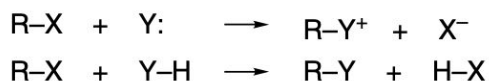


## Nucleophilic Substitution Reaction

Nucleophilic substitution is a fundamental class of reactions in which a leaving group is replaced by an electron-rich compound, called the nucleophile. The nucleophile essentially attempts to replace the leaving group as the primary substituent in the reaction itself.

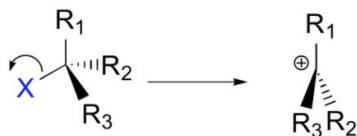


Nucleophilic substitutions on aliphatic carbon centres can proceed by two different mechanisms, unimolecular nucleophilic substitution ( $\text{S}_{\text{N}}1$ ) and bimolecular nucleophilic substitution ( $\text{S}_{\text{N}}2$ ).

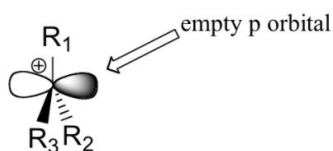
### Unimolecular Nucleophilic Substitution ( $\text{S}_{\text{N}}1$ )

#### 1. Mechanism

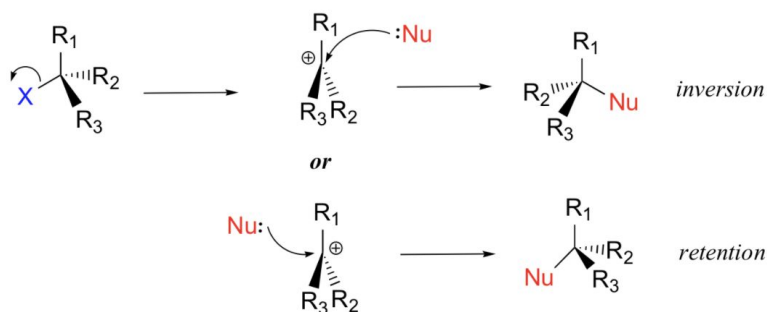
Its a two-step reaction. The C-X bond breaks first before the nucleophile approaches.



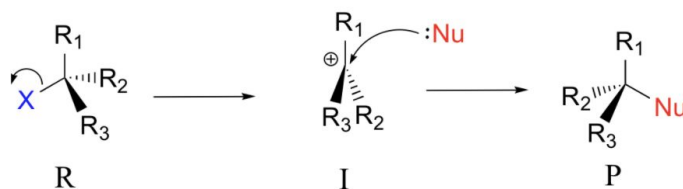
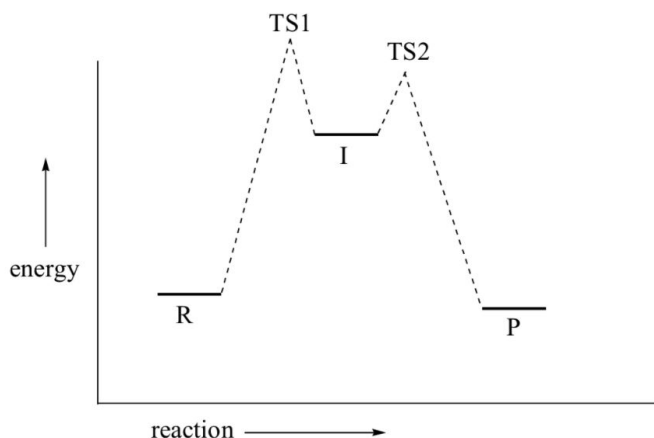
This results in a carbocation formation: because the central carbon has only three bonds, it bears a formal charge of +1. The carbocation should be pictured as  $\text{sp}^2$  hybridised, with trigonal planar geometry. Perpendicular to the plane formed by the three  $\text{sp}^2$  hybrid orbitals is an empty, unhybridised p orbital.



In the second step of this two-step reaction, the nucleophile attacks the empty, 'electron hungry' p orbital of the carbocation to form a new bond and return the carbon to tetrahedral geometry.



## 2. Potential Energy Curve for S<sub>N</sub>1



## 3. Relative reactivity of different alkyl halides towards S<sub>N</sub>1 mechanism

Since S<sub>N</sub>1 reactions involve the formation of carbocation as intermediate in the rate-determining step; more is the stability of carbocation higher will be reactivity of alkyl halides towards SN1 route.

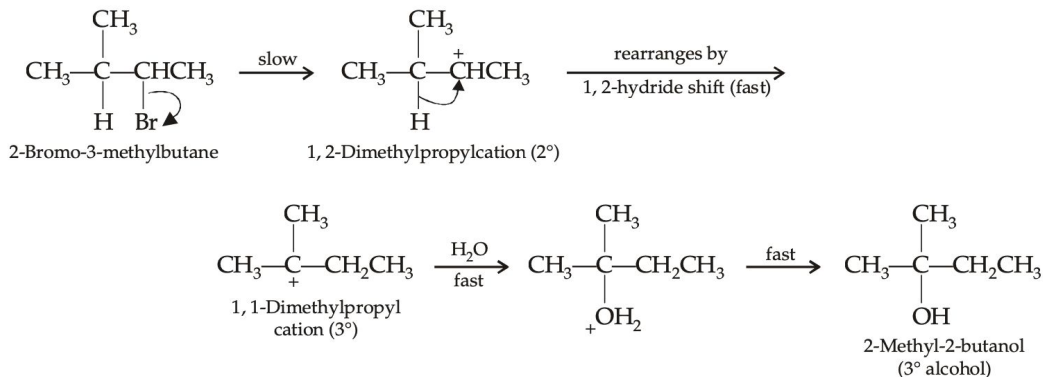
Since the stability of carbocations follows the order : 3° > 2° > 1° > Methyl, so S<sub>N</sub>1 reactivity should also follow the same order.

Alkyl bromide	Class	Relative rate
CH <sub>3</sub> Br	Unsubstituted	1
CH <sub>3</sub> CH <sub>2</sub> Br	Primary	2
(CH <sub>3</sub> ) <sub>2</sub> CHBr	Secondary	43
(CH <sub>3</sub> ) <sub>3</sub> CBr	Tertiary	100,000,000

Steric crowding plays no role in S<sub>N</sub>1 reactions.

The electronic effect, specifically the stabilisation of carbocation intermediate by alkyl substituents, is the decisive factor for S<sub>N</sub>1 reactions.

For example, hydrolysis of 2-bromo-3-methylbutane (a secondary alkyl halide) yields 2-methyl- 2-butanol (tertiary alcohol) as the exclusive product of hydrolysis.

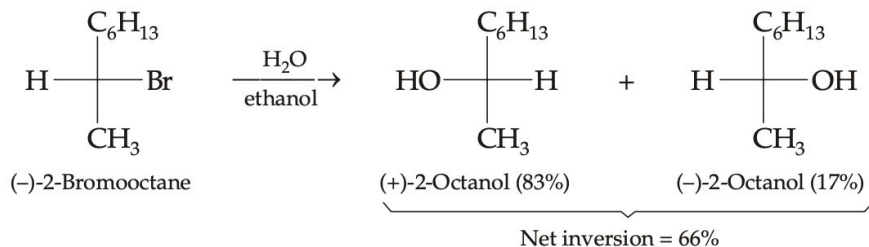


#### 4. Stereochemistry of S<sub>N</sub>1 reactions

Reactions proceed both with inversion as well as retention of configuration.

The number of inverted molecules is always more than the molecules having an original configuration.

For example, hydrolysis of optically pure (–)-2-bromooctane gives 83% (+)- and 17% (–)-2-octanols, i.e. reaction proceeds with 66% net inversion.



#### 5. Effect of Leaving Group

The better the leaving group, the faster will be the reaction.

The weaker the base, the better the leaving group.

Since the leaving group breaks away as a base, it is easier to displace weaker bases than stronger bases. Thus, we can say that the less basic the substituent, the more easily it is displaced by the solvent in S<sub>N</sub>1 reactions.

Relative Leaving-Group Abilities

Leaving group	Relative rate	Conjugate acid* of leaving group	K <sub>a</sub> of conjugate acid
F <sup>–</sup>	10 <sup>–5</sup>	HF	3.5 × 10 <sup>–4</sup>
Cl <sup>–</sup>	10 <sup>10</sup>	HCl	10 <sup>7</sup>
Br <sup>–</sup>	10 <sup>1</sup>	HBr	10 <sup>9</sup>
I <sup>–</sup>	10 <sup>2</sup>	HI	10 <sup>10</sup>
H <sub>2</sub> O	10 <sup>1</sup>	H <sub>3</sub> O <sup>+</sup>	55
TsO <sup>–</sup>	10 <sup>5</sup>	TsOH	6 × 10 <sup>2</sup>
CF <sub>3</sub> SO <sub>2</sub> O <sup>–</sup>	10 <sup>8</sup>	CF <sub>3</sub> SO <sub>2</sub> OH	10 <sup>6</sup>

#### 6. Effect of Concentration of Nucleophile

It does not play any direct role in S<sub>N</sub>1 reactions.

## 7. Effect of solvent

Change in the solvent in a particular reaction may increase or decrease the rate of reaction, even in some cases, it may change the mechanism.

In the presence of good ionizing solvents which increases the ionisation rate of the alkyl halide, the rate of  $S_N1$  reaction increases.

Dielectric constants and ionization rates of *t*-butyl chloride in common solvents.

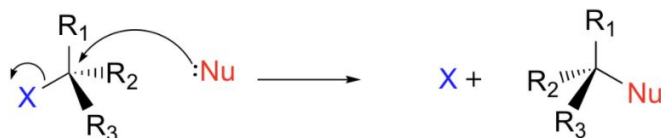
Solvent	Dielectric constant	Relative rate of ionization
Water	78	8000
Methanol	33	1000
Ethanol	24	200
Acetone	21	1
Diethyl ether	4.3	0.001
Hexane	2.0	<0.0001

## Bimolecular Nucleophilic Substitution ( $S_N2$ )

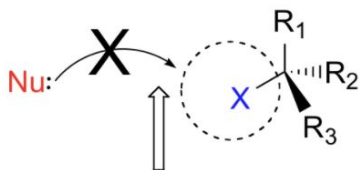
### 1. Mechanism

The reaction takes place in a single step, and bond-forming and bond-breaking occur simultaneously.

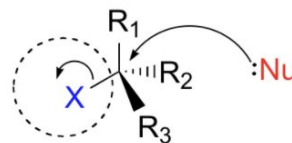
The overall rate depends on a step in which two separate molecules (the nucleophile and the electrophile) collide



The nucleophile, being an electron-rich species, must attack the electrophilic carbon from the backside relative to the location of the leaving group. Approach from the front side simply doesn't work: the leaving group - which is also an electron-rich group - blocks the way.



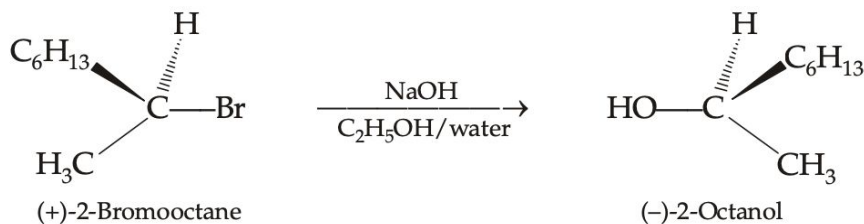
nucleophilic attack is blocked from the front side . . .



. . .so attack occurs from the back side

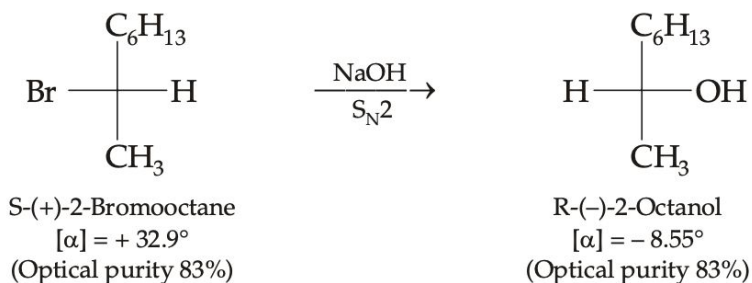
### 2. Stereochemistry of $S_N2$ reactions

This can best be demonstrated by taking alkyl halide having chiral carbon, e.g. 2-bromooctane. When (+)-2-bromooctane is allowed to react with NaOH under  $S_N2$  conditions, (–)-2-octanol is obtained.

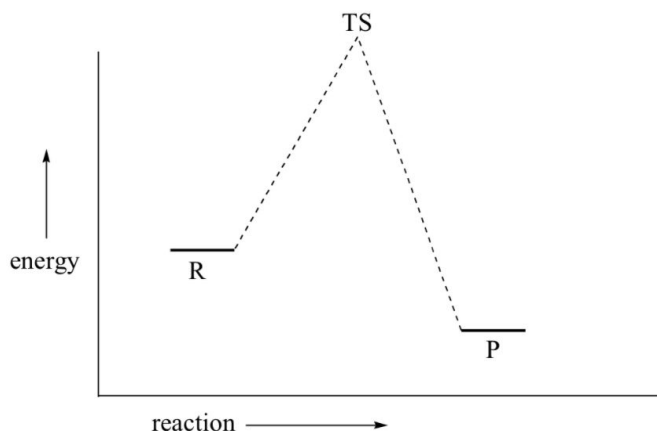


It can be concluded that an  $\text{S}_{\text{N}}2$  reaction proceeds with inversion of configuration usually referred to as **Walden inversion**.

An  $\text{S}_{\text{N}}2$  reaction proceeds with complete inversion of configuration. This can be proved by the fact that a sample of 83% optically pure (+)-2-bromooctane gives 83% optically pure (-)-2-octanol on  $\text{S}_{\text{N}}2$  reaction.



### 3. Potential Energy Curve for $\text{S}_{\text{N}}2$



### 4. Steric Effects in $\text{S}_{\text{N}}2$ Reactions

Large difference in rate can be because of the degree of steric hindrance offered by an increasing number of alkyl groups on the carbon bearing the leaving group, to the nucleophile.

### 5. Effect of Leaving Group

The better the leaving group, the faster will be the reaction.

Since the leaving group breaks away as a base, it is easier to displace weaker bases than stronger bases. Thus, we can say that the less basic the substituent, the more easily it is displaced by an attacking nucleophile in S<sub>N</sub>2 reactions.

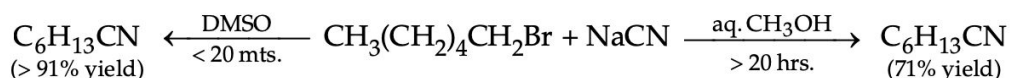
Leaving group	Relative rate	Conjugate acid* of leaving group	K <sub>a</sub> of conjugate acid
F <sup>-</sup>	10 <sup>-5</sup>	HF	3.5 × 10 <sup>-4</sup>
Cl <sup>-</sup>	10 <sup>10</sup>	HCl	10 <sup>7</sup>
Br <sup>-</sup>	10 <sup>1</sup>	HBr	10 <sup>9</sup>
I <sup>-</sup>	10 <sup>2</sup>	HI	10 <sup>10</sup>
H <sub>2</sub> O	10 <sup>1</sup>	H <sub>3</sub> O <sup>+</sup>	55
TsO <sup>-</sup>	10 <sup>5</sup>	TsOH	6 × 10 <sup>2</sup>
CF <sub>3</sub> SO <sub>2</sub> O <sup>-</sup>	10 <sup>8</sup>	CF <sub>3</sub> SO <sub>2</sub> OH	10 <sup>6</sup>

In  $S_N2$  reactions, a nucleophile transfers its electron pair to the carbon of the substrate leading to the formation of the transition state. Hence, a stronger nucleophile will react with the substrate faster.

### Nucleophilicity of some common nucleophiles in water and alcohol

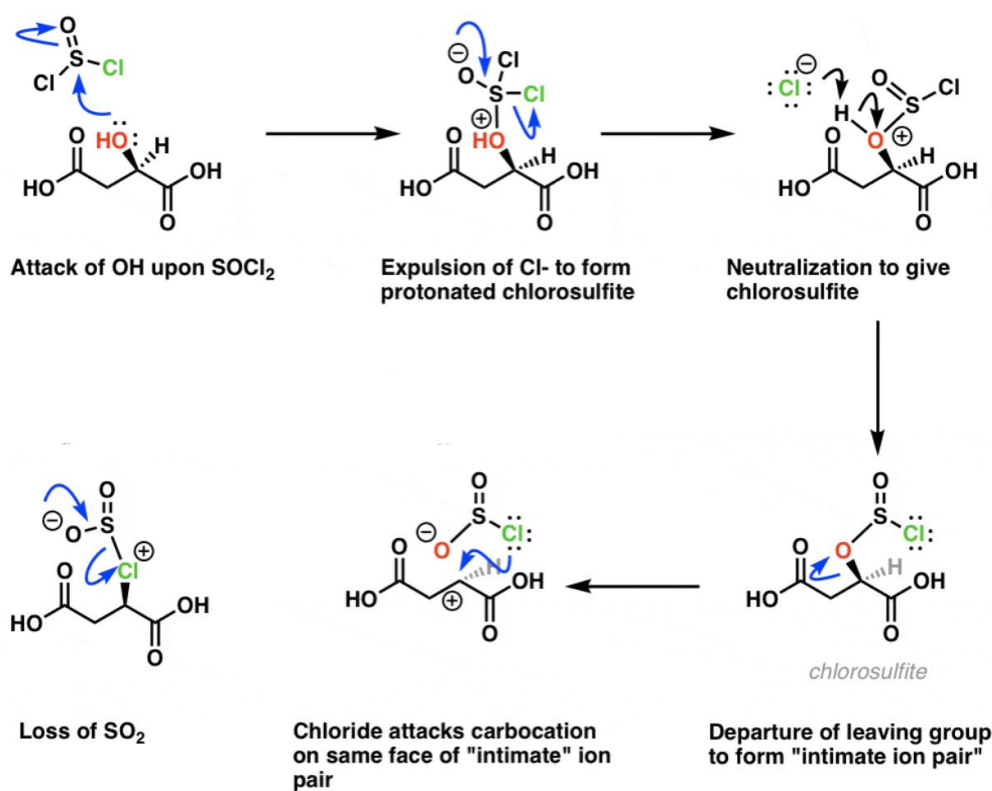
<i>Class of nucleophile</i>	<i>Nucleophile</i>	<i>Relative reactivity</i>
Very good	$\text{R}_3\text{P:}$ , $\text{I}^-$ , $\text{HS}^-$ , $\text{RS}^-$	$> 10^5$
Good	$\text{R}_2\text{NH}$ , $\text{HO}^-$ , $\text{RO}^-$ , $\text{CN}^-$ , $\text{N}_3^-$	$10^4$
Fair	$\text{Br}^-$ , $\text{NH}_3$ , $\text{Cl}^-$ , $\text{RCOO}^-$	$10^3$
Weak	$\text{F}^-$ , $\text{H}_2\text{O}$ , $\text{ROH}$	1
Very weak	$\text{RCOOH}$	$10^{-2}$

Change in the solvent in a particular reaction may increase or decrease the rate of reaction, even in some cases it may change the mechanism.



### Other mechanisms (S<sub>N</sub>i)

- $S_Ni$  or Substitution Nucleophilic internal stands for a specific but not often encountered nucleophilic aliphatic substitution reaction mechanism.
- A typical representative organic reaction displaying this mechanism is the chlorination of alcohols with thionyl chloride, or the decomposition of alkyl chloroformates, the main feature is the retention of stereochemical configuration
- $\text{SOCl}_2$  coordinates to the alcohol, with loss of  $\text{HCl}$  and formation of a good leaving group ("chlorosulfite"). The chlorosulfite leaving group can spontaneously depart, forming a carbocation, and when it does so, an "intimate ion pair" is formed, where the carbocation and negatively charged leaving group are held tightly together in space. From here, the chlorine can act as a nucleophile – attacking the carbocation on the same face from which it was expelled – and after the expulsion of  $\text{SO}_2$ , we have the formation of an alkyl chloride with retention of configuration.



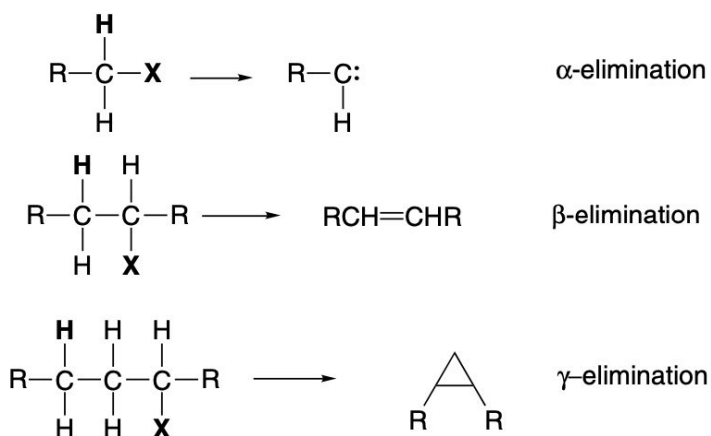
## Elimination Reaction

An elimination reaction is a type of organic reaction in which two substituents are removed from a molecule in either a one- or two-step mechanism.

The one-step mechanism is known as the E2 reaction, and the two-step mechanism is known as the E1 reaction.

E2 is bimolecular (second-order) while E1 is unimolecular (first-order).

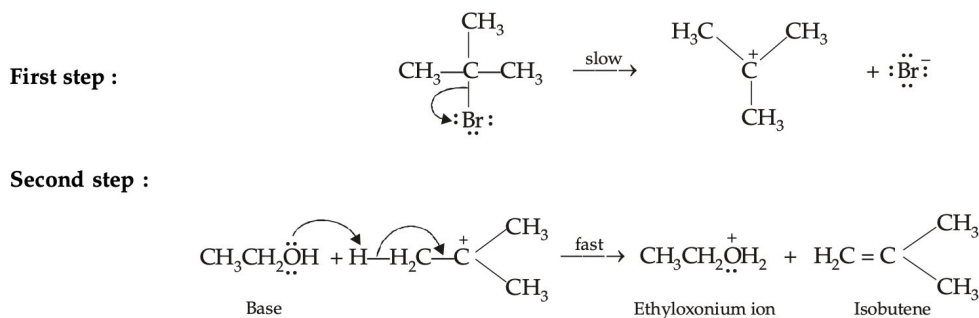
Eliminations of  $\gamma$ - and higher leaving groups result in cyclization.



## Unimolecular Elimination (E1)

### 1. Mechanism

E1 reaction proceeds by first-order kinetics. The mechanism is similar to that of  $\text{S}_{\text{N}}1$  reactions except that here the carbocation loses a proton to form an alkene.



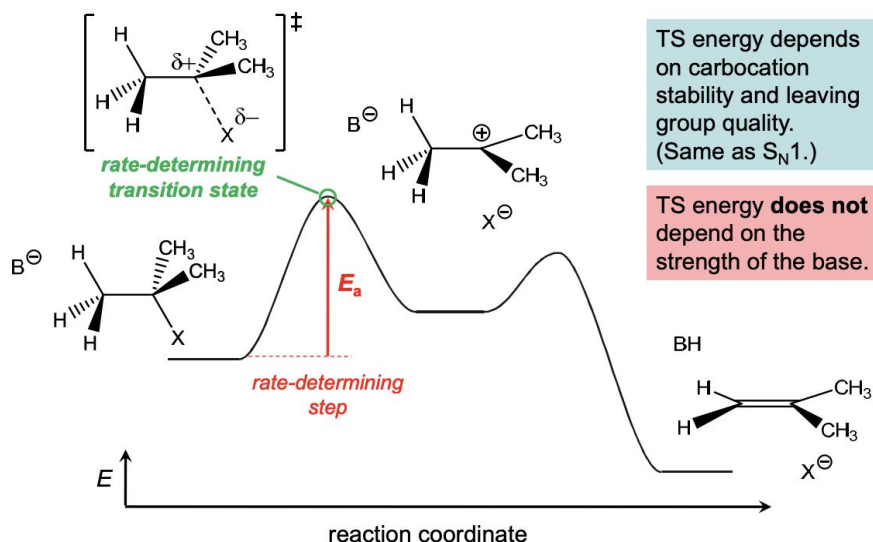
### 2. Stereochemistry of E1 reactions

Since the carbocation is planar, the electrons from the departing hydrogen can move towards the positively charged carbon from either side and thus both syn, as well as anti-elimination, can occur.

However, E-isomer having bulkier groups on the opposite sides will be major product because of its higher stability than the Z-isomer.



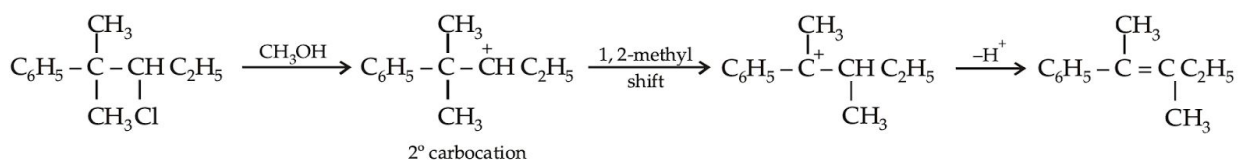
### 3. Potential Energy Curve for E1



### 4. Relative reactivity of different alkyl halides towards E1 mechanism

Since here carbocations are formed as intermediates, the relative order of reactivity of alkyl halides towards E1 should be  $3^\circ > 2^\circ > 1^\circ$ .

The formation of carbocation may result in a rearranged product, in the case when less stable carbocation may change to the more stable by 1, 2-shift.



### 5. Effect of Leaving Group

Since in the rate-determining step of E1 reaction, the leaving group is removed, and a carbocation is formed as an intermediate, the rate of E1 reaction depends on both of these factors and follows the order.

$3^\circ$  benzylic  $>$   $3^\circ$  allylic  $>$   $2^\circ$  benzylic  $>$   $2^\circ$  allylic  $>$   $3^\circ >$   $1^\circ$  benzylic  $>$   $1^\circ$  allylic  $>$   $2^\circ >$   $1^\circ >$  vinyl

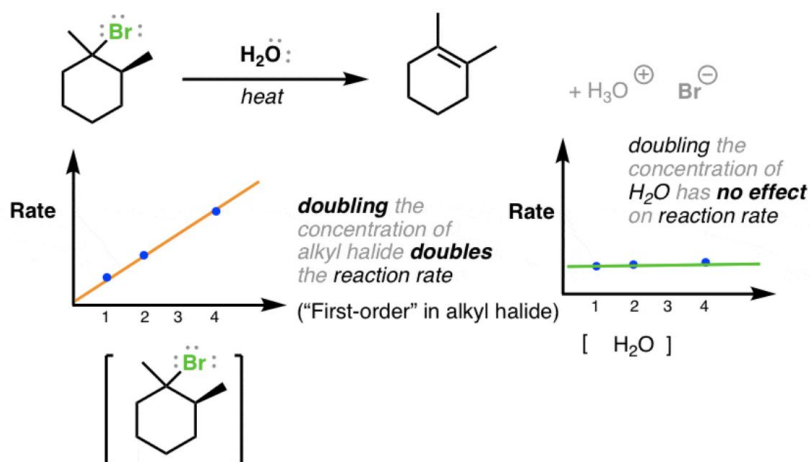
### 6. Effect of Neucleophile

A weak base facilitates the E1 reaction.

### 7. Effect of Concentration of Substrate and Water

When we vary the concentration of the substrate, the reaction rate increases accordingly. In other words, there is a "first-order" dependence of rate on the concentration of substrate.

The reaction rate depends **ONLY** on the concentration of substrate



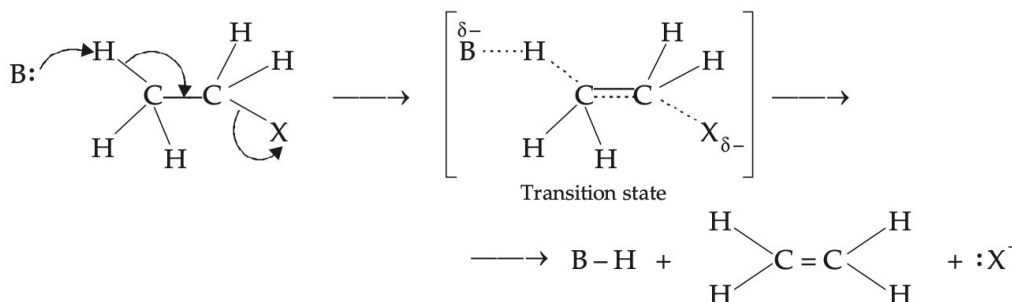
## 8. Effect of Solvent

Good ionizing solvents (polar protic) favour the E1 mechanism by stabilizing the carbocation intermediate.

## Bimolecular Elimination (E2)

### 1. Mechanism

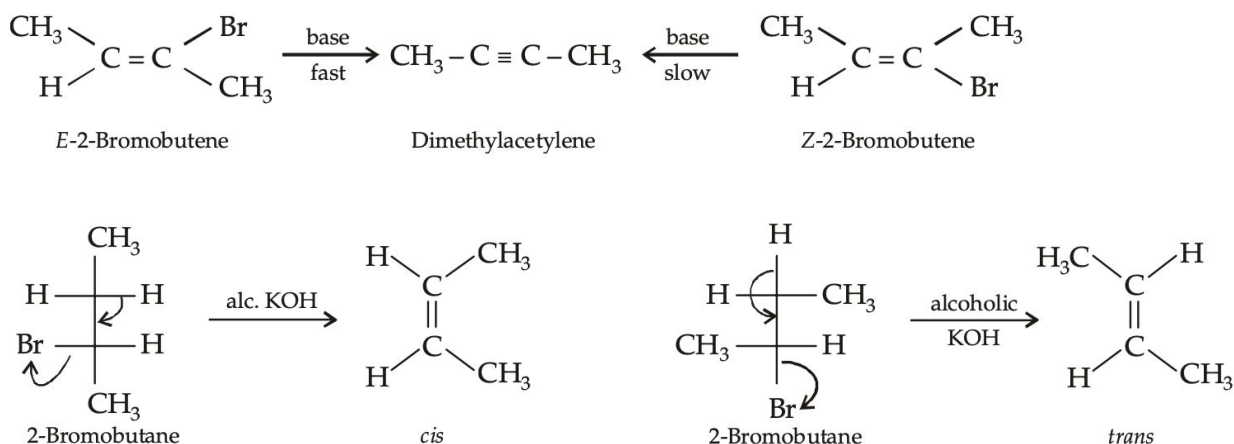
Base pulls a proton away from carbon and simultaneously a halide leaving group departs from the molecule forming the double bond.



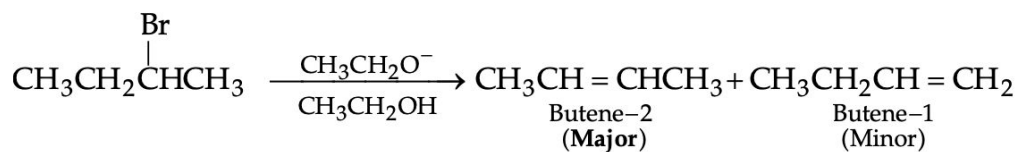
### 2. Stereochemistry of E2 reactions

The two groups or atoms are eliminated from anti positions because anti elimination requires the molecule to be in a staggered conformation (a more stable conformer), while syn elimination requires eclipsed conformation.

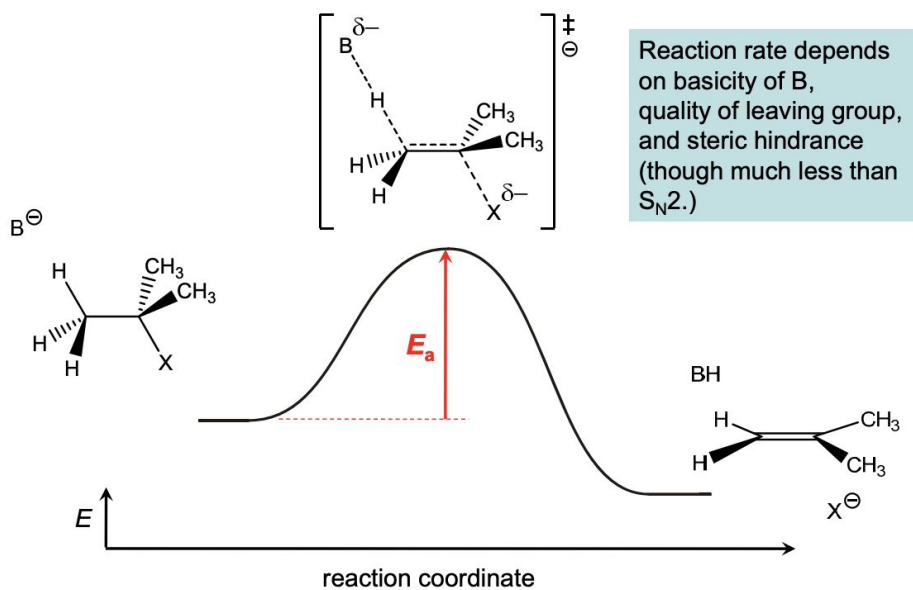
Following example indicates that E2 reaction is stereospecific, i.e. different stereoisomer of the starting material gives different stereoisomer of the product. This is also reflected from compounds having chiral carbon atoms; meso-isomer gives cis-isomer while d- or l-gives trans-isomer on E2 elimination.



Another interesting example of E2 reaction is dehydrohalogenation of alkyl halides leading to two products.



### 3. Potential Energy Curve for E1



### 4. Relative reactivity of different alkyl halides towards E2 mechanism

Among different halide leaving groups, the reactivity of alkyl halides increases with decreasing strength of the carbon-halogen bond.



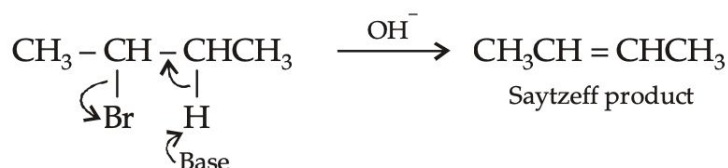
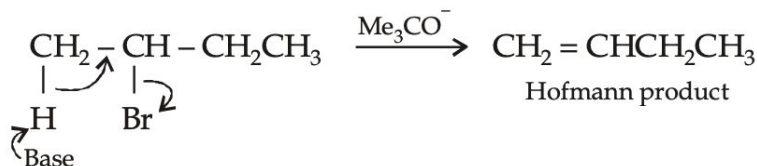
Dehydrohalogenation of alkyl halide yields more than one alkene, the alkene having a greater number of alkyl groups to the doubly bonded carbons will be preferred product. The more stable alkene is thus known as the **Saytzeff product**, while the less stable alkene is known as **Hoffmann product**.



Thus, the ease of formation and stability of various alkenes is  $\text{R}_2\text{C}=\text{CR}_2 > \text{R}_2\text{C}=\text{CHR} > \text{R}_2\text{C}=\text{CH}_2, \text{RCH}=\text{CHR} > \text{RCH}=\text{CH}_2$ .

Most E2 reactions give Saytzeff product, however, Hofmann product is preferred under one of the following conditions:

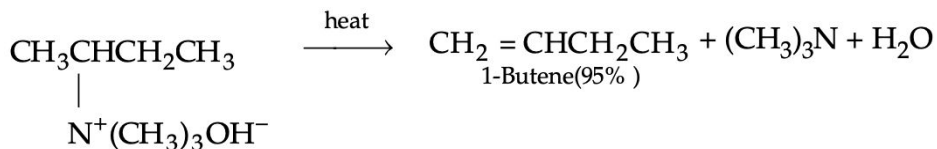
1.) The base used is large, e.g.  $\text{Me}_3\text{CO}^-$ .



2.) The alkyl halide is an alkyl fluoride.

3.) The alkyl halide contains one or more double bonds. Remember that a conjugated alkene is always preferred to a non-conjugated alkene.

4.) Eliminations involving charged substances, e.g. when a quaternary hydroxide is heated strongly (to 125°C or higher), it decomposes to form an alkene and a tertiary amine.



## 5. Effect of Leaving Group

Better leaving group leads to faster reactions. More discussed in point number 4.

## 6. Effect of Neucleophile

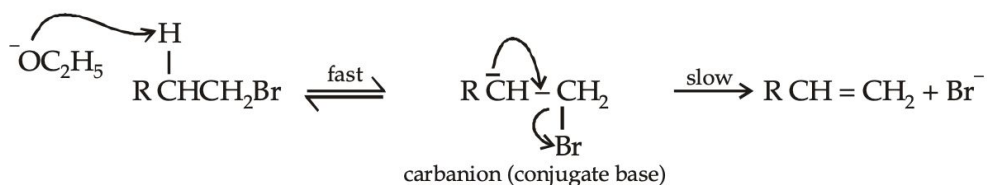
High concentration of a strong base is needed to facilitate the reaction.

## 7. Effect of Solvent

Solvent is not important for E1 reactions.

### Other Reactions (E1<sub>c</sub>B)

- In cases where the molecule is able to stabilize an anion but possesses a poor leaving group, the third type of reaction, E1<sub>c</sub>B, exists.
- This is a two-step reaction. The first step involves the rapid formation of carbanion by an alkyl halide under the influence of a base.
- The second step is slow and involves the loss of the leaving group (halide ion).



- Since the rate-determining step is dependent on the concentration of the conjugate base of the substrate (carbanions) and thus unimolecular, the reaction is known as E1<sub>c</sub>B (elimination, unimolecular from the conjugate base).
- Reactions proceeding by E1<sub>c</sub>B pathway are exceedingly rare.

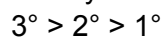
## Elimination vs Substitution

Since the most common substrate for 1, 2-elimination as well as for substitution is alkyl halides and alkyl sulphonates. Furthermore, the reagent required for the two reactions (bases and nucleophiles) is similar. Both reagents are electron-rich. Thus, there will always be a competition between substitution and elimination.

- **S<sub>N</sub>2 vs E2 Reaction**

While acting as a nucleophile, the reagent :Z attacks the substrate on carbon and causes substitution while acting as a base it attacks the substrate on hydrogen and brings about elimination.

The relative order of reactivity for the two kinds of reactions is:

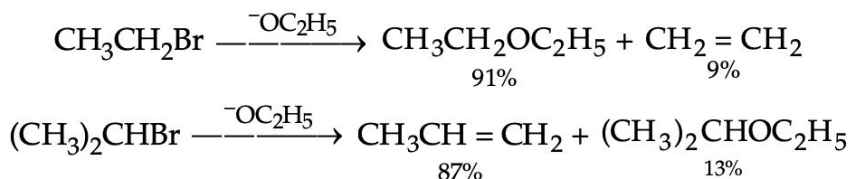
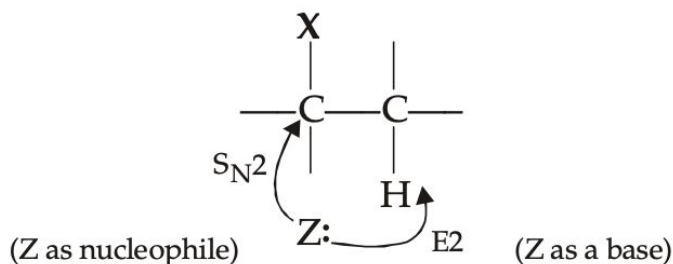


For E2 reactions

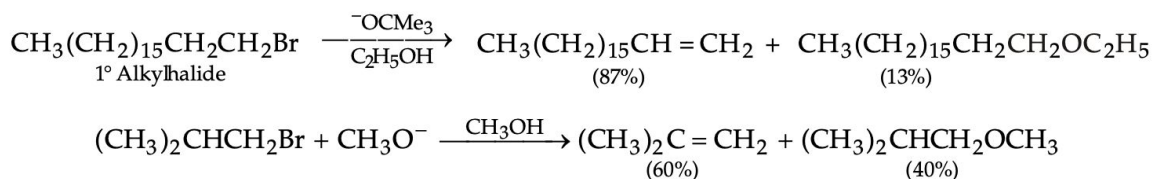


For S<sub>N</sub>2 reactions

It can be concluded that primary substrates undergo elimination slowest and substitution fastest, while tertiary substrates undergo elimination fastest and substitution slowest.

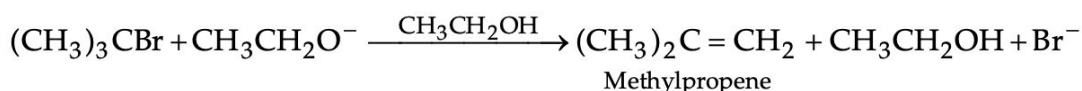


A bulky nucleophile or bulky alkyl halide (even primary) will favour E2 reactions, because of steric factor



Nucleophiles which are also strong bases like  $\text{OH}^-$  favour elimination while good nucleophiles, which are weak bases (e.g.  $\text{CN}^-$ , azide  $\text{N}_3^-$ ,  $\text{SH}^-$  etc.) favour substitution.

A tertiary alkyl halide is the least reactive toward  $S_N2$  reaction but most reactive toward E2 reaction, thus when a tert-alkyl halide is treated with a nucleophile under  $S_N2/E2$  conditions, only the elimination product is formed.



### • $S_N1$ vs $E1$ reaction

Both are involved in the formation of a carbocation in the rate-determining step. Hence the least stable carbocation ( $1^\circ$ ) will react immediately with the anion to form substitution product. On the other hand, the  $3^\circ$  cation, having sufficient stability will lose a proton to form the more stable (more branched) alkene.

For a particular alkyl halide substitution reactions are favoured by nucleophiles which are weak bases, viz.  $\text{H}_2\text{O}$ ,  $\text{C}_2\text{H}_5\text{OH}$ ,  $\text{CN}^-$ ,  $\text{N}_3^-$ ,  $\text{RS}^-$ ,  $\text{HS}^-$  etc., and using low temperature (room temperature); while elimination reactions are favoured by strong bases like  $\text{OH}^-$ ,  $\text{OC}_2\text{H}_5^-$  etc. and using high temperature.

## References

- **Books**

General Organic Chemistry for JEE Main & JEE Advanced by Dr O.P. Tandon  
Francis A. Carey, Richard J. Sundberg - Advanced Organic Chemistry Part A. Structure and Mechanisms

- **Websites**

[https://en.wikipedia.org/wiki/Nucleophilic\\_substitution](https://en.wikipedia.org/wiki/Nucleophilic_substitution)  
[https://en.wikipedia.org/wiki/Elimination\\_reaction](https://en.wikipedia.org/wiki/Elimination_reaction)  
<http://www.masterorganicchemistry.com/2014/02/10/socl2-and-the-sni-mechanism/>  
<https://home.iitk.ac.in/~madhavr/CHM102/Lec13.pdf>  
[http://www1.chem.umn.edu/groups/taton/chem2301/Handouts/7\\_10.pdf](http://www1.chem.umn.edu/groups/taton/chem2301/Handouts/7_10.pdf)  
<https://www.masterorganicchemistry.com/2012/09/19/the-e1-reaction/#:~:text=When%20we%20vary%20the%20concentration,doesn't%20change%20at%20all>  
[https://chem.libretexts.org/Bookshelves/General\\_Chemistry/Map%3AGeneral\\_Chemistry\\_\(Petrucchi\\_et\\_al.\)/27%3A\\_Reactions\\_of\\_Organic\\_Compounds/27.02%3A\\_Introduction\\_to\\_Substitution\\_Reactions](https://chem.libretexts.org/Bookshelves/General_Chemistry/Map%3AGeneral_Chemistry_(Petrucchi_et_al.)/27%3A_Reactions_of_Organic_Compounds/27.02%3A_Introduction_to_Substitution_Reactions)  
[https://chem.libretexts.org/Courses/Sacramento\\_City\\_College/SCC%3A\\_Chem\\_420\\_-\\_Organic\\_Chemistry\\_I/Text/07%3A\\_Alkyl\\_Halides%3A\\_Nucleophilic\\_Substitution\\_and\\_Elimination/7.18%3A\\_Comparison\\_of\\_E1\\_and\\_E2\\_Reactions#:~:text=1](https://chem.libretexts.org/Courses/Sacramento_City_College/SCC%3A_Chem_420_-_Organic_Chemistry_I/Text/07%3A_Alkyl_Halides%3A_Nucleophilic_Substitution_and_Elimination/7.18%3A_Comparison_of_E1_and_E2_Reactions#:~:text=1)