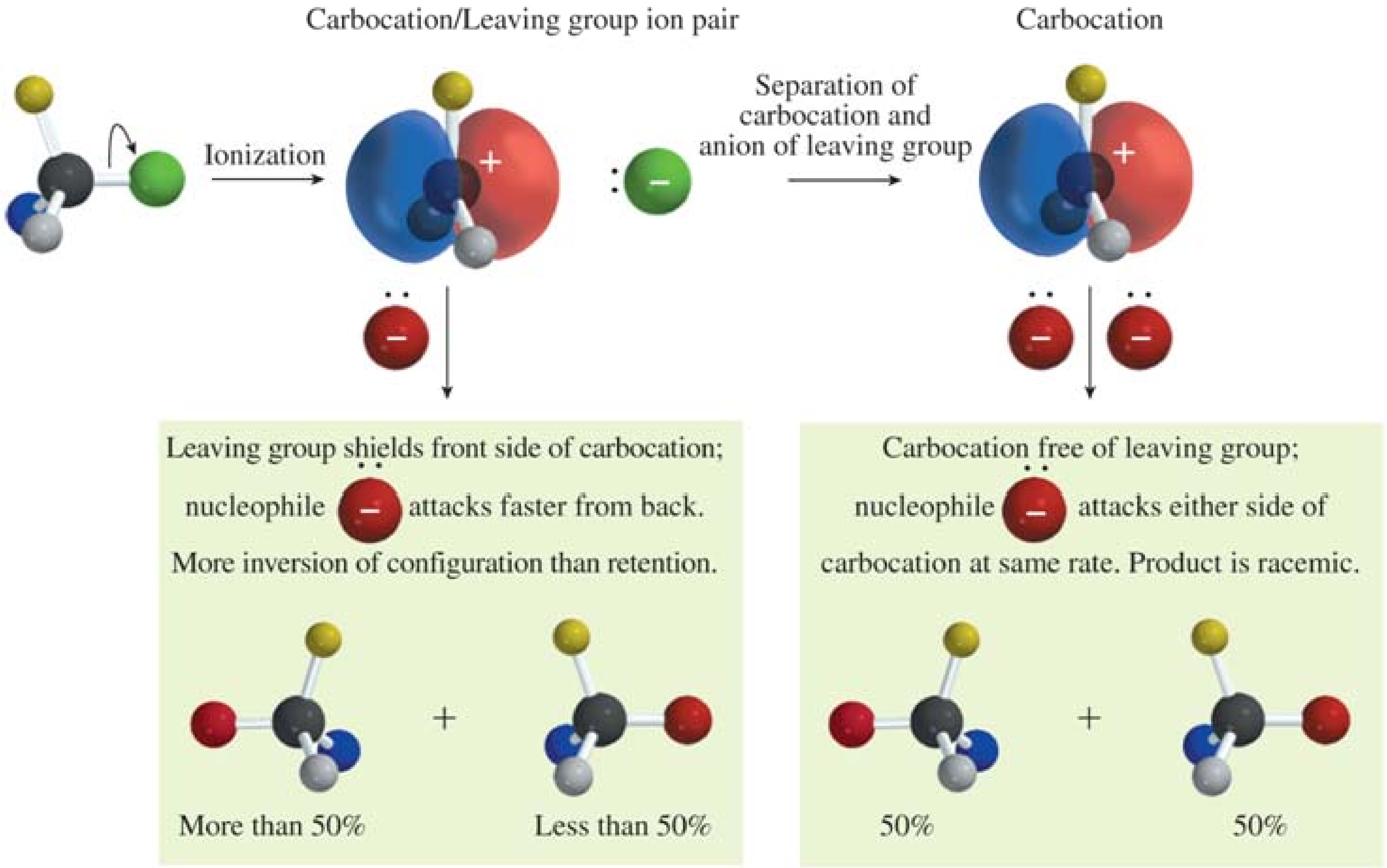


R-(–)-2-Bromooctane

(*S*)-(+)-2-Octanol (83%)

(*R*)-(–)-2-Octanol (17%)

Figure 8.6



Leaving group shields front side of carbocation; nucleophile − attacks faster from back. More inversion of configuration than retention.

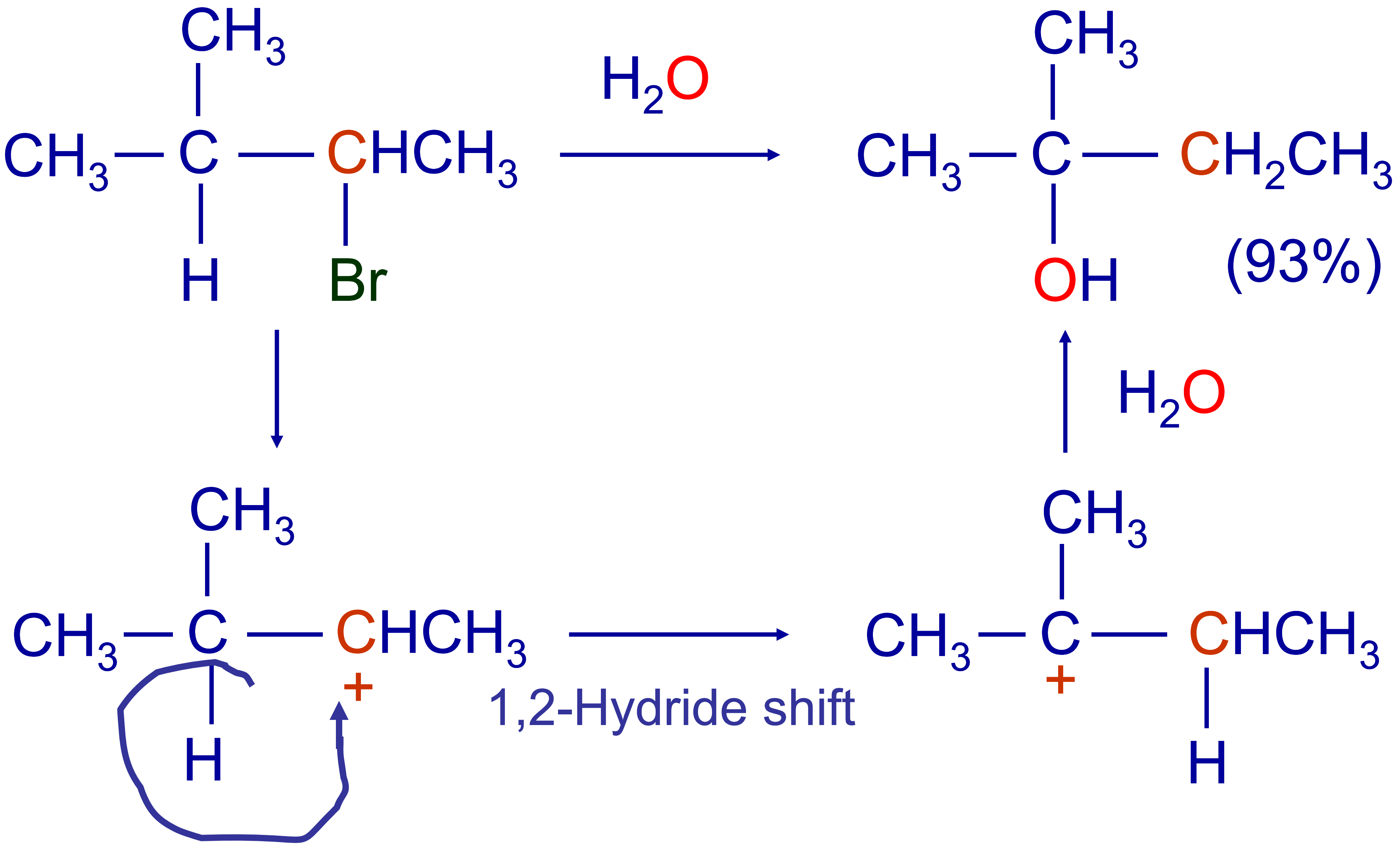
Carbocation free of leaving group; nucleophile − attacks either side of carbocation at same rate. Product is racemic.

8.9. Carbocation Rearrangements in S_N1 Reactions

Because...

Carbocations are intermediates
in S_N1 reactions, rearrangements
are possible.

Example



8.10. Effect of Solvent on the Rate of Nucleophilic Substitution

In general...

S_N1 Reaction Rates Increase
in Polar Solvents!

Table 8.6

S_N1 Reactivity versus Solvent Polarity

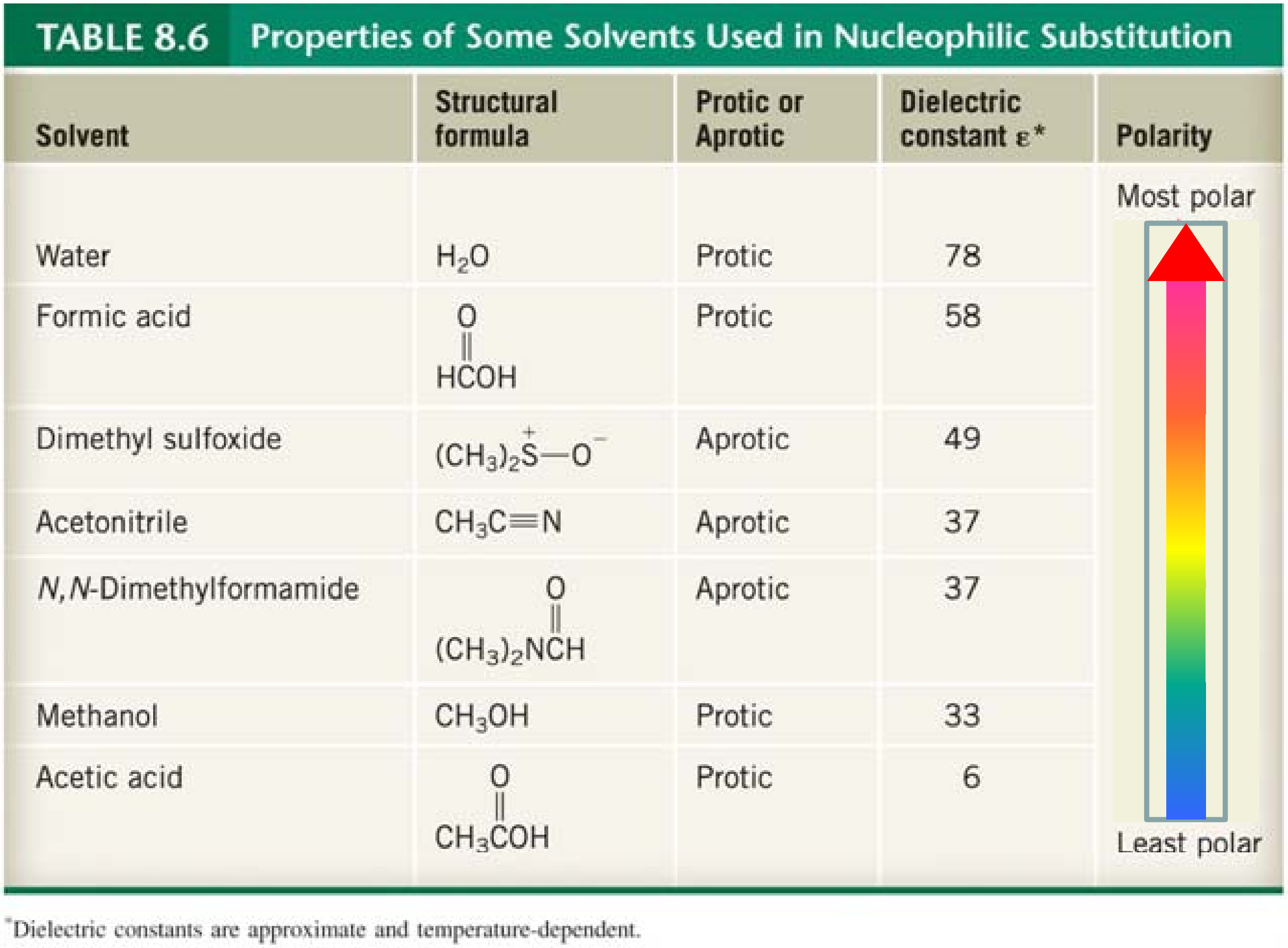


TABLE 8.6 Properties of Some Solvents Used in Nucleophilic Substitution

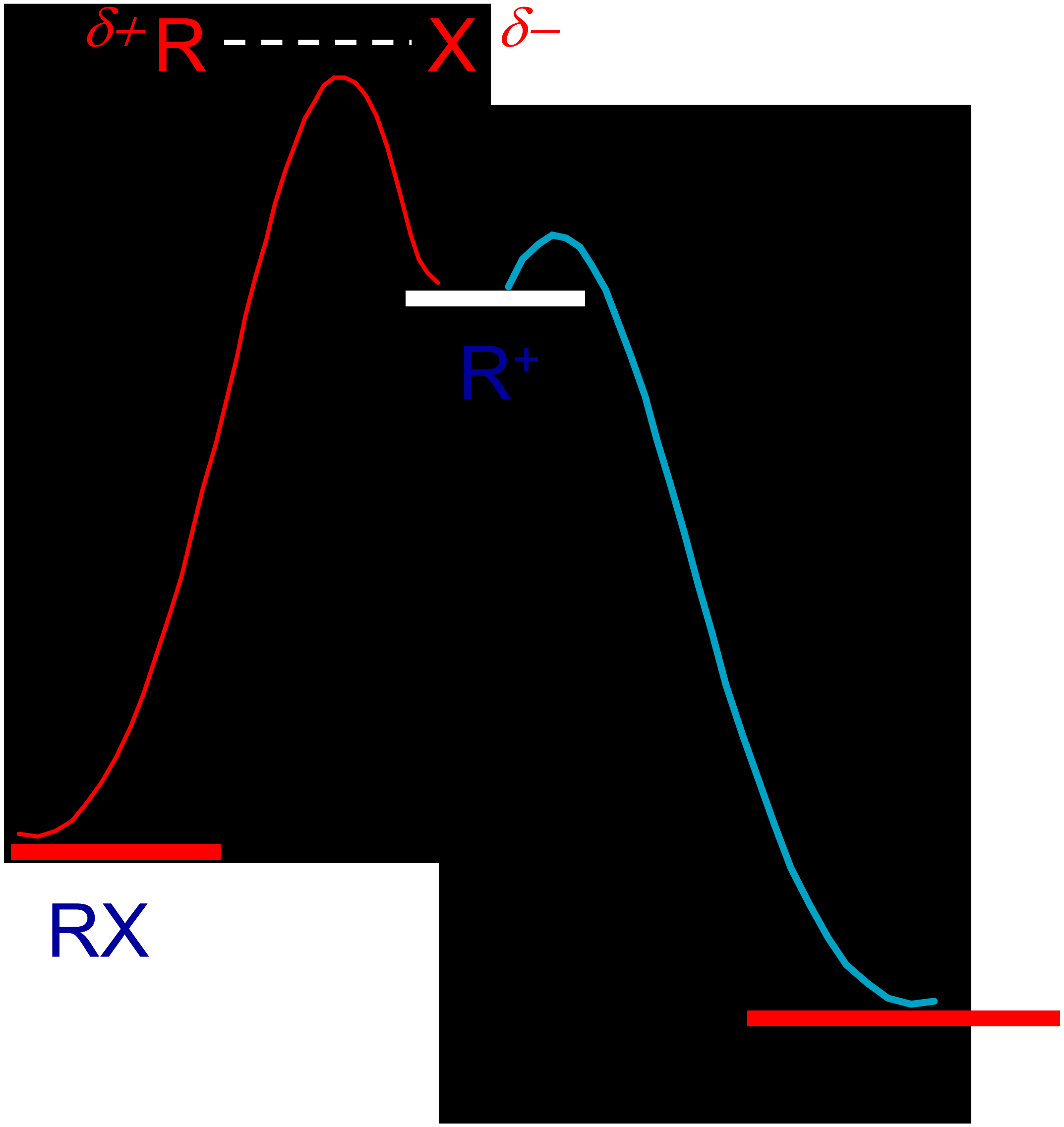
Solvent	**Structural formula**	**Protic or Aprotic**	**Dielectric constant ε***	**Polarity**
Water	H_2O	Protic	78	Most polar
Formic acid	$H\overset{\overset{O}{\|}}{C}OH$	Protic	58	
Dimethyl sulfoxide	$(CH_3)_2\overset{+}{S}{-}O^-$	Aprotic	49	
Acetonitrile	$CH_3C{\equiv}N$	Aprotic	37	
N,N-Dimethylformamide	$(CH_3)_2N\overset{\overset{O}{\|}}{C}H$	Aprotic	37	
Methanol	CH_3OH	Protic	33	
Acetic acid	$CH_3\overset{\overset{O}{\|}}{C}OH$	Protic	6	Least polar

*Dielectric constants are approximate and temperature-dependent.

Most polar

Fastest rate

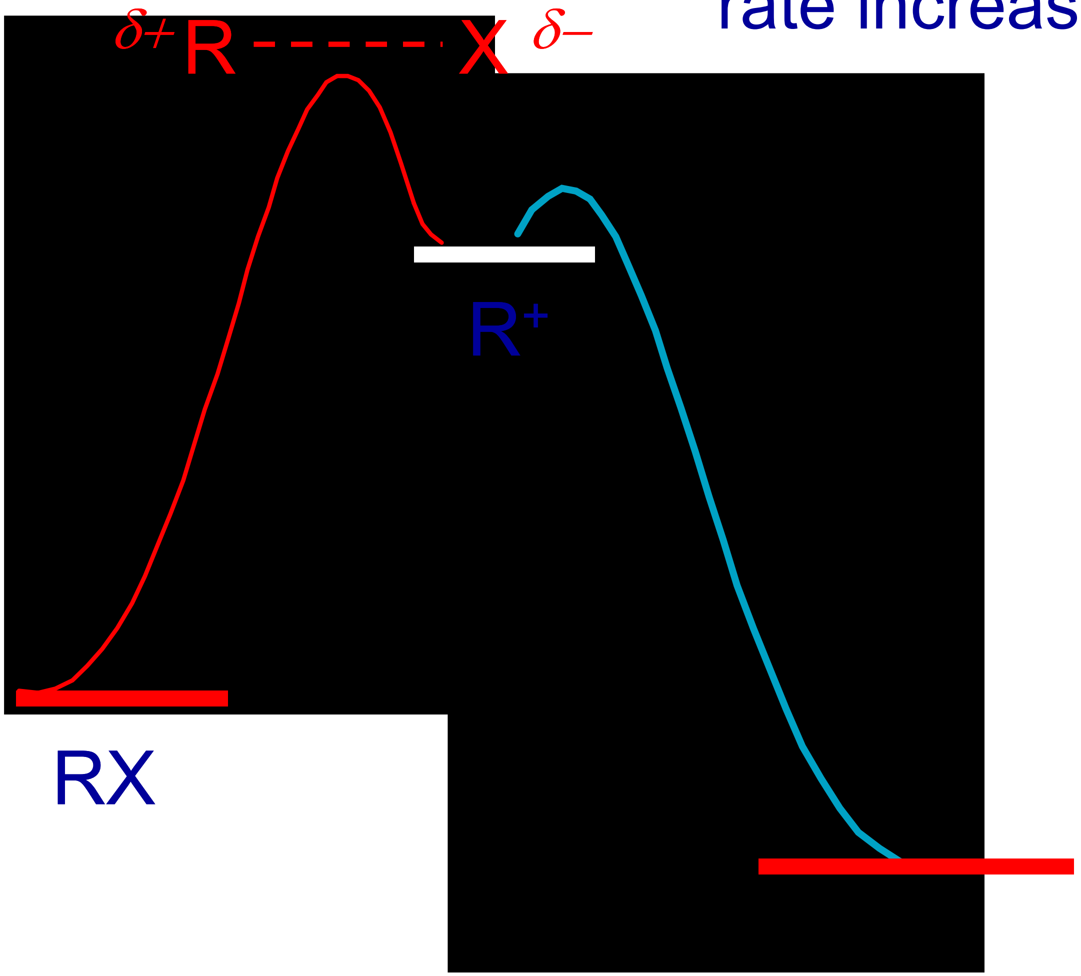
Transition state stabilized by polar solvent.



Energy of RX not much affected by polarity of solvent.

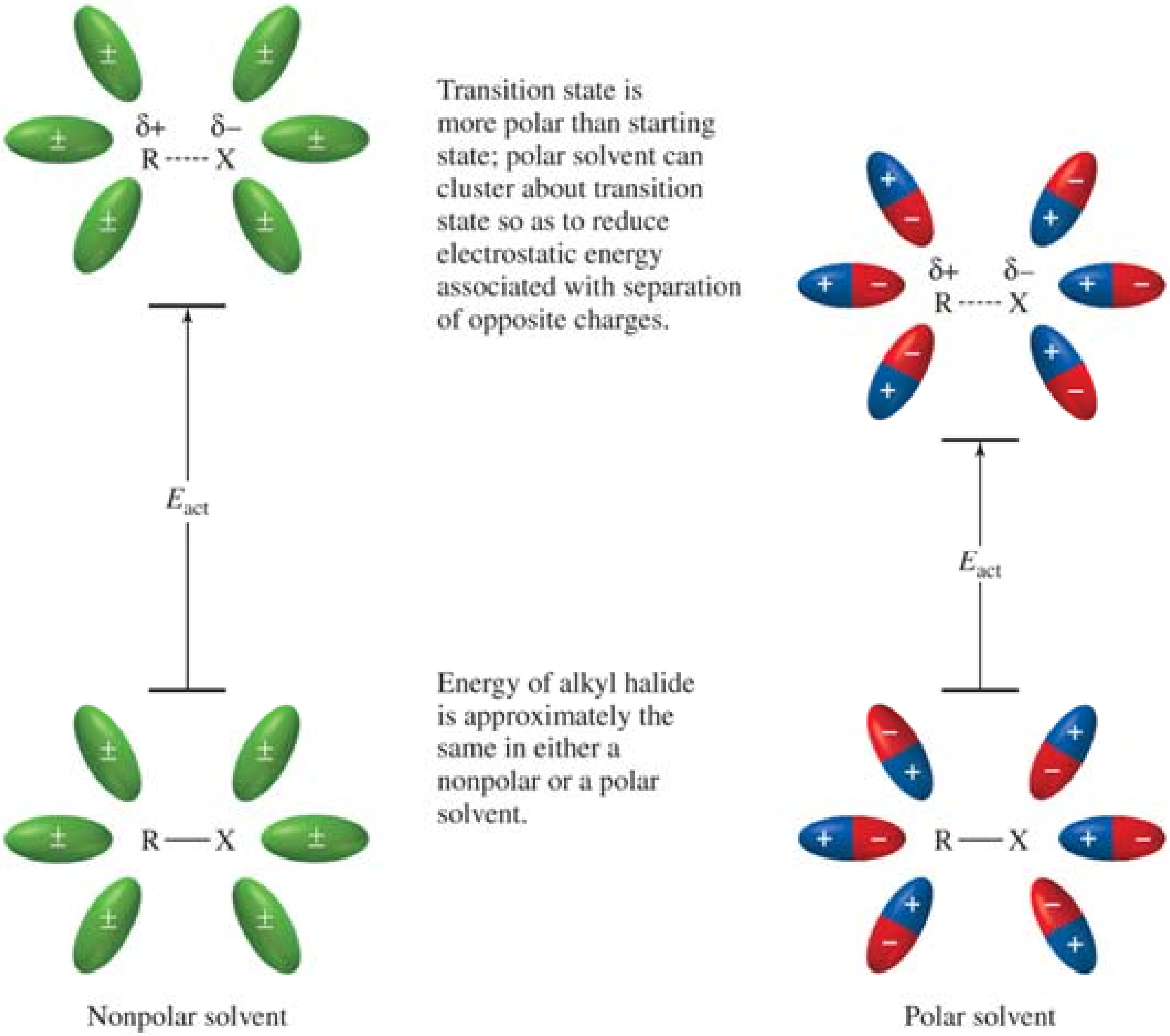
Transition state stabilized by polar solvent.

Activation energy decreases; rate increases.



Energy of RX not much affected by polarity of solvent.

S_N1 Reaction: Solvent Effect on Substrate



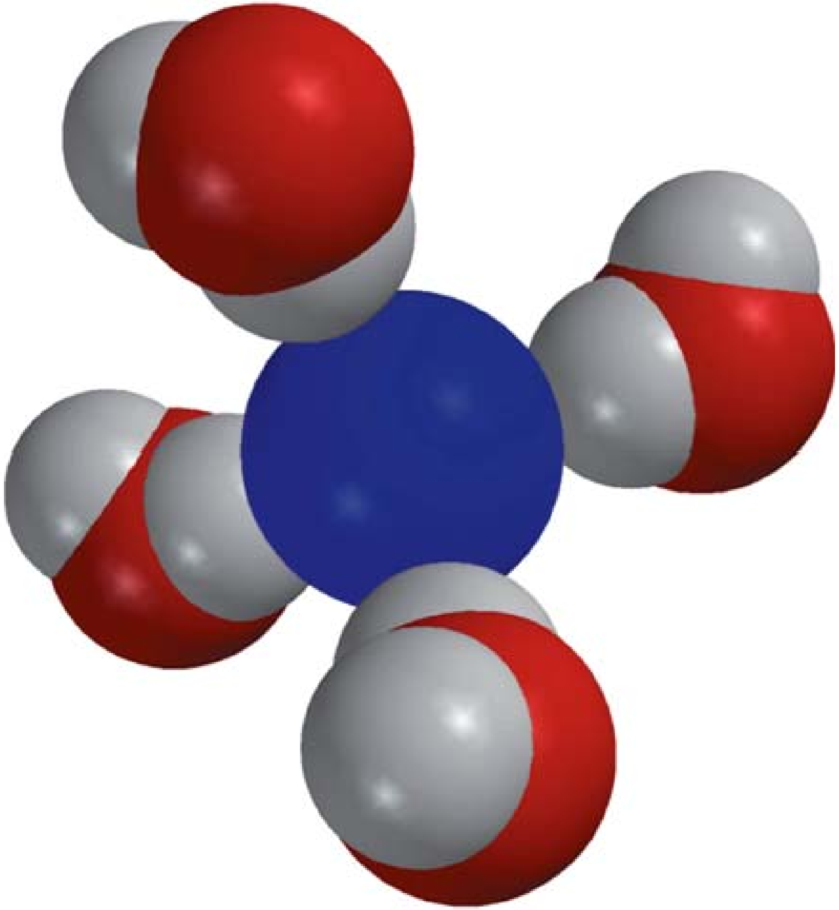
Transition state is more polar than starting state; polar solvent can cluster about transition state so as to reduce electrostatic energy associated with separation of opposite charges.

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

S_N2 Reaction: Solvent Effect on Nucleophile

- Polar protic solvents form H-bonds to anionic nucleophiles.

- Solvation forces stabilize the anion and supress its nucleophilicity.



In general...

S_N2 Reaction Rates Increase in Polar Aprotic Solvents.

An aprotic solvent is one that does not have an —OH group.

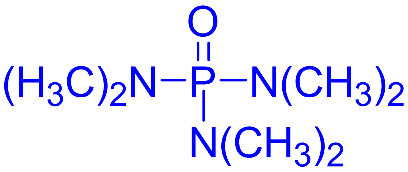
The Solvent

$$CH_3CH_2CH_2CH_2Br + N_3^- \longrightarrow CH_3CH_2CH_2CH_2N_3 + Br^-$$

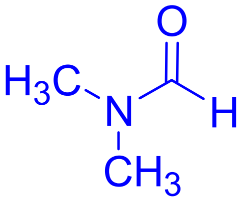
	HMPA	CH_3CN	DMF	DMSO	H_2O	CH_3OH
Relative reactivity	200,000	5000	2800	1300	7	1

More reactive

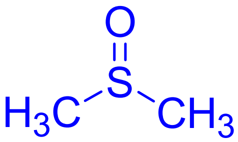
Less reactive



HMPA = Hexamethylphosphoramide



DMF= *N*,*N*-Dimethylformamide



DMSO= Dimethyl sulfoxide

Table 8.7

S_N2 Reactivity versus Type of Solvent

$CH_3CH_2CH_2CH_2Br + N_3^-$

Solvent	Type	Relative rate
CH_3OH	polar protic	1
H_2O	polar protic	7
DMSO	polar aprotic	1300
DMF	polar aprotic	2800
Acetonitrile	polar aprotic	5000

Table 8.8
S_N1 Reactivity versus Type of Solvent

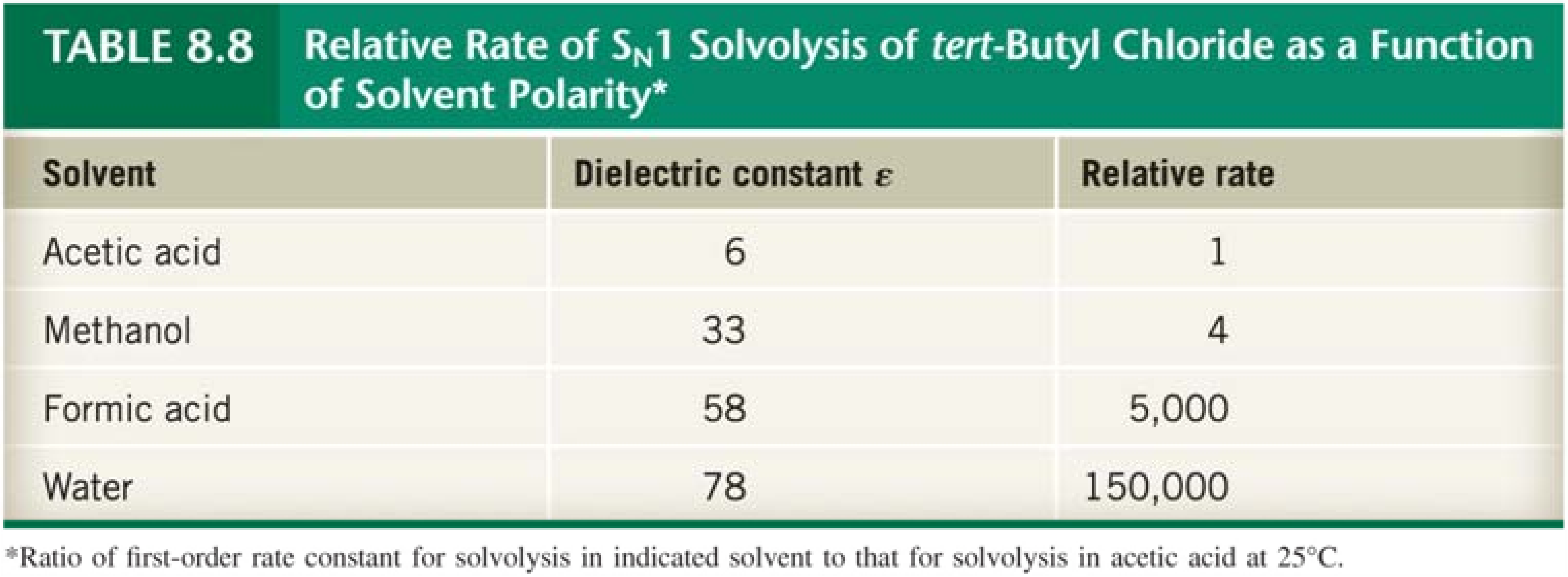


TABLE 8.8 Relative Rate of S_N1 Solvolysis of *tert*-Butyl Chloride as a Function of Solvent Polarity*

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.

S_N1 Reaction Characteristic

- Substrate-The best substrates are those that yield the most stable carbocations-best for tertiary, allylic, and benzylic substrates.

- Leaving group- Good leaving groups lower the energy of the transition state leading to carbocation formation.

- Nucleophile- The nucleophile must be nonbasic to prevent a competitive E2 elimination, but otherwise does not affect the reaction rate.

- Solvent- Polar solvents, such as water, stabilize the carbocation.

  intermediate by solvation, thereby increasing the reaction rate.

Mechanism Summary S_N1 and S_N2

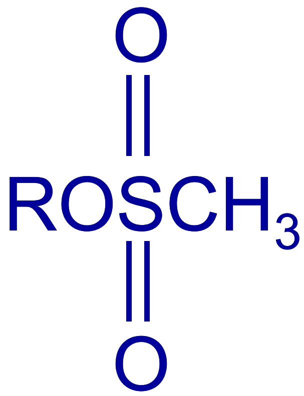
- ➢ Primary alkyl halides undergo nucleophilic substitution, they always react by the S_N2 mechanism.
- ➢ Tertiary alkyl halides undergo nucleophilic substitution, they always react by the S_N1 mechanism.
- ➢ Secondary alkyl halides undergo nucleophilic substitution, they react by the:
  - S_N1 mechanism in the presence of a weak nucleophile (solvolysis).
  - S_N2 mechanism in the presence of a good nucleophile.

Leaving Groups

- We have seen numerous examples of nucleophilic substitution in which X in RX is a halogen.

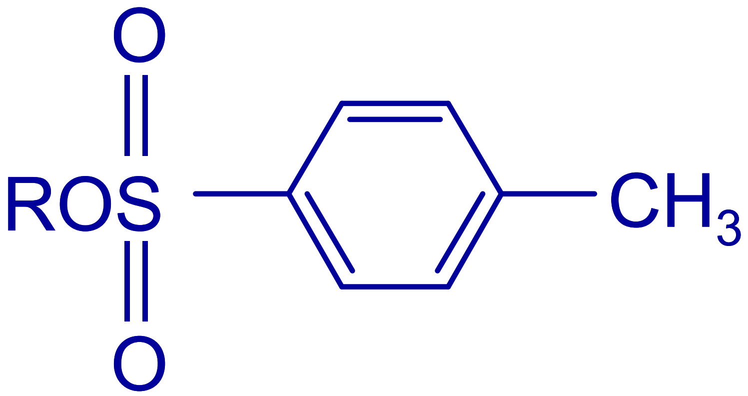
- Halogen is not the only possible leaving group though.

8.12. Nucleophilic Substitution of Alkyl Sulfonates



$$\mathrm{RO}\overset{\overset{\displaystyle \mathrm{O}}{\|}}{\underset{\underset{\displaystyle \mathrm{O}}{\|}}{\mathrm{S}}}\mathrm{CH_3}$$

Alkyl
methanesulfonate
(mesylate)

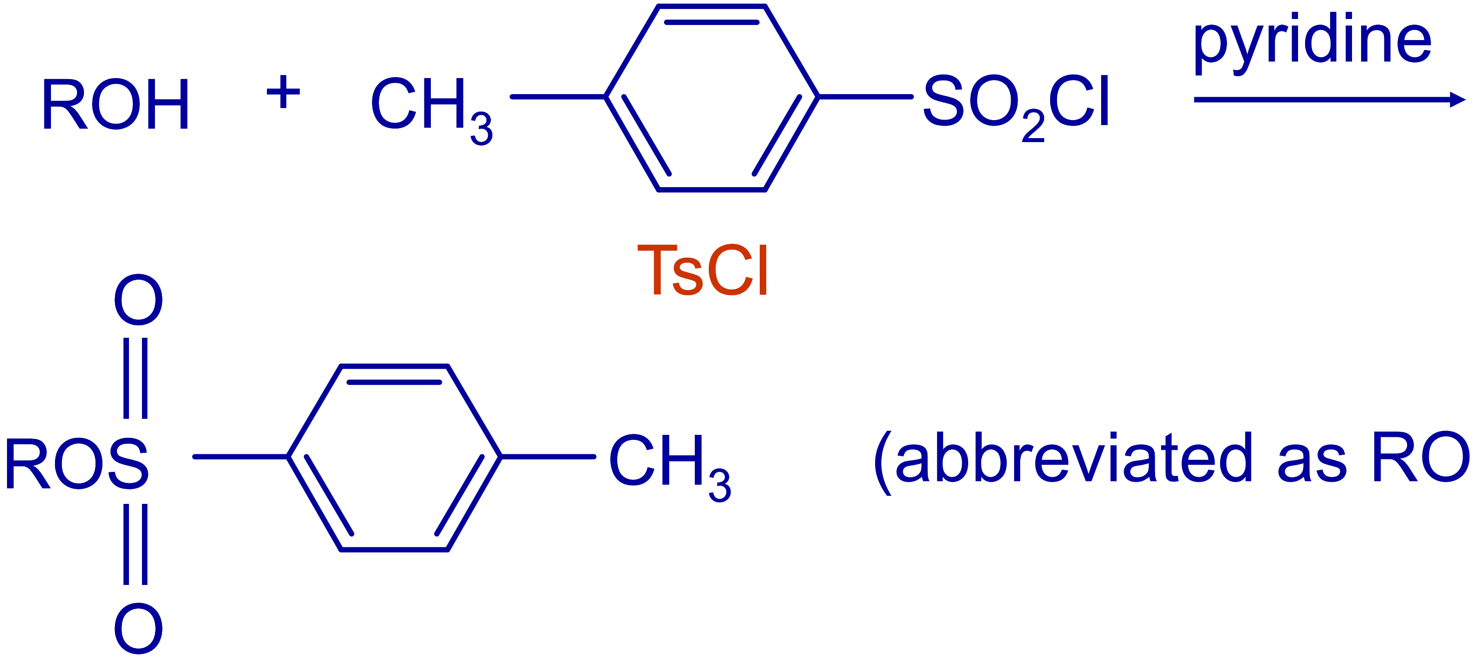


Alkyl
p-toluenesulfonate
(tosylate)

Undergo same kinds of reactions as alkyl halides.

Preparation

- Tosylates are prepared by the reaction of alcohols with *p*-toluenesulfonyl chloride (usually in the presence of pyridine).



TsCl

(abbreviated as ROTs)

Tosylates undergo typical nucleophilic substitution reactions

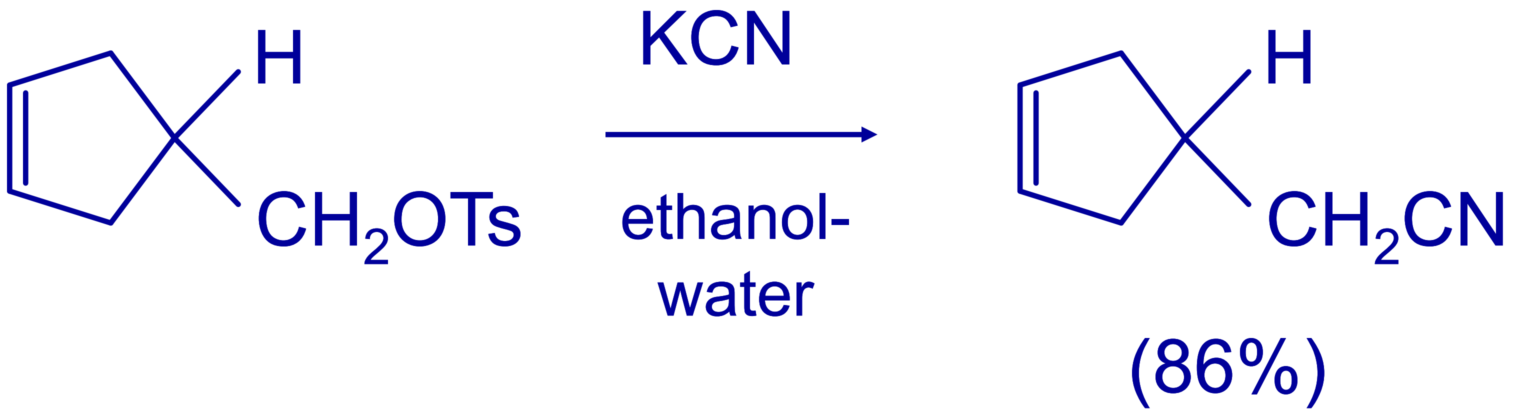


Table 8.9. Approximate Relative Reactivity of Leaving Groups

The best leaving groups are weakly basic!

Leaving Group	Relative Rate	Conjugate acid of leaving group	pK_a of conj. acid
F^-	10^{-5}	HF	3.5
Cl^-	1	HCl	-7
Br^-	10^1	HBr	-9
I^-	10^2	HI	-10
H_2O	10^1	H_3O^+	-1.7
TsO^-	10^5	TsOH	-2.8
$CF_3SO_2O^-$	10^8	CF_3SO_2OH	-6

Table 8.9. Approximate Relative Reactivity of Leaving Groups

The best leaving groups are weakly basic!

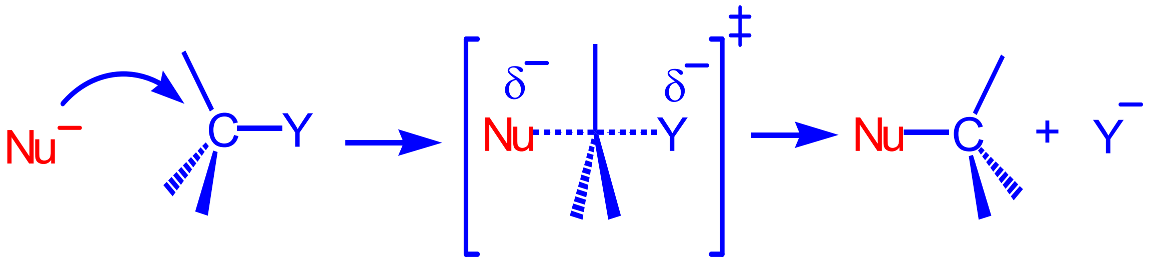
Leaving Group	Relative Rate	Conjugate acid of leaving group	pK_a of conj. acid
Br	10	HBr	-9
I^-	10^2	HI	-10
H_2O	10^1	H_3O^+	-1.7
TsO^-	10^5	TsOH	-2.8
$CF_3SO_2O^-$	10^8	CF_3SO_2OH	-6

Sulfonate esters are extremely good leaving groups; sulfonate ions are very weak bases.

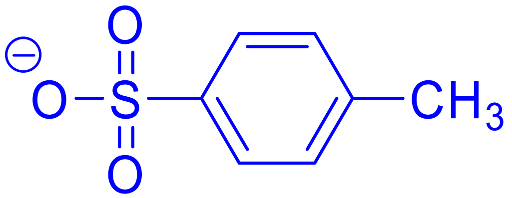
The Leaving Group

	TsO^-	I^-	Br^-	Cl^-	F^-	HO^-, H_2N^-, RO^-
Relative reactivity	60,000	30,000	10,000	200	1	~0

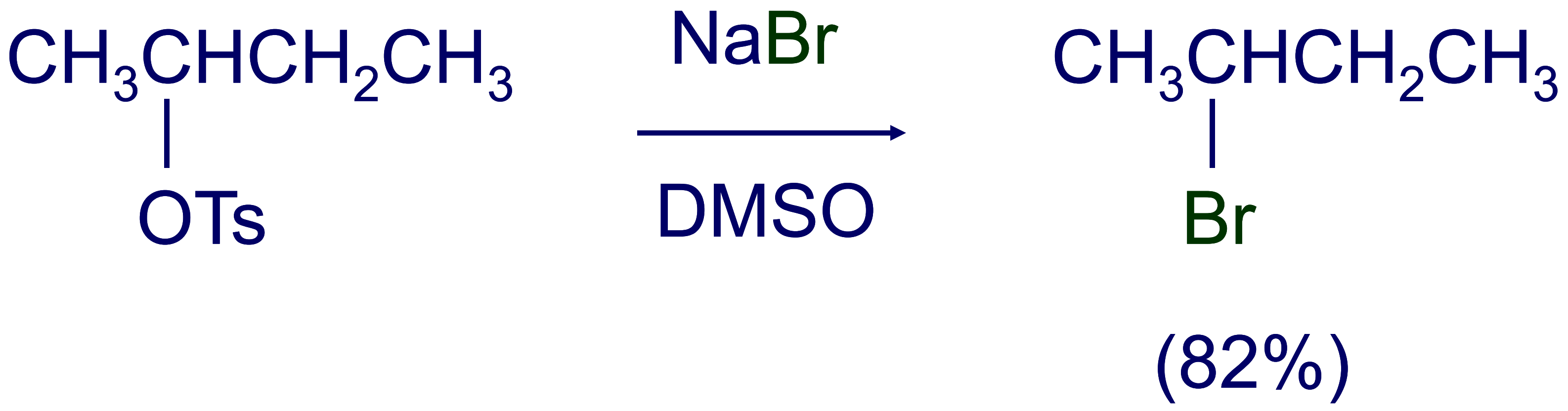
More reactive ← Less reactive



$^{\ominus}OTs$ =



Tosylates can be converted to alkyl halides



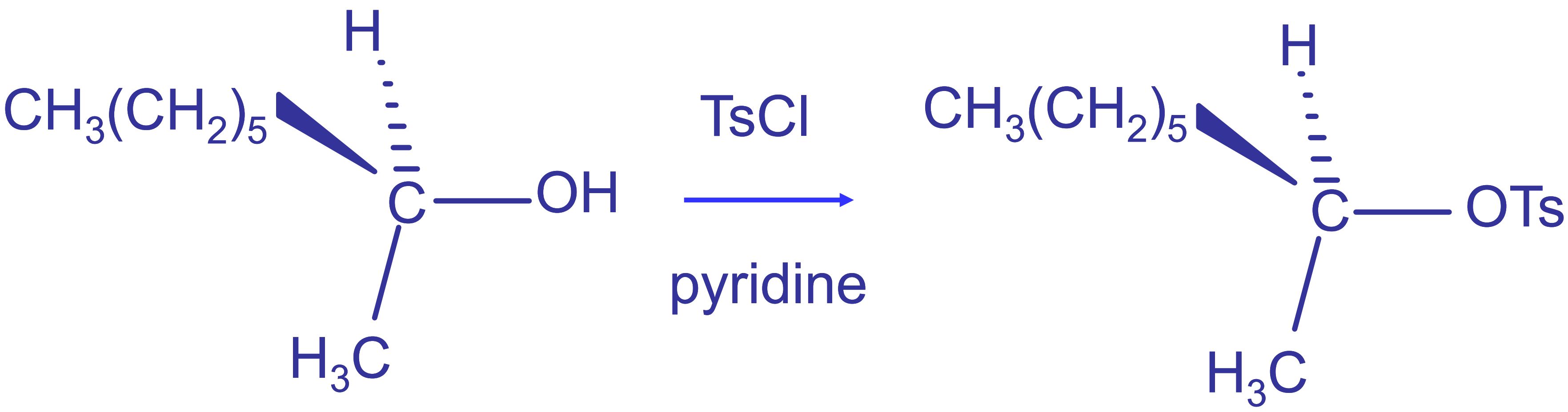
$$CH_3\underset{\text{OTs}}{\underset{|}{C}}HCH_2CH_3 \xrightarrow[\text{DMSO}]{\text{NaBr}} CH_3\underset{\text{Br}}{\underset{|}{C}}HCH_2CH_3$$

(82%)

- Tosylate is a better leaving group than bromide.

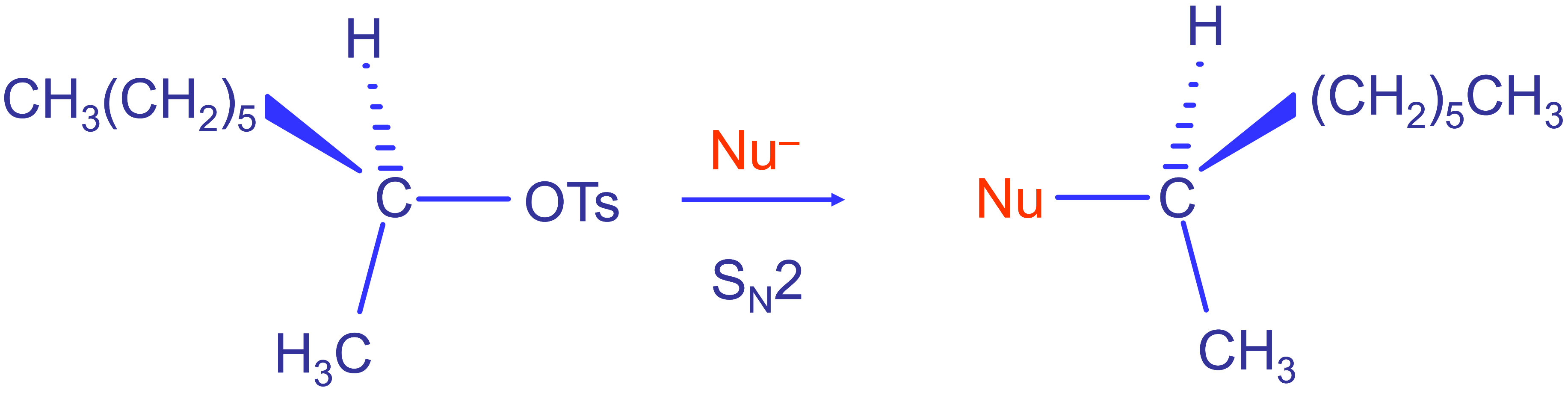
Tosylates allow control of stereochemistry

- Preparation of tosylate does not affect any of the bonds to the chirality center, so configuration and optical purity of tosylate is the same as the alcohol from which it was formed.



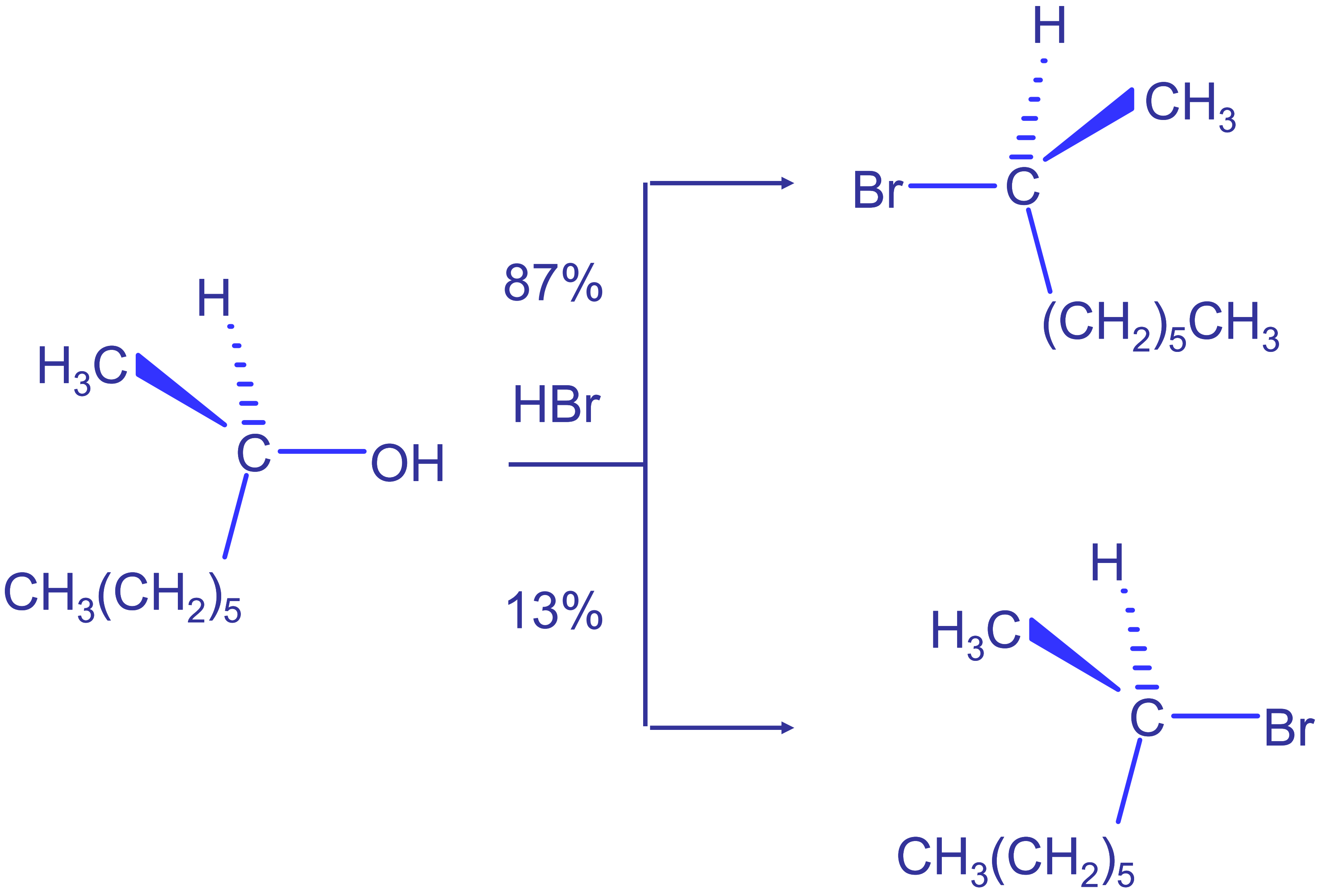
Tosylates allow control of stereochemistry

- Having a tosylate of known optical purity and absolute configuration then allows the preparation of other compounds of known configuration by S_N2 processes.

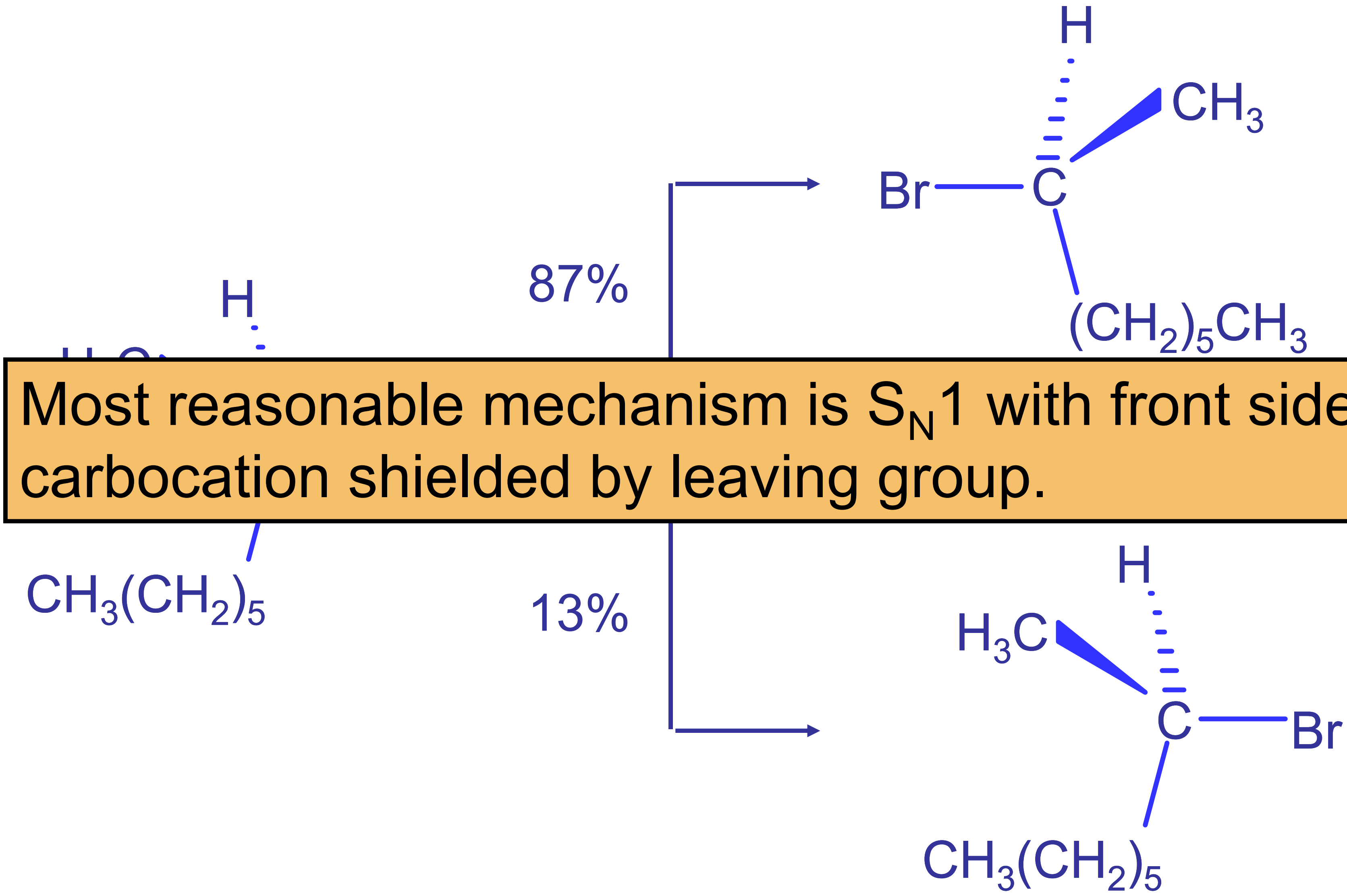


Looking Back:
Reactions of Alcohols
with
Hydrogen Halides

Secondary alcohols react with hydrogen halides with incomplete inversion of configuration

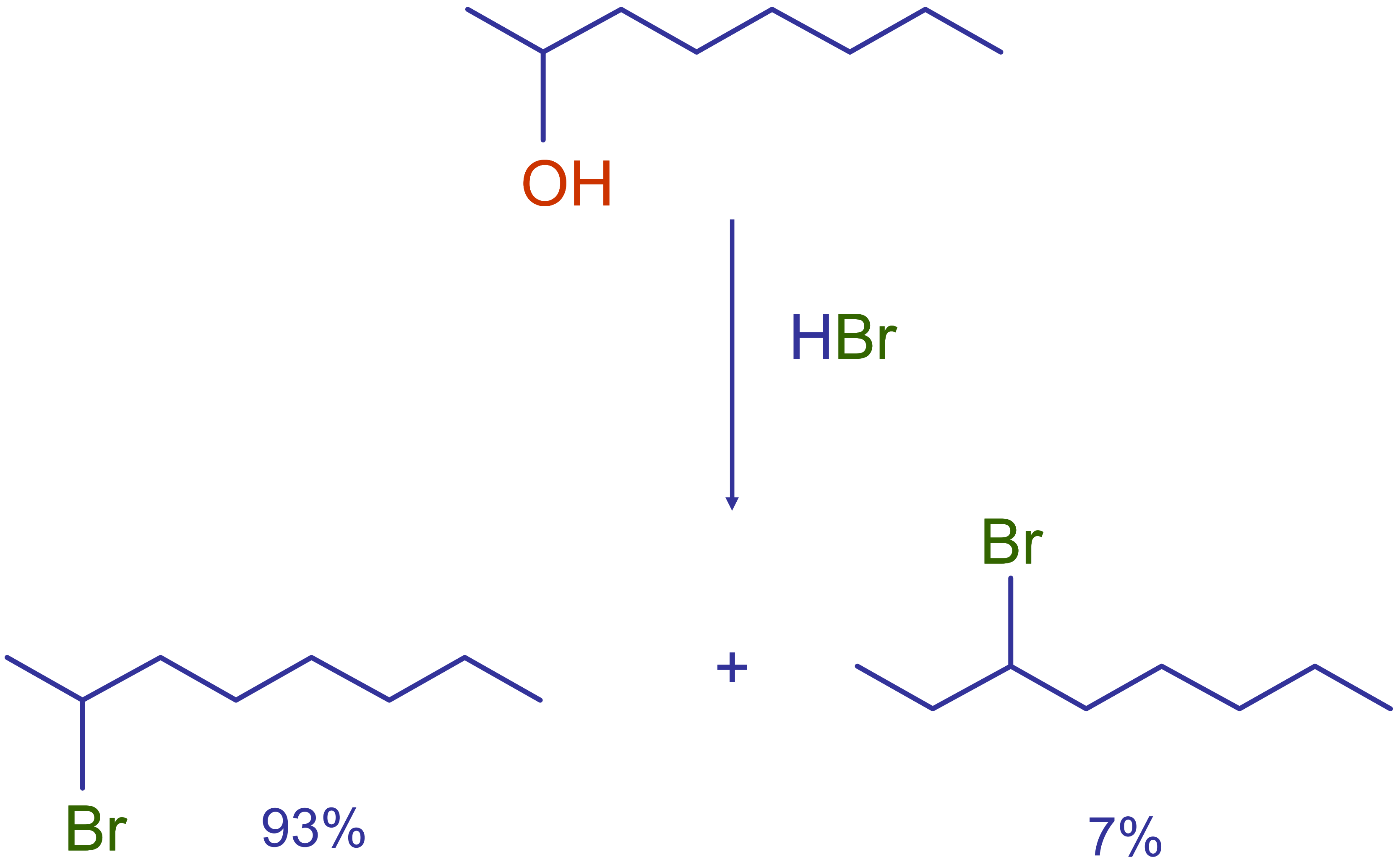


Secondary alcohols react with hydrogen halides with incomplete inversion of configuration

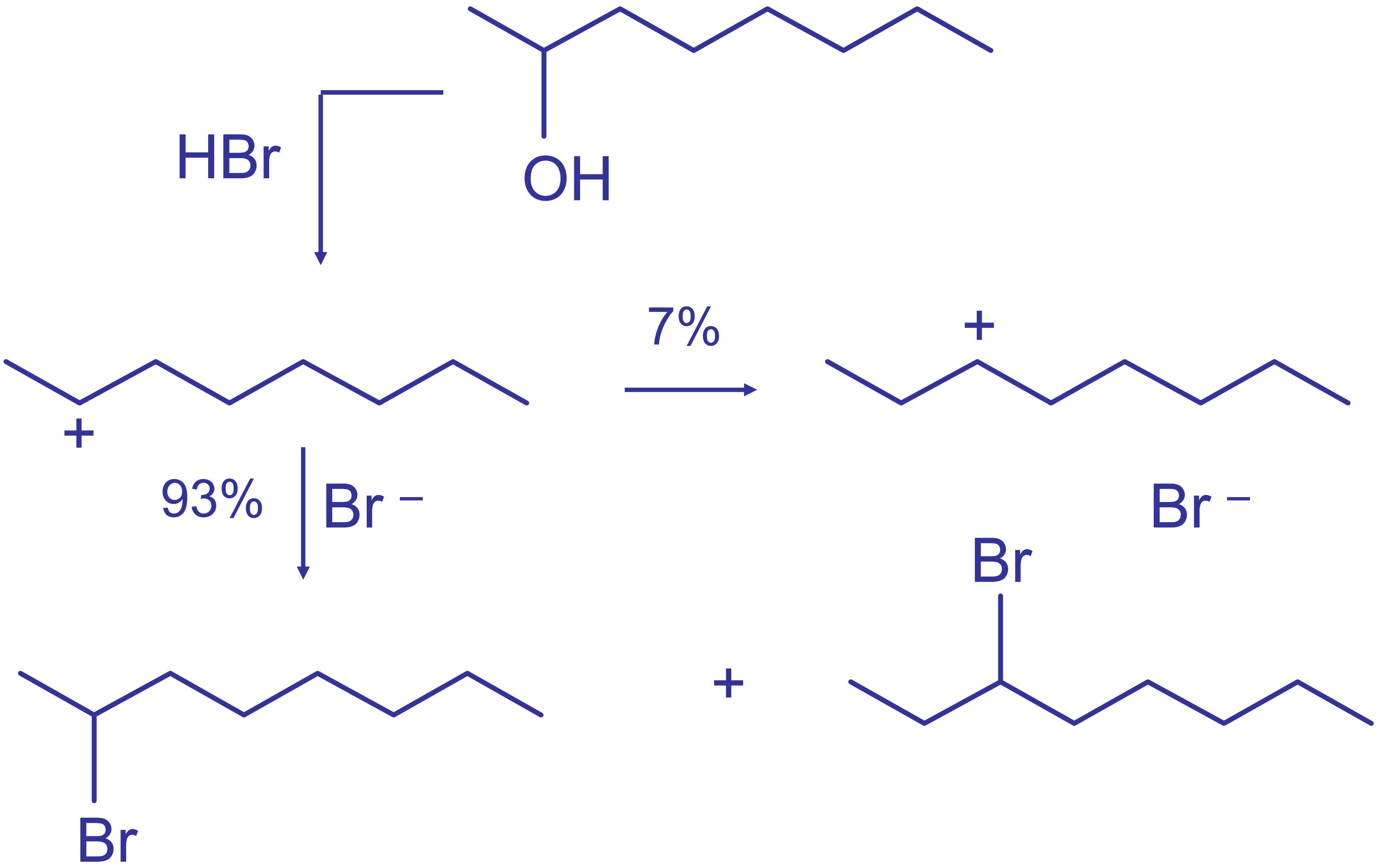


Most reasonable mechanism is S_N1 with front side of carbocation shielded by leaving group.

Rearrangements can occur in the reaction of alcohols with hydrogen halides



Rearrangements can occur in the reaction of alcohols with hydrogen halides



4.14. Other Methods for Converting Alcohols to Alkyl Halides

Reagents for ROH to RX

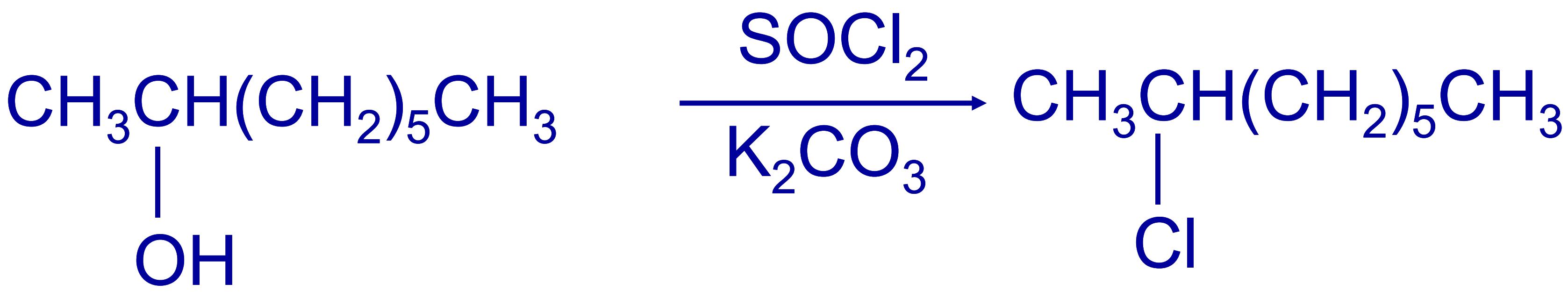
Thionyl chloride

$SOCl_2 + ROH \rightarrow RCl + HCl + SO_2$

Phosphorus tribromide

$PBr_3 + 3ROH \rightarrow 3RBr + H_3PO_3$

Examples



$$CH_3\underset{\displaystyle OH}{\underset{|}{C}}H(CH_2)_5CH_3 \xrightarrow[K_2CO_3]{SOCl_2} CH_3\underset{\displaystyle Cl}{\underset{|}{C}}H(CH_2)_5CH_3$$

(81%)

(pyridine often used instead of K_2CO_3)

$$(CH_3)_2CHCH_2OH \xrightarrow{PBr_3} (CH_3)_2CHCH_2Br$$

(55-60%)

PBr_3 reaction occurs with inversion of configuration.

4.15. Halogenation of Alkanes

Energetics

$RH + X_2 \rightarrow RX + HX$

Explosive for F_2

Exothermic for Cl_2 and Br_2

Endothermic for I_2

Reactivity of halogens: $F_2 > Cl_2 > Br_2 > I_2$

4.16. Chlorination of Methane

Carried out at high temperature (400 °C)

$CH_4 + Cl_2 \rightarrow CH_3Cl + HCl$

$CH_3Cl + Cl_2 \rightarrow CH_2Cl_2 + HCl$

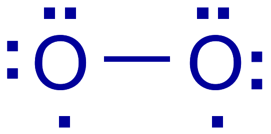
$CH_2Cl_2 + Cl_2 \rightarrow CHCl_3 + HCl$

$CHCl_3 + Cl_2 \rightarrow CCl_4 + HCl$

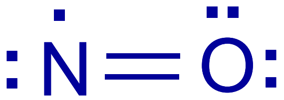
4.17. Structure and Stability of Free Radicals

Free radicals contain unpaired electrons

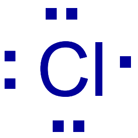
Examples: O_2



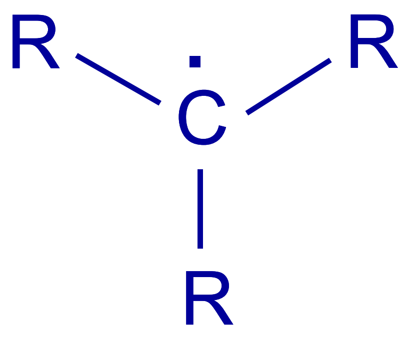
NO



Cl

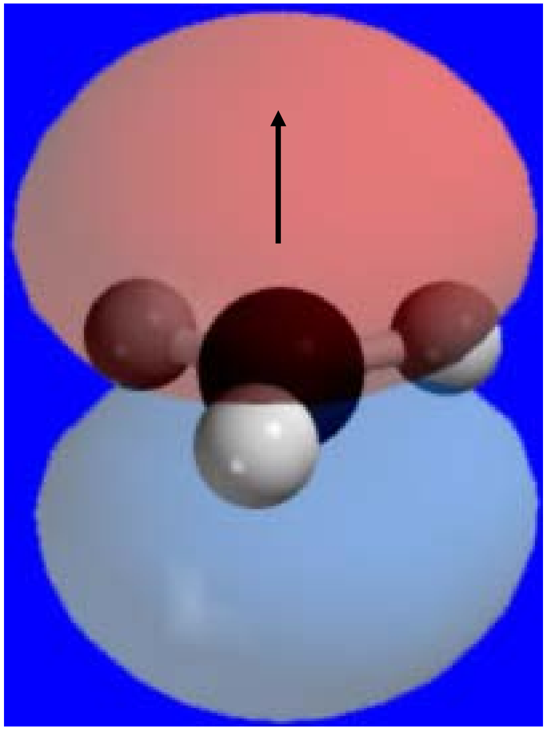


Alkyl Radicals



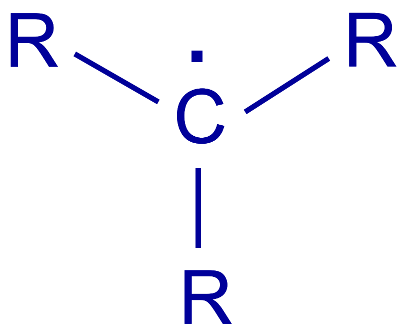
- Most free radicals in which carbon bears the unpaired electron are too unstable to be isolated.
- Alkyl radicals are classified as primary, secondary, or tertiary in the same way that carbocations are.

Figure 4.17. Structure of methyl radical



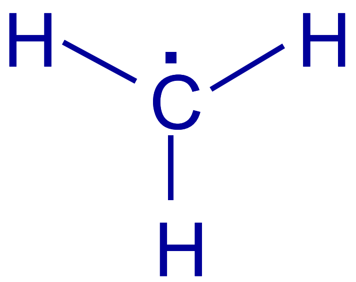
- Methyl radical is planar, which suggests that carbon is sp^2 hybridized and that the unpaired electron is in a *p* orbital.

Alkyl Radicals



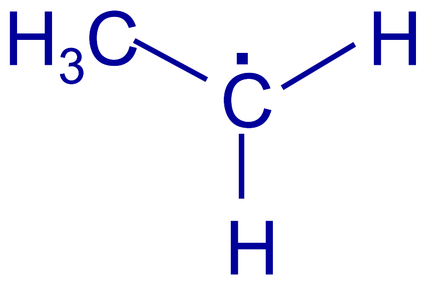
- The order of stability of free radicals is the same as for carbocations.

Alkyl Radicals



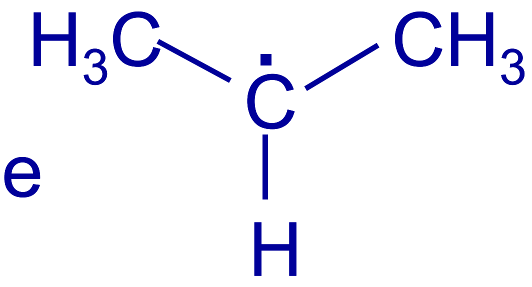
Methyl radical

less stable than



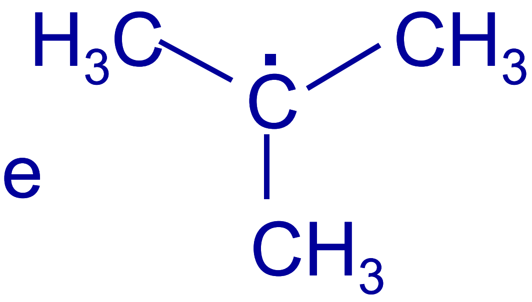
Ethyl radical (primary)

less stable than



Isopropyl radical (secondary)

less stable than



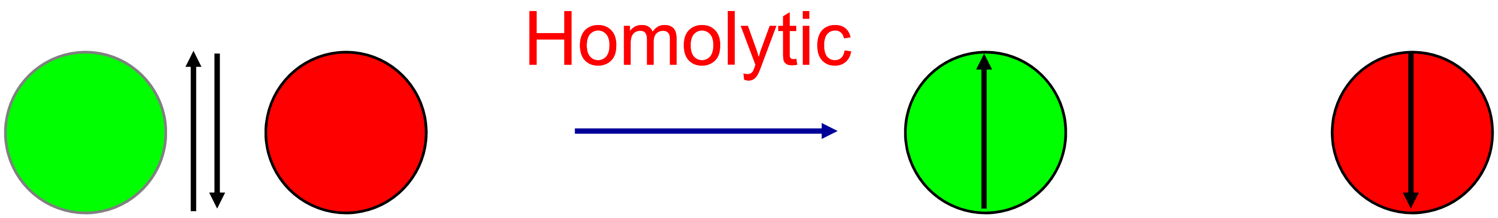
tert-Butyl radical (tertiary)

Alkyl Radicals

- The order of stability of free radicals can be determined by measuring bond strengths.

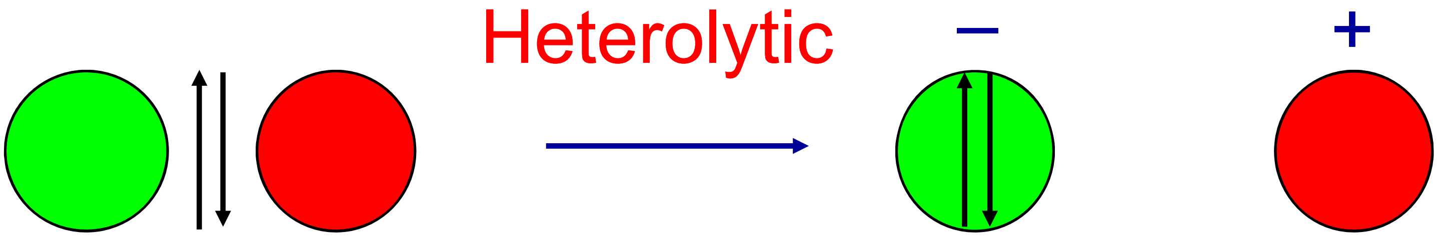
- By "bond strength" we mean the energy required to break a covalent bond.

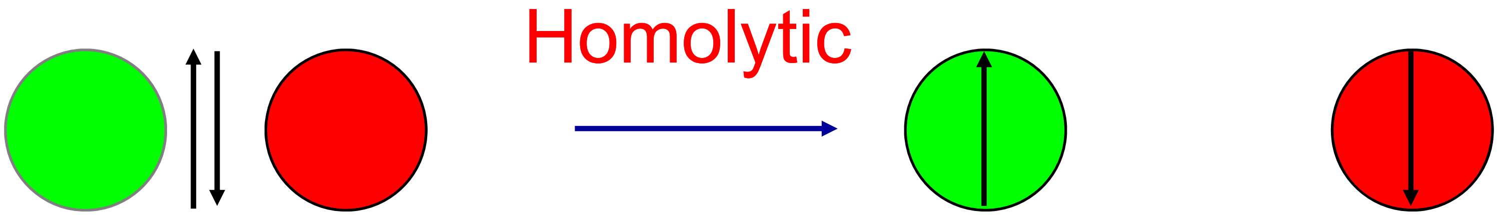
- A chemical bond can be broken in two different ways—heterolytically or homolytically.



- In a homolytic bond cleavage, the two electrons in the bond are divided equally between the two atoms. One electron goes with one atom, the second with the other atom.

- In a heterolytic cleavage, one atom retains both electrons.



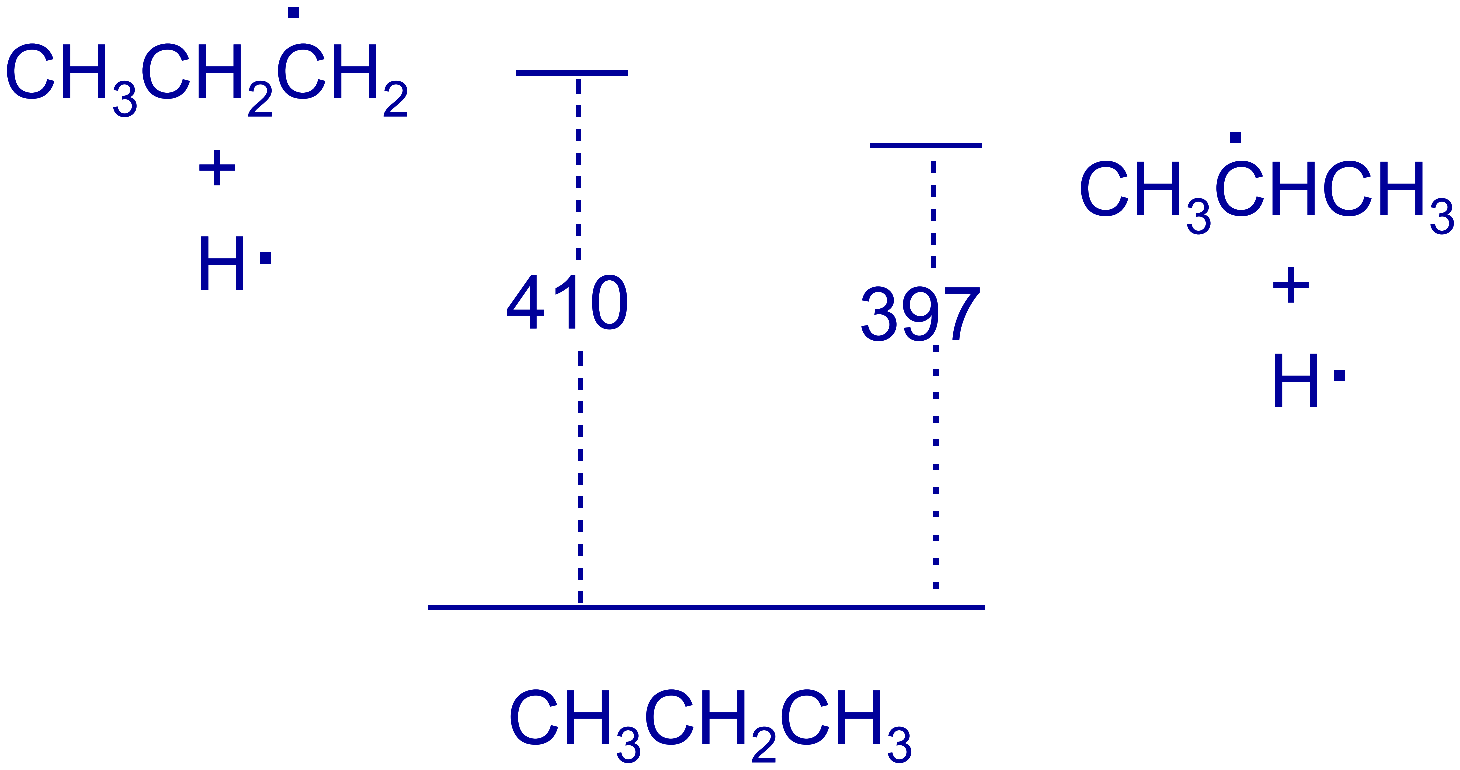


- The species formed by a homolytic bond cleavage of a neutral molecule are free radicals. Therefore, measure energy cost of homolytic bond cleavage to gain information about stability of free radicals.

- The more stable the free-radical products, the weaker the bond, and the lower the bond-dissociation energy.

Measures of Free Radical Stability

- Bond-dissociation energy measurements tell us that isopropyl radical is 13 kJ/mol more stable than propyl.



$CH_3CH_2\dot{C}H_2$ + $H\cdot$

410

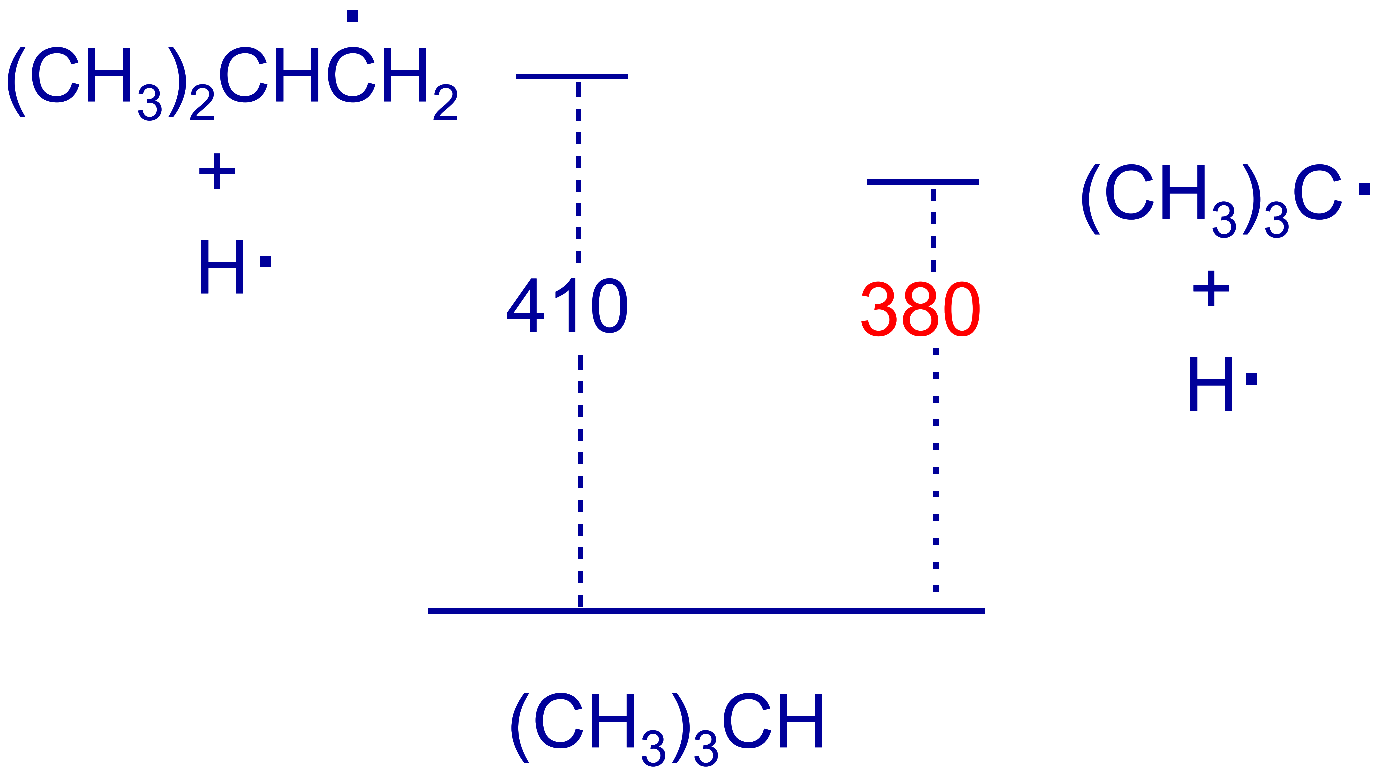
397

$CH_3\dot{C}HCH_3$ + $H\cdot$

$CH_3CH_2CH_3$

Measures of Free Radical Stability

- Bond-dissociation energy measurements tell us that *tert*-butyl radical is 30 kJ/mol more stable than isobutyl.



$(CH_3)_2CH\dot{C}H_2$
+
$H\cdot$

410

380

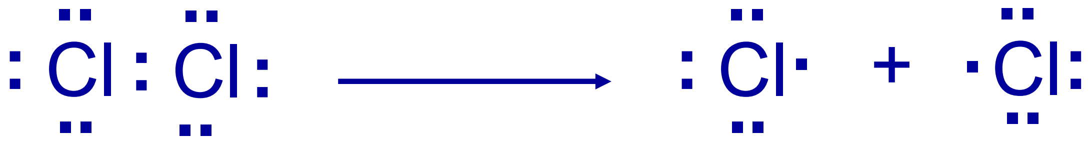
$(CH_3)_3C\cdot$
+
$H\cdot$

$(CH_3)_3CH$

4.18. Mechanism of Chlorination of Methane

Free-radical chain mechanism.

Initiation step:

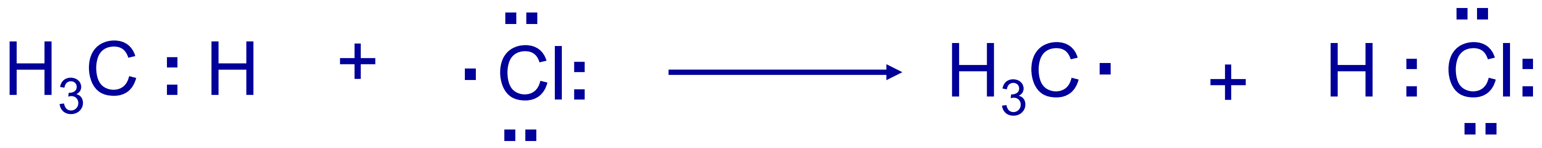


$$:\overset{..}{\underset{..}{\mathrm{Cl}}}:\overset{..}{\underset{..}{\mathrm{Cl}}}: \longrightarrow\ :\overset{..}{\underset{..}{\mathrm{Cl}}}\cdot\ +\ \cdot\overset{..}{\underset{..}{\mathrm{Cl}}}:$$

- ➢ The initiation step "gets the reaction going“ by producing free radicals—chlorine atoms from chlorine molecules in this case.
- ➢ Initiation step is followed by propagation steps. Each propagation step consumes one free radical but generates another one.

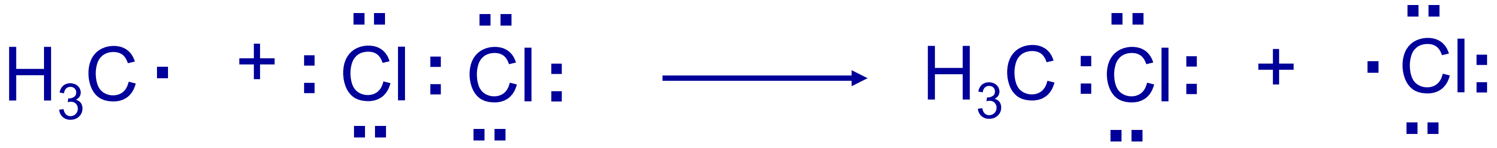
Mechanism of Chlorination of Methane

First propagation step:



$$H_3C:H + \cdot\overset{\cdot\cdot}{\underset{\cdot\cdot}{Cl}}: \longrightarrow H_3C\cdot + H:\overset{\cdot\cdot}{\underset{\cdot\cdot}{Cl}}:$$

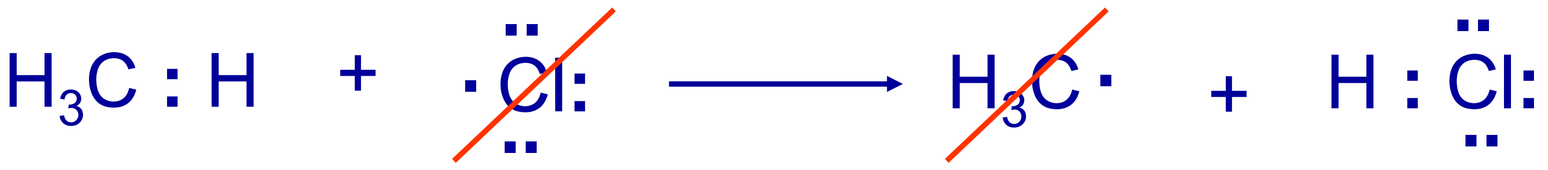
Second propagation step:



$$H_3C\cdot + :\overset{\cdot\cdot}{\underset{\cdot\cdot}{Cl}}:\overset{\cdot\cdot}{\underset{\cdot\cdot}{Cl}}: \longrightarrow H_3C:\overset{\cdot\cdot}{\underset{\cdot\cdot}{Cl}}: + \cdot\overset{\cdot\cdot}{\underset{\cdot\cdot}{Cl}}:$$

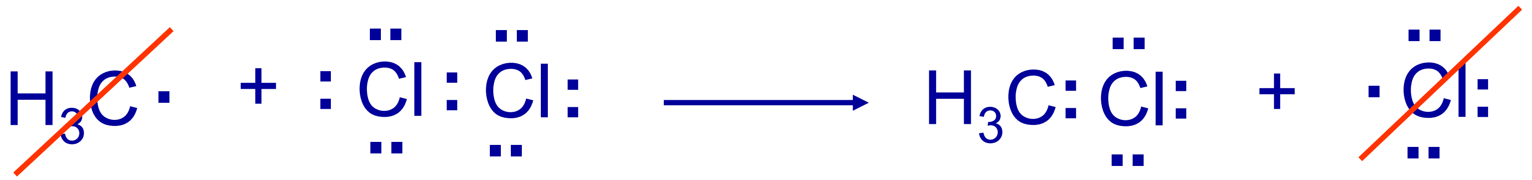
Mechanism of Chlorination of Methane

First propagation step:

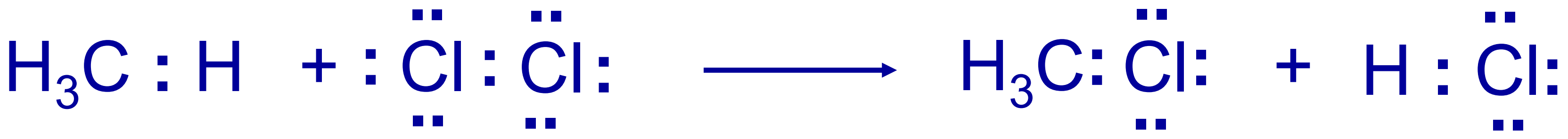


$$H_3C:H + \cancel{\cdot\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{Cl}}}:} \longrightarrow \cancel{H_3C\cdot} + H:\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{Cl}}}:$$

Second propagation step:



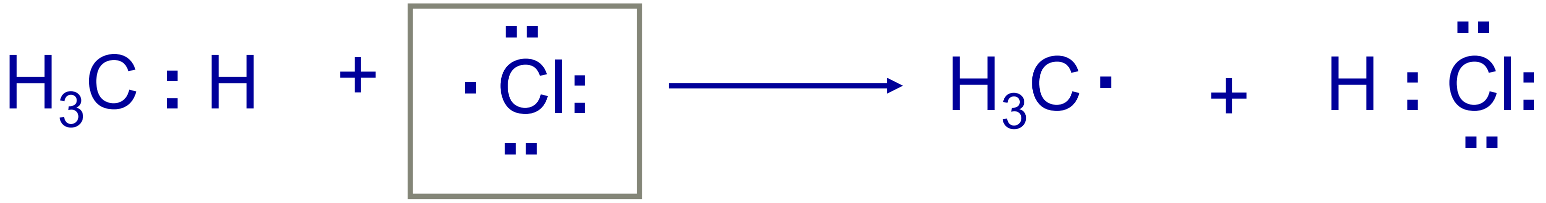
$$\cancel{H_3C\cdot} + :\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{Cl}}}:\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{Cl}}}: \longrightarrow H_3C:\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{Cl}}}: + \cancel{\cdot\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{Cl}}}:}$$



$$H_3C:H + :\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{Cl}}}:\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{Cl}}}: \longrightarrow H_3C:\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{Cl}}}: + H:\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{Cl}}}:$$

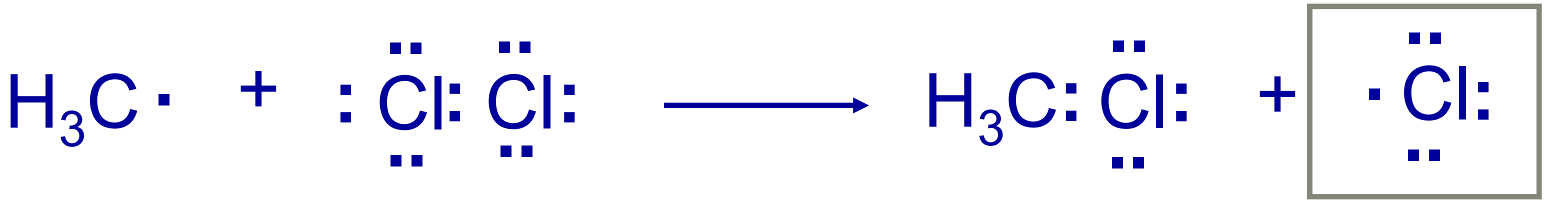
Almost all of the product is formed by repetitive cycles of the two propagation steps.

First propagation step:

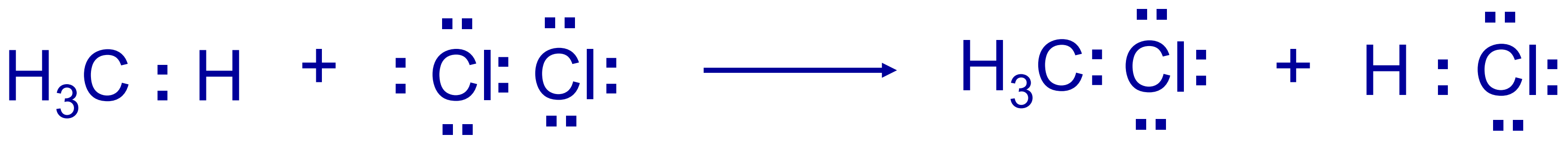


$$H_3C:H + \boxed{\cdot\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}}:} \longrightarrow H_3C\cdot + H:\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}}:$$

Second propagation step:



$$H_3C\cdot + :\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}}: \longrightarrow H_3C:\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}}: + \boxed{\cdot\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}}:}$$



$$H_3C:H + :\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}}: \longrightarrow H_3C:\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}}: + H:\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}}:$$

Termination Steps

- Stop chain reaction by consuming free radicals.

$$H_3C\cdot \;+\; \cdot\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}}: \longrightarrow H_3C:\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}}:$$

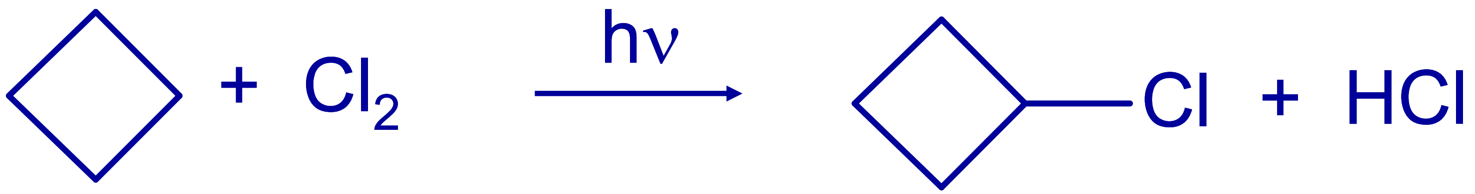
- Hardly any product is formed by termination step because concentration of free radicals at any instant is extremely low.

4.19. Halogenation of Higher Alkanes

- Can be used to prepare alkyl chlorides from alkanes in which all of the hydrogens are equivalent to one another.

$$CH_3CH_3 + Cl_2 \xrightarrow{420^\circ C} CH_3CH_2Cl + HCl$$

(78%)



(73%)

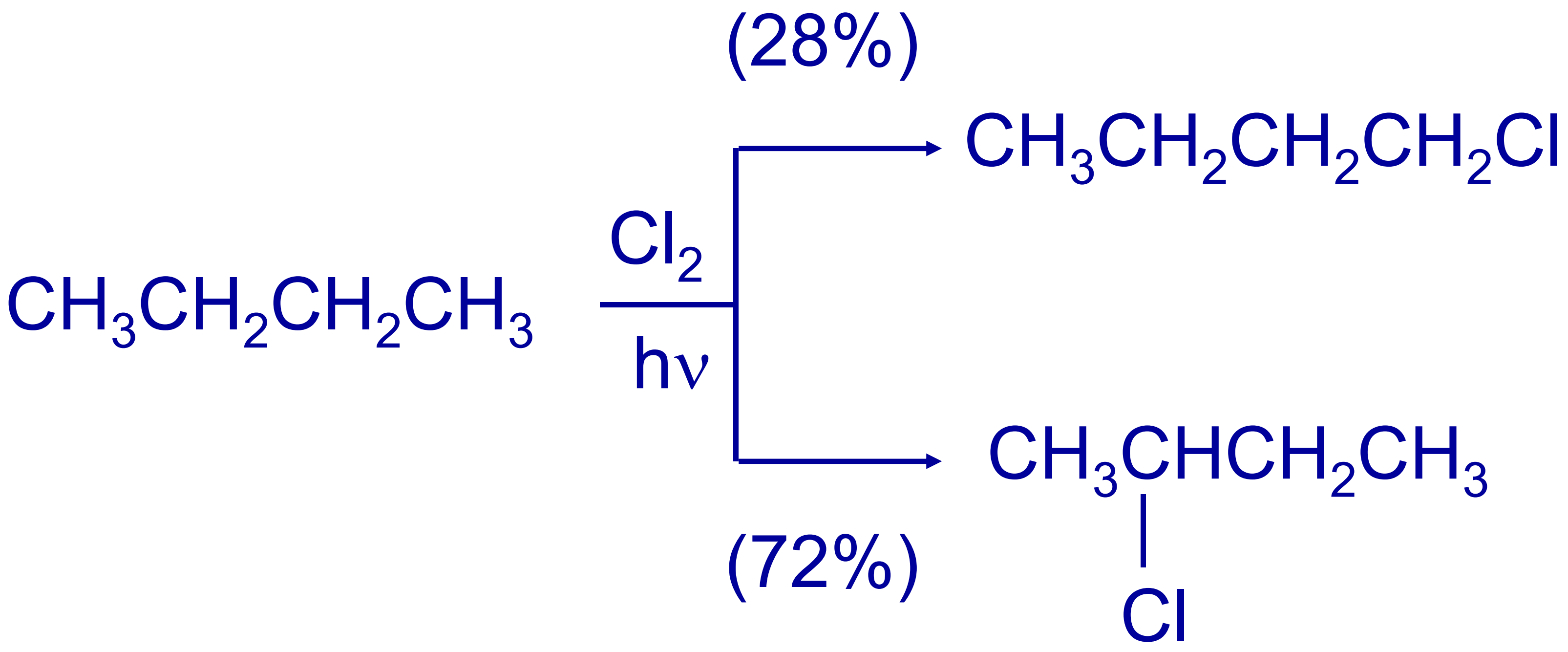
Chlorination of Alkanes

Major limitation:

- Chlorination gives every possible monochloride derived from original carbon skeleton.

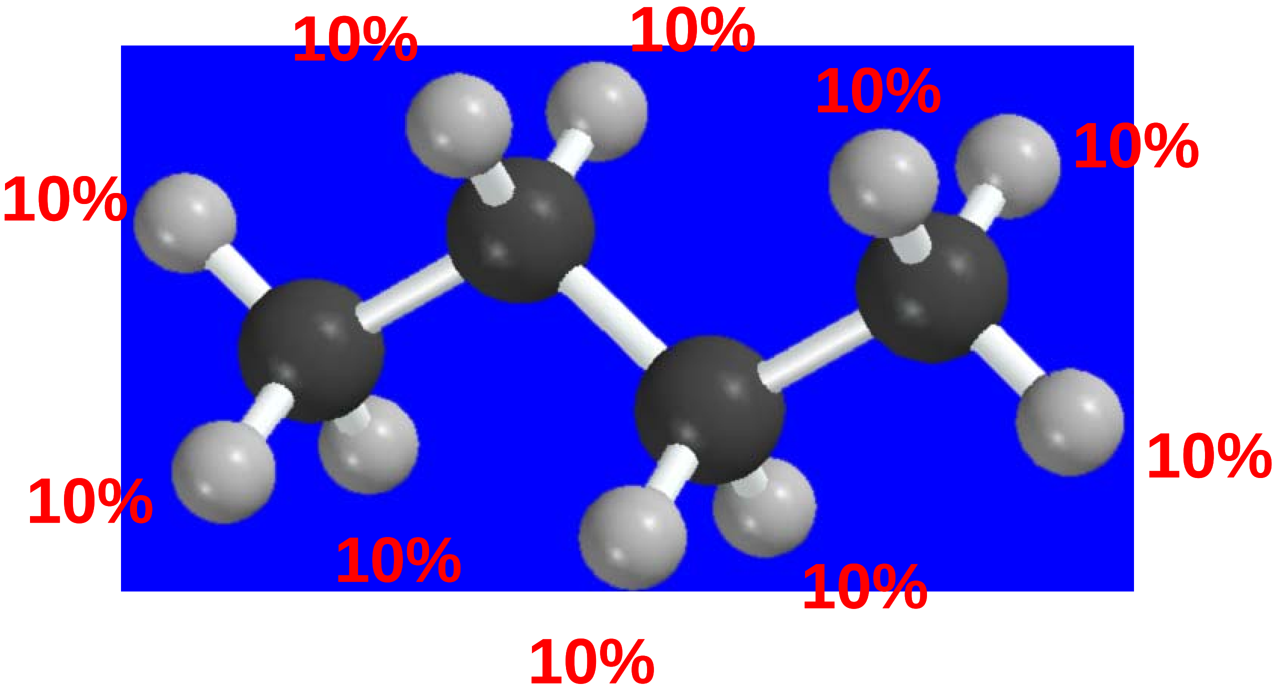
Example

- Chlorination of butane gives a mixture of 1-chlorobutane and 2-chlorobutane.

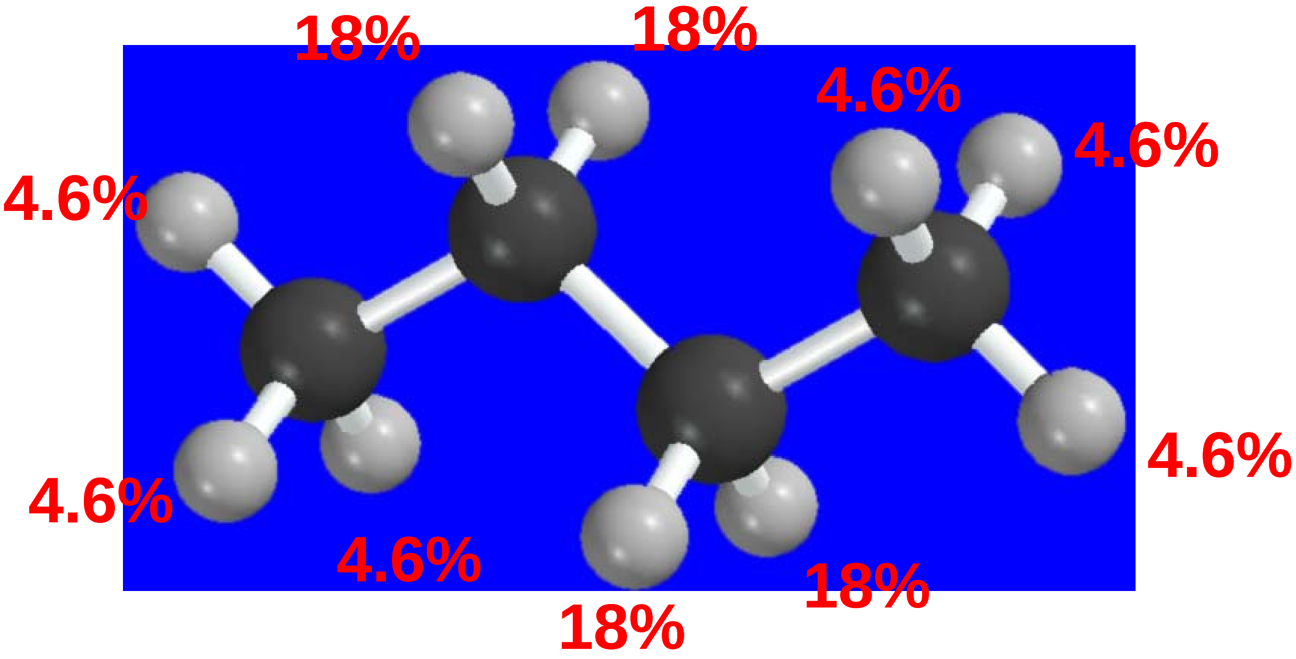


$$CH_3CH_2CH_2CH_3 \xrightarrow[h\nu]{Cl_2} \begin{cases} CH_3CH_2CH_2CH_2Cl & (28\%) \\ CH_3\underset{\displaystyle Cl}{\underset{|}{C}}HCH_2CH_3 & (72\%) \end{cases}$$

- Percentage of product that results from substitution of indicated hydrogen if every collision with chlorine atoms is productive.



- Percentage of product that actually results from replacement of indicated hydrogen.

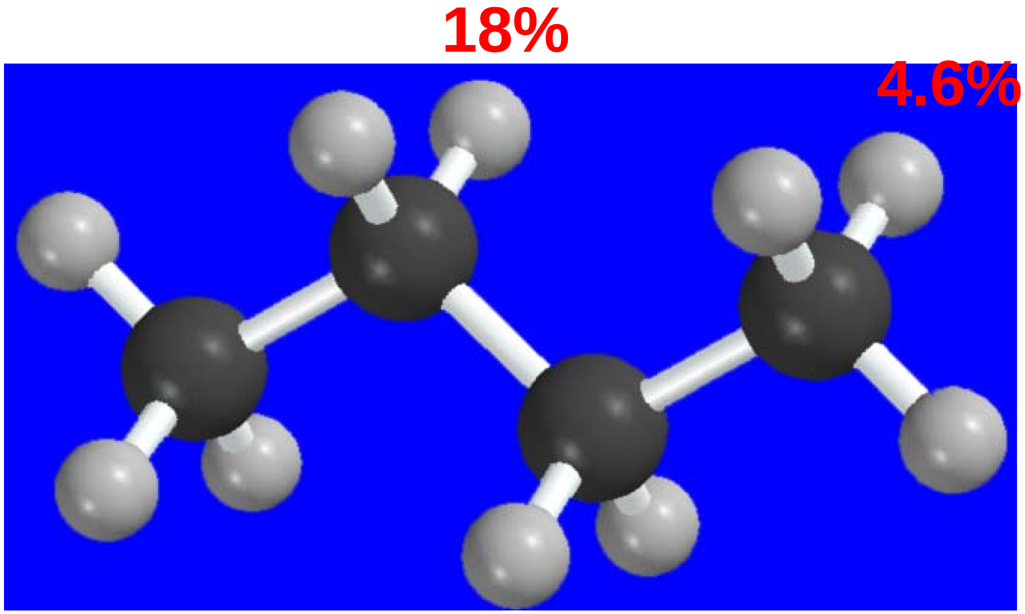


Relative rates of hydrogen atom abstraction

Divide by 4.6

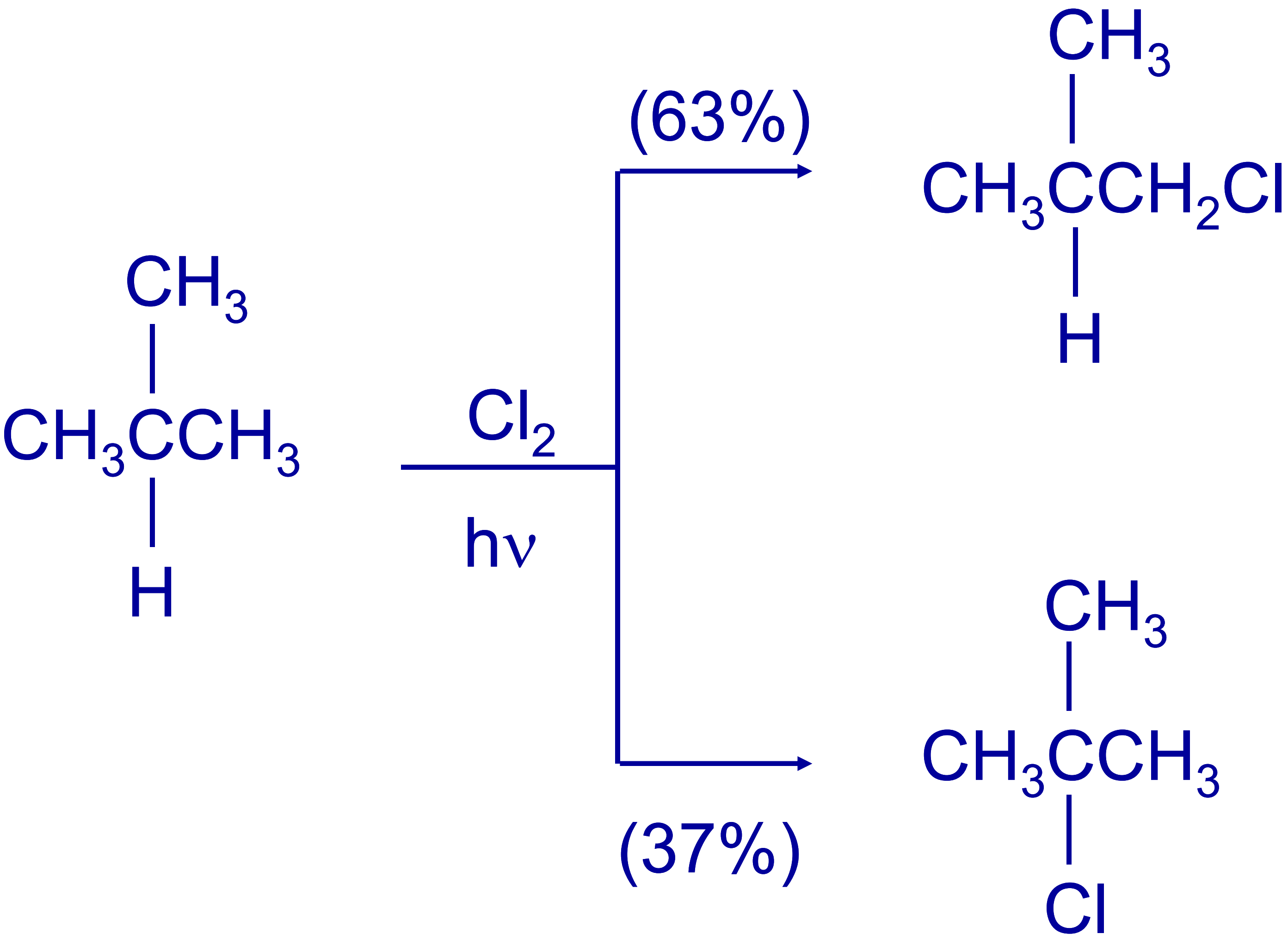
$$\frac{4.6}{4.6} = 1$$

$$\frac{18}{4.6} = 3.9$$



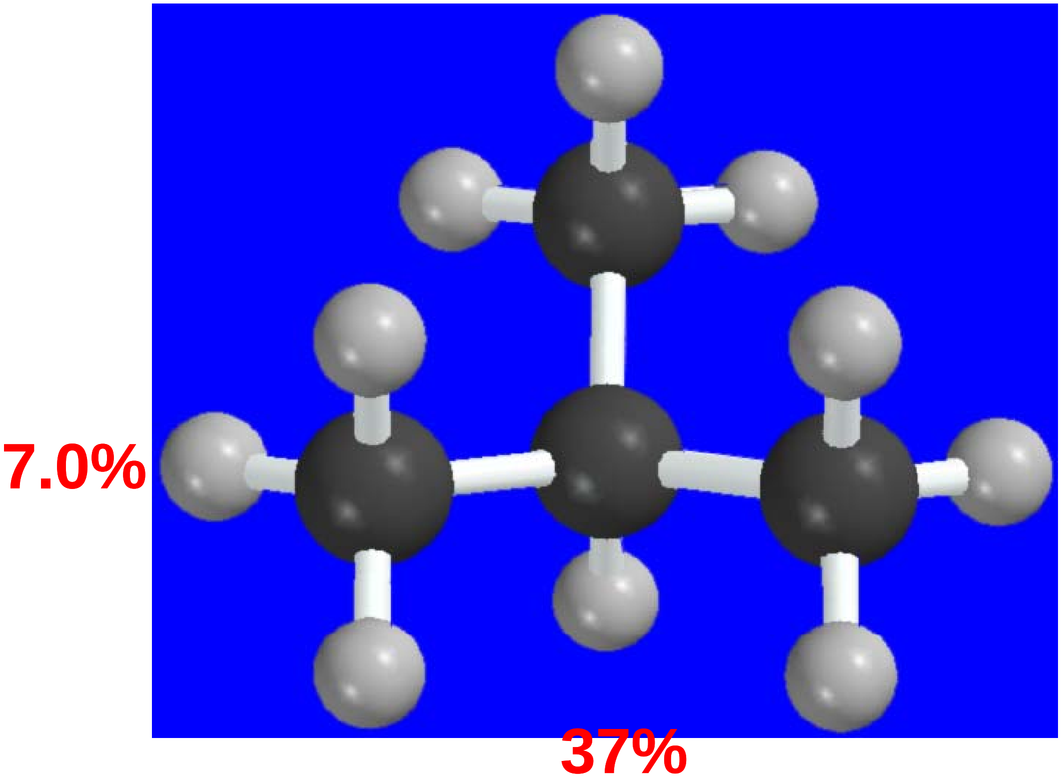
A <u>secondary</u> hydrogen is abstracted 3.9 times faster than a <u>primary</u> hydrogen by a chlorine atom.

- Similarly, chlorination of 2-methylbutane gives a mixture of isobutyl chloride and *tert*-butyl chloride.



$$\underset{\displaystyle H}{\overset{\displaystyle CH_3}{CH_3\overset{|}{\underset{|}{C}}CH_3}} \xrightarrow[h\nu]{Cl_2} \underset{\displaystyle H}{\overset{\displaystyle CH_3}{CH_3\overset{|}{\underset{|}{C}}CH_2Cl}}\ (63\%) + \underset{\displaystyle Cl}{\overset{\displaystyle CH_3}{CH_3\overset{|}{\underset{|}{C}}CH_3}}\ (37\%)$$

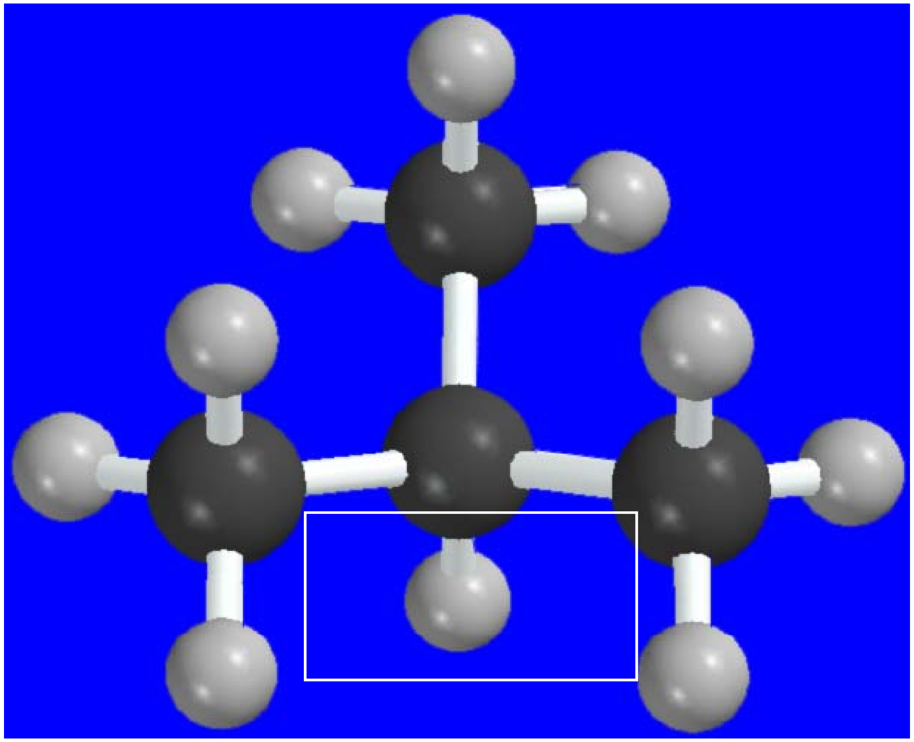
Percentage of product that results from replacement of indicated hydrogen



Relative rates of hydrogen atom abstraction

Divide by 7

$$\frac{7.0}{7} = 1$$



$$\frac{37}{7} = 5.3$$

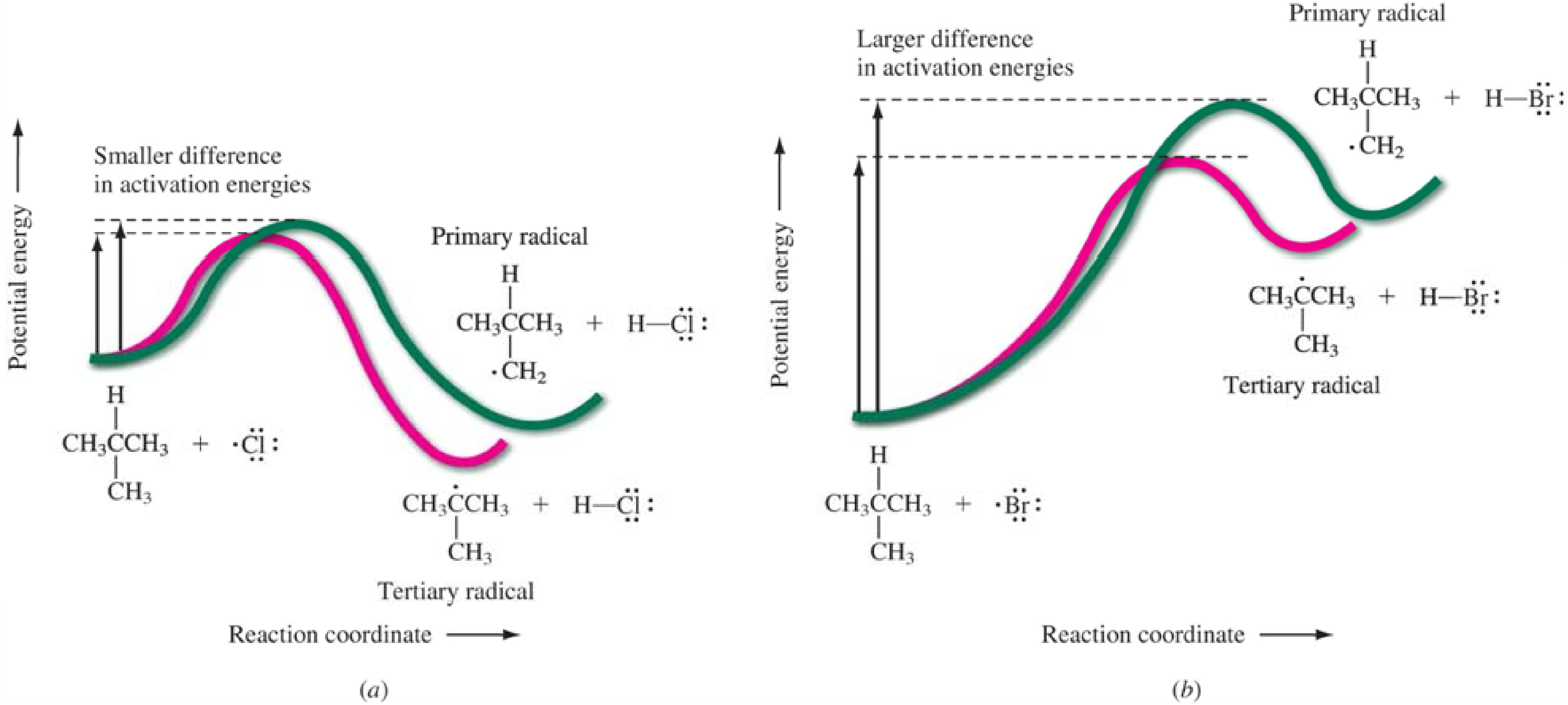
A <u>tertiary</u> hydrogen is abstracted 5.3 times faster than a <u>primary</u> hydrogen by a chlorine atom.

Selectivity of free-radical halogenation

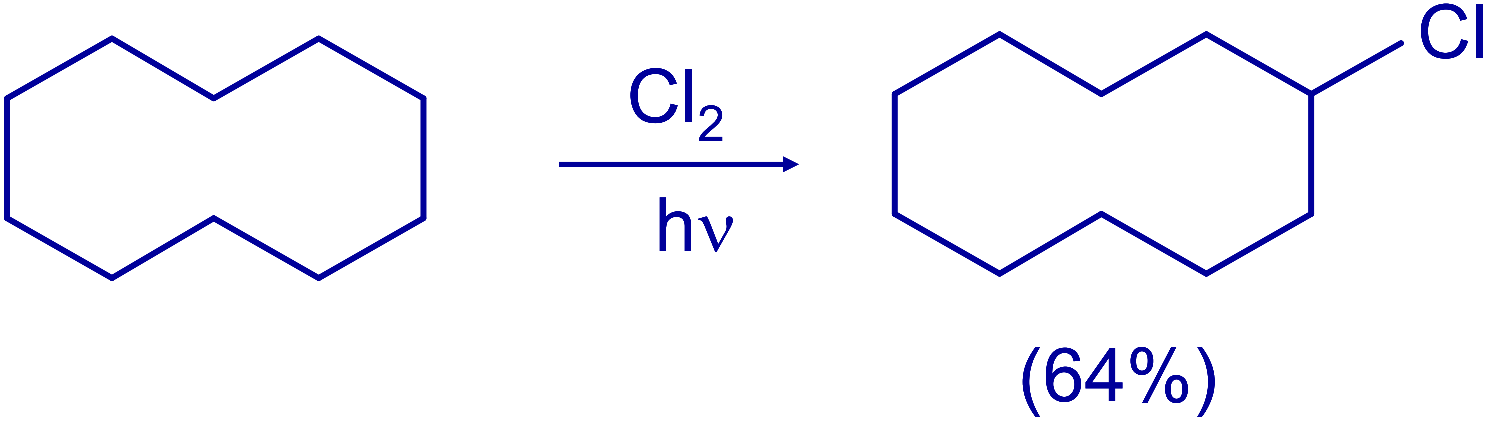
	R_3CH >	R_2CH_2 >	RCH_3
Chlorination:	5	4	1
Bromination:	1640	82	1

- Chlorination of an alkane gives a mixture of every possible isomer having the same skeleton as the starting alkane. Useful for synthesis only when all hydrogens in a molecule are equivalent.
- Bromination is highly regioselective for substitution of tertiary hydrogens. Major synthetic application is in synthesis of tertiary alkyl bromides.

Figure 4.20. Selectivity of Bromination

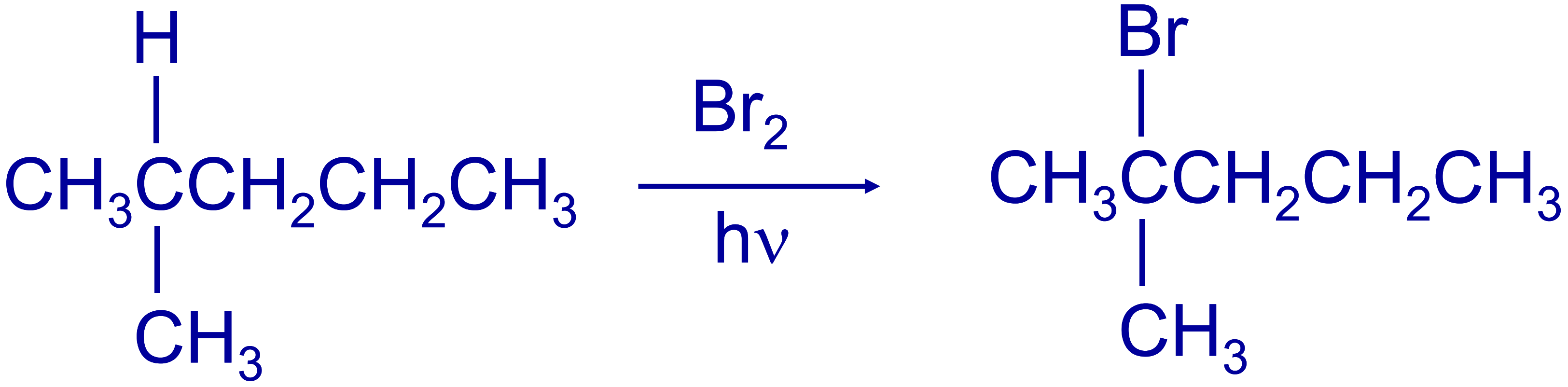


Synthetic application of chlorination of an alkane



- Chlorination is useful for synthesis only when all of the hydrogens in a molecule are equivalent.

Synthetic application of bromination of an alkane



$$CH_3\overset{H}{\underset{CH_3}{C}}CH_2CH_2CH_3 \xrightarrow[h\nu]{Br_2} CH_3\overset{Br}{\underset{CH_3}{C}}CH_2CH_2CH_3$$

(76%)

- Bromination is highly selective for substitution of tertiary hydrogens.
- Major synthetic application is in synthesis of tertiary alkyl bromides.

Assigned Problems

Chapter 4: All problems.
Chapter 8: All problems except those dealing with elimination (for now).