



Nucleophilic Substitution Reactions

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Organic chemistry is basically the study of synthesis, reactions, properties, and structures of carbon-containing compounds. Organic reactions can be classified into four main types: addition, elimination (E), substitution, and rearrangement reactions. The movement of electrons during these reactions play a vital role in understanding and identifying the processes behind them. Electron movement is involved in bond breaking, bond forming and when depicting resonance structures. During **homolytic** cleavage, a single bond cleaves leaving one electron at each side while in the **heterolytic** cleavage, a single bond is cleaved leaving both electrons on one side of the bond. Homolytic bond cleavage is shown with a curved **fishhook** arrow () and heterolytic bond cleavage using a normal **curved** arrow (). This phenomenon is used in bond formation and depicting

resonance structures as shown below.

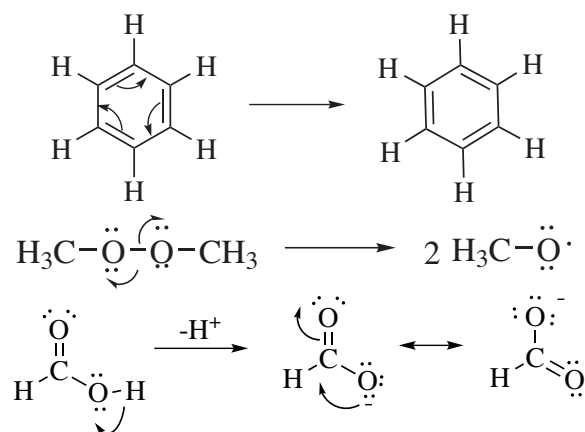


Fig. 1: Examples for resonance structures, homolytic and heterolytic bond cleavages

In **substitution reactions**, the incoming group

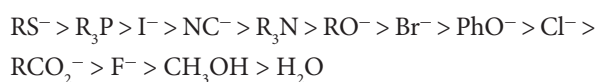
(a **nucleophile or electrophile**) attacks the **substrate** replacing a similar group (called **leaving group** or nucleofuge) present in the substrate. Here, we will discuss only the nucleophilic substitution reactions, *e.g.*



Nucleophile can be considered as a negatively charged ion, group or molecule with a lone pair of electrons (Lewis base) or π -electron pair of a multiple bond, *e.g.* halide, RO^- , HO^- , HS^- , H_2O , amine, alkene, alkyne *etc.*

Nucleophilicity is the reactivity of the nucleophile which increases with the basicity and the atomic number of an ion. But nucleophilicity decreases with increasing solvation.

← Nucleophilicity increases



There are three types of nucleophilic substitution reactions.

- **Bimolecular** nucleophilic substitution (S_N^2)
- **Unimolecular** nucleophilic substitution (S_N^1)
- **Internal** nucleophilic substitution (S_N^i)

Sometimes the carbocation intermediate formed may undergo a rearrangement reaction, *e.g.* S_N^1 (**SN one prime**).

S_N^2 Reactions

S_N^2 reactions are concerted and stereospecific with the inversion of configuration. Thus, the **bond breaking** and **bond forming** happens in a **single step** or simultaneously. S_N^2 reactions show second order kinetics, *i.e.*

$$\text{Rate} = k[\text{substrate}][\text{nucleophile}]$$

Generally, substitution occurs on a sp^3 -hybridized carbon bonded to an electronegative atom/group. The nucleophile attacks the carbon from the **opposite** side of the leaving group while forming a **trigonal planar** transition state. Since nucleophile and the leaving group

are in the same axis the product shows the **inverse** configuration.

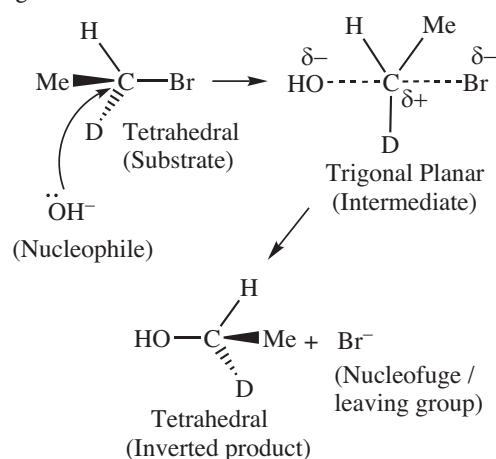


Fig. 2: Mechanism of a S_N^2 reaction

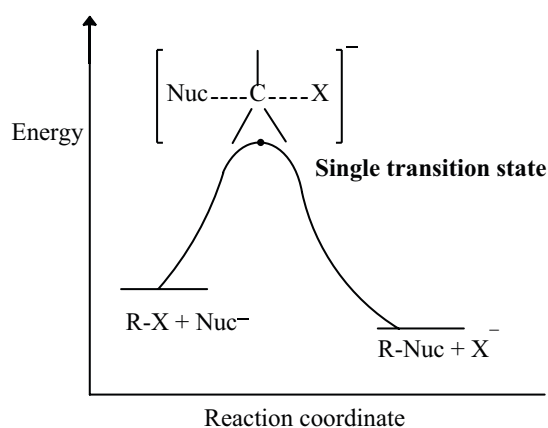


Fig. 3: Energy diagram of a S_N^2 reaction

Factors that affect S_N^2 reactions

Main factors that affect S_N^2 reactions are: the nature of the substrate, nucleophile/base, solvent and leaving group.

Nature of the substrate

Unhindered substrates (*e.g.* MeX , RCH_2X) show higher reactivity since the attack of the nucleophile takes place from the side opposite to the leaving group, X. Therefore, **primary substrates** react faster. **Vinyl** and **aryl** substrates are unreactive towards S_N^2 or S_N^1 reactions since the π -electron cloud tends to block the nucleophile from attacking the carbon atom. S_N^2 reactions do not occur with **tertiary substrates** (R_3CX).

Nature of the nucleophile/base

Negatively **charged** nucleophiles are much more

reactive than neutral nucleophiles. S_N^2 reactions are favored by **primary** and **allylic** substrates. **Secondary** alkyl halides can undergo either S_N^2 or E^2 reactions. S_N^2 reactions are favored by strong ionic nucleophiles/weak bases. E^2 reaction is favored by strong bases (e.g. DBN, DBU, $t\text{BuO}^-$).

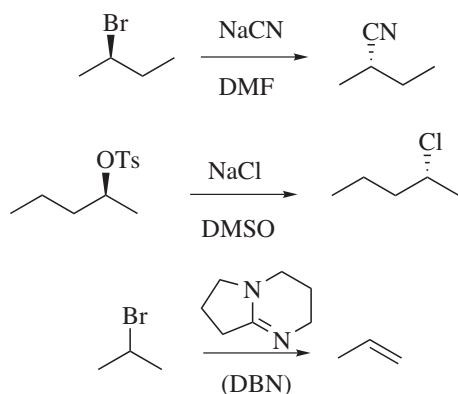


Fig. 4: Examples with secondary substrates for S_N^2 and E^2 reactions

HO^- and H_2N^- are strong bases as well as good nucleophiles.

Nature of the Solvent

Polar solvents favorably increase the reaction rate than non-polar solvents. Polar **aprotic** solvents e.g. Acetone, MeCN, DMF (Me_2NCHO), HMPA [$\text{P}(\text{NMe}_2)_3$] and DMSO (Me_2SO) promote S_N^2 reactions. The presence of protons can form hydrogen bonds with the nucleophile and hinder the attack by the nucleophile. **Protic** solvents (e.g. H_2O , ROH, HOAc) promote S_N^1 reactions.

Nature of the leaving group

Since leaving groups depart as anions, the leaving ability is higher when the negative charge is stabilised. Generally, **weak** bases are **good** leaving groups. Leaving ability decreases in the following order.



S_N^1 Reactions

In a S_N^1 reaction, the substitution takes place *via* **two steps** (Fig. 5). In the **first step**, the leaving group departs and the substrate forms a **carbocation** intermediate; this is the rate determining step. The **second step** involves bond formation with the new nucleophile.

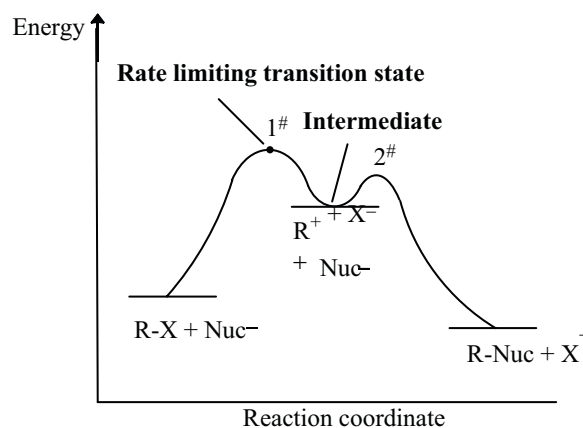


Fig. 5: The energy diagram of S_N^1 reaction

Since the rate of the reaction depends only on the substrate concentration, it shows first order kinetics, *i.e.* $\text{Rate} = k[\text{Substrate}]$. Thus, the configuration of the substrate not retained and leads to a racemic mixture (Fig.6).

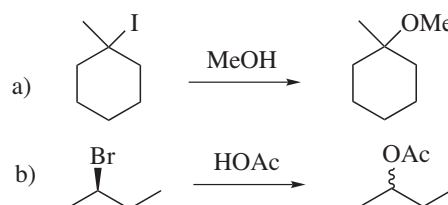


Fig. 6: Examples for S_N^1 reactions

Factors that affect S_N^1 reactions

Since the reaction passes through an intermediate, the substrate should be able to form a **stable carbocation**. Therefore, tertiary (3°) substrates undergo S_N^1 reactions more favorably.

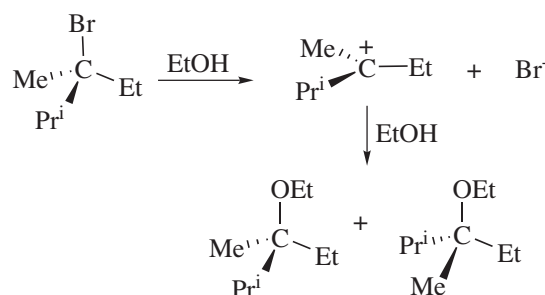


Fig. 7: Mechanism of the S_N^1 reaction where EtOH act as the nucleophile which attacks the tertiary carbocation, forming a mixture of two products.

The stability of the carbocation increases in the following order. $\text{Me} < 1^\circ < 2^\circ < 3^\circ$

As the concentration of the nucleophile does not

affect the rate of the reaction, the nature of the nucleophile does not play a vital role. Usually, **polar** solvents are used to stabilize the carbocation intermediate *via* solvation. Good leaving groups also promote faster formation of carbocations.

S_N^1 reactions are prone to side reactions, *e.g.* elimination and carbocation rearrangements. For example, in water, neopentyl bromide (Fig.8) does not undergo S_N^2 reaction (due to steric factors) to form a primary alcohol, instead the attack of the Me group generates a **stable tertiary** carbocation, affording a tertiary alcohol. In boiling water, Me_3CBr produces an **alkene** *via* E^1 mechanism.

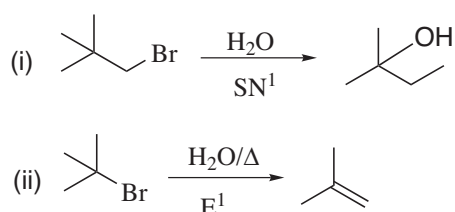


Fig. 8: Examples for S_N^1 with a Me group transfer and E^1 reactions

S_N^i Reactions (i = internal)

In S_N^i reactions, the attacking nucleophile is a part of the substrate, which is produced by ionizing the substrate. Even though all parameters are similar to that of S_N^1 , the reaction always proceeds with the **retention of configuration**.

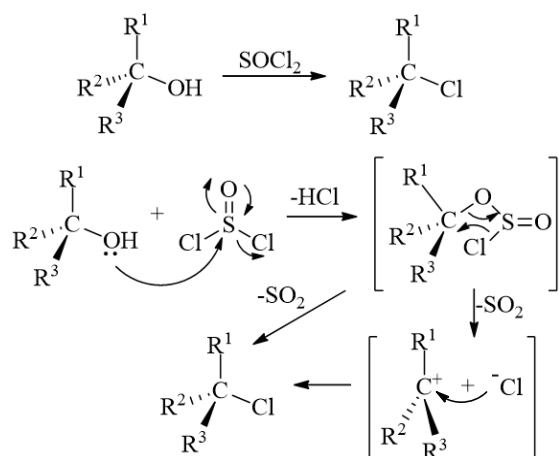
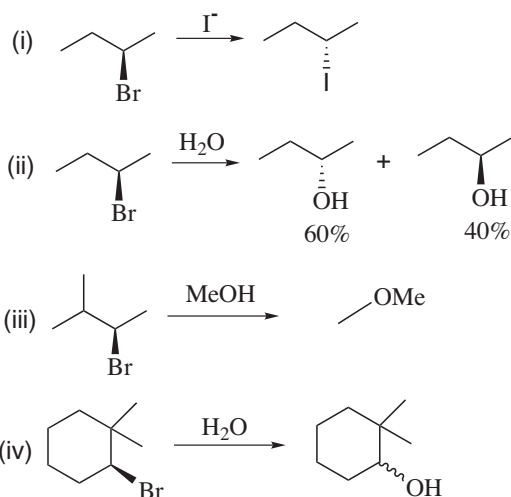


Fig. 9: Example for an internal nucleophilic substitution (S_N^i) reaction

Problems

1. Draw the resonance structures of allyl group. Propose the S_N^i (S_N one prime) mechanism for the reaction between $\text{CH}_2=\text{CHCH}_2\text{Br}$ and HO^- ion.
2. Write the reaction mechanisms for conversions given in Figs. 4, 6 and 7.
3. Write the reaction mechanisms for the following conversions.



4. Discuss the nucleophilicity and basicity of halide ions in protic and aprotic solvents.
5. Write the reaction mechanisms for the following conversions.

