

# **Factors Affecting Aliphatic Nucleophilic Substitution Reactions**

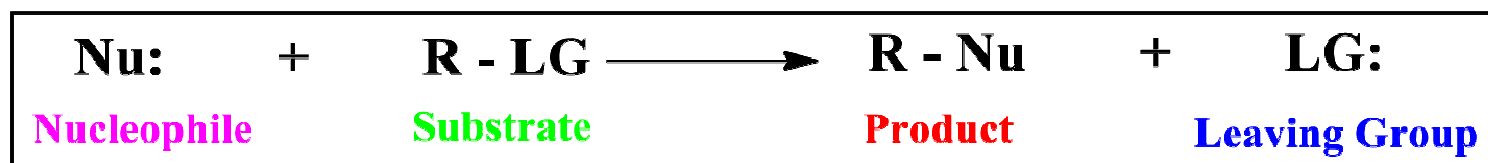
*by*

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# Nucleophilic Substitution Reaction

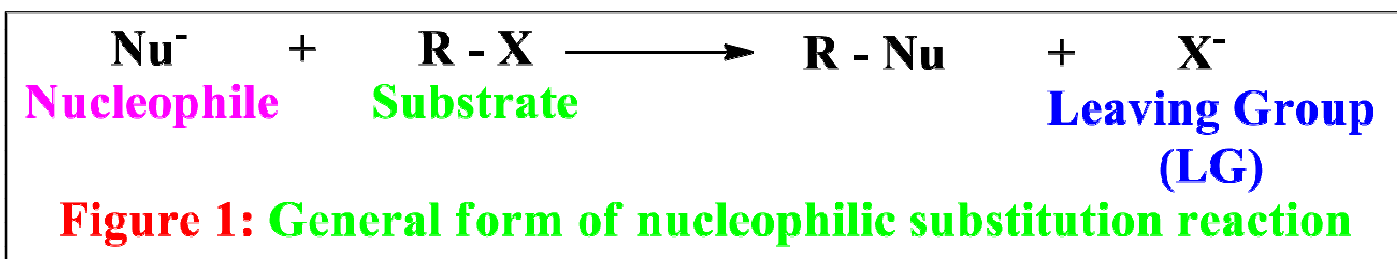
- A substitution reaction is a chemical reaction during which an atom or one functional group in a chemical compound is replaced by another atom or functional group.
- In organic chemistry, **nucleophilic substitution** is a class of reactions in which a **leaving group (LG)** is replaced by an electron rich species (**nucleophile**). The whole molecular entity of which the electrophile and the leaving group are part is usually called the **substrate**.



- The electron pair from the nucleophile (**Nu:**) attacks the substrate (**R-LG**) forming a new bond, while the leaving group (**LG:**) departs with an electron pair. The principal product in this case is **R-Nu**.

# General Features of Nucleophilic Substitution Reactions

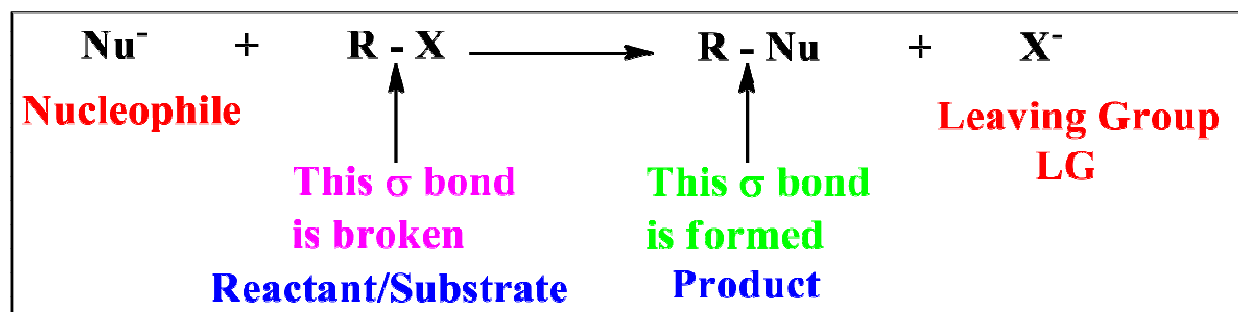
- The nucleophile may be electrically neutral or negatively charged, whereas the substrate is typically neutral or positively charged.



- Three components are necessary in any nucleophilic substitution reactions as abbreviated in its general form (**Figure 1**):
  - R- in R-X:** An alkyl group R containing an  $\text{sp}^3$  hybridized carbon atom bonded to X in the substrate, R-X.
  - X- in R-X:** An atom (or group of atoms) called a leaving group, which is capable of accepting the electron density in the C-X bond.
  - Nu: or Nu<sup>-</sup>:** A nucleophile is an electron rich (a neutral or an anion) species that tends to attack the substrate at a position of low electron density.

# Possible Mechanisms for Nucleophilic Substitution

- Overall a nucleophilic substitution can be represented as follows:



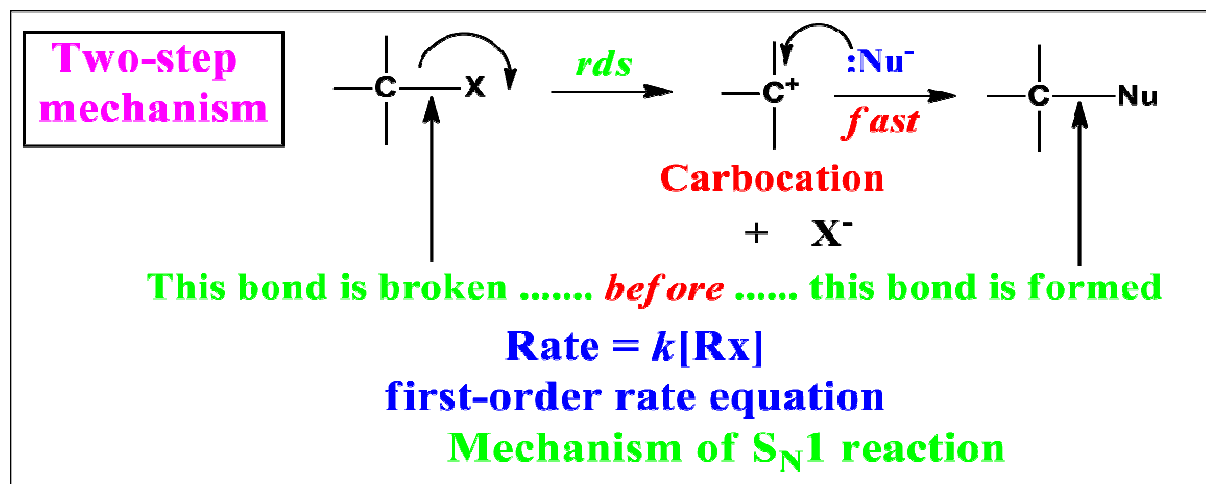
- There are two fundamental events in a nucleophilic substitution reaction:
  - breaking of the  $\sigma$  bond to the leaving group
  - formation of the new  $\sigma$  bond to the nucleophile
- Nucleophilic substitution at an  $\text{sp}^3$  hybridised carbon, therefore, involves two  $\sigma$  bonds: the bond to the leaving group, which is broken, and the bond to the nucleophile, which is formed.

# Nucleophilic Substitution Unimolecular Reactions (S<sub>N</sub>1)

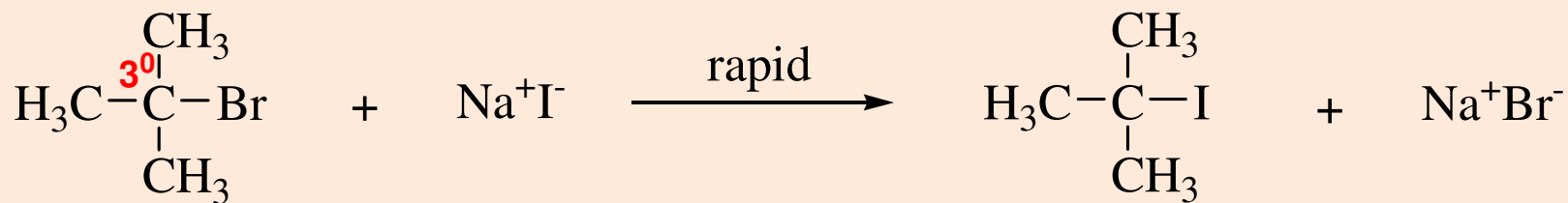
# Mechanisms for Nucleophilic Substitution

## Unimolecular Reactions ( $S_N1$ )

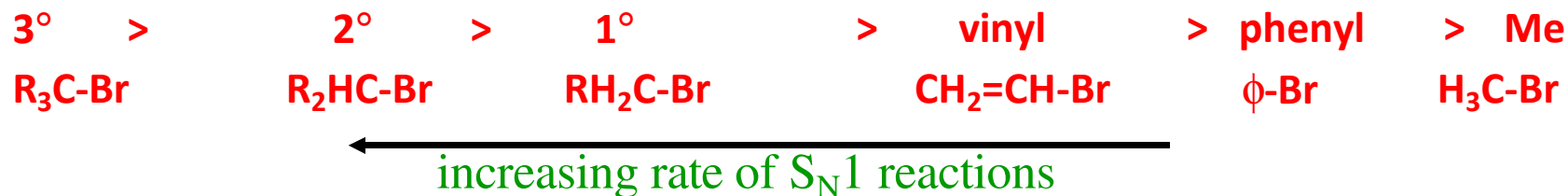
- Bond breaking occurs before bond formation.



- Here, the C-X bond is broken first and then the C-Nu bond is formed, the mechanism has **two-steps** and a **carbocation** is formed as a reactive intermediate. The **first step is rate-determining**, and the rate of such a **unimolecular reaction** depends on the concentration of RX only; therefore, the rate equation is **first order**.



- ❑ 3° alkyl halides are essentially inert to substitution by S<sub>N</sub>2 mechanism because of steric hindrance.
- ❑ Despite this, 3° alkyl halides undergo nucleophilic substitution reactions quite rapidly, but by a different mechanism, i.e., the S<sub>N</sub>1 mechanism.
- ❑ S<sub>N</sub>1 = Substitution, Nucleophilic, 1st order (unimolecular).
- ❑ S<sub>N</sub>1 reactions obey 1st order kinetics, i.e., Rate = k[RX].
- ❑ The rate depends upon the concentration of only 1 reactant, the alkyl halide-not the nucleophile
- ❑ The order of reactivity of substrates for S<sub>N</sub>1 reactions is the reverse of S<sub>N</sub>2



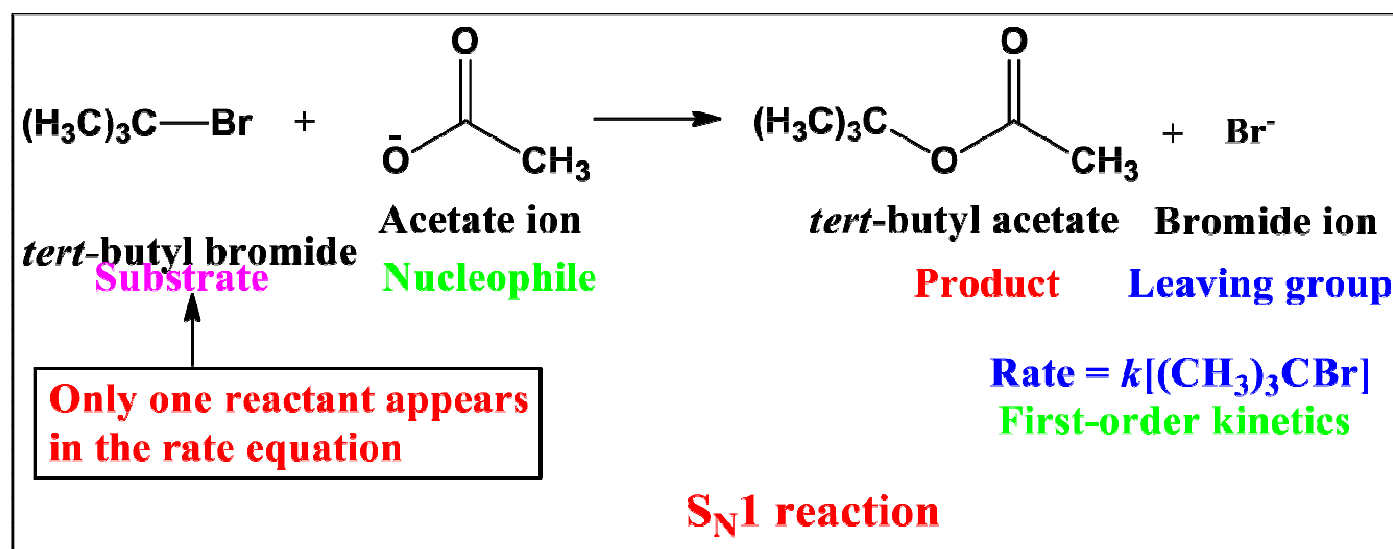




# Mechanisms for Nucleophilic Substitution

## Unimolecular Reactions ( $S_N1$ )

- This reaction illustrates a similar nucleophilic substitution reaction with *t*-butyl bromide  $[(CH_3)_3CBr]$ , which also leads to substitution of  $Br^-$  by  $CH_3CO_2^-$ . Kinetic data show that this reaction rate depends on the concentration of only one reactant, the alkyl halide; that is, the rate equation is *first order*. This suggests a **two-step mechanism** in which the rate-determining step involves the alkyl halide only.



## The rate of an $S_N1$ reaction depends upon 3 factors:

1. The nature of the substrate (the alkyl halide) i.e. the stability of carbocation
2. The ability of the leaving group to leave
3. The nature of the solvent

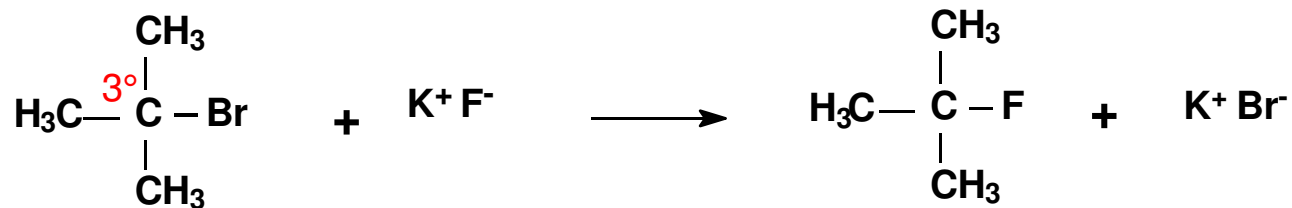
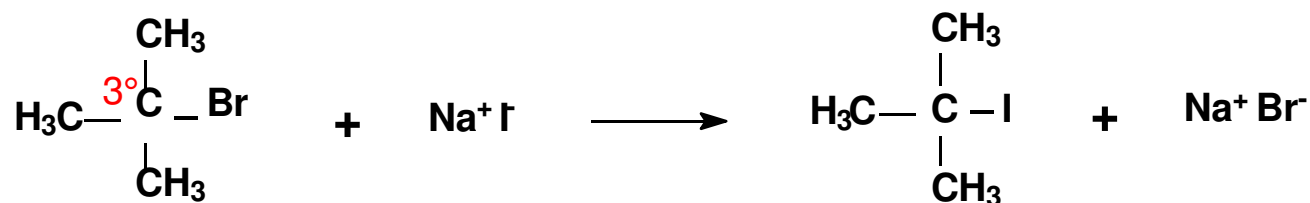
- The rate is independent on the power of the nucleophile.





## Effect of the nucleophile on rate of S<sub>N</sub>1 reactions:

- Recall again that the nature of the nucleophile has no effect on the rate of S<sub>N</sub>1 reactions because the slowest (rate-determining) step of an S<sub>N</sub>1 reaction is the dissociation of the leaving group and formation of the carbocation.
- All carbocations are very good electrophiles (electron acceptors) and even weak nucleophiles, like H<sub>2</sub>O and methanol, will react quickly with them.
- The two S<sub>N</sub>1 reactions will proceed at essentially the same rate since the only difference is the nucleophile.



# Effect of nature of the leaving group on rate of

## $S_N1$ reactions:

- The nature of the leaving group has the same effect on both  $S_N1$  and  $S_N2$  reactions.
- The better the leaving group, the faster a  $C^+$  can form and hence the faster will be the  $S_N1$  reaction.
- The leaving group usually has a negative charge
- Groups which best stabilize a negative charge are the best leaving groups, i.e., the weakest bases are stable as anions and are the best leaving groups.
- Weak bases are readily identified. They have high  $pK_b$  values.

$pK_b = 23$	$pK_b = 22$	$pK_b = 21$	$pK_b = 11$	$pK_b = -1.7$	$pK_b = -2$	$pK_b = -21$
$I^-$	$Br^-$	$Cl^-$	$F^-$	$OH^-$	$OR^-$	$NH_2^-$
30,000	10,000	200	1	0	0	0



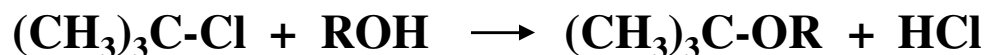
Increasing leaving ability

- Iodine ( $-I$ ) is a good leaving group because iodide ( $I^-$ ) is non basic.
- $OH^-$  and  $NH_2^-$  are poor leaving groups because they are strong bases.

## Effect of solvent on rate of S<sub>N</sub>1 reactions:

- ❑ For S<sub>N</sub>1 reactions, the solvent affects the rate only if it influences the stability of the charged transition state, i.e., the C<sup>+</sup>.
- ❑ The Nu<sup>-</sup> is not involved in the rate determining step, so solvent effects on the Nu<sup>-</sup> do not affect the rate of S<sub>N</sub>1 reactions.
- ❑ Polar protic solvents (H<sub>2</sub>O, MeOH, EtOH, NH<sub>3</sub>, tBuOH, AcOH) will solvate and stabilize the charged transition state (C<sup>+</sup> intermediate), lowering the activation energy and accelerating S<sub>N</sub>1 reactions.
- ❑ Nonpolar solvents do not lower the activation energy and thus make S<sub>N</sub>1 reactions relatively slower.

**The relative rates of an S<sub>N</sub>1 reaction due to solvent effects are given below:**



H <sub>2</sub> O	20% EtOH (aq)	40% EtOH (aq)	EtOH
<b>100,000</b>	<b>14,000</b>	<b>100</b>	<b>1</b>

← reaction rate increases with polarity of solvent

## Effect of the solvent on rate of $S_N1$ reactions:

- ❑ Solvent polarity is usually expressed by the “dielectric constant”,  $\epsilon$ , which is a measure of the ability of a solvent to act as an electric insulator.
- ❑ Polar solvents are good electric insulators because their dipoles surround and associate with charged species.

**Dielectric constants of some common solvents are given in the following table**

name	dielectric constant	name	dielectric constant
<b>aprotic solvents</b>		<b>protic solvents</b>	
hexane	1.9	acetic acid	6.2
benzene	2.3	acetone	20.7
diethyl ether	4.3	ethanol	24.3
chloroform	4.8	methanol	33.6
HMPA	30	formic acid	58.0
DMF	38	<b>water</b>	<b>80.4</b>
DMSO	48		

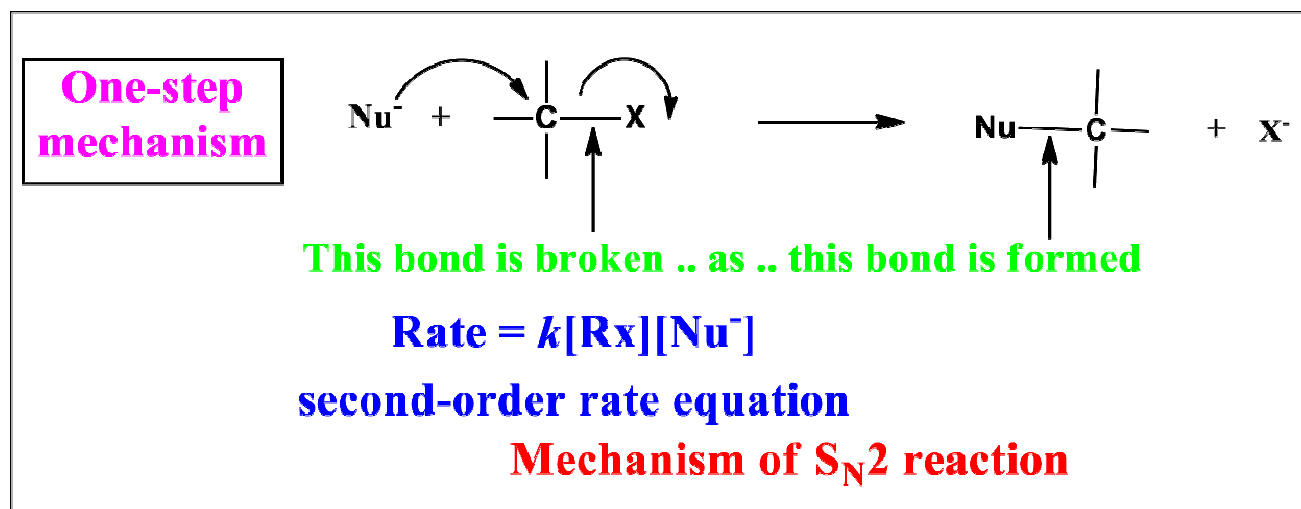


# Nucleophilic Substitution Bimolecular Reactions (S<sub>N</sub>2)

# Mechanisms for Nucleophilic Substitution

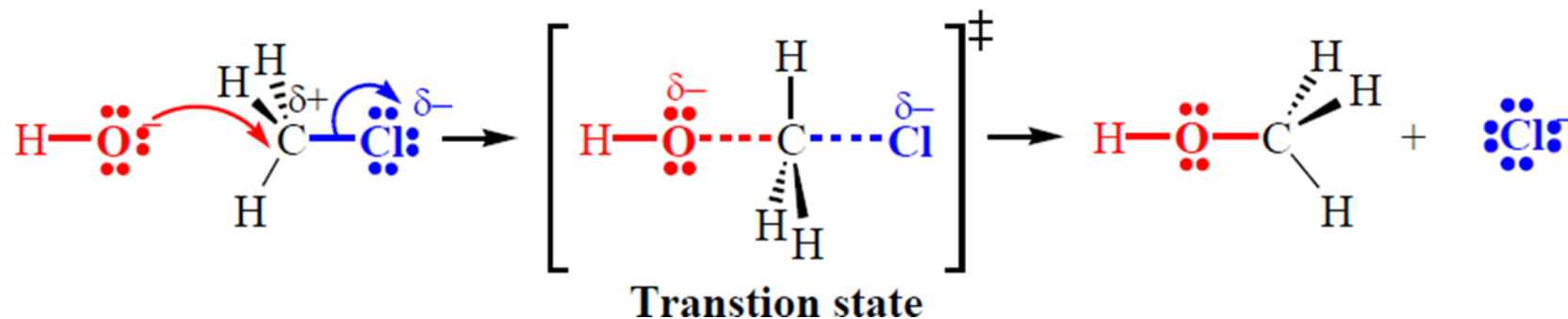
## Bimolecular Reactions ( $S_N2$ )

- Bond breaking and bond formation occur at the same time.



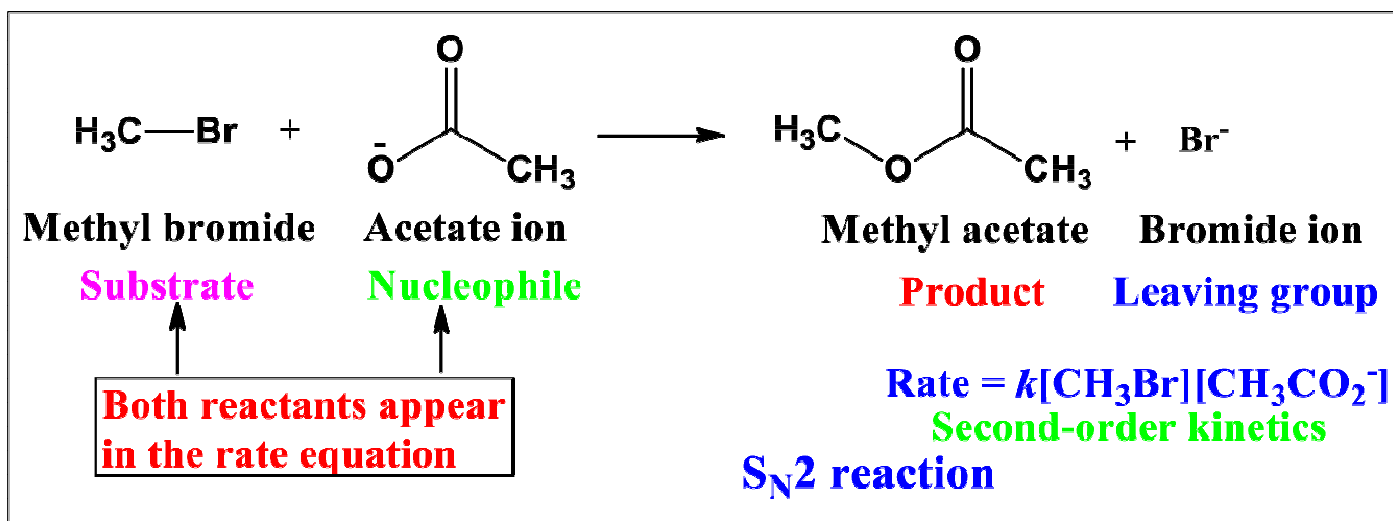
- Here, the C-X bond is broken as the C-Nu bond is formed, the **mechanism has one-step**. The rate of such a **bimolecular reaction** depends on the concentration of both the reactants; that is, the rate equation is **second order**.

**Mechanism:**



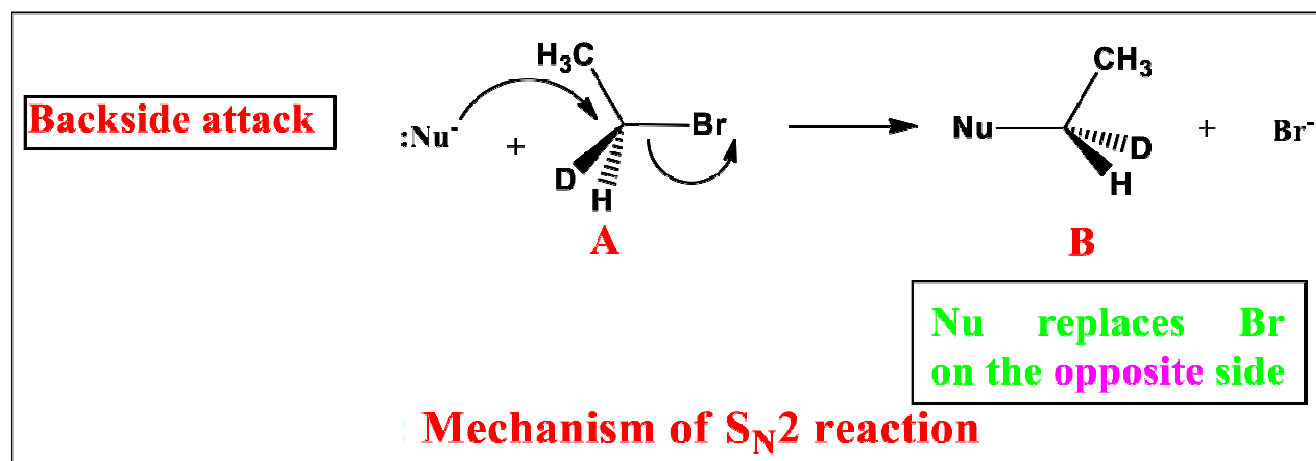
- Because bond formation and bond breaking occur simultaneously in a single transition state, the  $S_N2$  reaction is a concerted reaction.

- Reaction of methyl bromide ( $\text{CH}_3\text{Br}$ ) with the nucleophile acetate ( $\text{CH}_3\text{CO}_2^-$ ) affords the substitution product methyl acetate ( $\text{CH}_3\text{CO}_2\text{CH}_3$ ) with loss of  $\text{Br}^-$  as the leaving group.
- The rate of reaction depends on the concentration of both reactants; that is, the rate equation is *second order*. This bimolecular reaction involves a **one-step mechanism** in which the C-X bond is broken as the C-Nu bond formed.



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

- In **backside attack**, the nucleophile approaches from the opposite side to the leaving group of the substrate (**A**), forming **B**. In this example, the leaving group was drawn on the right, so the nucleophile attacks from the left. Because the nucleophile and leaving group are in the opposite position relative to the other three groups on carbon, **backside attack** results in *inversion* of configuration around the stereogenic centre. The configuration of the carbon atom becomes inverted during S<sub>N</sub>2 reaction.



**The rate of an  $S_N2$  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**

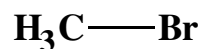
## Nature of the substrate on the rate of an $S_N2$ reaction :

- Unhindered alkyl halides, those in which the back side of the  $\alpha$ -carbon is not blocked, will react fastest in  $S_N2$  reactions.

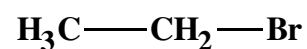


- While a methyl halides reacts quickly in  $S_N2$  reactions, a  $3^\circ$  does not react. The back side of an  $\alpha$ -carbon in a  $3^\circ$  alkyl halide is completely blocked.

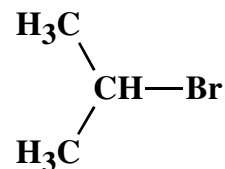
# Effect of nature of substrate on rate of $S_N2$ reactions:



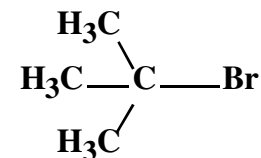
methyl bromide



ethyl bromide

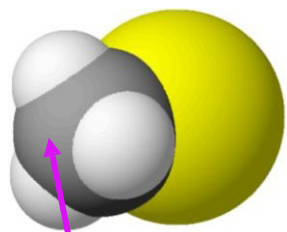


isopropyl bromide

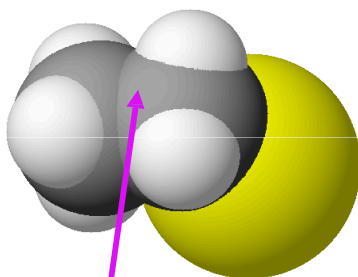


t-butyl bromide

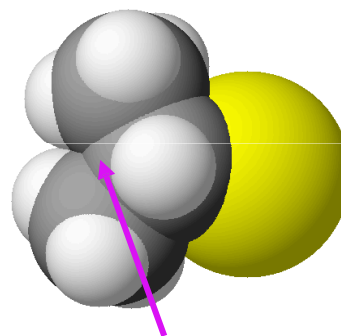
SPACE FILLING MODELS SHOW ACTUAL SHAPES AND RELATIVE SIZES



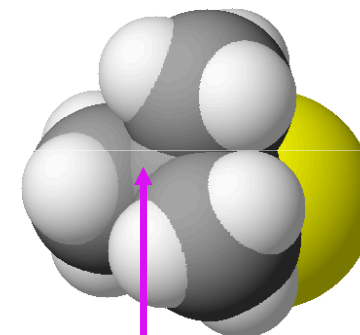
Back side of  $\alpha$ -C of a methyl halide is unhindered.



Back side of  $\alpha$ -C of a  $1^\circ$  alkyl halide is slightly hindered.



Back side of  $\alpha$ -C of a  $2^\circ$  alkyl halide is mostly hindered.



Back side of  $\alpha$ -C of a  $3^\circ$  alkyl halide is completely blocked.

Me

>>

$1^\circ$

>>

$2^\circ$

>>

$3^\circ$



decreasing rate of  $S_N2$  reactions



# Effect of nucleophile on rate of S<sub>N</sub>2 reactions:

- The better the nucleophile, the faster the rate of S<sub>N</sub>2 reactions.
- The table below show the relative power or various nucleophiles.
- The best nucleophiles are the best electron donors.

Reactivity	Nu: <sup>-</sup>	Relative Reactivity
very weak	HSO <sub>4</sub> <sup>-</sup> , H <sub>2</sub> PO <sub>4</sub> <sup>-</sup> , RCOOH	< 0.01
weak	ROH	1
	HOH, NO <sub>3</sub> <sup>-</sup>	100
fair	F <sup>-</sup>	500
	Cl <sup>-</sup> , RCOO <sup>-</sup>	20 × 10 <sup>3</sup>
	NH <sub>3</sub> , CH <sub>3</sub> SCH <sub>3</sub>	300 × 10 <sup>3</sup>
good	N <sub>3</sub> <sup>-</sup> , Br <sup>-</sup>	600 × 10 <sup>3</sup>
	OH <sup>-</sup> , CH <sub>3</sub> O <sup>-</sup>	2 × 10 <sup>6</sup>
very good	CN <sup>-</sup> , HS <sup>-</sup> , RS <sup>-</sup> , (CH <sub>3</sub> ) <sub>3</sub> P:, NH <sub>2</sub> <sup>-</sup> , RMgX, I <sup>-</sup> , H <sup>-</sup>	> 100 × 10 <sup>6</sup>

↑  
increasing  
↓

# Effect of nature of the leaving group on rate of $S_N2$ reactions:

- ❑ The leaving group usually has a negative charge
- ❑ Groups which best stabilize a negative charge are the best leaving groups, i.e., the weakest bases are stable as anions and are the best leaving groups.
- ❑ Weak bases are readily identified. They have high  $pK_b$  values.

$pK_b = 23$	$pK_b = 22$	$pK_b = 21$	$pK_b = 11$	$pK_b = -1.7$	$pK_b = -2$	$pK_b = -21$
I <sup>-</sup>	Br <sup>-</sup>	Cl <sup>-</sup>	F <sup>-</sup>	OH <sup>-</sup>	OR <sup>-</sup>	NH <sub>2</sub> <sup>-</sup>
30,000	10,000	200	1	0	0	0

←  
Increasing leaving ability

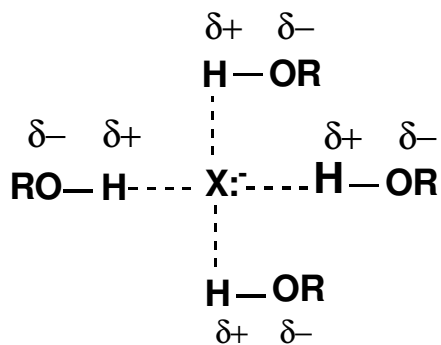
- ❑ Iodine (-I) is a good leaving group because iodide (I<sup>-</sup>) is non basic.
- ❑ OH<sup>-</sup> and NH<sub>2</sub><sup>-</sup> are poor leaving groups because they are strong bases.

# Effect of solvent on rate of $S_N2$ reactions:

## There are 3 classes of organic solvents:

- ❑ Protic solvents, which contain  $-OH$  or  $-NH_2$  groups. Protic solvents slow down  $S_N2$  reactions.
- ❑ Polar aprotic solvents like acetone, which contain strong dipoles but no  $-OH$  or  $-NH_2$  groups. Polar aprotic solvents speed up  $S_N2$  reactions.
- ❑ Non polar solvents, e.g., hydrocarbons.  $S_N2$  reactions are relatively slow in non polar solvents.

**Protic Solvents** (e.g., H<sub>2</sub>O, MeOH, EtOH, CH<sub>3</sub>COOH, etc.) cluster around the Nu:, solvate it and lower its energy (stabilize it) and reduce its reactivity via H-bonding.

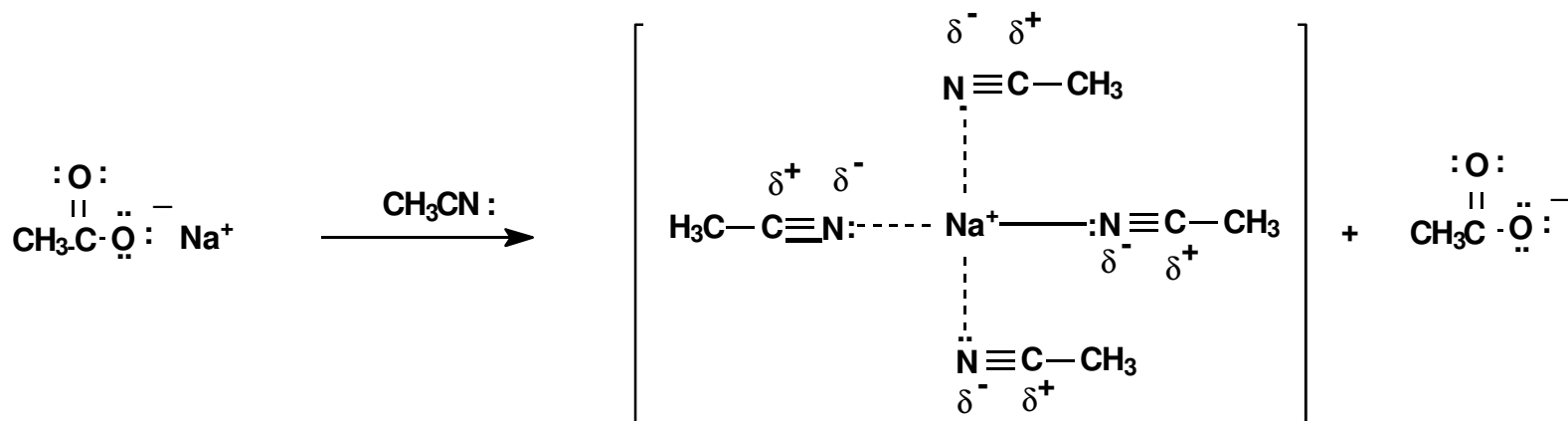


**A solvated anion (Nu:) has reduced nucleophilicity, reduced reactivity and increased stability.**

**A solvated nucleophile has difficulty hitting the  $\alpha$ -carbon.**

□ Polar Aprotic Solvents solvate the cation counterion of the nucleophile but not the nucleophile.

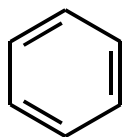
□ Examples include acetonitrile ( $\text{CH}_3\text{CN}$ ), acetone ( $\text{CH}_3\text{COCH}_3$ ), dimethylformamide (DMF)  $[(\text{CH}_3)_2\text{NC}=\text{OH}]$ , dimethyl sulfoxide, DMSO  $[(\text{CH}_3)_2\text{SO}]$ , hexamethylphosphoramide, HMPA  $\{[(\text{CH}_3)_2\text{N}]_3\text{PO}\}$  and dimethylacetamide (DMA).



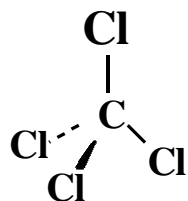
**Polar aprotic solvents solvate metal cations leaving the anion counterion (Nu:) bare and thus more reactive**

• Non polar solvents (benzene, carbon tetrachloride, hexane, etc.) do not solvate or stabilize nucleophiles.

- $S_N2$  reactions are relatively slow in non polar solvents similar to that in protic solvents.



benzene



carbon  
tetrachloride

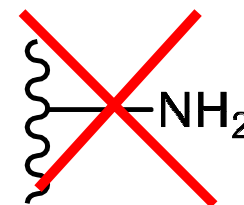
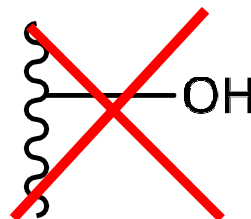


n-hexane

# Solvent requirement for $S_N2$ reactions:

- Requires a polar, aprotic solvent...

- NO alcohols or amines







*Thank  
you*

