

NUCLEOPHILIC SUBSTITUTION REACTIONS

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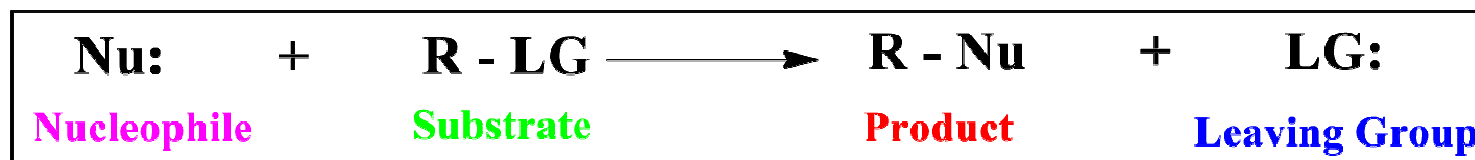
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Nucleophilic Substitution Reaction

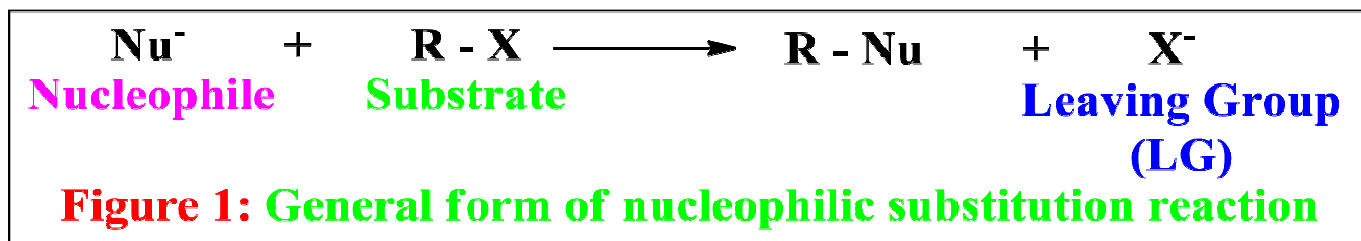
- A substitution reaction is a chemical reaction during which an atom or one functional group in a chemical compound is replaced by another atom or functional group. In organic chemistry, nucleophilic substitution is a class of reactions in which a leaving group (LG) is replaced by an electron rich species (nucleophile). The whole molecular entity of which the electrophile and the leaving group are part is usually called the substrate.
- The most general form of substitution reaction may be given as the following:



- The electron pair from the nucleophile (**Nu:**) attacks the substrate (**R-LG**) forming a new bond, while the leaving group (**LG:**) departs with an electron pair. The principal product in this case is **R-Nu**.

General Features of Nucleophilic Substitution Reactions

- The nucleophile may be electrically neutral or negatively charged, whereas the substrate is typically neutral or positively charged.



- Three components are necessary in any nucleophilic substitution reactions as abbreviated in its general form (**Figure 1**):
 - R- in R-X:** An alkyl group R containing an sp^3 hybridized carbon atom bonded to X in the substrate, R-X.
 - X- in R-X:** An atom (or group of atoms) called a leaving group, which is capable of accepting the electron density in the C-X bond.
 - Nu: or Nu⁻:** A nucleophile is an electron rich (a neutral or an anion) species that tends to attack the substrate at a position of low electron density.

General Features of Nucleophilic Substitution

- As these substitution reactions involve electron rich species, i.e., nucleophiles, they are called **nucleophilic substitution reactions**. Nucleophilic substitutions are **Lewis acid-base reactions**. The nucleophile (Lewis base) donates its electron pair, the alkyl halide (Lewis acid) accepts it, and the C-X bond is heterolytically cleaved.
- Nucleophilic substitution reactions can be broadly categorised as taking place at a saturated aliphatic carbon or at (less often) an aromatic or other unsaturated carbon centre.
- Nucleophilic substitution reactions occur when an electron rich species, the **nucleophile**, reacts at an electrophilic saturated carbon atom attached to an electronegative group, the **leaving group**, that can be displaced as shown in the general scheme in **Figure 1**.

Nucleophilic Substitution Reaction

- A common example of nucleophilic substitution reaction is the alkaline hydrolysis of an alkyl halide, e.g., R-Br to the corresponding alcohol (R-OH), where the attacking nucleophile is the OH⁻ and the leaving group is Br⁻.



- Kinetic measurement on reactions in which **alkyl halides** (R-X) react with a variety of different nucleophiles, **Nu:**, have revealed two essentially extreme types: one in which, rate of the reaction is dependent of [Nu:],

$$\text{Rate} = k_2[\text{R-X}][\text{Nu:}] \quad \text{----- I}$$

and another in which, the rate is independent of [Nu:],

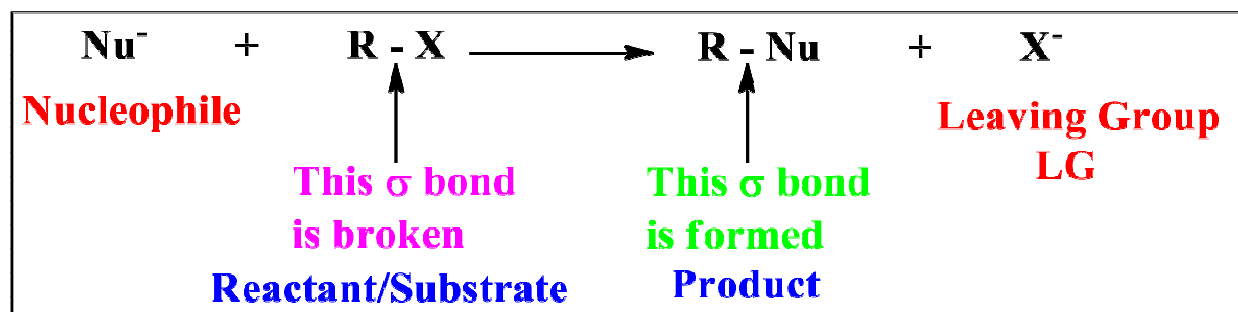
$$\text{Rate} = k_1[\text{R-X}] \quad \text{-----II}$$

Nucleophiles

- **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*.
- A nucleophile is, therefore, a chemical species that donates an electron pair to form a chemical bond in relation to a reaction. All molecules or ions with a free pair of electrons or at least one π bond can act as nucleophiles. Since nucleophiles donate electrons, they are by definition Lewis bases.
- The term '**Nucleophilic**' describes the affinity of a nucleophile to the nuclei.

Possible Mechanisms for Nucleophilic Substitution

- Overall a nucleophilic substitution can be represented as follows:



- There are two fundamental events in a nucleophilic substitution reaction:
 - breaking of the σ bond to the leaving group
 - formation of the new σ bond to the nucleophile
- Nucleophilic substitution at an sp^3 hybridised carbon, therefore, involves two σ bonds: the bond to the leaving group, which is broken, and the bond to the nucleophile, which is formed.

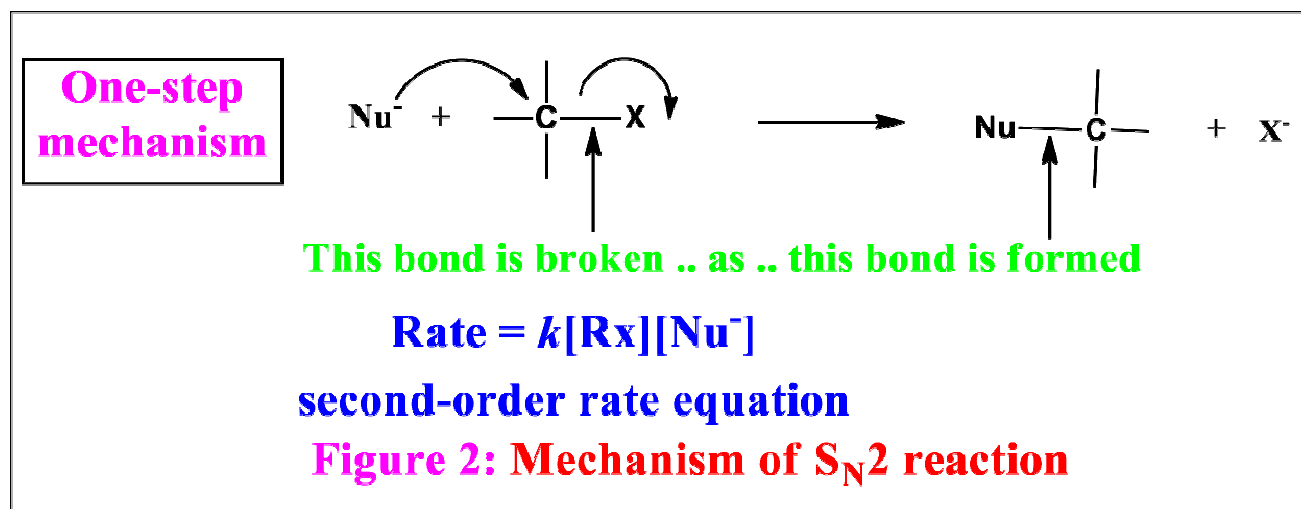
Two Mechanisms for Nucleophilic Substitution

1. The S_N2 mechanism (substitution nucleophilic bimolecular), illustrated by the reaction in **Figure 2**.
 2. The S_N1 mechanism (substitution nucleophilic unimolecular), illustrated by the reaction in **Figure 3**.
- The numbers **1** and **2** in the names S_N1 and S_N2 refer to the kinetic order of the reactions. It may also indicate the molecularity of the reaction. For example, S_N2 means that the kinetics are second order. The number **2** does not refer to the number of steps in the mechanism. S_N2 reaction is a single-step process whereas S_N1 reaction is a two-step process.

Mechanisms for Nucleophilic Substitution

Bimolecular Reactions (S_N2)

- Bond breaking and bond formation occur at the same time.

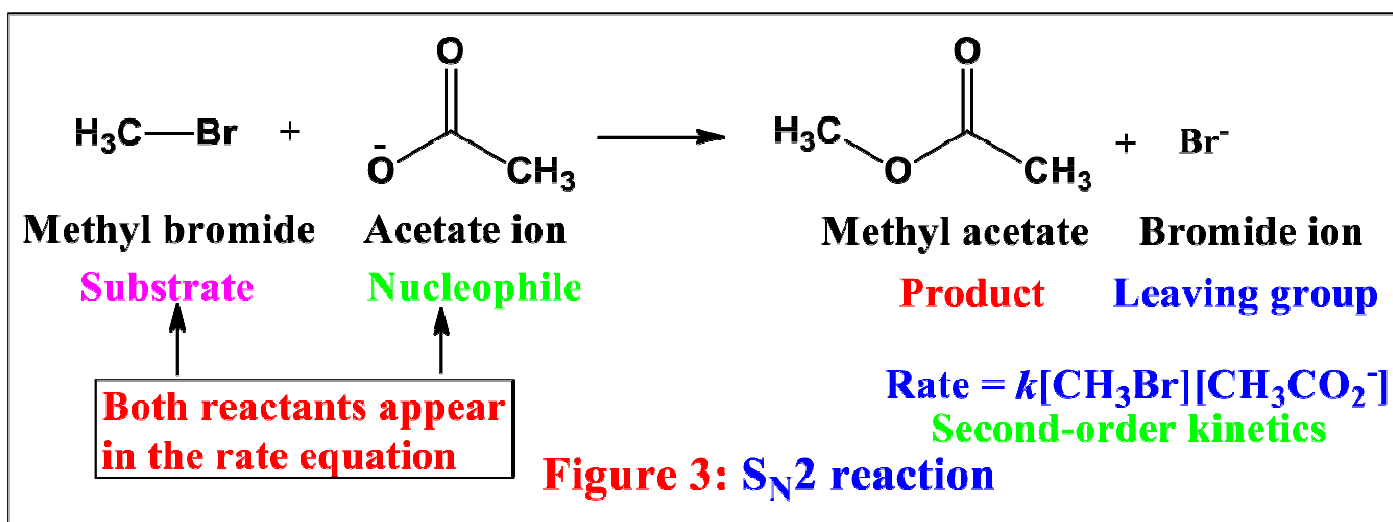


- Here, the C-X bond is broken as the C-Nu bond is formed, the **mechanism has one-step**. The rate of such a **bimolecular reaction** depends on the concentration of both the reactants; that is, the rate equation is **second order**.

Mechanisms for Nucleophilic Substitution

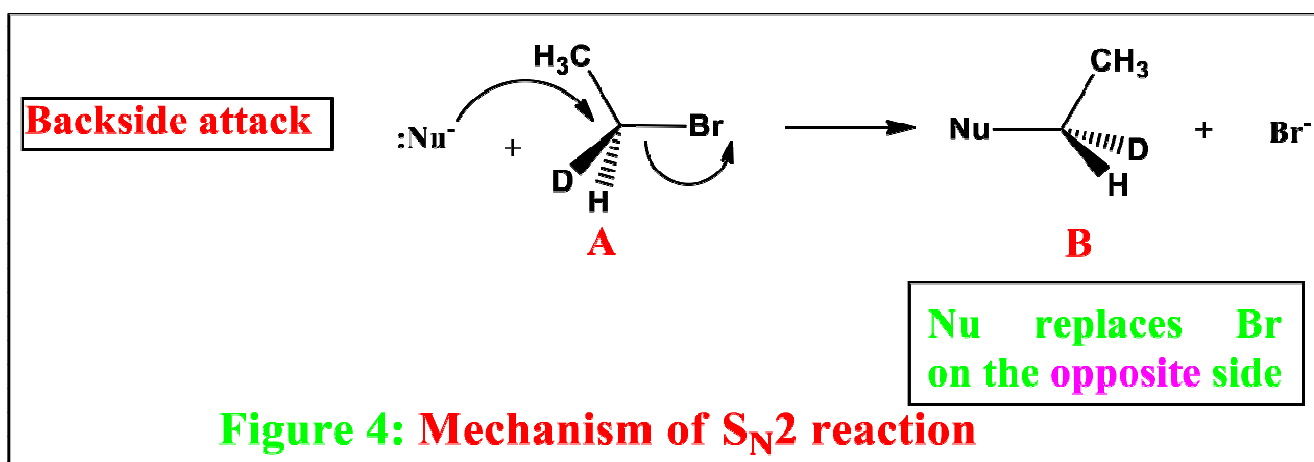
Bimolecular Reactions (S_N2)

- Reaction of methyl bromide (CH_3Br) with the nucleophile acetate (CH_3CO_2^-) affords the substitution product methyl acetate ($\text{CH}_3\text{CO}_2\text{CH}_3$) with loss of Br^- as the leaving group.
- The rate of reaction depends on the concentration of both reactants; that is, the rate equation is *second order*. This bimolecular reaction involves a **one-step mechanism** in which the C-X bond is broken as the C-Nu bond formed.



Stereochemistry of the S_N2 Reaction

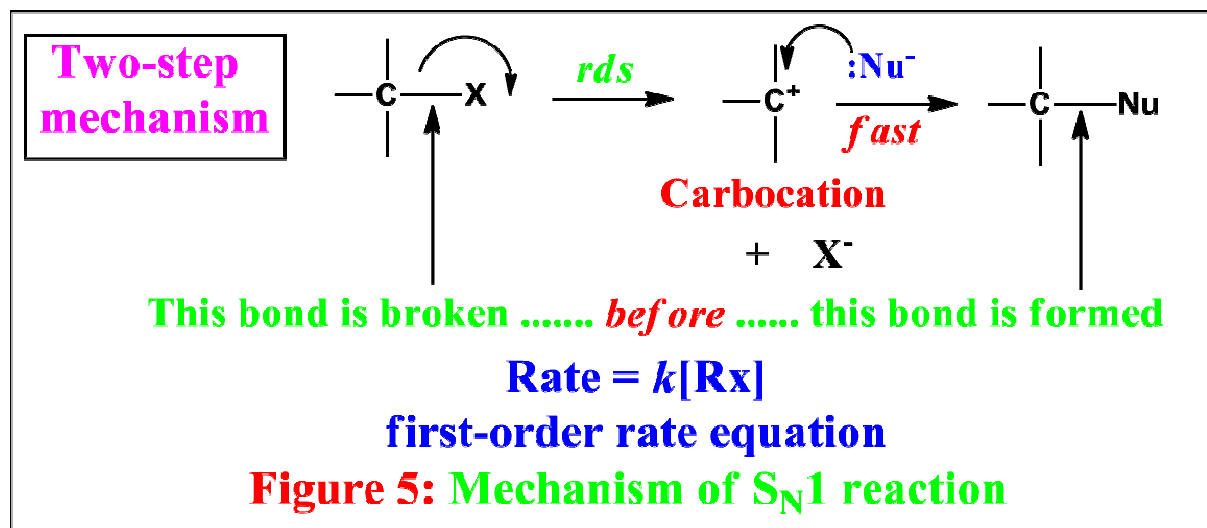
- In **backside attack**, the nucleophile approaches from the opposite side to the leaving group of the substrate (**A**), forming **B**. In this example, the leaving group was drawn on the right, so the nucleophile attacks from the left. Because the nucleophile and leaving group are in the opposite position relative to the other three groups on carbon, **backside attack** results in *inversion* of configuration around the stereogenic centre. **Figure 4** illustrates the nucleophilic approach.



Mechanisms for Nucleophilic Substitution

Unimolecular Reactions (S_N1)

- Bond breaking occurs before bond formation.

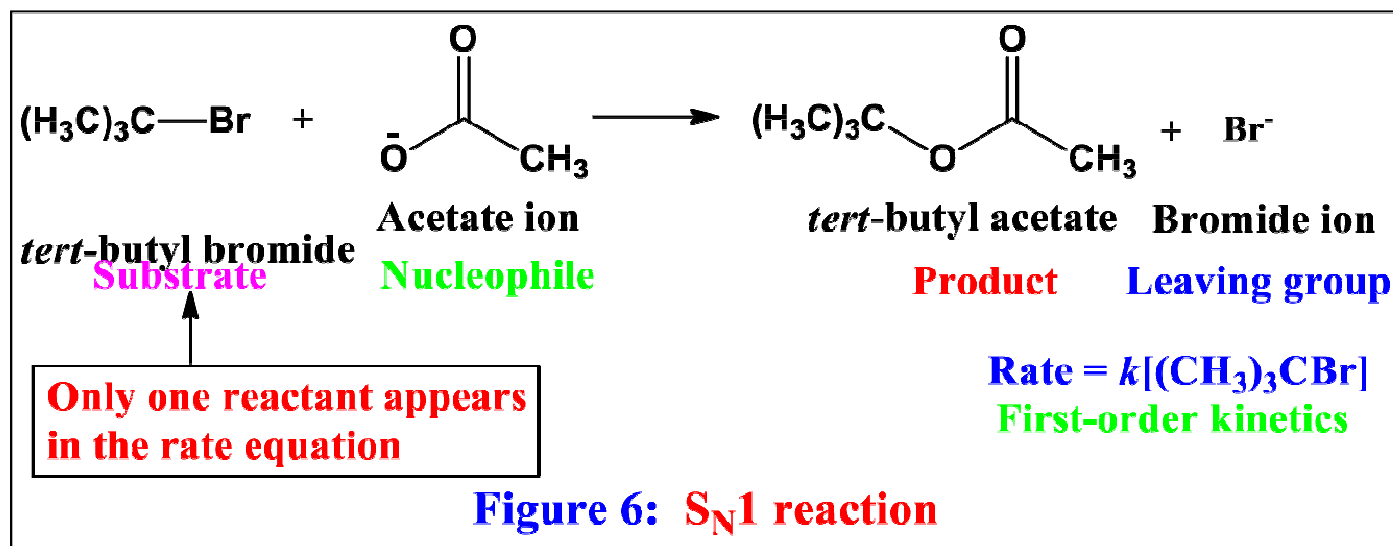


- Here, the C-X bond is broken first and then the C-Nu bond is formed, the mechanism has **two-steps** and a **carbocation** is formed as a reactive intermediate. The **first step is rate-determining**, and the rate of such a **unimolecular reaction** depends on the concentration of RX only; therefore, the rate equation is **first order**.

Mechanisms for Nucleophilic Substitution

Unimolecular Reactions (S_N1)

- Figure 6** illustrates a similar nucleophilic substitution reaction with *t*-butyl bromide $[(CH_3)_3CBr]$, which also leads to substitution of Br by $CH_3CO_2^-$. Kinetic data show that this reaction rate depends on the concentration of only one reactant, the alkyl halide; that is, the rate equation is *first order*. This suggests a **two-step mechanism** in which the rate-determining step involves the alkyl halide only.



THANK YOU