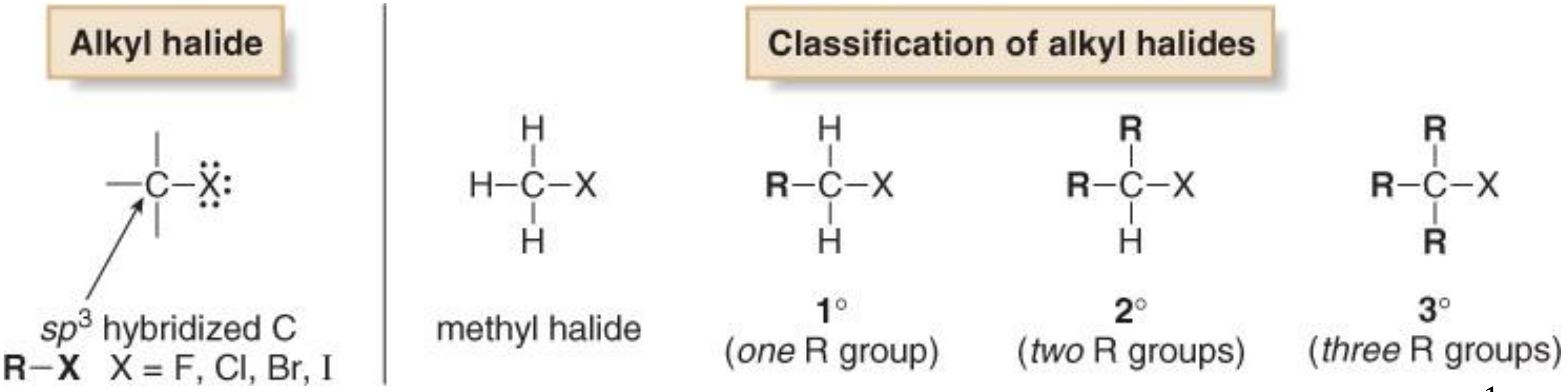
Alkyl Halides and Nucleophilic Substitution

Introduction to Alkyl Halides

- Alkyl halides are organic molecules containing a halogen atom bonded to an *sp*^{3} hybridized carbon atom.

- Alkyl halides are classified as primary (1°), secondary (2°), or tertiary (3°), depending on the number of carbons bonded to the carbon with the halogen atom.

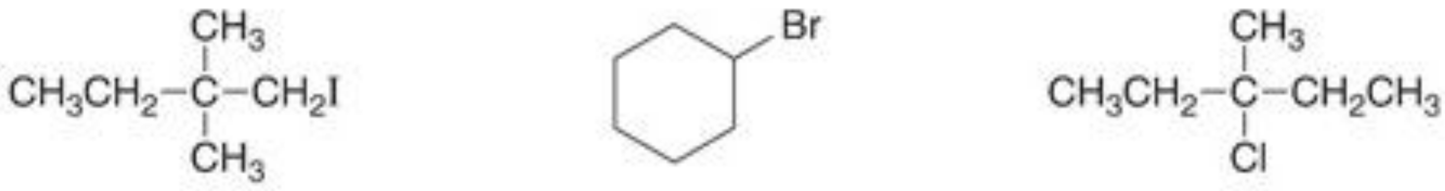
- The halogen atom in halides is often denoted by the symbol "X".



- There are other types of organic halides. These include **vinyl halides**, **aryl halides**, **allylic halides** and **benzylic halides**.
- **Vinyl halides** have a halogen atom (X) bonded to a C—C double bond.
- **Aryl halides** have a halogen atom bonded to a benzene ring.
- **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 7.1

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



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

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

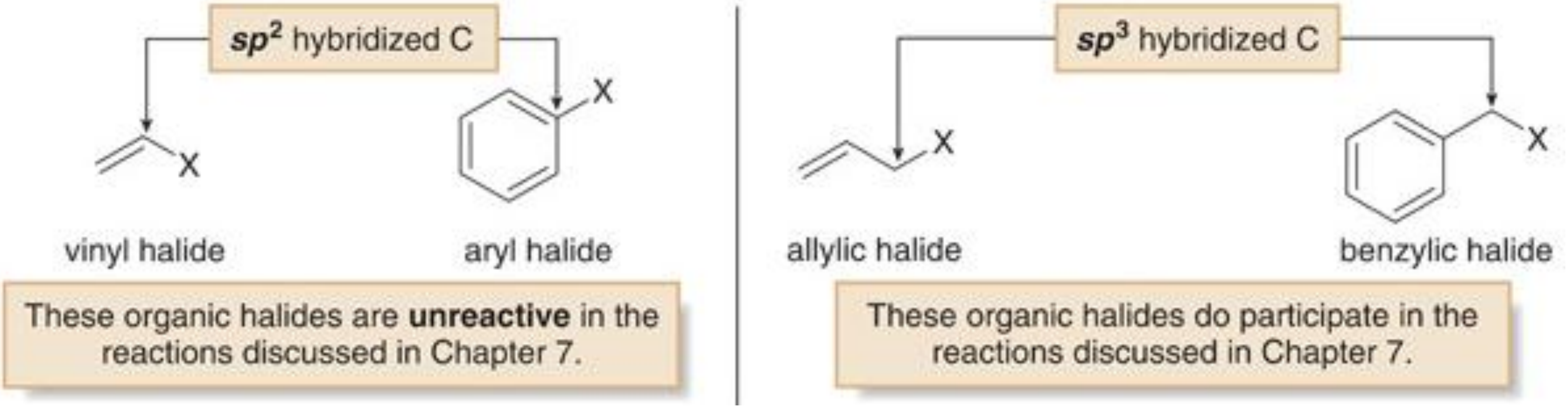
1° iodide

2° bromide

3° chloride

Figure 7.2

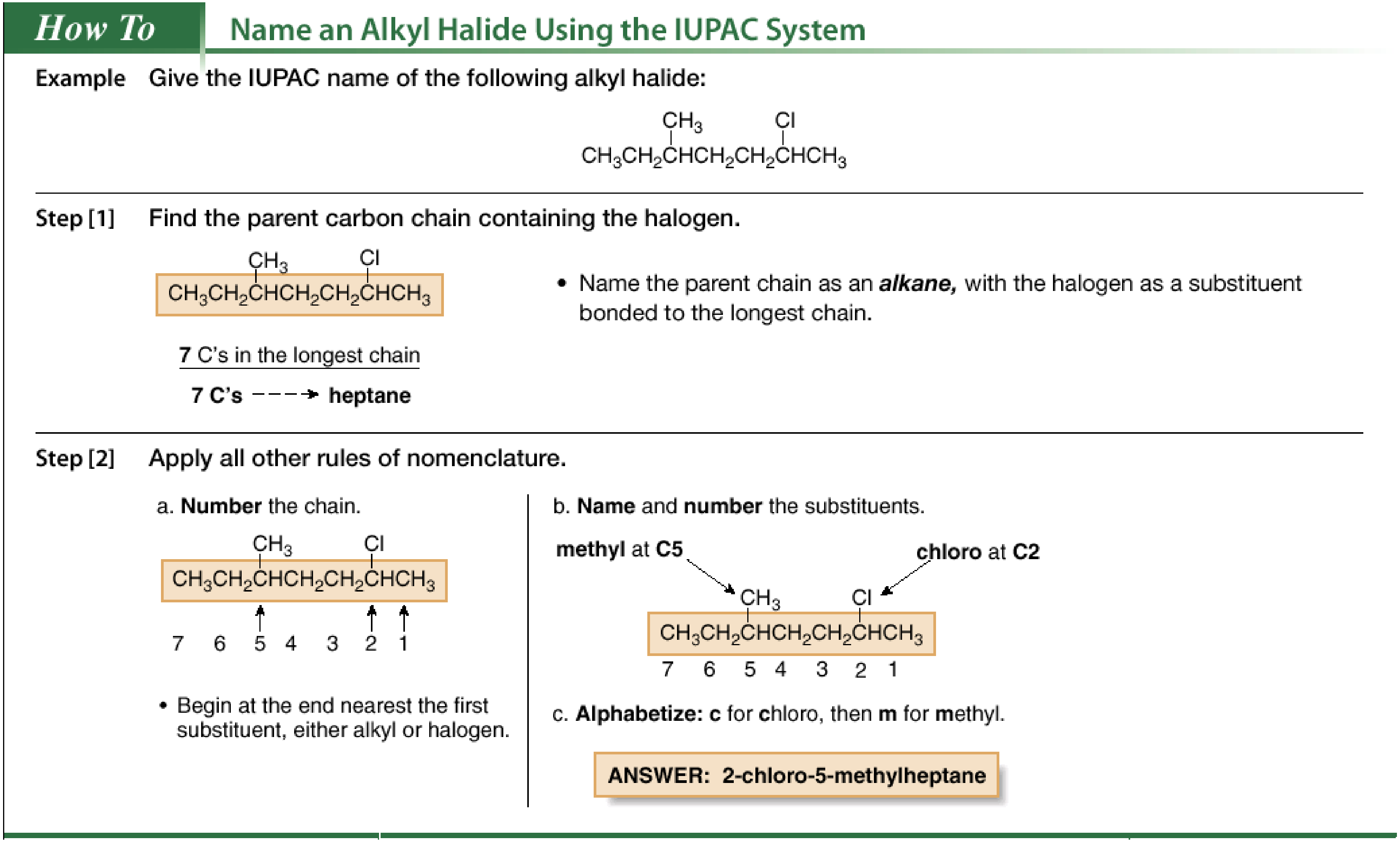
Four types of organic halides (RX) having X near a π bond



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

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

Nomenclature



How To Name an Alkyl Halide Using the IUPAC System

Example Give the IUPAC name of the following alkyl halide:

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

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

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

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.

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

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**

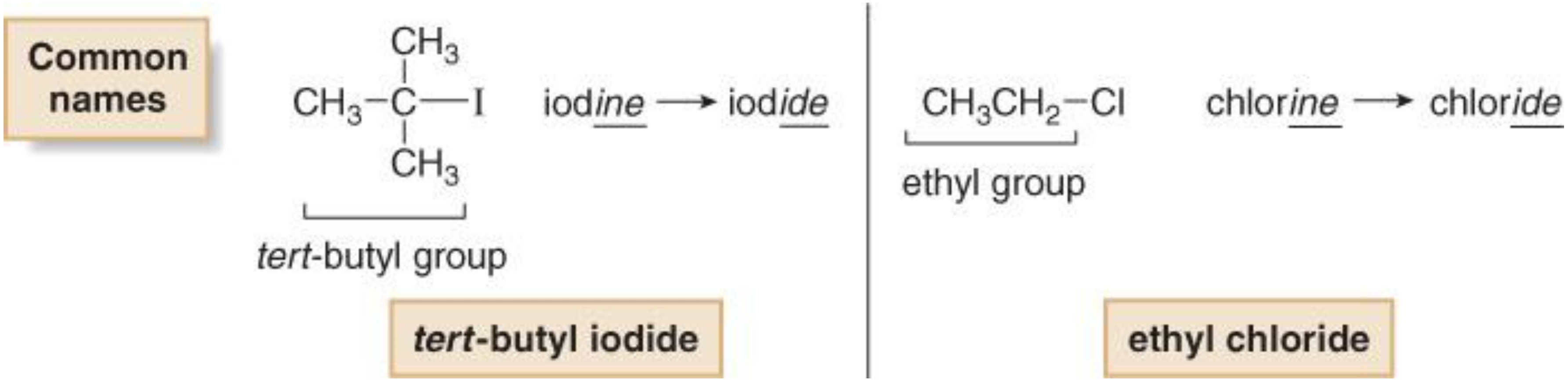
$$\boxed{CH_3CH_2\overset{CH_3}{\overset{|}{C}}HCH_2CH_2\overset{Cl}{\overset{|}{C}}HCH_3}$$

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 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.**



Physical Properties

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

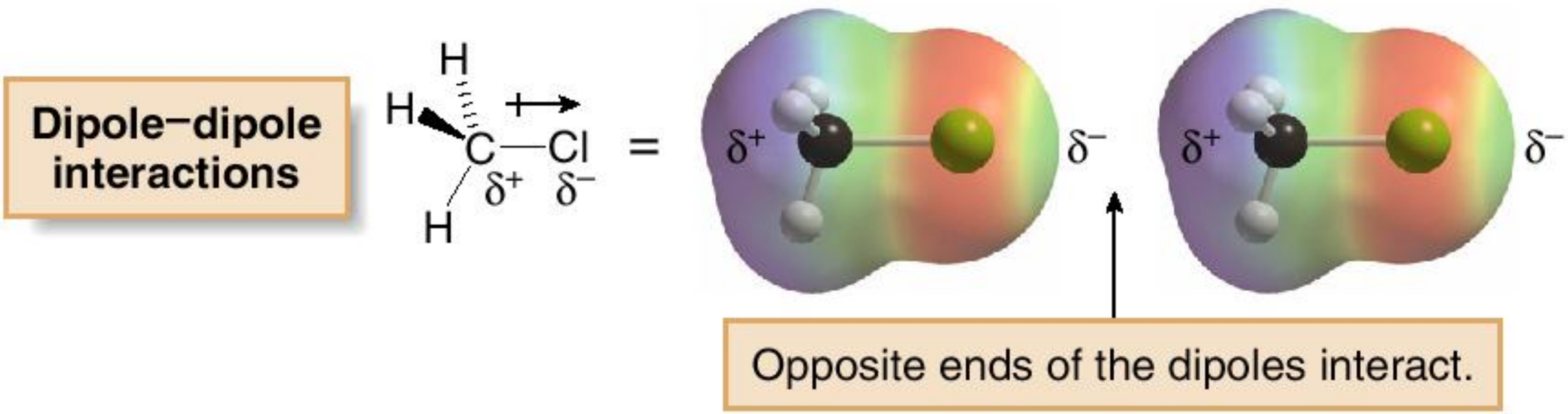


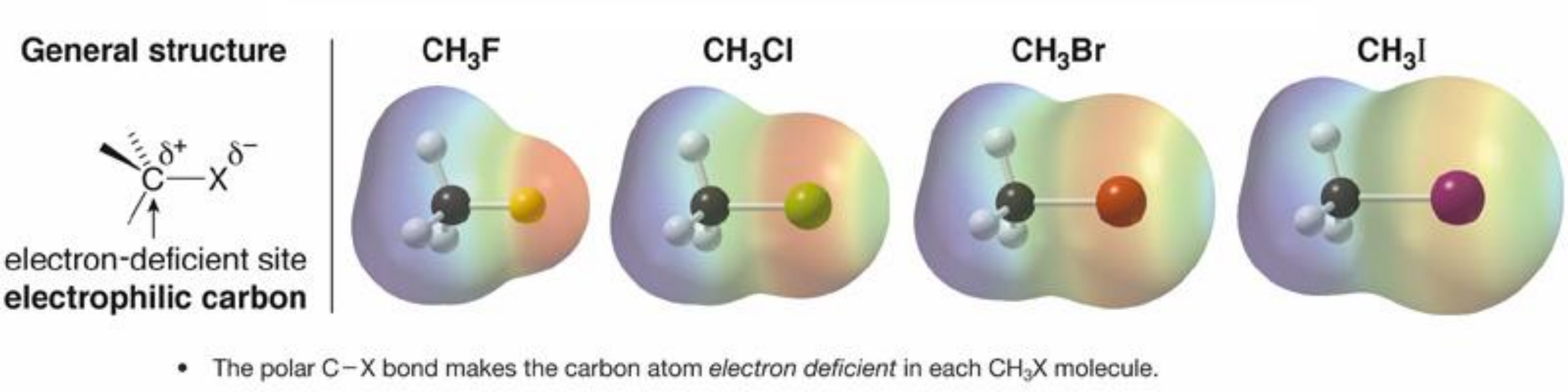
Table 7.1 Physical Properties of Alkyl Halides

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

The Polar Carbon-Halogen Bond

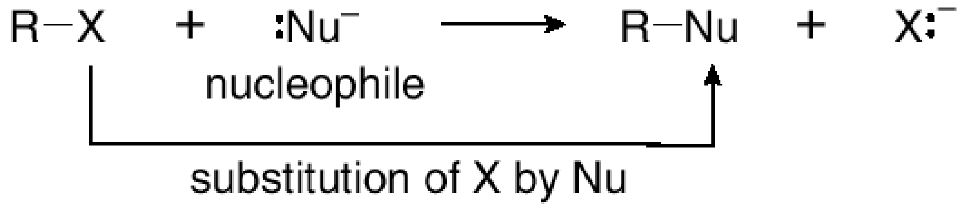
- The electronegative halogen atom in alkyl halides creates a polar C—X bond, making the carbon atom electron deficient. Electrostatic potential maps of four simple alkyl halides illustrate this point.

Figure 7.5
Electrostatic potential maps of four halomethanes (CH_3X)

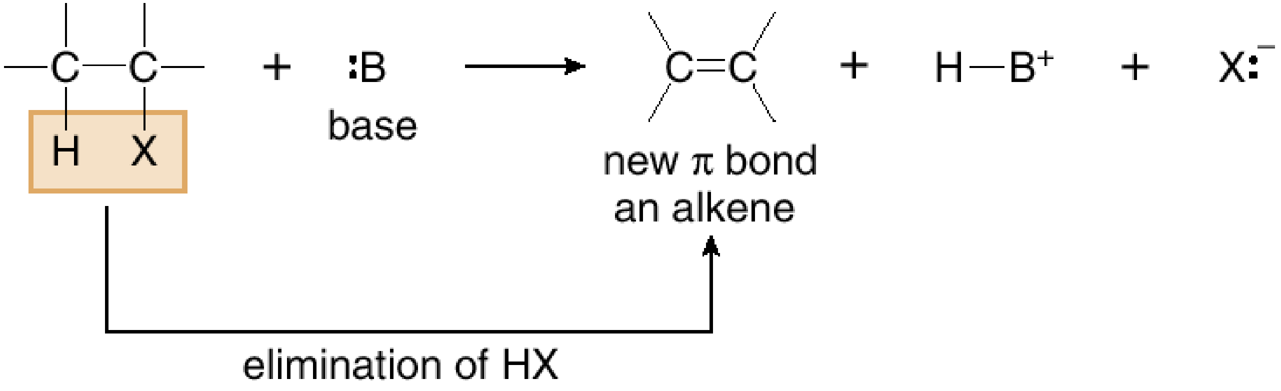


- The polar C−X bond makes the carbon atom *electron deficient* in each CH_3X molecule.

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

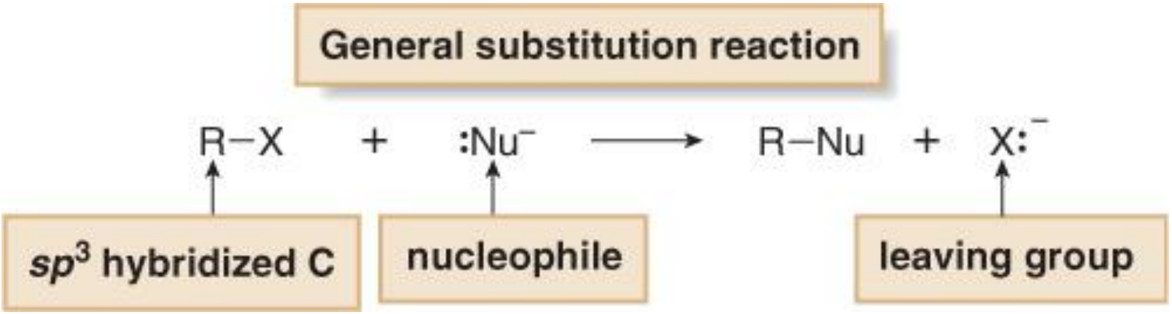


- **Alkyl halides undergo elimination reactions with Brønsted–Lowry bases.**



General Features of Nucleophilic Substitution

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



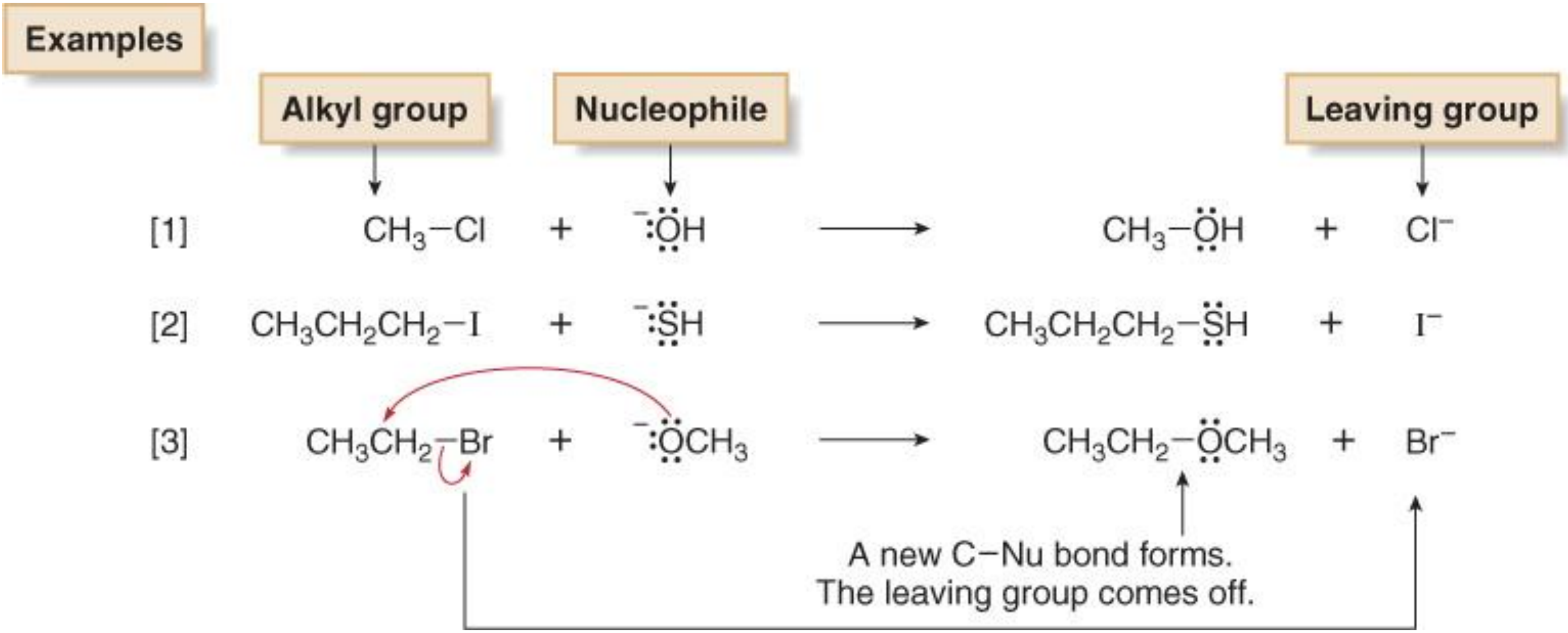
General substitution reaction

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

sp^3 **hybridized C**

nucleophile

leaving group



Examples

Alkyl group

Nucleophile

Leaving group

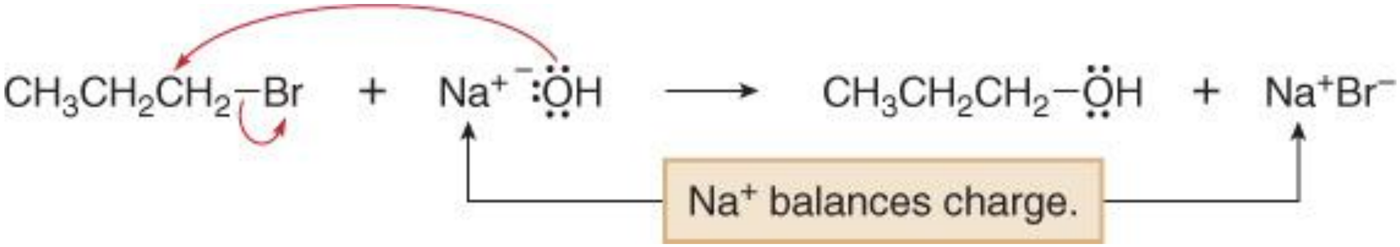
[1] $CH_3{-}Cl + {}^-{:}\ddot{\underset{..}{O}}H \longrightarrow CH_3{-}\ddot{\underset{..}{O}}H + Cl^-$

[2] $CH_3CH_2CH_2{-}I + {}^-{:}\ddot{\underset{..}{S}}H \longrightarrow CH_3CH_2CH_2{-}\ddot{\underset{..}{S}}H + I^-$

[3] $CH_3CH_2{-}Br + {}^-{:}\ddot{\underset{..}{O}}CH_3 \longrightarrow CH_3CH_2{-}\ddot{\underset{..}{O}}CH_3 + Br^-$

A new C−Nu bond forms.
The leaving group comes off.

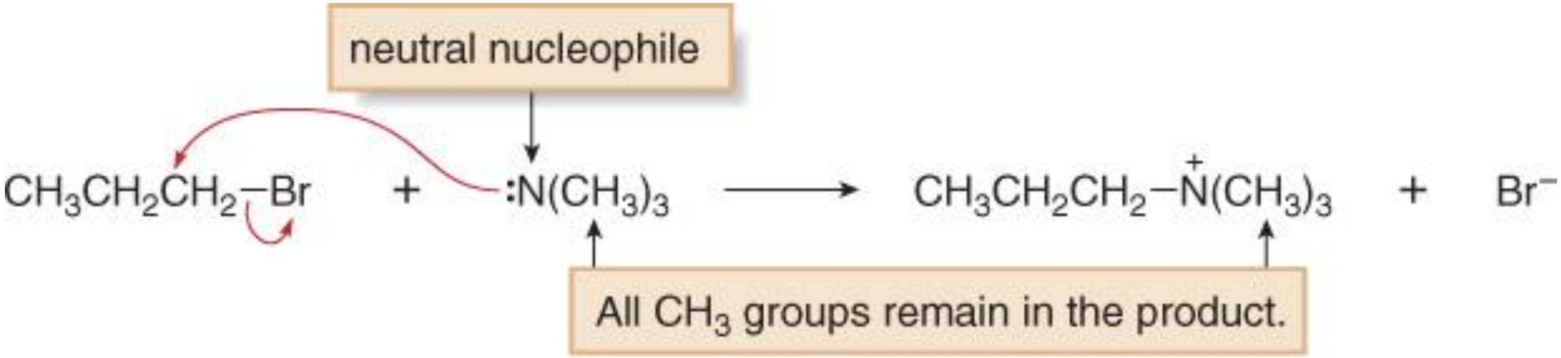
- **Negatively charged nucleophiles like HO^- and HS^- are used as salts with Li^+, Na^+, or K^+ counterions to balance the charge. Since the identity of the counterion is usually inconsequential, it is often omitted from the chemical equation.**



Na^+ balances charge.

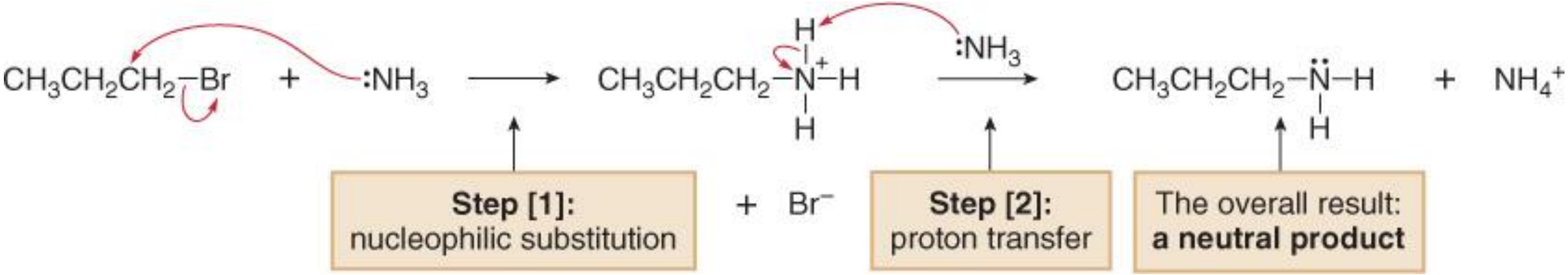
- **When a neutral nucleophile is used, the substitution product bears a positive charge.**

neutral nucleophile



All CH_3 groups remain in the product.

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

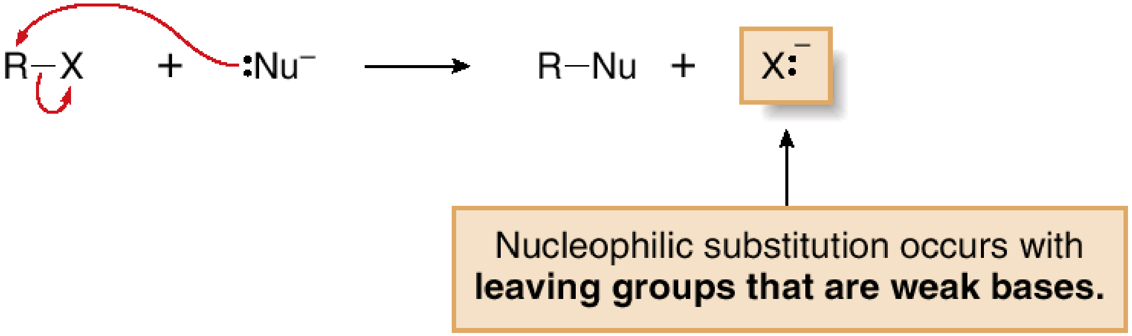


- **To draw any nucleophilic substitution product:**
  - **Find the *sp*^{3} hybridized carbon with the leaving group.**
  - **Identify the nucleophile, the species with a lone pair or π bond.**
  - **Substitute the nucleophile for the leaving group and assign charges (if necessary) to any atom that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

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.

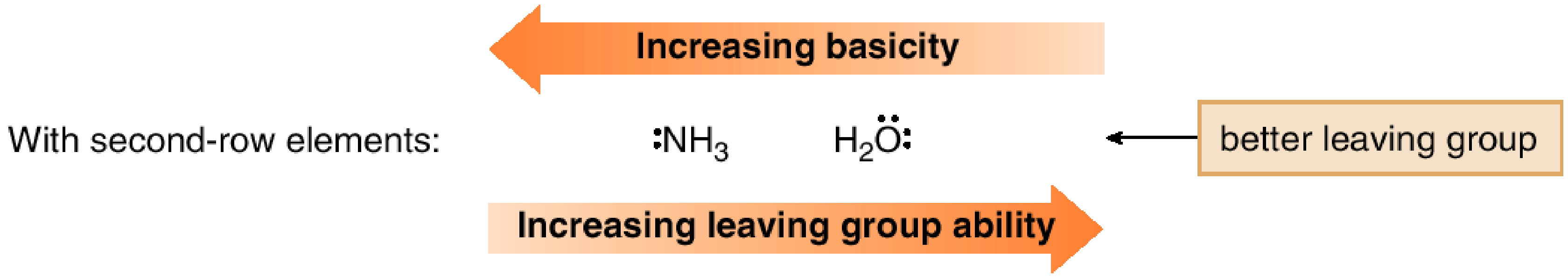


Nucleophilic substitution occurs with **leaving groups that are weak bases.**

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

- **There are periodic trends in leaving group ability:**

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



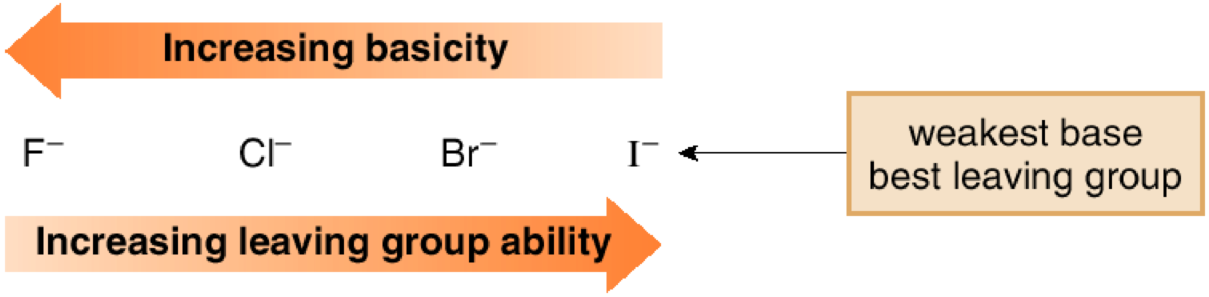
Increasing basicity

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

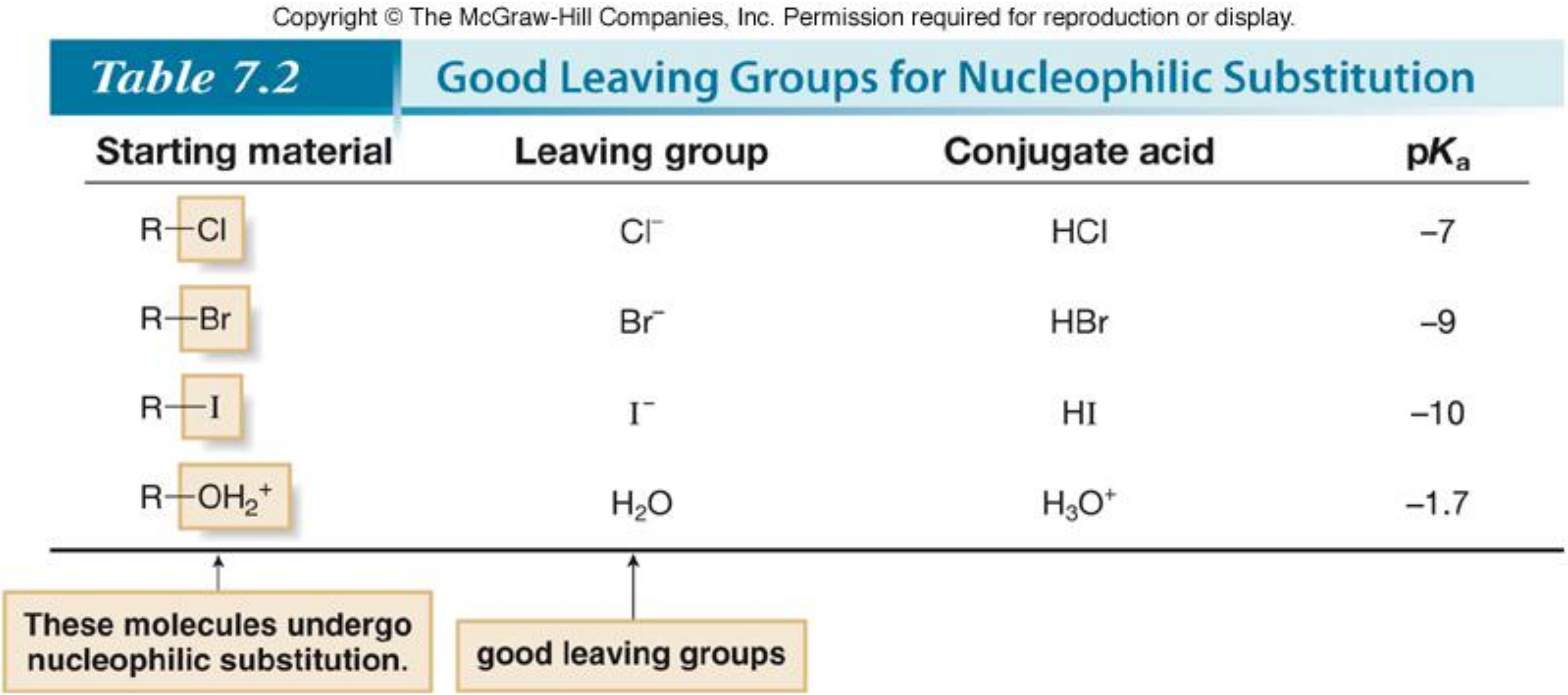


Table 7.2 Good Leaving Groups for Nucleophilic Substitution

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

These molecules undergo nucleophilic substitution.

good leaving groups

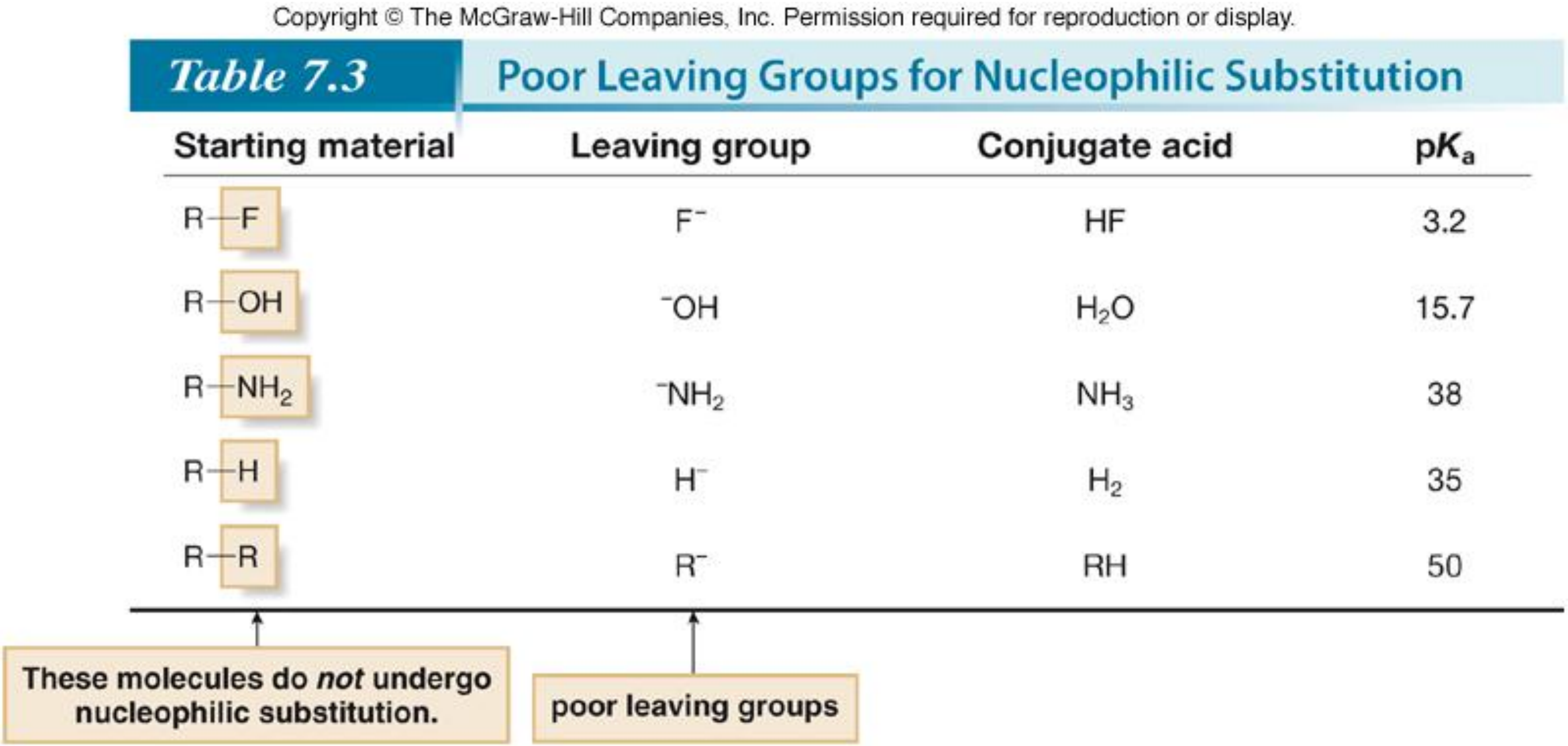


Table 7.3 Poor Leaving Groups for Nucleophilic Substitution

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

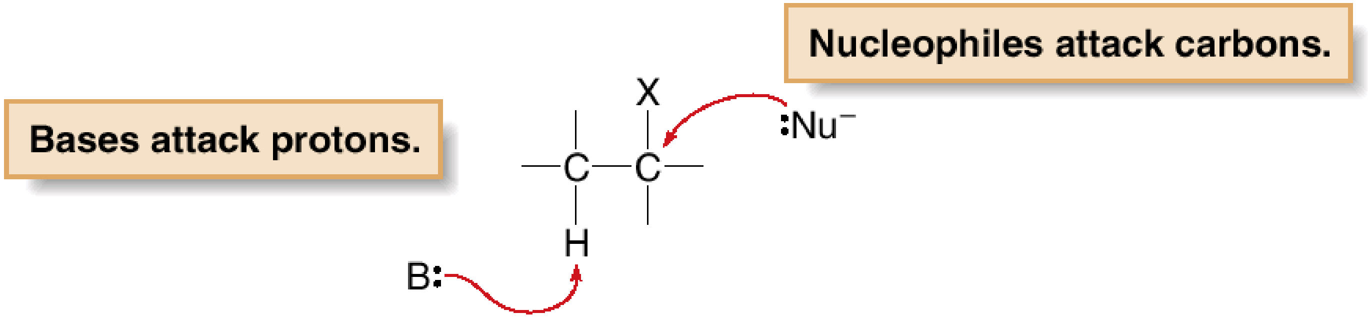
These molecules do *not* undergo nucleophilic substitution.

poor leaving groups

The Nucleophile

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

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



- **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 in three instances:**

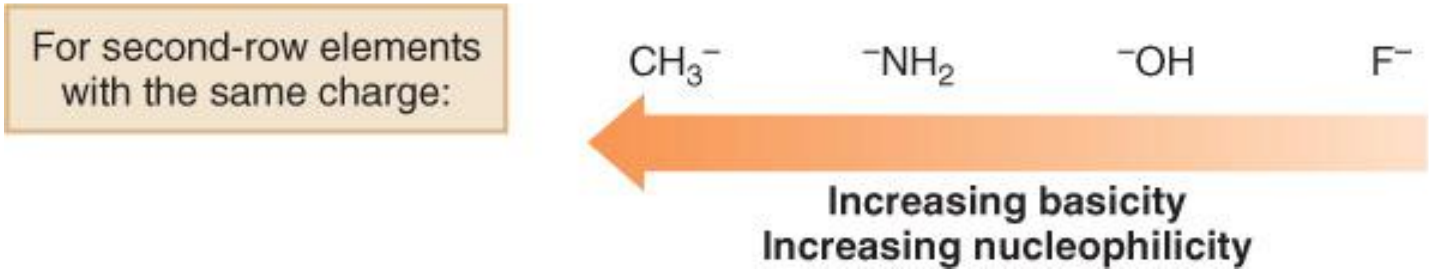
1. **For two nucleophiles with the same nucleophilic atom, the stronger base is the stronger nucleophile.**

   The relative nucleophilicity of HO^- and CH_3COO^-, two oxygen nucleophiles, 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^-.

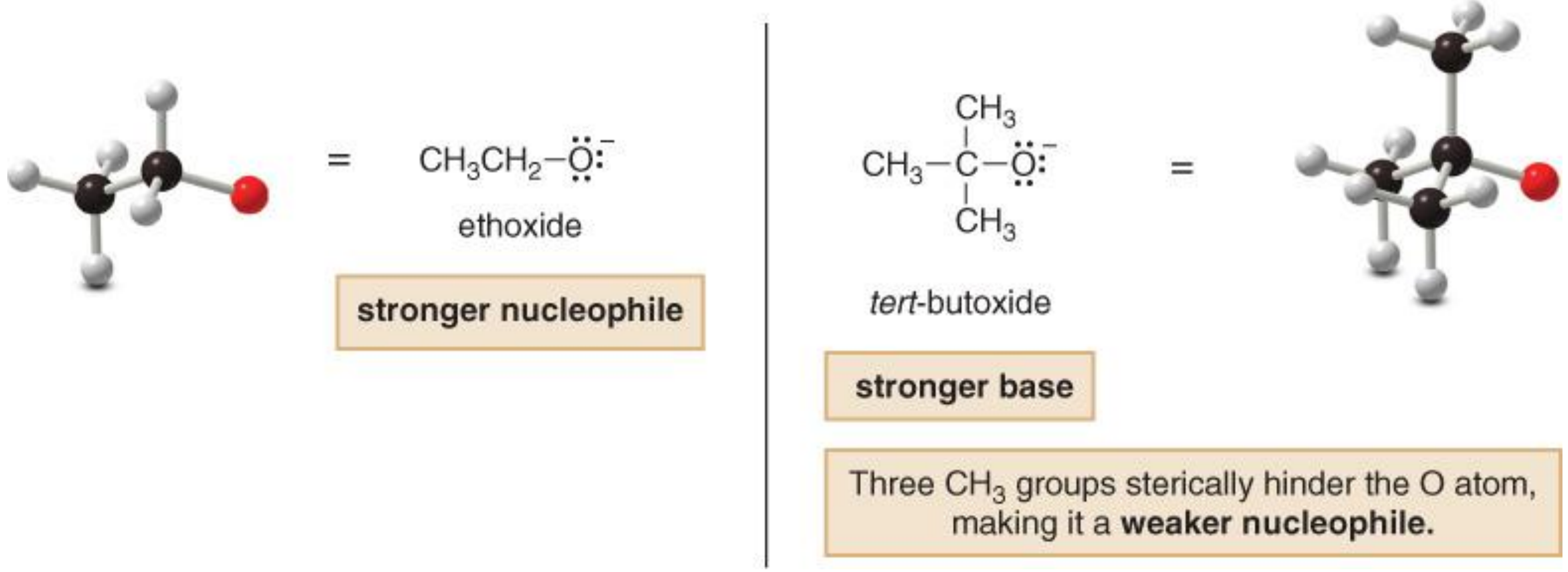
2. **A negatively charged nucleophile is always a stronger nucleophile than its conjugate acid.**

   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:**

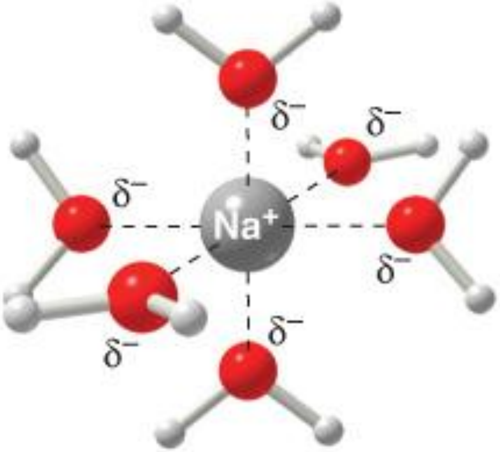


- **Nucleophilicity does not parallel basicity when steric hindrance becomes important.**
- **Steric hindrance is a decrease in reactivity resulting from the presence of bulky groups at the site of a reaction.**
- **Steric hindrance decreases nucleophilicity but not basicity.**
- **Sterically hindered bases that are poor nucleophiles are called nonnucleophilic bases.**

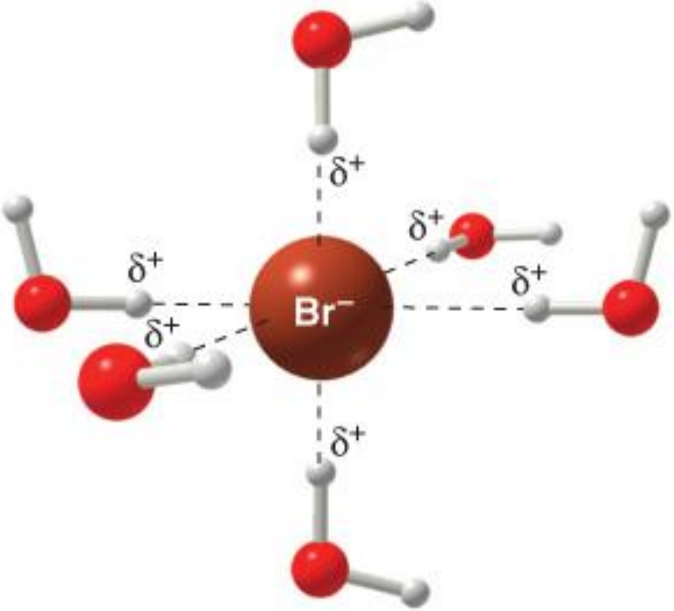


Three CH_3 groups sterically hinder the O atom, making it a **weaker nucleophile.**

- **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, and the Br^- anions are solvated by strong hydrogen bonding interactions.**

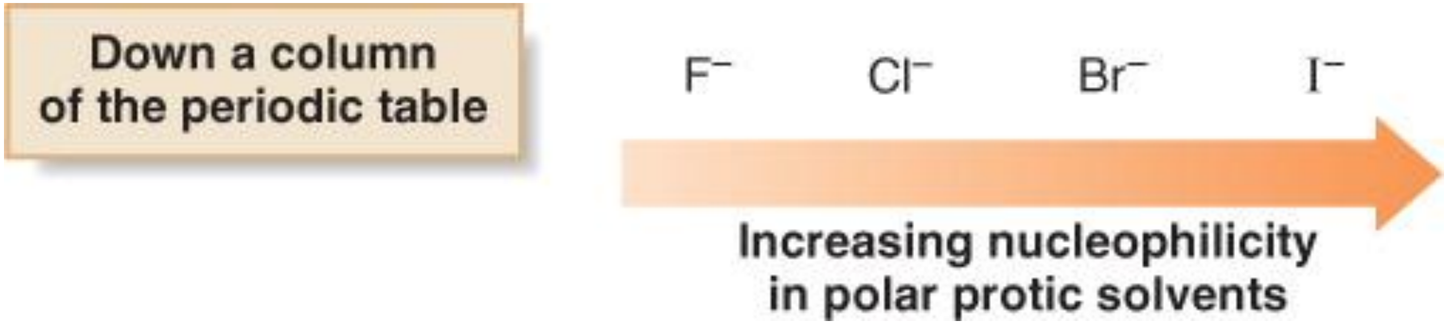


Na^+ is solvated by ion–dipole interactions with H_2O.



Br^- is solvated by hydrogen bonding with H_2O.

- **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.**

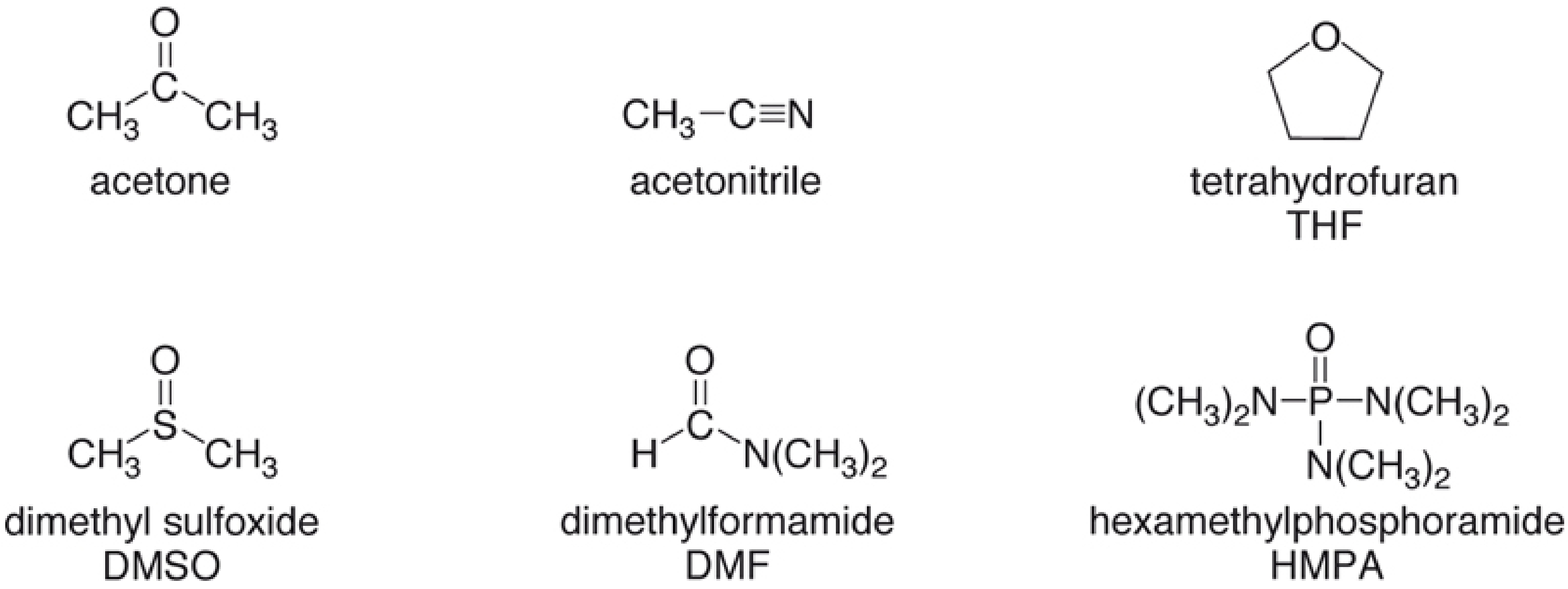


H_2O	CH_3OH	CH_3CH_2OH	$(CH_3)_3COH$	CH_3COOH
	methanol	ethanol	*tert*-butanol	acetic acid

Figure 7.6
Example of polar protic solvents

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

Figure 7.7
Examples of polar aprotic solvents



acetone

acetonitrile

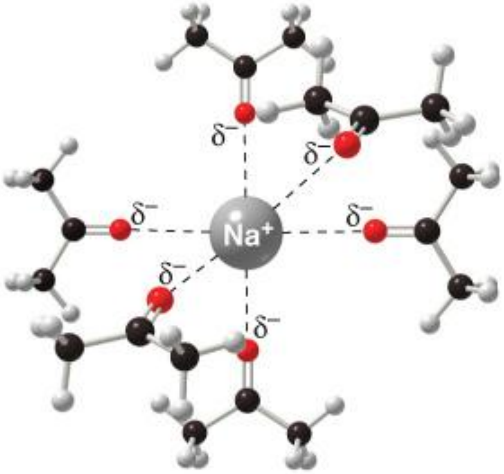
tetrahydrofuran
THF

dimethyl sulfoxide
DMSO

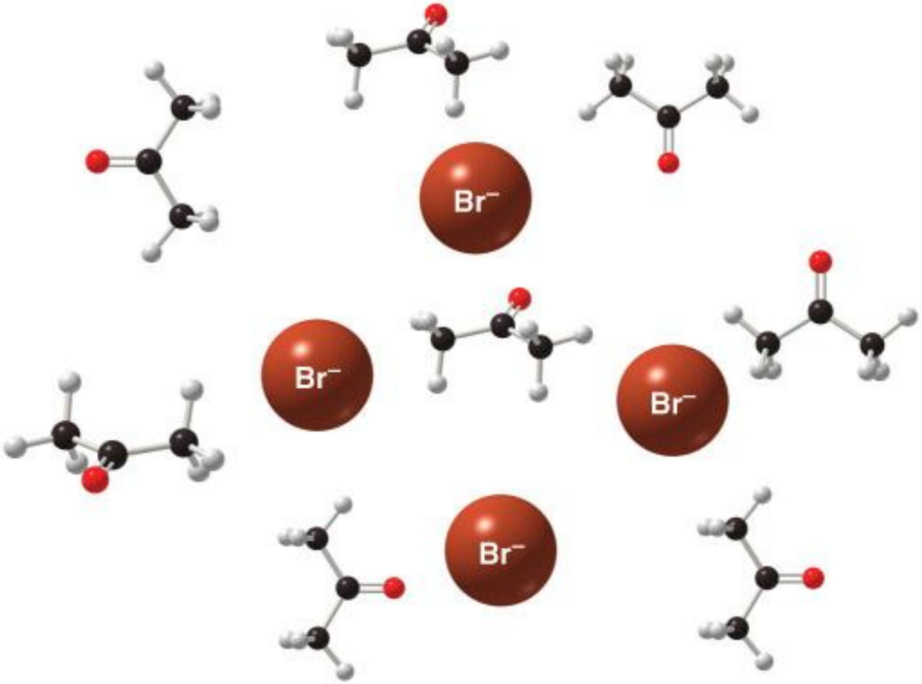
dimethylformamide
DMF

hexamethylphosphoramide
HMPA

- **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”.**

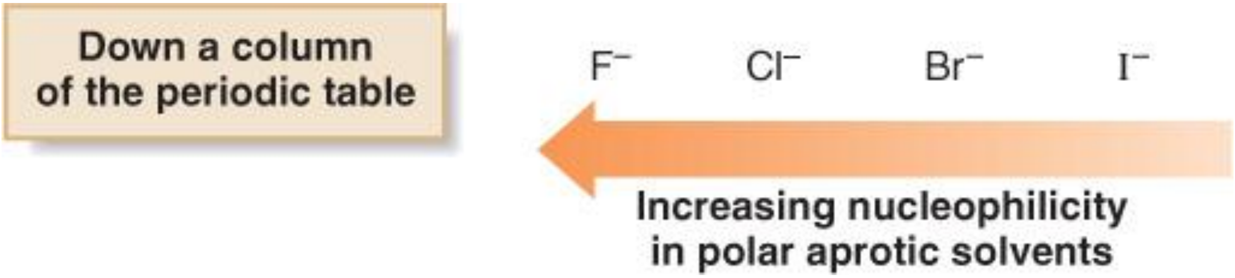


$(CH_3)_2C{=}O$ solvates Na^+ well by ion–dipole interactions.



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

- 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.



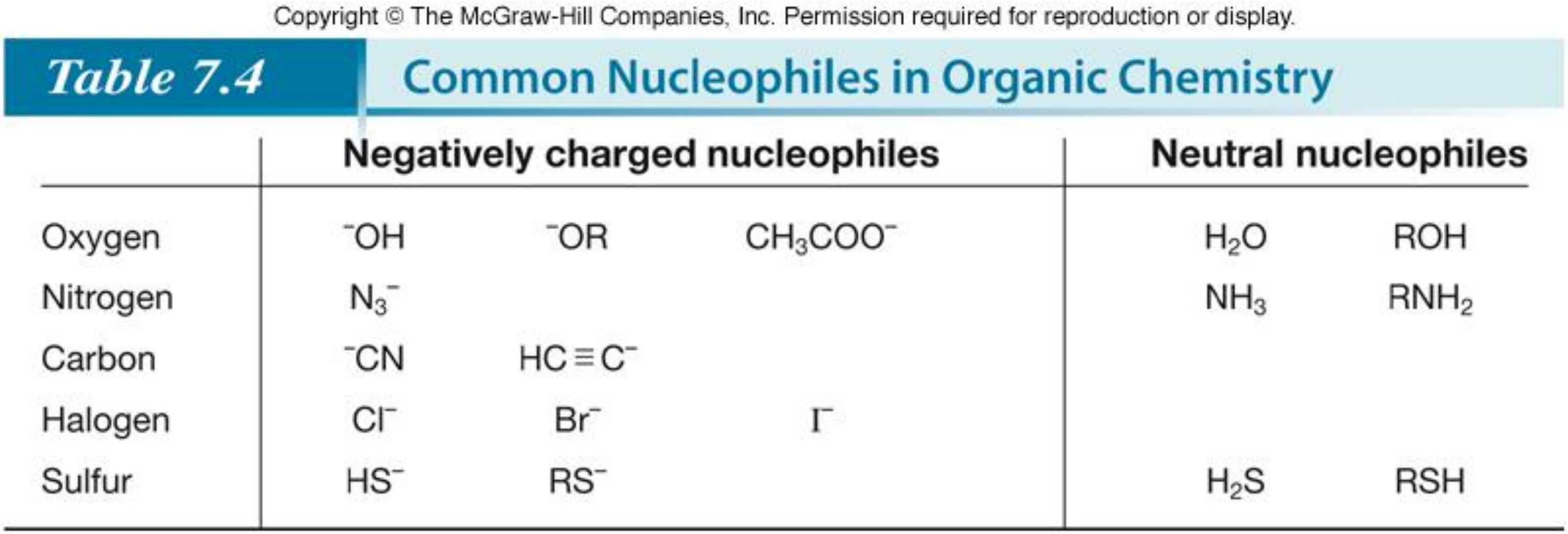
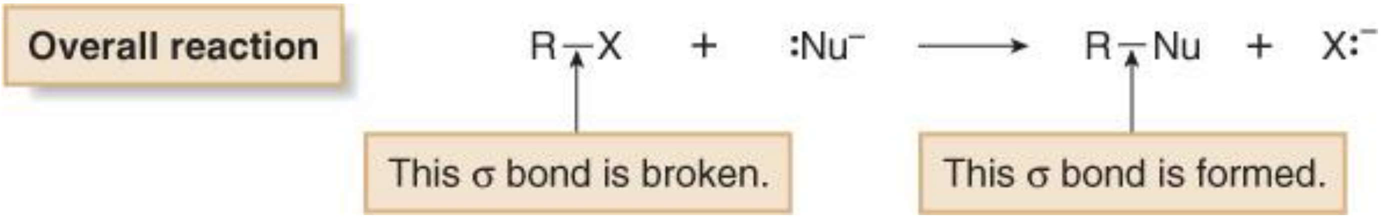


Table 7.4 Common Nucleophiles in Organic Chemistry

	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

Mechanisms of Nucleophilic Substitution

In a nucleophilic substitution:



Overall reaction

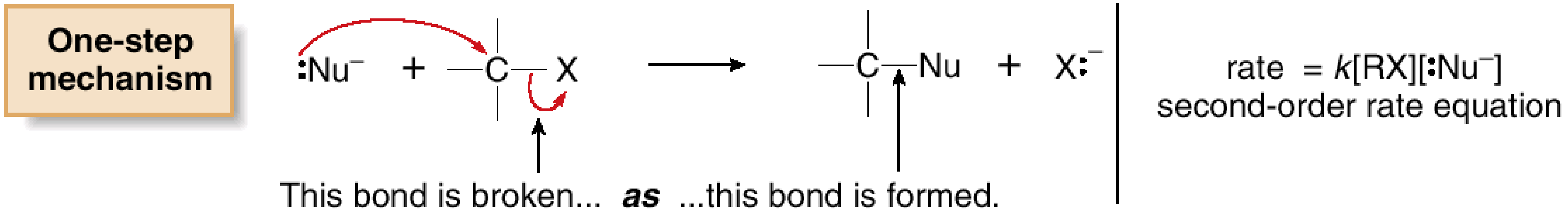
$R-X + :Nu^- \longrightarrow R-Nu + X:^-$

This σ bond is broken.

This σ bond is formed.

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

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



One-step mechanism

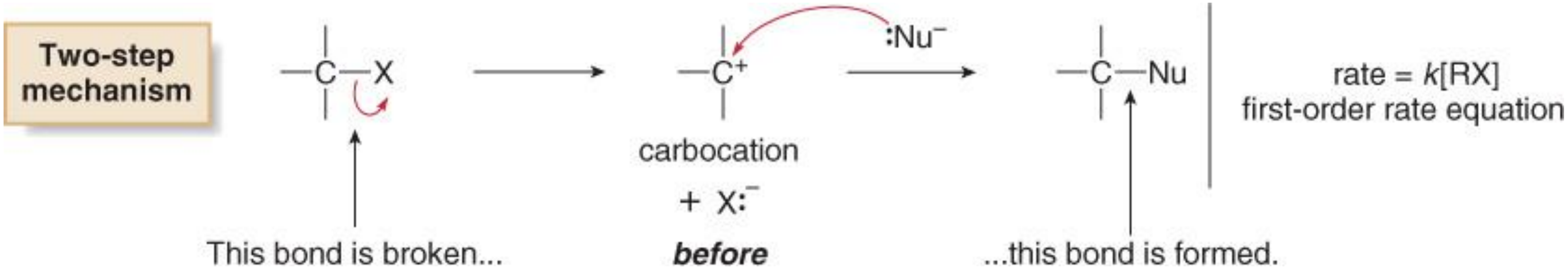
$:Nu^- + -C-X \longrightarrow -C-Nu + X:^-$

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

rate = k[RX][:Nu⁻]
second-order rate equation

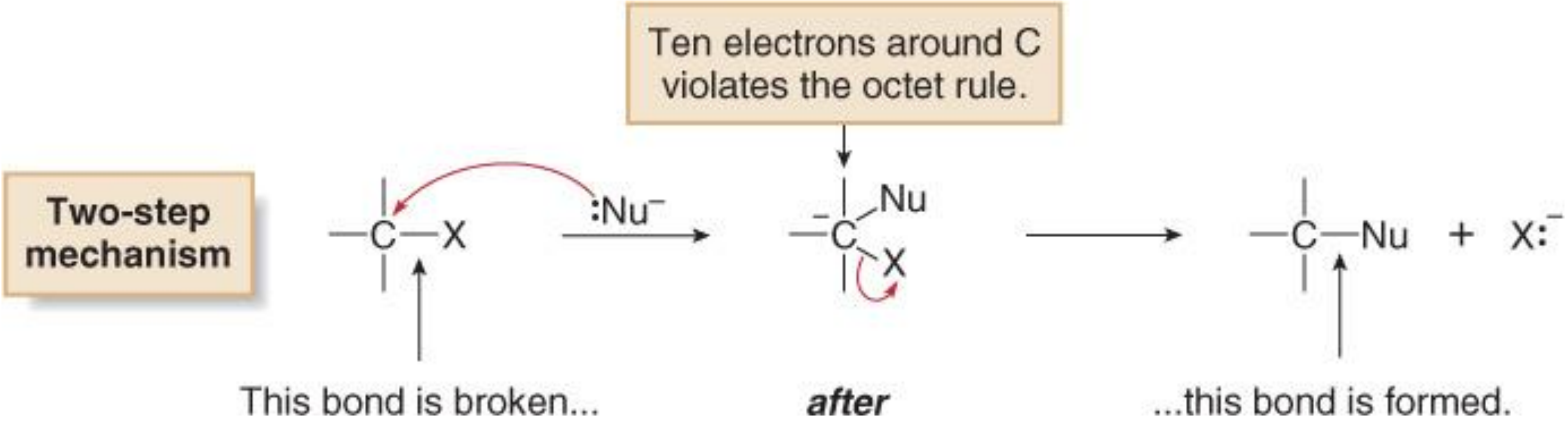
In this scenario, the mechanism is comprised of one step. In such a bimolecular reaction, the rate depends upon the concentration of both reactants, that is, the rate equation is second order.

[2] Bond breaking occurs before bond making.



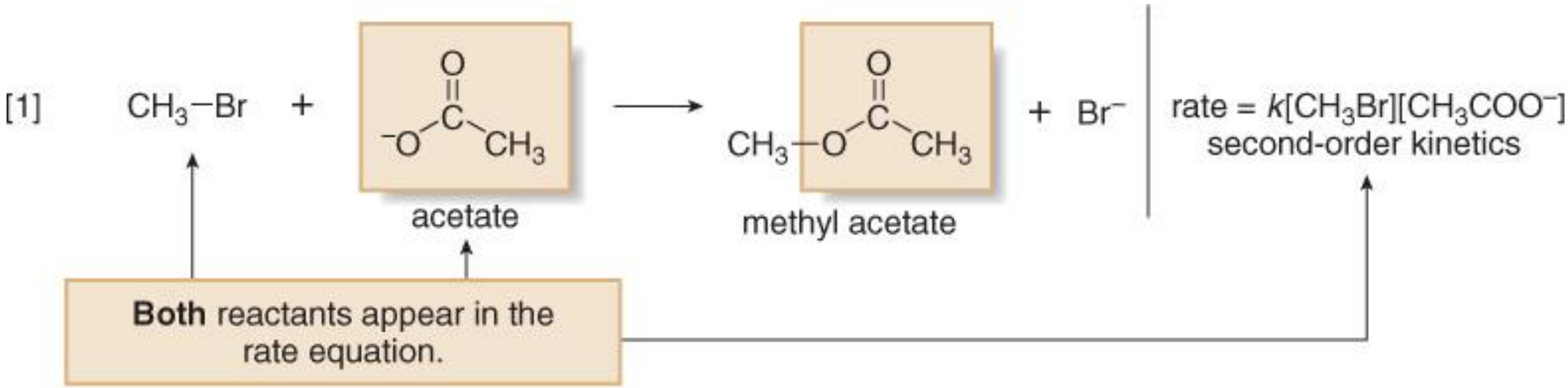
In this scenario, the mechanism has two steps and a carbocation is formed as an intermediate. Because the first step is rate-determining, the rate depends on the concentration of RX only; that is, the rate equation is first order.

[3] Bond making occurs before bond breaking.



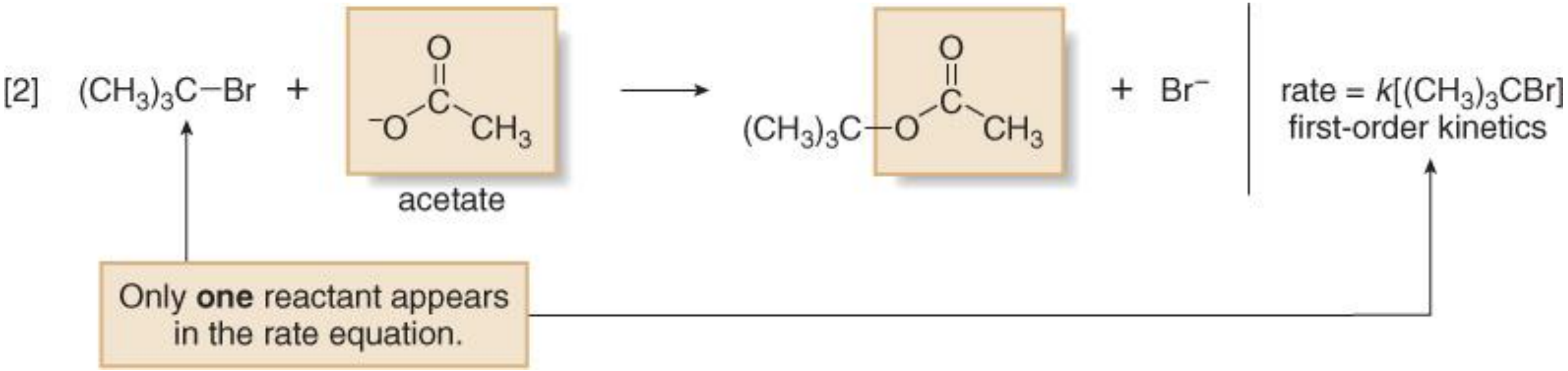
This mechanism has an inherent problem. The intermediate generated in the first step has 10 electrons around carbon, violating the octet rule. Because two other mechanistic possibilities do not violate a fundamental rule, this last possibility can be disregarded.

Consider reaction [1] below:



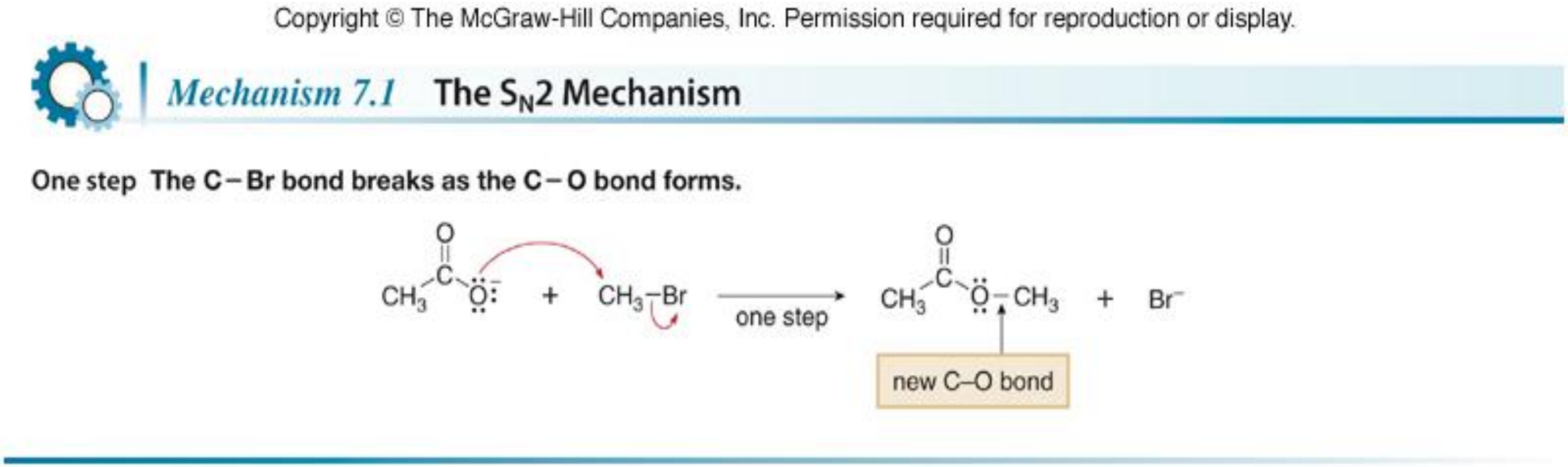
Kinetic data show that the rate of reaction [1] depends on the concentration of both reactants, which suggests a bimolecular reaction with a one-step mechanism. This is an example of an S_N2 (substitution nucleophilic bimolecular) mechanism.

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 (substitution nucleophilic unimolecular) mechanism.

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



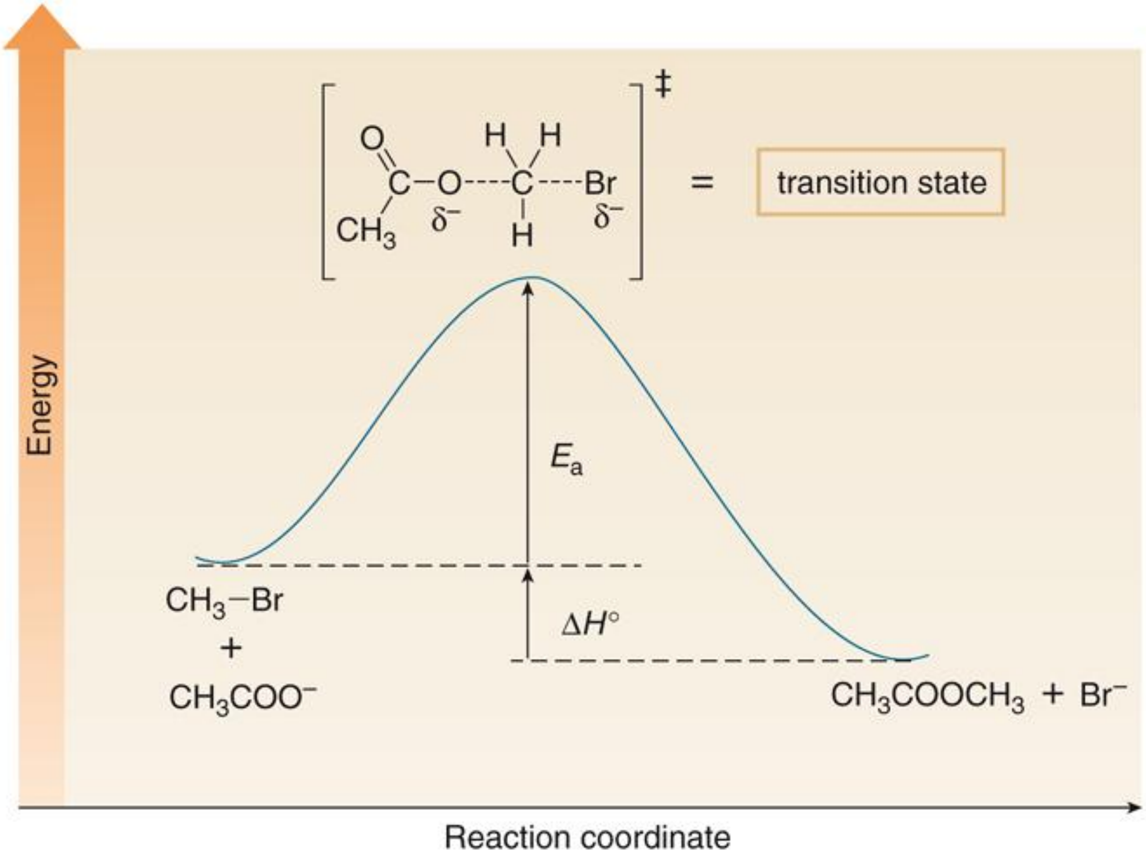
Mechanism 7.1 The S_N2 Mechanism

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

Figure.8

An energy diagram for the S_N2 reaction:

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

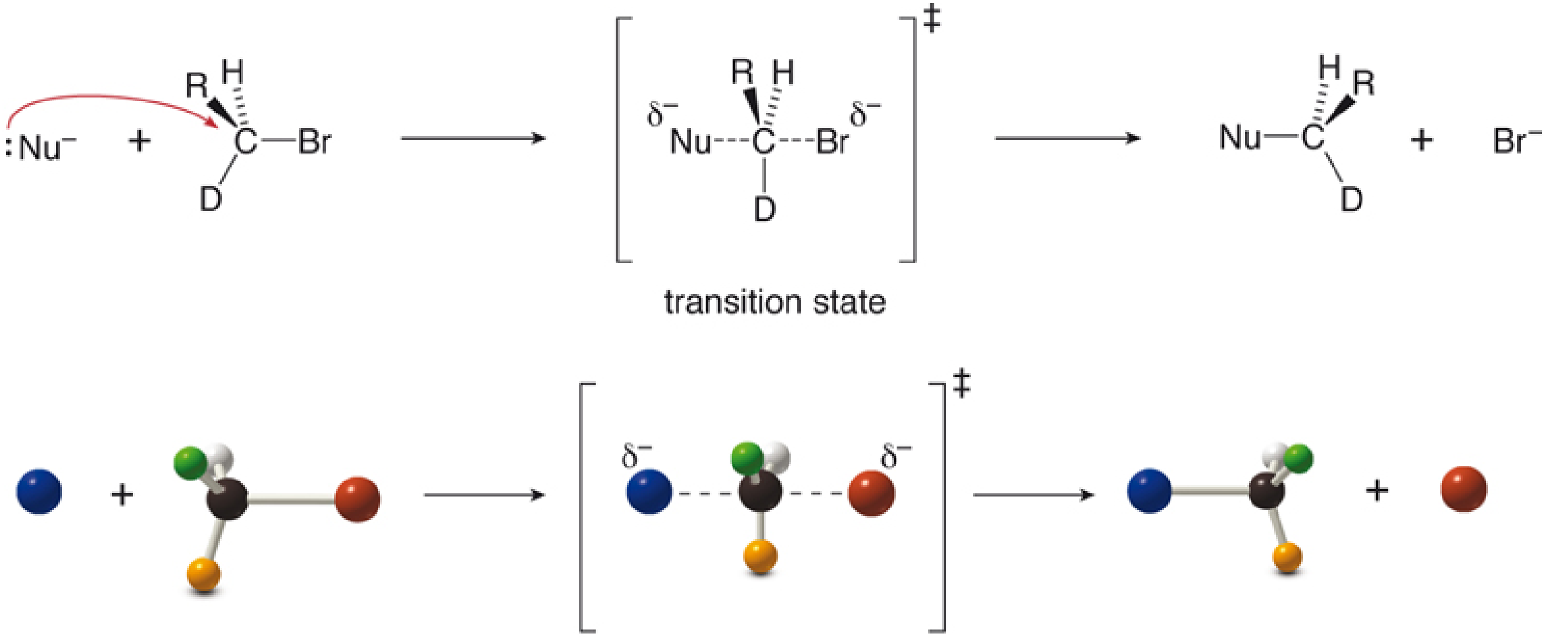


- In the transition state, the C–Br bond is partially broken, the C–O bond is partially formed, and both the attacking nucleophile and the departing leaving group bear a partial negative charge.

Stereochemistry

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

Figure 9
Stereochemistry of the S_N2 reaction

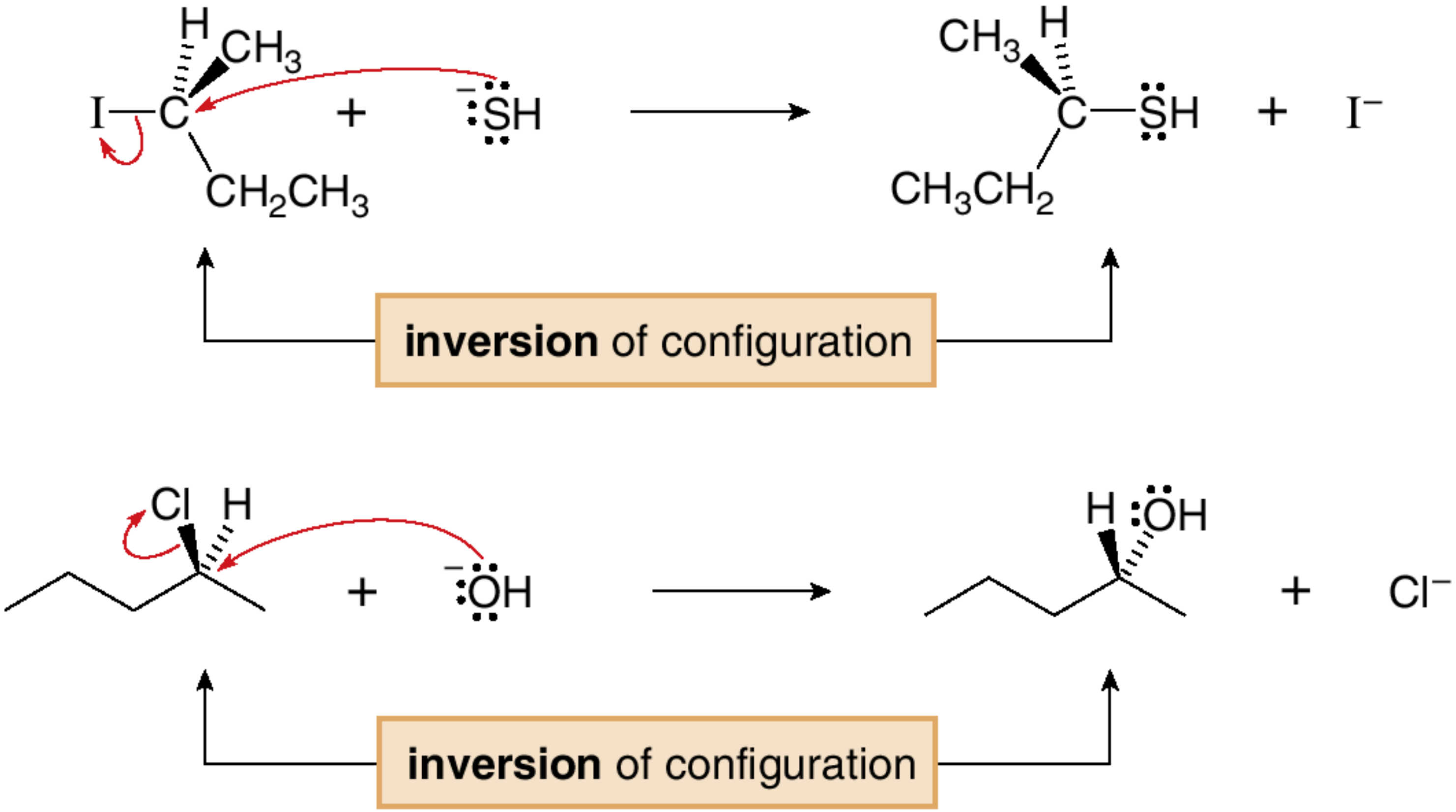


:Nu⁻ and Br⁻ are 180Υaway from each other, on either side of a plane containing R, H, and D.

Figure 10

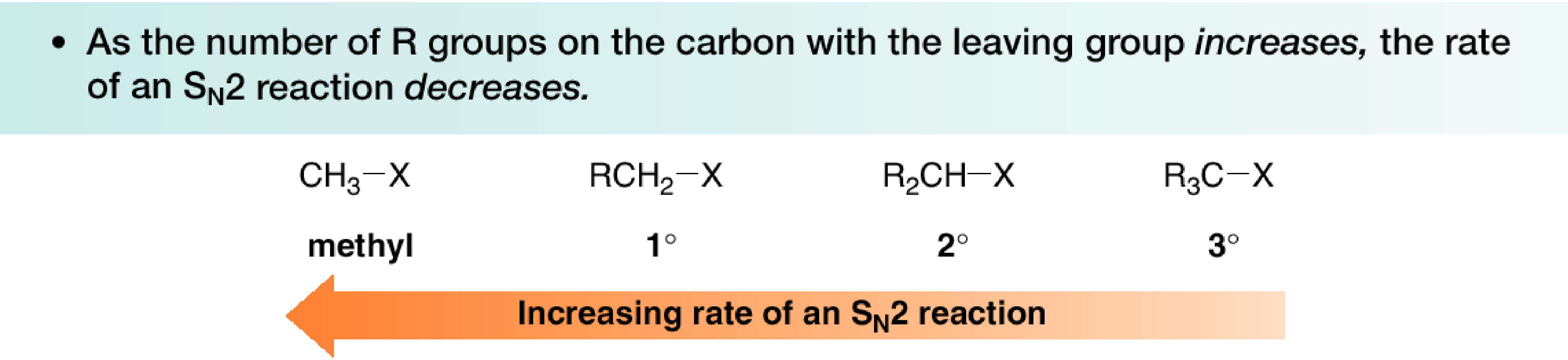
Two examples of inversion of configuration in the S_N2 reaction

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



inversion of configuration

inversion of configuration



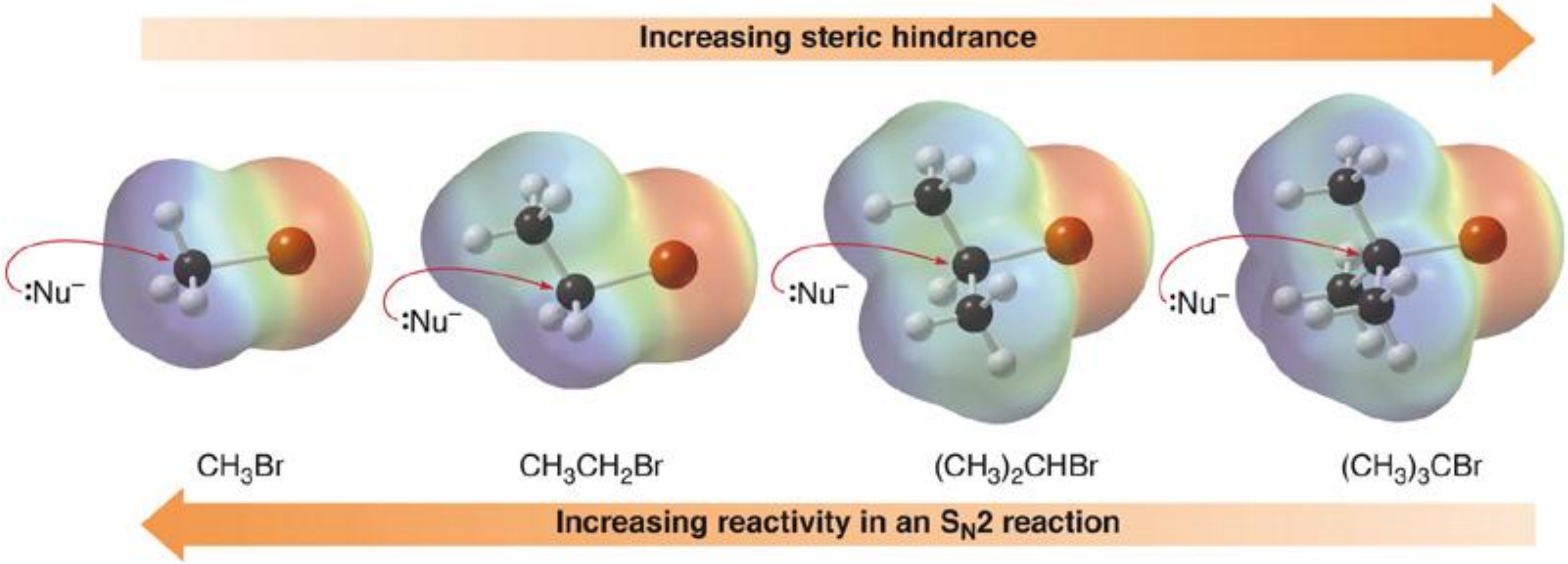
- As the number of R groups on the carbon with the leaving group *increases*, the rate of an S_N2 reaction *decreases.*

- **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. This order of reactivity can be explained by steric effects. Steric hindrance caused by bulky R groups makes nucleophilic attack from the backside more difficult, slowing the reaction rate.**

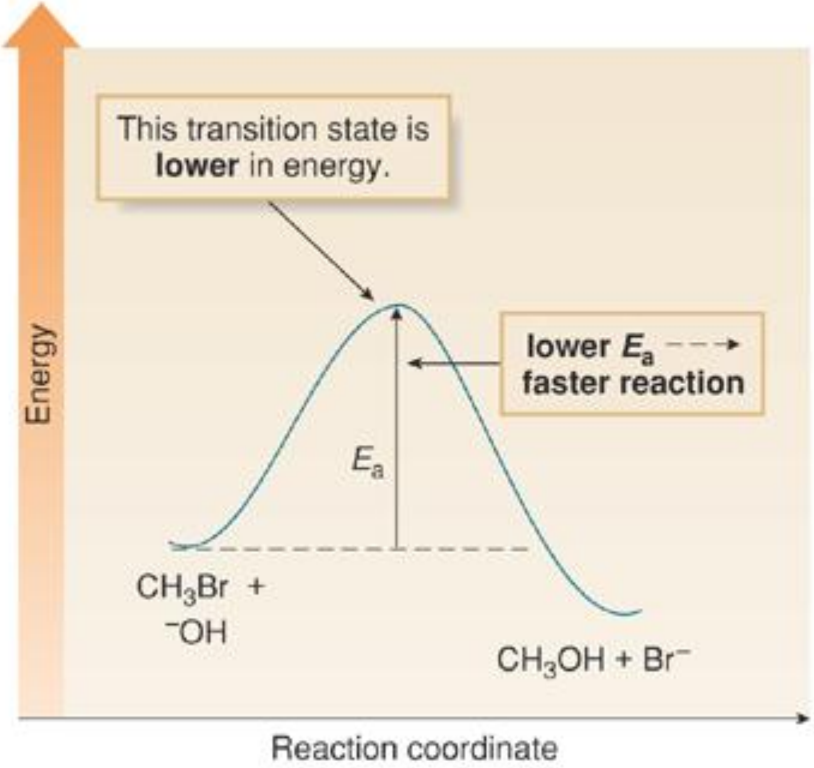
Electrostatic potential maps illustrate the effects of steric hindrance around the carbon bearing the leaving group in a series of alkyl halides.

Figure 7.11

Steric effects in the S_N2 reaction

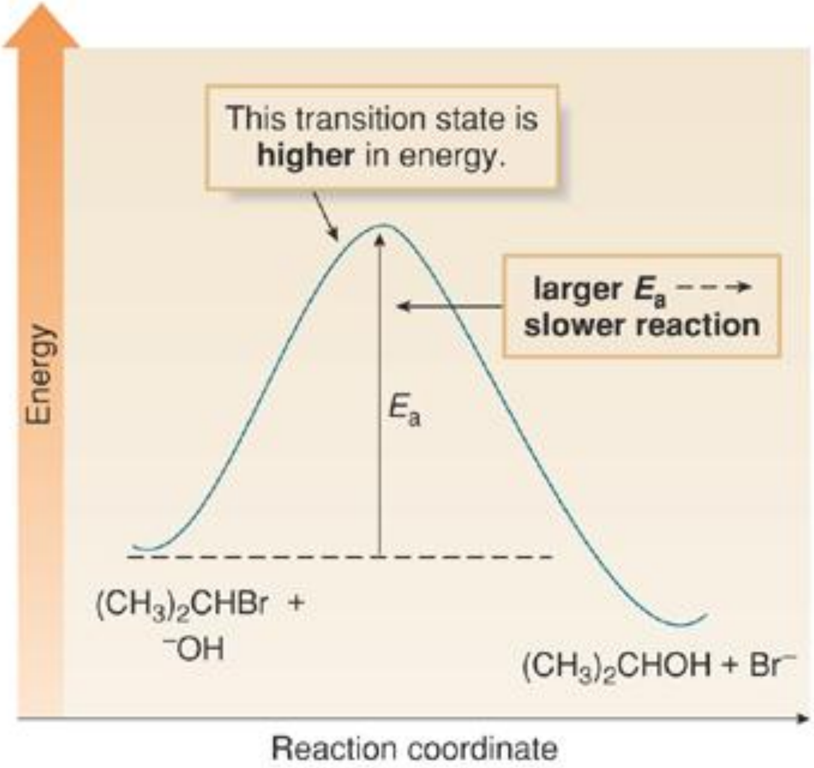


- **The higher the E_a, the slower the reaction rate. Thus, any factor that increases E_a decreases the reaction rate.**



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

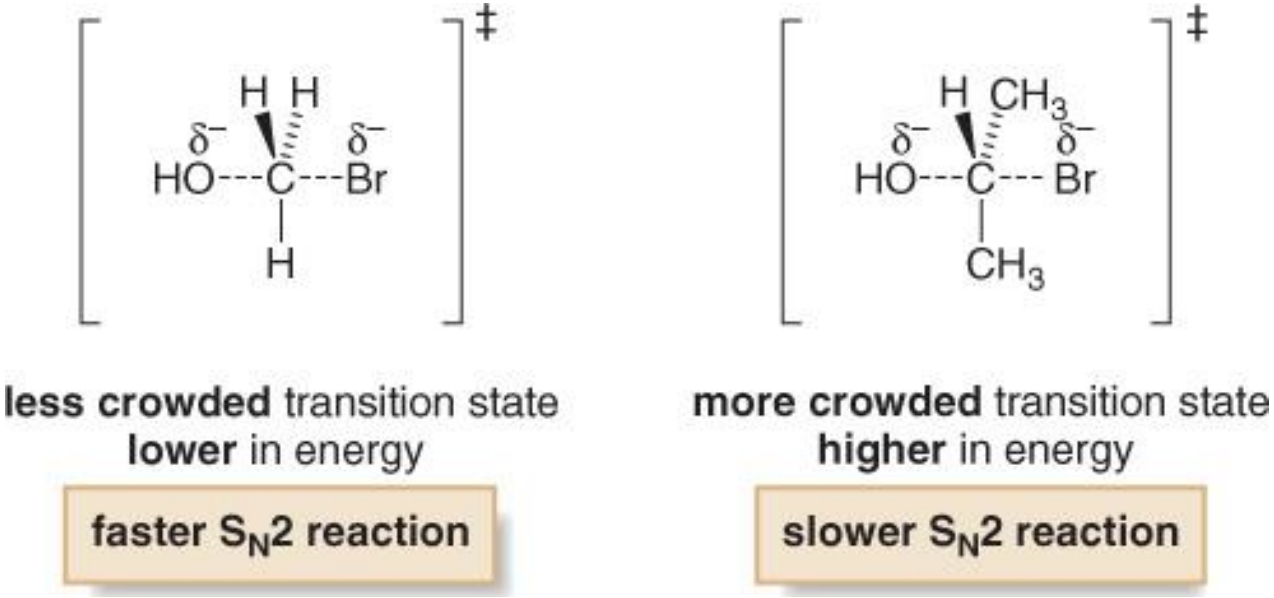
- CH_3Br is an unhindered alkyl halide. The transition state in the S_N2 reaction is lower in energy, making E_a lower and increasing the reaction rate.



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

- $(CH_3)_2CHBr$ 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.

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



less crowded transition state
lower in energy
faster S_N2 reaction

more crowded transition state
higher in energy
slower S_N2 reaction

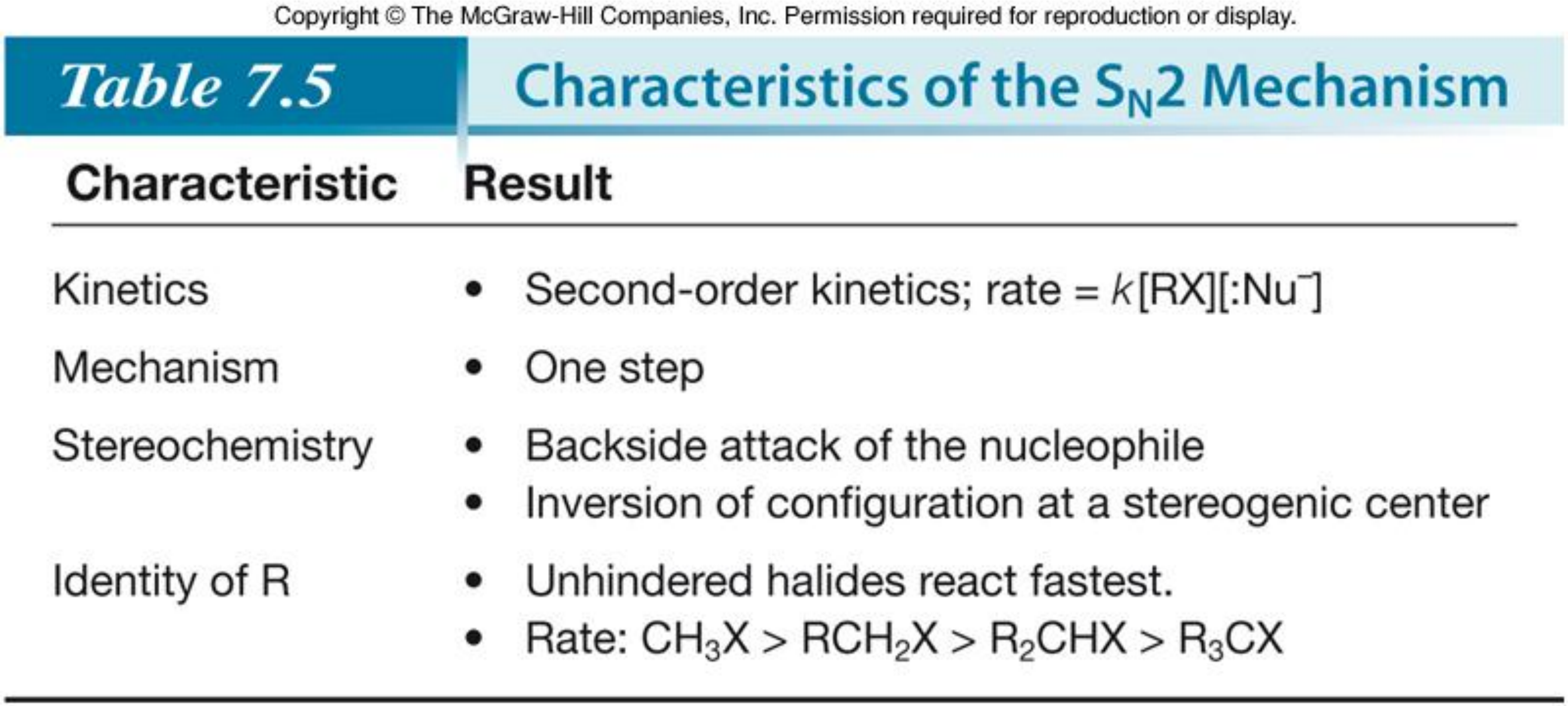
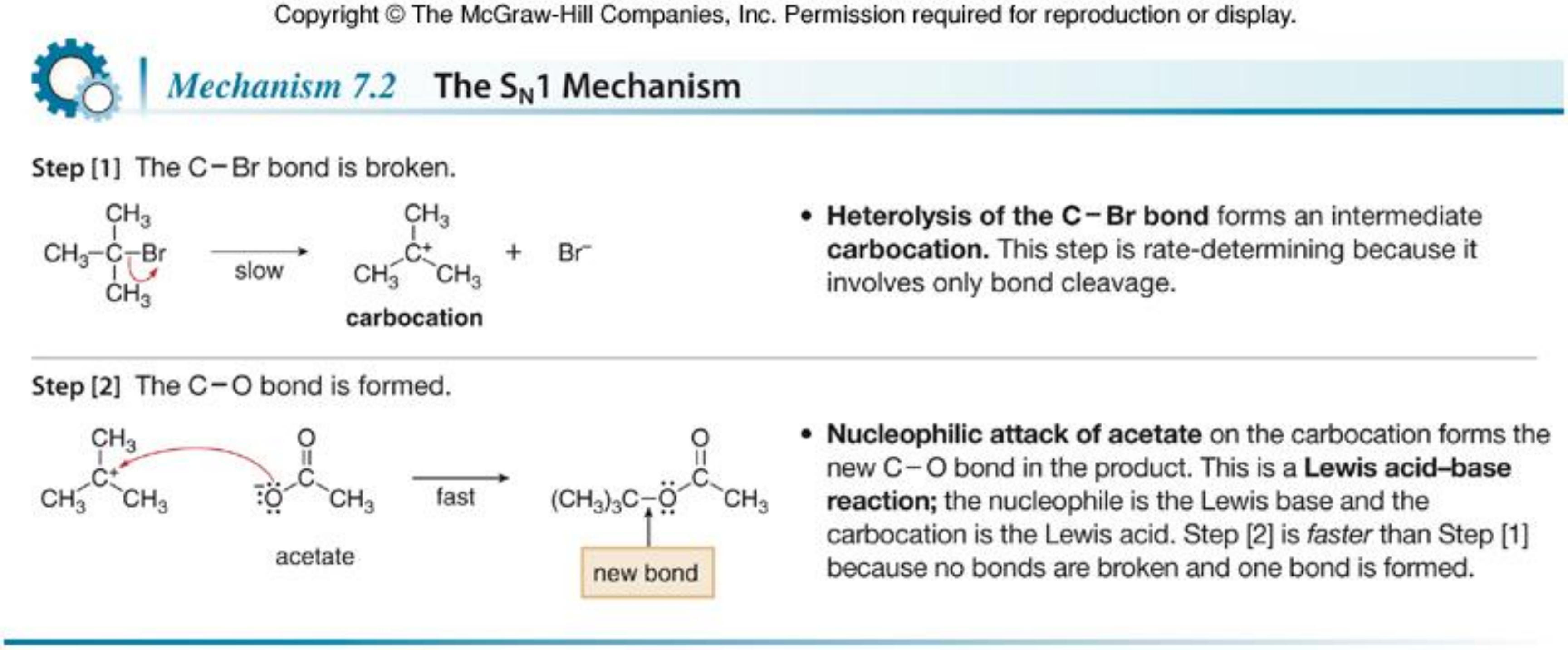


Table 7.5 Characteristics of the S_N2 Mechanism

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 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.

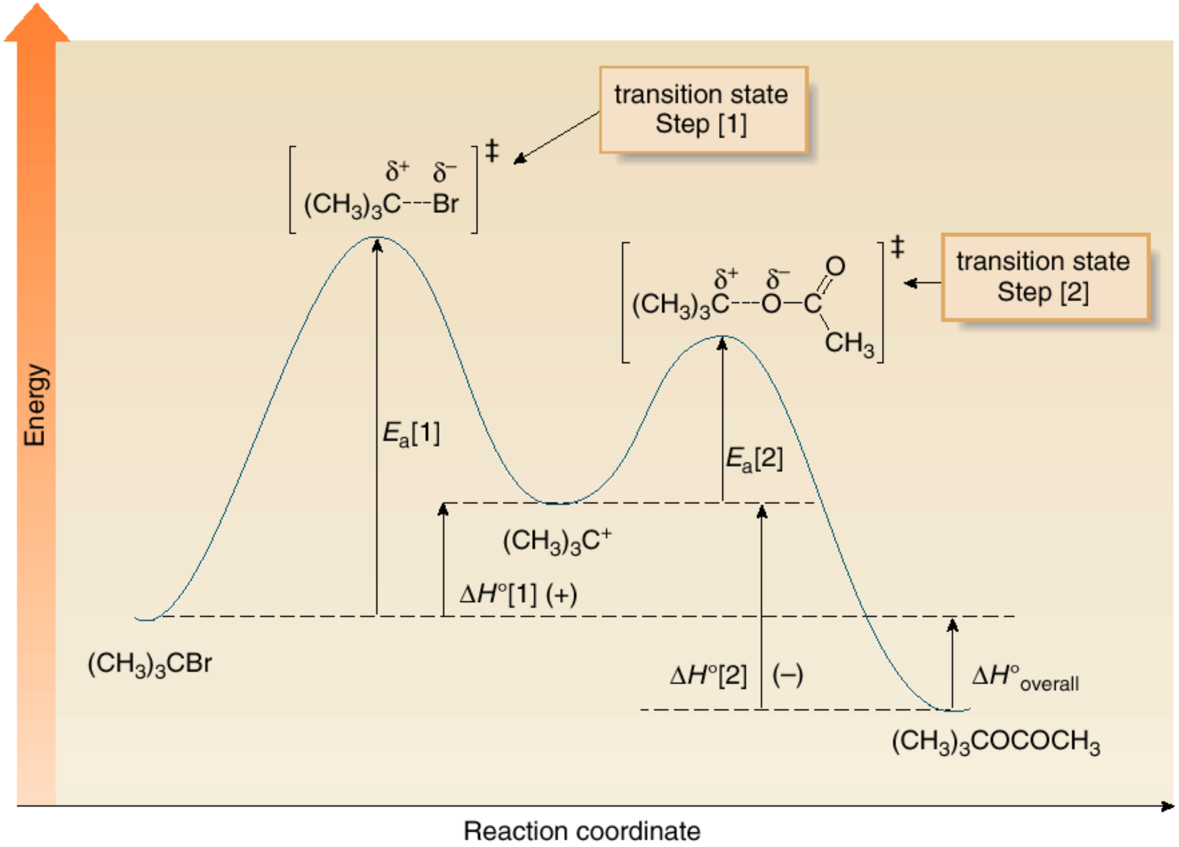
- **Nucleophilic attack of acetate** on the carbocation forms the new C–O bond in the product. This is a **Lewis acid–base reaction;** the nucleophile is the Lewis base and the carbocation is the Lewis acid. Step [2] is *faster* than Step [1] because no bonds are broken and one bond is formed.

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

Figure 7.15

An energy diagram for the S_N1 reaction:

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

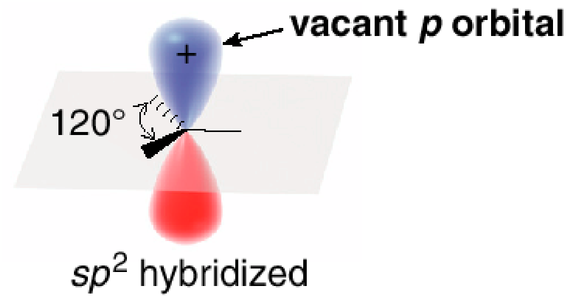


- Since the S_N1 mechanism has two steps, there are two energy barriers.
- $E_a[1] > E_a[2]$ since Step [1] involves bond breaking and Step [2] involves bond formation.
- In each step only one bond is broken or formed, so the transition state for each step has one partial bond.
- The reaction is drawn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

Stereochemistry

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

A trigonal planar carbocation



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

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

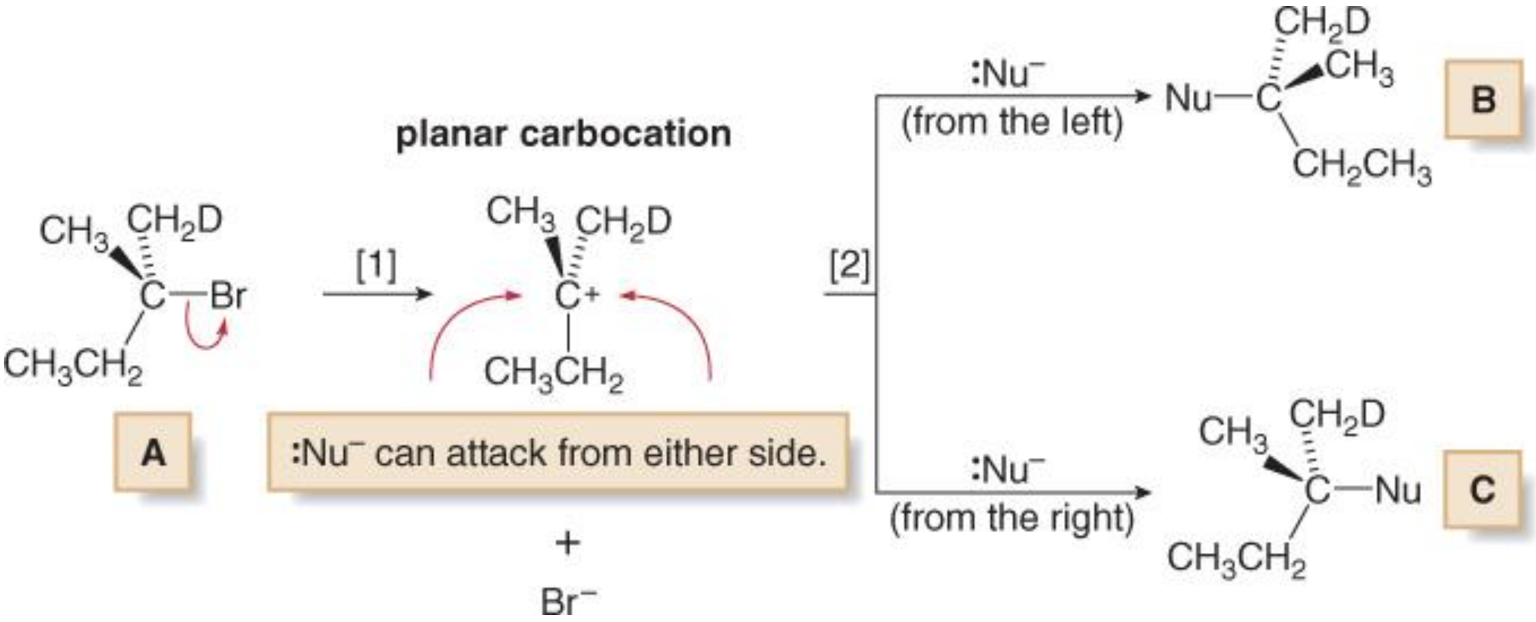
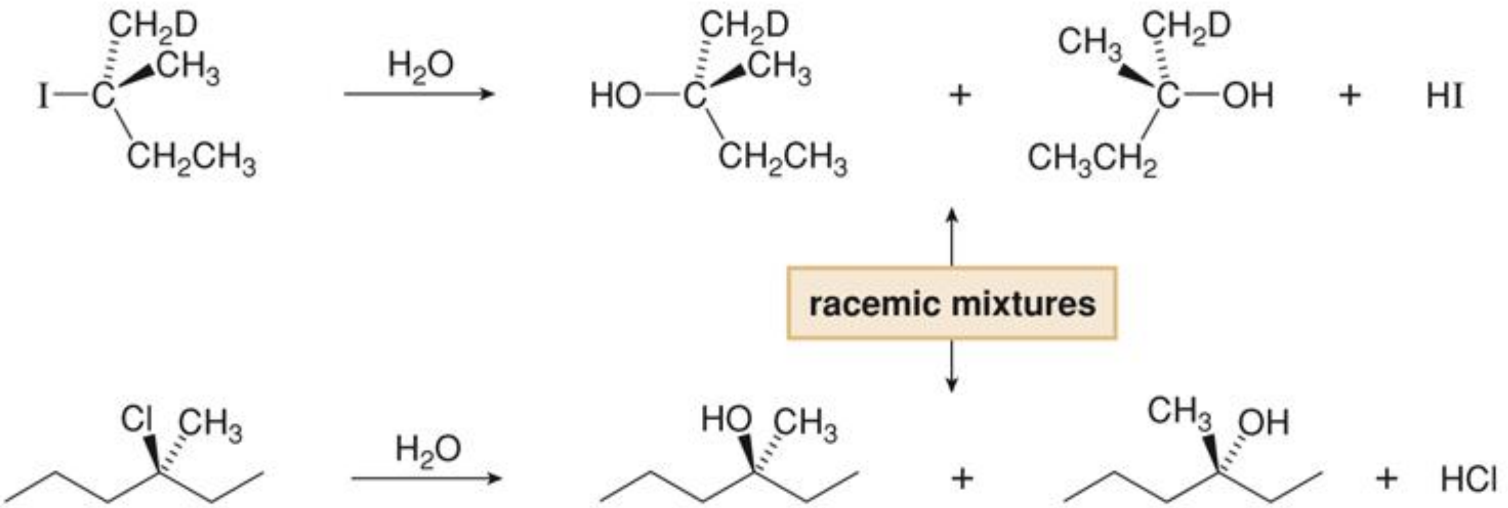


Figure 7.16

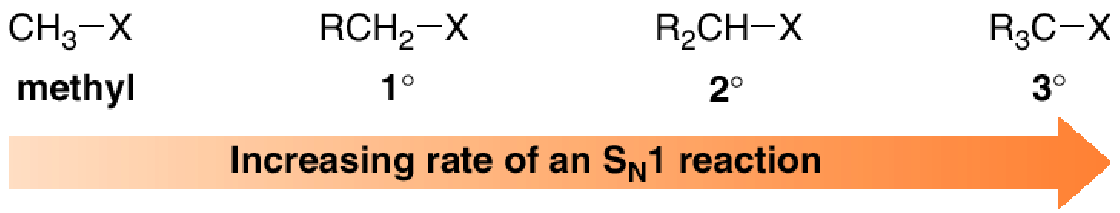
Two examples of racemization in the S_N1 reaction



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

- **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.*



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

methyl **1°** **2°** **3°**

Increasing rate of an S_N1 reaction

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

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

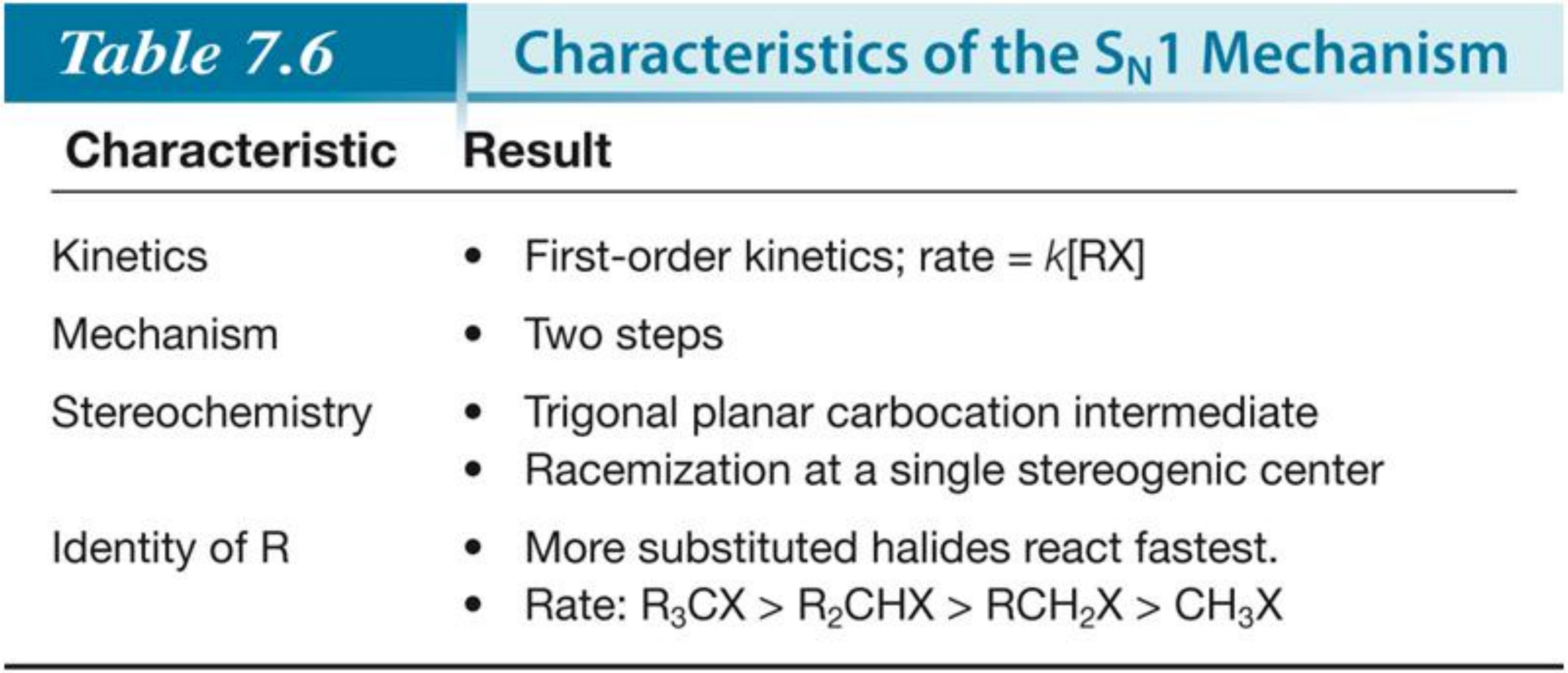
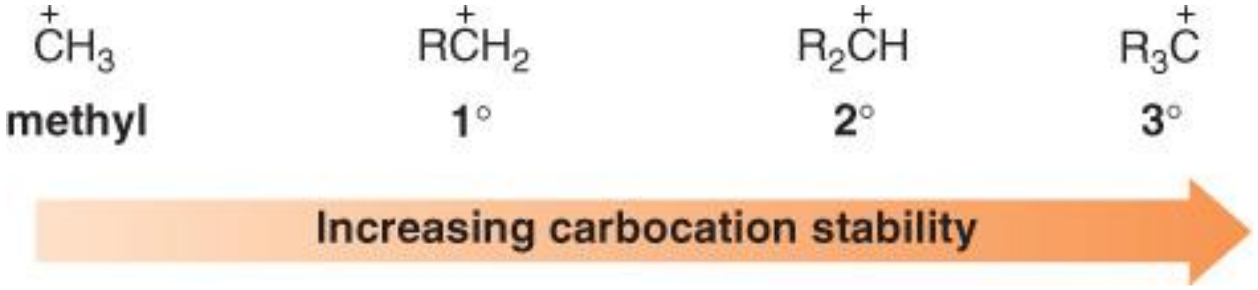


Table 7.6 Characteristics of the S_N1 Mechanism

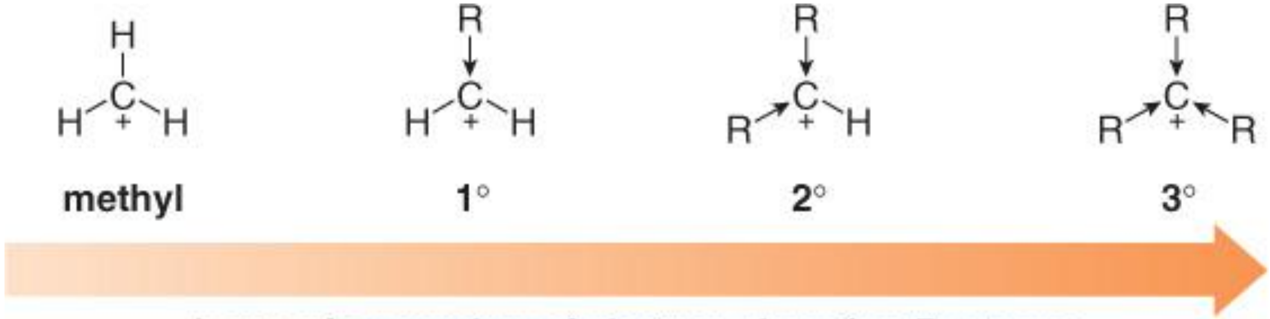
Characteristic	Result
Kinetics	• First-order kinetics; rate = k[RX]
Mechanism	• Two steps
Stereochemistry	• Trigonal planar carbocation intermediate • Racemization at a single stereogenic center
Identity of R	• More substituted halides react fastest. • Rate: $R_3CX > R_2CHX > RCH_2X > CH_3X$

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.

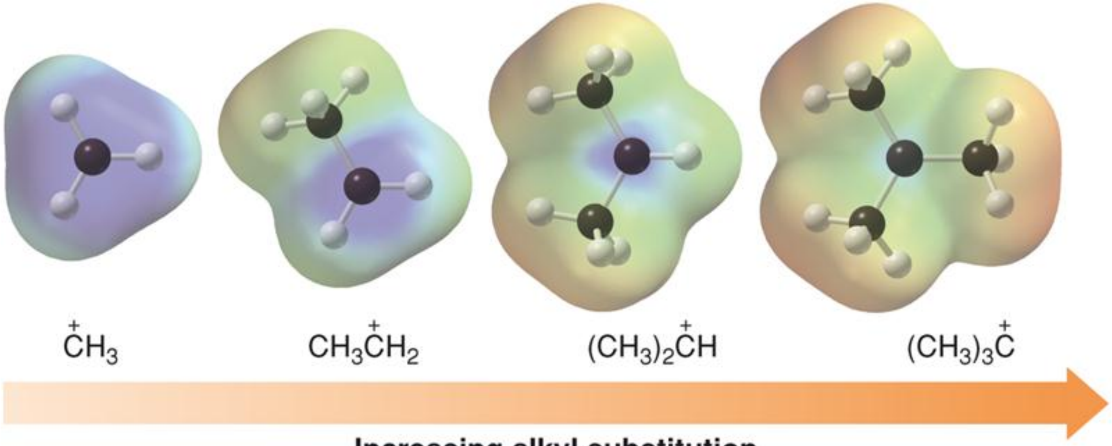


- The order of carbocation stability can be rationalized through inductive effects and hyperconjugation.
- Inductive effects are electronic effects that occur through σ bonds. Specifically, the inductive effect is the pull of electron density through σ bonds caused by electronegativity differences between atoms.
- Alkyl groups are electron donating groups that stabilize a positive charge. Since an alkyl group has several σ bonds, each containing electron density, it is more polarizable than a hydrogen atom, and better able to donate electron density.
- In general, the greater the number of alkyl groups attached to a carbon with a positive charge, the more stable will be the cation.



Increasing number of electron-donating R groups
Increasing carbocation stability

Figure 7.17
Electrostatic potential maps for differerent carbocations



Increasing alkyl substitution
Increasing dispersal of positive charge

- 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.

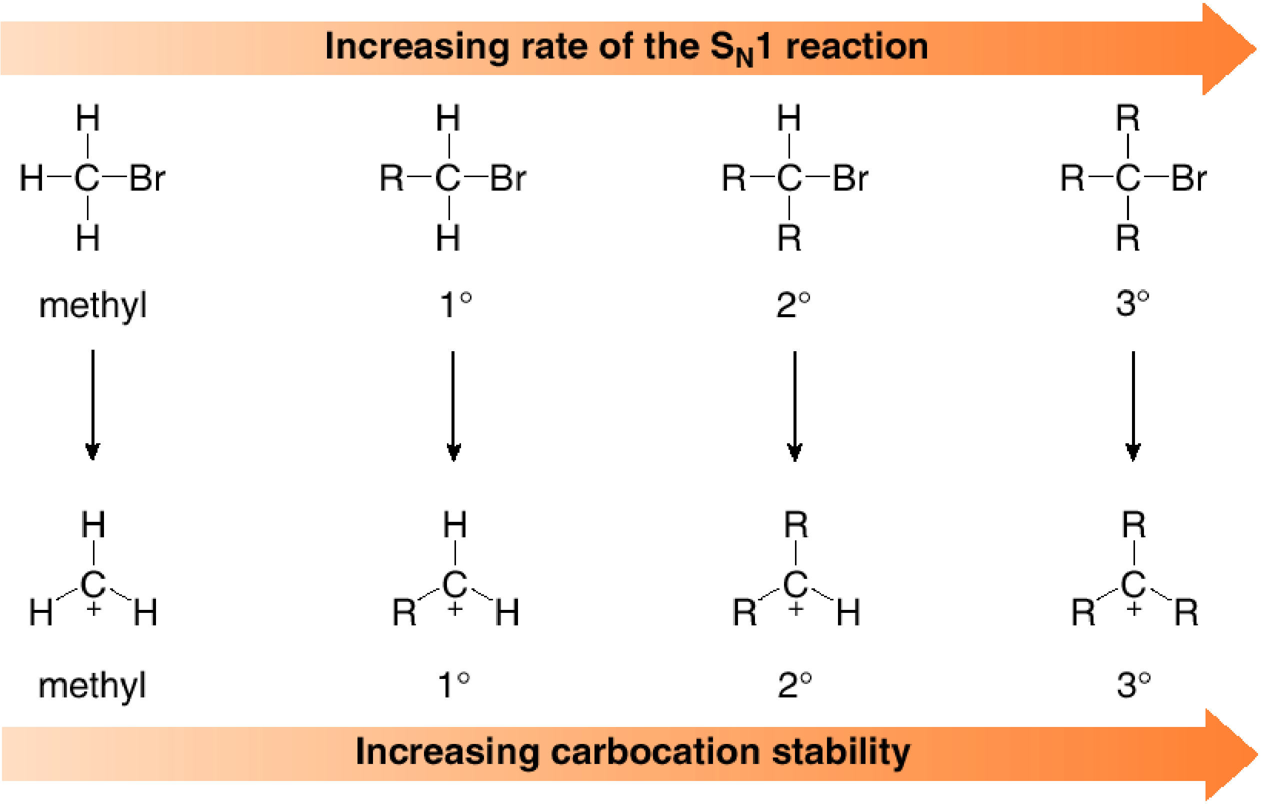
- The order of carbocation stability is also a consequence of hyperconjugation.
- **Hyperconjugation** is the spreading out of charge by the overlap of an empty *p* orbital with an adjacent σ bond. This overlap (hyperconjugation) delocalizes the positive charge on the carbocation, spreading it over a larger volume, and this stabilizes the carbocation.
- Example: CH_3^+ cannot be stabilized by hyperconjugation, but $(CH_3)_2CH^+$ can.

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

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

The Hammond Postulate

- The rate of an S_N1 reaction *increases* as the number of R groups on the carbon with the leaving group *increases.*
- The stability of a carbocation *increases* as the number of R groups on the positively charged carbon *increases.*



Increasing rate of the S_N1 reaction

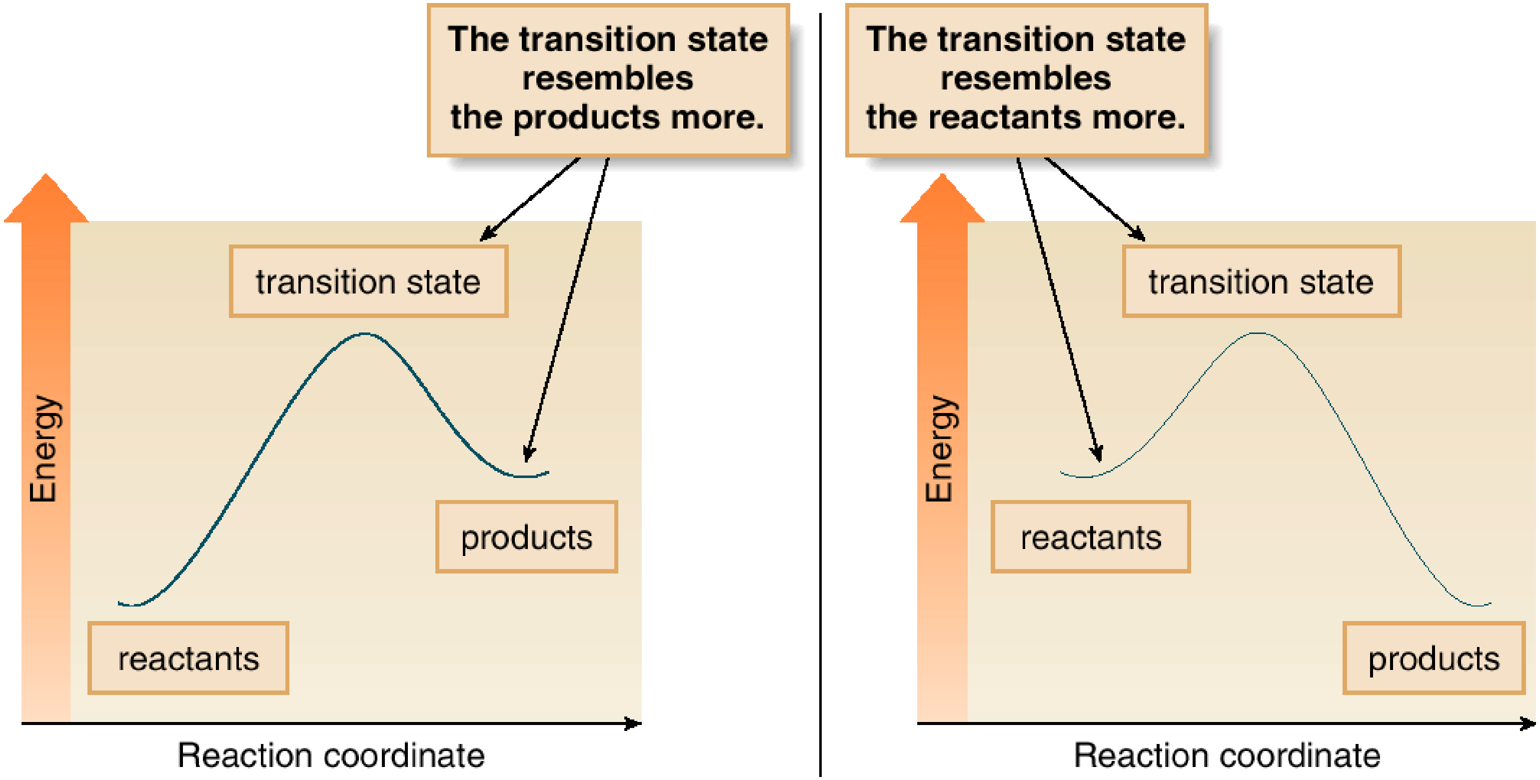
Increasing carbocation stability

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

The reaction is faster with a more stable carbocation.

- **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.**

- **In endothermic reactions, the transition state is closer in energy to the products.**
- **In exothermic reactions, the transition state is closer in energy to the reactants.**



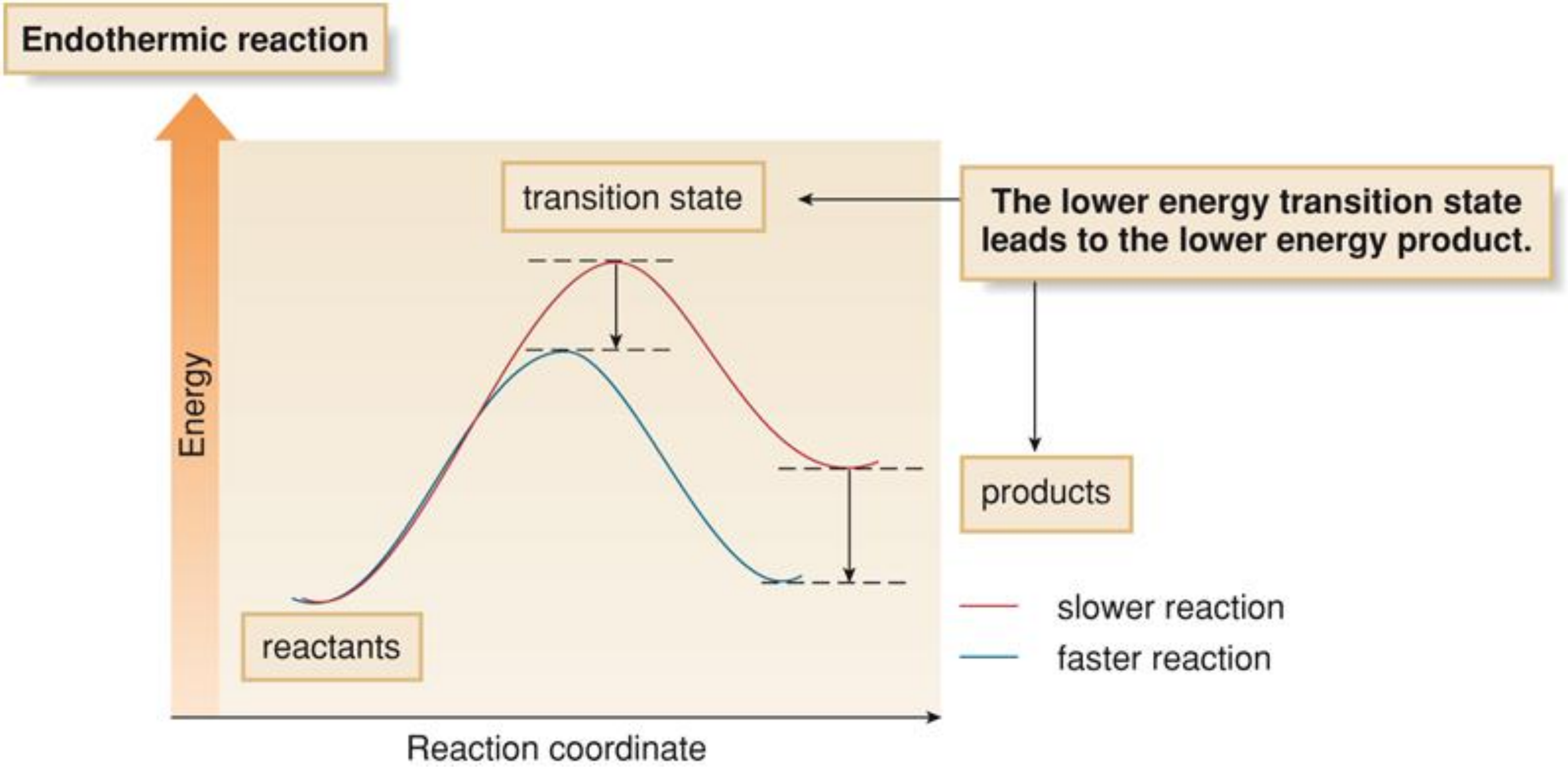
[1] An endothermic reaction

[2] An exothermic reaction

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

- **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 in an endothermic reaction, but one is more stable than the other, the transition state that leads to the formation of the more stable product is lower in energy, so this reaction should occur faster.**

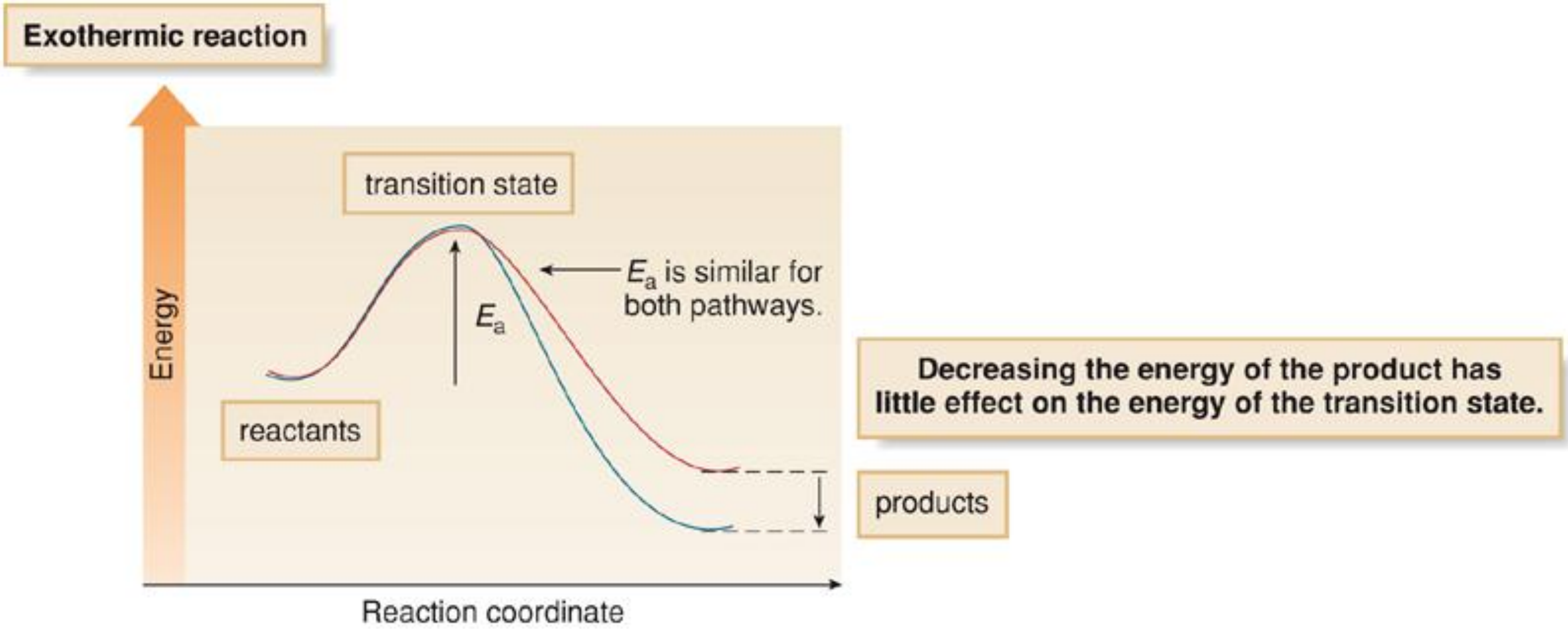
Figure 7.18
An endothermic reaction—How the energy of the transition state and products are related



- **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.**

Figure 7.19

An exothermic reaction—How the energy of the transition state and products are related



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

- **The Hammond postulate estimates the relative energy of transition states, and thus it can be used to predict the relative rates of two reactions.**
- **According to the Hammond postulate, the stability of the carbocation determines the rate of its formation.**

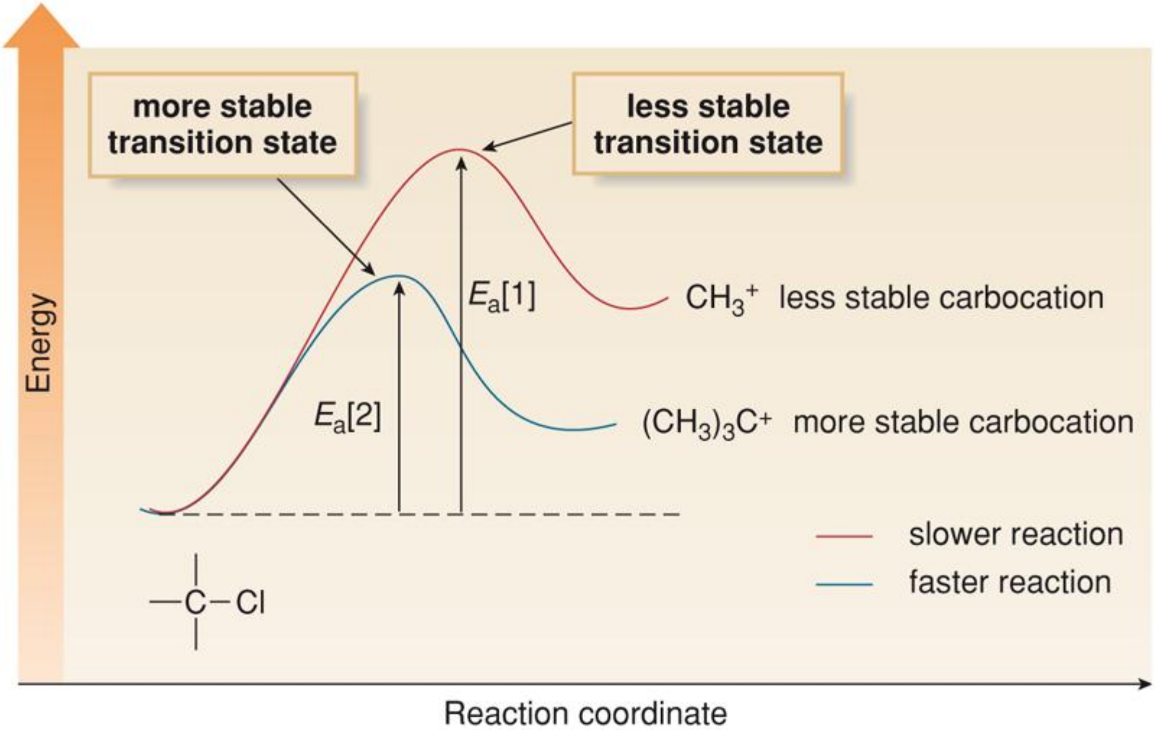


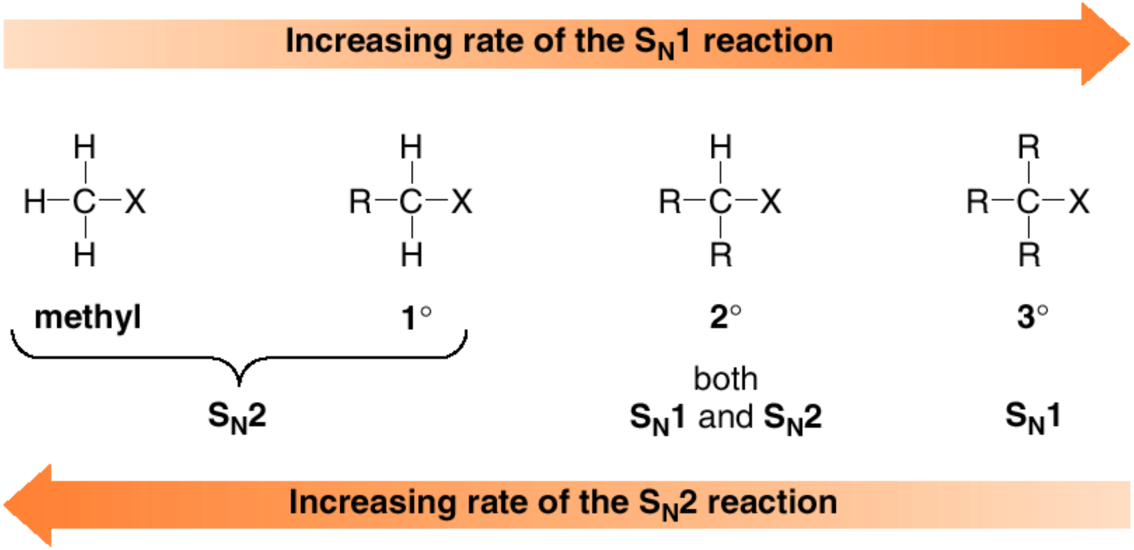
Figure 7.20
Energy diagram for carbocation formation in two different S_N1 reactions

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

Predicting the Likely Mechanism of a Substitution Reaction.

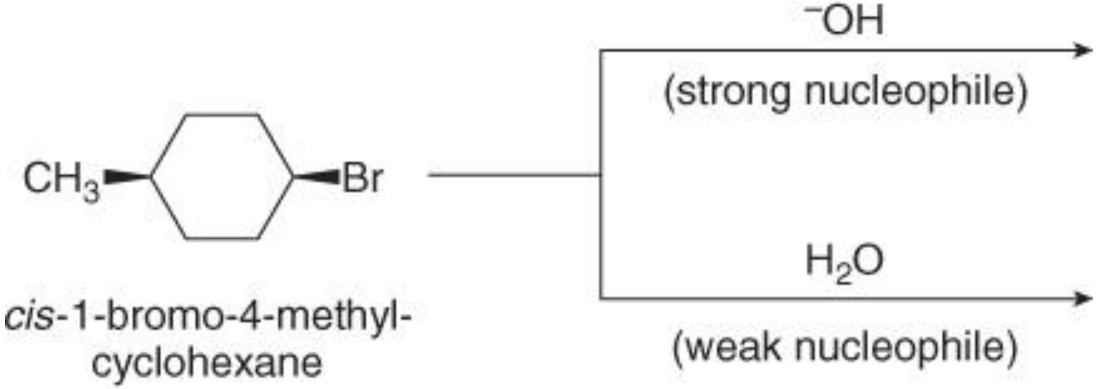
- Four factors are relevant in predicting whether a given reaction is likely to proceed by an S_N1 or an S_N2 reaction—The most important is the identity of the alkyl halide.

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



- Methyl and 1° halides (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.

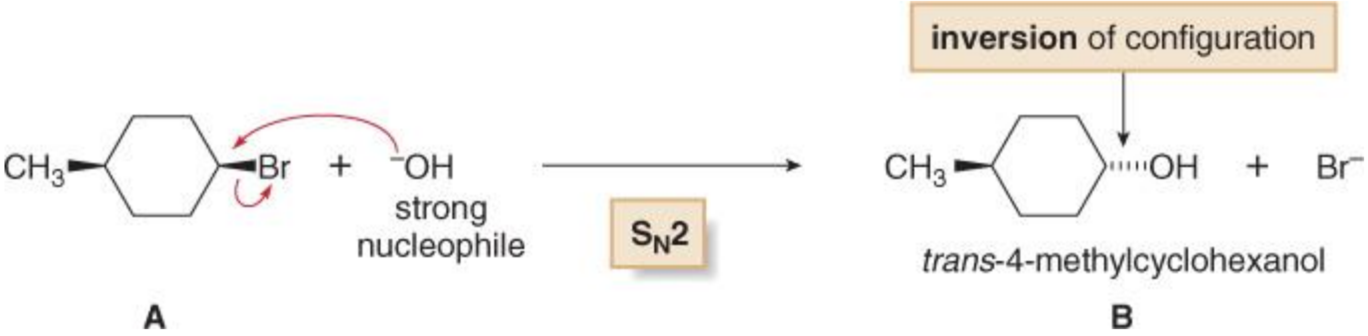
- **The nature of the nucleophile is another factor.**
- **Strong nucleophiles (which usually bear a negative charge) present in high concentrations favor S_N2 reactions.**
- **Weak nucleophiles, such as H_2O and ROH favor S_N1 reactions by decreasing the rate of any competing S_N2 reaction.**
- **Let us compare the substitution products formed when the 2° alkyl halide A is treated with either the strong nucleophile HO^- or the weak nucleophile H_2O. Because a 2° alkyl halide can react by either mechanism, the strength of the nucleophile determines which mechanism takes place.**



cis-1-bromo-4-methyl-cyclohexane

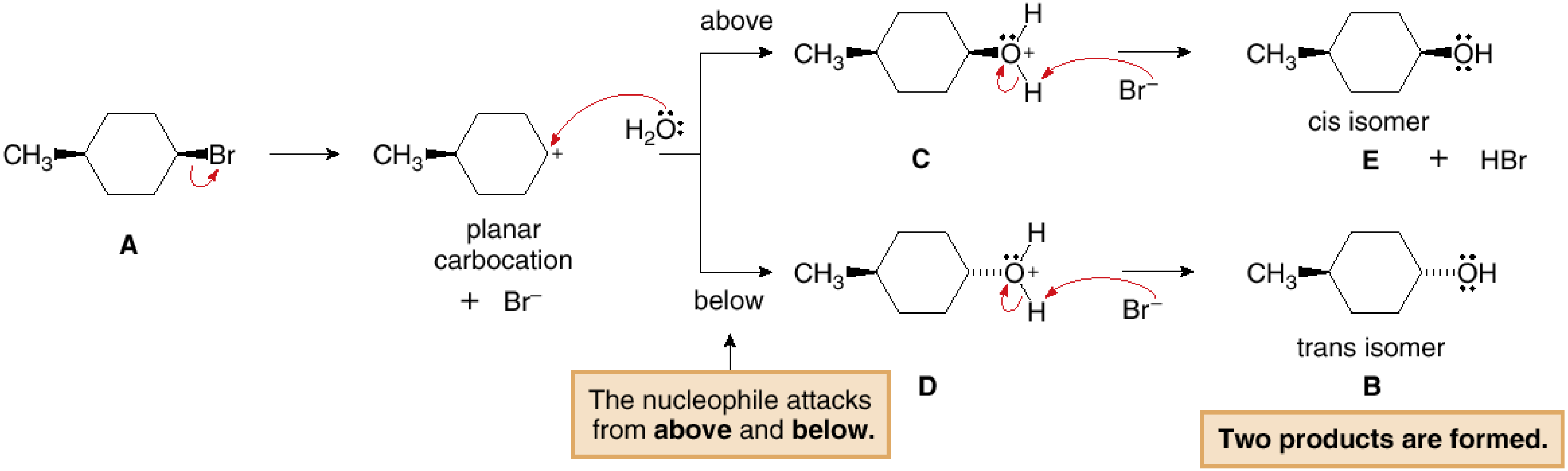
A

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



inversion of configuration

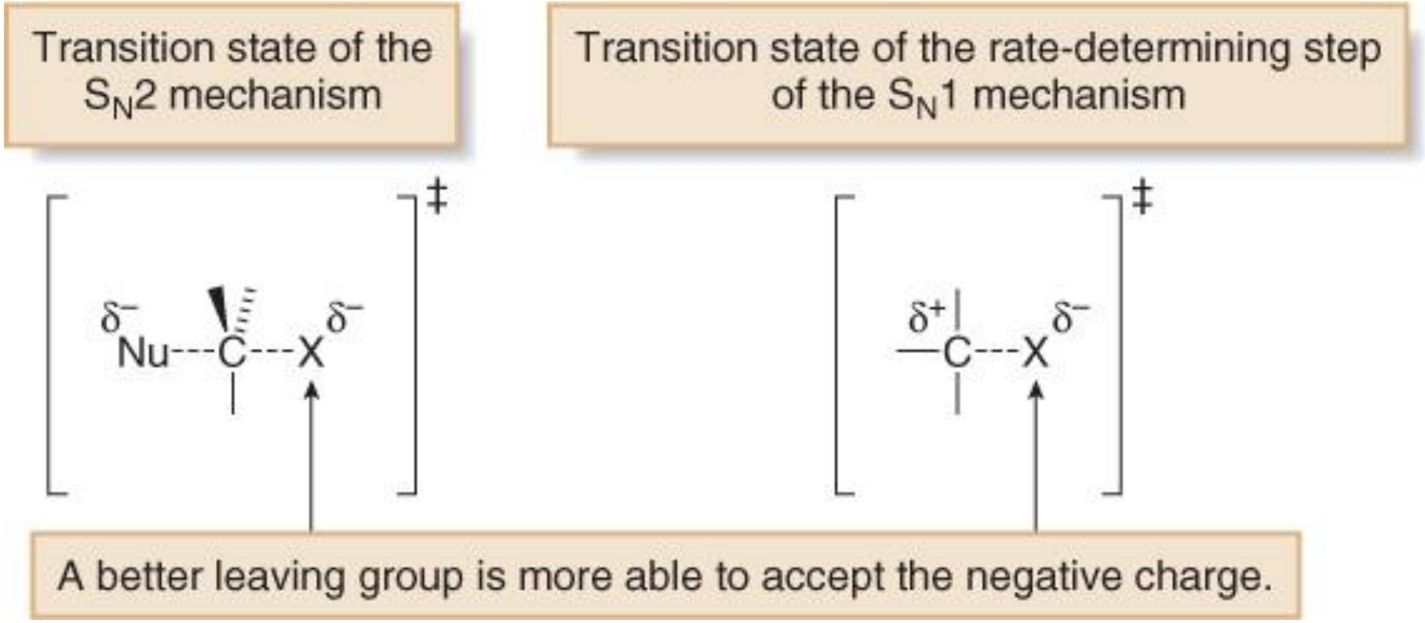
- **The weak nucleophile favors an S_N1 mechanism.**



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

Two products are formed.

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



Transition state of the S_N2 mechanism

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

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

Increasing leaving group ability
Increasing rate of S_N1 and S_N2 reactions

- **The nature of the solvent is a fourth factor.**
- **Polar protic solvents like 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.**

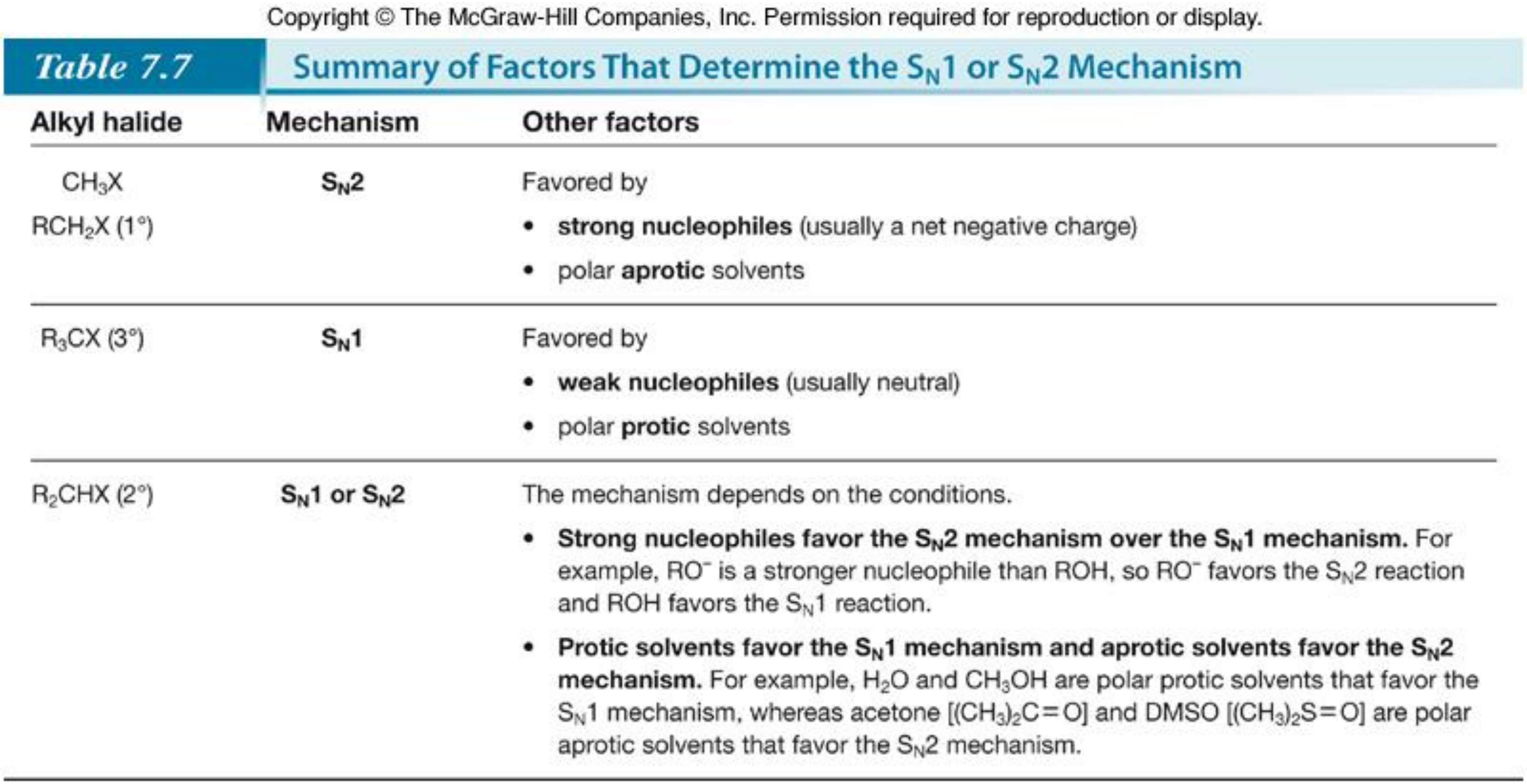


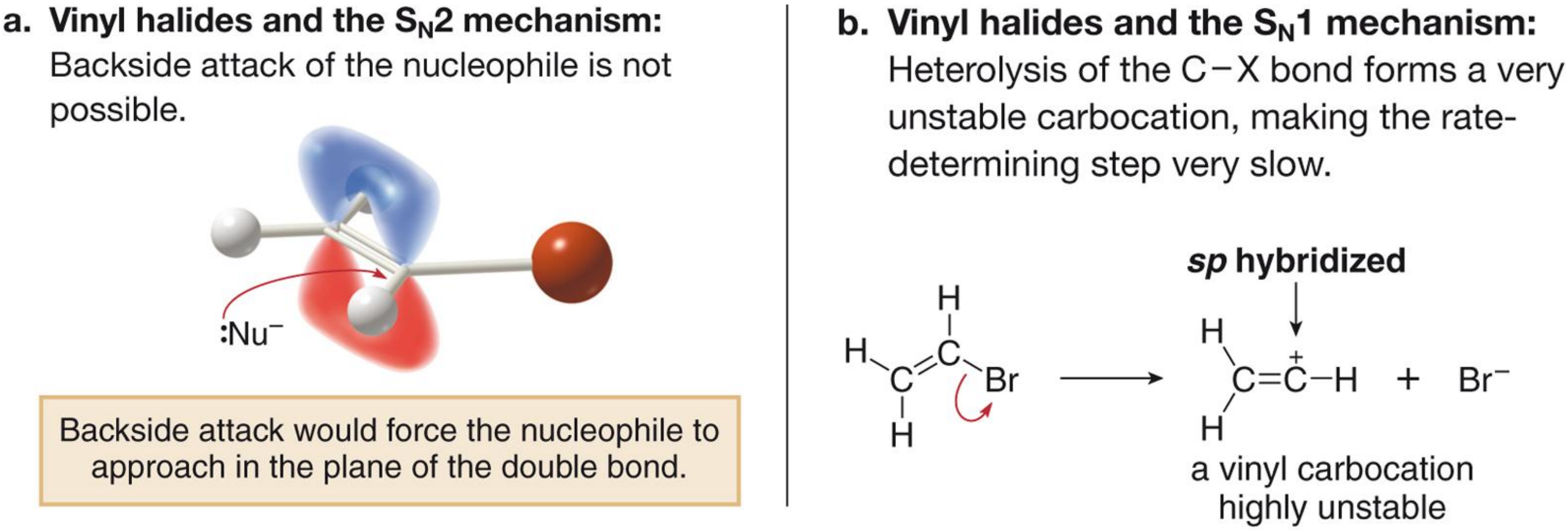
Table 7.7 Summary of Factors That Determine the S_N1 or S_N2 Mechanism

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 Halides and Aryl Halides.

- **Vinyl and aryl halides do not undergo S_N1 or S_N2 reactions, because heterolysis of the C—X bond would form a highly unstable vinyl or aryl cation.**

Figure 7.22
Vinyl halides and nucleophilic substitution mechanisms



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

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

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

a vinyl carbocation
highly unstable

Alkyl Halides and Nucleophilic Substitution

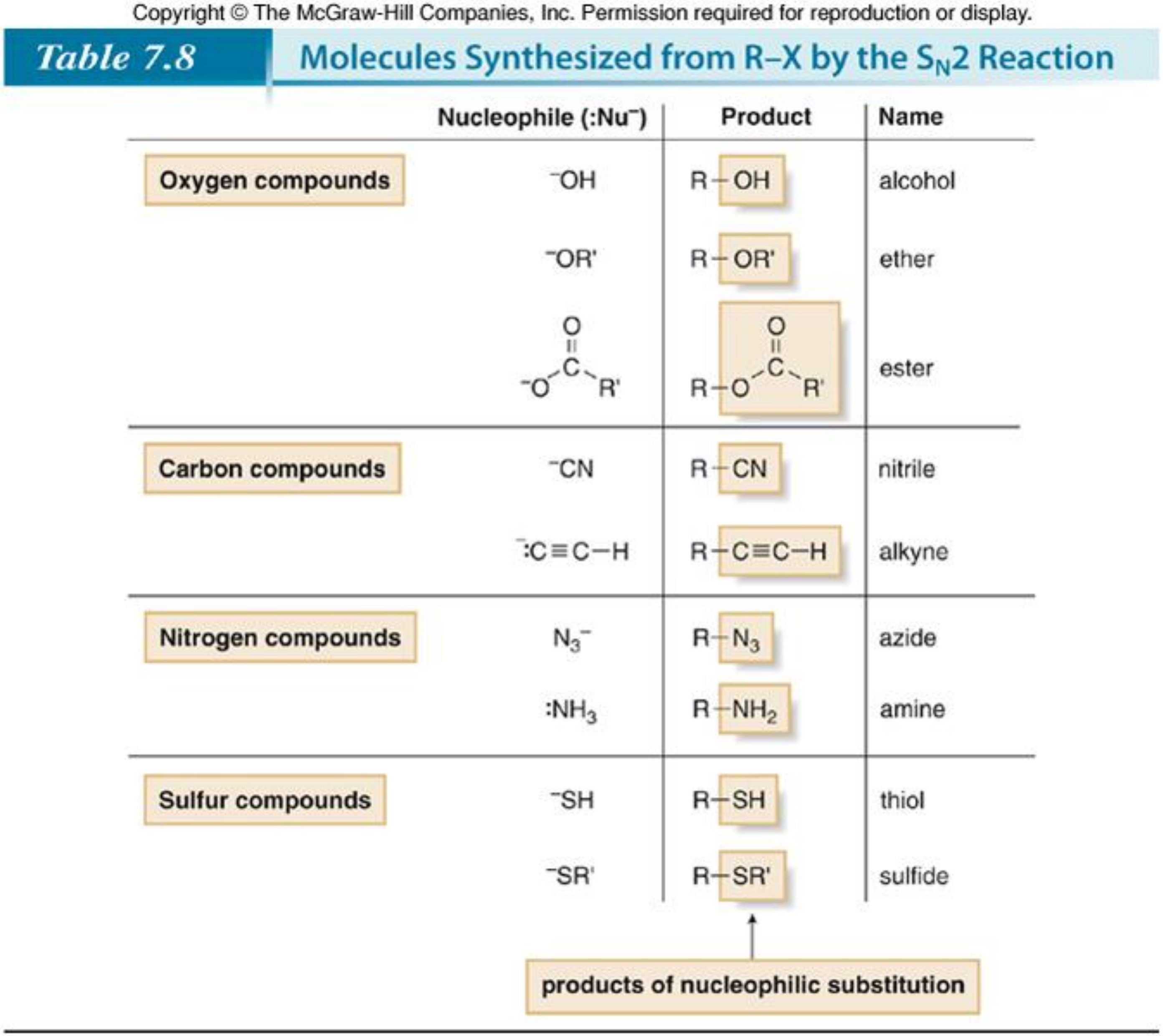


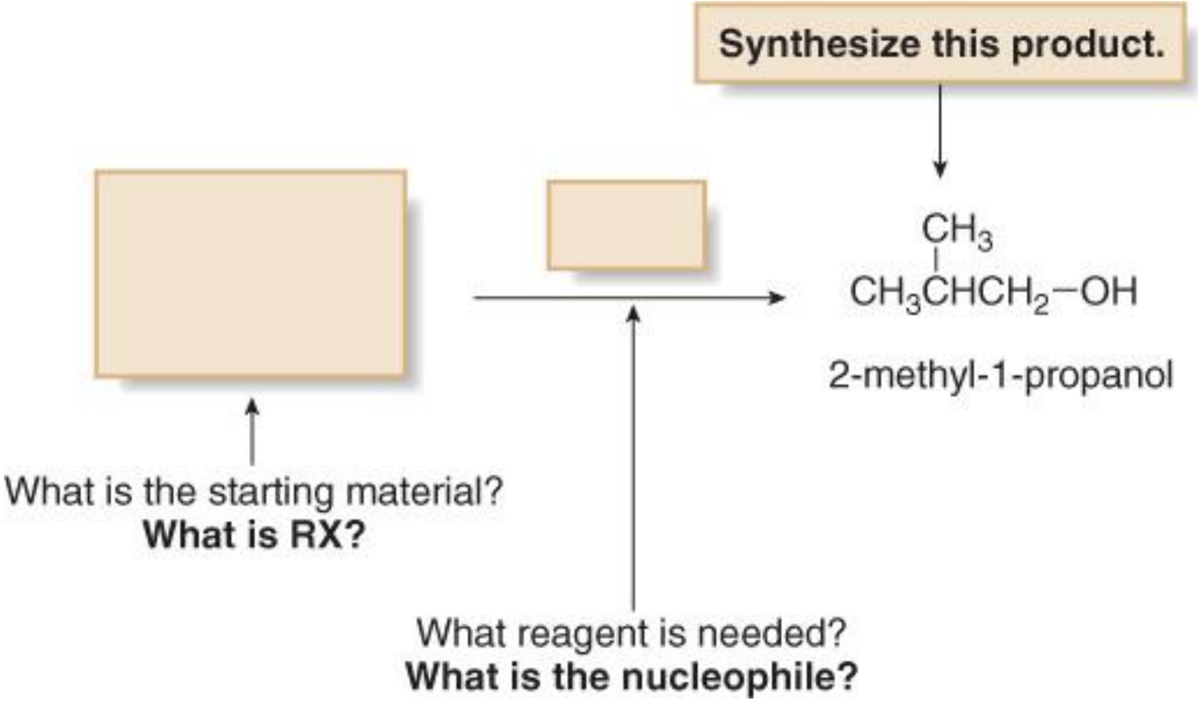
Table 7.8 Molecules Synthesized from R–X by the S_N2 Reaction

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

products of nucleophilic substitution

Nucleophilic Substitution and Organic Synthesis.

- 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 we are using nucleophilic substitution, we must determine what alkyl halide and what nucleophile can be used to form a specific product.



Synthesize this product.

$CH_3CH(CH_3)CH_2-OH$

2-methyl-1-propanol

What is the starting material?
What is RX?

What reagent is needed?
What is the nucleophile?

- **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.**