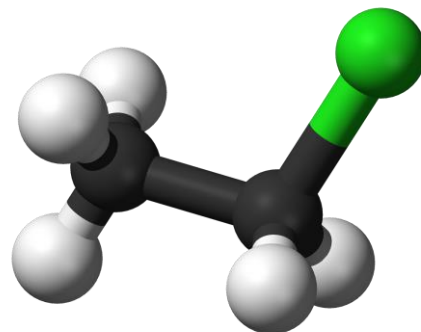


## Alkyl Halides – S<sub>N</sub>2 Reaction

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*Instructor: Asst. Prof. Dr. Tanatorn Khotavivattana*

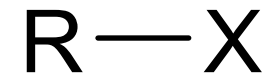
*E-mail: [tanatorn.k@chula.ac.th](mailto:tanatorn.k@chula.ac.th)*

**Recommended Textbook:**

Chapter 6 in *Organic Chemistry*, 8<sup>th</sup> Edition, L. G. Wade, Jr., 2010, Prentice Hall (Pearson Education)

# Typical Reactions of Alkyl Halides

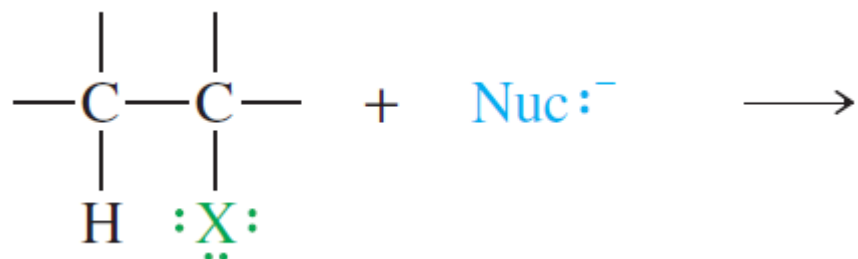
Halide is a good \_\_\_\_\_



Stability:

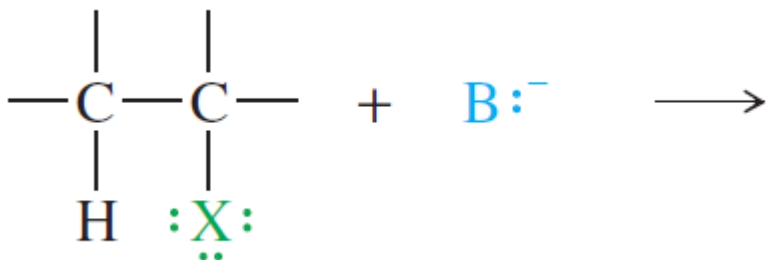
## 1) Nucleophilic Substitution

A nucleophile replaces a leaving group from a carbon atom, using its lone pair of electrons to form a new bond to the carbon atom.



## 2) Elimination

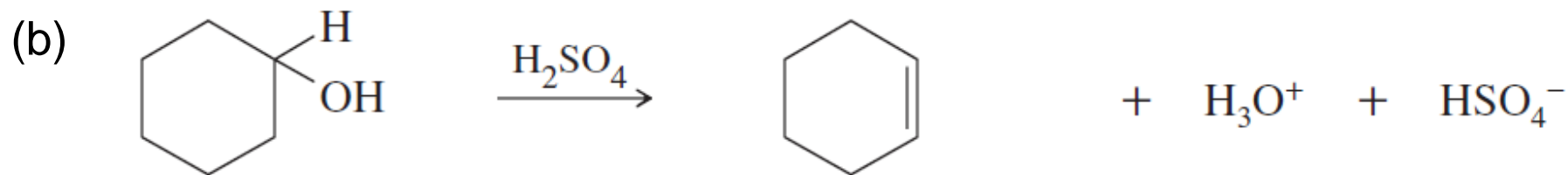
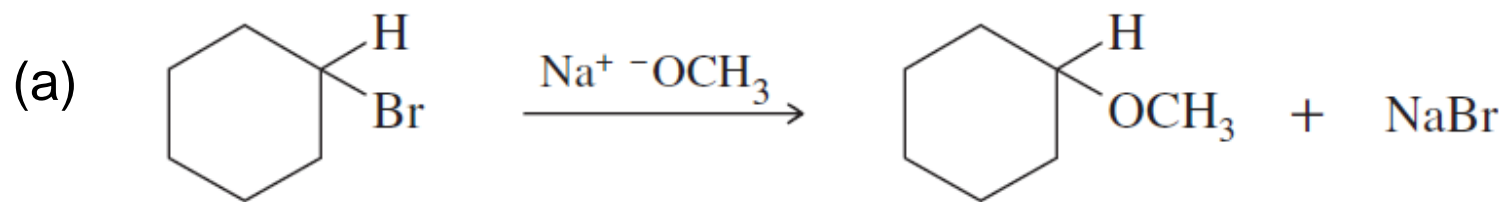
Both the halide ion and another substituent are lost. A new bond is formed. The reagent reacts as a base, abstracting a proton from the alkyl halide.



**Most nucleophiles are also basic and can engage in either substitution or elimination, depending on the alkyl halide and the reaction conditions.**

## Example 1

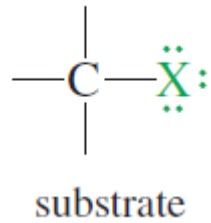
Classify each reaction as a substitution, elimination. Identify the leaving group in each reaction, and the nucleophile in substitutions.



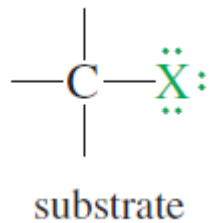
# Nucleophilic Substitution



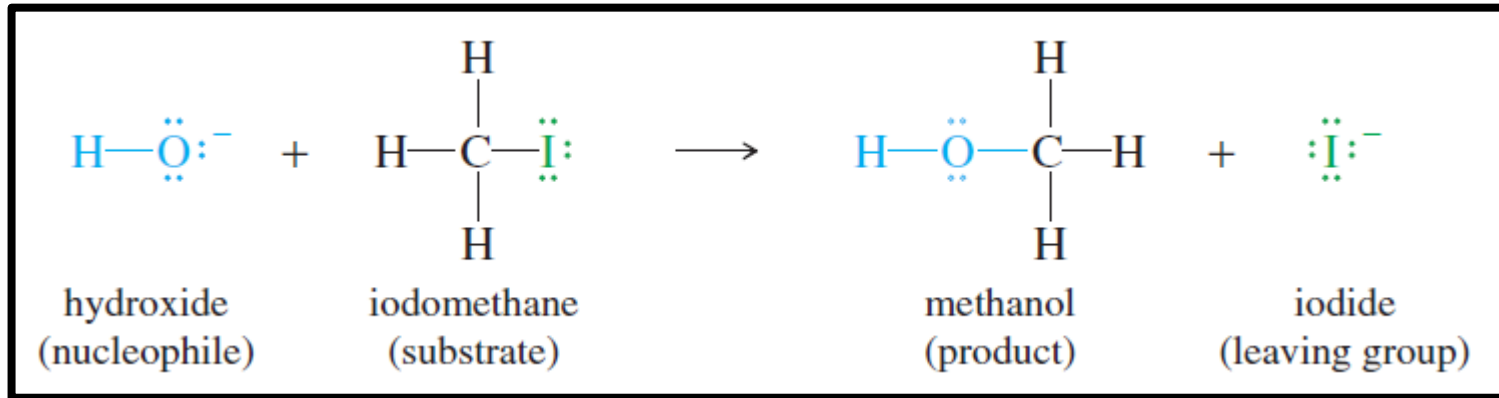
## 1) Second-Order Nucleophilic Substitution ( $S_N2$ )



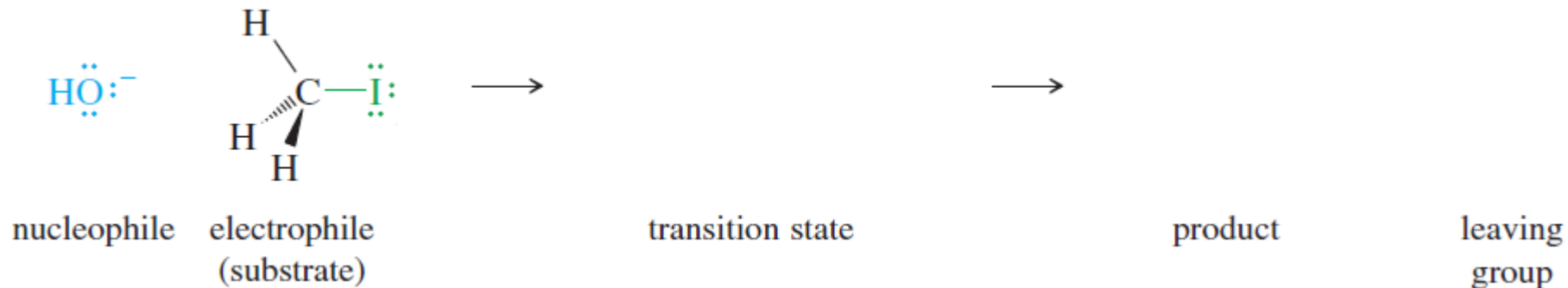
## 2) First-Order Nucleophilic Substitution ( $S_N1$ )



# S<sub>N</sub>2 Reaction

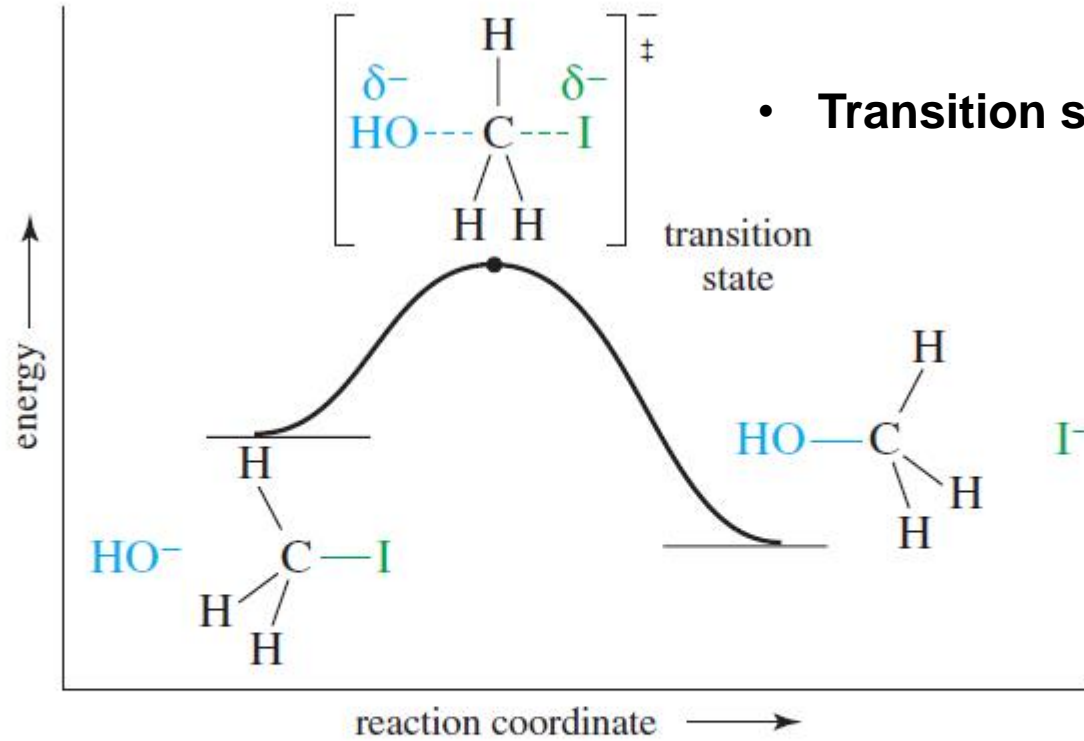


## Mechanism

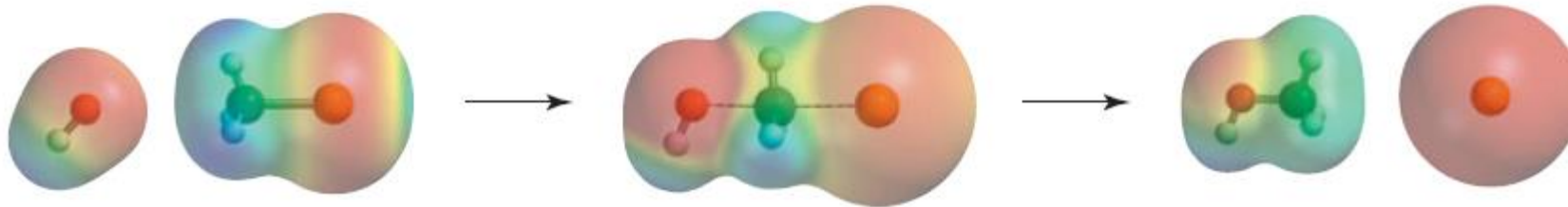


Rate =

# S<sub>N</sub>2 - The reaction-energy diagram

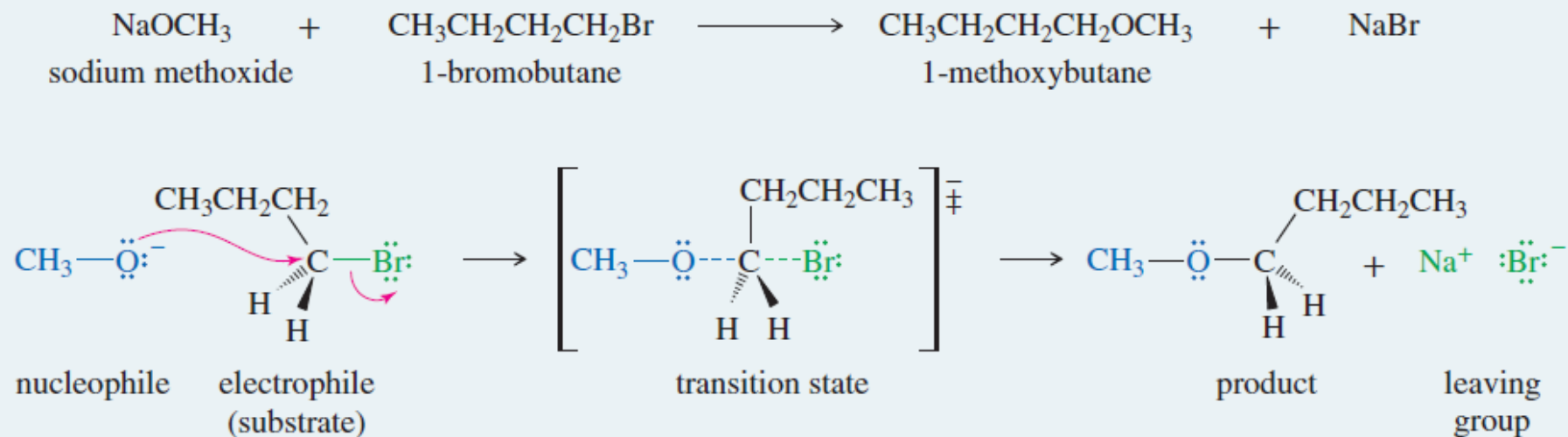


- **Transition state**, a point of maximum energy



- **Concerted reaction**, taking place in a single step with bonds breaking and forming at the same time.

**EXAMPLE:** Reaction of 1-bromobutane with sodium methoxide gives 1-methoxybutane.



### Example 2

Show another S<sub>N</sub>2 reaction using a different combination of an alkoxide and an alkyl bromide that also produces 1-methoxybutane.



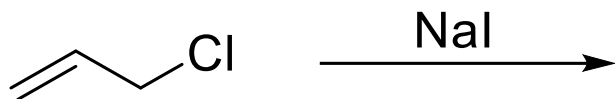
**Example 3**

Consider the reaction of **1-bromobutane** with a large excess of **ammonia** (NH<sub>3</sub>). Draw the reactants, the transition state, and the products. Note that the initial product is the salt of an amine (RNH<sub>3</sub><sup>+</sup>Br<sup>-</sup>), which is deprotonated by the excess ammonia to give the amine.

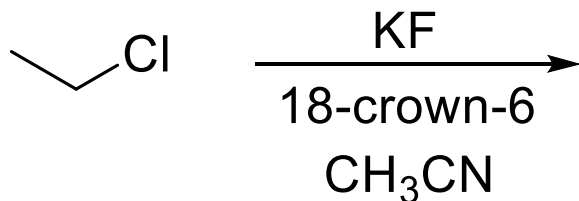
- **Halogen Exchange Reactions**

The reaction provides a useful method for synthesizing **alkyl iodides** and **fluorides**, which are more difficult to make than alkyl chlorides and bromides.

- Iodide is a good nucleophile, and many alkyl chlorides/bromides react with **sodium iodide** to give alkyl iodides.



- Alkyl fluorides are often made by treating alkyl chlorides/bromides with **KF with a crown ether** to dissolve the fluoride salt in an aprotic solvent, which enhances the normally weak nucleophilicity of the fluoride ion



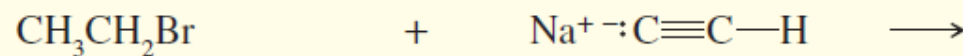
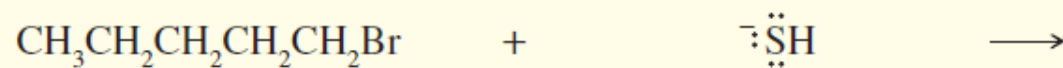
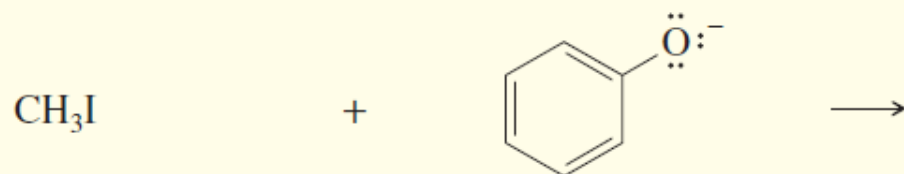
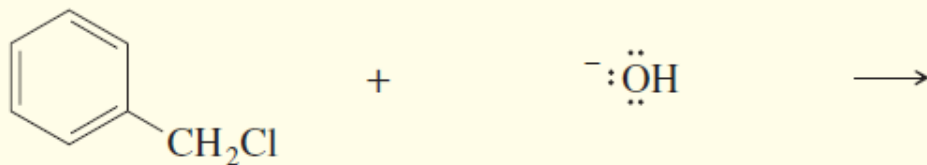
# Generality of S<sub>N</sub>2 reactions - Summary

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

<i>Nucleophile</i>	<i>Product</i>	<i>Class of Product</i>
R-X + $\text{:I:}^-$		alkyl halide
R-X + $\text{:OH}^-$		alcohol
R-X + $\text{:OR}'^-$		ether
R-X + $\text{:SH}^-$		thiol (mercaptan)
R-X + $\text{:SR}'^-$		thioether (sulfide)
R-X + $\text{:NH}_3$		amine salt
R-X + $\text{:N}^+=\text{N}=\text{N}^-$		azide
R-X + $\text{:C}\equiv\text{C-R}'$		alkyne
R-X + $\text{:C}\equiv\text{N:}$		nitrile
R-X + $\text{:O}=\text{C-R}'$		ester
R-X + $\text{:PPh}_3$		phosponium salt

# Generality of S<sub>N</sub>2 reactions - Summary

Examples

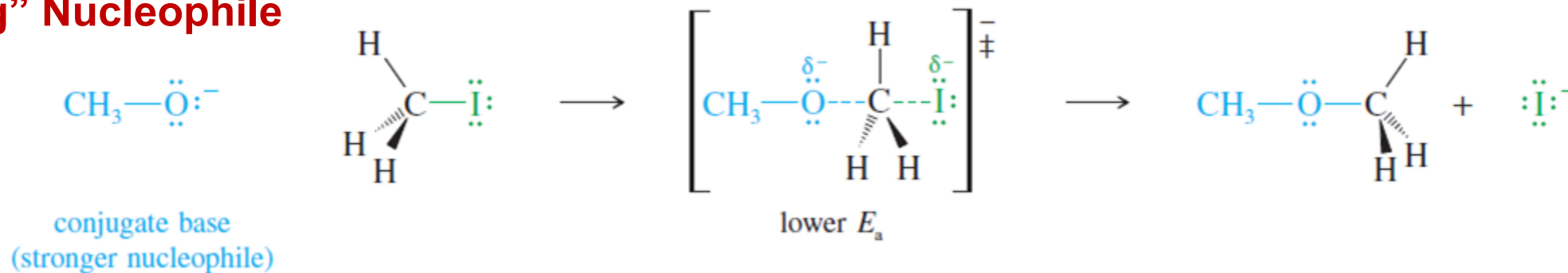


# Factors Affecting S<sub>N</sub>2 Reactions:

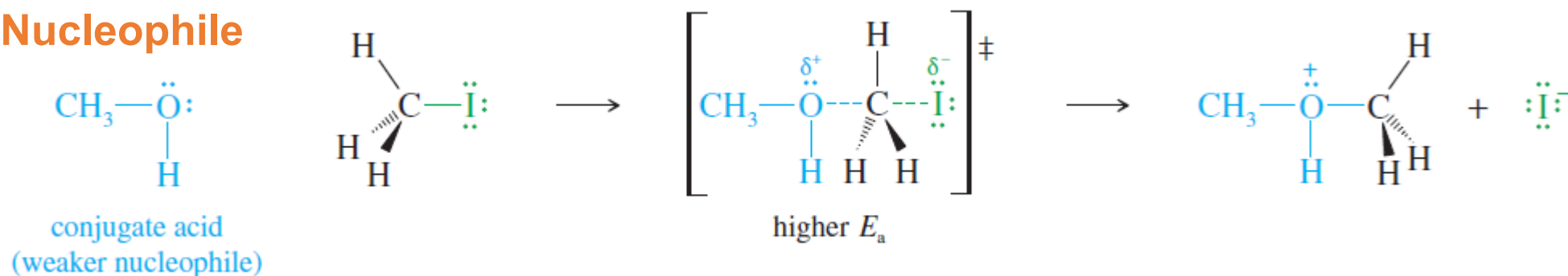
## 1A) Strength of the Nucleophile

A **“stronger”** nucleophile is an ion or molecule that reacts faster in the reaction than a **“weaker”** nucleophile under the same conditions

### “Strong” Nucleophile



### “Weak” Nucleophile



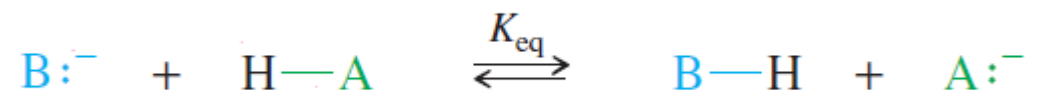
**A base is always a stronger nucleophile than its conjugate acid.**

# Factors Affecting S<sub>N</sub>2 Reactions:

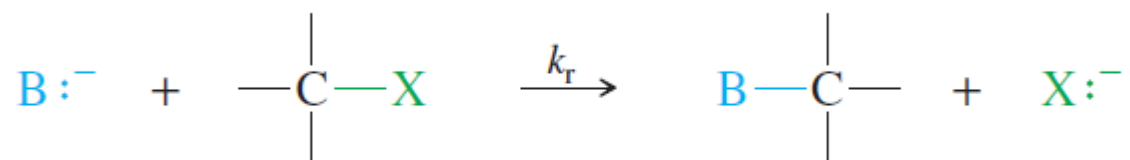
## 1A) Strength of the Nucleophile

**! Note: Basicity ≠ Nucleophilicity**

**Basicity** is defined by the \_\_\_\_\_ for abstracting a \_\_\_\_\_



**Nucleophilicity** is defined by the \_\_\_\_\_ of attack on an \_\_\_\_\_

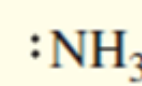
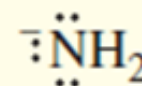
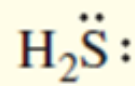
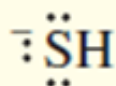
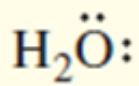
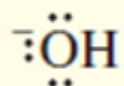


- If the new bond is to a **proton**, it has reacted as a **base**; if the new bond is to **carbon**, it has reacted as a **nucleophile**.
- Predicting which way a species will react may be difficult; **most (but not all)** good nucleophiles are also strong bases, and vice versa.

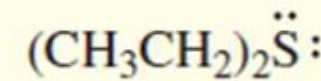
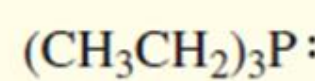
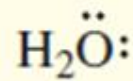
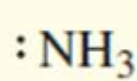
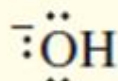
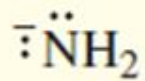
# Factors Affecting S<sub>N</sub>2 Reactions:

## 1A) Strength of the Nucleophile – Trends:

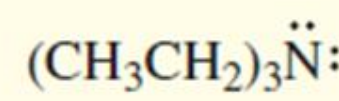
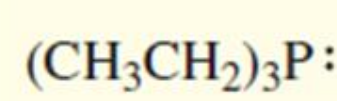
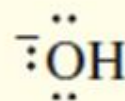
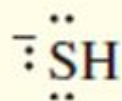
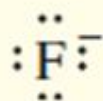
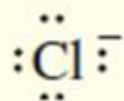
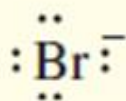
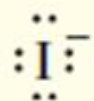
- A species with a **negative charge** is a stronger nucleophile than a **similar neutral** species.



- Nucleophilicity decreases from **left** to **right** in the periodic table, following the increase in **electronegativity**.



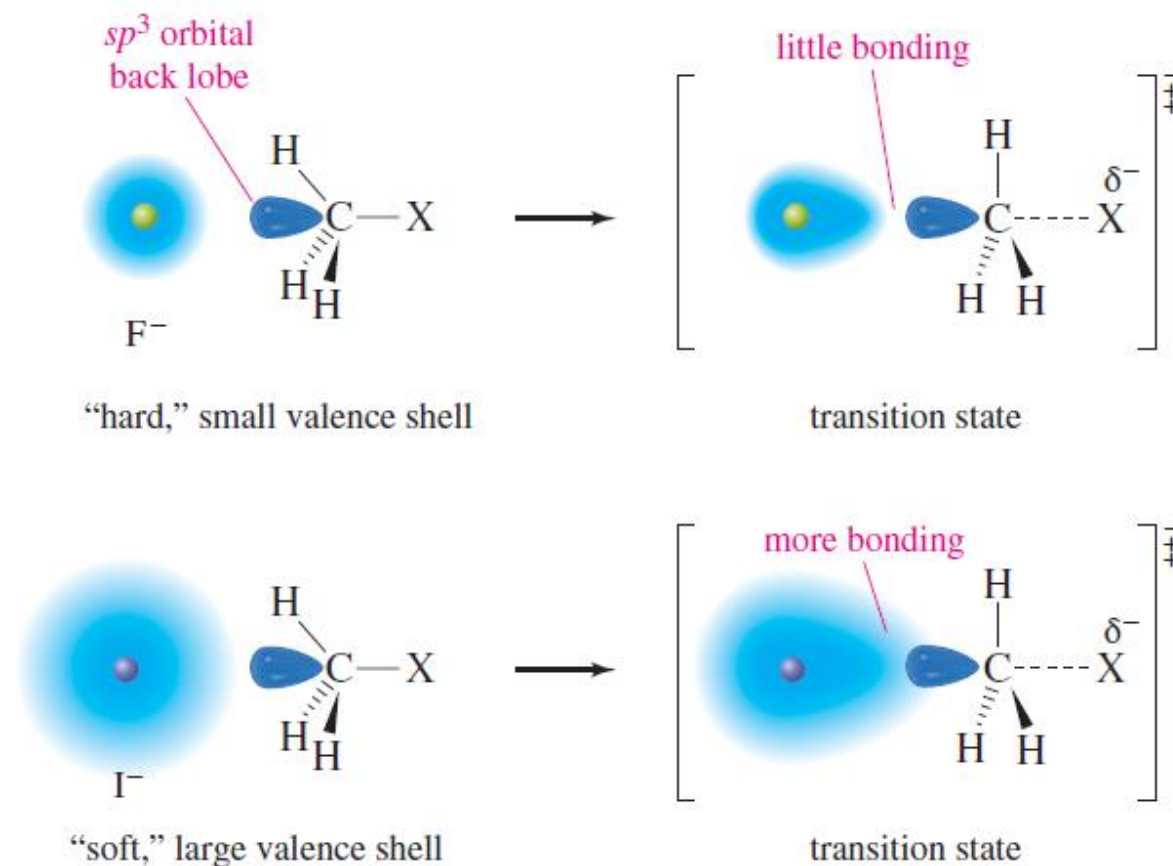
- Nucleophilicity **increases down the periodic table**, following the increase in **size** and **polarizability**, and the decrease in **electronegativity**.



# Factors Affecting S<sub>N</sub>2 Reactions:

## 1A) Strength of the Nucleophile – Trends:

- Nucleophilicity **increases down the periodic table**, following the increase in **size** and **polarizability**, and the decrease in **electronegativity**.



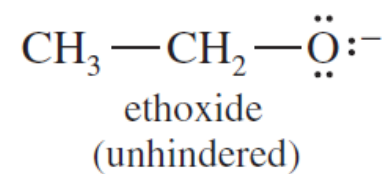
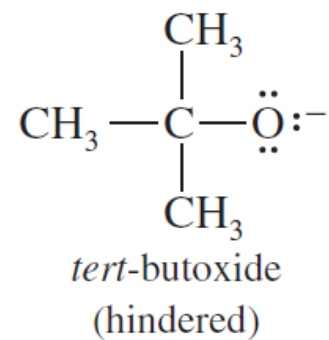
**more polarizable:** Its electrons can move more freely toward a positive charge, resulting in stronger bonding in the transition state.





# Factors Affecting S<sub>N</sub>2 Reactions:

## 1B) Steric effect on the Nucleophile



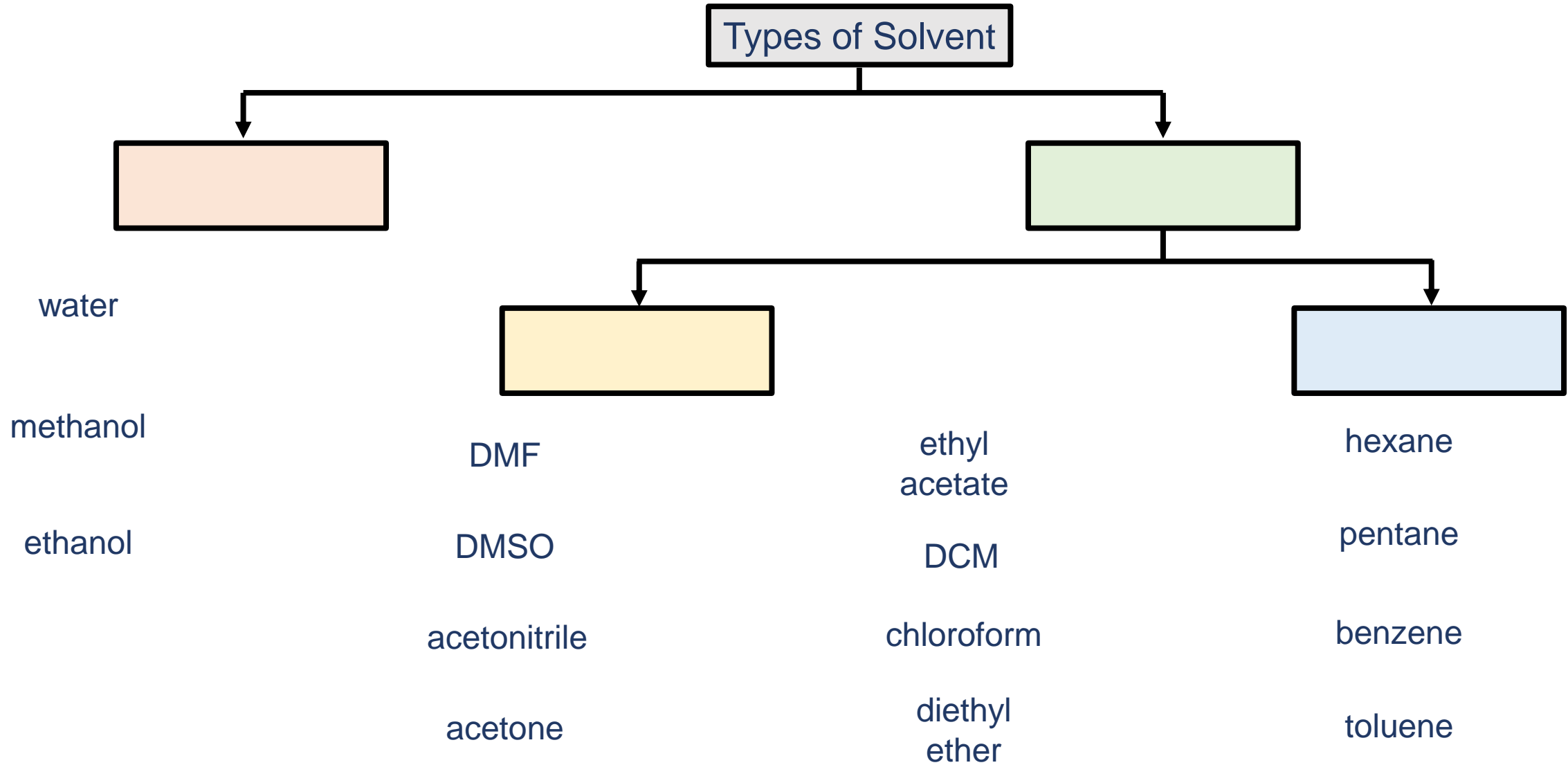
# Factors Affecting S<sub>N</sub>2 Reactions:

## 1B) Steric effects on the Nucleophile



# Factors Affecting S<sub>N</sub>2 Reactions:

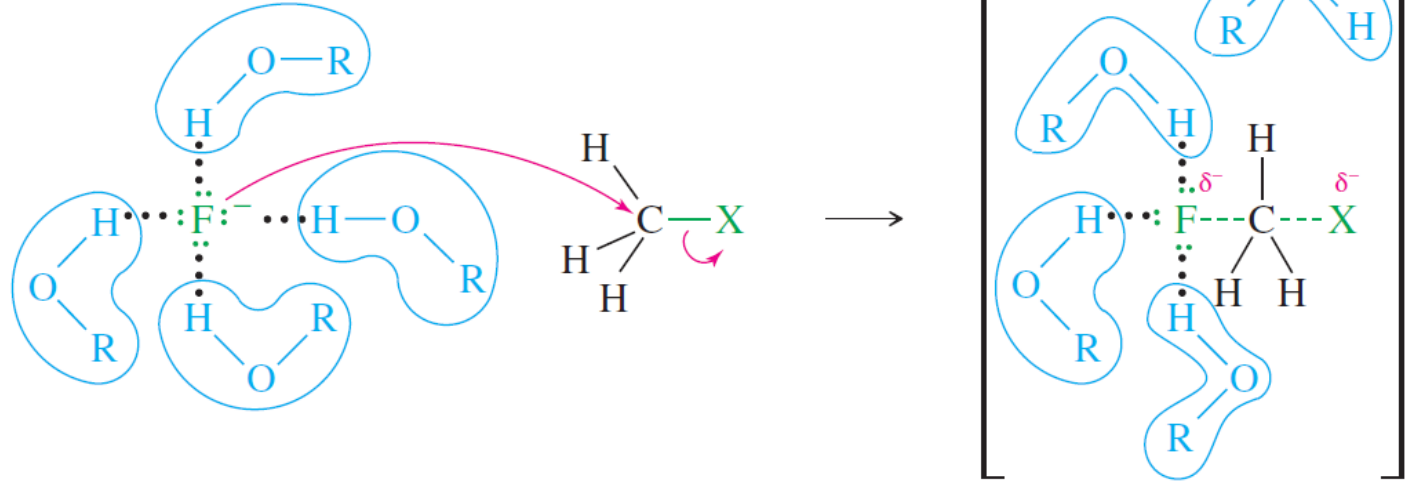
## 1C) Solvent effects on the Nucleophile



# Factors Affecting S<sub>N</sub>2 Reactions:

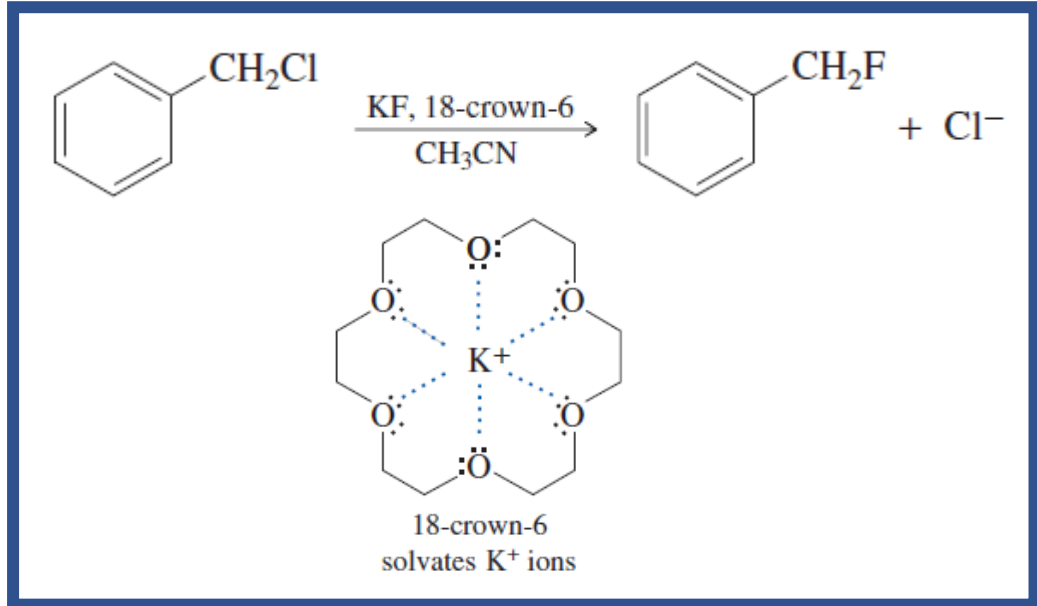
## 1C) Solvent effects on the Nucleophile

Protic Solvent

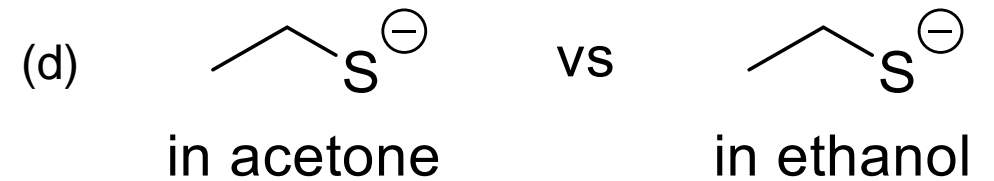
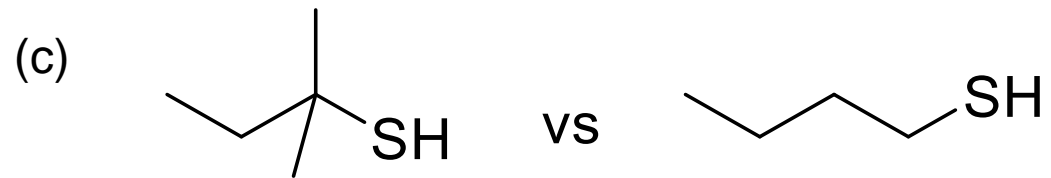
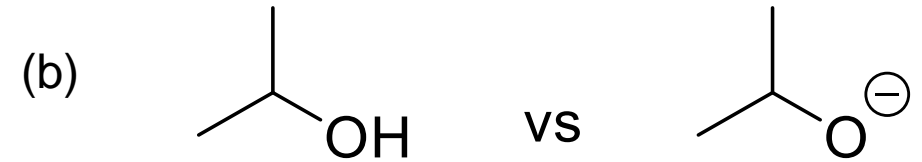


Polar Aprotic Solvent

Non-polar Aprotic Solvent



**Example 4** Which is the better nucleophile in the S<sub>N</sub>2 mechanism.



# Factors Affecting S<sub>N</sub>2 Reactions:

## 2A) Leaving-Group Effects on the Substrate

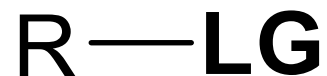
A leaving group serves **two purposes** in the reaction:

1. It **polarizes the bond**, making the carbon atom electrophilic.
2. It **leaves with the pair of electrons** that once bonded it to the electrophilic carbon atom.

For good leaving group:

1. **electron withdrawing**,  
to polarize the carbon atom

3. **stable once it has left**



2. **polarizable**, to stabilize  
the transition state

# Factors Affecting S<sub>N</sub>2 Reactions:

## 2A) Leaving-Group Effects on the Substrate

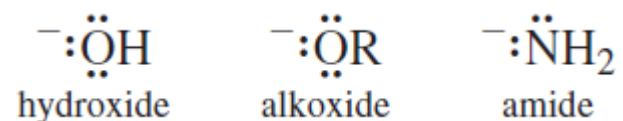
### 3. stable once it has left

Good leaving groups should be \_\_\_\_\_ bases;  
therefore, they are the conjugate bases of \_\_\_\_\_ acids.

TABLE 6-4 Weak Bases That Are Common Leaving Groups

<b>Ions:</b>	$\text{:}\ddot{\text{Cl}}\text{:}^-$	$\text{:}\ddot{\text{Br}}\text{:}^-$	$\text{:}\ddot{\text{I}}\text{:}^-$	$\text{:}\ddot{\text{O}}\text{--}\overset{\overset{\text{:}\ddot{\text{O}}\text{:}}{\parallel}}{\text{S}}\text{--}\text{R}$	$\text{:}\ddot{\text{O}}\text{--}\overset{\overset{\text{:}\ddot{\text{O}}\text{:}}{\parallel}}{\text{S}}\text{--}\ddot{\text{O}}\text{R}$	$\text{:}\ddot{\text{O}}\text{--}\overset{\overset{\text{:}\text{O:}^-}{\parallel}}{\text{P}}\text{--}\ddot{\text{O}}\text{R}$
	halides			sulfonate	sulfate	phosphate
<b>Neutral molecules:</b>	$\text{:}\ddot{\text{O}}\text{--}\text{H}$	$\text{:}\ddot{\text{O}}\text{--}\text{R}$	$\begin{array}{c} \text{R} \\   \\ \text{:}\ddot{\text{N}}\text{--}\text{R} \\   \\ \text{R} \end{array}$	$\begin{array}{c} \text{R} \\   \\ \text{:}\ddot{\text{S}}\text{--}\text{R} \end{array}$	$\begin{array}{c} \text{R} \\   \\ \text{:}\ddot{\text{P}}\text{--}\text{R} \\   \\ \text{R} \end{array}$	
	water	alcohols	amines	sulfides	phosphines	

**Ions that are strong bases and poor leaving groups:**

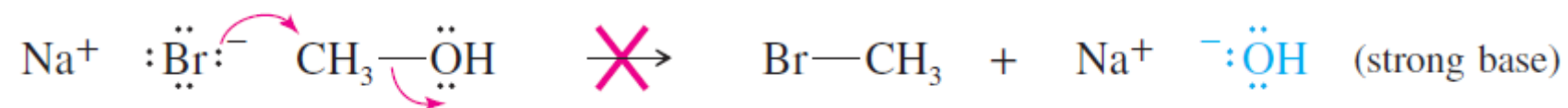




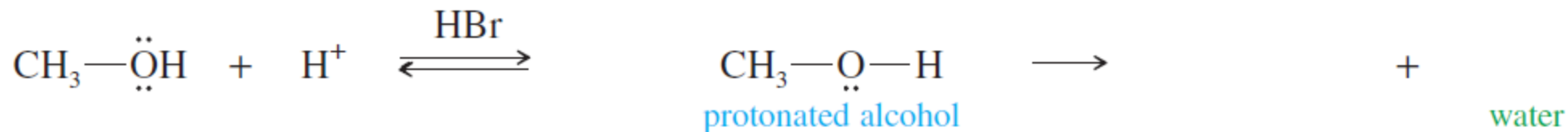
# Factors Affecting S<sub>N</sub>2 Reactions:

## 2A) Leaving-Group Effects on the Substrate

Ions that are strong bases and poor leaving groups:



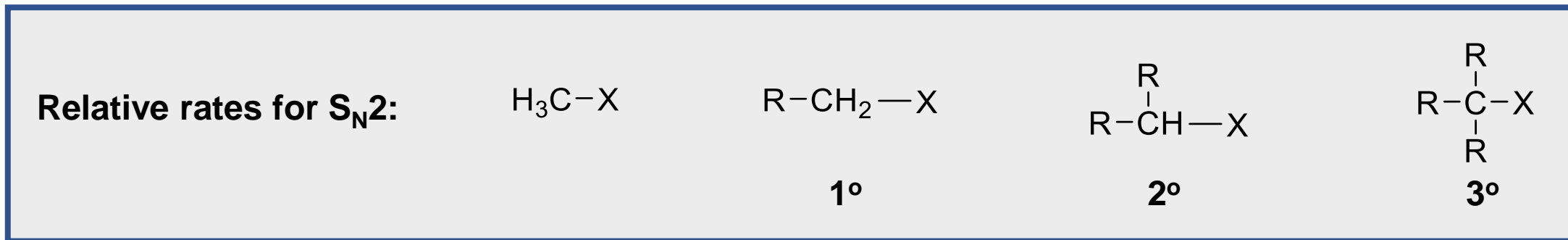
**Solution:** under \_\_\_\_\_ conditions, the hydroxyl group can be \_\_\_\_\_ to form a **positively charged** species. Water then serves as the leaving group.



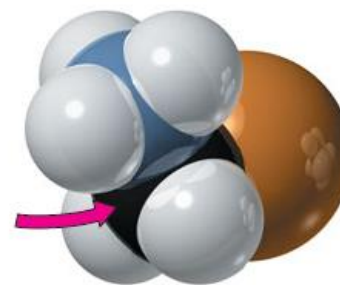
Note that the need to protonate the alcohol (requiring acid) **limits the choice of nucleophiles** to those few that are weak bases, such as bromide and iodide. A **strongly basic nucleophile would become protonated** in acid.

# Factors Affecting S<sub>N</sub>2 Reactions:

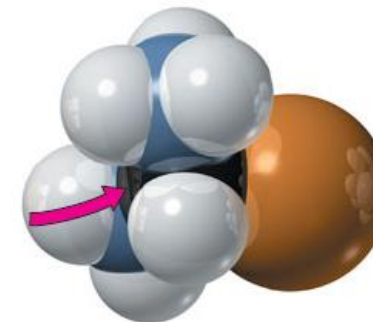
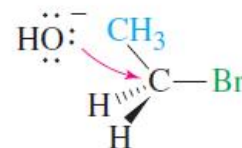
## 2B) Steric Effects on the Substrate



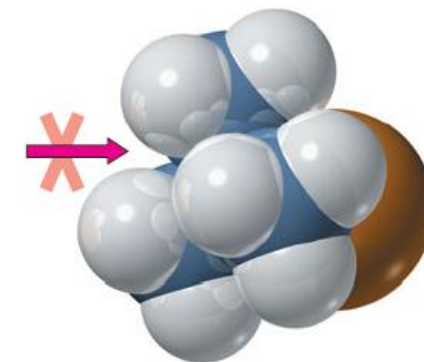
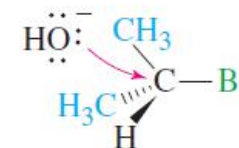
Class of Halide	Example	Relative Rate
methyl	$\text{CH}_3-\text{Br}$	>1000
primary (1°)	$\text{CH}_3\text{CH}_2-\text{Br}$	50
secondary (2°)	$(\text{CH}_3)_2\text{CH}-\text{Br}$	1
tertiary (3°)	$(\text{CH}_3)_3\text{C}-\text{Br}$	<0.001
<i>n</i> -butyl (1°)	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2-\text{Br}$	20
isobutyl (1°)	$(\text{CH}_3)_2\text{CHCH}_2-\text{Br}$	2
neopentyl (1°)	$(\text{CH}_3)_3\text{CCH}_2-\text{Br}$	0.0005



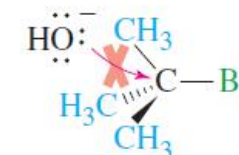
ethyl bromide (1°)  
attack is easy



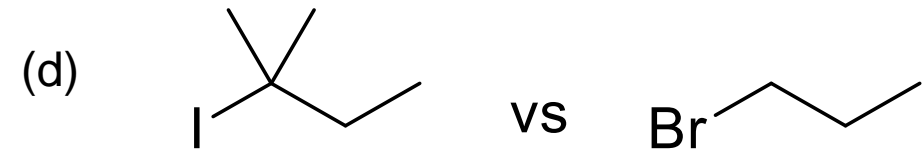
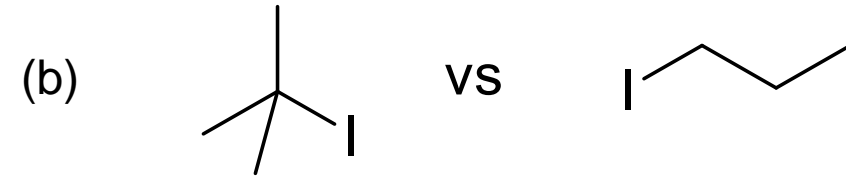
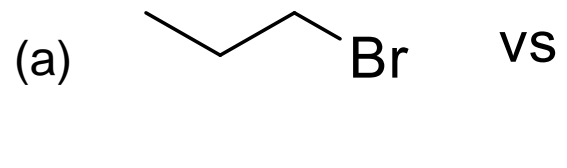
isopropyl bromide (2°)  
attack is possible



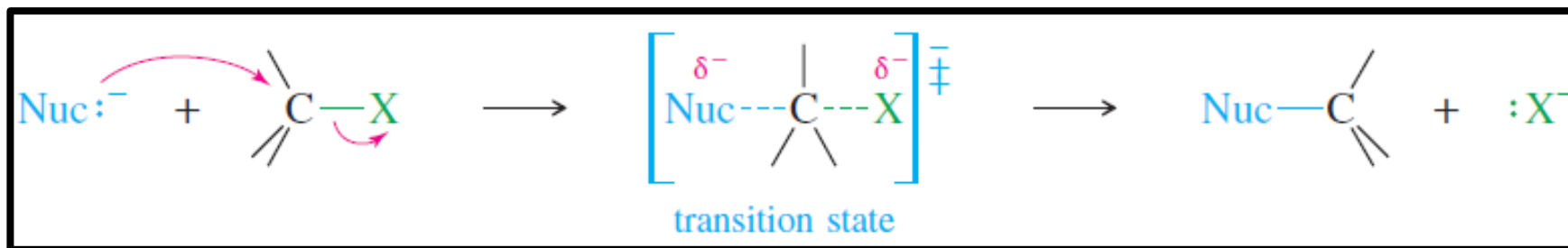
*tert*-butyl bromide (3°)  
attack is impossible



**Example 5** Which substrate will react faster by the S<sub>N</sub>2 mechanism.



## Summary



### 1) Nucleophile

1A) Strength

1B) Steric effect

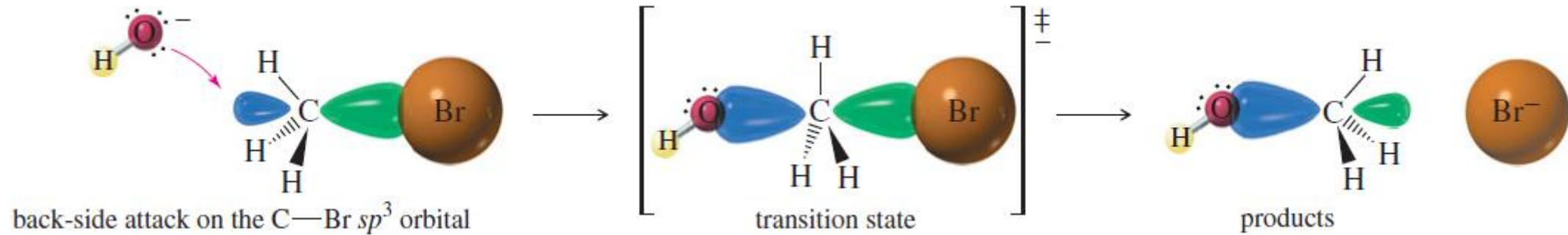
1C) Solvent effects

### 2) Substrate

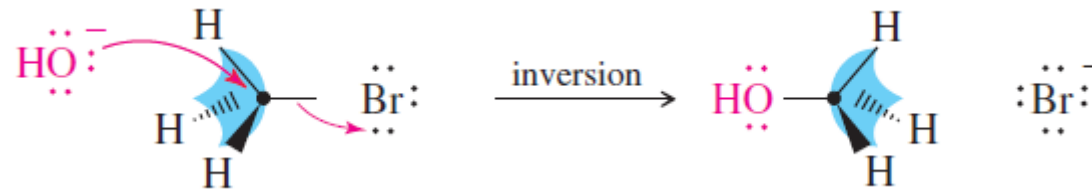
2A) Leaving-Group Effects

2B) Steric effect

# Stereochemistry of S<sub>N</sub>2 Reaction

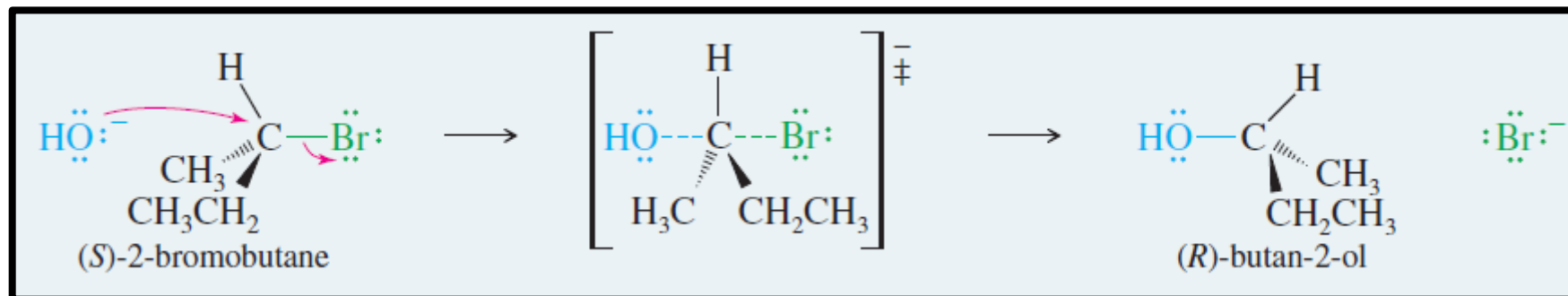


**Back-side attack** literally turns the tetrahedron of the carbon atom inside out, like an umbrella caught by the wind



# Stereochemistry of S<sub>N</sub>2 Reaction

In the case of an asymmetric carbon atom, back-side attack gives the **opposite configuration** of the carbon atom. We call this result an **inversion of configuration** at the carbon atom.



**Example 6** Predict the stereochemistry of the product in the following reaction

