Substitution Reactions
2 – Introduction and Properties of – S_N2 and S_N1

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Nucleophilic Substitution Reactions

In nucleophilic substitution reactions a nucleophile displaces a leaving group bonded to an electrophile to give a product. The nucleophile, a species with an unshared electron pair (electron rich) displaces a leaving group which is on the electrophile (electron poor).

A leaving group is substituted by a nucleophile

	R-**X**	+	**Nu:$^-$**	$\longrightarrow$	R – **Nu**	+	**X$^-$**
	Substrate		**Nucleophile**		**Product**		**Leaving group**
Shorthand	***Subs***		***Nu$^-$***		***Prod***		***LG***

Examples of nucleophilic substitution

$$HO^- + CH_3 - I \longrightarrow CH_3OH + I^-$$

$$CH_3O^- + CH_3CH_2Br \longrightarrow CH_3CH_2\text{-}OCH_3 + Br^-$$

Kinetics of Chemical Reactions

It is good to review kinetics of reactions, specifically rate law. Order of reaction is determined experimentally to see which reactants affect the rate of reaction when their concentration is changed.

- 0 order is when rate of reaction is unaffected by change in concentration of the reactants.
- 1st order is when rate of reaction doubles when one of the reactants is doubled.
- 2nd order is when rate of reaction quadruples when two of the reactants are doubled.

Order of reaction help to understand how the reactions work: which reactants are involved in the transition state.

- A *transition state* is the high energy state of the reaction , it is an unstable entity with a very brief existence ($<10^{-12}$ s).
- In the transition state bonds are partially formed and broken.

The $S_N{}^2$ Reaction

This type of substitution reaction indicates:

S is for substitution.

N (subscript) is for nucleophilic.

2 (superscript) is bimolecular, indicating that both nucleophile and substrate are in rate determining step.

An S_N2 Reaction

Consider the reaction given below. The initial rate of the reaction is measured by analytical methods and the data given in the table is obtained.

$$CH_3Cl + OH^- \longrightarrow CH_3\text{-}OH + Cl^-$$

Experiment	**Initial $[CH_3Cl]$**	**Initial $[OH^-]$**	**Initial Rate (Mol L^{-1} s^{-1})**
1	0.0010	1.0	4.9×10^{-7}
2	0.0020	1.0	9.8×10^{-7}
3	0.0010	2.0	9.8×10^{-7}
4	0.0020	2.0	19.6×10^{-7}

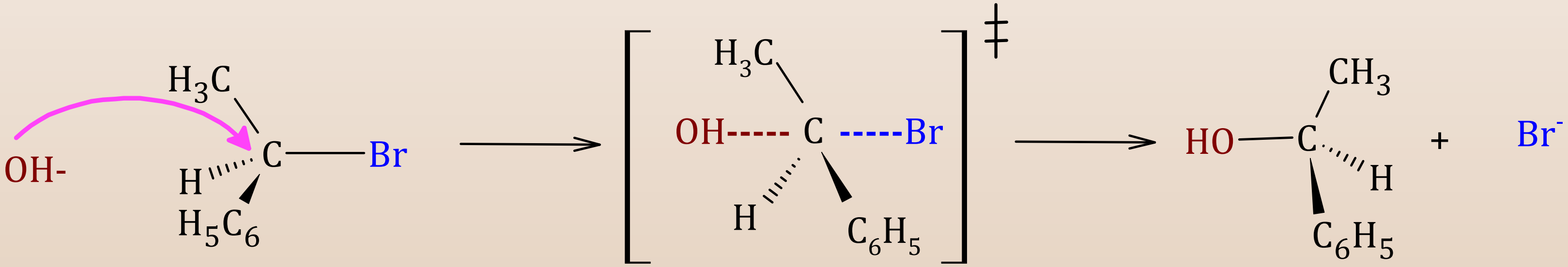
- It is seen that the rate is directly proportional to the initial concentrations of both methyl chloride (substrate) and hydroxide (nucleophile).
- The rate equation can be written as below.

$$\textbf{Rate} = k[CH_3Cl]\,[OH^-]$$

- This indicates that the reaction above is bimolecular, both substrate and nucleophile are involved in the transition state.

S_N2 Reaction Mechanism

The mechanism of the reaction can be proposed as shown below where both the substrate and nucleophile are in the transition state.



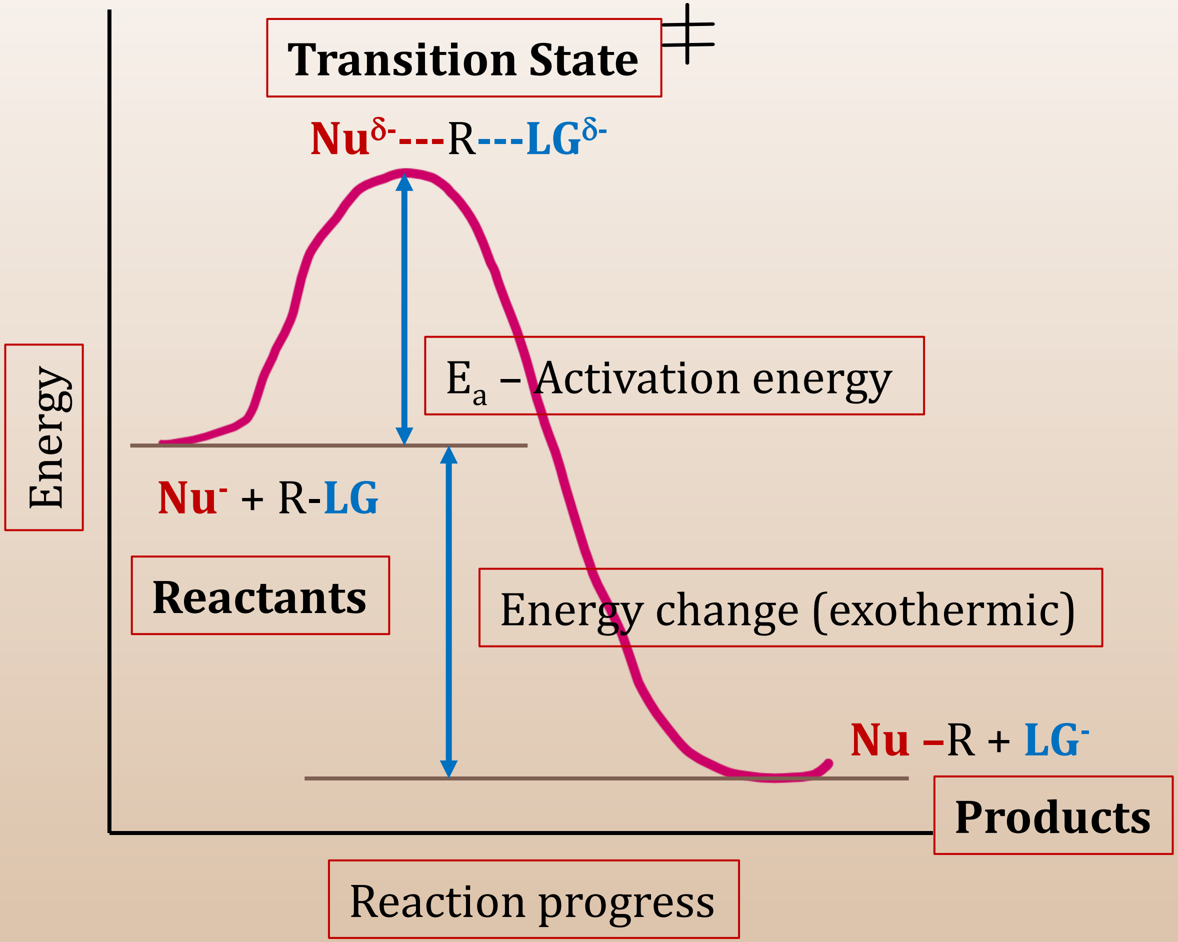
Nucleophile (Nu) attacks from back side of the electrophilic (E) carbon, where the leaving group (LG) is.

The transition state forms in which both Nu and LG are in the process of bond formation and bond breaking. Square brackets and crosshair symbol, indicate transition state.

Product forms with new bond between Nu and E. LG bond is now broken. The carbon tetrahedral has inverted in the process.

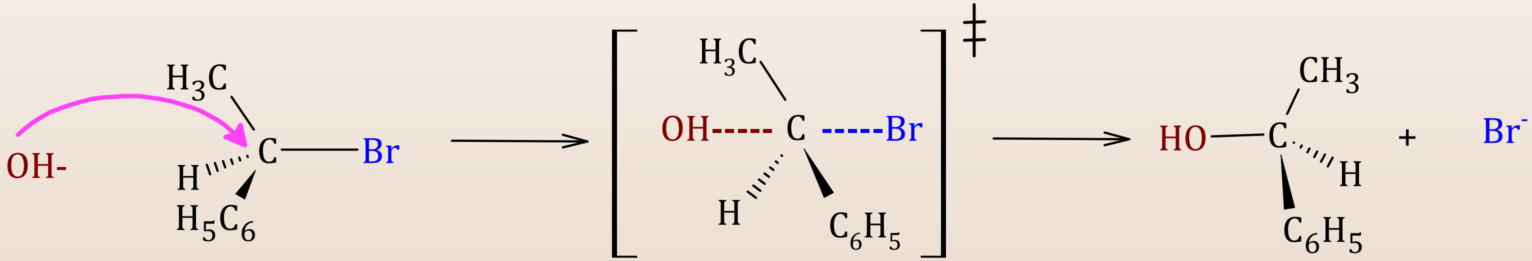
S_N2 Energy Diagram

- One-step reaction hence ONE transition state.
- Transition state is highest in energy.
- In this graph the reaction is exothermic.



S_N2 Stereochemistry

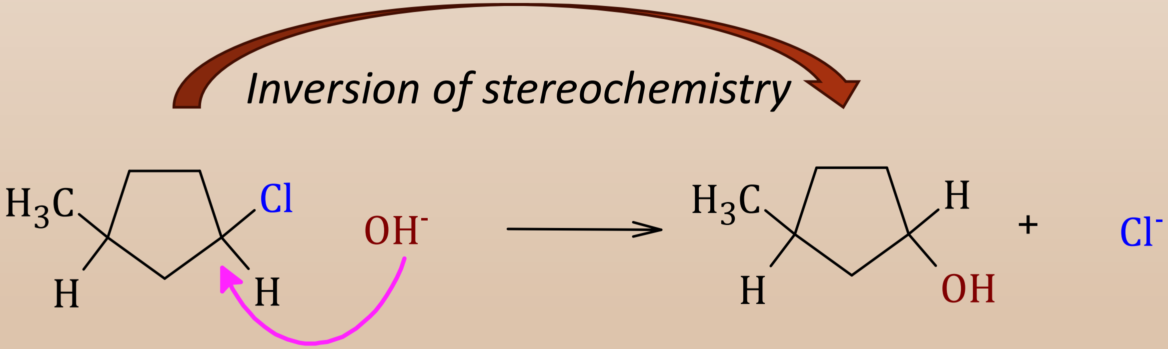
- Backside attack of nucleophile results in an **inversion of configuration**.



R enantiomer

S enantiomer

- In cyclic systems a cis compound can react and become trans product.



cis-1-chloro-3-methylcyclopentane

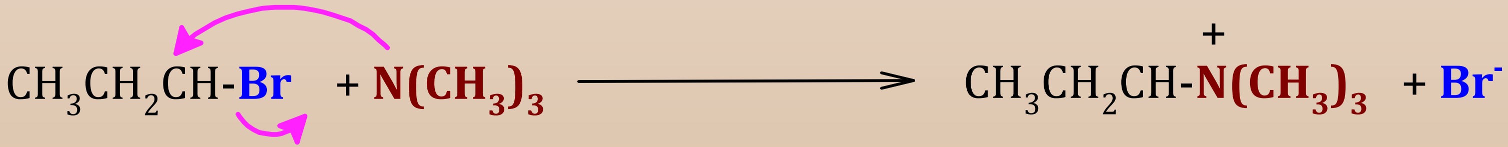
trans-3-methylcyclopentanol

Examples of S_N^2 Nucleophilic Substitution

- 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.
- The Na^+ in the reaction below will balance the charge on both sides. It is also the spectator ion hence not written all the time.

$$CH_3CH_2CH\text{-}\mathbf{Br} + Na^+\ \mathbf{OH}^- \longrightarrow CH_3CH_2CH\text{-}\mathbf{OH} + Na^+\ \mathbf{Br}^-$$

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



$$CH_3CH_2CH\text{-}\mathbf{Br} + \mathbf{N(CH_3)_3} \longrightarrow CH_3CH_2CH\text{-}\overset{+}{\mathbf{N}}\mathbf{(CH_3)_3} + \mathbf{Br}^-$$

Nucleophile is neutral

All the methyl groups in the nucleophile are still present

Applications for S_N^2 Reactions

- The most important application of S_N2 reactions is the synthesis of other classes/functional groups of compounds.
- Halogen exchange reaction can be done to make a suitable substrate or product.

R-**X**	+	**Nu:$^-$**	$\longrightarrow$	R – **Nu**	+	**X$^-$**
Substrate		**Nucleophile**		**Product**		**Leaving group**

Substrate	Nu		Product	Functional Group
R-X	I^-	$\longrightarrow$	R-I	Alkyl halide
R-X	^-OH* or OH^-	$\longrightarrow$	R-OH	Alcohol
R-X	^-OR* or OR^-	$\longrightarrow$	R-OR	Ether
R-X	^-SH* or SH^-	$\longrightarrow$	R-SH	Thiol
R-X	$^-NH_2$* or NH_2^-	$\longrightarrow$	$R\text{-}NH_2$	Thioether
R-X	CN^-	$\longrightarrow$	R-CN	Nitrile
R-X	$C\equiv C^-$	$\longrightarrow$	$R\text{-}C\equiv C$	alkyne

** Note: The negative sign indicates where the formal charge is on the ion, but we also write the minus at the end of the polyatomic ion. Either is okay.*

The S_N^1 Reaction

This type of substitution reaction indicates:

S is for substitution.

N (subscript) is for nucleophilic.

1 (superscript) is unimolecular, indicating that only one species either nucleophile or substrate are in rate determining step.

An S_N1 Reaction

Consider the reaction given below. The initial rate of the reaction is measured by analytical methods and the data given in the table is obtained.

$$(CH_3)_3CCl + OH^- \longrightarrow CH_3\text{-}OH + Cl^-$$

Experiment	Initial $[(CH_3)_3CCl]$	Initial $[OH^-]$	Initial Rate (Mol L^{-1} s^{-1})
1	0.0010	1.0	4.9×10^{-7}
2	0.0020	1.0	9.8×10^{-7}
3	0.0010	2.0	4.9×10^{-7}

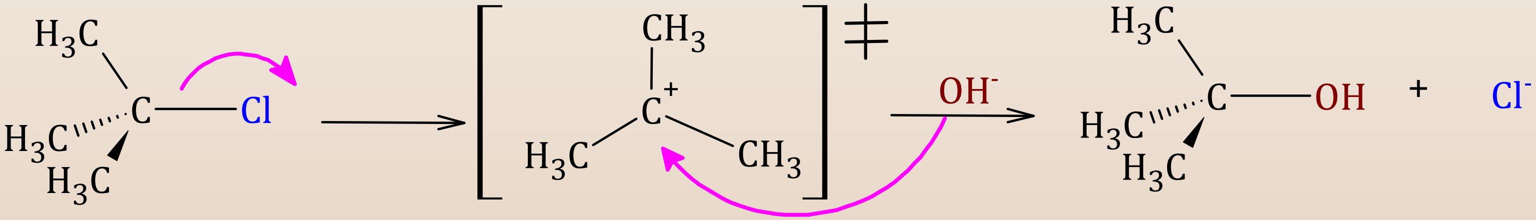
- The rate is directly proportional to the initial concentrations of only the substrate. Hydroxide concentration does not affect the rate of reaction.
- The rate equation can be written as below.

$$\textbf{Rate} = k[(CH_3)_3CCl]$$

- This indicates that the reaction above is unimolecular, only the substrate is involved in the transition state.

S_N1 Mechanism

The mechanism of the reaction can be proposed as shown below where only the substrate is in the transition state.



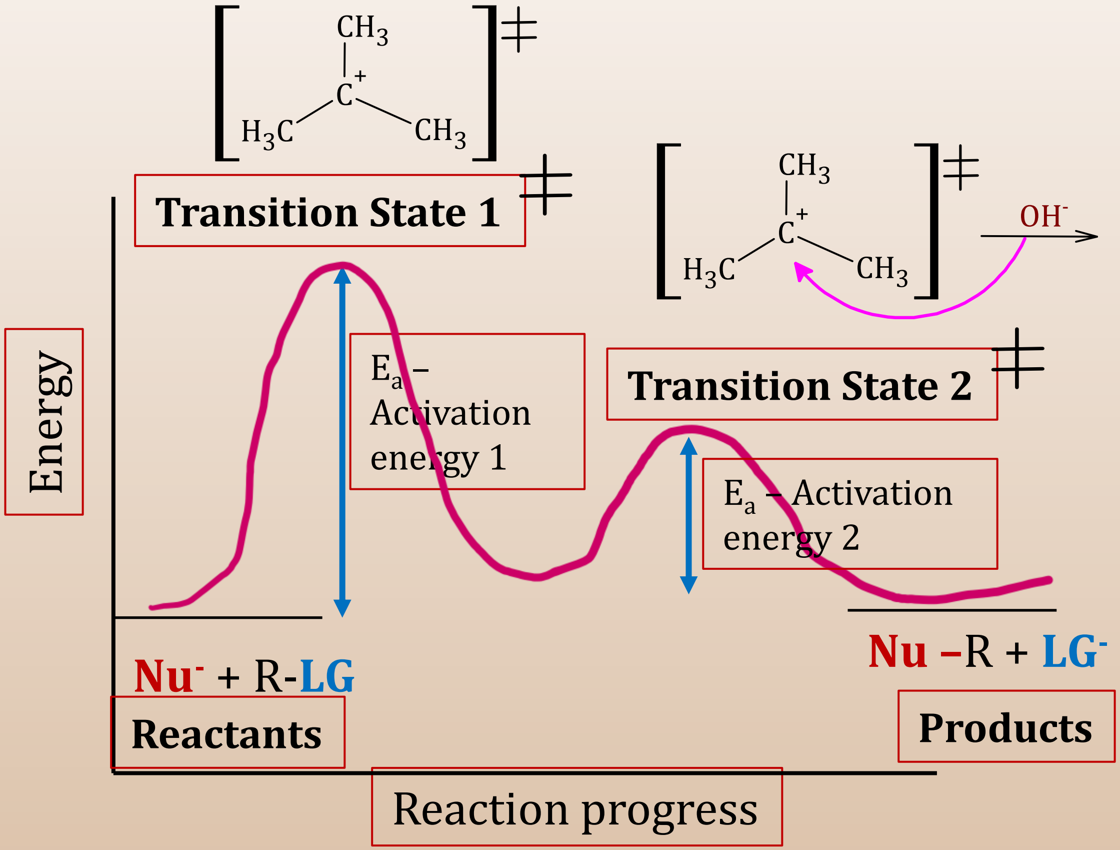
The leaving group (LG) leaves first.

Transition state in this is a carbocation, which is sp^2, trigonal planar species. Square brackets and crosshair symbol, indicate transition state.

Product forms with new bond between Nu and E. The product here retains and inverts in stereochemistry giving a racemic mixture.

S_N1 Energy Diagram

- Two-step reaction hence TWO transition states.
- The second transition state is when Nu attacks the carbocation.
- In this graph the reaction is exothermic.



Transition State 1 ‡

Transition State 2 ‡

Energy

E_a – Activation energy 1

E_a – Activation energy 2

Nu^- + R-LG

Reactants

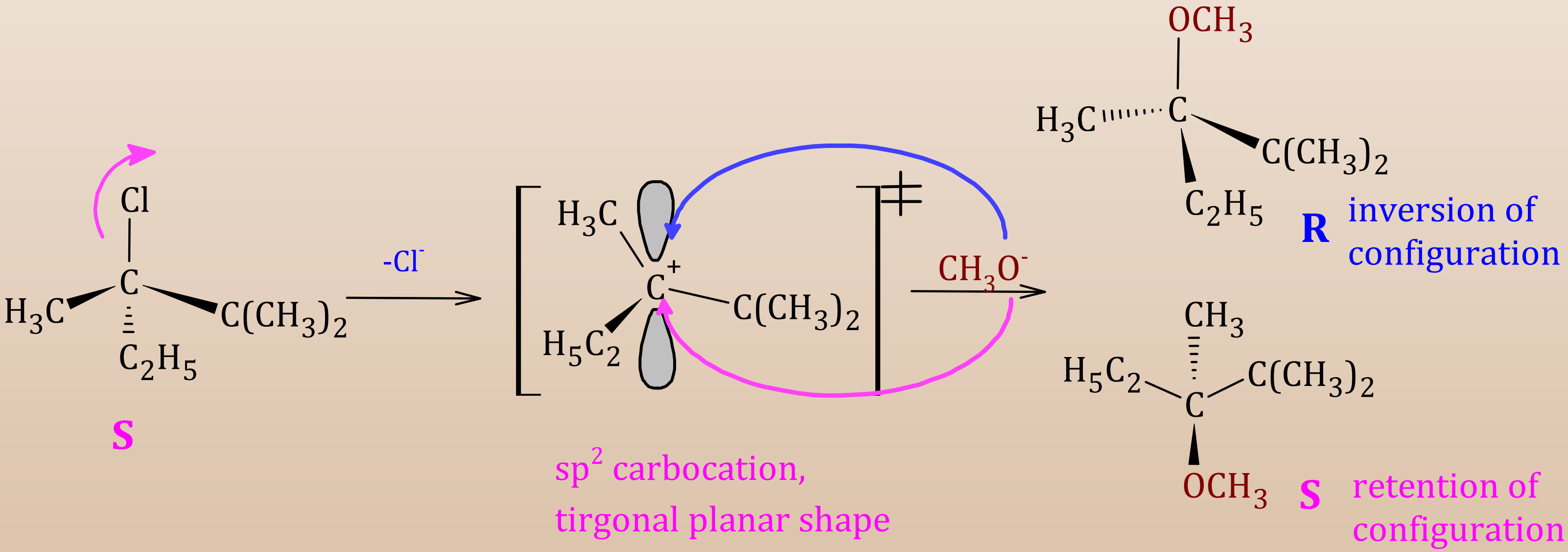
Nu –R + LG^-

Products

Reaction progress

S_N1 Stereochemistry

The carbocation is sp^2, which is trigonal planar. The nucleophile can form a bond from either side of the plane. The final product will be and equal mixture of R and S (racemic mixture) which is inversion and retention of stereochemistry.



S

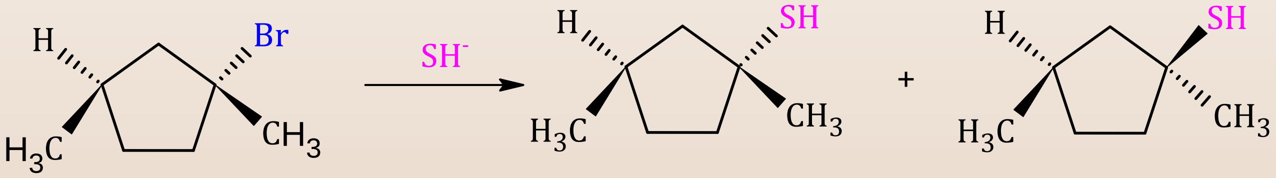
sp^2 carbocation,
tirgonal planar shape

R inversion of configuration

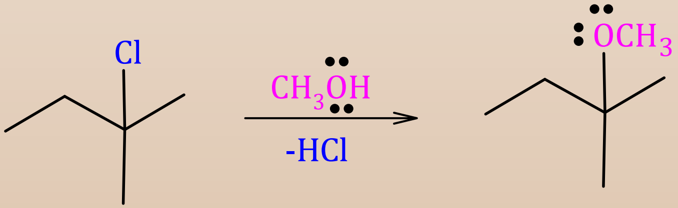
S retention of configuration

Examples of $S_N{}^1$ Nucleophilic Substitution

- The nucleophile in these reactions are not required to be strong, hence can be negative or neutral.



- Water, alcohols and amines are common neutral nucleophiles. Note that these nucleophiles have a lone pair of electrons to be electron rich.



Key Words/Concepts

- Substitution Reaction
- Nucleophile
- Electrophile
- Leaving group
- 1st order reaction (unimolecular)
- 2nd order reaction (bimolecular)
- Transition state
- Rate determining step
- Carbocation
- Configuration (inversion and retention)