SN2 REACTIONS

Introduction
Nucleophilic substitution reaction occurs when the substrate is attacked by a nucleophile and the leaving group departs. The reaction takes place at the saturated carbon atom i.e sp3 hybridized.

SN2 Reaction

- Nucleophilic substitution reactions which follow the second order kinetics are known as SN2 reactions.
- The rate of second order reaction depends upon the concentration of both, the substrate and the reagent.
- The term SN2 stands for biomolecular nucleophilic substitution. These reactions are completed in a single step, by the displacement of a leaving group by a nucleophile and no intermediate is formed.
- SN2 reactions always goes through a possible transition state.
- During the transition state, the bond to the nucleophile forms at the same time that the bond to the leaving group breaks, because at no time can the carbon have more than eight electrons in its outer shell.
- Therefore, the nucleophile is required to approach from the back, and configuration at carbon is inverted.
- Other way round we can say, if nucleophile attacks the substrate carbon 180° away from the leaving group, which is regarded as rear side or backside attack, resulting the inversion of configuration. The mechanism of these reactions is as follows.

- During the formation of transition state, the substrate carbon loses the sp3 hybridized state and attains the sp2 hybridized state with one unhybridized p orbital in a perpendicular direction to the trigonal plane containing the carbon with the non reacting groups.
- One lobe of this p orbital overlaps with the leaving groups and its opposite lobe may overlap with the nucleophile.
- Therefore, the nucleophile can undergo rear side attack in these reactions. In the transition state, the carbon and non reacting groups are almost coplanar. If the leaving group and nucleophile are identical then the geometry of the transition state should be perfectly planar. The energy required to break the C–X bond had been supplied by the simultaneous formation of C–Y bond.
- SN2 products are stereospecific because stereoisomeric reactants give stereochemically different products. They are also stereoselective because they form exclusively or predominantly only one of a possible pair of enantiomers or one of the possible distereoisomers.

Example:
- The reaction between methyl bromide (CH₃Br) and a strong base (OH– ion of NaOH).
• The rate determining step involves both CH$_3$Br and OH$^-$.
• The reaction between two reactants resulting in the direct displacement of Br$^-$ and OH$^-$
  group occurs in such a way that a new C–OH bond is being formed while the old C–Br bond
  starts breaking.
• Thus the bond formation and bond breaking occur simultaneously. Hence the reaction is
  one step reaction without any intermediate. While the reaction is taking place, the energetic
  OH$^-$ ion approaches the CH$_3$Br molecule from the opposite side of the bromine to avoid
  repulsion between OH$^-$ and Br$^-$ ions.
• In the reaction medium the OH$^-$ ion approaches the electron deficient carbon atom
  following which the C–Br bond starts stretching.
• At one stage, both Br and OH are partially bonded to the central C atom (HO-----C-----Br)
  which is known as the transition state. In the transition state partial negative charge of OH$^-$
  ion is transferred to Br through the central carbon atom.
• At last the approaching OH$^-$ ion results in the formation of the complete C–OH bond and in
  this process Br$^-$ ion departs. In the transition stage a total of five atoms or groups are
  attached to the central carbon atom.
• As we move in the series, from methyl bromide to t-butyl chloride (i.e. from $1^\circ$ to $3^\circ$), a
  decrease in the nucleophilic attack was found at the carbon bearing the bromine atom due
  to steric hindrance of the attached groups or atoms, or we can say that the nucleophile
  does not get any space to attack. The +I effect along the series makes the carbon bearing
  the bromine progressively less positively polarized and consequently less readily attacked
  by the nucleophile.

When there is a chiral centre, inversion occurs, known as Walden Inversion.

• The rate for hydrolysis of alkyl halide is in the order of halides
  \[ \text{MeX} > 1^\circ > 2^\circ > 3^\circ. \]
• Thus, we can say the steric factor is more important than the electronic factor. The Fact for
  the transition state will be highest for $3^\circ$ while least for the MeX.
• The reaction is thermodynamically favorable only when a stronger base displaces a weaker
  base. Hence, successful displacements are exothermic.
• The energy difference between the transition state and the starting materials of the reaction
  is known as activation energy.
• This amount of energy is needed for a reaction to occur.
• Transition state represents an energy maximum on the reaction coordinate and can’t be
  measured directly due to their extremely short lifetime interval.
• Their lifetime is approximately 10-12 seconds. In bimolecular reactions, the transition state
  represents one specific orientation of the reactants.
The entropy of activation, $\Delta S$ is negative. In the beginning of the reaction, the infinite number of arrangements in space that the reactants might assume are later reduced to only one. This results in the decrease in entropy.

The higher the amount of activation entropy (as negative), the higher is the free energy of activation;

$$\Delta G = \Delta H - T\Delta S$$

While, $\Delta S = \text{(entropy of the transition state)} - \text{(entropy of the substrates)}$

**An energy diagram of the SN2 reaction**

**Kinetics of SN2 Reactions**

In the above mentioned reaction both the substrate (CH$_3$Br) and the nucleophile (OH$^-$) take part in the rate determining step (the only step), the reaction should be first order in each component, second order overall and satisfy the below mentioned rate expression. Thus the reaction follows 2nd order kinetics. Hence, the rate equation is:

$$\text{Rate} = k \ [\text{CH}_3\text{Br}] \ [\text{OH}]$$

This law was found to apply for many reactions in chemistry. But for reactions involving excess of nucleophile (solvent), even though the mechanism is bimolecular, experimentally determined rate will be 1st order. This is because the rate is dependent on the concentration of the substrate molecule, the kinetics involved in this reaction is referred as pseudo first order:

$$\text{Rate} = k \ [\text{CH}_3\text{OH}]$$

The unfortunate part is that the reaction mechanism can’t be operated for the substrate containing the leaving group at bridgehead carbon atom of any polycyclic systems. The reason is that the back side of this carbon can’t be free to allow the nucleophile from that side during the formation of transition state. Example:
The reaction between [2.2.2] system with ethoxide ion and [3.3.1] system with NaI, where acetone is used as a solvent does not result in product formation. But their open chain analogues underwent the reactions gradually.

**Stereochemical Factors of SN2 Reaction**

- From the above discussion it can be concluded that the molecule is turning inside out or we can say direct displacement, thus Walden inversion (named Paul Walden 1863-1957) is expected to be take place.
- When a substitution takes place in a chiral carbon, inversion of configuration occurs and this is known as Walden inversion and was observed long before the SN2 mechanism was formulated by Hughes and Ingold.
- In SN2 reaction the alkyl halide converted into alcohol in presence of strong base results inversion of configuration. The change of configuration can be established by observing the directions of optical rotation.

**Examples for Walden inversion:** In these reactions one must be an inversion while the other must be retention of configuration, but it is not possible to predict the exact point of inversion.

**Chlorination of (+)-malic acid:** When (+)-malic acid is treated with SO2Cl, it results in (+)-chlorosuccinic acid, where retention in configuration is there. On the other hand, when (+)-malic acid is treated with PCl5, it results in (-)-chlorosuccinic acid, i.e inversion in configuration is there.

**Hydrolysis of (+)-chlorosuccinic acid:** When (+)-chlorosuccinic acid is hydrolysed with silver hydroxide or aqueous silver oxide, it results in (+)-malic acid, where retention in configuration is there. On the other hand, when (+)-chlorosuccinic acid is hydrolysed with KOH, it results in (-) malic
Hughes & Ingold did fabulous work to establish the inversion of configuration in SN2 reaction. For example; reaction of (+)-2-iodooctane with KI* (radioactive iodide) results in (-)-iodooctane. The rate of this reaction is as follows:

$$\text{Rate } \alpha [C_6H_{13}CHICH_3] [I^-]^*$$

Thus the exchange of actual iodide with the radioactive iodide results the loss of optical activity, which indicates the formation of (-) isomer from (+) isomer. Thus, inversion of configuration indicates the SN2 reaction.

Factors Influencing SN2 Reaction

Solvent:

- Nucleophiles are more stabilized than the transition state in polar protic solvents due to solvation where the ground state energy of nucleophile is reduced in comparison to the transition state's energy.
- Due to this, reaction progress leads to a higher activation energy and thus to a lower reaction rate. The nucleophiles are less solvated in polar aprotic solvents (DMSO, DMF and HMPT) which results in the less stabilized ground state when compared to the polar protic solvents.
- Thus, the nucleophile is more reactive which leads to the lowering of activation energy, and a higher rate of the reaction. Thus, for SN2 mechanism, increasing solvent polarity usually decreases the rate of reaction.

Nucleophile:

- In SN2 reaction, the nucleophile is involved in the rate determining step, so the nature and concentration of nucleophile affect the rate of SN2 reaction.
- The stronger the nucleophile, the faster is the SN2 reaction. In SN2 reaction the high energy transition is required.
- Therefore, a high concentration of strong nucleophile is required for SN2 reaction. Good nucleophiles having higher energy in the ground state, and are less stable than the poor nucleophiles.
- Thus, the activation energy in SN2 reaction is lower and the reaction rate is consequently higher than in SN1 reaction with a comparatively stable nucleophile. The reactivity of small nucleophiles is rapid than the sterically demanding nucleophiles. Basic and negatively charged nucleophiles are more reactive as compared to uncharged nucleophiles.
Substrate:

- Activation energy of the transition state in SN2 reaction increases as the steric hindrance in the substrate increases, while at the same time reaction rate is decreased. The reaction rate of SN2 reactions will be in the order of $1^\circ > 2^\circ > 3^\circ$ alkyl halide
  - $(\text{CH}_3\text{–X} > \text{RCH}_2\text{–X} > \text{R}_2\text{CH–X} > \text{R}_3\text{C–X})$.
- In the cases of secondary and tertiary alkyl compounds, SN2 reaction is largely superseded by an SN1 reaction or elimination. Rates of SN2 reactions for allylic and benzylic systems are also increased because of resonance in the transition state.

Leaving Group:

- A leaving group which becomes a more stable species after it departs is a better leaving group.
- The best leaving groups are the weakest bases. Stable anions are good leaving groups which results in the lowering of activation energy while reaction rate is higher.
- For example, iodide anions are better leaving groups than chloride anions. Hydroxide anions, alkoxides, fluoride anions, and amide anions are poor leaving groups thus SN2 reactions with fluoroalkanes, alcohols, ethers, or amines virtually never occur. However, acid-catalysed SN2 reactions with alcohols or amines can take place, as the leaving group does not consist of the hydroxide anion. Thus the
- leaving groups can be arranged in the order: $\text{MsO–, TsO–} > \text{I–} > \text{Br–} > \text{Cl–} > \text{F–} > (–\text{OH, –NH}_2)$
- Where, MsO– and TsO– are extremely good leaving groups due to resonance stabilization.
- Thus, the nature of leaving group not only affect the rate of reaction but may also change the reaction mechanism.