

## St Peter's Institute of Pharmaceutical Sciences

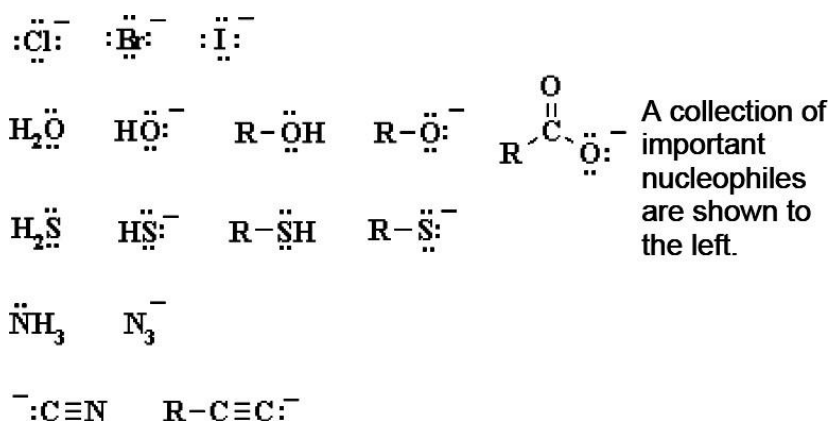
Course : Bachelor of Pharmacy

Subject : Pharmaceutical Organic Chemistry 1

Subject Code:BP202T

### 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 ( $\text{CH}_3\text{OH}$ ):

Very Good	$\text{I}^-$ , $\text{HS}^-$ , $\text{RS}^-$
Good	$\text{Br}^-$ , $\text{HO}^-$ , $\text{RO}^-$ , $\text{NC}^-$ , $\text{N}_3^-$
Fair	$:\text{NH}_3$ , $\text{Cl}^-$ , $\text{F}^-$ , $\text{RCO}_2^-$
Weak	$\text{H}_2\text{O}$ , $\text{ROH}$
Very Weak	$\text{RCO}_2\text{H}$

- **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  $\text{OH}^-$  is negatively charged, but

the O in  $\text{H}_2\text{O}$  is neutral.)

Neutral Nucleophiles

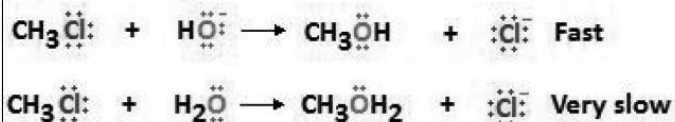
$\text{H}_2\text{O}$ ,  $\text{NH}_3$ ,  $\text{RNH}_2$ ,  $\text{R}_2\text{NH}$ ,  $\text{R}_3\text{N}$ ,  
 $\text{ROH}$ ,  $\text{RCOOH}$ ,  $\text{RSH}$ , and  $\text{PR}_3$

Charged Nucleophiles

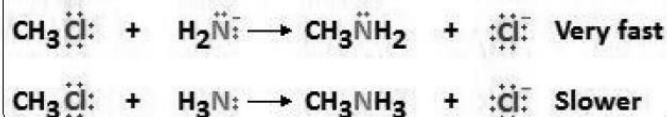
$\text{RO}^-$ ,  $^- \text{NH}_2$ ,  $\text{R}^- \text{NH}$ ,  $\text{R}_2\text{N}^-$ ,  $\text{HS}^-$ ,  $\text{RS}^-$ ,  
 $\text{RSe}^-$ ,  $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{I}^-$ ,  $\text{F}^-$ ,  $\text{CN}^-$ ,  $^- \text{OH}$ ,  $\text{RCO}_2^-$

- 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 H<sub>2</sub>O, and results in a faster reaction rate. Similarly, when nitrogen is part of NH<sub>2</sub><sup>-</sup>, it bears a negative charge, and when it is part of NH<sub>3</sub>, it is neutral. The N of NH<sub>2</sub><sup>-</sup> is a better nucleophile than the N of NH<sub>3</sub>, and results in a faster reaction rate.

#### Experiment #1



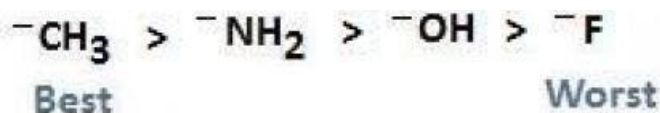
#### Experiment #2



- 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.

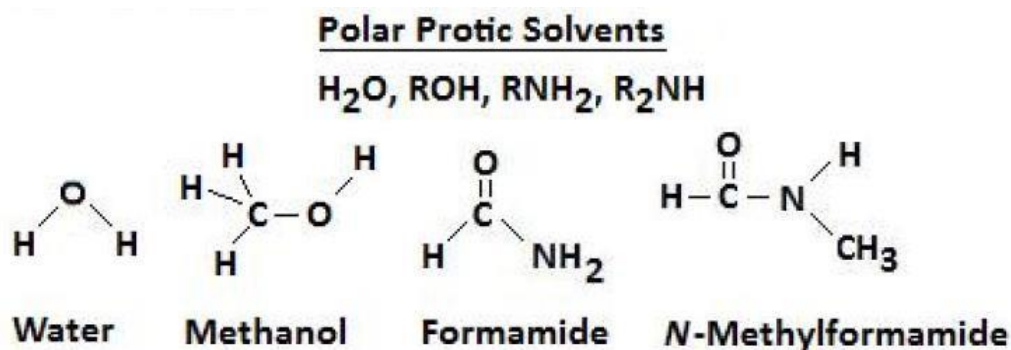


## ➤ Solvents and Nucleophilicity:

- In general solvents as being either polar or nonpolar. Polar solvents can be further subdivided into **protic** and **aprotic solvents**.

### • PROTIC SOLVENTS

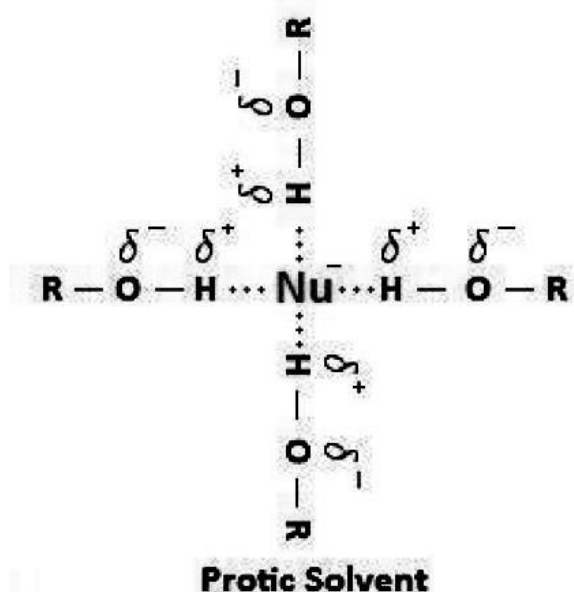
- A protic solvent is a solvent that has a hydrogen atom bound to an oxygen or nitrogen. A few examples of protic solvents include  $\text{H}_2\text{O}$ ,  $\text{ROH}$ ,  $\text{RNH}_2$ , and  $\text{R}_2\text{NH}$ , where water is an example of an inorganic **protic solvent** and alcohols and amides 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

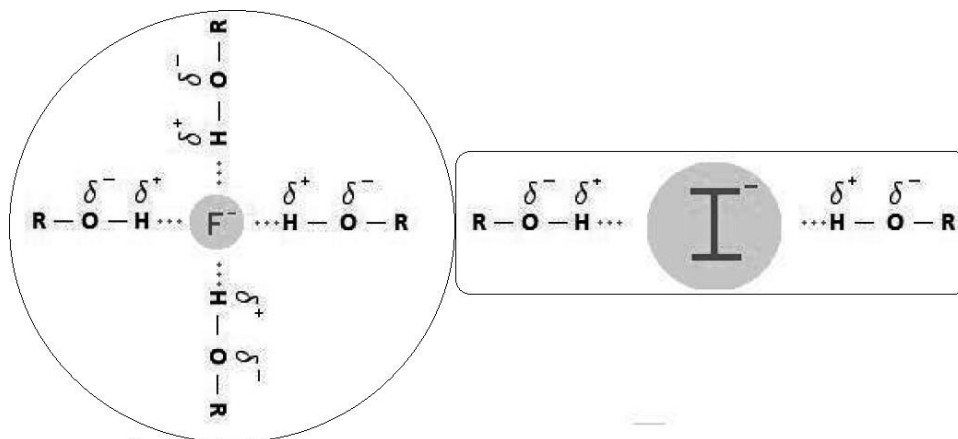
### hydrogen bonds.

- 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 ( $\text{ROH}$ ) 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  $\text{RNH}_2$  and  $\text{R}_2\text{NH}$ .



## • 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.

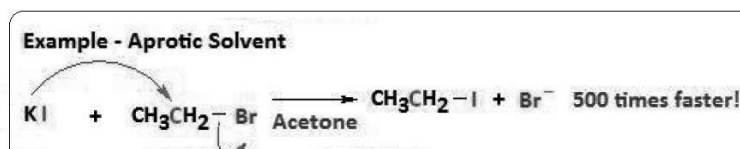
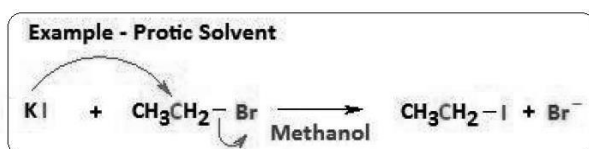
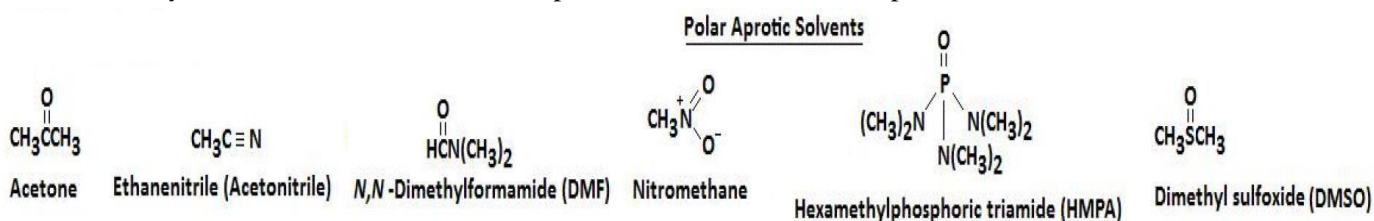


- Nucleophilicity follows basicity when moving across a row. But, the effect of protic solvents on nucleophilicity, we learned that solvation weakens the nucleophile, having the greatest effect on smaller anions. In effect, when using protic solvents, nucleophilicity does not follow basicity when moving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



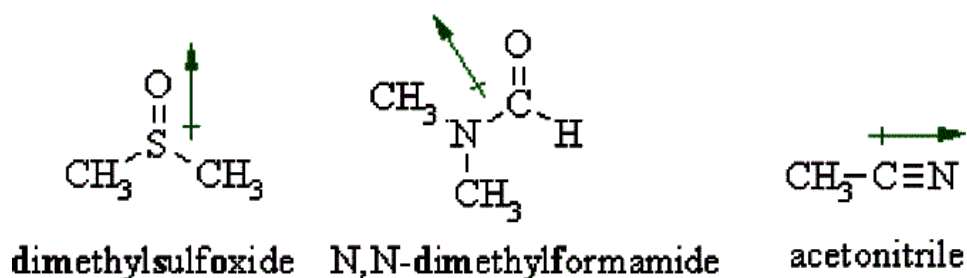
## • APROTIC SOLVENTS

- An aprotic solvent is a solvent that lacks of positively polarized hydrogen.
- Aprotic solvents, like protic solvents, are polar but, because they have lack of 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 H<sub>2</sub>O 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



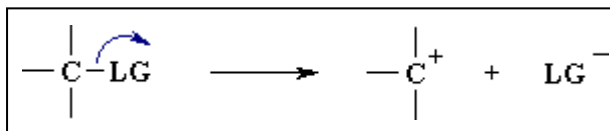
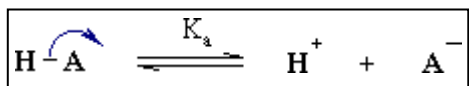
## • OVERALL

- 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<sup>-</sup>).
- Polar aprotic solvents are typically only used when a polar protic solvent gives poor results due to having a weak Nu, (esp. F<sup>-</sup>, <sup>-</sup>CN, RCO<sub>2</sub><sup>-</sup>)

Solvent	Dipole moment, $\mu$	Dielectric constant, $\epsilon$	Relative Rate	Type
CH <sub>3</sub> OH	2.87	33	1	protic
H <sub>2</sub> O	1.84	78	7	protic
DMSO	3.96	49	1,300	aprotic
DMF	3.82	37	2,800	aprotic
CH <sub>3</sub> CN	3.92	38	5,000	aprotic

## ➤ Leaving Groups:

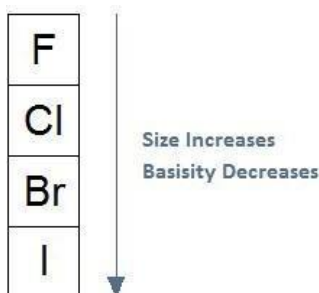
- A leaving group (**LG**), is an atom (or a group of atoms) that is displaced as stable species taking with it the bonding electrons. Typically the leaving group is an anion (e.g. Cl<sup>-</sup>) or a neutral molecule (e.g. H<sub>2</sub>O).
- The better the leaving group, the more likely it is to depart.
- 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.



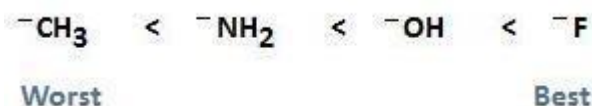
- **As Size Increases, Basicity Decreases:** In general, if we move from the top of the periodic table to the bottom of the periodic table as shown in the diagram below, the size of an atom will increase. As size increases, basicity will decrease, meaning a species will be less likely to act as a base;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

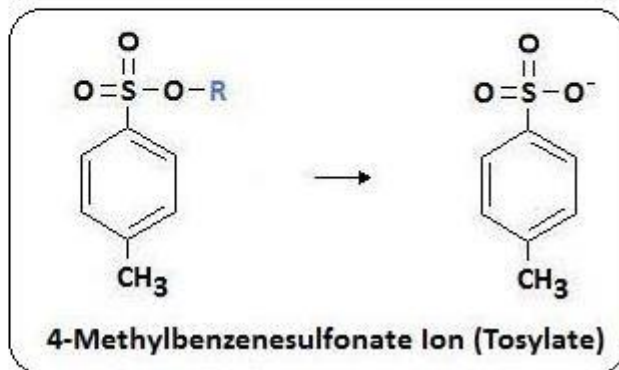
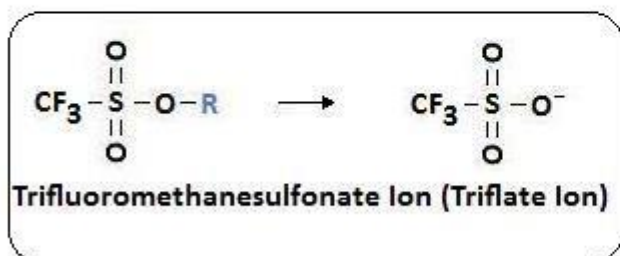
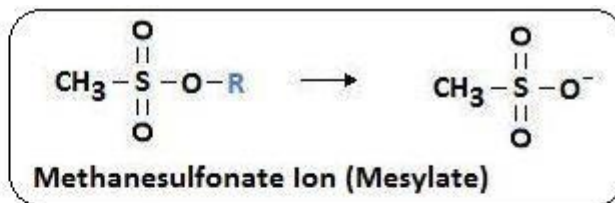
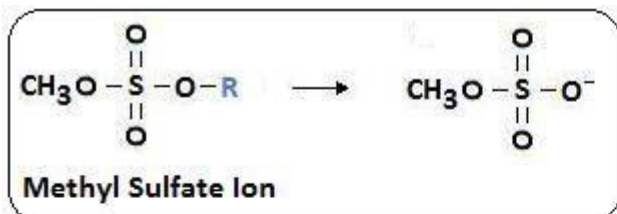
- As mentioned previously, if we move from left to right on the periodic table, electronegativity increases. With an increase in electronegativity, basicity decreases, and the ability of the leaving group to leave increases. This is because an increase in electronegativity results in a species that wants to hold onto its electrons rather than donate them. The following diagram illustrates this concept, showing <sup>-</sup>CH<sub>3</sub> to be the worst leaving group and F<sup>-</sup> to be the best leaving group.
- For example, fluoride is such a poor leaving group that S<sub>N</sub>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.



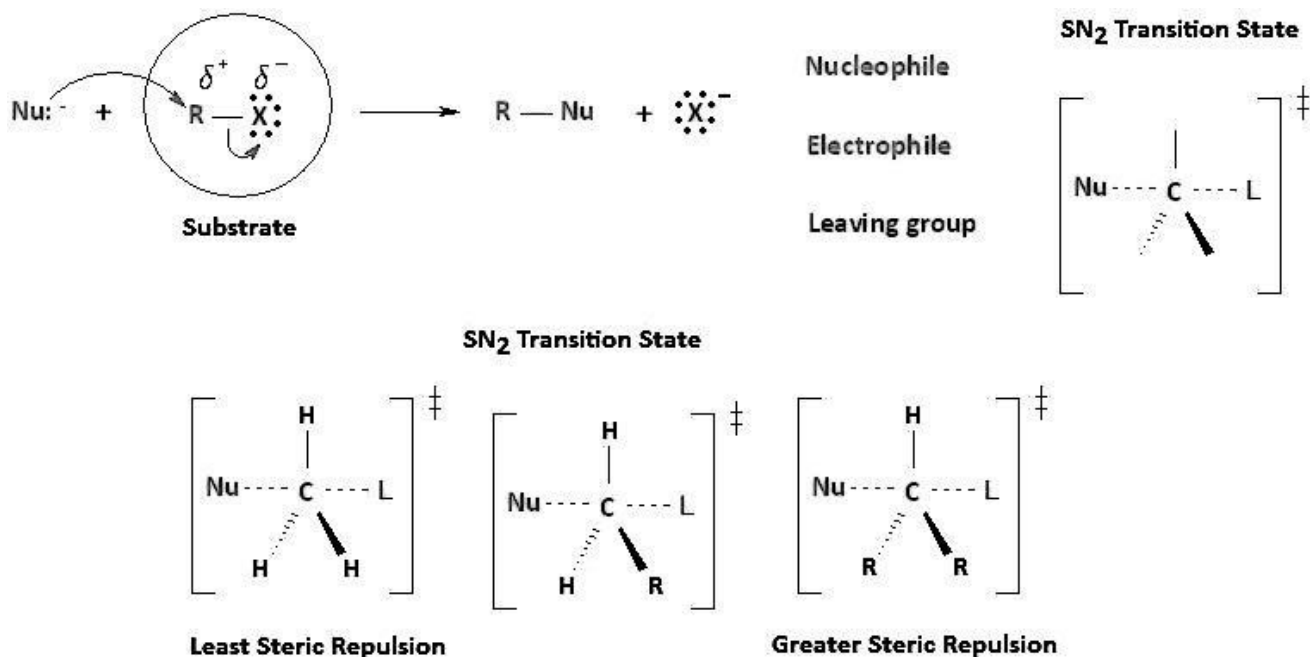
- **Resonance Increases the Ability of the Leaving Group to Leave:** As we learned previously, resonance stabilized structures are weak bases. Therefore, leaving groups that form resonance structures upon leaving are considered to be excellent leaving groups. The following diagram shows sulfur derivatives of the type  $\text{ROSO}_3^-$  and  $\text{RSO}_3^-$ . 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.





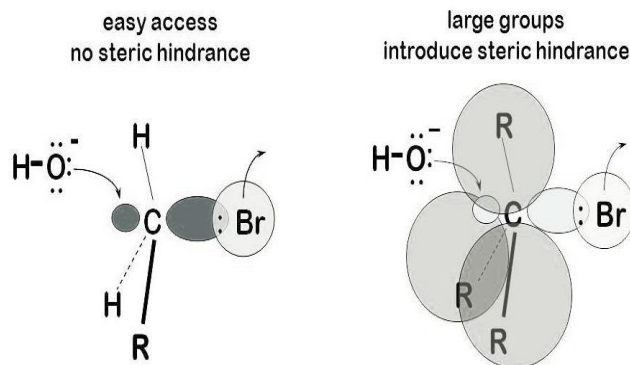
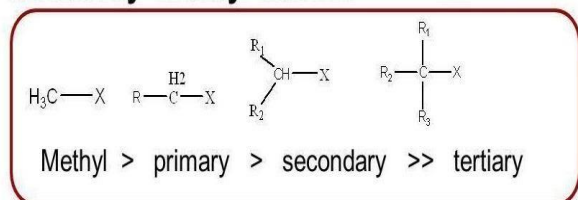
## ➤ Substrate influence in nucleophilic substitution reactions:

- Sterically Hindered Substrates will reduce the  $S_N2$  reaction rate.

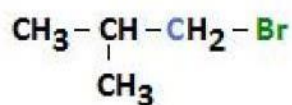


- Steric hindrance affects the rate at which an  $S_N2$  reaction will occur. As each hydrogen is replaced by an **R-group**, the rate of reaction is significantly diminished. This is because the addition of one or two **R-groups** shields the backside of the electrophilic carbon, impeding nucleophilic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

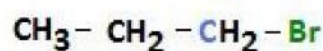
### Reactivity of alkyl halides $S_N2$ Reaction



- **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.



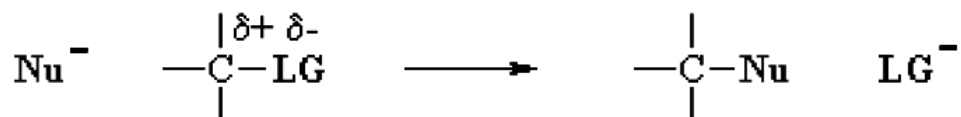
**2-methyl-1-bromopropane**



**1-bromopropane**

## ➤ 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  $\sigma$  bond to the nucleophile
- breaking of the  $\sigma$  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<sub>N</sub>1 reaction**
- Simultaneous bond formation and bond breaking: **S<sub>N</sub>2 reaction**
- S<sub>N</sub>i** 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 stereochemical configuration.

### Bonding in the halogen-alkanes

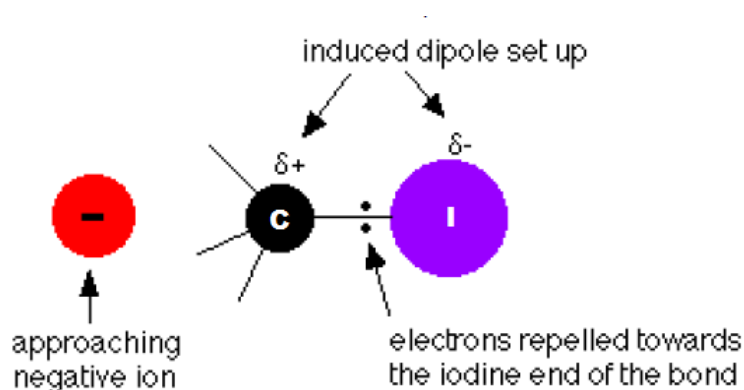
- Halogen-alkanes (also known as halo-alkanes or alkyl halides) are compounds containing a halogen atom (fluorine, chlorine, bromine or iodine) joined to one or more carbon atoms in a chain.
- The interesting thing about these compounds is the carbon-halogen bond, and all the nucleophilic substitution 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 ( $\delta^-$ ) and the carbon slightly positive ( $\delta^+$ ) 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**

### Reference Books:

- Organic Chemistry by Morrison and Boyd
- Organic Chemistry by I.L. Finar , Volume-I
- Textbook of Organic Chemistry by B.S. Bahl & Arun Bahl.
- Organic Chemistry by P.L.Soni
- Practical Organic Chemistry by Mann and Saunders.
- Vogel's text book of Practical Organic Chemistry
- Advanced Practical organic chemistry by N.K. Vishnoi.
- Introduction to Organic Laboratory techniques by Pavia, Lampman and Kriz.
- Reaction and reaction mechanism by Ahluwalia/Chatwal.