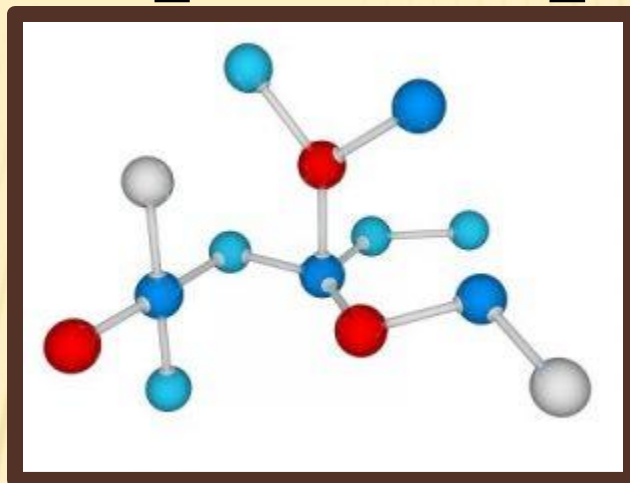


# Nucleophilic Substitution Reactions

## $SN_1$ and $SN_2$



**Dr Syed Gohar Taqi Kazimi**

Department of Chemistry  
University of Sargodha



# Substitution reaction

A chemical **reaction** in which an atom or group of atoms (functional group) of a molecule is replaced by another atom or functional group.

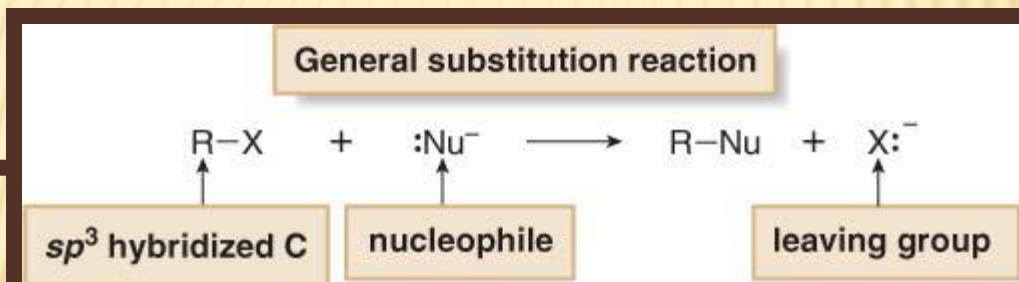
There are mainly two types of this reaction

**Electrophilic substitutions** involve displacement of a functional group by an electrophile (generally a hydrogen atom). Electrophiles are species that are attracted to electrons.

**Nucleophilic substitutions** involve attack of a positively charged (or partially positively charged) atom or group by a nucleophile.

# Nucleophilic Substitution Reaction

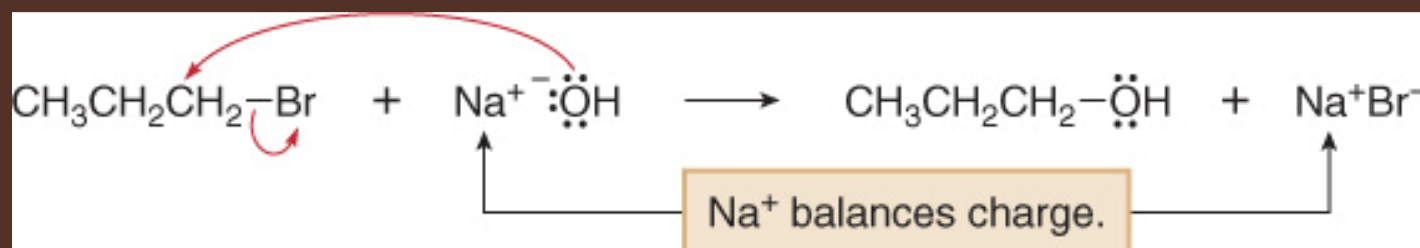
- In nucleophilic substitution reactions, the C–X bond of the substrate undergoes heterolysis, and the lone-pair electrons of the nucleophile is used to form a new bond to the carbon atom. Three components are necessary in any substitution reaction.



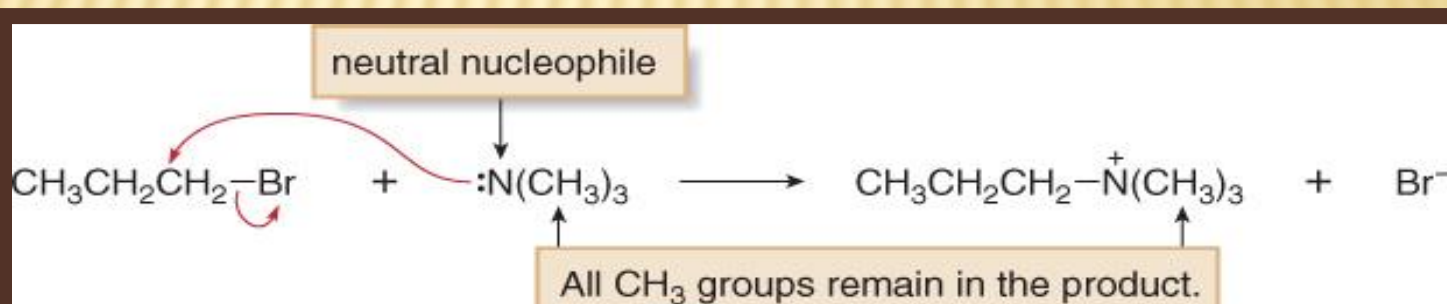
General Reaction for Nucleophilic Substitution of an Alkyl Halide by Hydroxide Ion.



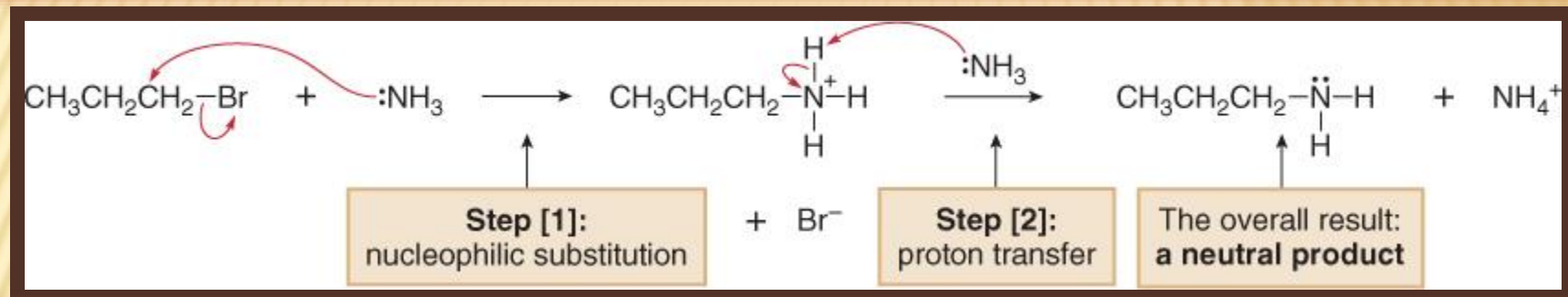
Negatively charged nucleophiles like  $\text{HO}^-$  and  $\text{HS}^-$  are used as salts with  $\text{Li}^+$ ,  $\text{Na}^+$ , or  $\text{K}^+$  counter ions to balance the charge. Since the identity of the counter ion is usually in consequential, it is often omitted from the chemical equation.



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



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 Bronsted-Lowry acid-base reaction, forming a neutral product.



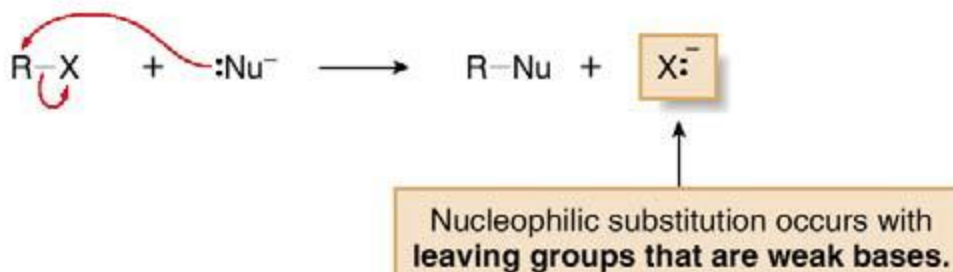
To draw any nucleophilic substitution product:

- Find the *sp<sup>3</sup> hybridized carbon with the leaving group*.
- Identify the nucleophile, the species with a lone pair or  $\pi$  bond.
- Substitute the nucleophile for the leaving group and assign charges (if necessary) to any atom that is involved in bond breaking or bond formation.

# The Leaving Group

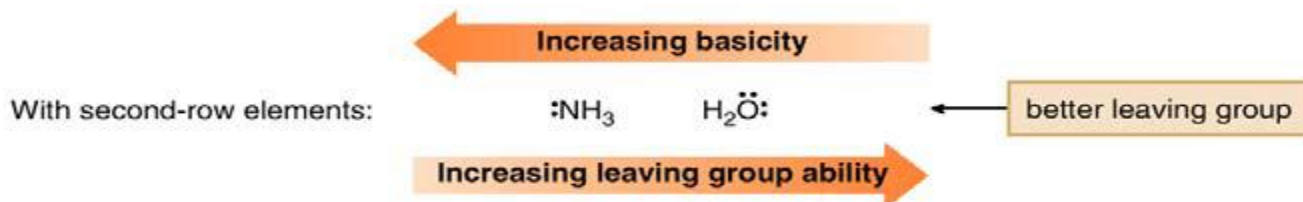
In a nucleophilic substitution reaction of  $R-X$ , the  $C-X$  bond is heterolytically cleaved, and the leaving group departs with the electron pair in that bond, forming  $X:^-$ . The more stable the leaving group  $X:^-$ , the better able it is to accept an electron pair. For example,  $H_2O$  is a better leaving group than  $HO^-$  because  $H_2O$  is a weaker base.

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

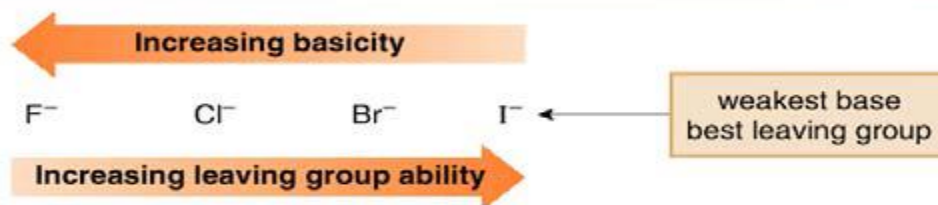


There are periodic trends in leaving group ability:

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



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



**Table 7.2**

**Good Leaving Groups for Nucleophilic Substitution**

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

These molecules undergo nucleophilic substitution.

good leaving groups

**Table 7.3**

**Poor Leaving Groups for Nucleophilic Substitution**

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

These molecules do *not* undergo nucleophilic substitution.

poor leaving groups

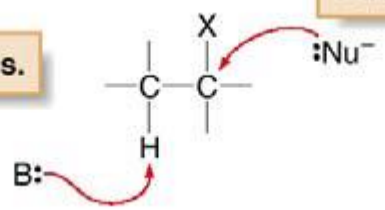
# Nucleophile

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).

Bases attack protons.

Nucleophiles attack 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<sub>a</sub>* 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  $\text{HO}^-$  and  $\text{CH}_3\text{COO}^-$ , two oxygen nucleophiles, is determined by comparing the *pK<sub>a</sub>* values of their conjugate acids ( $\text{H}_2\text{O} = 15.7$ , and  $\text{CH}_3\text{COOH} = 4.8$ ).  $\text{HO}^-$  is a stronger base and stronger nucleophile than  $\text{CH}_3\text{COO}^-$ .
2. A negatively charged nucleophile is always a stronger nucleophile than its conjugate acid.  $\text{HO}^-$  is a stronger base and stronger nucleophile than  $\text{H}_2\text{O}$ .
3. Right-to-left-across a row of the periodic table, nucleophilicity increases as basicity increases:

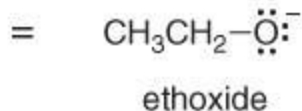
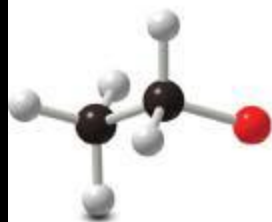
For second-row elements  
with the same charge:



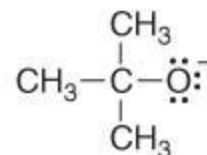
Increasing basicity  
Increasing nucleophilicity

## 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.



stronger nucleophile



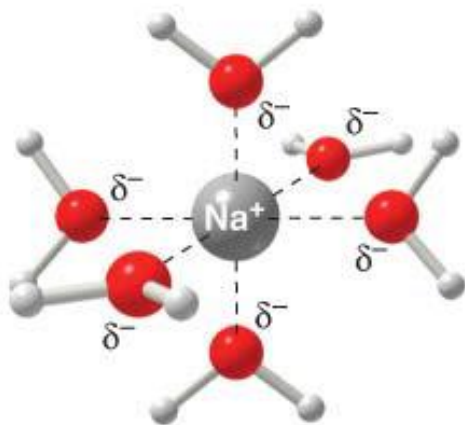
*tert*-butoxide

stronger base

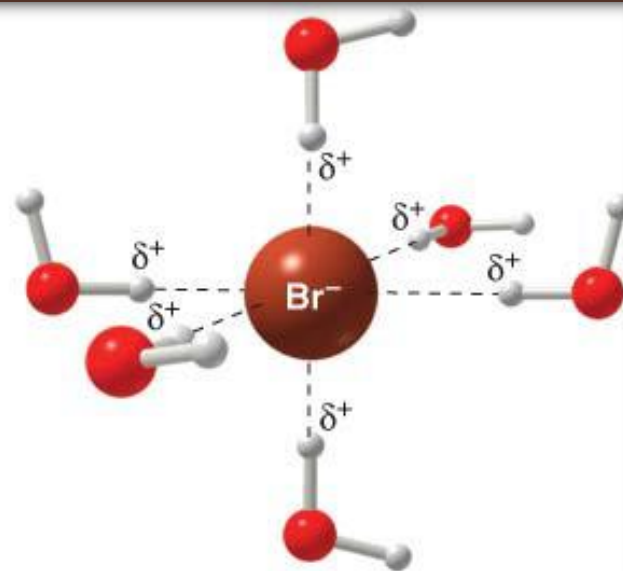


Three  $\text{CH}_3$  groups sterically hinder the O atom,  
making it a **weaker nucleophile**.

If the salt NaBr is used as a source of the nucleophile  $\text{Br}^-$  in  $\text{H}_2\text{O}$ , the  $\text{Na}^+$  cations are solvated by ion-dipole interactions with  $\text{H}_2\text{O}$  molecules, and the  $\text{Br}^-$  anions are solvated by strong hydrogen bonding interactions.



$\text{Na}^+$  is solvated by ion-dipole interactions with  $\text{H}_2\text{O}$ .



$\text{Br}^-$  is solvated by hydrogen bonding with  $\text{H}_2\text{O}$ .

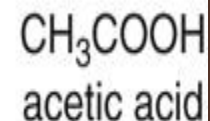
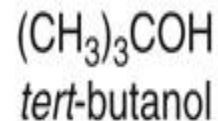
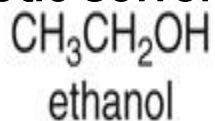
In polar protic solvents, nucleophilicity increases down a column of the periodic table as the size of the anion increases. This is the opposite of basicity.

Down a column  
of the periodic table



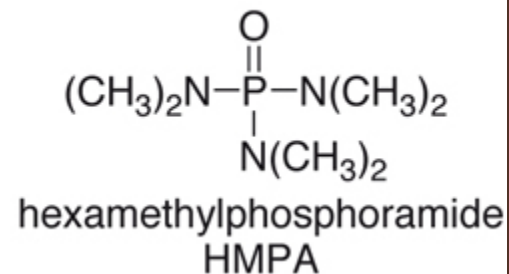
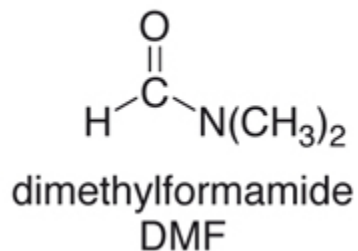
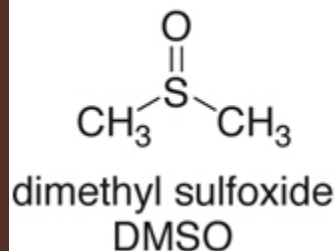
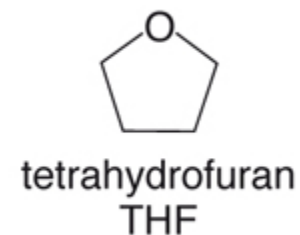
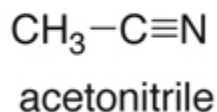
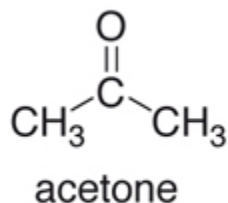
Increasing nucleophilicity  
in polar protic solvents

### Polar protic solvents



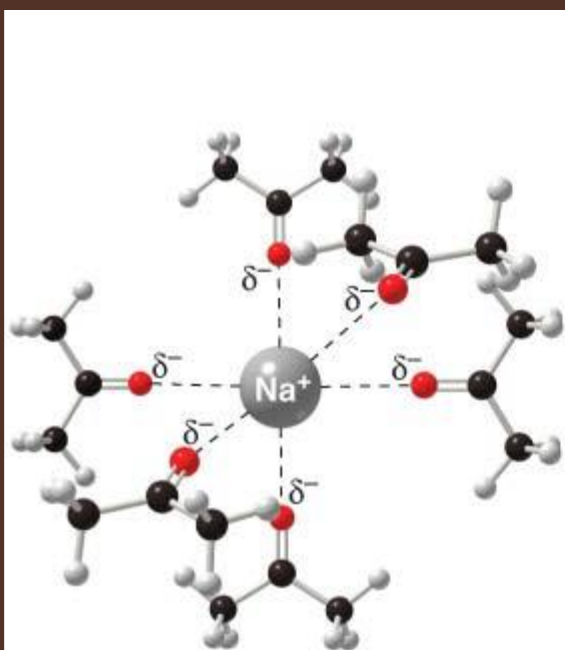
Polar aprotic solvents also exhibit dipole—dipole interactions, but they have no O—H or N—H bonds. Thus, they are incapable of hydrogen bonding.

### Polar aprotic solvents

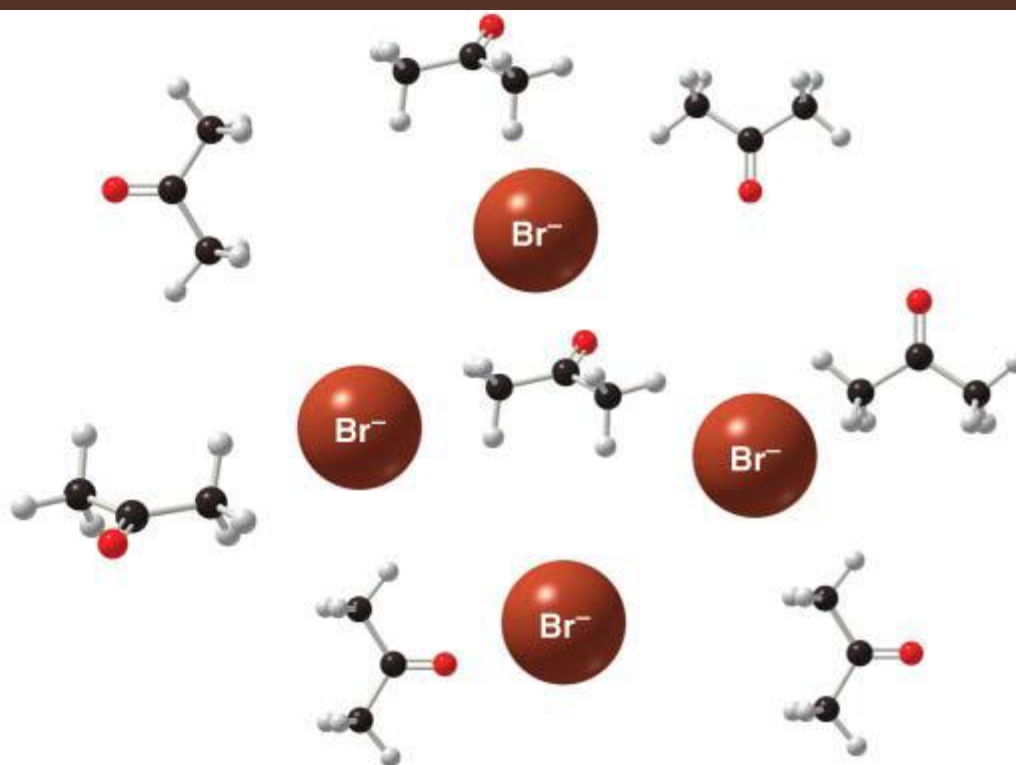


Polar aprotic solvents solvate cations by ion–dipole interactions.

- Anions are not well solvated because the solvent cannot hydrogen bond to them. These anions are said to be “naked”.



$(\text{CH}_3)_2\text{C}=\text{O}$  solvates  $\text{Na}^+$  well by ion–dipole interactions.



$\text{Br}^-$  anions are surrounded by solvent but not well solvated by the  $(\text{CH}_3)_2\text{C}=\text{O}$  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.

Down a column  
of the periodic table



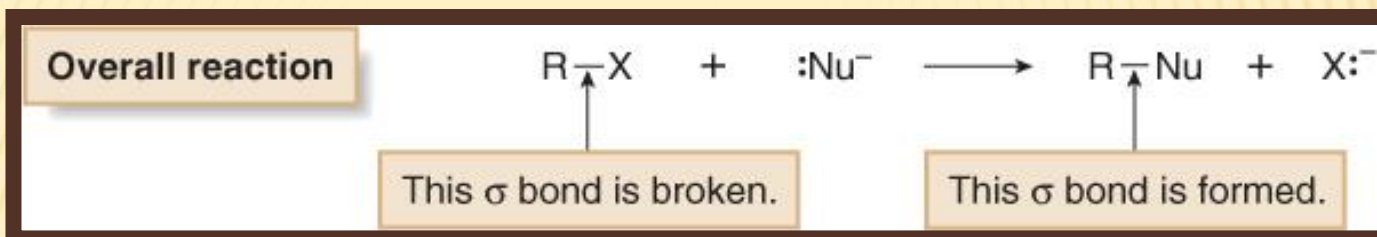
Increasing nucleophilicity  
in polar aprotic solvents

**Table 7.4**

**Common Nucleophiles in Organic Chemistry**

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

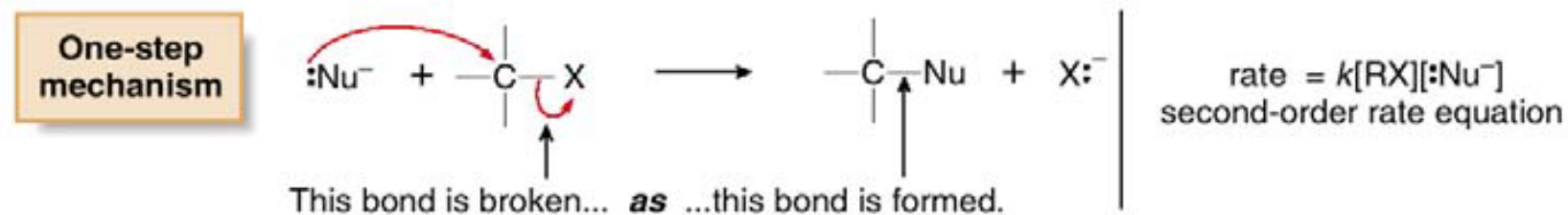
# Possible Mechanisms of Nucleophilic Substitution



But what is the order of bond making and bond breaking? There are three possibilities.

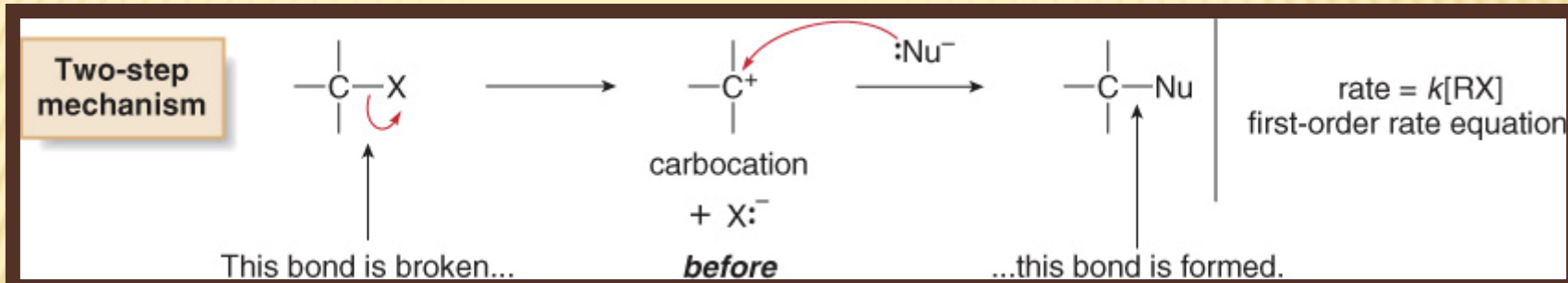
[1] ***Bond making and bond breaking occur at the same time.***

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.



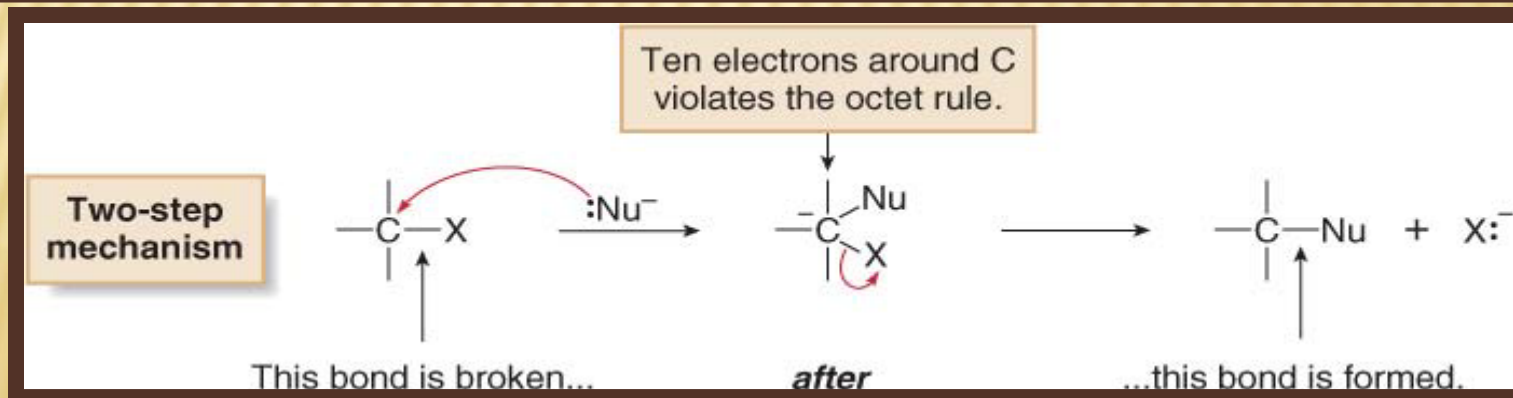
## [2] *Bond breaking occurs before bond making.*

In this case 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



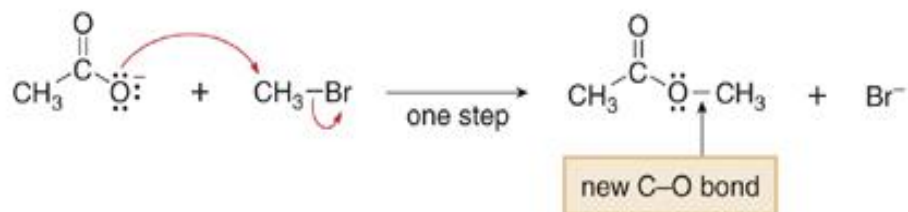


## Nucleophilic Substitution Bimolecular Reaction SN<sub>2</sub>

- The rate of the reaction depends on the concentration of Alkyl halide and the concentration of nucleophile.
- The reaction is second order overall.
- The reaction is first order with respect to alkyl halide and first order with respect to nucleophile.

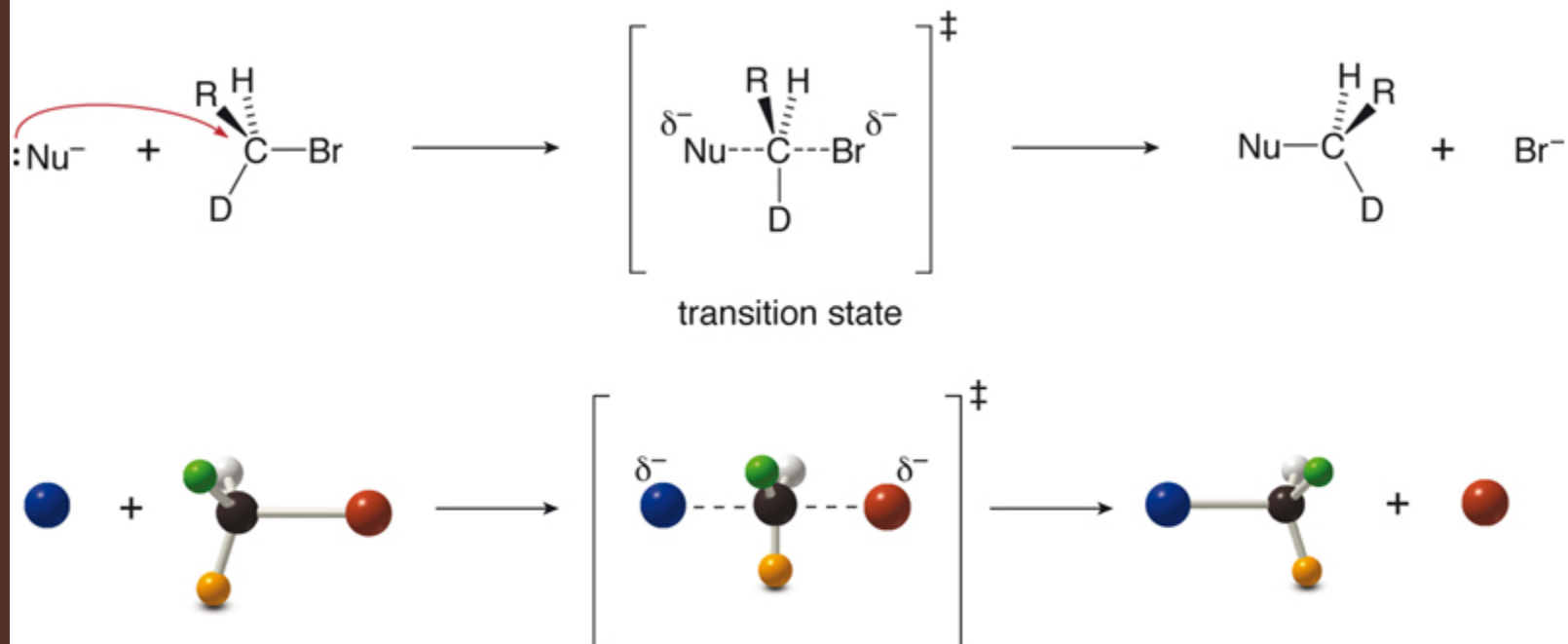
### SN<sub>2</sub> Mechanism

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



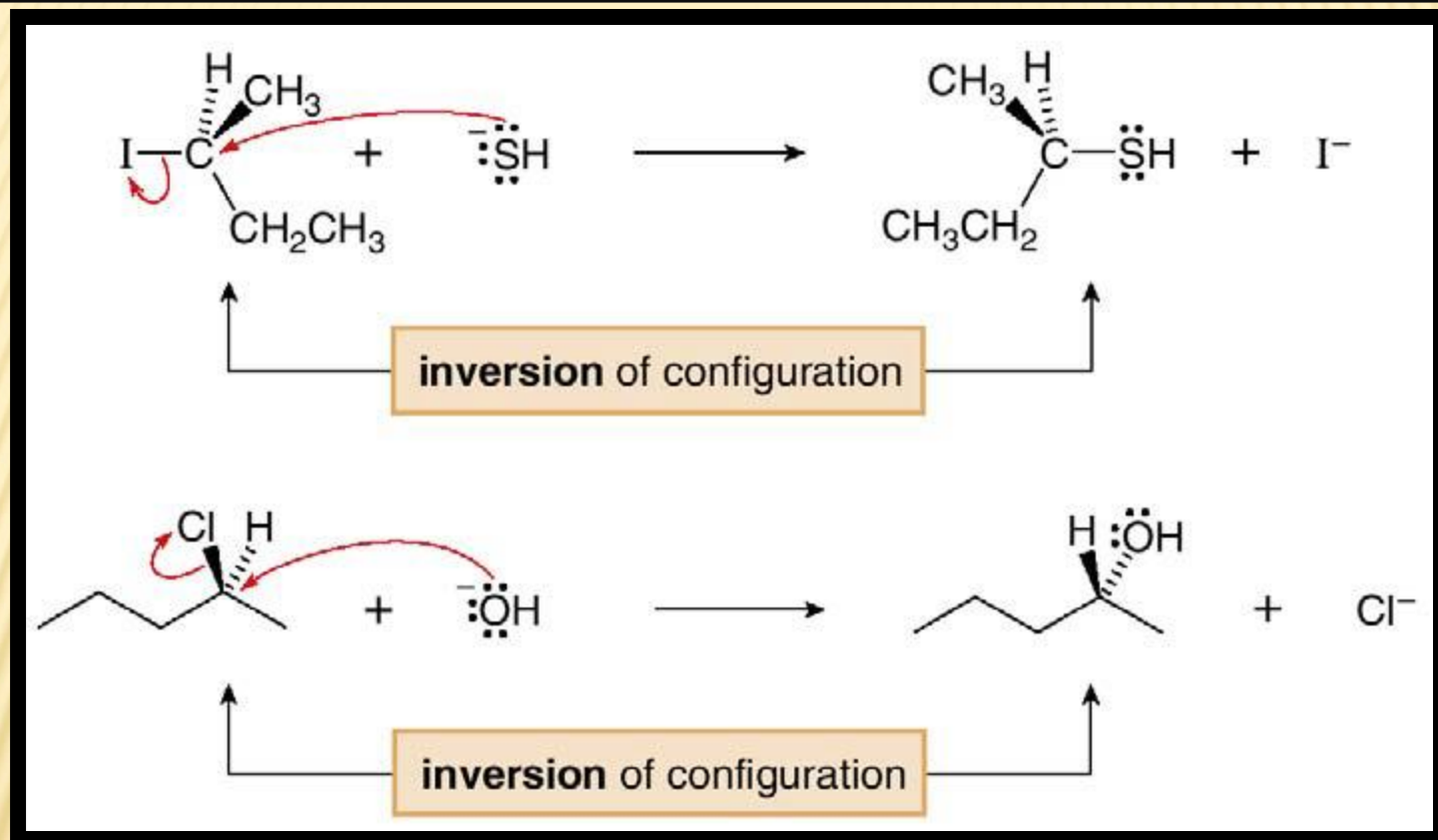
# Stereochemistry of the $S_N2$ Reaction

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



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

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



The rate of an SN<sub>2</sub> reaction depends upon 4 factors:

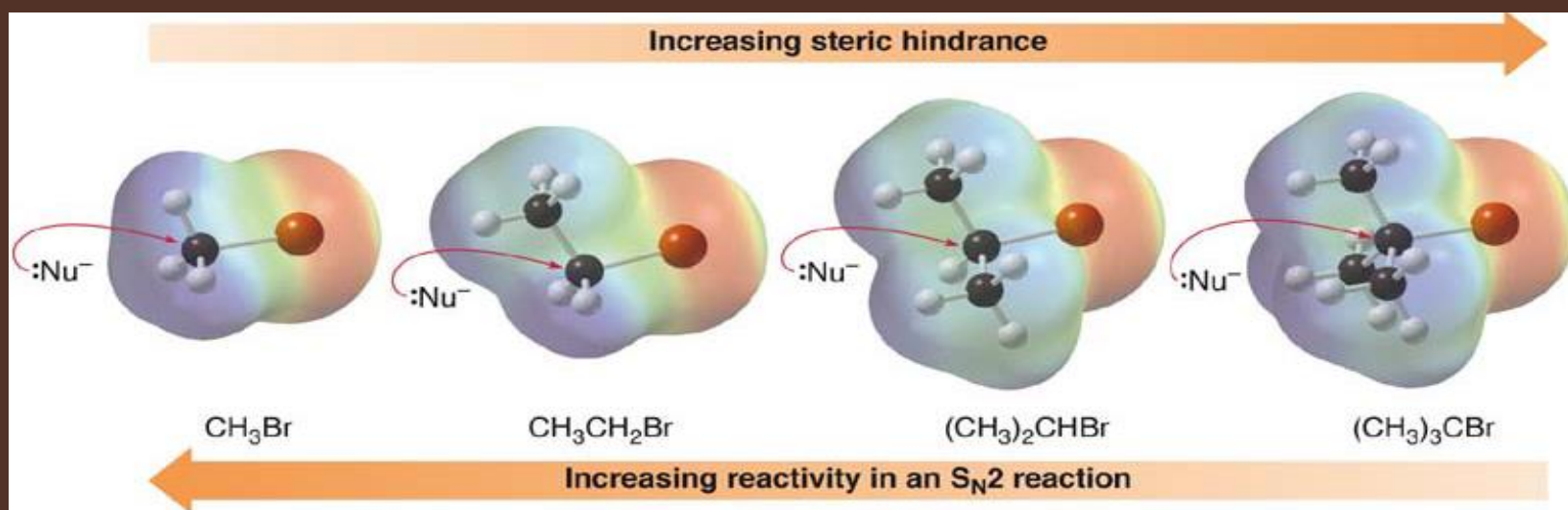
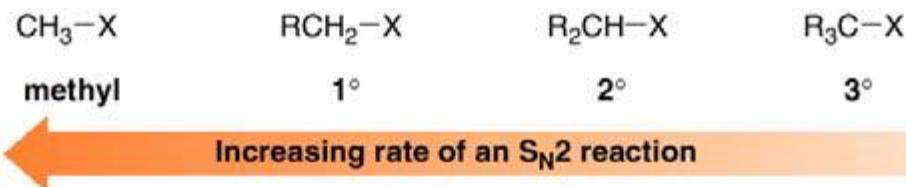
1. The nature of the substrate (the alkyl halide)
2. The power of the nucleophile
3. The ability of the leaving group to leave
4. The nature of the solvent

# Nature of the substrate

Methyl and 1° alkyl halides undergo S<sub>N</sub>2 reactions with ease.

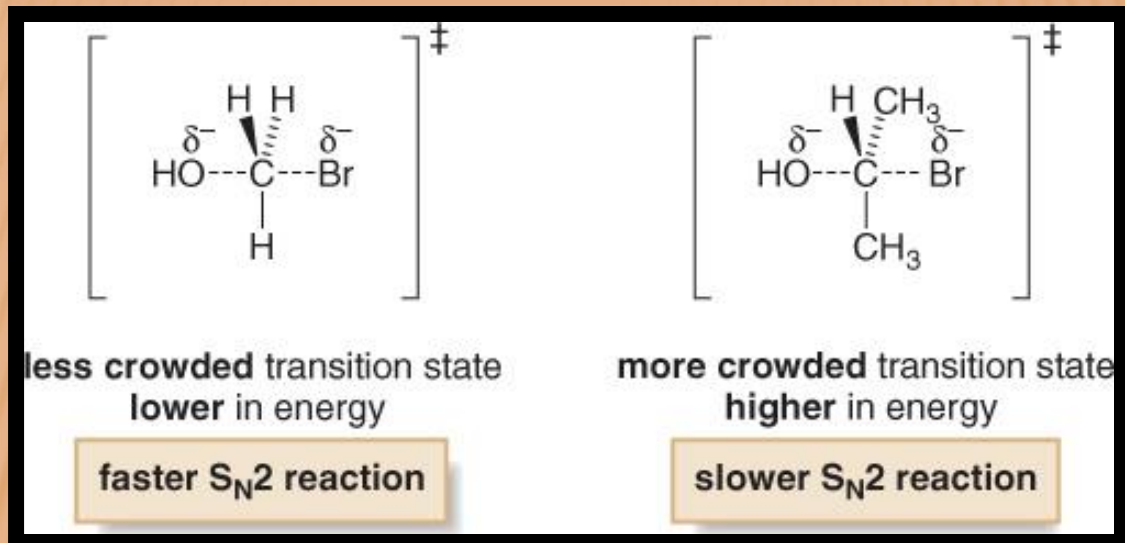
- 2° Alkyl halides react more slowly.
- 3° Alkyl halides do not undergo S<sub>N</sub>2 reactions. This order of reactivity can be explained by steric effects. Steric hindrance caused by bulky R groups makes nucleophilic attack from the backside more difficult, slowing the reaction rate.

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



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.



To be a good leaving group the substituent must be able to leave as a relatively stable, weakly basic molecule or ion.

- In alkyl halides the leaving group is the halogen substituent -- it leaves as a halide ion.
- Because halide ions are relatively stable and very weak bases, they are good leaving groups.

## Overview

- The nucleophile attacks the carbon bearing the leaving group from the back side.
  - The bond formation between the nucleophile and the carbon atom, and the bond breaking between the carbon atom and the leaving group occurs simultaneously.
  - The configuration of the carbon atom becomes inverted during  $\text{SN}_2$  reaction.
  - Because bond formation and bond breaking occur simultaneously in a single transition state, the  $\text{SN}_2$  reaction is a concerted reaction.
- Rate of reaction depends upon two species i.e., alkyl halide and attacking nucleophile.

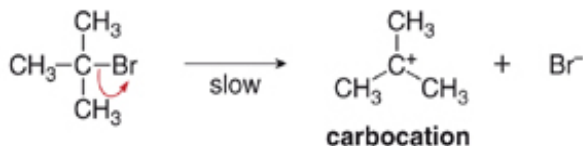
# Nucleophilic Substitution Unimolecular Reaction SN1

The rate of this reaction depends only on the concentration of one reactant, alkyl halide

- SN1 reactions happen in two steps: 1. The leaving group leaves, and the substrate forms a carbocation intermediate. 2. The nucleophile attacks the carbocation, forming the product.

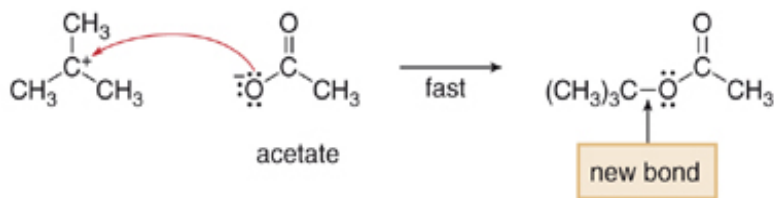
## SN1 Mechanism

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.

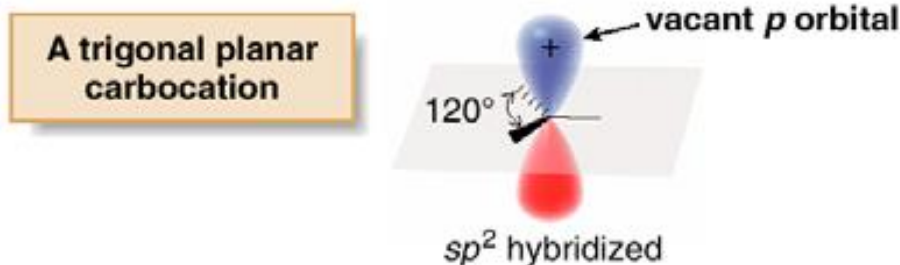
Step [2] The C-O bond is formed.



- **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.

## Stereochemistry of the $S_N1$ Reaction

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

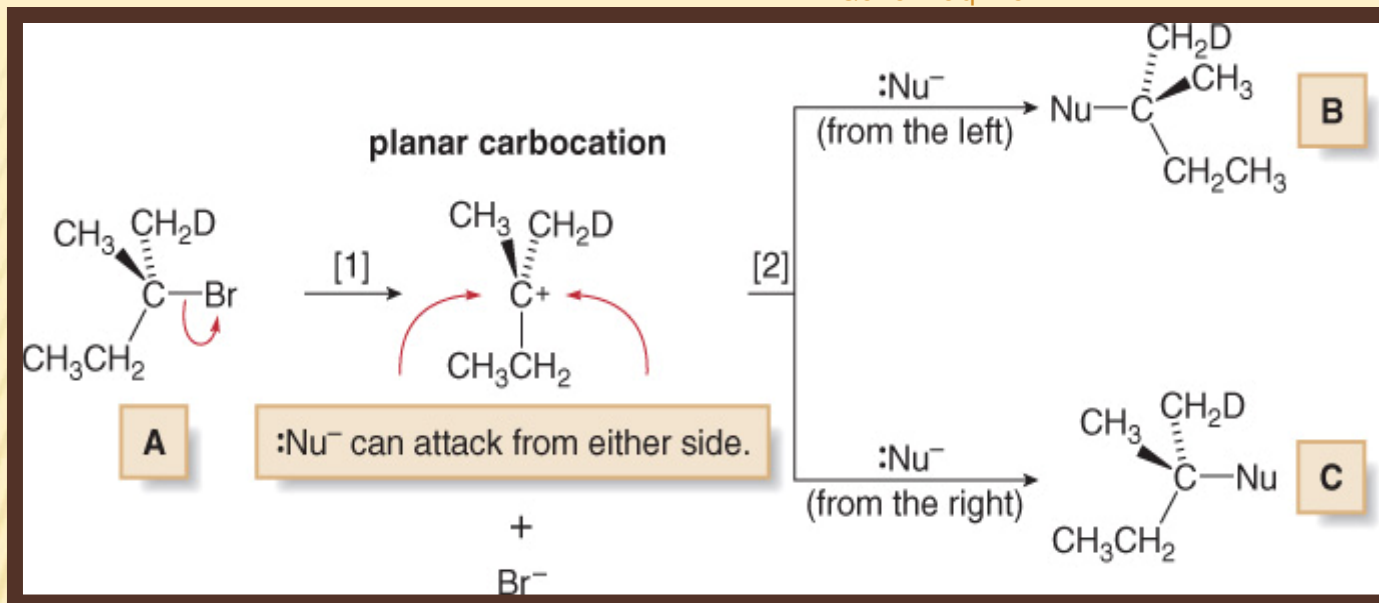


- A carbocation (with three groups around C) is  $sp^2$  hybridized and trigonal planar, and contains a vacant  $p$  orbital extending above and below the plane.

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.

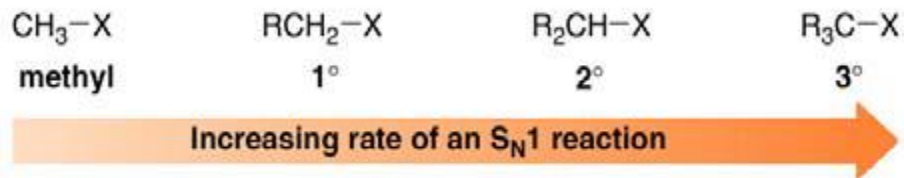




## Nature of Substrate

The rate of an  $\text{S}_{\text{N}}1$  reaction is affected by the type of alkyl halide involved

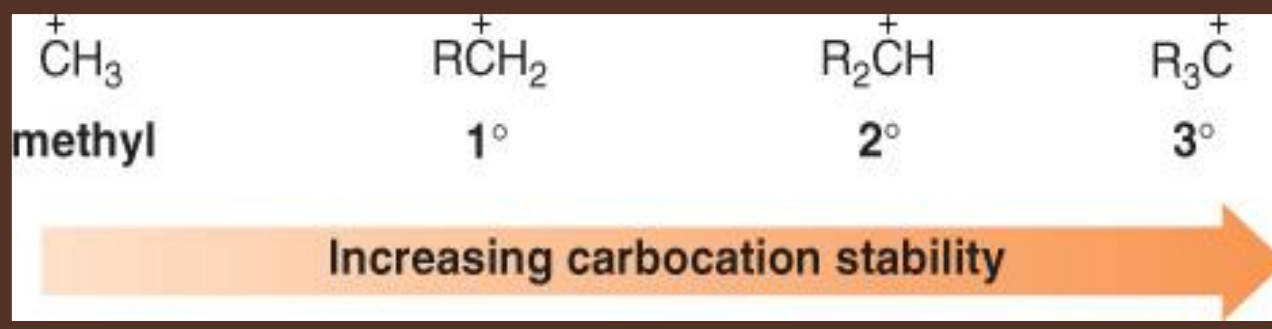
- As the number of R groups on the carbon with the leaving group *increases*, the rate of an  $\text{S}_{\text{N}}1$  reaction *increases*.



This trend is exactly opposite to that observed in  $\text{S}_{\text{N}}2$  reactions.

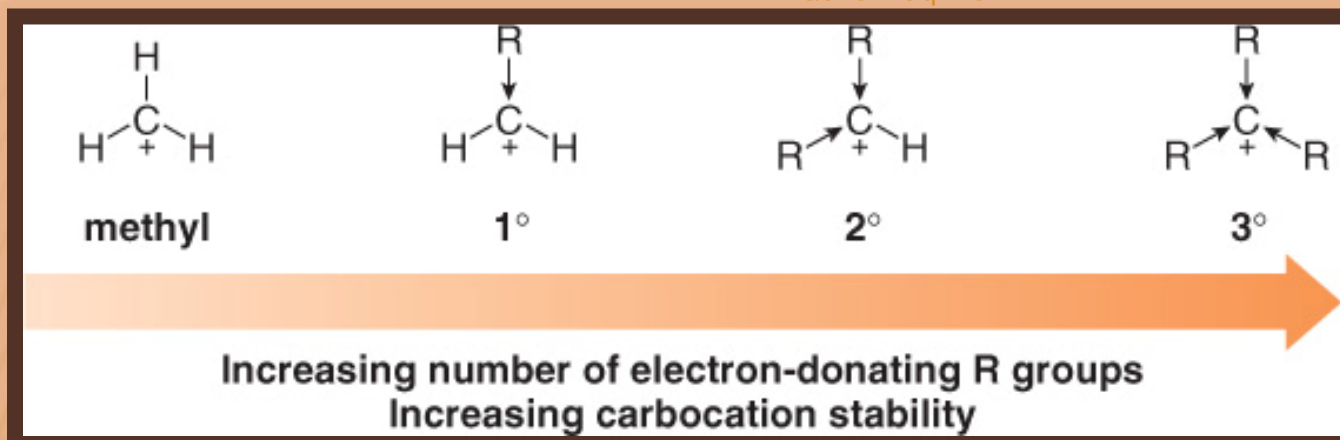
# Carbocation Stability

- 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 ( $1^\circ$ ), secondary ( $2^\circ$ ), or tertiary ( $3^\circ$ ), based on the number of R groups bonded to the charged carbon atom. As the number of R groups increases, carbocation stability increases.

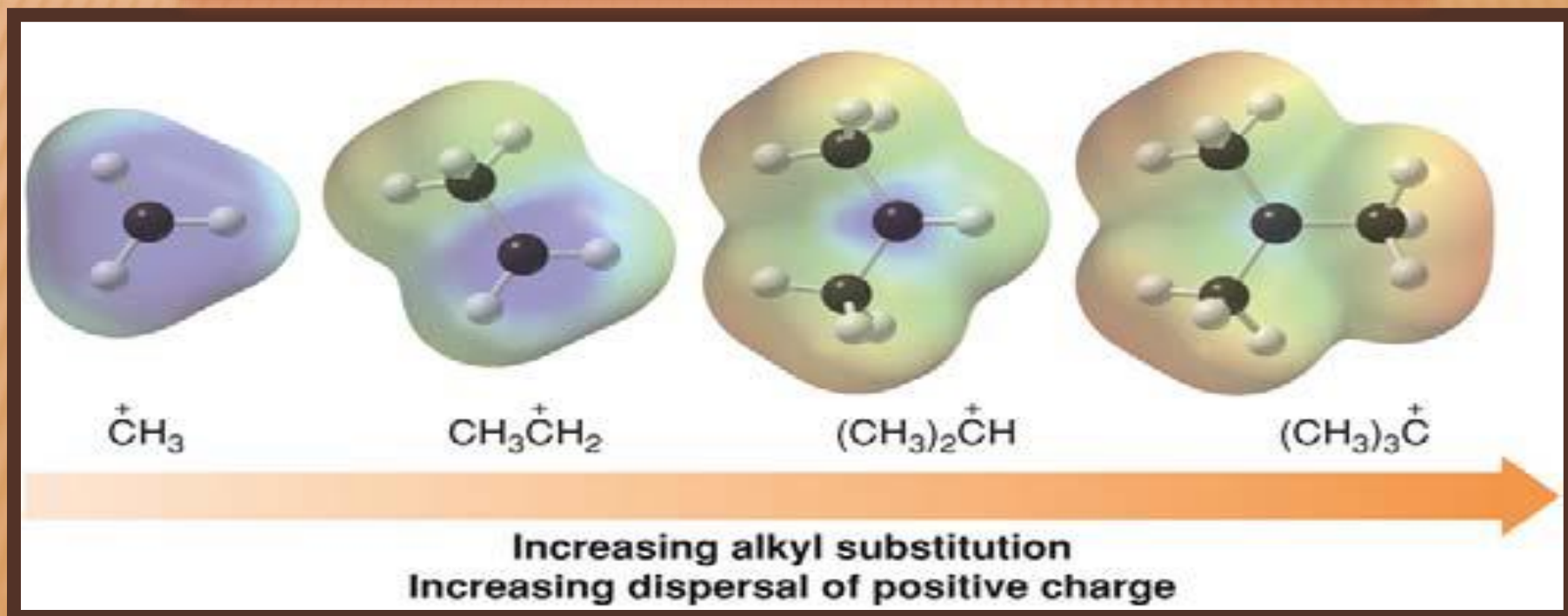


## Inductive Effect

- Carbocation stability depends upon inductive effects & hyperconjugation.
- Inductive effects are electronic effects that occur through  $\sigma$  bonds. The inductive effect is the pull of electron density through  $\sigma$  bonds caused by EN differences between Atoms.
- Alkyl groups are electron donating groups that stabilize a positive charge. Since an alkyl group has several  $\sigma$  bonds, each containing electron density, it is more polarizable than a hydrogen atom, and better able to donate electron density.
- The greater the no. of alkyl groups attached to a carbon with a positive charge, the more stable will be the cation.

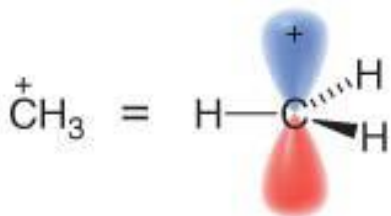


### Electrostatic potential maps for different carbocations

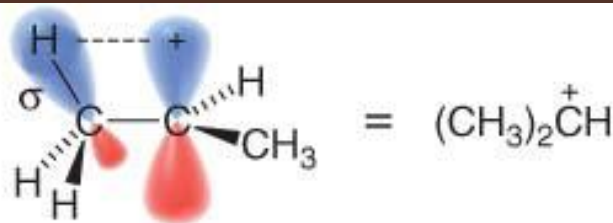


# Hyperconjugation

- 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  $\sigma$  bond. This overlap (hyperconjugation) delocalizes the positive charge on the carbocation, spreading it over a larger volume, and this stabilizes the carbocation.*
- Example:  $\text{CH}_3^+$  cannot be stabilized by hyperconjugation, but  $(\text{CH}_3)_2\text{CH}^+$  can



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

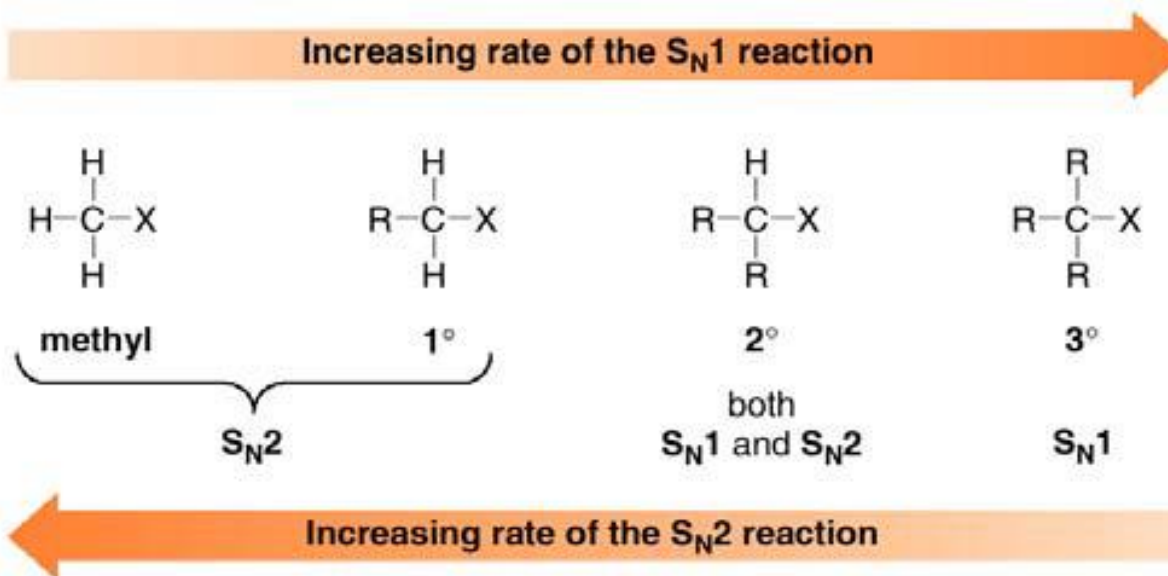


Overlap of the C—H  $\sigma$  bond with the adjacent vacant *p* orbital stabilizes the carbocation.

## The Alkyl Halide-The Most Important Factor

- Among Four factors the most important is the identity of the alkyl halide.

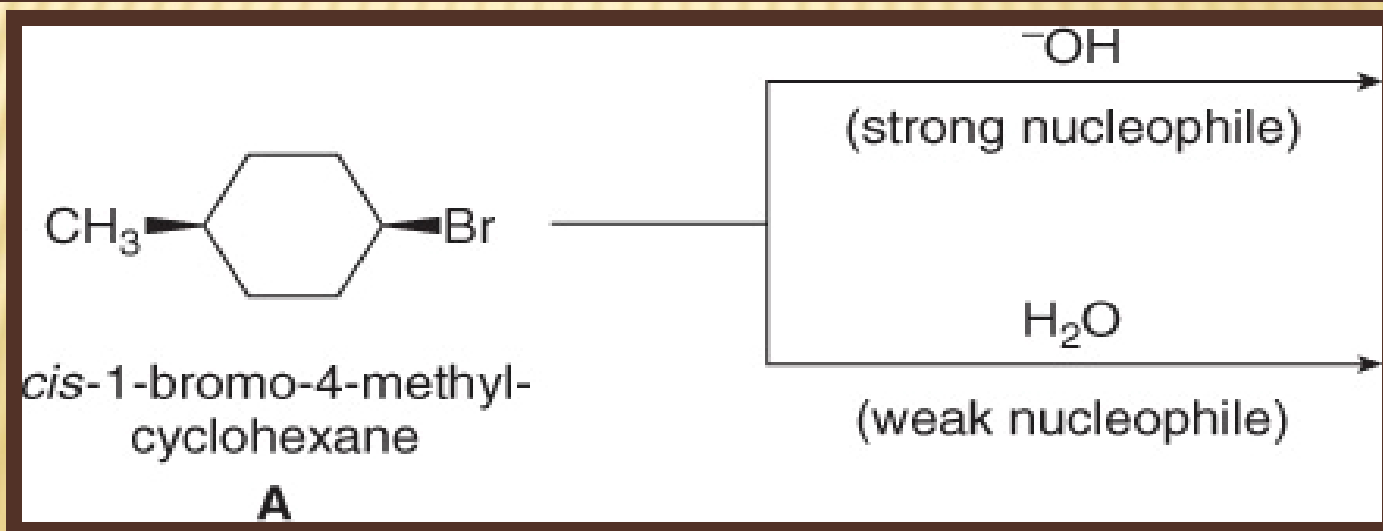
- Increasing alkyl substitution favors  $S_N1$ .
- Decreasing alkyl substitution favors  $S_N2$ .



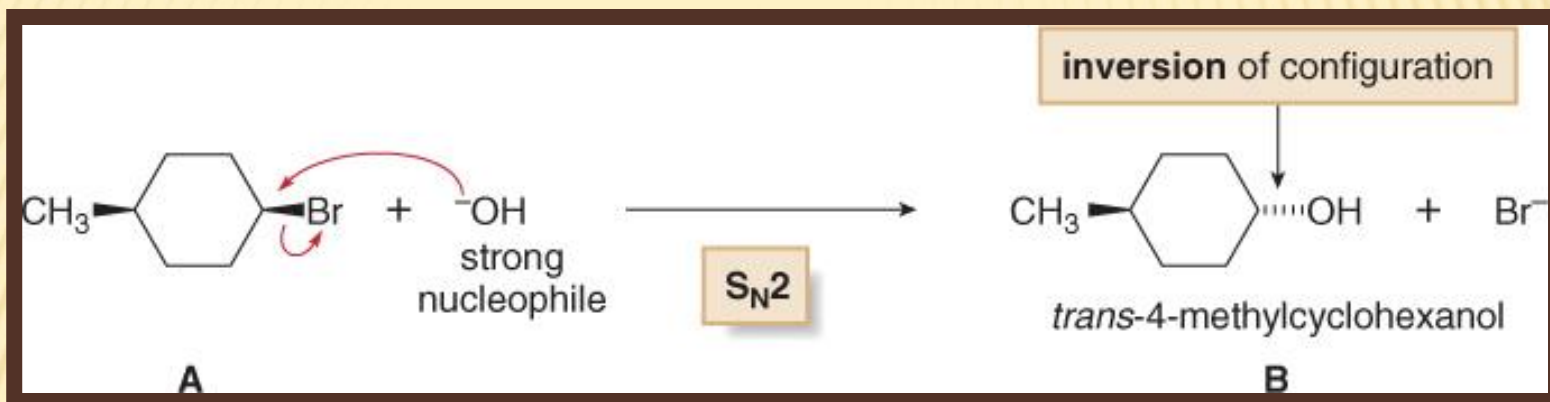
- Methyl and  $1^\circ$  halides ( $\text{CH}_3\text{X}$  and  $\text{RCH}_2\text{X}$ ) undergo  $S_N2$  reactions only.
- $3^\circ$  Alkyl halides ( $\text{R}_3\text{CX}$ ) undergo  $S_N1$  reactions only.
- $2^\circ$  Alkyl halides ( $\text{R}_2\text{CHX}$ ) undergo both  $S_N1$  and  $S_N2$  reactions.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

# The Nucleophile

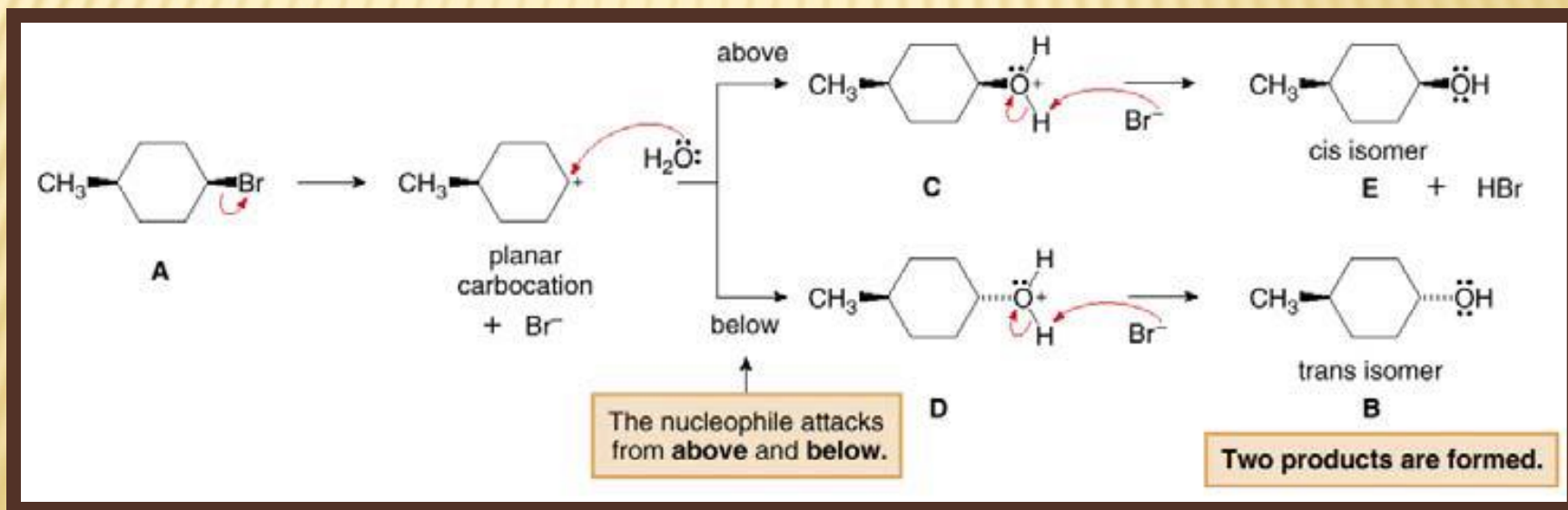
- Rate of SN also depends on nucleophile.
- Strong nucleophiles having negative charge and present in high concentrations favor SN<sub>2</sub> reactions.
- Weak nucleophiles, such as H<sub>2</sub>O and ROH favor SN<sub>1</sub> reactions by decreasing the rate of any competing SN<sub>2</sub> reaction.
- Let us see the products formed when the 2° alkyl halide A is treated with either the strong nucleophile HO<sup>-</sup> or the weak nucleophile H<sub>2</sub>O. Since a 2° alkyl halide can react by either mechanism, the strength of the nucleophile determines which mechanism takes place.



## The strong nucleophile favors an $S_N2$ mechanism.



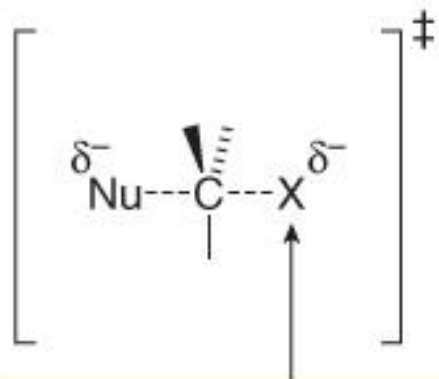
## The weak nucleophile favors an $S_N1$ mechanism.



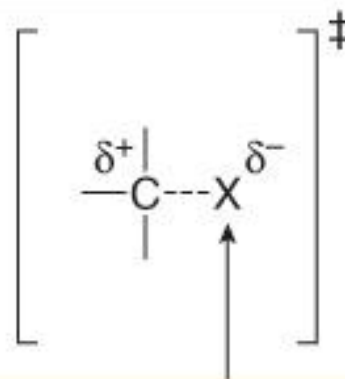
# The Leaving Group

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.

R-F

R-Cl

R-Br

R-I

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



# The Solvent

- The nature of the solvent is a fourth factor.
- Polar protic solvents like H<sub>2</sub>O and ROH favor S<sub>N</sub>1 reactions because the ionic intermediates are stabilized by solvation.
- Polar aprotic solvents favor S<sub>N</sub>2 reactions because nucleophiles are not well solvated, and therefore, are more nucleophilic.

## Summary of Factors that Determine the S<sub>N</sub>1 or S<sub>N</sub>2 Mechanism

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