

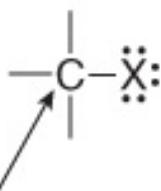
# **Alkyl Halides, Nucleophilic Substitution and Elimination Reactions**

**S<sub>N</sub>1, S<sub>N</sub>2, E1 and E2**

# Introduction to Alkyl Halides

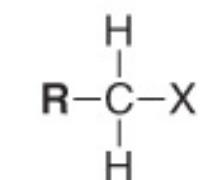
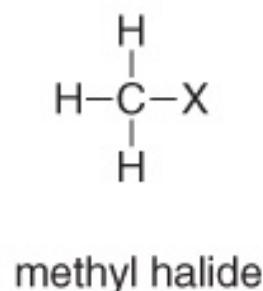
- Alkyl halides are organic molecules containing a halogen atom bonded to an  $sp^3$  hybridized carbon atom.
- Alkyl halides are classified as primary ( $1^\circ$ ), secondary ( $2^\circ$ ), or tertiary ( $3^\circ$ ), depending on the number of carbons bonded to the carbon with the halogen atom.
- The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

Alkyl halide

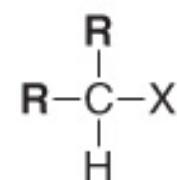


$R-X$     $X = F, Cl, Br, I$

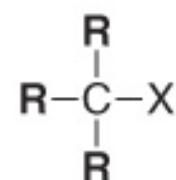
Classification of alkyl halides



$1^\circ$   
(one R group)



$2^\circ$   
(two R groups)



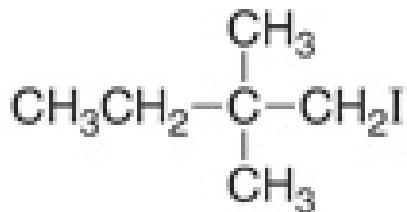
$3^\circ$   
(three R groups)

## Introduction to Alkyl Halides

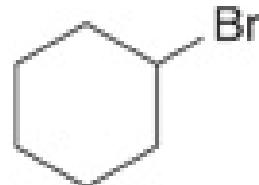
- There are other types of organic halides. These include vinyl halides, aryl halides, allylic halides and benzylic halides.
- Vinyl halides have a halogen atom (X) bonded to a  $C=C$  bond ( $>C=C-Cl$ ).
- Aryl halides have a halogen atom bonded to an aromatic ring ( $ArCl$ ).
- Allylic halides have X bonded to the carbon atom adjacent to a  $C=C$  bond ( $>C=C-CH_2Cl$ ).
- Benzylic halides have X bonded to the carbon atom adjacent to a benzene ring ( $PhCH_2Cl$ ).

# Introduction to Alkyl Halides

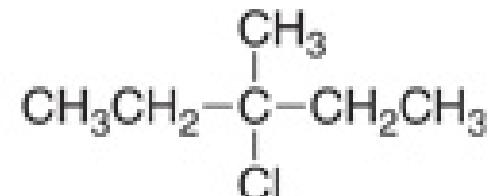
Examples of 1°, 2°, and 3° alkyl halides



1° iodide

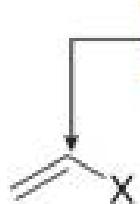


2° bromide

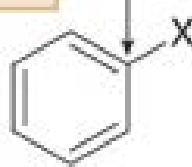


3° chloride

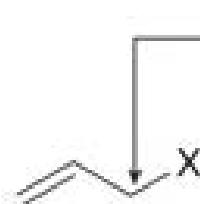
Four types of organic halides ( $\text{RX}$ ) having  $\text{X}$  near a  $\pi$  bond



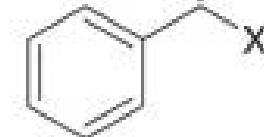
$sp^2$  hybridized C



Vinyl halide



$sp^3$  hybridized C



Aryl halide

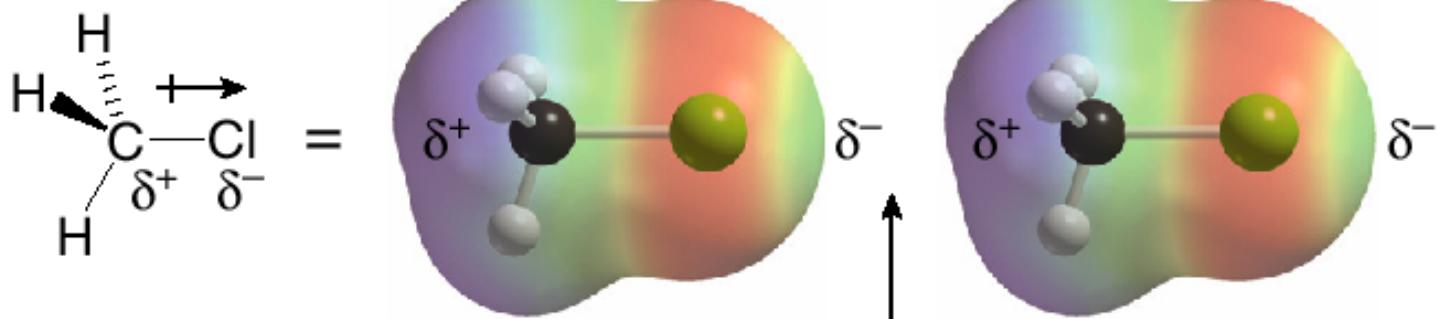
Allylic halide

benzylic halide

## Physical Properties

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

Dipole-dipole interactions



Opposite ends of the dipoles interact.

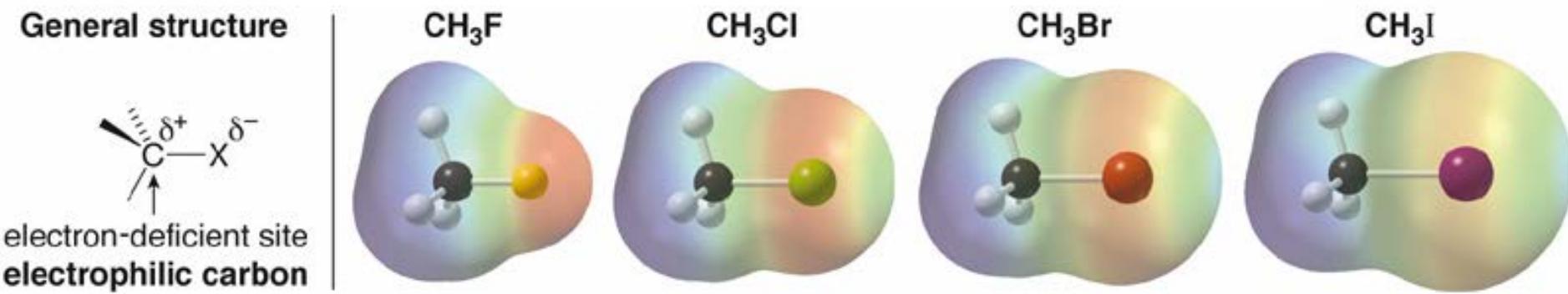
# Physical Properties

Property	Observation
Boiling point and melting point	<ul style="list-style-type: none"><li>Alkyl halides have higher bp's and mp's than alkanes having the same number of carbons.</li></ul> <p style="text-align: center;"><math>\text{CH}_3\text{CH}_3</math> and <math>\text{CH}_3\text{CH}_2\text{Br}</math> bp = <math>-89^\circ\text{C}</math>                                    bp = <math>39^\circ\text{C}</math></p> <ul style="list-style-type: none"><li>Bp's and mp's increase as the size of R increases.</li></ul> <p style="text-align: center;"><math>\text{CH}_3\text{CH}_2\text{Cl}</math> and <math>\text{CH}_3\text{CH}_2\text{CH}_2\text{Cl}</math> mp = <math>-136^\circ\text{C}</math>                                    mp = <math>-123^\circ\text{C}</math> bp = <math>12^\circ\text{C}</math>    bp = <math>47^\circ\text{C}</math></p> <ul style="list-style-type: none"><li>Bp's and mp's increase as the size of X increases.</li></ul> <p style="text-align: center;"><math>\text{CH}_3\text{CH}_2\text{Cl}</math> and <math>\text{CH}_3\text{CH}_2\text{Br}</math> mp = <math>-136^\circ\text{C}</math>                                    mp = <math>-119^\circ\text{C}</math> bp = <math>12^\circ\text{C}</math>    bp = <math>39^\circ\text{C}</math></p> <p style="margin-left: 200px;"></p> <p style="margin-left: 200px;"></p>
Solubility	<ul style="list-style-type: none"><li><math>\text{RX}</math> is soluble in organic solvents.</li><li><math>\text{RX}</math> is insoluble in water.</li></ul>

# 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.

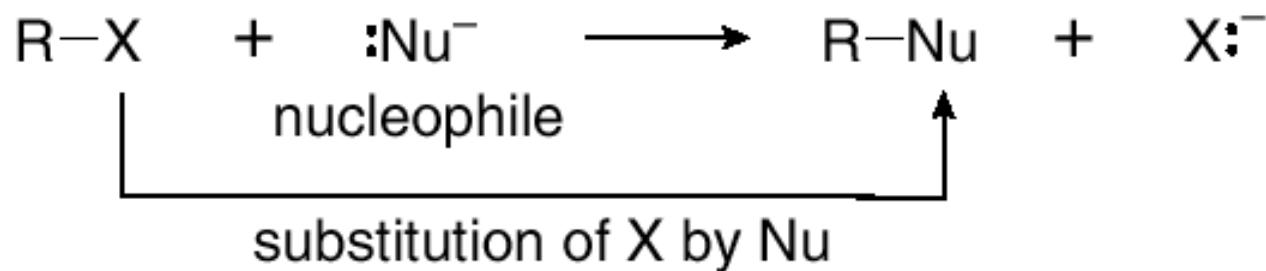
## Electrostatic potential maps of four halomethanes ( $\text{CH}_3\text{X}$ )



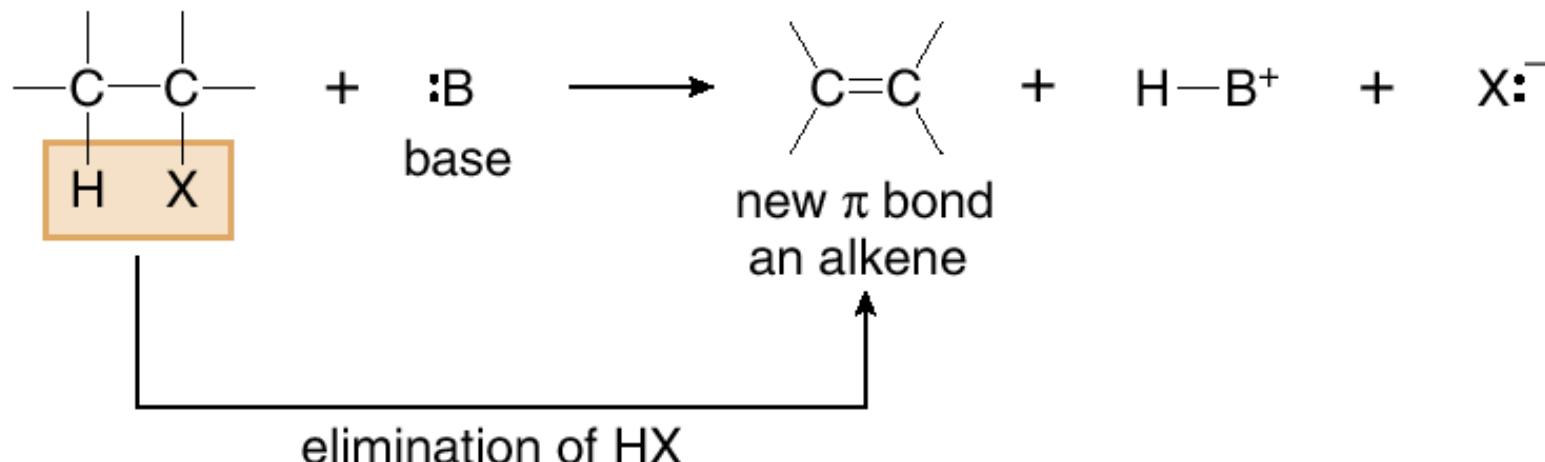
- The polar C—X bond makes the carbon atom electron deficient in each  $\text{CH}_3\text{X}$  molecule.

# The Polar Carbon-Halogen Bond

Alkyl halides undergo substitution reactions with nucleophiles.

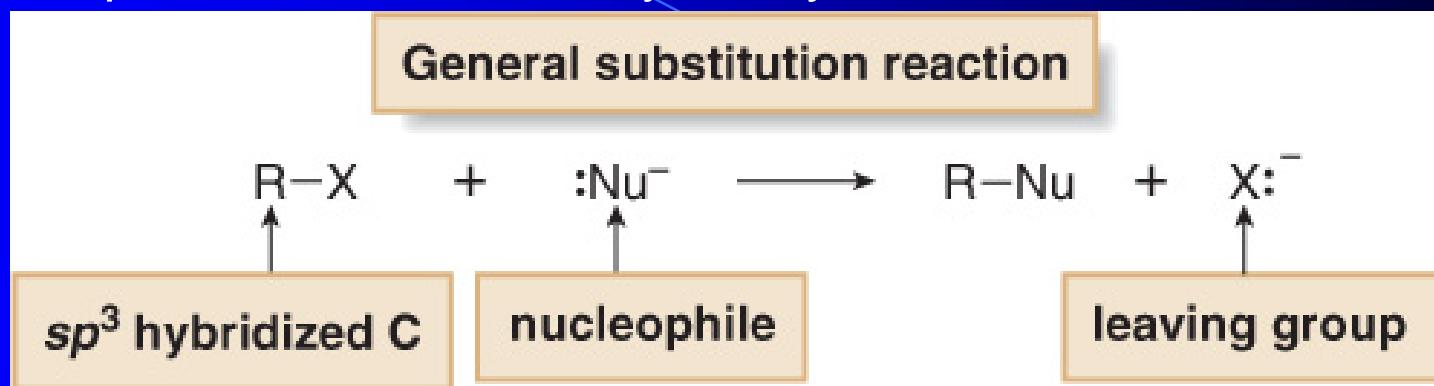


Alkyl halides undergo elimination reactions with Brønsted–Lowry bases.

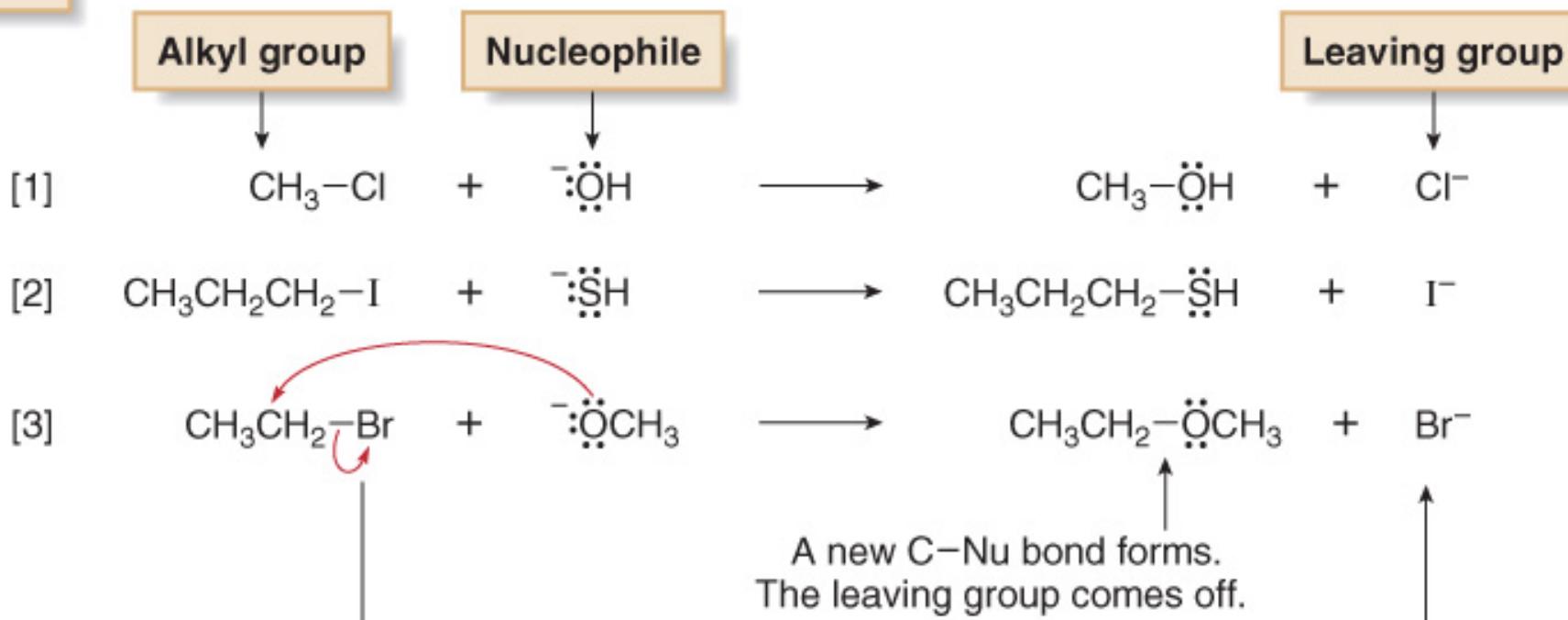


# General Features of Nucleophilic Substitution

- Three components are necessary in any substitution reaction.

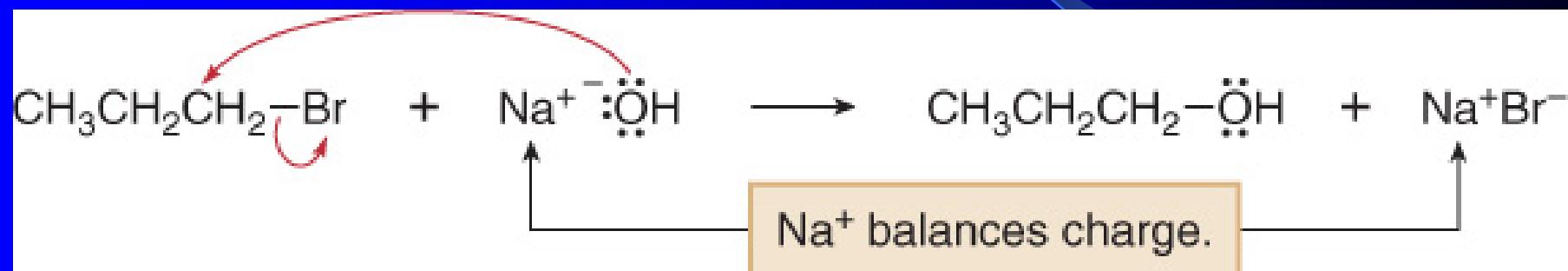


## Examples

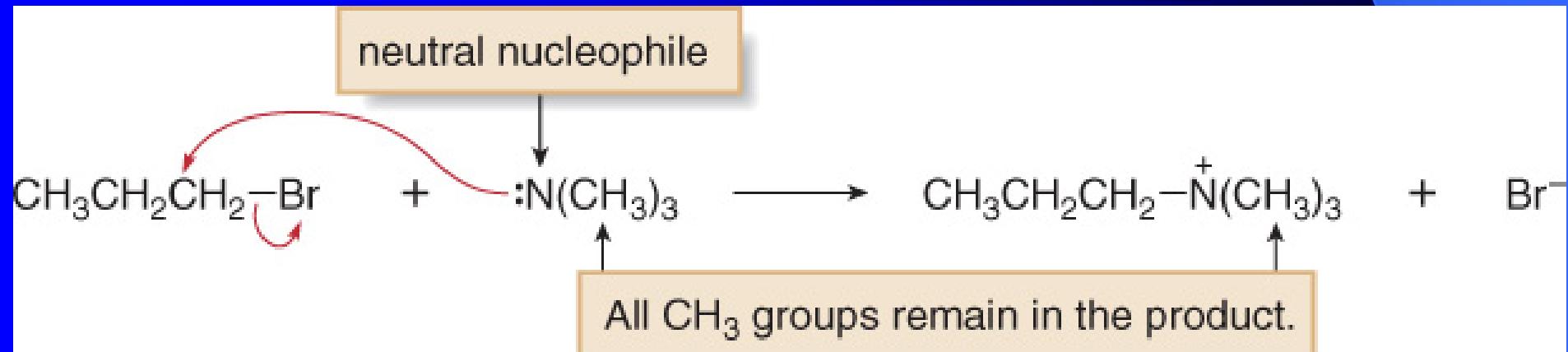


# General Features of Nucleophilic Substitution

- Negatively charged nucleophiles like  $\text{HO}^-$  and  $\text{HS}^-$  are used as salts with  $\text{Li}^+$ ,  $\text{Na}^+$ , or  $\text{K}^+$  counter-ions to balance the charge. Since the identity of the counter-ion is usually inconsequential, it is often omitted from the chemical equation.

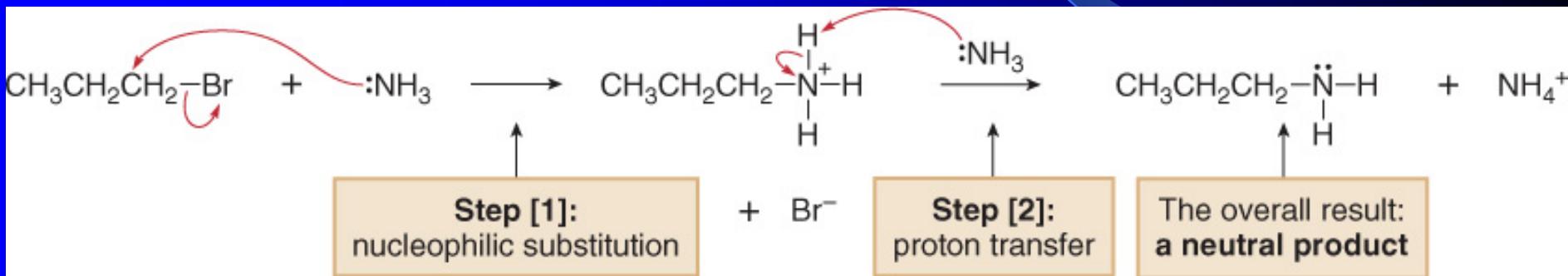


- When a neutral nucleophile is used, the substitution product bears a positive charge.



# General Features of Nucleophilic Substitution

- Furthermore, when the substitution product bears a positive charge and also contains a proton bonded to O or N, the initially formed substitution product readily loses a proton in a Brønsted-Lowry acid-base reaction, forming a neutral product.

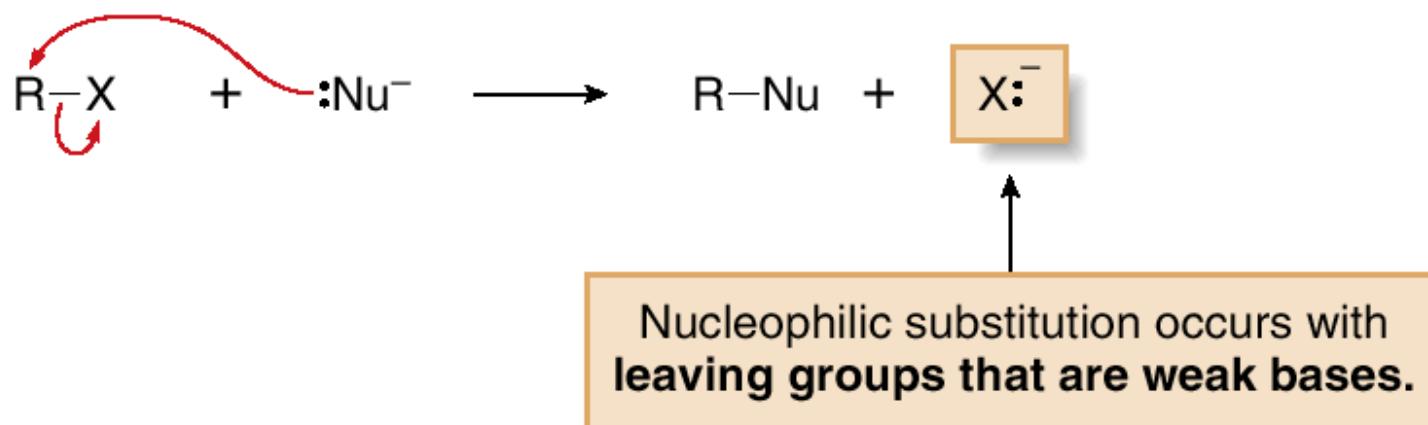


- To draw any nucleophilic substitution product:
  - Find the  $sp^3$  hybridized carbon with the leaving group.
  - Identify the nucleophile, the species with a lone pair or  $\pi$  bond.
  - Substitute the nucleophile for the leaving group and assign charges (if necessary) to any atom that is involved in bond breaking or bond formation.

# The Leaving Group

- In a nucleophilic substitution reaction of R—X, the C—X bond is heterolytically cleaved, and the leaving group departs with the electron pair in that bond, forming  $\text{X}^-$ . The more stable the leaving group  $\text{X}^-$ , the better able it is to accept an electron pair.

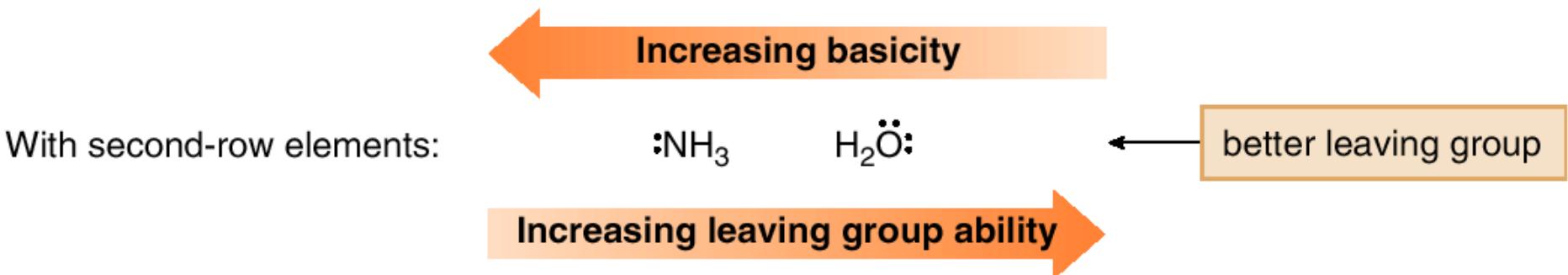
In comparing two leaving groups, the better leaving group is the weaker base.



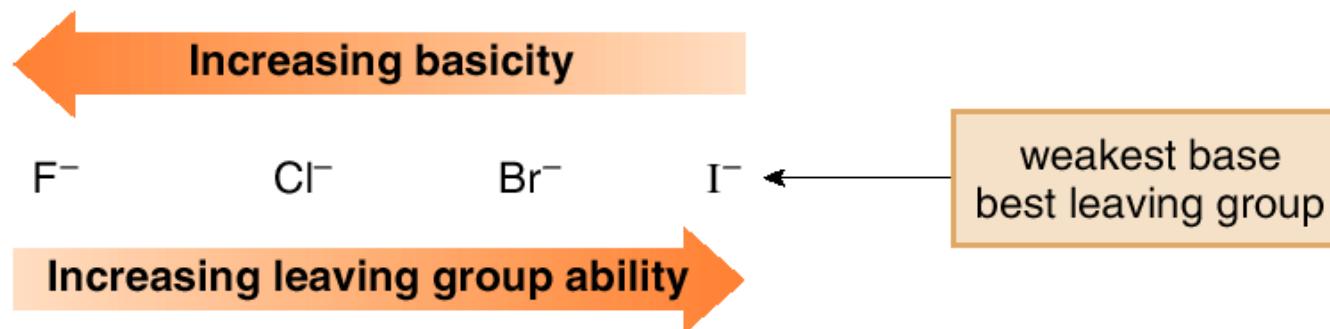
- For example,  $\text{H}_2\text{O}$  is a better leaving group than  $\text{HO}^-$  because  $\text{H}_2\text{O}$  is a weaker base.

# The Leaving Group

Left-to-right across a row of the periodic table, basicity decreases so leaving group ability *increases*.



Down a column of the periodic table, basicity decreases so leaving group ability *increases*.



# The Leaving Group

## Good Leaving Groups for Nucleophilic Substitution Reaction

Starting material	Leaving group	Conjugate acid	pK <sub>a</sub>
R—Cl	Cl <sup>−</sup>	HCl	−7
R—Br	Br <sup>−</sup>	HBr	−9
R—I	I <sup>−</sup>	HI	−10
R—OH <sub>2</sub> <sup>+</sup>	H <sub>2</sub> O	H <sub>3</sub> O <sup>+</sup>	−1.7

These molecules undergo nucleophilic substitution.

good leaving groups

# The Leaving Group

## Good Leaving Groups for Nucleophilic Substitution Reaction

Starting material	Leaving group	Conjugate acid	pK <sub>a</sub>
R—F	F <sup>-</sup>	HF	3.2
R—OH	OH <sup>-</sup>	H <sub>2</sub> O	15.7
R—NH <sub>2</sub>	NH <sub>2</sub> <sup>-</sup>	NH <sub>3</sub>	38
R—H	H <sup>-</sup>	H <sub>2</sub>	35
R—R	R <sup>-</sup>	RH	50

These molecules do *not* undergo nucleophilic substitution.

poor leaving groups

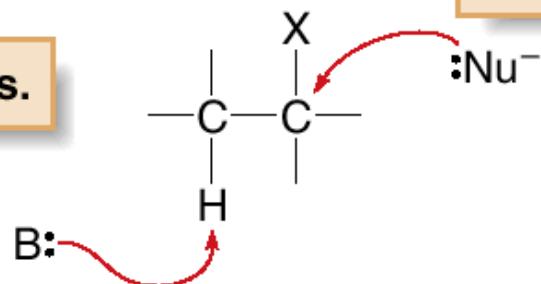
# The Nucleophile

- Nucleophiles and bases are structurally similar: both have a lone pair or a  $\pi$  bond. They differ in what they attack.

Bases attack protons. Nucleophiles attack other electron-deficient atoms (usually carbons).

Bases attack protons.

Nucleophiles attack carbons.



## The Nucleophile

- Although nucleophilicity and basicity are interrelated, they are fundamentally different.
  - ▶ Basicity is a measure of how readily an atom donates its electron pair to a proton. It is characterized by an equilibrium constant,  $K_a$  in an acid-base reaction, making it a thermodynamic property.
  - ▶ Nucleophilicity is a measure of how readily an atom donates its electron pair to other atoms. It is characterized by a rate constant,  $k$ , making it a kinetic property.

# The Nucleophile

- Nucleophilicity parallels basicity in three instances:
  1. For two nucleophiles with the same nucleophilic atom, the stronger base is the stronger nucleophile.

The relative nucleophilicity of  $\text{HO}^-$  and  $\text{CH}_3\text{COO}^-$ , two oxygen nucleophiles, is determined by comparing the  $pK_a$  values of their conjugate acids ( $\text{H}_2\text{O} = 15.7$ , and  $\text{CH}_3\text{COOH} = 4.8$ ).  $\text{HO}^-$  is a stronger base and stronger nucleophile than  $\text{CH}_3\text{COO}^-$ .
  2. A negatively charged nucleophile is always a stronger nucleophile than its conjugate acid.

$\text{HO}^-$  is a stronger base and stronger nucleophile than  $\text{H}_2\text{O}$ .
  3. Right-to-left-across a row of the periodic table, nucleophilicity increases as basicity increases:

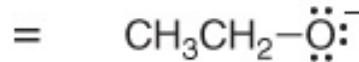
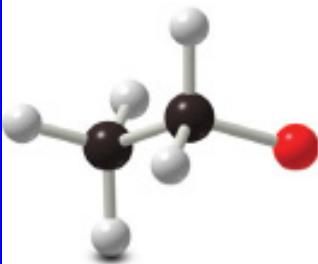
For second-row elements  
with the same charge:



Increasing basicity  
Increasing nucleophilicity

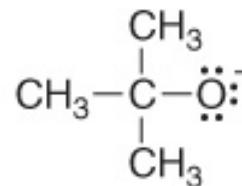
# The Nucleophile

- Nucleophilicity does not parallel basicity when steric hindrance becomes important.
- Steric hindrance decrease the reactivity resulting 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, they are called non-nucleophilic bases.



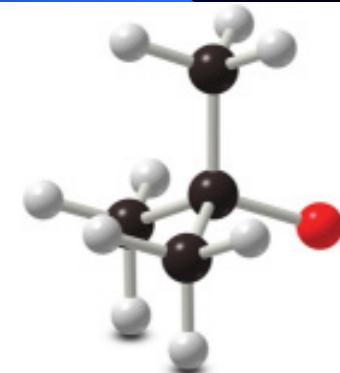
ethoxide

stronger nucleophile



*tert*-butoxide

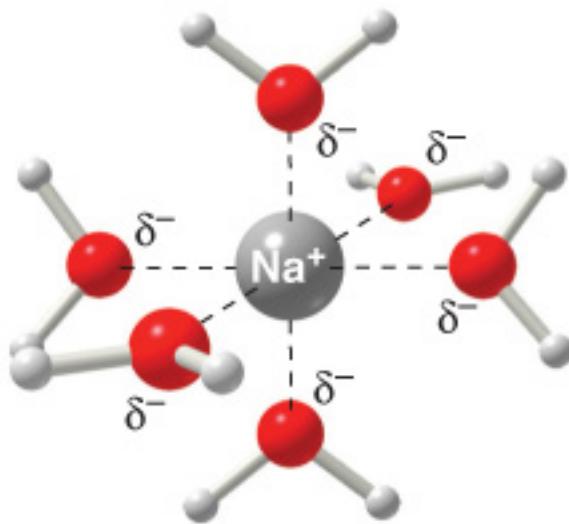
stronger base



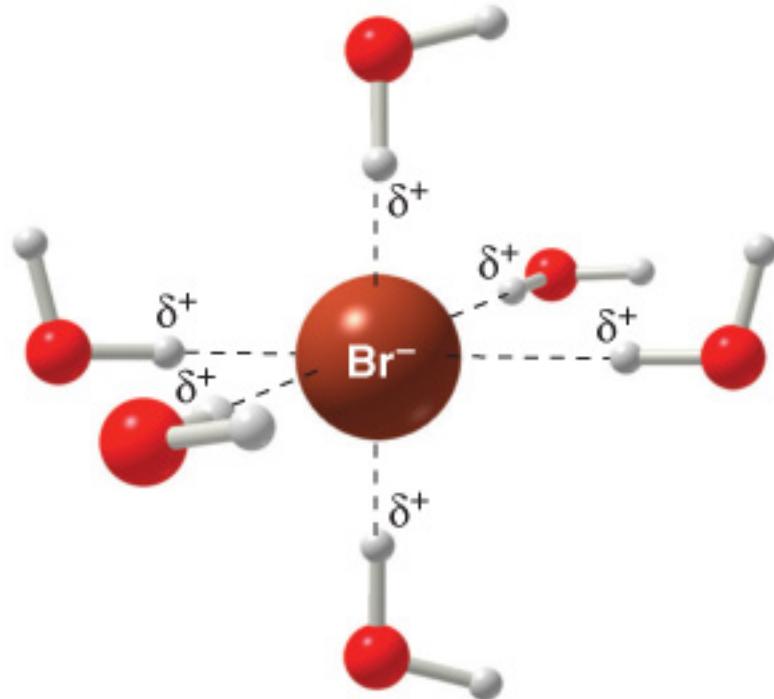
Three  $\text{CH}_3$  groups sterically hinder the O atom, making it a **weaker nucleophile**.

# The Nucleophile

- If the salt NaBr is used as a source of the nucleophile Br<sup>-</sup> in H<sub>2</sub>O, the Na<sup>+</sup> cations are solvated by ion-dipole interactions with H<sub>2</sub>O molecules, and the Br<sup>-</sup> anions are solvated by strong hydrogen bonding interactions.



Na<sup>+</sup> is solvated by ion-dipole interactions with H<sub>2</sub>O.



Br<sup>-</sup> is solvated by hydrogen bonding with H<sub>2</sub>O.

# The Nucleophile

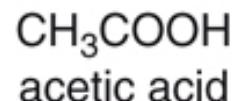
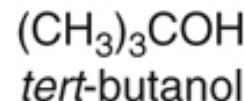
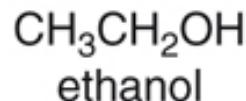
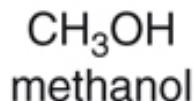
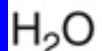
- In polar protic solvents, nucleophilicity increases down a column of the periodic table as the size of the anion increases. This is the opposite of basicity.

Down a column  
of the periodic table



Increasing nucleophilicity  
in polar protic solvents

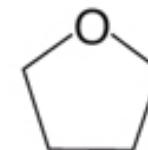
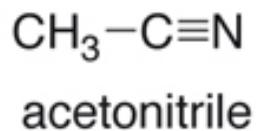
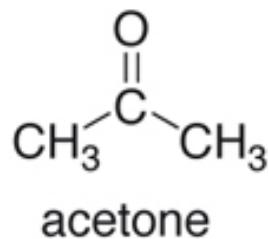
## Examples of polar protic solvents



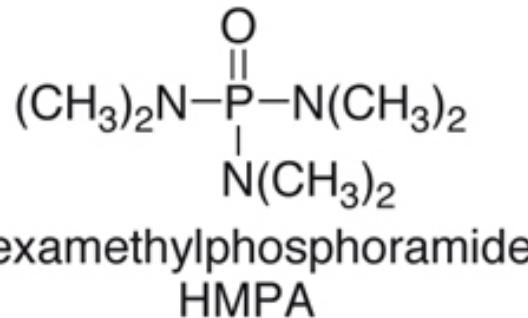
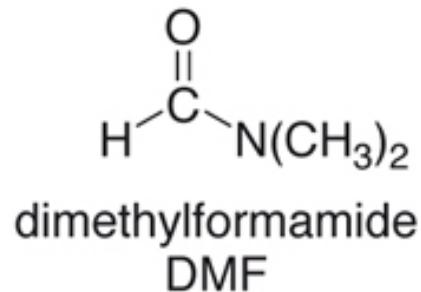
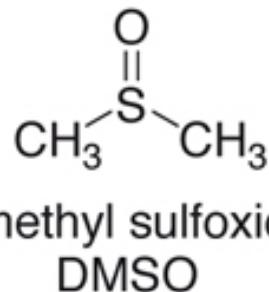
# The Nucleophile

- Polar aprotic solvents also exhibit dipole–dipole interactions, but they have no O—H or N—H bonds. Thus, they are incapable of hydrogen bonding.

## Examples of polar aprotic solvents

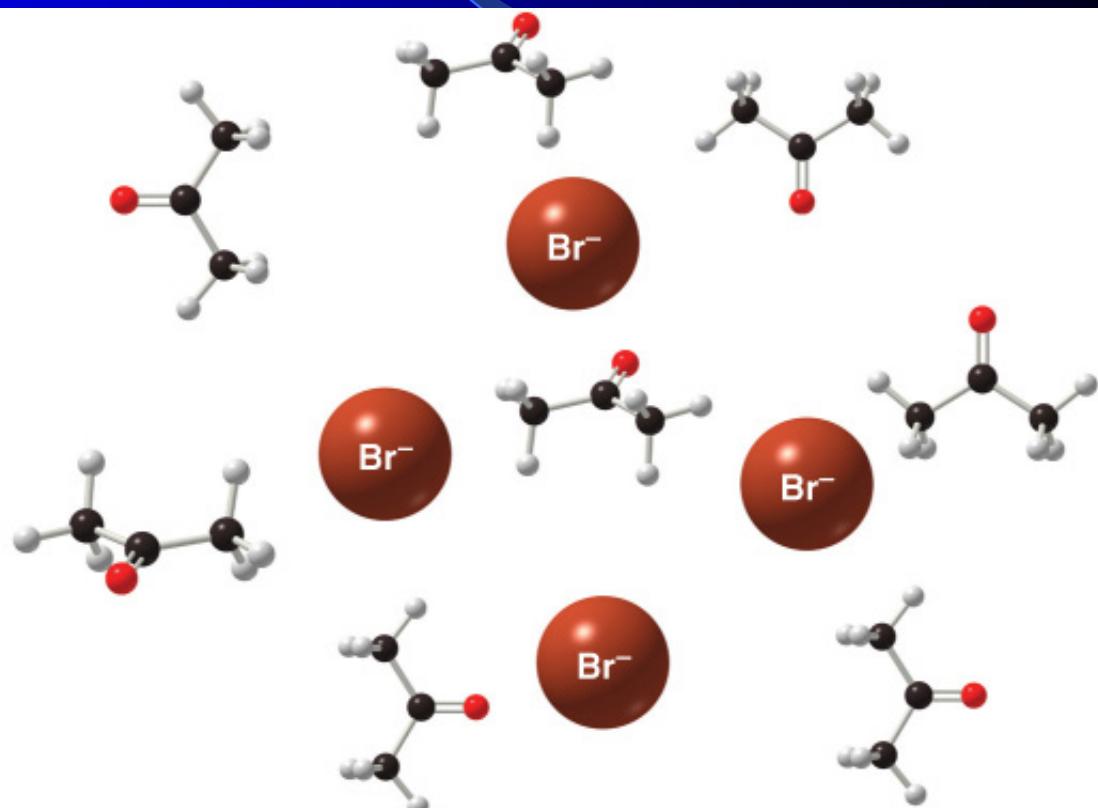
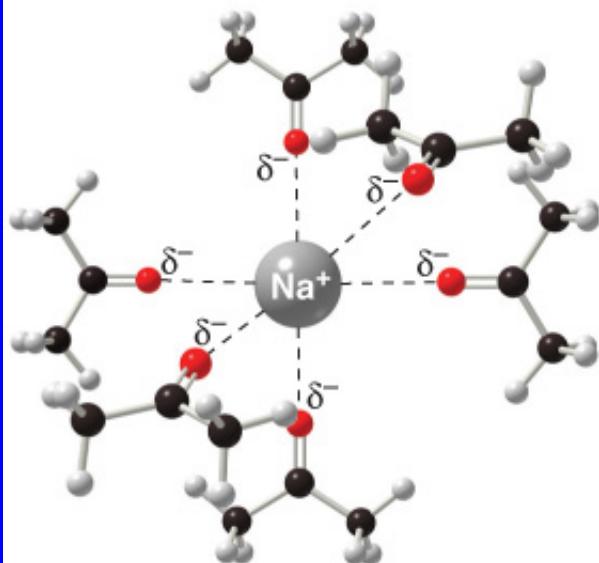


tetrahydrofuran  
THF



# The Nucleophile

- Polar aprotic solvents solvate cations by ion—dipole interactions.
- Anions are not well solvated because the solvent. These anions are said to be “naked”.



Br<sup>-</sup> anions are surrounded by solvent but not well solvated by the (CH<sub>3</sub>)<sub>2</sub>C=O molecules.

# The Nucleophile

- In polar aprotic solvents, nucleophilicity parallels basicity, and the stronger base is the stronger nucleophile.
- Because basicity decreases as size increases down a column, nucleophilicity decreases as well.

Down a column  
of the periodic table



Increasing nucleophilicity  
in polar aprotic solvents

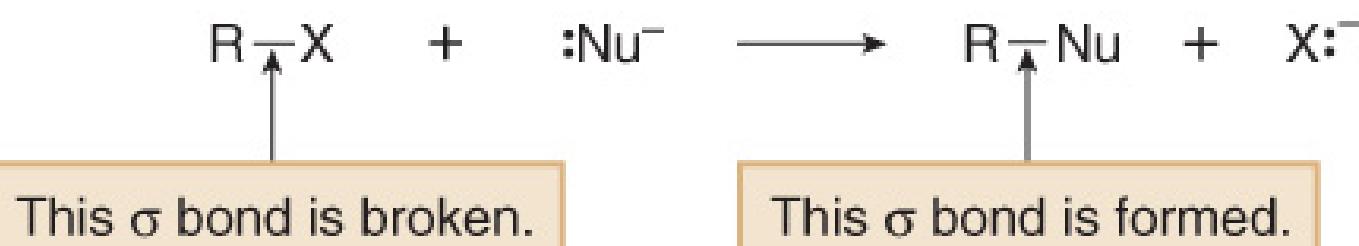
# The Nucleophile

	Negatively charged nucleophiles			Neutral nucleophiles	
Oxygen	$\text{^-OH}$	$\text{^-OR}$	$\text{CH}_3\text{COO}^-$	$\text{H}_2\text{O}$	$\text{ROH}$
Nitrogen	$\text{N}_3^-$			$\text{NH}_3$	$\text{RNH}_2$
Carbon	$\text{^-CN}$	$\text{HC}\equiv\text{C}^-$			
Halogen	$\text{Cl}^-$	$\text{Br}^-$	$\text{I}^-$		
Sulfur	$\text{HS}^-$	$\text{RS}^-$		$\text{H}_2\text{S}$	$\text{RSH}$

# Mechanisms of Nucleophilic Substitution

In a nucleophilic substitution:

Overall reaction

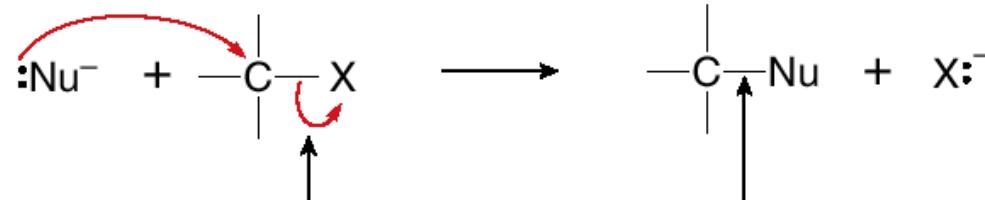


But what is the order of bond making and bond breaking? In theory, there are three possibilities.

# Mechanisms of Nucleophilic Substitution

[1] Bond making and bond breaking occur at the same time.

One-step mechanism



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

$$\text{rate} = k[\text{RX}][\text{:Nu}^-]$$

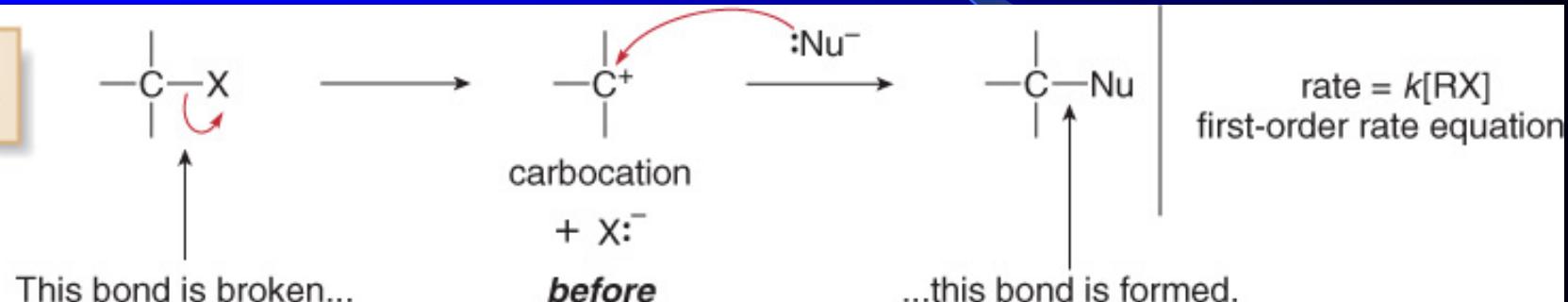
second-order rate equation

In this scenario, the mechanism is comprised of one step. In such a **bimolecular reaction**, the rate depends upon the concentration of both reactants, that is, the rate equation is **second order**.

# Mechanisms of Nucleophilic Substitution

[2] Bond breaking occurs before bond making.

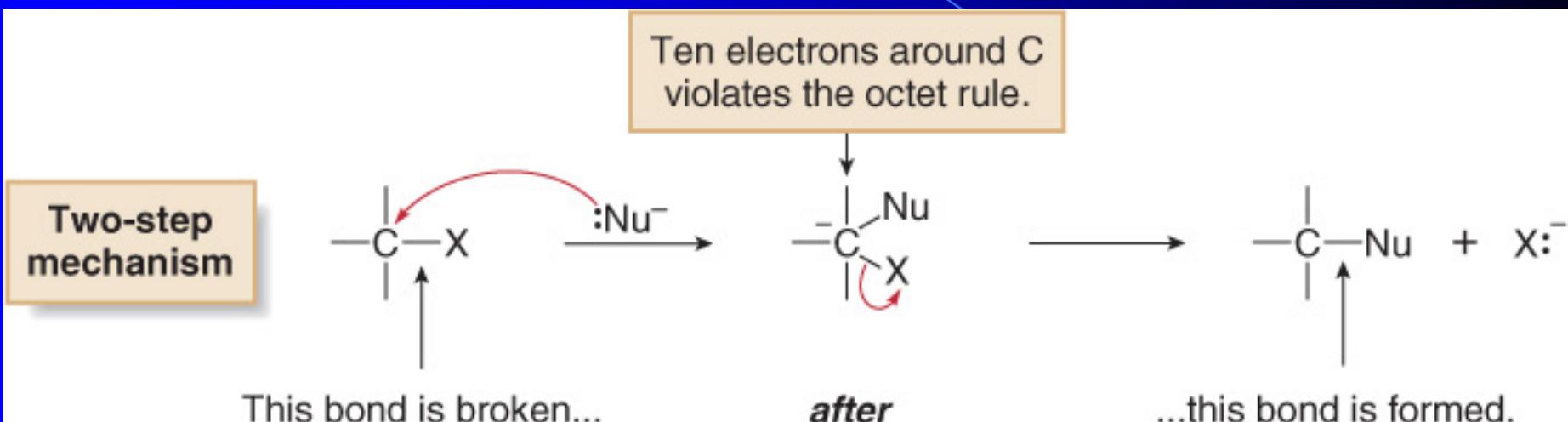
Two-step mechanism



In this scenario, the mechanism has two steps and a carbocation is formed as an intermediate. Because the first step is rate-determining, the rate depends on the concentration of  $\text{RX}$  only; that is, the rate equation is first order.

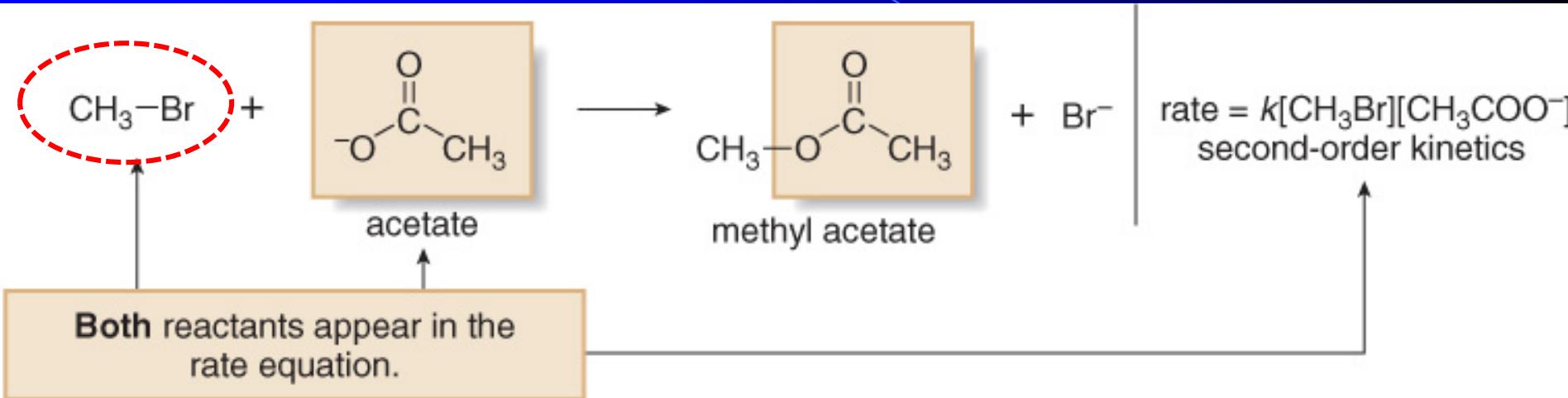
# Mechanisms of Nucleophilic Substitution

[3] Bond making occurs before bond breaking.



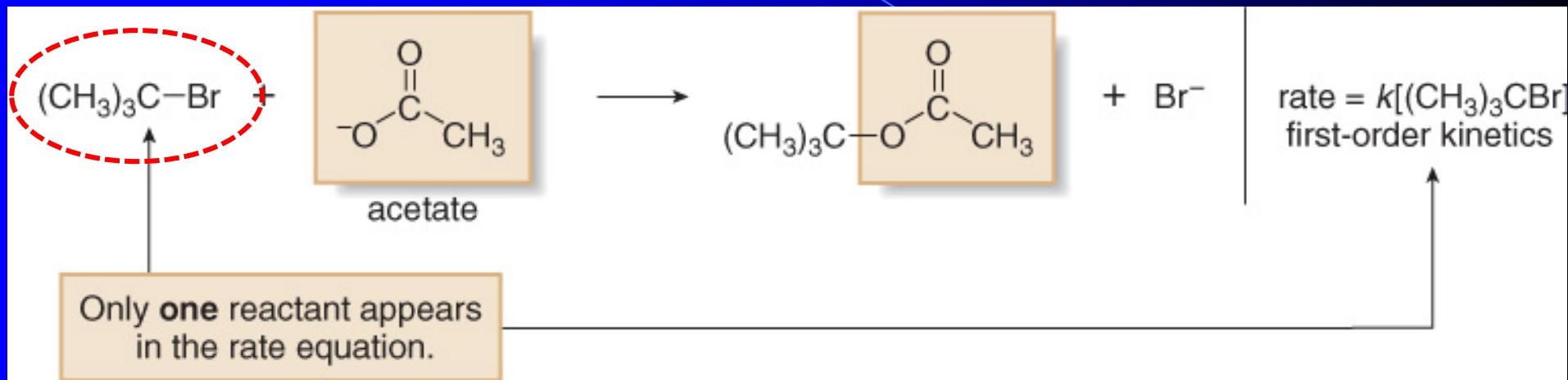
This mechanism has an inherent problem. The intermediate generated in the first step has 10 electrons around carbon, violating the octet rule. Because two other mechanistic possibilities do not violate a fundamental rule, this last possibility can be disregarded.

# Mechanisms of Nucleophilic Substitution



Kinetic data show that the rate of reaction depends on the concentration of both reactants, which suggests a bimolecular reaction with a one-step mechanism. This is an example of an  $S_N2$  (substitution nucleophilic bimolecular) mechanism.

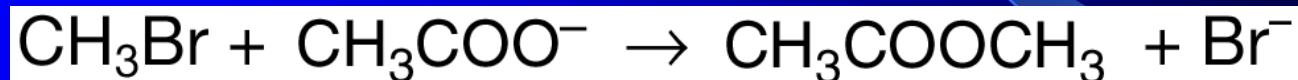
# Mechanisms of Nucleophilic Substitution



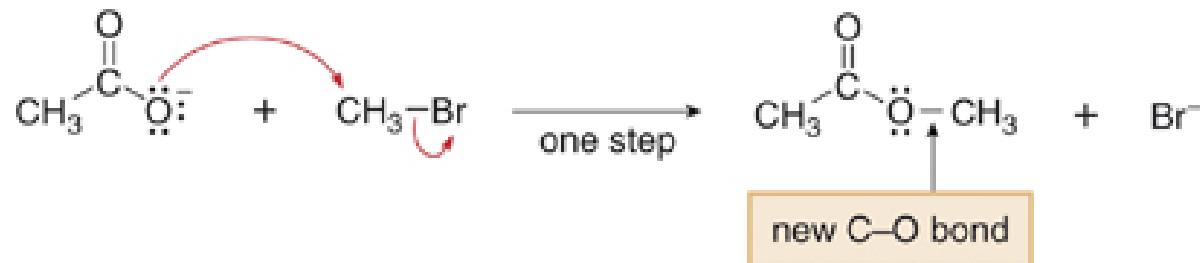
Kinetic data show that the rate of reaction depends on the concentration of only the alkyl halide. This suggests a two-step mechanism in which the rate-determining step involves the alkyl halide only. This is an example of an  $S_N1$  (substitution nucleophilic unimolecular) mechanism.

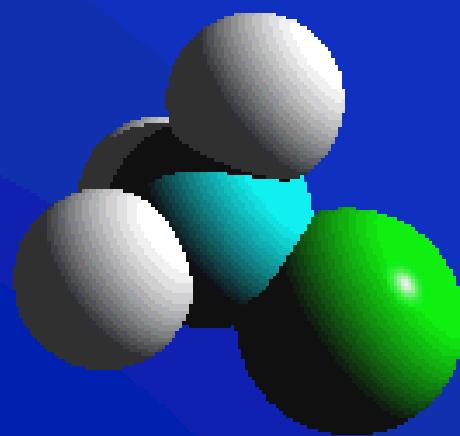
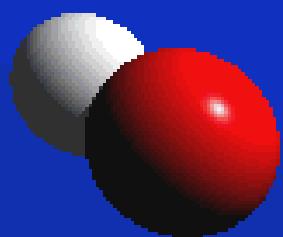
# Mechanisms of Nucleophilic Substitution

The mechanism of an S<sub>N</sub>2 reaction would be drawn as follows. Note the curved arrow notation that is used to show the flow of electrons.



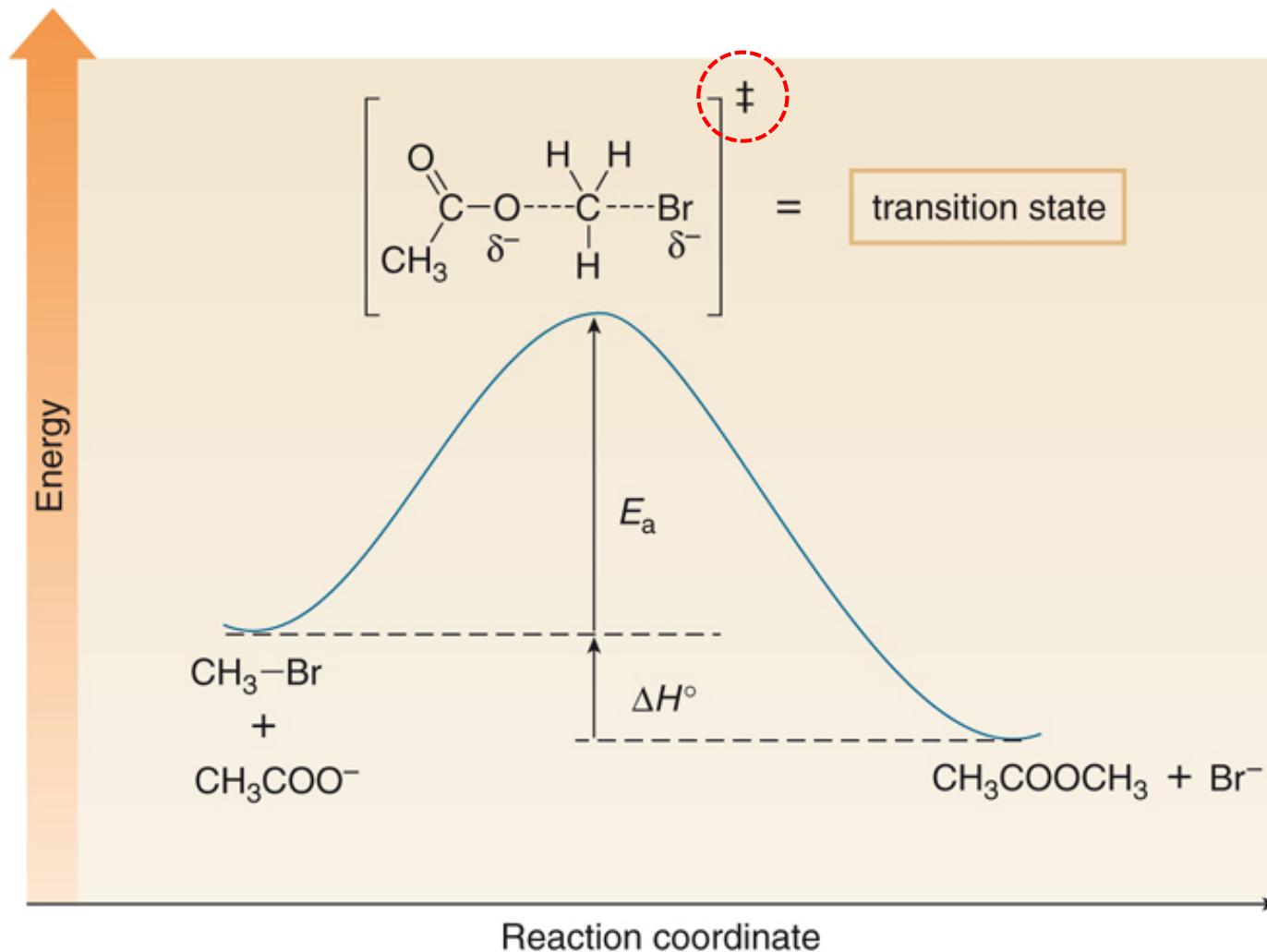
One step The C – Br bond breaks as the C – O bond forms.





## Mechanisms of Nucleophilic Substitution

### An energy diagram for the S<sub>N</sub>2 reaction

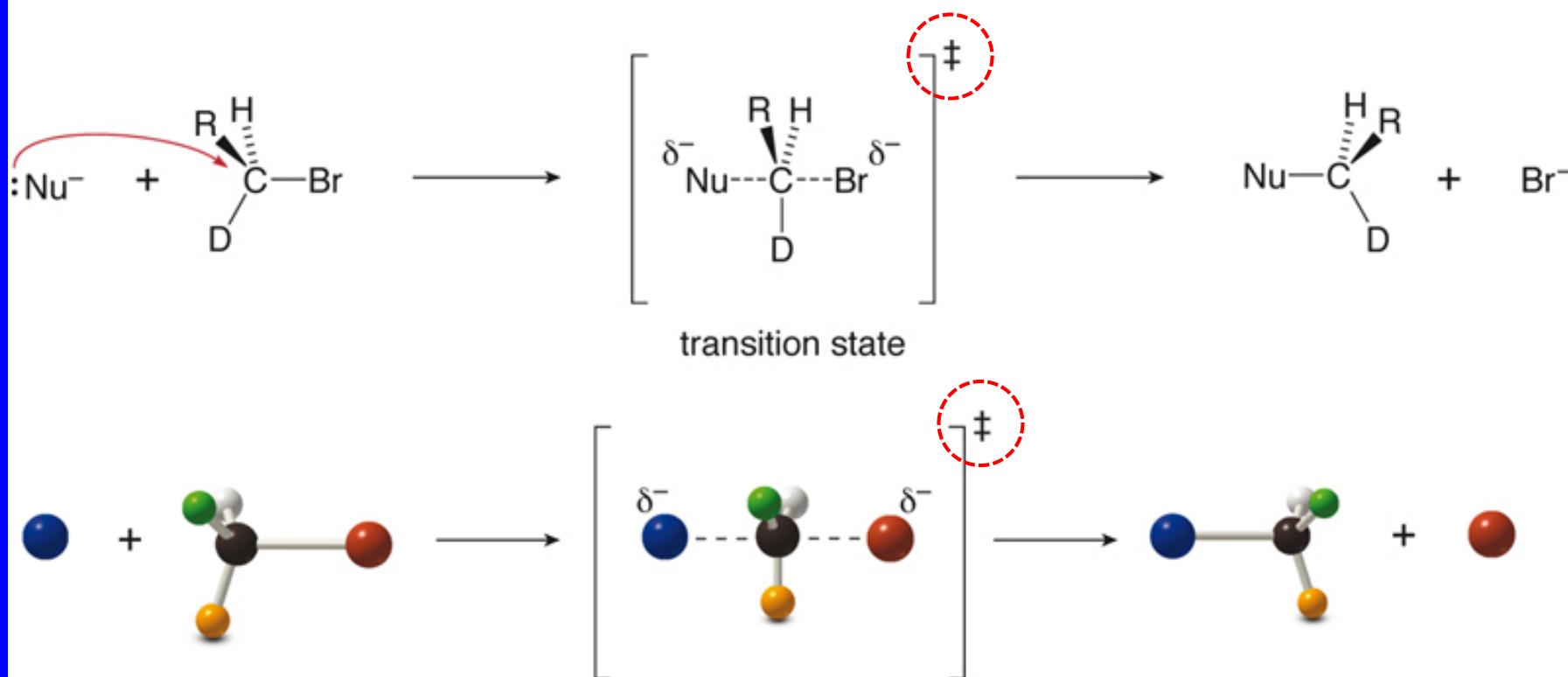


- In the transition state, the C–Br bond is partially broken, the C–O bond is partially formed, and both the attacking nucleophile and the departing leaving group bear a partial negative charge.

# Mechanisms of Nucleophilic Substitution—Stereochemistry

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

## Stereochemistry of the $S_N2$ reaction

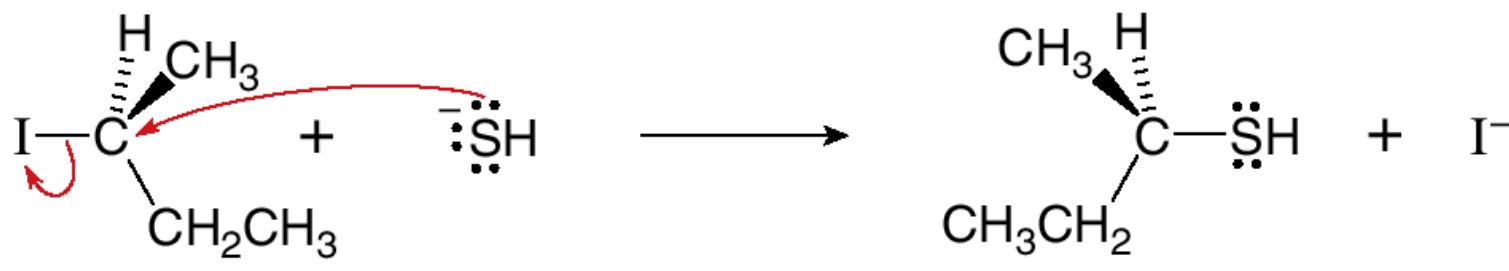


$:Nu^-$  and  $Br^-$  are  $180^\circ$  away from each other, on either side of a plane containing  $R$ ,  $H$ , and  $D$ .

# Mechanisms of Nucleophilic Substitution—Stereochemistry

Two examples of inversion of configuration in the  $S_N2$  reaction

- 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.



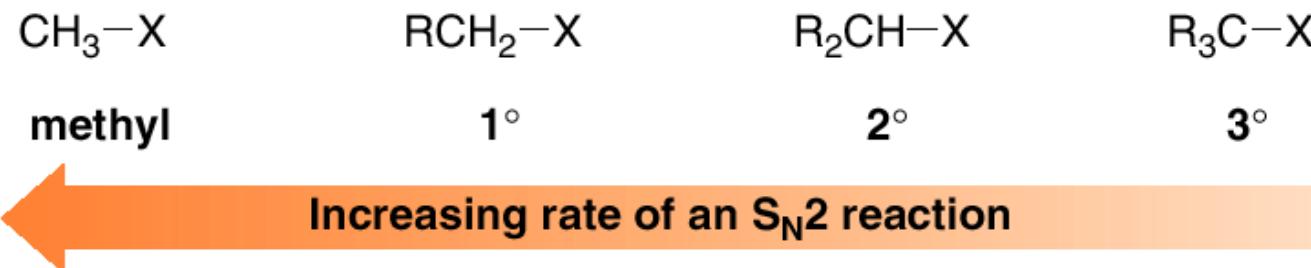
inversion of configuration



inversion of configuration

# Mechanisms of Nucleophilic Substitution

As the number of R groups on the carbon with the leaving group *increases*, the rate of an S<sub>N</sub>2 reaction *decreases*.

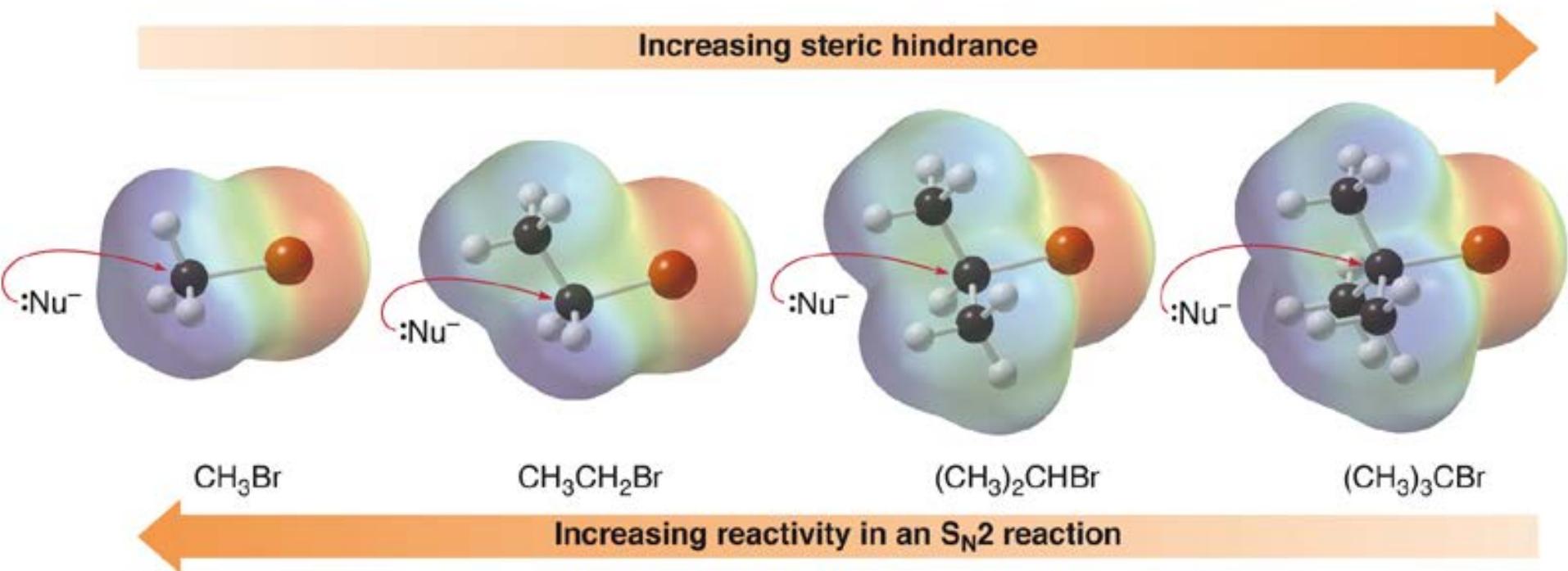


- Methyl and 1° alkyl halides undergo S<sub>N</sub>2 reactions with ease.
- 2° Alkyl halides react slowly (at a lower rate).
- 3° Alkyl halides do not undergo S<sub>N</sub>2 reactions. This order of reactivity can be explained by steric effects. Steric hindrance caused by bulky R groups makes nucleophilic attack from the backside more difficult, slowing the reaction rate.

# Mechanisms of Nucleophilic Substitution

Electrostatic potential maps illustrate the effects of steric hindrance around the carbon bearing the leaving group in a series of alkyl halides.

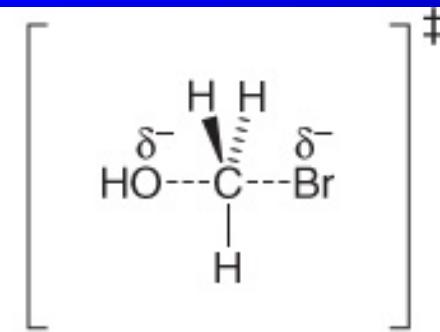
## Steric effects in the $S_N2$ reaction



# Mechanisms of Nucleophilic Substitution

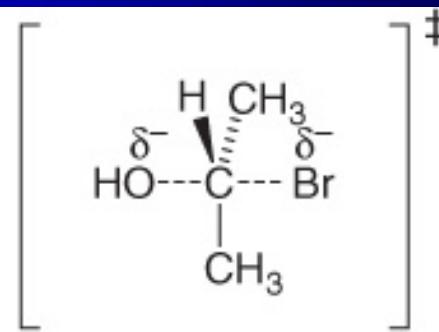
## Mechanisms of Nucleophilic Substitution

- Increasing the number of R groups on the carbon with the leaving group increases crowding in the transition state, thereby decreasing the reaction rate.
- The  $S_N2$  reaction is fastest with unhindered halides.



less crowded transition state  
lower in energy

faster  $S_N2$  reaction



more crowded transition state  
higher in energy

slower  $S_N2$  reaction

## Mechanisms of Nucleophilic Substitution

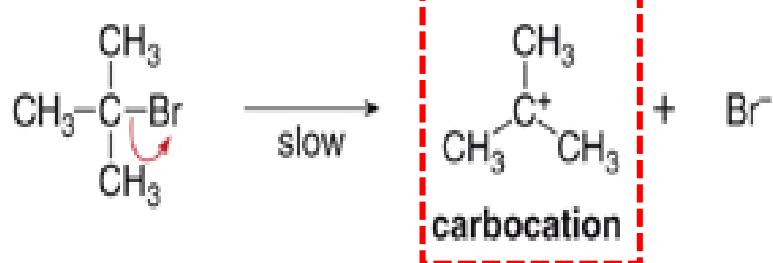
### Characteristics of $S_N2$ mechanism

Characteristic	Result
Kinetics	<ul style="list-style-type: none"><li>Second-order kinetics; rate = <math>k[RX][:\text{Nu}^-]</math></li></ul>
Mechanism	<ul style="list-style-type: none"><li>One step</li></ul>
Stereochemistry	<ul style="list-style-type: none"><li>Backside attack of the nucleophile</li><li>Inversion of configuration at a stereogenic center</li></ul>
Identity of R	<ul style="list-style-type: none"><li>Unhindered halides react fastest.</li><li>Rate: <math>\text{CH}_3\text{X} &gt; \text{RCH}_2\text{X} &gt; \text{R}_2\text{CHX} &gt; \text{R}_3\text{CX}</math></li></ul>

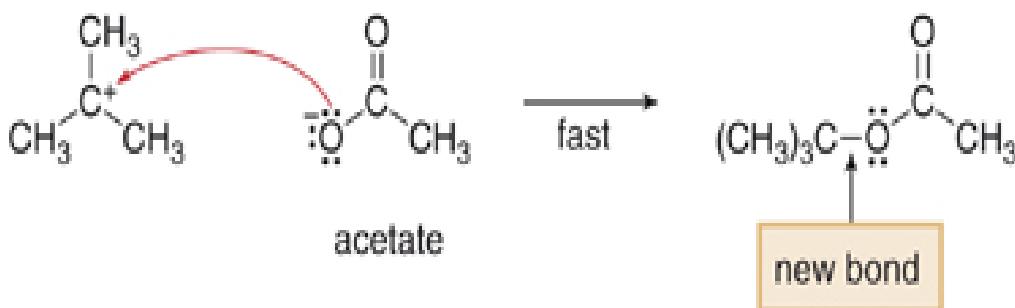
# Mechanisms of Nucleophilic Substitution

The mechanism of an  $S_N1$  reaction involves the formation of an intermediate Carbocation. Note the curved arrow formalism that is used to show the flow of electrons.

Step [1] The C–Br bond is broken.



Step [2] The C–O bond is formed.

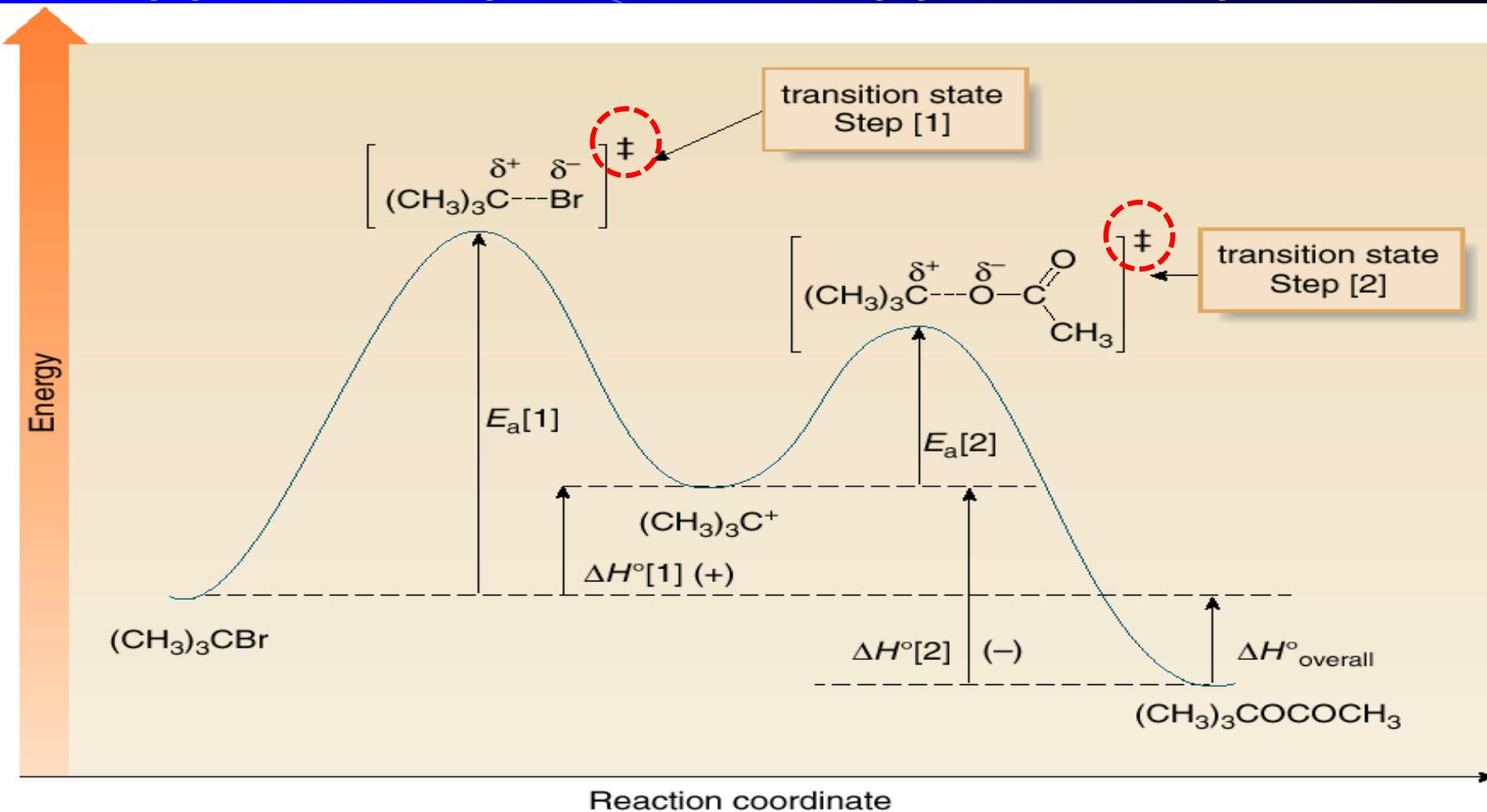


Heterolytic breaking of C–Br bond leave a +ve charge on the C and forms the carbocation. This is the slowest step as a bond is breaking, hence it is the rate determining step

Nucleophilic attack of attack on carbocation leads to the formation of product. This step is faster as a new chemical bond is formed.

Key features of the  $S_N1$  mechanism are that it has two steps, and carbocations are formed as reactive intermediates.

# An energy diagram for the S<sub>N</sub>1 reaction

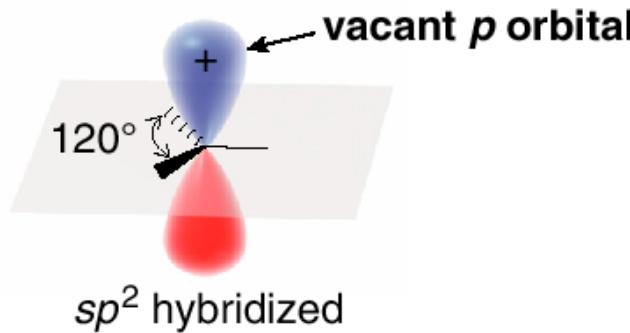


- Since the  $\text{S}_{\text{N}}1$  mechanism has two steps, there are two energy barriers.
- $E_a[1] > E_a[2]$  since Step [1] involves bond breaking and Step [2] involves bond formation.
- In each step only one bond is broken or formed, so the transition state for each step has one partial bond.
-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

# Mechanisms of Nucleophilic Substitution and Stereochemistry

To understand the stereochemistry of the  $S_N1$  reaction, we must examine the geometry of the carbocation intermediate.

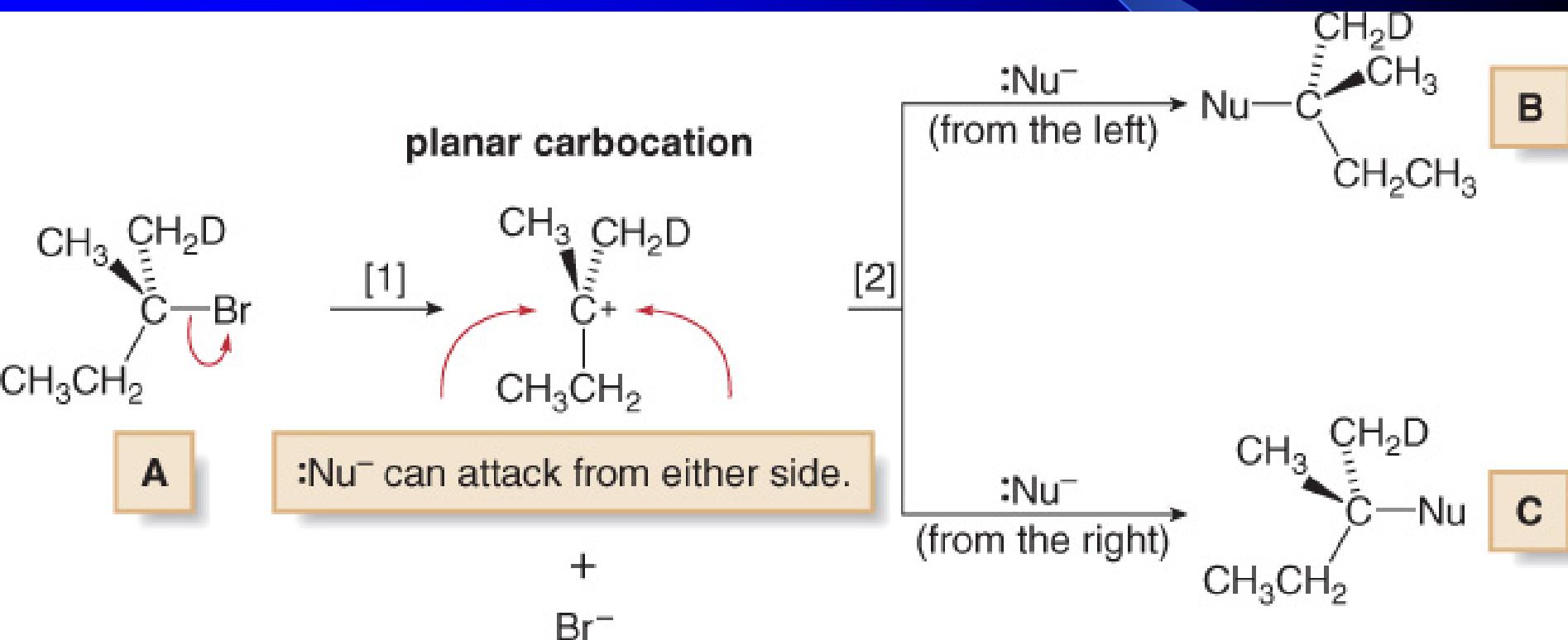
A trigonal planar carbocation



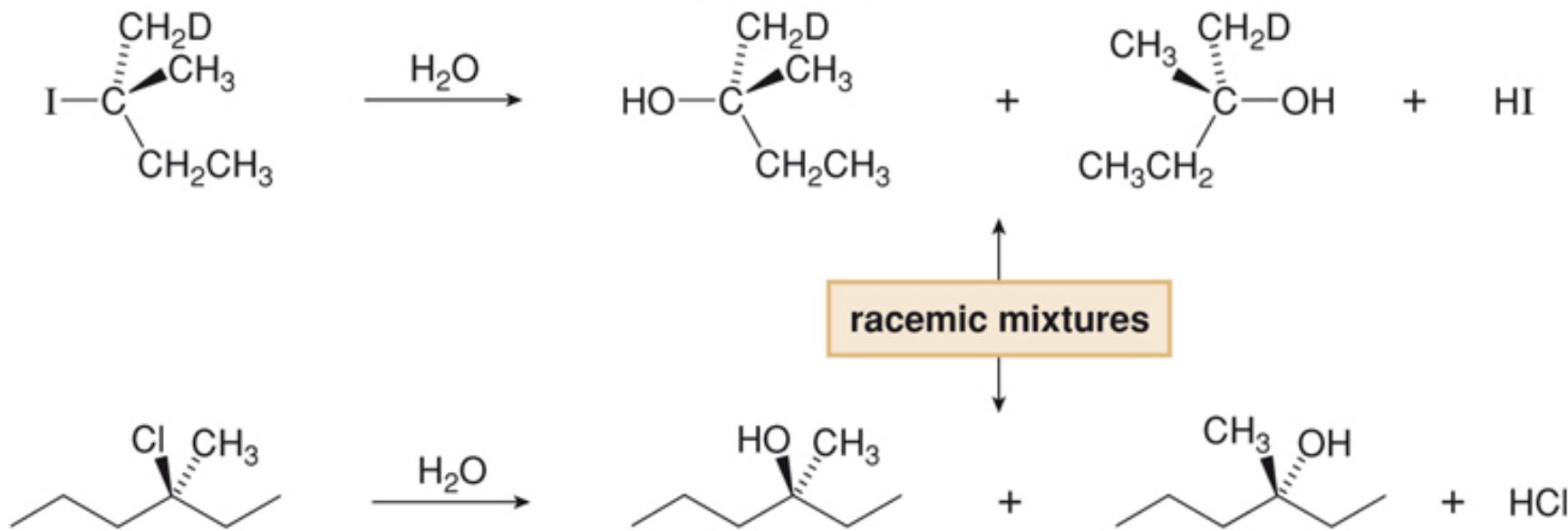
- A carbocation (with three groups around C) is  $sp^2$  hybridized and trigonal planar, and contains a vacant  $p$  orbital extending above and below the plane.

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.

Because there is no preference for nucleophilic attack from either direction, an equal amount of the two enantiomers is formed—a racemic mixture. We say that **racemization** has occurred.



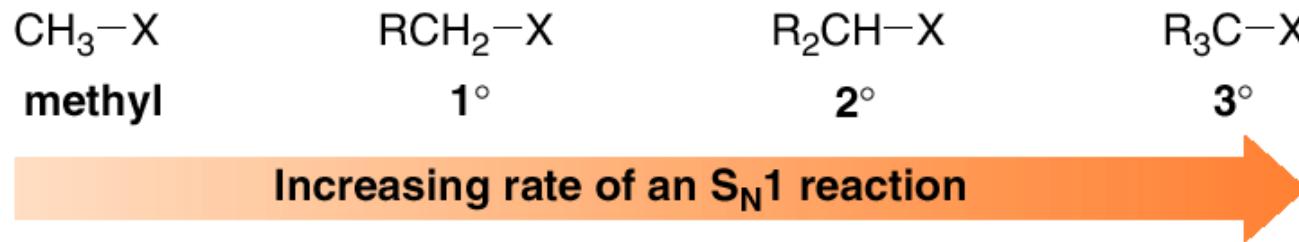
## Two examples of racemization in the $S_N1$ reaction



- 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).

# Mechanisms for Nucleophilic Substitution

- 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*.



- $3^\circ$  Alkyl halides undergo  $S_N1$  reactions rapidly.
  - $2^\circ$  Alkyl halides react more slowly.
  - Methyl and  $1^\circ$  alkyl halides do *not* undergo  $S_N1$  reactions.
- 
- This trend is exactly opposite to that observed in  $S_N2$  reactions.

# Mechanisms for Nucleophilic Substitution

## *Characteristics of $S_N1$ Mechanism*

Characteristic	Result
Kinetics	<ul style="list-style-type: none"><li>First-order kinetics; rate = <math>k[RX]</math></li></ul>
Mechanism	<ul style="list-style-type: none"><li>Two steps</li></ul>
Stereochemistry	<ul style="list-style-type: none"><li>Trigonal planar carbocation intermediate</li><li>Racemization at a single stereogenic center</li></ul>
Identity of R	<ul style="list-style-type: none"><li>More substituted halides react fastest.</li><li>Rate: <math>R_3CX &gt; R_2CHX &gt; RCH_2X &gt; CH_3X</math></li></ul>

# Carbocation Stability

- The effect of the type of alkyl halide on  $S_N1$  reaction rates can be explained by considering carbocation stability.
- Carbocations are classified as primary ( $1^\circ$ ), secondary ( $2^\circ$ ), or tertiary ( $3^\circ$ ), based on the number of R groups bonded to the charged carbon atom. As the number of R groups increases, carbocation stability increases.



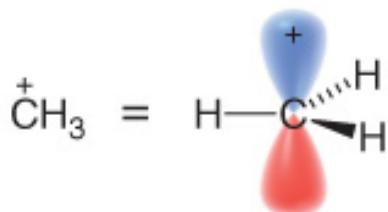
Increasing carbocation stability

# Carbocation Stability

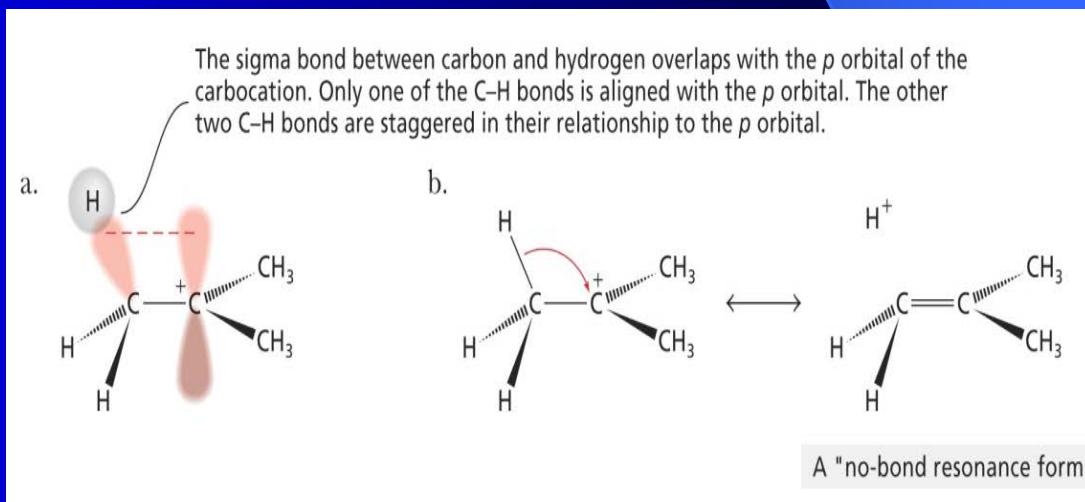
- Order of carbocation stability: inductive effects and hyperconjugation.
- Inductive effects: Electronic effects occurring through  $\sigma$  bonds. Electron density is pulled through  $\sigma$  bonds due to electronegativity differences between atoms/groups.
- Alkyl groups are electron donating groups. Since an alkyl group has several  $\sigma$  bonds, each containing electron density, it is more polarizable than a hydrogen atom, and better able to donate electron density.
- The greater the number of alkyl groups attached to a positively charged carbon, the more stable will be the cation.

# Carbocation Stability

- Hyperconjugation: It 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:  $\text{CH}_3^+$  cannot be stabilized by hyperconjugation, but  $(\text{CH}_3)_2\text{CH}^+$  can.

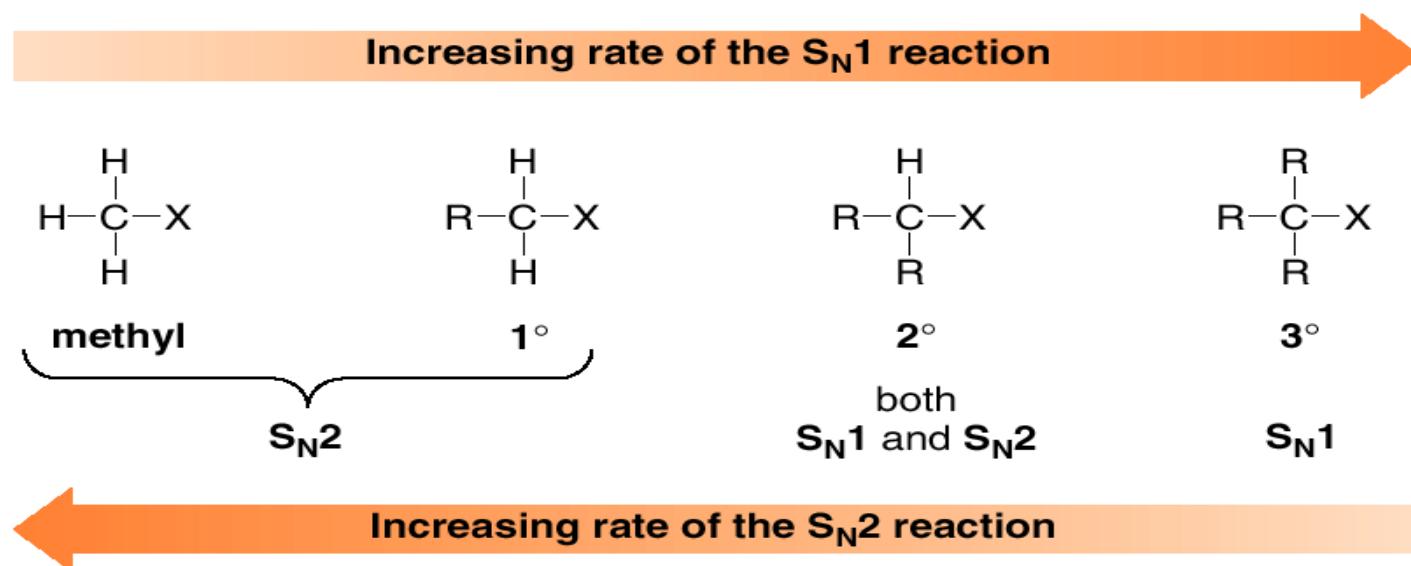


This carbocation has no opportunity for orbital overlap with the vacant p orbital.



# Predicting the Likely Mechanism of a Substitution Reaction

- Four factors are relevant in predicting whether a given reaction is likely to proceed by an  $S_N1$  or an  $S_N2$  reaction—The most important is the identity of the alkyl halide.
- Increasing alkyl substitution favors  $S_N1$ .
- Decreasing alkyl substitution favors  $S_N2$ .

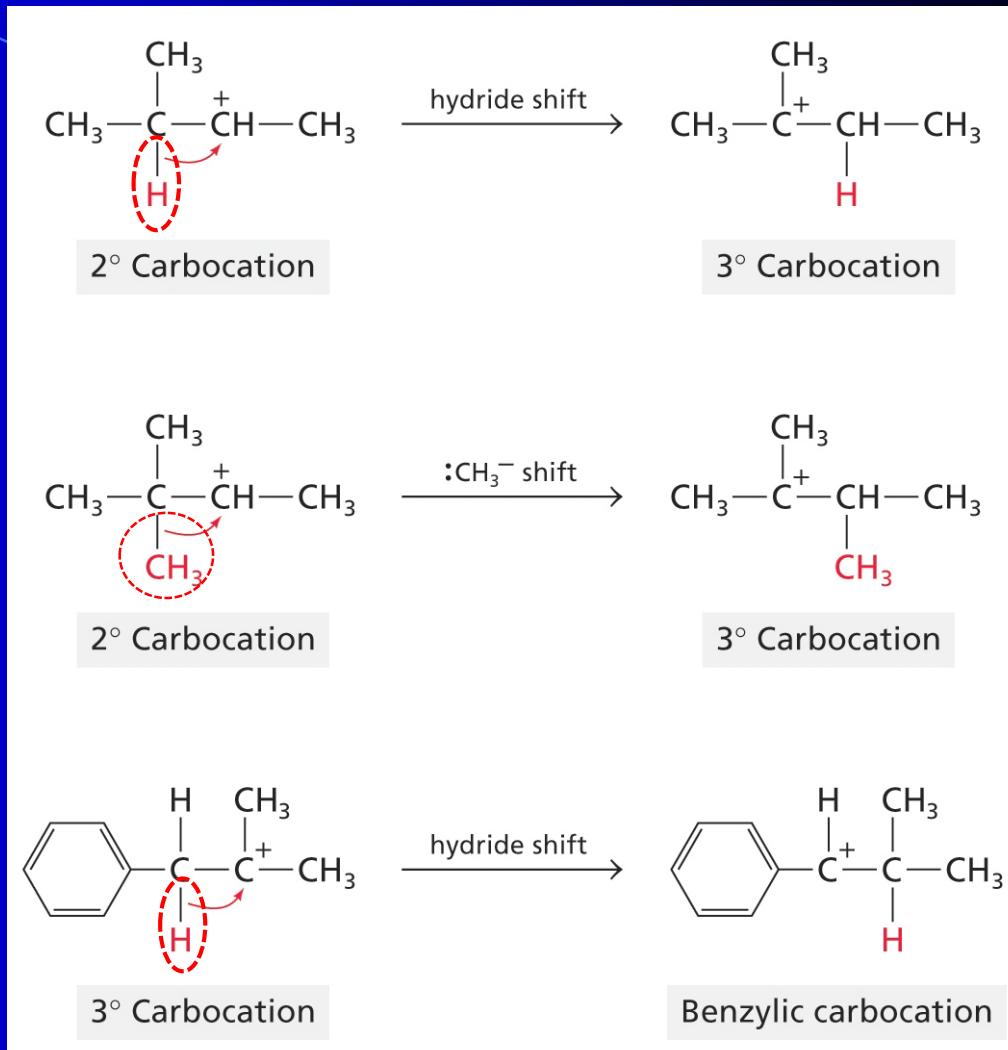


- Methyl and 1° halides ( $\text{CH}_3\text{X}$  and  $\text{RCH}_2\text{X}$ ) undergo  $S_N2$  reactions only.
- 3° Alkyl halides ( $\text{R}_3\text{CX}$ ) undergo  $S_N1$  reactions only.
- 2° Alkyl halides ( $\text{R}_2\text{CHX}$ ) undergo both  $S_N1$  and  $S_N2$  reactions. Other factors determine the mechanism.

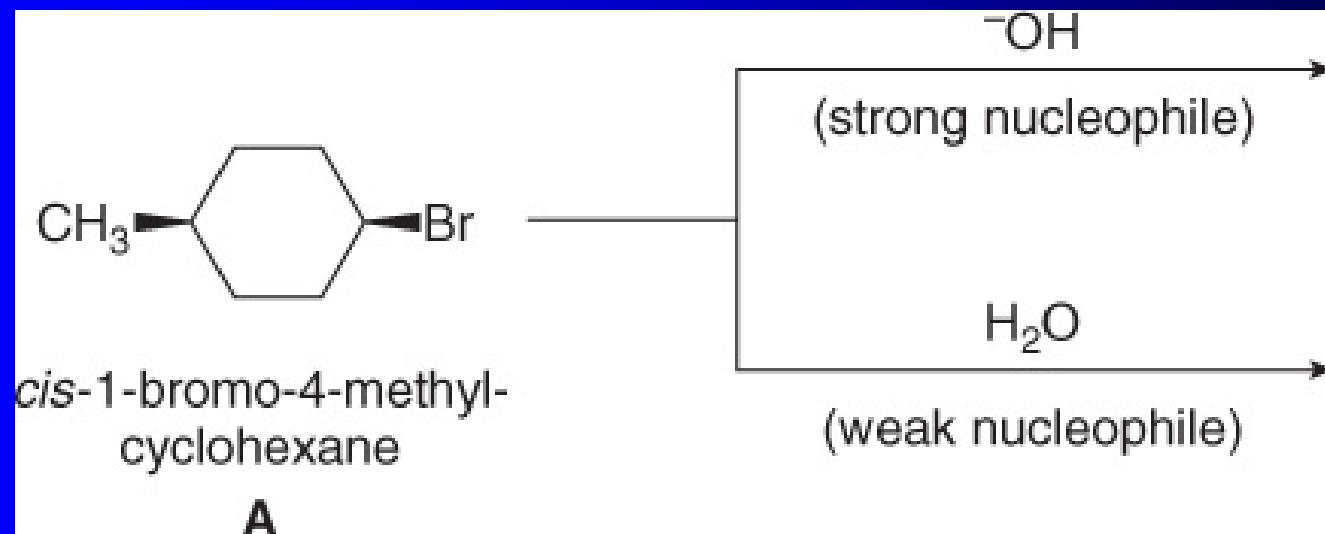
# $S_N1$ Rearrangements

It is worth noting that carbocation rearrangements can involve shifting either a hydride ion or a methyl anion. In either case, you will always be forming a more stable carbocation.

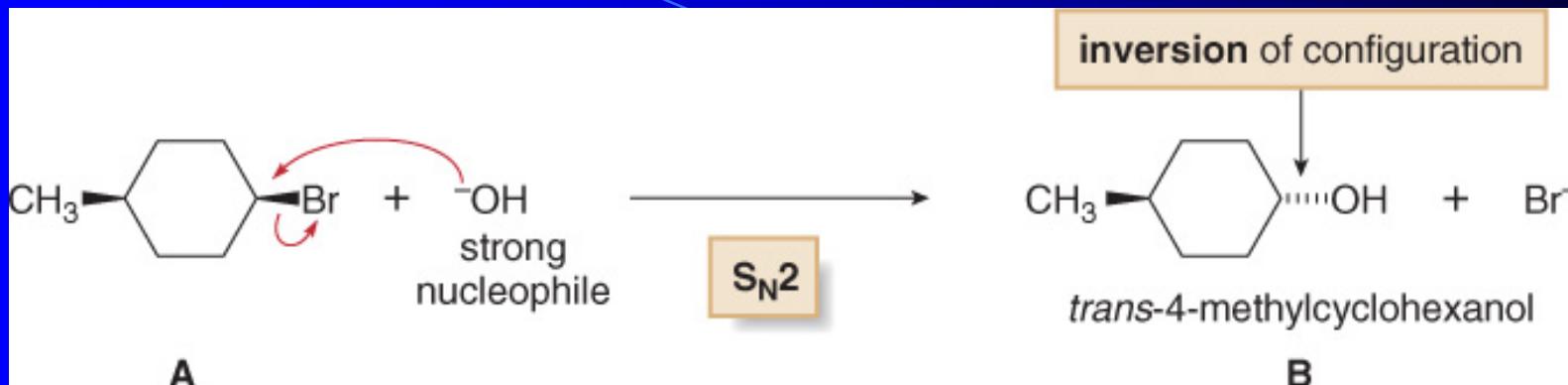
Pay close attention to the way curly arrows are drawn when proposing a hydride or methyl shift. We should be able to tell if you're proposing a hydride shift or generation of a pi bond.



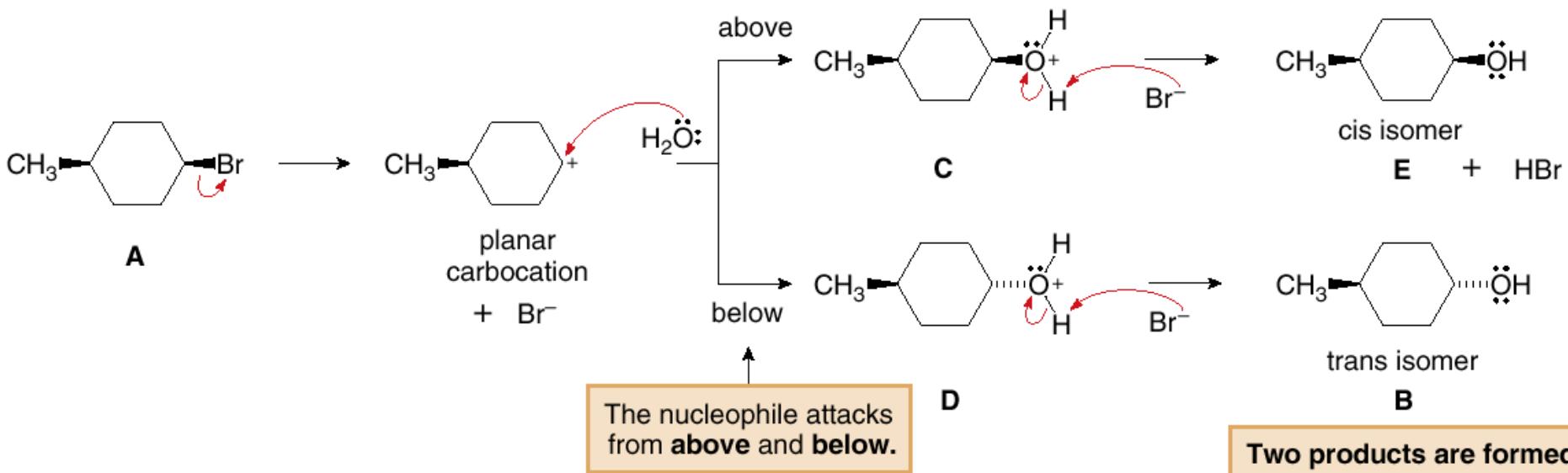
- The nature of the nucleophile is another factor.
- Strong nucleophiles (which usually bear a negative charge) present in high concentrations favor  $S_N2$  reactions.
- Weak nucleophiles, such as  $H_2O$  and  $ROH$  favor  $S_N1$  reactions by decreasing the rate of any competing  $S_N2$  reaction.



• The strong nucleophile favors an  $S_N2$  mechanism.

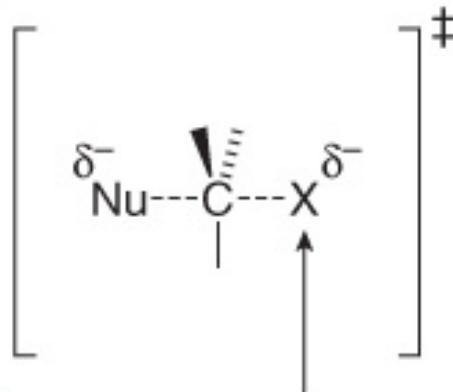


• The weak nucleophile favors an  $S_N1$  mechanism.

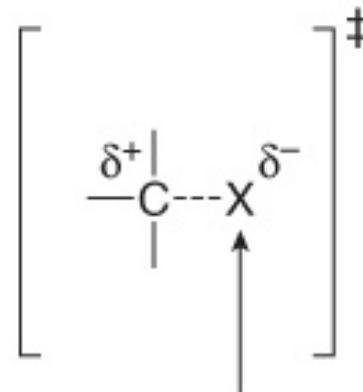


- A better leaving group increases the rate of both  $S_N1$  and  $S_N2$  reactions.

Transition state of the  $S_N2$  mechanism



Transition state of the rate-determining step of the  $S_N1$  mechanism



A better leaving group is more able to accept the negative charge.

$\text{R-F}$

$\text{R-Cl}$

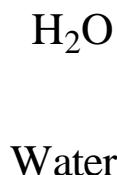
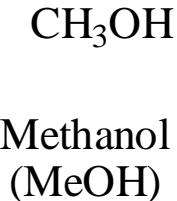
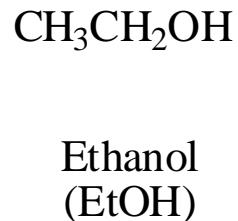
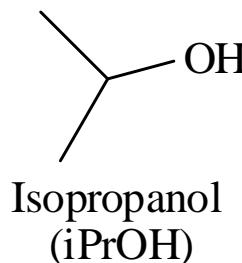
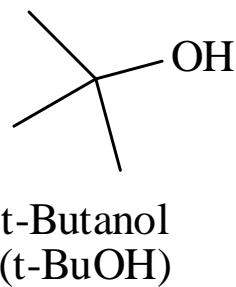
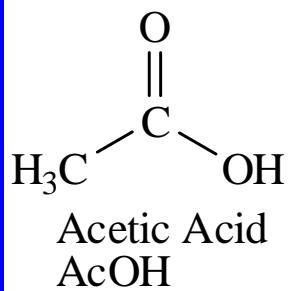
$\text{R-Br}$

$\text{R-I}$

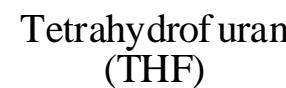
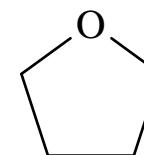
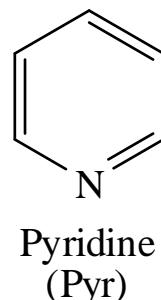
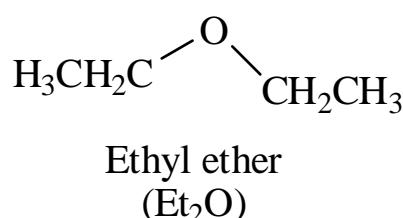
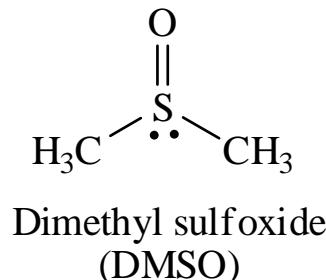
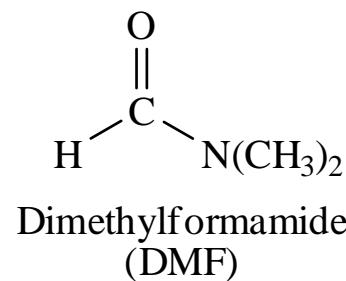
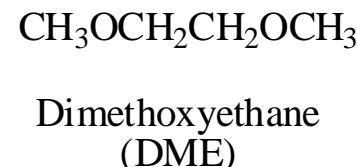
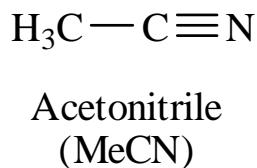
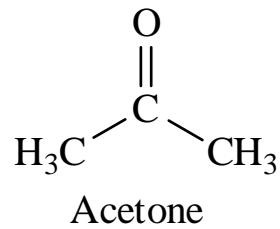
Increasing leaving group ability  
Increasing rate of  $S_N1$  and  $S_N2$  reactions

- The nature of the solvent is a fourth factor.
- Polar protic solvents like  $\text{H}_2\text{O}$  and  $\text{ROH}$  favor  $\text{S}_{\text{N}}1$  reactions because the ionic intermediates (both cations and anions) are stabilized by solvation.
- Polar aprotic solvents favor  $\text{S}_{\text{N}}2$  reactions because nucleophiles are not well solvated, and therefore, are more nucleophilic.

## Some common polar protic solvents:



## Some common polar aprotic solvents:



# Predicting the Likely Mechanism of a Substitution Reaction

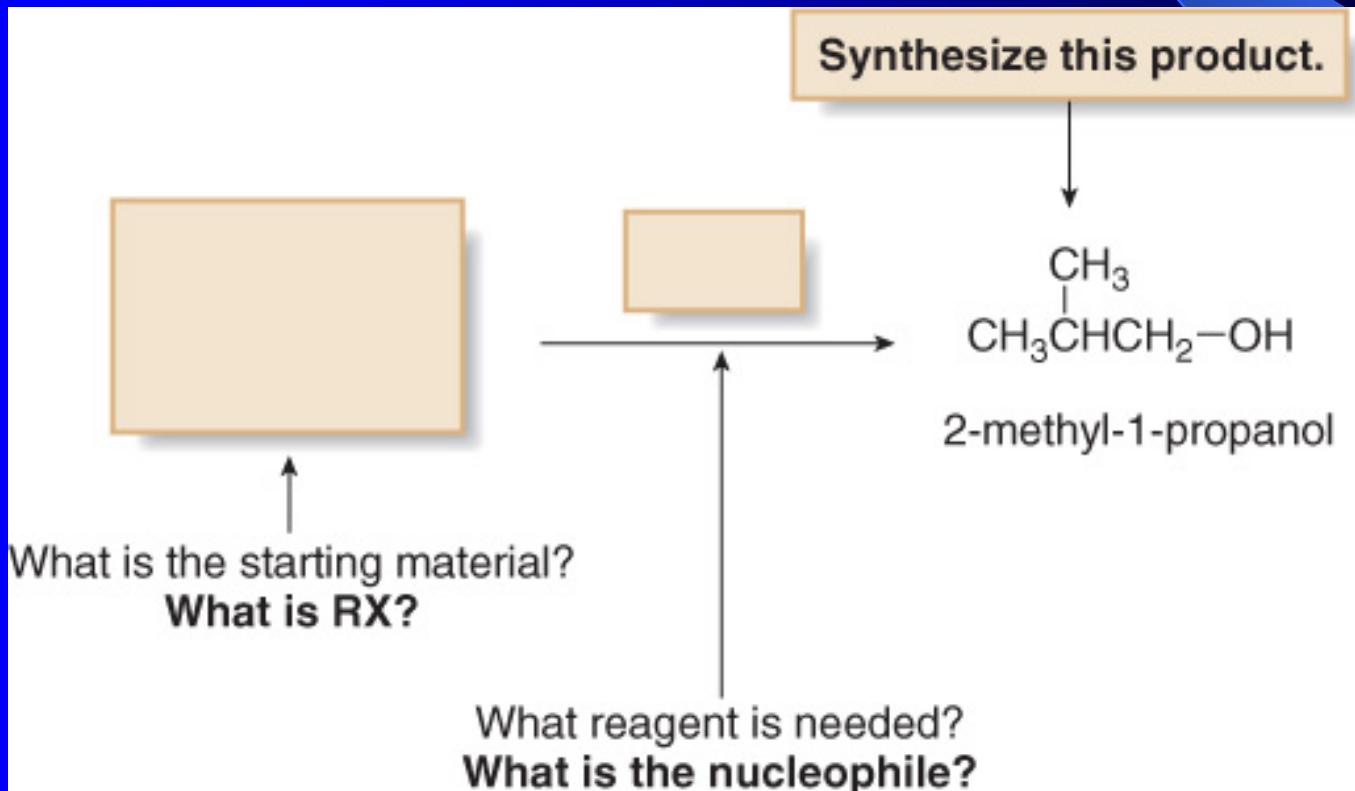
## Summary of $S_N1$ and $S_N2$ mechanisms

Alkyl halide	Mechanism	Other factors
$\text{CH}_3\text{X}$	$S_N2$	Favored by <ul style="list-style-type: none"><li>• <u>strong nucleophiles</u> (usually a net negative charge)</li><li>• <u>polar aprotic solvents</u></li></ul>
$\text{RCH}_2\text{X}$ ( $1^\circ$ )		
$\text{R}_3\text{CX}$ ( $3^\circ$ )	$S_N1$	Favored by <ul style="list-style-type: none"><li>• <u>weak nucleophiles</u> (usually neutral)</li><li>• <u>polar protic solvents</u></li></ul>
$\text{R}_2\text{CHX}$ ( $2^\circ$ )	$S_N1$ or $S_N2$	The mechanism depends on the conditions. <ul style="list-style-type: none"><li>• <u>Strong nucleophiles favor the <math>S_N2</math> mechanism over the <math>S_N1</math> mechanism.</u> For example, <math>\text{RO}^-</math> is a stronger nucleophile than <math>\text{ROH}</math>, so <math>\text{RO}^-</math> favors the <math>S_N2</math> reaction and <math>\text{ROH}</math> favors the <math>S_N1</math> reaction.</li><li>• <u>Protic solvents favor the <math>S_N1</math> mechanism and aprotic solvents favor the <math>S_N2</math> mechanism.</u> For example, <math>\text{H}_2\text{O}</math> and <math>\text{CH}_3\text{OH}</math> are polar protic solvents that favor the <math>S_N1</math> mechanism, whereas acetone <math>[(\text{CH}_3)_2\text{C}=\text{O}]</math> and DMSO <math>[(\text{CH}_3)_2\text{S}=\text{O}]</math> are polar aprotic solvents that favor the <math>S_N2</math> mechanism.</li></ul>

	Nucleophile ( $:Nu^-$ )	Product	Name
Oxygen compounds	$-OH$	$R-OH$	alcohol
	$-OR'$	$R-OR'$	ether
	$\begin{matrix} O \\ \parallel \\ -O-C-R' \end{matrix}$	$R-O-C(=O)R'$	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			

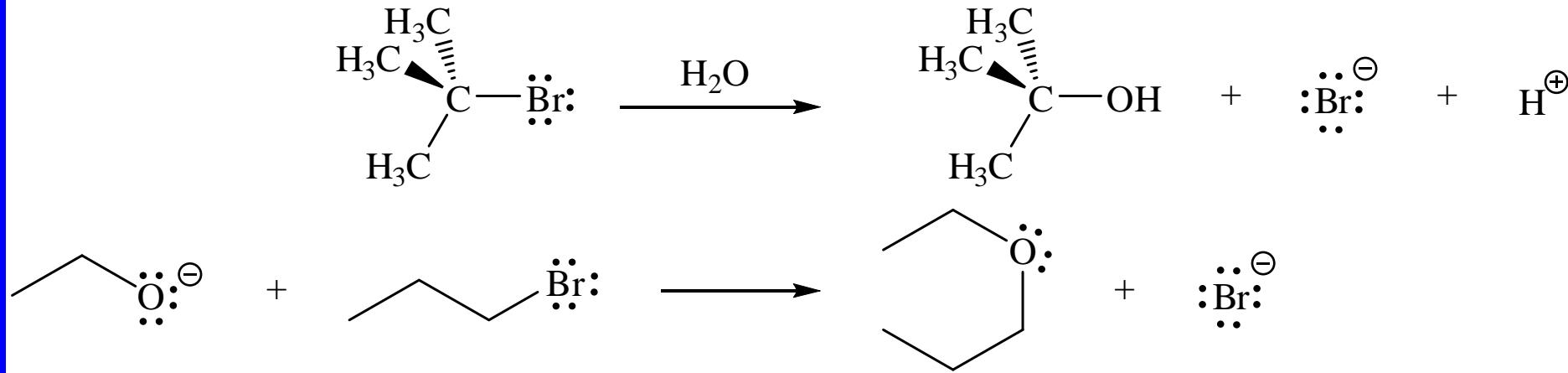
# Nucleophilic Substitution and Organic Synthesis

- What starting material and reagents are needed to make it?
- If we are using nucleophilic substitution, we must determine what alkyl halide and what nucleophile can be used to form a specific product.



# Elimination Reactions

Consider the following reactions:

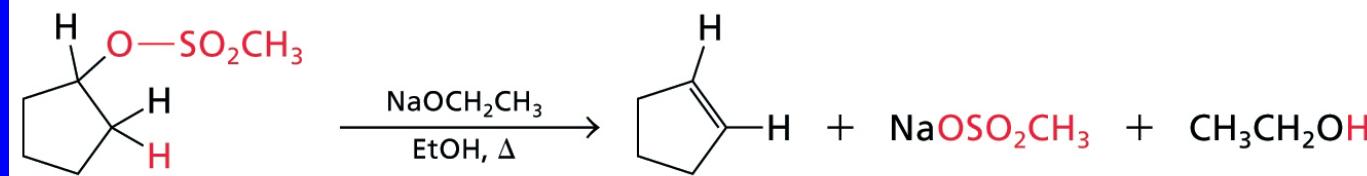
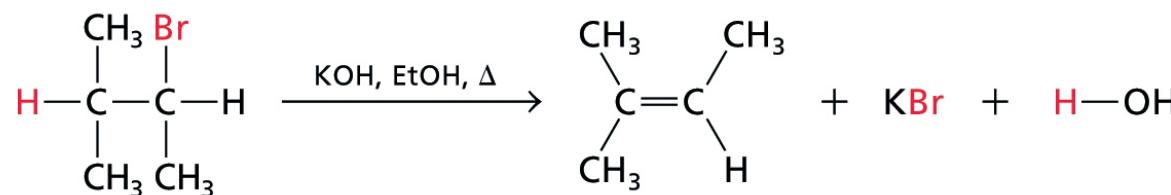
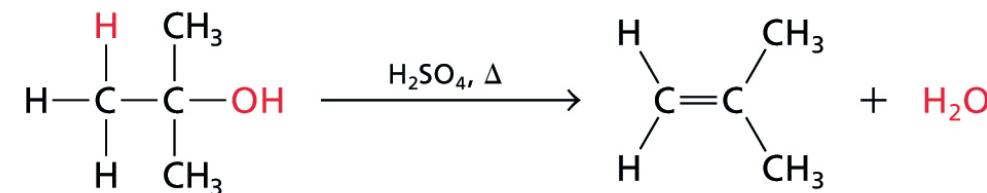


Are these reactions as simple as this? No.

With any substitution reaction we must always consider the possibility of competing elimination reactions. In the examples above, the nucleophiles can attack the electrophilic site to give the substitution product or they can act as bases giving the elimination products.

Whenever substitution reactions are possible, we must also consider whether or not elimination reactions might occur under the same reaction conditions.

In elimination reactions, a “neutral” molecule is ‘eliminated’ from the substrate to form a  $\pi$  bond. The  $\pi$  bond is formed between the two carbon atoms that bore the two parts of the eliminated molecule:



As there are two major classes of substitution reactions, there are two major classes of elimination reactions:

- E1 Reactions - in E1 elimination reactions only one molecule (the substrate) is involved in the rate determining step.
- E2 Reactions - in E2 elimination reactions two molecules (the substrate and base/nucleophile) are involved in the rate determining step.

As with substitution reactions, the mechanistic pathway followed in an elimination reaction is dependent on:

- The nature of the leaving group (for E1 and E2).
- Stability of the carbocation (for E1).
- The strength of the base (for E1 and E2). This is analogous to the strength of the nucleophile for substitution reactions.

## Elimination Reactions – The E1 Mechanism

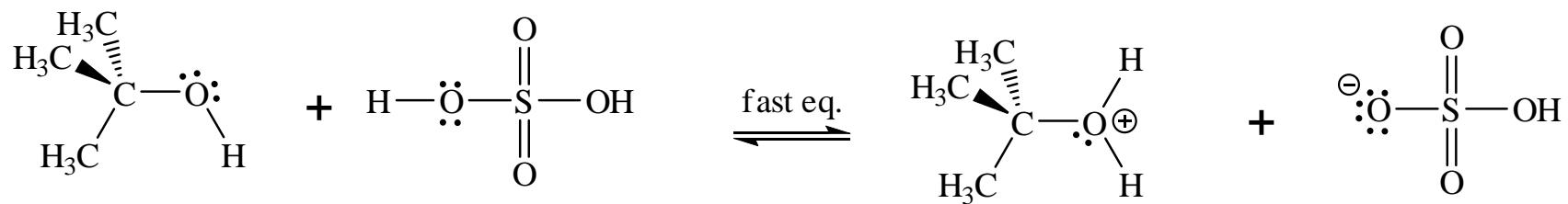
The substrates that favour E1 reactions are the same that favour S<sub>N</sub>1 reactions:

- A substrate bearing a good leaving group attached to a tetrahedral carbon atom.
- A substrate that can form a relatively stable carbocation.

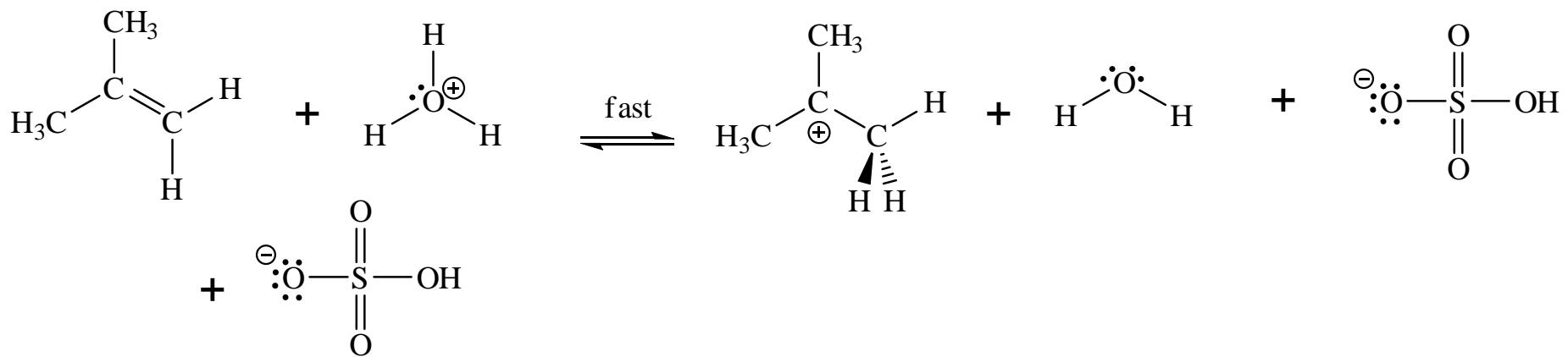
The difference between E1 and S<sub>N</sub>1 reactions is in the type species which reacts with the substrate. E1 reactions are favoured with:

- Bases that are poor nucleophiles (good nucleophiles will favour substitution reactions).
- Remember: Substitution and Elimination reactions are always competing (whenever possible).

## Elimination Reactions – The E1 Mechanism



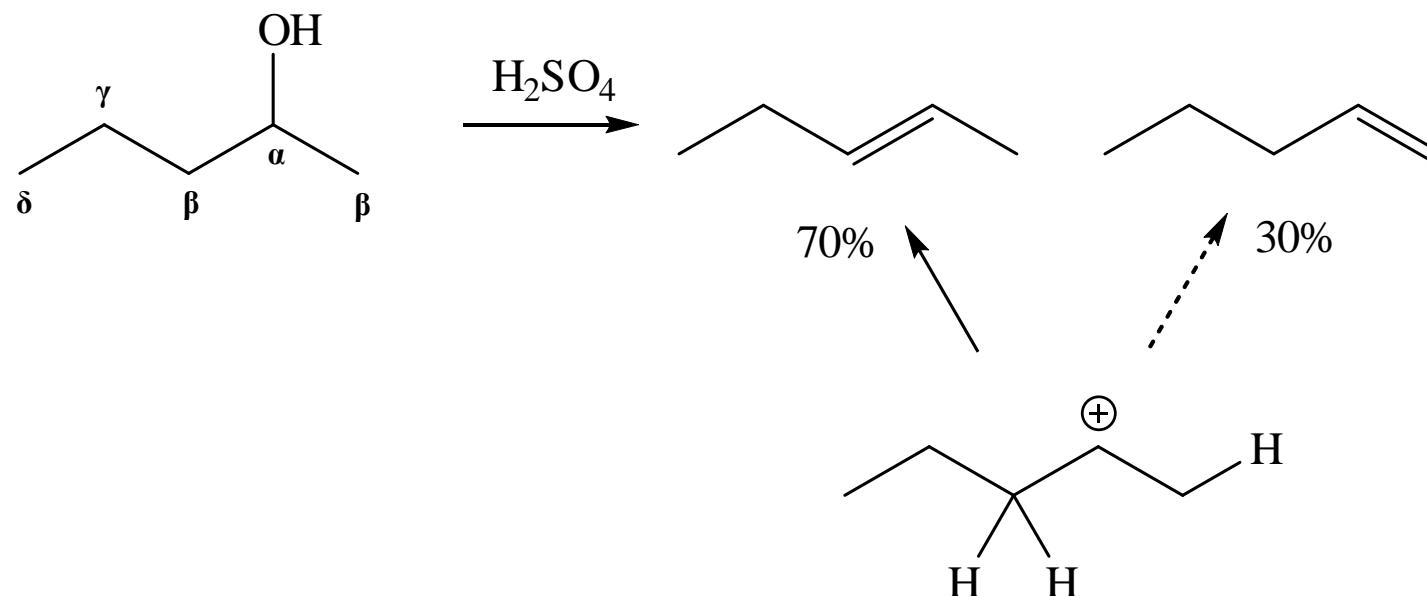
↓ slow



Why no substitution?

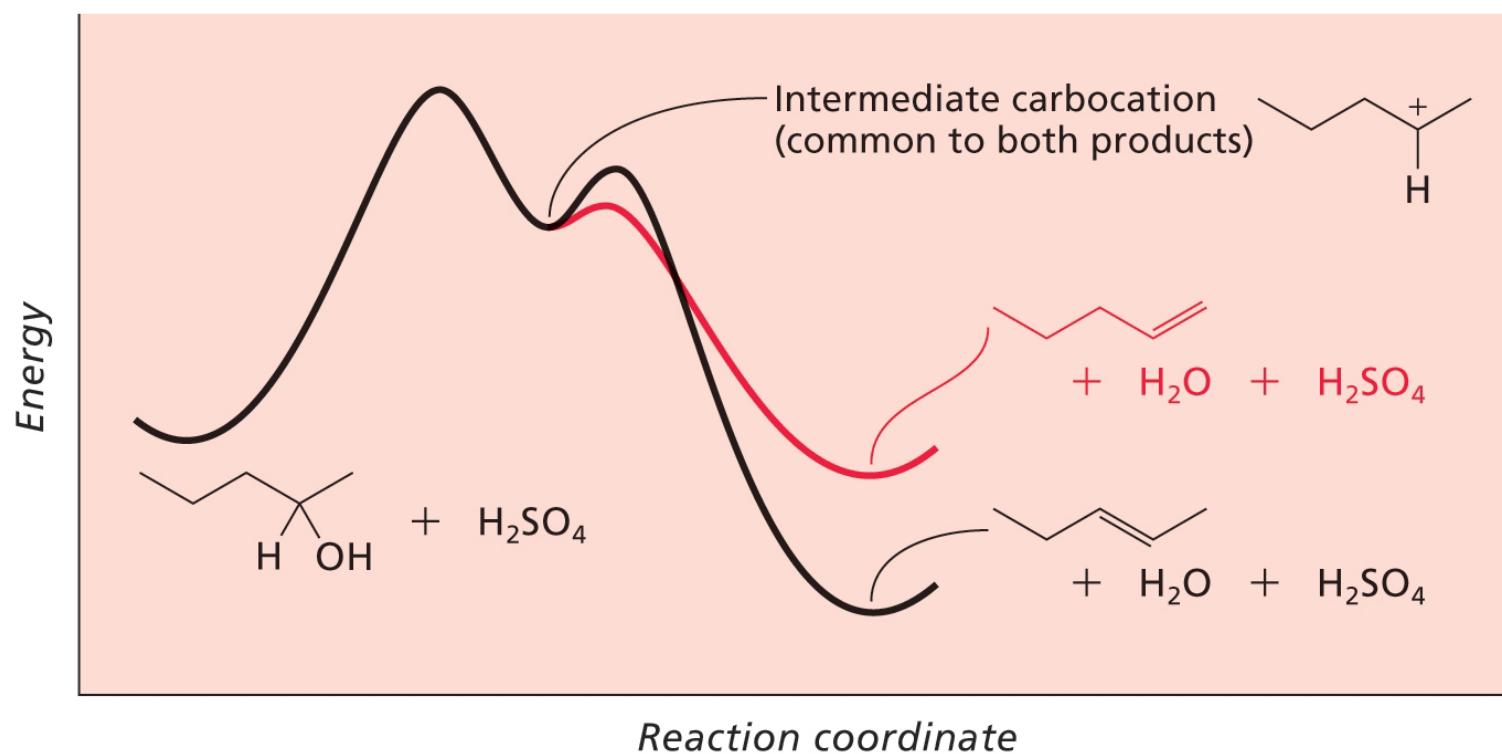
## E1 Reactions – Stereochemistry and Regiochemistry

A different elimination product is possible for every unique type of H beta ( $\beta$ ) to the carbocation carbon.



## Elimination Reactions - Kinetic vs. Thermodynamic Products

In the previous reaction, 1-pentene is the kinetic product (meaning it is easier to form) and 2-pentene is the thermodynamic product (meaning it is more stable).

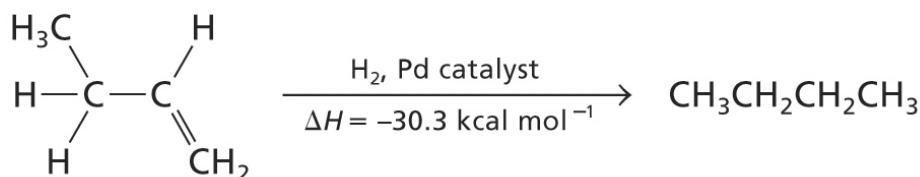


Elimination reactions that occur under thermodynamic control are said to form the Saytzeff products.

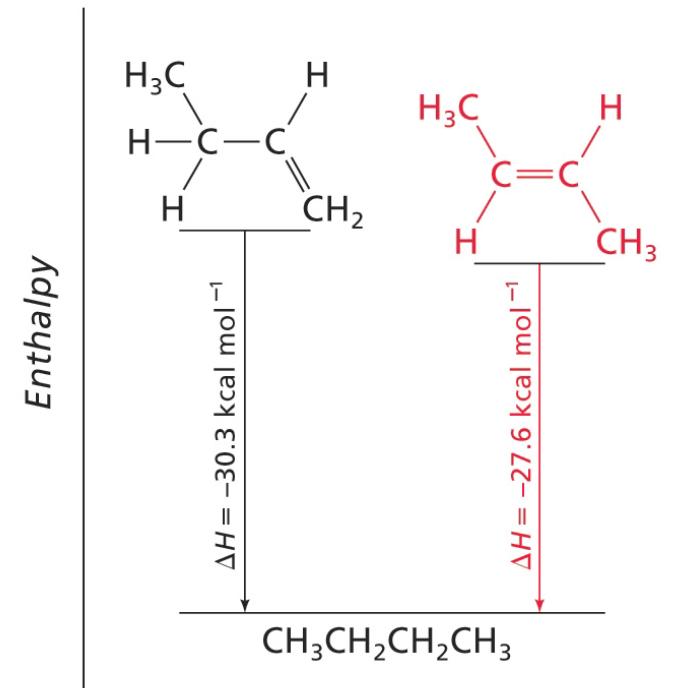
# Elimination Reactions - Kinetic vs. Thermodynamic Products

Remember: the stability of alkenes is determined by their heats of hydrogenation. Generally, the more substituted the alkene, the more stable it is.

a.

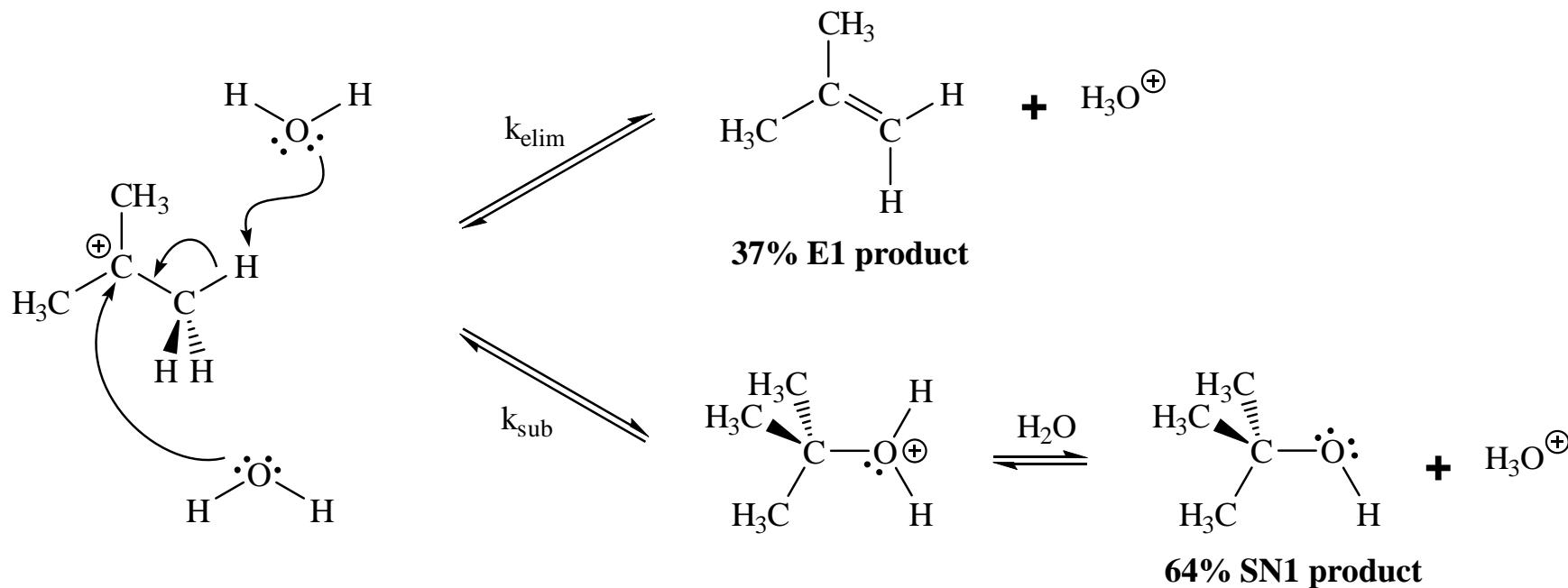
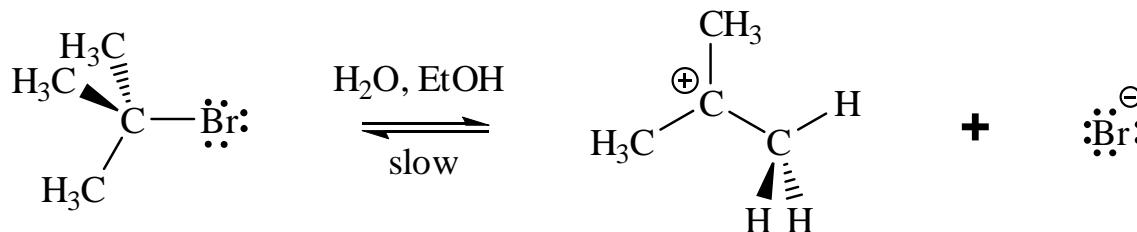


b.



## E1 Reactions – Alkyl Halides

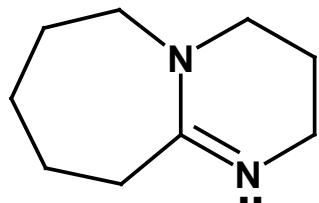
Alkyl halides can also undergo E1 reactions. Because the bases used for these reactions ( $\text{H}_2\text{O}$ ,  $\text{EtOH}$ ) are also nucleophilic, the  $\text{S}_{\text{N}}1$  reaction will also compete.



## Elimination Reactions – E2 Reaction

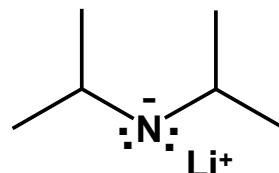
The previous example demonstrates a common problem in synthetic chemistry – the problem of competing reactions which lead to numerous products. In the previous example, our base ( $\text{H}_2\text{O}$ ) was also nucleophilic. What if we used a base that was a poor nucleophile?

Below are some examples of strong bases which are poor nucleophiles:



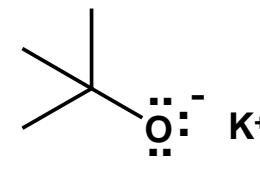
DBU

(1,8-diazabicyclo[5.4.0]undec-7-ene)



LDA

(lithium diisopropylamide)



KOtBu

(potassium *tert*-butoxide)

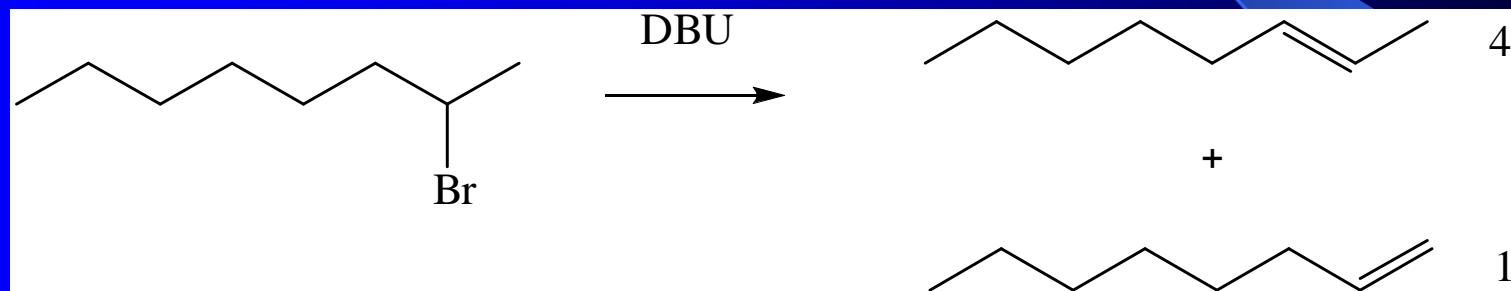
Why are these molecules poor nucleophiles?

## Elimination Reactions – E2 Reaction

E2 reactions are favoured for:

- Substrates bearing a good leaving group attached to a tetrahedral carbon atom.
- Strong non-nucleophilic bases .

The Saytzeff product is generally the major product:

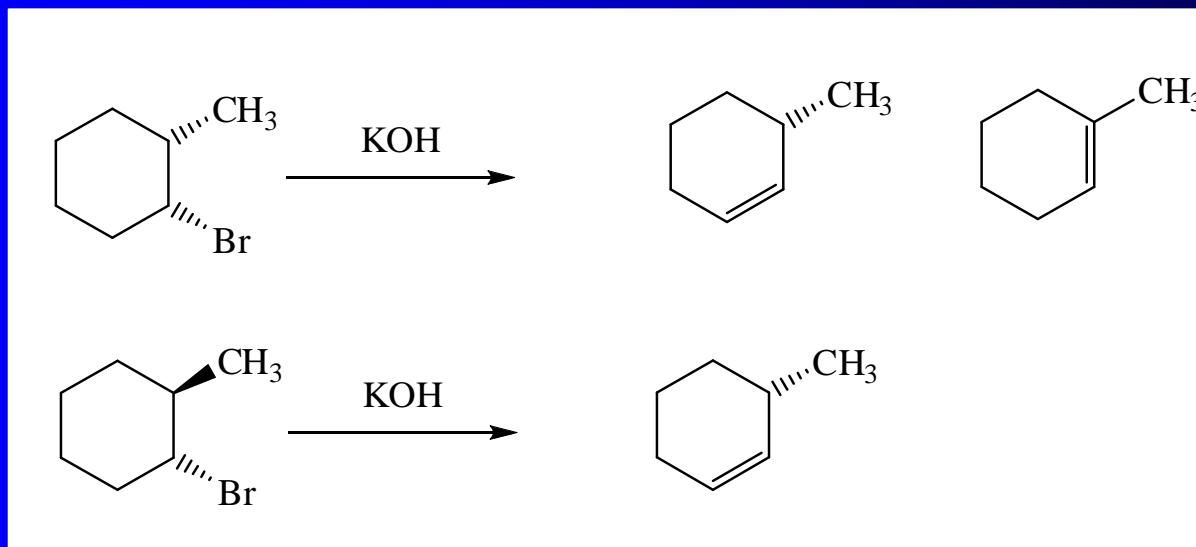


Propose a mechanism to account for the two products formed:

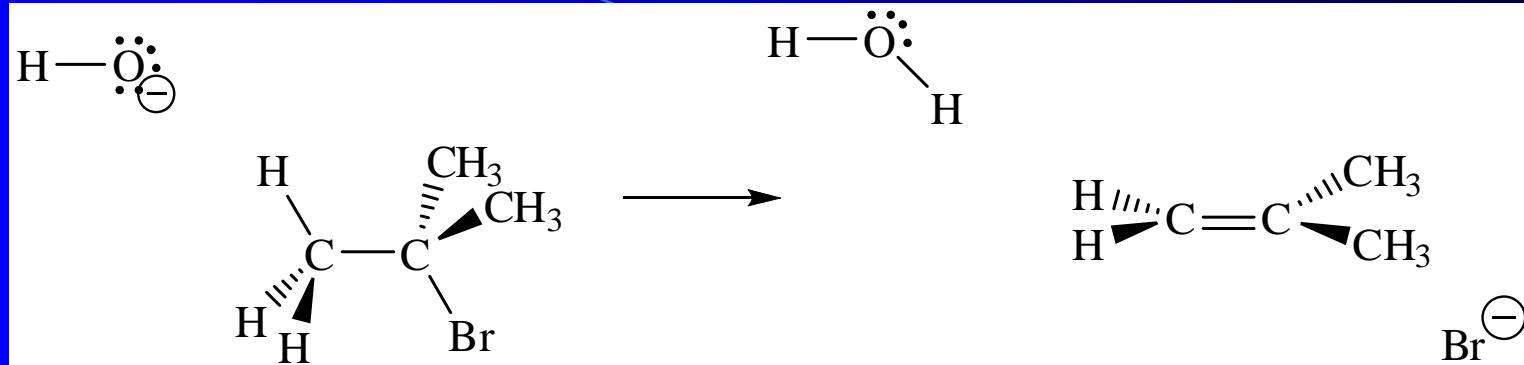
## E2 Reactions – Stereochemistry and Regiochemistry

For  $S_N2$  reactions, you saw that the nucleophile had to attack from the backside of the electrophilic site. This restriction is still valid for E2 reactions. In E2, since we are concerned with bases and not nucleophiles, this restriction reads 'the proton removed must be anti-periplanar to the leaving group'.

Consider the following reactions:

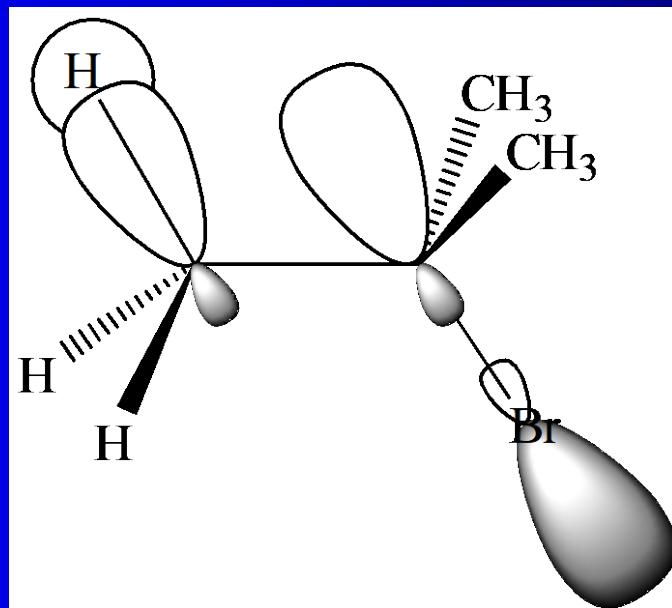


## E2 Reactions - Stereochemistry and Regiochemistry



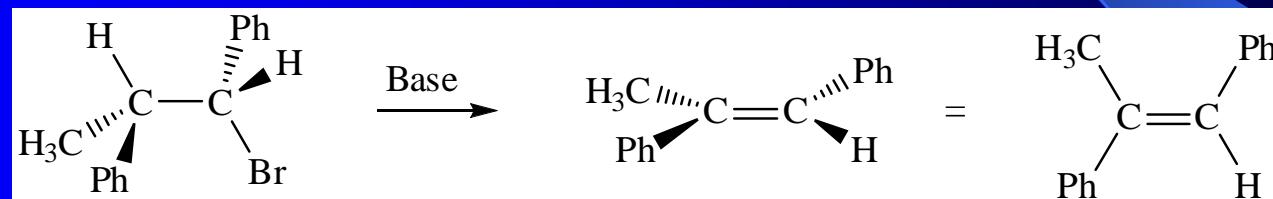
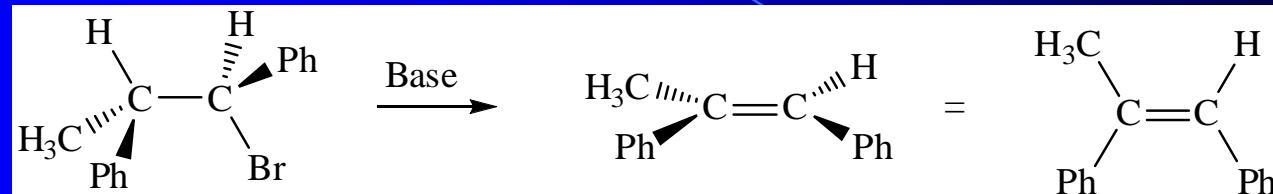
The  $\beta$ -proton pulled off by the base must be anti-periplanar to the leaving group. This reaction is referred to as a "beta-elimination".

Why?



## E2 Reactions – Stereochemistry and Regiochemistry

This restriction also applies non-cyclic systems:

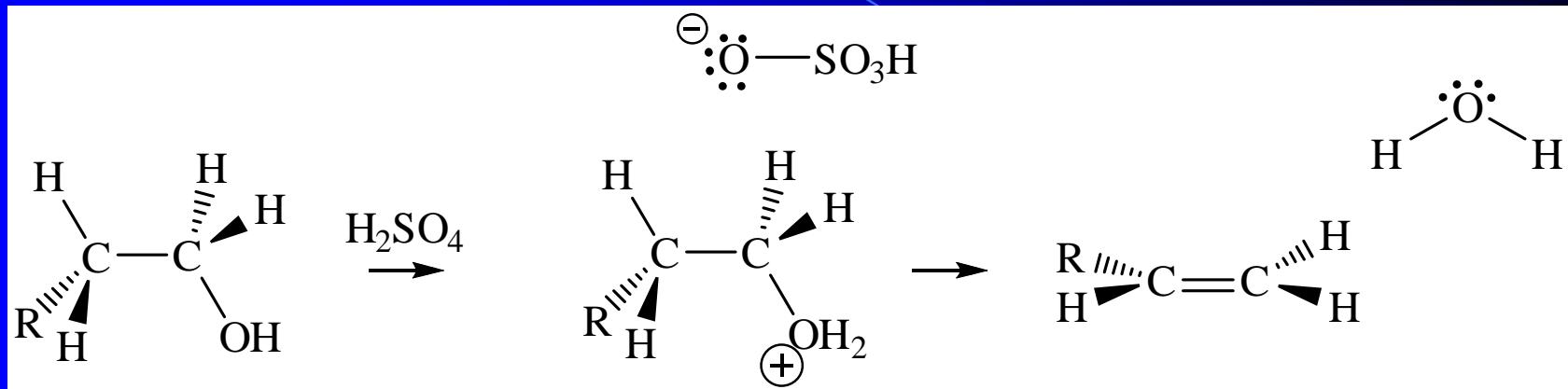


Notice here that a pair of diastereomers react to produce different products which are stereoisomers. This type of reaction is known as a stereospecific reaction.

These stereospecific elimination reactions only occur for E2 and not for E1. Why?

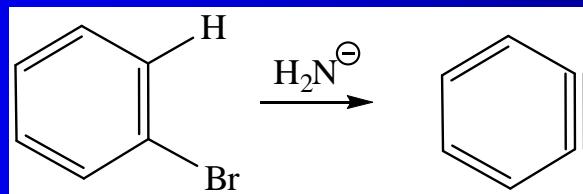
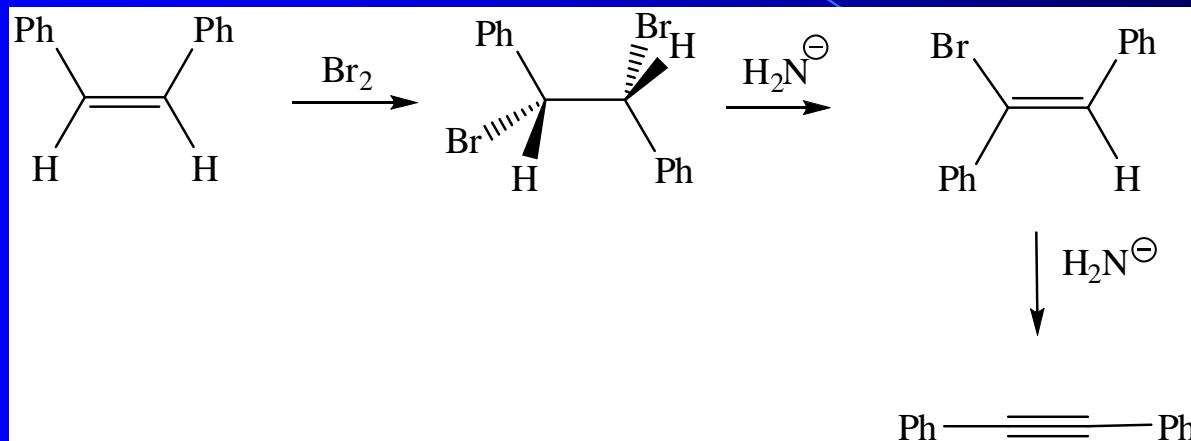
## E2 Reactions - Elimination of Primary Alcohols

It is possible to convert 1° alcohols to alkenes:



## E2 Reactions – Preparation of Alkynes

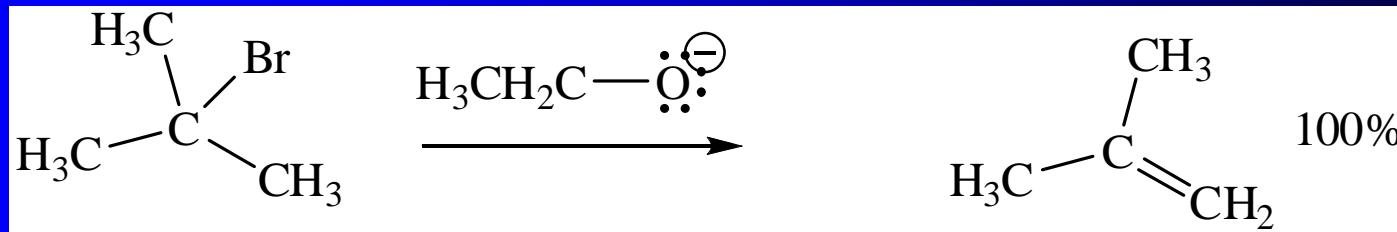
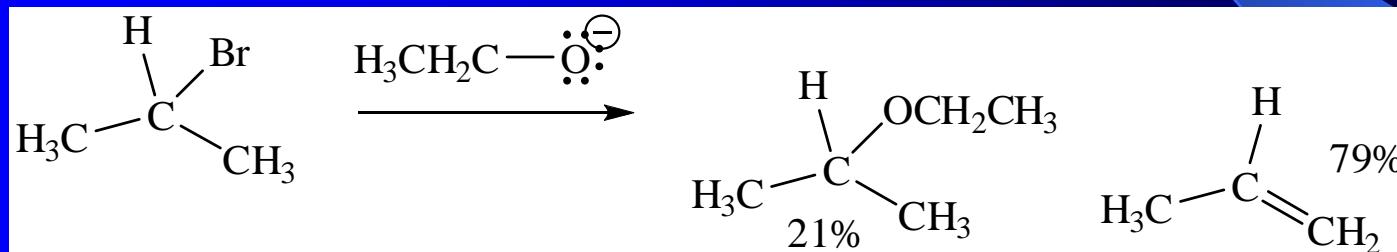
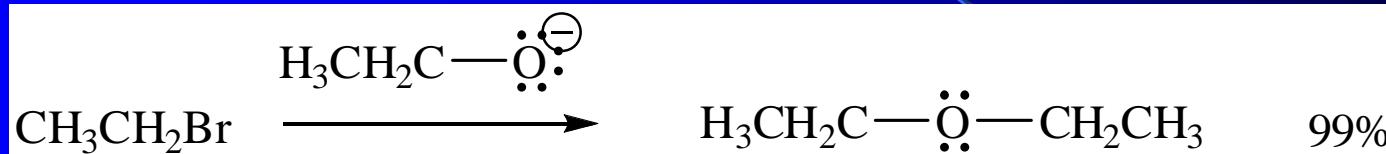
Elimination reactions can be used to prepare alkynes:



In this reaction, benzyne is formed from the elimination reaction of a substituted benzene. As expected from its structure, benzyne is extremely reactive.

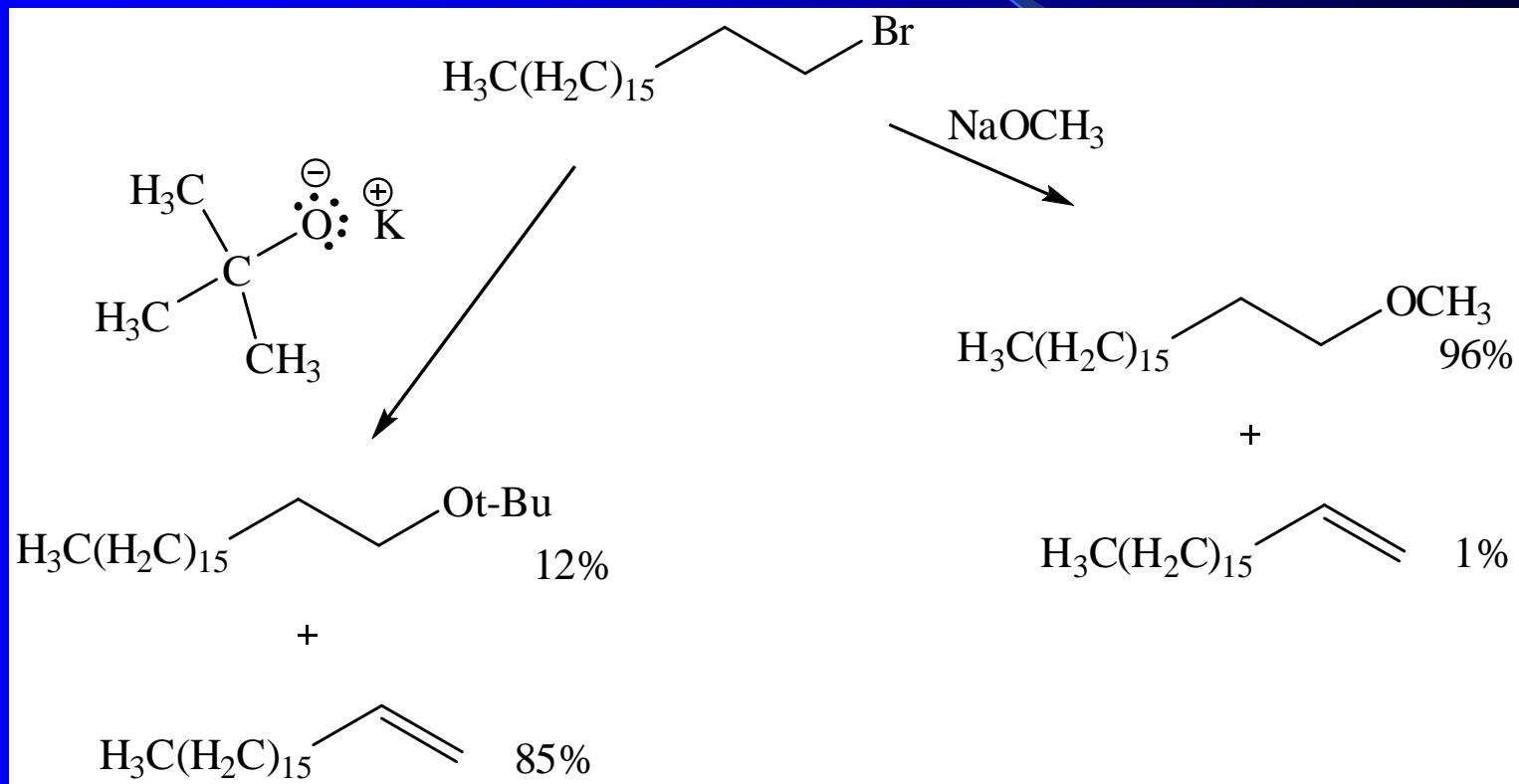
## E2 Reactions – E2 vs. S<sub>N</sub>2

Because many good nucleophiles are also good bases, S<sub>N</sub>2 often competes with E2 for those substrates that are good for S<sub>N</sub>2



## E2 Reactions – E2 vs. S<sub>N</sub>2

To promote E2 over S<sub>N</sub>2 we need to use strong bases that are non-nucleophilic.

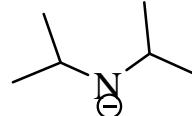


## E1 vs. E2 vs. S<sub>N</sub>1 vs. S<sub>N</sub>2

- As a general rule, elimination reactions can always compete with substitution reactions. We can, however, alter the reaction conditions to favour one process over another.
- To favour E1 over S<sub>N</sub>1 for alcohols, use an acid with a non-nucleophilic conjugate base (H<sub>2</sub>SO<sub>4</sub>, H<sub>3</sub>PO<sub>4</sub>). To favour S<sub>N</sub>1 over E1, use a good nucleophile.
- To favour E2 over S<sub>N</sub>2, use a strong, bulky non-nucleophilic base. To favour S<sub>N</sub>2 over E2, use good nucleophiles that are relatively weak bases.
- It is important to keep in mind that although you might choose reaction conditions that will favour one reaction over another, more often than not you will still see traces of the competing reaction.
- Before you even consider the possibility of an elimination reaction, make sure there are  $\beta$ -hydrogen atoms available to eliminate!

# $S_N1$ , $S_N2$ , $E1$ and $E2$

	$S_N1$	$S_N2$	$E1$	$E2$
Mechanism	2 or more steps involving carbocation intermediate	1 step bimolecular process	2 or more steps involving carbocation intermediate	1 step bimolecular process
Kinetics	First order in substrate	Second order, first in substrate and nucleophile	First order in substrate	Second order, first in substrate and base
Substrate Dependence	Those substrates that form stable carbocations. 3, allylic, benzylic	Those substrates that are uncluttered at the reaction site: 1, 2. Good nucleophiles.	Those substrates that form stable carbocations. 3, allylic, benzylic	Requires strong base and any substrate with beta proton.
Stereochem	Racemization.	Stereospecific inversion.	Usually mixtures.	Stereospecific involving antiperiplanar relationship of beta-proton and leaving group.
Importance of Base/nucleophile	Not involved in RDS, but less basic form of nucleophile will limit E2.	Reactivity of nucleophile is important since it is involved in RDS.	If a good, non-basic nucleophile is present (halides, bisulfate) then $S_N1$ .	Strong, non-nucleophilic bases (KOtBu, LDA) best to limit $S_N2$ .
Importance of Leaving group	Involved in RDS so is important.	Involved in RDS so is important.	Involved in RDS so is important.	Involved in RDS so is important.
Competes with..	$E1$ and $E2$	$E2$ when basic nucleophiles employed.	$S_N1$	$S_N2$
Solvent	Polar protic best	Polar aprotic best	Polar protic best	Varies.

Weak base/ poor Nu	Weak base/ good Nu	Moderate/strong base/good Nu	Strong base/ poor Nu
H <sub>2</sub> O, ROH	Br-, I-, H <sub>2</sub> S	RS-, NC-, RNH <sub>2</sub> , NH <sub>3</sub> N <sub>3</sub> - HO-, RO-	t-Bu—O-  LDA

Methyl, CH <sub>3</sub> X	NR	S <sub>N</sub> 2	S <sub>N</sub> 2	S <sub>N</sub> 2
1°, RCH <sub>2</sub> X	NR	S <sub>N</sub> 2	S <sub>N</sub> 2	E2
2°, RCHXR	S <sub>N</sub> 1 E1	S <sub>N</sub> 2	S <sub>N</sub> 2 E2	E2
3°, R <sub>3</sub> CX	S <sub>N</sub> 1 E1	S <sub>N</sub> 1 E1	E2	E2
1° benzylic	S <sub>N</sub> 1	S <sub>N</sub> 2	S <sub>N</sub> 2	S <sub>N</sub> 2
2° benzylic	S <sub>N</sub> 1 E1	S <sub>N</sub> 2	S <sub>N</sub> 2 E2	E2
3° benzylic	S <sub>N</sub> 1 E1	S <sub>N</sub> 1 E1	E2	E2
1° allylic	S <sub>N</sub> 1	S <sub>N</sub> 2	S <sub>N</sub> 2	S <sub>N</sub> 2
2° allylic	S <sub>N</sub> 1 E1	S <sub>N</sub> 2	S <sub>N</sub> 2 E2	E2
3° allylic	S <sub>N</sub> 1 E1	S <sub>N</sub> 1 E1	E2	E2
Aryl, PhX	NR	NR	NR	E2
Alkenyl, H <sub>2</sub> C=CHX	NR	NR	NR	E2