

Organic Chemistry, *Fourth Edition*

Janice Gorzynski Smith
University of Hawai'i

Chapter 7 Alkyl Halides and Nucleophilic Substitution

Prepared by Layne A. Morsch
The University of Illinois - Springfield

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Alkyl Halides

Introduction

- Nomenclature

- Physical properties

General features of nucleophilic substitution

- The leaving group

- The nucleophile

Possible mechanisms for nucleophilic substitution

- The S_N2 mechanism

- The S_N1 mechanism

- Carbocation stability

- When is the mechanism S_N1 or S_N2?

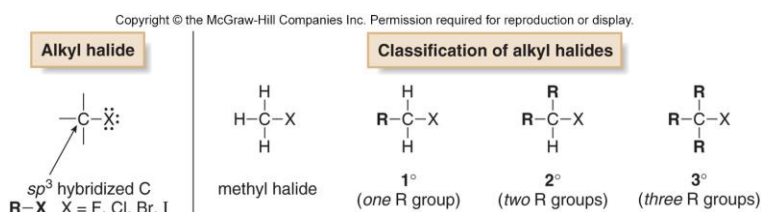
- Vinyl halides and aryl halides

- Organic synthesis

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Alkyl Halides

- **Alkyl halides** are organic molecules containing a halogen atom bonded to an sp^3 hybridized carbon atom.
- The halogen atom in halides is often denoted by the symbol "X".
- 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.

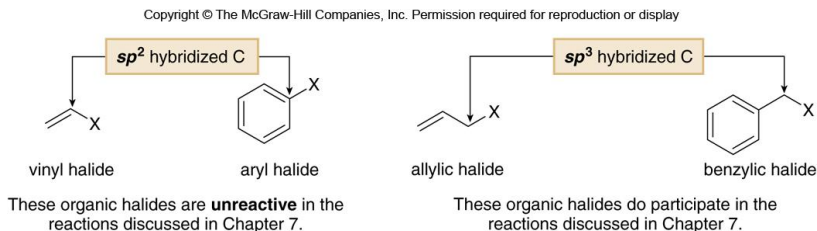


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Types of Alkyl Halides

- **Vinyl halides** have a halogen atom (X) bonded to a C-C double bond.
- **Aryl halides** have a halogen atom bonded to a benzene ring.

Figure 7.2

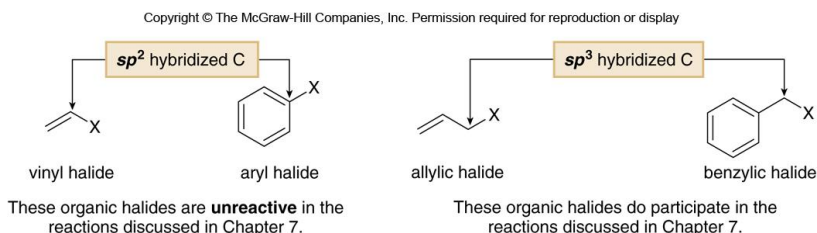


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Types of Alkyl Halides

- **Allylic halides** have X bonded to the carbon atom adjacent to a C-C double bond.
- **Benzylic halides** have X bonded to the carbon atom adjacent to a benzene ring.

Figure 7.2



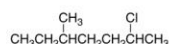
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Naming Alkyl Halides

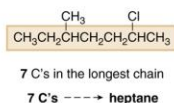
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HOW TO Name an Alkyl Halide Using the IUPAC System

Example Give the IUPAC name of the following alkyl halide:



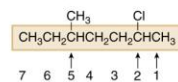
Step [1] Find the parent carbon chain containing the halogen.



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

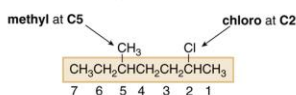
Step [2] Apply all other rules of nomenclature.

a. **Number** the chain.



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

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



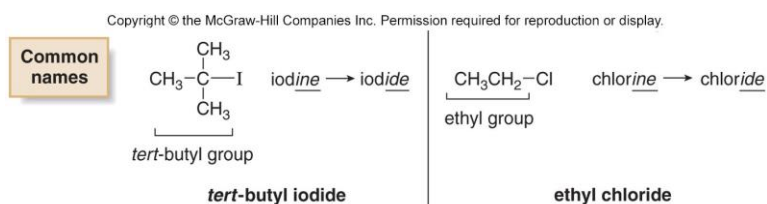
c. **Alphabetize**: c for chloro, then m for methyl.

ANSWER: 2-chloro-5-methylheptane

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Common Names of Alkyl Halides

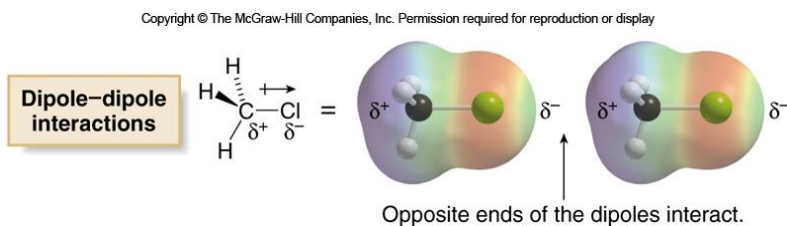
- **Common names** are often used for simple alkyl halides.
- To assign a common name:
 - Name **all the carbon atoms** of the molecule as a single alkyl group.
 - Name the **halogen bonded** to the alkyl group.
 - **Combine** the names of the alkyl group and halide, separating the words with a space.



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Polarity of Alkyl Halides

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



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Physical Properties of Alkyl Halides

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Table 7.1 Physical Properties of Alkyl Halides

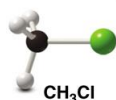
Property	Observation
Boiling point and melting point	Alkyl halides have higher bp's and mp's than alkanes having the same number of carbons. CH_3CH_3 bp = -89°C and $\text{CH}_3\text{CH}_2\text{Br}$ bp = 39°C
	Bp's and mp's increase as the size of R increases. $\text{CH}_3\text{CH}_2\text{Cl}$ mp = -136°C bp = 12°C and $\text{CH}_3\text{CH}_2\text{CH}_2\text{Cl}$ 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. $\text{CH}_3\text{CH}_2\text{Cl}$ mp = -136°C bp = 12°C and $\text{CH}_3\text{CH}_2\text{Br}$ mp = -119°C bp = 39°C more polarizable halogen higher mp and bp
	- RX is soluble in organic solvents. - RX is insoluble in water.

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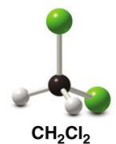
Simple Alkyl Halides

Figure 7.4

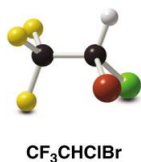
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- Chloromethane (CH_3Cl)** is produced by giant kelp and algae and also found in emissions from volcanoes such as Hawaii's Kilauea. Almost all of the atmospheric chloromethane results from these natural sources.



- 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.

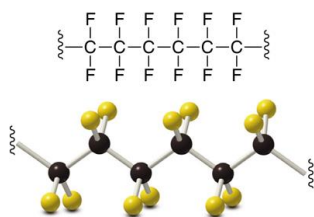


- Halothane (CF_3CHClBr)** is a safe general anesthetic that has now replaced other organic anesthetics such as CHCl_3 , which causes liver and kidney damage, and $\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_3$ (diethyl ether), which is very flammable.

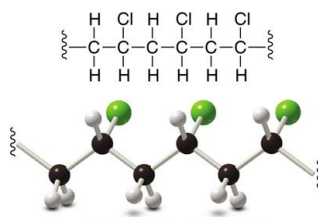
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Common Alkyl Halides

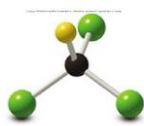
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Teflon
(nonstick coating)

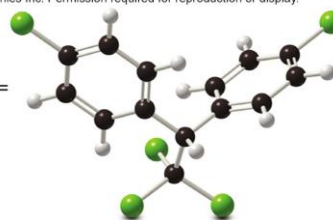
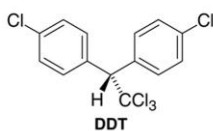


poly(vinyl chloride) (PVC)
(plastic used in films, pipes, and insulation)



CFCl₃
CFC 11
Freon 11

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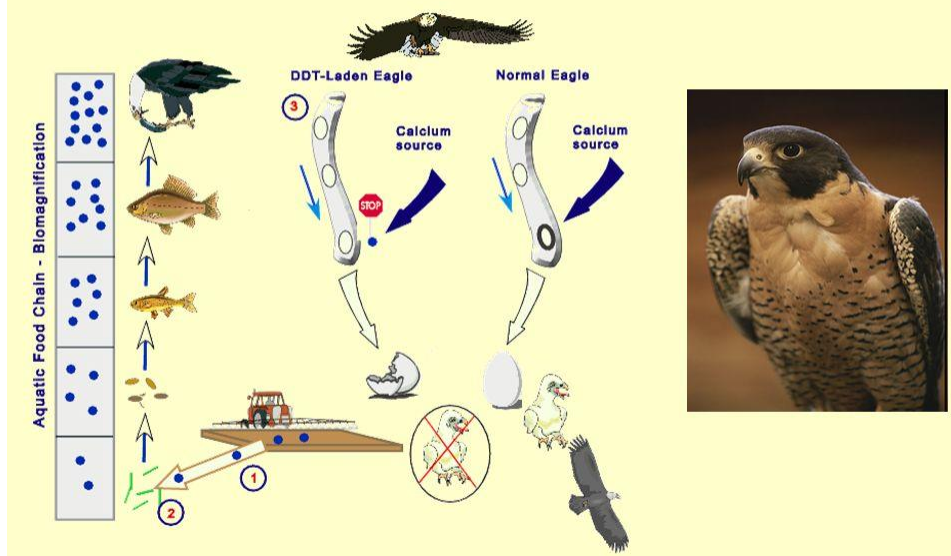


DDT kills insects that spread diseases such as malaria and typhus

DDT accumulates in fatty tissues

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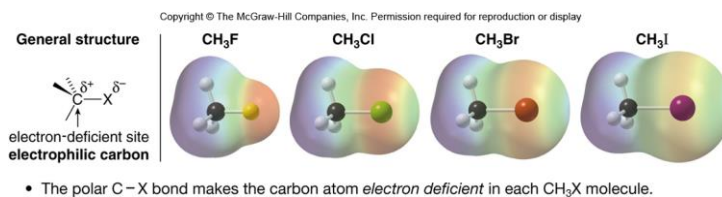
- The peregrine falcon almost became extinct in Canada because of DDT use.



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.
- This electron deficient carbon is a key site in the reactivity of alkyl halides.

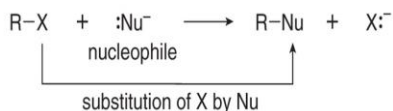
Figure 7.5



Reaction Types for Alkyl Halides

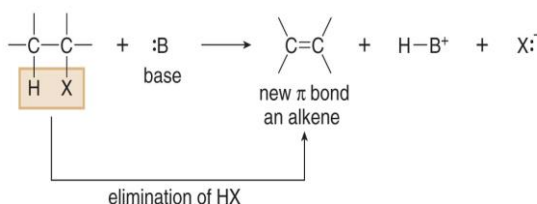
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- Alkyl halides undergo substitution reactions with nucleophiles.



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

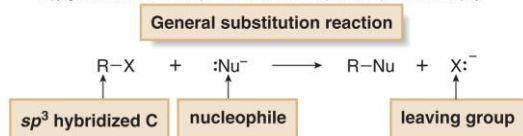


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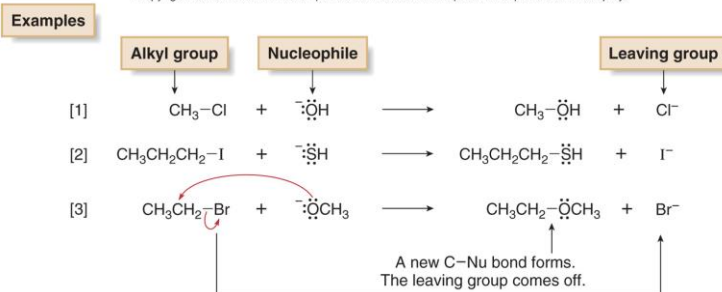
Substitution Reactions

- Three components are necessary in any substitution reaction.

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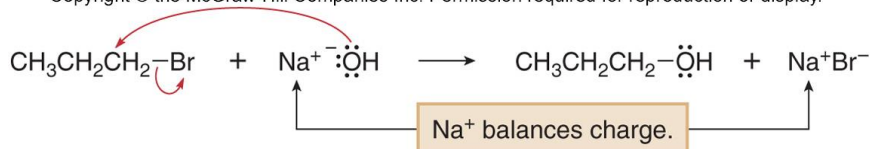
Nucleophiles in Substitution Reactions

- Nucleophiles are **Lewis bases** that can be **negatively charged or neutral**.

1. Negatively charged nucleophiles like HO^- and HS^- are used as salts with Li^+ , Na^+ , or K^+ **counterions to balance the charge**.

- Since the identity of the counterion is usually inconsequential, it is often omitted from the chemical equation.

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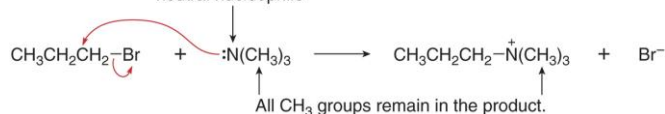


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Neutral Nucleophiles

2. Neutral nucleophile: the substitution product bears a **positive charge**.

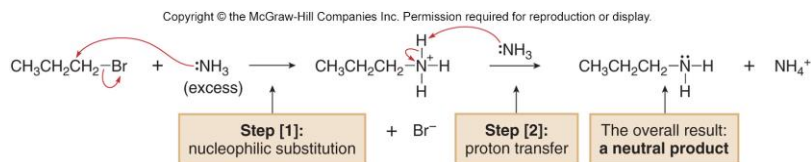
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neutral nucleophile



- The substitution product's positive charge is usually caused by a **proton bonded to O or N**.
- That proton is readily lost from this in a Brønsted-Lowry acid-base reaction, forming a neutral product.

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Drawing Products of Nucleophilic Substitution Reactions



- The overall effect of any nucleophilic substitution is the replacement of the **leaving group** by the **nucleophile**.
- To draw any nucleophilic substitution product:
 - Find the **sp³ hybridized** carbon with the leaving group.
 - Identify **the nucleophile**, the species with a lone pair or π 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.

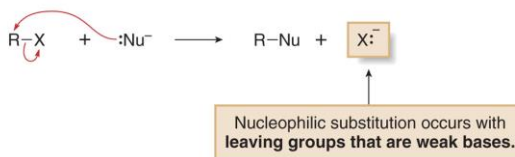
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The Leaving Group

- 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 X:⁻.
- The **more stable** the leaving group X:⁻, the better able it is to accept an electron pair.

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



- For example, H₂O is a **better leaving** group than HO⁻ because H₂O is a **weaker base**.

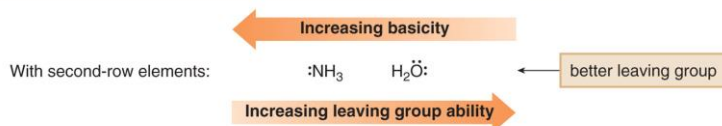
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Trends in Leaving Group Ability

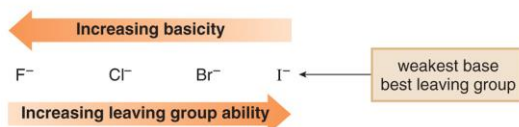
- The weaker the base, the better the leaving group.

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- 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*.



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Good Leaving Groups

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Table 7.2 Good Leaving Groups for Nucleophilic Substitution

Starting material	Leaving group	Conjugate acid	$\text{p}K_{\text{a}}$
$\text{R}-\text{Cl}$	Cl^-	HCl	-7
$\text{R}-\text{Br}$	Br^-	HBr	-9
$\text{R}-\text{I}$	I^-	HI	-10
$\text{R}-\text{OH}_2^+$	H_2O	H_3O^+	-1.7

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Poor Leaving Groups

- Conjugate bases of weaker acids are poorer leaving groups.

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Table 7.3 Poor Leaving Groups for 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

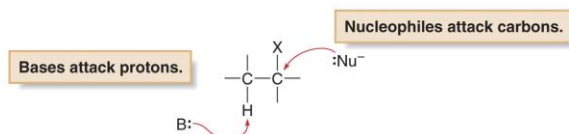
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Nucleophiles and Bases

- Nucleophiles and bases are **structurally similar**: both have a lone pair or a π bond.
- They differ in what they attack.
 - Bases attack **protons**. $Base + H$
 - Nucleophiles attack other **electron-deficient** atoms (usually carbons). $Nu + C$

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



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Nucleophiles vs. Bases

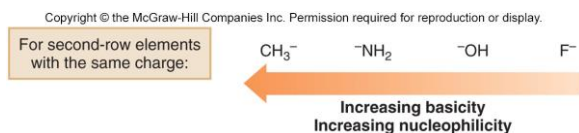
- Although nucleophilicity and basicity are interrelated, they are fundamentally different.
 - **Basicity** is a measure of how readily an atom donates its electron pair to a proton.
 - It is characterized by an equilibrium constant, K_a in an acid-base reaction, making it a thermodynamic property.
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

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Nucleophilicity Parallels Basicity

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 HO^- and CH_3COO^- , is determined by comparing the $\text{p}K_a$ values of their conjugate acids ($\text{H}_2\text{O} = 15.7$, and $\text{CH}_3\text{COOH} = 4.8$).
 - HO^- is a stronger base and stronger nucleophile than CH_3COO^- .
2. A negatively charged nucleophile is always a **stronger nucleophile** than its conjugate acid.
 - HO^- is a stronger base and stronger nucleophile than H_2O .
3. Right-to-left across a row of the periodic table, **nucleophilicity increases as basicity increases**:

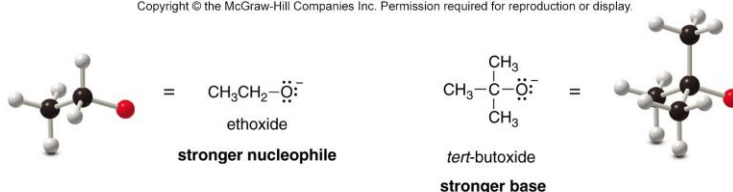


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Steric Effects on Nucleophile Strength

- Nucleophilicity does not parallel basicity when steric hindrance becomes important.
 - Steric hindrance** is a decrease in 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 are called **nonnucleophilic bases**.

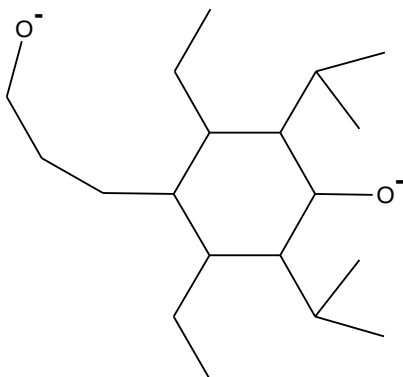
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Three CH_3 groups sterically hinder the O atom, making it a **weaker nucleophile**.

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Steric Effects on Nucleophile Strength



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Solvent Effects on Nucleophilicity

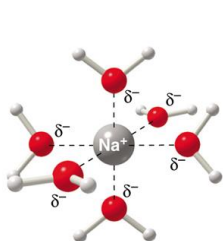
- Most organic reactions are performed in a **liquid solvent** capable of dissolving the reactants, at least to some extent.
- Since substitution reactions involve **polar starting materials**, polar solvents are used to dissolve them.
- There are two types of polar solvents: **protic and aprotic**.
- Nucleophilicity can be affected by the **nature of the solvent**.

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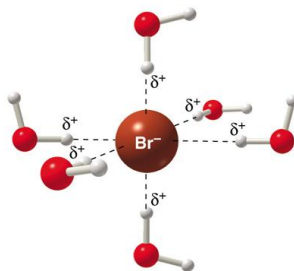
Solvation by Polar Protic Solvents

- **Polar protic** solvents solvate both cations and anions well.
- If the salt NaBr is used as a source of the nucleophile Br^- in H_2O :
 - The Na^+ cations are solvated by **ion-dipole** interactions with H_2O molecules.
 - The Br^- anions are solvated by strong **hydrogen bonding** interactions.

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Na^+ is solvated by ion-dipole interactions with H_2O .



Br^- is solvated by hydrogen bonding with H_2O .

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Nucleophilicity in Polar Protic Solvents

- **Smaller, more electronegative** anions are solvated more strongly, effectively shielding them from reaction.
- 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.

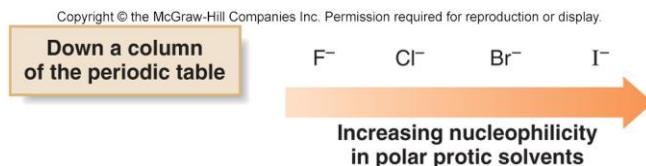
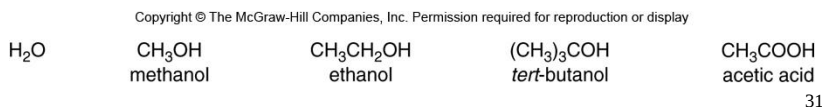


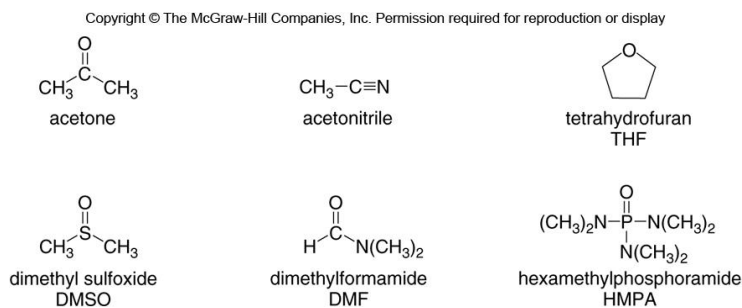
Figure 7.6



Polar Aprotic Solvents

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

Figure 7.7

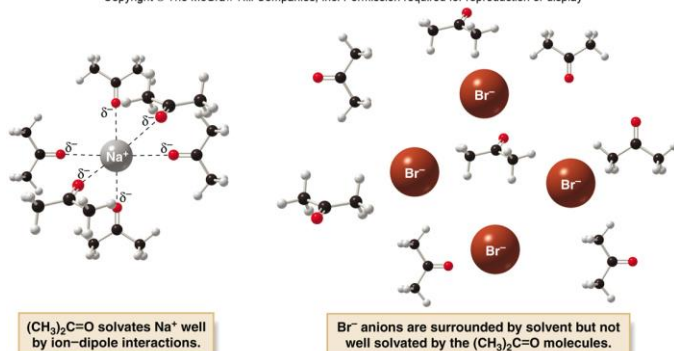


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Nucleophilicity in Polar Aprotic Solvents

- Polar aprotic solvents solvate cations by **ion-dipole** interactions.
- Anions are not well solvated because the **solvent cannot hydrogen bond** to them.
- These anions are said to be “**naked**” and therefore, more reactive.

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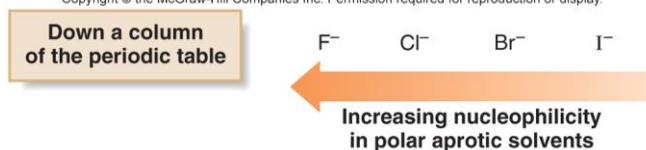


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Nucleophilicity vs. Basicity in Polar Aprotic Solvents

- 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.

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Common Nucleophiles

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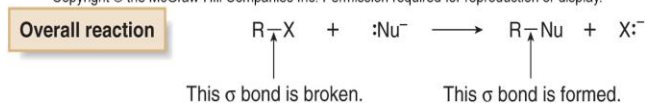
Table 7.4 Common Nucleophiles in Organic Chemistry

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

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Bond Breaking and Making in Nucleophilic Substitution Mechanisms

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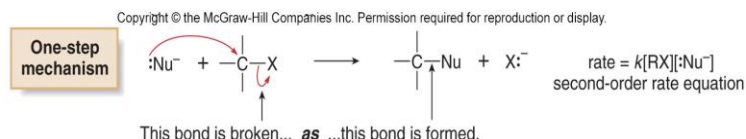


- But what is the order of bond making and bond breaking?
- In theory, there are **three possibilities**.
 - Bond making and breaking occur at the same time.
 - Bond breaking occurs first.
 - Bond making occurs first.

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Nucleophilic Substitution Mechanisms— Concerted

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

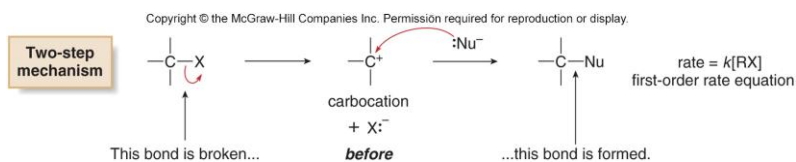


- The mechanism is comprised of **one step**.
- In such a bimolecular reaction, the **rate** depends upon the concentration of **both reactants**.
- The rate equation is **second order**.

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Nucleophilic Substitution Mechanisms— Bond Breaking First

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

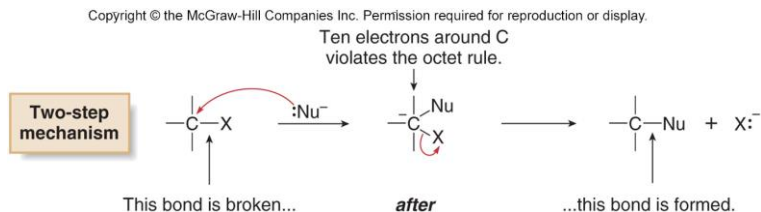


- The mechanism has **two steps** and a carbocation is formed as an intermediate.
- The first step is **rate-determining**.
- The rate depends on the **concentration of RX only**.
- The rate equation is **first order**.

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Nucleophilic Substitution Mechanisms– Bond Making First

3. Bond making occurs before bond breaking.

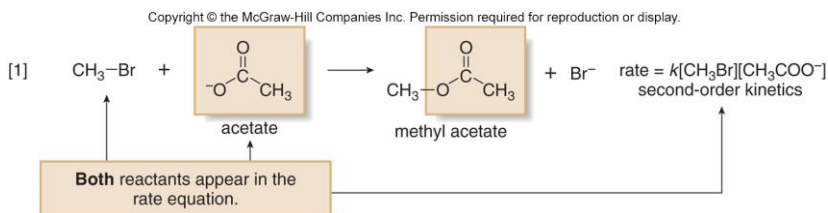


- This mechanism has an **inherent problem**.
- The intermediate generated in the first step has **10 electrons** around carbon, violating the octet rule.
- Because two other mechanistic possibilities do not violate a fundamental rule, this last possibility **can be disregarded**.

39

Kinetics and Mechanisms

Consider reaction 1 below:

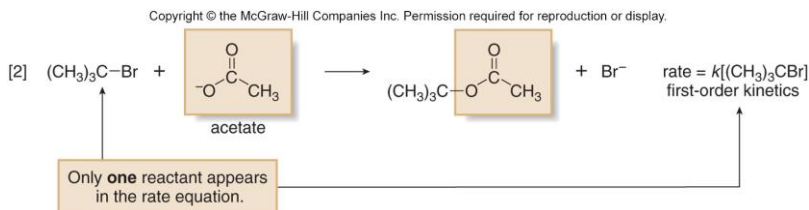


- **Kinetic data** show that the rate of reaction 1 depends on the concentration of both reactants, which suggests a **bimolecular** reaction with a one-step mechanism.
- This is an example of an **S_N2** (bimolecular nucleophilic substitution) mechanism.

40

Kinetics and Mechanisms

Consider reaction 2 below:



- **Kinetic data** show that the rate of reaction 2 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** (unimolecular nucleophilic substitution) mechanism.

41

S_N2 Reaction Mechanism

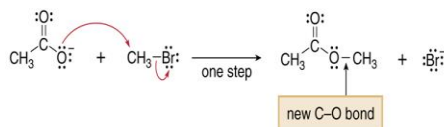
- The mechanism of an S_N2 reaction would be drawn as follows.
- Curved arrow notation is used to show the flow of electrons.

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Mechanism 7.1 The S_N2 Mechanism

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



42

S_N2 Kinetics

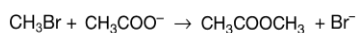
- S_N2 reactions exhibit **2nd order kinetics**.
- The reaction is **bimolecular** – both the alkyl halide and the nucleophile appear in the rate equation.

$$\text{rate} = k[\text{CH}_3\text{Br}][\text{CH}_3\text{COO}^-]$$

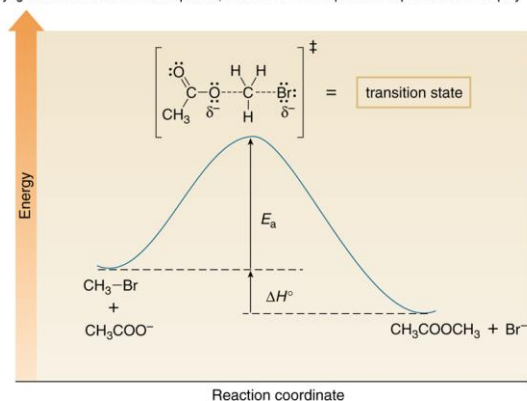
43

Energy Diagrams for S_N2 Reactions

Figure 7.8



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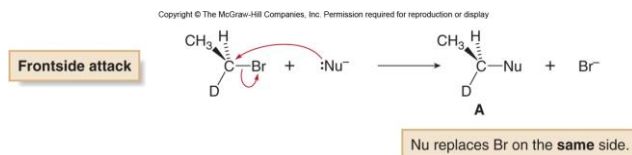


- In the transition state, the C–Br bond is partially broken, the C–O bond is partially formed, and both the attacking nucleophile and the departing leaving group bear a partial negative charge.

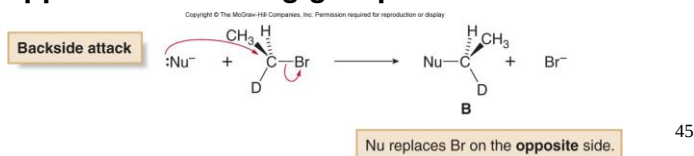
44

Stereochemistry of the S_N2 Reaction

- There are two possibilities for which direction the nucleophile will approach the substrate.
 - Frontside** Attack: The nucleophile approaches from the same side as the leaving group.



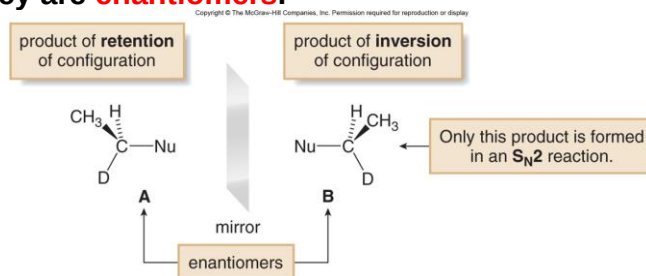
- Backside** Attack: The nucleophile approaches from the side opposite the leaving group.



45

Stereochemistry of the S_N2 Reaction

- The products of **frontside** and **backside** attack are different compounds.
 - They are **enantiomers**.

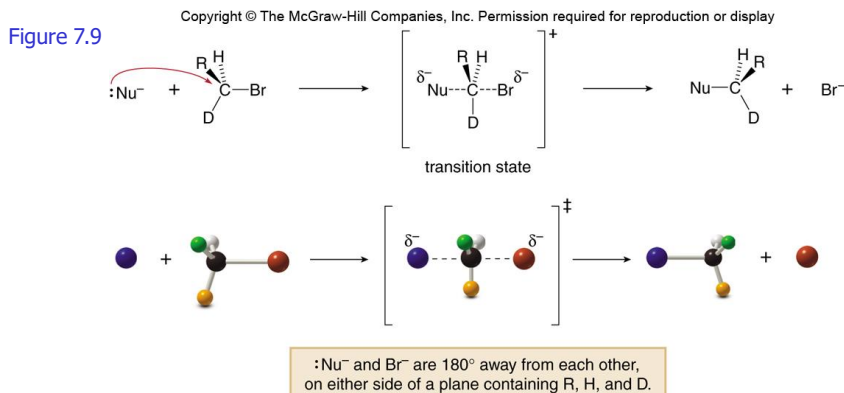


- All **S_N2 reactions** proceed with **backside attack** of the nucleophile.
- They result in **inversion of configuration** at the stereocenter.

46

Transition States of S_N2 Reactions

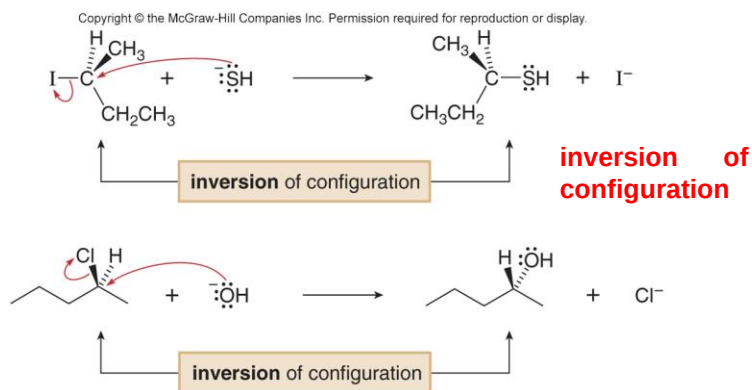
- The transition state always has **partial bonds** to the nucleophile and the leaving group.
- There can also be **partial charges** on the nucleophile and/or leaving group.



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Inversion in S_N2 Reactions

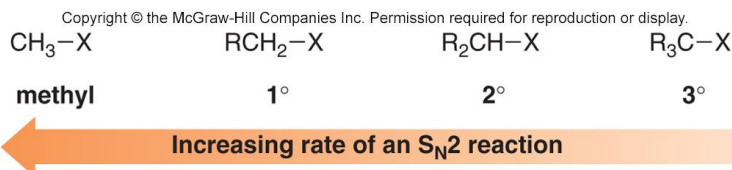
- Examples**



48

Substrate Reactivity in S_N2 Reactions

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



- 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** due to steric effects.

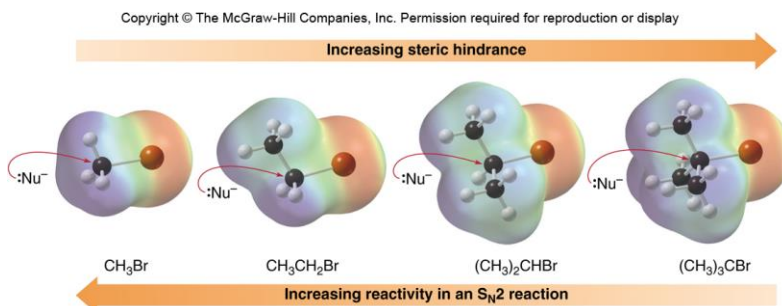
Bulky R groups near the reaction site make nucleophilic attack from the backside more difficult, slowing the reaction rate.

49

Steric Effects in S_N2 Reactions

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

Figure 7.11

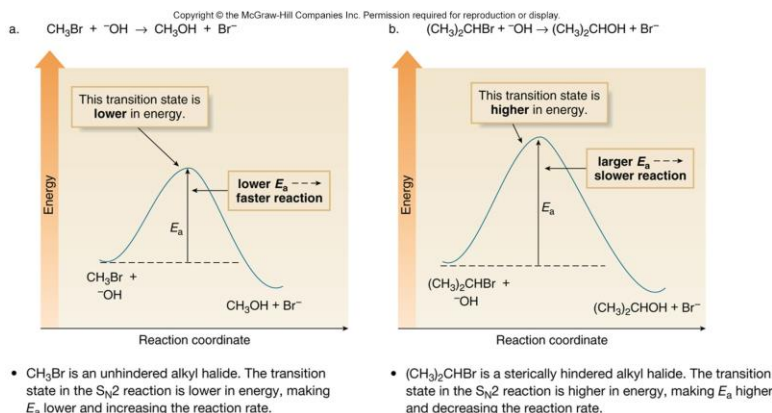


50

Energy Diagrams for S_N2 Reactions

- The higher the E_a , the **slower the reaction rate**.
- Thus, any factor that increases E_a decreases the reaction rate.

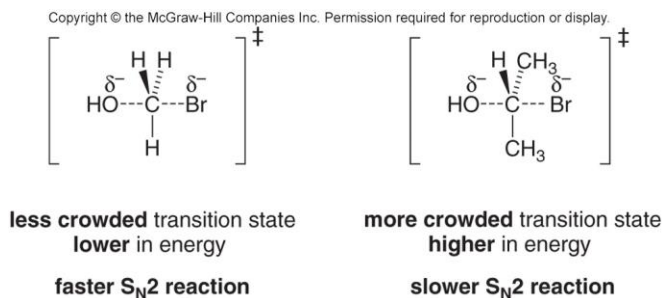
Figure 7.12



51

Effect of Sterics on Rate of S_N2 Reactions

- 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.



52

Characteristics of the S_N2 Mechanism

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Table 7.5 Characteristics of the S_N2 Mechanism

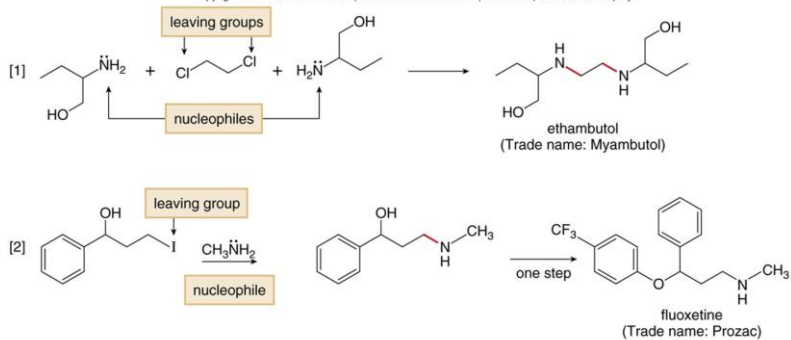
Characteristic	Result
Kinetics	Second-order kinetics; rate = $k[\text{RX}][\text{Nu}^-]$
Mechanism	One step
Stereochemistry	- Backside attack of the nucleophile - Inversion of configuration at a stereogenic center
Identity of R	- Unhindered halides react fastest. - Rate: $\text{CH}_3\text{X} > \text{RCH}_2\text{X} > \text{R}_2\text{CHX} > \text{R}_3\text{CX}$

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The S_N2 Reaction in the Synthesis of Drugs

Figure 7.13

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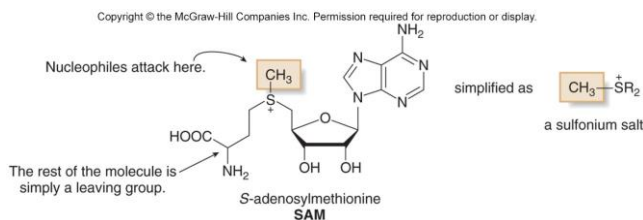


- In both examples, the initial substitution product bears a positive charge and goes on to lose a proton to form the product drawn.
- The NH₂ group serves as a neutral nucleophile to displace halogen in each synthesis. The new bonds formed by nucleophilic substitution are drawn in red in the products.

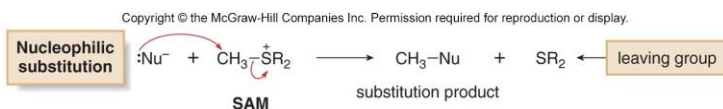
54

Nucleophilic Substitution Reactions in Biological Systems

- Nucleophilic substitution reactions are important in biological systems as well.



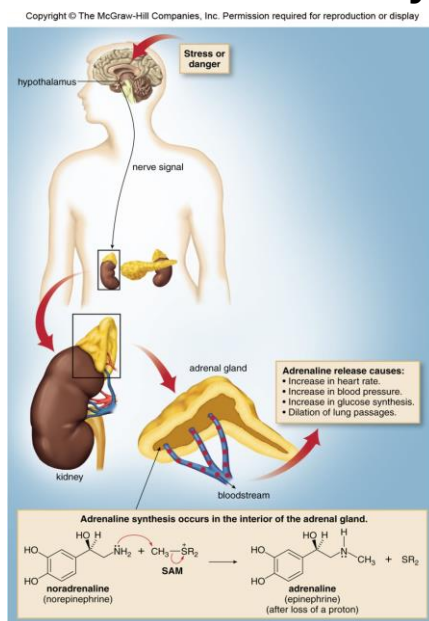
- This reaction is called methylation because a CH_3 group is transferred from one compound (SAM) to another ($:\text{Nu}^-$).



55

$\text{S}_{\text{N}}2$ Reaction in Adrenaline Synthesis

Figure 7.14
Adrenaline synthesis
from noradrenaline in
response to stress



56

S_N1 Reaction Mechanism

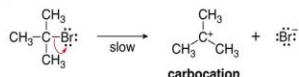
- The mechanism of an S_N1 reaction would be drawn as follows: Note the curved arrow formalism that is used to show the flow of electrons.

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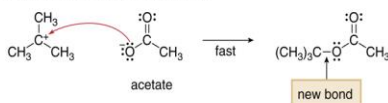
Mechanism 7.2 The S_N1 Mechanism

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.

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

57

S_N1 Kinetics

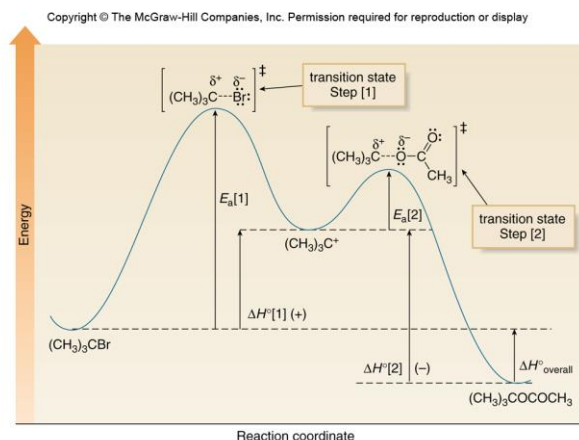
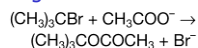
- S_N1 reactions exhibit **1st order kinetics**.
- The reaction is **unimolecular** – involving only the alkyl halide.
- The identity and concentration of the nucleophile have **no effect on the reaction rate**.
- Therefore, the nucleophile does not appear in the rate equation.

$$\text{rate} = k[\text{CH}_3\text{Br}]$$

58

Energy Diagrams for S_N1 Reactions

Figure 7.15



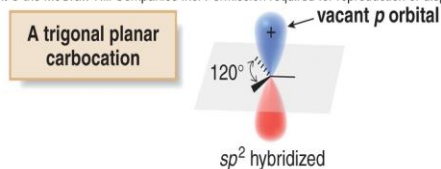
- Since the S_N1 mechanism has two steps, there are two energy barriers.
- $E_a[1] > E_a[2]$ since Step [1] involves bond breaking and Step [2] involves bond formation.
- In each step only one bond is broken or formed, so the transition state for each step has one partial bond.

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Stereochemistry of S_N1 Reactions

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

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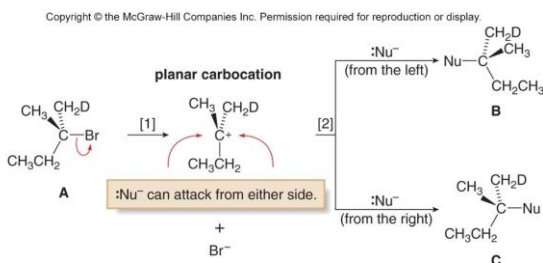


- A carbocation (with three groups around C) is *sp*² hybridized and trigonal planar, and contains a vacant *p* orbital extending above and below the plane.

60

Racemization in S_N1 Reactions

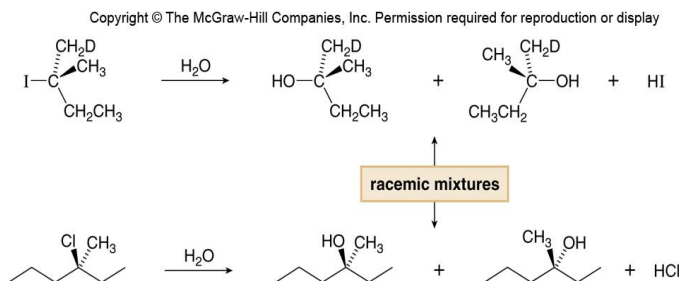
- Step [1]: **Loss of the leaving group** generates a planar carbocation that is achiral.
- In Step [2]: **attack of the nucleophile** can occur on either side to afford two products which are a pair of enantiomers.
- Because there is no preference for nucleophilic attack from either direction, **an equal amount** of the two enantiomers is formed—a racemic mixture.
- This process is called **racemization**.



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Racemization in S_N1 Reactions

Examples:



- 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).

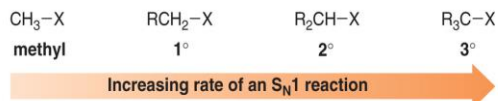
62

Substrate Reactivity in S_N1 Reactions

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

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



- 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.

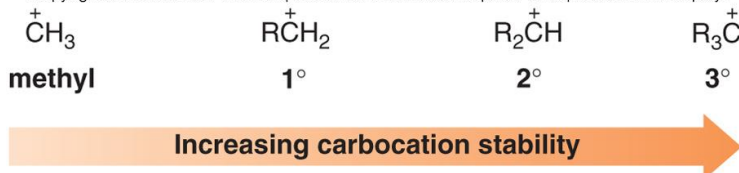
- This trend is exactly opposite to that observed in S_N2 reactions.

63

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°)**, **secondary (2°)**, or **tertiary (3°)**, based on the number of R groups bonded to the charged carbon atom.
- As the number of **R groups increases**, carbocation **stability increases**.

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Inductive Effects and Carbocation Stability

- The order of carbocation stability can be rationalized through **inductive effects** and **hyperconjugation**.
- **Inductive effects** occur by the pull of electron density through σ bonds caused by electronegativity differences between atoms.
- Alkyl groups are **electron donor** groups that stabilize a positive charge because they contain several σ bonds, each containing electron density.
- As a result, **alkyl groups are more polarizable** than a hydrogen atom, and better able to donate electron density.
- In general, the **more alkyl groups** attached to a carbon with a positive charge, the more stable the cation will be.

65

Carbocation Stability

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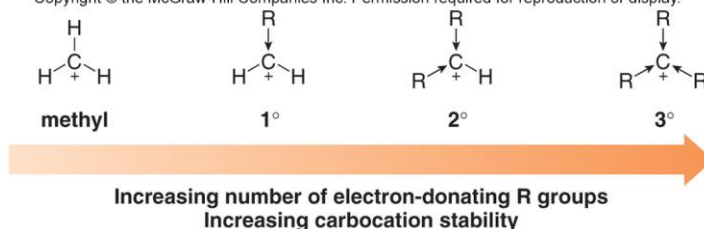
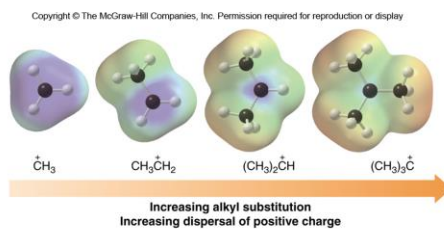


Figure 7.17
Electrostatic potential maps for
different carbocations



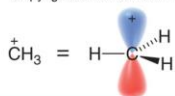
- Dark blue areas in electrostatic potential plots indicate regions low in electron density. As alkyl substitution increases, the region of positive charge is less concentrated on carbon.

66

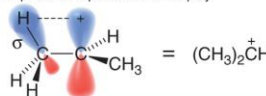
Hyperconjugation and Carbocation Stability

- The order of carbocation stability is also a consequence of **hyperconjugation**.
- **Hyperconjugation** is the **spreading out of charge** by the overlap of an empty p orbital with an adjacent σ bond.
- This overlap **delocalizes the positive charge** on the carbocation over a larger volume, thus stabilizing it.
- For example: $(\text{CH}_3)_2\text{CH}^+$ can be stabilized by hyperconjugation, but CH_3^+ cannot.

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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.

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Characteristics of the $\text{S}_{\text{N}}1$ Mechanism

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Table 7.6 Characteristics of the $\text{S}_{\text{N}}1$ Mechanism

Characteristic	Result
Kinetics	• First-order kinetics; rate = $k[\text{RX}]$
Mechanism	• Two steps
Stereochemistry	• Trigonal planar carbocation intermediate • Racemization at a single stereogenic center
Identity of R	• More substituted halides react fastest. • Rate: $\text{R}_3\text{CX} > \text{R}_2\text{CHX} > \text{RCH}_2\text{X} > \text{CH}_3\text{X}$

68

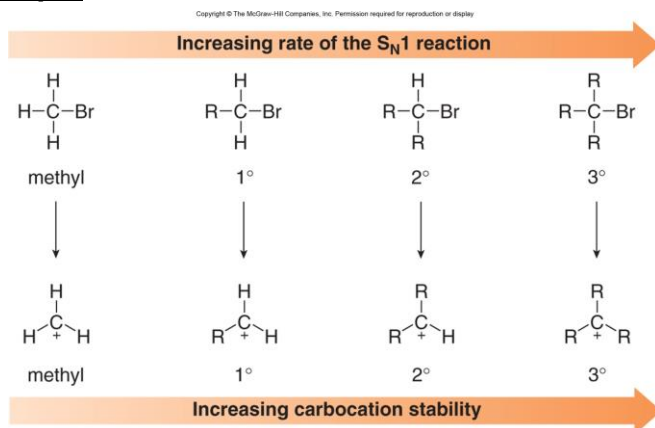
The Hammond Postulate

- The **Hammond postulate** relates reaction rate to stability.
- It provides a quantitative estimate of the energy of a transition state.
- The **Hammond postulate** states that the transition state of a reaction resembles the structure of the species (reactant or product) to which it is closer in energy.

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The Hammond Postulate

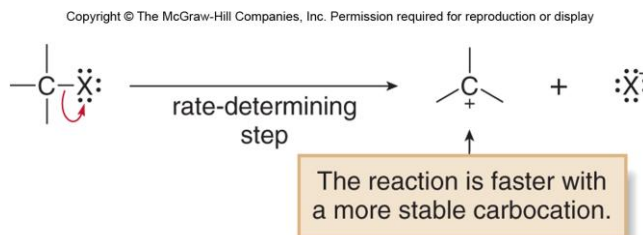
- The **rate of S_N1** reaction increases as the number of R groups on carbon increases.
- The **stability of a carbocation** increases as the number of R groups on the C⁺ increases.



70

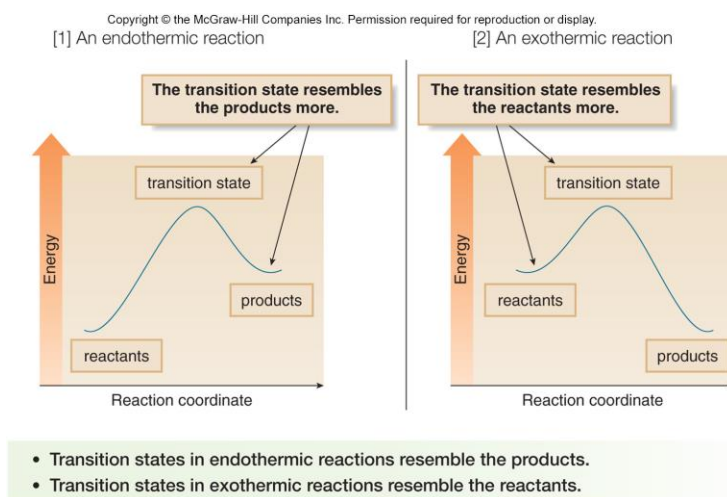
The Hammond Postulate and S_N1 reactions

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



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Transition State Energy and the Hammond Postulate



72

Endothermic Reaction Transition States

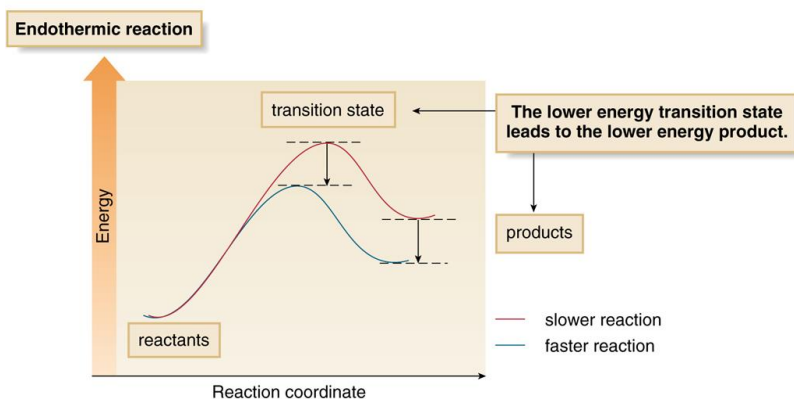
- In an **endothermic reaction**, the transition state resembles the products more than the reactants, so anything that stabilizes the product stabilizes the transition state also.
- Thus, **lowering the energy of the transition state** decreases E_a , which **increases the reaction rate**.
- If there are **two possible products** of different stability in an endothermic reaction, the transition state leading to the more stable product is lower in energy, so this reaction should occur more quickly.

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Transition State Energy of an Endothermic Reaction

Figure 7.18

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Exothermic Reaction Transition States

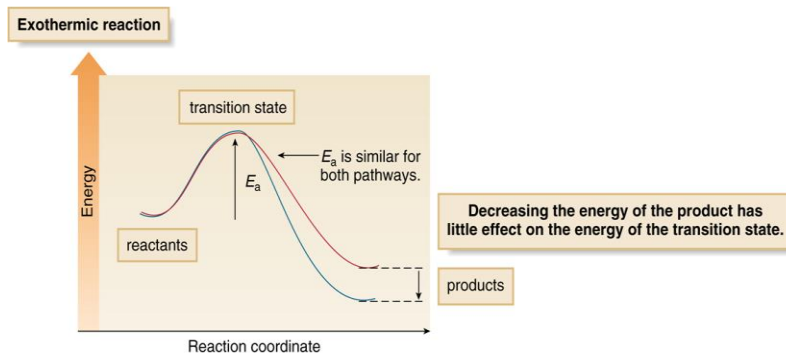
- In the case of an exothermic reaction, the **transition state resembles the reactants** more than the products.
- Thus, **lowering the energy** of the products has little or no effect on the energy of the transition state.
- Since **E_a is unaffected**, the reaction rate is unaffected.
- The conclusion is that **in an exothermic** reaction, the more stable product may or may not form faster, since E_a is similar for both products.

75

Transition State Energy of an Exothermic Reaction

Figure 7.19

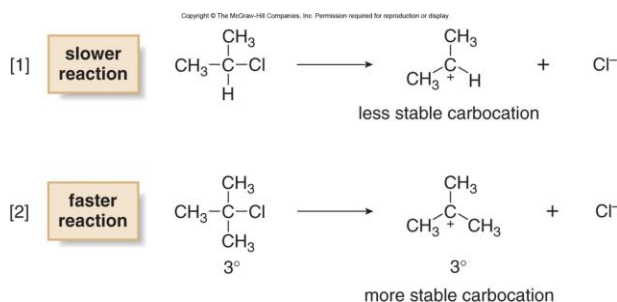
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Application of the Hammond Postulate to the S_N1 Reaction

- In the S_N1 reaction, the rate determining step is the formation of the carbocation, an endothermic process.
- According to the Hammond postulate, the stability of the carbocation determines the rate of its formation.

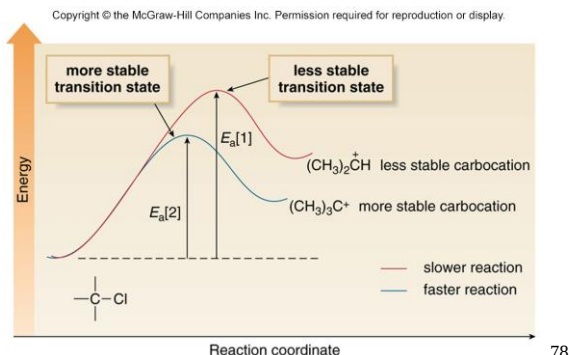


77

Application of the Hammond Postulate to the S_N1 Reaction

- Since (CH₃)₂CH⁺ is less stable than (CH₃)₃C⁺
- E_a[1] > E_a[2]
- Reaction [1] is slower

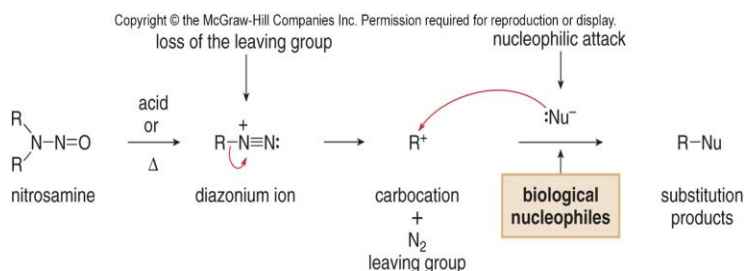
Figure 7.20
Energy diagram for carbocation formation in two different S_N1 reactions



78

Nitrosamines: S_N1 Reactions

- nitrosamines (R₂NN=O): act as toxins and carcinogens.
- With acid and heat, they can break down to form carbocations, which react with biological nucleophiles.



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Predicting the Mechanism of Nucleophilic Substitutions Reactions

- **Four factors** are relevant in predicting whether a given reaction is likely to proceed by an **S_N1** or an **S_N2** mechanism:

1. The alkyl halide—CH₃X, RCH₂X, R₂CHX or R₃CX
2. The nucleophile—strong or weak
3. The leaving group—good or poor
4. The solvent—protic or aprotic

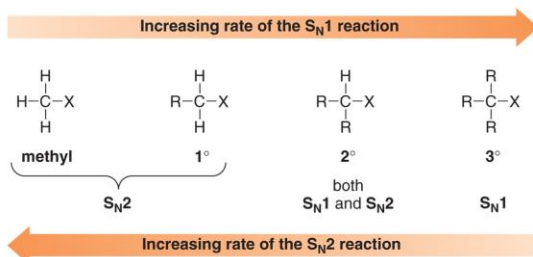
80

1. Nature of the Alkyl Halide

- The most important factor is the **identity of the alkyl halide**.

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- Increasing alkyl substitution favors S_N1 .
- Decreasing alkyl substitution favors S_N2 .



- Methyl and 1° halides (CH_3X and RCH_2X) undergo S_N2 reactions only.
- 3° Alkyl halides (R_3CX) undergo S_N1 reactions only.
- 2° Alkyl halides (R_2CHX) undergo both S_N1 and S_N2 reactions. Other factors determine the mechanism.

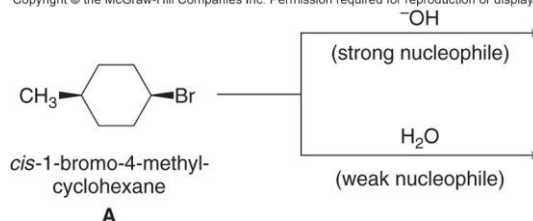
81

2. Effect of the Nucleophile

- 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.

Example: Consider what happens when the 2° alkyl halide A, which can react by either mechanism, is treated with either the strong nucleophile HO^- or the weak nucleophile H_2O .

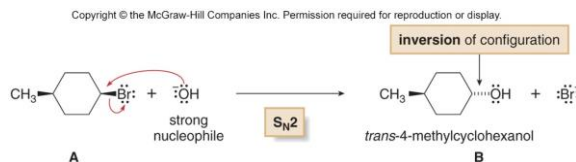
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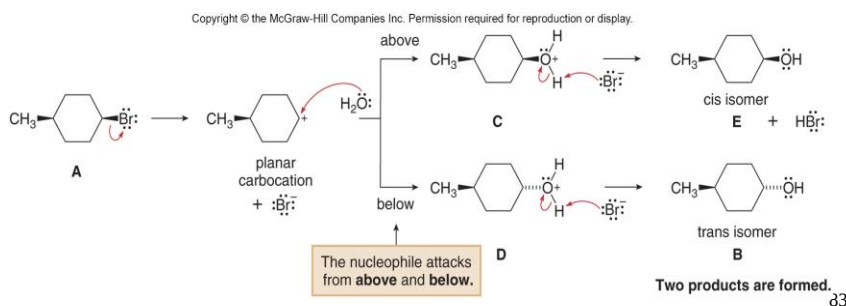
82

2. Effect of the Nucleophile

- The **strong nucleophile** favors an **S_N2** mechanism.

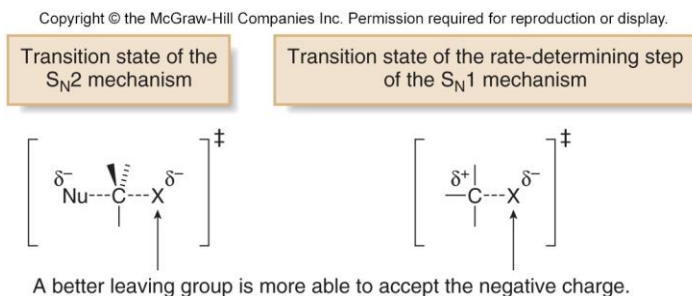


- The **weak nucleophile** favors an **S_N1** mechanism.



3. Effect of Leaving Groups

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



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R-F R-Cl R-Br R-I



Increasing leaving group ability
Increasing rate of S_N1 and S_N2 reactions

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4. Effect of Solvent

- **Polar protic** solvents like H_2O and 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.

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Predicting $\text{S}_{\text{N}}1$ or an $\text{S}_{\text{N}}2$ —Summary

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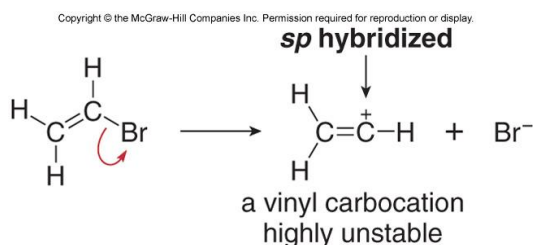
Table 7.7 Summary of Factors That Determine the $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$ Mechanism

Alkyl halide	Mechanism	Other factors
CH_3X RCH_2X (1°)	$\text{S}_{\text{N}}2$	Favored by • strong nucleophiles (usually a net negative charge) • polar aprotic solvents
R_3CX (3°)	$\text{S}_{\text{N}}1$	Favored by • weak nucleophiles (usually neutral) • polar protic solvents
R_2CHX (2°)	$\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$	The mechanism depends on the conditions. • Strong nucleophiles favor the $\text{S}_{\text{N}}2$ mechanism over the $\text{S}_{\text{N}}1$ mechanism. For example, RO^- is a stronger nucleophile than ROH, so RO^- favors the $\text{S}_{\text{N}}2$ reaction and ROH favors the $\text{S}_{\text{N}}1$ reaction. • Protic solvents favor the $\text{S}_{\text{N}}1$ mechanism and aprotic solvents favor the $\text{S}_{\text{N}}2$ mechanism. For example, H_2O and CH_3OH are polar protic solvents that favor the $\text{S}_{\text{N}}1$ mechanism, whereas acetone [$(\text{CH}_3)_2\text{C}=\text{O}$] and DMSO [$(\text{CH}_3)_2\text{S}=\text{O}$] are polar aprotic solvents that favor the $\text{S}_{\text{N}}2$ mechanism.

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Vinyl and Aryl Halides

- S_N1 or S_N2 reactions occur on sp^3 hybridized carbons.
- **Vinyl and aryl halides**, which have a halogen attached to a **sp^2 hybridized** carbon, do not undergo S_N1 or S_N2 reactions.
- **Heterolysis** of the C-X bond would form a highly unstable vinyl or aryl cation.



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Organic Synthesis

- **Organic synthesis** is the systematic preparation of a compound from a readily available starting material by one or many steps.
- **Nucleophilic substitution reactions**, especially S_N2 , are used to introduce a wide variety of functional groups into a molecule, depending on the nucleophile.
- Organic synthesis has produced many useful compounds (e.g., pharmaceuticals, pesticides, and polymers used in everyday life).
 - Chemists may rely on synthesis to prepare useful substances such as a **natural product** produced by organisms, but in only minute amounts (e.g., Taxol used in cancer treatment).

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Organic Synthesis Using Alkyl Halides

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Table 7.8 Molecules Synthesized from R-X by the S_N2 Reaction

	Nucleophile (:Nu ⁻)	Product	Name
Oxygen compounds	⁻ OH	R-OH	alcohol
	⁻ OR'	R-OR'	ether
			ester
Carbon compounds	⁻ CN	R-CN	nitrile
	⁻ C≡C-H	R-C≡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

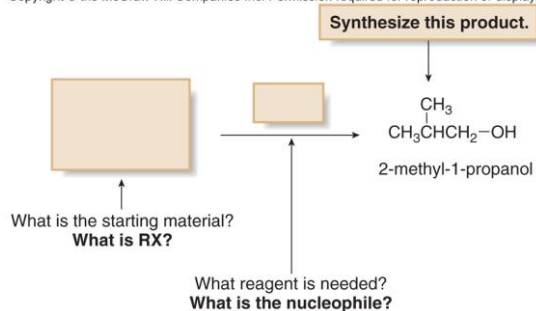
↑
products of nucleophilic substitution

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Thinking Backwards in 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?”
- If a **nucleophilic substitution** is being used, determine what alkyl halide and what nucleophile can be used to form a specific product.

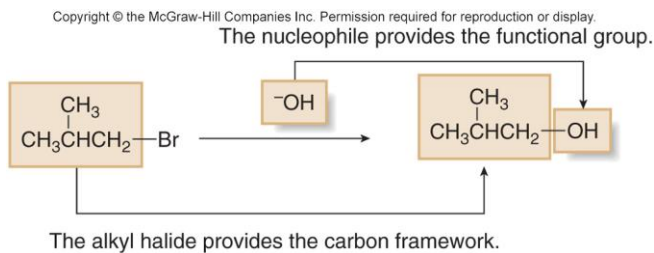
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Approaches Used in Organic Synthesis

- To determine the two components needed for synthesis, remember that the **carbon atoms** come from the organic starting material, in this case, a 1° alkyl halide.
- The **functional group** comes from the nucleophile, HO^- in this case.
- With these two components, we can “fill in the boxes” to complete the synthesis.



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