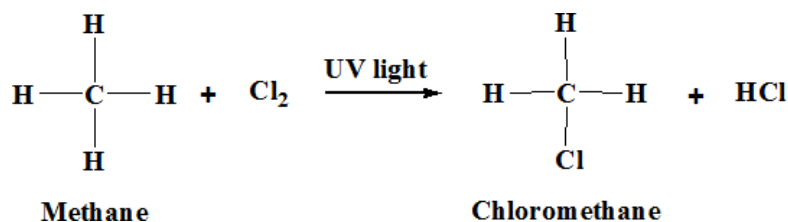
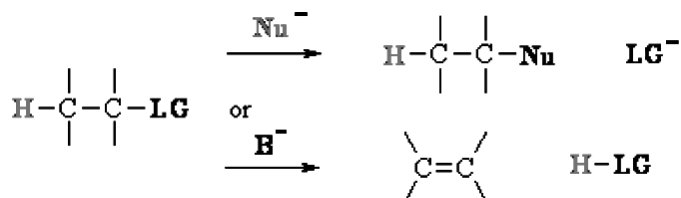


SUBSTITUTION REACTIONS

- Substitution Reactions are those reaction in which atoms or groups of atoms are directly attached to a carbon in the substrate molecule is replaced by another atom or group of atoms.



- Substitution reaction also known as single displacement reaction or single substitution reaction.
- Substitution reactions in organic chemistry are classified either as electrophilic, free radical or nucleophilic depending upon the reagent involved.
- **Substitution versus Elimination**: Substitution and elimination reactions often compete with each other because due to it's nucleophilic or basic properties.

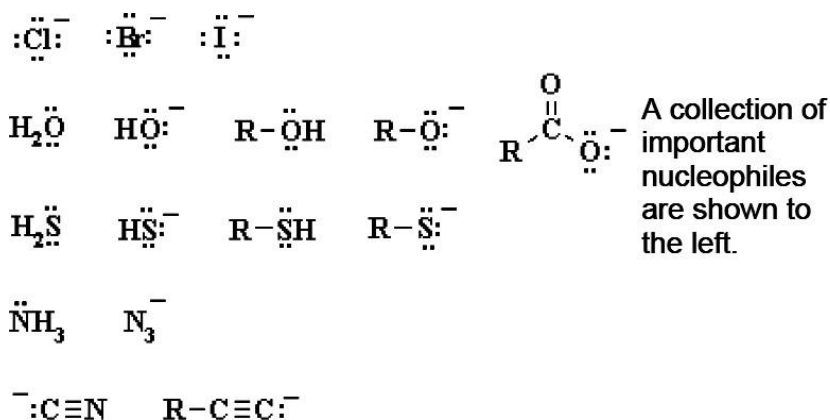


- **Substitution and elimination reactions are strongly influenced by:**
 1. Increasing the temperature tends to increase elimination due to disorder / entropy effects
 2. Increasing steric effects (look at both "R" and the "Nu/B") tends to increase elimination.
 3. The basicity / nucleophilicity of the attacking species *i.e.* switching from **ROH** to **RO⁻** will increase the amount of elimination

Reaction	Substrate	Nu or Base	Leaving Group (LG)	Solvent	Examples
S_N1	Strong (3° or resonance Stabilised)	Weak (Good Nu and weak base)	Strong (Good LG)	Very Strong (Polar solvents)	alkyl halide / AgNO ₃ / aq. EtOH alcohol / HX (note X is a good Nu)
S_N2	Strong (Methyl or 1°)	Strong (Good Nu and weak base)	Strong (Good LG)	Strong (Polar aprotic Solvents)	alkyl halide / NaI / acetone alcohol / SOCl ₂ or PCl ₃
E1	Strong (3° or resonance Stabilised)	Weak (weak base)	Strong (Good LG)	Very Strong (Polar solvents)	alcohol / H ₂ SO ₄ / heat tertiary alkyl halide / weak base (ROH or H ₂ O)
E2	Strong (3°)	Strong (Poor Nu and strong base)	Strong (Good LG)	Strong (Polar aprotic solvents)	alkyl halide / KOH / heat, primary alcohols / alcohol / H ₂ SO ₄ / heat

➤ Nucleophiles (Nu):

- Nucleophile means "**nucleus loving**" which describes the tendency of an electron rich species to be attracted to the positive nuclear charge of an electron poor species, the electrophile.
- The more available the electrons, the more nucleophilic the system. Hence the first step should be to locate the nucleophilic center.
- **Nu** that contain lone pairs and may be anionic, however the high electron density of a **C=C** is also a nucleophile.



- **Nucleophilicity trends (compared with basicity)**
1. Across a row in the periodic table nucleophilicity (lone pair donation) $\text{C}^- > \text{N}^- > \text{O}^- > \text{F}^-$ since increasing electronegativity decreases the lone pair availability. This is the same order as for basicity.
 2. If one is comparing the same central atom, higher electron density will increase the nucleophilicity, e.g. an anion will be a better **Nu** (lone pair donor) than a neutral atom such as $\text{HO}^- > \text{H}_2\text{O}$. This is the same order as for basicity.
 3. Within a group in the periodic table, increasing polarisation of the nucleophile as you go down a group enhances the ability to form the new CX bond and increases the nucleophilicity, so $\text{I}^- > \text{Br}^- > \text{Cl}^- > \text{F}^-$. The electron density of larger atoms is more readily distorted i.e. polarised, since the electrons are further from the nucleus.
 - Note that is the opposite order to basicity (acidity increases down a group) where polarisability is much less important for bond formation to the very small proton.
 - Here is a table of relative nucleophilicities as measured in methanol (CH_3OH):

Very Good	I^- , HS^- , RS^-
Good	Br^- , HO^- , RO^- , NC^- , N_3^-
Fair	$:\text{NH}_3$, Cl^- , F^- , RCO_2^-
Weak	H_2O , ROH
Very Weak	RCO_2H

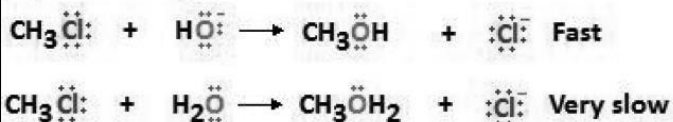
- **Increasing the Negative Charge Increases Nucleophilicity**
 - Nucleophiles can be neutral or negatively charged. In either case, it is important that the nucleophile be a good Lewis base, meaning it has electrons it wants to share. (For example, the **O** in OH^- is negatively charged, but the **O** in H_2O is neutral.)

Neutral Nucleophiles
 H_2O , NH_3 , RNH_2 , R_2NH , R_3N ,
 ROH , RCOOH , RSH , and PR_3

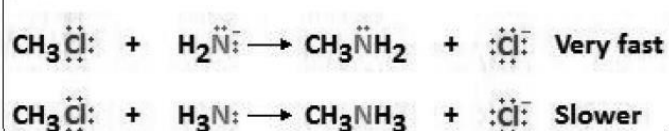
Charged Nucleophiles
 RO^- , $^-\text{NH}_2$, R^-NH , R_2N^- , HS^- , RS^- ,
 RSe^- , Cl^- , Br^- , I^- , F^- , CN^- , ^-OH , RCO_2^-

- It has been experimentally shown that a nucleophile containing a negatively charged reactive atom is better than a nucleophile containing a reactive atom that is neutral. For example, when oxygen is part of the hydroxide ion, it bears a negative charge, and when it is part of a water molecule, it is neutral. The O of OH is a better nucleophile than the O of H₂O, and results in a faster reaction rate. Similarly, when nitrogen is part of NH₂⁻, it bears a negative charge, and when it is part of NH₃, it is neutral. The N of NH₂⁻ is a better nucleophile than the N of NH₃, and results in a faster reaction rate.

Experiment #1



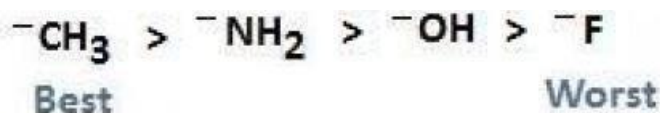
Experiment #2



- To say that nucleophilicity follows basicity across a row means that, as basicity increases from *right to left* on the *periodic table*, nucleophilicity also increases. As basicity decreases from *left to right* on the *periodic table*, nucleophilicity also decreases. When it comes to nucleophilicity, do not assign this same rule when making comparisons between the *halogens* located in a column. In this case of moving up and down a column, nucleophilicity does not always follow basicity. It depends on the type of solvent you are using.

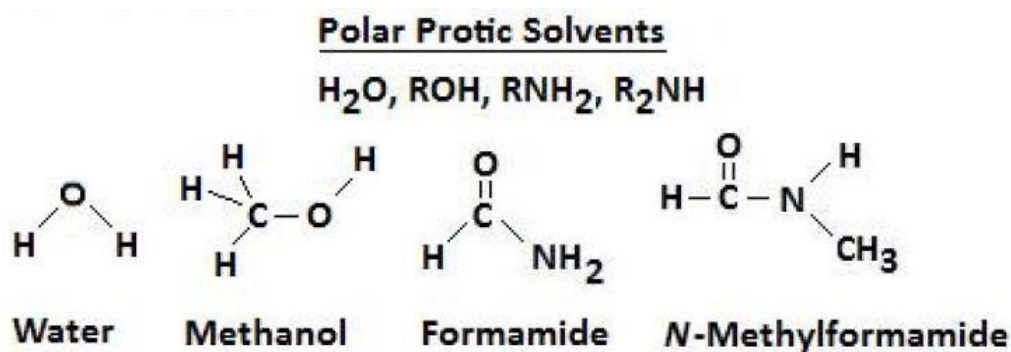


- In the section Nucleophilic Substitution, we assigned a relationship to leaving groups containing C, N, O, and F, showing that the strength of the leaving group follows electronegativity. This is based on the fact that the best leaving groups are those that are weak bases that do not want to share their electrons. The best nucleophiles however, are good bases that want to share their electrons with the electrophilic carbon. The relationship shown below, therefore, is the exact opposite of that shown for the strength of a leaving group.

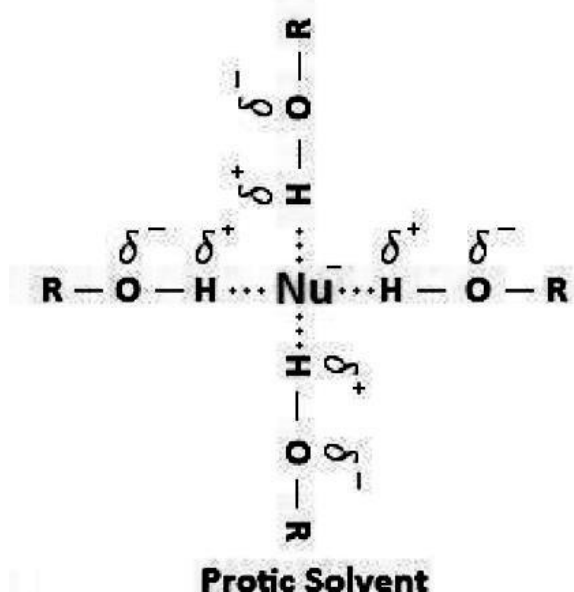


➤ Solvents and Nucleophilicity:

- In general solvents as being either polar or nonpolar. Polar solvents can be further subdivided into **protic** and **aprotic solvents**.
- **PROTIC SOLVENTS**
 - A protic solvent is a solvent that has a hydrogen atom bound to an oxygen or nitrogen. A few examples of protic solvents include H_2O , ROH , RNH_2 , and R_2NH , where water is an example of an inorganic **protic solvent** and alcohols and amides are examples of organic solvents.

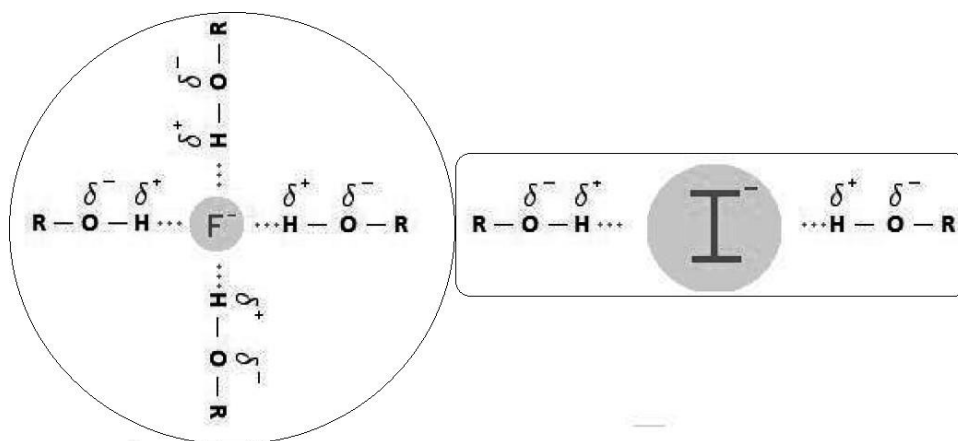


- Since oxygen and nitrogen are highly electronegative atoms, the **O-H** and **N-H** bonds that are present in protic solvents result in a hydrogen that is positively polarized. When protic solvents are used in nucleophilic substitution reactions, the positively polarized hydrogen of the solvent molecule can interact with the negatively charged nucleophile. In solution, molecules or ions that are surrounded by these solvent molecules are said to be solvated. Solvation is the process of attraction and association of solvent molecules with ions of a solute. The solute, in this case, is a negatively charged nucleophile.
- When interaction between a **protic solvent** and a **negatively charged nucleophile**. The interactions are called **hydrogen bonds**.
- The **hydrogen bond** results from a **dipole-dipole force** between an **electronegative atom**, such as a halogen, and a hydrogen atom bonded to nitrogen, oxygen or fluorine.
- In the case using an alcohol (ROH) as an example of a protic solvent, then interaction can occur with other solvents containing a positively polarized hydrogen atom, such as a molecule of water, or amides of the form RNH_2 and R_2NH .

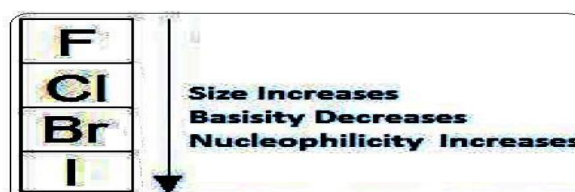


• IMPORTANT OF SOLVATION

- Solvation weakens the nucleophile; that is, solvation decreases nucleophilicity. This is because the solvent forms a "shell" around the nucleophile, impeding the nucleophile's ability to attack an electrophilic carbon.
- Furthermore, because the charge on smaller anions is more concentrated, small anions are more tightly solvated than large anions.
- For example the smaller fluoride anion is represented as being more heavily solvated than the larger iodide anion. This means that the fluoride anion will be a weaker nucleophile than the iodide anion because fluoride will not function as a nucleophile at all in protic solvents. It is so small that solvation creates a situation whereby fluoride's lone pair of electrons are no longer accessible, meaning it is unable to participate in a nucleophilic substitution reaction.

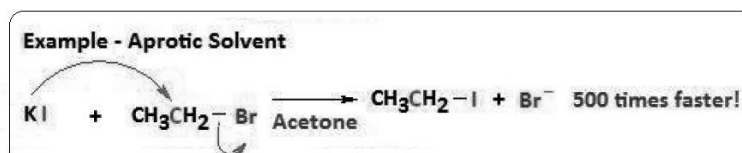
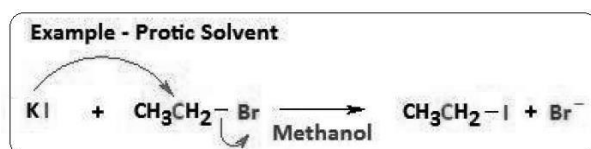
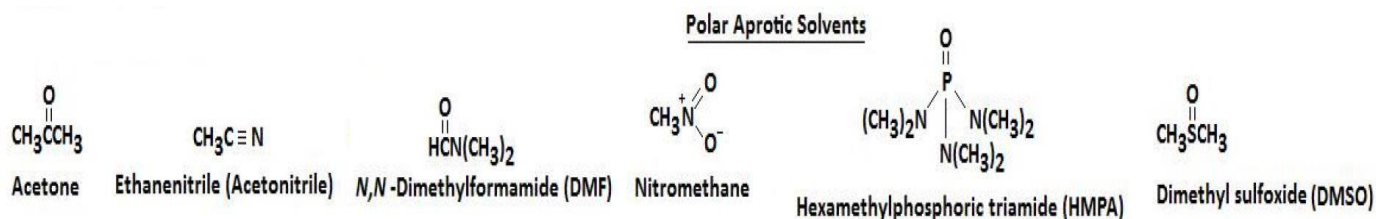


- Nucleophilicity follows basicity when moving across a row. But, the effect of protic solvents on nucleophilicity, we learned that solvation weakens the nucleophile, having the greatest effect on smaller anions. In effect, when using protic solvents, nucleophilicity does not follow basicity when moving up and down a column. In fact, it's the exact opposite: when basicity decreases, nucleophilicity increases and when basicity increases, nucleophilicity decreases.



• APROTIC SOLVENTS

- An aprotic solvent is a solvent that lacks a positively polarized hydrogen.
- Aprotic solvents, like protic solvents, are polar but, because they lack a positively polarized hydrogen, they do not form hydrogen bonds with the anionic nucleophile. The result, with respect to solvation, is a relatively weak interaction between the aprotic solvent and the nucleophile.



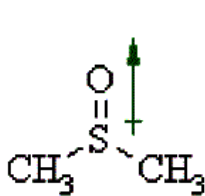
• SUMMARY

✓ POLAR PROTIC SOLVENTS (polar and ability to be **H-bond donor**)

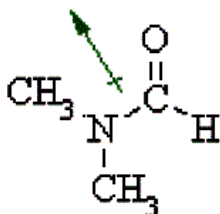
- have dipoles due to polar bonds
- can H atoms that can be donated into a H-bond
- examples are the more common solvents like H₂O and ROH
- remember basicity is also usually measured in water
- anions will be solvated due to H-bonding, inhibiting their ability to function as **Nu**

✓ POLAR APROTIC SOLVENTS (polar but no ability to be **H-bond donor**)

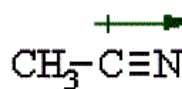
- have dipoles due to polar bonds
- don't have H atoms that can be donated into a **H-bond**
- examples are acetone, acetonitrile, DMSO, DMF
- anions are not solvated and are "**naked**" and reaction is not inhibited



dimethylsulfoxide



N,N-dimethylformamide



acetonitrile

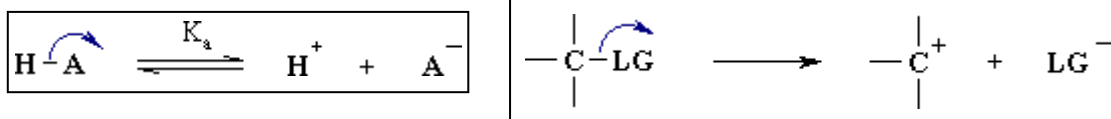
• OVERALL

- All nucleophiles will be more reactive in aprotic than protic solvents
- Those species that were most strongly solvated in polar protic solvents will "gain" the most reactivity in polar aprotic (e.g. F⁻).
- Polar aprotic solvents are typically only used when a polar protic solvent gives poor results due to having a weak Nu, (esp. F⁻, ⁻CN, RCO₂⁻)

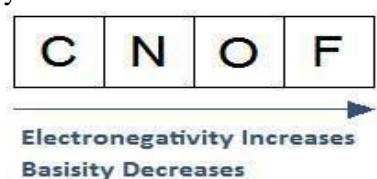
Solvent	Dipole moment, μ	Dielectric constant, ϵ	Relative Rate	Type
CH ₃ OH	2.87	33	1	protic
H ₂ O	1.84	78	7	protic
DMSO	3.96	49	1,300	aprotic
DMF	3.82	37	2,800	aprotic
CH ₃ CN	3.92	38	5,000	aprotic

➤ Leaving Groups:

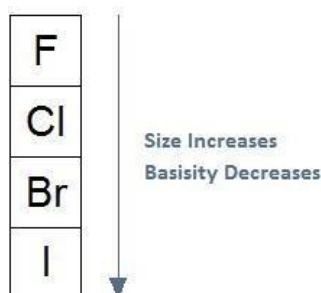
- A leaving group (**LG**), is an atom (or a group of atoms) that is displaced as stable species taking with it the bonding electrons. Typically the leaving group is an anion (e.g. Cl^-) or a neutral molecule (e.g. H_2O).
- The better the leaving group, the more likely it is to depart.
- A "good" leaving group can be recognised as being the conjugate base of a strong acid.



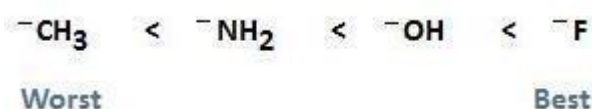
- The Nature of the **Leaving Group** (LG) depends on electronegativity, size, and resonance.
- **As Electronegativity Increases, Basicity Decreases:** In general, if we move from the left of the periodic table to the right of the periodic table as shown in the diagram below, electronegativity increases. As electronegativity increases, basicity will decrease, meaning a species will be less likely to act as base; that is, the species will be less likely to share its electrons.



- **As Size Increases, Basicity Decreases:** In general, if we move from the top of the periodic table to the bottom of the periodic table as shown in the diagram below, the size of an atom will increase. As size increases, basicity will decrease, meaning a species will be less likely to act as a base; that is, the species will be less likely to share its electrons.



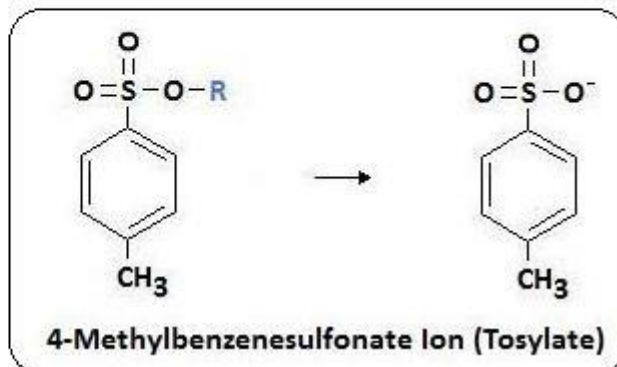
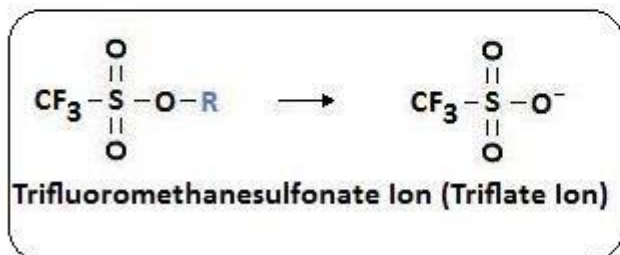
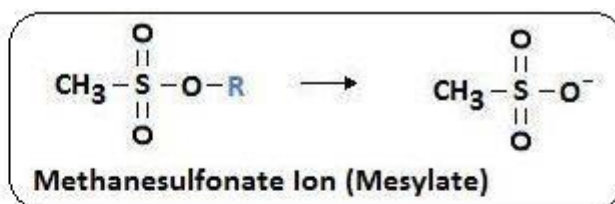
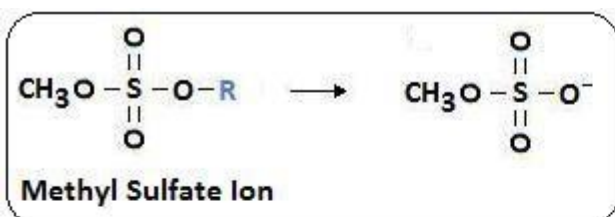
- **Resonance Decreases Basicity:** The third factor to consider in determining whether or not a species will be a strong or weak base is resonance. As you may remember from general chemistry, the formation of a resonance stabilized structure results in a species that is less willing to share its electrons. Since strong bases, by definition, want to share their electrons, resonance stabilized structures are weak bases.
- **Weak Bases are the Best Leaving Groups**
 - As mentioned previously, if we move from left to right on the periodic table, electronegativity increases. With an increase in electronegativity, basicity decreases, and the ability of the leaving group to leave increases. This is because an increase in electronegativity results in a species that wants to hold onto its electrons rather than donate them. The following diagram illustrates this concept, showing CH_3^- to be the worst leaving group and F^- to be the best leaving group.
 - For example, fluoride is such a poor leaving group that $\text{S}_{\text{N}}2$ reactions of *fluoroalkanes* are rarely observed.



- **As Size Increases, the Ability of the Leaving Group to Leave Increases:** If we move down the periodic table, size increases. With an increase in size, basicity decreases, and the ability of the leaving group to leave increases.

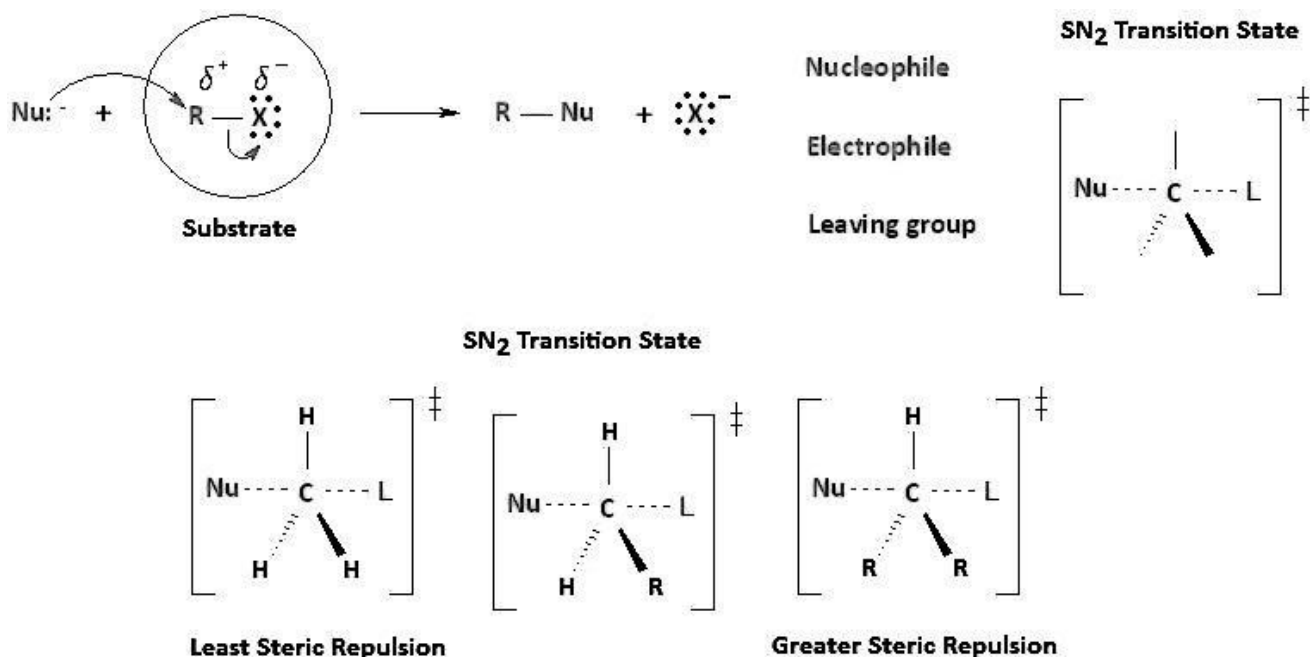


- **Resonance Increases the Ability of the Leaving Group to Leave:** As we learned previously, resonance stabilized structures are weak bases. Therefore, leaving groups that form resonance structures upon leaving are considered to be excellent leaving groups. The following diagram shows sulfur derivatives of the type ROSO_3^- and RSO_3^- . Alkyl sulfates and sulfonates like the ones shown make excellent leaving groups. This is due to the formation of a resonance stabilized structure upon leaving.



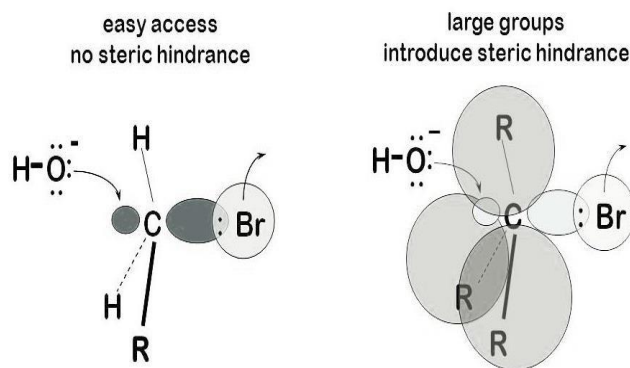
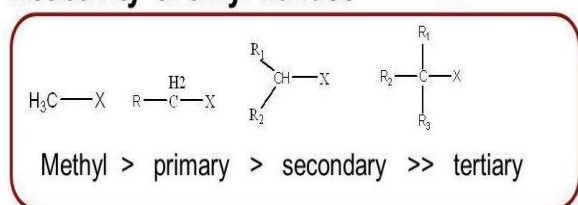
➤ Substrate influence in nucleophilic substitution reactions:

- Sterically Hindered Substrates will reduce the S_N2 reaction rate.

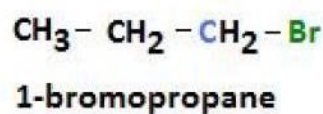
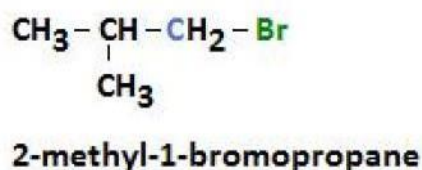


- Steric hindrance affects the rate at which an S_N2 reaction will occur. As each hydrogen is replaced by an **R-group**, the rate of reaction is significantly diminished. This is because the addition of one or two **R-groups** shields the backside of the electrophilic carbon, impeding nucleophilic attack.

Reactivity of alkyl halides S_N2 Reaction

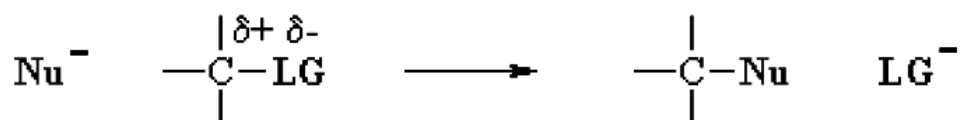


- **Substitutes on Neighboring Carbons Slow Nucleophilic Substitution Reactions**, As for example below, **2-methyl-1-bromopropane** differ from **1-bromopropane** in that it has a methyl group attached to the carbon that neighbors the electrophilic carbon. The addition of this methyl group results in a significant decrease in the rate of a nucleophilic substitution reaction. If **R groups** were added to carbons farther away from the electrophilic carbon, we would still see a decrease in the reaction rate. However, branching at carbons farther away from the electrophilic carbon would have a much smaller effect.



➤ Nucleophilic Substitution Reaction:

- Overall a nucleophilic substitution can be represented as follows:



- There are two fundamental events in a nucleophilic substitution reaction:

- formation of the new σ bond to the nucleophile
- breaking of the σ bond to the leaving group

- Depending on the relative timing of these events, three different mechanisms are possible:

- Bond breaking to form a carbocation proceeds the formation of the new bond: **S_N1 reaction**
- Simultaneous bond formation and bond breaking: **S_N2 reaction**
- S_Ni** or **Substitution Nucleophilic internal**: It stands for a specific but not often encountered nucleophilic aliphatic substitution reaction mechanism. A typical representative organic reaction displaying this mechanism is the chlorination of alcohols with thionyl chloride, or the decomposition of alkyl chloroformates, the main feature is retention of stereo chemical configuration.

- Bonding in the halogen-alkanes**

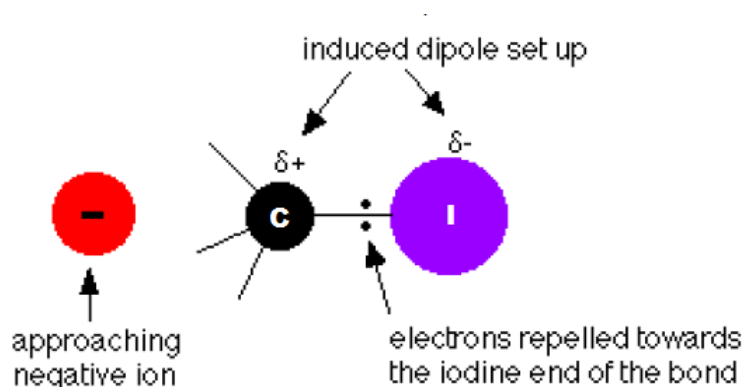
- Halogen-alkanes (also known as halo-alkanes or alkyl halides) are compounds containing a halogen atom (fluorine, chlorine, bromine or iodine) joined to one or more carbon atoms in a chain.
- The interesting thing about these compounds is the carbon-halogen bond, and all the nucleophilic substitution reactions of the halogen alkanes involve breaking that bond

- The polarity of the carbon-halogen bonds**

- With the exception of iodine, all of the halogens are more electronegative than carbon.

Electronegativity values				
C = 2.5	F = 4.0	Cl = 3.0	Br = 2.8	I = 2.5

- That means that the electron pair in the carbon-halogen bond will be dragged towards the halogen end, leaving the halogen slightly negative (δ^-) and the carbon slightly positive (δ^+) except in the carbon-iodine case.
- Although the **carbon-iodine bond** doesn't have a permanent dipole, the bond is very easily polarised by anything approaching it. Imagine a negative ion approaching the bond from the far side of the carbon atom:



The fairly small polarity of the carbon-iodine bond will be increased by the same effect

- *The strengths of the carbon-halogen bonds*

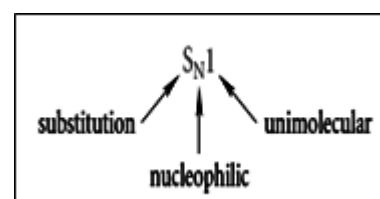
Strengths of various bonds (kJ/mol)	
C-H	413
C-F	467
C-Cl	346
C-Br	290
C-I	228

- In all of these **nucleophilic substitution** reactions, the **carbon-halogen bond** has to be broken at some point during the reaction. The harder it is to break, the slower the reaction will be.
- The **carbon-fluorine bond** is very strong (stronger than **C-H**) and isn't easily broken. It doesn't matter that the **carbon-fluorine bond** has the greatest polarity the strength of the bond is much more important in determining its reactivity, Therefore expect **fluoro-alkanes** to be very unreactive and they are.
- In the other halogeno-alkanes, the bonds get weaker as you go from **chlorine** to **bromine** to **iodine**.
- That means that **chloro-alkanes** react most slowly, **bromo-alkanes** react faster, and **iodo-alkanes** react faster still: *Rates of reaction:* **R-Cl < R-Br < R-I**

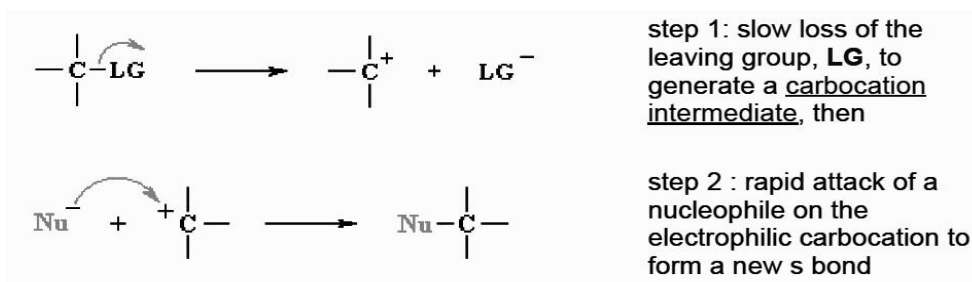
➤ Nucleophilic Aliphatic Substitution

1. S_N1 Reaction

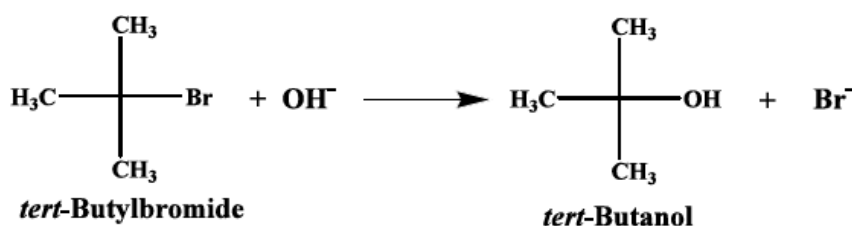
- The **S_N1 reaction** is a substitution reaction in organic chemistry. "SN" stands for nucleophilic substitution and the "1" represents the fact that the rate determining step is unimolecular.
- Thus, the rate equation is often shown as having **first order dependence on electrophile** and **zero order dependence on nucleophile**.
- In S_N1 reaction, substitution at **Sp^3 carbon** in which a Carbon-Leaving group bond ionizes to form a carbocation intermediate before the Carbon-Nucleophile bond is formed.
- **Making faster S_N1 reaction:** Use a better leaving group, create a more stable carbocation by increasing number of carbon groups on **Sp^3 carbon**, or add **resonance** to structure. Remember that resonance from **one pi bonds** outweighs stability from one alkyl group (ex: tertiary without resonance is slower than secondary with resonance).
- **S_N1 reaction is:**
 - Non-stereospecific (attack by nucleophile occurs from both sides)
 - Non-concerted - has carbocation intermediate
 - Unimolecular - rate depends on concentration of only the substrate.
- **Substrate for S_N1 reaction:**
 - Best if tertiary or conjugated (benzylic or allylic) carbocation can be formed as leaving group departs
 - never primary
- **Formation of carbonium ion.**
 - Reactivity of an alkyl halide depends chiefly upon how stable a carbonium ion it can form.
 - In **S_N1 reactions** the order of reactivity of alkyl halides is **Allyl, benzyl $> 3^0 > 2^0 > 1^0 > CH_3X$** .
 - **3^0 alkyl halides** undergo **S_N1 reaction** very fast because of the high stability of 3^0 carbocations.
- **Nucleophile character in S_N1 reaction:**
 - Best if more reactive (i.e. more anionic or more basic)
- **Leaving Group nature:**
 - Best if more stable (i.e. can support negative charge well)
 - Examples: **TsO^-** (very good) $> I^- > Br^- > Cl^- > F^-$ (poor)
 - However, tertiary or allylic **ROH** or **ROR'** can be reactive under strongly acidic conditions to replace **OH** or **OR**.
- **Solvent used in S_N1 reaction:**
 - **Protic solvents** used in S_N1 reaction because formation of carbocation intermediate is the rate determining step. Since for the formation of stable intermediate carbocation highly polar solvent is required. The negative part of the polar protic solvent interacts with the highly positive part and minimises the energy and makes it stable.



• ***S_N1* Reaction mechanism:**

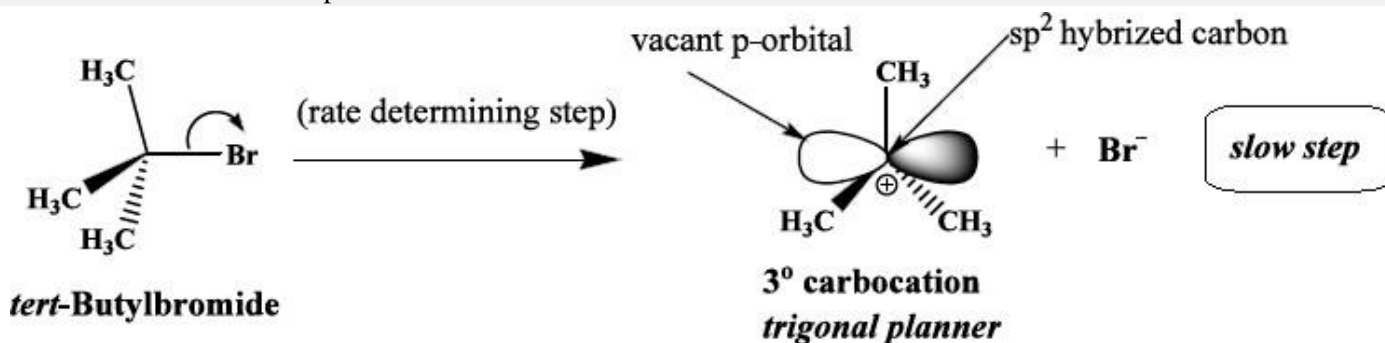


- For example: The reaction between ***tert*-butylbromide** and **aqueous sodium hydroxide ion** to give ***tert*-butyl alcohol** and **bromide ion** follows **S_N1** mechanism.



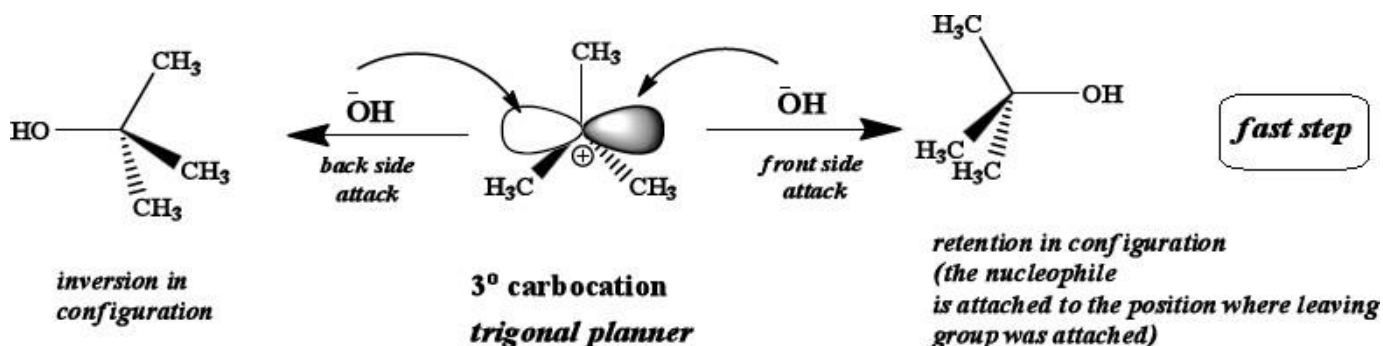
In the first step

The Carbon-Halogen (C-Br) bond of the substrates slowly breaks by heterolytic fission (halogen departs with the shared pairs of electrons) forming a carbocation. This is the slowest step and hence is the rate determining step. The formed carbocation has trigonal planar structure.



In the second step

The nucleophile rapidly attacks the free carbocation giving the product. The nucleophile can attack the carbocation from either sides of the plane giving racemized product (with inversion and retention configuration).



Note: Since the product ***tert*-butanol** is achiral, both the product formed in this case is the same.

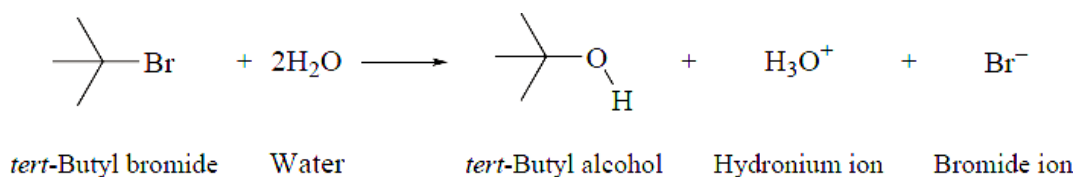
If the leaving group departing from the substrate exists in the form of ion pair with the carbocation, partial Racemisation occurs.

• **Rate of S_N1 reaction:**

- Rate of S_N1 reaction follow **first-order rate law**.
- According to the **kinetics of reactions**, their rate depends only on the **substrate's concentration [S]**:

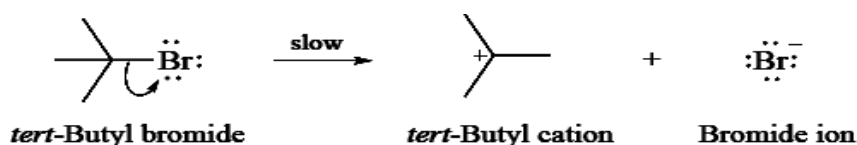
Reaction rate \propto [S]

- As for example: hydrolysis of *tert*-butyl bromide

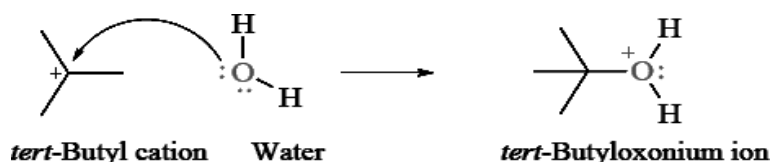


The overall reaction Mechanism

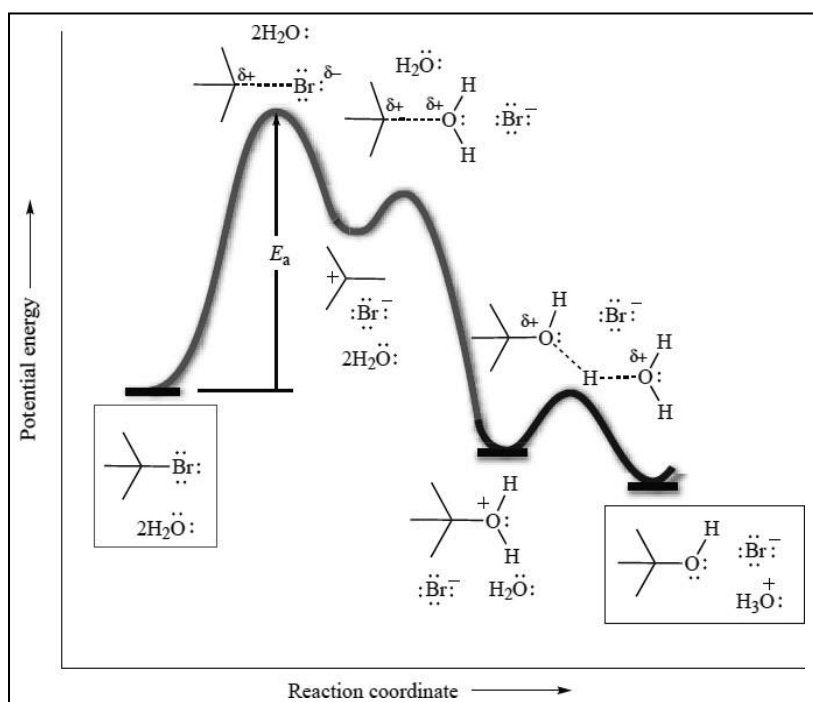
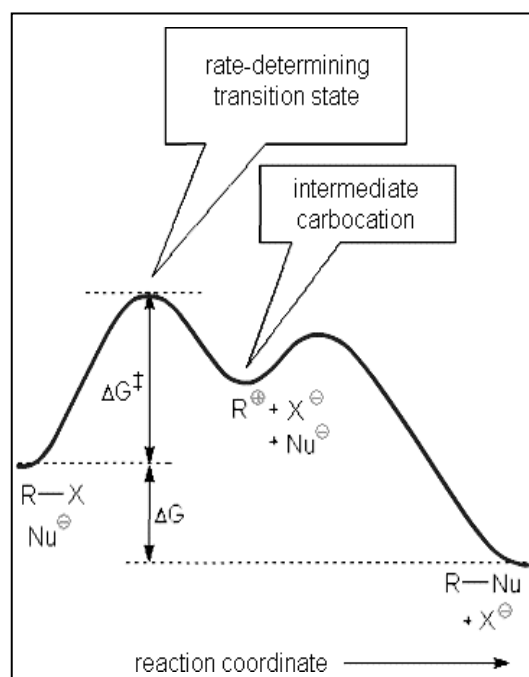
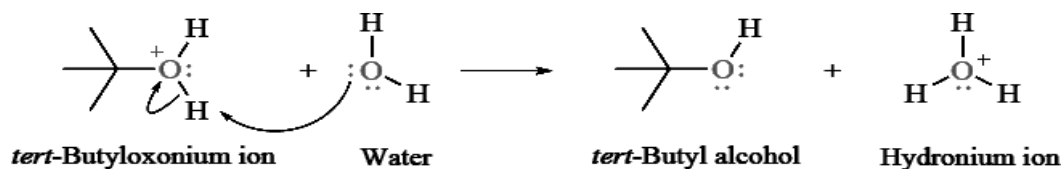
Step 1: The alkyl halide dissociates to a *carbocation* and a *halide ion*.



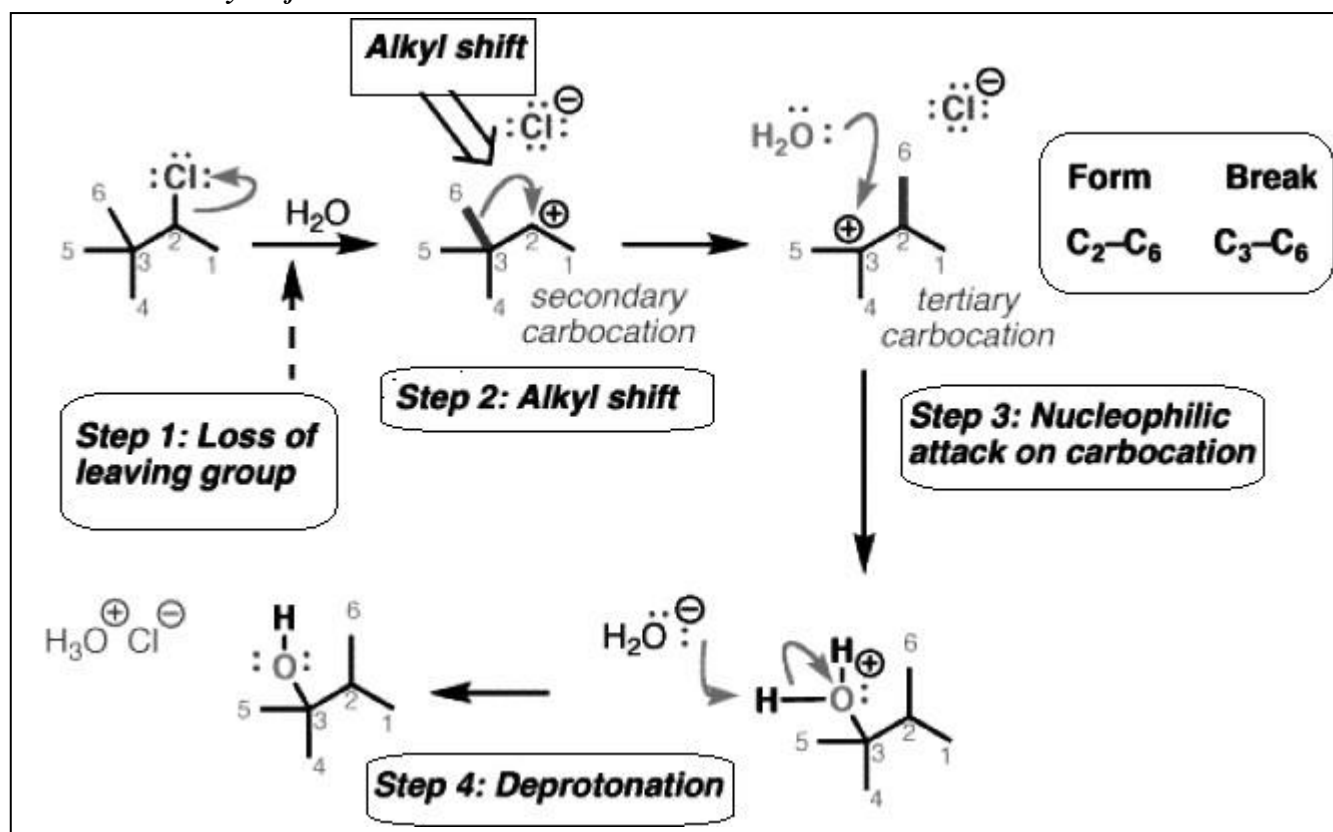
Step 2: The carbocation formed in step 1 reacts rapidly with water, which acts as a nucleophile. This step completes the nucleophilic substitution stage of the mechanism and yields an *alkyloxonium ion*.



Step 3: This step is a fast acid–base reaction that follows the nucleophilic substitution. Water acts as a base to remove a proton from the *alkyloxonium ion* to give the observed product of the reaction, *tert*-butyl alcohol.

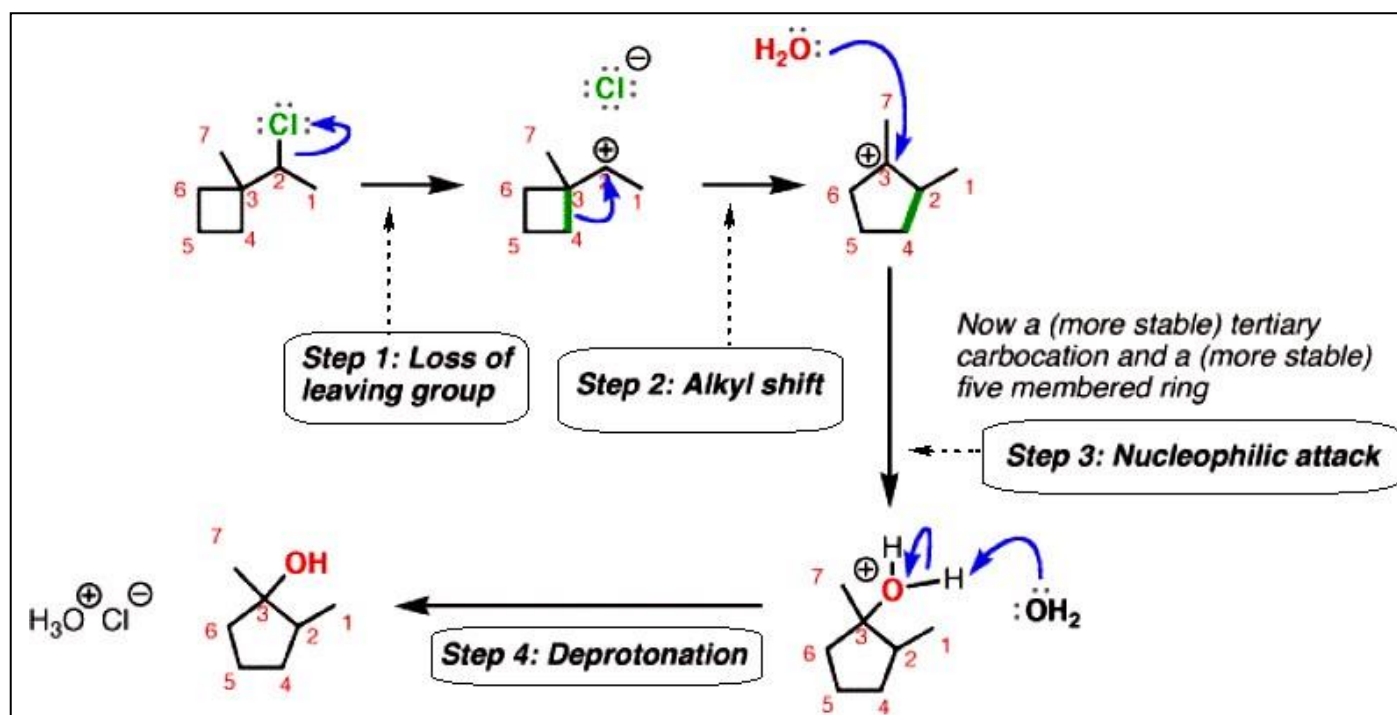


• *S_N1 reaction with Alkyl Shift:*



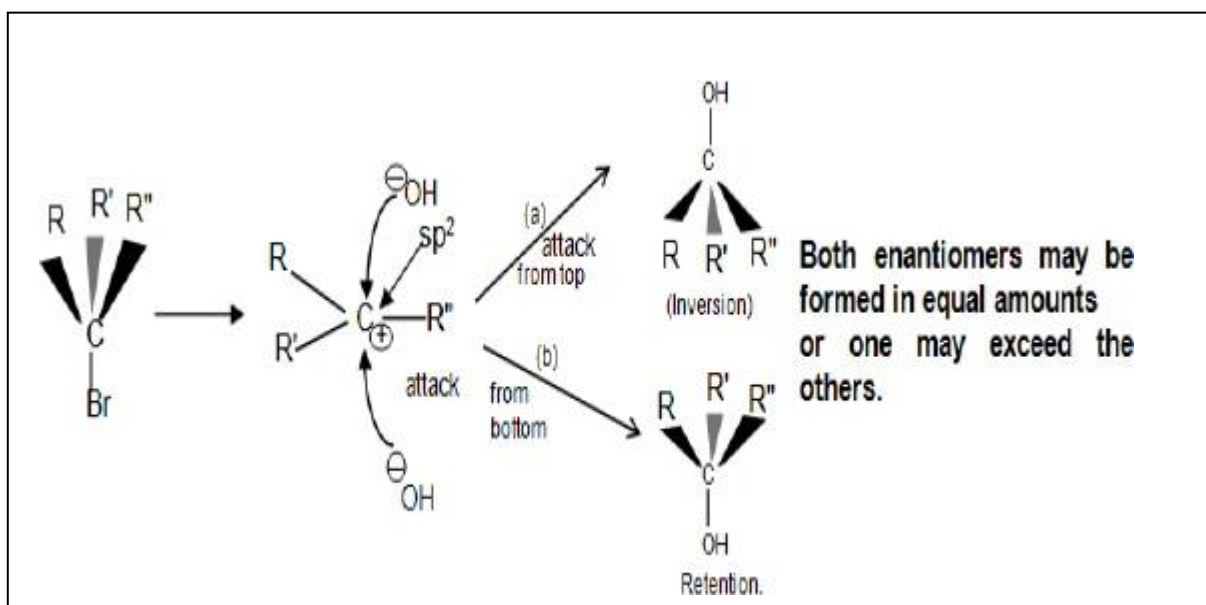
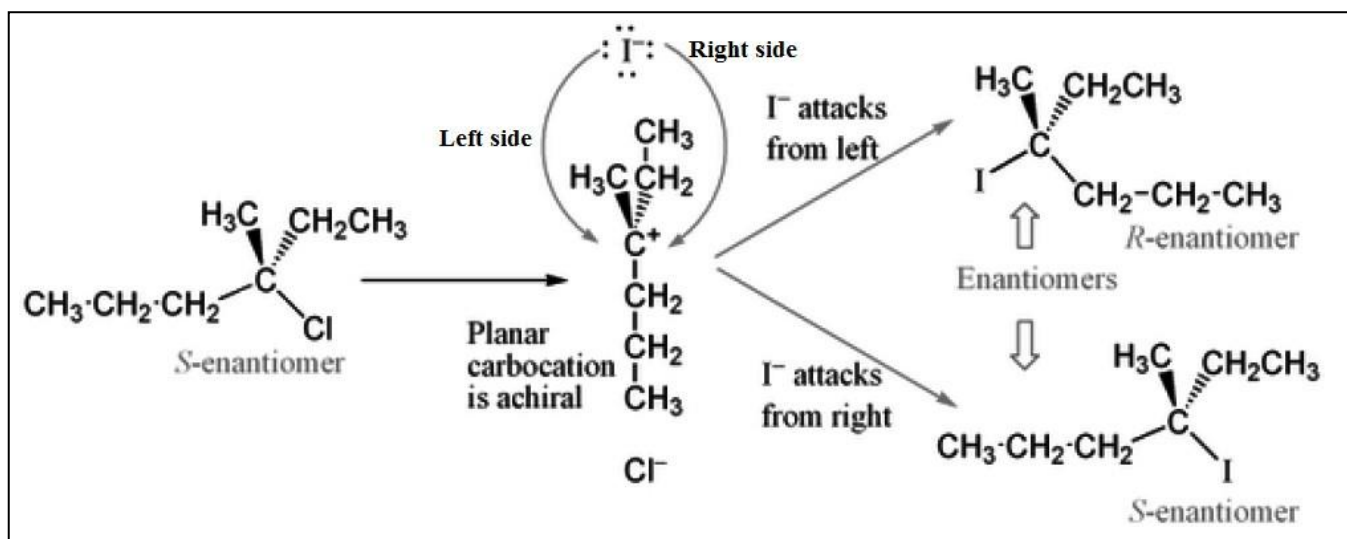
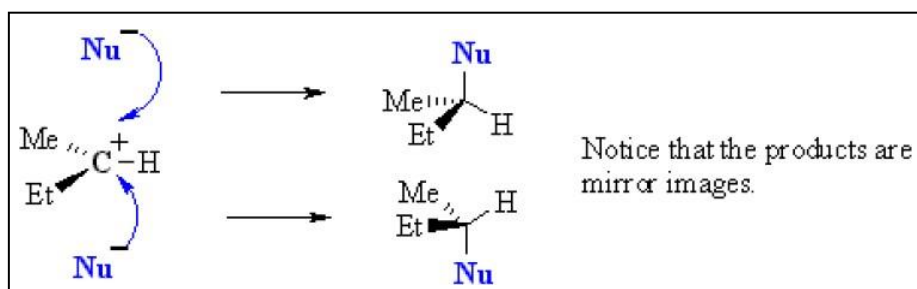
• *S_N1 reaction with Alkyl Shift leads to ring expansion:*

- It doesn't always have to be a methyl group that moves. One interesting example is when a carbocation is formed adjacent to a strained ring, such as a **cyclobutane**. Even though the **CH₃** could potentially migrate in this case, it's favourable to shift one of the alkyl groups in the ring, which leads to ring expansion and the formation of a **less strained, five membered ring**.



• **Stereochemistry in S_N1 reaction:**

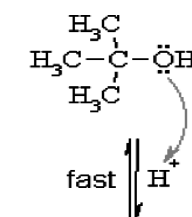
- In **S_N1 reaction**, the nucleophile attacks the **planar carbocation**. Since there is an equally probability of attack on each face there will be a loss of stereochemistry at the reactive center as both products will be observed.
- **S_N1 reaction** proceeds with racemization though may not be complete.



• **S_N1 mechanism for reaction of alcohols with HBr**

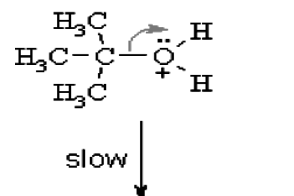
Step 1:

An acid/base reaction. Protonation of the alcoholic oxygen to make a better leaving group. This step is very fast and reversible. The lone pairs on the oxygen make it a Lewis base.



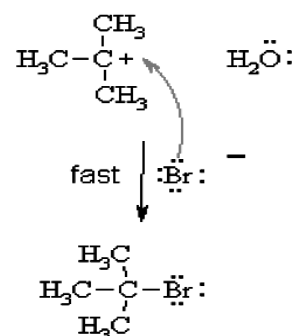
Step 2:

Cleavage of the C-O bond allows the loss of the good leaving group, a neutral water molecule, to give a carbocation intermediate. This is the rate determining step (bond breaking is endothermic)



Step 3:

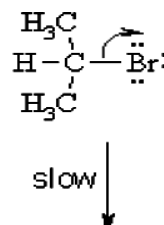
Attack of the nucleophilic bromide ion on the electrophilic carbocation creates the alkyl bromide.



• **S_N1 mechanism for reaction of alkyl halides with H₂O**

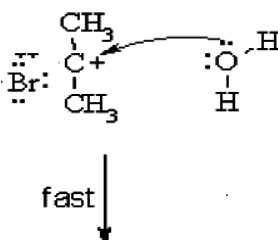
Step 1:

Cleavage of the already polar C-Br bond allows the loss of the good leaving group, a halide ion, to give a carbocation intermediate. This is the rate determining step (bond breaking is endothermic)



Step 2:

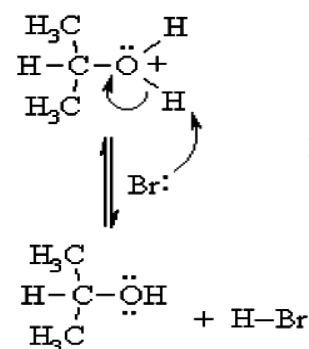
Attack of the nucleophile, the lone pairs on the **O-atom** of the water molecule, on the electrophilic carbocation creates an oxonium species.



Step 3:

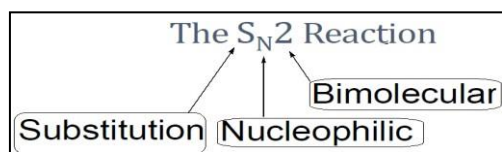
Deprotonation by a base yields the alcohol as the product.

- Note that this is the reverse of the reaction of an alcohol with HBr.
- In principle, the nucleophile here, H₂O, could be replaced with any nucleophile, in which case the final deprotonation may not always be necessary.

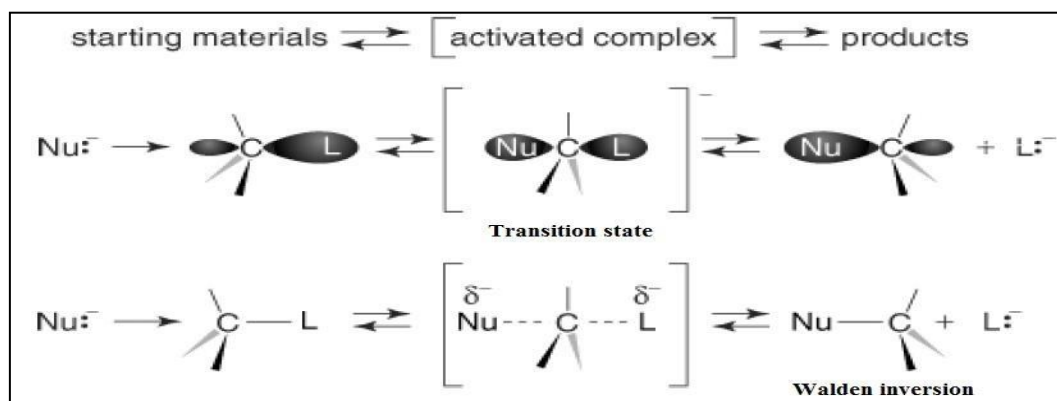


2. S_N2 Reaction

- S_N2 reaction stands for **Substitution Nucleophilic Bimolecular Reaction**.
- In this mechanism, one bond is broken and one bond is formed synchronously, i.e., in one step.

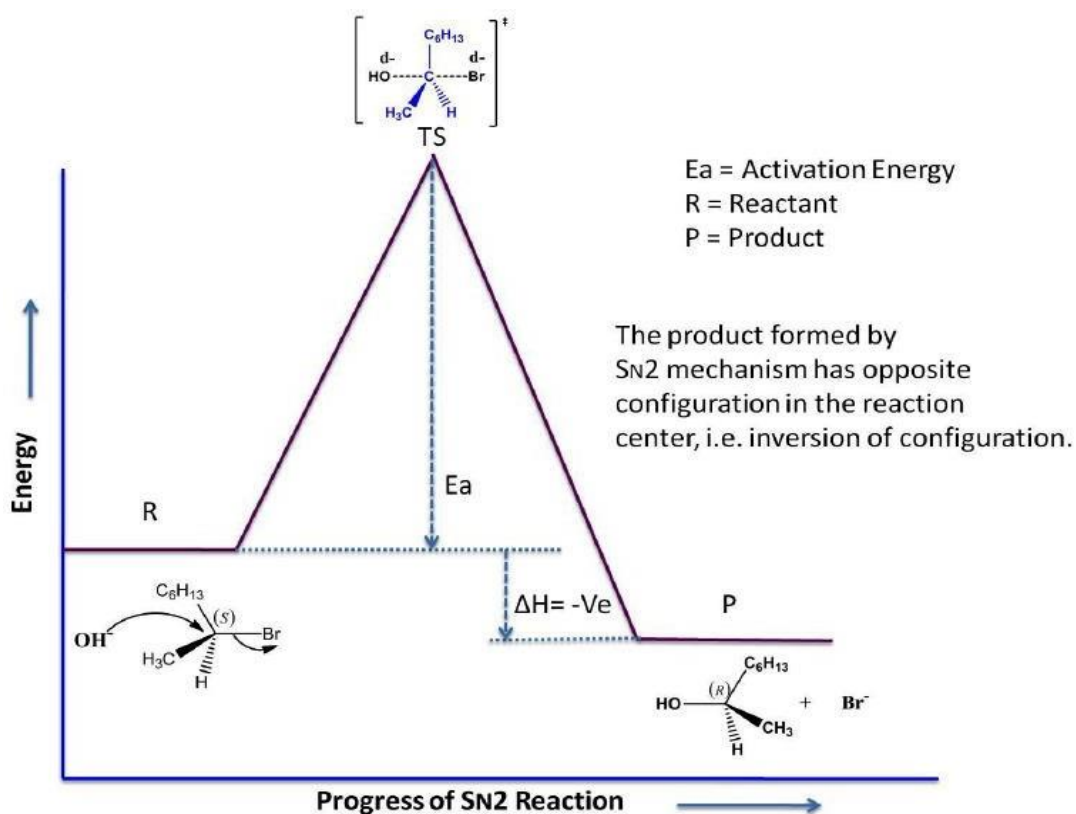


- The S_N2 **mechanism** begins when an electron pair of the nucleophile attacks the back lobe of the leaving group. Carbon in the resulting complex is **trigonal bipyramidal** in shape. With the loss of the leaving group, the carbon atom again assumes a **pyramidal** shape; however, its configuration is inverted.
- In an S_N2 **reaction**, **Nucleophile** attacks opposite side of the **leaving group**. This occurs because the nucleophilic attack is always on the back lobe (antibonding orbital) of the carbon atom acting as the nucleus. The bond between **nucleophile (Nu)** and **carbon (C)** forms at the exact same time that the bond between **carbon** and **Leaving Group (L)** breaks. In other words, **Nu-C** bond formation and **C-Leaving Group** bond breakage happen simultaneously. In the **transition state**, the carbon is partially attached to both.
- S_N2 **mechanisms** always proceed via rearward attack of the nucleophile on the substrate. This process results in the inversion of the relative configuration, going from starting material to product. This inversion is often called the **Walden inversion**.



• **The Rate of S_N2 Reaction**

- The rate of the reaction depends on the concentration of both the **Substrate [S]** and the **Nucleophile [Nu]** and the reaction is of second order and is represented as **S_N2 . Rate $\propto [\text{Substrate}][\text{Nucleophile}]$**
- **S_N2 Mechanism:** a substitution at an sp^3 carbon in which the nucleophile-carbon bond formation and the leaving group-carbon bond breakage occur at the same time.
- **Transition state:** highest point of an energy structure on a reaction profile graph for any mechanism step
- S_N2 reactions are bimolecular, meaning the rate-determining step involves the nucleophile and the starting molecule (electrophile).
- For an S_N2 reaction, the rate-determining step occurs when the nucleophile attacks the sp^3 carbon and the leaving group leaves. As depicted on the graph to the right, the energy barrier of the transition state of the nucleophile carbon bond formation and the carbon-leaving group bond scission must be overcome for the reaction to occur.

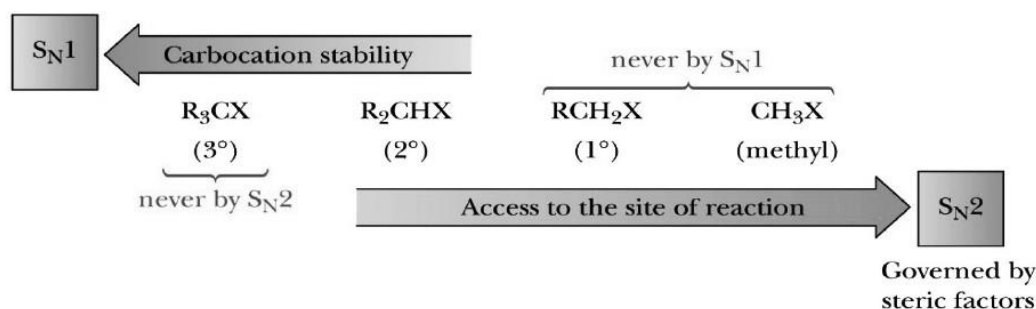


Energy Profile of the reaction

- **Factors affecting the rates of S_N2 reactions:**

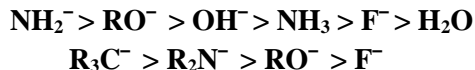
1. Structure of Substrate

- In S_N2 reaction the substrate plays the most important part in determining the rate of the reaction.
- This is because the nucleophile attacks from the back of the substrate, thus breaking the carbon leaving group bond and forming the carbon nucleophile bond. Therefore, to maximise the rate of the S_N2 reaction, the back of the substrate must be as unhindered as possible.
- Overall, this means that **methyl** and **primary substrates** react the fastest, followed by **secondary substrates**.
- Tertiary substrates do not participate in S_N2 reactions, because of steric hindrance



2. The Nature of the Nucleophile

- For **S_N2 reaction** in solution there are some principles that govern the effect of nucleophile on the rate.
- A nucleophile with a negative charge is always more powerful than its conjugate acid. Thus OH^- is more powerful than H_2O , NH_2^- is more powerful than NH_3 , CH_3O^- is more powerful than CH_3OH , etc.
- In comparing nucleophiles whose attacking atom is in the same row of the periodic table, nucleophilicity is approximately in order of basicity as following:



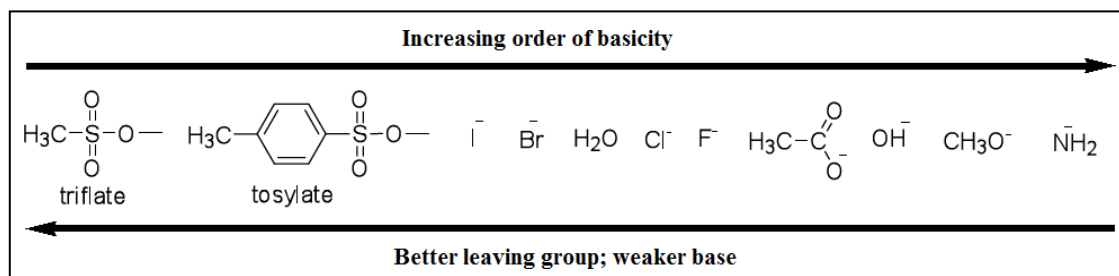
- Going down the periodic table, nucleophilicity increases, though basicity decreases. Thus the usual order of halide nucleophilicity is: $I^- > Br^- > Cl^- > F^-$
- So, a strong/anionic nucleophile always favours S_N2 manner of nucleophilic substitution.

3. Effect of Solvent

- Polar aprotic solvent (without OH) favors S_N2 .
- For examples of polar aprotic solvents are **acetone**, **dimethylsulfoxide**, **N,N'-dimethylformamide**, etc.
- In **S_N2 reaction**, freer the nucleophile, faster is the reaction.
- The stronger the solvation of the nucleophile, the greater the energy required to remove the nucleophile from its solvation cage to reach the transition state, and hence lower is the rate of the S_N2 reaction.
- For example when NaOH is added to aprotic solvent like acetone or dimethyl sulfoxide, sodium is solvated by the solvent whereas OH^- is not. Thus the nucleophile is free and can easily attack the positively charged carbon for S_N2 .
- In polar protic solvent both the sodium and hydroxide ions are strongly solvated and more energy is needed to free the nucleophile from the solvent cage to carry out S_N2 .

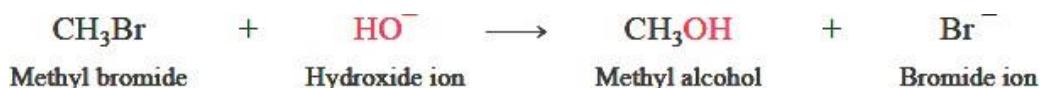
4. The nature of the leaving group

- The ability of leaving group is related to how stable it is as an anion.
- The most stable anions and the best leaving group are the conjugate bases of strong acid i.e., are weaker bases. Conversely, poor leaving groups form ions of poor to moderate stability.
- Strong bases, such as OH^- , NH_2^- , and RO^- , make poor leaving groups. Water, which is less basic than a hydroxide ion, is a better leaving group.
- Some good leaving groups are the sulfate ion and the *p*-toluenesulfonate (tosylate ion). The following list ranks atoms and molecules in order of their stability as leaving groups, from most to least stable.



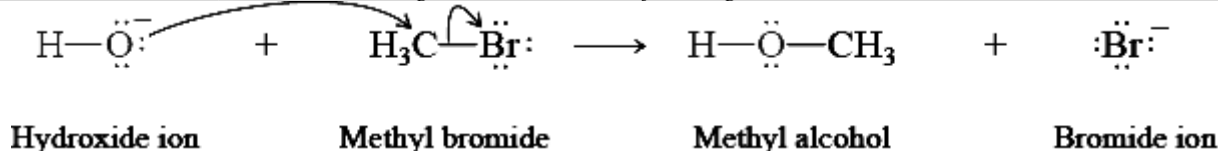
• The $\text{S}_{\text{N}}2$ Mechanism of Nucleophilic Substitution

The Overall Reaction



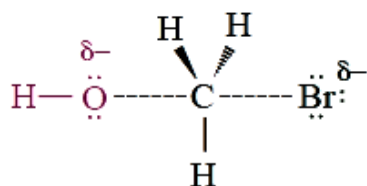
The Mechanism

The reaction proceeds in a single step. Hydroxide ion acts as a nucleophile. While the C–Br bond is breaking, the C–O bond is forming.

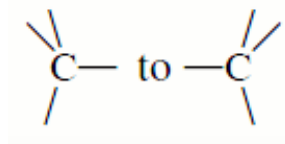


The Transition State

Hydroxide ion attacks carbon from the side opposite the C–Br bond

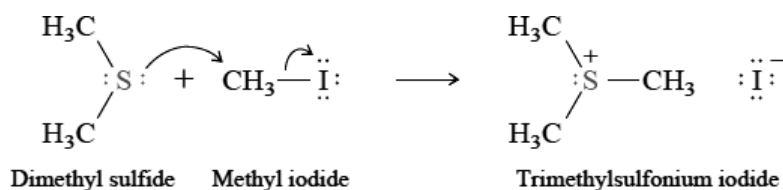


Carbon is partially bonded to both hydroxide and bromide. The arrangement of bonds undergoes tetrahedral inversion from as the reaction progresses.

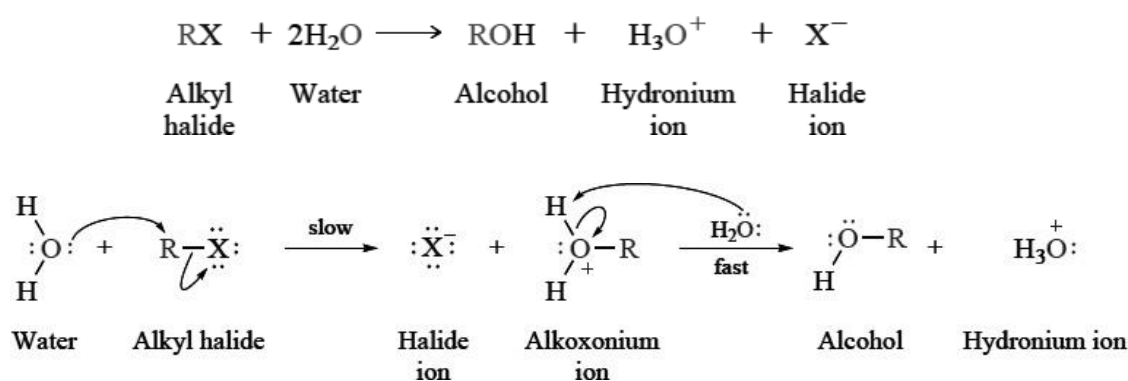


• **Nucleophiles and Nucleophilicity:**

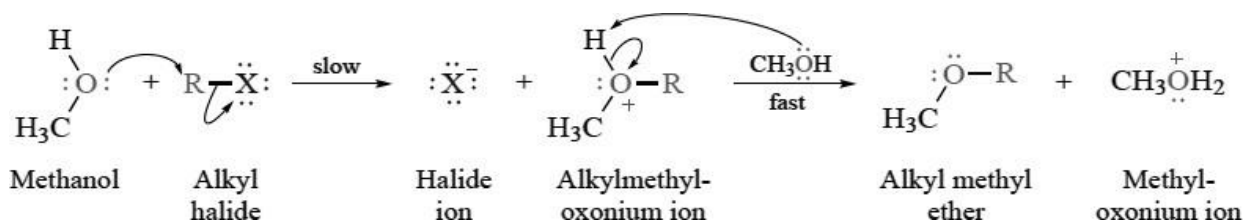
- The Lewis base that acts as the nucleophile often is, but need not always be, an anion. Neutral Lewis bases such as **amines** ($R_3N:$), **phosphines** ($R_3P:$), and **sulfides** ($R_2S:$) can also serve as nucleophiles.



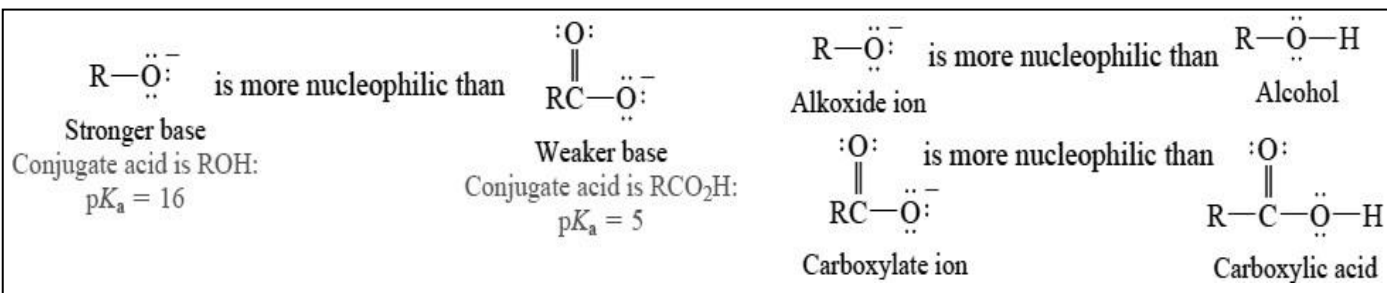
- Other common examples of substitutions involving neutral nucleophiles include solvolysis reactions- substitutions where the nucleophile is the solvent in which the reaction is carried out. Solvolysis in water (hydrolysis) converts an alkyl halide to an alcohol. The reaction occurs in two steps. The first yields an alkyloxonium ion by nucleophilic substitution and is rate-determining. The second gives the alcohol by proton transfer-a rapid Bronsted acid-base reaction.



- **Solvolysis in methanol (methanolysis)** gives a **methyl ether**.



Nucleophilicity of Some Common Nucleophiles		
Reactivity class	Nucleophile	Relative reactivity
Very good nucleophiles	I^- , HS^- , RS^-	$>10^5$
Good nucleophiles	Br^- , HO^- , RO^- , CN^- , N_3^-	10^4
Fair nucleophiles	NH_3 , Cl^- , F^- , RCO_2^-	10^3
Weak nucleophiles	H_2O , ROH	1
Very weak nucleophiles	RCO_2H	10^{-2}



3. Comparison of S_N1 and S_N2

Points	S _N 1	S _N 2
<i>Steps</i>	Two steps	One step
<i>Molecularity</i>	Unimolecular, only substrate is involved in rate determining step	Bimolecular, both substrate and nucleophile are involved in the reaction
<i>Kinetics and rate</i>	First order	Second order
<i>Stereochemistry</i>	Racemisation or partial racemization favouring product with inverted configuration	Complete inversion
<i>Effect of substrate structure on rate</i>	Stability of carbocation: Tertiary > secondary > primary > methyl	Steric hindrance decreases the rate of reaction: Methyl > primary > secondary > tertiary
<i>Effect of solvents on rate</i>	Polar protic solvents like water favours S _N 1.	Polar aprotic solvent (without OH) favours S _N 2, like acetone, DMSO
<i>Nucleophilicity and concentration of nucleophiles</i>	Weak nucleophiles of low concentration too can make the reaction to occur	Strong nucleophiles of high concentration increases the rate
<i>Leaving group effect</i>	Weakly basic and highly polarizable group increase the rate	Weakly basic and highly polarizable group increases the rate.
<i>Reaction intermediate</i>	carbocation	None
<i>Competition Reaction</i>	E1 (Elimination Unimolecular) and rearrangement	E2 (Elimination Bimolecular)

❖ Note By: Classification of Solvents

Solvent is a liquid substance capable to dissolve other substances (solutes) without chemical changes.

1. Molecular structure of solvents
2. Inorganic solvents
3. Organic solvents

1. MOLECULAR STRUCTURE OF SOLVENTS

- Ability of a substance to dissolve another substance is determined by compatibility of their molecular structures (like dissolves like). Types of molecular structures of the solvents are as follows:

(i) **Polar protic solvents**

- A polar protic molecule consists of a polar group OH and a non-polar tail.
- The structure may be represented by a formula R-OH.
- Polar protic solvents dissolve other substances with polar protic molecular structure. Polar protic solvents are miscible with water (hydrophilic).
- Examples of polar protic solvents: water (H-OH), acetic acid (CH₃CO-OH), methanol (CH₃-OH), ethanol (CH₃CH₂-OH), n-propanol (CH₃CH₂CH₂-OH), n-butanol (CH₃CH₂CH₂CH₂-OH).

(ii) **Dipolar aprotic solvents**

- Dipolar aprotic molecules possess a large bond dipole moment (a measure of polarity of a molecule chemical bond).
- They do not contain OH group.
- Examples of dipolar aprotic solvents: acetone [(CH₃)₂C=O], ethyl acetate (CH₃CO₂CH₂CH₃), dimethyl sulfoxide [(CH₃)₂SO], acetonitrile (CH₃CN), dimethylformamide [(CH₃)₂NC(O)H].

(iii) **Non-polar solvents**

- Electric charge in the molecules of non-polar solvents is evenly distributed; therefore the molecules have low dielectric constant.
- Non-polar solvents are hydrophobic (immiscible with water).
- Non-polar solvents are lipophilic as they dissolve non-polar substances such as oils, fats, greases.
- Examples of non-polar solvents: carbon tetrachloride (CCl_4), benzene (C_6H_6), and diethyl ether ($\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_3$), hexane [$\text{CH}_3(\text{CH}_2)_4\text{CH}_3$], methylene chloride (CH_2Cl_2).

2. INORGANIC SOLVENTS

- The most popular inorganic (not containing carbon) solvents are water (H_2O) and aqueous solutions containing special additives (surfactants, detergents, PH buffers, inhibitors).
- Other inorganic solvents are liquid anhydrous Ammonia (NH_3), concentrated sulfuric acid (H_2SO_4), sulfuryl chloride fluoride (SO_2ClF).

3. ORGANIC SOLVENTS

(i) **Oxygenated solvents**

- Oxygenated solvent is an organic solvent, molecules of which contain oxygen.
- Oxygenated solvents are widely used in the paints, inks, pharmaceuticals, fragrance sectors, adhesives, cosmetics, detergents, food industries. Examples of oxygenated solvents: alcohols, glycol ethers, methyl acetate, ethyl acetate, ketones, esters, and glycol ether/esters.

(ii) **Hydrocarbon solvents**

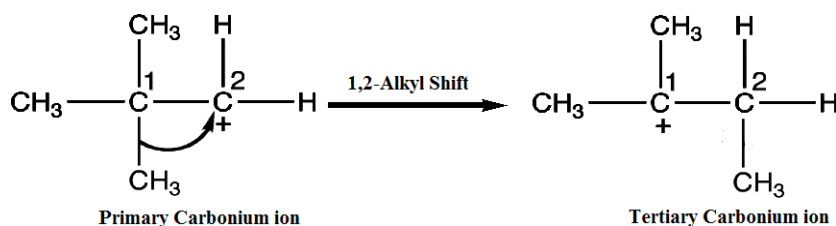
- Molecules of hydrocarbon solvents consist only of Hydrogen and carbon atoms.
 - Aliphatic solvents: Molecules of aliphatic solvents have straight-chain structure. Hexane, gasoline, kerosene are aliphatic solvents. -White spirits
 - White spirit (mineral turpentine spirits): It is a mixture of aromatic and paraffinic hydrocarbons.
 - Pure aromatic solvents: Molecules of pure aromatic solvents have benzene ring structure. Examples of pure aromatic solvents are benzene, toluene and xylene.

(iii) **Halogenated solvents**

- Halogenated solvent is an organic solvent, molecules of which contain halogenic atoms: chlorine (Cl), fluorine (F), bromine (Br) or iodine (I).
- Accordingly to the type of halogen halogenated solvents are classified into the following categories:
 - Chlorinated solvents: The common chlorinated solvents are trichlorethylene ($\text{ClCH}-\text{CCl}_2$), perchlorethylene (tetrachlorethylene, $\text{Cl}_2\text{C}-\text{CCl}_2$), methylene chloride (CH_2Cl_2), carbon tetrachloride (CCl_4), chloroform (CHCl_3), 1,1,1-trichlorethane (methyl chloroform, CH_3-CCl_3).
 - Fluorocarbon solvents: Examples of fluorocarbon solvents: dichlorofluoromethane (freon 21, CHCl_2F), trichlorofluoromethane (freon 11, CCl_3F), tetrafluoromethane (freon 14, CF_4), difluorodichloromethane (freon 12, CHCl_2F_2), hydrochlorofluorocarbon (freon 22, HCFC).
 - Brominated solvents: Examples of brominated solvents: ethylene dibromide (1,2-dibromoethane, $\text{BrCH}_2-\text{CH}_2\text{Br}$), methylene chlorobromide (bromochloromethane, CH_2BrCl), methyl bromine (bromomethane, CH_3Br).
 - Iodinated solvents: Examples of iodinated solvents: n-butyl iodide (1-iodobutane, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{I}$), methyl iodide (iodomethane, CH_3I), ethyl iodide (iodoethane, $\text{C}_2\text{H}_5\text{I}$), n-propyl iodide (1-iodopropane, $\text{CH}_3\text{CH}_2\text{CH}_2\text{I}$).

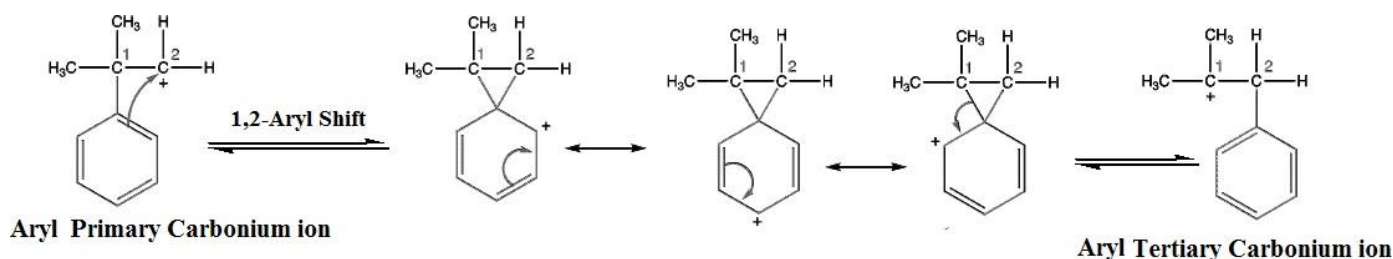
❖ Note By: 1,2-Alkyl Shift

- A *1,2-alkyl shift* is a carbocation rearrangement in which an alkyl group migrates to the carbon atom bearing the formal charge of +1 (**Carbon 2**) from an adjacent carbon atom (**Carbon 1**).



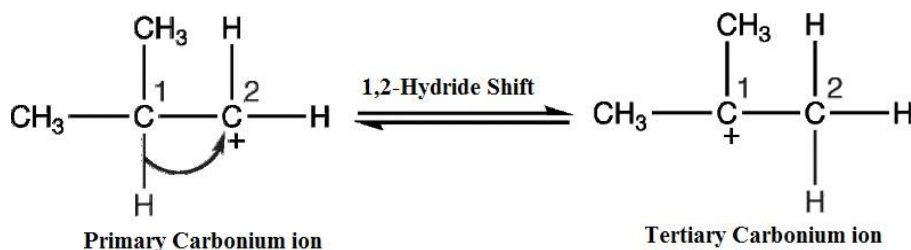
❖ Note By: 1,2-Aryl Shift

- A *1,2-aryl shift* is a carbocation rearrangement in which an aryl group in a carbocation migrates to the carbon atom bearing the formal charge of +1 (**Carbon 2**) from an adjacent carbon atom (**Carbon 1**).



❖ Note By: 1,2-Hydride Shift

- A *1,2-hydride shift* is a carbocation rearrangement in which a hydrogen atom in a carbocation migrates to the carbon atom bearing the formal charge of +1 (**Carbon 2**) from an adjacent carbon atom (**Carbon 1**).



❖ Note By: Alkyl Shift leads to ring expansion

- It doesn't always have to be a *methyl group* that moves. One interesting example is when a carbocation is formed adjacent to a strained ring, such as a **cyclobutane**. Even though the CH₃ could potentially migrate in this case, it's favourable to shift one of the alkyl groups in the ring, which leads to ring expansion and the formation of a less strained, **five membered ring**.

