Organic Chemistry, *Fourth Edition*

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Chapter 7

Alkyl Halides and Nucleophilic Substitution

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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**

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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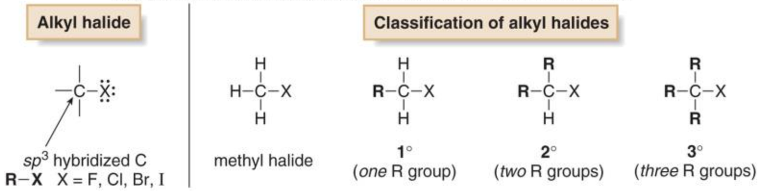

Types of Alkyl Halides

- **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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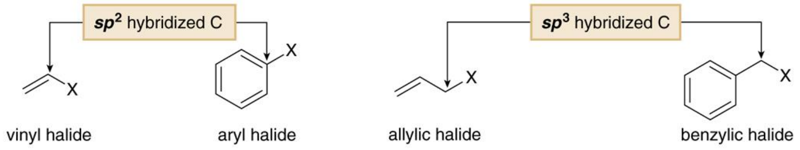


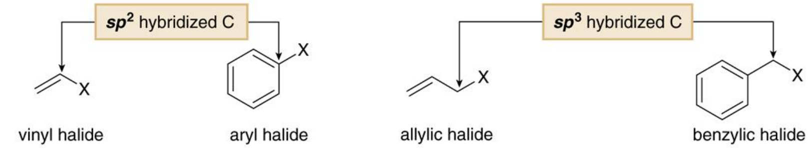
These organic halides are **unreactive** in the reactions discussed in Chapter 7.

These organic halides do participate in the reactions discussed in Chapter 7.

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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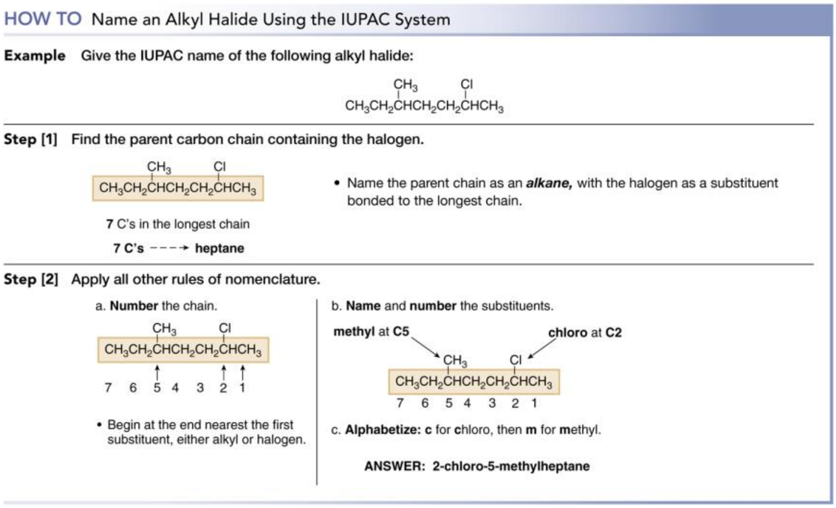
Naming Alkyl Halides



HOW TO Name an Alkyl Halide Using the IUPAC System

Example Give the IUPAC name of the following alkyl halide:

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

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

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

7 C's in the longest chain

7 C's ---→ **heptane**

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

Step [2] Apply all other rules of nomenclature.

a. **Number** the chain.

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

7 6 5 4 3 2 1

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

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

methyl at **C5** **chloro** at **C2**

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

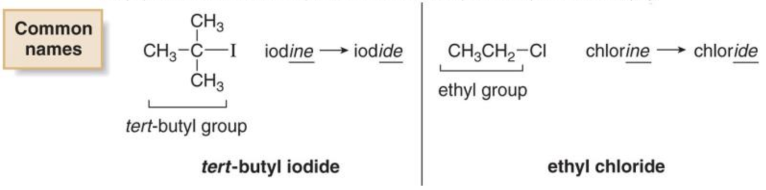
7 6 5 4 3 2 1

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

ANSWER: 2-chloro-5-methylheptane

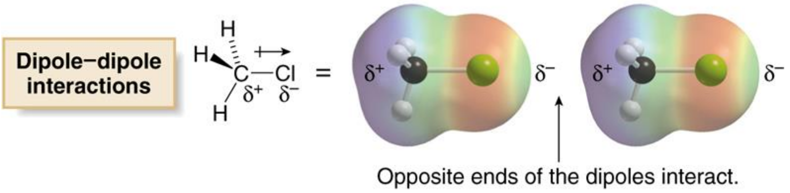
Common Names of Alkyl Halides

- **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.**



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.**



Physical Properties of Alkyl Halides

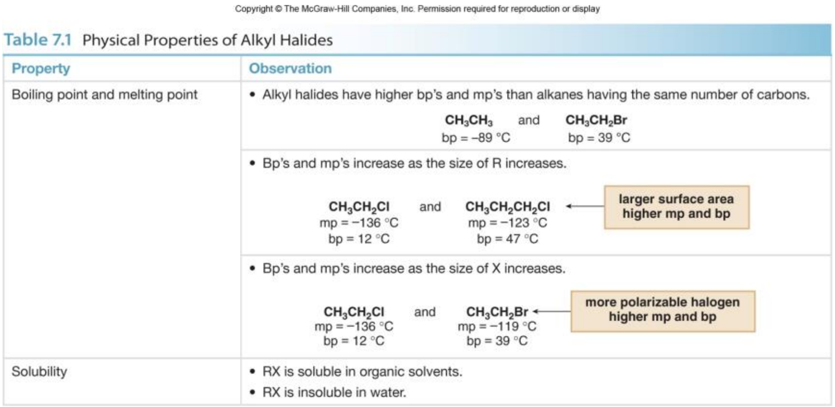
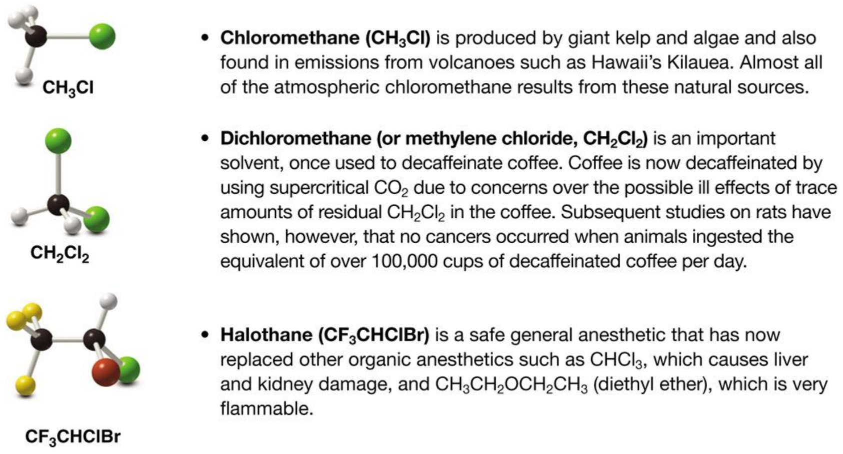


Table 7.1 Physical Properties of Alkyl Halides

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** and **CH_3CH_2Br** bp = −89 °C bp = 39 °C
	• Bp's and mp's increase as the size of R increases. **CH_3CH_2Cl** mp = −136 °C bp = 12 °C and **$CH_3CH_2CH_2Cl$** mp = −123 °C bp = 47 °C ← **larger surface area higher mp and bp**
	• Bp's and mp's increase as the size of X increases. **CH_3CH_2Cl** mp = −136 °C bp = 12 °C and **CH_3CH_2Br** mp = −119 °C bp = 39 °C ← **more polarizable halogen higher mp and bp**
Solubility	• RX is soluble in organic solvents. • RX is insoluble in water.

Simple Alkyl Halides

Figure 7.4



CH_3Cl

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

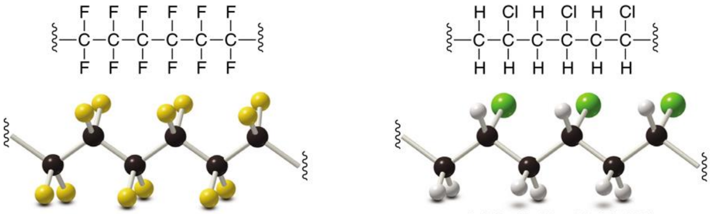
CH_2Cl_2

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

$CF_3CHClBr$

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

Common Alkyl Halides



Teflon
(nonstick coating)

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

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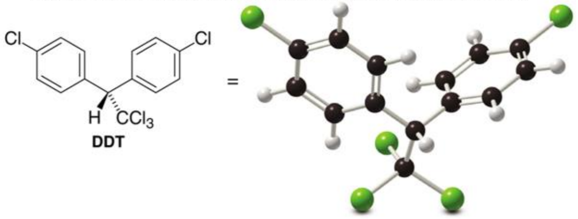
$CFCl_3$
CFC 11
Freon 11



DDT

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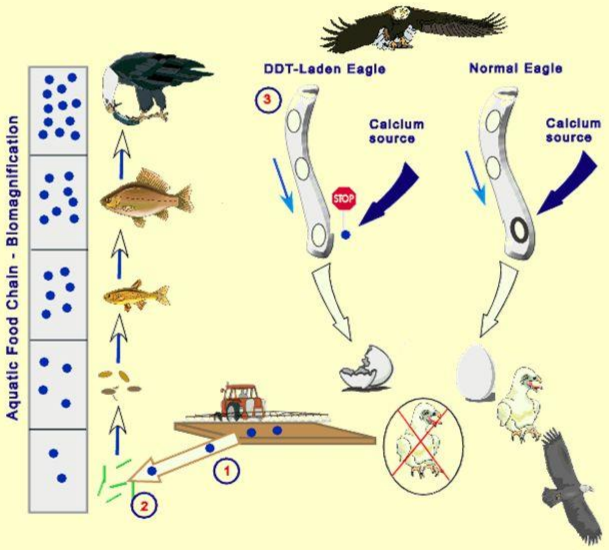
DDT kills insects that spread diseases such as malaria and typhus

DDT accumulates in fatty tissues

- 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

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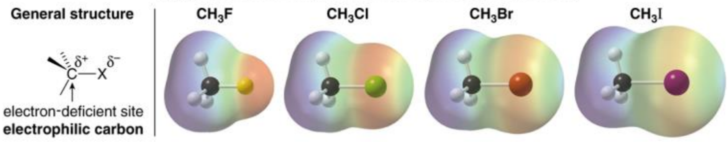
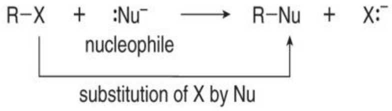


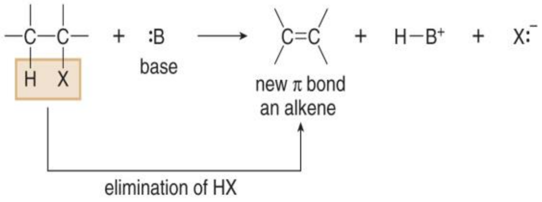
- The polar C – X bond makes the carbon atom *electron deficient* in each CH_3X molecule.

Reaction Types for Alkyl Halides

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

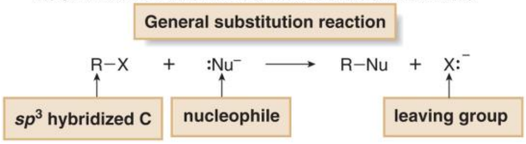


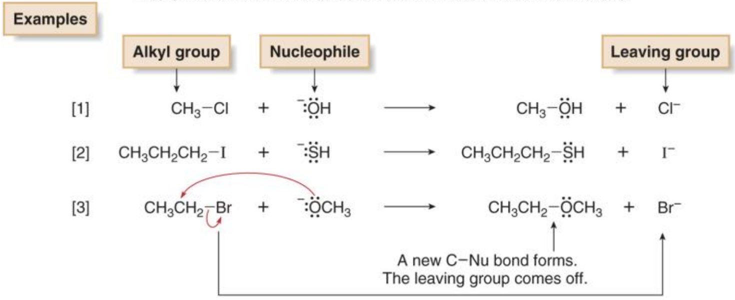
- **Alkyl halides undergo elimination reactions with Brønsted–Lowry bases.**



Substitution Reactions

- **Three components are necessary in any substitution reaction.**





Nucleophiles in Substitution Reactions

- **<u>Nucleophiles</u> are Lewis bases that can be negatively charged or neutral.**

<u>1. Negatively charged</u> 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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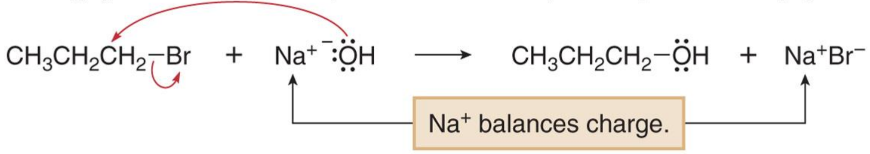

Neutral Nucleophiles

2. <u>Neutral nucleophile</u>: the substitution product bears a positive charge.

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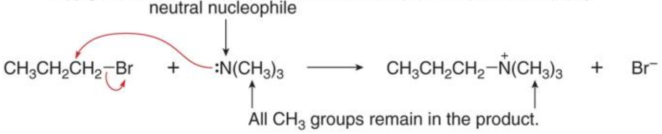
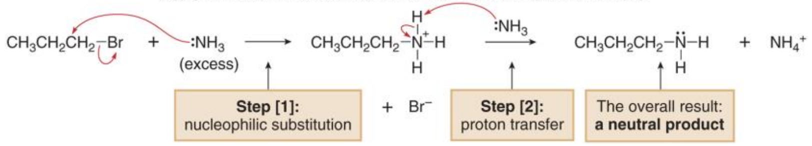


- **The substitution product's positive charge is usually caused by a proton bonded to O or N.**
- **That proton is readily lost from this in a Brønsted-Lowry acid-base reaction, forming a neutral product.**

Drawing Products of Nucleophilic Substitution Reactions

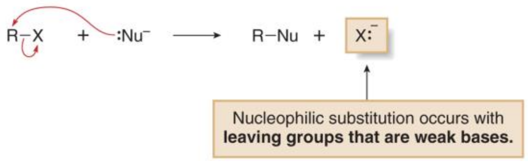


- The overall effect of any nucleophilic substitution is the replacement of the leaving group by the nucleophile.
- To draw any nucleophilic substitution product:
  1. Find the *sp*^{3} hybridized carbon with the leaving group.
  2. Identify the nucleophile, the species with a lone pair or π bond.
  3. 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 X:$^-$.
- The more stable the leaving group X:$^-$, the better able it is to accept an electron pair.

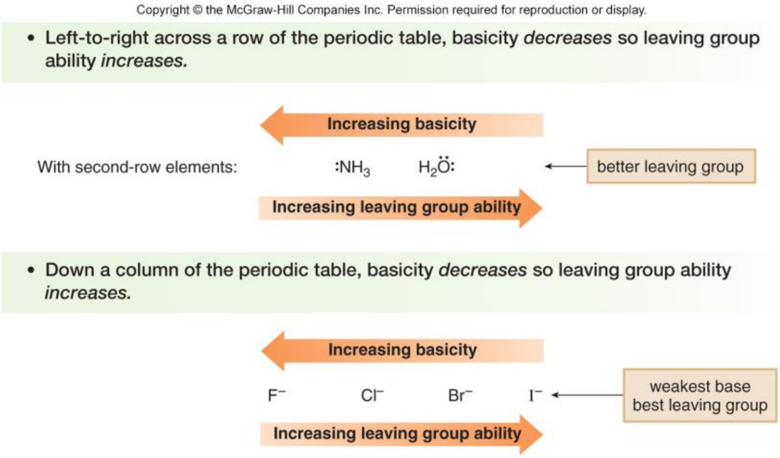
- In comparing two leaving groups, the better leaving group is the weaker base.



- For example, H_2O is a better leaving group than HO^- because H_2O is a weaker base.

Trends in Leaving Group Ability

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



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

Increasing basicity

With second-row elements: $:NH_3$ $H_2\ddot{O}:$ ← better leaving group

Increasing leaving group ability

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

Increasing basicity

F^- Cl^- Br^- I^- ← weakest base best leaving group

Increasing leaving group ability

Good Leaving Groups

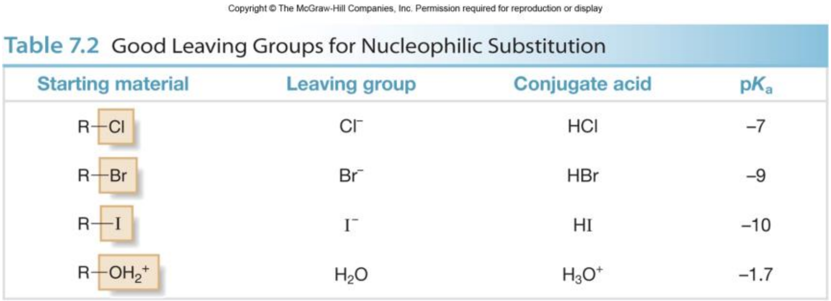


Table 7.2 Good Leaving Groups for Nucleophilic Substitution

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

Poor **Leaving Groups**

- **Conjugate bases of weaker acids are poorer leaving groups.**

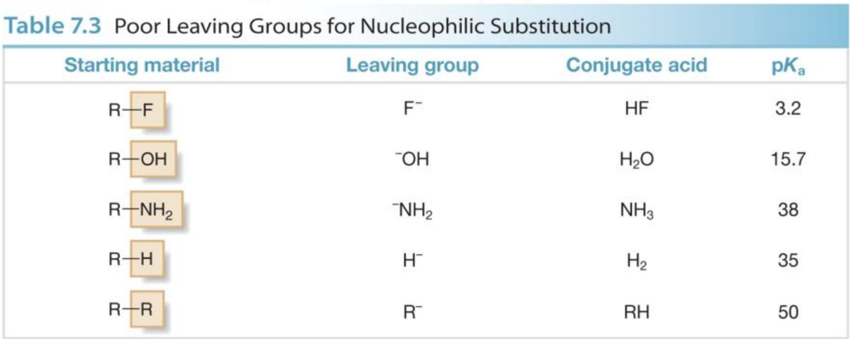
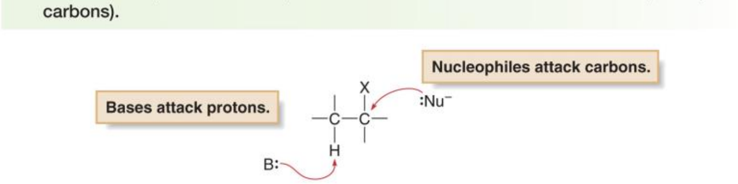


Table 7.3 Poor Leaving Groups for Nucleophilic Substitution

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

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



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

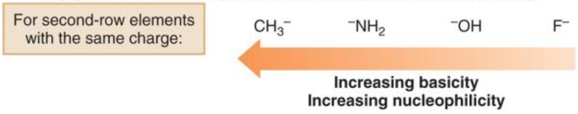
Nucleophiles vs. Bases

- 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.

Nucleophilicity Parallels Basicity

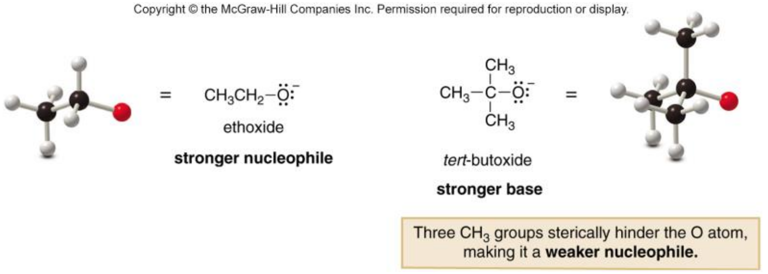
Nucleophilicity parallels basicity in three instances:

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 pK_a values of their conjugate acids (H_2O = 15.7, and CH_3COOH = 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:



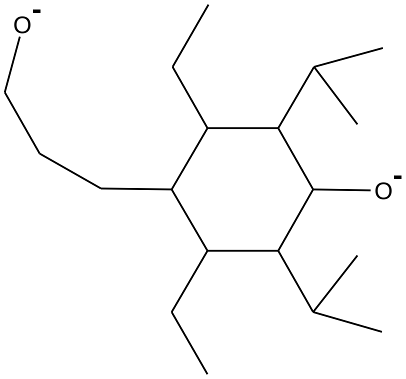
Steric Effects on Nucleophile Strength

- **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.**



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

Steric Effects on Nucleophile Strength



Solvent Effects on Nucleophilicity

- **Most organic reactions are performed in a liquid solvent capable of dissolving the reactants, at least to some extent.**

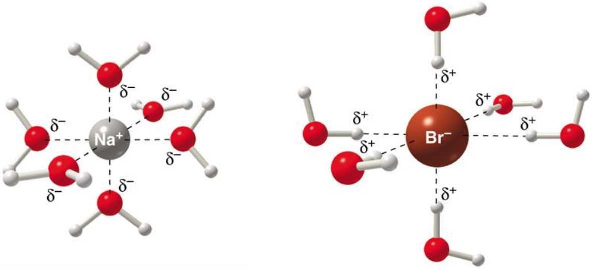
- **Since substitution reactions involve polar starting materials, polar solvents are used to dissolve them.**

- **There are two types of polar solvents: protic and aprotic.**

- **Nucleophilicity can be affected by the nature of the solvent.**

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.**



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

Br^- is solvated by hydrogen bonding with H_2O.

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.**

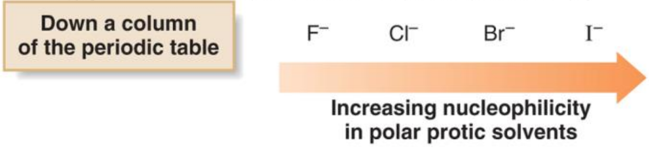


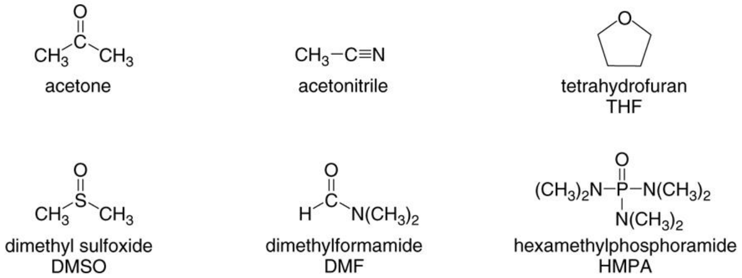
Figure 7.6

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

Polar Aprotic Solvents

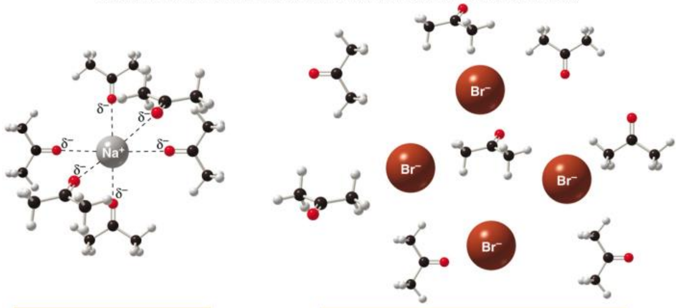
- **Polar aprotic solvents also exhibit dipole-dipole interactions, but they have no O-H or N-H bonds.**
  - **They are incapable of hydrogen bonding.**

Figure 7.7



Nucleophilicity in <u>Polar Aprotic</u> Solvents

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

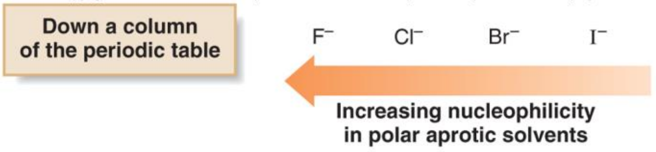


$(CH_3)_2C{=}O$ solvates Na^+ well by ion–dipole interactions.

Br^- anions are surrounded by solvent but not well solvated by the $(CH_3)_2C{=}O$ molecules.

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.



Down a column of the periodic table

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

Increasing nucleophilicity in polar aprotic solvents

Common Nucleophiles

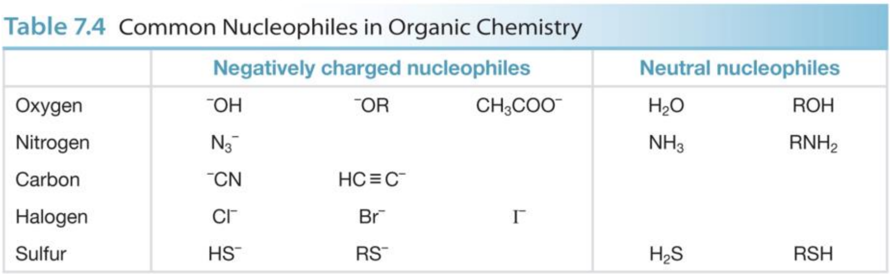
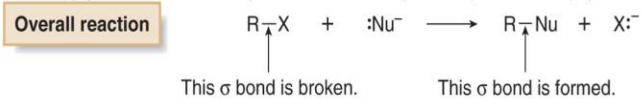


Table 7.4 Common Nucleophiles in Organic Chemistry

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

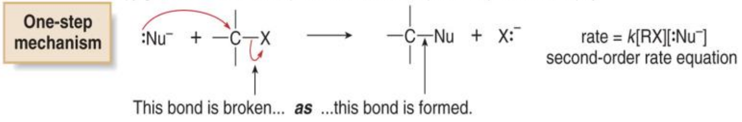
Bond Breaking and Making
in Nucleophilic Substitution Mechanisms



- **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.**

Nucleophilic Substitution Mechanisms– Concerted

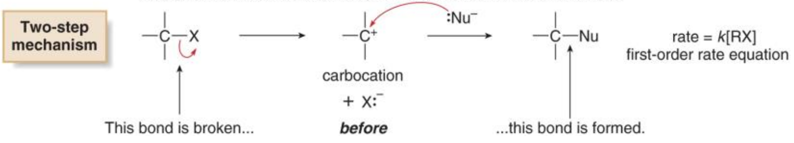
1. **Bond making and bond breaking occur at the same time.**



- **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.**

Nucleophilic Substitution Mechanisms– Bond Breaking First

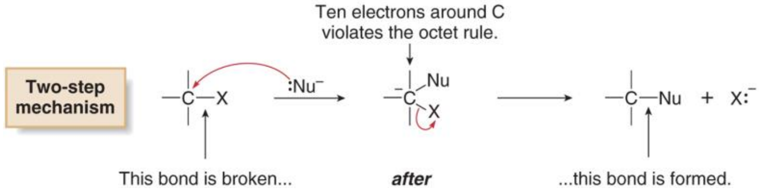
2. **Bond breaking occurs before bond making.**



- **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.**

Nucleophilic Substitution Mechanisms–Bond Making First

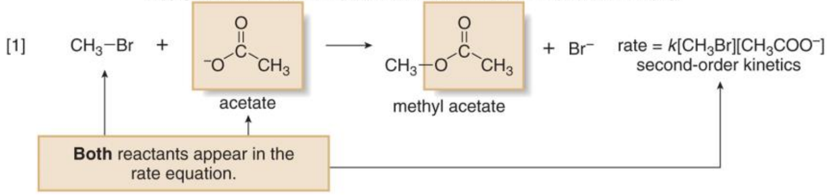
3. Bond making occurs before bond breaking.



- **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.**

Kinetics and Mechanisms

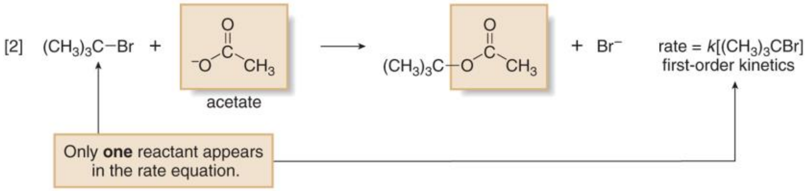
Consider reaction 1 below:



- **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.**

Kinetics and Mechanisms

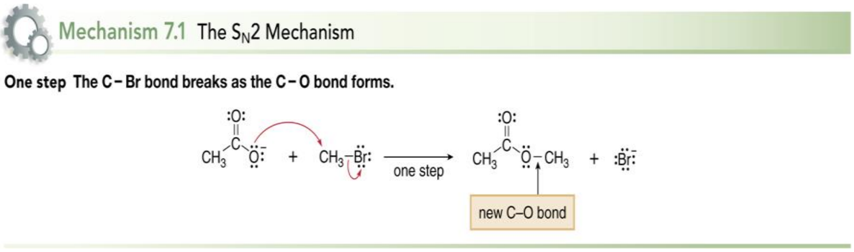
Consider reaction 2 below:



- **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.**

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.**



S_N2 Kinetics

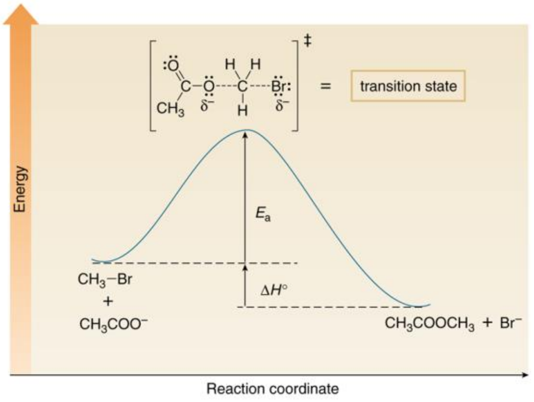
- **S_N2 reactions exhibit 2nd order kinetics.**
- **The reaction is bimolecular – both the alkyl halide and the nucleophile appear in the rate equation.**

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

Energy Diagrams for S_N2 Reactions

Figure 7.8

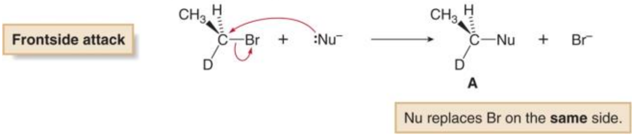
$CH_3Br + CH_3COO^- \rightarrow CH_3COOCH_3 + Br^-$



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

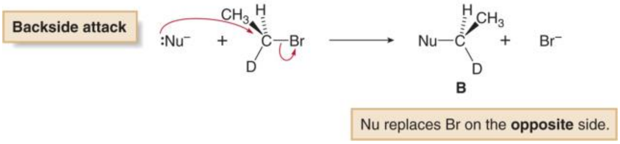
Stereochemistry of the S_N2 Reaction

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



Nu replaces Br on the **same** side.

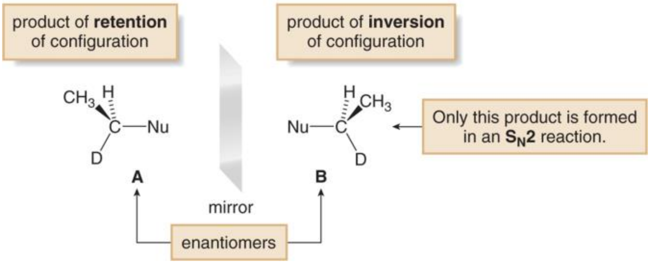
- **Backside Attack: The nucleophile approaches from the side opposite the leaving group.**



Nu replaces Br on the **opposite** side.

Stereochemistry of the S_N2 Reaction

- **The <u>products</u> of frontside and backside attack are different compounds.**
  - **They are enantiomers.**



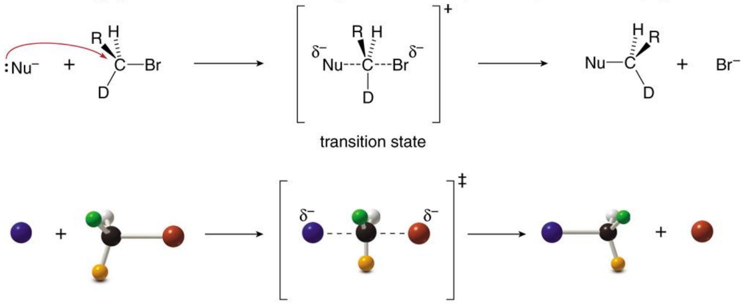
Only this product is formed in an S_N2 reaction.

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

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.

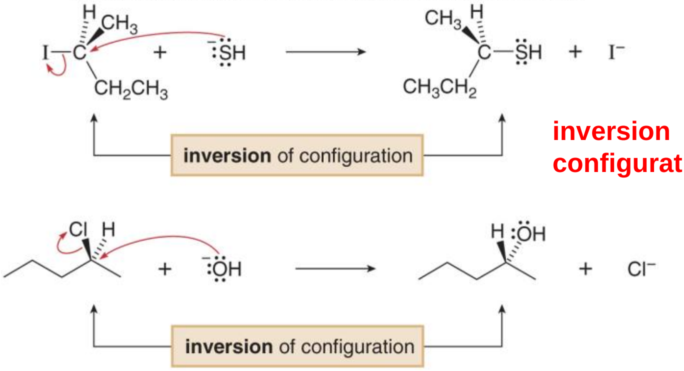
Figure 7.9



:Nu⁻ and Br⁻ are 180° away from each other, on either side of a plane containing R, H, and D.

Inversion in S_N2 Reactions

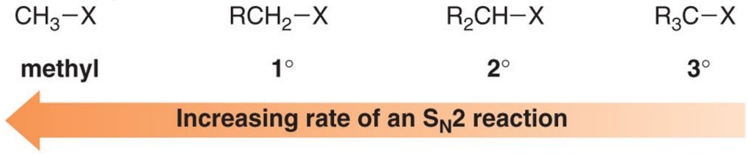
- Examples



inversion of configuration

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*.



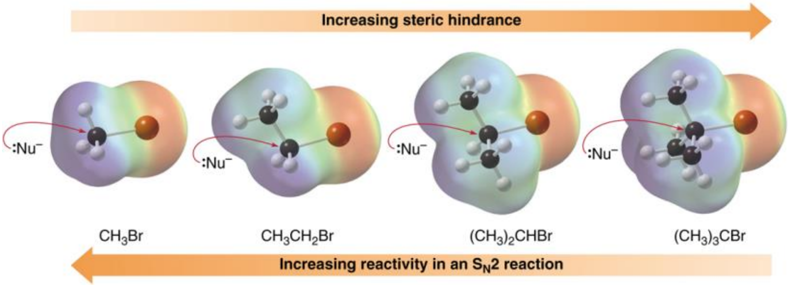
- Methyl and 1° alkyl halides undergo S_N2 reactions with ease.
- 2° Alkyl halides react more slowly.
- 3° Alkyl halides do not undergo S_N2 reactions due to steric effects.

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

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.

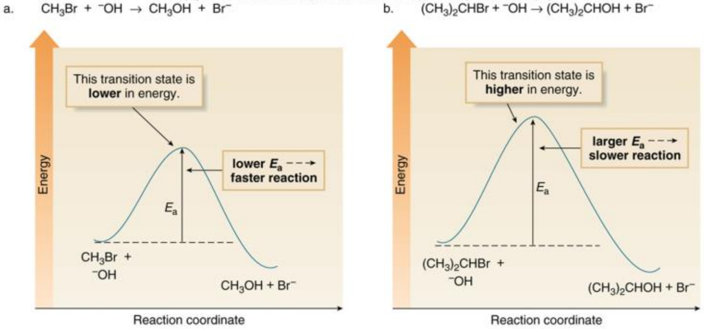
Figure 7.11



Energy Diagrams for S_N2 Reactions

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

Figure 7.12



a. $CH_3Br + {}^-OH \rightarrow CH_3OH + Br^-$

b. $(CH_3)_2CHBr + {}^-OH \rightarrow (CH_3)_2CHOH + Br^-$

- CH_3Br is an unhindered alkyl halide. The transition state in the S_N2 reaction is lower in energy, making E_a lower and increasing the reaction rate.
- $(CH_3)_2CHBr$ is a sterically hindered alkyl halide. The transition state in the S_N2 reaction is higher in energy, making E_a higher and decreasing the reaction rate.

Effect of Sterics on Rate of S_N2 Reactions

- **Increasing the <u>number of R groups</u> 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

Characteristics of the S_N2 Mechanism

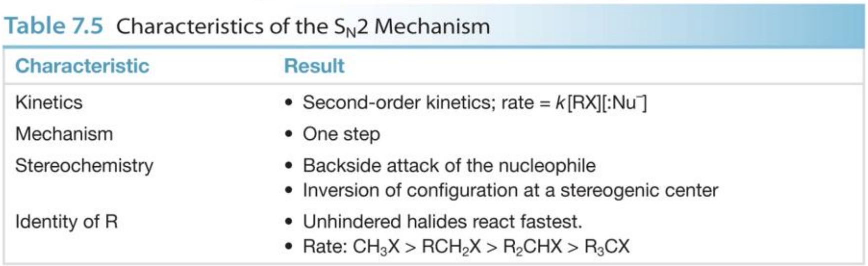
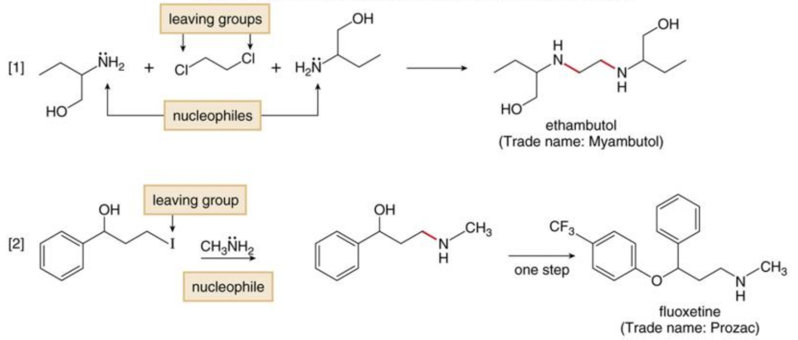


Table 7.5 Characteristics of the S_N2 Mechanism

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

The S_N2 Reaction in the Synthesis of Drugs

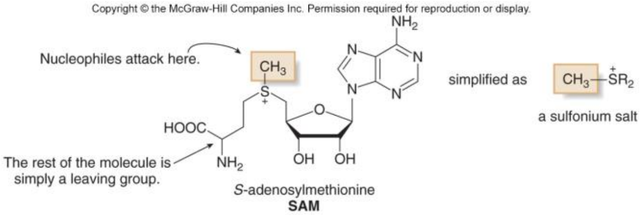
Figure 7.13



- In both examples, the initial substitution product bears a positive charge and goes on to lose a proton to form the product drawn.
- The NH_2 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.

Nucleophilic Substitution Reactions in Biological Systems

- **Nucleophilic substitution reactions are important in biological systems as well.**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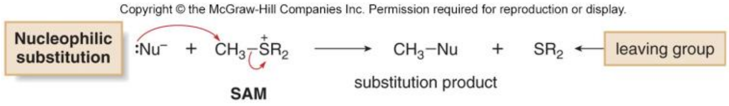
- **This reaction is called methylation because a CH_3 group is transferred from one compound (SAM) to another (:Nu¯).**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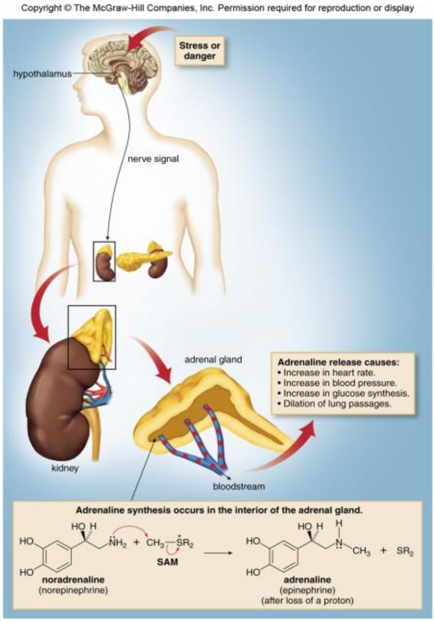
S_N2 Reaction in Adrenaline Synthesis

Figure 7.14
Adrenaline synthesis from noradrenaline in response to stress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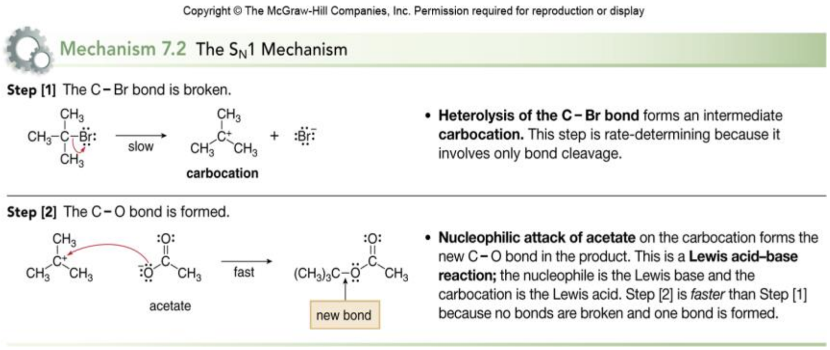
S_N1 Reaction Mechanism

- **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.**



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.**

S_N1 Kinetics

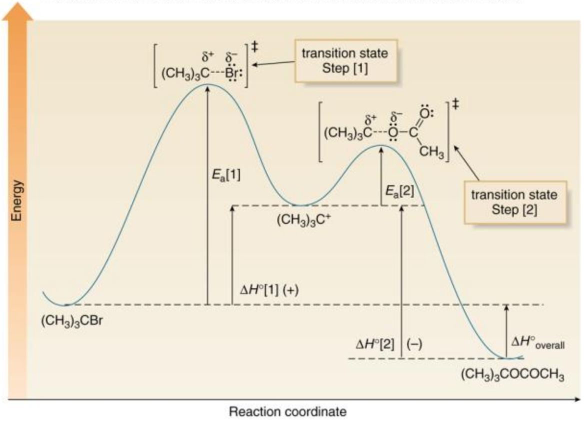
- **S_N1 reactions exhibit 1^{st} order kinetics.**
- **The reaction is unimolecular – involving only the alkyl halide.**
- **The identity and concentration of the nucleophile have no effect on the reaction rate.**
- **Therefore, the nucleophile does not appear in the rate equation.**

$$\text{rate} = k[CH_3Br]$$

Energy Diagrams for S_N1 Reactions

Figure 7.15

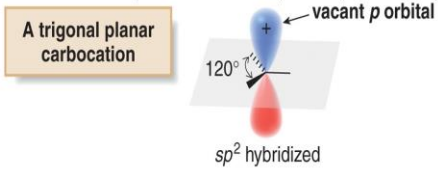
$(CH_3)_3CBr + CH_3COO^- \rightarrow (CH_3)_3COCOCH_3 + Br^-$



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

Stereochemistry of S_N1 Reactions

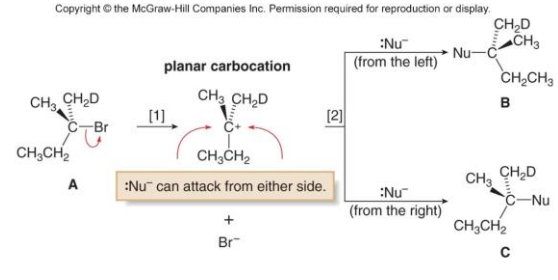
To understand the stereochemistry of the S_N1 reaction, we must examine the geometry of the carbocation intermediate.



- 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.

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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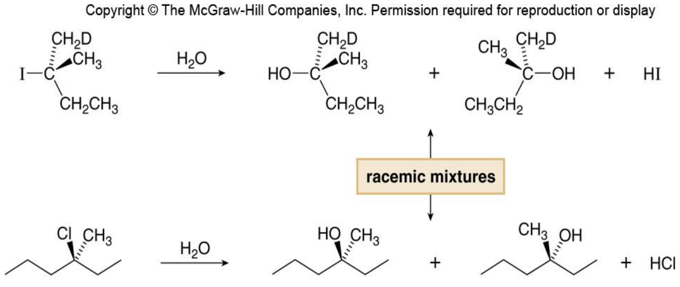
Racemization in S_N1 Reactions

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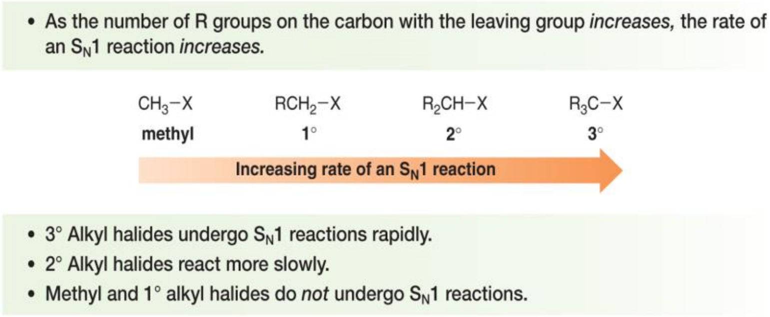
- Nucleophilic substitution of each starting material by an S_N1 mechanism forms a **racemic mixture** of two products.
- With H_2O, a neutral nucleophile, the initial product of nucleophilic substitution (ROH_2^+) loses a proton to form the final neutral product, ROH (Section 7.6).

Substrate Reactivity in S_N1 Reactions

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



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

CH_3-X methyl, RCH_2-X 1°, R_2CH-X 2°, R_3C-X 3°

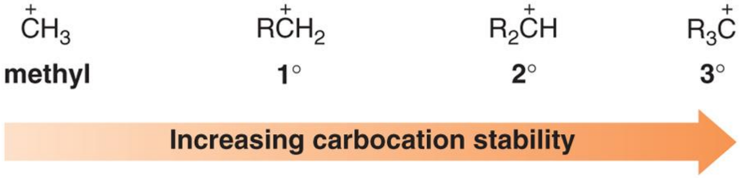
Increasing rate of an S_N1 reaction

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

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

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.**



$\overset{+}{C}H_3$ methyl, $R\overset{+}{C}H_2$ 1°, $R_2\overset{+}{C}H$ 2°, $R_3\overset{+}{C}$ 3°

Increasing carbocation stability

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.**

Carbocation Stability

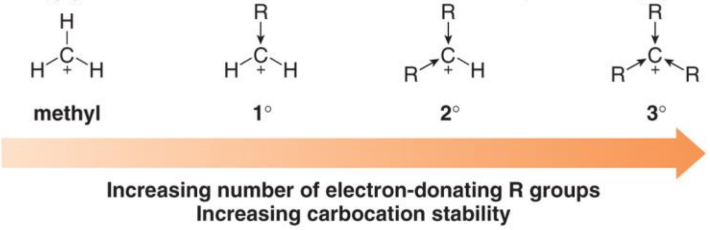
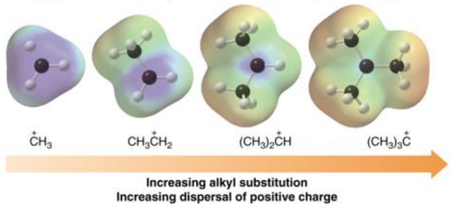


Figure 7.17
Electrostatic potential maps for differerent carbocations



- 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.

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

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.

Characteristics of the S_N1 Mechanism

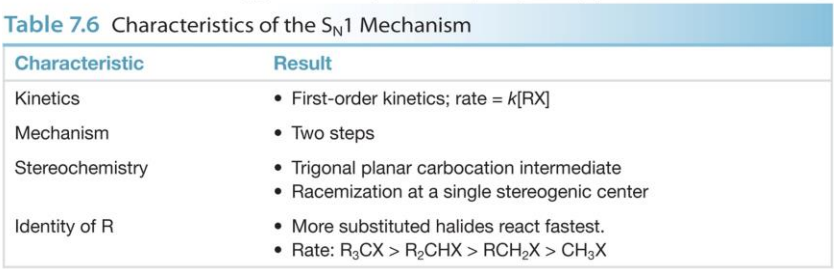


Table 7.6 Characteristics of the S_N1 Mechanism

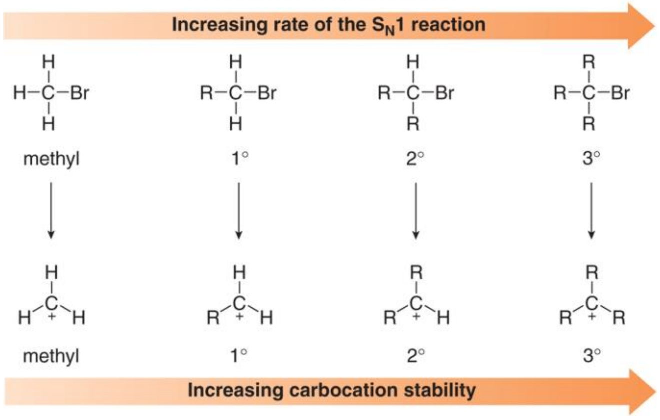
Characteristic	Result
Kinetics	• First-order kinetics; rate = k[RX]
Mechanism	• Two steps
Stereochemistry	• Trigonal planar carbocation intermediate • Racemization at a single stereogenic center
Identity of R	• More substituted halides react fastest. • Rate: $R_3CX > R_2CHX > RCH_2X > CH_3X$

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.

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.



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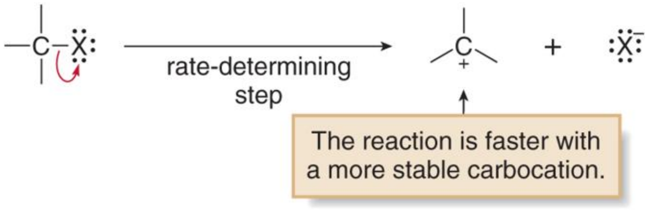
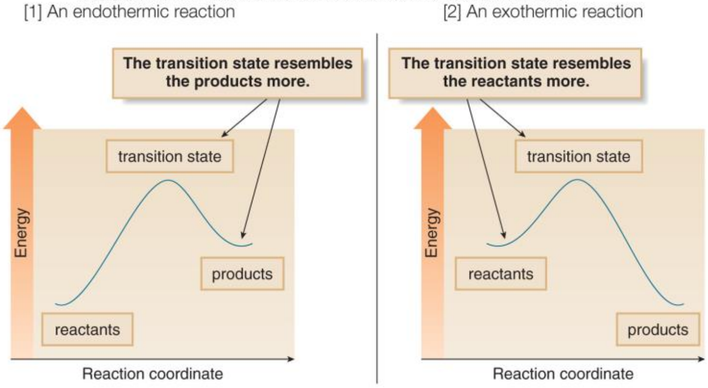
The Hammond Postulate and S_N1 reactions

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



Transition State Energy and the Hammond Postulate



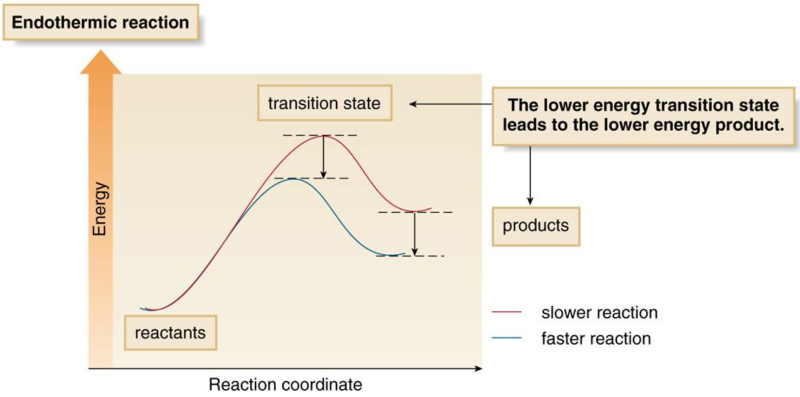
- Transition states in endothermic reactions resemble the products.
- Transition states in exothermic reactions resemble the reactants.

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.**

Transition State Energy of an Endothermic Reaction

Figure 7.18

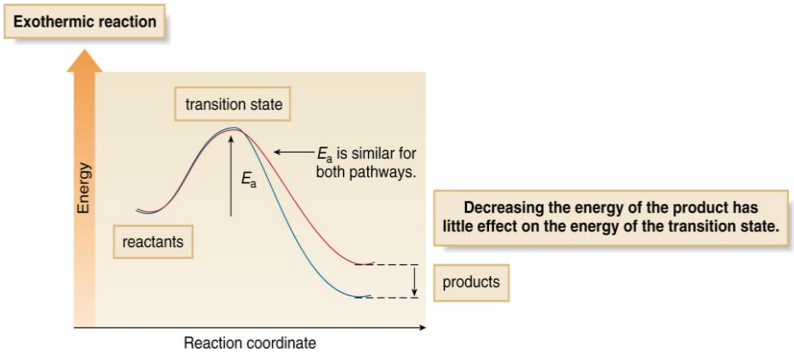


Exothermic Reaction Transition States

- 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.

Transition State Energy of an Exothermic Reaction

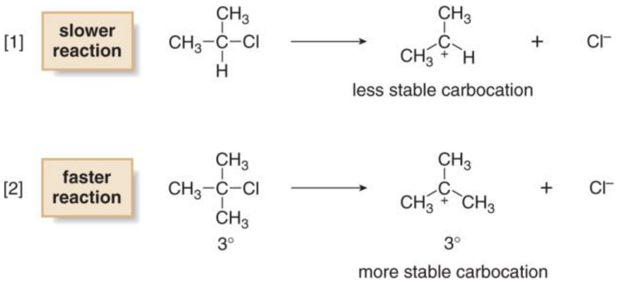
Figure 7.19



Decreasing the energy of the product has little effect on the energy of the transition state.

Application of the Hammond Postulate to the S_N1 Reaction

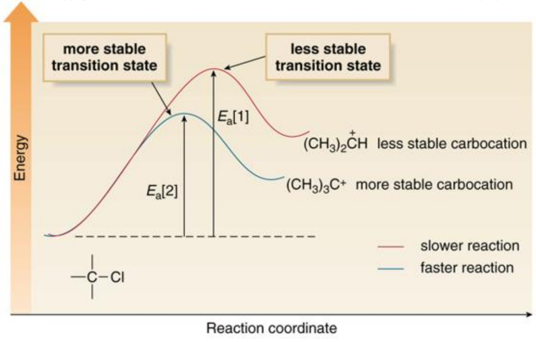
- In the S_N1 reaction, the rate determining step is the formation of the carbocation, an endothermic process.
- According to the Hammond postulate, the stability of the carbocation determines the rate of its formation.



Application of the Hammond Postulate to the S_N1 Reaction

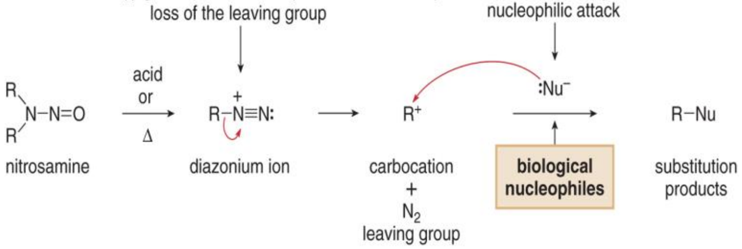
- Since $(CH_3)_2CH^+$ is less stable than $(CH_3)_3C^+$
- $E_a[1] > E_a[2]$
- Reaction [1] is slower

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



Nitrosamines: S_N1 Reactions

- nitrosamines ($R_2NN=O$): act as toxins and carcinogens.
- With acid and heat, they can break down to form carbocations, which react with biological nucleophiles.



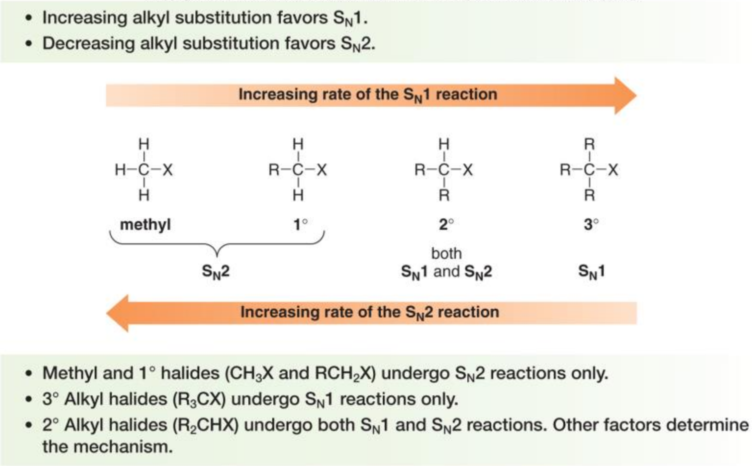
Predicting the Mechanism of Nucleophilic Substitutions Reactions

- 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—CH_3X, RCH_2X, R_2CHX or R_3CX
2. The nucleophile—strong or weak
3. The leaving group—good or poor
4. The solvent—protic or aprotic

1. Nature of the Alkyl Halide

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



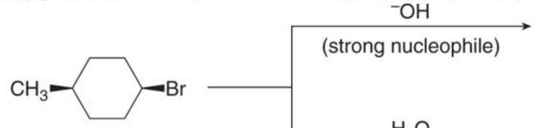
- Increasing alkyl substitution favors S_N1.
- Decreasing alkyl substitution favors S_N2.

- 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.

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.

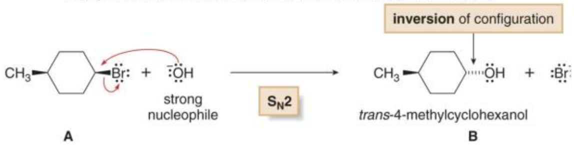


cis-1-bromo-4-methyl-cyclohexane

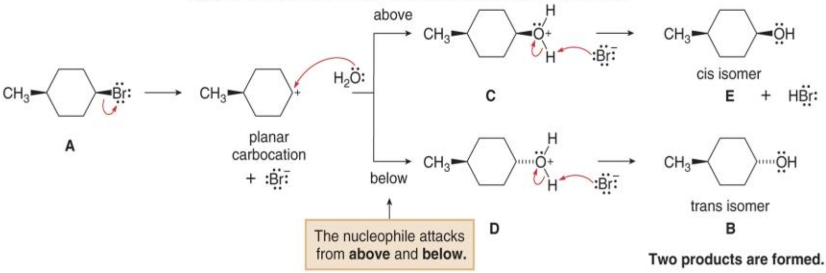
A

2. Effect of the Nucleophile

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

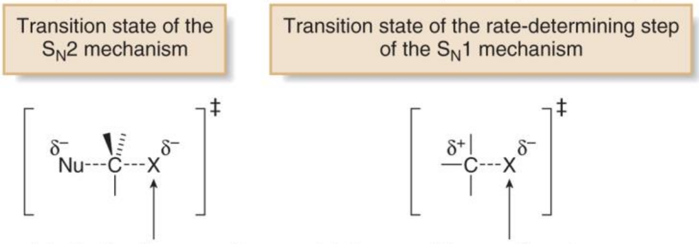


- **The weak nucleophile favors an S_N1 mechanism.**



3. Effect of Leaving Groups

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



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

Increasing leaving group ability
Increasing rate of S_N1 and S_N2 reactions

4. Effect of Solvent

- **Polar protic** solvents like H_2O and ROH favor S_N1 reactions because the ionic intermediates (both cations and anions) are stabilized by solvation.

- **Polar aprotic** solvents favor S_N2 reactions because nucleophiles are not well solvated, and therefore, are more nucleophilic.

Predicting S_N1 or an S_N2–Summary

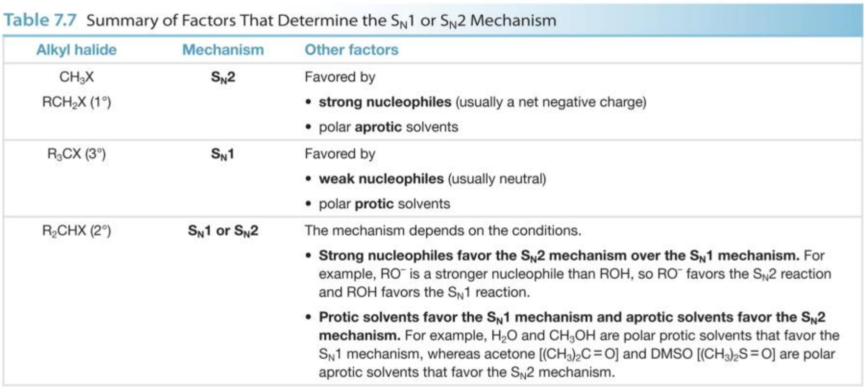


Table 7.7 Summary of Factors That Determine the S_N1 or S_N2 Mechanism

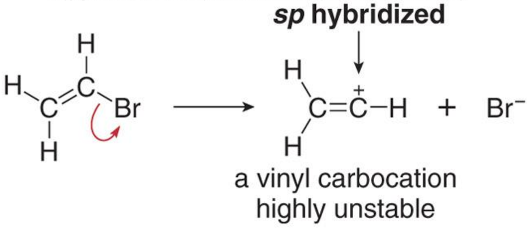
Alkyl halide	Mechanism	Other factors
CH_3X RCH_2X (1°)	**S_N2**	Favored by • **strong nucleophiles** (usually a net negative charge) • polar **aprotic** solvents
R_3CX (3°)	**S_N1**	Favored by • **weak nucleophiles** (usually neutral) • polar **protic** solvents
R_2CHX (2°)	**S_N1 or S_N2**	The mechanism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

Vinyl and Aryl Halides

- **S$_N$1 or S$_N$2 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$_N$1 or S$_N$2 reactions.**

- **Heterolysis of the C-X bond would form a highly unstable vinyl or aryl cation.**



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$_N$2, 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).**

Organic Synthesis Using Alkyl Halides

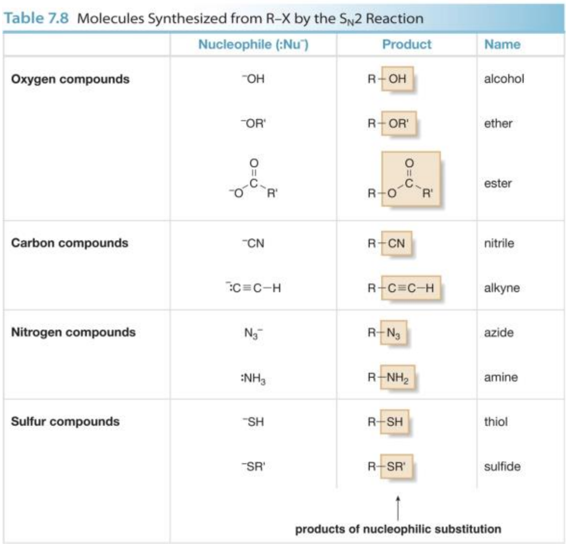


Table 7.8 Molecules Synthesized from R–X by the S_N2 Reaction

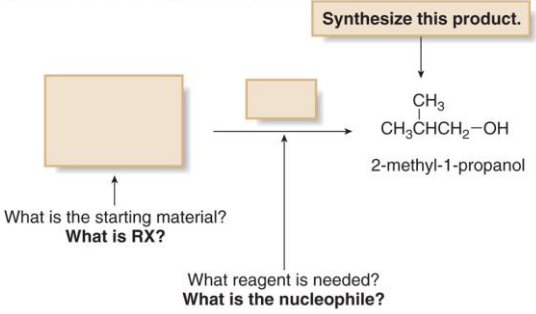
	Nucleophile (:Nu⁻)	Product	Name
Oxygen compounds	^-OH	$R-OH$	alcohol
	$^-OR'$	$R-OR'$	ether
	$^-O-C(=O)-R'$	$R-O-C(=O)-R'$	ester
Carbon compounds	^-CN	$R-CN$	nitrile
	$^-:C\equiv C-H$	$R-C\equiv C-H$	alkyne
Nitrogen compounds	N_3^-	$R-N_3$	azide
	$:NH_3$	$R-NH_2$	amine
Sulfur compounds	^-SH	$R-SH$	thiol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

↑ **products of nucleophilic substitution**

Thinking Backwards in Organic Synthesis

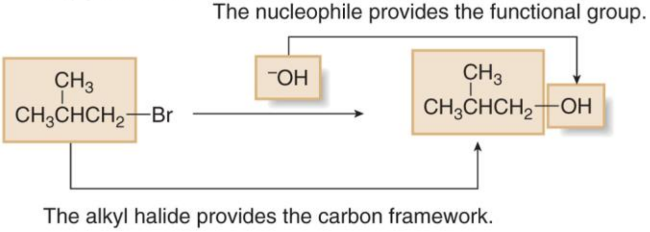
- **To carry out the synthesis of a particular compound, we must think backwards, and ask ourselves the question:**
  "What starting material and reagents are needed to make it?"

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



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.



The nucleophile provides the functional group.

The alkyl halide provides the carbon framework.