Nucleophilic Substitution of Alkyl Halides

Nucleophilic substitution is a reaction in which an incoming nucleophile substitutues (replaces) an outgoing leaving group. The term nucleophile comes from the Greek meaning '*nucleus loving*', in other words nucleophiles seek positive charged centres. Nucleophiles have lone pairs of electrons and may carry a negative charge. There are many examples of nucleophiles, such as **NH_3**, **H_2O**, **CN^-**, **$HC\equiv C^-$**, and **OH^-**.

Alkyl halides contain a halogen (X = **F**, **Cl**, **Br** or **I**) covalently bonded to a carbon atom. Due to the electronegativity differences between carbon and the halide, the **C-X** bond is polar with a partial positive charge ($\delta+$) on the carbon atom and a partial negative charge ($\delta-$) on the halogen. Halogens are good leaving groups and can be replaced by an incoming nucleophile as in the general reaction shown here.

$$\mathbf{Nu:^-} \quad + \quad \overset{\delta+}{\mathbf{R}}\mathbf{\text{--}}\overset{\delta-}{\mathbf{X}} \quad \rightarrow \quad \mathbf{R\text{--}Nu} \quad + \quad \mathbf{X^-}$$

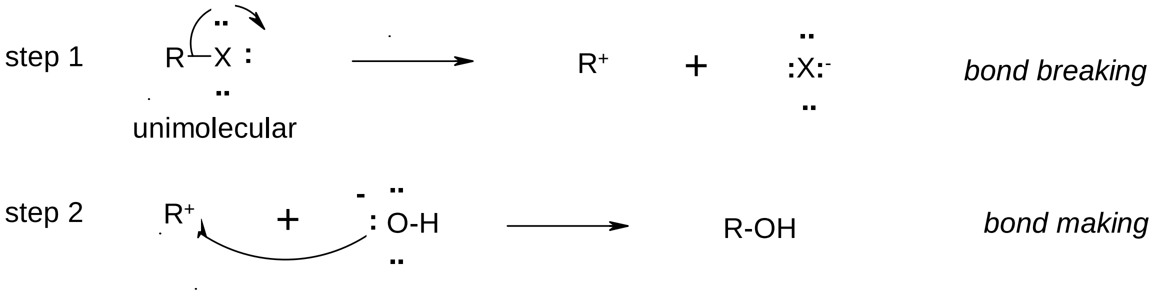
where R represents any carbon containing group, such as **CH_3-**, **CH_3CH_2-** or **$(CH_3)_2CH$-**

Although many different nucleophiles can be used in substitution reactions, leading to the formation of a wide range of organic products, we will focus on the use of **OH^-**. When hydroxide is substituted for a chlorine as shown in the case below, an alkyl halide is transformed into an alcohol.

$$\mathbf{OH^-} \quad + \quad \mathbf{R\text{-}Cl} \quad \rightarrow \quad \mathbf{R\text{-}OH} \quad + \quad \mathbf{Cl^-}$$

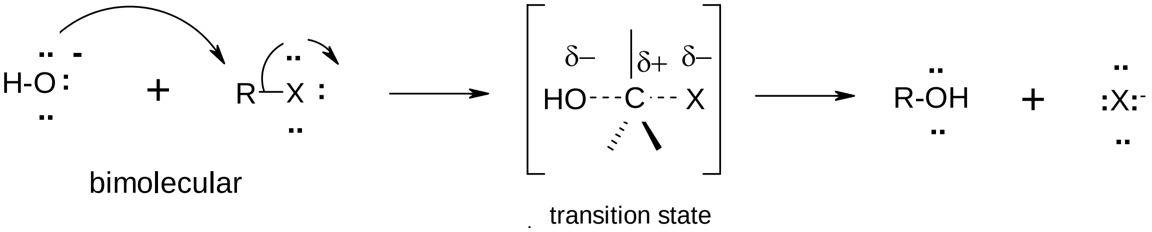
Mechanisms of Nucleophilic Substitution

Although the overall reaction is straightforward, the sequence of bond making and bond breaking (known as the pathway or mechanism) may occur in several different ways. For instance, from the overall chemical equation it can be seen that a **C-X** bond must be broken and a new **C-OH** bond is formed. One could imagine that the bond breaking step might occur first followed by a bond making step, as depicted in the two step mechanism shown below.



where R^+ is a short lived electron deficient carbocation intermediate and the curved arrows are used to illustrate the flow of electrons in the bond breaking and making steps. Because bond breaking is much slower than the bond making, step 1 is the rate determining step and this process is *unimolecular*. In other words, the rate of the reaction depends only on the concentration of one species, **R-X**. This mechanism is referred to as S_N1, where S indicates substitution, N indicates nucleophilic and the 1 indicates unimolecular.

Alternately, one might imagine that the bond making and bond breaking occur simultaneously in a one step concerted mechanism shown here.



Since there is only one *bimolecular* step in this mechanism, the rate of reaction will depend on the concentration of both **R-X** and $\mathbf{OH^-}$. This mechanism is referred to as S_N2, where S indicates substitution, N indicates nucleophilic and the 2 indicates bimolecular.

A third option, which would involve bond making followed by bond breaking is not possible, since the carbon atom bearing the leaving group cannot accommodate five bonds (remember the octet rule).

Kinetics of Nucleophilic Substitution Reactions

S_N1: The kinetics of tertiary alkyl halides $\mathbf{R_3C\text{-}X}$ are found to be first order overall, consistent with a unimolecular slow step as in the S_N1 mechanism.

Rate = k [$\mathbf{R_3C\text{-}X}$], where k is a rate constant for a particular alkyl halide and temperature (the square brackets are used to indicate molar concentration). Note that for tertiary alkyl halides the rate of reaction does not depend on [$\mathbf{OH^-}$].

S_N2: The kinetics of primary alkyl halides ($\mathbf{R\text{-}CH_2\text{-}X}$) are found to be second order overall, consistent with a bimolecular slow step as in the S_N2 mechanism.

Rate = k [$\mathbf{R\text{-}CH_2\text{-}X}$] [$\mathbf{OH^-}$]

This evidence indicates that different mechanisms are occurring depending on the nature of the alkyl halide. The main factors that govern the pathway for this reaction are the steric hinderence of the alkyl halide and the stability of the carbocation intermediate. As the various groups surrounding the carbon atom bearing the halide become bulkier it becomes increasing difficult for the nucleophile to approach and the crowded transition state encountered in the S_N2 mechanism is destabilized. At the same time, groups attached to the carbon bearing the halide stabilize the energy of the carbocation intermediate making it more likely to be formed, thus favouring the S_N1 mechanism.

In general, methyl and primary alkyl halides undergo substitution via S_N2; tertiary alkyl halides undergo S_N1 and secondary alkyl halides react via both S_N1 and S_N2 mechanisms.