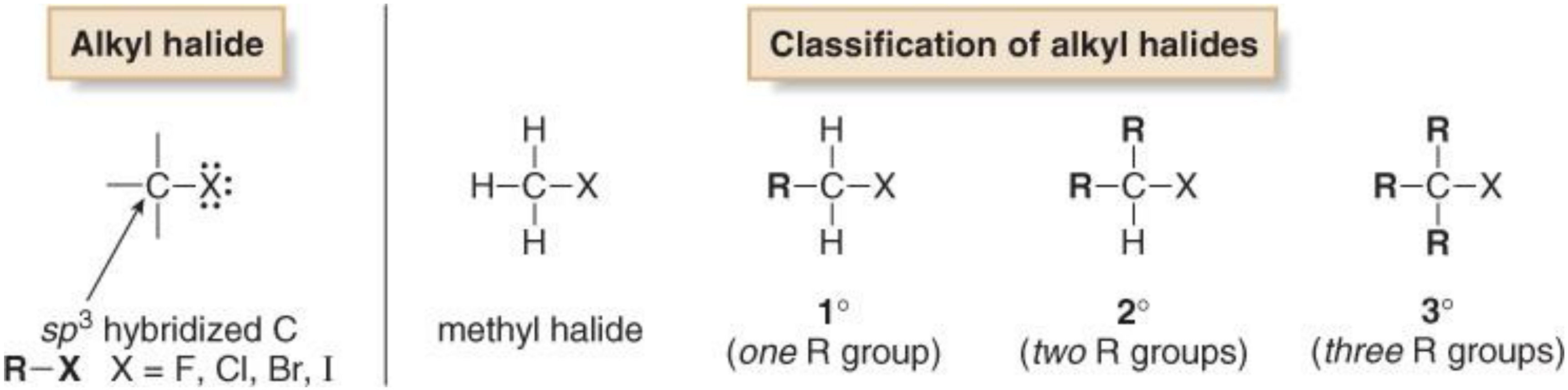
Alkyl Halides

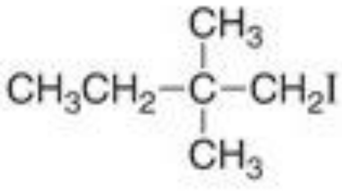
Chapter 10
Organic Chemistry, *8th Edition*
John McMurry

Introduction to Alkyl Halides

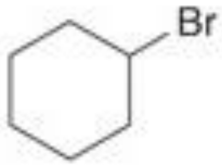
- Alkyl halides are organic molecules containing a halogen atom bonded to an sp^3 hybridized carbon atom.
- Alkyl halides are classified as primary (1°), secondary (2°), or tertiary (3°), depending on the number of carbons bonded to the carbon with the halogen atom.
- The halogen atom in halides is often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



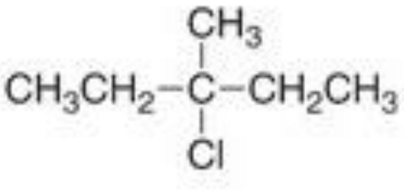
Introduction to Alkyl Halides


$CH_3CH_2-C(CH_3)_2-CH_2I$

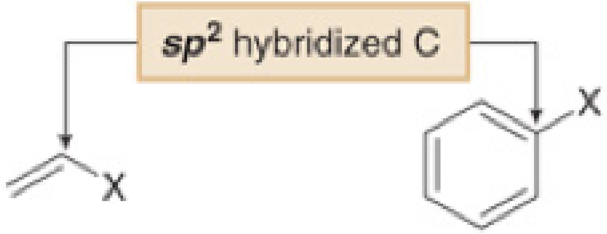
1° iodide



2° bromide


$CH_3CH_2-C(CH_3)(Cl)-CH_2CH_3$

3° chloride



vinyl halide

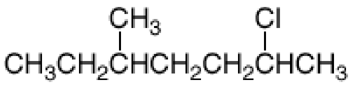
aryl halide

Different reactivity

Nomenclature

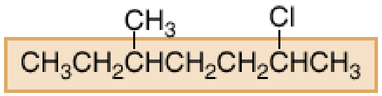
How To Name an Alkyl Halide Using the IUPAC System

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.



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

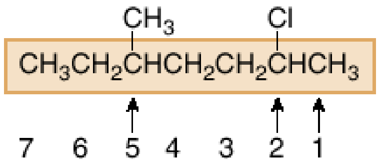
7 C's in the longest chain

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.

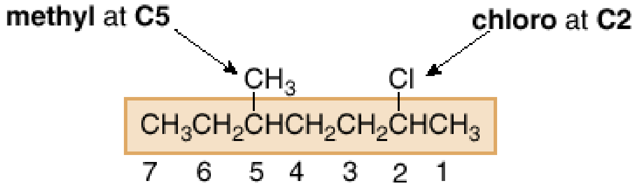
a. **Number** the chain.



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

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

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



methyl at **C5**

chloro at **C2**

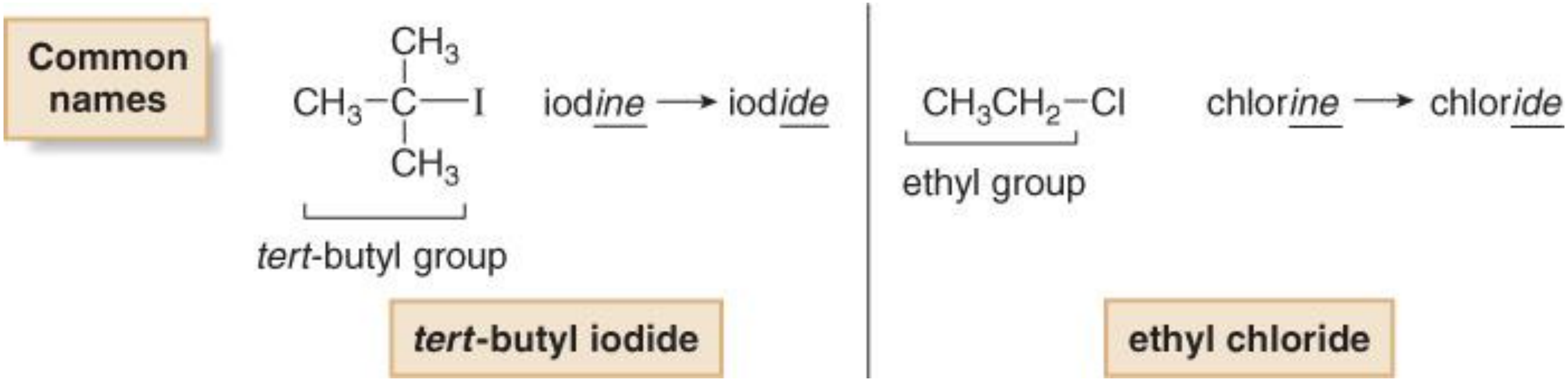
$CH_3CH_2\overset{\overset{CH_3}{|}}{C}HCH_2CH_2\overset{\overset{Cl}{|}}{C}HCH_3$

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

ANSWER: 2-chloro-5-methylheptane

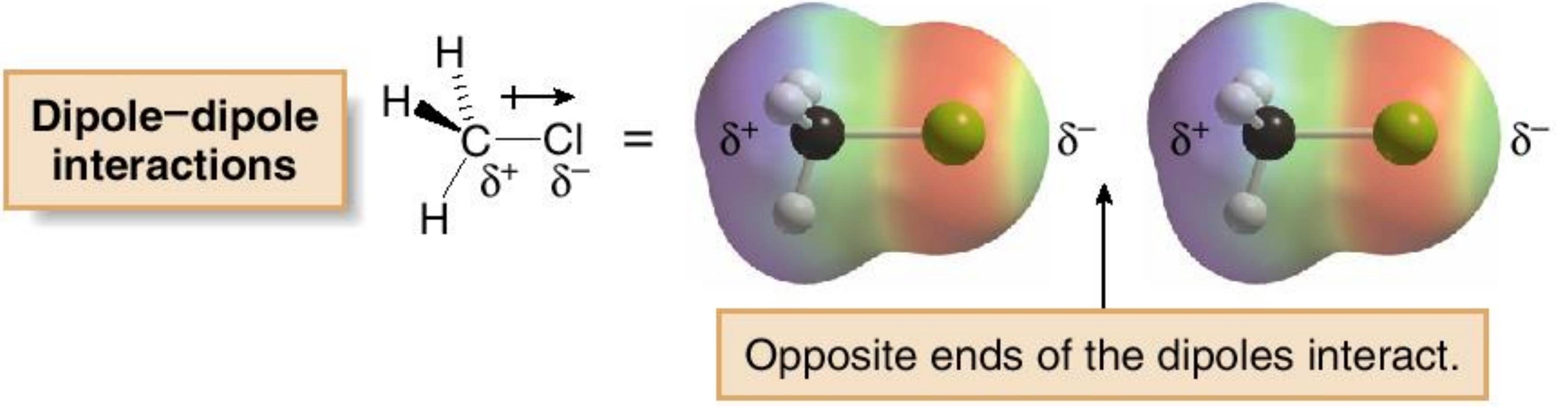
Nomenclature

- 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.



Physical Properties

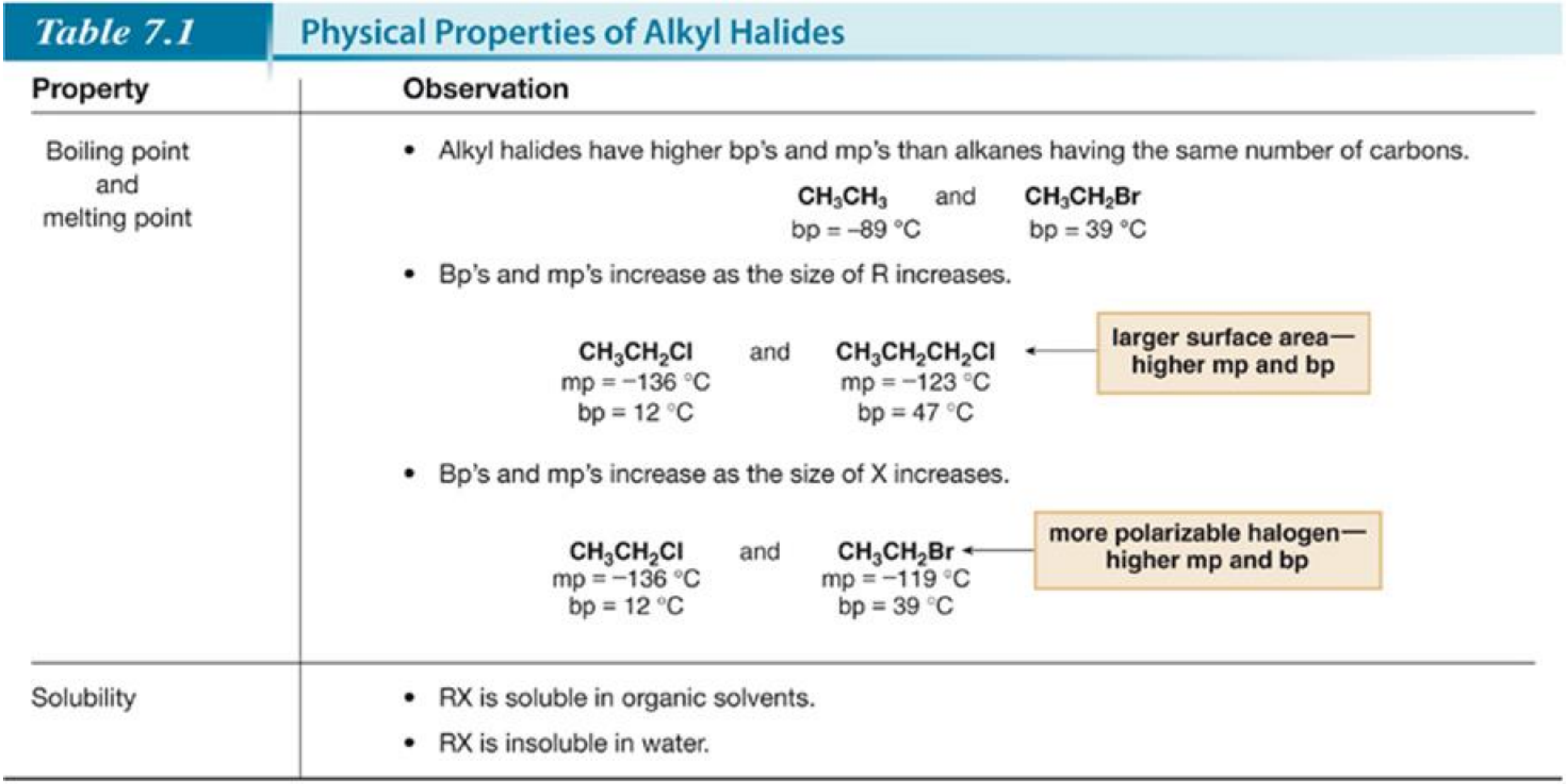


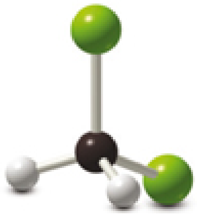
Table 7.1 Physical Properties of Alkyl Halides

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.

Interesting Alkyl Halides

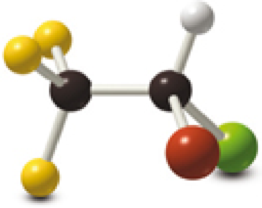
CH_3Cl

- **Chloromethane (CH_3Cl)** is produced by giant kelp and algae and also found in emissions from volcanoes such as Hawaii's Kilauea. Almost all of the atmospheric chloromethane results from these natural sources.



CH_2Cl_2

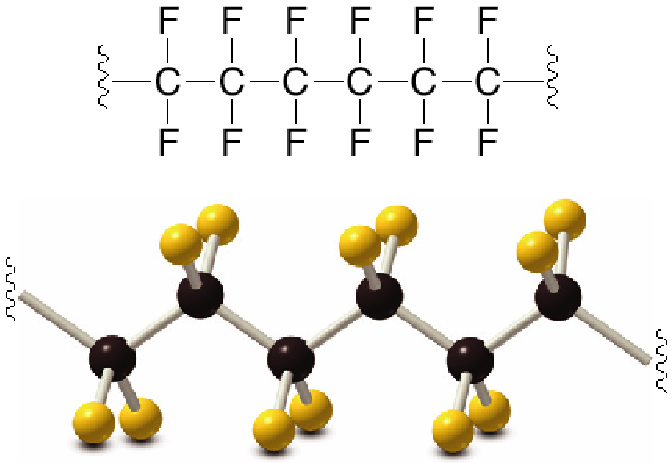
- **Dichloromethane (or methylene chloride, CH_2Cl_2)** is an important solvent, once used to decaffeinate coffee. Coffee is now decaffeinated by using supercritical CO_2 due to concerns over the possible ill effects of trace amounts of residual CH_2Cl_2 in the coffee. Subsequent studies on rats have shown, however, that no cancers occurred when animals ingested the equivalent of over 100,000 cups of decaffeinated coffee per day.



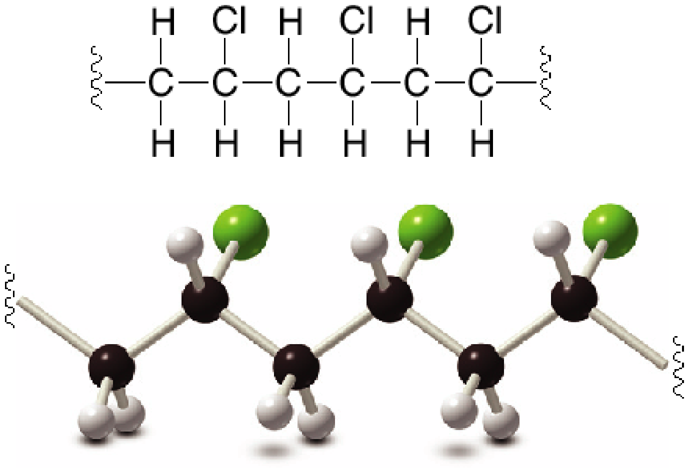
$CF_3CHClBr$

- **Halothane ($CF_3CHClBr$)** is a safe general anesthetic that has now replaced other organic anesthetics such as $CHCl_3$, which causes liver and kidney damage, and $CH_3CH_2OCH_2CH_3$ (diethyl ether), which is very flammable.

Interesting Alkyl Halides

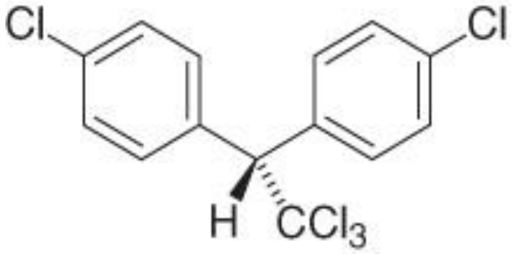


Teflon
(nonstick coating)



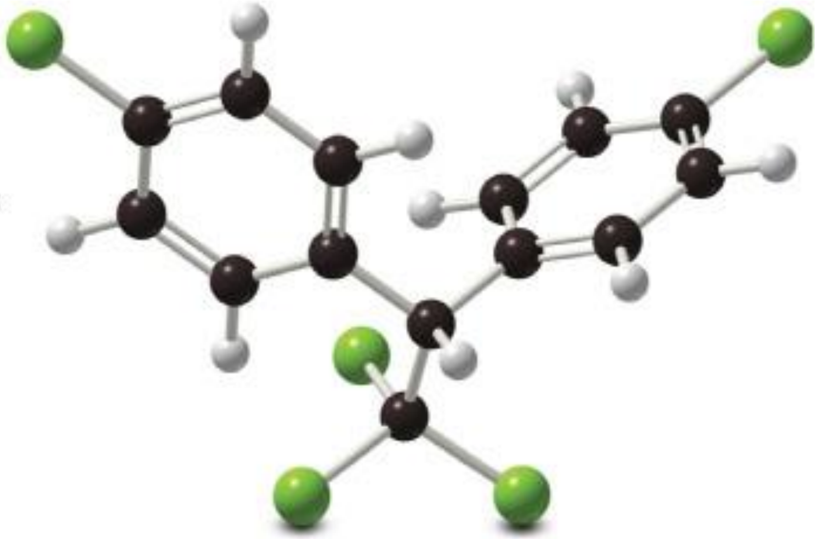
poly(vinyl chloride) (PVC)
(plastic used in films, pipes, and insulation)

$CFCl_3$
CFC 11
Freon 11



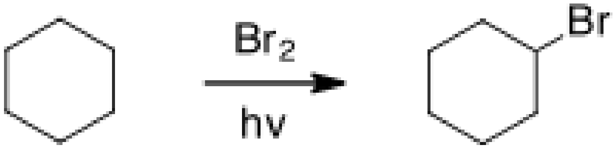
DDT

=

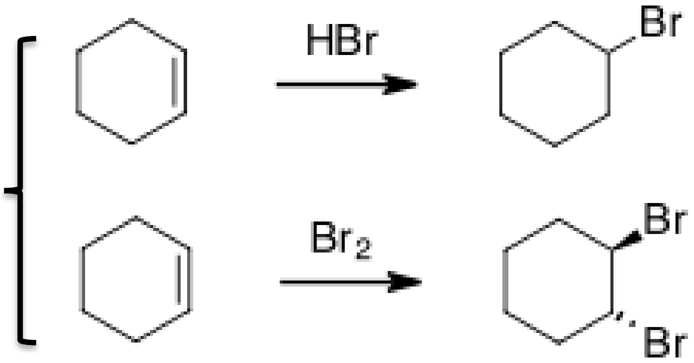


Preparation

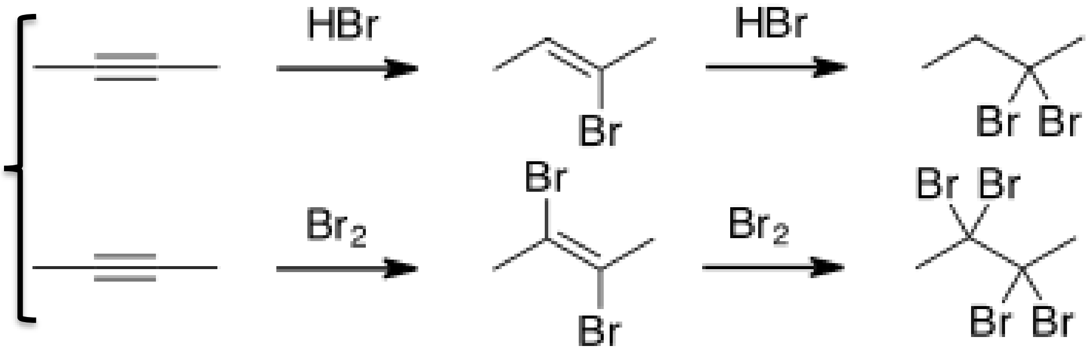
From alkanes



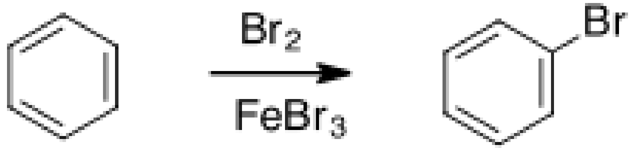
From alkenes



From alkynes

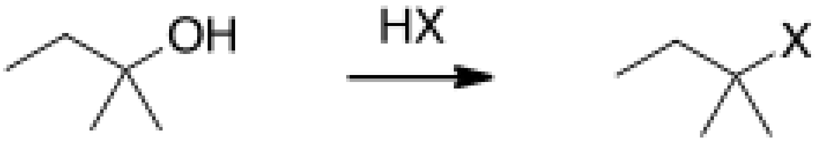


Aryl halides:

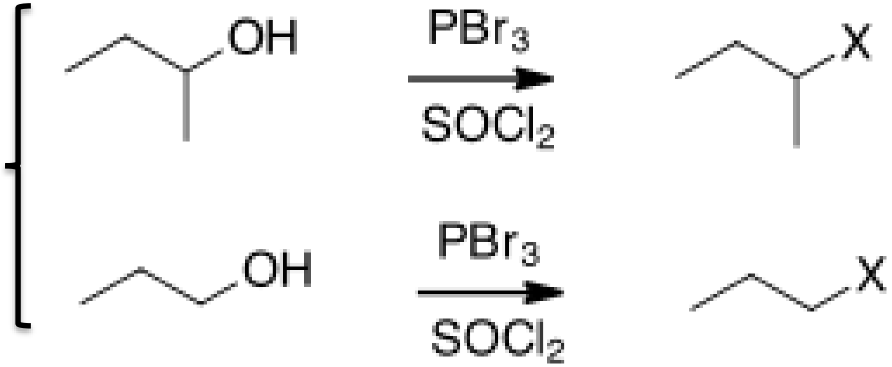


Preparation from alcohols

tertiary

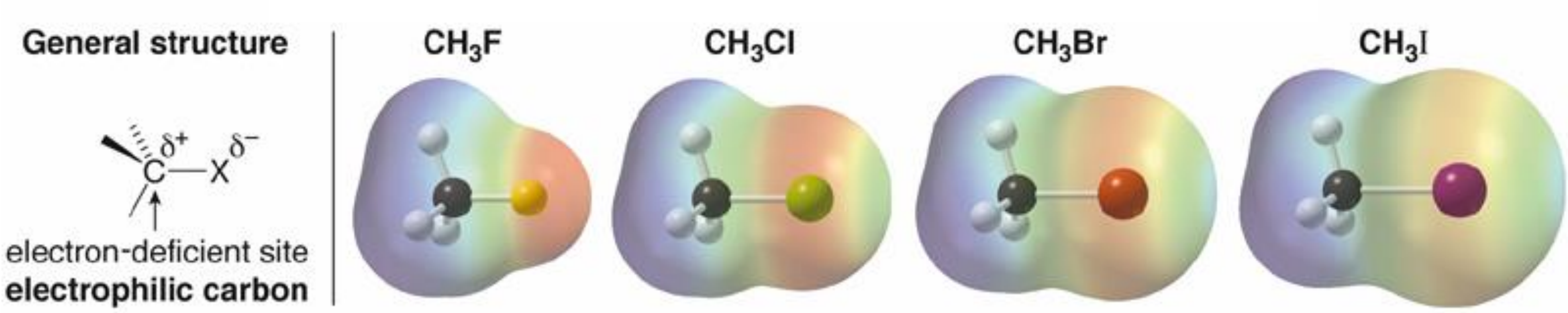


primary
and
secondary



The Polar Carbon-Halogen Bond

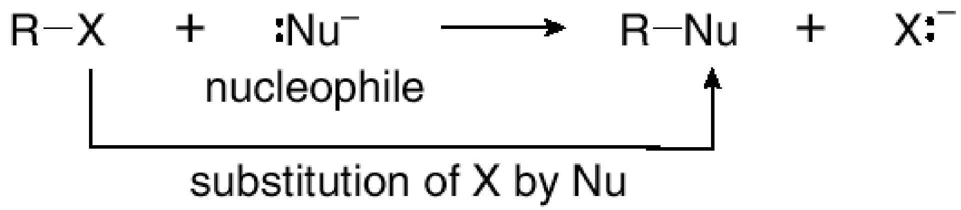
- The electronegative halogen atom in alkyl halides creates a polar C—X bond, making the carbon atom electron deficient. Electrostatic potential maps of four simple alkyl halides illustrate this point.



- 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.

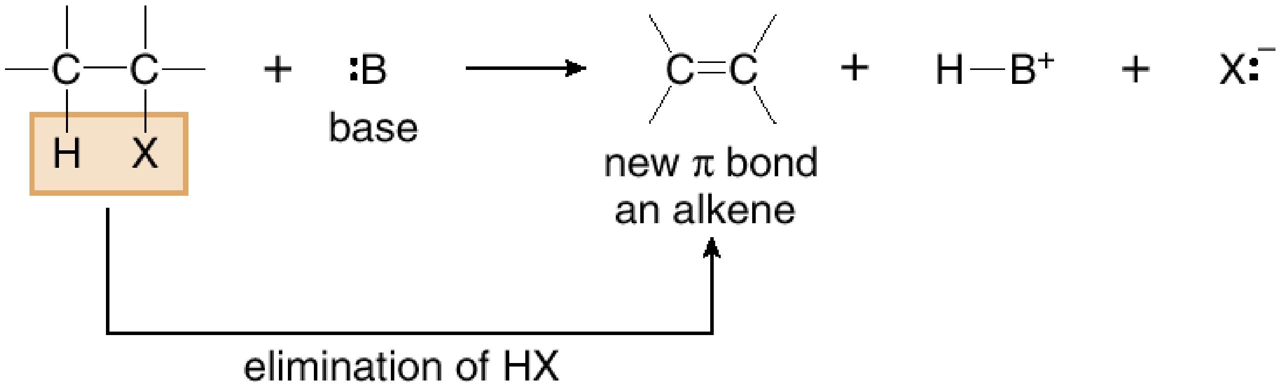


$$R{-}X + :Nu^- \longrightarrow R{-}Nu + X:^-$$

nucleophile

substitution of X by Nu

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



base

new π bond
an alkene

elimination of HX

Nucleophilic Substitution

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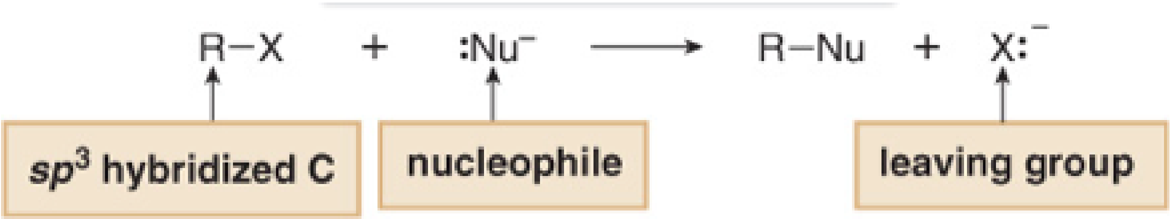
General Features of Nucleophilic Substitution



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

sp^3 hybridized C

nucleophile

leaving group

Examples

Alkyl group

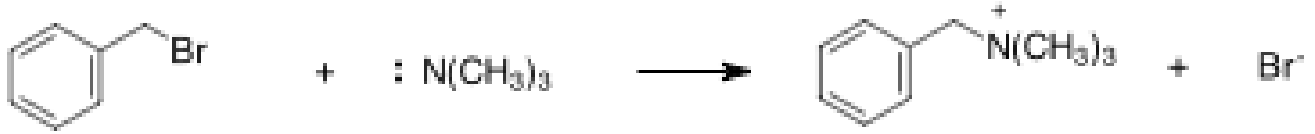
Nucleophile

Leaving group

[1] $\text{CH}_3{-}\text{Cl} \;+\; {}^{-}:\ddot{\underset{\cdot\cdot}{\text{O}}}\text{H} \longrightarrow \text{CH}_3{-}\ddot{\underset{\cdot\cdot}{\text{O}}}\text{H} \;+\; \text{Cl}^{-}$

[2] $\text{CH}_3\text{CH}_2\text{CH}_2{-}\text{I} \;+\; {}^{-}:\ddot{\underset{\cdot\cdot}{\text{S}}}\text{H} \longrightarrow \text{CH}_3\text{CH}_2\text{CH}_2{-}\ddot{\underset{\cdot\cdot}{\text{S}}}\text{H} \;+\; \text{I}^{-}$

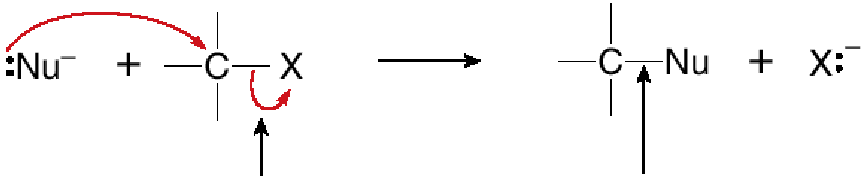
[3]



Mechanism

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

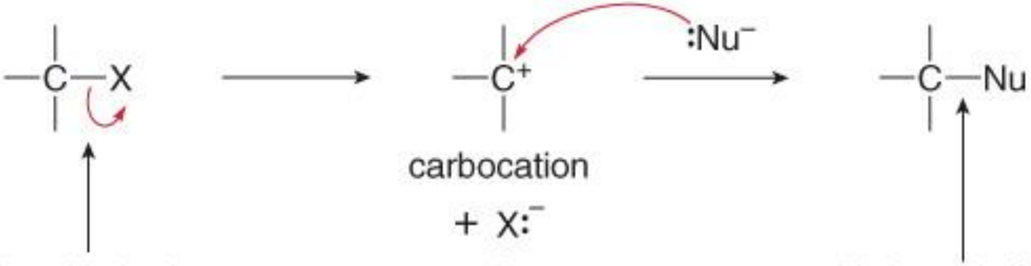
One-step mechanism



This bond is broken... ***as*** ...this bond is formed.

Bond breaking occurs before bond making. **S_N1**

Two-step mechanism



This bond is broken... ***before*** ...this bond is formed.

The Nucleophile

- Although nucleophilicity and basicity are interrelated, they are fundamentally different.

  - Basicity is a thermodynamic property.

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

  - Nucleophilicity is a kinetic property.

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

The Nucleophile

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

  HO^{-} is a stronger base and 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.

- Going down along a group nucleophilicity increases as polarizability increases:

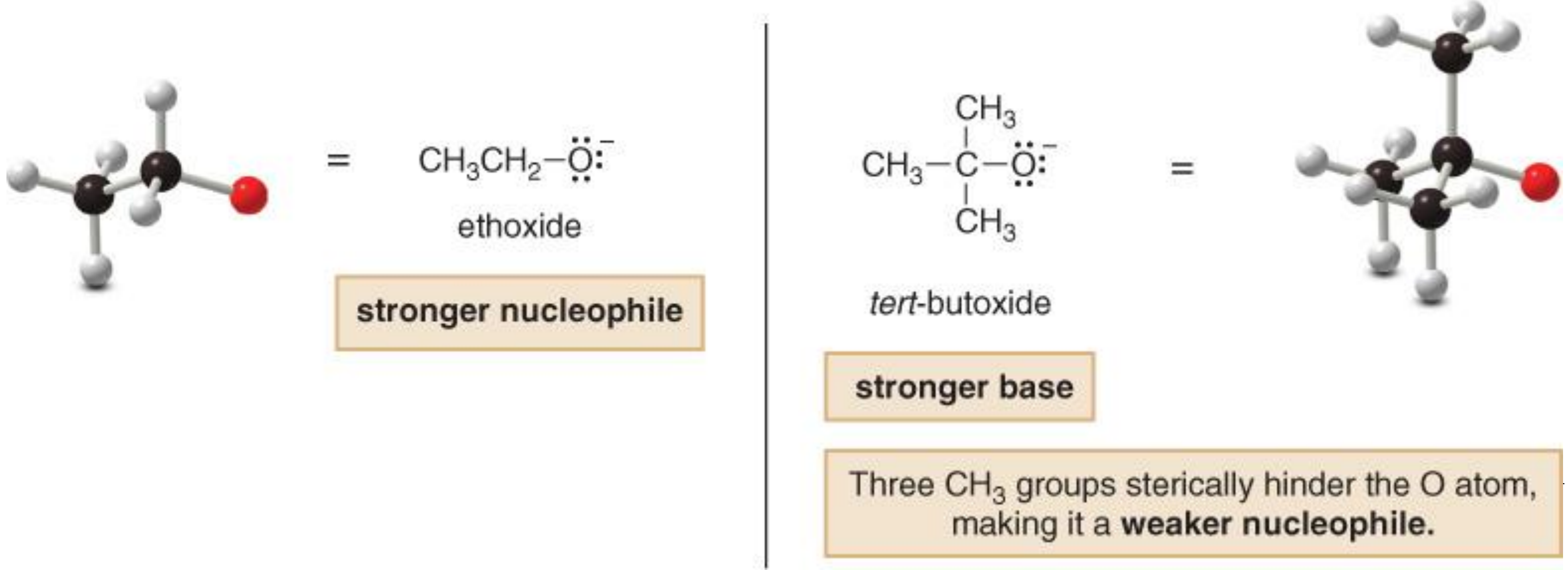
H_2S is a weaker base but a stronger nucleophile than H_2O. Nucleophilicity increases following the order $F^{-}<Cl^{-}<Br^{-}<I^{-}$ while basicity follow the opposite order

- 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

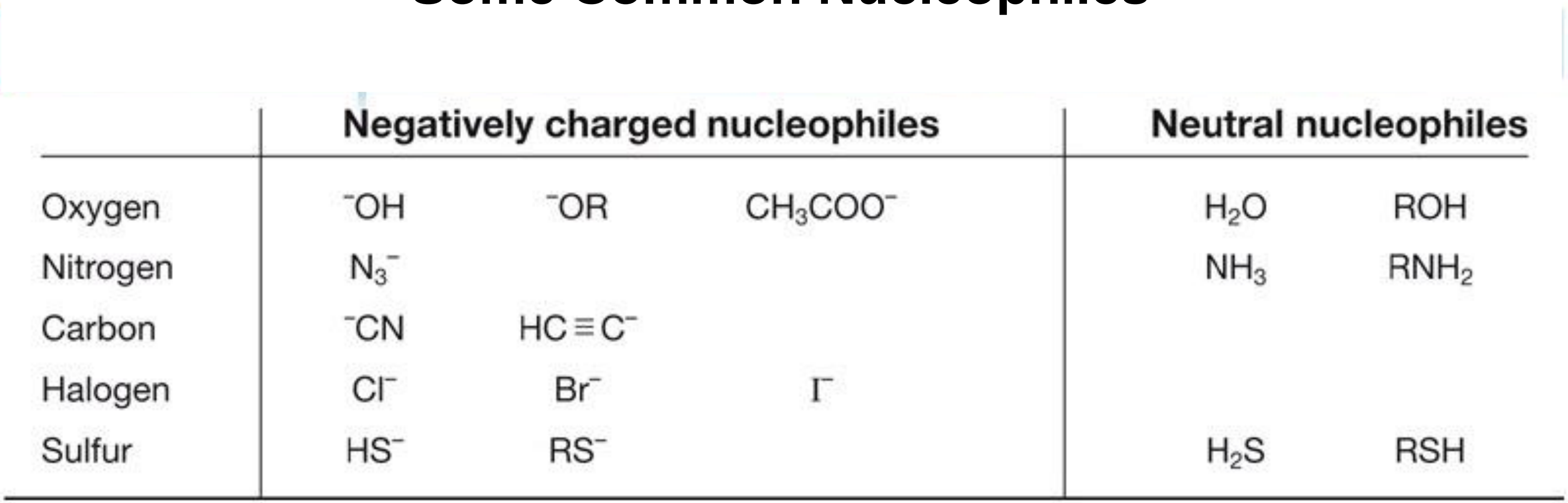
- Nucleophilicity does not parallel basicity when steric hindrance becomes important.
- Steric hindrance results from the presence of bulky groups at the site of a reaction.
- Steric hindrance decreases nucleophilicity but not basicity.
- Sterically hindered bases that are poor nucleophiles are called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



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

The Nucleophile

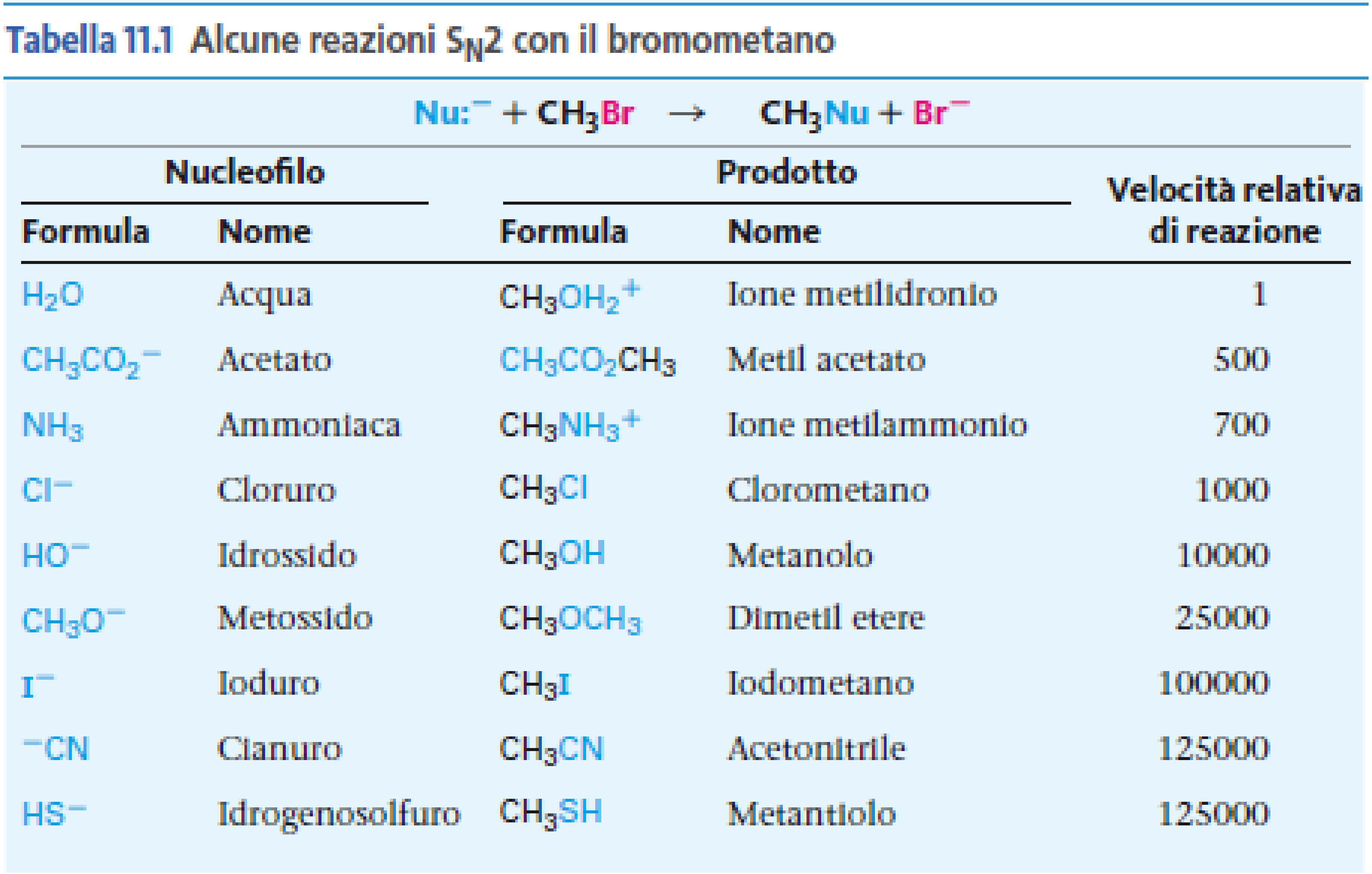


Tabella 11.1 Alcune reazioni S_N2 con il bromometano

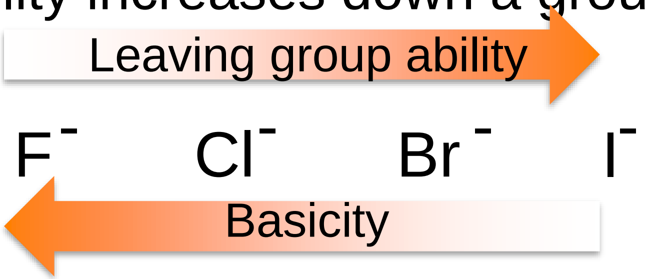
$$Nu:^- + CH_3Br \rightarrow CH_3Nu + Br^-$$

Nucleofilo		Prodotto		Velocità relativa di reazione
Formula	**Nome**	**Formula**	**Nome**	
H_2O	Acqua	$CH_3OH_2^+$	Ione metilidronio	1
$CH_3CO_2^-$	Acetato	$CH_3CO_2CH_3$	Metil acetato	500
NH_3	Ammoniaca	$CH_3NH_3^+$	Ione metilammonio	700
Cl^-	Cloruro	CH_3Cl	Clorometano	1000
HO^-	Idrossido	CH_3OH	Metanolo	10000
CH_3O^-	Metossido	CH_3OCH_3	Dimetil etere	25000
I^-	Ioduro	CH_3I	Iodometano	100000
^-CN	Cianuro	CH_3CN	Acetonitrile	125000
HS^-	Idrogenosolfuro	CH_3SH	Metantiolo	125000

The Leaving Group

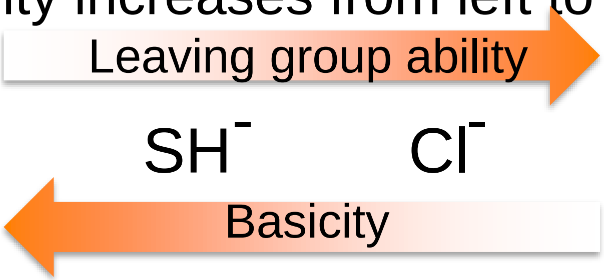
Stable (weak bases) species are good leaving groups.

- Leaving group ability increases down a group:



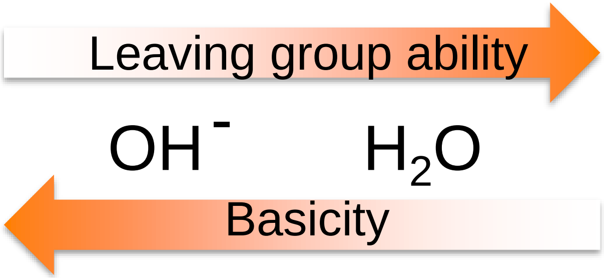
F^- Cl^- Br^- I^-

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



SH^- Cl^-

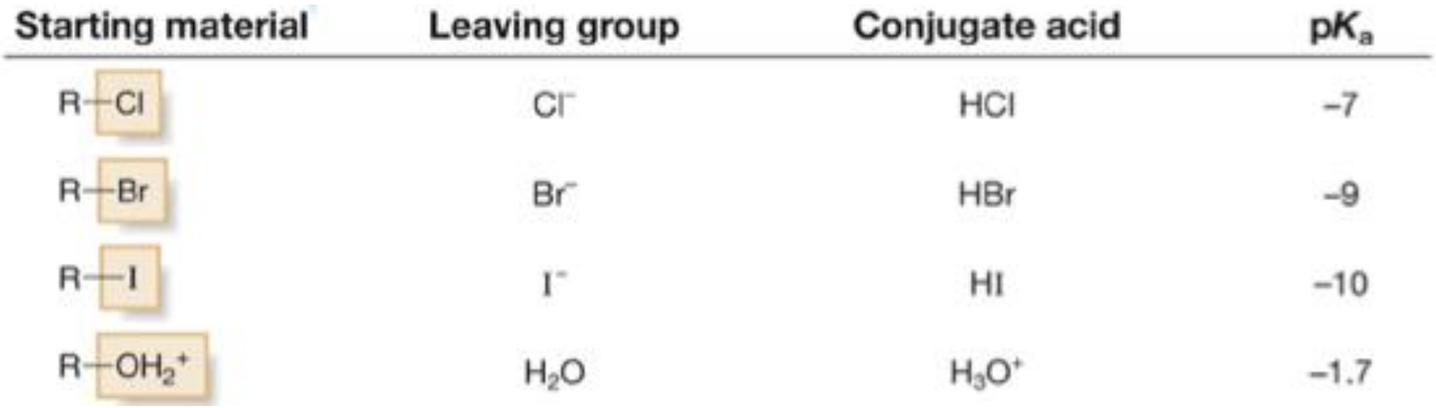
- Neutral leaving groups are better than charged ones



OH^- H_2O

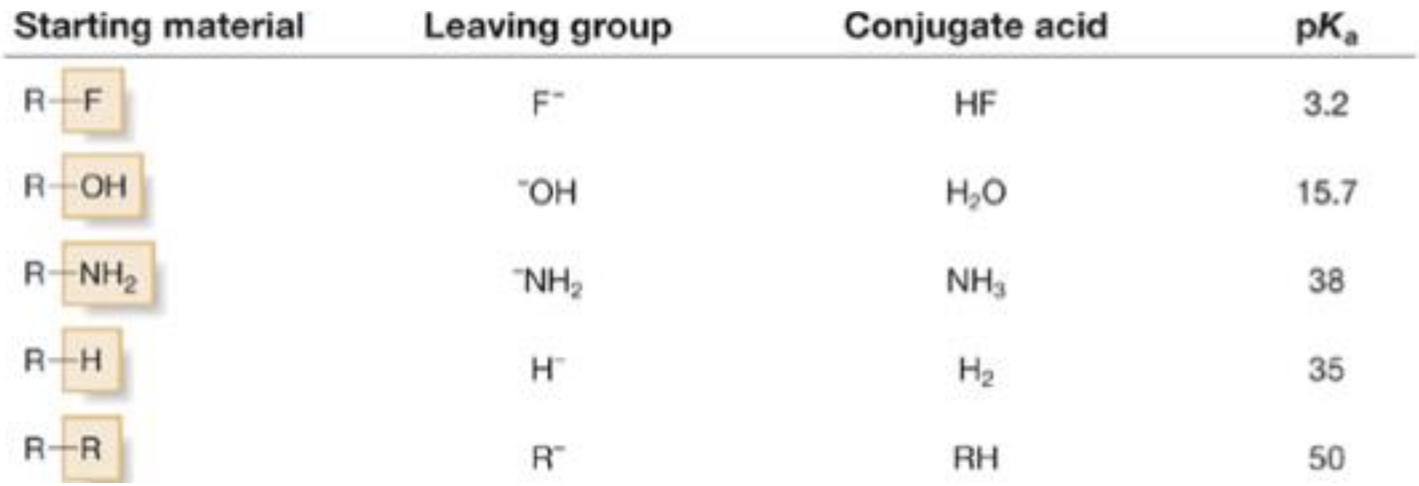
The Leaving Group

These molecules undergo nucleophilic substitution



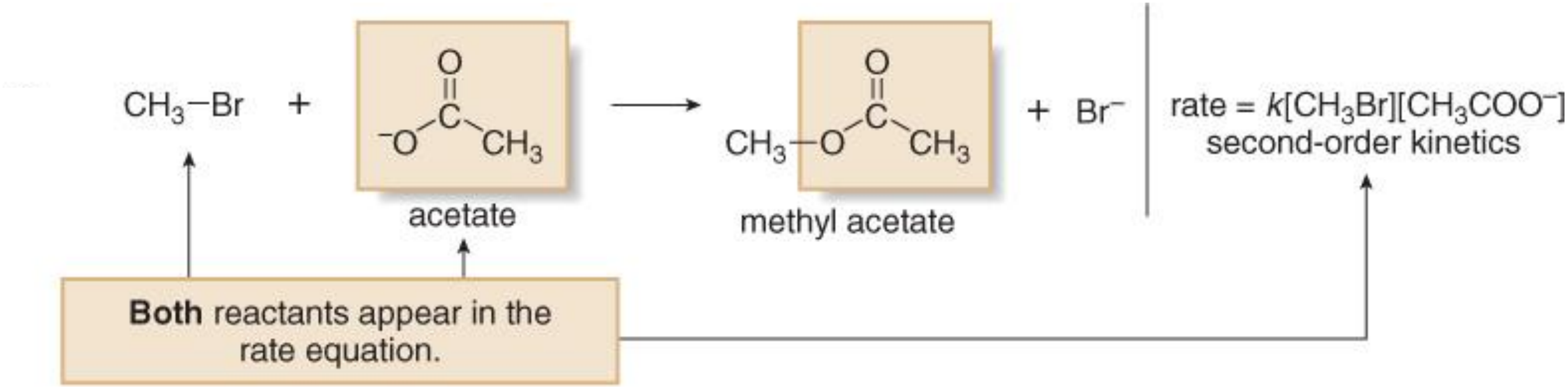
Starting material	Leaving group	Conjugate acid	pK_a
R—Cl	Cl^-	HCl	–7
R—Br	Br^-	HBr	–9
R—I	I^-	HI	–10
R—OH_2^+	H_2O	H_3O^+	–1.7

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

S_N2 Mechanism: Kinetics



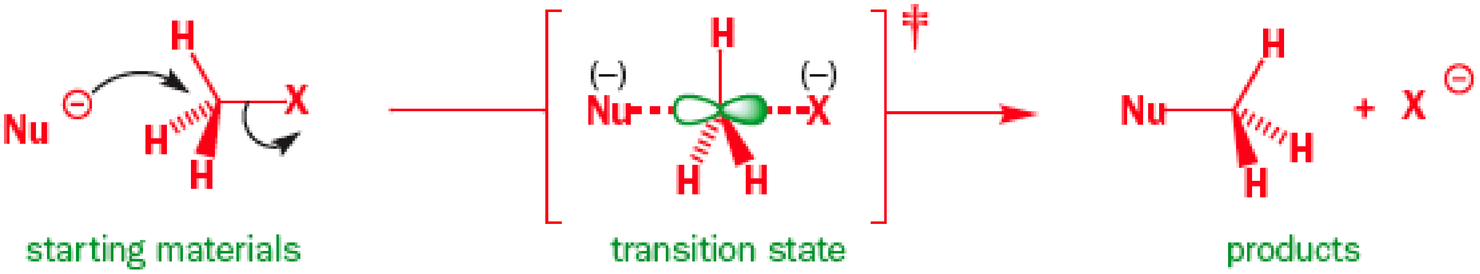
$\text{rate} = k[CH_3Br][CH_3COO^-]$

second-order kinetics

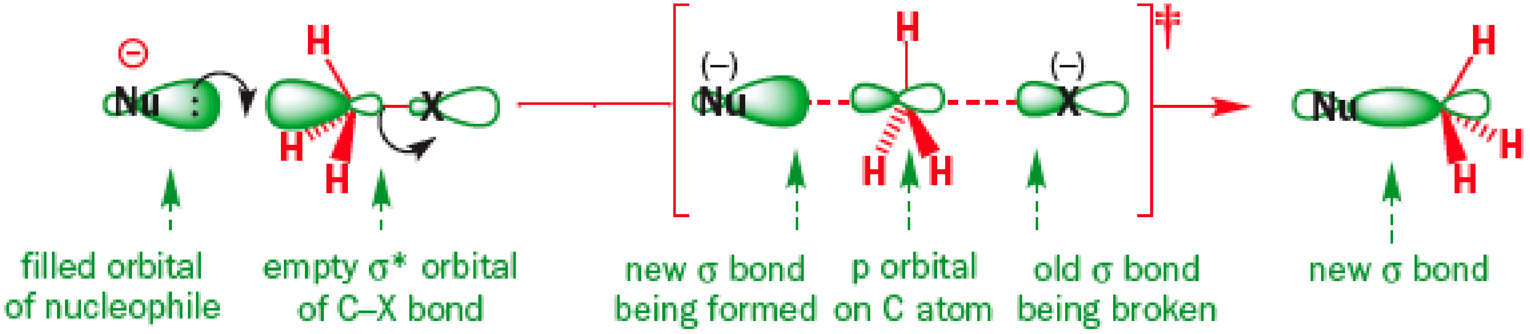
Both reactants appear in the rate equation.

S_N2 Mechanism: Stereochemistry

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

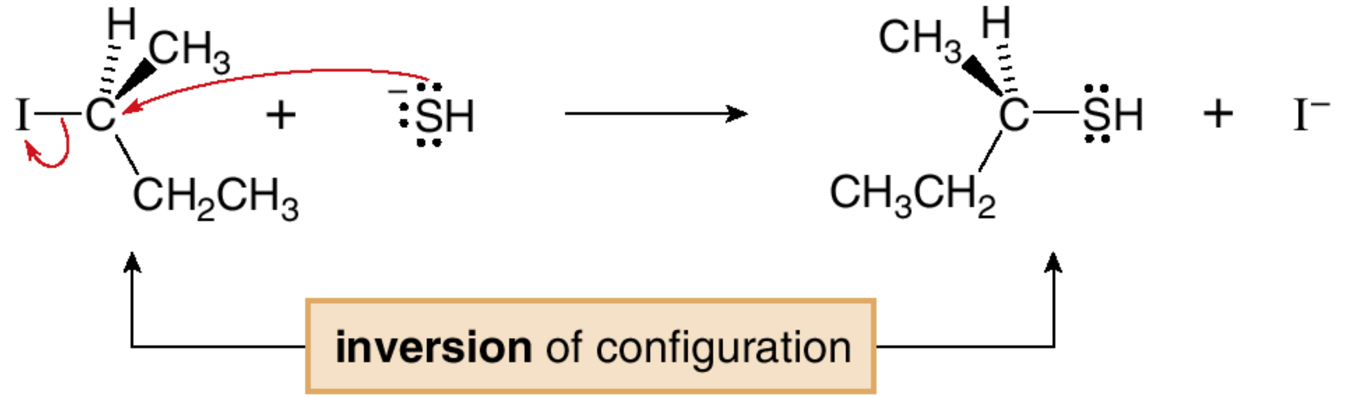


:Nu^- and X^- are 180° away from each other,
on either side of a plane containing C, H, H, H

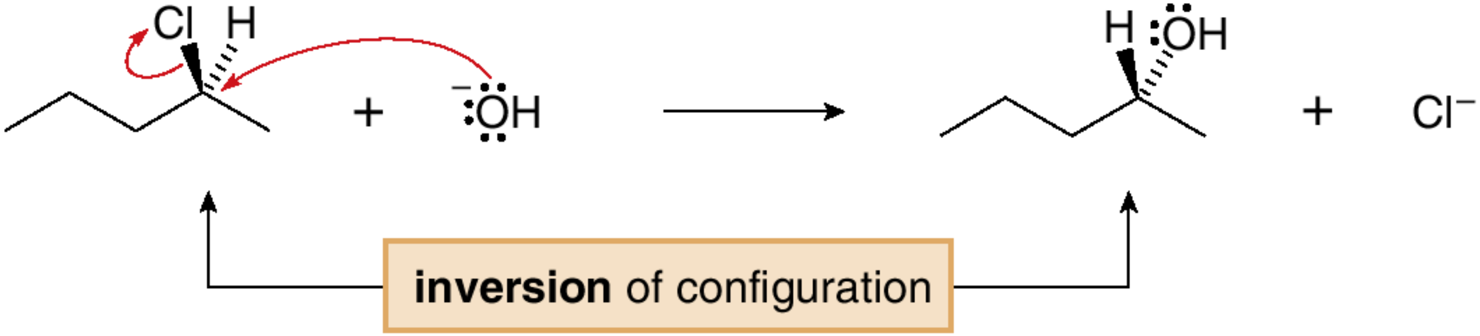


S_N2 Mechanism: Stereochemistry

- 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.



inversion of configuration

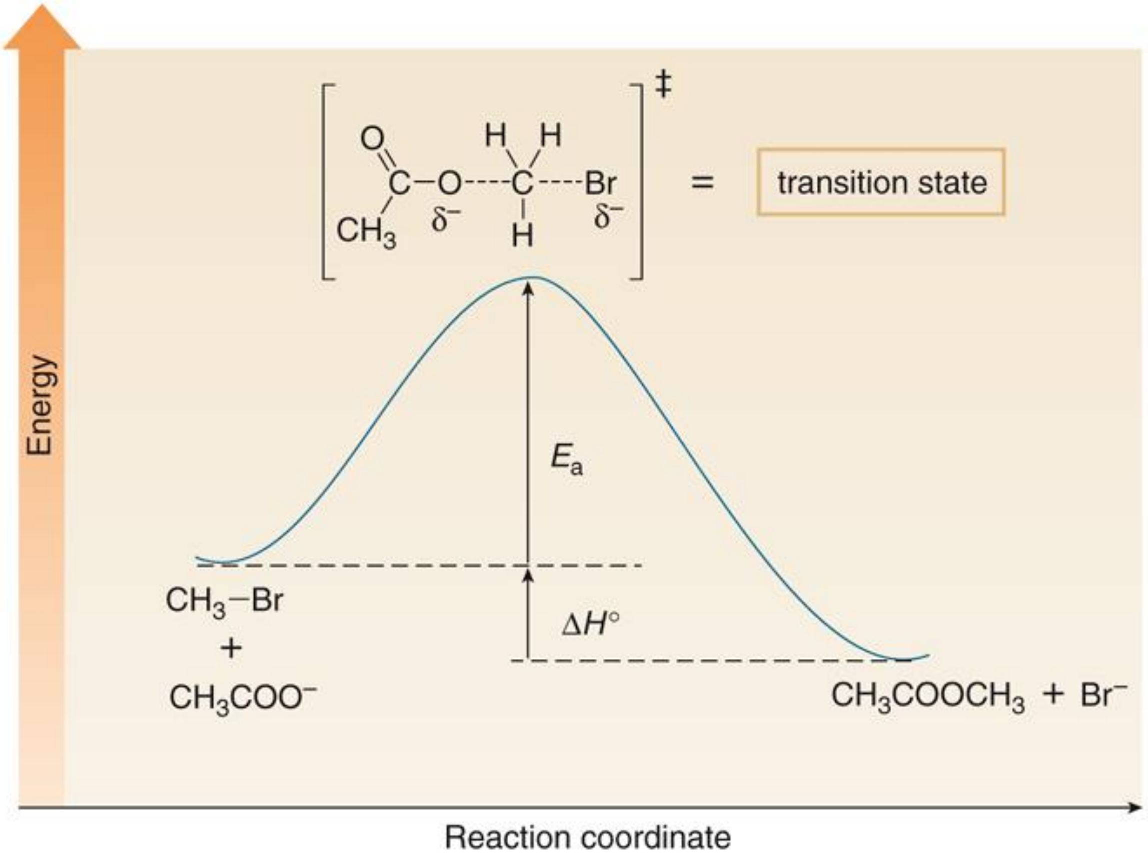


inversion of configuration

S_N2 Mechanism: Energy Profile

Energy profile for the reaction:

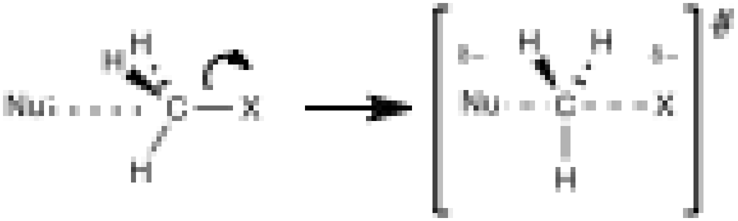
$CH_3Br + CH_3COO^- \rightarrow CH_3COOCH_3 + Br^-$

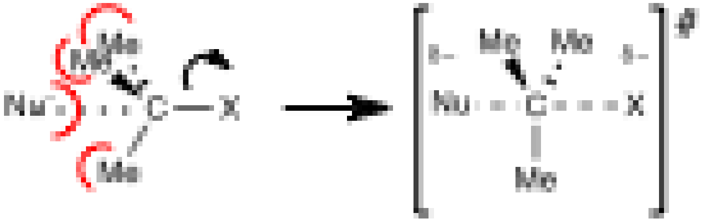


- In the transition state, the C–Br bond is partially broken, the C–O bond is partially formed, and both the attacking nucleophile and the departing leaving group bear a partial negative charge.

S_N2 Reaction: The Alkyl Substrate

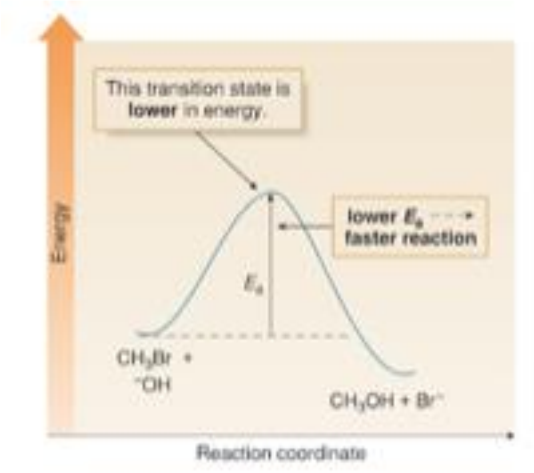
- Increasing the number of R groups on the carbon with the leaving group makes the approach of the nucleophile more difficult and increases crowding in the transition state.
- The S_N2 reaction is fastest with unhindered halides.

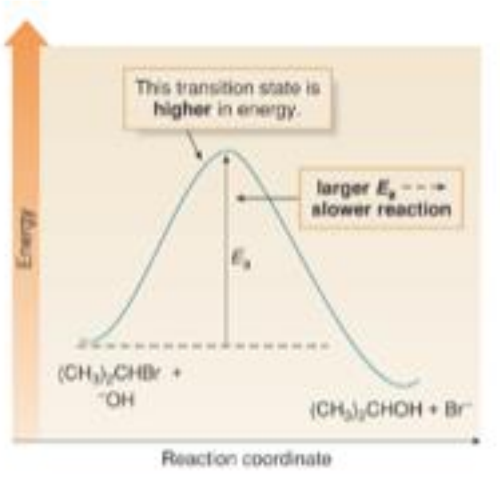




hindered approach

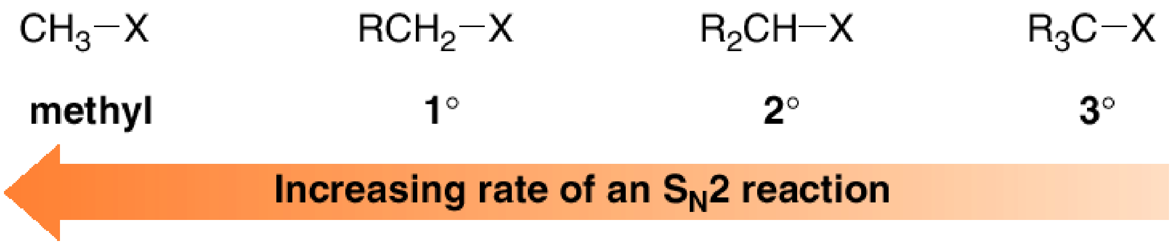
crowded transition state





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.*



$CH_3{-}X$	$RCH_2{-}X$	$R_2CH{-}X$	$R_3C{-}X$
methyl	**1°**	**2°**	**3°**

Increasing rate of an S_N2 reaction

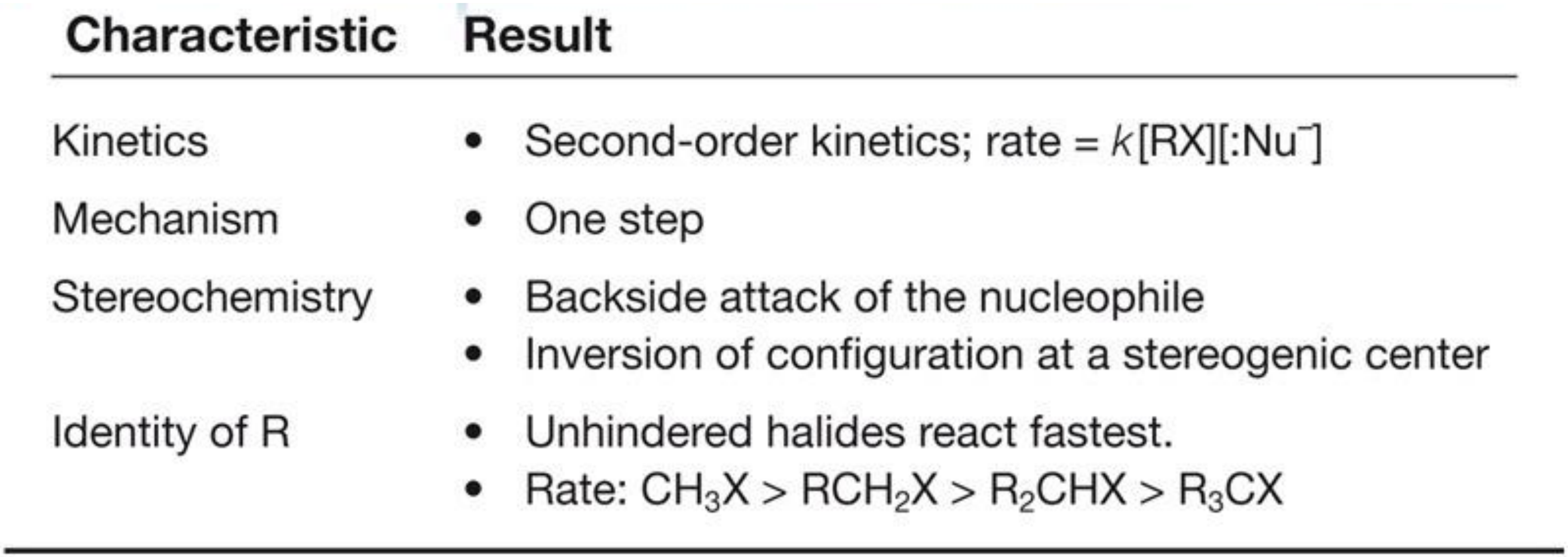
This order of reactivity can be explained by steric effects.

- 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.

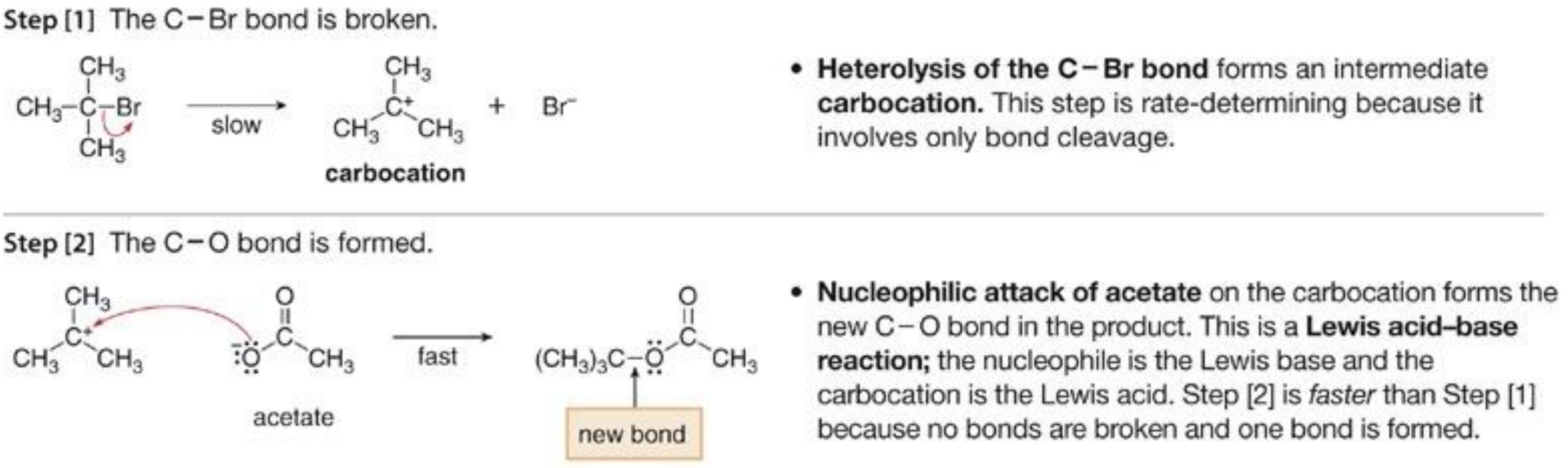
S_N2 Mechanism



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

The S_N1 mechanism has two steps, and carbocations are formed as reactive intermediates.



Step [1] The C–Br bond is broken.

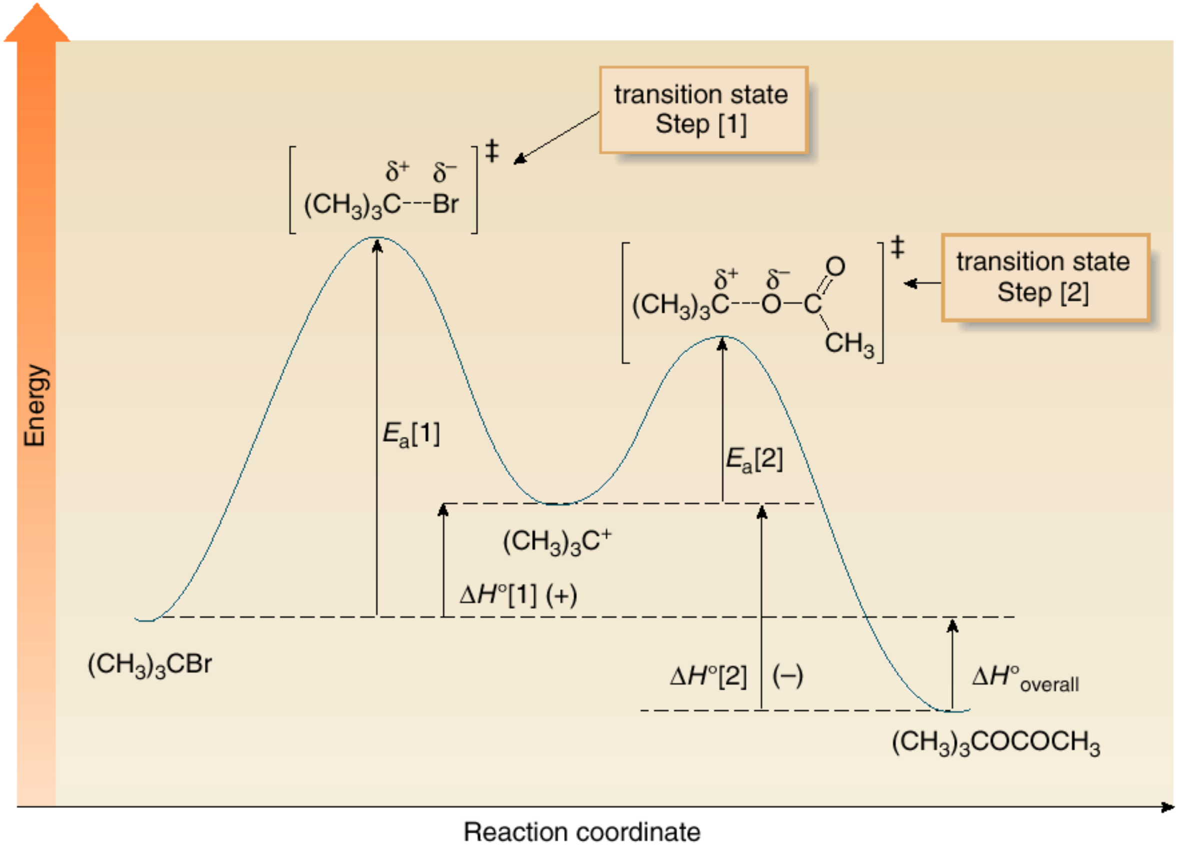
- **Heterolysis of the C–Br bond** forms an intermediate **carbocation.** This step is rate-determining because it involves only bond cleavage.

Step [2] The C–O bond is formed.

- **Nucleophilic attack of acetate** on the carbocation forms the new C–O bond in the product. This is a **Lewis acid–base reaction;** the nucleophile is the Lewis base and the carbocation is the Lewis acid. Step [2] is *faster* than Step [1] because no bonds are broken and one bond is formed.

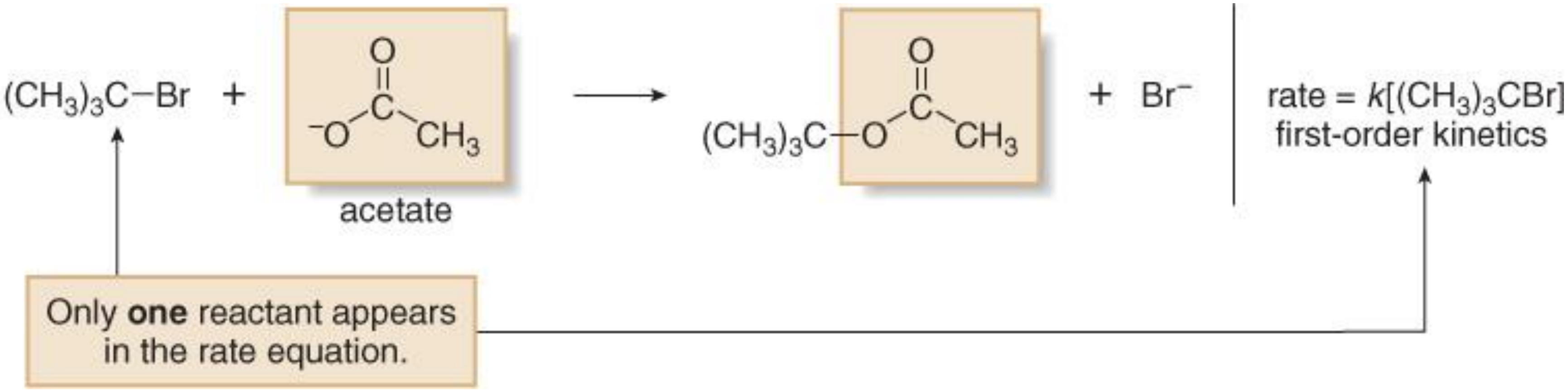
S_N1 Mechanism: Energetics

$(CH_3)_3CBr + CH_3COO^- \rightarrow$
$(CH_3)_3COCOCH_3 + Br^-$



- Since the S_N1 mechanism has two steps, there are two energy barriers.
- $E_a[1] > E_a[2]$ since Step [1] involves bond breaking and Step [2] involves bond formation.
- In each step only one bond is broken or formed, so the transition state for each step has one partial bond.
- The reaction is drawn with $\Delta H°_{overall}$ as a negative value, since the products are lower in energy than the starting materials.

S_N1 Mechanism: Kinetics

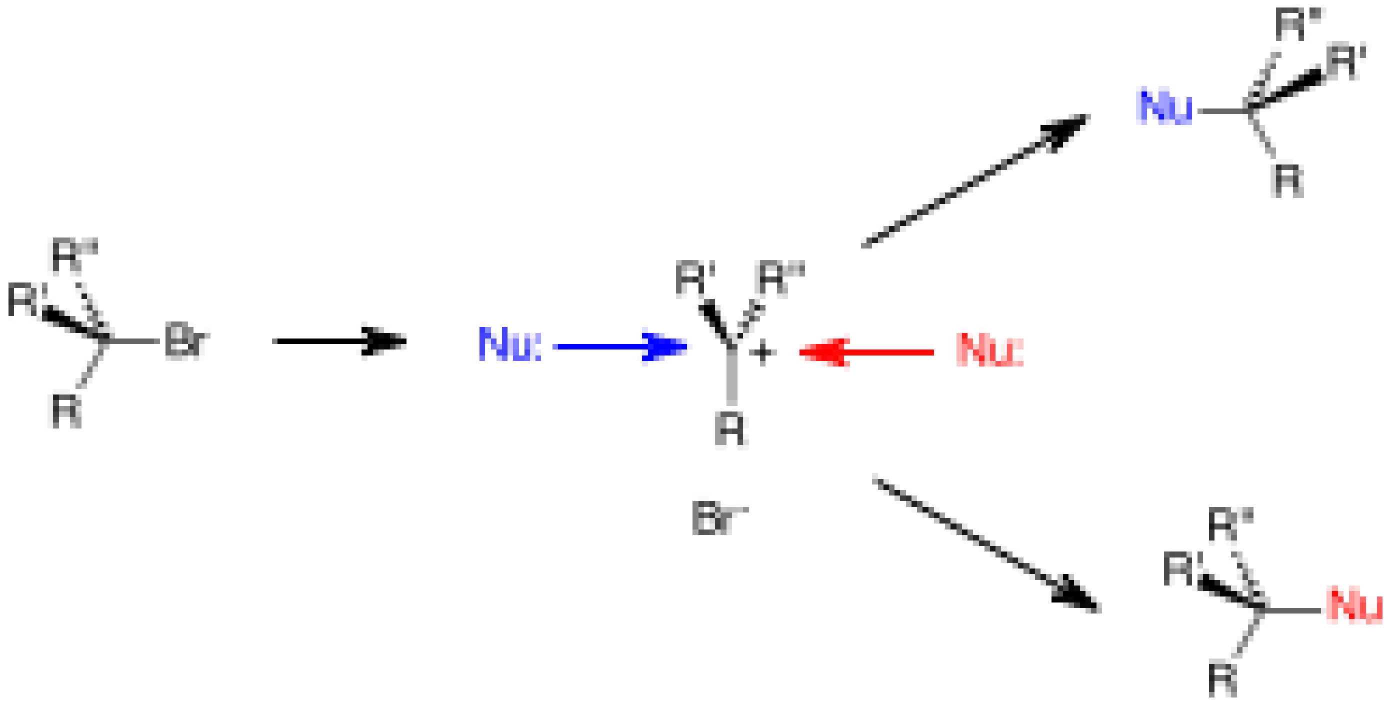


rate = $k[(CH_3)_3CBr]$
first-order kinetics

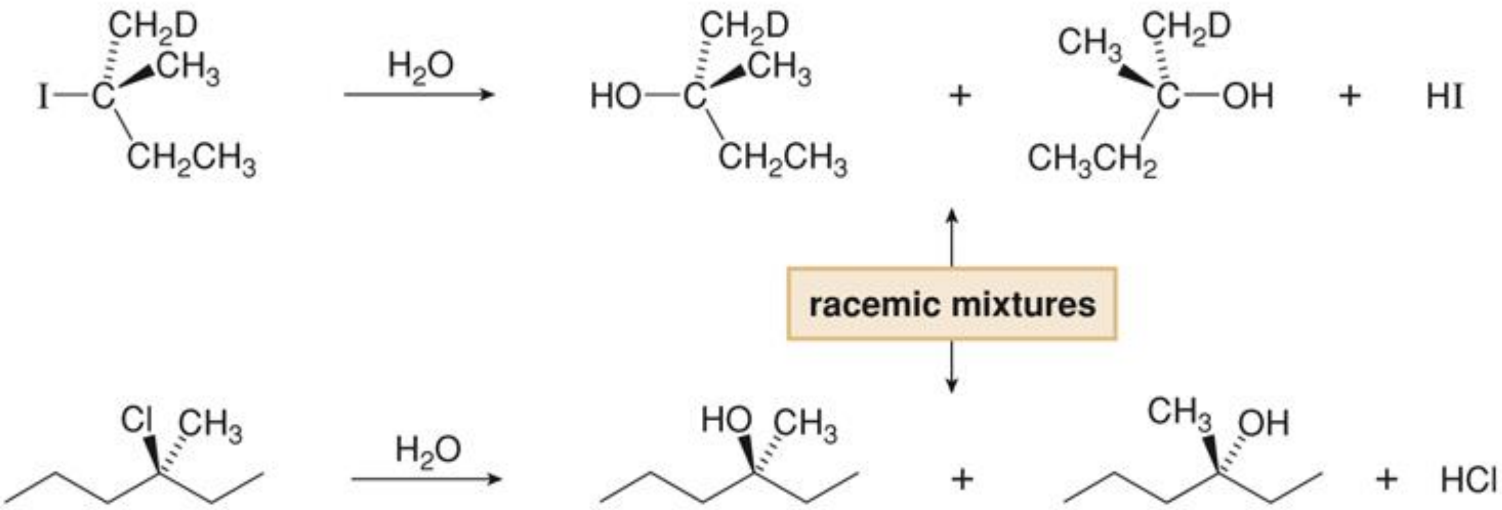
Only **one** reactant appears in the rate equation.

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

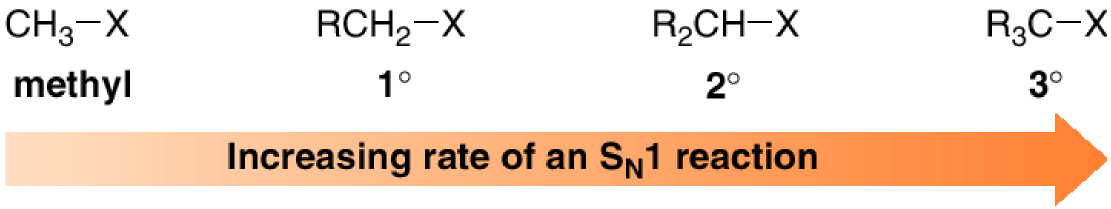


- Nucleophilic substitution of each starting material by an S_N1 mechanism forms a **racemic mixture** of two products.
- With H_2O, a neutral nucleophile, the initial product of nucleophilic substitution (ROH_2^+) loses a proton to form the final neutral product, ROH (Section 7.6).

The Alkyl Substrate

- The rate of an S_N1 reaction is affected by the type of alkyl halide involved.

- 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 **methyl**

RCH_2-X **1°**

R_2CH-X **2°**

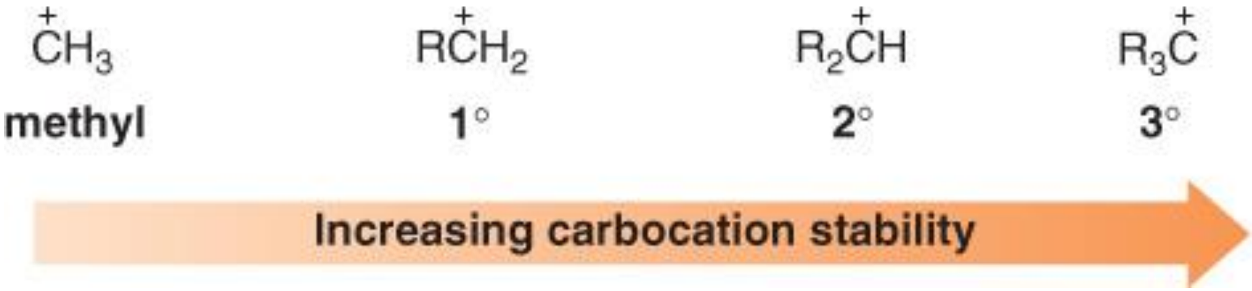
R_3C-X **3°**

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



$\overset{+}{C}H_3$ **methyl**

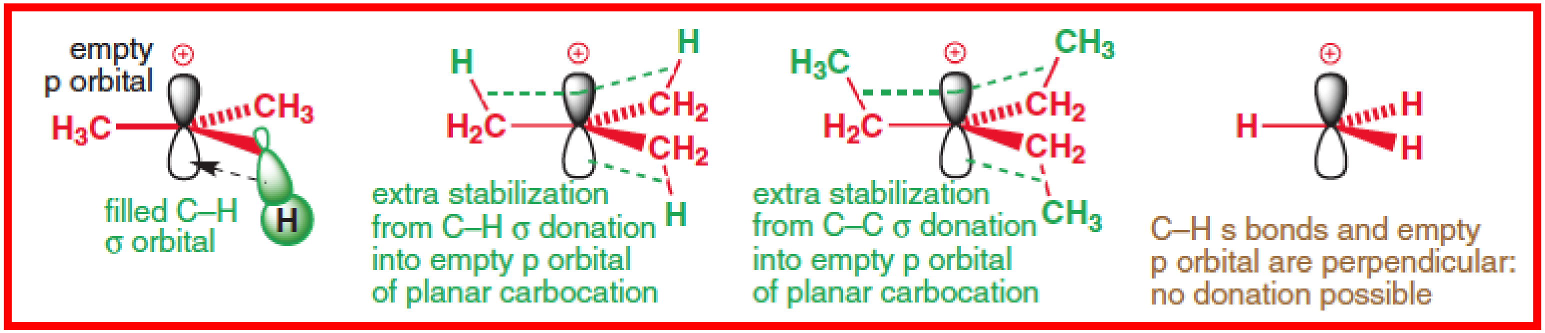
$R\overset{+}{C}H_2$ **1°**

$R_2\overset{+}{C}H$ **2°**

$R_3\overset{+}{C}$ **3°**

Increasing 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.



filled C–H σ orbital

extra stabilization from C–H σ donation into empty p orbital of planar carbocation

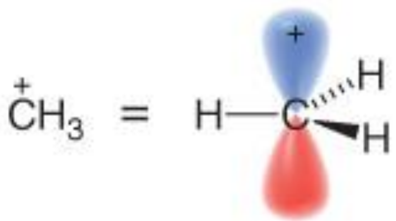
extra stabilization from C–C σ donation into empty p orbital of planar carbocation

C–H s bonds and empty p orbital are perpendicular: no donation possible

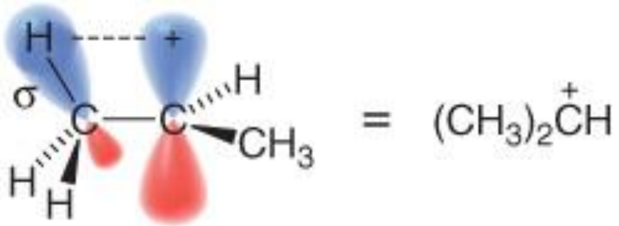
Carbocation Stability

- Hyperconjugation is the spreading out of charge by the overlap of an empty *p* orbital with an adjacent σ bond. This overlap (hyperconjugation) delocalizes the positive charge on the carbocation, spreading it over a larger volume, and this stabilizes the carbocation.

- Example: CH_3^+ cannot be stabilized by hyperconjugation, but $(CH_3)_2CH^+$ can.



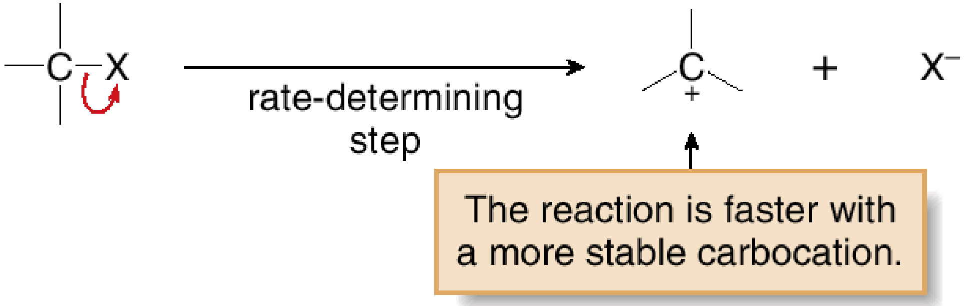
This carbocation has no opportunity for orbital overlap with the vacant *p* orbital.



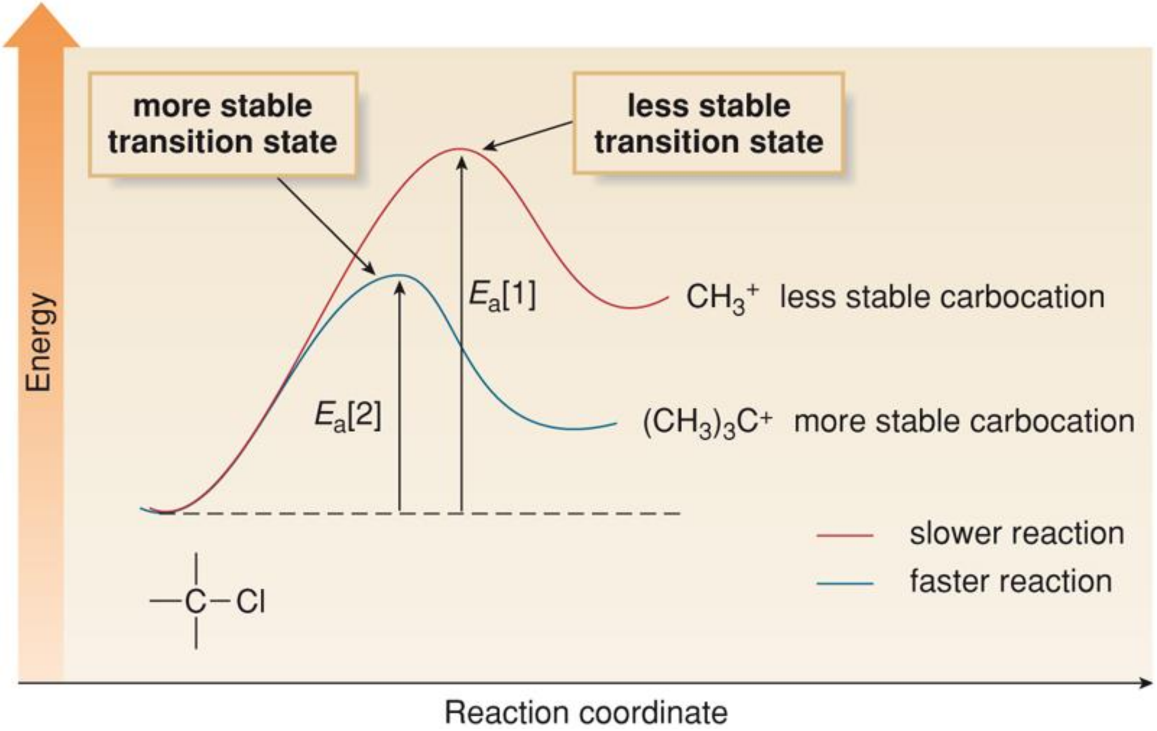
Overlap of the C–H σ bond with the adjacent vacant *p* orbital stabilizes the carbocation.

The Hammond Postulate

- Thus, the rate of an S_N1 reaction *increases* as the stability of the carbocation *increases.*

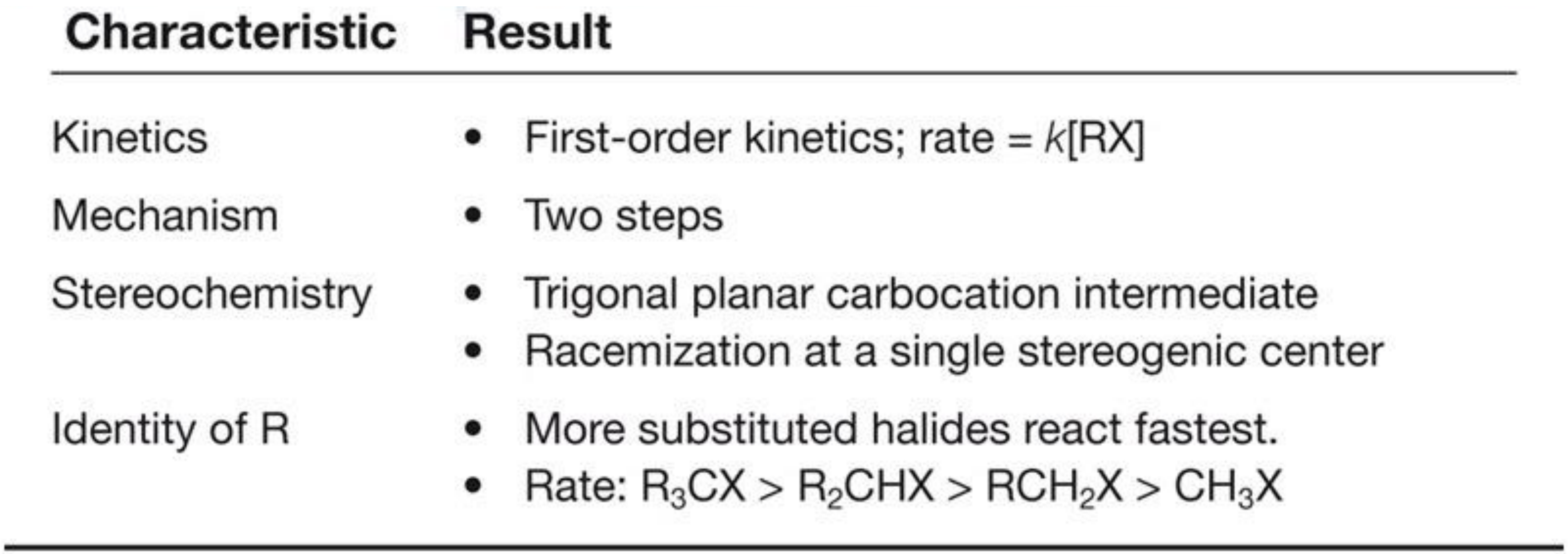


The reaction is faster with a more stable carbocation.



- Since CH_3^+ is less stable than $(CH_3)_3C^+$, $E_a[1] > E_a[2]$, and Reaction [1] is slower.

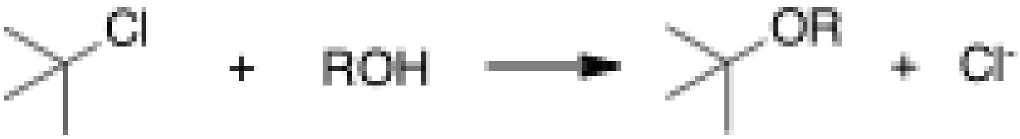
S_N1 Mechanism



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: $R_3CX > R_2CHX > RCH_2X > CH_3X$

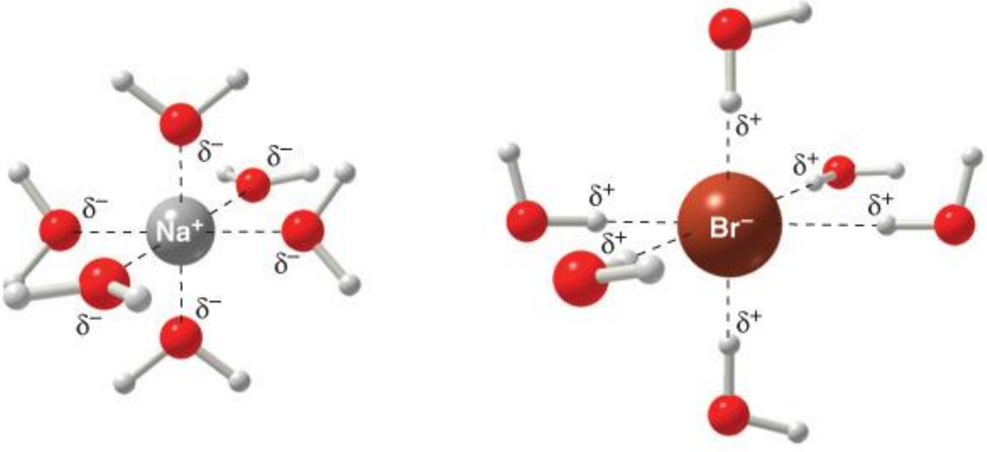
S_N1 Mechanism

- Leaving group: the same reactivity order as in S_N2 reactions.
- Nucleophile: has little effect in S_N1 reactions because it reacts after the slow step (must be nonbasic to prevent elimination) bur good nucleophiles favour S_N2 reactions.
- Solvent: polar solvents favor the reaction by stabilizing the intermediate carbocation (Hammond postulate).



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

The Solvent



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

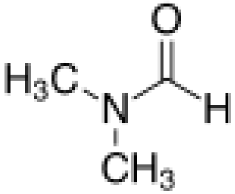
Br− is solvated by hydrogen bonding with H_2O.

- Protic solvents slow down SN_2 reactions

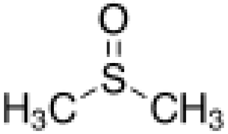
H_2O	CH_3OH	CH_3CH_2OH	$(CH_3)_3COH$	CH_3COOH
	methanol	ethanol	*tert*-butanol	acetic acid

- SN_2 reations are best carried out in polar aprotic solvents

acetonitrile



N,N-dimethylformamide
DMF

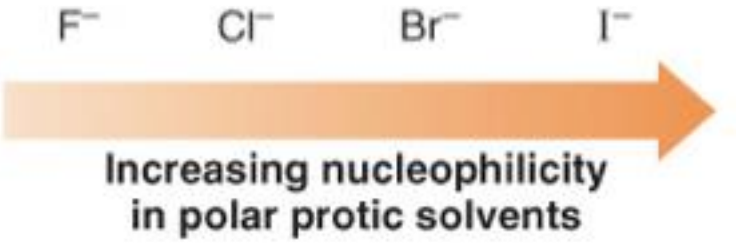


dimethylsulfoxide
DMSO

Solvent Effects on Nucleophilicity

- Hydrogen bonds are stronger with small anions

  In polar protic solvents:



- In polar aprotic solvents, nucleophilicity parallels basicity.

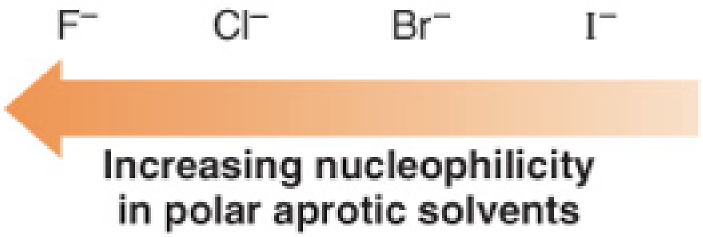
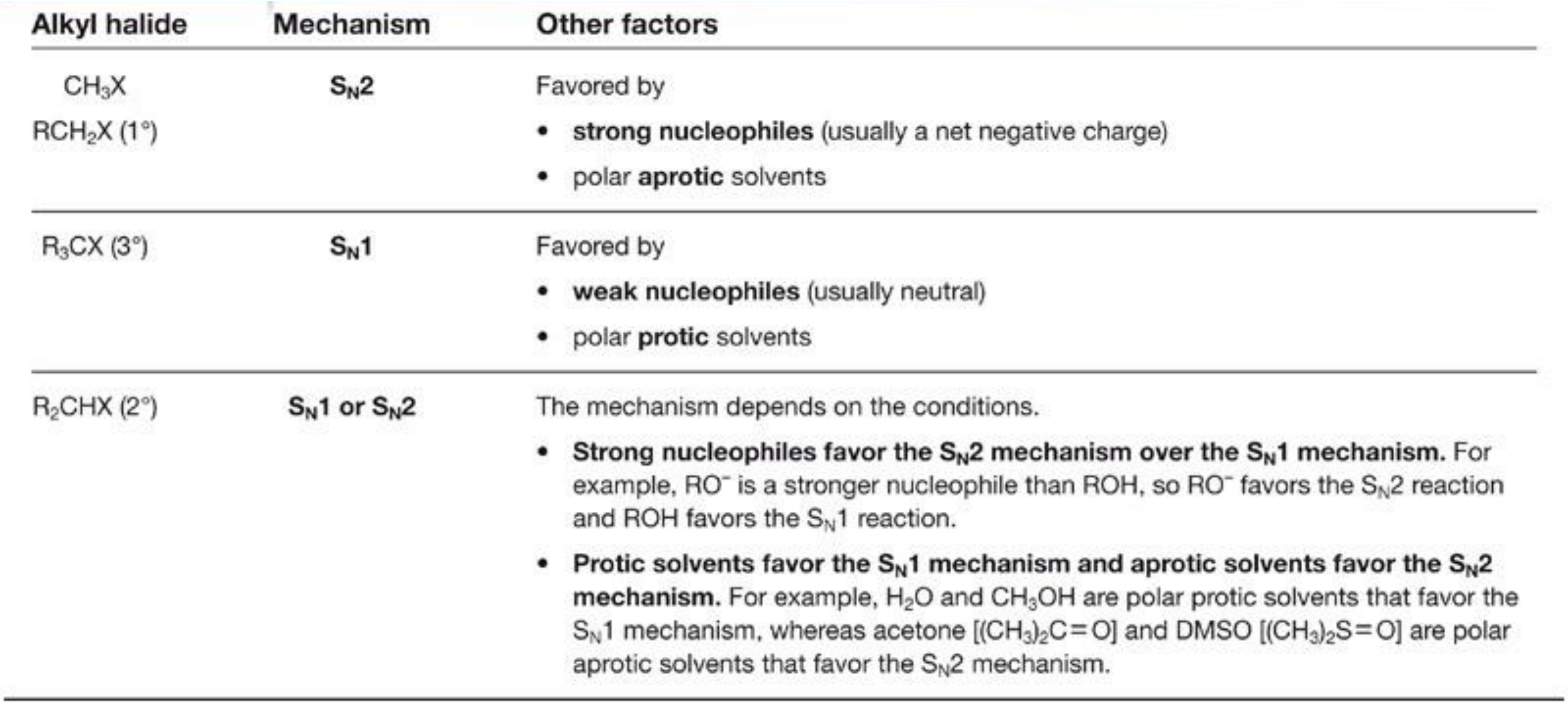


Table 2. Properties of some common solvents

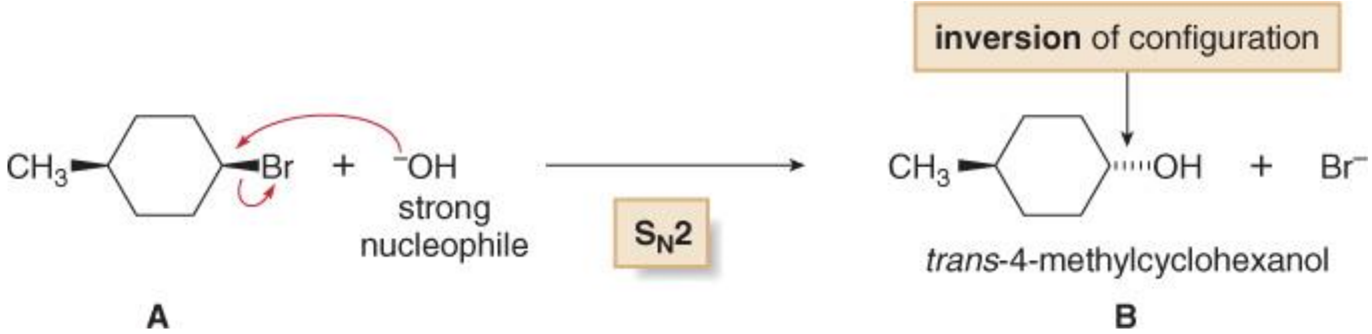
Solvent	Chemical formula	Water solubility in solvent	Dielectric constant (κ)	Dipole moment (μ)
		percentage		*debye*
Pentane	C_5H_{12}	0.01	1.84	—*
Hexane	C_6H_{14}	0.01	1.88	—
Cyclohexane	C_6H_{12}	0.012	2.02	—
Carbon disulfide	CS_2	0.005	2.64	0
Carbon tetrachloride	CCl_4	0.008	2.24	0
Benzene	C_6H_6	0.058	2.30	0
Diethyl ether	$(C_2H_5)_2O$	1.3	4.3	1.15
Chloroform	$CHCl_3$	0.07	4.8	1.01
Methyl chloride	CH_2Cl_2	0.17	8.9	1.60
Tetrahydrofuran	C_4H_8O	miscible	7.6	1.63
Acetone	CH_3COCH_3	miscible	—	2.88
Dioxane	$C_4H_8O_2$	miscible	2.2	0
Ethyl acetate	$CH_3COOC_2H_5$	9.8	6.0	1.78
1-Pentanol	$C_5H_{11}OH$	10.0	15.0	—
Acetonitrile	CH_3CN	miscible	—	3.92
1-Propanol	C_3H_8OH	miscible	20.3	1.68
Dimethylsulfoxide	$(CH_3)_2SO$	miscible	4.7	3.96
Dimethylformamide	$HCON(CH_3)_2$	miscible	36.7	3.82
Methanol	CH_3OH	miscible	32.7	1.70
Water	H_2O	—	80.0	1.85

Predicting the Mechanism

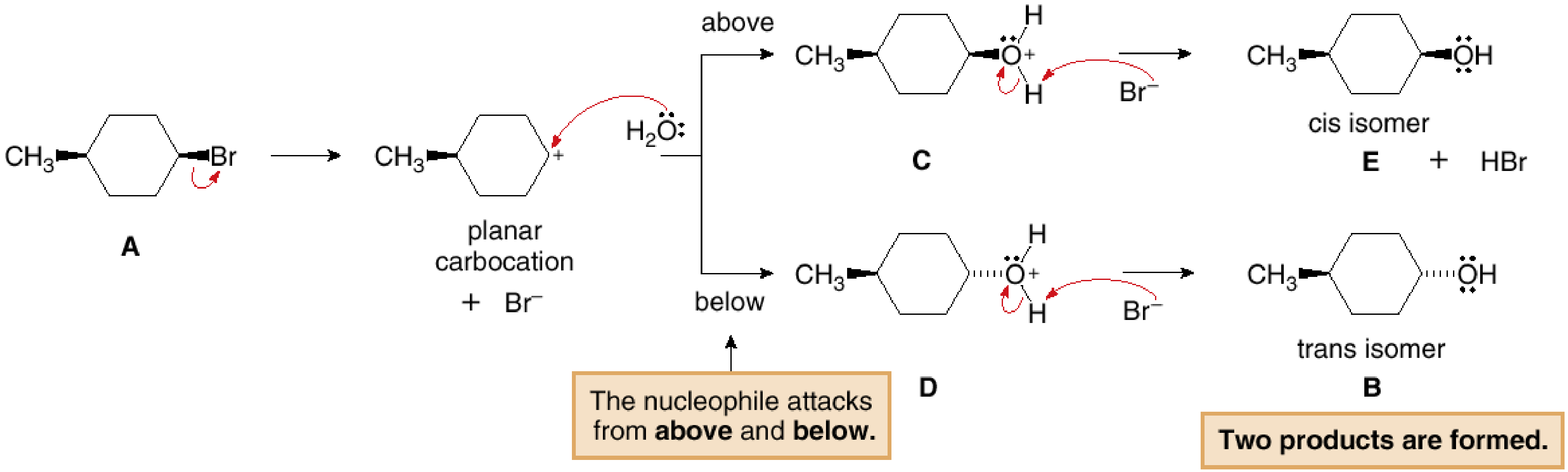


Alkyl halide	Mechanism	Other factors
CH_3X RCH_2X (1°)	**S_N2**	Favored by • **strong nucleophiles** (usually a net negative charge) • polar **aprotic** solvents
R_3CX (3°)	**S_N1**	Favored by • **weak nucleophiles** (usually neutral) • polar **protic** solvents
R_2CHX (2°)	**S_N1 or S_N2**	The mechanism depends on the conditions. • **Strong nucleophiles favor the S_N2 mechanism over the S_N1 mechanism.** For example, RO^- is a stronger nucleophile than ROH, so RO^- favors the S_N2 reaction and ROH favors the S_N1 reaction. • **Protic solvents favor the S_N1 mechanism and aprotic solvents favor the S_N2 mechanism.** For example, H_2O and CH_3OH are polar protic solvents that favor the S_N1 mechanism, whereas acetone $[(CH_3)_2C{=}O]$ and DMSO $[(CH_3)_2S{=}O]$ are polar aprotic solvents that favor the S_N2 mechanism.

Predicting the Mechanism



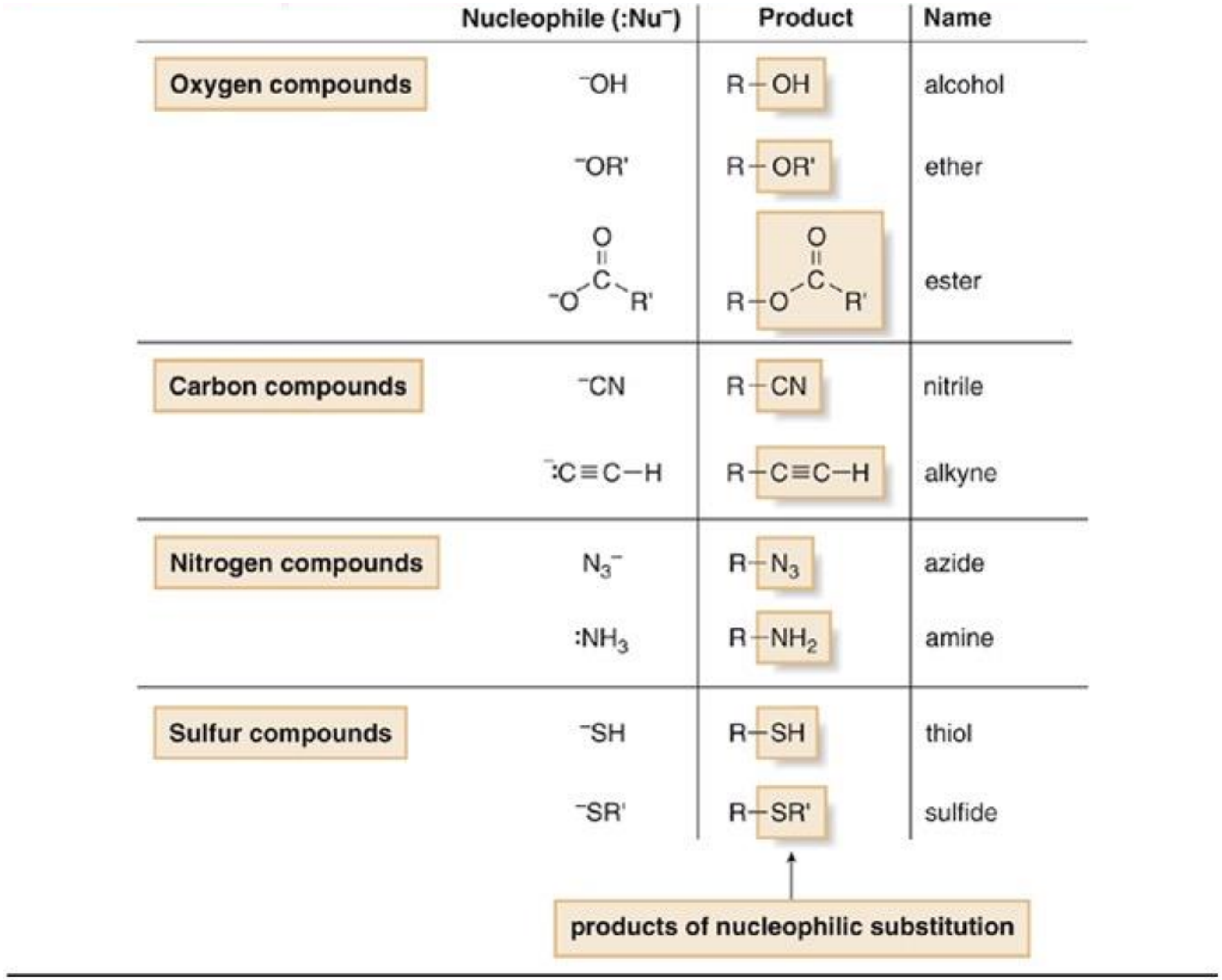
inversion of configuration



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

Two products are formed.

Organic Synthesis

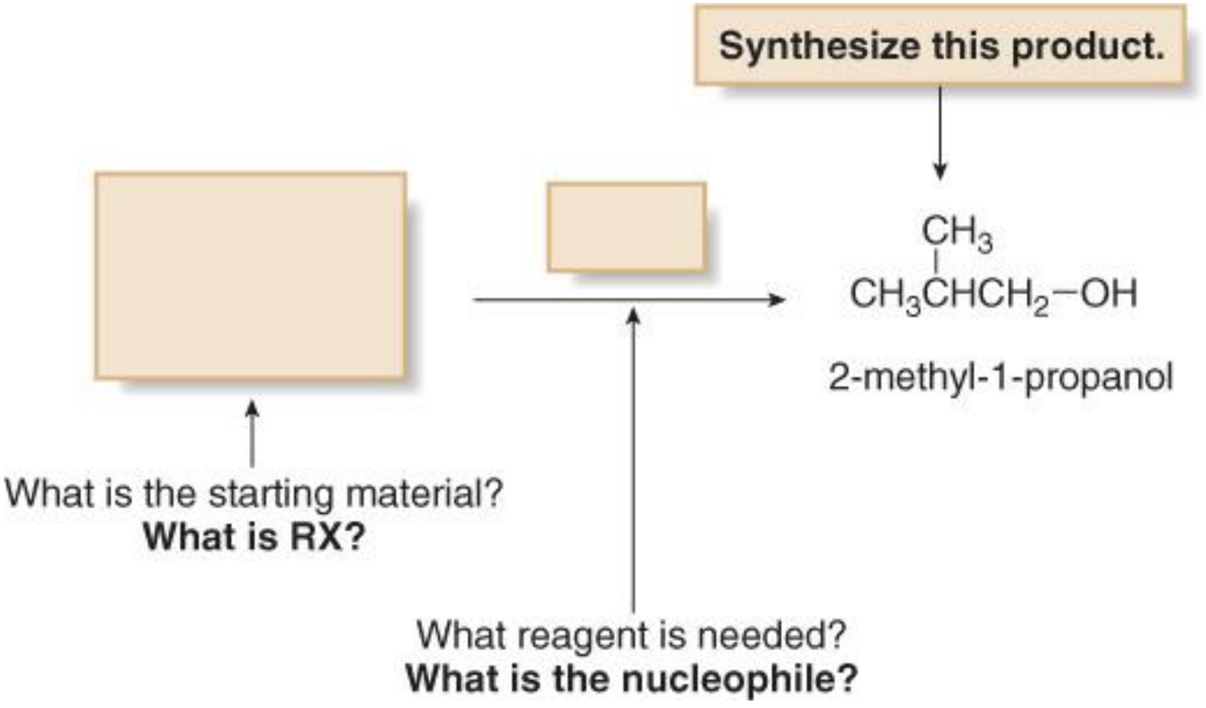


	Nucleophile (:Nu⁻)	Product	Name
Oxygen compounds	^{-}OH	$R-OH$	alcohol
	$^{-}OR'$	$R-OR'$	ether
	$^{-}O-C(=O)-R'$	$R-O-C(=O)-R'$	ester
Carbon compounds	^{-}CN	$R-CN$	nitrile
	$^{-}:C \equiv C-H$	$R-C \equiv C-H$	alkyne
Nitrogen compounds	N_3^-	$R-N_3$	azide
	$:NH_3$	$R-NH_2$	amine
Sulfur compounds	^{-}SH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

products of nucleophilic substitution

Organic Synthesis

- To carry out the synthesis of a particular compound, we must think backwards, and ask ourselves the question: What starting material and reagents are needed to make it?



Synthesize this product.

$$\overset{\displaystyle CH_3}{\overset{|}{CH_3CHCH_2{-}OH}}$$

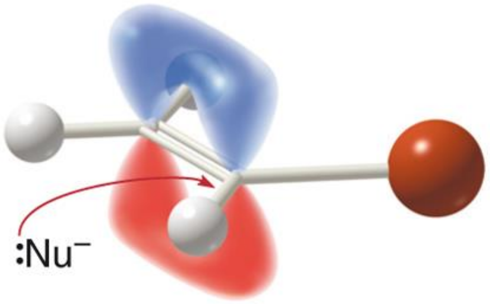
2-methyl-1-propanol

What is the starting material?
What is RX?

What reagent is needed?
What is the nucleophile?

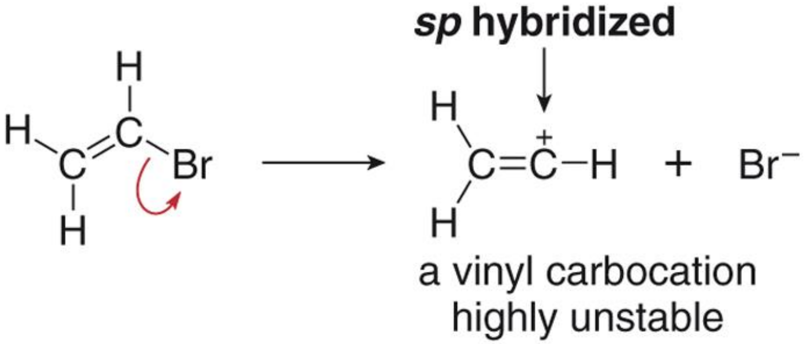
Vinyl Halides

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



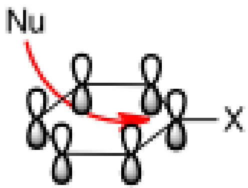
Backside attack would force the nucleophile to approach in the plane of the double bond.

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.



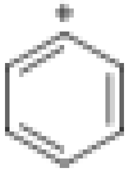
Aryl Halides

S_N2



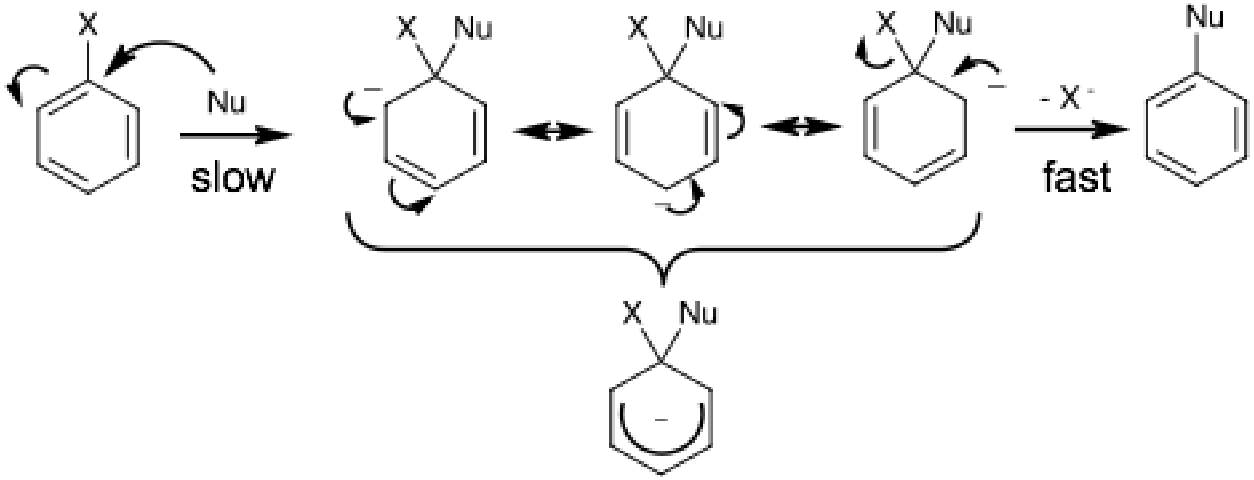
Backside attack
is impossible

S_N1



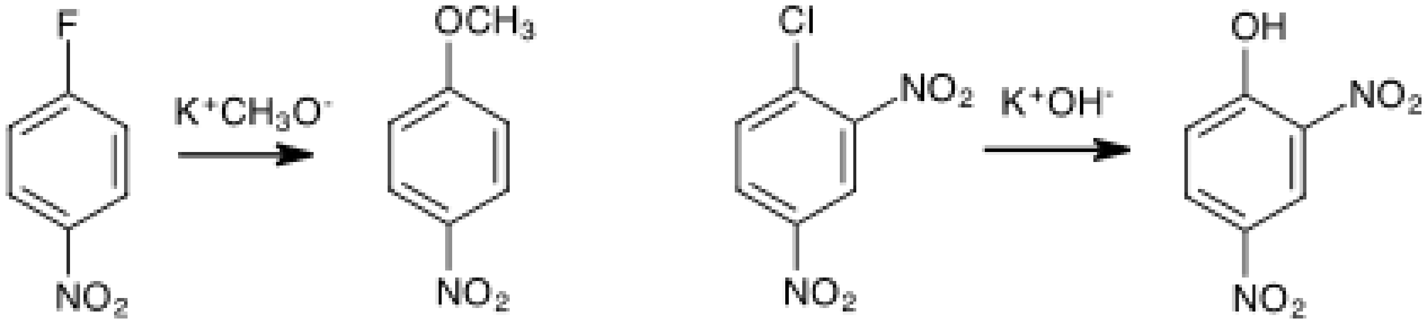
Very unstable
sp^2 carbocation

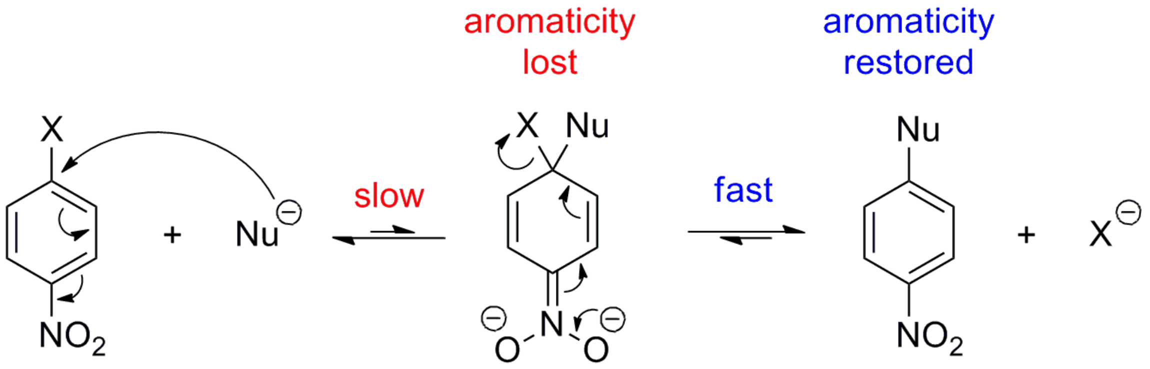
S_NAr



Aryl Halides

- Aromatic compounds are electron rich.
- They react only when strong –R substituents are present.
- The order of reactivity is F>Cl>Br>I





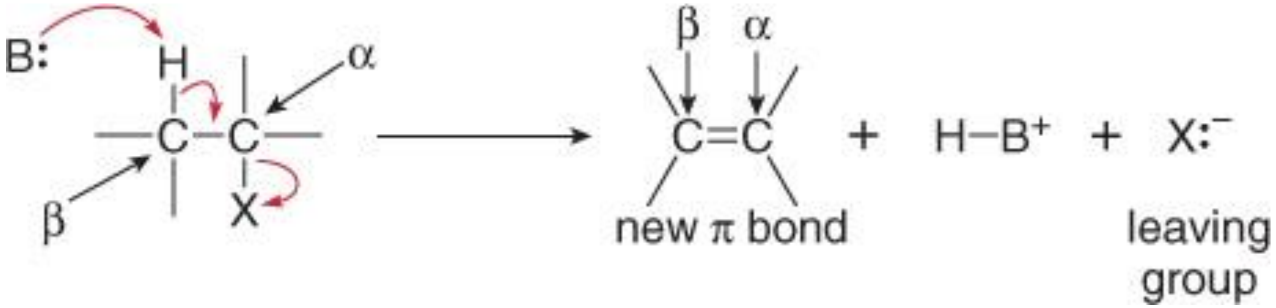
Meisenheimer complex

Eliminations

Chapter 11
Organic Chemistry, *8th Edition*
John McMurry

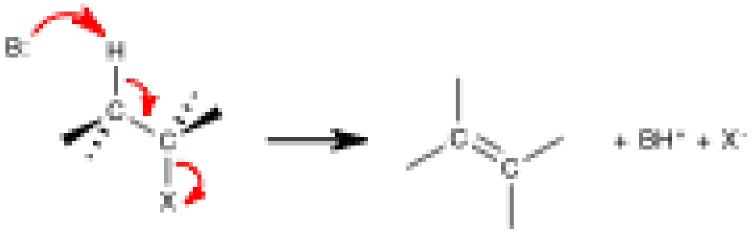
General Features of Elimination

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



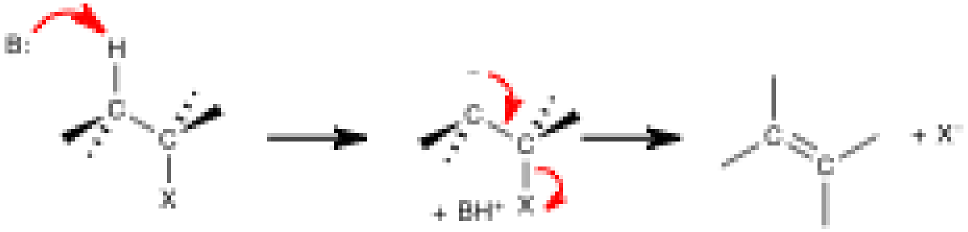
Elimination Mechanisms

E2



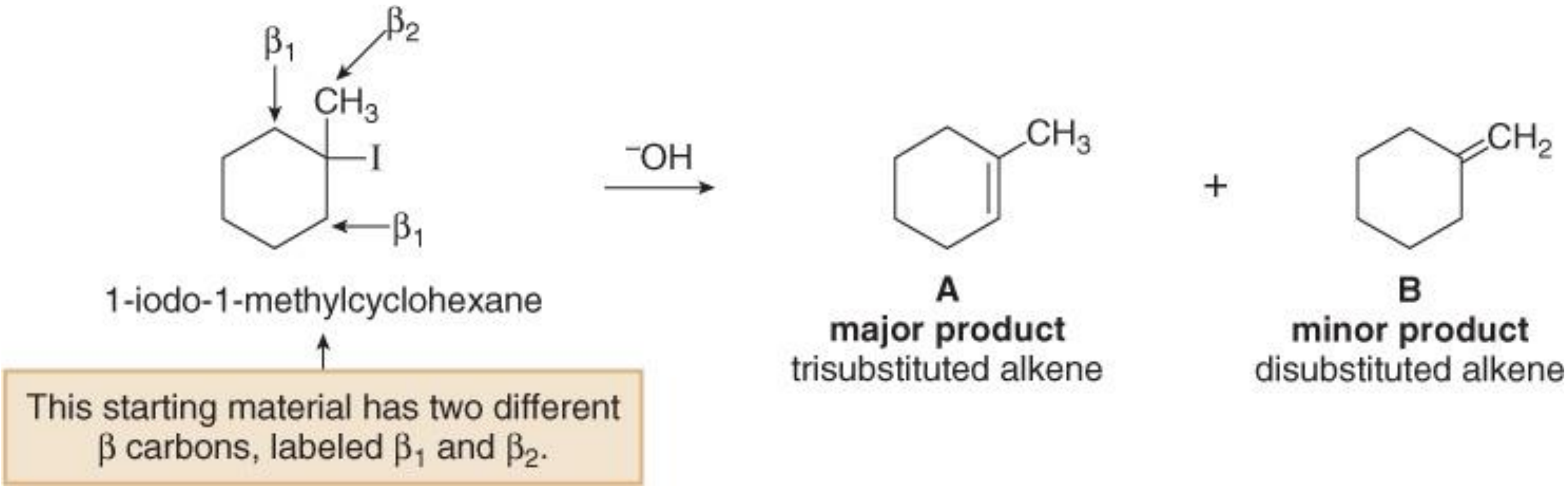
E1

E1cb



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.

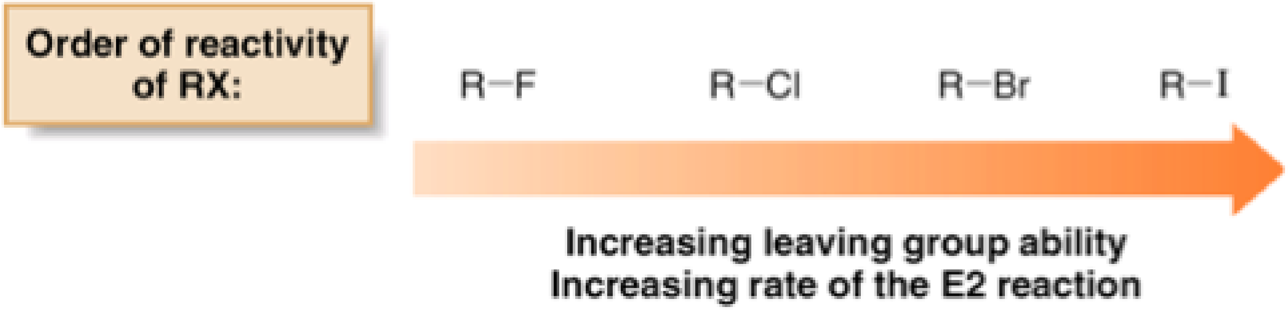
A
major product
trisubstituted alkene

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.

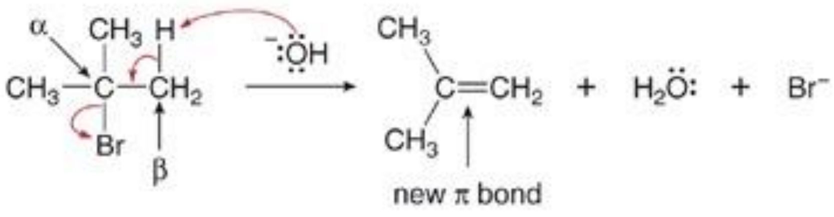
Leaving Groups in Elimination Reactions

Elimination reactions are faster with good leaving groups:



Mechanisms of Elimination—E2

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



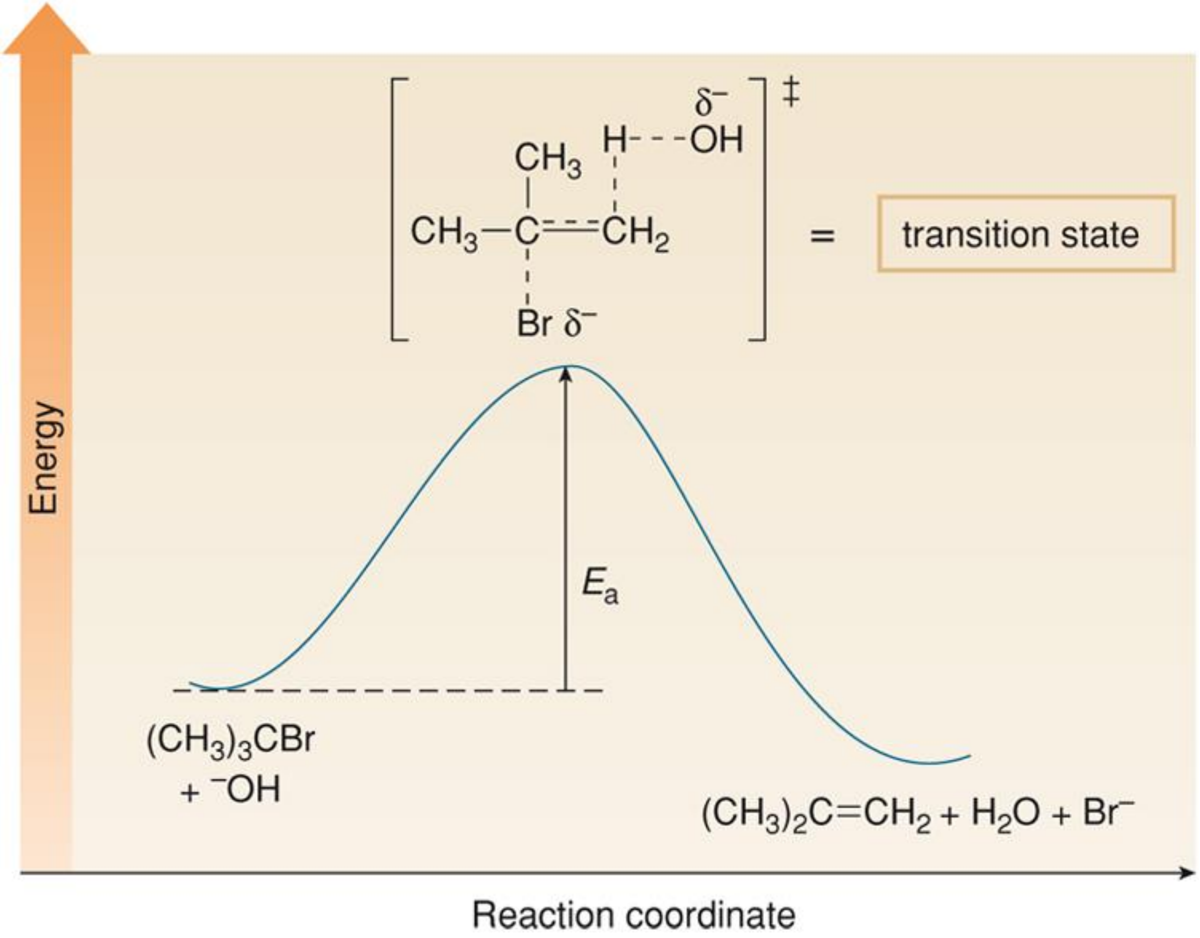
- The base ⁻OH removes a proton from the β carbon, forming H_2O (a by-product).
- The electron pair in the β C–H bond forms the new π bond.
- The leaving group Br^- comes off with the electron pair in the C–Br bond.

- 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.,

$$\textbf{rate} = k[(CH_3)_3CBr][^{-}OH]$$

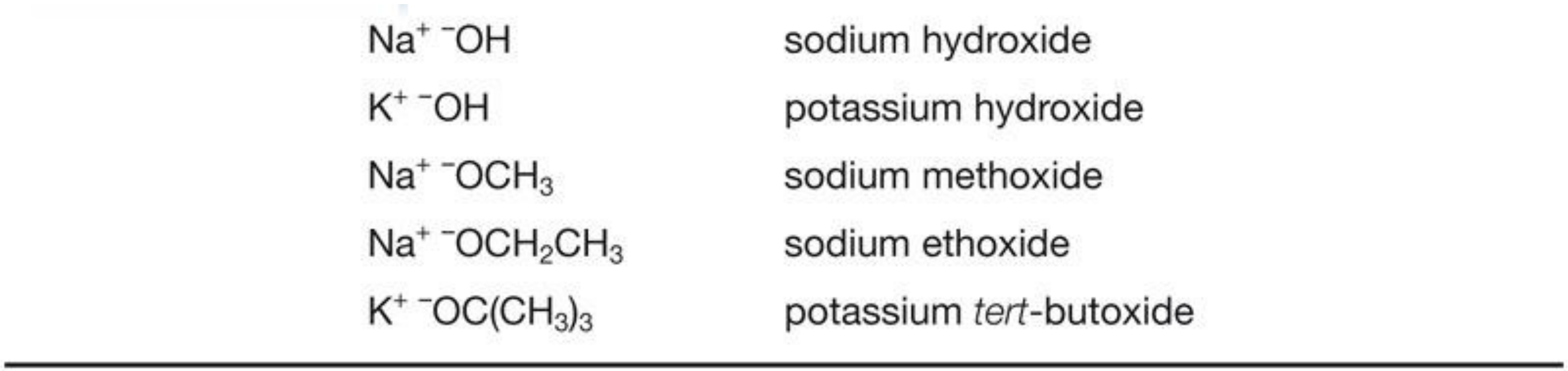
Mechanisms of Elimination—E2

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



Mechanisms of Elimination—E2

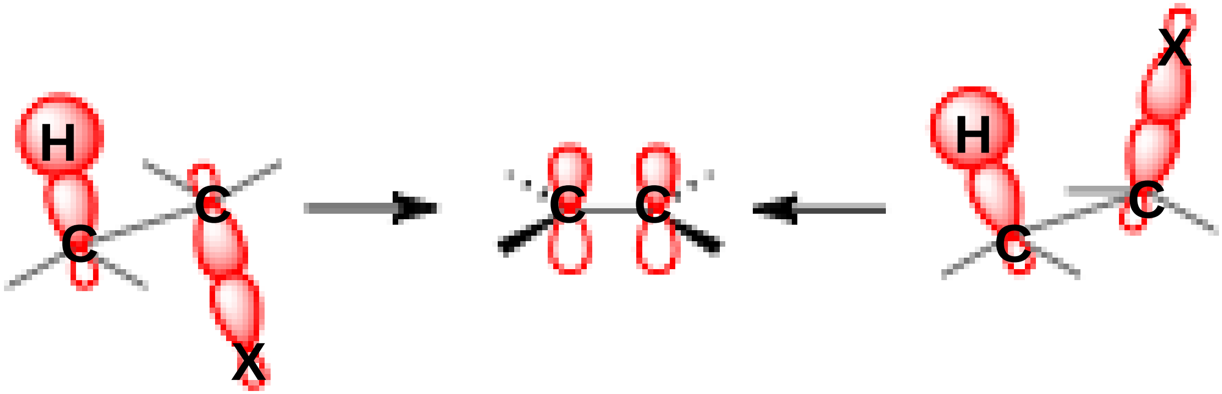
- E2 reactions are favoured by strong negatively charged bases, such as HO^- and its alkyl derivatives, RO^-, called alkoxides.
- Potassium t-butoxide is a strong, non-nucleophilic base.



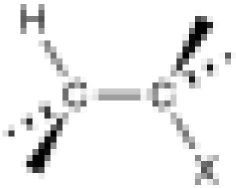
$Na^+\ {}^-OH$	sodium hydroxide
$K^+\ {}^-OH$	potassium hydroxide
$Na^+\ {}^-OCH_3$	sodium methoxide
$Na^+\ {}^-OCH_2CH_3$	sodium ethoxide
$K^+\ {}^-OC(CH_3)_3$	potassium *tert*-butoxide

Stereochemistry of the E2 Reaction

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

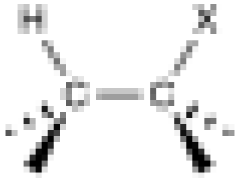


anti periplanar



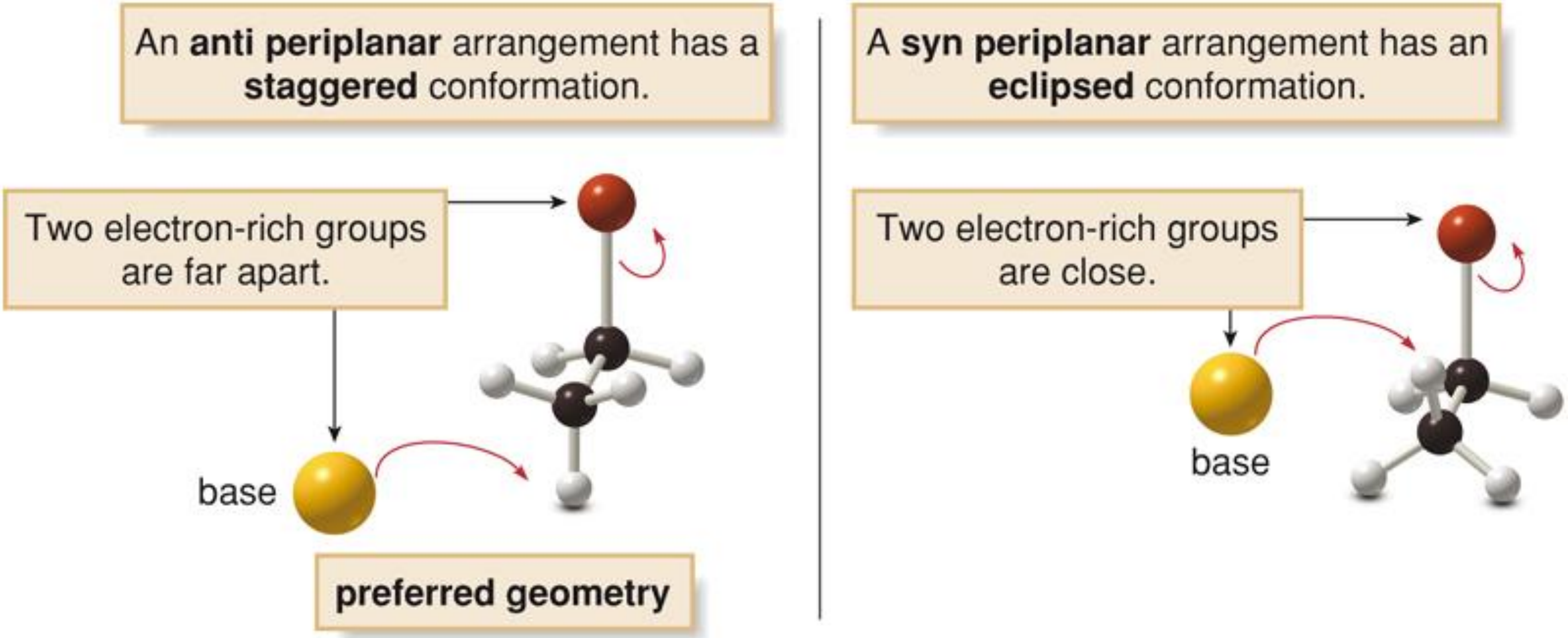
dihedral angle: 180°
staggered
favoured

syn periplanar



dihedral angle: 0°
eclipsed
disfavoured

Stereochemistry of the E2 Reaction



An **anti periplanar** arrangement has a **staggered** conformation.

Two electron-rich groups are far apart.

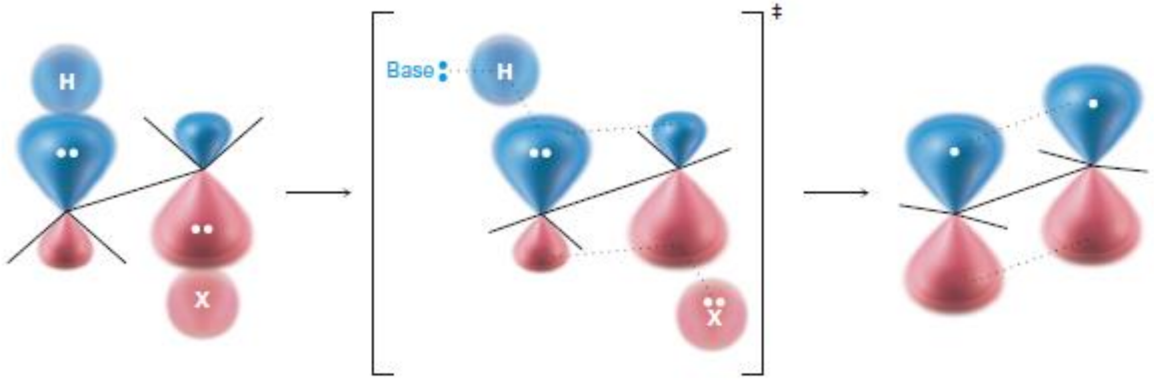
preferred geometry

A **syn periplanar** arrangement has an **eclipsed** conformation.

Two electron-rich groups are close.

- E2 elimination occurs most often in the anti periplanar geometry.

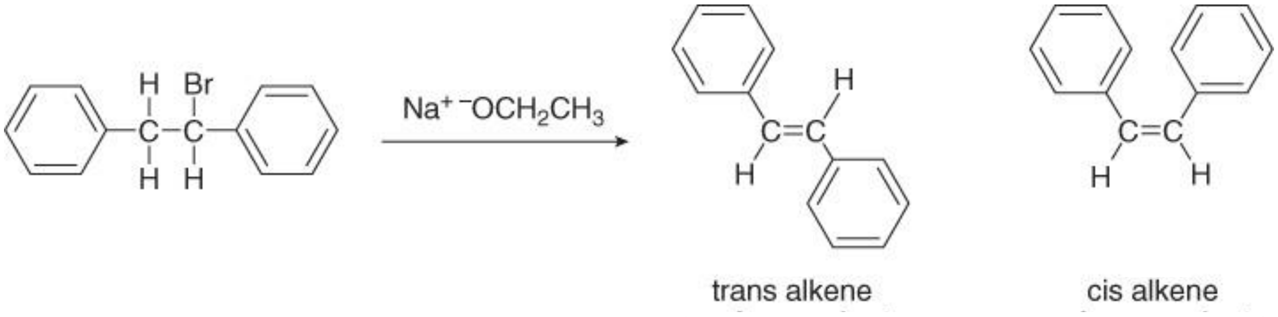
Stereochemistry of the E2 Reaction

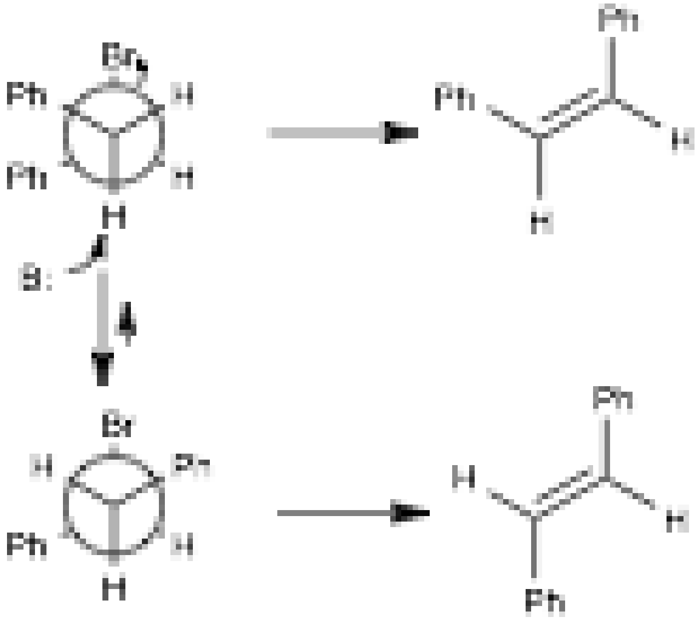


Reagente anti-periplanare **Stato di transizione anti** **Alchene prodotto**

Figura 11.18 Lo stato di transizione per la reazione E2 di un alogenuro alchilico con una base. La sovrapposizione degli orbitali *p* che si formano nello stato di transizione richiede che il reagente abbia geometria periplanare.

Stereochemistry of the E2 Reaction



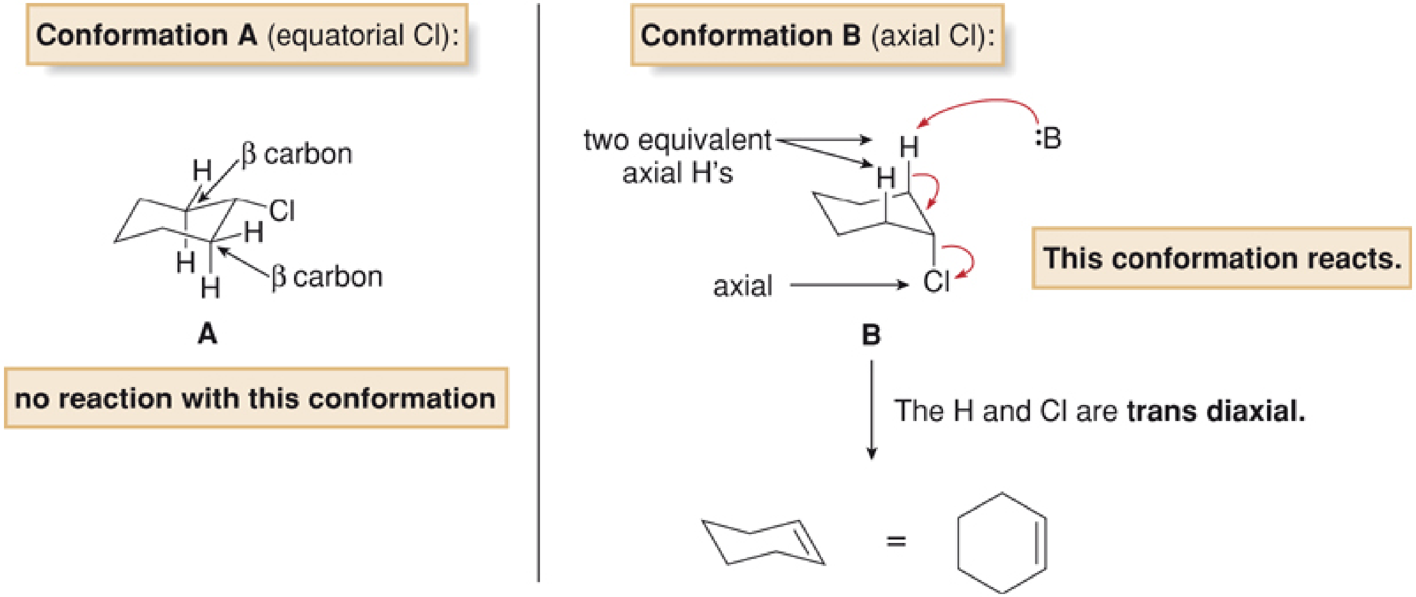


Minor product

Major product

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

Stereochemistry of the E2 Reaction



Conformation A (equatorial Cl):

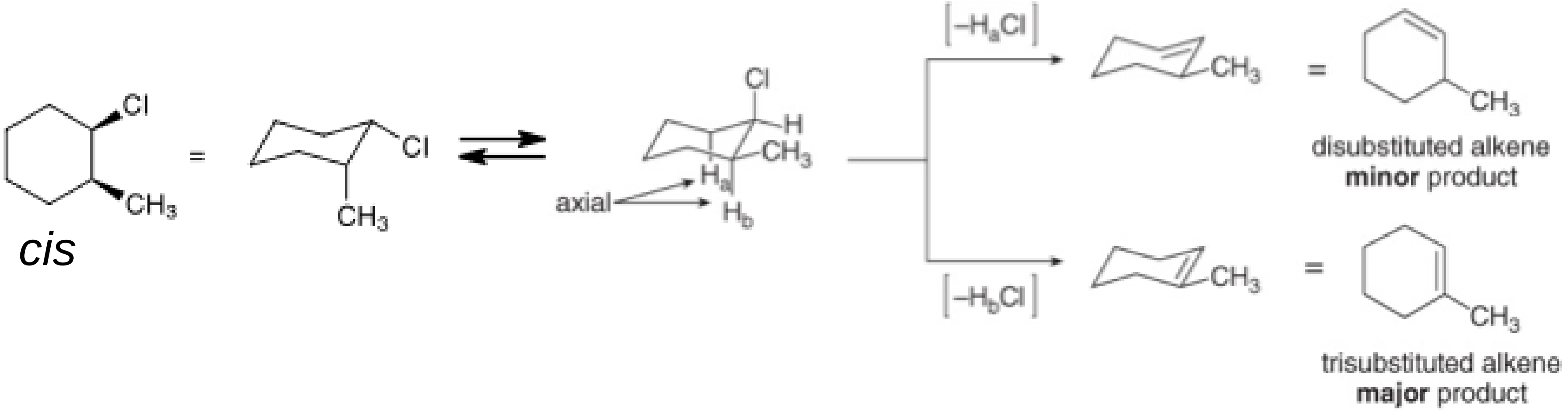
no reaction with this conformation

Conformation B (axial Cl):

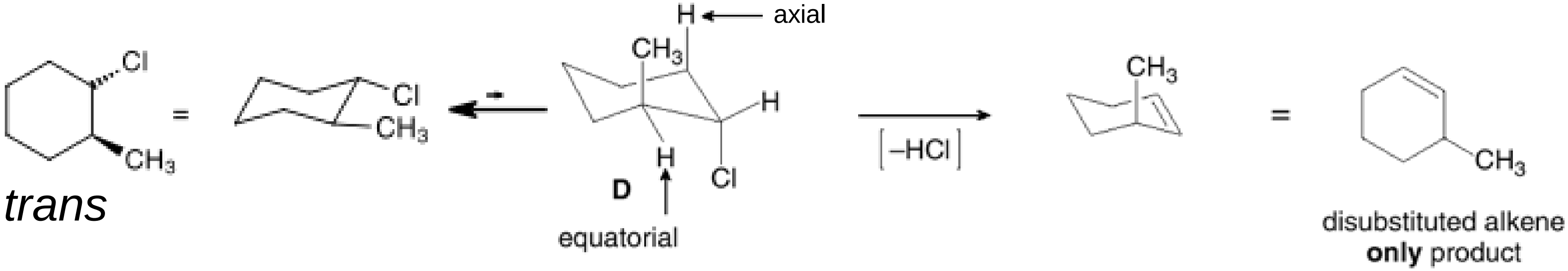
This conformation reacts.

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

Stereochemistry of the E2 Reaction

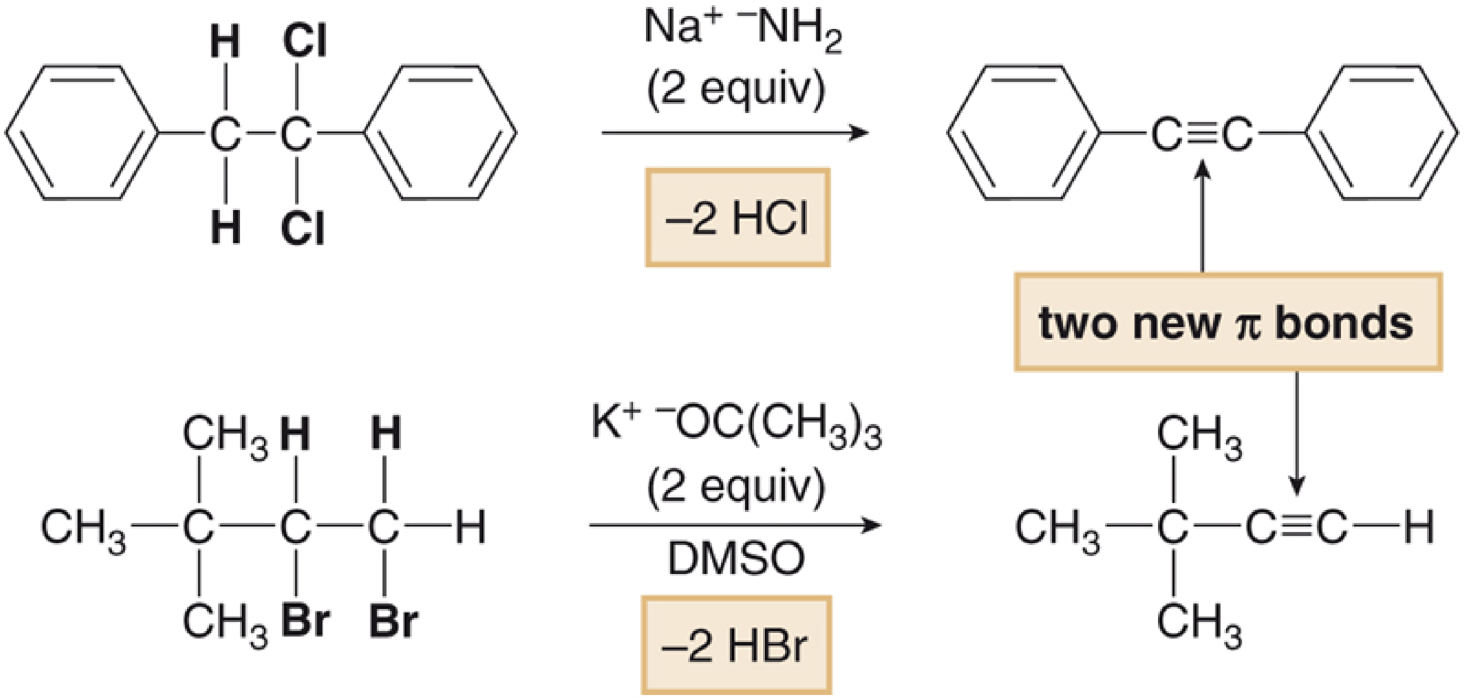


cis

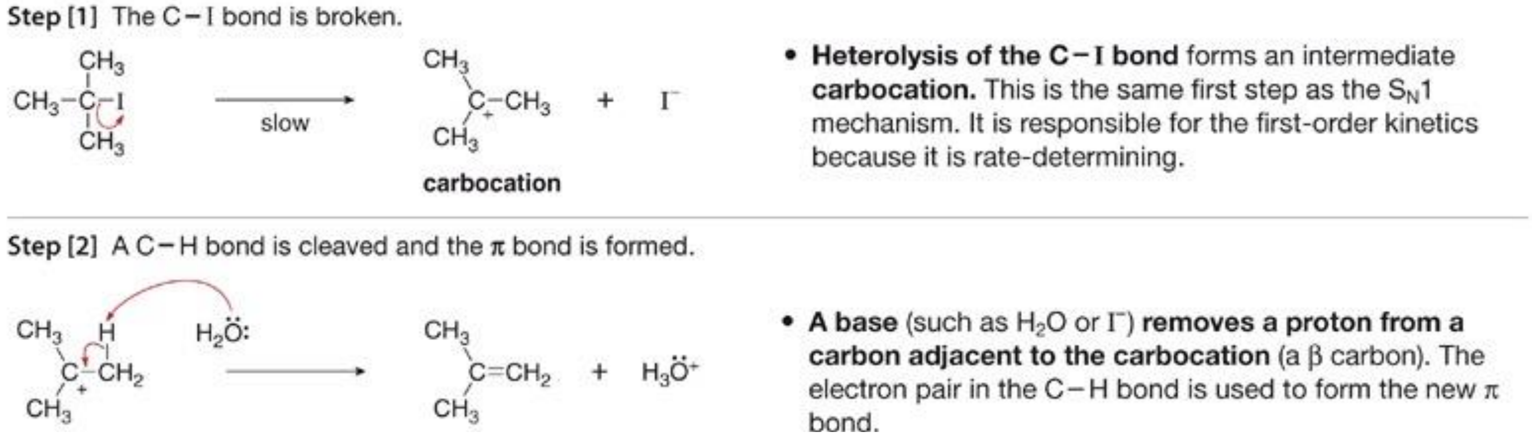


trans

E2 Reactions and Alkyne Synthesis



Mechanisms of Elimination—E1



Step [1] The C–I bond is broken.

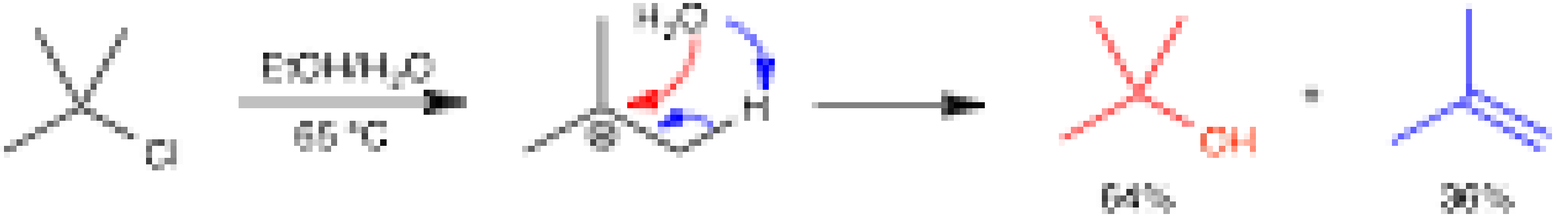
- **Heterolysis of the C–I bond** forms an intermediate **carbocation.** This is the same first step as the S_N1 mechanism. It is responsible for the first-order kinetics because it is rate-determining.

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.

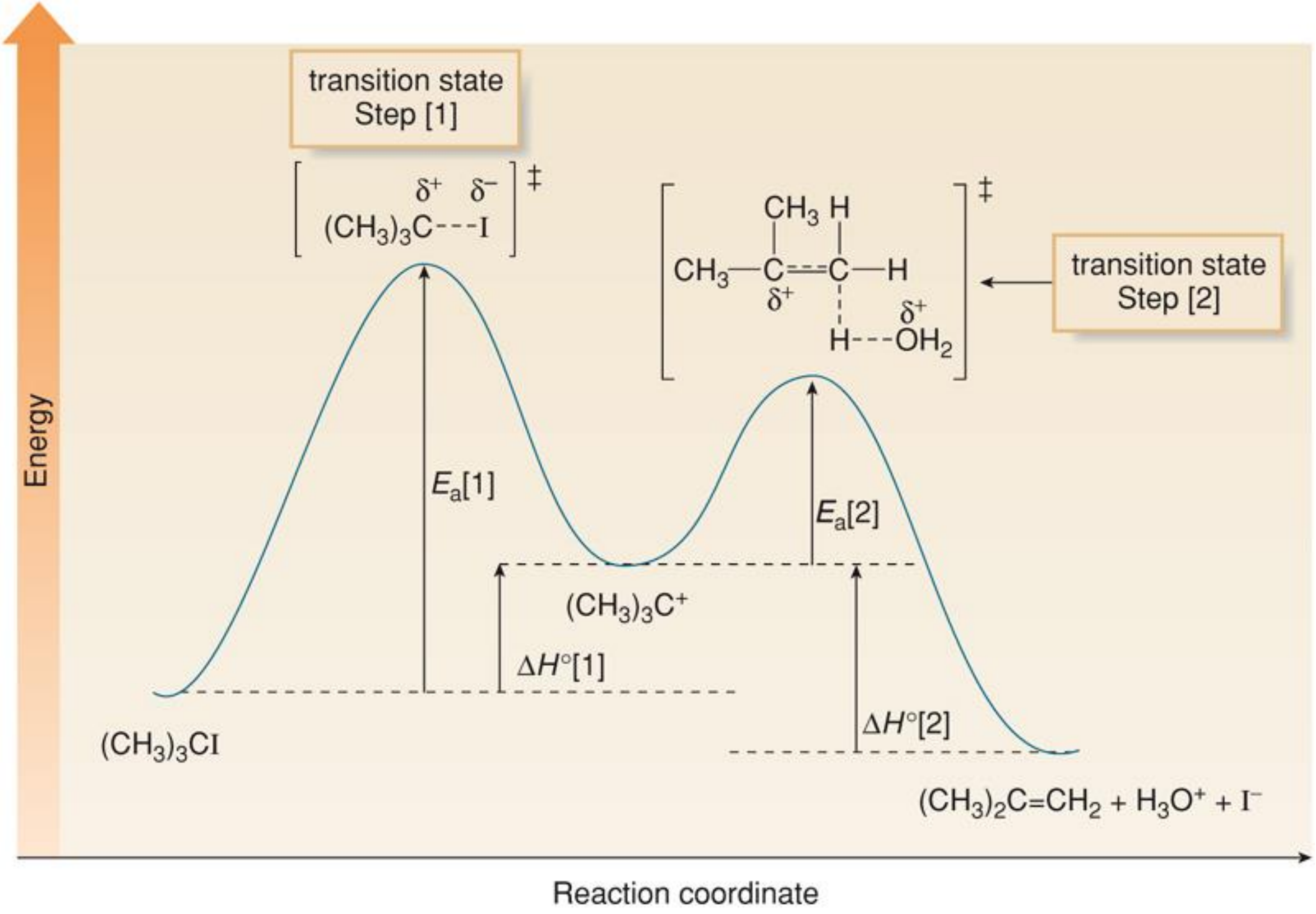
- E1 reactions exhibit first-order kinetics: **$v = k[(CH_3)_3I]$**

- E1 reactions frequently accompany SN1 reactions



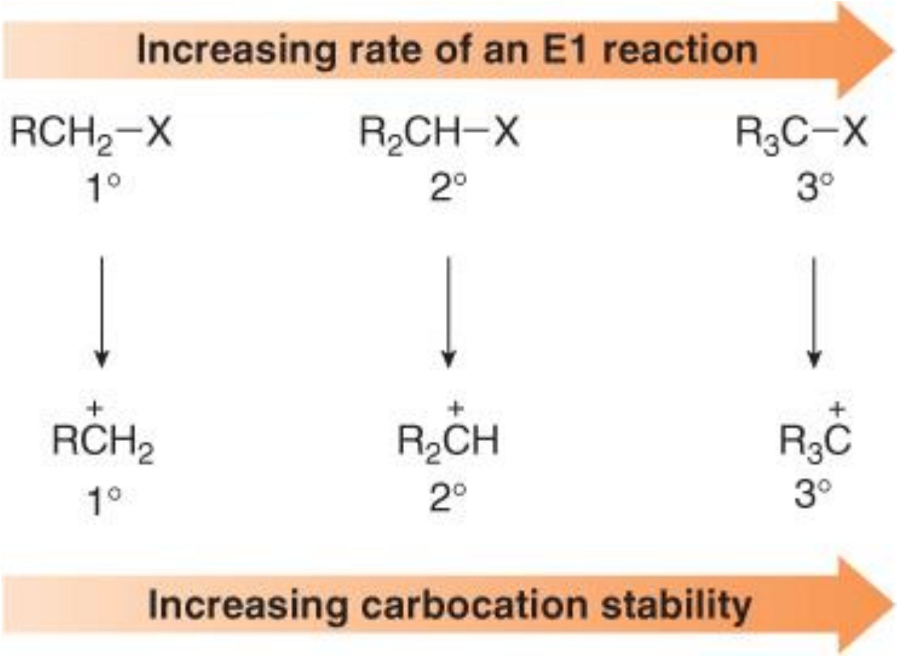
Mechanisms of Elimination—E1

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



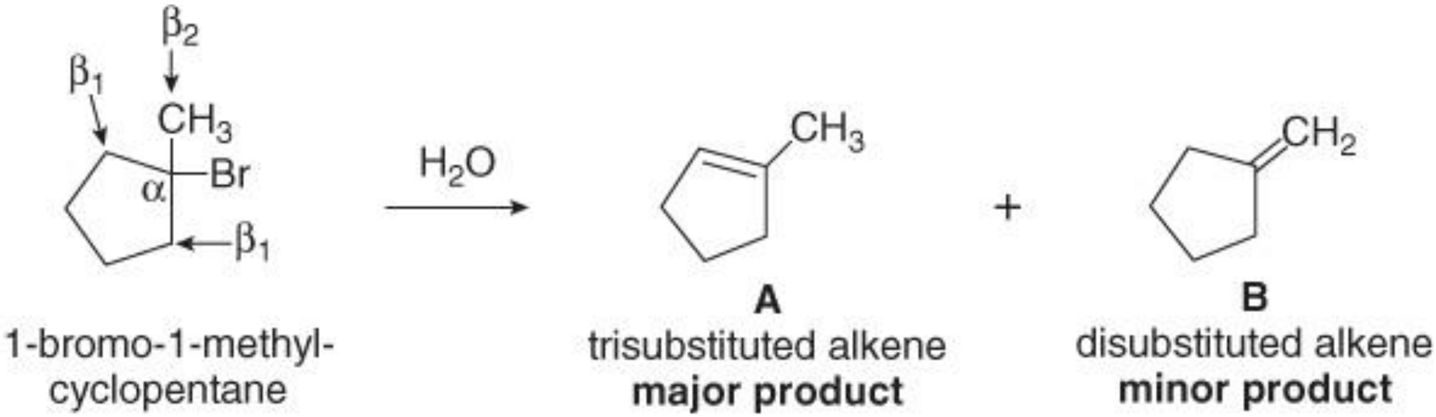
Mechanisms of Elimination—E1

- 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)

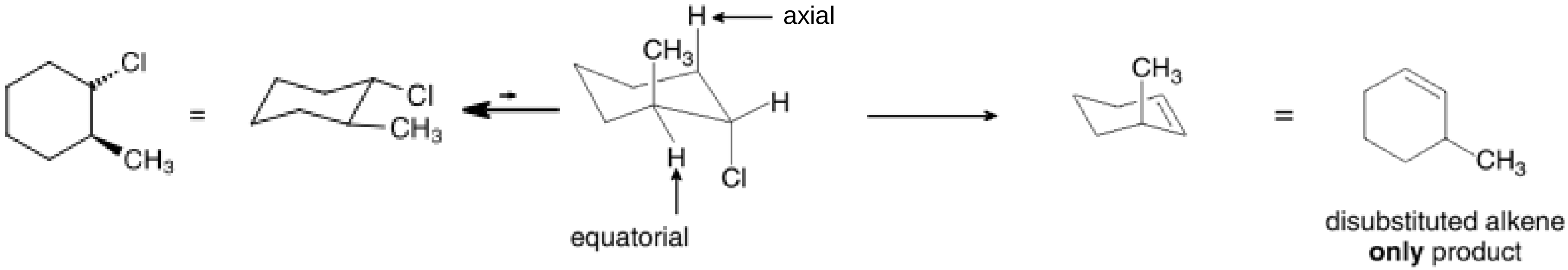


Mechanisms of Elimination

	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	Favors the most stable alkene
Solvent	Favored by dipolar aprotic solvents	Favored by polar protic solvents.

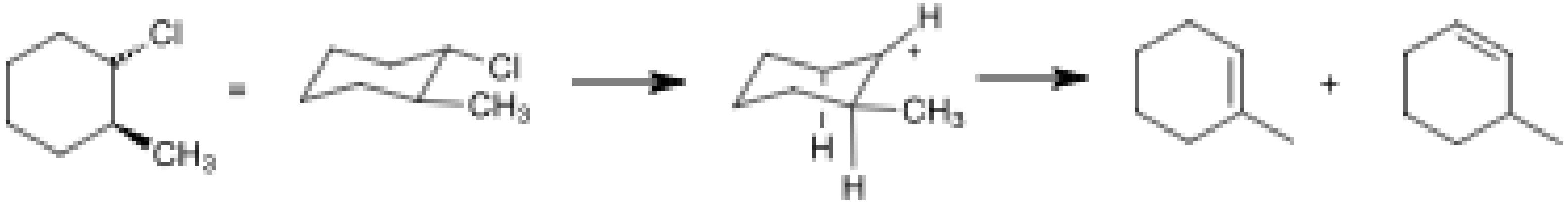
When is the Mechanism E1 or E2?

E2 conditions: 1M NaOEt, EtOH, 100 °C



disubstituted alkene **only** product

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



When is the Mechanism E1 or E2?

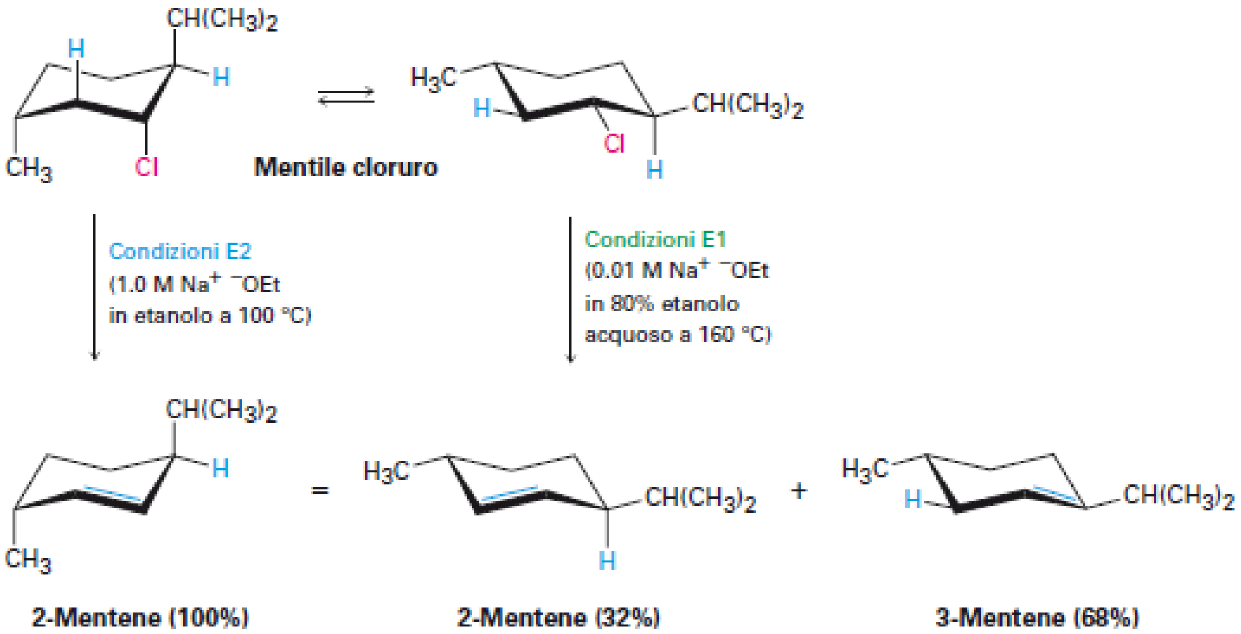
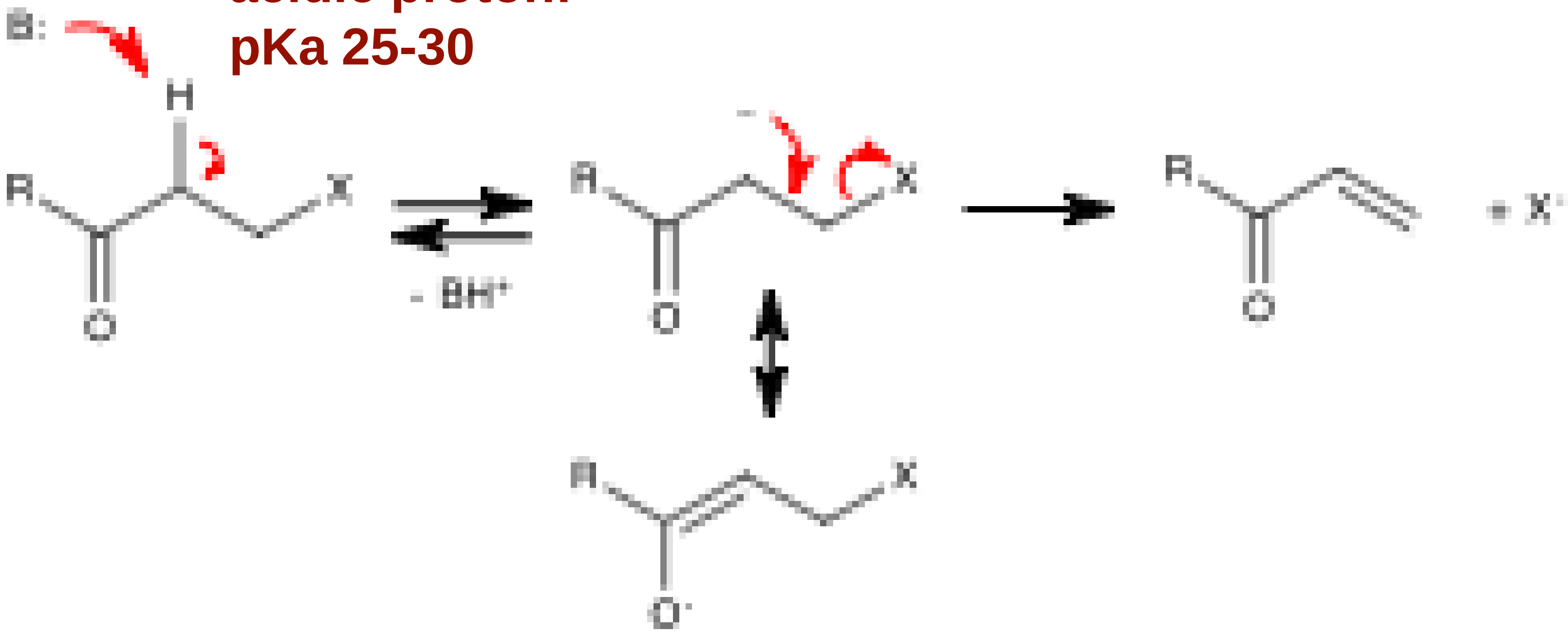


Figura 11.22 Reazioni di eliminazione del mentile cloruro. Condizioni E2 (①, base forte in etanolo 100%) portano al 2-mentene tramite un'eliminazione anti–periplanare, mentre condizioni E1 (② base molto diluita in etanolo acquoso 80%) portano ad una miscela di 2-mentene e 3-mentene.

Mechanisms of Elimination—E1cb

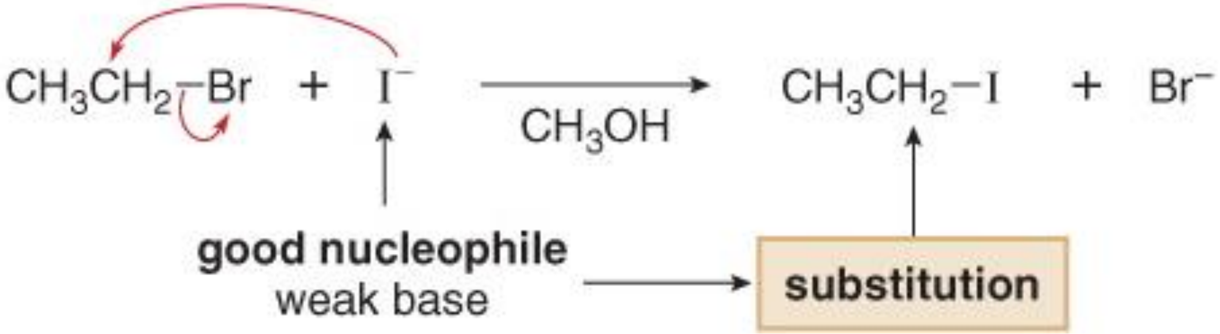


acidic proton:
pKa 25-30

carbanion stabilized
by delocalization

Substitution *vs* Elimination

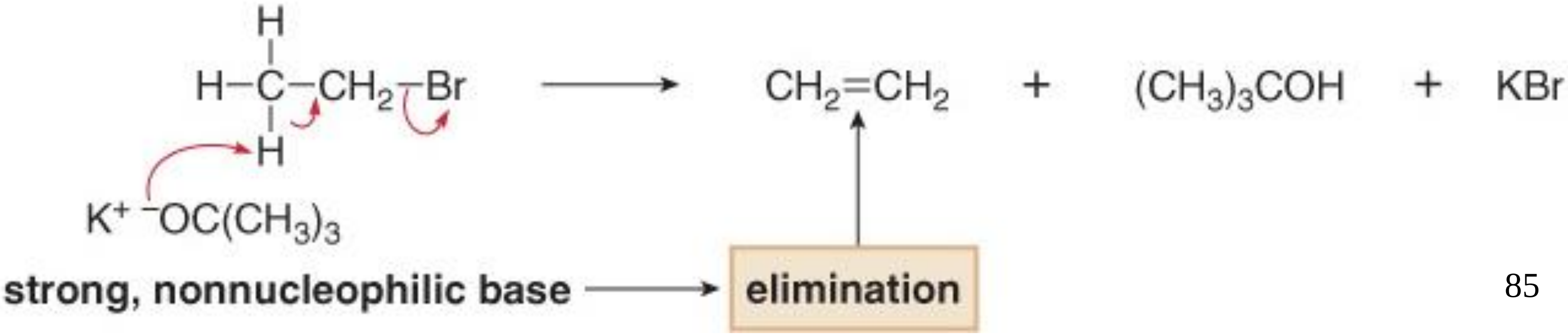
- Good nucleophiles that are weak bases favor substitution over elimination. These include I^-, Br^-, HS^-, ^-CN, and CH_3COO^-.



$$CH_3CH_2{-}Br + I^- \xrightarrow[CH_3OH]{} CH_3CH_2{-}I + Br^-$$

good nucleophile
weak base → **substitution**

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

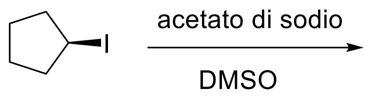


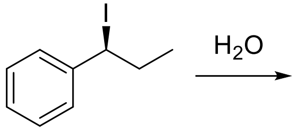
$$H_3C{-}CH_2{-}Br + K^+\ {}^-OC(CH_3)_3 \longrightarrow CH_2{=}CH_2 + (CH_3)_3COH + KBr$$

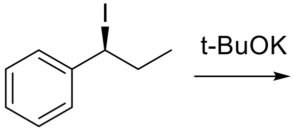
strong, nonnucleophilic base → **elimination**

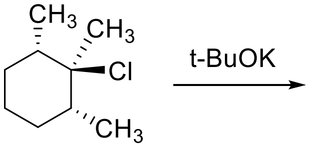
Substitution and Elimination

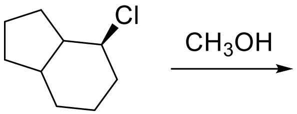
Alkyl halide	**SN2**	**SN1**	**E2**	**E1**	**E1cb**
methyl	***yes***				
primary	***with good, weakly basic nucleophiles***		***with strong, non-nucleophilic bases***		***yes***
secondary allylic benzylic	***with good nucleophiles in polar aprotic solvents***	***with weak nucleophiles in protic solvents***	***with strong bases in aprotic solvents***	***with weak bases in protic solvents***	***yes***
tertiary		***with non basic nucleophiles***	***with strong bases***	***with weak bases***	***yes***

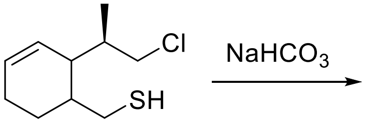

I
acetato di sodio
DMSO

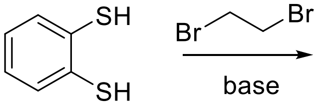

I
H2O


I
t-BuOK


CH3
CH3
Cl
CH3
t-BuOK


Cl
CH3OH

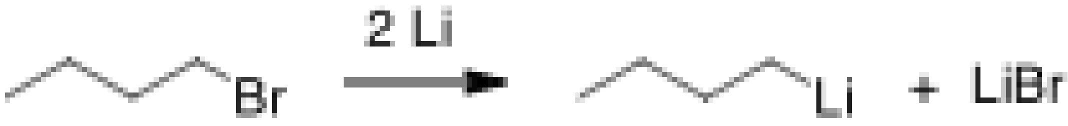

Cl
SH
NaHCO3


SH
SH
Br
Br
base

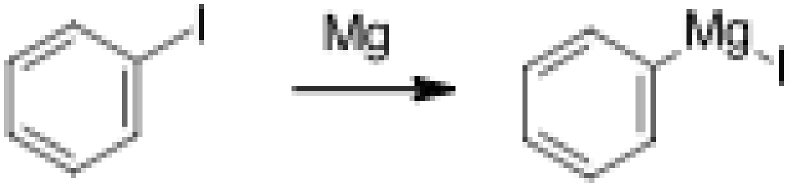
Reverse of Polarity. Organometallic Compounds

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

Examples:



organolithium



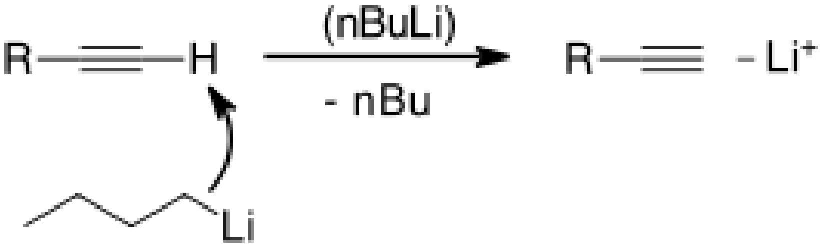
organomagnesium
(Grignard reagents)

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

organocuprates
(Gilman reagents)

Reverse of Polarity.
Organometallic Compounds

strong bases:



strong nucleophiles: