

## Principles of Nucleophilic Substitution

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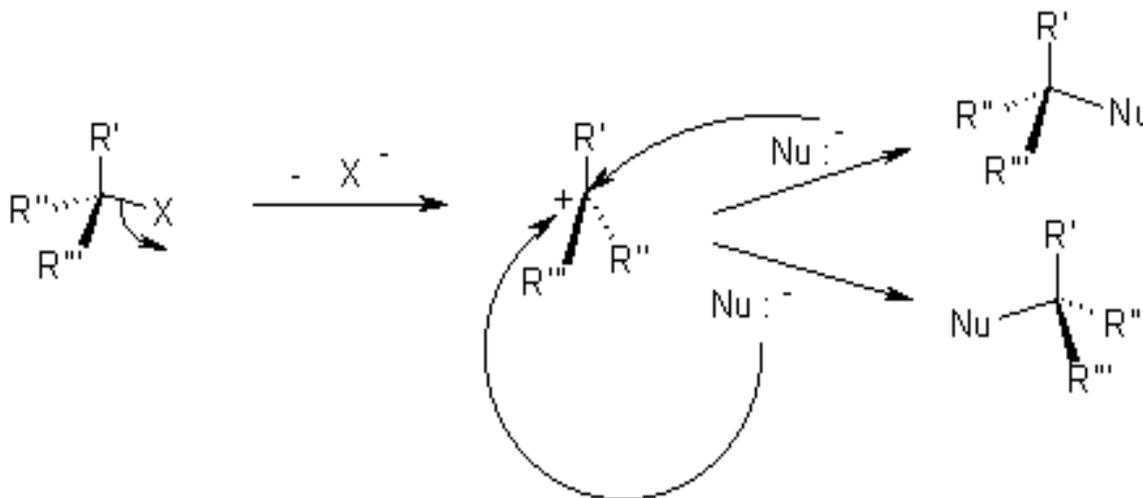
### Abstract

The work reported in this theoretical paper deals with types of substitution reaction ( $sn_1$  ,  $sn_2$  , conditions of both reactions , methods of both reactions , diagram of reactions , energy for reactions, types of reactants , products, rate of reactions , steps of reactions, transition state for reaction) and other reactions.

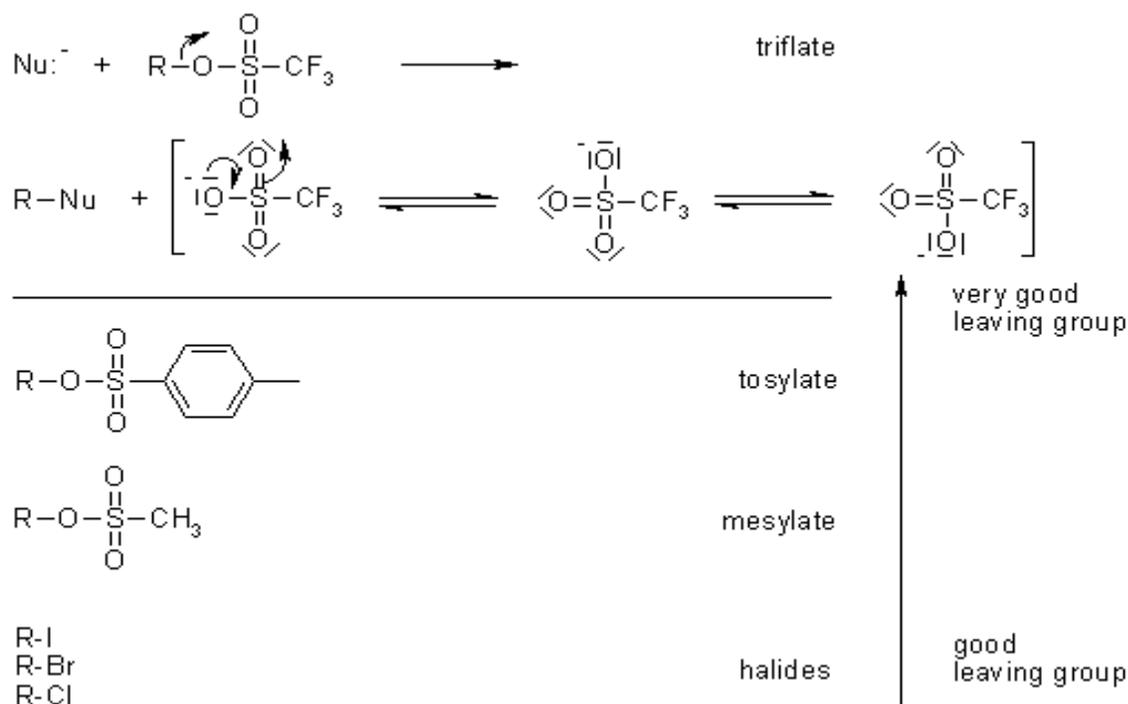
**Keywords:** reactant , product.

### Introduction

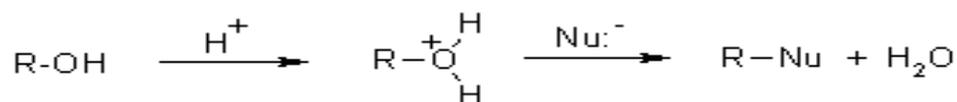
In the  $S_N1$  reaction , a planar carbenium ion is formed first, which then reacts further with the nucleophile. Since the nucleophile is free to attack from either side, this reaction is associated with racemization.



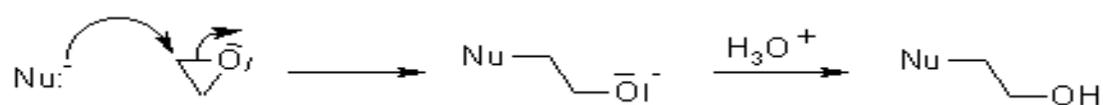
In reaction, the nucleophile competes with the leaving group. Because of this, one must realize what properties a leaving group should have, and what constitutes a good nucleophile. Very good leaving groups, such as triflate, tosylate and mesylate, stabilize an incipient negative charge. The delocalization of this charge is reflected in the fact that these ions are not considered to be nucleophilic.



Hydroxide and alkoxide ions are not good leaving groups; however, they can be activated by means of Lewis or Brønsted acids.



Epoxides are an exception, since they relieve their ring strain when they undergo nucleophilic substitution, with activation by acid being optional:

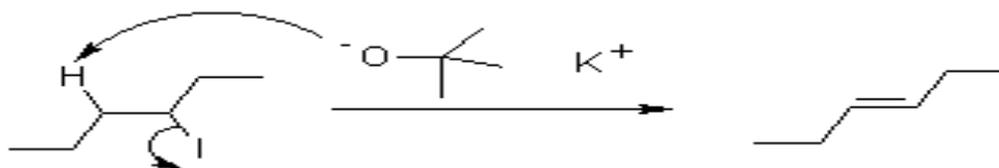


Triflate, tosylate and

mesylate are the anions of strong acids. The weak conjugate bases are poor nucleophiles. Nucleophilicity increases in parallel with the base strength. Thus, amines, alcohols and alkoxides are very good nucleophiles. Base strength is a rough measure of how reactive the nonbonding electron pair is; thus, it is not necessary for a nucleophile to be anionic.

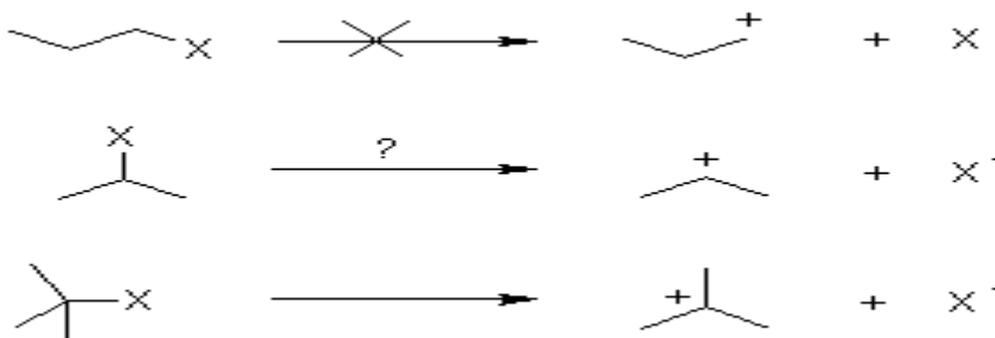
Under substitution conditions, amines proceed all the way to form quaternary salts, which makes it difficult to control the extent of the reaction.

However, as a nucleophile's base strength and steric hindrance increase, its basicity tends to be accentuated. If there are abstractable protons at the  $\beta$ -position of the electrophile, an elimination pathway can compete with the nucleophilic substitution.



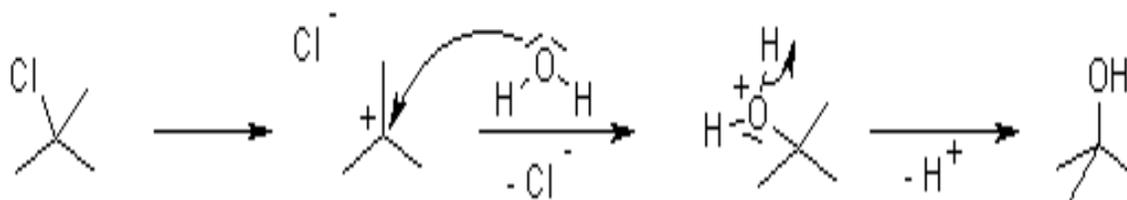
An additional factor that plays a role is the character of the solvent. Increasing stabilization of the nucleophile by the solvent results in decreasing reactivity. Thus, polar protic solvents will stabilize the chloride and bromide ions through the formation of hydrogen bonds to these smaller anions. Iodide is a comparatively better nucleophile in these solvents. The reverse behavior predominates in a protic polar media.

The formation of the corresponding unstable primary carbenium ion is disfavored. Reaction by the  $S_N1$  pathway is highly probable for compounds with tertiary substitution, since the corresponding tertiary carbenium ion is stabilized through hyper conjugation:

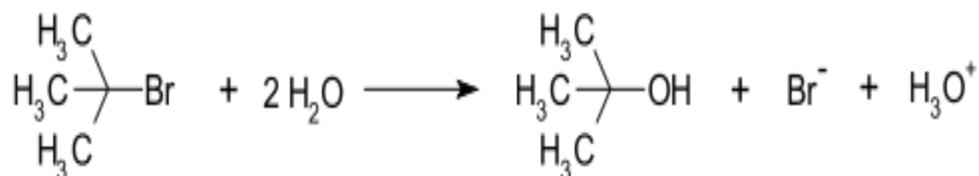


The better the solvent stabilizes the ions, the more probable that the reaction will follow an  $S_N1$  pathway (e.g., in polar protic solvents such as water in acetone). The more highly substituted is the incipient carbenium ion, the more probable that the reaction will follow an  $S_N1$  pathway. The more unreactive the nucleophile, the more probable it becomes that a reaction with secondary and tertiary electrophiles will follow an  $S_N1$  pathway. A weaker nucleophile is not as effective in the backside attack, since this location is sterically shielded, especially in the case of tertiary substrates. Carbenium ions are planar and therefore less sterically hindered, and are naturally more reactive as electrophiles than the uncharged parent compound.

The hydrolysis of *tert*-butyl chloride is a typical  $S_N1$  reaction:



An example of a reaction taking place with an  $S_N1$  reaction mechanism is the hydrolysis of *tert*-butyl bromide with water forming *tert*-butanol:

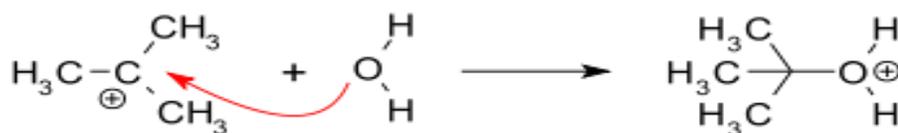


This  $S_N1$  reaction takes place in three steps:

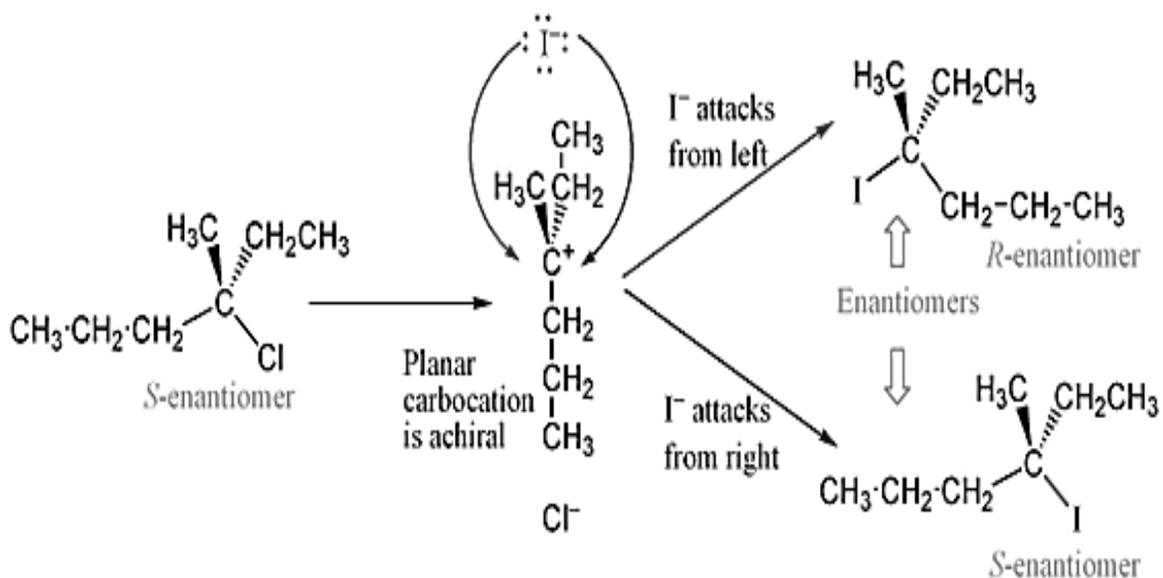
- Formation of a *tert*-butyl carbocation by separation of a leaving group (a bromide anion) from the carbon atom: this step is slow and reversible.



**Nucleophilic attack:** the carbocation reacts with the nucleophile. If the nucleophile is a neutral molecule (i.e. a solvent) a third step is required to complete the reaction. When the solvent is water, the intermediate is an oxonium ion. This reaction step is fast.



Deprotonation: Removal of a proton on the protonated nucleophile by water acting as a base forming the alcohol and a hydronium ion. This reaction step is fast.



SN1 indicates a *substitution, nucleophilic, unimolecular* reaction, described by the expression rate =  $k[\text{R-LG}]$ . This implies that the rate determining step of the mechanism depends on the decomposition of a single molecular species.

Multi-step reactions have intermediates and a several transition states (TS).

In an S<sub>N</sub>1 there is loss of the leaving group generates an intermediate carbocation which is then undergoes a rapid reaction with the nucleophile..

Let's look at how the various components of the reaction influence the reaction pathway:

### R-

Reactivity order :  $(\text{CH}_3)_3\text{C}^- > (\text{CH}_3)_2\text{CH}^- > \text{CH}_3\text{CH}_2^- > \text{CH}_3^-$

In an S<sub>N</sub>1 reaction, the rate determining step is the loss of the leaving group to form the intermediate carbocation. The more stable the carbocation is, the easier it is to form, and the faster the S<sub>N</sub>1 reaction will be. Some students fall into the trap of thinking that the system with the less stable carbocation will react fastest, but they are forgetting that it is the generation of the carbocation that is rate determining. Since a carbocation intermediate is formed, there is the possibility of rearrangements (*e.g.* 1,2-hydride or 1,2-alkyl shifts) to generate a more stable carbocation. This is usually indicated by a change in the position of the substituent or a change in the carbon skeleton of the product when compared to the starting material.

The following images show a selection of alkyl bromides and their relative rates of reaction in an S<sub>N</sub>1 hydrolysis. Try to correlate the structure of the alkyl bromide with the type of carbocation that will be formed. If you need help, click the L button to show you where the carbocation will be formed.

You should have found that the carbocations get more stable as you go left to right in the table. As the carbocation gets easier to form, so the rate of reaction increases.

### -LG

The only event in the rate determining step of the S<sub>N</sub>1 is breaking the **C-LG** bond. Therefore, there is a very strong dependence on the nature of the leaving group, the better the leaving, the faster the S<sub>N</sub>1 reaction will be.

### Nu

Since the nucleophile is not involved in the rate determining step, the nature of the nucleophile is unimportant in an S<sub>N</sub>1 reaction. However, the more reactive the nucleophile, the more likely an S<sub>N</sub>2 reaction becomes.

### Stereochemistry

In an S<sub>N</sub>1, the nucleophile attacks the planar carbocation. Since there is an equally probability of attack on each face there will be a **loss of stereochemistry** at the reactive center as both products will be observed.

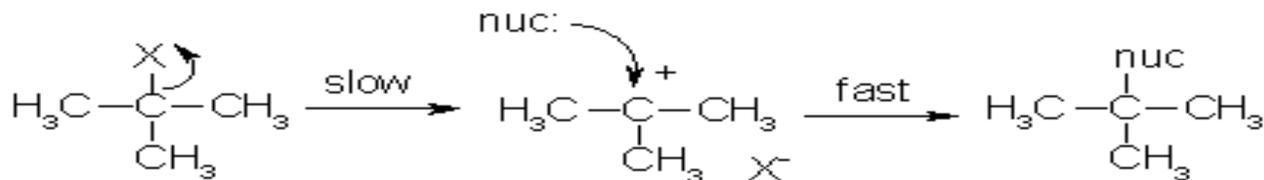
### Solvent

Polar solvents which can stabilise carbocations which can favour the S<sub>N</sub>1 reaction (*e.g.* H<sub>2</sub>O, ROH)

### Summary

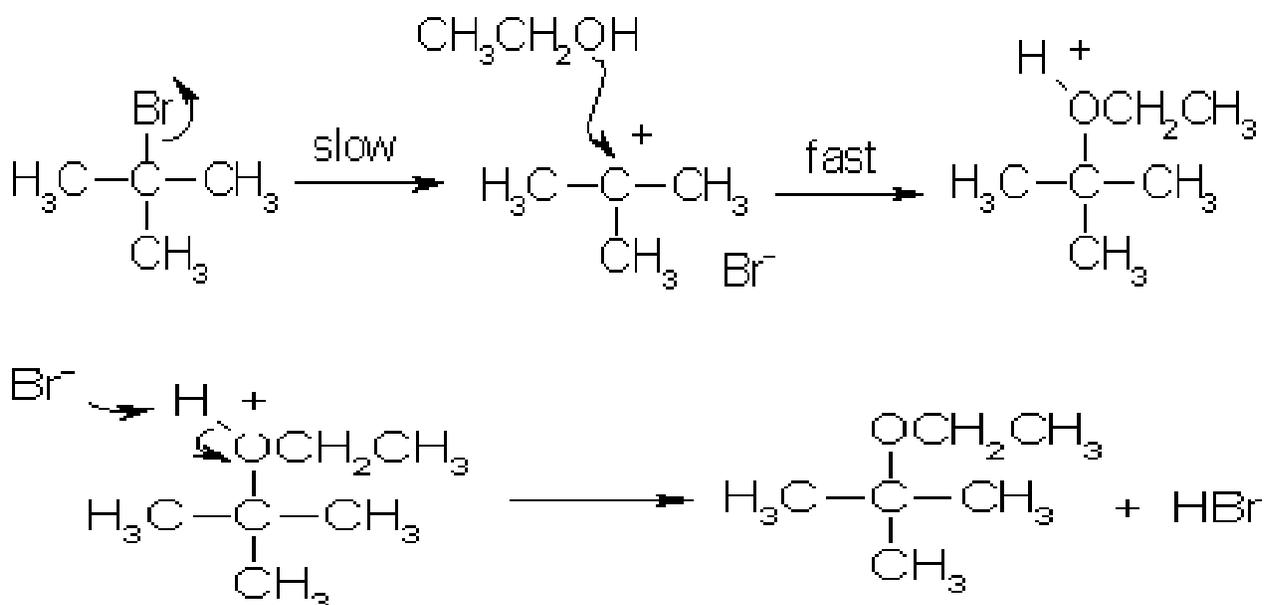
This pathway is most common for systems with good leaving groups, stable carbocations and weaker nucleophiles. A typical example is the reaction of HBr with a tertiary alcohol.

The general form of the S<sub>N</sub>1 mechanism is as follows:



Because the mechanism goes through a carbocation, the leaving group must be attached to either a tertiary or secondary carbon to stabilize the intermediate. A methyl or primary leaving group will not form a carbocation. Since it goes through a carbocation intermediate, there are possibilities for alkyl and hydrogen rearrangements (HINT: In mechanism problems if you see a change in the carbon skeleton between the reactant and the product, automatically suspect a carbocation intermediate (ie, E1, Sn1) stabilized by an alkyl or hydrogen rearrangement).

An example of the Sn1 Mechanism



**Base Strength:** Base strength is unimportant, since the base is not involved in the rate determining step (the formation of the carbocation).

**Leaving groups:** A good leaving group is required, such as a halide or a tosylate, since the leaving group is involved in the rate-determining step.

**Notes:** Be wary of rearrangements that can occur with the  $\text{S}_{\text{N}}1$  reaction. Because it goes through a carbocation intermediate, both hydrogen shifts and alkyl shifts can occur!

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