

Nucleophilic Substitution and Elimination Reaction

After the completion of this chapter students should be familiar with substitution and elimination reactions, know the mechanism of S_N1 , S_N2 , $E1$ and $E2$ reactions, and know the factors that affect S_N1 , S_N2 , $E1$ and $E2$ reaction. The students should understand basic concepts like rate determining step, order of reaction, transition state, steric hinderance, polar aprotic solvent, polar protic solvents, stability of carbocations, retention and inversion in configuration, etc.

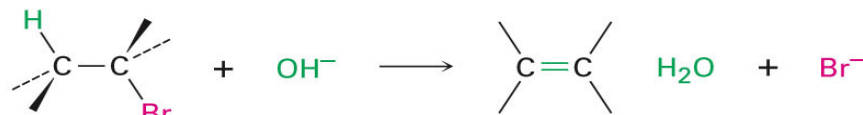
In chemistry, **nucleophilic substitution** is a fundamental class of reactions in which a nucleophile attacks a positively charged or partially positively charged carbon of a substrate forming a covalent bond and replacing a leaving group. In 1935, Hughes and Ingold studied nucleophilic substitution reactions of alkyl halides and related compounds and proposed two main mechanisms; namely S_N1 and S_N2 reactions, both of them competing with each other. S stands for substitution, N stands for nucleophilic, and the number represents the kinetic order of the reaction (1 and 2 for first and second order, respectively).

Elimination reactions are the competing reactions of substitution reactions. In an elimination reaction, two atoms or groups are generally eliminated from the adjacent carbons resulting in the formation of unsaturated compound. If β -hydrogen is eliminated as proton, the elimination reaction is called β elimination, a characteristic elimination reaction. In elimination reactions two sigma bonds are broken and one pi bond is formed. Elimination reactions are broadly classified under two different types: $E1$ (elimination unimolecular) and $E2$ (elimination bimolecular).

Substitution

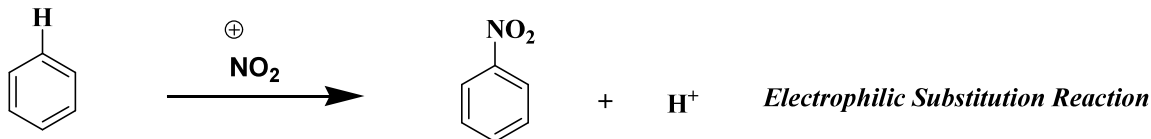
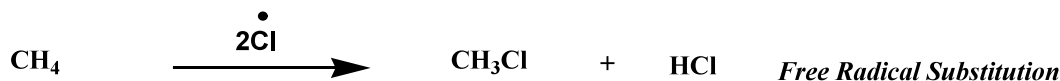


Elimination

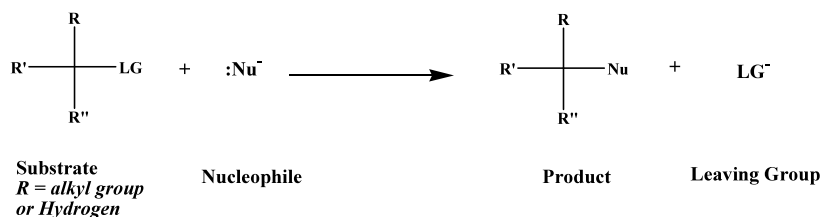


Substitution Reaction:

In a substitution reaction, a atom or group is substituted from a substrate by a atom or group. There are three kinds of substitution reaction: Electrophilic substitution reaction, free radical substitution reaction, and nucleophilic substitution reaction. However, in this chapter we will focus on nucleophilic substitution reaction.



In a nucleophilic substitution reaction, a nucleophile, species with an unshared electron pair, substitutes an atom or a group from a substrate as shown below.

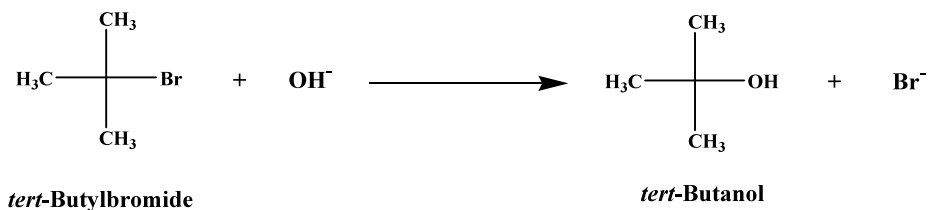


Based on the timing of bond breaking and bond formation in the reaction, substitution reaction is classified into two main types: S_N1 and S_N2

S_N1 (Substitution Nucleophilic Unimolecular Reaction)

In S_N1 reaction, the rate of the reaction depends only on the concentration of the substrate but not on the concentration of nucleophiles.

For example: The reaction between *tert*-butylbromide and aqueous sodium hydroxide ion to give *tert*-butyl alcohol and bromide ion follows S_N1 mechanism.



1. Rate of Reaction

The rate of reaction depends only on the concentration of alkyl halide and is independent on the concentration of hydroxide ions. If the concentration of *tert*-butylbromide is doubled the rate of reactions is doubled and if the concentration of *tert*-butylbromide is halved the rate of the reaction is also halved. But, the change in

concentration of hydroxide ion in the reaction mixture has no effect on the rate of reaction. Hence, SN1 reaction is first order reaction.

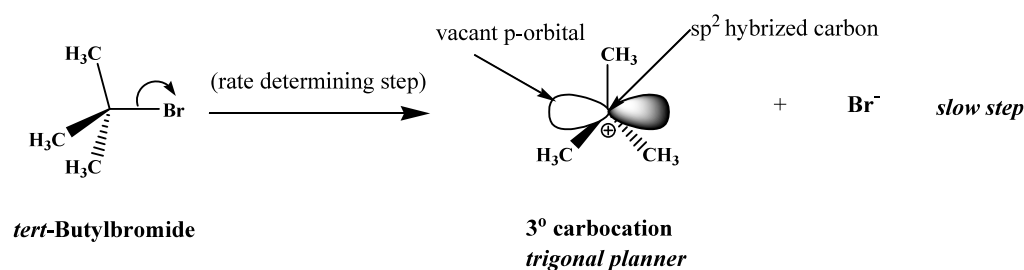
Therefore,

$$\text{Rate of Reaction} = k [\text{tert-butylbromide}]$$

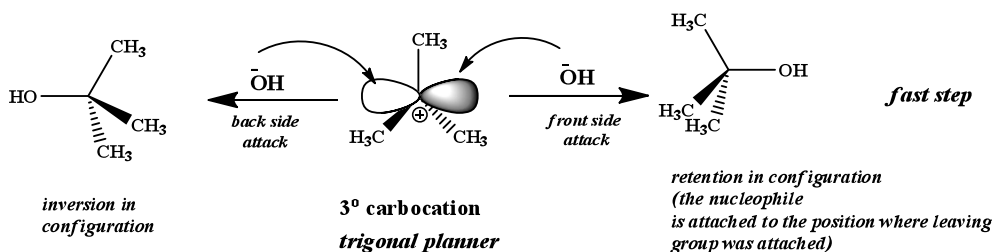
Where, **k** is rate constant for first order reaction

2. Mechanism of S_N1 reaction

- a) The reaction completes in two steps. In the first step, the Carbon-Halogen (C-Br) bond of the substrates slowly breaks by heterolytic fission (halogen departs with the shared pairs of electrons) forming a carbocation. This is the slowest step and hence is the rate determining step. The formed carbocation has trigonal planar structure.



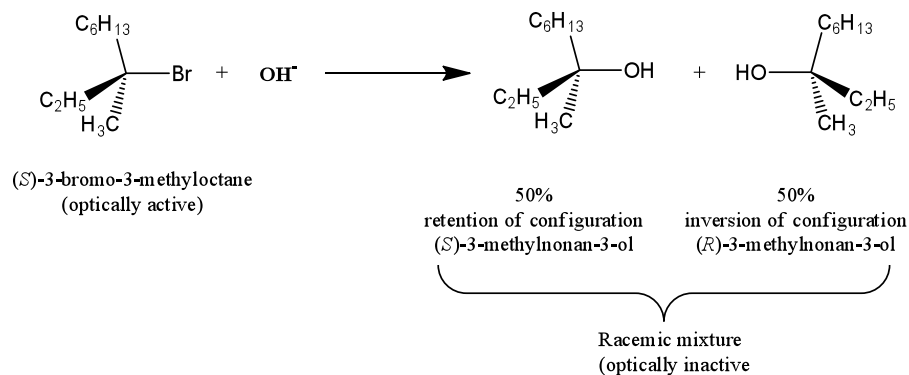
- b) In the second step, the nucleophile rapidly attacks the free carbocation giving the product. The nucleophile can attack the carbocation from either sides of the plane giving racemized product (with inversion and retention configuration).



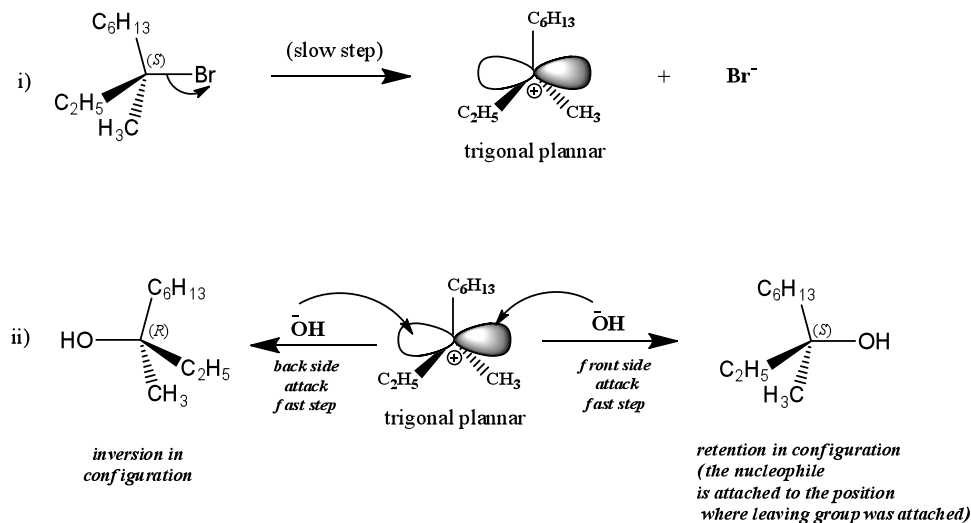
Note: Since the product *tert*-butanol is achiral, both the product formed in this case is the same.

If the leaving group departing from the substrate exists in the form of ion pair with the carbocation, partial racemization occurs.

Proof of racemization via the formatin of carbocation in S_N1 reaction

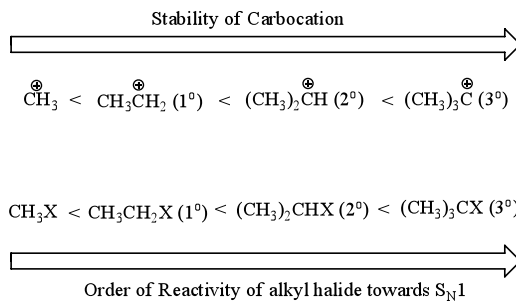


Mechanism



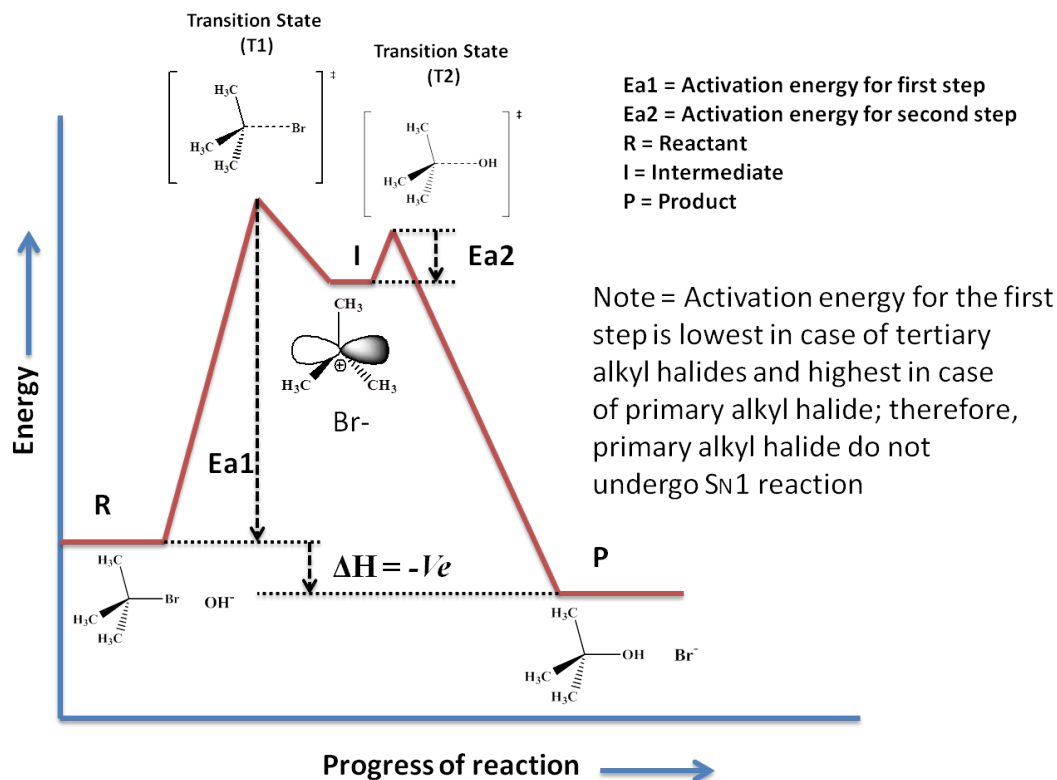
3. The order of reactivity of alkyl halides towards S_N1 reaction

Since the rate of reaction depends on the ionization of C-X (carbon halogen) bond in alkyl halide to form carbocation. More stable the carbocation formed, faster is the reaction. Therefore, the order of reactivity of alkyl halides towards S_N1 reaction is:



S_N1 reaction does not take place with methyl or primary alkyl halide

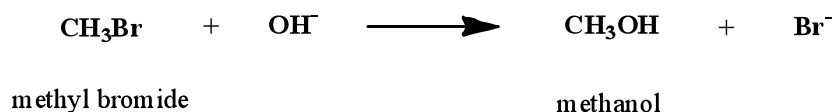
4. Energy Profile of the reaction



S_N2 (Substitution Nucleophilic Bimolecular Reaction)

In S_N2 reaction, the rate of the reaction depends only on the concentration of both substrate and the nucleophile.

For example: The reaction between methyl bromide and aqueous sodium hydroxide ion to give methanol and bromide ion follows S_N2 mechanism.



Rate of Reaction

The rate of reaction depends only on the concentration of both alkyl halide and hydroxide ions. If the concentration of methyl bromide is doubled, the rate of reactions is doubled and if the concentration of methyl bromide is halved the rate of the reaction is also halved. Similarly, if the concentration of hydroxide ion is doubled, the rate of reaction is doubled and if the concentration of hydroxide is halved, the rate of reaction is also halved. Hence, S_N2 reaction is second order reaction.

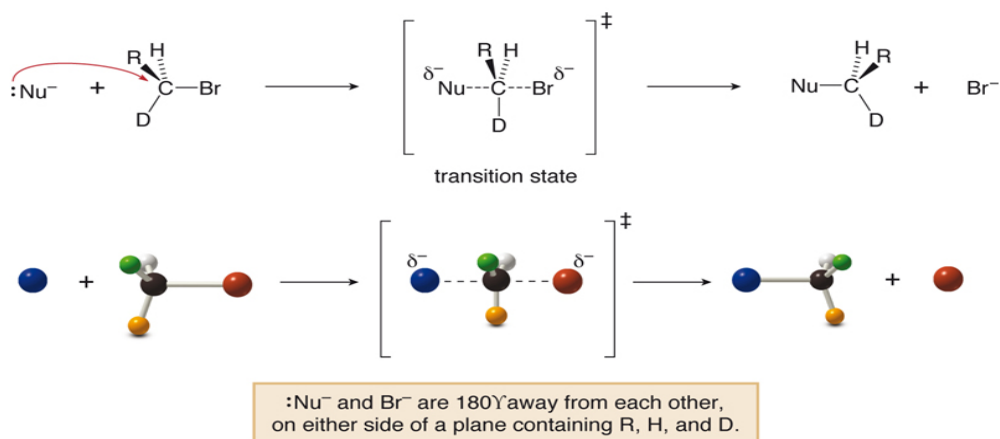
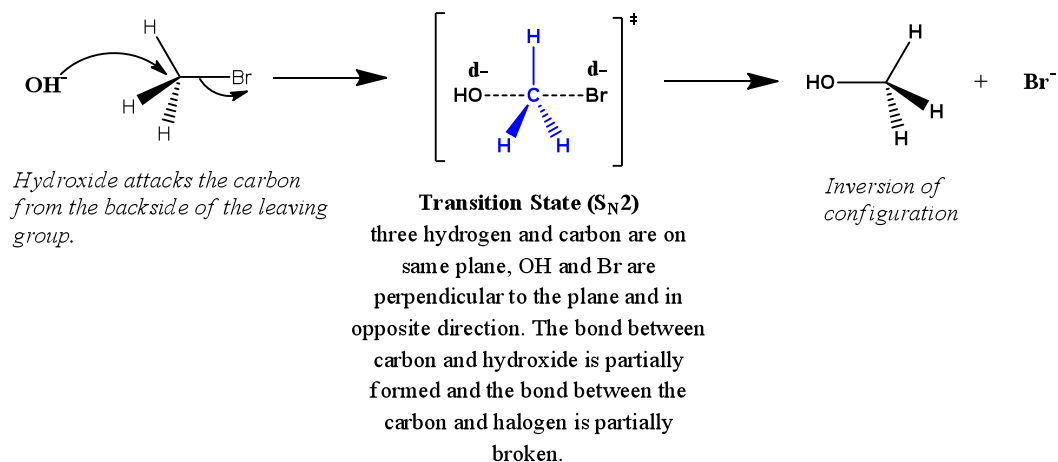
Therefore,

$$\text{Rate of Reaction} = k [\text{methyl bromide}] [\text{OH}^-]$$

Where, **k** is rate constant for second order reaction

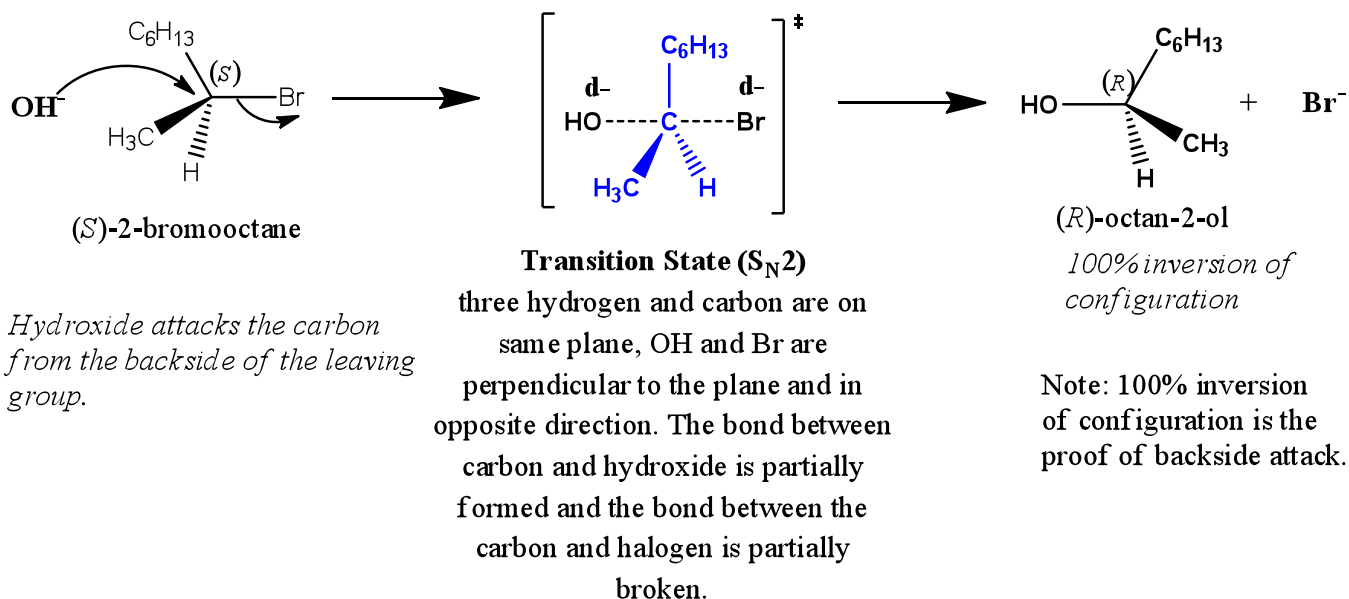
Mechanism of S_N2 reaction

The reaction completes in one step. The nucleophile attacks the carbon bearing the leaving group from the opposite direction of the leaving group resulting in the departure of leaving group. Nucleophile donates the lone pair of electrons in the formation of new covalent bond, whereas, the leaving group takes the shared pair of electrons with it. The forming of covalent bond between the carbon and nucleophile and breaking of the covalent bond between carbon and the leaving group takes place simultaneously. Reaction taking place in one step is called concerted reaction and takes place as through the formation of transition state as shown below.



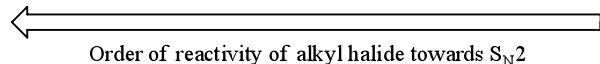
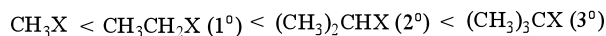
Proof of inversion of configuration by back side attack of the nucleophile

The inversion of configuration during S_N2 reaction can be proved by taking a chiral alkyl halide. For example, hydrolysis of (*S*)-2-bromooctane in the presence of aqueous sodium hydroxide gives only (*R*)-octa-2-ol with inversion of configuration.

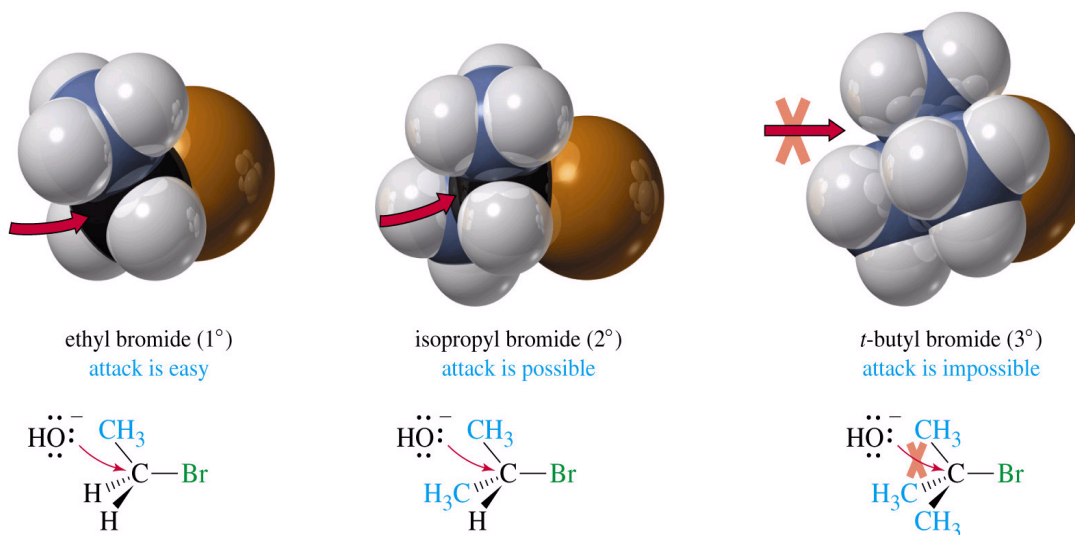


The order of reactivity of alkyl halides towards S_N2 reaction

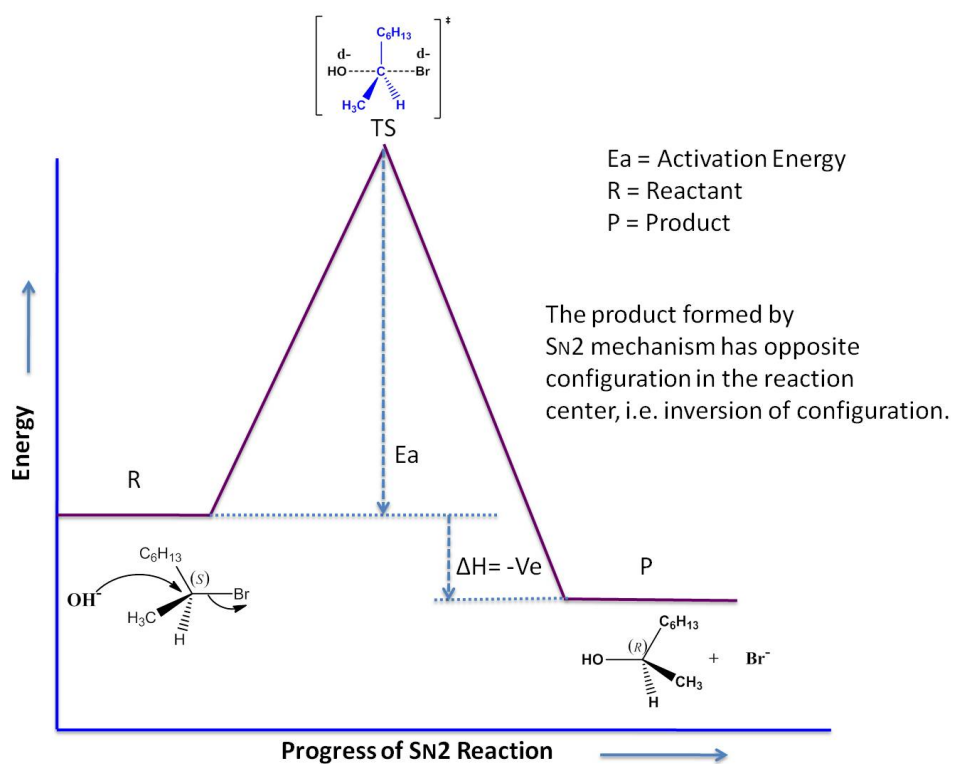
Simple alkyl halides show the following general order of reactivity in S_N2 reaction.



The steric effect is the important factor behind the order of reactivity. A steric effect is an effect on relative rates caused by the space-filling properties of those parts of a molecule attached at or near the reacting site. Availability of space for attack on the carbon site by the nucleophile decreases with the increasing steric effect and consequently the rate of reaction decreased largely. For example, in methyl halide three hydrogen atoms are connected to the reacting carbon and afford no obstacle to the incoming nucleophile for the backside attack, so the reaction is fast. On the other hand, in tertiary alkyl halides there are three alkyl groups attached to the reacting carbon which obstructs the nucleophile for the back side attack, making the reaction impossible by S_N2 .



1. Energy Profile of the reaction



Factors affecting the rates of S_N1 and S_N2 reactions

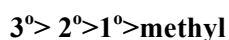
The most important factors that affect the relative rates of S_N1 and S_N2 reactions are:

1. Structure of substrate
2. Nature of nucleophile
3. Solvent
4. Nature of leaving group

1. Structure of Substrate

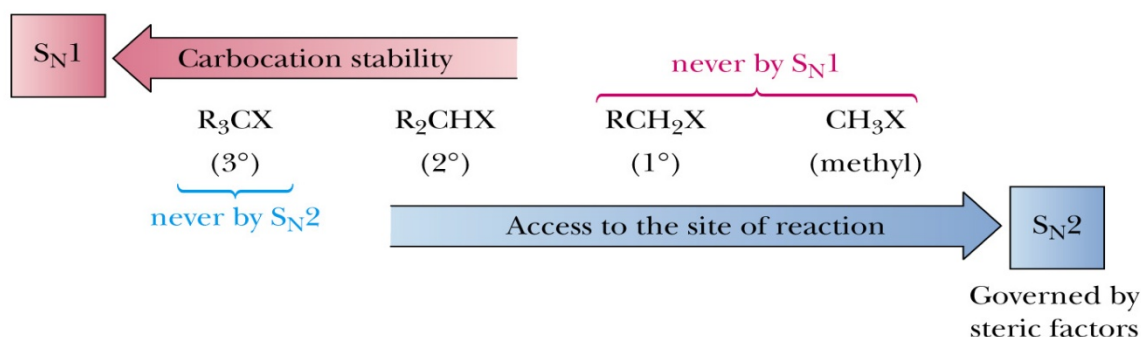
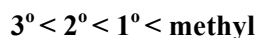
Effect of the substrate structure in S_N1

S_N1 reaction proceeds through the formation of carbocation. More stable the formed carbocation, higher is the rate of reaction. For example, any compound that gives tertiary carbocation as intermediate has highest reactivity towards S_N1. Since primary or methyl carbocation do not form, primary substituted compounds do not react by S_N1. The order of reactivity of alkyl halides towards S_N1 is mentioned below:



Effect of the structure of substrate in S_N2

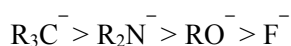
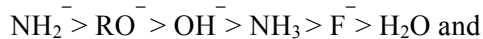
In S_N2 the rate of reaction depends on how easily the nucleophile gets access to the reacting carbon center for back side attack. We have discussed this in the previous section.



The nature of the nucleophile

Since the nucleophile does not participate in the rate determining step in S_N1 reaction, the rates of S_N1 reaction is unaffected by the nature of the nucleophile. For S_N2 reaction in solution there are some principles that govern the effect of nucleophile on the rate.

1. A nucleophile with a negative charge is always more powerful than its conjugate acid. Thus OH[−] is more powerful than H₂O, NH₂[−] is more powerful than NH₃, CH₃O[−] is more powerful than CH₃OH, etc.
2. In comparing nucleophiles whose attacking atom is in the same row of the periodic table, nucleophilicity is approximately in order of basicity as following:

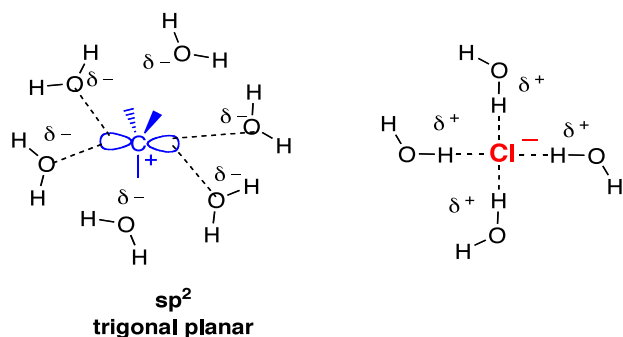


3. Going down the periodic table, nucleophilicity increases, though basicity decreases. Thus the usual order of halide nucleophilicity is: $I^- > Br^- > Cl^- > F^-$

The nature of the solvent

Solvent for S_N1 reaction

In an S_N1 reaction the C-X bond dissociates heterolytically giving rise to positive (carbocation) and negative charged species. Polar protic solvents (having OH group) having higher dielectric constant are good solvent for S_N1 reaction because they favor ionization, solvate the ions and stabilize them. For example: *tert*-butyl chloride in aqueous sodium hydroxide ionizes and the carbocation and chloride anion are stabilized by the solvation as following. **Thus polar protic solvents like water favors S_N1 .**

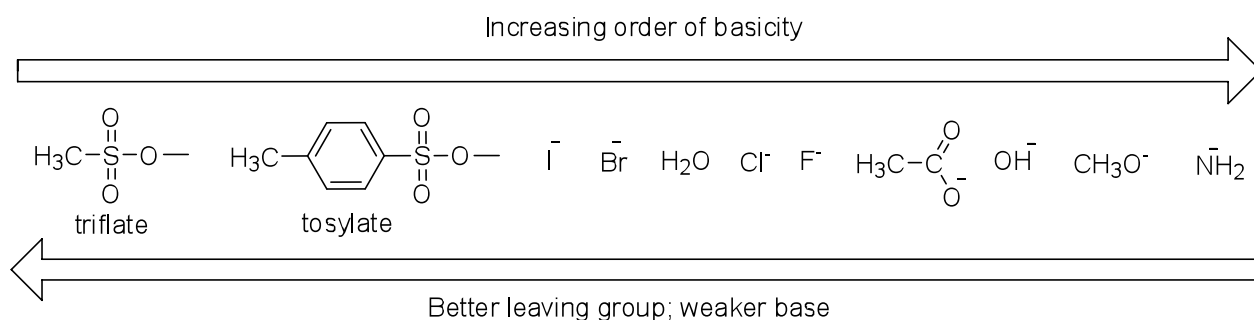


Effect of solvent in S_N2

Polar aprotic solvent (without OH) favors S_N2 . Examples of polar aprotic solvents are acetone, dimethylsulfoxide, N,N' -dimethylformamide, etc. In S_N2 reaction: freer the nucleophile, faster is the reaction. The stronger the solvation of the nucleophile, the greater the energy required to remove the nucleophile from its solvation cage to reach the transition state, and hence lower is the rate of the S_N2 reaction. For example when NaOH is added to aprotic solvent like acetone or dimethyl sulfoxide, sodium is solvated by the solvent whereas OH^- is not. Thus the nucleophile is free and can easily attack the positively charged carbon for S_N2 . In polar protic solvent both the sodium and hydroxide ions are strongly solvated and more energy is needed to free the nucleophile from the solvent cage to carry out S_N2 .

The nature of the leaving group

The ability of leaving group is related to how stable it is as an anion. The most stable anions and the best leaving group are the conjugate bases of strong acid i.e., are weaker bases. Conversely, poor leaving groups form ions of poor to moderate stability. Strong bases, such as OH^- , NH_2^- , and RO^- , make poor leaving groups. Water, which is less basic than a hydroxide ion, is a better leaving group. Some good leaving groups are the sulfate ion and the *p*-toluenesulfonate (tosylate ion). The following list ranks atoms and molecules in order of their stability as leaving groups, from most to least stable.

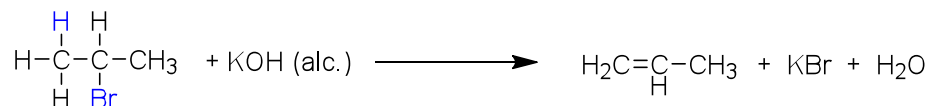


Comparison of S_N1 and S_N2

Points	S_N1	S_N2
1. Steps	Two steps	One step
2. Molecularity	Unimolecular, only substrate is involved in rate determining step (rds)	Bimolecular, both substrate and nucleophile are involved in rds
3. Kinetics and rate	First order	Second order
4. Stereochemistry	Racemisation or partial racemization favoring product with inverted configuration	Complete inversion
5. Effect of substrate structure on rate	Stability of carbocation: Tertiary > secondary > primary > methyl	Steric hinderance decreases the rate of reaction: Methyl > primary > secondary > tertiary
6. Effect of solvents on rate	polar protic solvents like water favors S_N1 .	Polar aprotic solvent (without OH) favors S_N2
7. Nucleophilicity and concentration of nucleophiles	Weak nucleophiles of low concentration too can make the reaction to occur	Strong nucleophiles of high concentration increases the rate
8. Leaving group effect	Weakly basic and highly polarizable group increase the rate	Weakly basic and highly polarizable group increases the rate.
9. Reaction intermediate	carbocation	None
10. Competition Reaction	E1 (Elimination Unimolecular) and rearrangement	E2 (Elimination Bimolecular)

Elimination Reaction

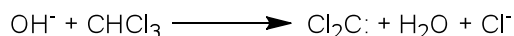
In an elimination reaction, two atoms or groups are generally eliminated from the adjacent carbons resulting in the formation of unsaturated compound. If β -hydrogen is eliminated as proton, the elimination reaction is called β elimination, a characteristic elimination reaction. In elimination reactions two sigma bonds are broken and one pi bond is formed. Elimination reactions are broadly classified under two different types: E1 (elimination unimolecular) and E2 (elimination bimolecular).



On the basis of the relative positions of the two eliminating groups or atoms, the elimination reactions may be classified as (a) 1,1- or α -elimination reaction and (b) 1,2- or β -elimination reaction.

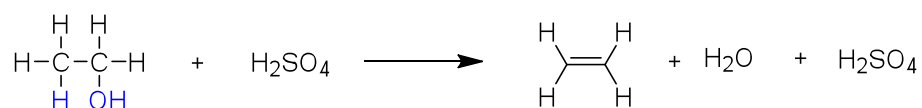
1,1- or α -elimination reaction

When the two atoms or groups are lost from one and the same atom of the substrate in an elimination reaction, the reaction is said to be 1,1- or α -elimination reaction. α -elimination reaction usually gives rise to a carbene, a reactive intermediate. For example, dichlorocarbene is obtained when chloroform is heated with alcoholic KOH solution.



1,2 – or β -elimination

When two atoms or groups are lost from the two adjacent atoms in an elimination reaction, it is said to be 1,2- or β -elimination reaction.



Elimination reactions are broadly classified into two types: E1 and E2

E1 (Elimination Unimolecular reaction)

In E1 reaction the rate of reaction only depends on the concentration of the substrate

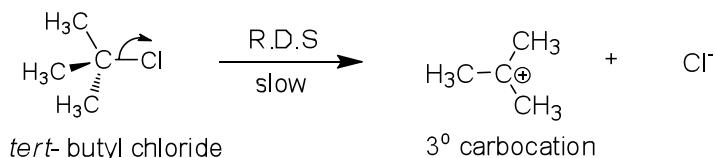
$$\text{Rate} = k [\text{substrate}]$$

For example, reaction of tert-butyl chloride with alcoholic KOH to give 2-methylprop-1-ene is an example of E1 reaction

E1 reaction takes place in two discrete steps via a carbocation intermediate formation

Step I: This involves the formation of carbocation

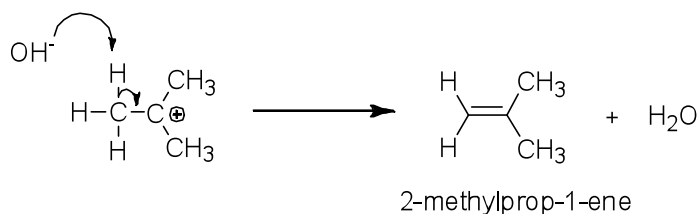
Ionisation of C-Cl bond



This is the slow step and hence the rate determining step.

Step II: This involves the loss of a proton from the carbon atom adjacent to the carbon bearing the positive charge. This is a fast step

Abstraction of beta-hydrogen by base

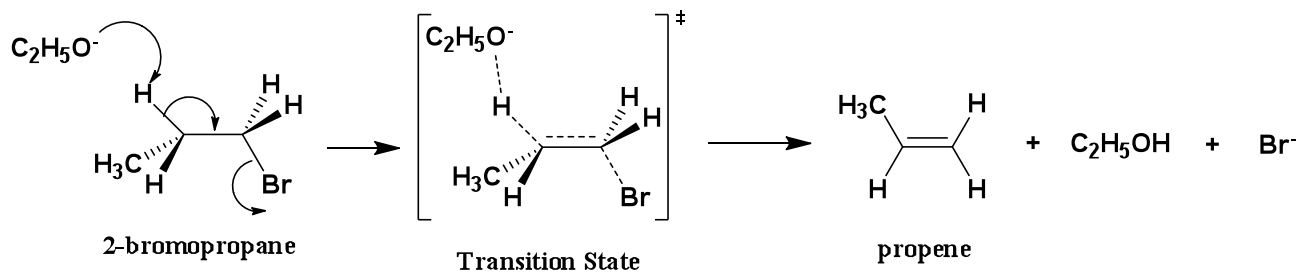


E2 reaction

The rate of E2 reaction depends on the concentration of both substrate and base.

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

For example: a reaction between 2-bromopropane with sodium ethoxide as a base in ethanol to give propene following E2 mechanism. E2 reaction takes place in a single concerted step in which two σ bonds break and a π bond forms simultaneously with the simultaneous departure of two groups, one of which is usually a proton. The abstraction of proton by base and departure of the leaving group takes place in a single step as shown below.

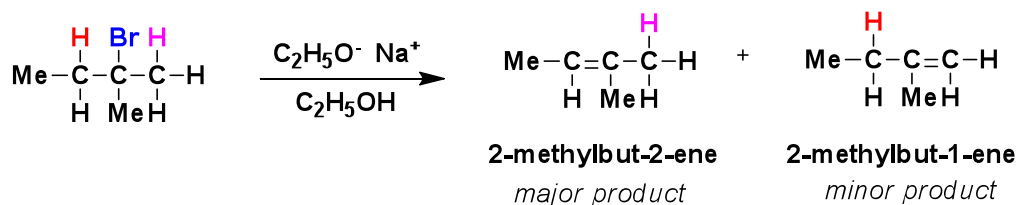


Hydrogen and the leaving group must be in anti-periplanar position for E2

The position of leaving group and departing proton should be anti-periplanar with respect to each other for E2 reaction.

Saytzeff's rule (pronounced Zaitsev's):

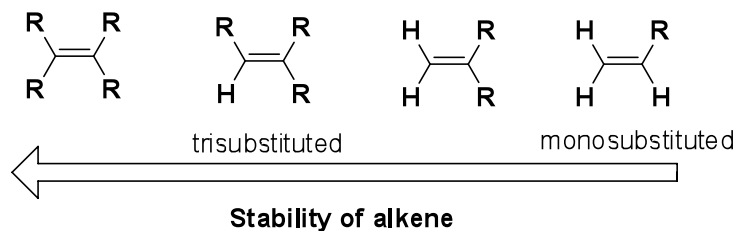
If the dehydrohalogenation (removal of proton and halogen) of alkyl halide can yield more than one alkene, then according to Saytzeff rule, the main product is the most highly substituted alkene. For example, two alkenes are possible when 2-bromo-2-methylbutane is heated with alcoholic sodium ethoxide (base).



According to Saytzeff rule, the main product is the trisubstituted alkene, 2-methylbut-2ene, rather than the disubstituted, 2-methylbut-1-ene.

tetrasubstituted

disubstituted



Higher substituted alkenes are more stable and formed in predominant amount.