

Nucleophilic Substitution Reactions

SN_1 and SN_2

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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.

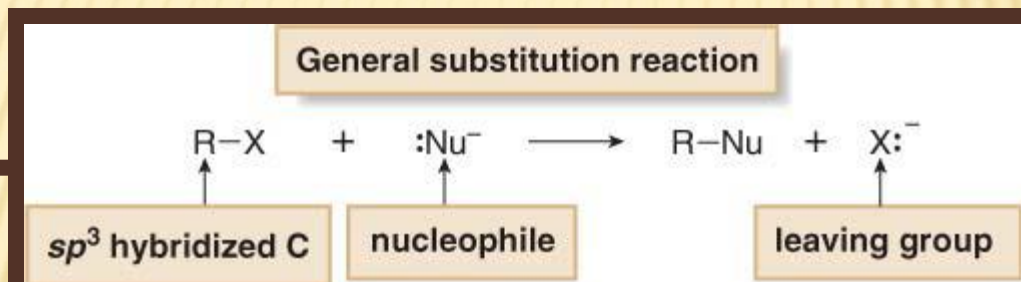
There are mainly two types of this reaction

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

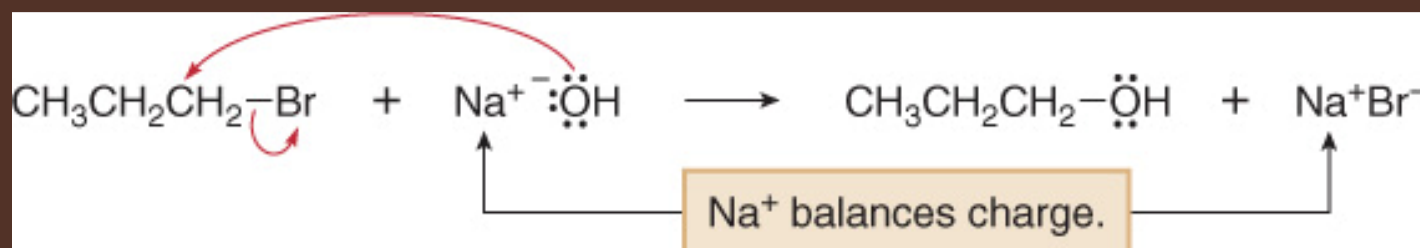
- In nucleophilic substitution reactions, the C–X bond of the substrate undergoes heterolysis, and the lone-pair electrons of the nucleophile is used to form a new bond to the carbon atom. Three components are necessary in any substitution reaction.



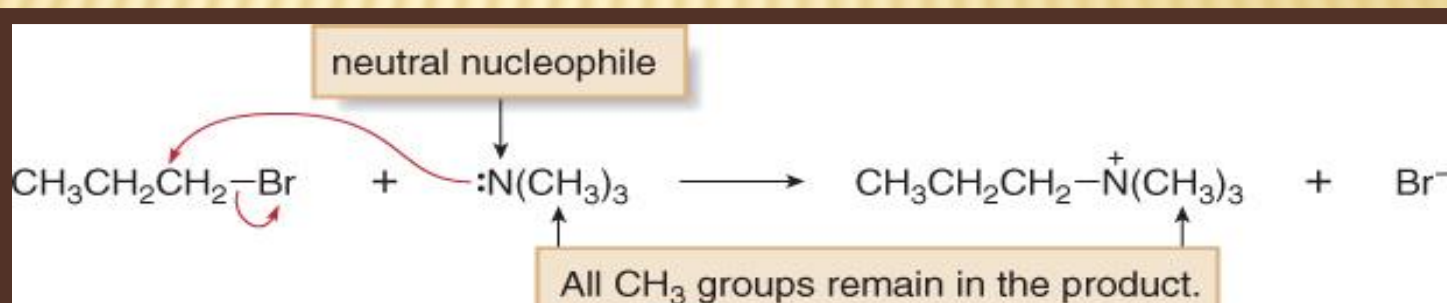
General Reaction for Nucleophilic Substitution of an Alkyl Halide by Hydroxide Ion.



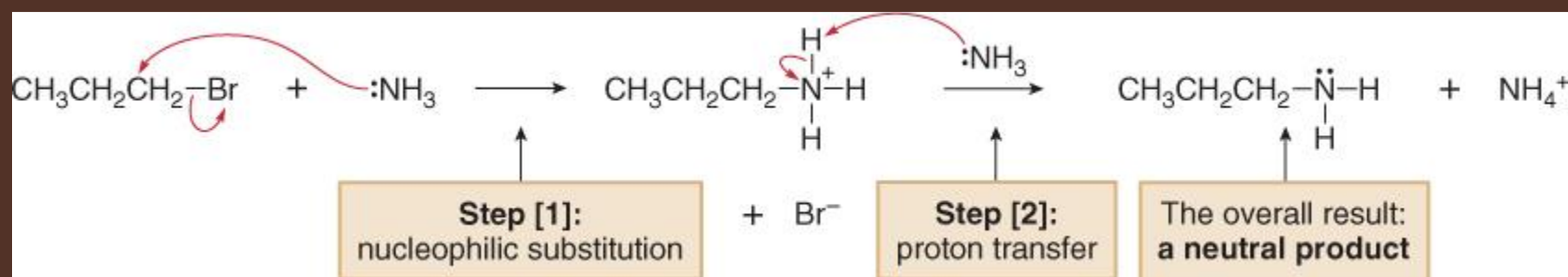
Negatively charged nucleophiles like HO^- and HS^- are used as salts with Li^+ , Na^+ , or K^+ counter ions to balance the charge. Since the identity of the counter ion is usually inconsequential, it is often omitted from the chemical equation.



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 *sp³ hybridized carbon with the leaving group*.
- Identify the nucleophile, the species with a lone pair or π bond.
- Substitute the nucleophile for the leaving group and assign charges (if necessary) to any atom that is involved in bond breaking or bond formation.

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.

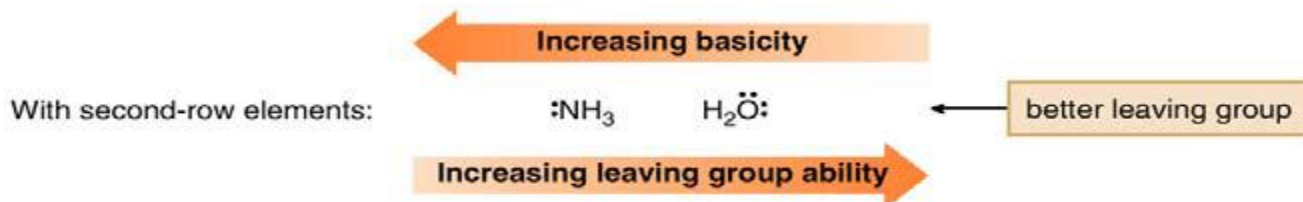
- In comparing two leaving groups, the better leaving group is the weaker base.



Nucleophilic substitution occurs with leaving groups that are weak bases.

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*.

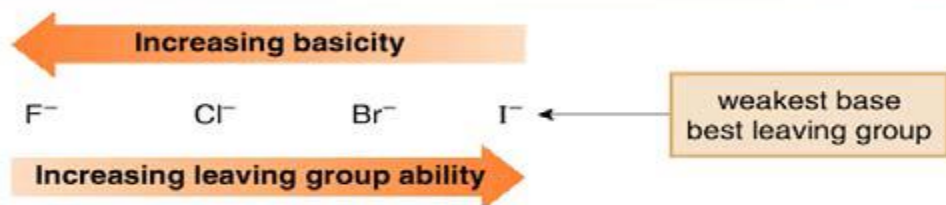


Table 7.2

Good Leaving Groups for Nucleophilic Substitution

Starting material	Leaving group	Conjugate acid	pK_a
R-Cl	Cl^-	HCl	-7
R-Br	Br^-	HBr	-9
R-I	I^-	HI	-10
R-OH ₂ ⁺	H ₂ O	H ₃ O ⁺	-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 ₂ O	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.

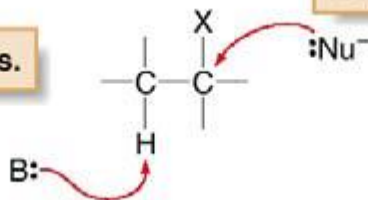
poor leaving groups

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_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 CH₃COO⁻, two oxygen nucleophiles, is determined by comparing the p*K_a* values of their conjugate acids (H₂O = 15.7, and CH₃COOH = 4.8). HO⁻ is a stronger base and stronger nucleophile than CH₃COO⁻.
2. A negatively charged nucleophile is always a stronger nucleophile than its conjugate acid. HO⁻ is a stronger base and stronger nucleophile than H₂O.
3. Right-to-left-across a row of the periodic table, nucleophilicity increases as basicity increases:

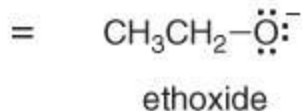
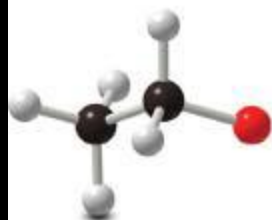
For second-row elements
with the same charge:



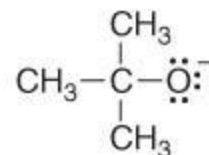
Increasing basicity
Increasing nucleophilicity

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



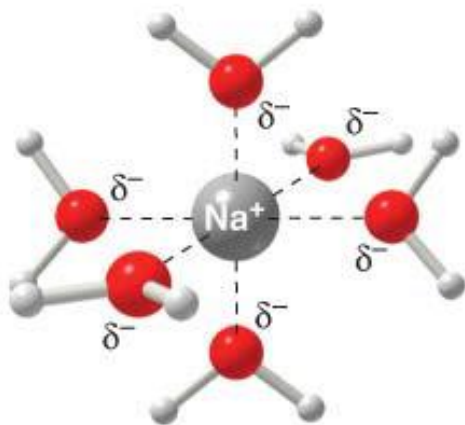
tert-butoxide

stronger base

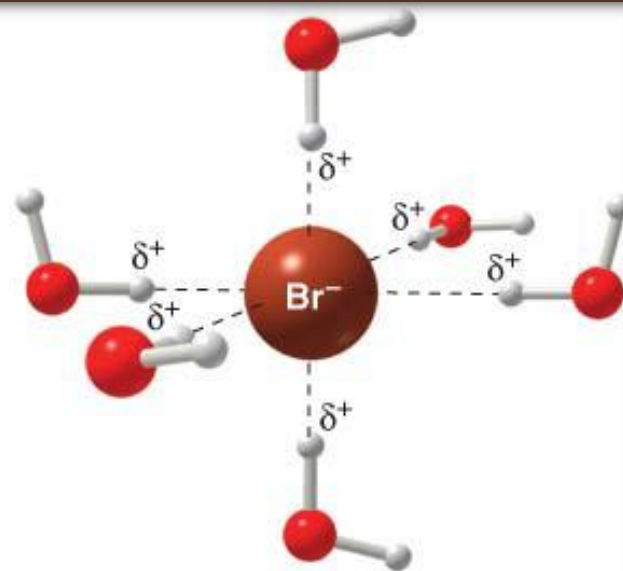


Three CH_3 groups sterically hinder the O atom, making it a **weaker nucleophile**.

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 .

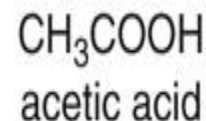
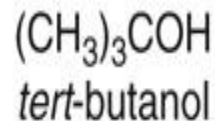
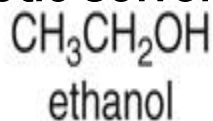
In polar protic solvents, nucleophilicity increases down a column of the periodic table as the size of the anion increases. This is the opposite of basicity.

Down a column
of the periodic table



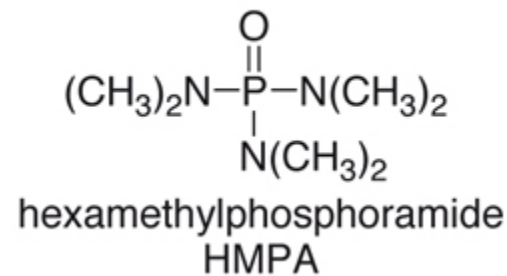
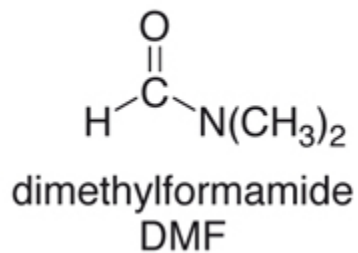
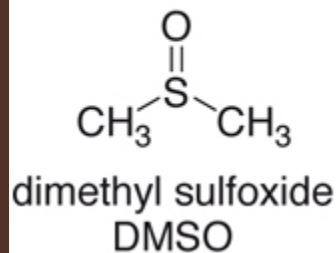
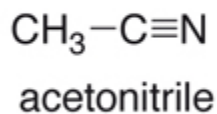
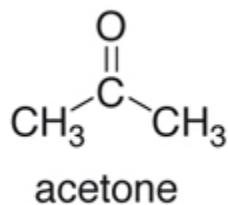
Increasing nucleophilicity
in polar protic solvents

Polar protic solvents



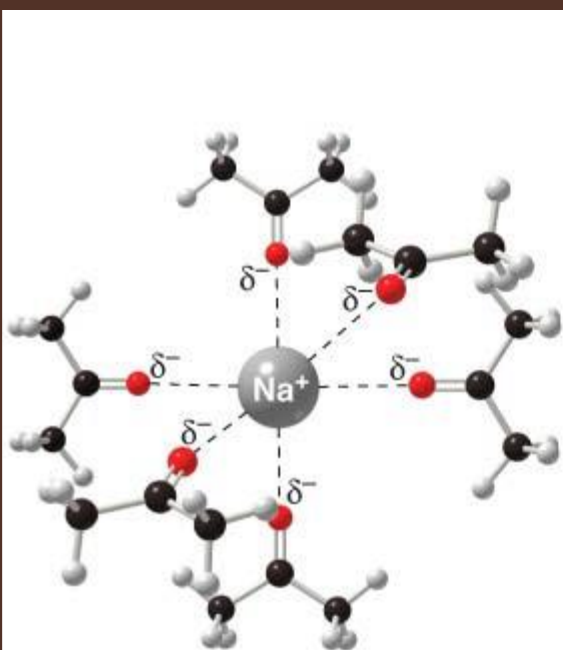
Polar aprotic solvents also exhibit dipole—dipole interactions, but they have no O—H or N—H bonds. Thus, they are incapable of hydrogen bonding.

Polar aprotic solvents

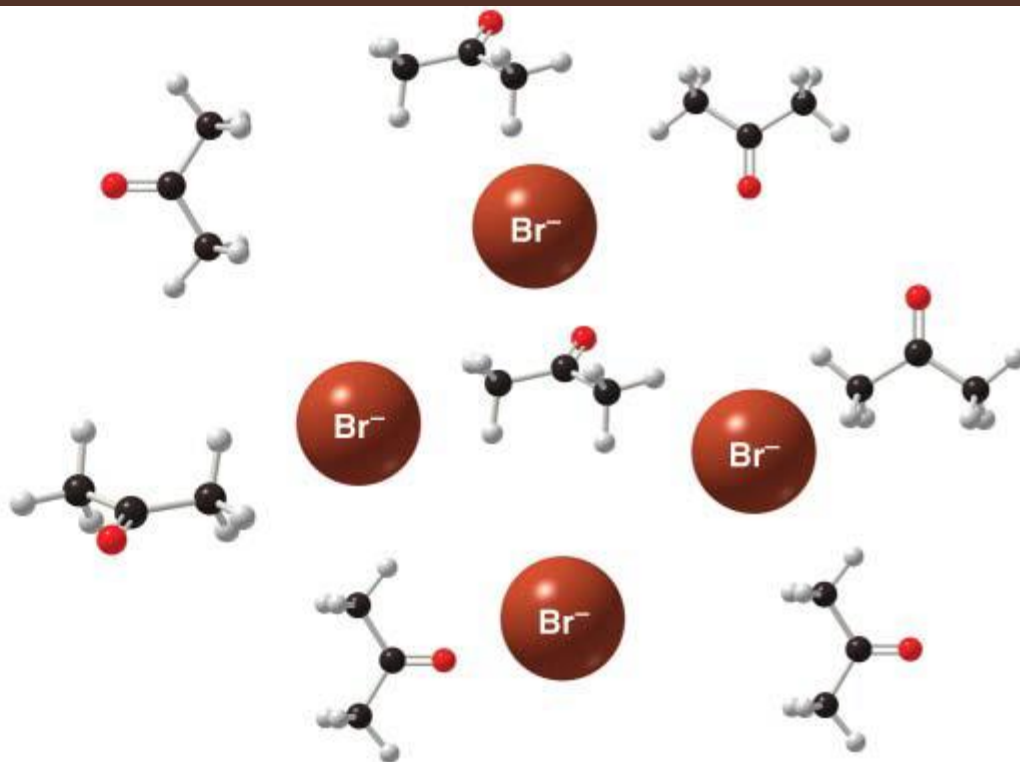


Polar aprotic solvents solvate cations by ion–dipole interactions.

- 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 Na^+ well by ion–dipole interactions.



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



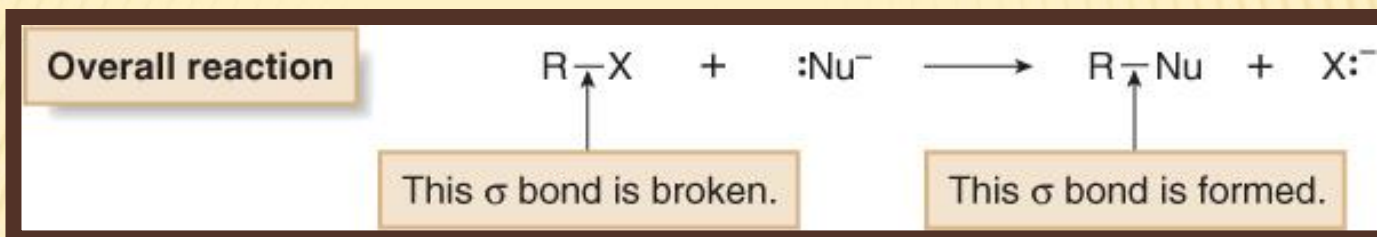
Increasing nucleophilicity
in polar aprotic solvents

Table 7.4

Common Nucleophiles in Organic Chemistry

	Negatively charged nucleophiles			Neutral nucleophiles	
Oxygen	^-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

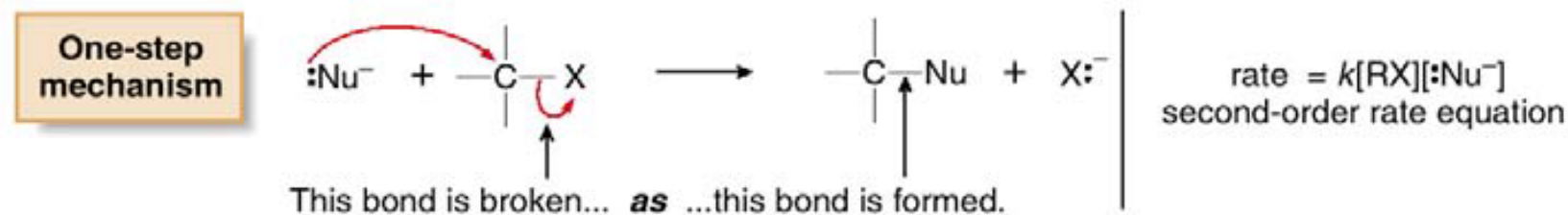
Possible Mechanisms of Nucleophilic Substitution



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

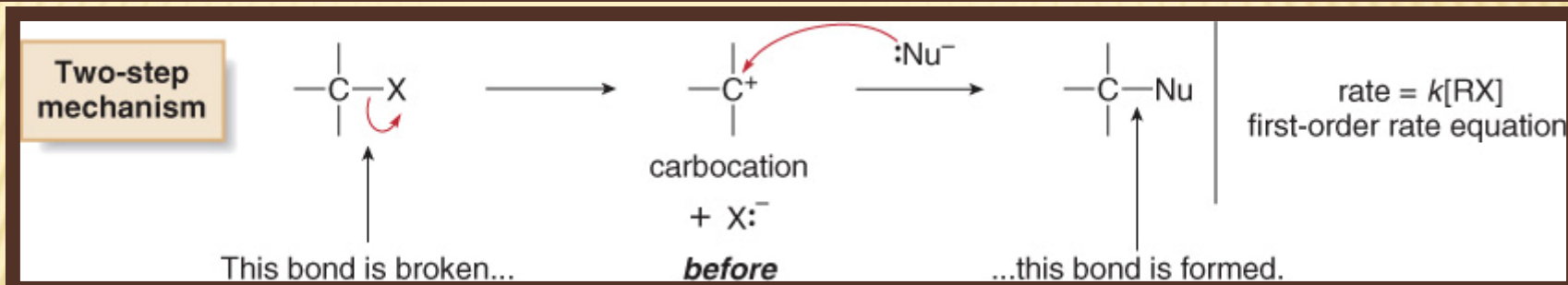
[1] ***Bond making and bond breaking occur at the same time.***

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.



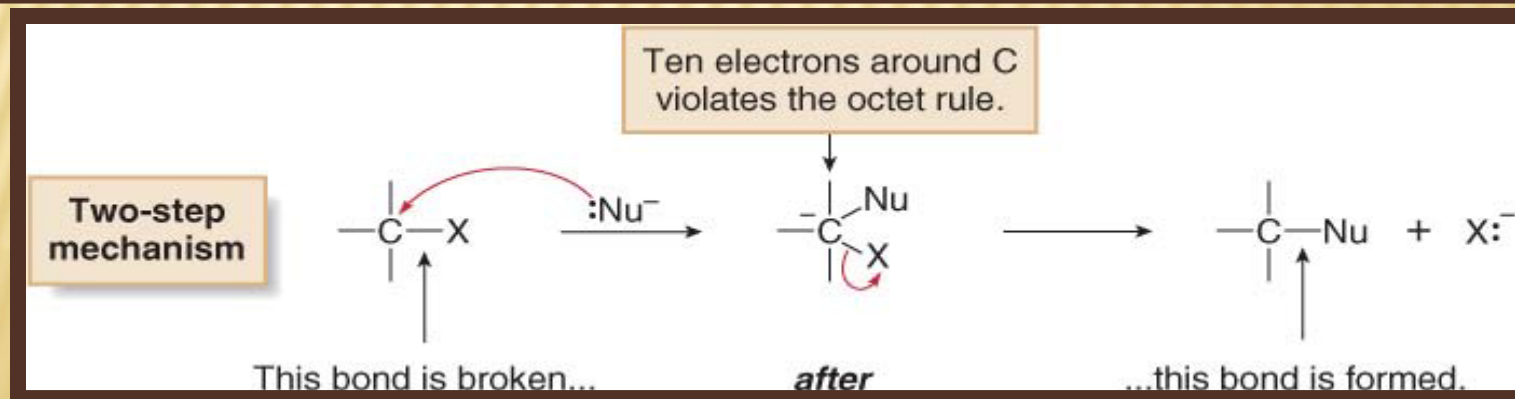
[2] *Bond breaking occurs before bond making.*

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

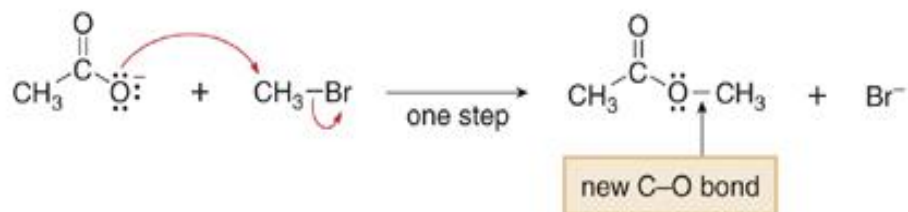


Nucleophilic Substitution Bimolecular Reaction SN2

- 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.

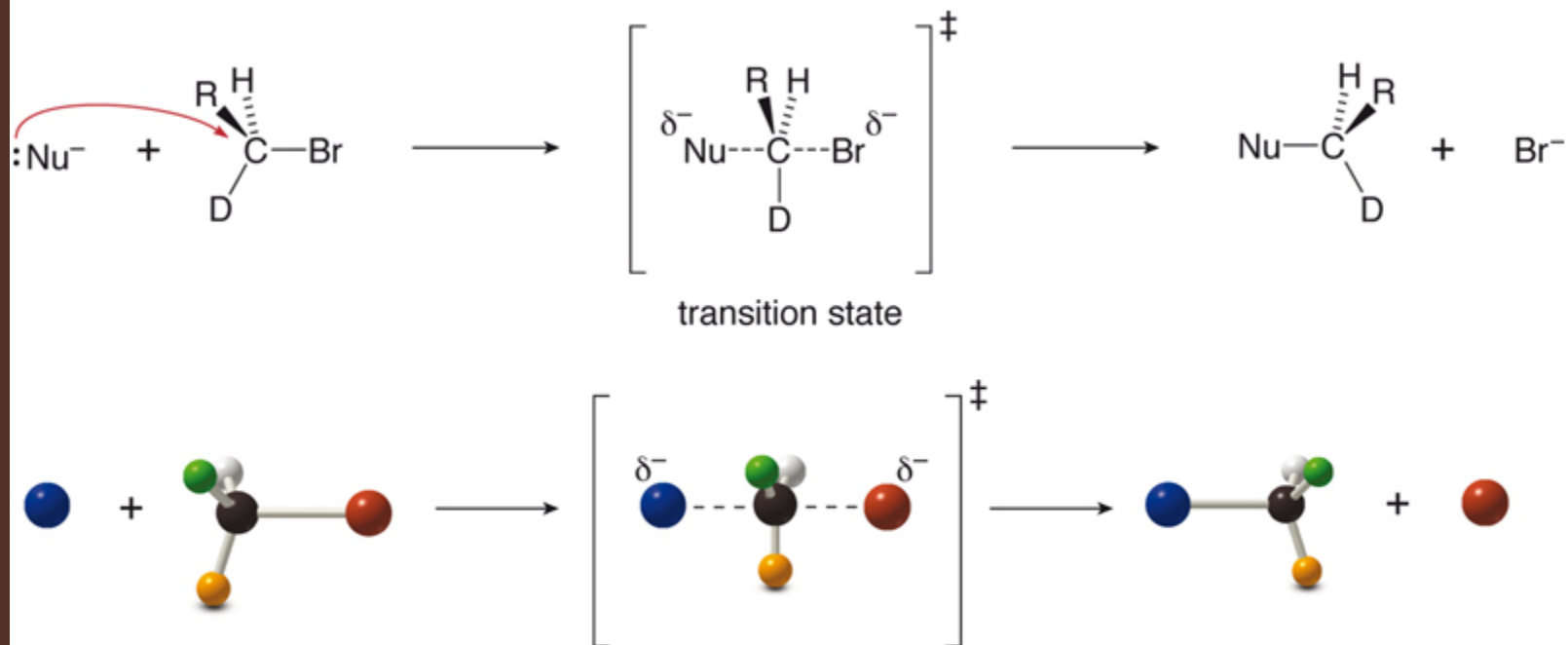
SN₂ Mechanism

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



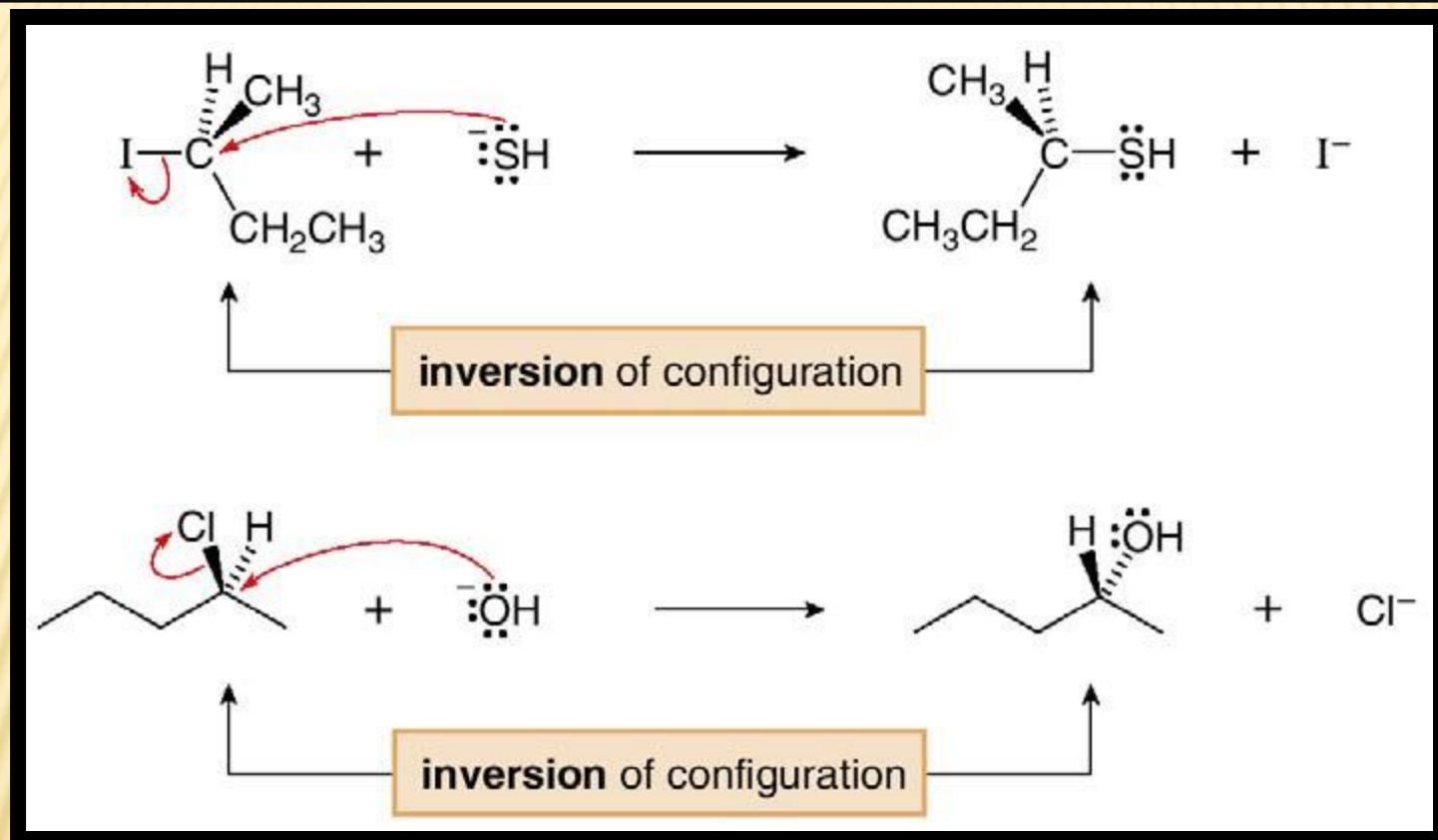
Stereochemistry of the SN₂ Reaction

All SN₂ reactions proceed with backside attack of the nucleophile, resulting in inversion of configuration at a stereogenic center.



:Nu⁻ and Br⁻ are 180° 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 SN₂ reaction depends upon 4 factors:

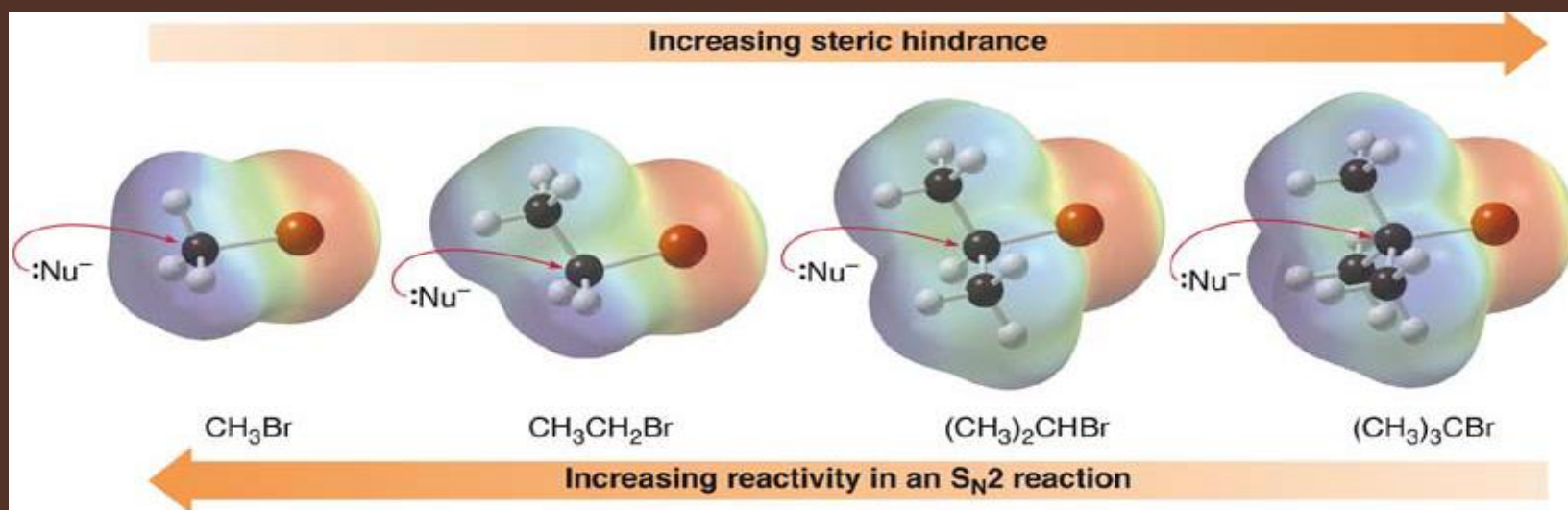
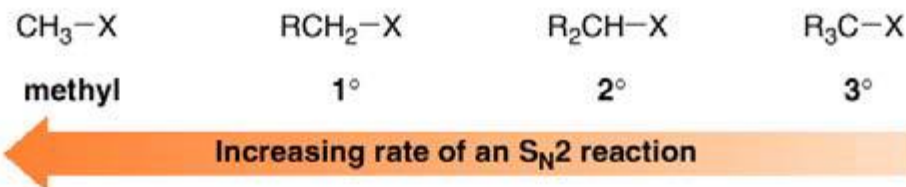
1. The nature of the substrate (the alkyl halide)
2. The power of the nucleophile
3. The ability of the leaving group to leave
4. The nature of the solvent

Nature of the substrate

Methyl and 1° alkyl halides undergo S_N2 reactions with ease.

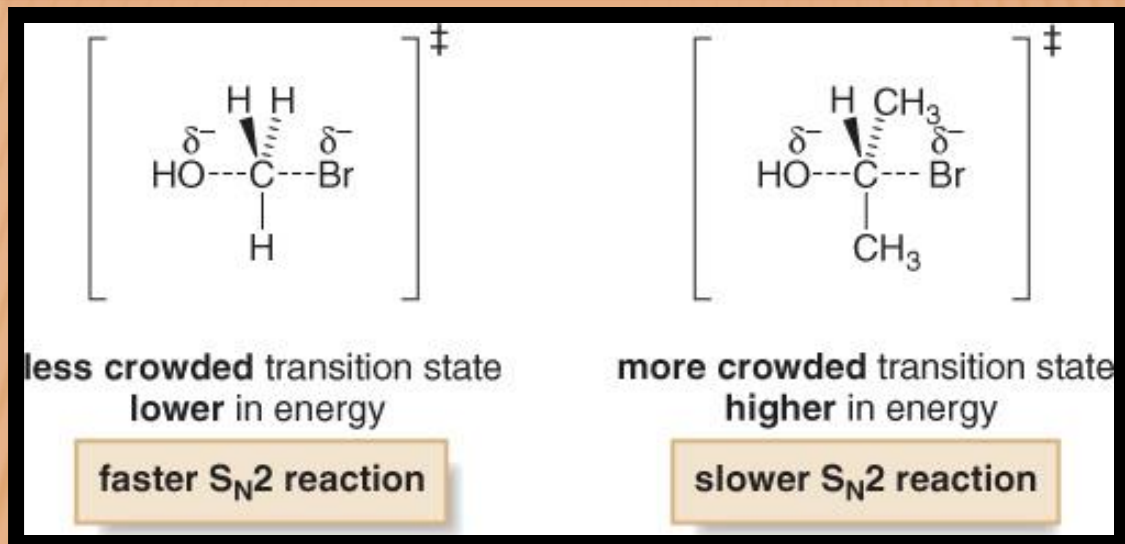
- 2° Alkyl halides react more slowly.
- 3° Alkyl halides do not undergo S_N2 reactions. This order of reactivity can be explained by steric effects. Steric hindrance caused by bulky R groups makes nucleophilic attack from the backside more difficult, slowing the reaction rate.

- As the number of R groups on the carbon with the leaving group *increases*, the rate of an S_N2 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 SN_2 reaction.
- Because bond formation and bond breaking occur simultaneously in a single transition state, the SN_2 reaction is a concerted reaction.

Rate of reaction depends upon two species i.e., alkyl halide and attacking nucleophile.

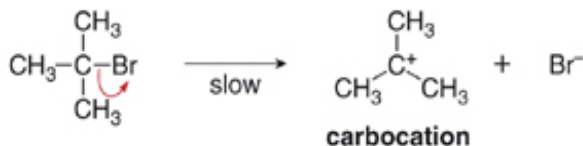
Nucleophilic Substitution Unimolecular Reaction SN1

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.

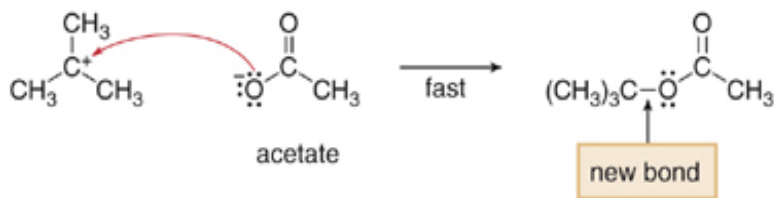
SN1 Mechanism

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.

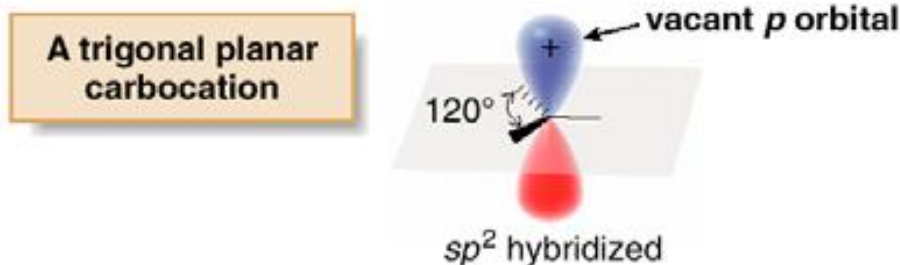
Step [2] The C-O bond is formed.



- **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 SN₁ Reaction

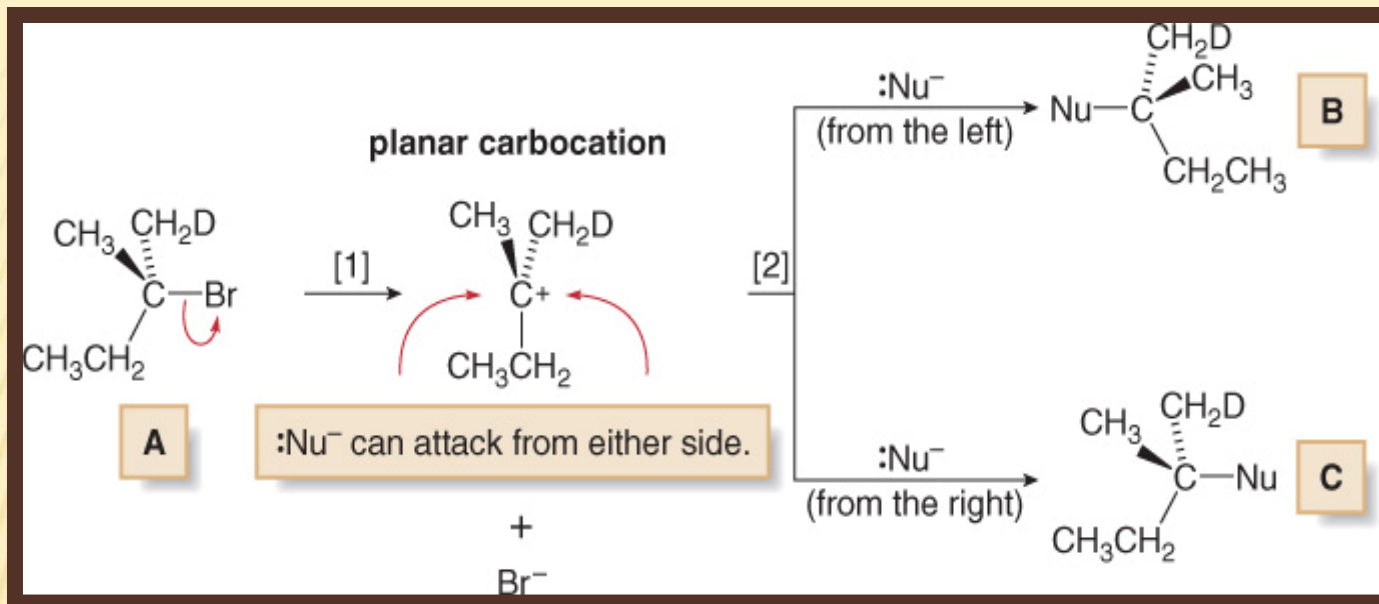
To understand the stereochemistry of the SN₁ reaction, we must examine the geometry of the carbocation intermediate



- 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.

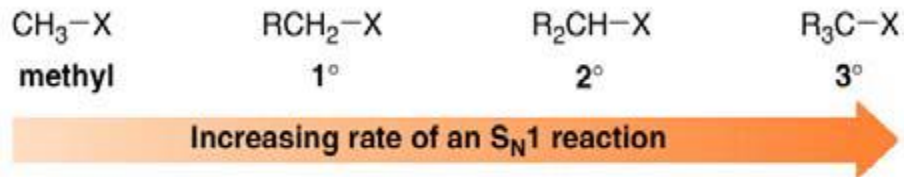
- Because there is no preference for nucleophilic attack from either direction, an equal amount of the two enantiomers is formed—a racemic mixture. We say that racemization has occurred.



Nature of Substrate

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

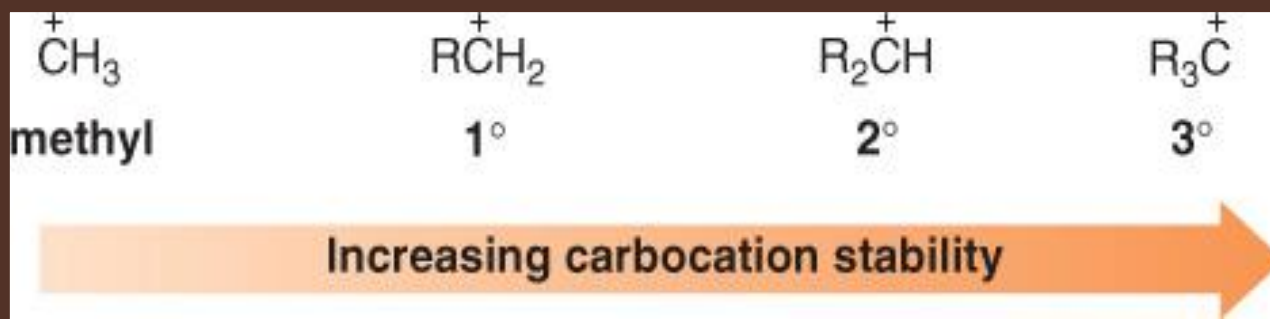
- As the number of R groups on the carbon with the leaving group *increases*, the rate of an $\text{S}_{\text{N}}1$ reaction *increases*.



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

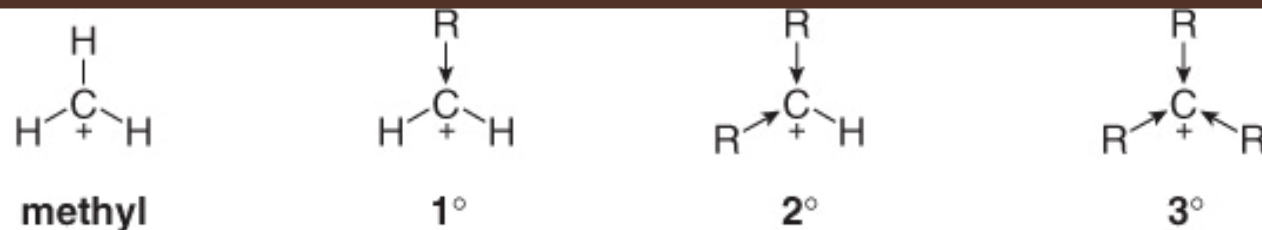
Carbocation Stability

- The effect of the type of alkyl halide on SN_1 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.



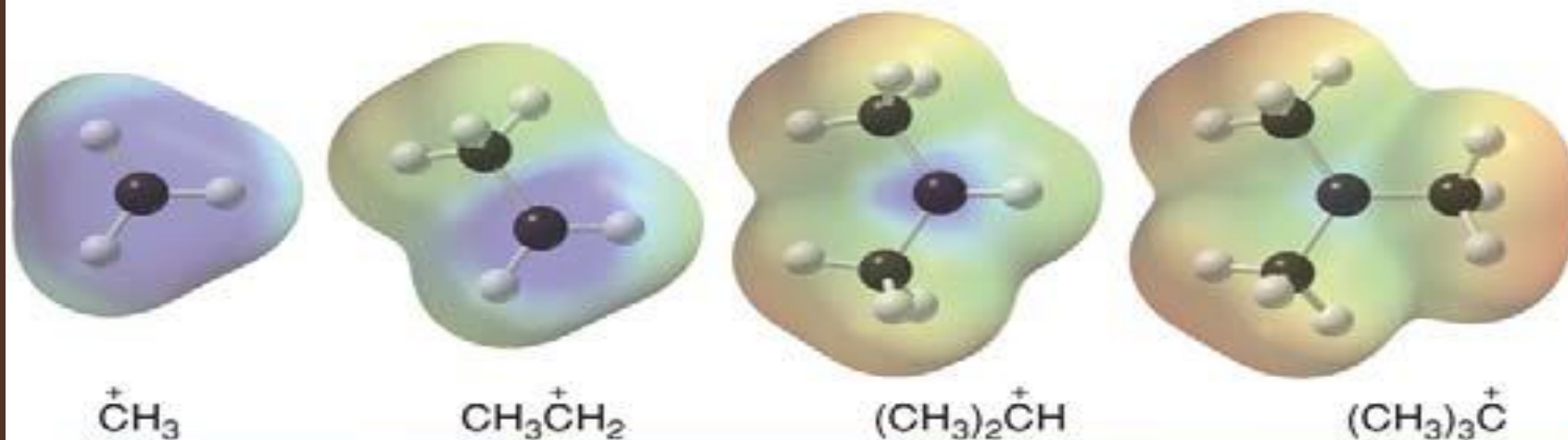
Inductive Effect

- Carbocation stability depends upon inductive effects & hyperconjugation.
- Inductive effects are electronic effects that occur through σ bonds. The inductive effect is the pull of electron density through σ bonds caused by EN 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.
- The greater the no. 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

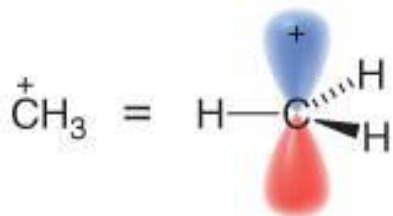
Electrostatic potential maps for different carbocations



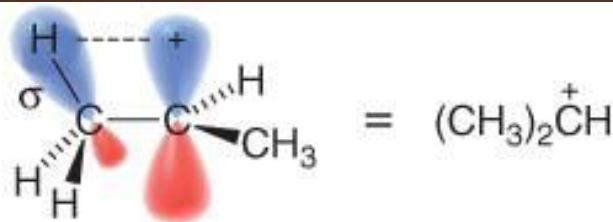
Increasing alkyl substitution
 Increasing dispersal of positive charge

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 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 $(\text{CH}_3)_2\text{CH}^+$ can



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

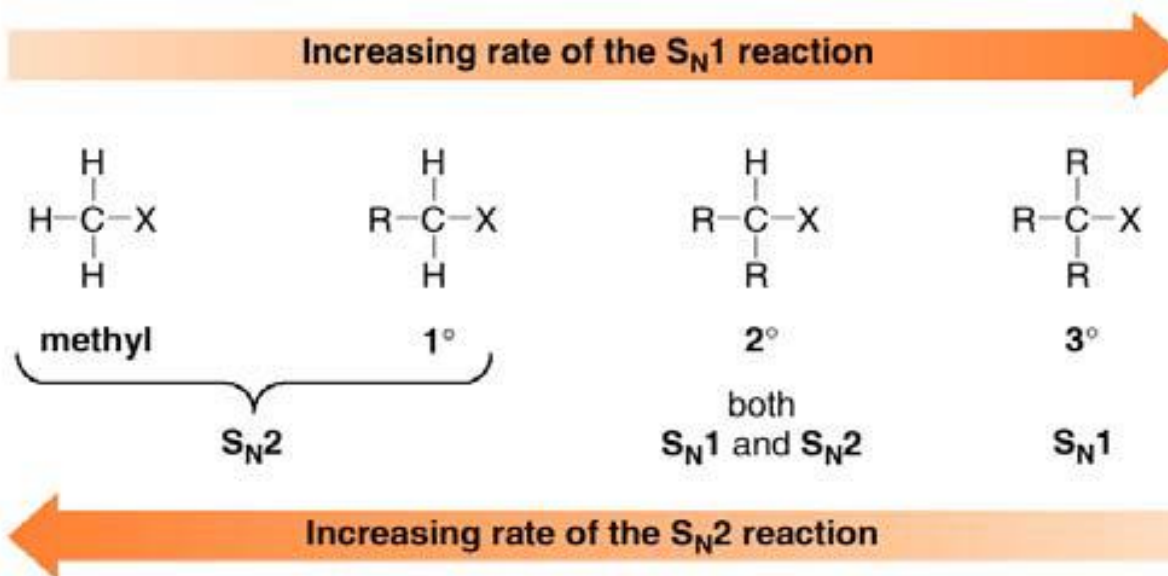


Overlap of the C—H σ bond with the adjacent vacant *p* orbital stabilizes the carbocation.

The Alkyl Halide-The Most Important Factor

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

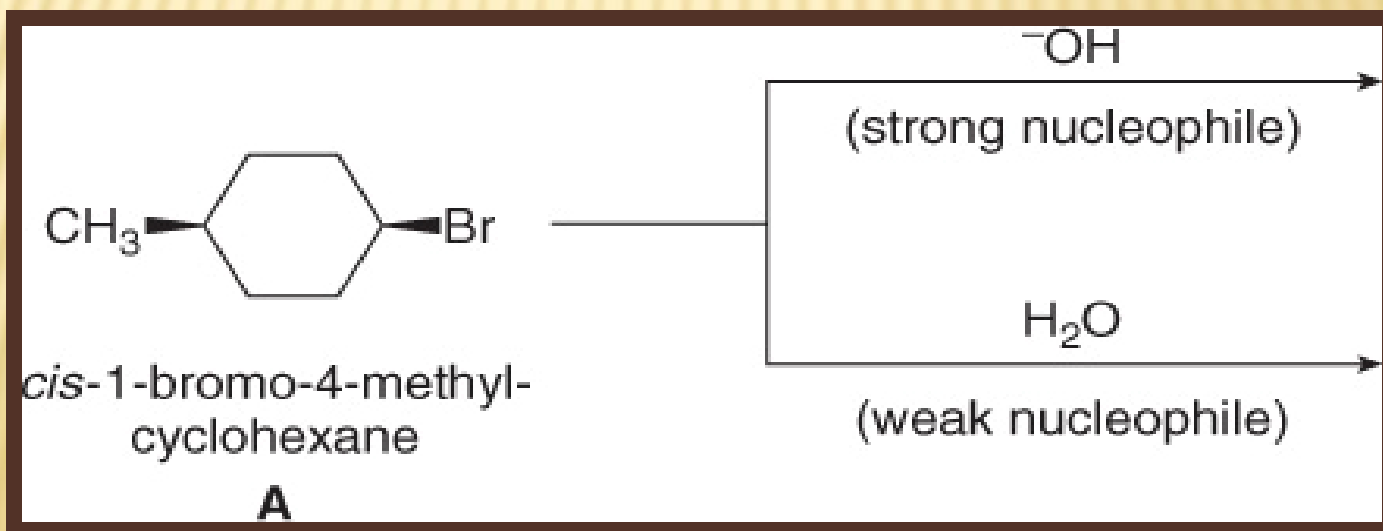
- Increasing alkyl substitution favors S_N1 .
- Decreasing alkyl substitution favors S_N2 .



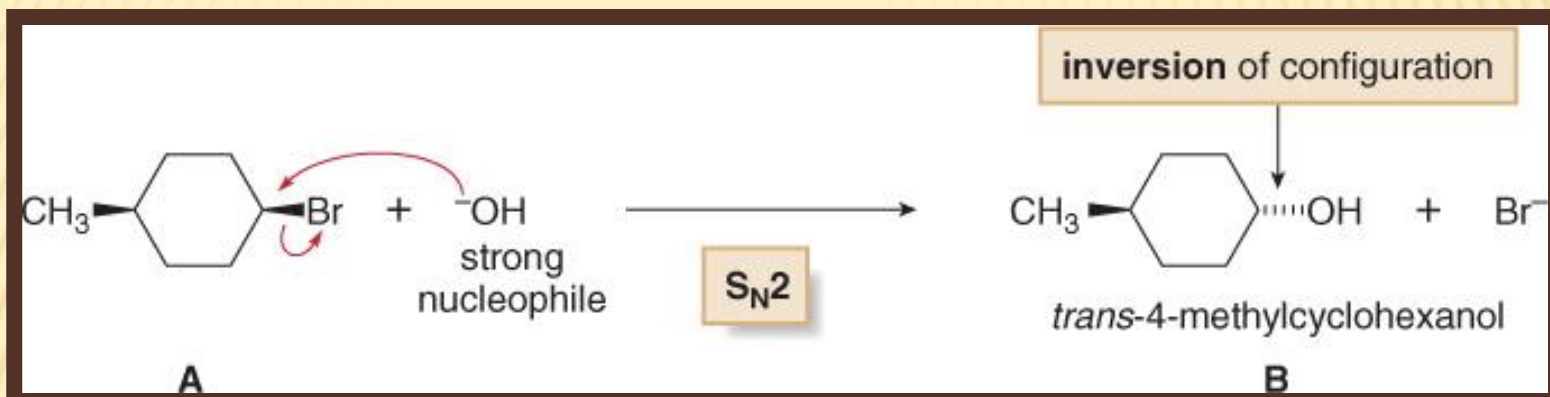
- Methyl and 1° halides (CH_3X and RCH_2X) undergo S_N2 reactions only.
- 3° Alkyl halides (R_3CX) undergo S_N1 reactions only.
- 2° Alkyl halides (R_2CHX) undergo both S_N1 and S_N2 reactions. Other factors determine the mechanism.

The Nucleophile

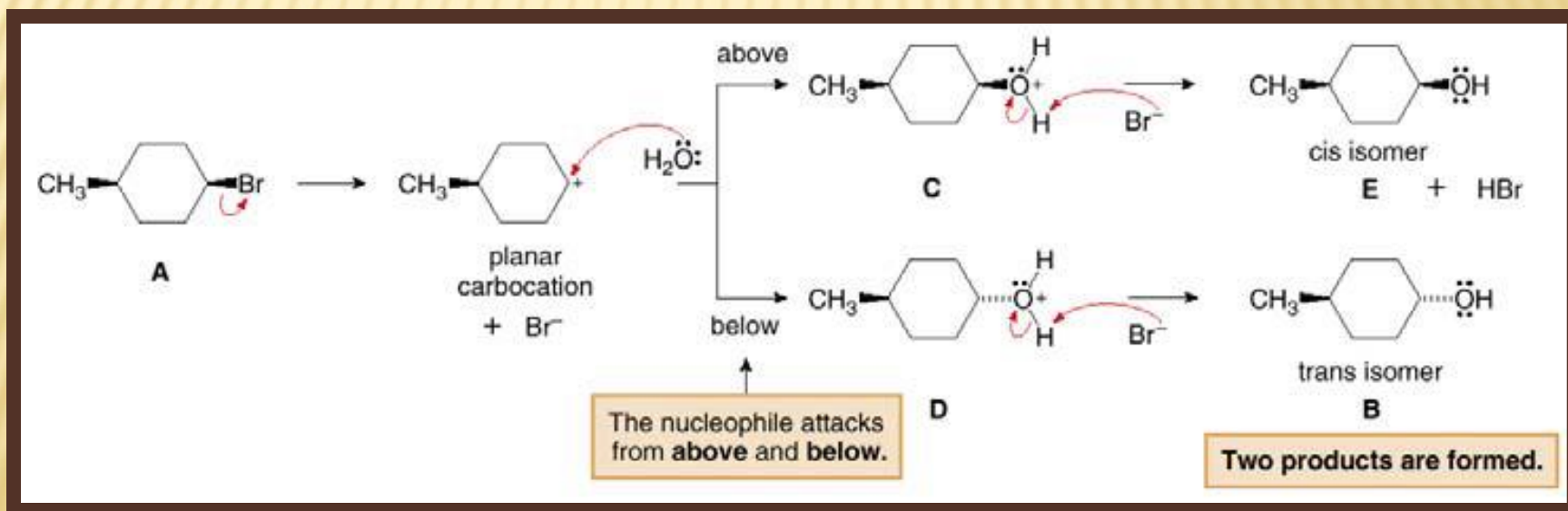
- Rate of SN also depends on nucleophile.
- Strong nucleophiles having negative charge and present in high concentrations favor SN₂ reactions.
- Weak nucleophiles, such as H₂O and ROH favor SN₁ reactions by decreasing the rate of any competing SN₂ reaction.
- Let us see the products formed when the 2° alkyl halide A is treated with either the strong nucleophile HO⁻ or the weak nucleophile H₂O. 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.



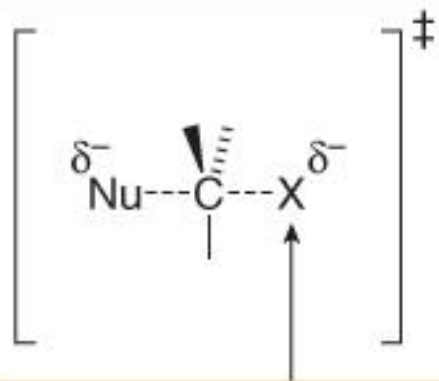
The weak nucleophile favors an S_N1 mechanism.



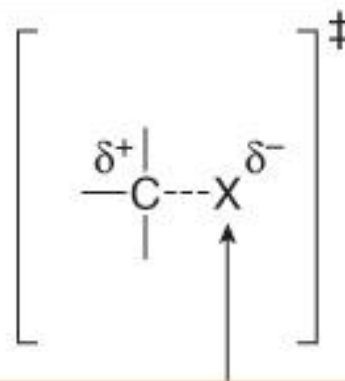
The Leaving Group

A better leaving group increases the rate of both SN1 and SN2 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 H₂O and ROH favor S_N1 reactions because the ionic intermediates are stabilized by solvation.
- Polar aprotic solvents favor S_N2 reactions because nucleophiles are not well solvated, and therefore, are more nucleophilic.

Summary of Factors that Determine the S_N1 or S_N2 Mechanism

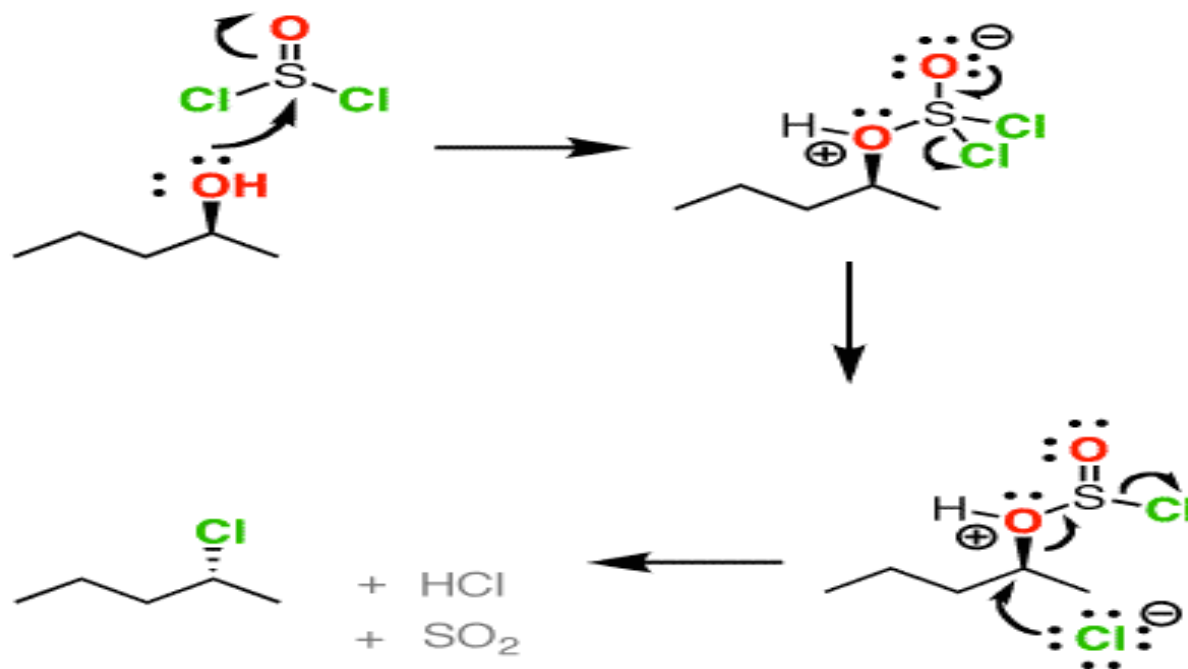
Alkyl halide	Mechanism	Other factors
CH ₃ X RCH ₂ X (1°)	S _N 2	Favored by <ul style="list-style-type: none">• strong nucleophiles (usually a net negative charge)• polar aprotic solvents
R ₃ CX (3°)	S _N 1	Favored by <ul style="list-style-type: none">• weak nucleophiles (usually neutral)• polar protic solvents
R ₂ CHX (2°)	S _N 1 or S _N 2	The mechanism depends on the conditions. <ul style="list-style-type: none">• 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, H₂O and CH₃OH are polar protic solvents that favor the S_N1 mechanism, whereas acetone [(CH₃)₂C=O] and DMSO [(CH₃)₂S=O] are polar aprotic solvents that favor the S_N2 mechanism.

S_Ni Reactions

Internal or intramolecular nucleophilic substitution reaction is known as **S_Ni reaction**. Best example of **S_Ni** is replacement of OH group by Cl, by reacting alcohols with thionyl chloride. This is second order **reaction** as rate of **reaction** depends upon concentration of alcohol molecule as well as thionyl chloride.



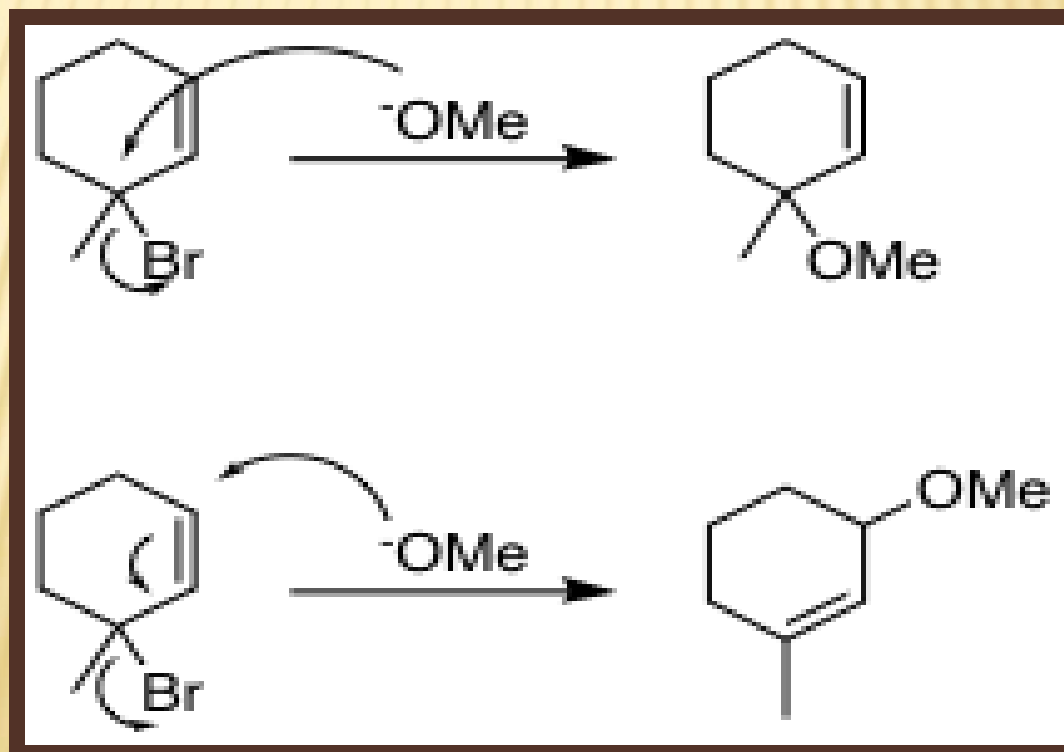
It differs from SN^1 reactions as there is no formation of a racemic mixture here. It is also different from SN^2 reactions as there is no inversion of configuration, and the stereochemistry of the reactant and the product is nearly the same. Hence the reaction is neither explained by SN^1 or SN^2 .



Prime Reactions

It is a nucleophilic substitution reactions in which allylic type substrate undergo substitution along with the rearrangement of double bond.

Such SN reactions are called prime reactions and rearrangements are known as allylic shifts.



S_N1' (Prime) Reaction

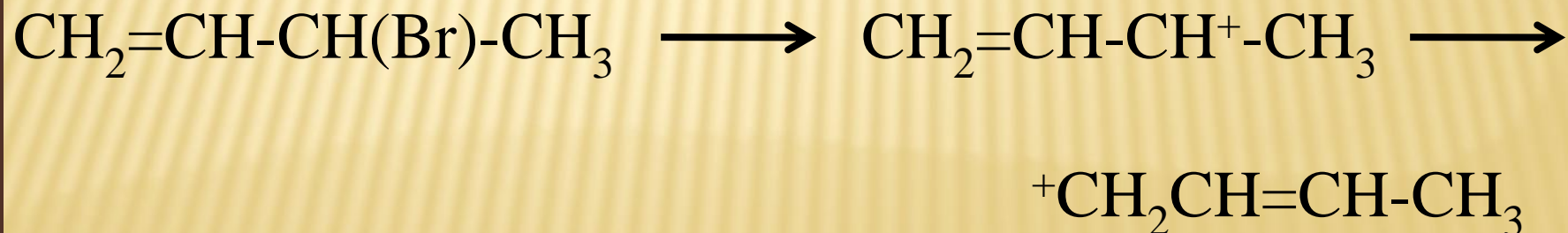
Rearranged product formed under S_N1 condition is S_N1' prime product and reaction is called S_N1' Prime reaction. It is a type of nucleophilic reaction in which molecularity of rate determining step is one. The rate of the reaction is proportional to the concentration of the substrate. It is a first order reaction.

For example $\text{CH}_3\text{CH}=\text{CHCH}_2\text{Cl}$ on solvolysis with 0.8 M NaOH at 25 C yields 60% of $\text{CH}_3\text{CH}=\text{CHCH}_2\text{OH}$ (Normal product) and 40% of $\text{CH}_3\text{CHOHCH}=\text{CH}_2$ (rearranged product).

In above example the nucleophile OH^- attacks gamma carbon instead of alpha carbon, as attacking nucleophile experiences steric repulsions from π e- cloud. OH^- undergo nucleophilic addition at gamma carbon, followed by π - bond rearrangement to next C-C bond & loss of leaving group Br^- forming product.

SN^1 and $\text{SN}^{1'}$ both are uni-molecular reaction and proceed through a carbocation intermediate. But the difference is, when the reaction occurs on an allylic system the carbonation formed is not localized, rather delocalized.

Another example is the reaction of 3-bromobut-1-ene, in which the bromine leaves instantly, double bond changes to the 2 position, and after that water attacks the 1 carbon which creates but-2-ene-1-ol.



Nucleophilic Conjugate Substitution – The S_N2' Mechanism

S_N2' prime reaction takes place when allyl halide reacts with any nucleophile. Here the nucleophile SH^- attacks gamma carbon instead of alpha carbon, as attacking nucleophile experiences steric repulsions from π e cloud and the saturated carbon being hindered (it is a secondary carbon), making the regular S_N2 mechanism less favorable. Many reactions proceed through a series of steps.

