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**NUCLEOPHILIC SUBSTITUTION REACTIONS**

One of the most important reactions in organic chemistry are nucleophilic substitution reactions. Basically a substitution occur between molecules where a reagent atom (or a group of atoms) replaces a current atom in the original molecule (substrate). For example, a hydrogen atom might get kicked off so that a different atom can be put on. There are two types of substitution reactions: nucleophilic  $S_N$  and electrophilic  $S_E$ . These two differ in the type of atom that is attaching to the original molecule. In  $S_E$  reactions the new atom has lack of electrons, while nucleophiles are always electron-rich, and they can be either neutral molecule ( $NH_3$ ,  $H_2O$ ,  $ROH$ , etc.) or negatively charged anion ( $OH^-$ ,  $Cl^-$ ,  $CN^-$ ).

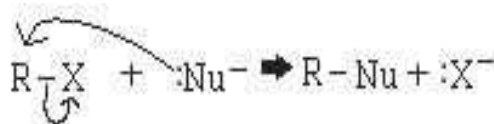
Sir Christopher Ingold studied nucleophilic substitution reactions of alkyl halides and related compounds. He proposed that there were two main mechanisms at work ( $S_N1$  and  $S_N2$ ), both of them competing with each other. Also he was responsible for the introduction into mainstream chemistry of concepts such as nucleophile, electrophile, inductive and resonance effects, and such descriptors as  $S_N1$ ,  $S_N2$ ,  $E1$ , and  $E2$  [1].

**General Mechanism.**

Nucleophilic substitution reactions can occur with any carbon chain that has a good leaving group. Often this leaving group is a halide (usually bromine or chlorine), but oxygen groups (typically in the form of water) can be a good leaving group as well. The leaving group increases in its ability to leave the less basic it is (in other words, when it has a lower  $pK_a$ ).

A nucleophile is similar to a base in that they both have a lone pair, or a pi bond. They differ only in which atom they attack. Nucleophiles attack the atom that is deficient in electrons (usually the carbon), while bases attack protons. A stronger base will be a strong nucleophile.

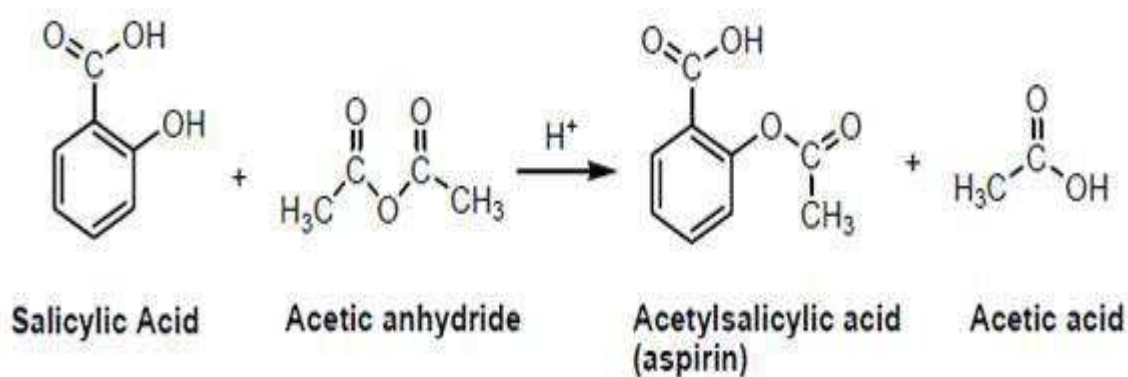
So remember the leaving group needs to be a poor base and have a lower  $pK_a$ , while the nucleophile needs to be a stronger base.



**Figure 1 – The general reaction for a nucleophilic substitution.**

In this figure, 'Nu' stands for the nucleophile, 'R' stands for a chain of carbons, and 'Br' is our leaving group. The nucleophile attacks the carbon (this carbon is called the “reaction center”). The arrows signify the flow of electrons. A pair of electrons from the electron-rich nucleophile attach to the carbon. Then the electrons from the C-Br bond leave with the bromine. If the leaving group is a particularly good, then it can leave on its own before the nucleophile attacks. Then even a weak nucleophile can attack, since the carbon will have a full positive charge and be highly deficient in electrons.

Now we should take a look at some of the most common reactions that use this mechanism:



The first one is the Williamson ether synthesis forming an ether from an organohalide or anhydride and a deprotonated alcohol (alkoxide). This process yields aspirin and acetic acid, which is considered as a byproduct. And the Aspirin is one of the most widely used medications in the world with an estimated 50 to 120 billion pills being consumed each year. It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system.

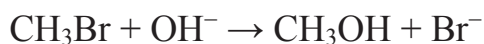
This reaction is important in the history of organic chemistry because it helped prove the structure of ethers. A typical Williamson reaction is conducted at 50–100 °C and is complete in 1–8 hours. Often the complete disappearance of the starting material is difficult to achieve, and side reactions are common. Yields of 50–95% are generally achieved in laboratory syntheses.

The second one is Sandmeyer reaction commonly used to synthesize aryl halides from aryl diazonium salts. The majority of variations of the Sandmeyer reactions consist of using various copper salts. For example, using cuprous cyanide produces benzonitriles. Substituting thiols or water for the copper salts generates thioethers or phenols, respectively.

Kolbe synthesis is vital when we need to prepare secondary amines or extend carbon chain. It is a typical  $S_N$  reaction, which runs best in polar aprotic solvents (DMSO, acetone). It's worth mentioning that cyanide is an ambident nucleophile so it has 2 pairs of electrons on each atom, and can also react on nitrogen to yield isonitriles. The result depends on the type of solvent and reaction mechanism. The more electronegative atom reacts when the mechanism is  $S_N1$  and the less electronegative one in a  $S_N2$  reaction [2].

The study of the Meisenheimer complex. In 1902 Jakob Meisenheimer investigated a red substance formed in the reaction of trinitrobenzene with sodium hydroxide in methanol. His reaction is the basis of the Zimmermann test used for the detection of ketosteroids with excess base to a strongly colored enolate.

Hydrolysis is a reaction of methyl bromine with hydroxide ion which gives us primary alcohol (methanol). Hydrolysis makes a good example of nucleophilic substitution



Finkelstein reaction can provide the exchange of one halide for another in aliphatic compounds that takes advantage of different solubility of halide salts.



To sum up what has been said the organic substitution reactions are not only used for synthesis of certain compound. Nucleophiles also can be applied in huge variety of situations. They can play the role as activating/deactivating part of benzene ring. Or be used as handy tool for the formation of carbon-carbon bonds with Grignard reagents. The fact that substitution reactions are versatile and flexible really proves their huge significance in Organic chemistry.

## REFERENCES

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