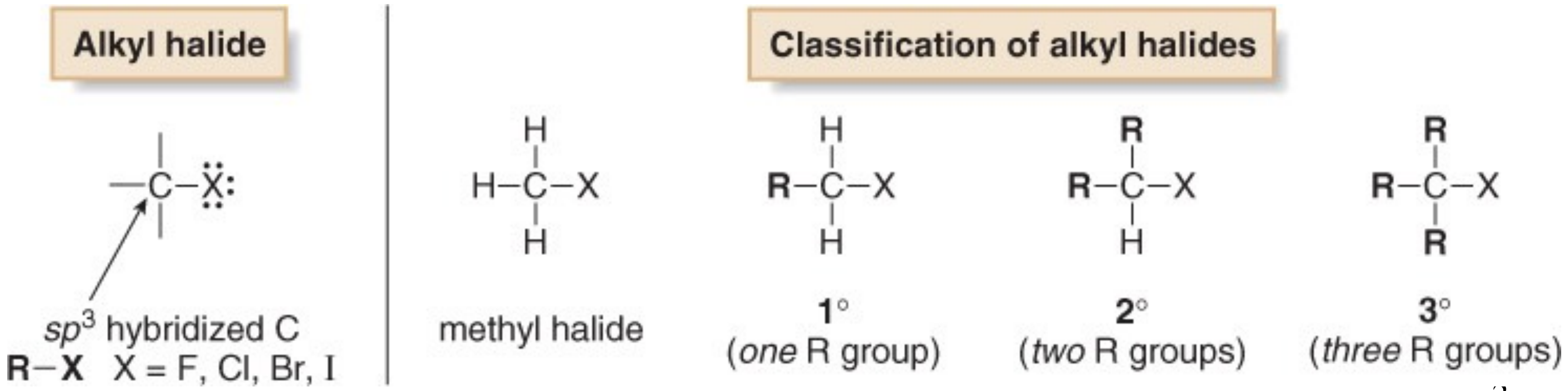
Alkyl Halides

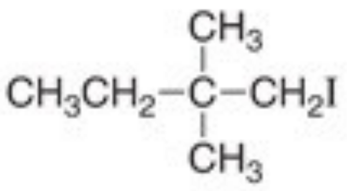
Chapter 10
Organic Chemistry, *8th Edition*
John McMurry

Introduction to Alkyl Halides

- **Alkyl halides** are organic molecules containing a halogen atom bonded to an *sp*^{3} hybridized carbon atom.
- Alkyl halides are classified as primary (1°), secondary (2°), or tertiary (3°), depending on the number of carbons bonded to the carbon with the halogen atom.
- The halogen atom in halides is often denoted by the symbol "X".

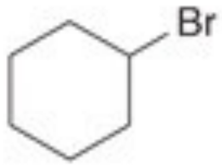


Introduction to Alkyl Halides

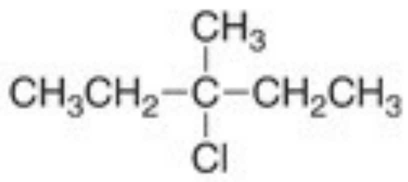


$\mathrm{CH_3CH_2-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{C}}-CH_2I}$

1° iodide

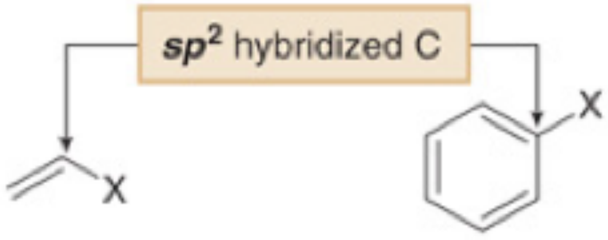


2° bromide



$\mathrm{CH_3CH_2-\underset{\displaystyle Cl}{\overset{\displaystyle CH_3}{C}}-CH_2CH_3}$

3° chloride



vinyl halide

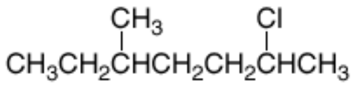
aryl halide

Different reactivity

Nomenclature

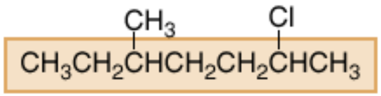
How To Name an Alkyl Halide Using the IUPAC System

Example Give the IUPAC name of the following alkyl halide:



$CH_3CH_2\overset{\overset{CH_3}{|}}{C}HCH_2CH_2\overset{\overset{Cl}{|}}{C}HCH_3$

Step [1] Find the parent carbon chain containing the halogen.



$CH_3CH_2\overset{\overset{CH_3}{|}}{C}HCH_2CH_2\overset{\overset{Cl}{|}}{C}HCH_3$

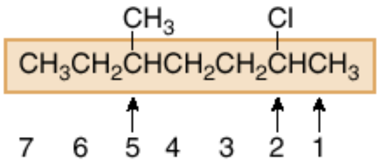
7 C's in the longest chain

7 C's ----→ **heptane**

- Name the parent chain as an ***alkane,*** with the halogen as a substituent bonded to the longest chain.

Step [2] Apply all other rules of nomenclature.

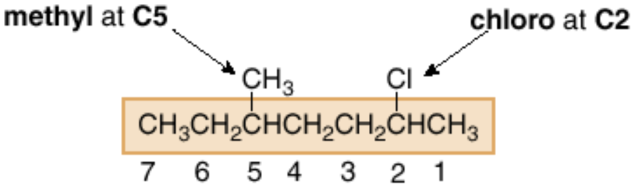
a. **Number** the chain.



$CH_3CH_2\overset{\overset{CH_3}{|}}{C}HCH_2CH_2\overset{\overset{Cl}{|}}{C}HCH_3$

- Begin at the end nearest the first substituent, either alkyl or halogen.

b. **Name** and **number** the substituents.



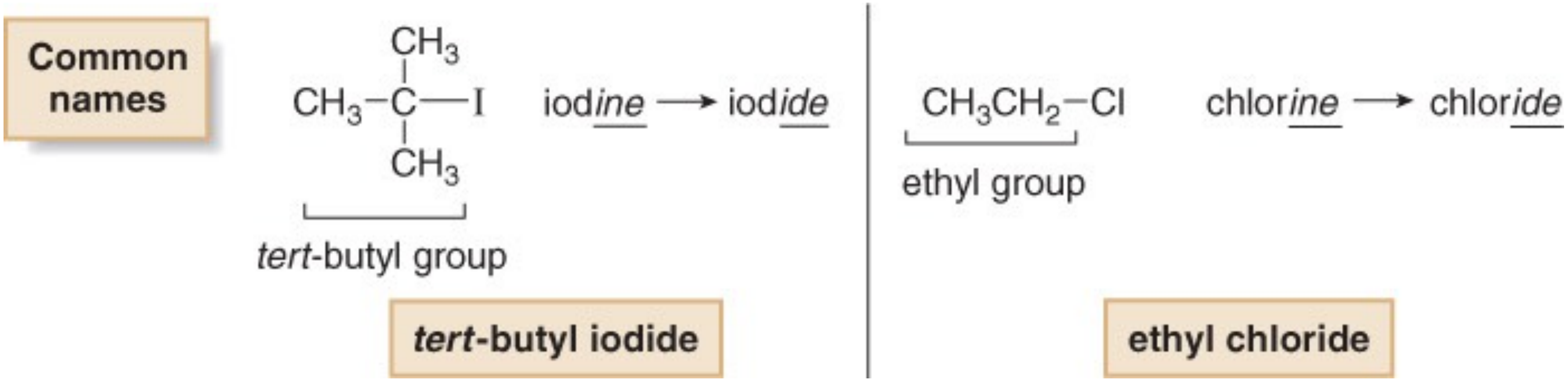
$CH_3CH_2\overset{\overset{CH_3}{|}}{C}HCH_2CH_2\overset{\overset{Cl}{|}}{C}HCH_3$

c. **Alphabetize: c** for **c**hloro, then **m** for **m**ethyl.

ANSWER: 2-chloro-5-methylheptane

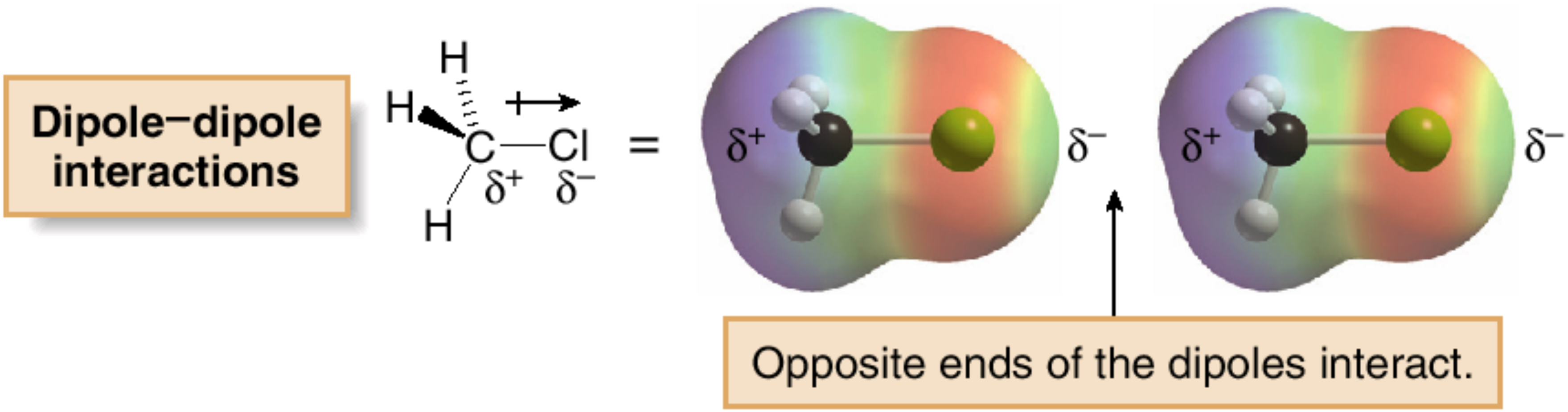
Nomenclature

Common names are often used for simple alkyl halides. To assign a common name:



Physical Properties

Alkyl halides are weak polar molecules. They exhibit dipole-dipole interactions because of their polar C—X bond, but because the rest of the molecule contains only C—C and C—H bonds, they are incapable of intermolecular hydrogen bonding.



Dipole–dipole interactions

Opposite ends of the dipoles interact.

Physical Properties

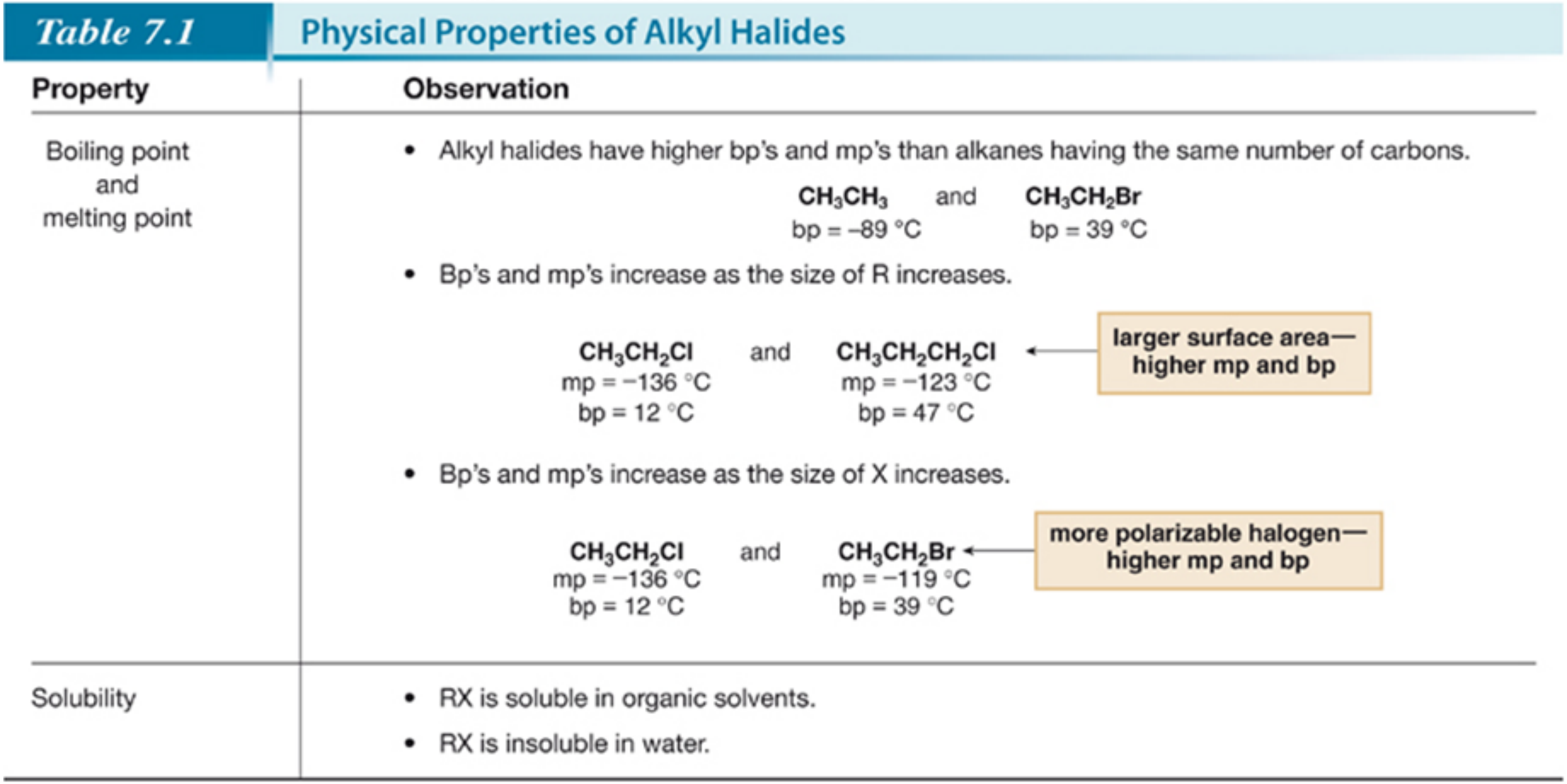
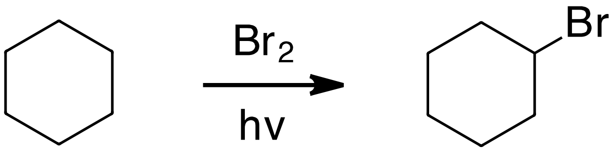


Table 7.1 Physical Properties of Alkyl Halides

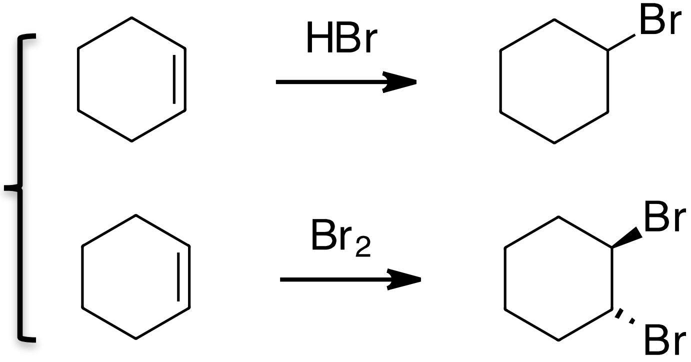
Property	Observation
Boiling point and melting point	• Alkyl halides have higher bp's and mp's than alkanes having the same number of carbons. CH_3CH_3 bp = –89 °C and CH_3CH_2Br bp = 39 °C • Bp's and mp's increase as the size of R increases. CH_3CH_2Cl mp = −136 °C bp = 12 °C and $CH_3CH_2CH_2Cl$ mp = −123 °C bp = 47 °C ← **larger surface area—higher mp and bp** • Bp's and mp's increase as the size of X increases. CH_3CH_2Cl mp = −136 °C bp = 12 °C and CH_3CH_2Br mp = −119 °C bp = 39 °C ← **more polarizable halogen—higher mp and bp**
Solubility	• RX is soluble in organic solvents. • RX is insoluble in water.

Preparation

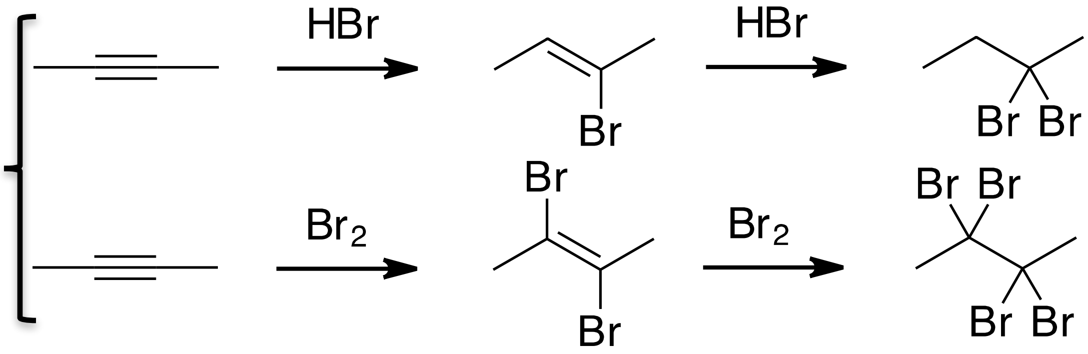
From alkanes



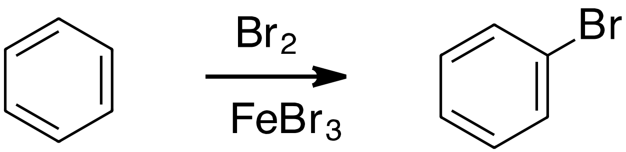
From alkenes



From alkynes



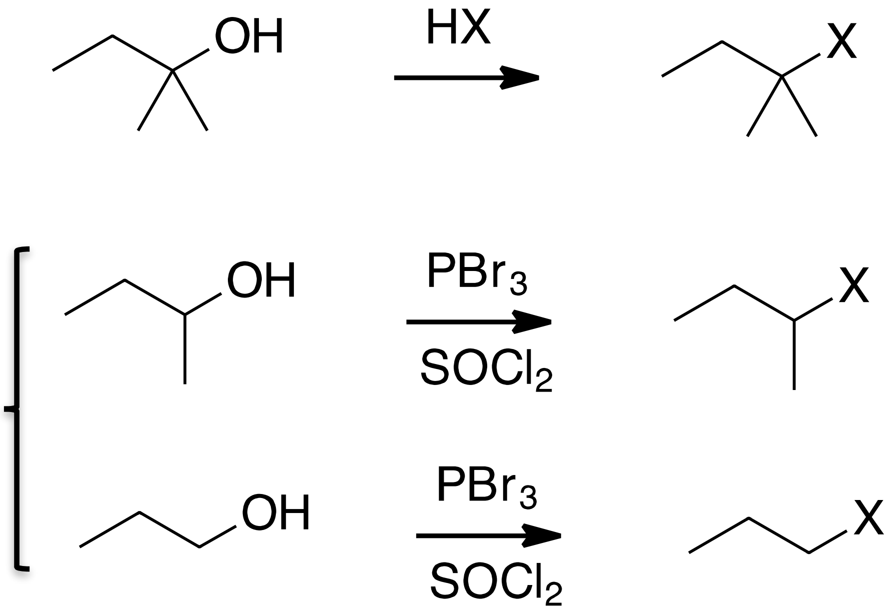
Aryl halides:



Preparation from alcohols

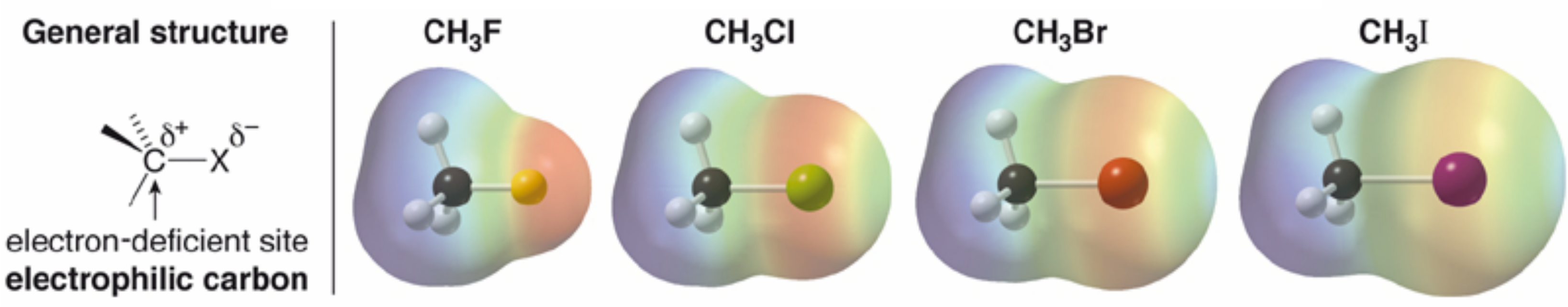
tertiary

primary and secondary



The Polar Carbon-Halogen Bond

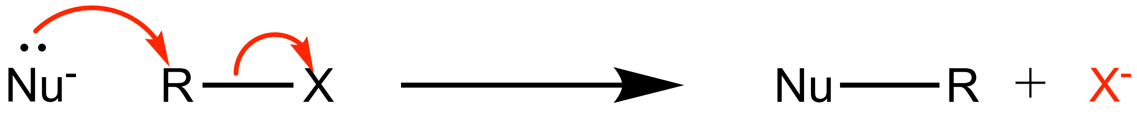
The electronegative halogen atom in alkyl halides creates a polar C—X bond, making the carbon atom electron deficient. Electrostatic potential maps of four simple alkyl halides illustrate this point.



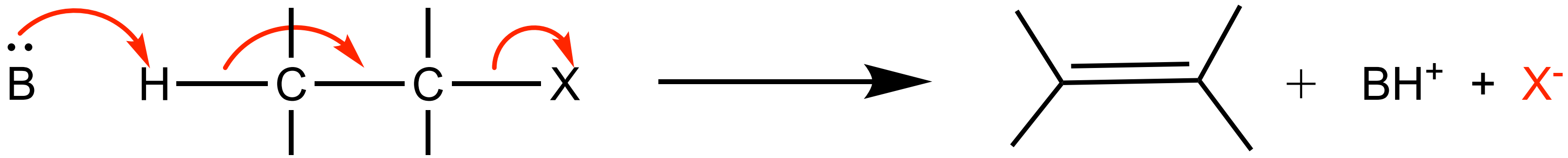
- The polar C−X bond makes the carbon atom *electron deficient* in each CH_3X molecule.

The Polar Carbon-Halogen Bond

- **Alkyl halides undergo substitution reactions with nucleophiles.**



- **Alkyl halides undergo elimination reactions with Brønsted–Lowry bases.**



Nucleophilic Substitution

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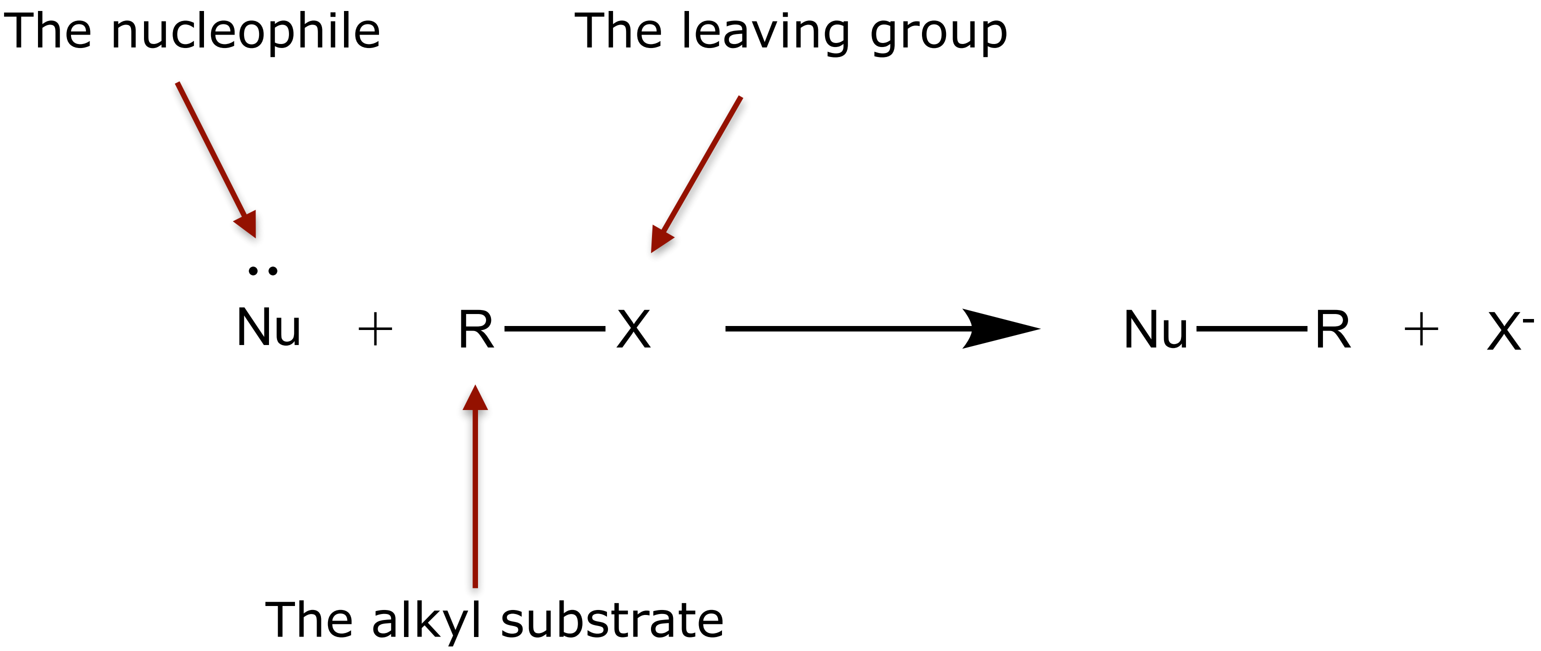
Nucleophilic Substitutions



The nucleophile

The leaving group

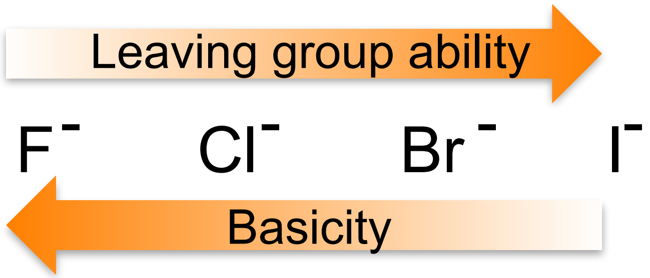
$$\ddot{Nu} + R-X \longrightarrow Nu-R + X^-$$

The alkyl substrate

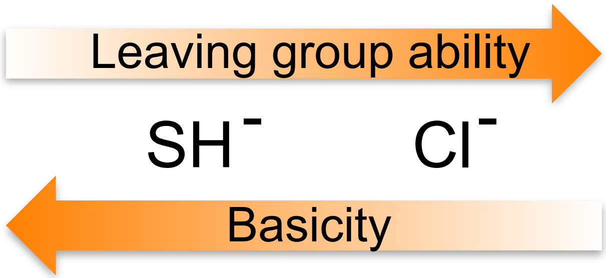
The Leaving Group

Stable species are good leaving groups.

- Leaving group ability increases down a period:

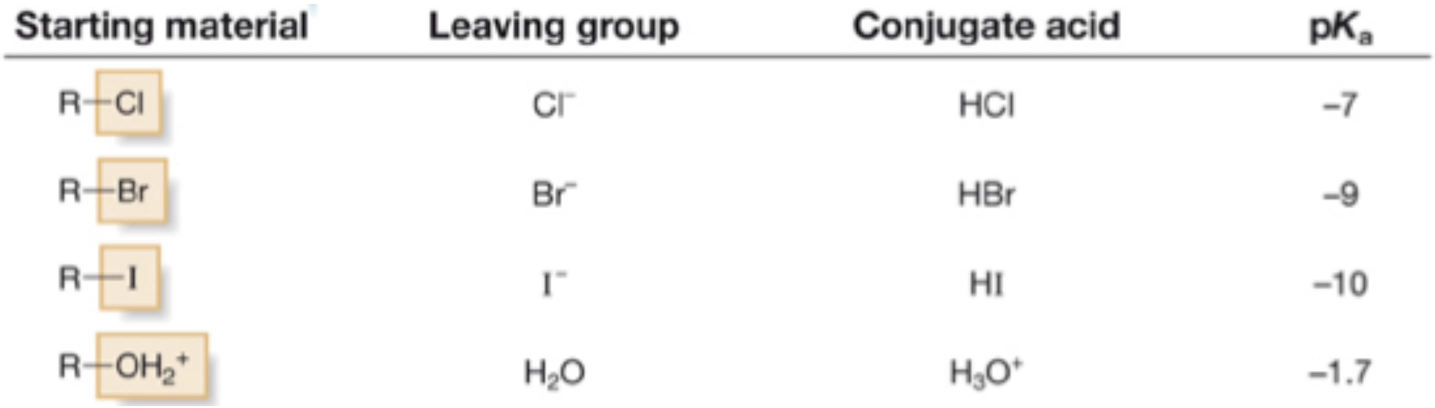


- Leaving group ability increases from left to right across a group:



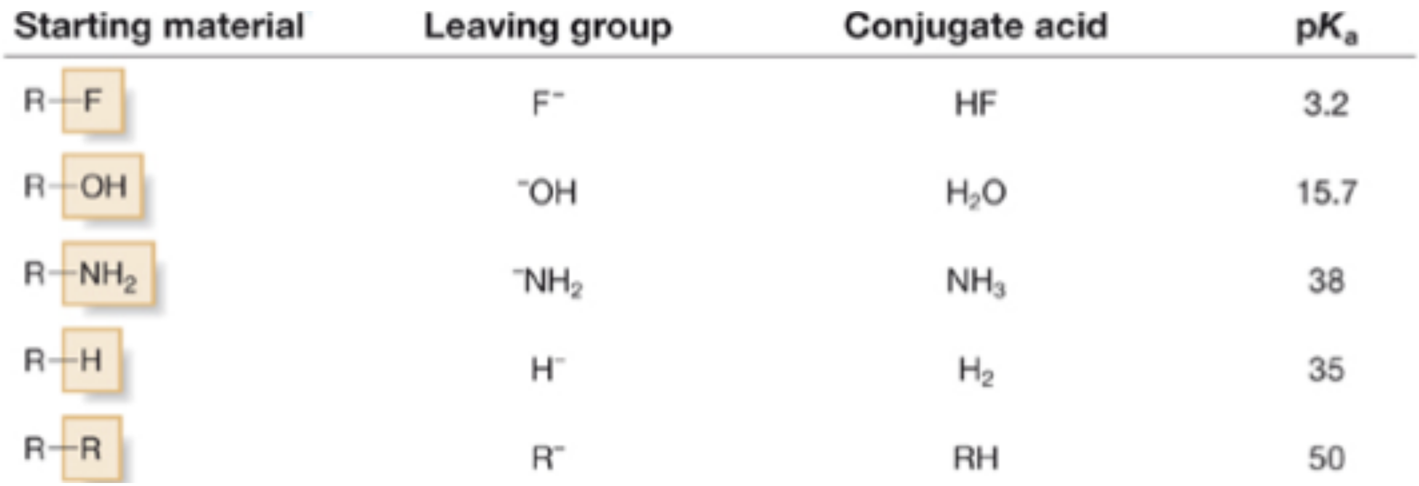
The Leaving Group

These molecules undergo nucleophilic substitution



Starting material	Leaving group	Conjugate acid	pK_a
$R-Cl$	Cl^-	HCl	–7
$R-Br$	Br^-	HBr	–9
$R-I$	I^-	HI	–10
$R-OH_2^+$	H_2O	H_3O^+	–1.7

These molecules do not undergo nucleophilic substitution



Starting material	Leaving group	Conjugate acid	pK_a
$R-F$	F^-	HF	3.2
$R-OH$	^-OH	H_2O	15.7
$R-NH_2$	$^-NH_2$	NH_3	38
$R-H$	H^-	H_2	35
$R-R$	R^-	RH	50

The Nucleophile

- Nucleophilicity is correlated to basicity.
- Although nucleophilicity and basicity are interrelated, they are fundamentally different.

  - Basicity is a thermodynamic property.

$$\mathrm{B{:}} + \mathrm{H_2O} \xrightleftharpoons{K_B} \mathrm{BH^+} + \mathrm{OH^-}$$

  - Nucleophilicity is a kinetic property.

$$\mathrm{Nu{:}} + \mathrm{E} \xrightarrow{k_{Nu}} \mathrm{Nu\text{-}E}$$

The Nucleophile

- For two nucleophiles with the same nucleophilic atom, the stronger base is the stronger nucleophile.

  HO^- is a stronger nucleophile than CH_3COO^-.
  (pK_a: $H_2O = 15.7$, $CH_3COOH = 4.8$).

- A negatively charged nucleophile is always a stronger nucleophile than its conjugate acid.

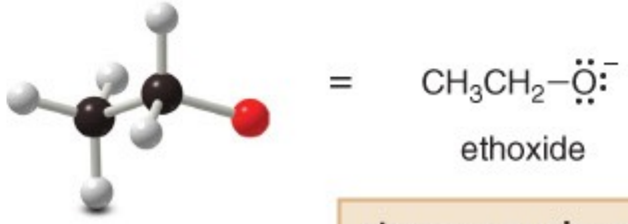
  HO^- is a stronger base and stronger nucleophile than H_2O.

- Right-to-left across a row of the periodic table, nucleophilicity increases as basicity increases:

  NH_3 is a stronger base and stronger nucleophile than H_2O.

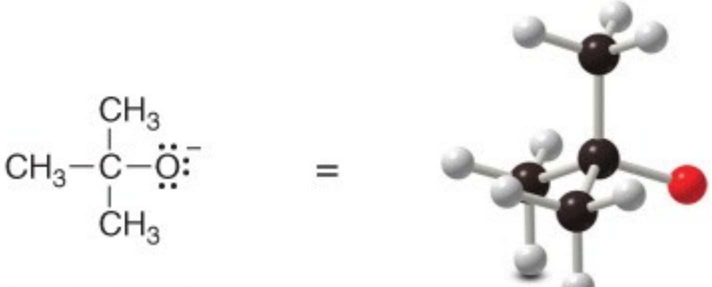
The Nucleophile

- Nucleophilicity does not parallel basicity when steric hindrance becomes important.
- Steric hindrance results from the presence of bulky groups at the site of a reaction.
- Steric hindrance decreases nucleophilicity but not basicity.
- Sterically hindered bases that are poor nucleophiles are called non-nucleophilic bases.


$$= CH_3CH_2-\ddot{\underset{\cdot\cdot}{O}}:^-$$

ethoxide

stronger nucleophile


$$CH_3-\overset{CH_3}{\underset{CH_3}{\overset{|}{\underset{|}{C}}}}-\ddot{\underset{\cdot\cdot}{O}}:^- =$$

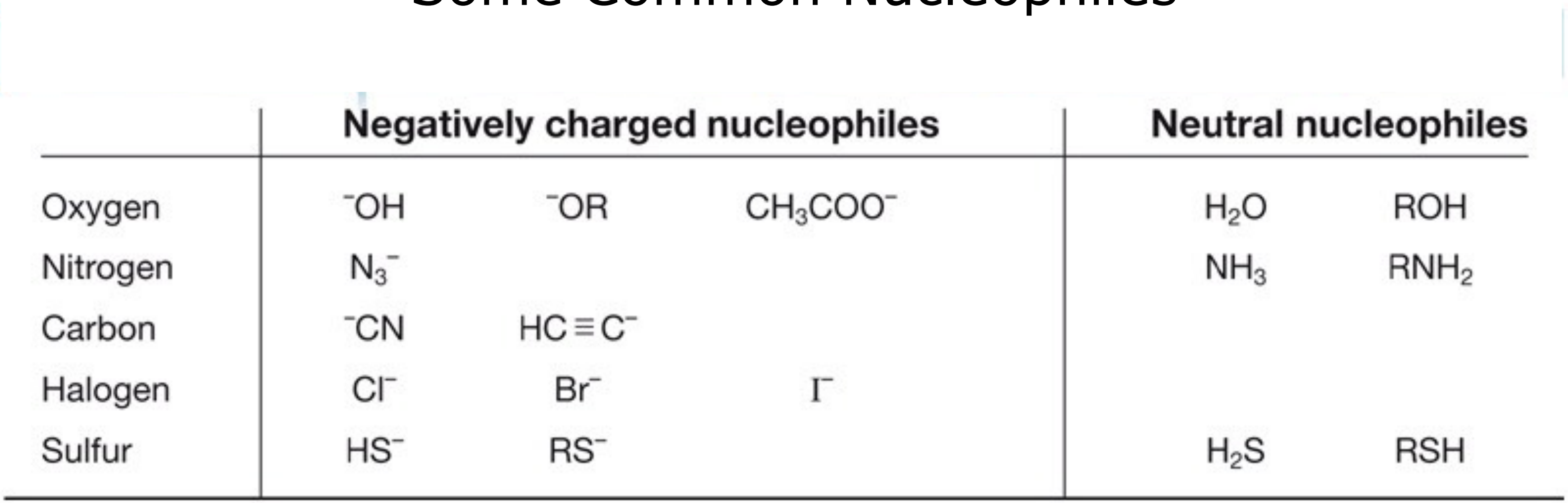
tert-butoxide

stronger base

Three CH_3 groups sterically hinder the O atom, making it a **weaker nucleophile.**

The Nucleophile

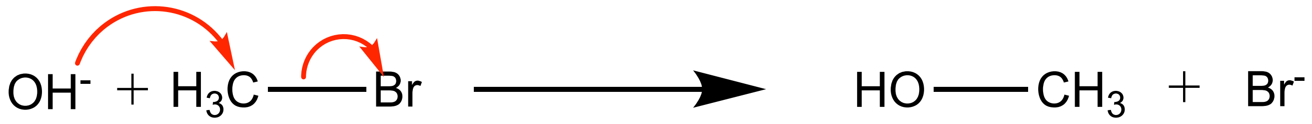
Some Common Nucleophiles



	Negatively charged nucleophiles			Neutral nucleophiles	
Oxygen	^-OH	^-OR	CH_3COO^-	H_2O	ROH
Nitrogen	N_3^-			NH_3	RNH_2
Carbon	^-CN	$HC\equiv C^-$			
Halogen	Cl^-	Br^-	I^-		
Sulfur	HS^-	RS^-		H_2S	RSH

Mechanisms

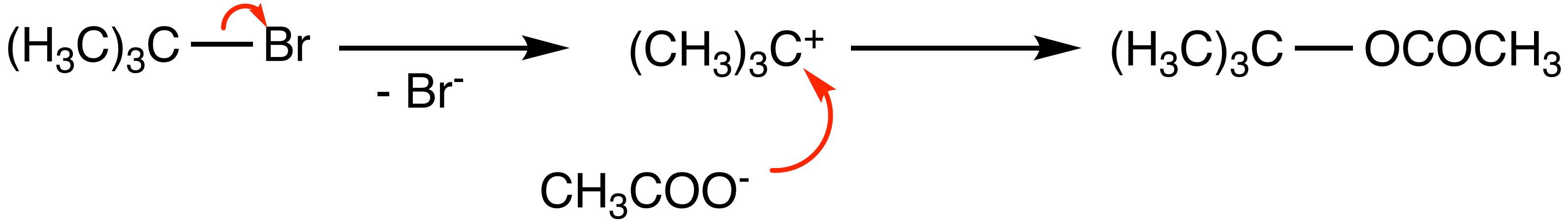
Bond making and bond breaking occur at the same time. S_N2



$$OH^- + H_3C{-}Br \longrightarrow HO{-}CH_3 + Br^-$$

one-step mechanism

Bond breaking occurs before bond making. S_N1



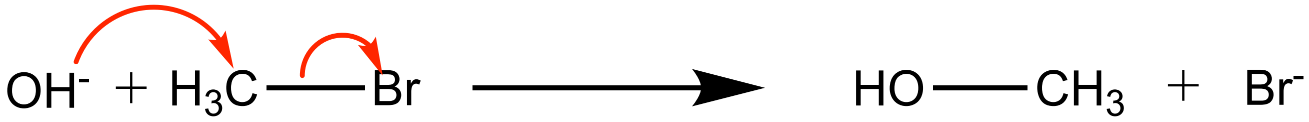
$$(H_3C)_3C{-}Br \xrightarrow[-\,Br^-]{} (CH_3)_3C^+ \longrightarrow (H_3C)_3C{-}OCOCH_3$$

CH_3COO^-

two-step mechanism

SN2 Mechanism: Kinetics

Bond making and bond breaking occur at the same time.

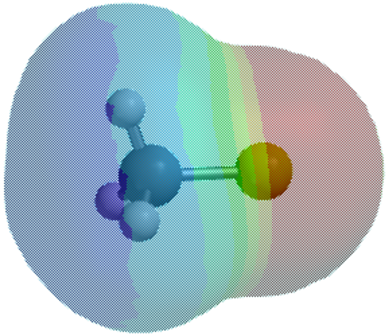


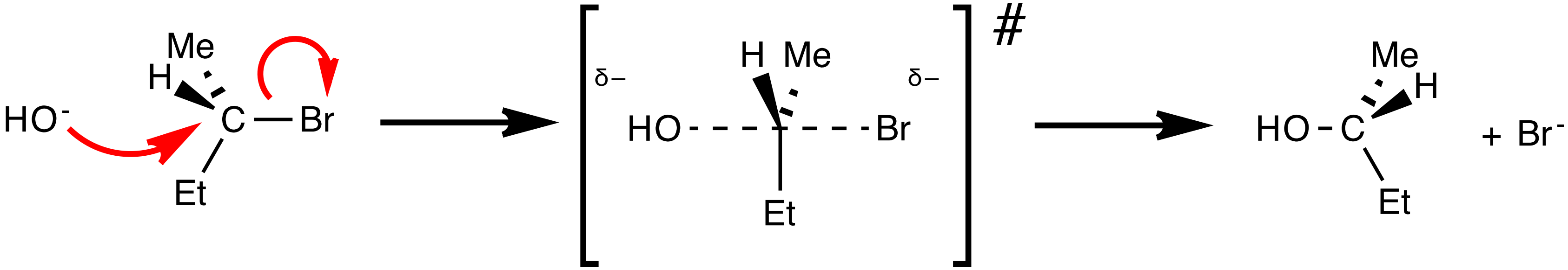
$$v = k[OH^-][CH_3Br]$$

2nd order rate equation; depends on both the nucleophile and the substrate

S_N2 Mechanism: Stereochemistry

All S_N2 reactions proceed with backside attack of the nucleophile, resulting in inversion of configuration at a stereogenic center.

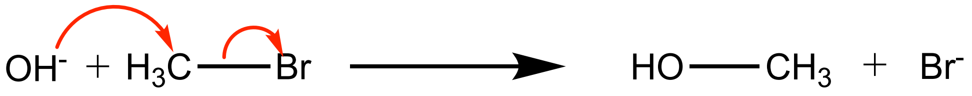




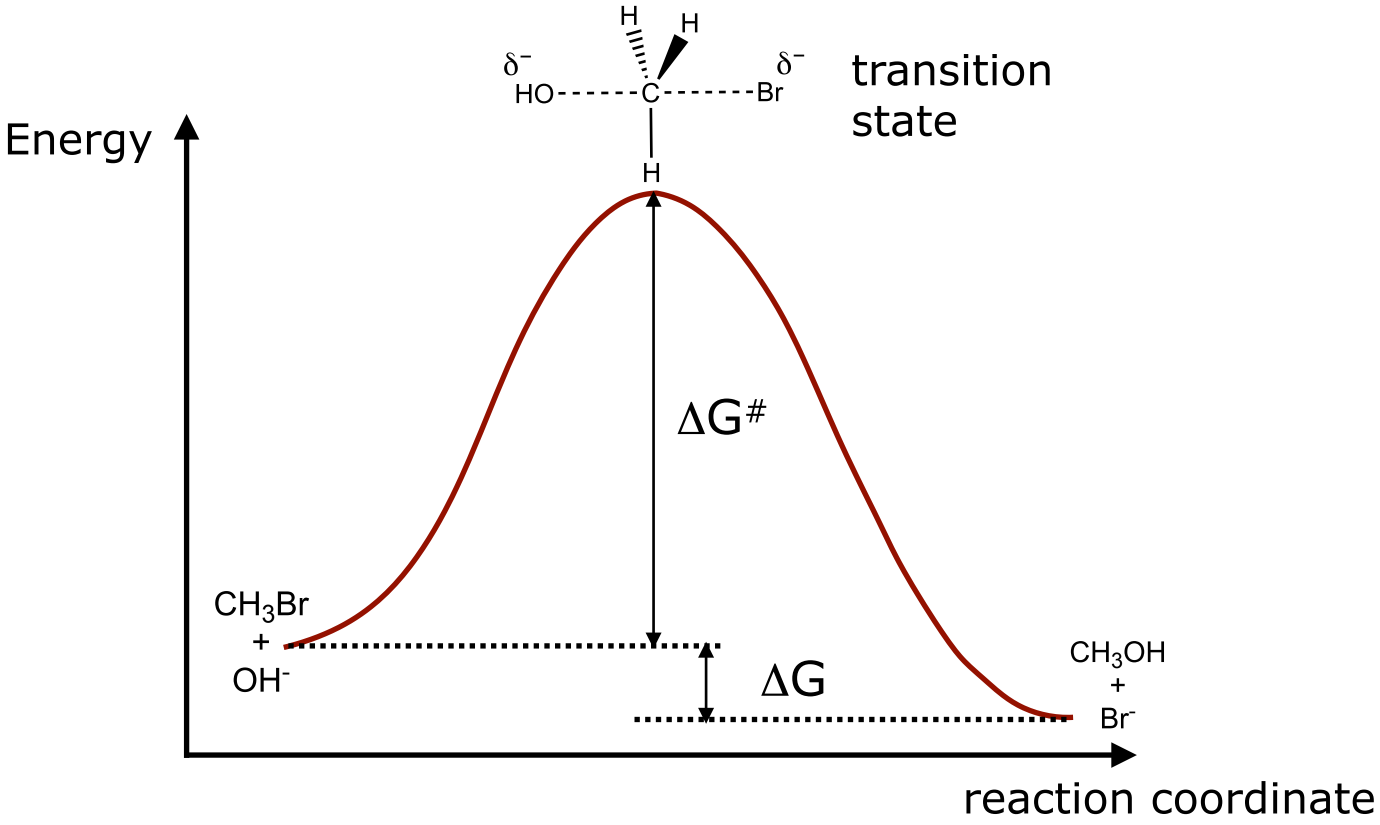
:Nu- and Br- are 180° away from each other, on either side of a plane containing C, H, Me, Et

S_N2 Mechanism: Energy Profile

Energy profile for the reaction:



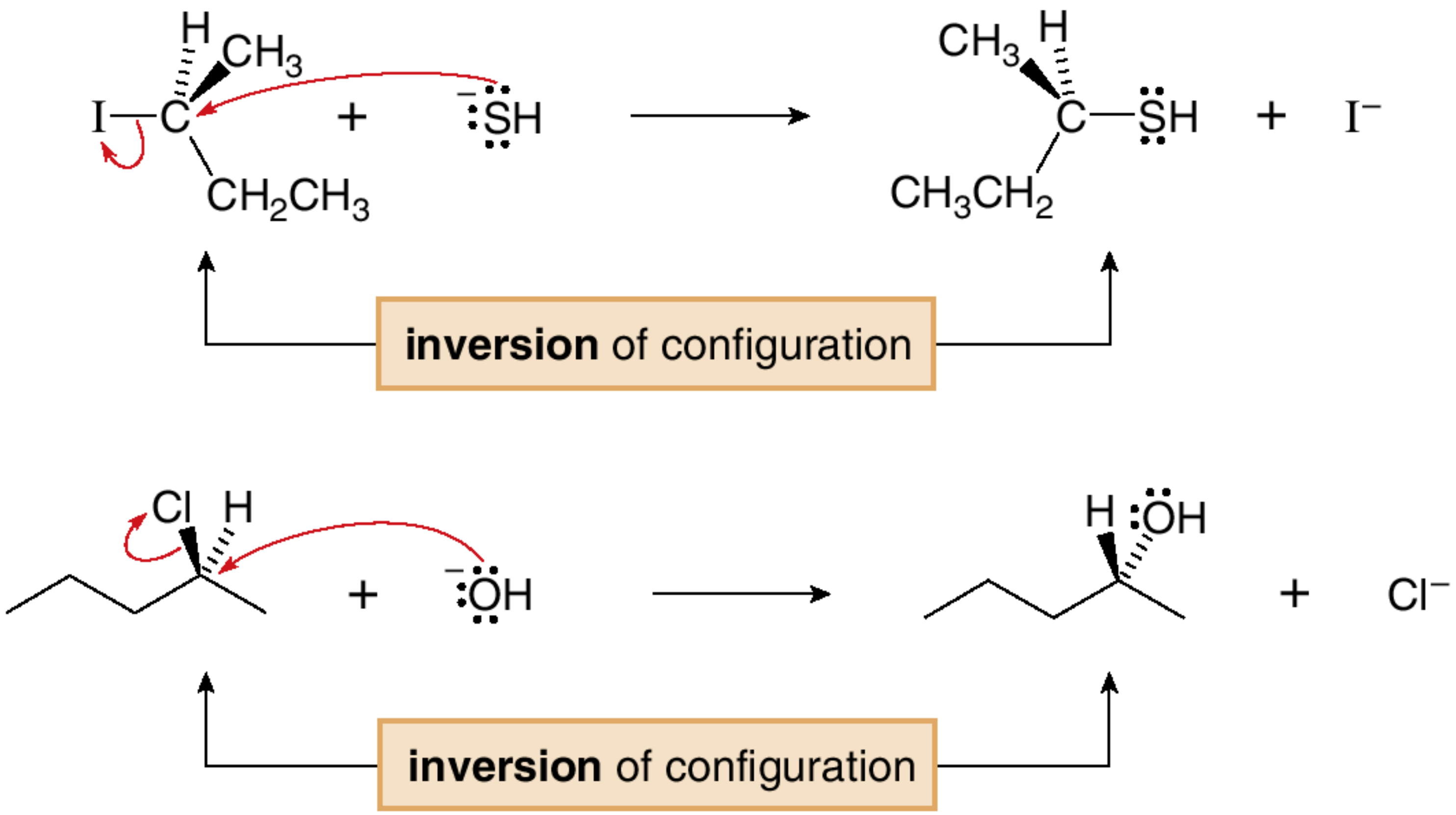
$OH^- + H_3C{-}Br \longrightarrow HO{-}CH_3 + Br^-$



- In the transition state, the C–Br bond is partially broken, the C–O bond is partially formed, and both the attacking nucleophile and the departing leaving group bear a partial negative charge.

S_N2 Mechanism: Stereochemistry

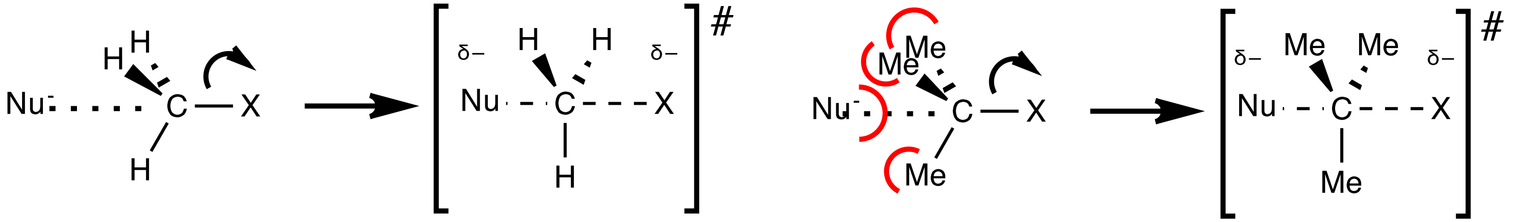
- The bond to the nucleophile in the product is always on the **opposite side** relative to the bond to the leaving group in the starting material.



S_N2 Reaction: The Alkyl Substrate

- Increasing the number of R groups on the carbon with the leaving group makes the approach of the nucleophile more difficult and increases crowding in the transition state.

- The S_N2 reaction is fastest with unhindered halides.

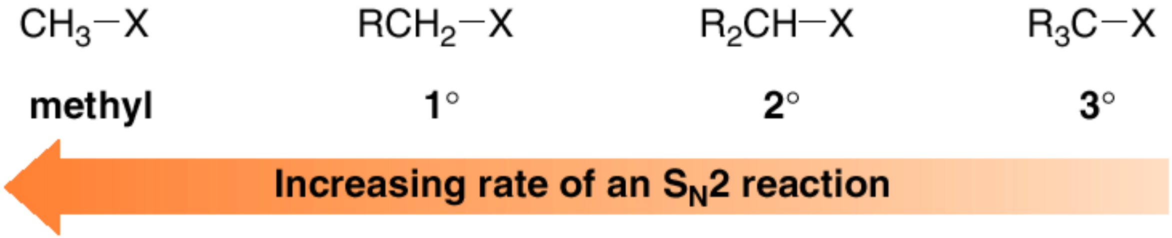


hindered approach

crowded transition state

The Alkyl Substrate

- As the number of R groups on the carbon with the leaving group *increases*, the rate of an S_N2 reaction *decreases*.



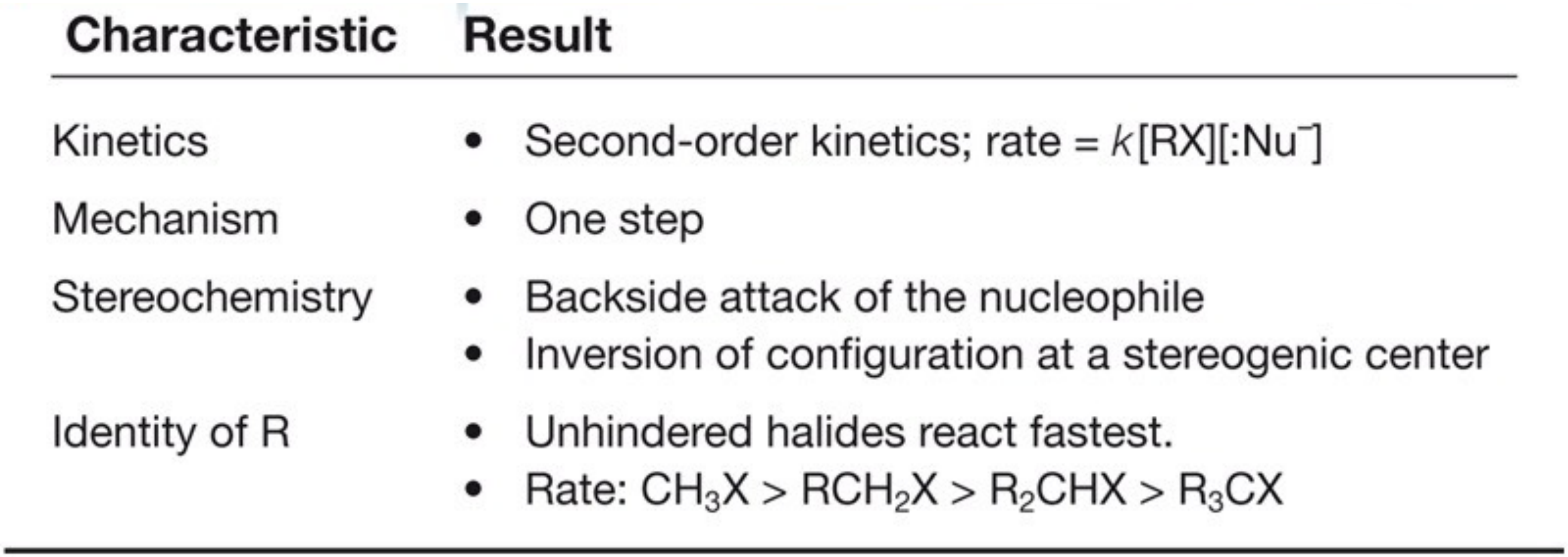
This order of reactivity can be explained by steric effects.

- Methyl and 1° alkyl halides undergo S_N2 reactions with ease.

- 2° Alkyl halides react more slowly.

- 3° Alkyl halides do not undergo S_N2 reactions.

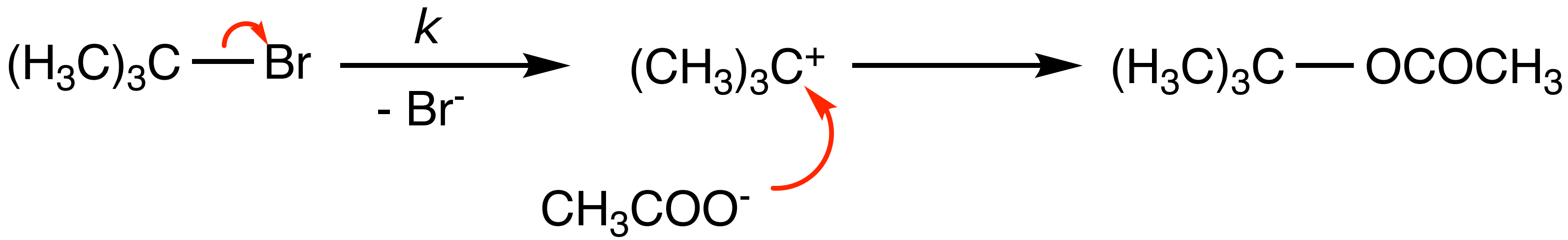
S_N2 Mechanism



Characteristic	Result
Kinetics	• Second-order kinetics; rate = k[RX][:Nu$^-$]
Mechanism	• One step
Stereochemistry	• Backside attack of the nucleophile • Inversion of configuration at a stereogenic center
Identity of R	• Unhindered halides react fastest. • Rate: $CH_3X > RCH_2X > R_2CHX > R_3CX$

S_N1 Mechanism: Kinetics

Bond breaking occurs before bond making.

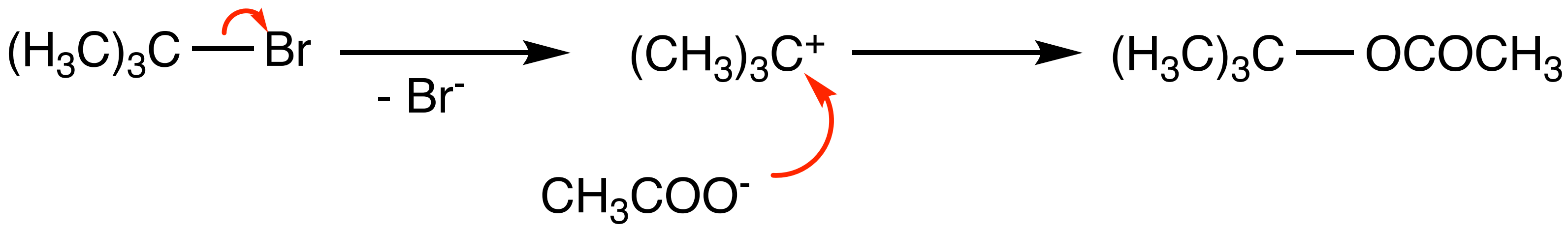


- In the S_N1 mechanism carbocations are formed as reactive intermediates.
- The first step (bond breaking) is slow; the second step (bond making) is fast.

$$v = k[(CH_3)_3CBr]$$

- 1st order rate equation; depends only on the substrate

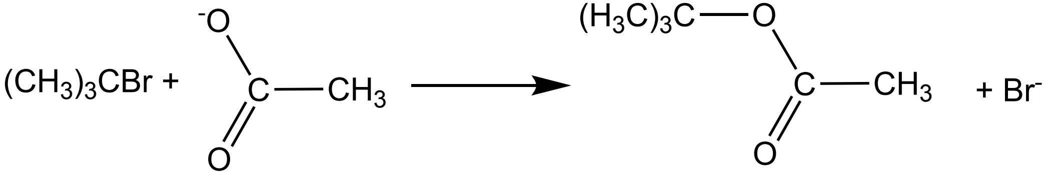
S_N1 Mechanism: Kinetics

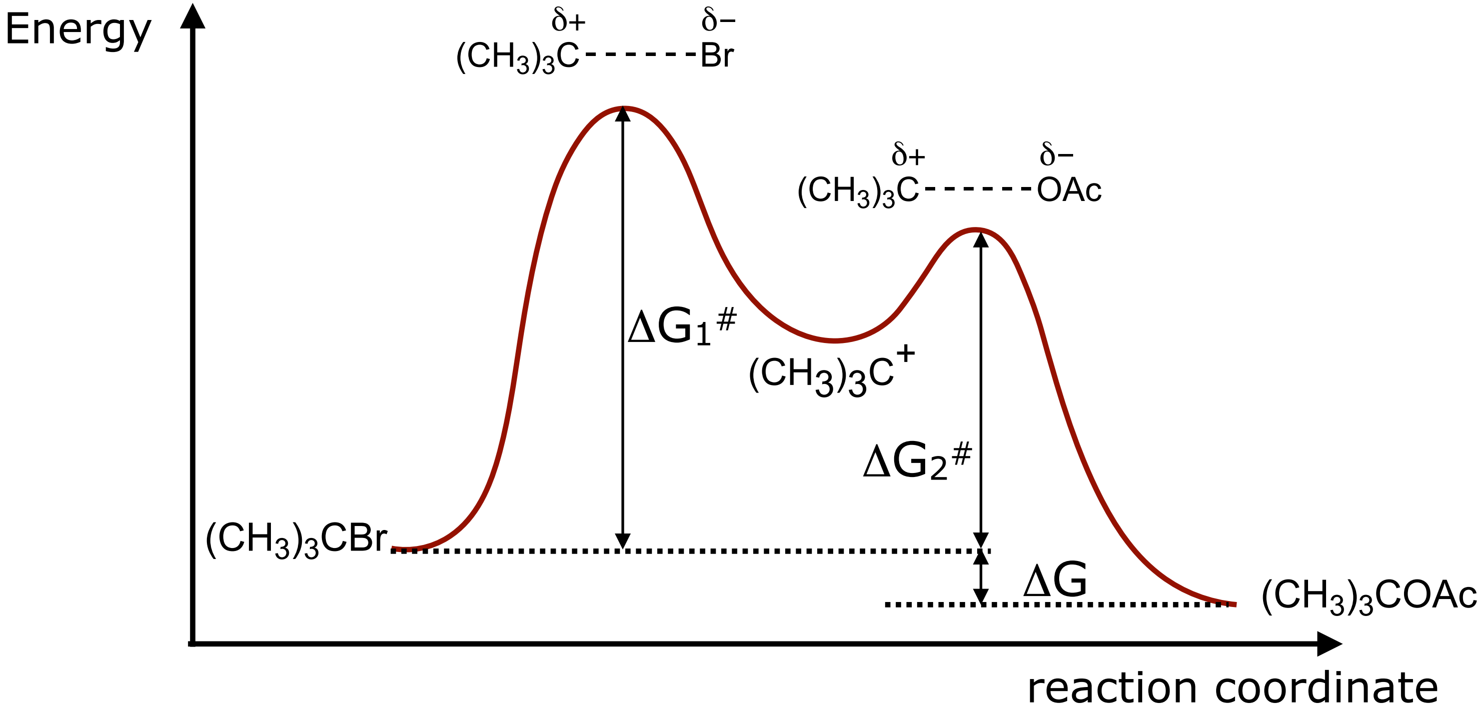


$$v = k[(CH_3)_3CBr]$$

1st order rate equation; depends only on the substrate

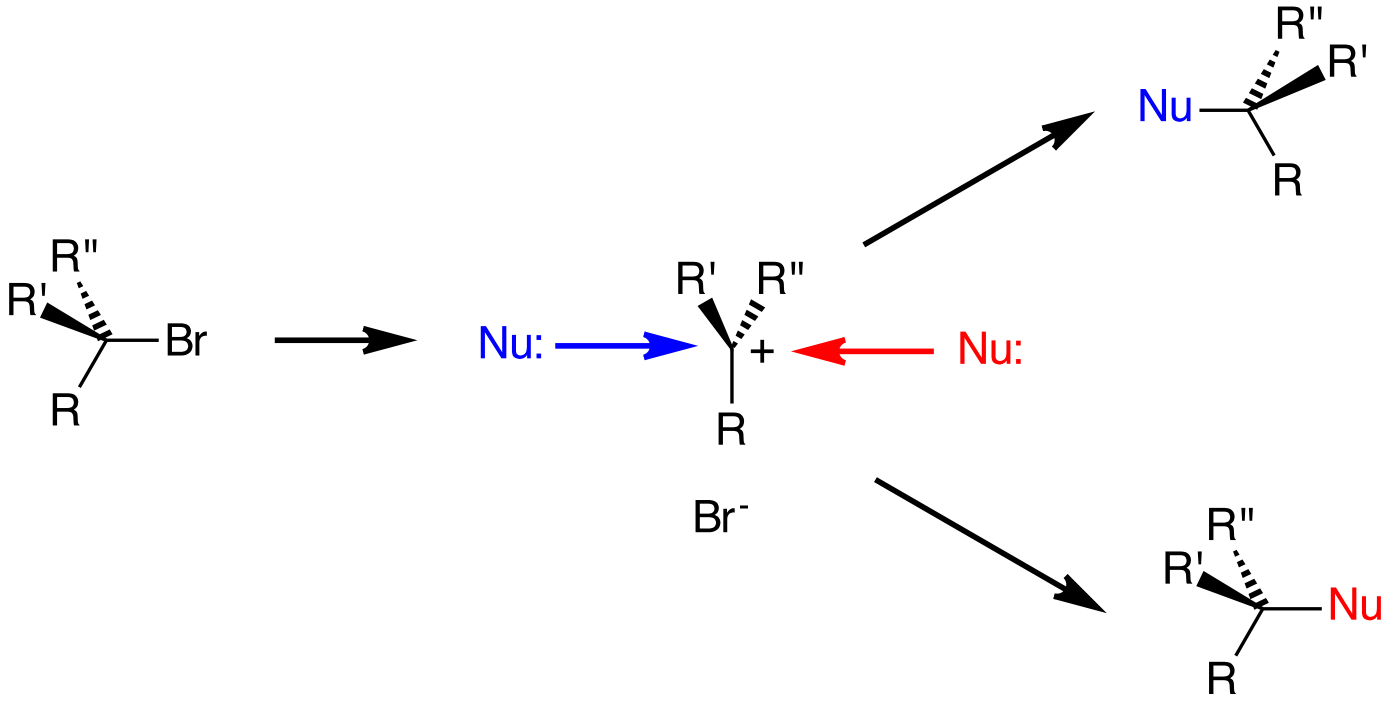
S_N1 Mechanism: Energetics



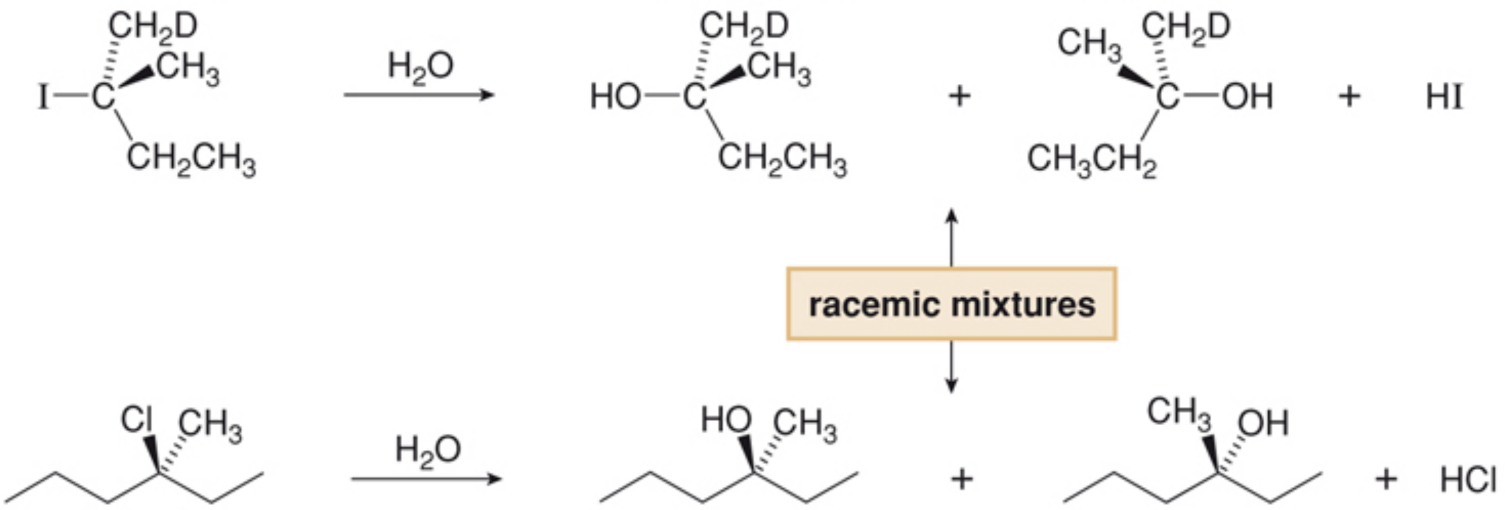


S_N1 Mechanism. Stereochemistry

- Loss of the leaving group in Step [1] generates a planar carbocation that is achiral.
- In Step [2], attack of the nucleophile can occur on either side to afford two products which are a pair of enantiomers. Racemization has occurred.



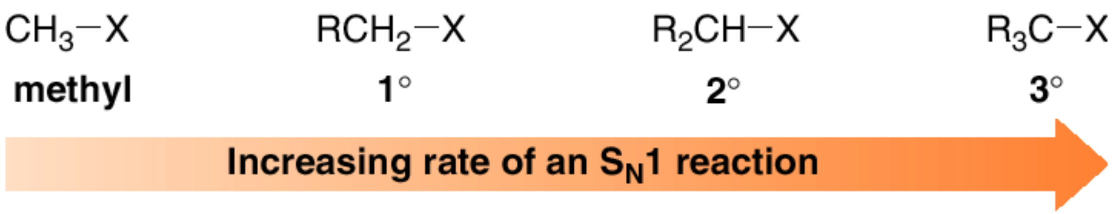
S_N1 Mechanism: Stereochemistry



- Nucleophilic substitution of each starting material by an S_N1 mechanism forms a **racemic mixture** of two products.
- With H_2O, a neutral nucleophile, the initial product of nucleophilic substitution (ROH_2^+) loses a proton to form the final neutral product, ROH (Section 7.6).

The Alkyl Substrate

- As the number of R groups on the carbon with the leaving group *increases,* the rate of an S_N1 reaction *increases.*



$CH_3{-}X$ | $RCH_2{-}X$ | $R_2CH{-}X$ | $R_3C{-}X$

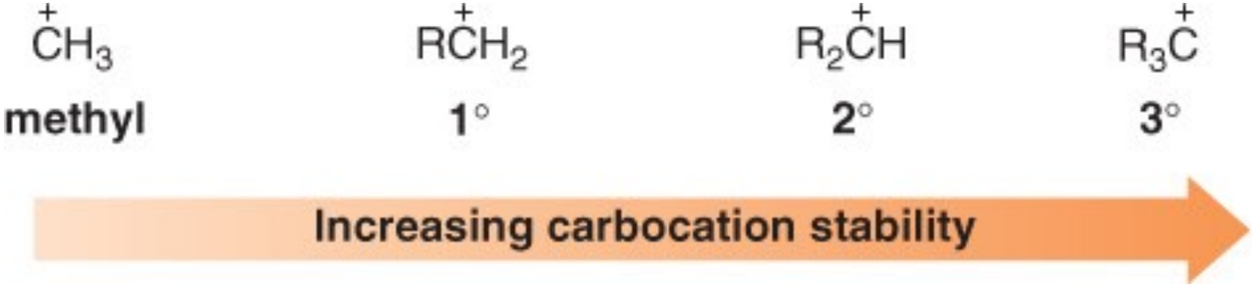
methyl | **1°** | **2°** | **3°**

Increasing rate of an S_N1 reaction

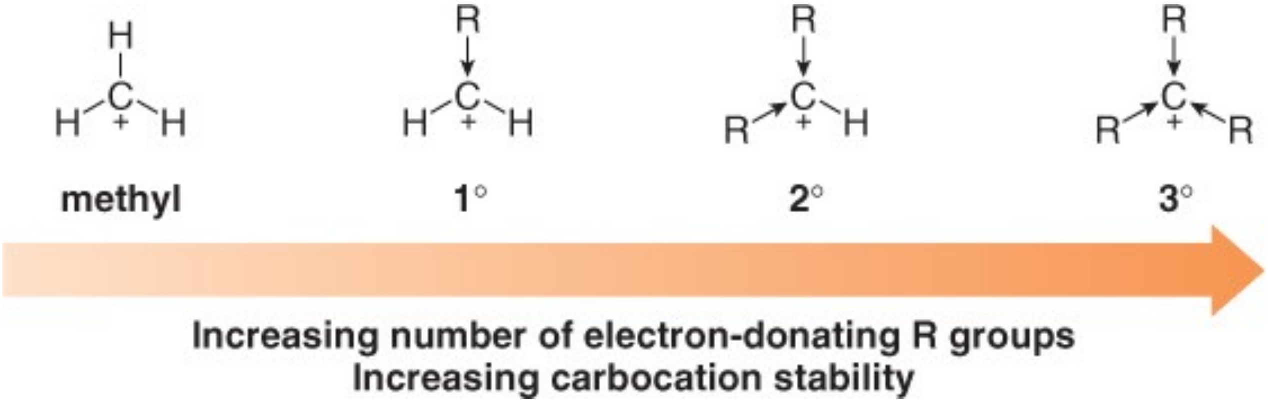
- 3° Alkyl halides undergo S_N1 reactions rapidly.
- 2° Alkyl halides react more slowly.
- Methyl and 1° alkyl halides do *not* undergo S_N1 reactions.

This trend is exactly opposite to that observed in S_N2 reactions and reflects the stability of the carbocation.

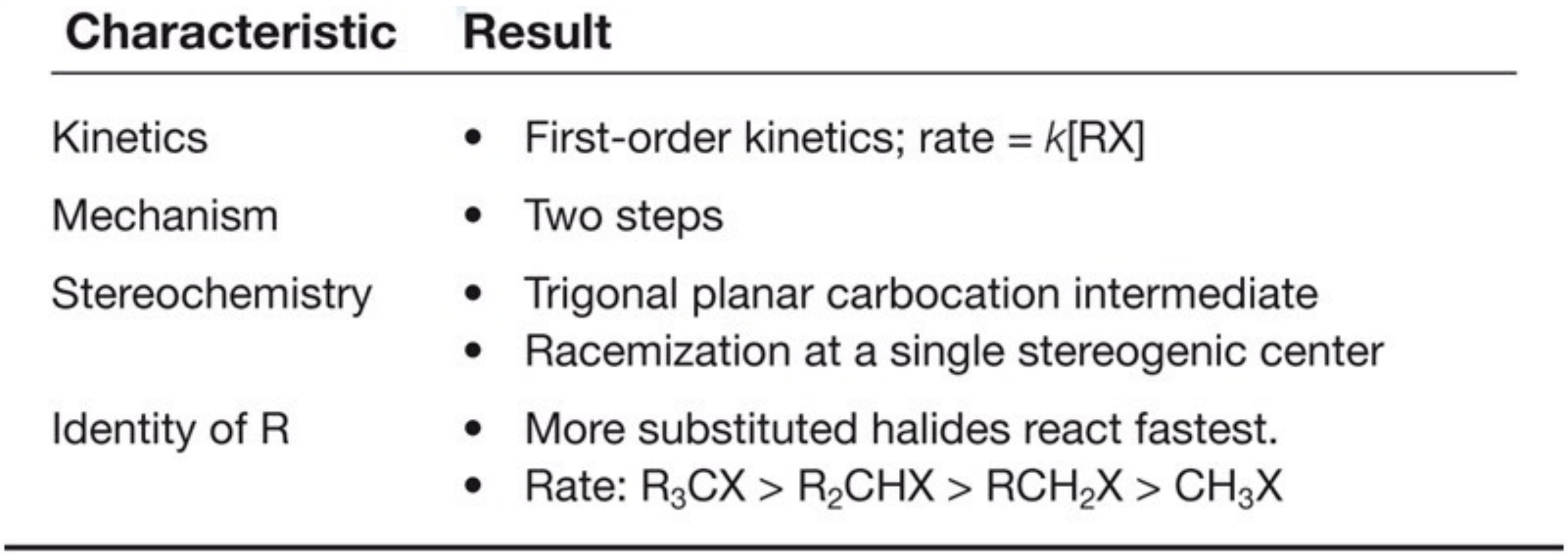
Carbocation Stability



Alkyl groups are electron donating. Since an alkyl group has several σ bonds, each containing electron density, it is more polarizable than a hydrogen atom, and better able to donate electron density.



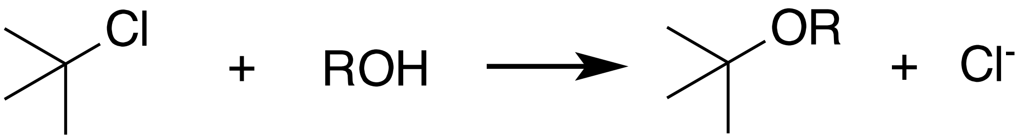
S_N1 Mechanism



Characteristic	Result
Kinetics	• First-order kinetics; rate = k[RX]
Mechanism	• Two steps
Stereochemistry	• Trigonal planar carbocation intermediate • Racemization at a single stereogenic center
Identity of R	• More substituted halides react fastest. • Rate: $R_3CX > R_2CHX > RCH_2X > CH_3X$

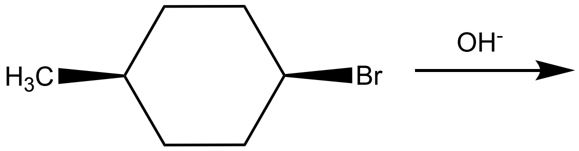
S_N1 and S_N2 Mechanisms

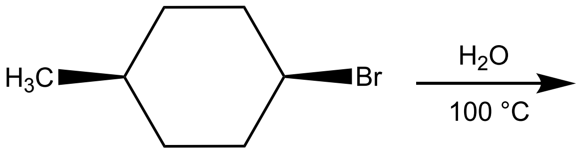
- Substrate: 1^{ry} - S_N2; 2^{ry} - S_N2 or S_N1; 3^{ry} - S_N1
- Leaving group: the same reactivity order in S_N1 and S_N2 reactions.
- Nucleophile: has little effect in S_N1 reactions because it reacts after the slow step (must be nonbasic to prevent elimination). Good nucleophiles favour S_N2 reactions.
- Solvent: polar solvents favor the S_N1 reaction by stabilizing the intermediate carbocation (Hammond postulate).



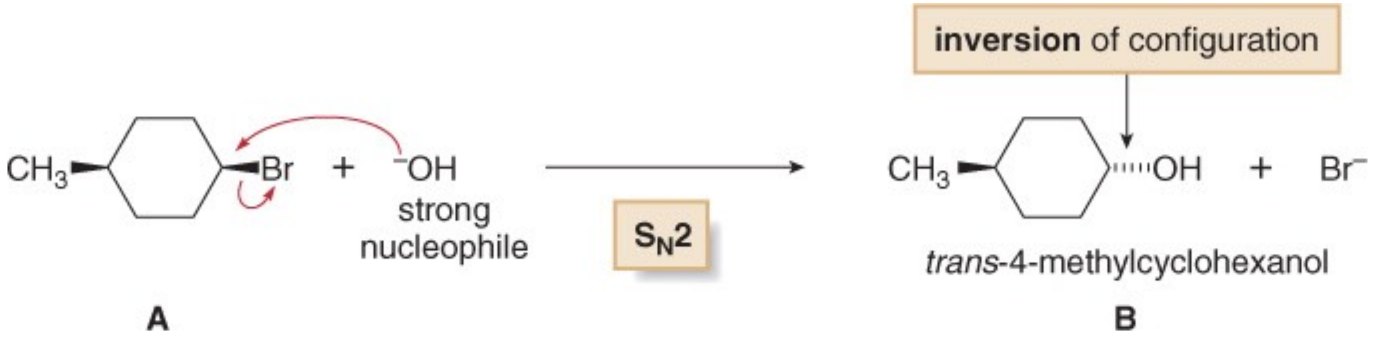
	ethanol	40% water/ 60% ethanol	80% water/20% ethanol	water
Relative reactivity	***1***	***100***	***14000***	***100000***

Predicting the Mechanism



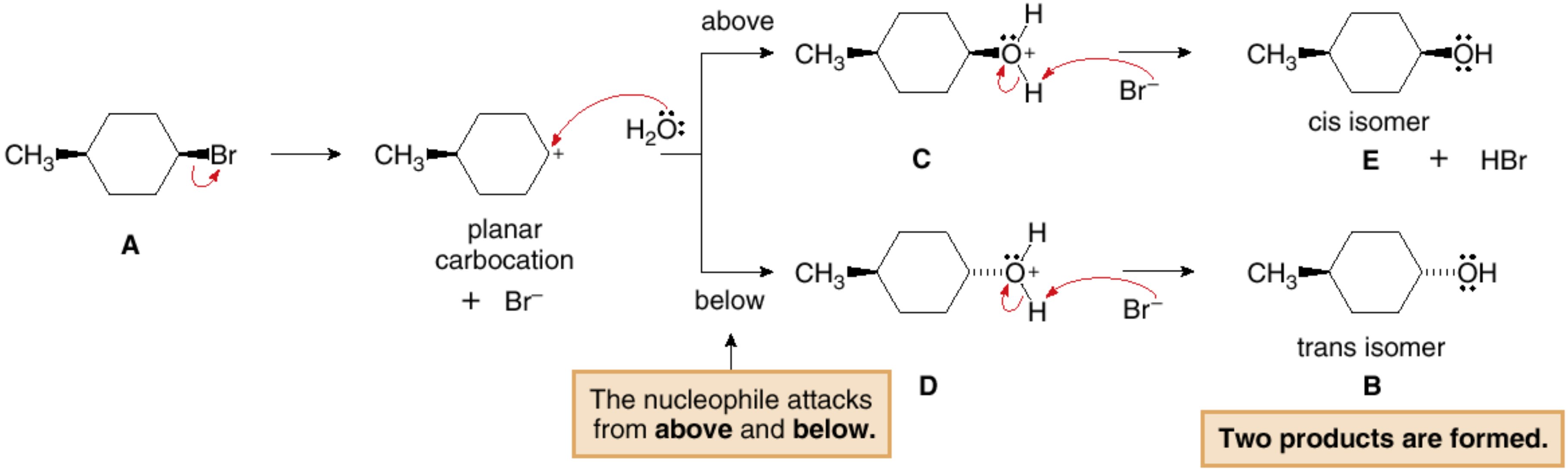


Predicting the Mechanism



inversion of configuration

S_N2

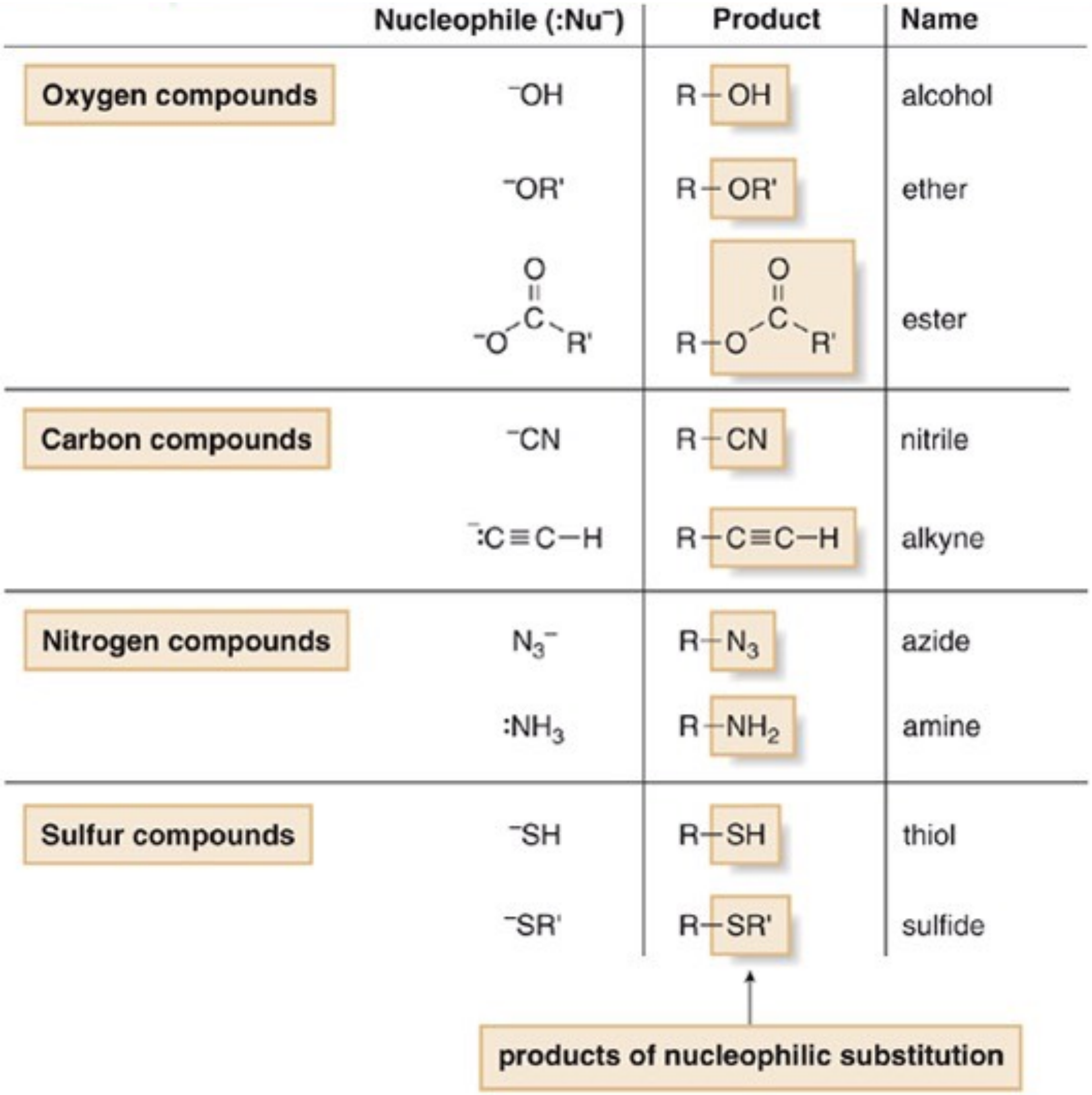


The nucleophile attacks from **above** and **below.**

Two products are formed.

Alkyl Halides in Organic Synthesis

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

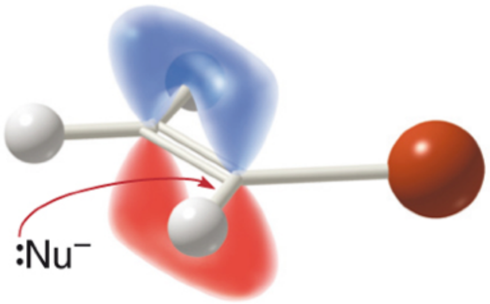


	Nucleophile ($:Nu^-$)	Product	Name
Oxygen compounds	^{-}OH	$R\text{–}OH$	alcohol
	$^{-}OR'$	$R\text{–}OR'$	ether
	$^{-}O\text{–}C(=O)\text{–}R'$	$R\text{–}O\text{–}C(=O)\text{–}R'$	ester
Carbon compounds	^{-}CN	$R\text{–}CN$	nitrile
	$^{-}:C{\equiv}C\text{–}H$	$R\text{–}C{\equiv}C\text{–}H$	alkyne
Nitrogen compounds	N_3^-	$R\text{–}N_3$	azide
	$:NH_3$	$R\text{–}NH_2$	amine
Sulfur compounds	^{-}SH	$R\text{–}SH$	thiol
	$^{-}SR'$	$R\text{–}SR'$	sulfide

products of nucleophilic substitution

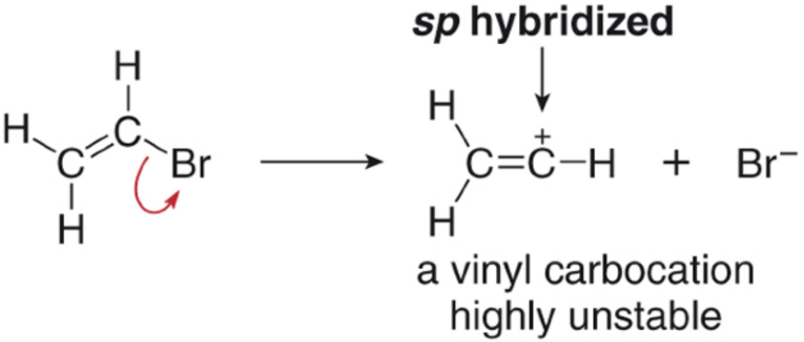
Vinyl Halides

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



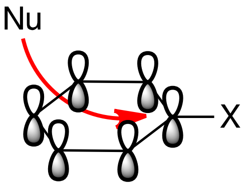
Backside attack would force the nucleophile to approach in the plane of the double bond.

b. Vinyl halides and the S_N1 mechanism: Heterolysis of the C−X bond forms a very unstable carbocation, making the rate-determining step very slow.



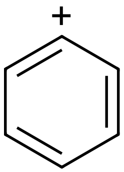
Aryl Halides

S_N2



Backside
attack is
impossible

S_N1



Very unstable
sp^2 carbocation

Eliminations

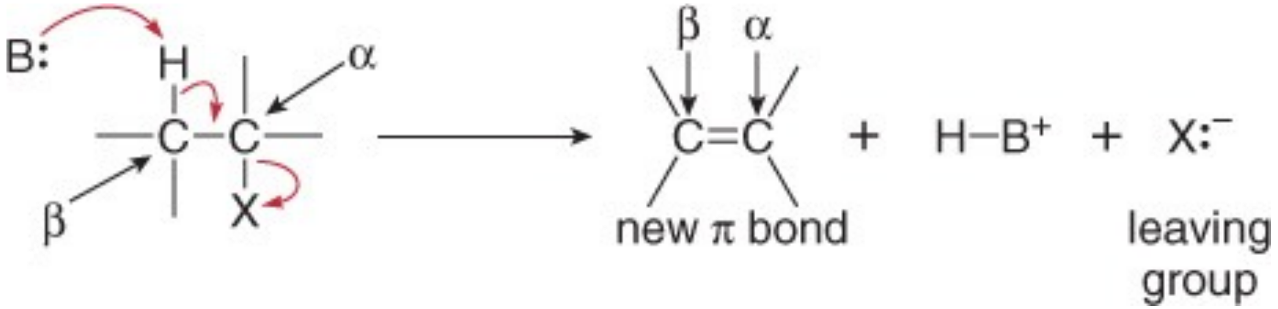
Chapter 11

Organic Chemistry, *8th Edition*

John McMurry

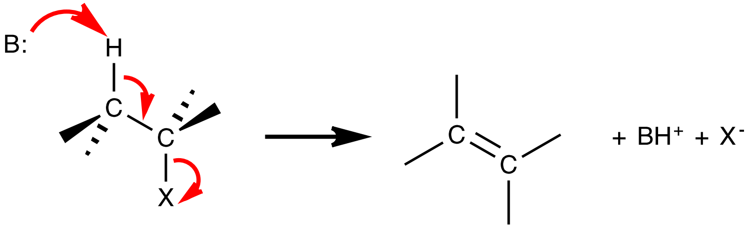
General Features of Elimination

- Alkyl halides undergo elimination reactions with Brønsted–Lowry bases. The elements of HX are lost and an alkene is formed.

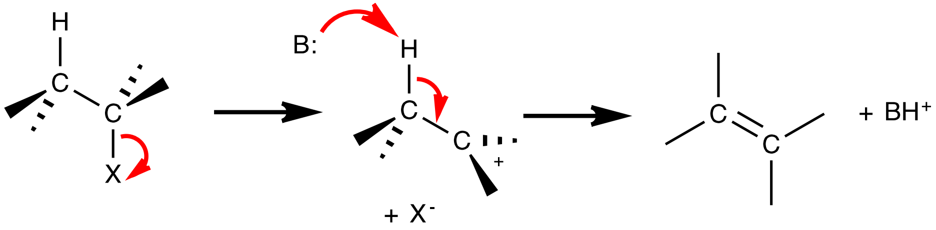


Elimination Mechanisms

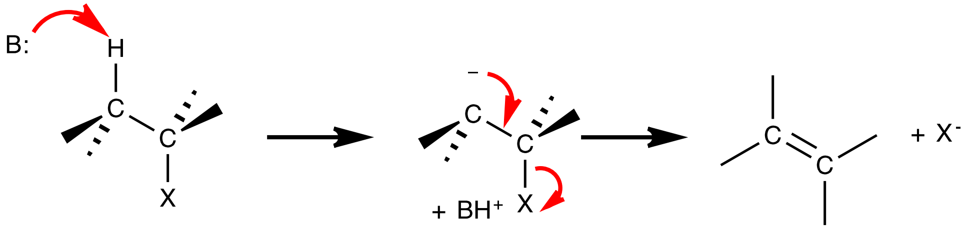
E2



E1

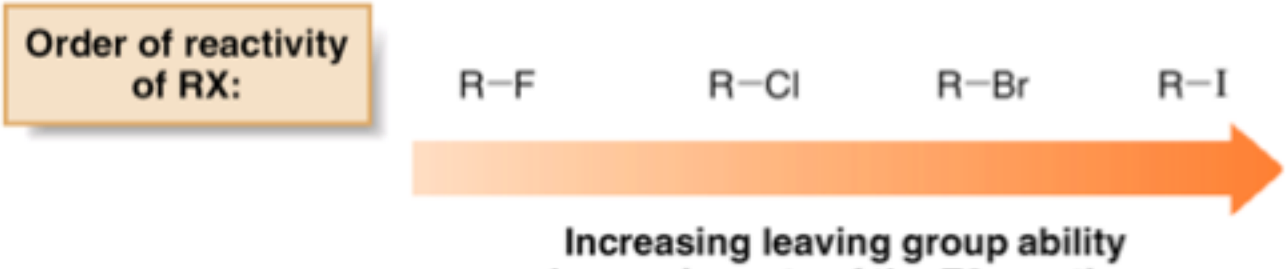


E1cb



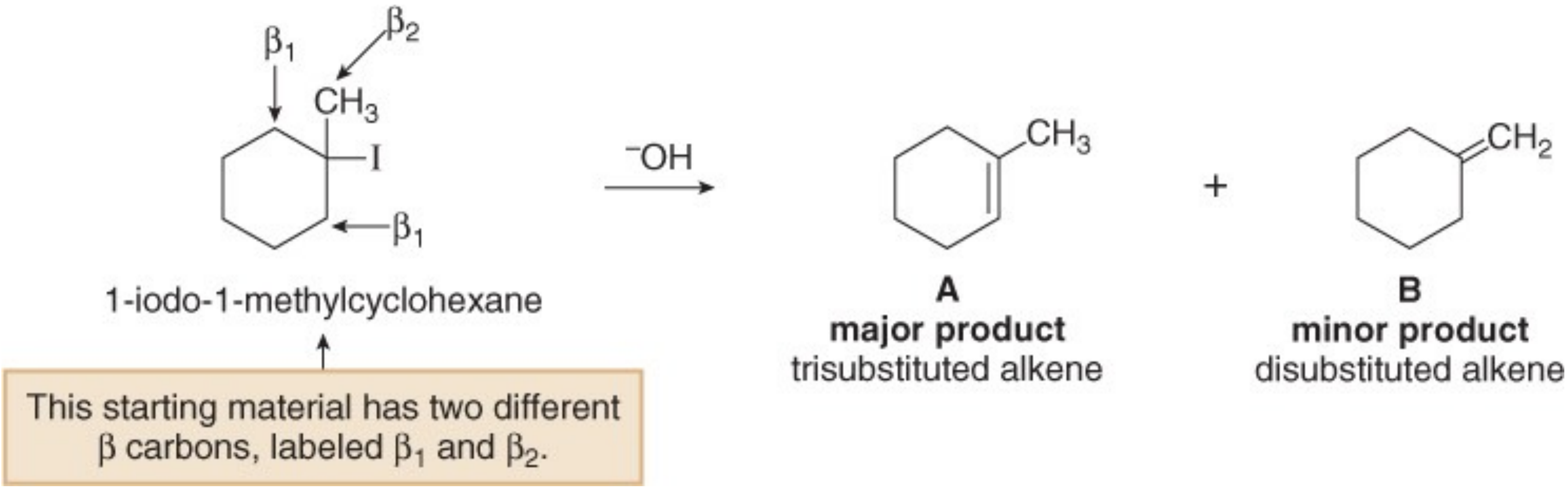
Leaving Groups in Elimination Reactions

Elimination reactions are faster with good leaving groups:



The Zaitsev (Saytzeff) Rule

- The major product is the more stable product—the one with the more substituted double bond.



1-iodo-1-methylcyclohexane

This starting material has two different β carbons, labeled β_1 and β_2.

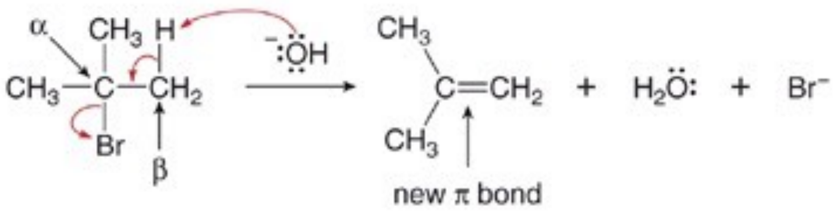
A
major product
trisubstituted alkene

B
minor product
disubstituted alkene

- A reaction is regioselective when it yields predominantly or exclusively one constitutional isomer when more than one is possible. Thus, elimination reactions are regioselective.

Mechanisms of Elimination: E2

- The most common mechanism for dehydrohalogenation is the E2 mechanism.



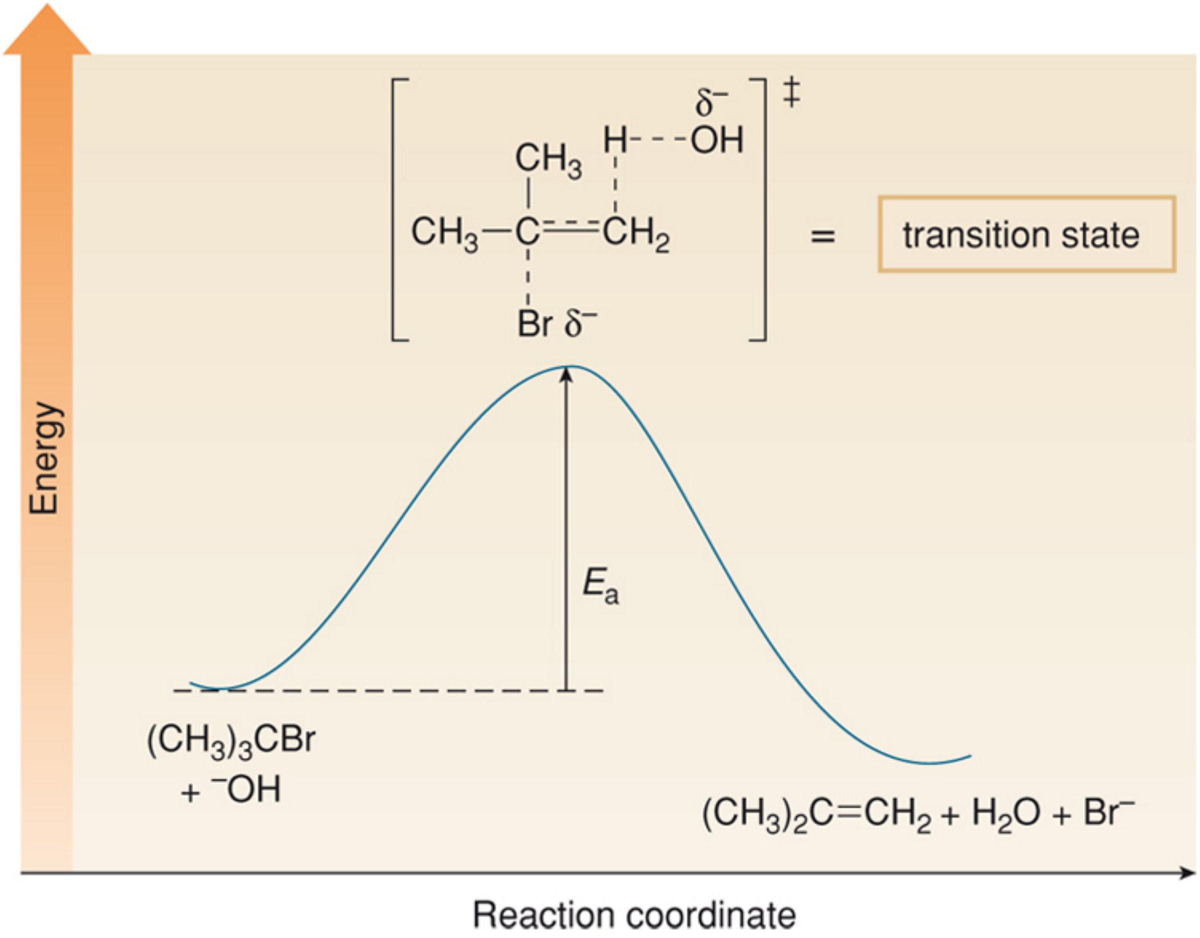
- The base ⁻OH removes a proton from the β carbon, forming H_2O (a by-product).
- The electron pair in the β C−H bond forms the new π bond.
- The leaving group Br^- comes off with the electron pair in the C−Br bond.

- The reaction is concerted—all bonds are broken and formed in a single step.
- It exhibits second-order kinetics, and both the alkyl halide and the base appear in the rate equation, i.e.,

$$v = k[(CH_3)_3CBr][^{-}OH]$$

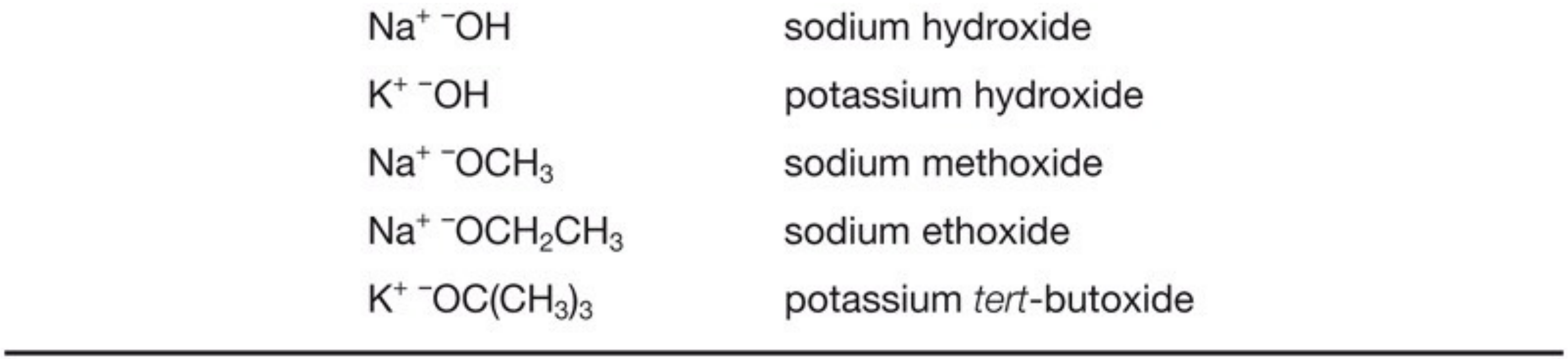
Mechanisms of Elimination: E2

$(CH_3)_3CBr + {}^{-}OH \rightarrow$
$(CH_3)_2C{=}CH_2 + H_2O + Br^{-}$



Mechanisms of Elimination: E2

- E2 reactions are favoured by strong negatively charged bases, such as HO^- and its alkyl derivatives, RO^-, called alkoxides.

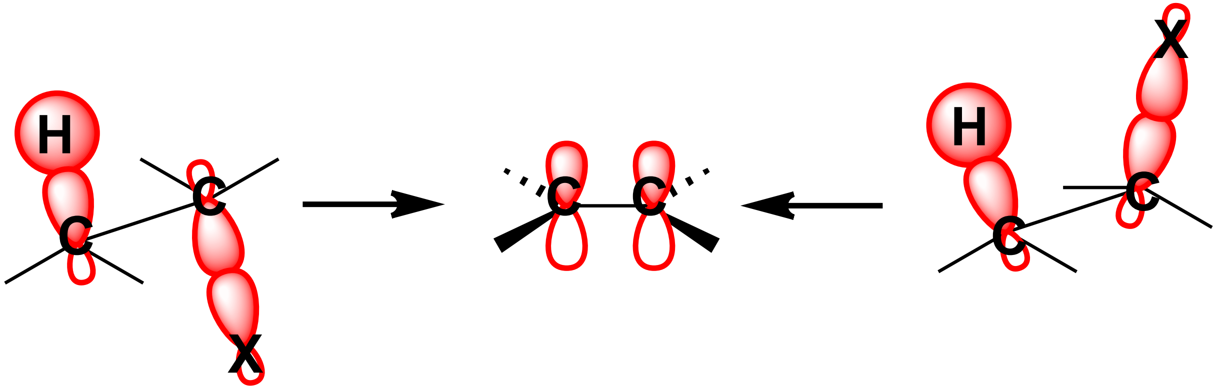


$Na^+ \ ^-OH$	sodium hydroxide
$K^+ \ ^-OH$	potassium hydroxide
$Na^+ \ ^-OCH_3$	sodium methoxide
$Na^+ \ ^-OCH_2CH_3$	sodium ethoxide
$K^+ \ ^-OC(CH_3)_3$	potassium *tert*-butoxide

- Potassium t-butoxide is a strong, non-nucleophilic base.

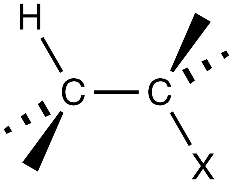
Stereochemistry of the E2 Reaction

- For efficient overlap the C—H and C—X bonds must be coplanar.

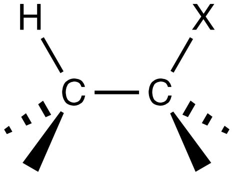


anti periplanar

syn periplanar

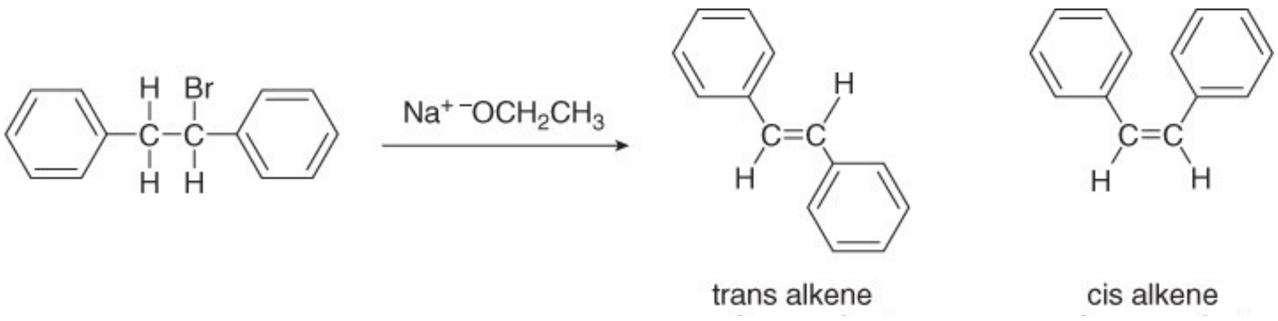


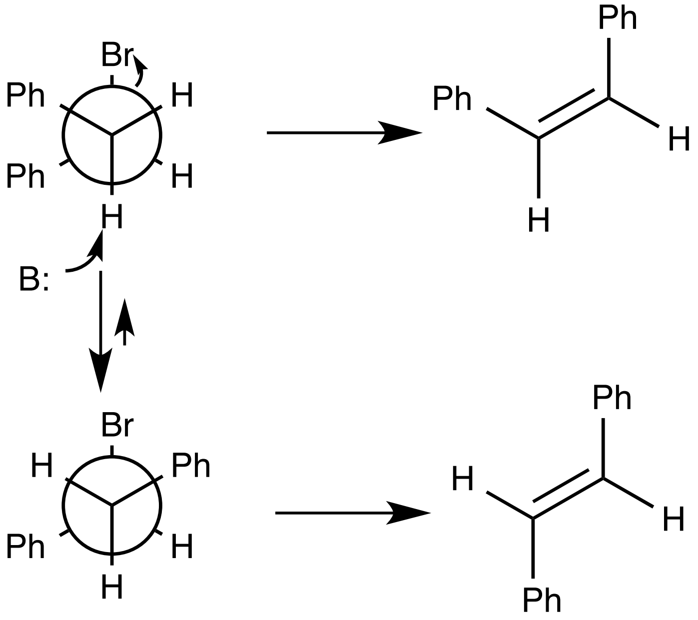
dihedral angle: 180°
staggered
favoured



dihedral angle: 0°
eclipsed
disfavoured

Stereochemistry of the E2 Reaction



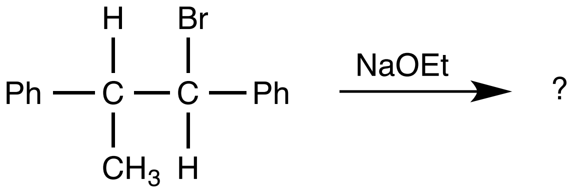


Minor product

Major product

The E2 reaction is stereoselective because one stereoisomer is formed preferentially.

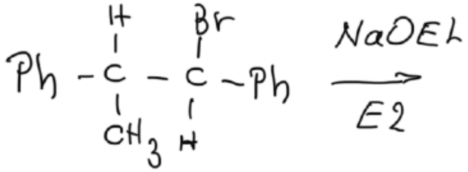
Stereochemistry of the E2 Reaction

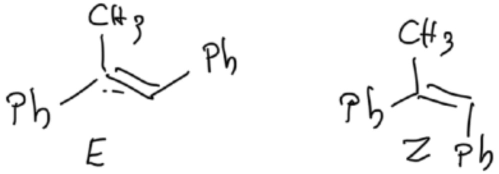


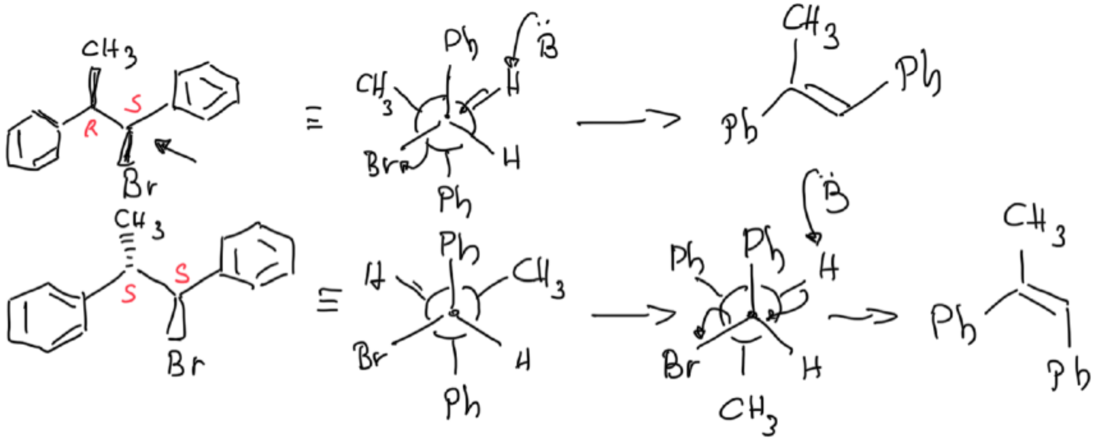
$$\mathrm{Ph{-}\overset{H}{\underset{CH_3}{C}}{-}\overset{Br}{\underset{H}{C}}{-}Ph} \xrightarrow{\text{NaOEt}} ?$$

(*R*,*R* or *S*,*S*)
(*R*,*S* or *S*,*R*)

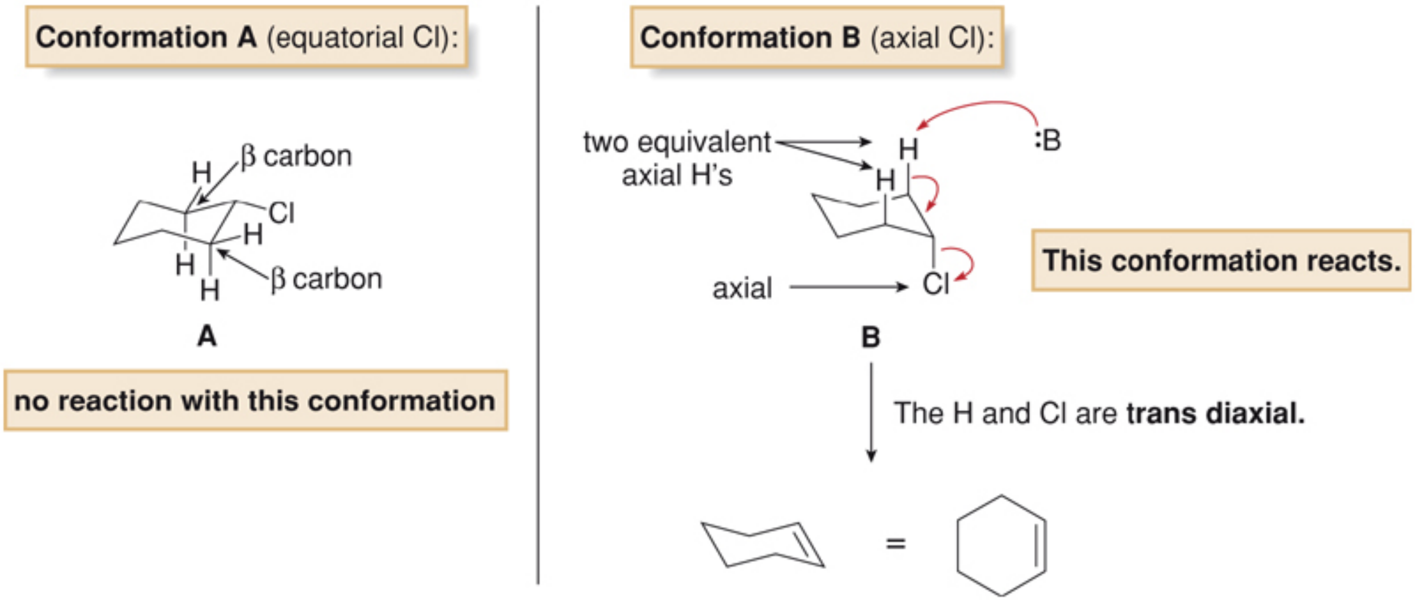
(R,R)/(S,S)
(R,S)/(S,R)







E2 Reactions in Cyclohexanes



Conformation A (equatorial Cl):

no reaction with this conformation

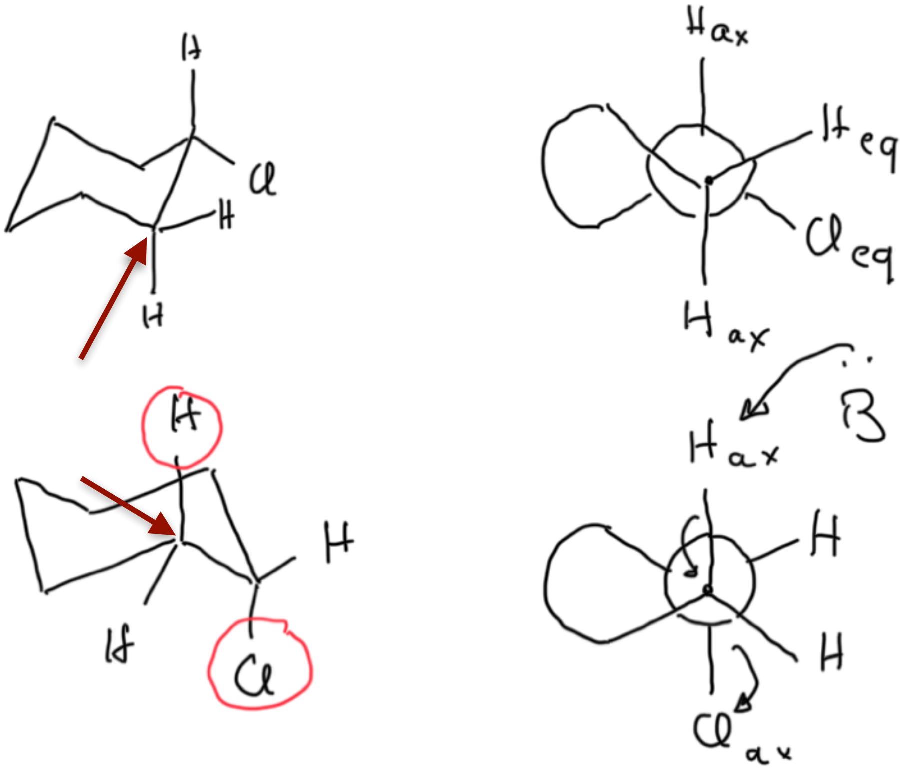
Conformation B (axial Cl):

This conformation reacts.

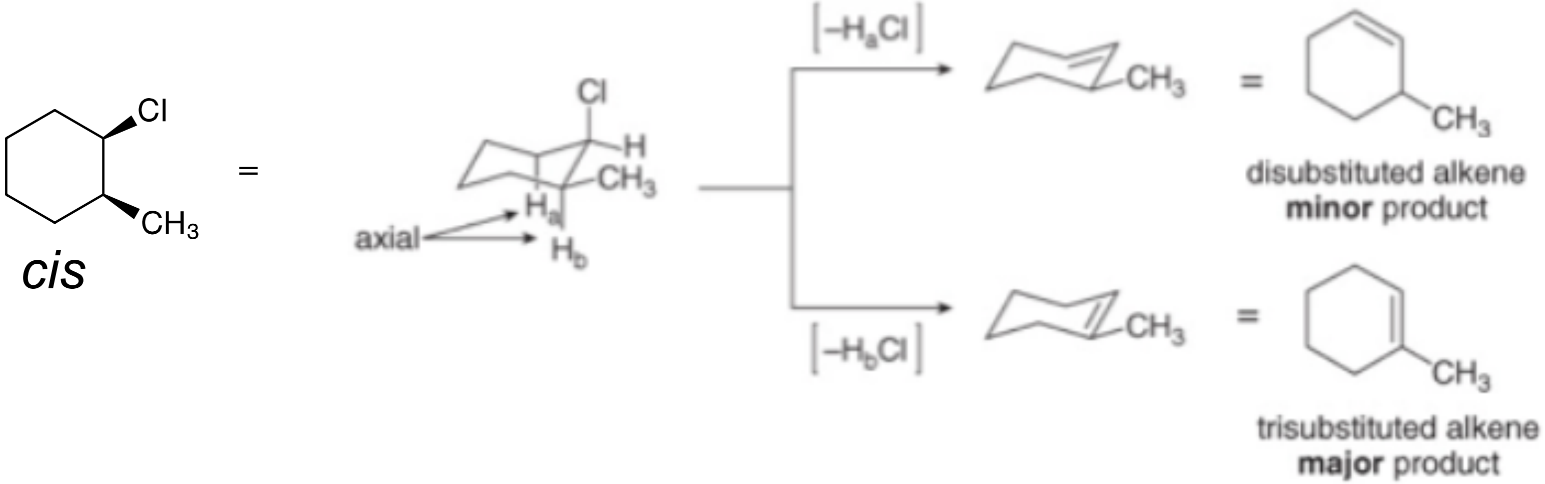
The H and Cl are **trans diaxial.**

E2 Reactions in Cyclohexanes

Proiezioni di Newman lungo i legami indicati dalla freccia



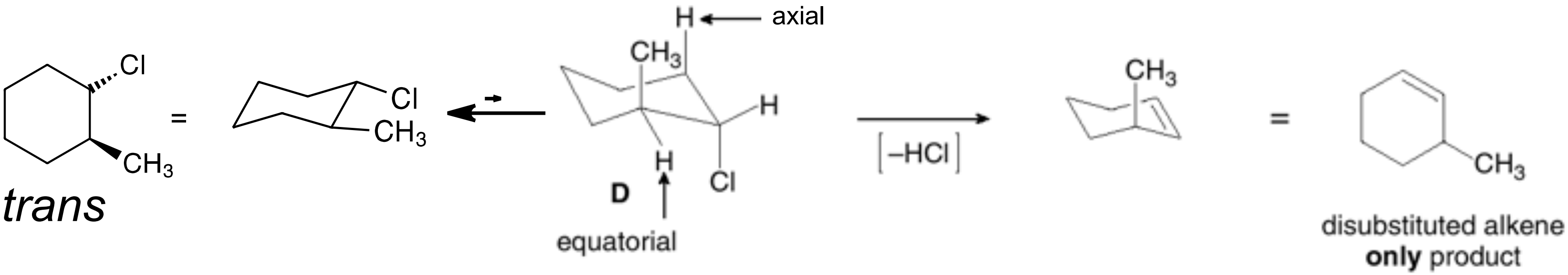
E2 Reactions in Cyclohexanes



cis

disubstituted alkene
minor product

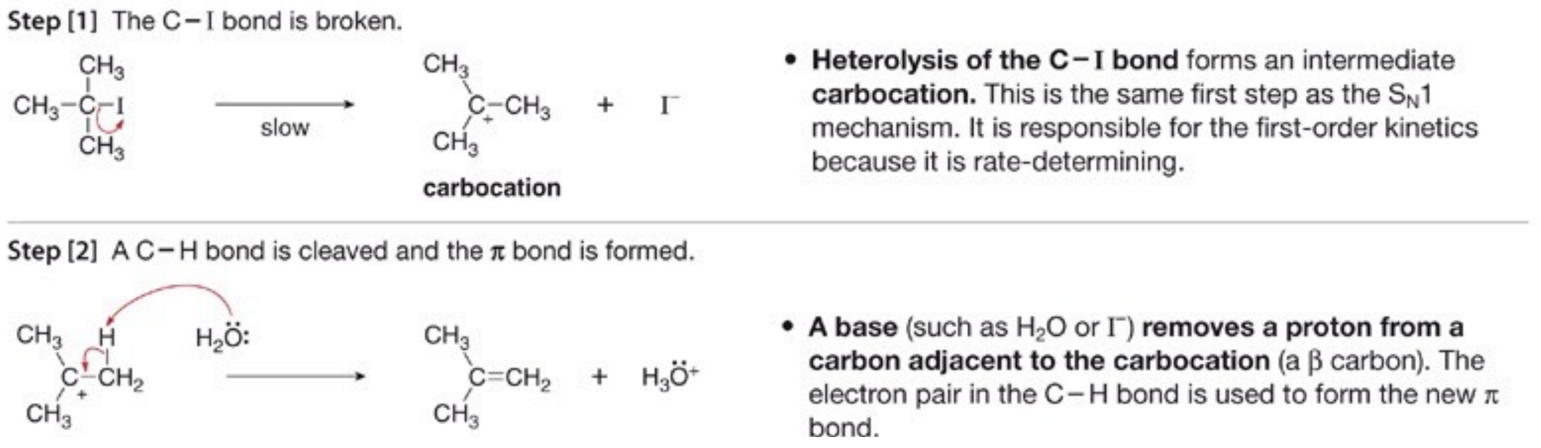
trisubstituted alkene
major product



trans

disubstituted alkene
only product

Mechanisms of Elimination: E1



Step [1] The C−I bond is broken.

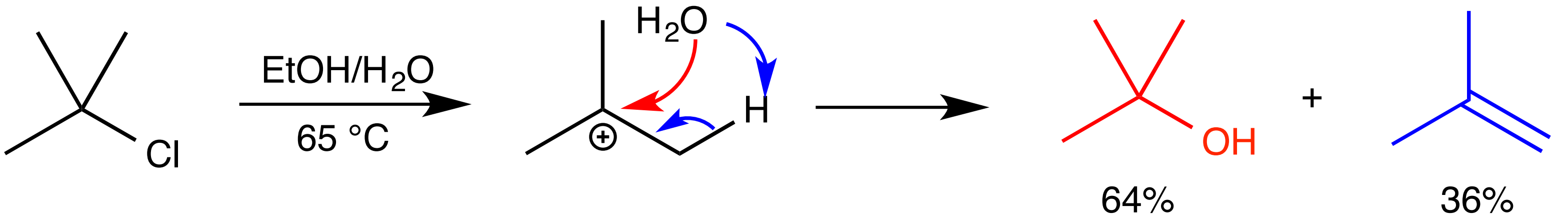
- **Heterolysis of the C−I bond** forms an intermediate **carbocation.** This is the same first step as the S_N1 mechanism. It is responsible for the first-order kinetics because it is rate-determining.

Step [2] A C−H bond is cleaved and the π bond is formed.

- **A base** (such as H_2O or I^-) **removes a proton from a carbon adjacent to the carbocation** (a β carbon). The electron pair in the C−H bond is used to form the new π bond.

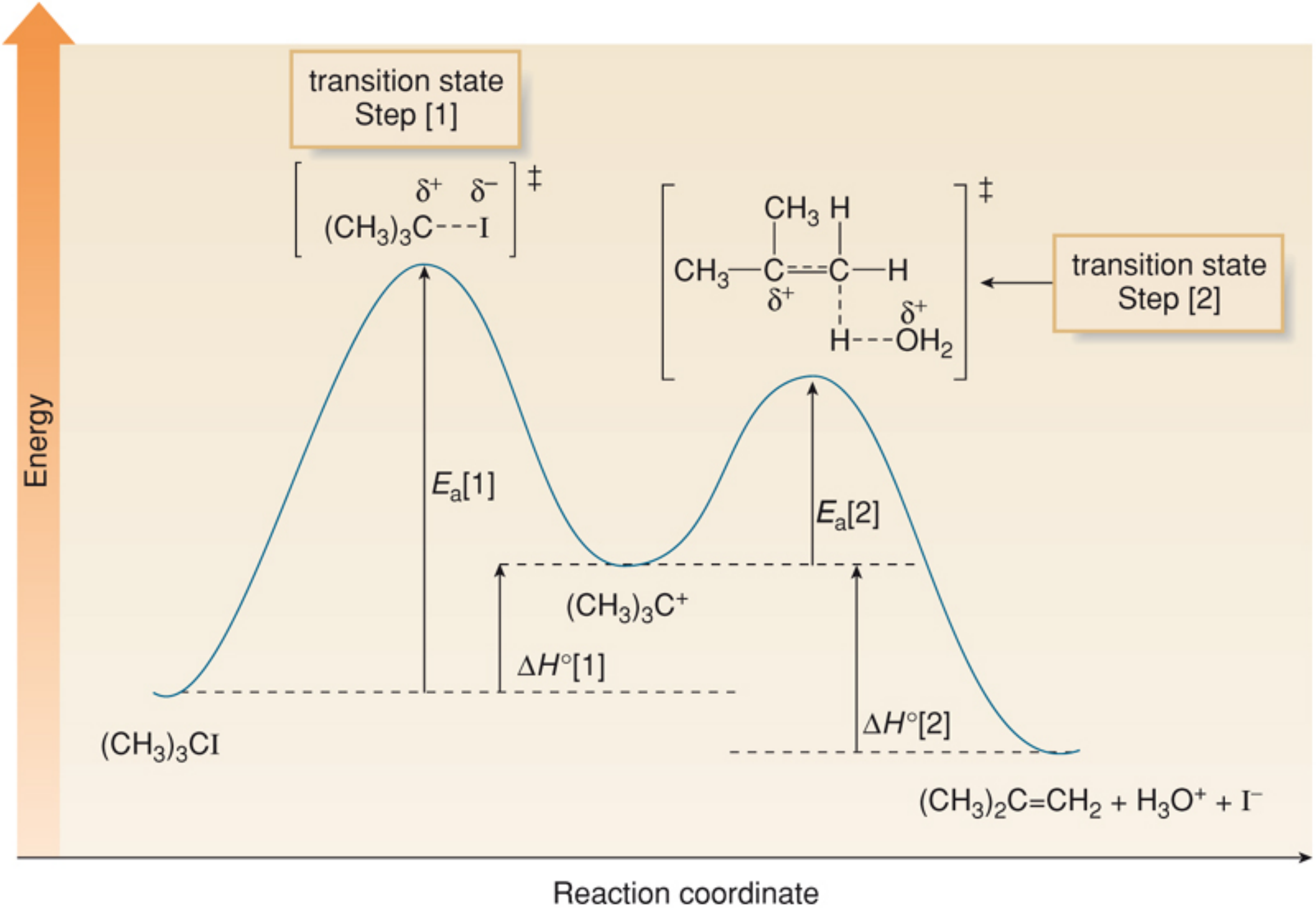
- E1 reactions exhibit first-order kinetics: $v = k[(CH_3)_3I]$

- E1 reactions frequently accompany SN1 reactions



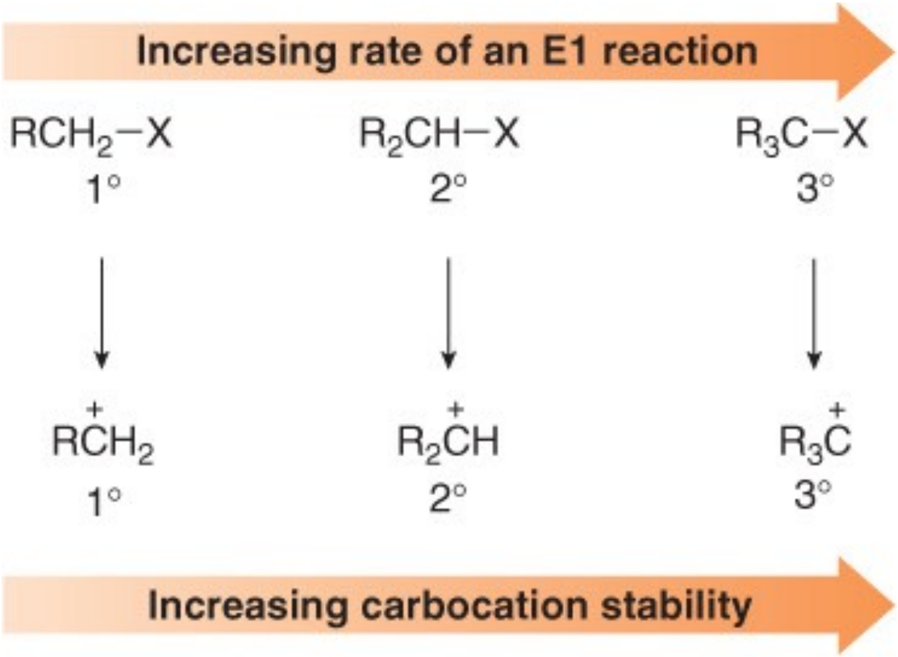
Mechanisms of Elimination: E1

$(CH_3)_3CI + H_2O \rightarrow$
$(CH_3)_2C{=}CH_2 + H_3O^+ + I^-$



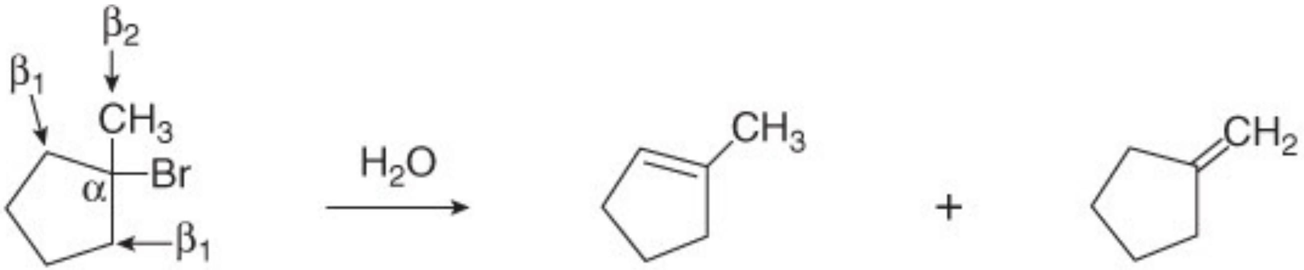
Mechanisms of Elimination: E1

The rate of an E1 reaction increases as the number of R groups on the carbon with the leaving group increases.



Mechanisms of Elimination: E1

E1 reactions are regioselective, favoring formation of the more substituted, more stable alkene (Zaitsev's rule)



1-bromo-1-methyl-
cyclopentane

A
trisubstituted alkene
major product

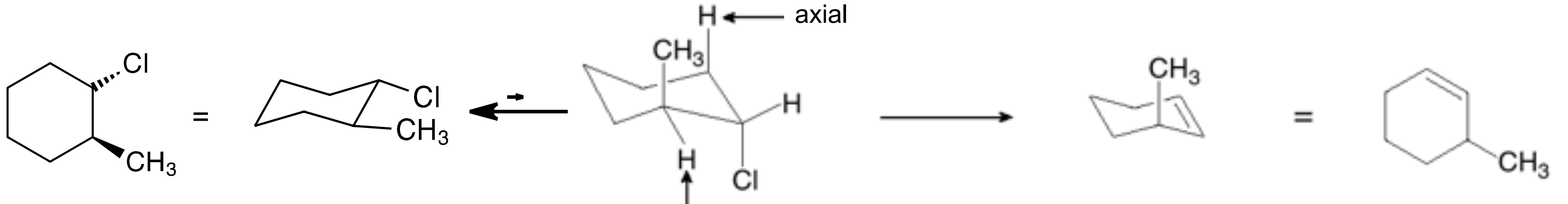
B
disubstituted alkene
minor product

Mechanisms of Elimination

	E2	E1
Mechanism	One step	Two steps
Kinetics	Second order	First order
Substrate	1ry, 2ry and 3ry halides	3ry (and 2ry) halides
Leaving group	Favored by good leaving groups	Favored by good leaving groups
Base	Favored by strong bases	Favored by weak bases (H_2O, ROH)
Stereochemistry	Antiperiplanar-stereoselective	Not stereoselective
Solvent	Favored by non polar solvents	Favored by polar protic solvents.

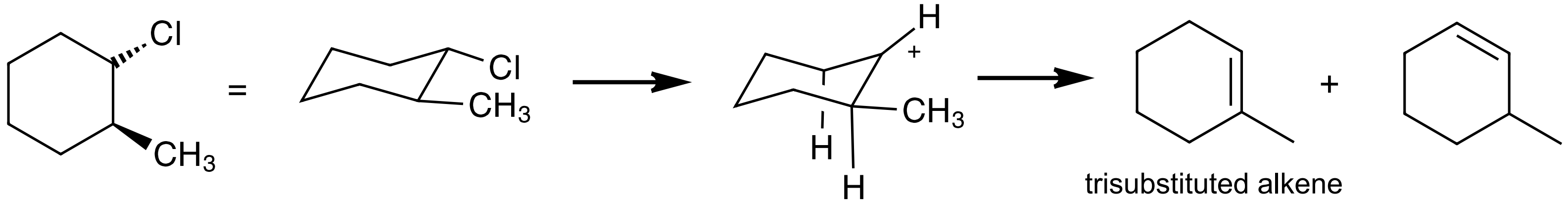
When is the Mechanism E1 or E2?

E2 conditions: 1M NaOEt, EtOH, 100 °C



disubstituted alkene
only product

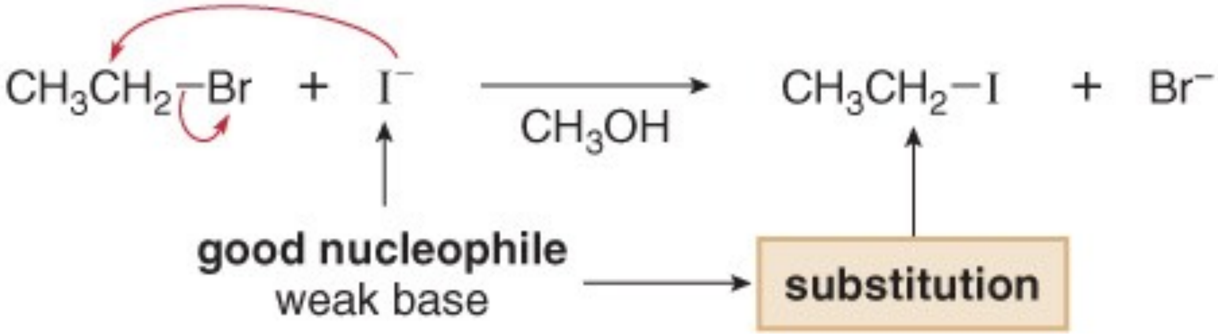
E1 conditions: 0.01M NaOEt, 80% EtOH, 160 °C



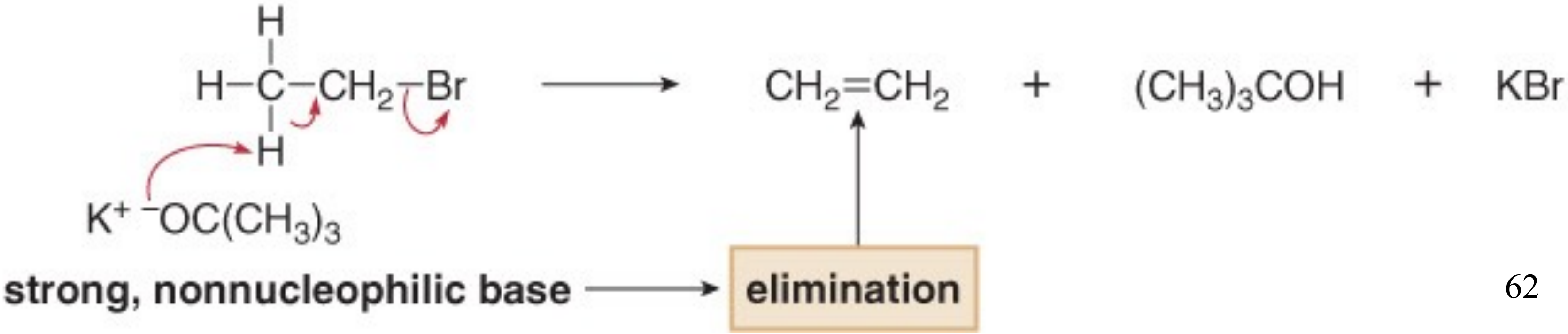
trisubstituted alkene
main product

Substitution *vs* Elimination

- Good nucleophiles that are weak bases favor substitution over elimination. These include I^{-}, Br^{-}, HS^{-}, ^{-}CN, and CH_3COO^{-}.



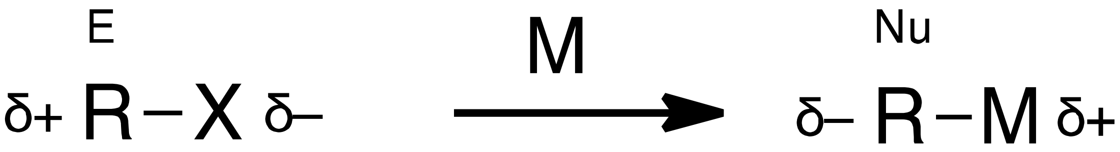
- Bulky nonnucleophilic bases ($KOC(CH_3)_3$) favor elimination over substitution.



Substitution and Elimination

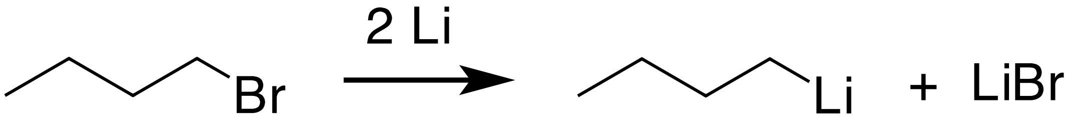
Alkyl halide	SN2	SN1	E2	E1
methyl	*yes*			
primary	*with good, weakly basic nucleophiles*		*with strong, non-nucleophilic bases*	
secondary allylic benzylic	*with good nucleophiles in aprotic solvents*	*with weak nucleophiles in protic solvents*	*with strong bases in aprotic solvents*	*with weak bases in protic solvents*
tertiary		*with non basic nucleophiles*	*with strong bases*	*with weak bases*

Reverse of Polarity. Organometallic Compounds

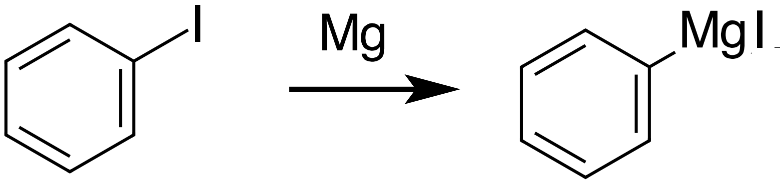


$$\delta+\ \overset{E}{R}-X\ \delta- \xrightarrow{M} \delta-\ \overset{Nu}{R}-M\ \delta+$$

Examples:



organolithium



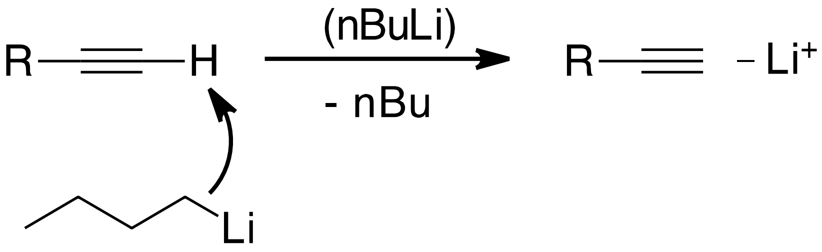
organomagnesium
(Grignard reagents)

$2\ CH_3Li \xrightarrow{CuI} (CH_3\text{-}Cu\text{-}CH_3)^-Li^+$

organocuprates
(Gilman reagents)

Reverse of Polarity. Organometallic Compounds

strong bases:



strong nucleophiles: