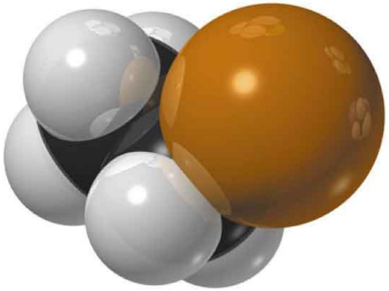


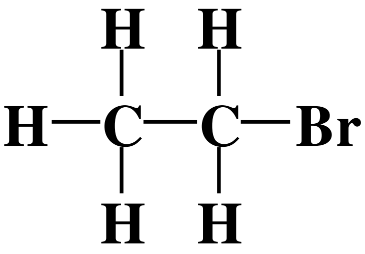
Organic Chemistry, 7th Edition
L. G. Wade, Jr.

Chapter 6

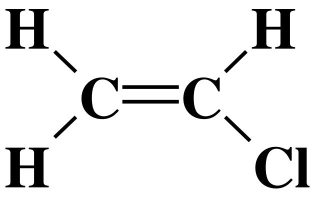
Alkyl Halides: Nucleophilic Substitution and Elimination

Classes of Halides

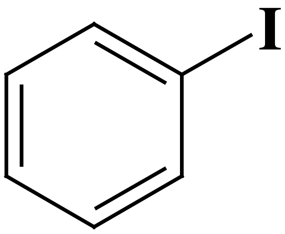
- Alkyl halides: Halogen, X, is directly bonded to *sp*^{3} carbon.
- Vinyl halides: X is bonded to *sp*^{2} carbon of alkene.
- Aryl halides: X is bonded to *sp*^{2} carbon on benzene ring.



alkyl halide

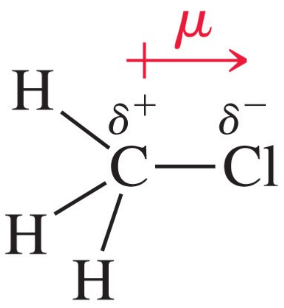


vinyl halide

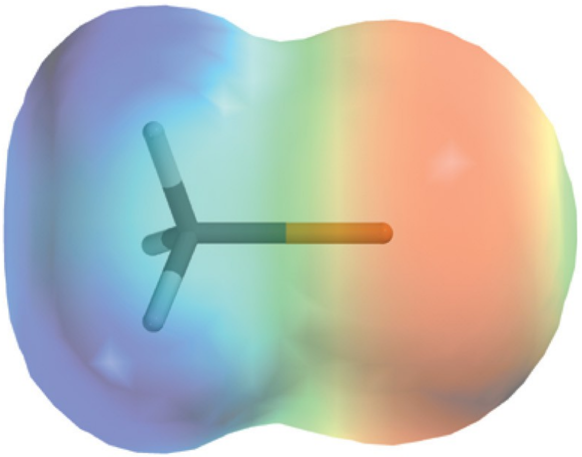


aryl halide

Polarity and Reactivity



chloromethane

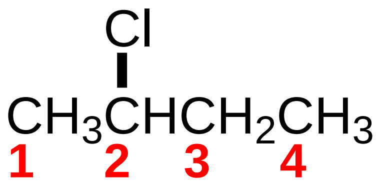


chloromethane

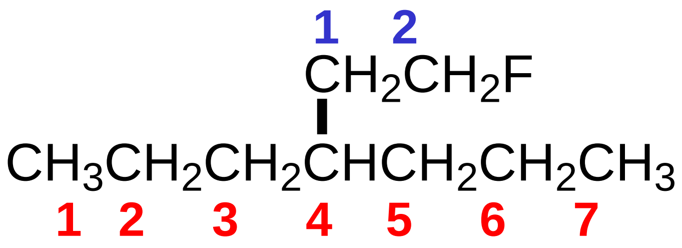
- Halogens are more electronegative than C.
- Carbon—halogen bond is polar, so carbon has partial positive charge.
- Carbon can be attacked by a nucleophile.
- Halogen can leave with the electron pair.

IUPAC Nomenclature

- Name as haloalkane.
- Choose the longest carbon chain, <u>even if</u> the halogen is not bonded to any of those C’s.
- Use lowest possible numbers for position.

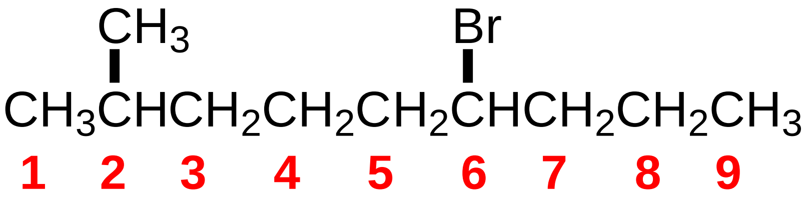

$CH_3\overset{Cl}{\overset{|}{C}}HCH_2CH_3$

2-chlorobutane


$CH_3CH_2CH_2\overset{CH_2CH_2F}{\overset{|}{C}}HCH_2CH_2CH_3$

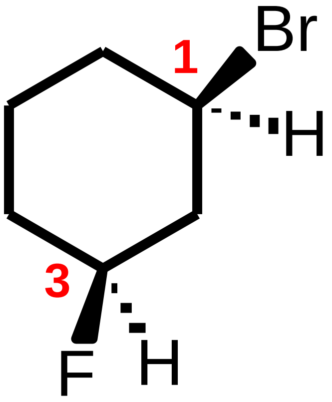
4-(2-fluoroethyl)heptane

Examples



$$CH_3\overset{CH_3}{\overset{|}{C}}HCH_2CH_2CH_2\overset{Br}{\overset{|}{C}}HCH_2CH_2CH_3$$

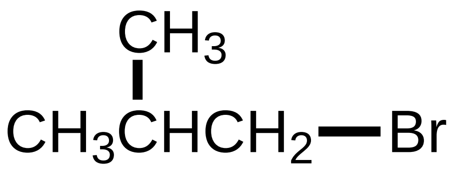
6-bromo-2-methylnonane



cis-1-bromo-3-fluorocyclohexane

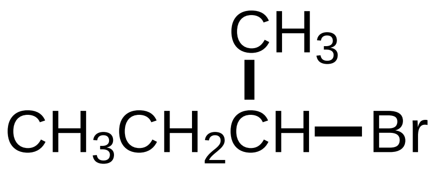
Systematic Common Names

- The alkyl groups is a substituent on halide.
- Useful only for small alkyl groups.



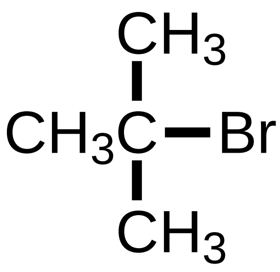
$CH_3\overset{\overset{CH_3}{|}}{C}HCH_2-Br$

iso-butyl bromide



$CH_3CH_2\overset{\overset{CH_3}{|}}{C}H-Br$

sec-butyl bromide



$CH_3\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-Br$

tert-butyl bromide

Common Names of Halides

- CH_2X_2 called methylene halide.
- CHX_3 is a haloform.
- CX_4 is carbon tetrahalide.
- Common halogenated solvents:

  CH_2Cl_2 is methylene chloride

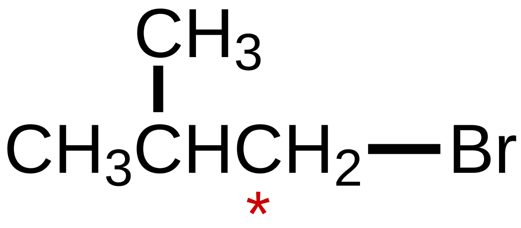
  $CHCl_3$ is chloroform

  CCl_4 is carbon tetrachloride.

Alkyl Halides Classification

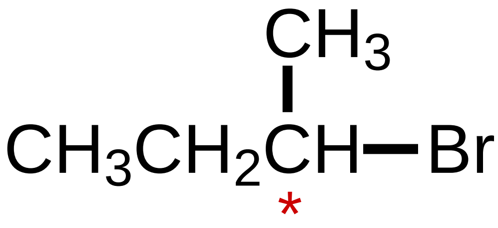
- **Methyl halides**: halide is attached to a methyl group.
- **Primary alkyl halide**: carbon to which halogen is bonded is attached to only one other carbon.
- **Secondary alkyl halide** : carbon to which halogen is bonded is attached to two other carbons.
- **Tertiary alkyl halide** : carbon to which halogen is bonded is attached to three other carbon.

Primary, Secondary, Tertiary Alkyl Halides



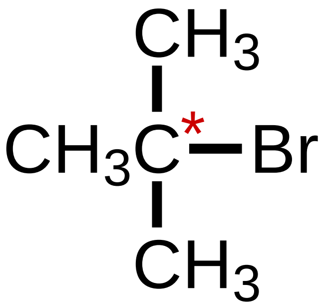
$\mathrm{CH_3\overset{\overset{\displaystyle CH_3}{|}}{C}H\underset{*}{C}H_2{-}Br}$

primary alkyl halide



$\mathrm{CH_3CH_2\underset{*}{\overset{\overset{\displaystyle CH_3}{|}}{C}}H{-}Br}$

secondary alkyl halide

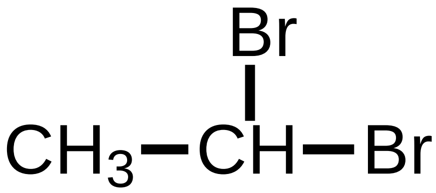


$\mathrm{CH_3\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C^{*}}}{-}Br}$

tertiary alkyl halide

Types of Dihalides

- **Geminal dihalide**: two halogen atoms are bonded to the same carbon.
- **Vicinal dihalide**: two halogen atoms are bonded to adjacent carbons.



$CH_3-\overset{\overset{Br}{|}}{C}H-Br$

geminal dihalide

$Br-CH_2CH_2-Br$

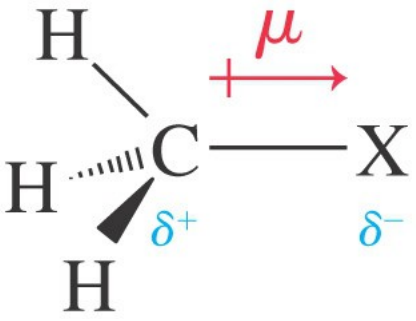
vicinal dihalide

Uses of Alkyl Halides

- Industrial and household cleaners.
- **Anesthetics:**
  - $CHCl_3$ used originally as general anesthetic but it is toxic and carcinogenic.
  - $CF_3CHClBr$ is a mixed halide sold as Halothane®
- **Freons** are used as refrigerants and foaming agents.
  - Freons can harm the ozone layer so they have been replaced by low-boiling hydrocarbons or carbon dioxide.
- **Pesticides** such as DDT are extremely toxic to insects but not as toxic to mammals.
  - Haloalkanes can not be destroyed by bacteria so they accumulate in the soil to a level which can be toxic to mammals, especially, humans.

Dipole Moments

- Electronegativities of the halides:
  F > Cl > Br > I
- Bond lengths increase as the size of the halogen increases:
  C—F < C—Cl < C—Br < C—I
- Bond dipoles:
  C—Cl > C—F > C—Br > C—I
  1.56 D 1.51 D 1.48 D 1.29 D
- Molecular dipoles depend on the geometry of the molecule.



Boiling Points

- Greater intermolecular forces, higher b.p.
  - dipole-dipole attractions not significantly different for different halides
  - London forces greater for larger atoms
- Greater mass, higher b.p.
- Spherical shape decreases b.p.

$(CH_3)_3CBr$	$CH_3(CH_2)_3Br$
73 C	102 C

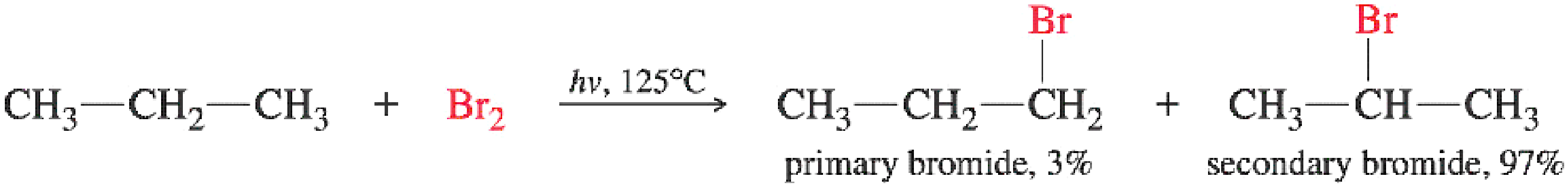
Densities

- Alkyl fluorides and chlorides less dense than water.
- Alkyl dichlorides, bromides, and iodides more dense than water.

Preparation of Alkyl Halides

- Free radical halogenation (Chapter 4)
  - Chlorination produces a mixtures of products. This reaction is not a good lab synthesis, except in alkanes where all hydrogens are equivalent.
  - Bromination is highly selective.
- Free radical allylic halogenation
  - Halogen is placed on a carbon directly attached to the double bond (allylic).

Halogenation of Alkanes

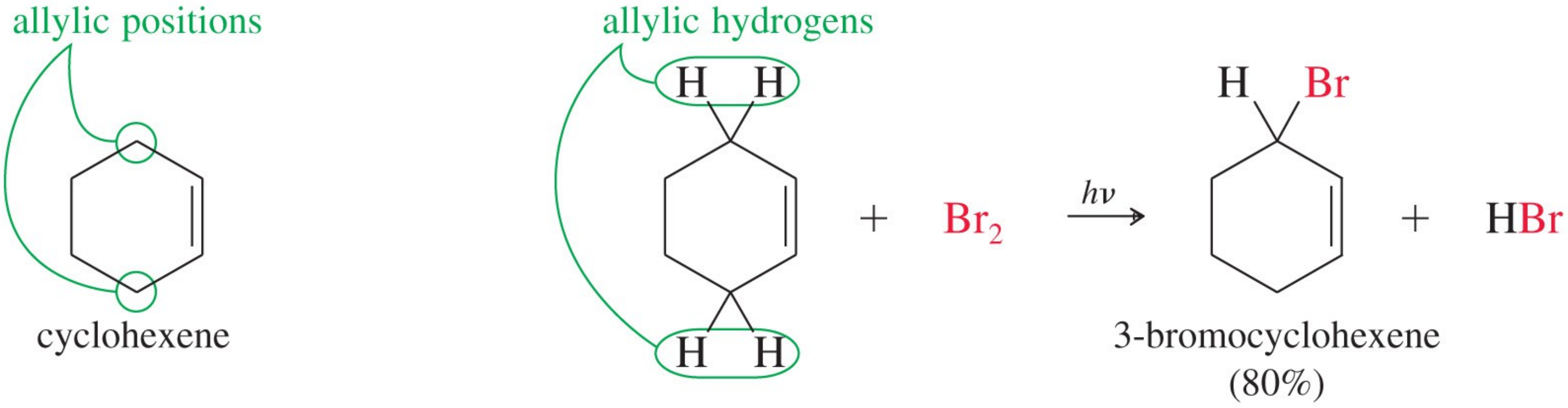


$$CH_3-CH_2-CH_3 + Br_2 \xrightarrow{h\nu,\ 125^\circ C} \underset{\text{primary bromide, 3\%}}{CH_3-CH_2-\overset{Br}{CH_2}} + \underset{\text{secondary bromide, 97\%}}{CH_3-\overset{Br}{CH}-CH_3}$$

- Bromination is highly selective:

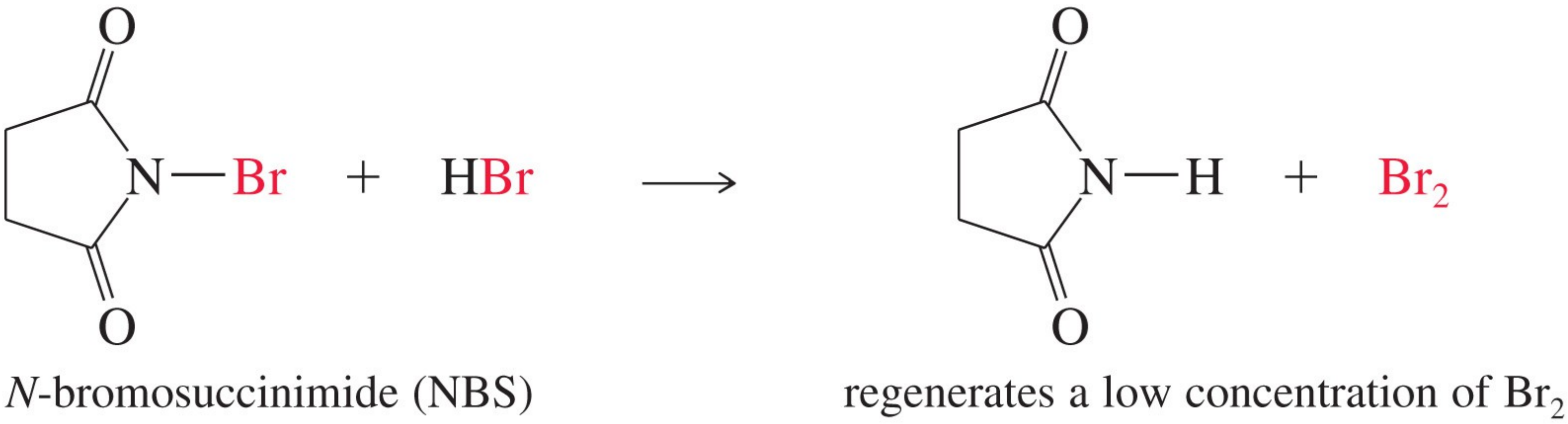
  3º carbons > 2º carbons > 1º carbons

Allylic Halogenation



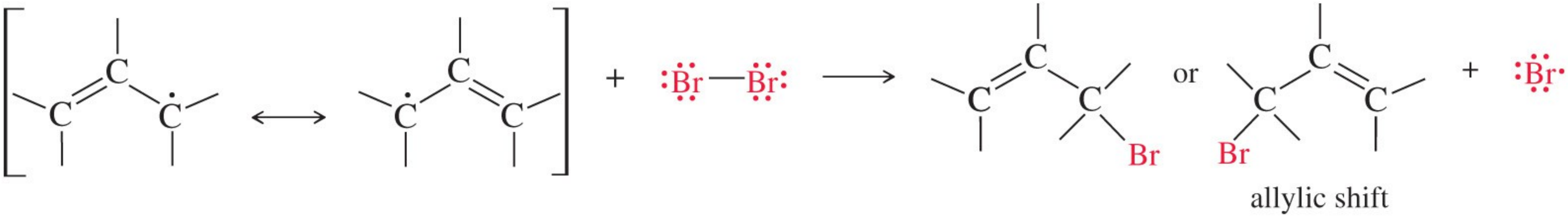
- Allylic radical is resonance stabilized.
- Bromination occurs with good yield at the allylic position (*sp*^{3} C next to C═C).

N-bromosuccinimide



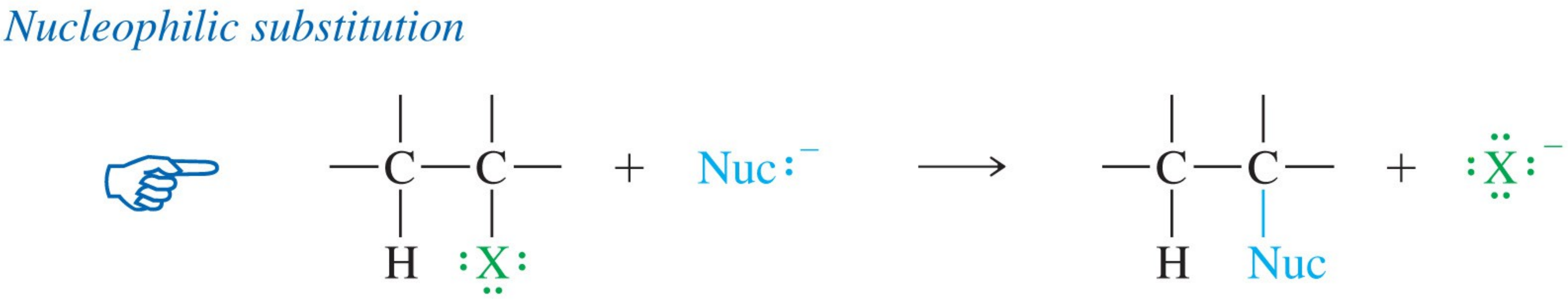
- N-bromosuccinimide (NBS) is an allylic brominating agent.
- Keeps the concentration of Br_2 low.

Reaction Mechanism



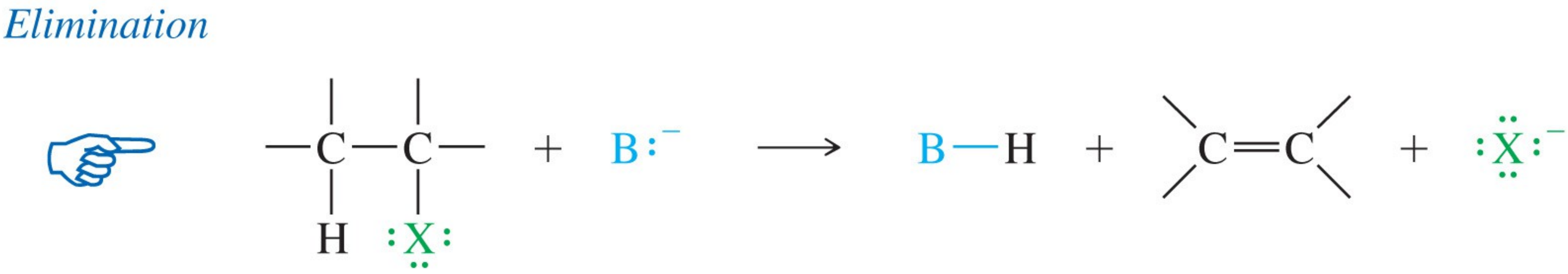
- The mechanism involves an allylic radical stabilized by resonance.
- Both allylic radicals can react with bromine.

Substitution Reactions



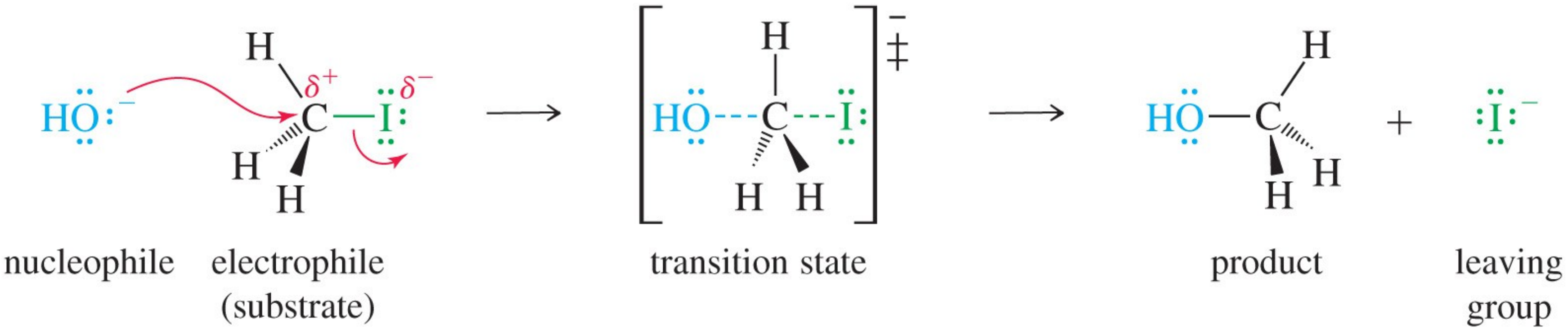
- The halogen atom on the alkyl halide is replaced with a nucleophile (Nuc^-).
- Since the halogen is more electronegative than carbon, the C—X bond breaks heterolytically and X^- leaves.

Elimination Reactions



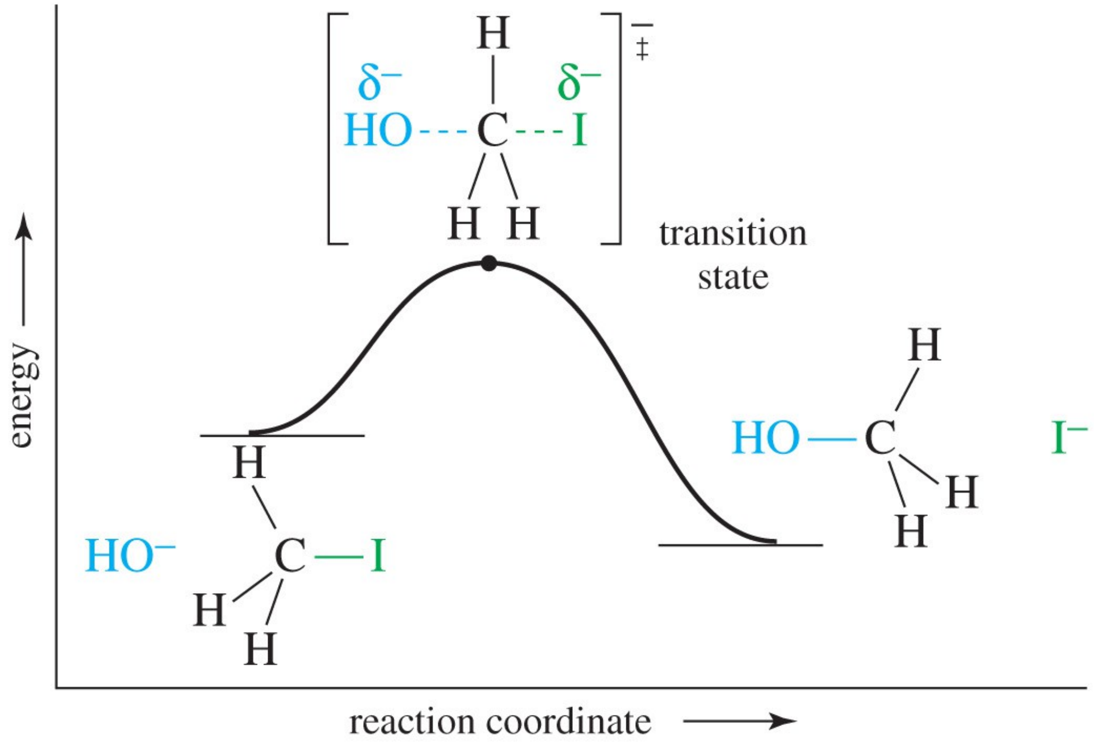
- Elimination reactions produce double bonds.
- The alkyl halides loses a hydrogen and the halide.
- Also called dehydrohalogenation (-HX).

S_N2 Mechanism



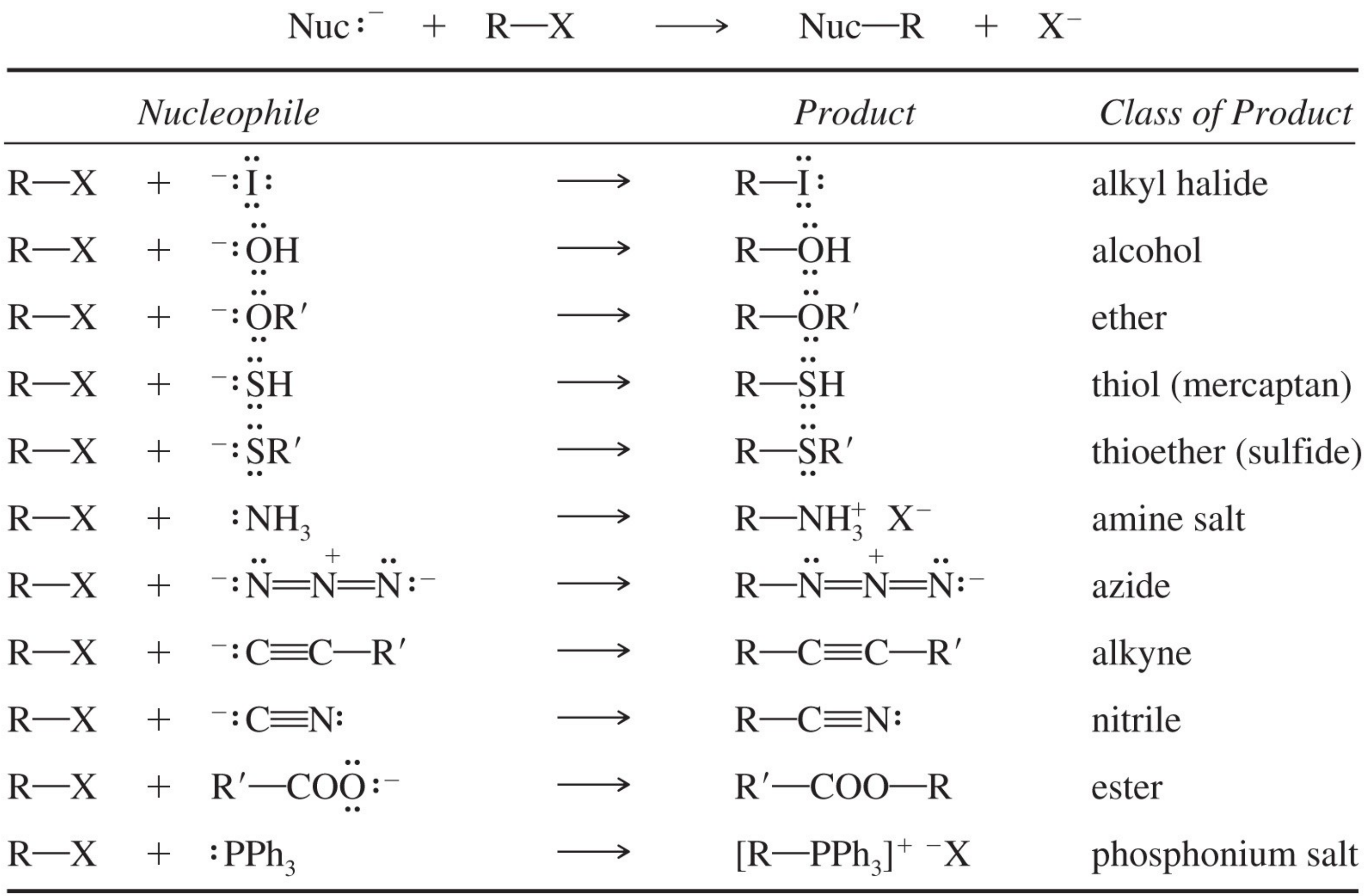
- Bimolecular nucleophilic substitution.
- Concerted reaction: new bond forming and old bond breaking at same time.
- Rate is first order in each reactant.
- Walden inversion.

S_N2 Energy Diagram



- The S_N2 reaction is a one-step reaction.
- Transition state is highest in energy.

Uses for S_N2 Reactions

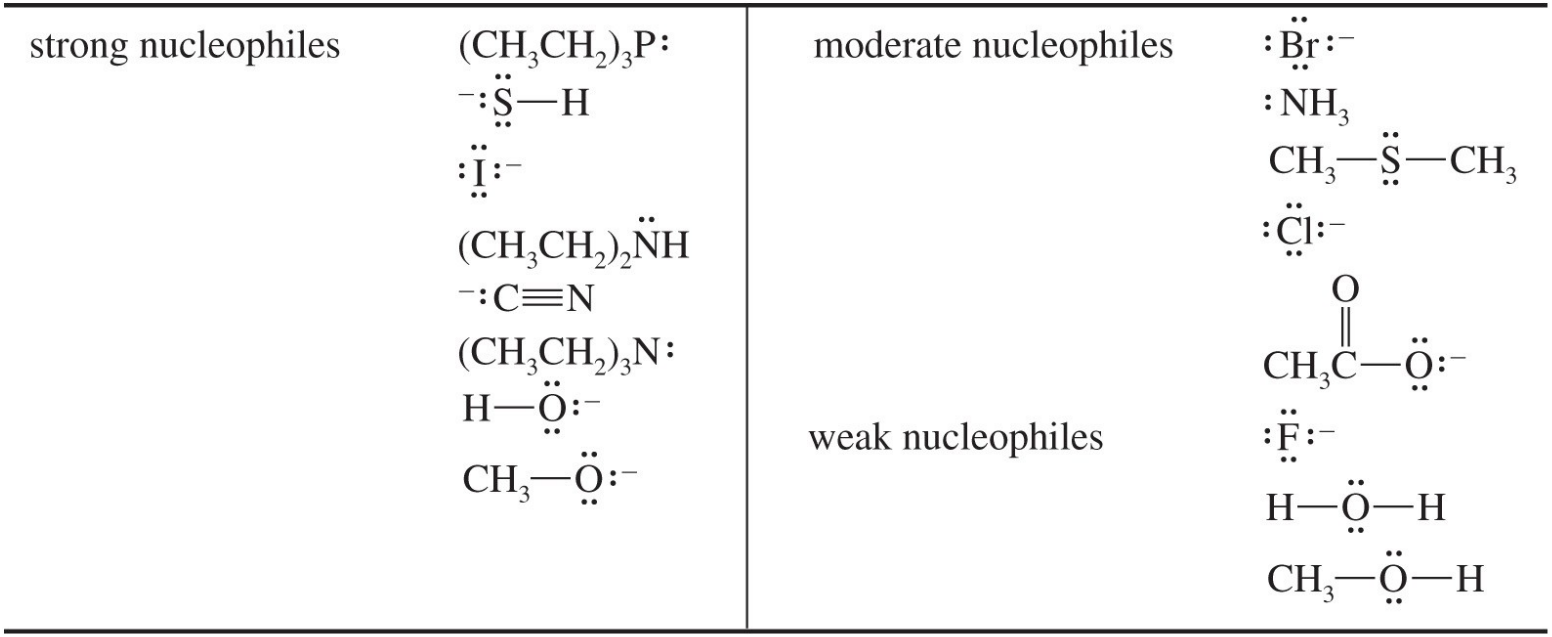


$$\mathrm{Nuc}:^{-} + \mathrm{R{-}X} \longrightarrow \mathrm{Nuc{-}R} + \mathrm{X}^{-}$$

		Nucleophile		*Product*	*Class of Product*
R—X	+	$^{-}:\ddot{\underset{\cdot\cdot}{\mathrm{I}}}:$	⟶	$\mathrm{R{-}}\ddot{\underset{\cdot\cdot}{\mathrm{I}}}:$	alkyl halide
R—X	+	$^{-}:\ddot{\underset{\cdot\cdot}{\mathrm{O}}}\mathrm{H}$	⟶	$\mathrm{R{-}}\ddot{\underset{\cdot\cdot}{\mathrm{O}}}\mathrm{H}$	alcohol
R—X	+	$^{-}:\ddot{\underset{\cdot\cdot}{\mathrm{O}}}\mathrm{R}'$	⟶	$\mathrm{R{-}}\ddot{\underset{\cdot\cdot}{\mathrm{O}}}\mathrm{R}'$	ether
R—X	+	$^{-}:\ddot{\underset{\cdot\cdot}{\mathrm{S}}}\mathrm{H}$	⟶	$\mathrm{R{-}}\ddot{\underset{\cdot\cdot}{\mathrm{S}}}\mathrm{H}$	thiol (mercaptan)
R—X	+	$^{-}:\ddot{\underset{\cdot\cdot}{\mathrm{S}}}\mathrm{R}'$	⟶	$\mathrm{R{-}}\ddot{\underset{\cdot\cdot}{\mathrm{S}}}\mathrm{R}'$	thioether (sulfide)
R—X	+	$:\mathrm{NH_3}$	⟶	$\mathrm{R{-}NH_3^+}\ \mathrm{X}^-$	amine salt
R—X	+	$^{-}:\ddot{\mathrm{N}}{=}\overset{+}{\mathrm{N}}{=}\ddot{\mathrm{N}}:^{-}$	⟶	$\mathrm{R{-}}\ddot{\mathrm{N}}{=}\overset{+}{\mathrm{N}}{=}\ddot{\mathrm{N}}:^{-}$	azide
R—X	+	$^{-}:\mathrm{C{\equiv}C{-}R'}$	⟶	$\mathrm{R{-}C{\equiv}C{-}R'}$	alkyne
R—X	+	$^{-}:\mathrm{C{\equiv}N}:$	⟶	$\mathrm{R{-}C{\equiv}N}:$	nitrile
R—X	+	$\mathrm{R'{-}CO}\ddot{\underset{\cdot\cdot}{\mathrm{O}}}:^{-}$	⟶	$\mathrm{R'{-}COO{-}R}$	ester
R—X	+	$:\mathrm{PPh_3}$	⟶	$[\mathrm{R{-}PPh_3}]^+\ {}^{-}\mathrm{X}$	phosphonium salt

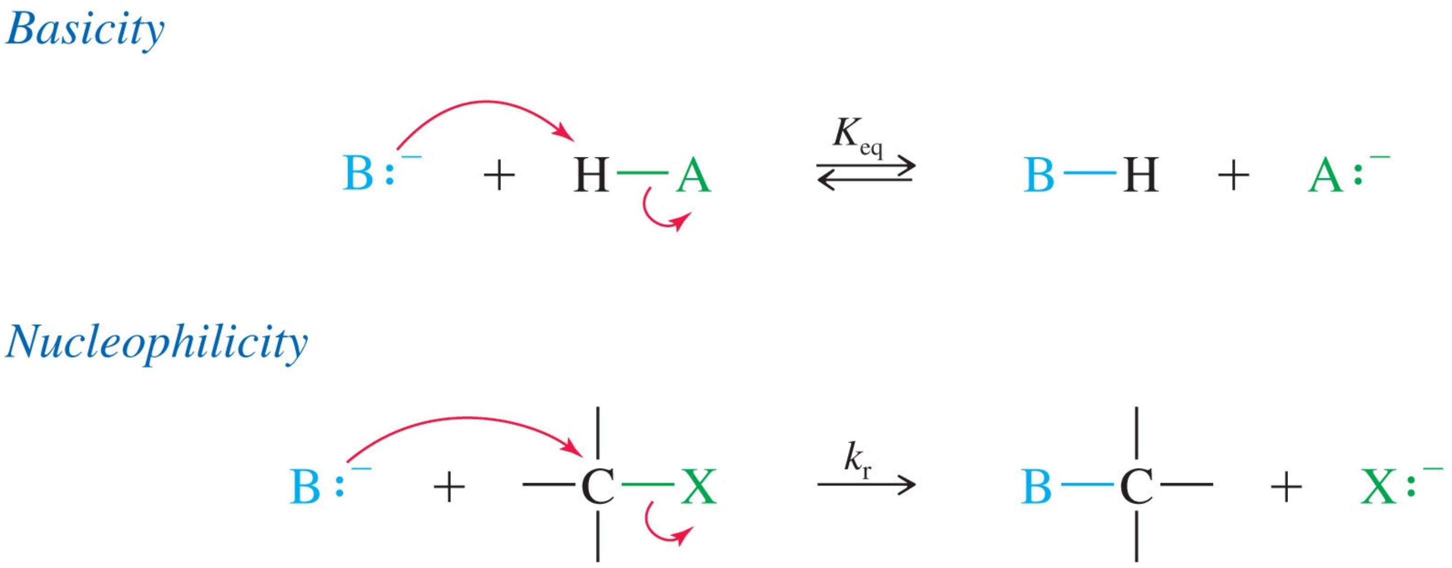
S_N2: Nucleophilic Strength

- Stronger nucleophiles react faster.
- Strong bases are strong nucleophiles, but not all strong nucleophiles are basic.



strong nucleophiles	$(CH_3CH_2)_3P$	moderate nucleophiles	Br^-
	^-S-H		NH_3
	I^-		CH_3-S-CH_3
	$(CH_3CH_2)_2NH$		Cl^-
	$^-C\equiv N$		$CH_3\overset{O}{\overset{\|}{C}}-O^-$
	$(CH_3CH_2)_3N$	weak nucleophiles	F^-
	$H-O^-$		$H-O-H$
	CH_3-O^-		CH_3-O-H

Basicity versus Nucleophilicity



- Basicity is defined by the equilibrium constant for abstracting a proton.
- Nucleophilicity is defined by the rate of attack on the electrophilic carbon atom

Trends in Nucleophilicity

- A negatively charged nucleophile is stronger than its neutral counterpart:

  $OH^- > H_2O$ $HS^- > H_2S$ $NH_2^- > NH_3$

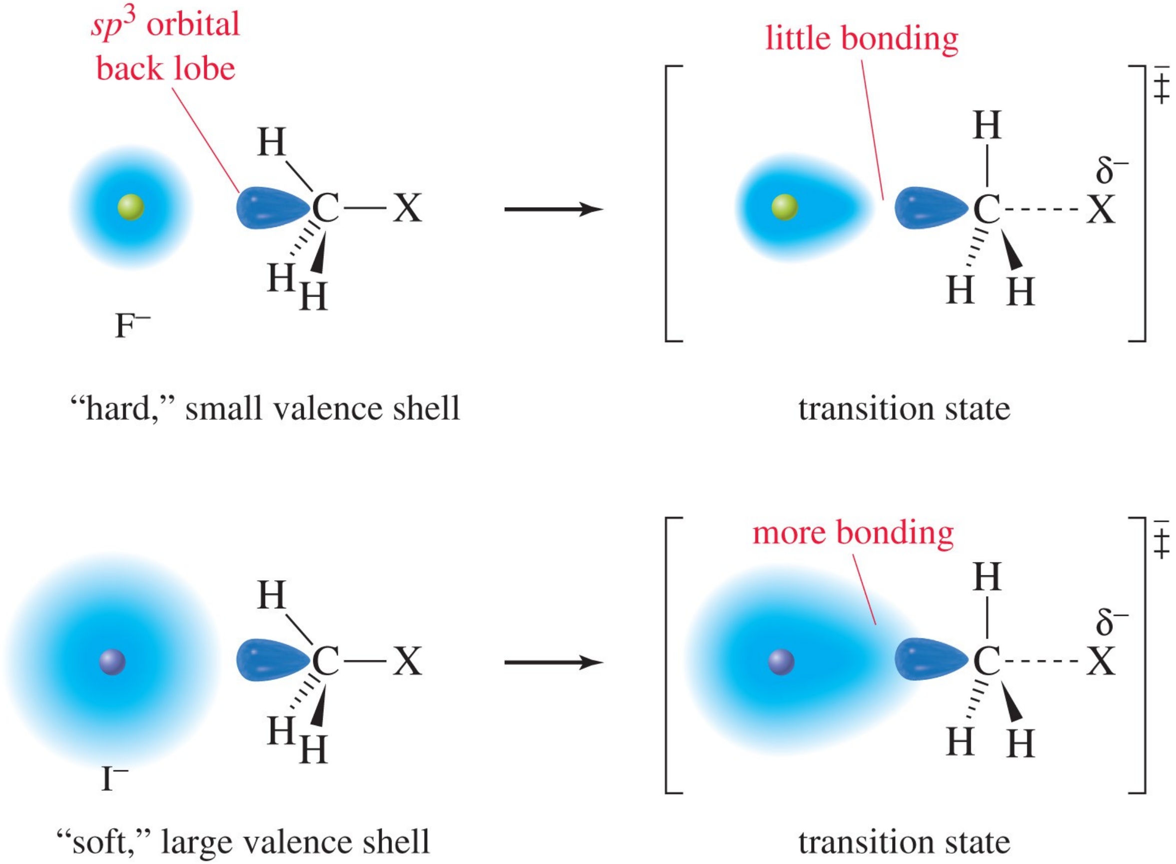
- Nucleophilicity decreases from left to right :

  $OH^- > F^-$ $NH_3 > H_2O$

- Increases down Periodic Table, as size and polarizability increase:

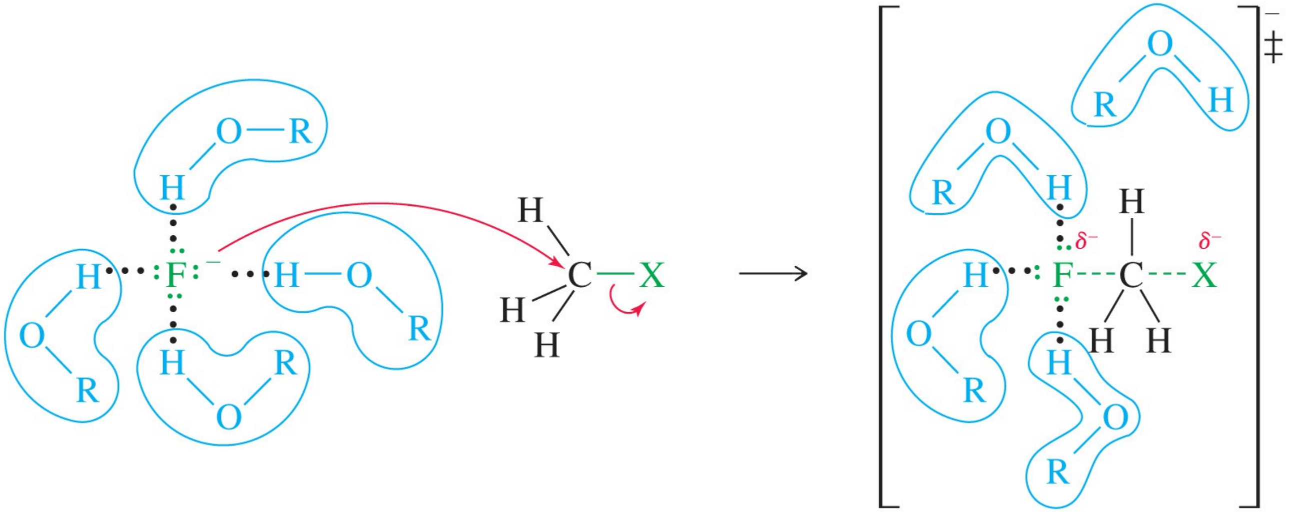
  $I^- > Br^- > Cl^-$

Polarizability Effect



Bigger atoms have a soft shell which can start to overlap the carbon atom from a farther distance.

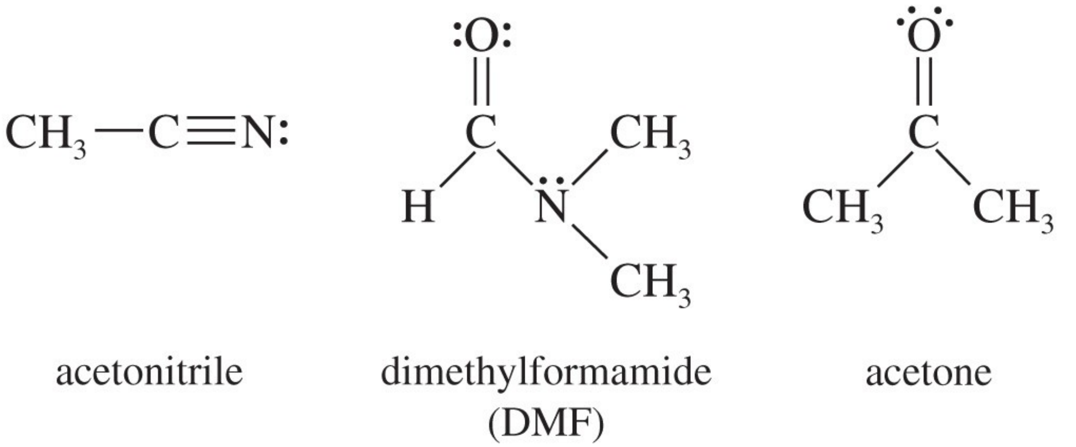
Solvent Effects: Protic Solvents



solvent partially stripped
off in the transition state

- Polar protic solvents have acidic hydrogens (O—H or N—H) which can solvate the nucleophile reducing their nucleophilicity.
- Nucleophilicity in protic solvents increases as the size of the atom increases.

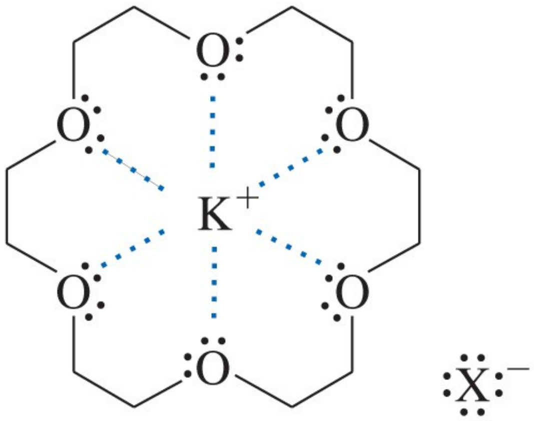
Solvent Effects: Aprotic Solvents



- Polar aprotic solvents do not have acidic protons and therefore cannot hydrogen bond.
- Some aprotic solvents are acetonitrile, DMF, acetone, and DMSO.

Crown Ethers

- Crown ethers solvate the cation, so the nucleophilic strength of the anion increases.
- Fluoride becomes a good nucleophile.



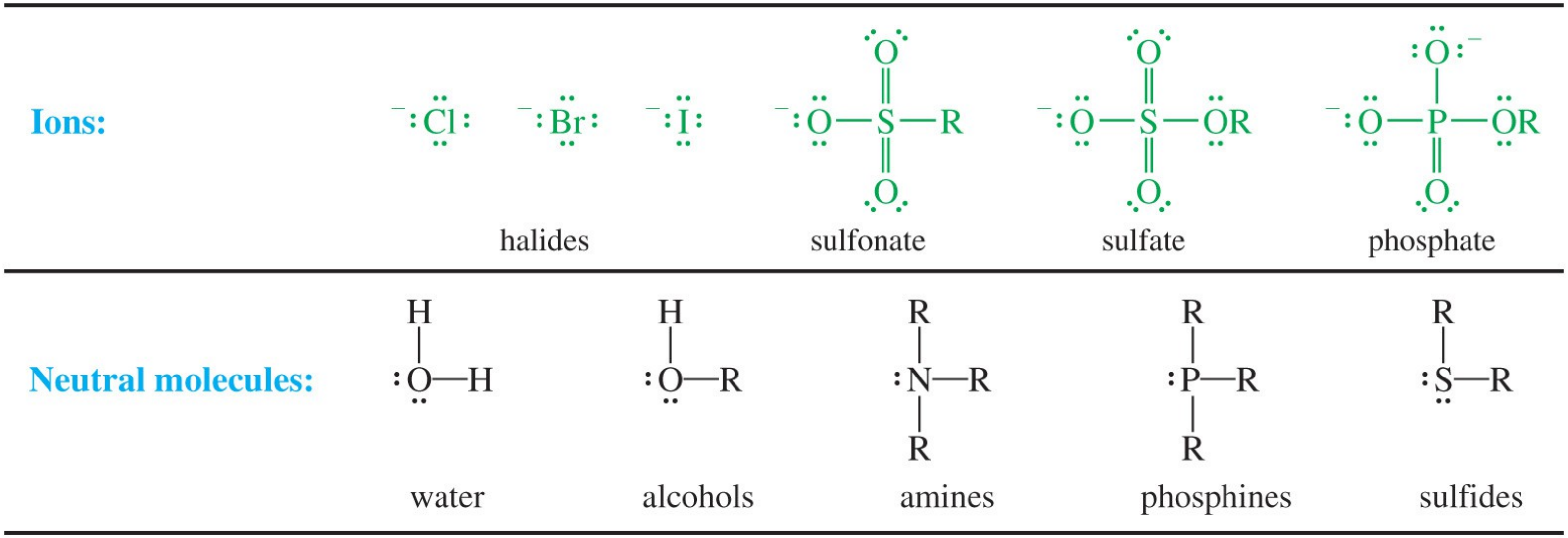
18-crown-6 solvates K$^+$ ions

$$R{-}X + KF \xrightarrow[CH_3CN]{\text{18-crown-6}} R{-}F + KX$$

Leaving Group Ability

The best leaving groups are:

- Electron-withdrawing, to polarize the carbon atom.
- Stable (not a strong base) once it has left.
- Polarizable, to stabilize the transition state.



Structure of Substrate on S_N2 Reactions

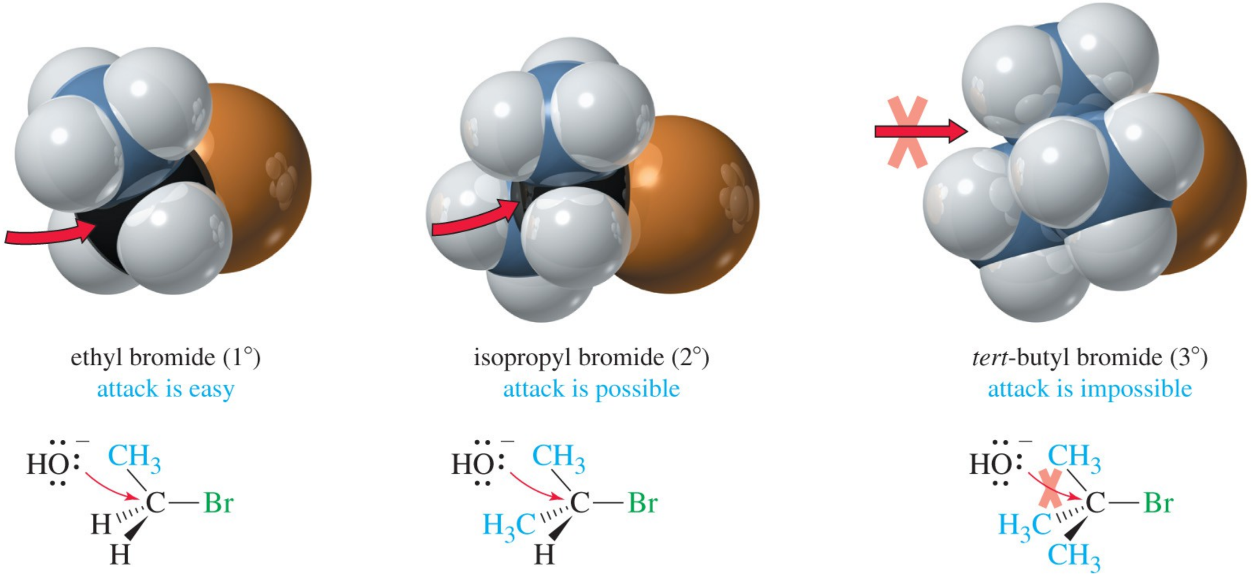
- Relative rates for S_N2:

CH_3X > 1° > 2° >> 3°

- Tertiary halides do not react via the S_N2 mechanism, due to steric hindrance.

Steric Effects of the Substrate on S_N2 Reactions

- Nucleophile approaches from the back side.
- It must overlap the back lobe of the C—X sp^3 orbital.



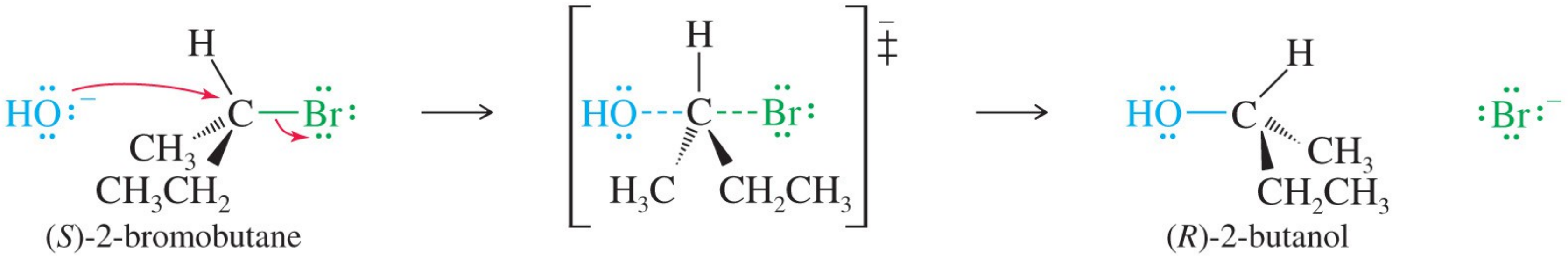
ethyl bromide (1°)
attack is easy

isopropyl bromide (2°)
attack is possible

tert-butyl bromide (3°)
attack is impossible

Stereochemistry of S_N2

S_N2 reactions will result in an inversion of configuration also called a Walden inversion.

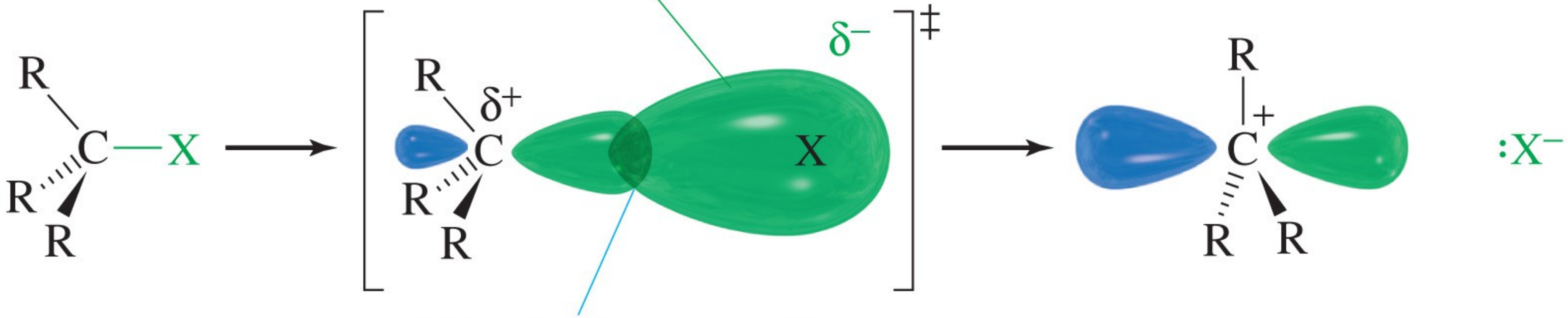


The S_N1 Reaction

- The S_N1 reaction is a unimolecular nucleophilic substitution.
- It is a two step reaction with a carbocation intermediate.
- Rate is first order in the alkyl halide, zero order in the nucleophile.
- Racemization occurs.

S_N1 Mechanism: Step 1

X is taking on a partial negative charge



partial bonding in the transition state

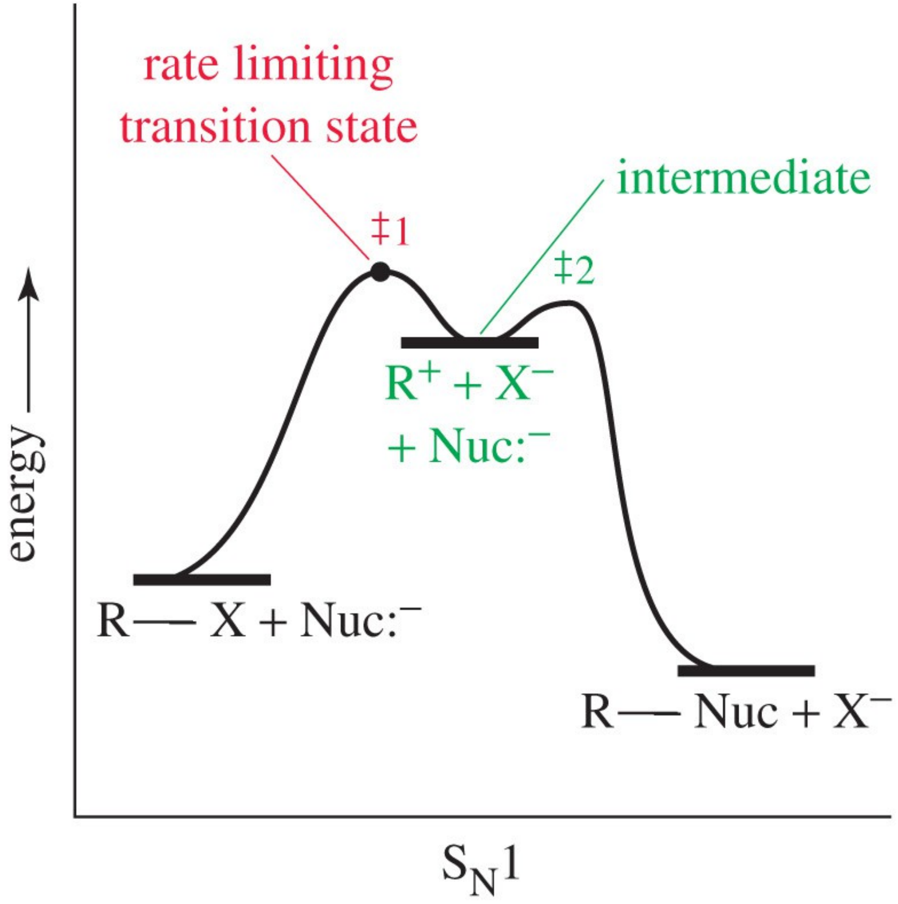
Formation of carbocation (rate determining step)

S_N1 Mechanism: Step 2

- The nucleophile attacks the carbocation, forming the product.
- If the nucleophile was neutral, a third step (deprotonation) will be needed.

S_N1 Energy Diagram

- Forming the carbocation is an endothermic step.
- Step 2 is fast with a low activation energy.

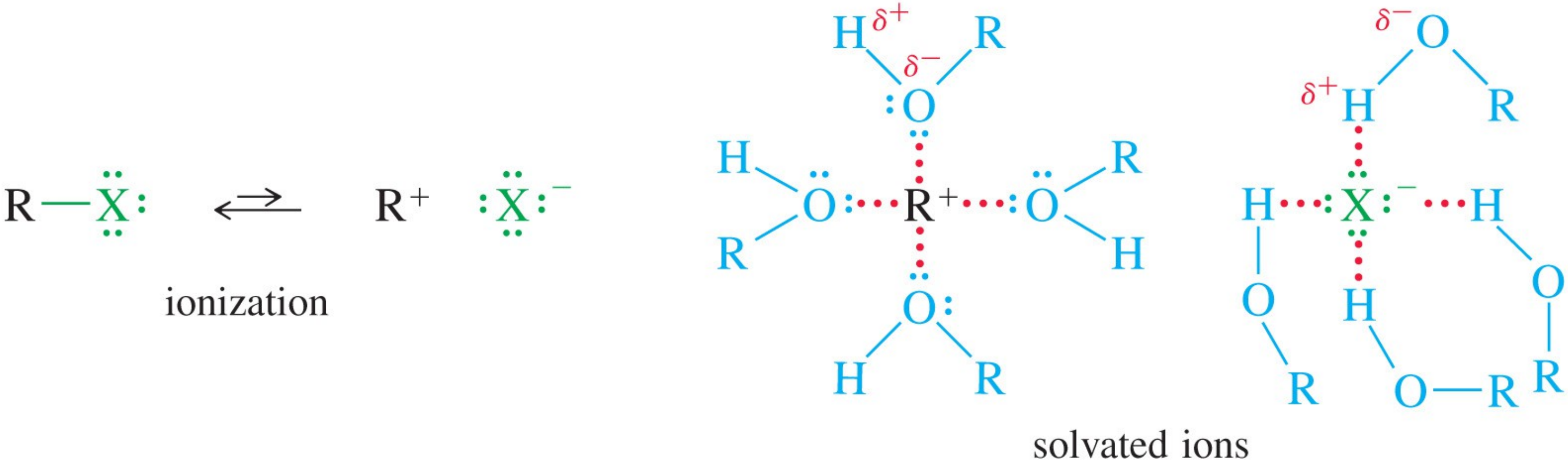


Rates of S_N1 Reactions

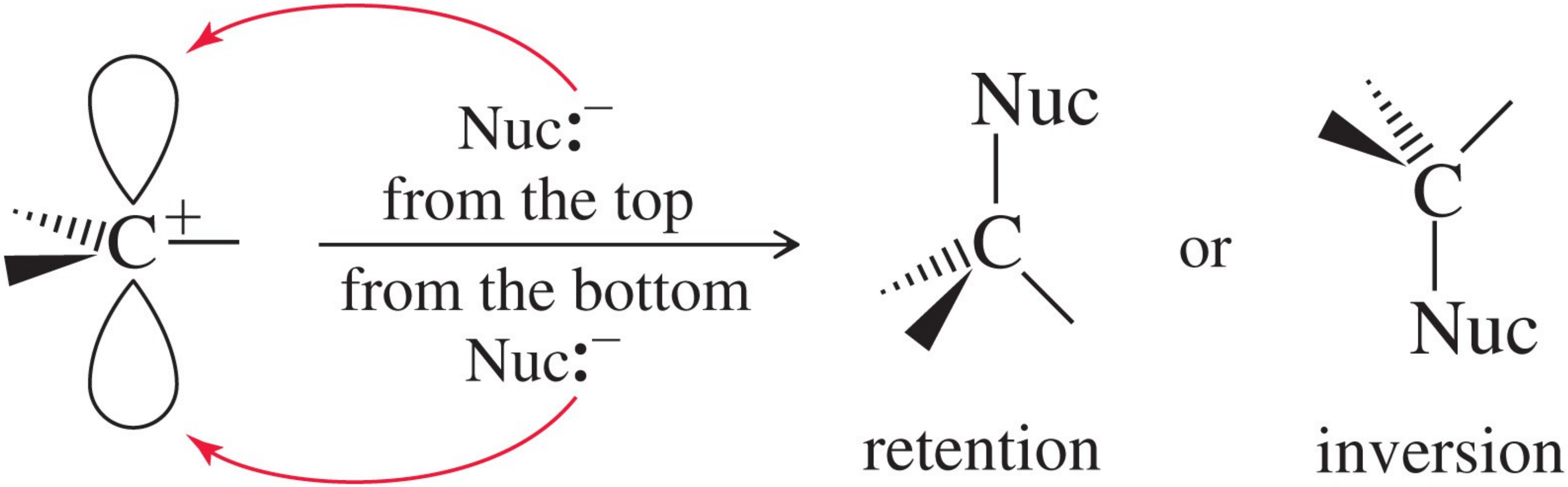
- Order of reactivity follows stability of carbocations (opposite to S_N2)
  - 3° > 2° > 1° >> CH_3X
  - More stable carbocation requires less energy to form.
- A better leaving group will increase the rate of the reaction.

Solvation Effect

- Polar protic solvent best because it can solvate both ions strongly through hydrogen bonding.

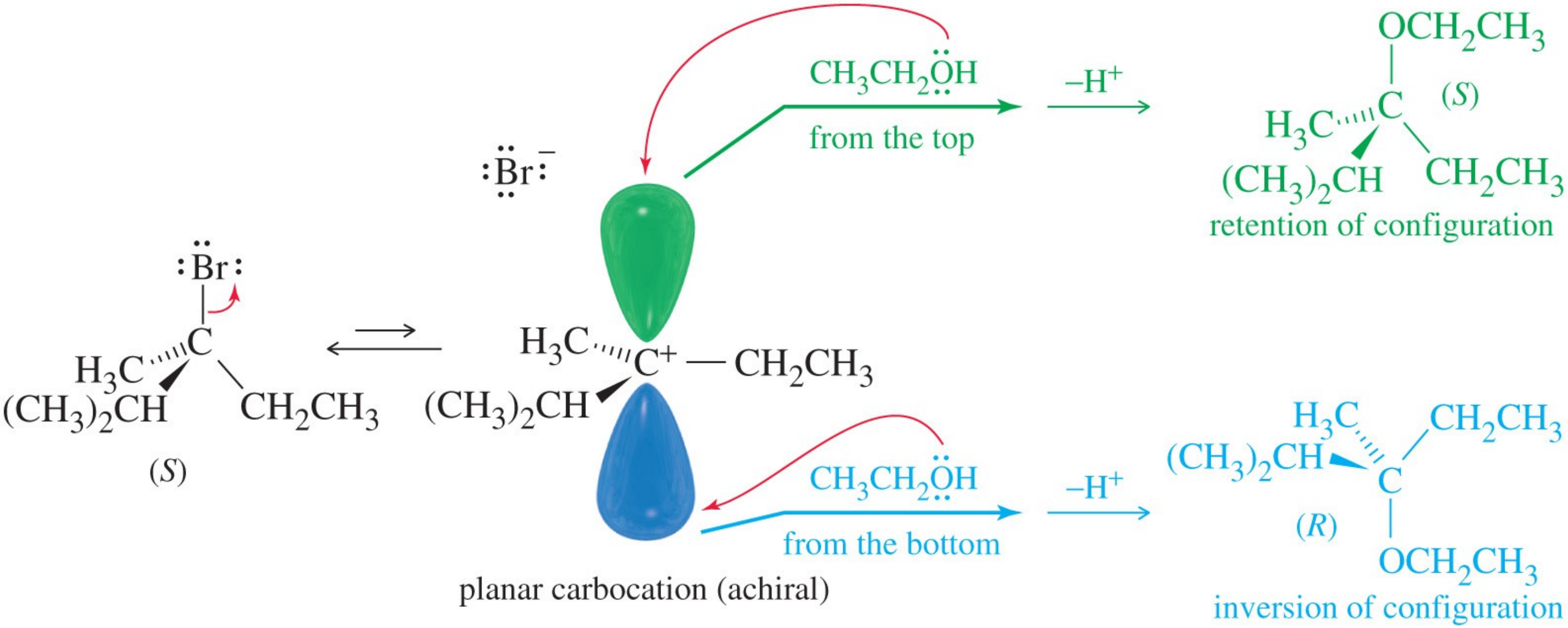


Structure of the Carbocation



- Carbocations are *sp*^{2} hybridized and trigonal planar. The lobes of the empty p orbital are on both sides of the trigonal plane.
- Nucleophilic attack can occur from either side producing mixtures of retention and inversion of configuration if the carbon is chiral.

Stereochemistry of S_N1

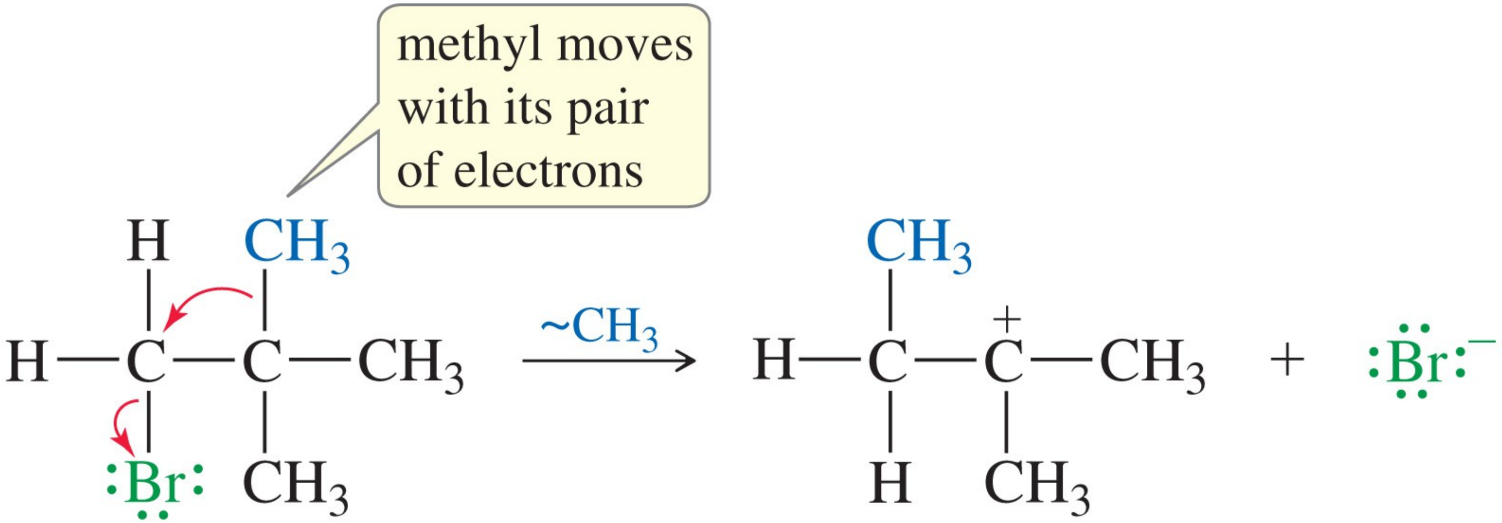


The S_N1 reaction produces mixtures of enantiomers. There is usually more inversion than retention of configuration.

Rearrangements

- Carbocations can rearrange to form a more stable carbocation.
- Hydride shift: H^- on adjacent carbon bonds with C^+.
- Methyl shift: CH_3^- moves from adjacent carbon <u>if</u> no hydrogens are available.

Hydride and Methyl Shifts



- Since a primary carbocation cannot form, the methyl group on the adjacent carbon will move (along with both bonding electrons) to the primary carbon displacing the bromide and forming a tertiary carbocation.
- The smallest groups on the adjacent carbon will move: if there is a hydrogen it will give a hydride shift.

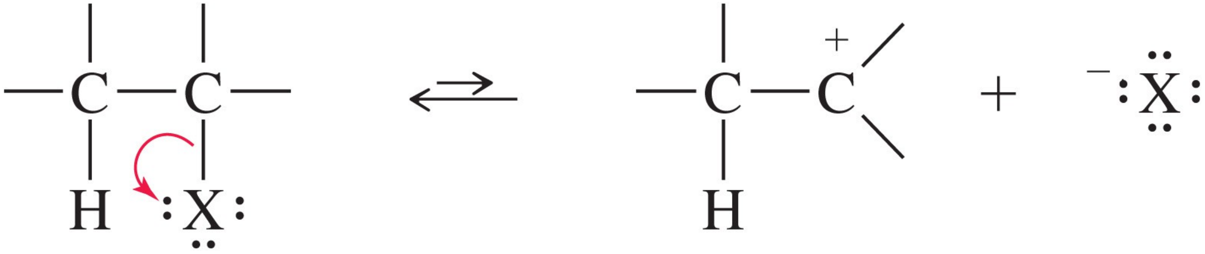
S_N1 or S_N2 Mechanism?

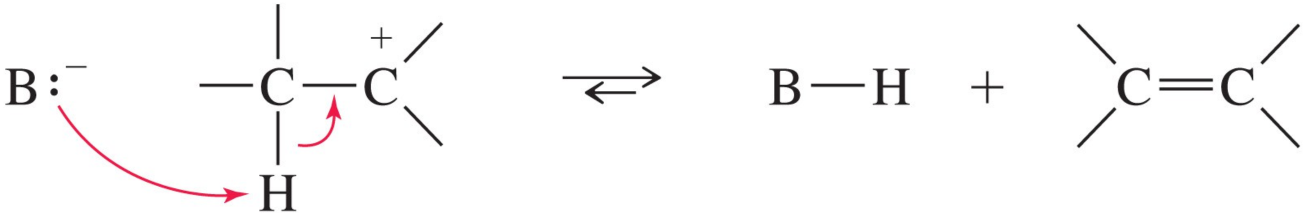
S_N2	**S_N1**
CH_3X > 1º > 2º	3º > 2º
Strong nucleophile	Weak nucleophile (may also be solvent)
Polar aprotic solvent	Polar protic solvent.
Rate = *k*[alkyl halide][Nuc]	Rate = *k*[alkyl halide]
Inversion at chiral carbon	Racemization
No rearrangements	Rearranged products

The E1 Reaction

- Unimolecular elimination.
- Two groups lost: a hydrogen and the halide.
- Nucleophile acts as base.
- The E1 and S_N1 reactions have the same conditions so a mixture of products will be obtained.

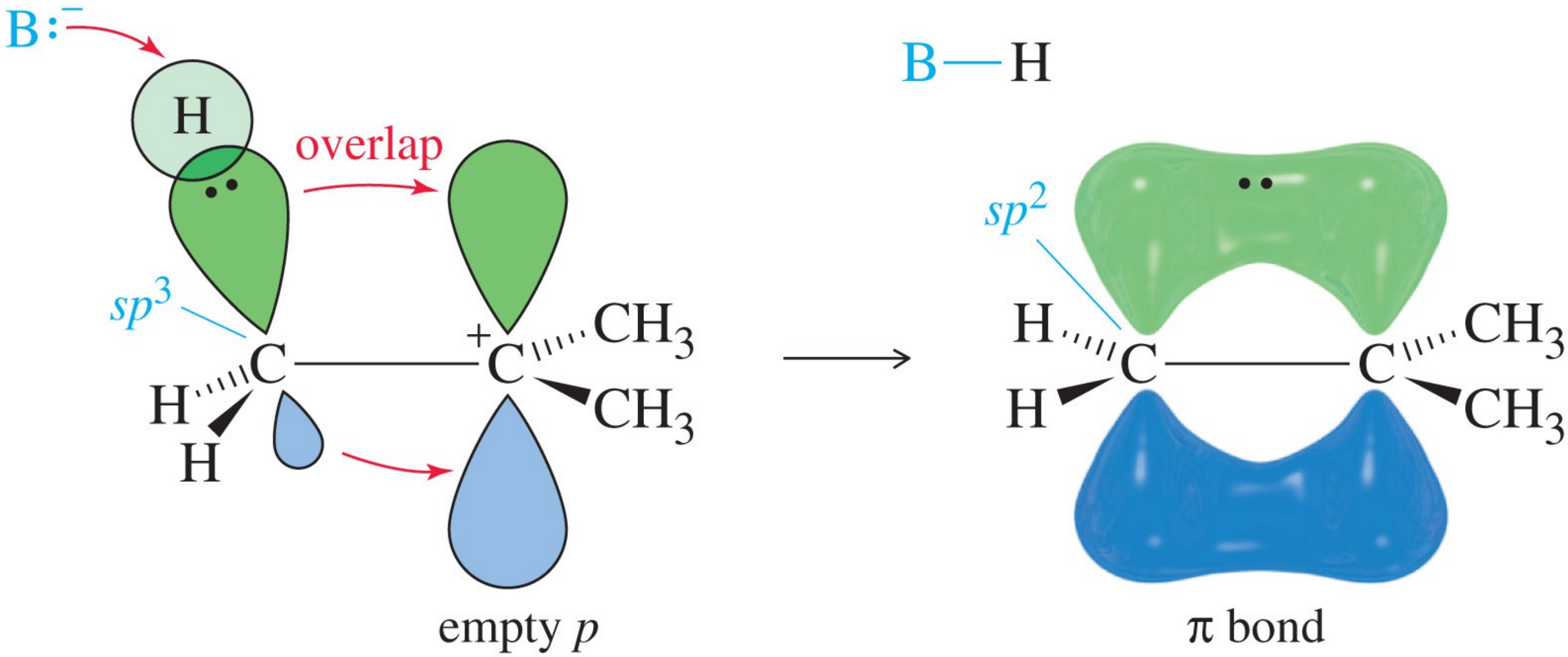
E1 Mechanism



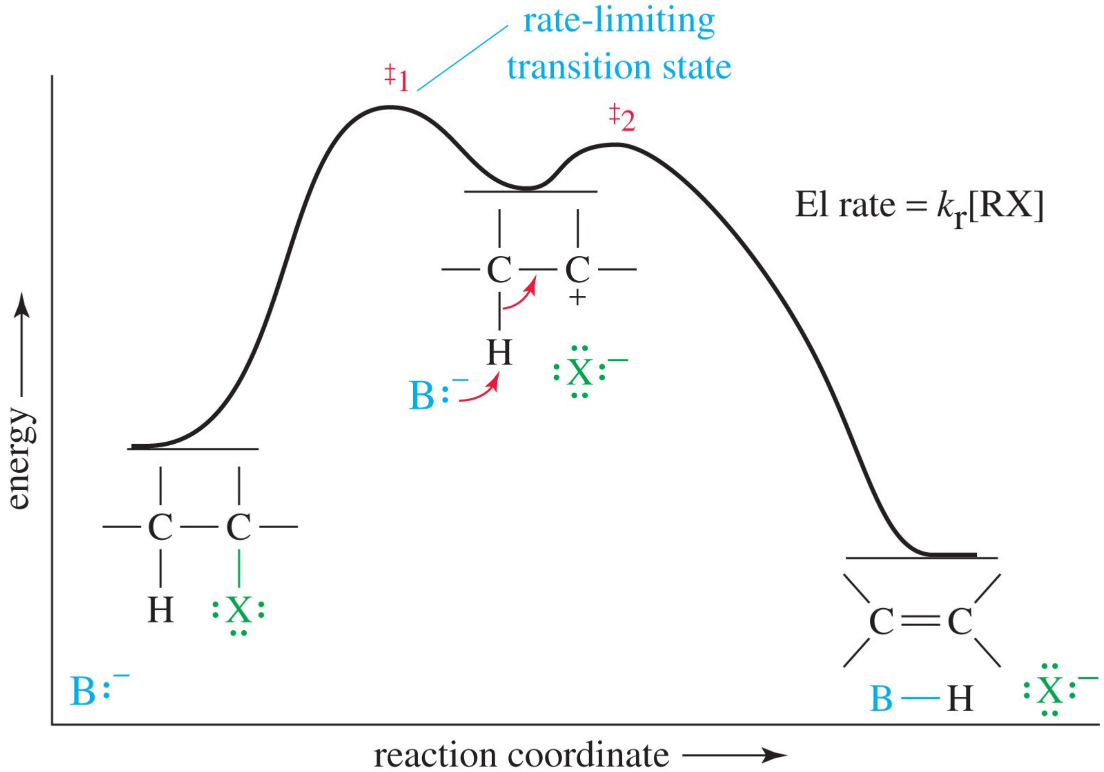


- Step 1: halide ion leaves, forming a carbocation.
- Step 2: Base abstracts H^+ from adjacent carbon forming the double bond.

A Closer Look

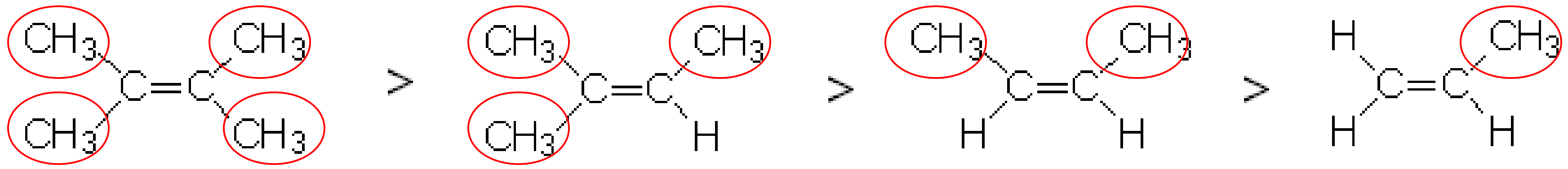


E1 Energy Diagram



The E1 and the S_N1 reactions have the same first step: carbocation formation is the rate determining step for both mechanisms.

Double Bond Substitution Patterns

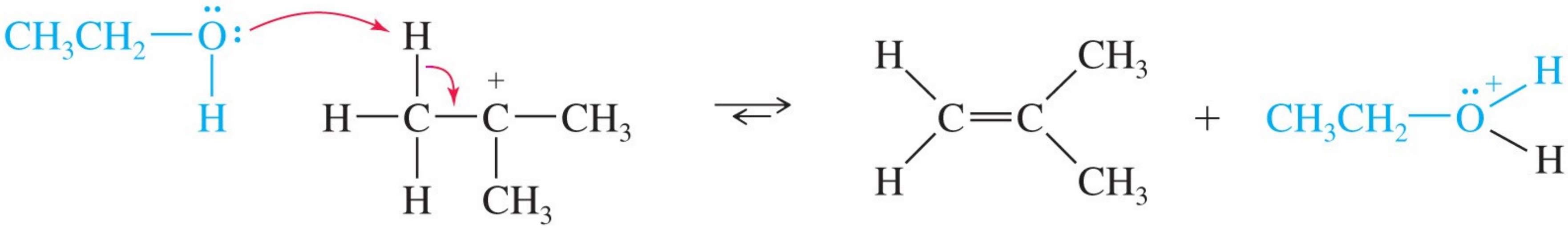


tetrasubstituted trisubstituted disubstituted monosubstituted

- The more substituted double bond is more stable.
- In elimination reactions, the major product of the reaction is the more substituted double bond: Zaitsev’s Rule.

Zaitsev's Rule

- If more than one elimination product is possible, the most-substituted alkene is the major product (most stable).

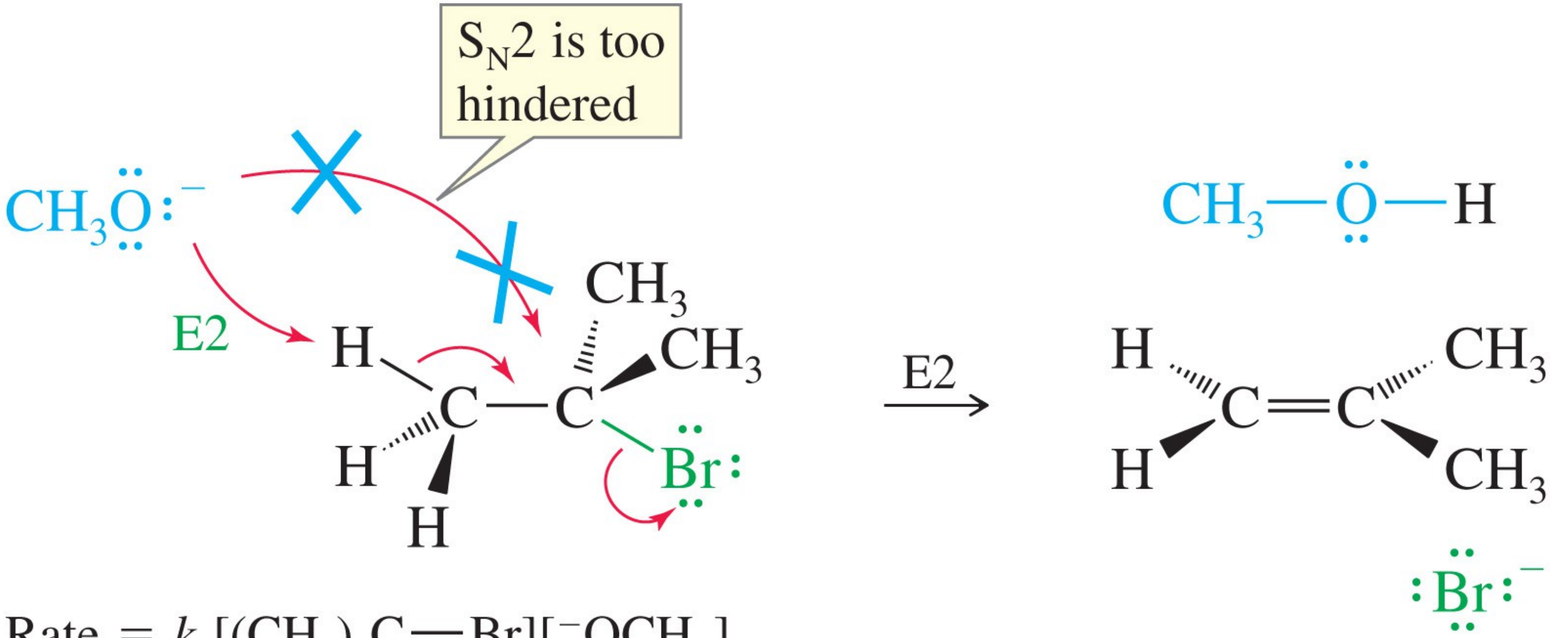


major product
(trisubstituted)

The E2 Reaction

- Elimination, bimolecular
- Requires a strong base
- This is a concerted reaction: the proton is abstracted, the double bond forms and the leaving group leaves, all in one step.

The E2 Mechanism



$\text{Rate} = k_r[(CH_3)_3C{-}Br][^{-}OCH_3]$

- Order of reactivity for alkyl halides:

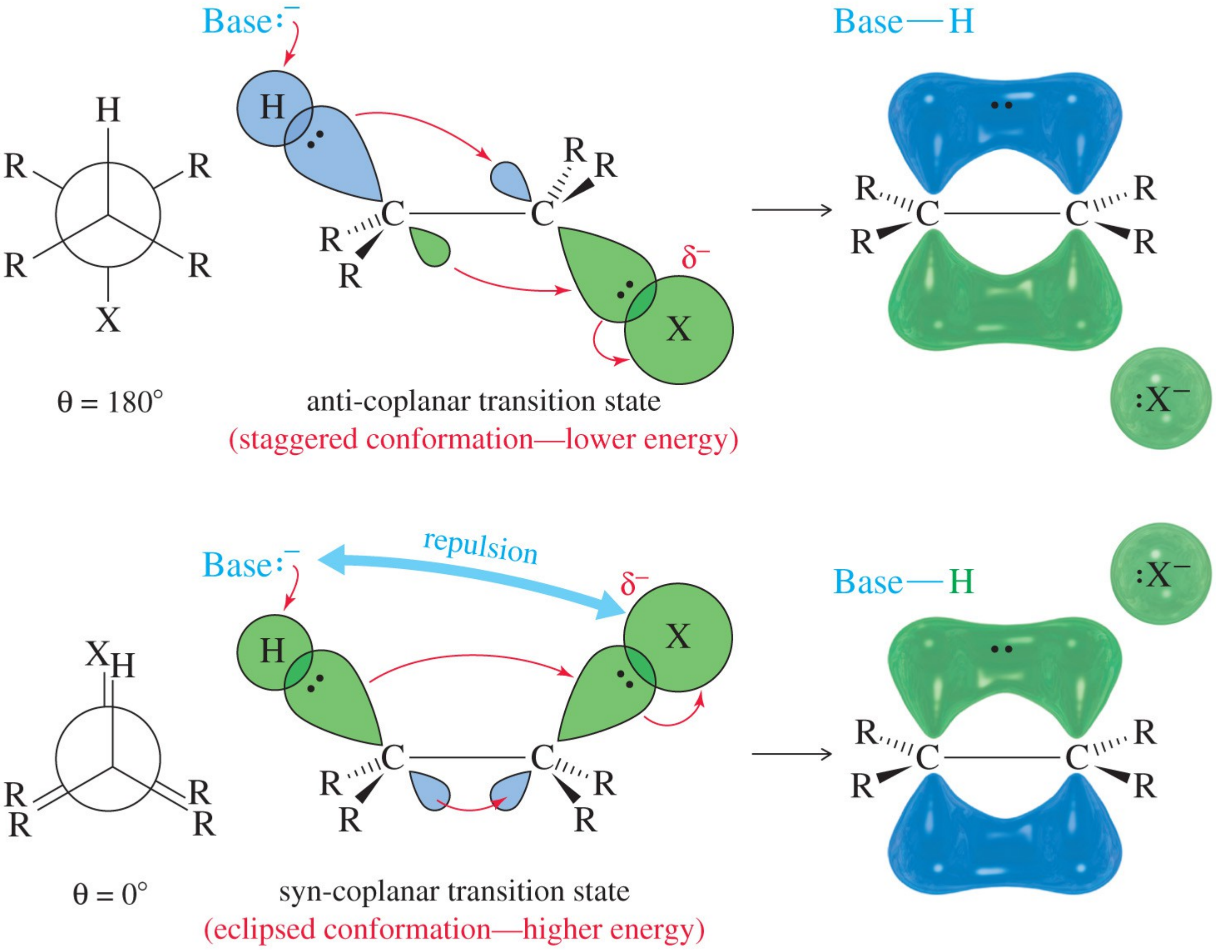
  3° > 2 ° > 1°

- Mixture may form, but Zaitsev product predominates.

E2 Stereochemistry

- The halide and the proton to be abstracted must be anti-coplanar (=180º) to each other for the elimination to occur.
- The orbitals of the hydrogen atom and the halide must be aligned so they can begin to form a pi bond in the transition state.
- The anti-coplanar arrangement minimizes any steric hindrance between the base and the leaving group.

E2 Stereochemistry



E1 or E2 Mechanism?

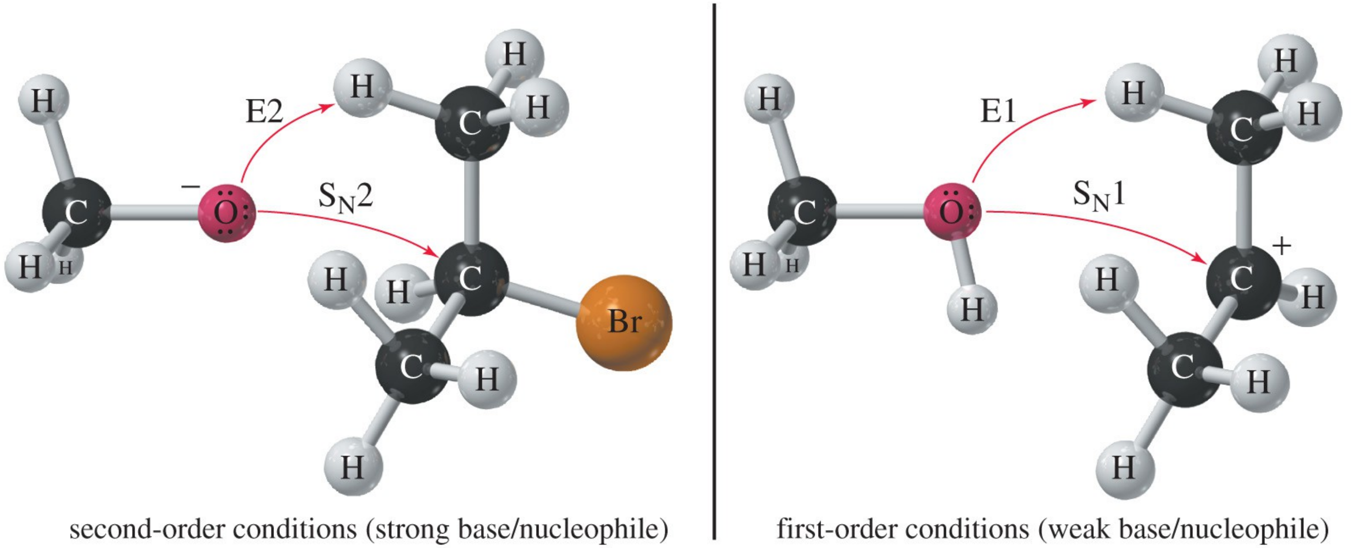
Tertiary > Secondary	Tertiary > Secondary
Base strength unimportant (usually weak)	Strong base required
Good ionizing solvent	Solvent polarity not important.
Rate = k[alkyl halide]	Rate = k[alkylhalide][base]
Zaitsev product	Zaitsev product
No required geometry	Coplanar leaving groups (usually anti)
Rearranged products	No rearrangements

Substitution or Elimination?

- Strength of the nucleophile determines order: Strong nucleophiles or bases promote bimolecular reactions.
- Primary halide usually undergo S_N2.
- Tertiary halide mixture of S_N1, E1 or E2. They cannot undergo S_N2.
- High temperature favors elimination.
- Bulky bases favor elimination.

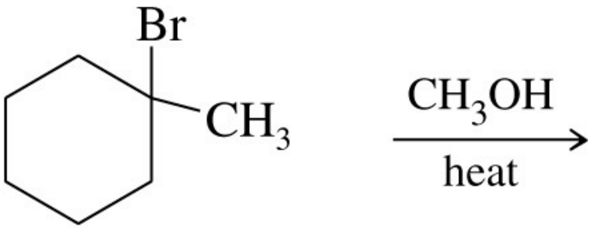
Secondary Alkyl Halides

- Secondary alkyl halides are more challenging:
  - Strong nucleophiles will promote S_N2/E2
  - Weak nucleophiles promote S_N1/E1
- Strong nucleophiles with limited basicity favor S_N2. Bromide and iodide are good examples of these.



Solved Problem 1

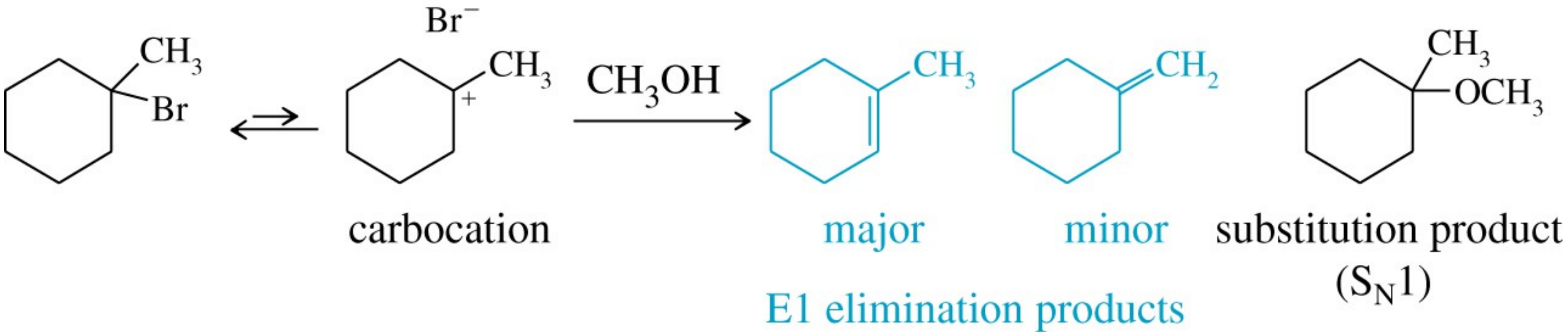
Predict the mechanisms and products of the following reaction.



1-bromo-1-methylcyclohexane

Solution

There is no strong base or nucleophile present, so this reaction must be first order, with an ionization of the alkyl halide as the slow step. Deprotonation of the carbocation gives either of two elimination products, and nucleophilic attack gives a substitution product.



Solved Problem 2

Predict the mechanisms and products of the following reaction.

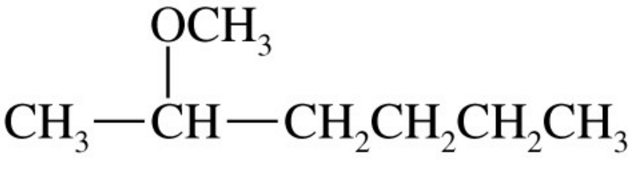
$$\overset{\displaystyle Br}{\overset{|}{CH_3-CH-CH_2CH_2CH_2CH_3}} \xrightarrow[CH_3OH]{NaOCH_3}$$

2-bromohexane

Solution

This reaction takes place with a strong base, so it is second order. This secondary halide can undergo both S_N2 substitution and E2 elimination. Both products will be formed, with the relative proportions of substitution and elimination depending on the reaction conditions.

$$\underbrace{\underset{\text{major}}{CH_3-CH=CH-CH_2CH_2CH_3} \quad \underset{\text{minor}}{CH_2=CH-CH_2CH_2CH_2CH_3}}_{\text{E2 products}}$$



$$\overset{\displaystyle OCH_3}{\overset{|}{CH_3-CH-CH_2CH_2CH_2CH_3}}$$

S_N2 product