Welcome to

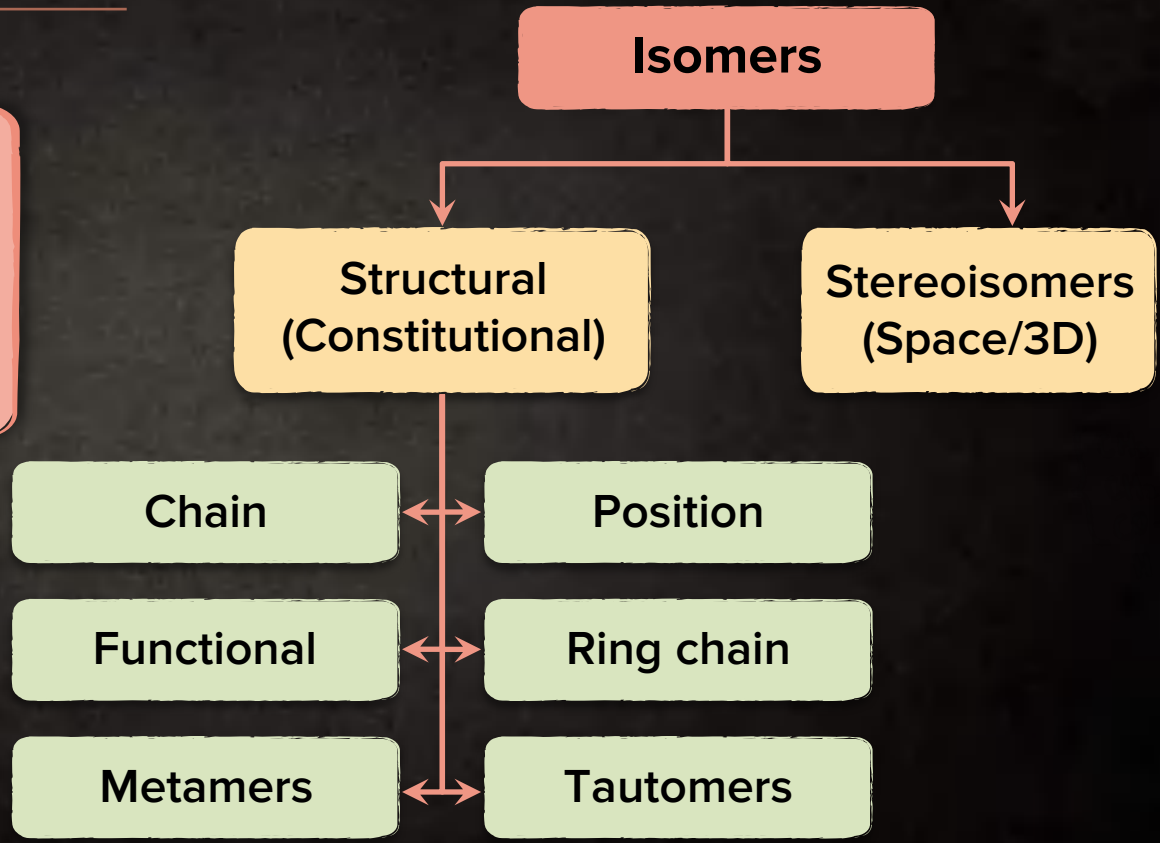
Aakash + BYJU'S LIVE

Reaction Mechanism and Stereoisomerism

Isomerism

The phenomenon of existence of two or more compounds possessing **the same molecular formula** but **different properties** is known as isomerism.

Such compounds are known as **isomers.**

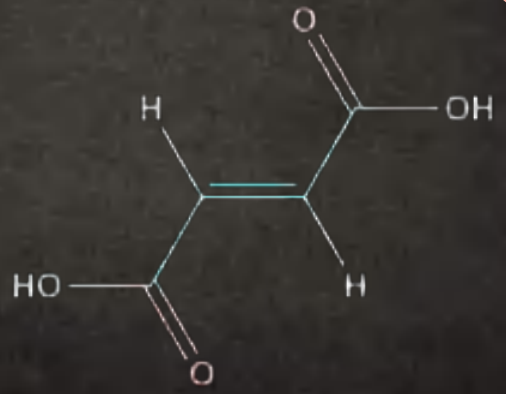


Stereoisomers

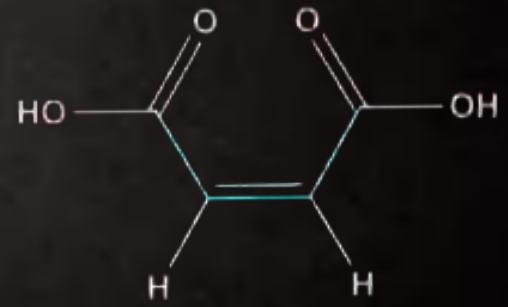
Stereoisomers have remarkably **different physical, chemical,** and **biological properties**.

Isomers that are different from each other only in the way the atoms are **oriented in space**.

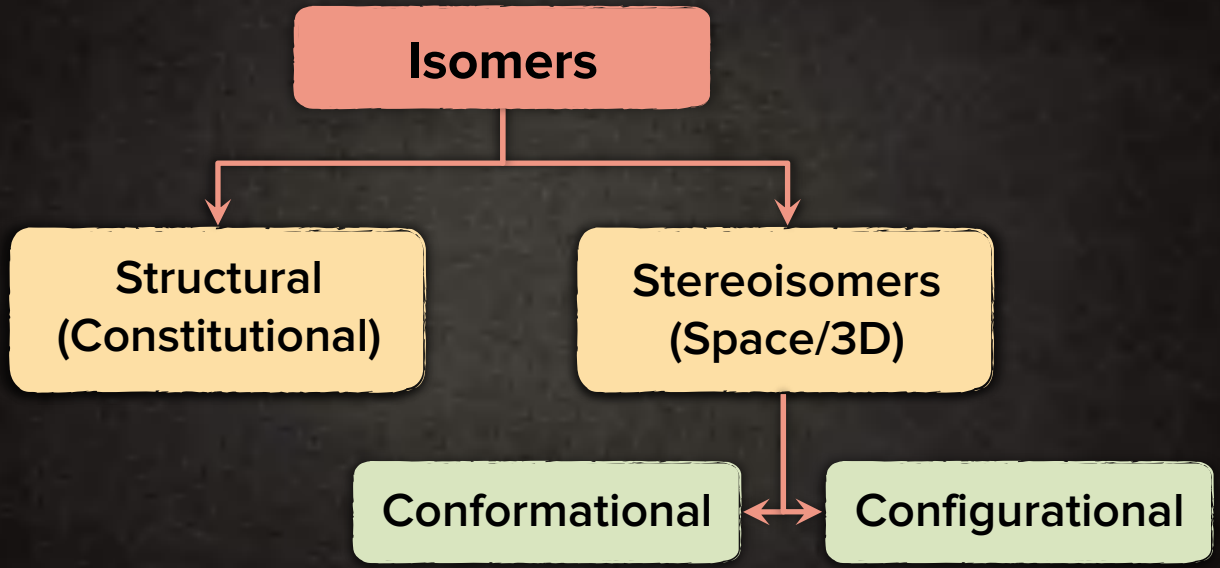
These isomers have **same connectivity** of atoms and groups.



Fumaric acid
M.P.: 287°C
Essential metabolite



Maleic acid
M.P.: 138°C
Toxic, irritant


Isomers
Structural (Constitutional)
Stereoisomers (Space/3D)
Conformational
Configurational

Conformational Isomers

There are **infinite arrangements (conformations)** which arise due to the free rotation around the C–C σ bond, out of which different conformations corresponding to **energy minima** are called **conformers.**

Configurational Isomers

Isomers which **differ in the configuration** i.e. the spatial arrangement of atoms that characterises a particular stereoisomer.

Arises due to **non-interconvertibility** at room temperature

Configurational Isomers

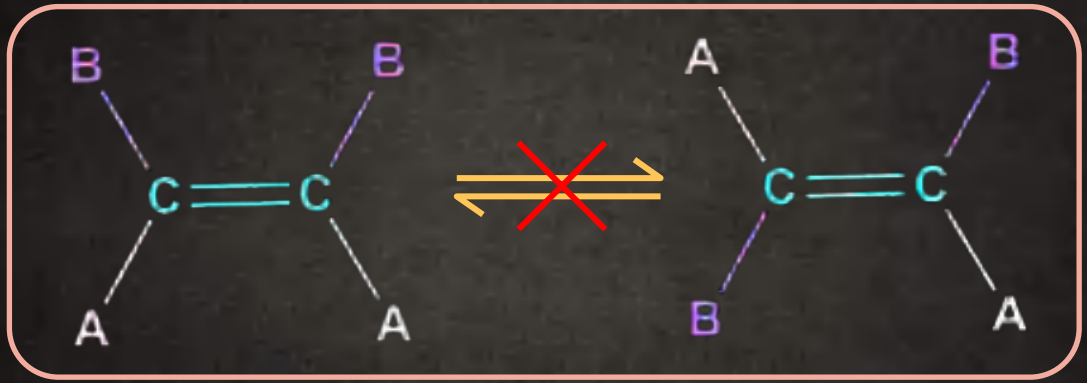
- Geometrical Isomers
- Optical Isomers

Geometrical Isomers

Isomers which possess the same molecular and structural formula but **differ in the arrangement** of atoms, or groups in space due to restricted rotation.

Restricted Rotation

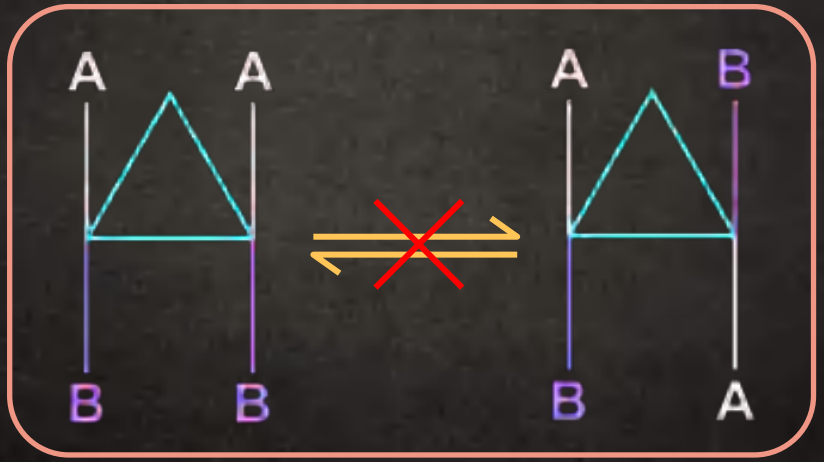
Restricted rotation by **double bond**



π bond prevents rotation
because the orbitals overlap both above and below the plane of atoms.

Restricted Rotation

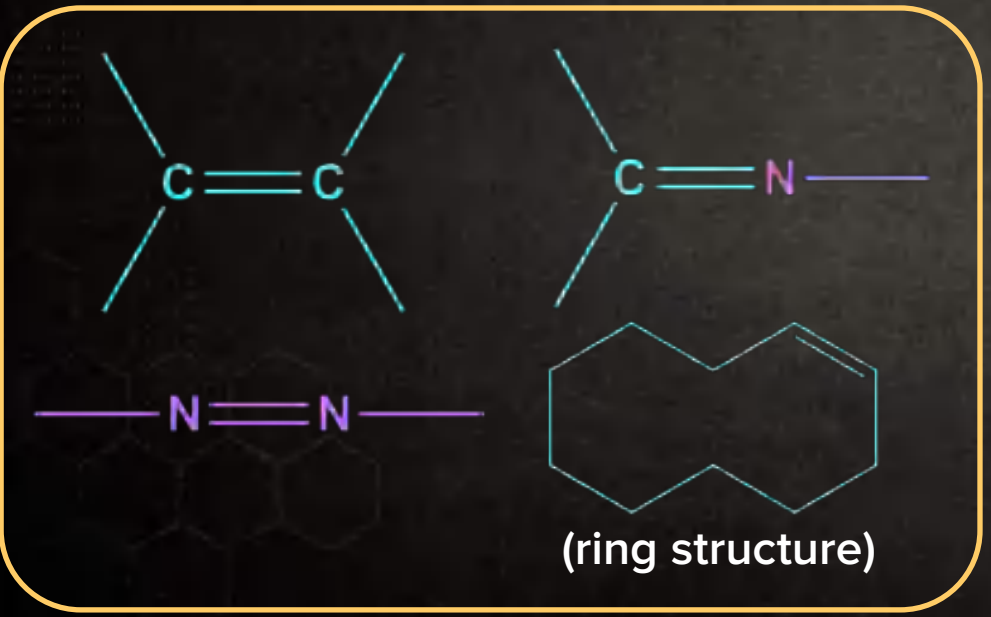
Restricted rotation along σ bond of cycloalkane

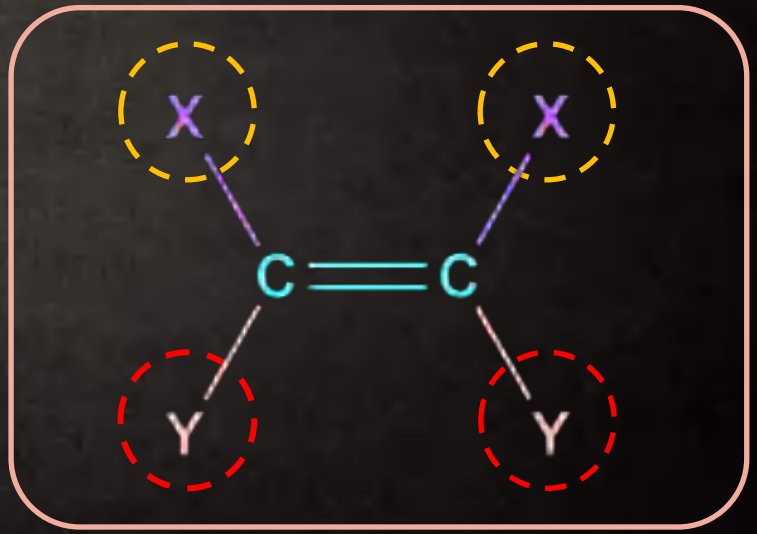


Conditions to Show G.I.

Restricted Rotation

Different groups should be attached to each atom of a restricted bond.





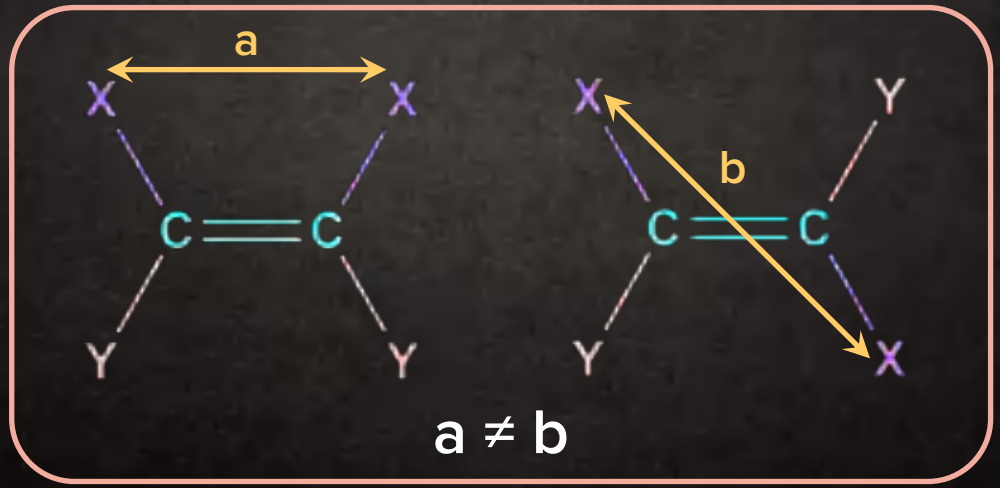
Note

1. Lone pair is also considered as a distinct group.

2. Isotopes are considered as different groups.

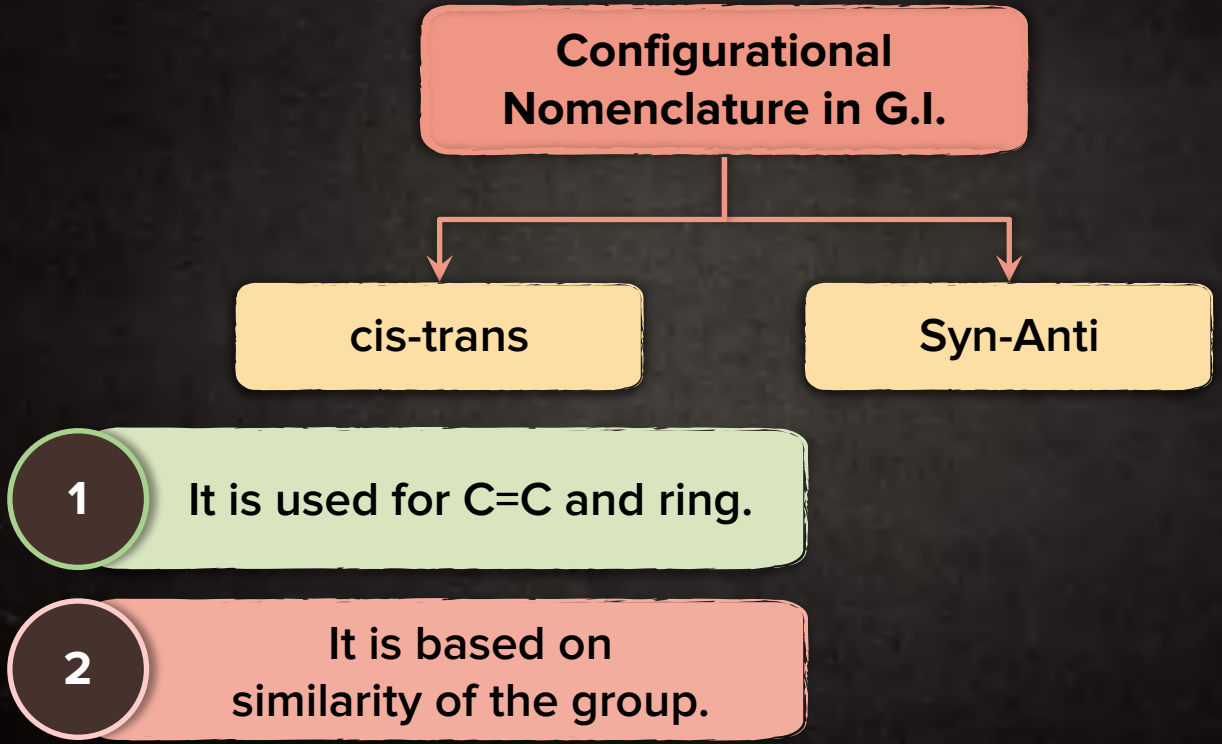
Conditions to Show G.I.

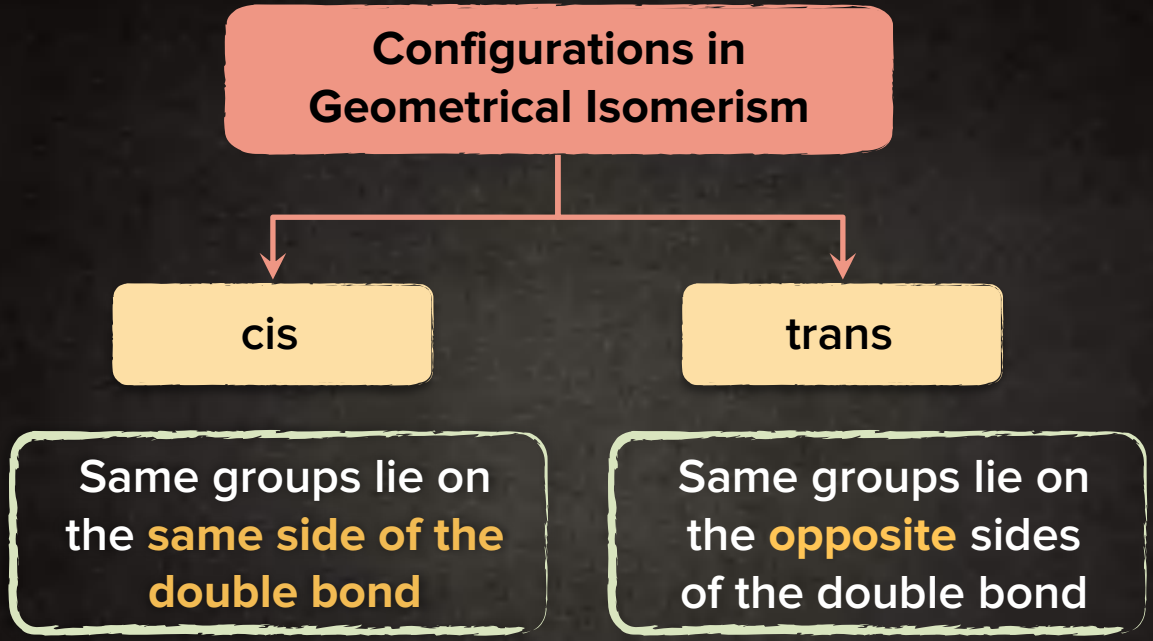
Distance between two particular group at different terminal of restricted rotation should be **different in G.I.**



$a \neq b$

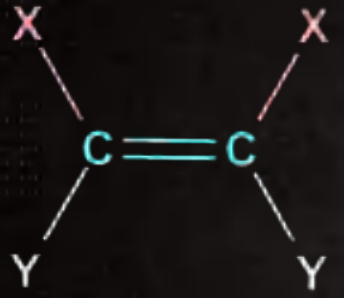
Configurational Nomenclature in G.I

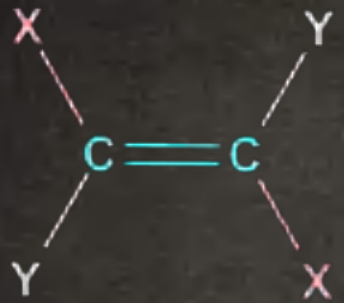



Configurations in Geometrical Isomerism
cis
trans
Same groups lie on the same side of the double bond
Same groups lie on the opposite sides of the double bond

cis-trans Configuration in Double Bond System

Examples





cis form

trans form

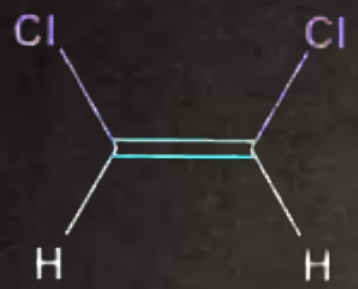
Same group- same side

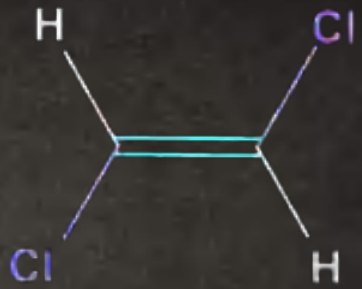
Same group- different side

cis form

trans form

cis-trans Configuration in Double Bond System





Same group-
Same side

Same group-
different side

cis form

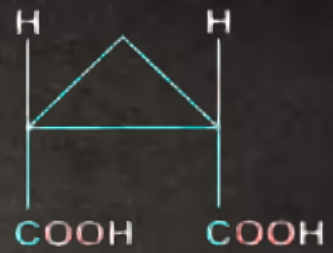
trans form

cis-trans Configuration in Cycloalkanes

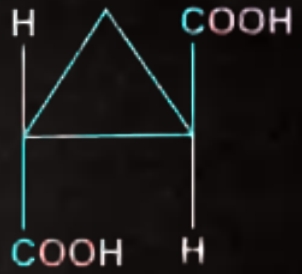
Examples

trans form

cis form



cis form



trans form

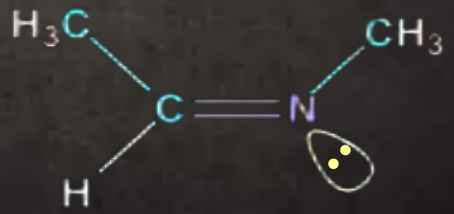
Syn-Anti Configuration

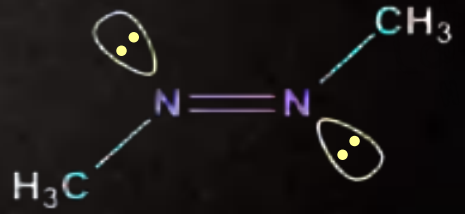
1. It is used for C = N, N = N

2. It is based on similarity of the group.

Syn → Same side

Anti → Opposite side

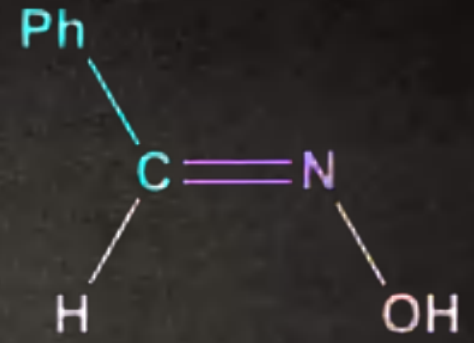




Syn-Anti Configuration

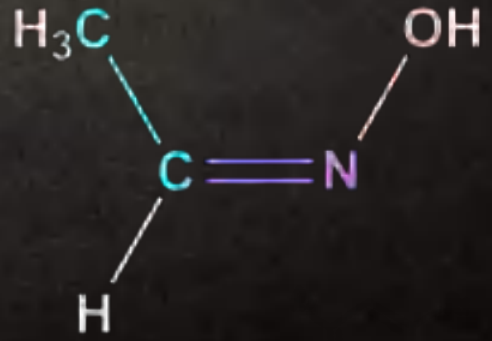
In case oximes,

Syn — If -H and -OH are on same side



Syn

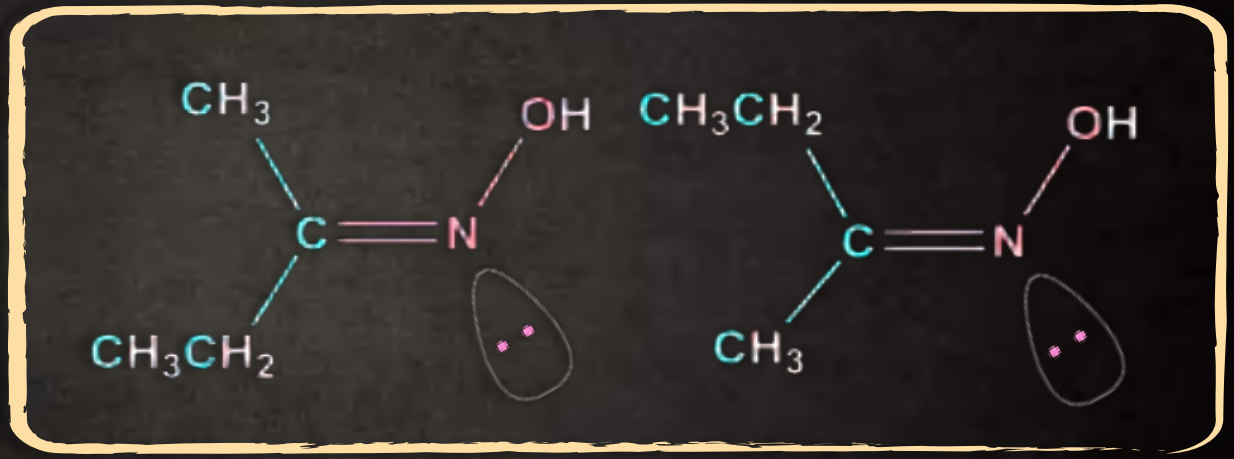
Anti — If -H and -OH are on opposite side



Anti

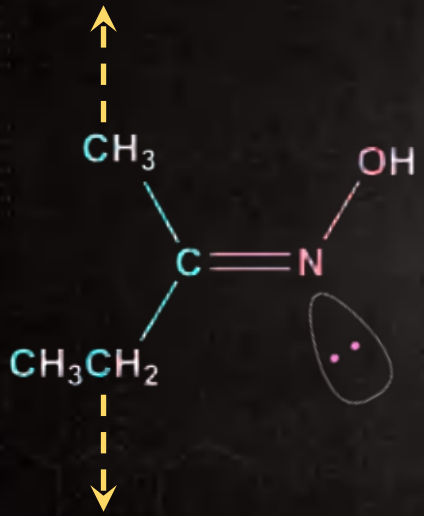
Syn-Anti Configuration

Example



Syn-Anti Configuration

Same side of -OH

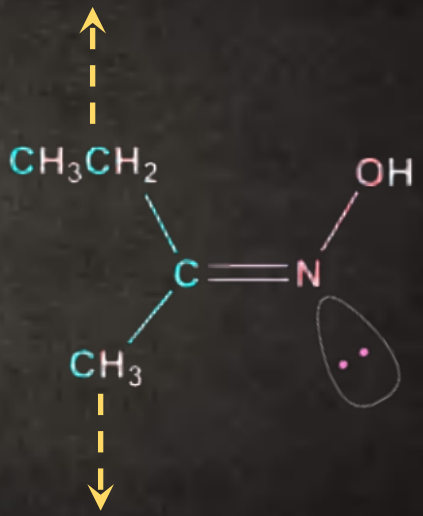


Opposite to -OH

Syn-Methyl ethyl ketoxime

Anti-Ethyl methyl ketoxime

Same side of -OH

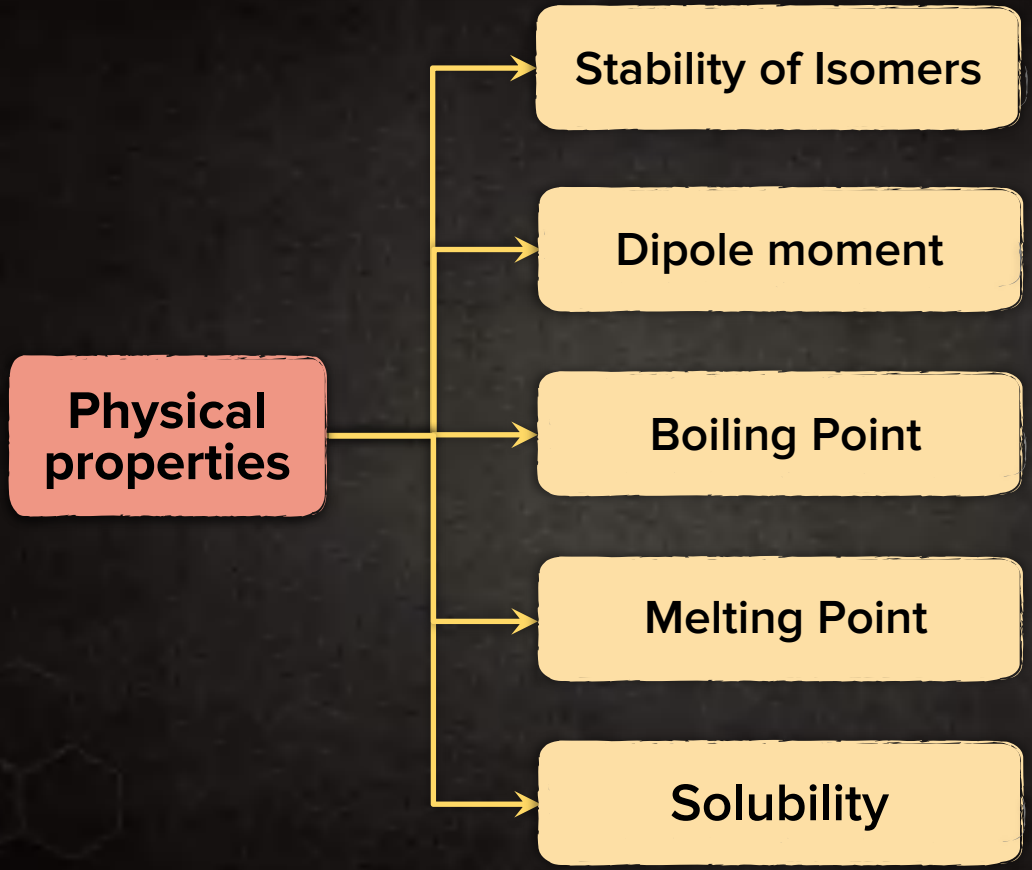


Opposite to -OH

Syn-Ethyl methyl ketoxime

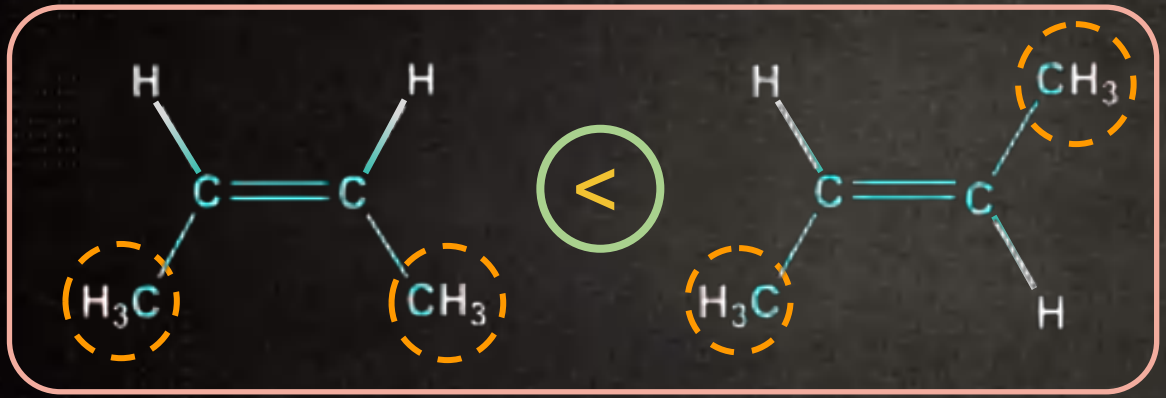
Anti-Methyl ethyl ketoxime

Physical Properties of Geometrical Isomers


Physical properties
Stability of Isomers
Dipole moment
Boiling Point
Melting Point
Solubility

Stability of Geometrical Isomers

$$\text{Stability} \propto \frac{1}{\text{Steric Hindrance}}$$



In general, **trans** isomer is **more stable than cis** isomer due to **lesser steric repulsions.**

cis-But-2-ene → **Higher** steric repulsion

trans-But-2-ene → **Lesser** steric repulsion

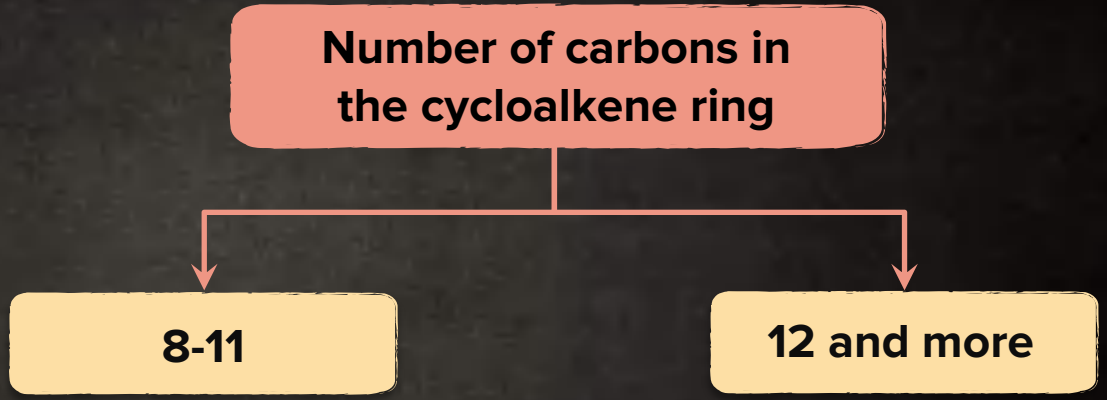
Stability of Geometrical Isomers in Cycloalkene

G.I. in Cycloalkenes

Cycloalkenes with **3 to 7 carbons** in the ring exist only in cis form, as trans form is unstable due to **angle strain.**

Cycloalkenes with 8 or more carbons in the ring exhibit **Geometrical Isomerism.**

Stability of Geometrical Isomers in Cycloalkenes



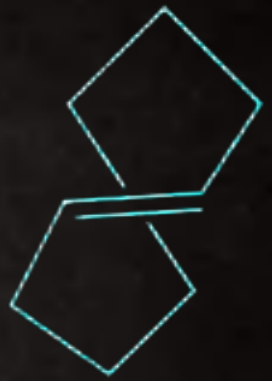
Stability of Geometrical Isomers

8-11 membered cycloalkenes show **cis-trans isomerism**

But, **cis isomers** are **more stable** for 8-11 membered cycloalkenes

Stability of Geometrical Isomers

Example



cis-Octene

trans-Octene

More stable

Less stable

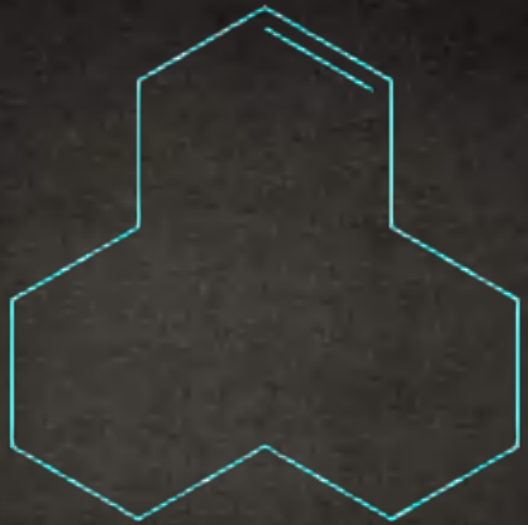
Stability of Geometrical Isomers

For 12-membered cycloalkenes and onwards, **trans isomers** are **more stable** than their **cis isomers.**

Because then cycloalkenes are large enough to form trans isomer easily due to flexibility (and we know that trans form are genrally more stable)

Stability of Geometrical Isomers

Example



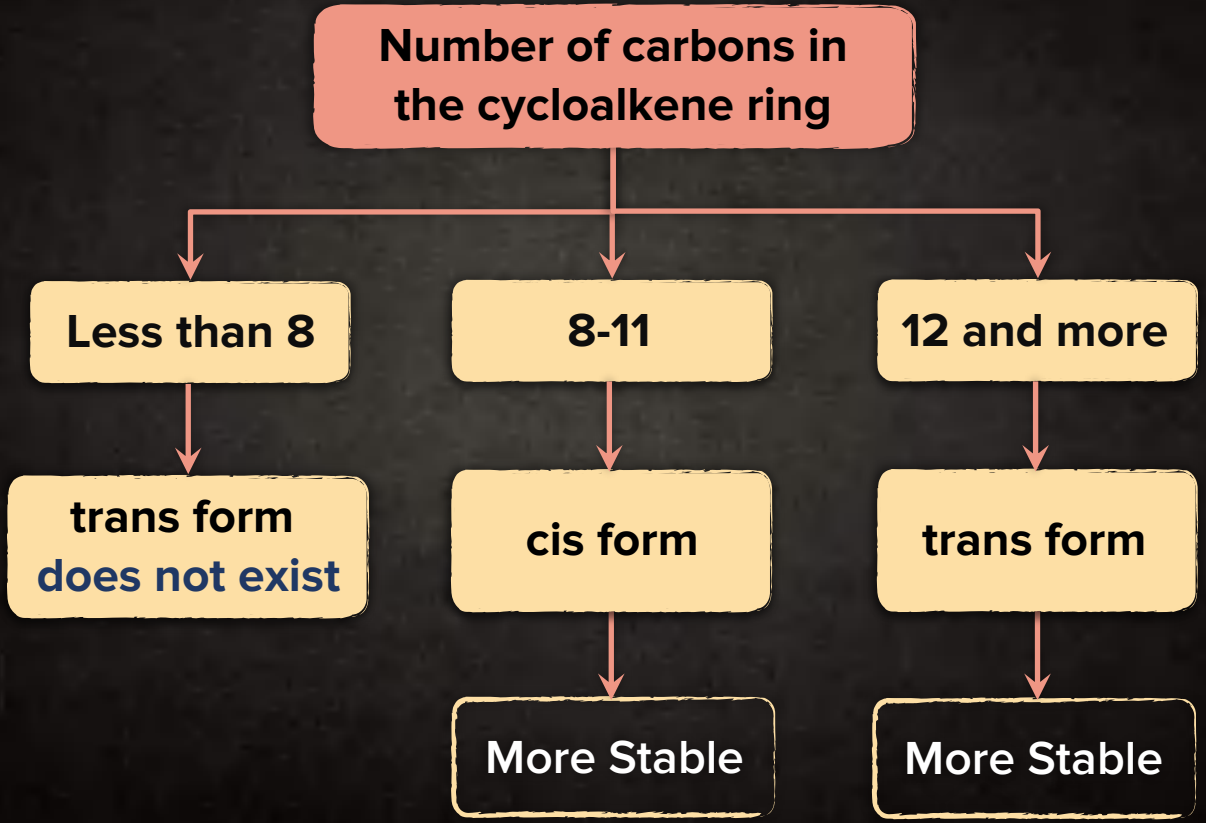
cis-Cyclododecene

trans-Cyclododecene

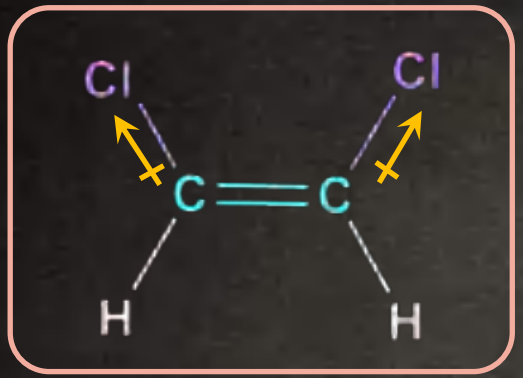
Less stable

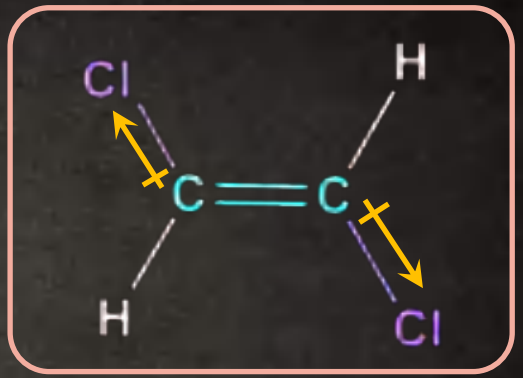
More stable

In a Nutshell!



Dipole Moment of Geometrical Isomers





$\mu_{net} \neq 0$

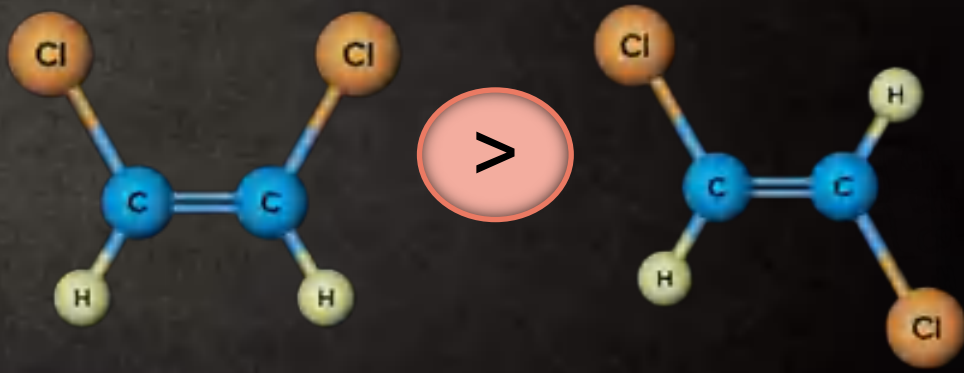
$\mu_{net} = 0$

So here, dipole moment of cis isomer is more than that of trans isomer.

Boiling Point of Geometrical Isomers

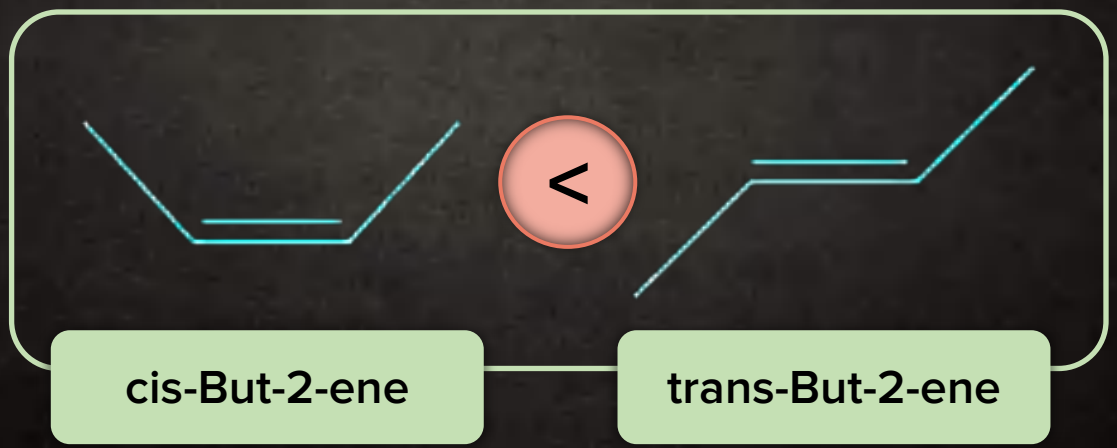
Generally, molecules with higher dipole moments have higher intermolecular forces of attraction.

Boiling point $\propto$ Dipole moment



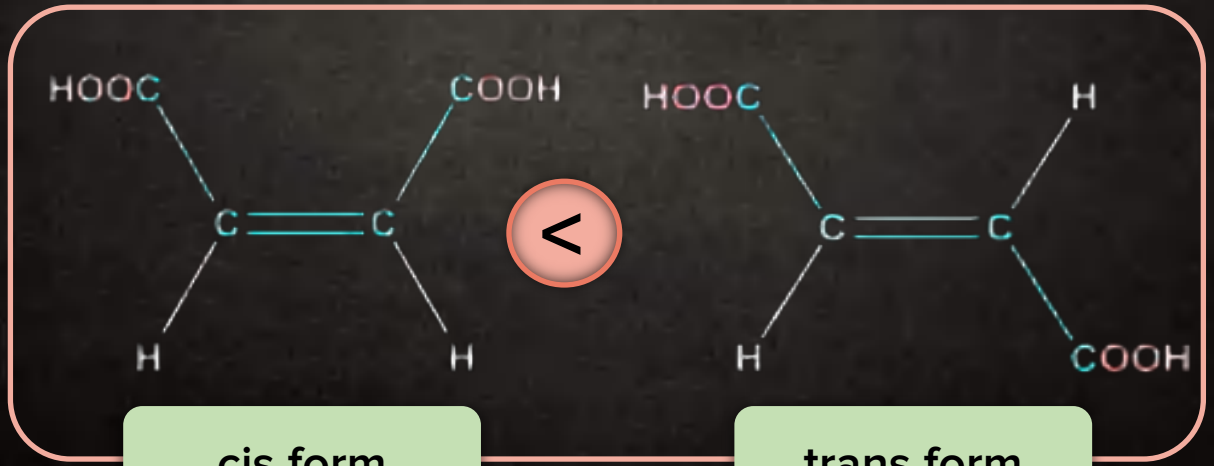
Melting Point of Geometrical Isomers

Melting point $\propto$ Packing



Melting Point

In general, the **trans** isomer has a **higher melting point than the cis** isomer.



cis form

trans form

Solubility

Like dissolves like

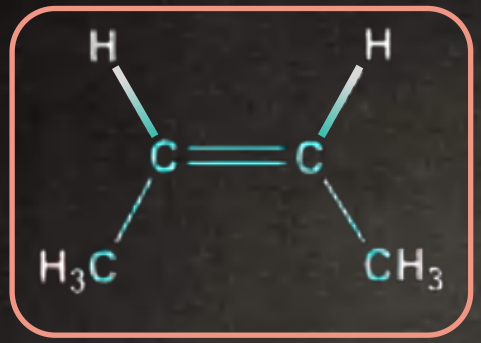
↓

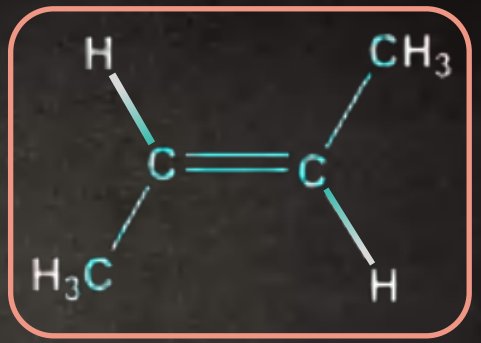
Polar compound is soluble in polar solvent.

Generally,

Solubility in water $\propto$ Dipole moment

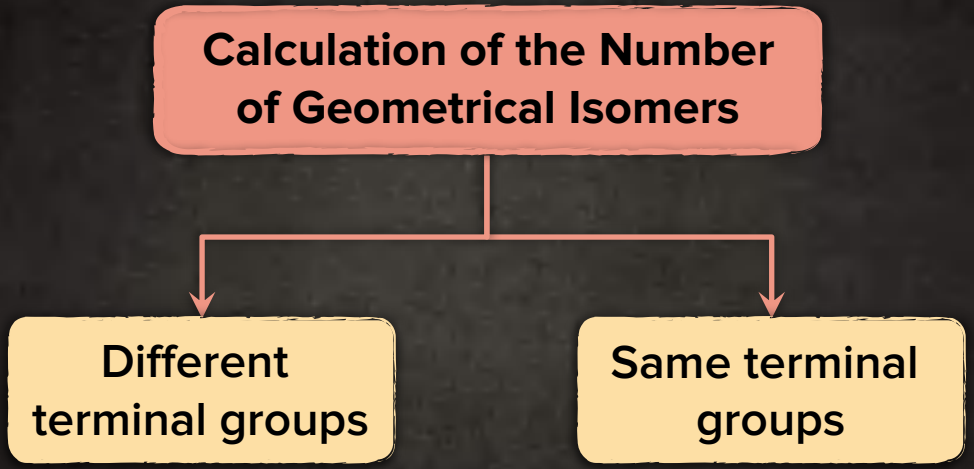
Solubility in Water



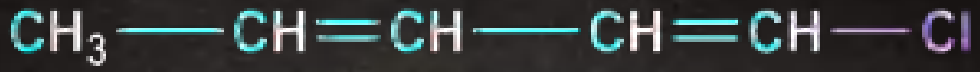


μ_{cis} > μ_{trans}

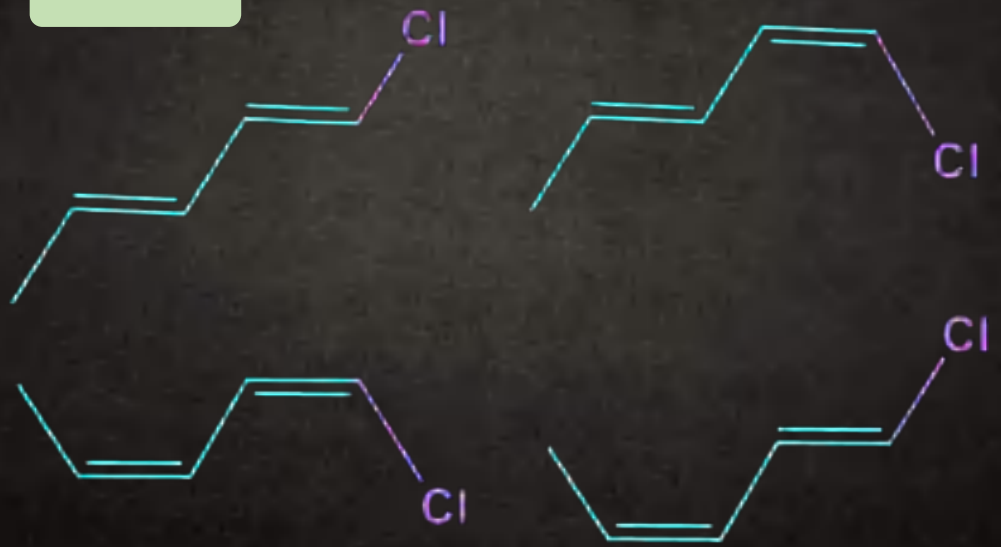
Solubility of cis isomer > Solubility of trans isomer


Calculation of the Number of Geometrical Isomers
Different terminal groups
Same terminal groups

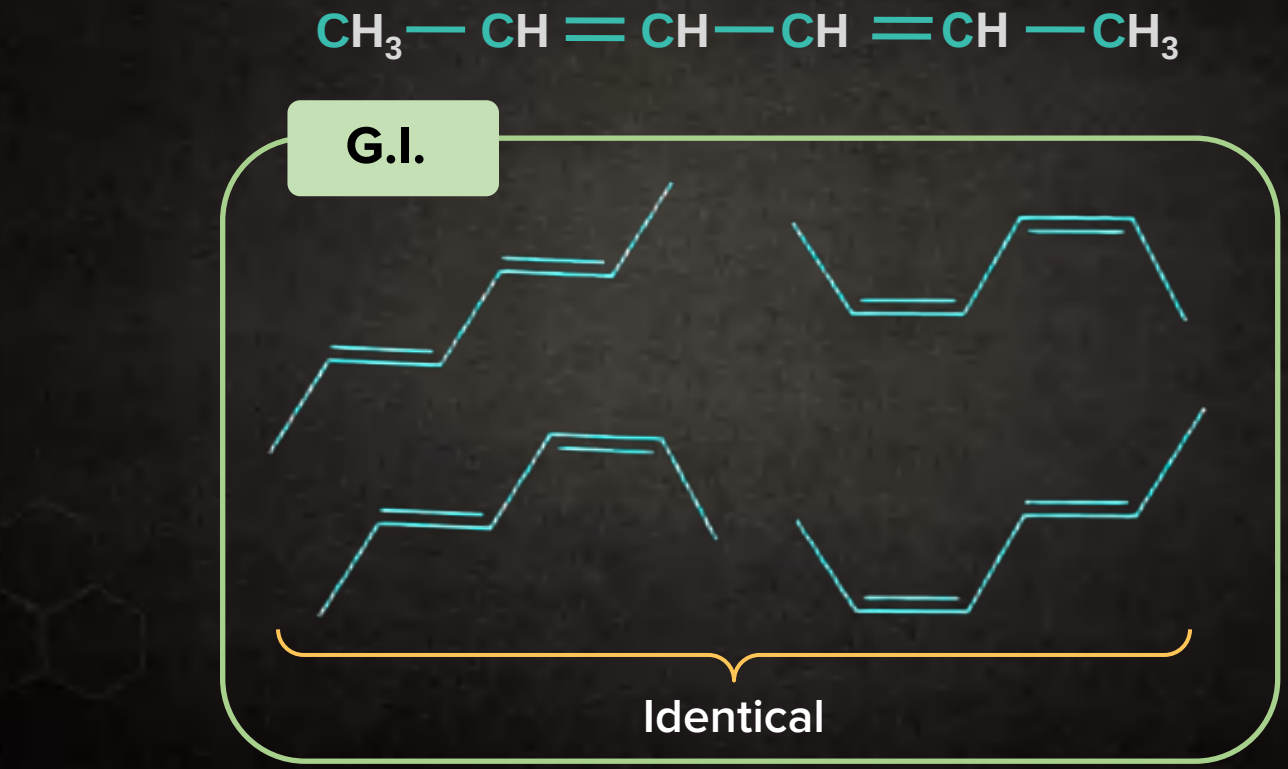
Calculation of the Number of G.I.



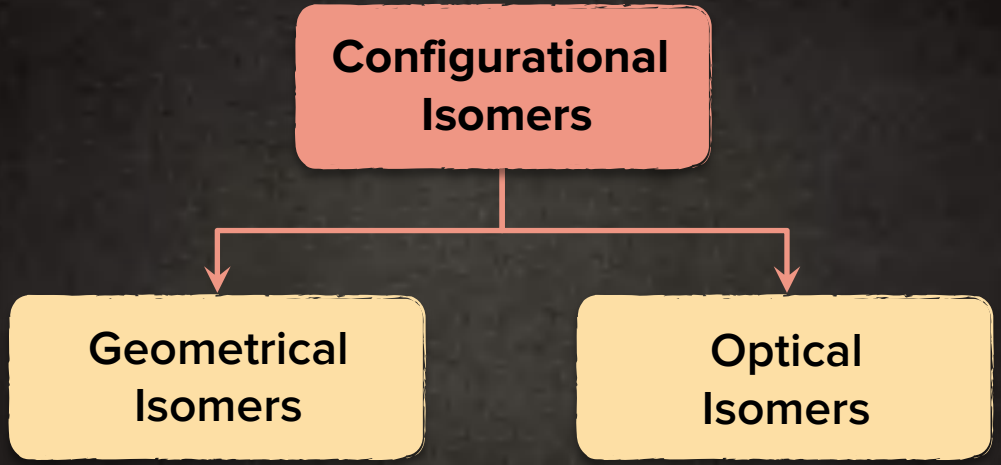
G.I.



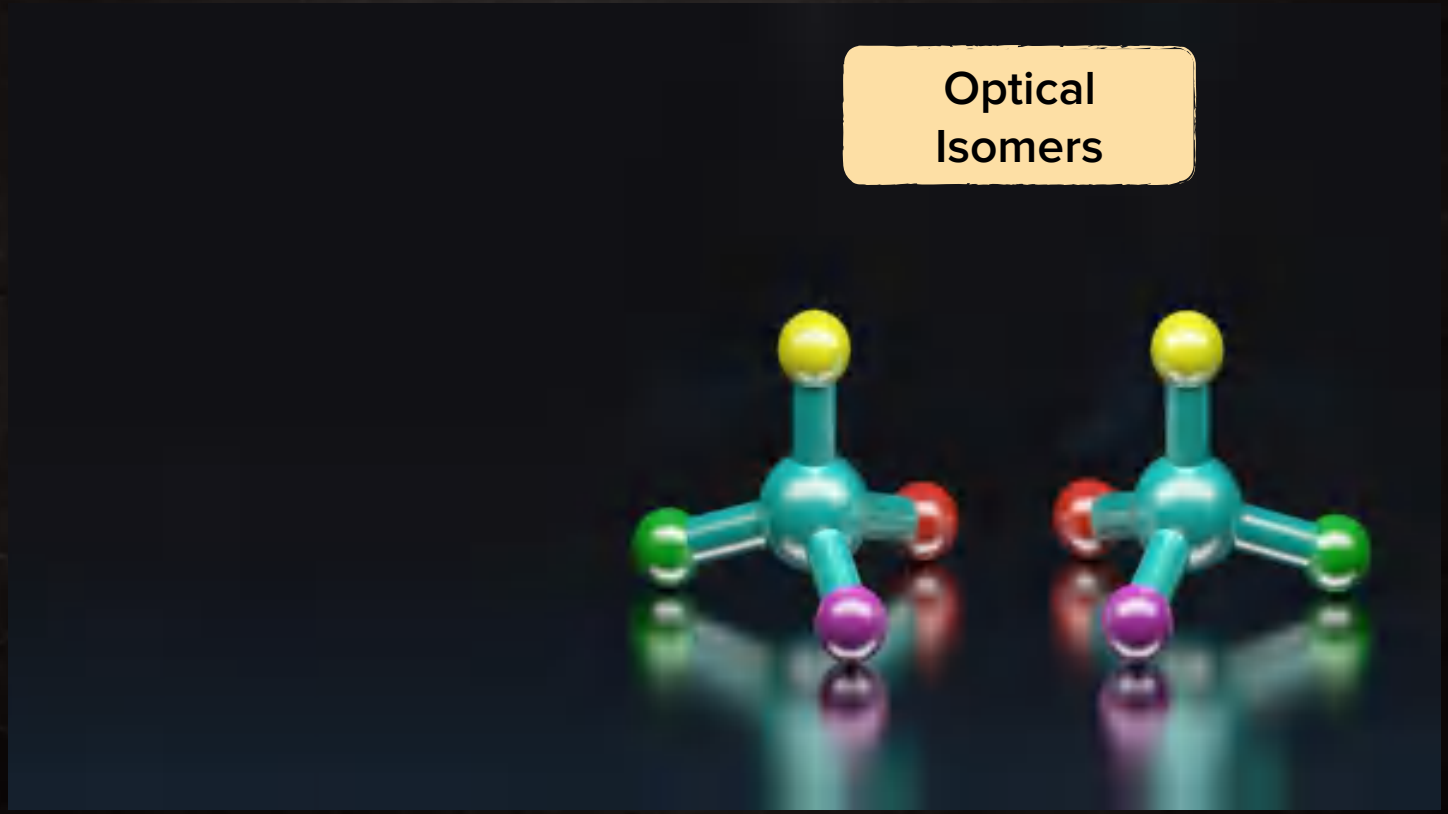
Calculation of the Number of G.I.



Configurational Isomers



Optical Isomers



Optical Isomers

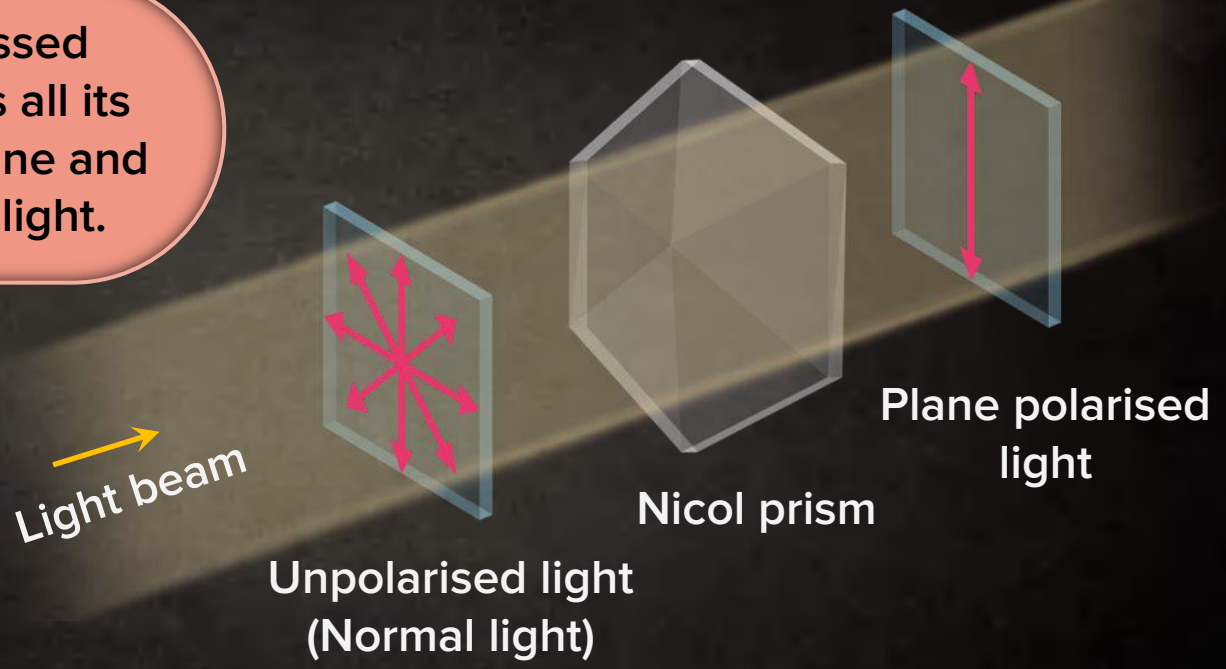
Stereoisomers that have **different behaviour towards plane polarised light (PPL)**.

Non-Polarised (Normal) Light

Normal light is an electromagnetic wave, which has oscillation in all the directions **perpendicular to the path of propagation.**

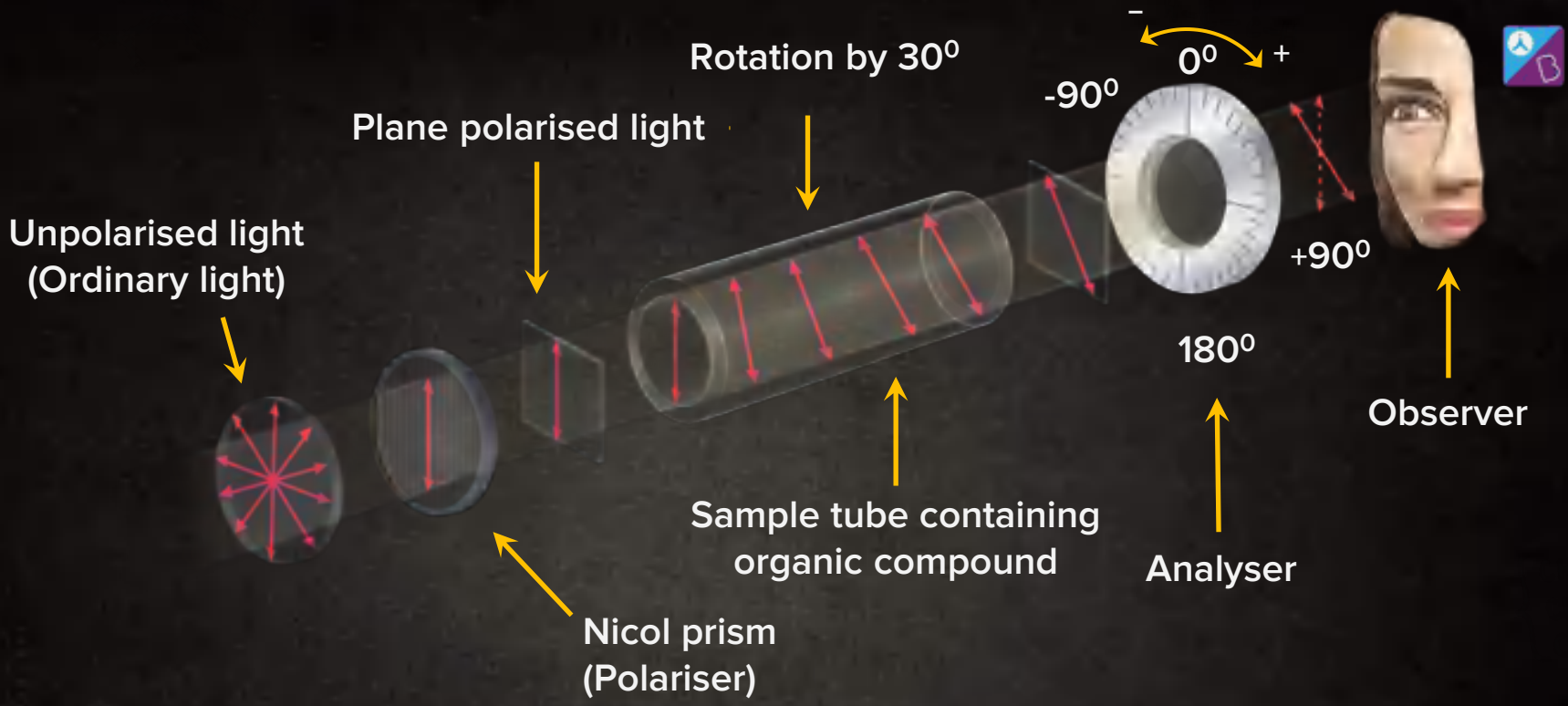
Nicol Prism (Polariser)

When normal light is passed through **Nicol prism**, it has all its oscillations in the same plane and is called **plane-polarised** light.

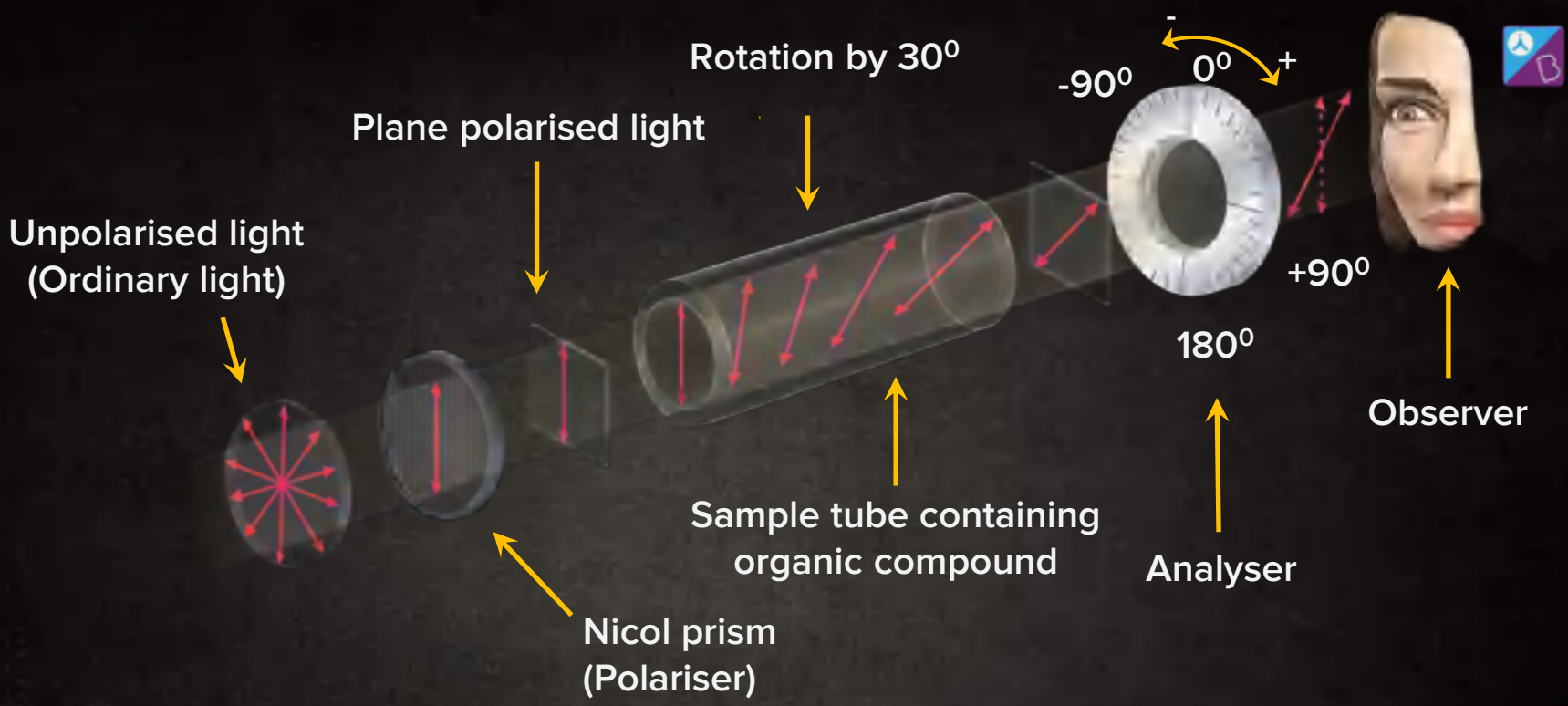


Polarimeter

An **instrument** that **measures the degree** to which a compound **rotates the plane** of polarisation of light.



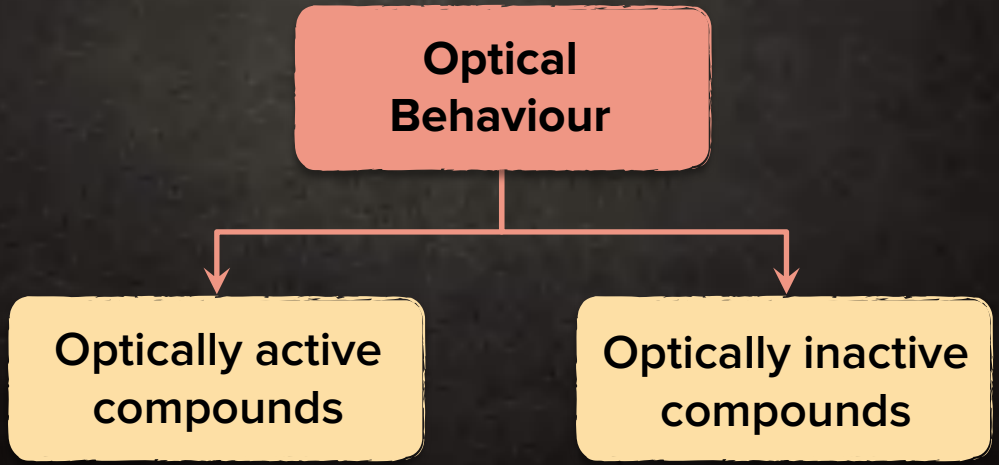
The plane polarised light is obtained when ordinary light is passed through the Nicol prism. When the same plane polarised light is passed through the sample containing l-isomer of an optically active compound, it gets deflected in the anticlockwise direction.



The plane polarised light is obtained when ordinary light is passed through the Nicol prism. When the same plane polarised light is passed through the sample containing d-isomer of an optically active compound, it gets deflected in the clockwise direction.

Optical Activity

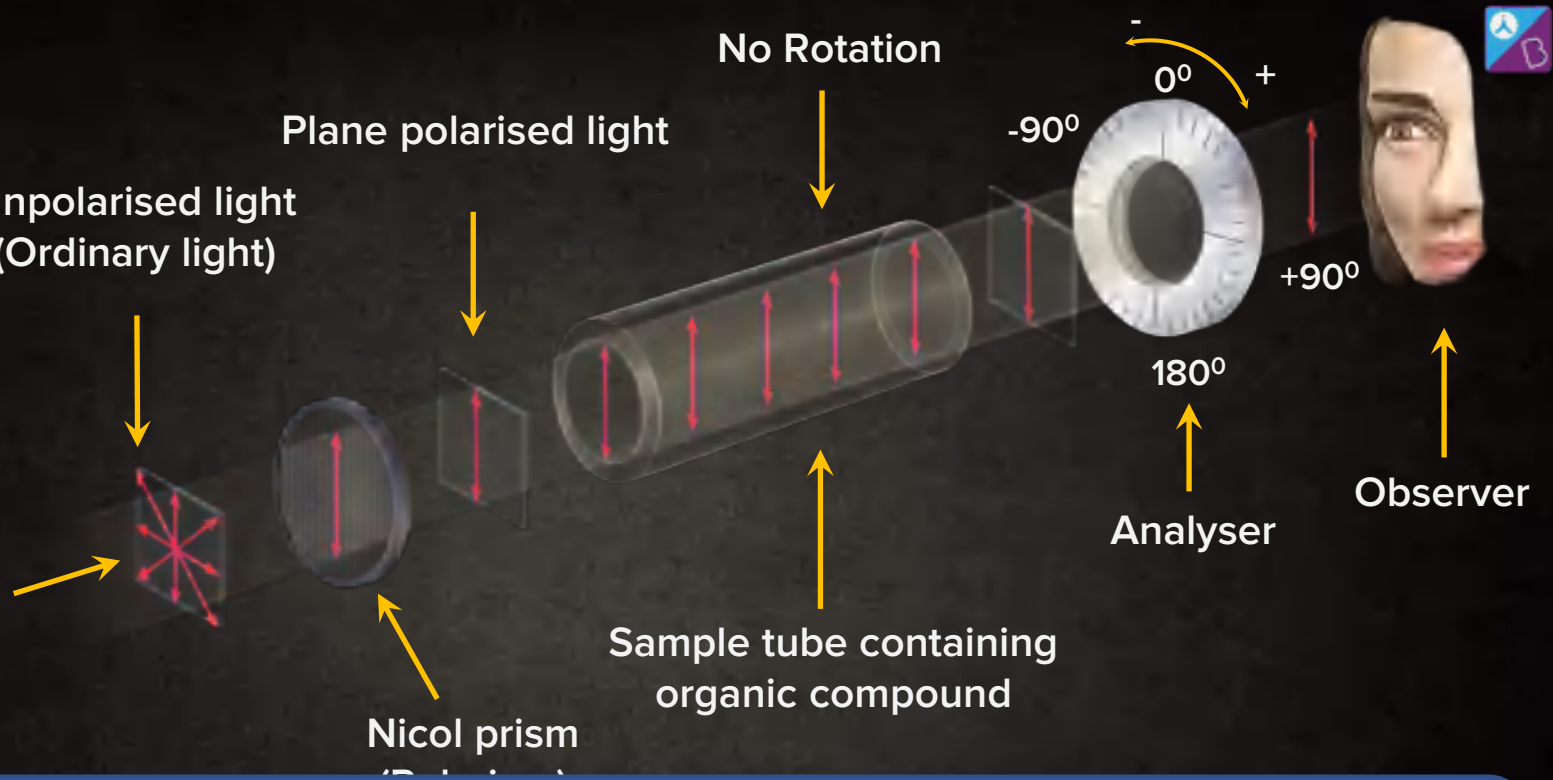
Based on optical activity or optical behaviour towards plane polarised light, we can classify compounds into two categories.



Optically Active Compounds

Compounds that **rotate the plane of polarised light** in a characteristic way when it is passed through their solutions.

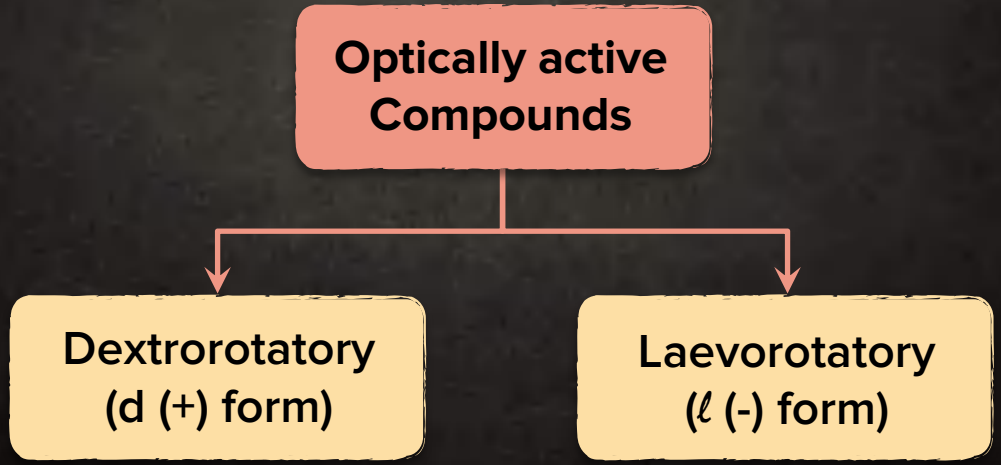
Compounds that **do not rotate the plane of polarised light** in a characteristic way when it is passed through their solutions.



The plane polarised light is obtained when ordinary light is passed through the Nicol prism. When the same plane polarised light is passed through the sample containing an optically inactive compound, it does not get deflected in any direction.

Optically Active Compounds

Based on the **direction of optical rotation**, optically active compounds can be categorised into **two types**.



Dextrorotatory and Levorotatory Compounds

If the substance rotates plane-polarised light to **the right (i.e., in clockwise direction)** then it is called dextrorotatory & indicated **by 'd' or (+).**

If the substance rotates plane-polarised light to the **left (i.e., in anti-clockwise direction)** then it is called laevorotatory & indicated by **'ℓ' or (-).**

Optically Active Compounds

d and ℓ forms of a compound are **experimental observations** that cannot be predicted by just looking at the structure of the molecule.

Optical Activity

van't Hoff and Le Bel proposed that all the four valencies of carbon are directed towards the four **corners of a regular tetrahedron.**

If **all the four substituents** attached to such a carbon **are different**, the resulting molecule lack symmetry and such a molecule is referred to as an **asymmetric molecule.**

Asymmetry of the molecule is responsible for the **optical activity** in such organic compounds.

Factors Affecting Rotation of PPL

The amount of rotation (θ) **is not constant** for a given optically active compound.

θ depends on

- Length of sample vessel
- Temperature
- Solvent
- Concentration (for solutions)
- Pressure (for gases)
- Wavelength of light

Factors Affecting Rotation of PPL

The length of the vessel and concentration or pressure determine the **number of molecules** in the path of the beam.

Rotations determined for a particular compound under the same conditions are **identical**.

Specific Rotation [α]

In order to place measured rotations on a **standard basis**, chemists calculate a quantity called specific rotation, **[α]**.

$$[\alpha]_t^{\lambda} = \frac{\theta}{\ell \times C}$$

[α] = Specific rotation
ℓ = Path length (dm)
λ = wavelength (nm)
θ = observed angle of rotation (degree)
C = concentration (g/mL)
t = temperature (25°C)

Specific rotation is the **number of degrees of rotation** observed if a 1 dm (10 cm) tube is used and the compound has concentration **1 g/mL**.

Note

Specific rotation of a compound is **independent** of the **length** of tube and **concentration** of the solution.

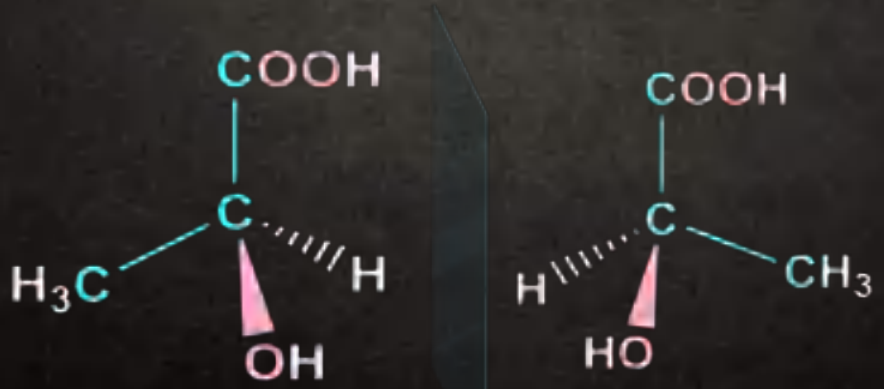
Since optical rotatory power is a **property of molecules**, if two substances have **unequal** molecular weights but are alike with respect to the power of rotating the plane of polarized light.

The substance of smaller molecular weight has the larger specific rotation, simply because it has **more molecules per unit weight**.

Optically Active Compounds

Ultimate criterion

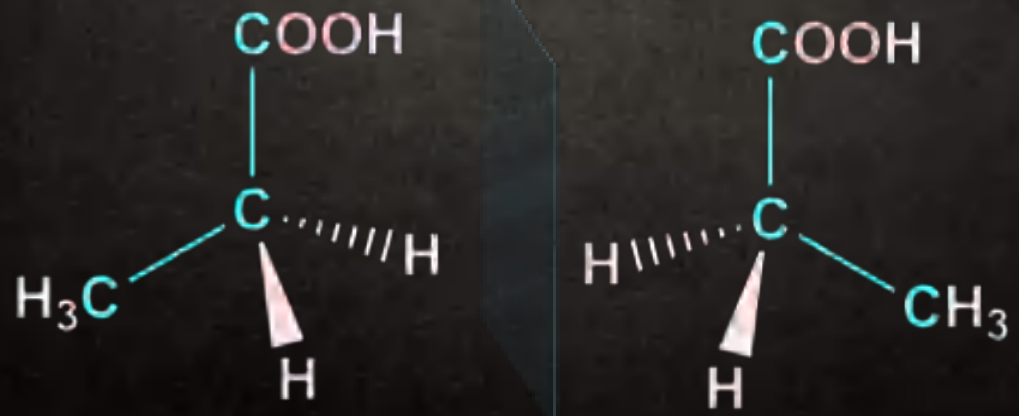
A compound which is **non-superimposable** to its mirror image is chiral.



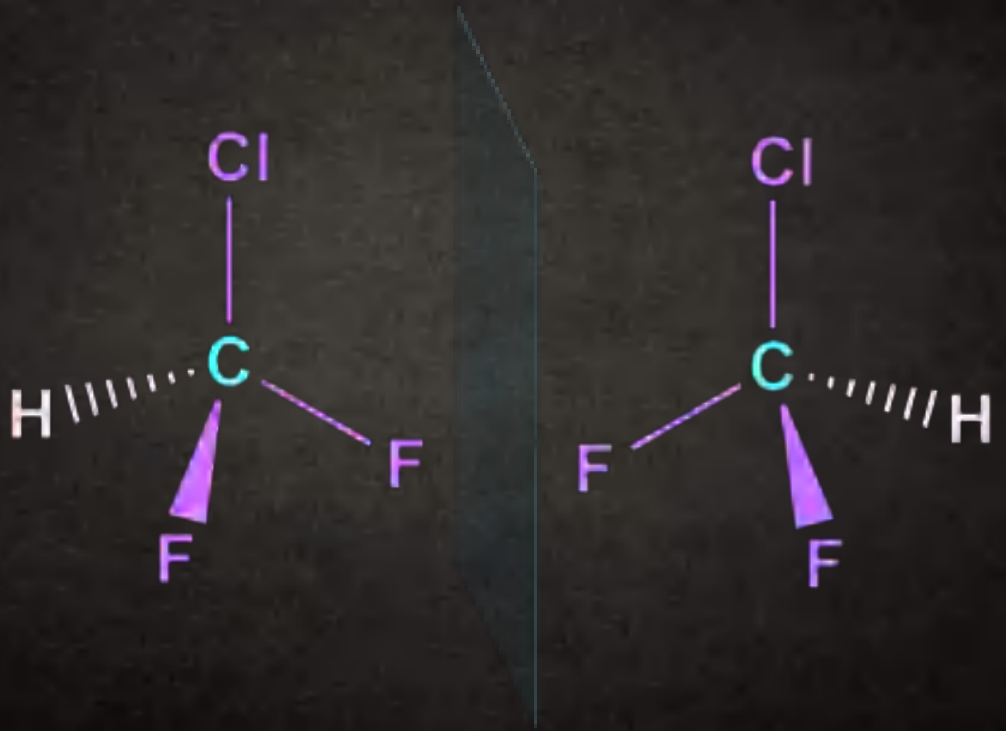
Examples

Optically Inactive Compounds

A compound which is **superimposable** to its mirror image.



Examples



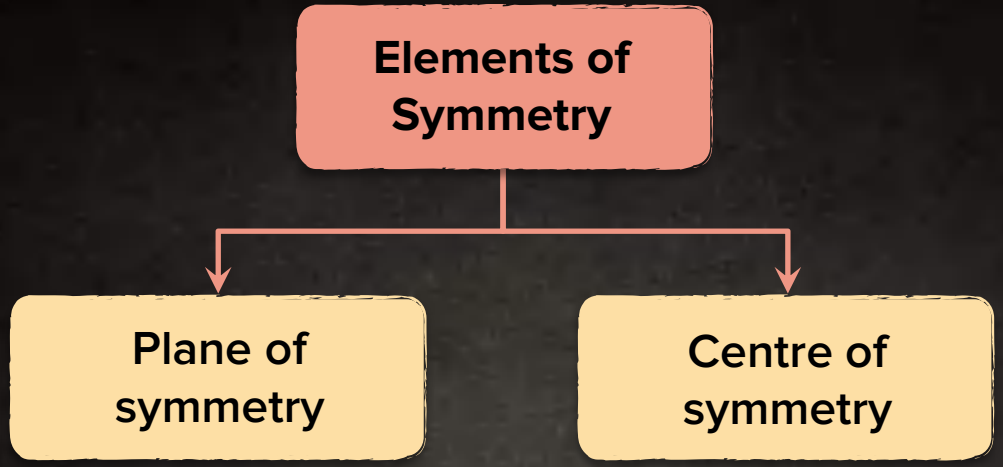
Optical Activity

Although the ultimate criterion is non-superimposability on the mirror image (chirality),

Other tests may be used that are **simpler to apply but not always accurate**.

Conditions for Optical Activity:

1. Absence of **P**lane **o**f **S**ymmetry **(POS)**
2. Absence of **C**entre **o**f **S**ymmetry **(COS)**



A plane passing through an object/ molecule such that the part on one side of the plane is the exact reflection of the part on the other side (the **plane acting as a mirror**).

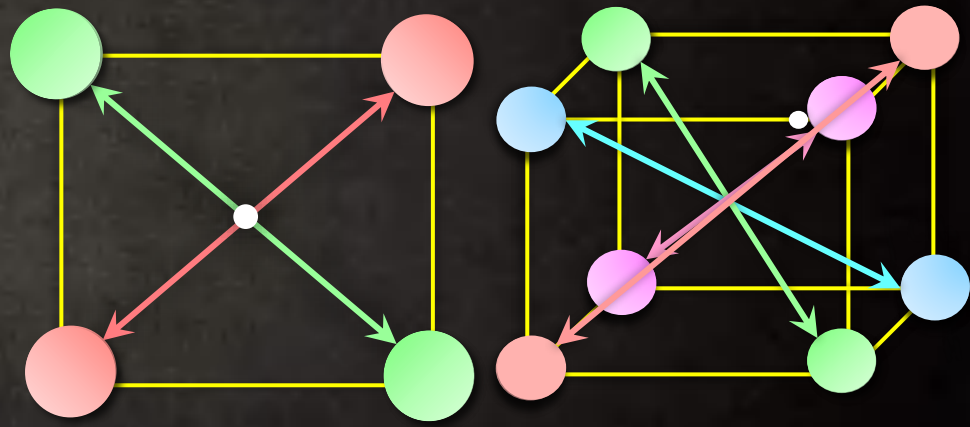
Optical Activity

Compounds possessing POS are always **optically inactive,** but there are a few cases known in which compounds lack POS and are **nevertheless inactive**.

Such compounds possess a **centre of symmetry (COS)**

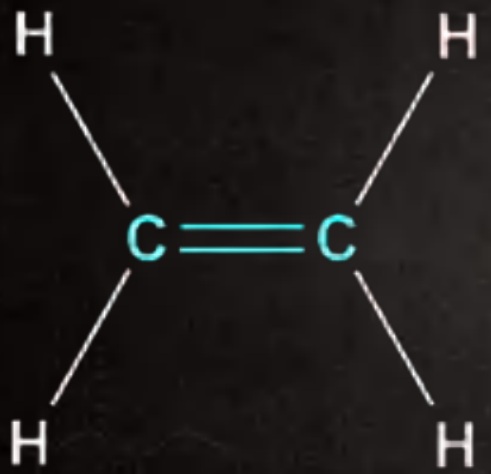
Centre of Symmetry (COS)

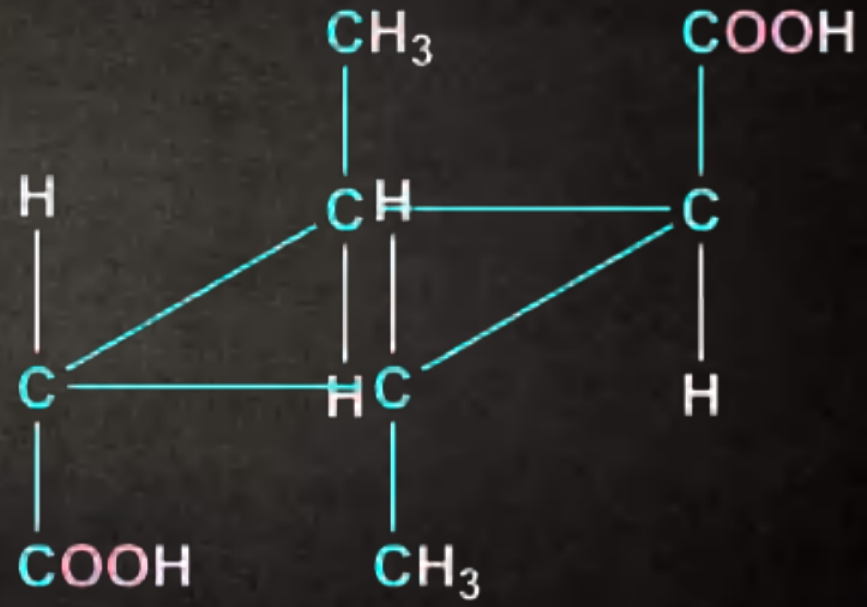
A **centre of symmetry** is a point within an object/compound such that a straight line **drawn from any part or element** of the object to the centre, and extended an equal distance on the other side encounters an **equal part** or element.



Centre of Symmetry

Centre of Symmetry





Optically Active Compounds

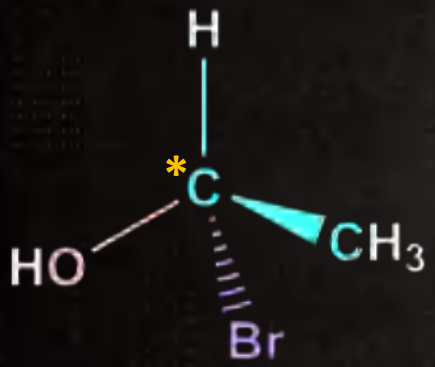
Generally, if a molecule **does not** possess **POS** and **COS**, it will be **optically active.**

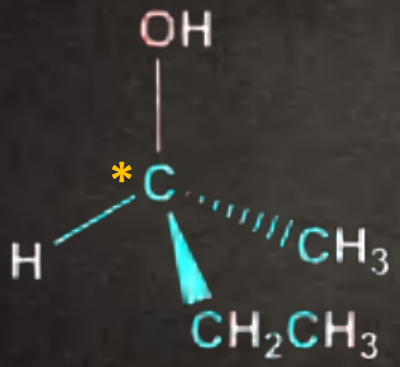
Chiral Carbon

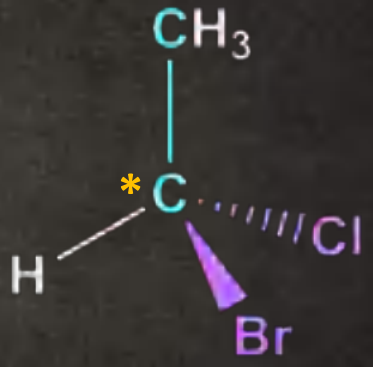
Chiral carbon/ Asymmetric carbon	Carbon atom connected to **four different groups**

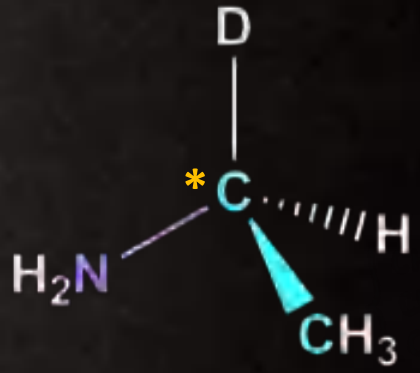
A molecule that contains just **one chiral carbon** atom is always chiral, and hence **optically active**.

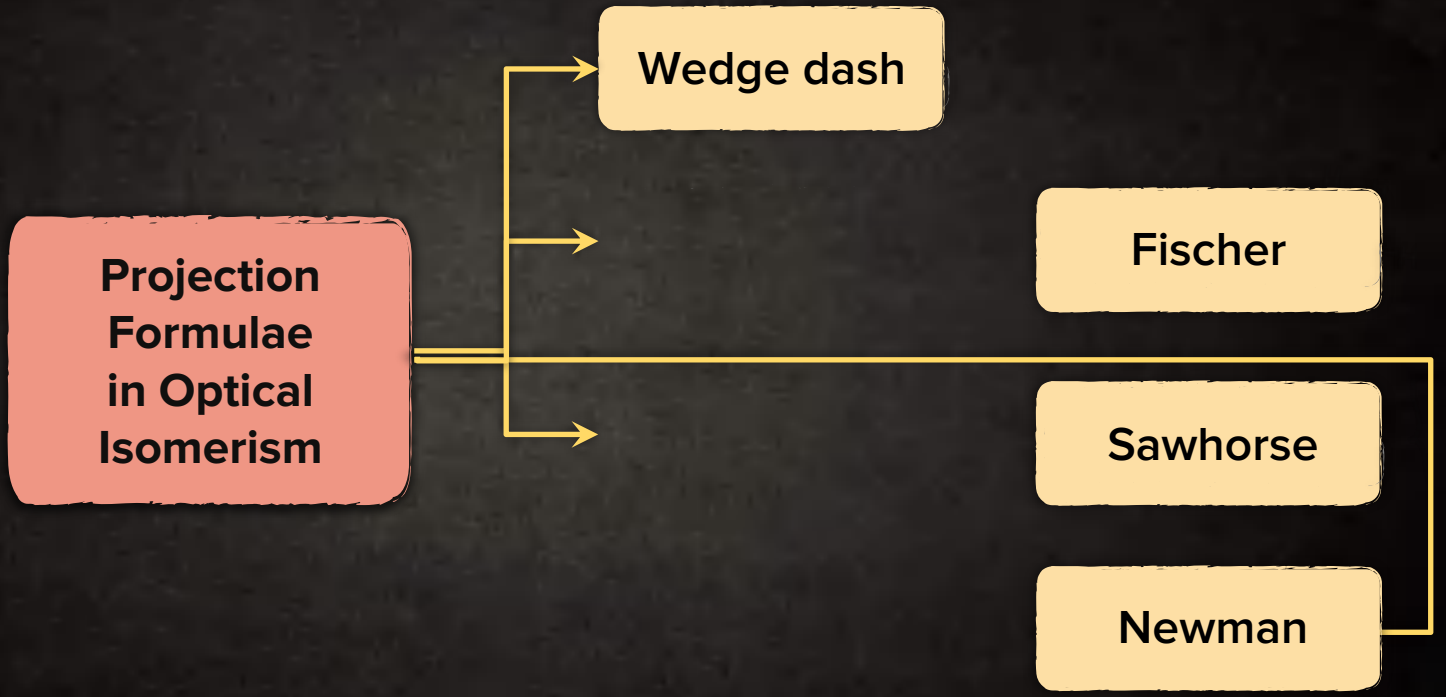
Chiral Carbon



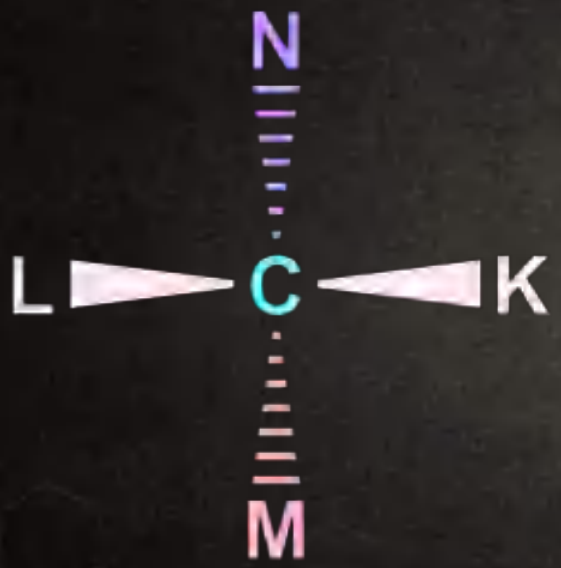


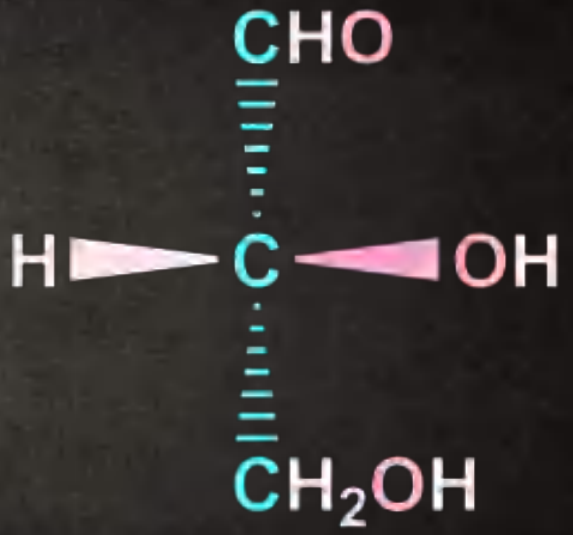





Projection Formulae in Optical Isomerism
Wedge dash
Fischer
Sawhorse
Newman

Wedge-Dash Projection Formula

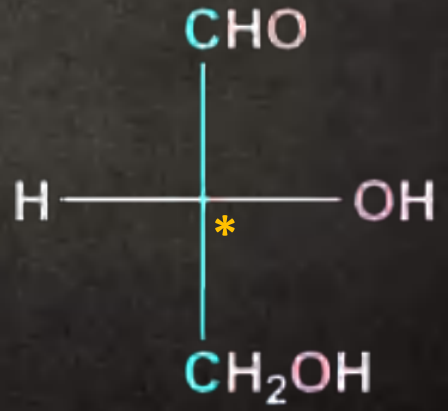




Rules for Writing Fischer Projection Formula

01 The molecule is drawn in the form of a **cross (+)** with the **chiral carbon at the intersection** of the horizontal and vertical lines.

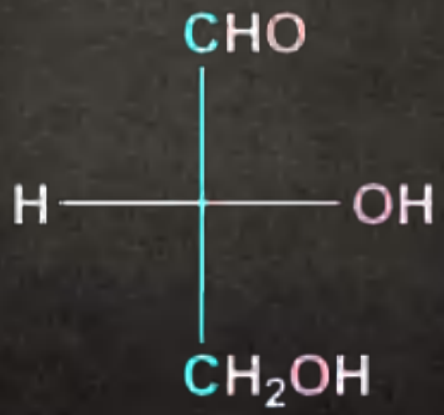
2D representation of a 3D molecule is called **Fischer Projection.**



Rules for Writing Fischer Projection Formula

02

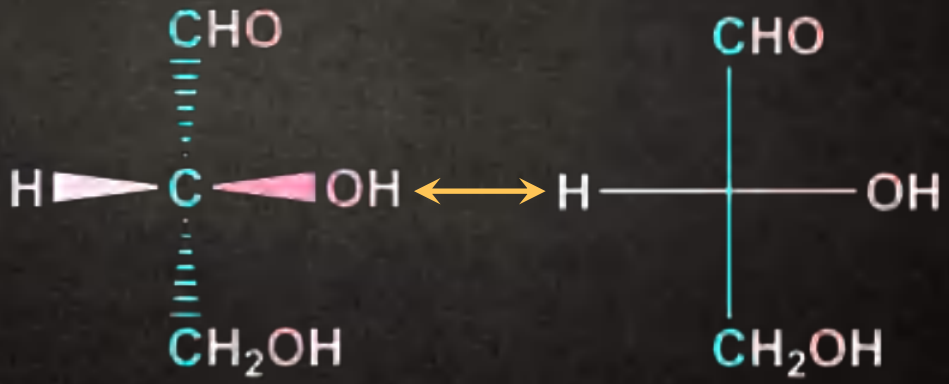
On the **vertical line, the main chain** is taken with the first carbon at the top.



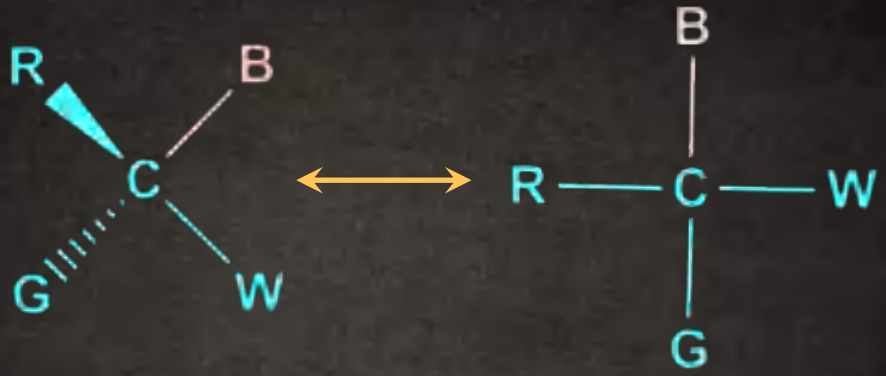
Rules for Writing Fischer Projection Formula

03

The **horizontal lines** represent the bonds directed **towards the viewer** and the **vertical lines** represent the bonds **away from the viewer**.



Wedge-Dash into Fischer

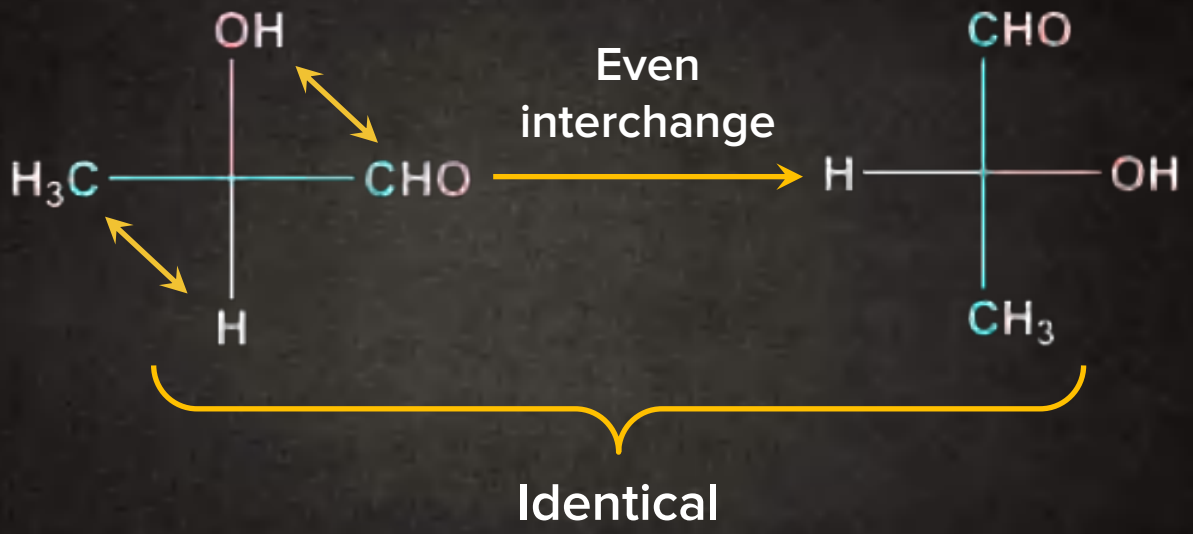


Note

Optical
isomers

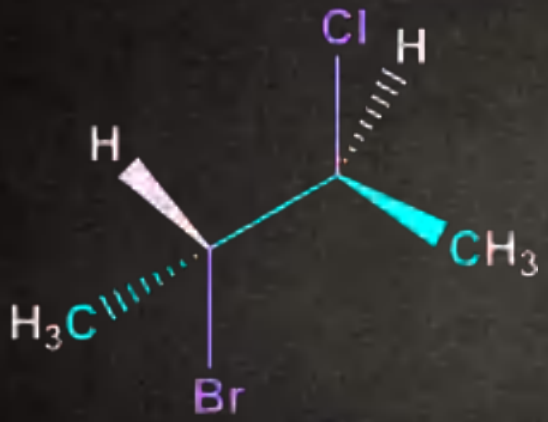
Odd interchange gives
isomer of the molecule

Note



Even interchange gives **identical** molecule

Wedge-Dash into Fischer



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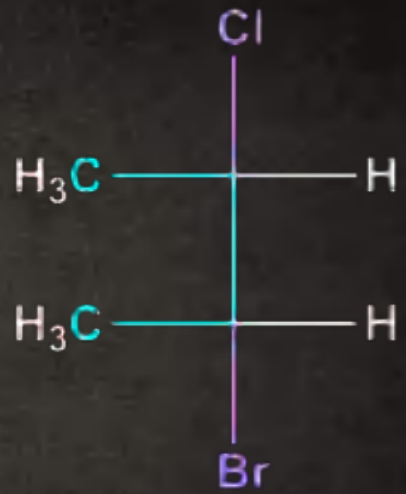
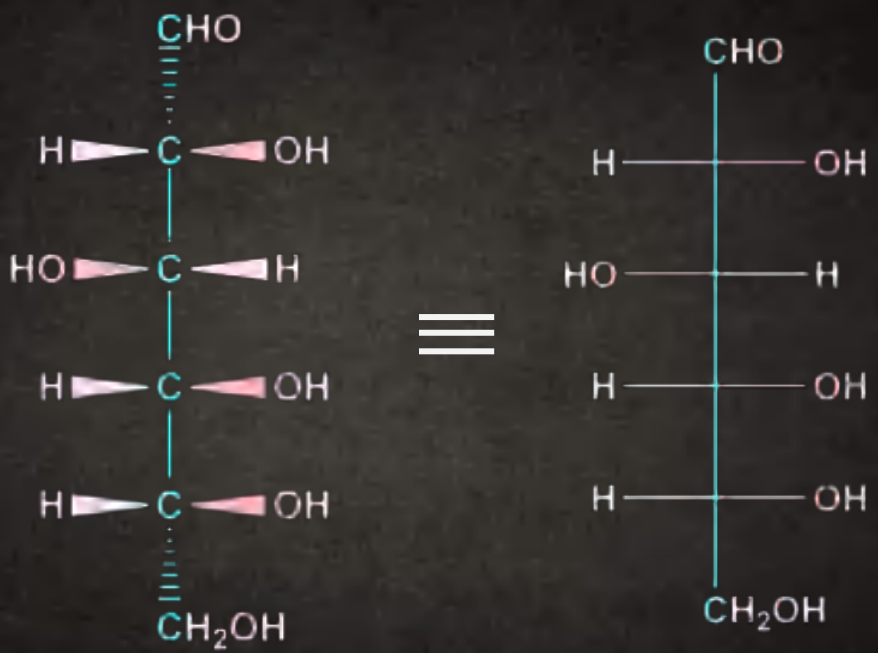


Wedge-dash formula

Fischer projection formula

Wedge-Dash into Fischer



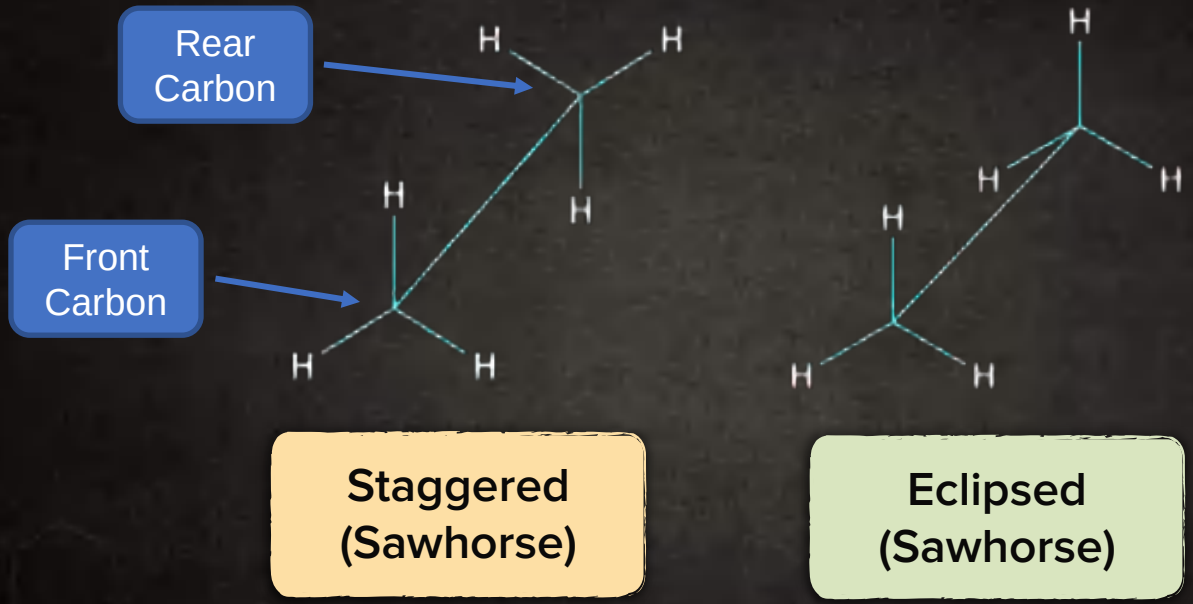
Wedge-dash formula

Fischer projection formula

Note

COS **cannot** be observed in Fisher projection formula.

Sawhorse Projection Formula



Staggered (Sawhorse)

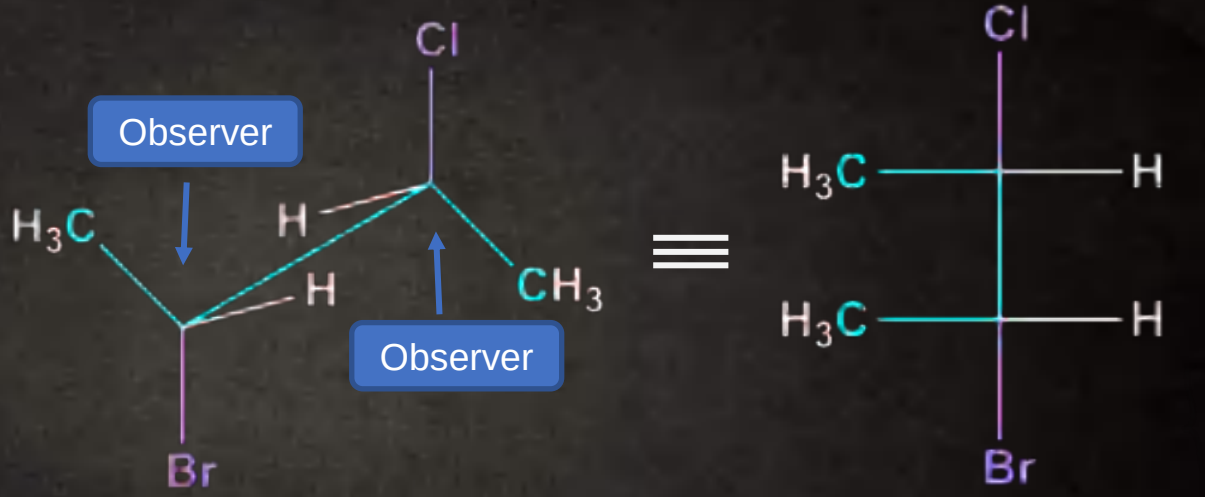
Eclipsed (Sawhorse)

Sawhorse into Fischer

First of all, convert **eclipsed** sawhorse into **staggered** form.

While observing, the **groups towards observer** are kept on **horizontal line** in Fisher projection and the **group** going **away from observer** are kept at the **vertical line.**

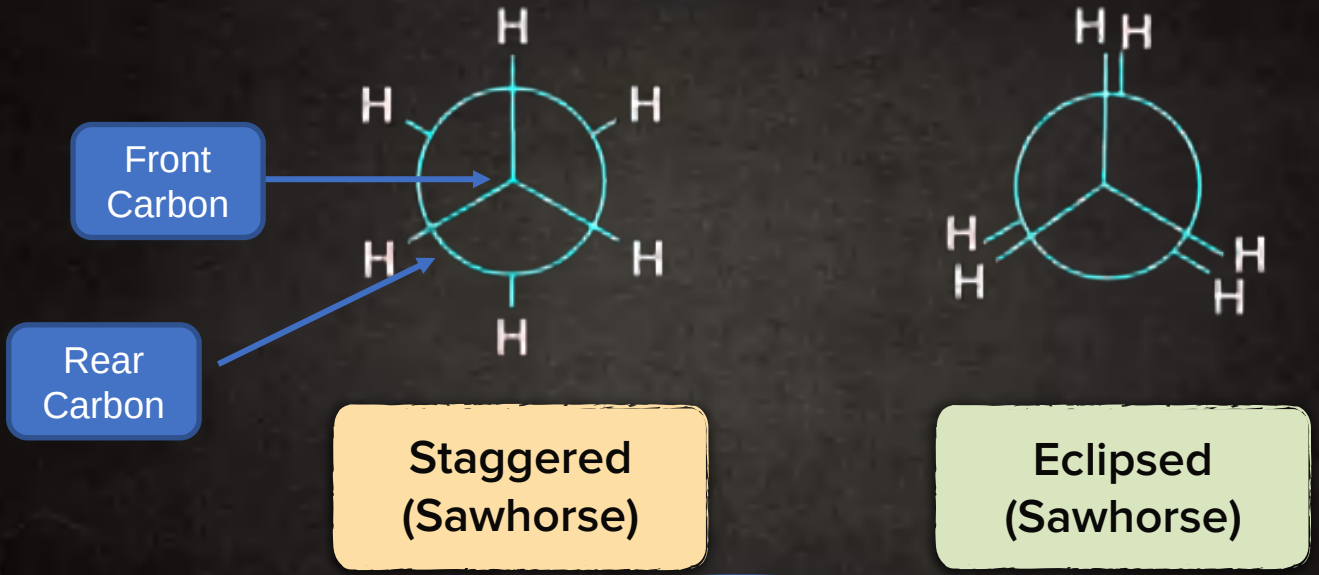
On **horizontal line**, the groups which comes **left** and **right** to the observer are kept on **left** and **right** side respectively in Fisher projection.



Sawhorse formula

Fischer projection formula

Newman Projection Formula

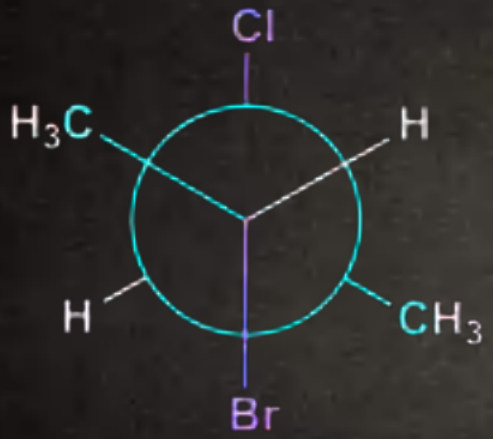


Staggered (Sawhorse)

Eclipsed (Sawhorse)

The rear carbon is represented by a circle which is just behind the front carbon

Newman into Fischer



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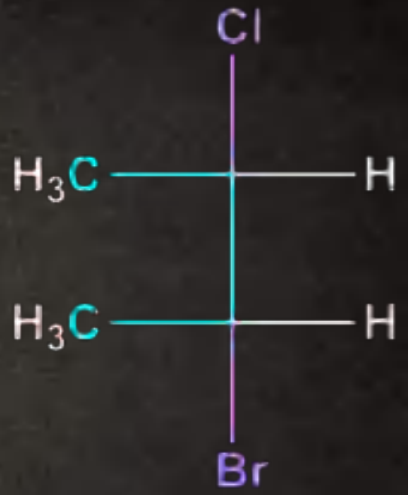


Newman formula

Fischer projection formula

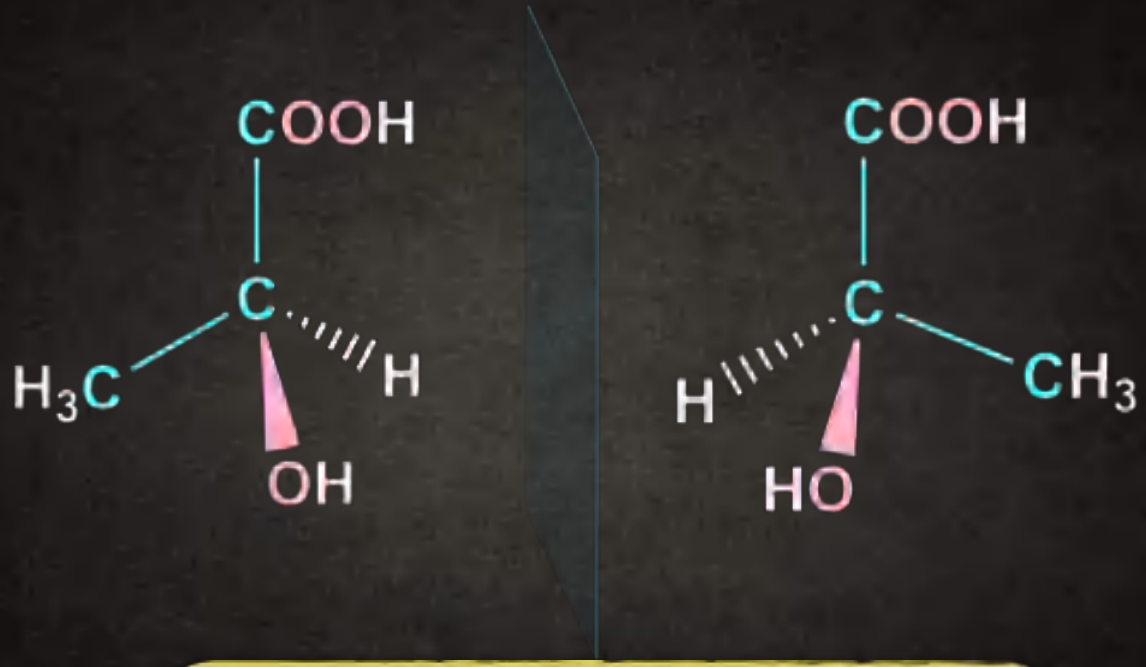
Compounds With Only One Chiral Carbon

Compounds with only one chiral carbon are **always optically active.**

These molecules have an **optical isomer.**

They are **non-superimposable** mirror images of each other.

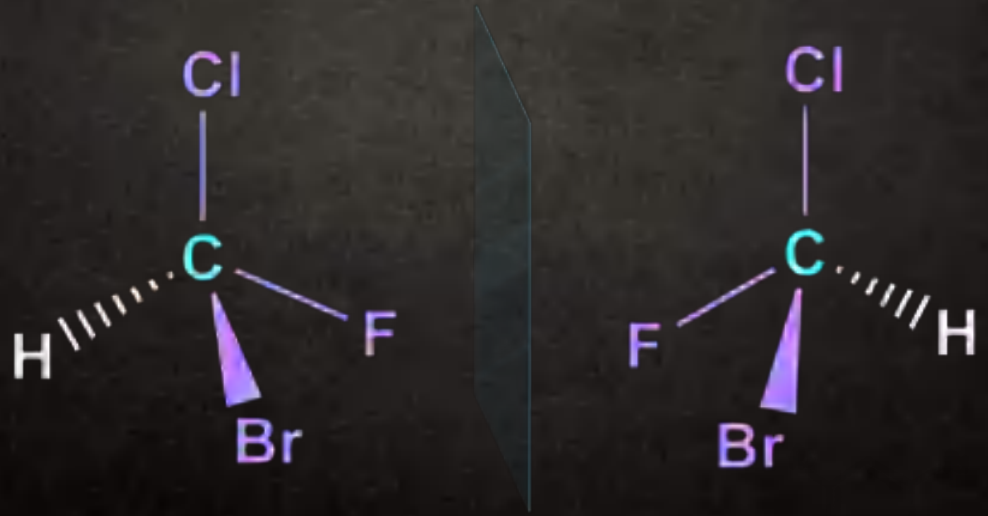
Chiral Compounds



Non-superimposable mirror images

Enantiomers

Stereoisomers that are **non-superimposable** mirror images of each other.



Racemic Mixture

A mixture of **equal amounts of enantiomers** is known as a racemic mixture.

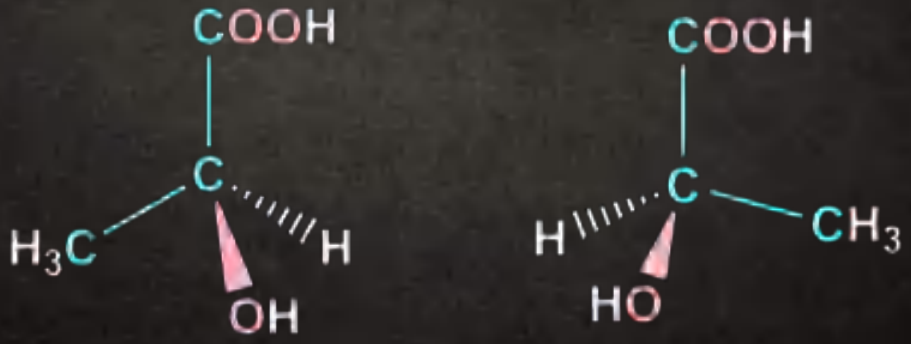
It is always optically **inactive.**

When enantiomers are mixed together in equal amounts, the **rotation caused by** one enantiomer is **exactly cancelled** by an equal and opposite rotation caused by another enantiomer.

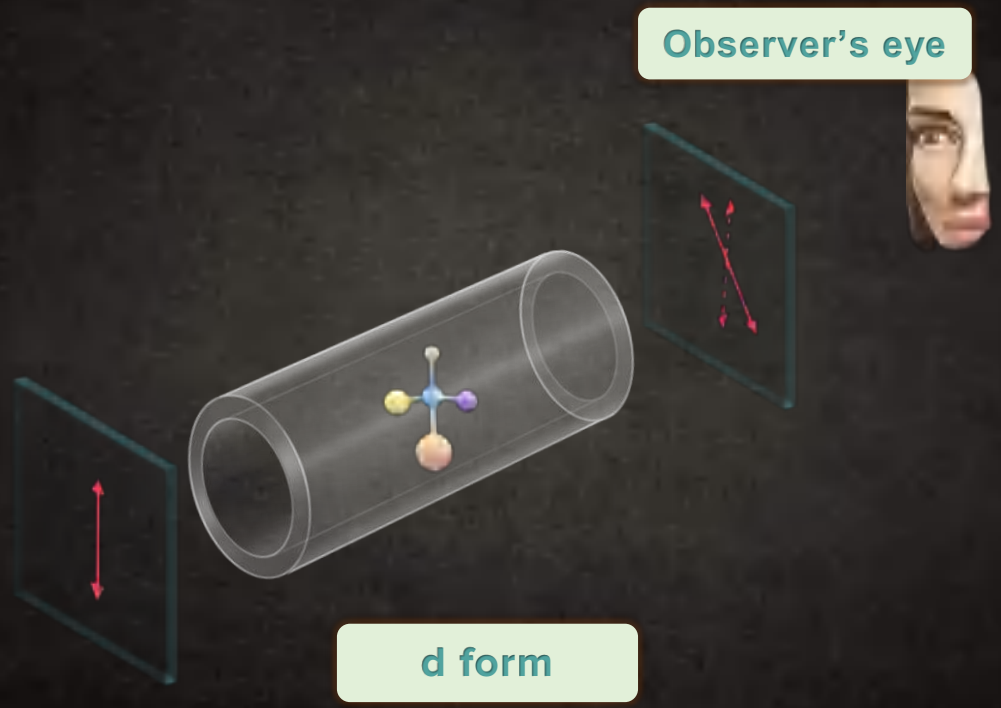
A prefix **(±)** is used to specify the racemic nature of the particular sample.

Example

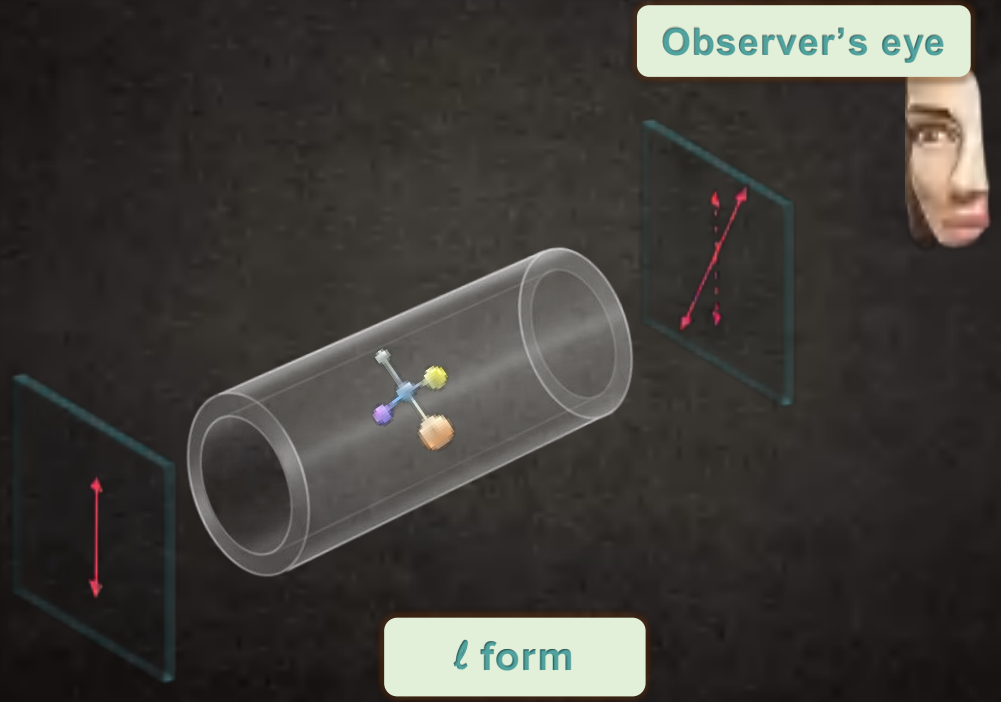
Equal amounts of the d and ℓ forms of lactic acid in a mixture **counter-balance the rotation** of each other.



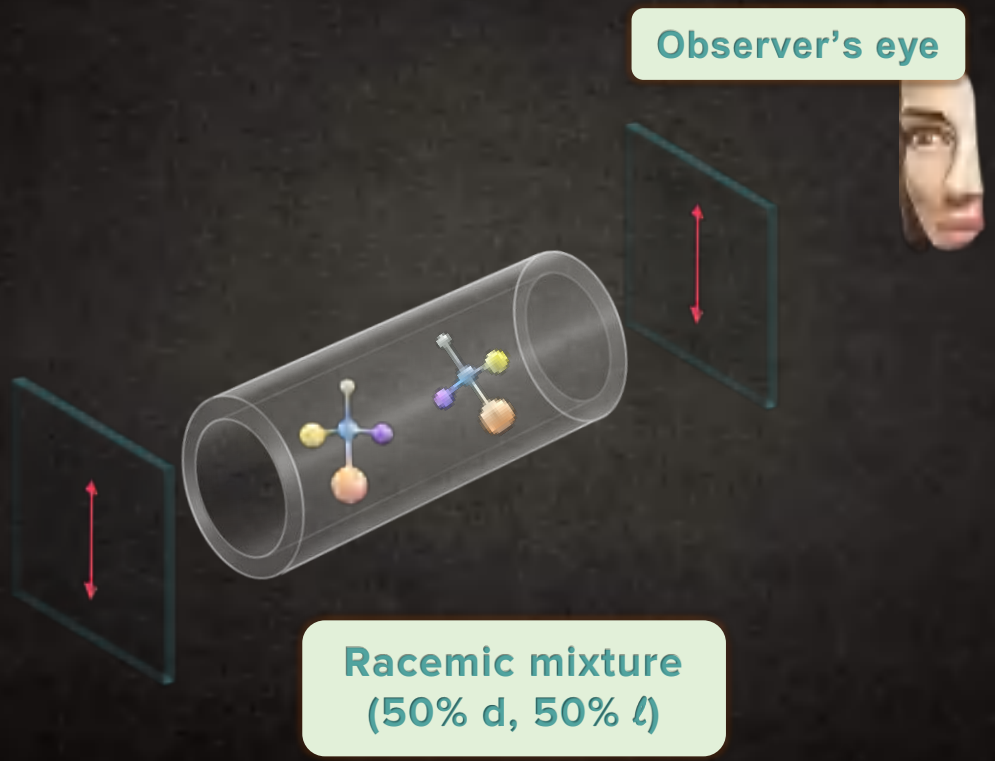
Clockwise Rotation



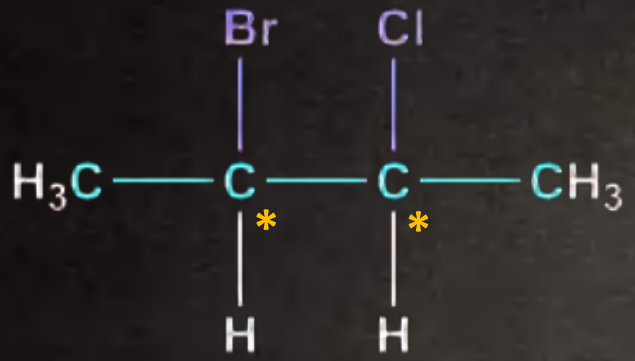
Anti-clockwise Rotation



Racemic Mixture



Check for Chirality



POS is absent

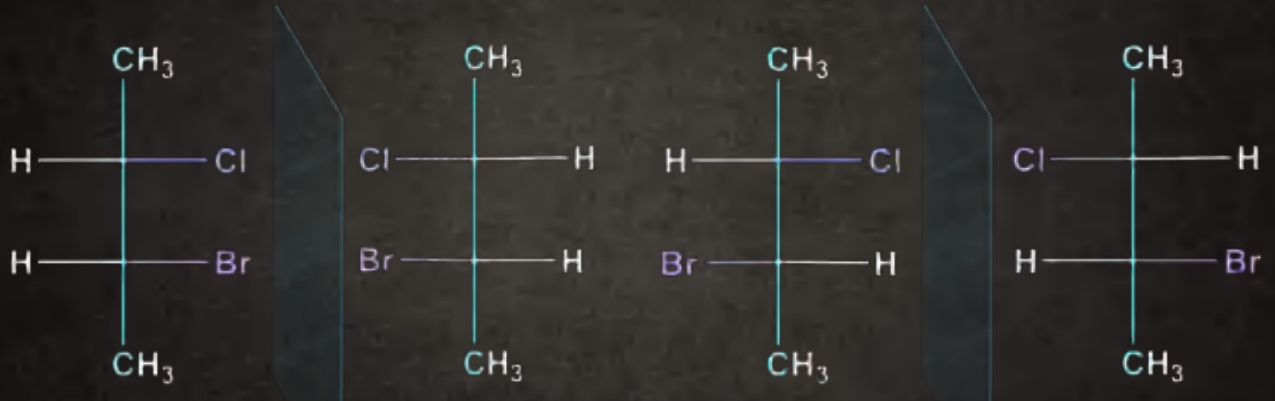
Optically active compound

COS is not checked for chirality in the Fischer projection.

Enantiomers

Enantiomers

Enantiomers

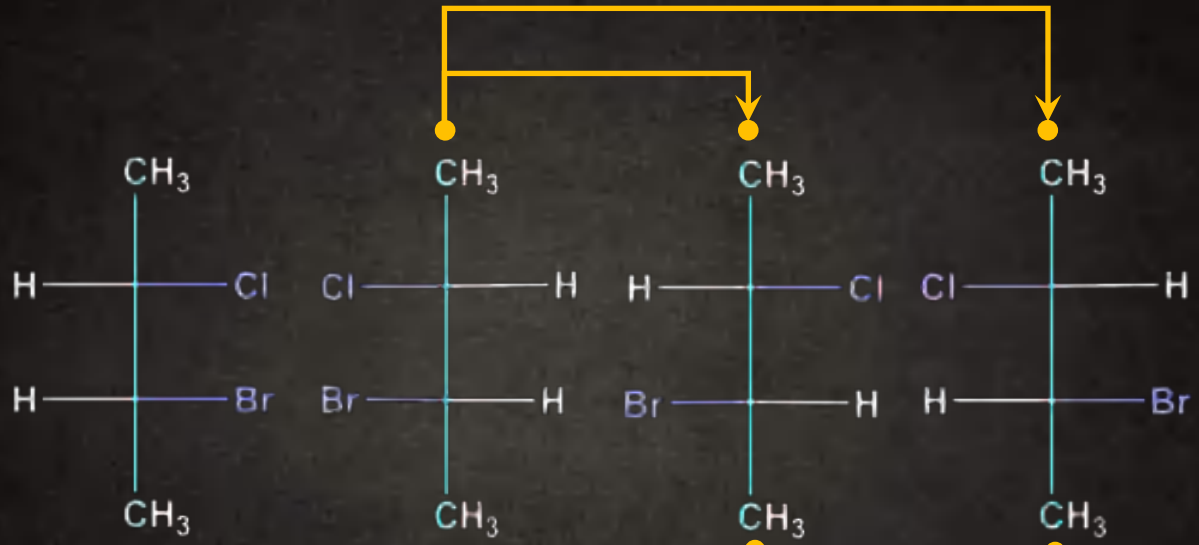


1 2 3 4

Diastereomers

Diastereomers are stereoisomers that are **not mirror images** of each other.

Diastereomers

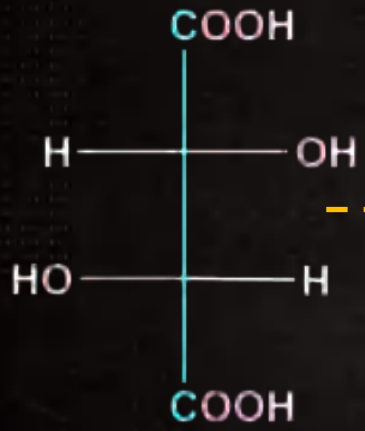


01 02 03 04

Properties	Enantiomers	Diastereomers
Molecular formula	Same	Same
Structural formula	Same	Same
Stereo chemical formula (structural formula with orientation)	Different	Different
Dipole Moment	Same	Different

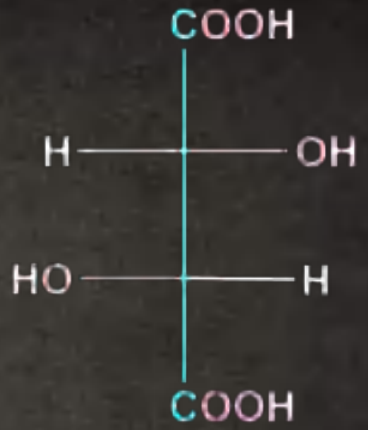
Properties	Enantiomers	Diastereomers
Physical properties (M.P., B.P., density, solubility, refractive index, etc.)	Same	Different
Angle of rotation of PPL	Same in magnitude but in different direction	Different

Check for Chirality



POS is absent

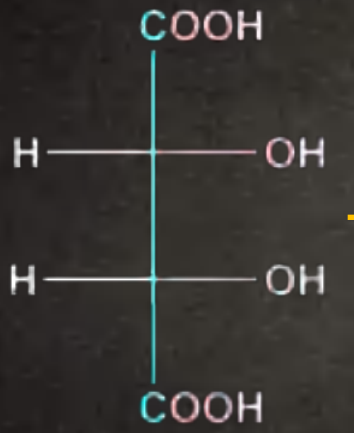
Optically **active** compound



POS is absent

Optically **active** compound

Check for Chirality



POS is present

Optically **inactive** compound

Meso Compounds

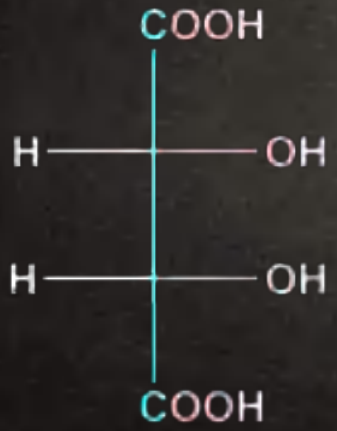
An **optically inactive** molecule whose at least one **diastereomer** is **optically active**

The molecule contains chiral centres and symmetry but are **optically inactive.**

The mirror images of meso compounds are **superimposable** over each other.

Meso Compounds

Optical inactivity is caused by **internal compensation.**



It contains 2 chiral carbons, but POS is present.

Optically **inactive**

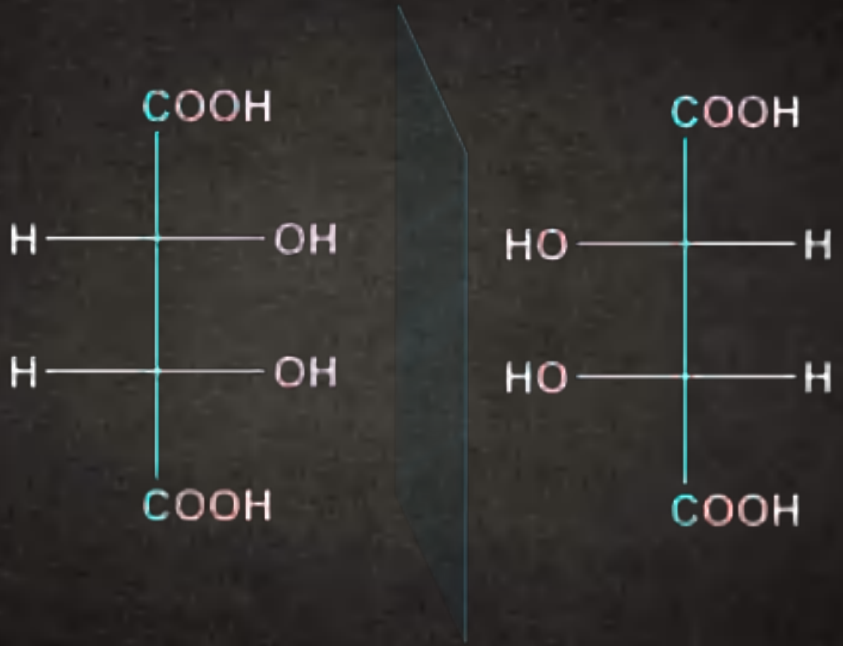
Meso Compounds

Example

Plane of symmetry

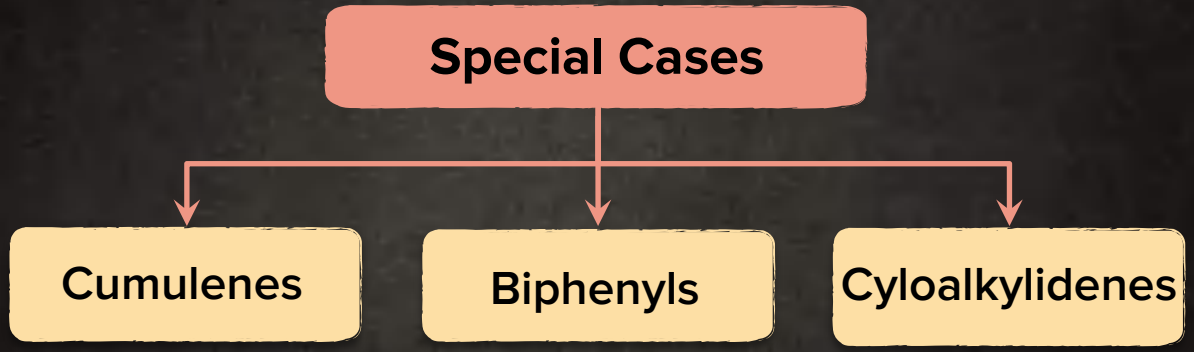
If two compounds are **meso, and mirror images** of each other, then they are **identical.**

Identical Compounds



Identical

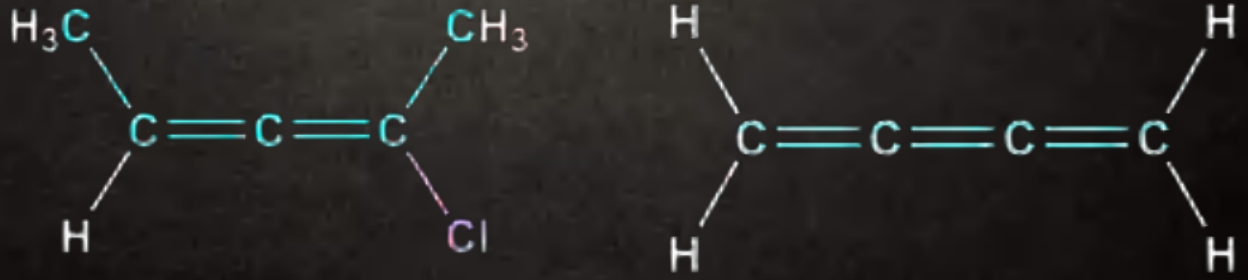
Special cases of Geometrical & Optical Isomers



Cumulenes

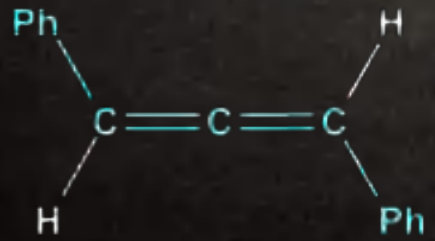
Hydrocarbons whose molecules have **cumulated double bonds** are known as cumulenes.

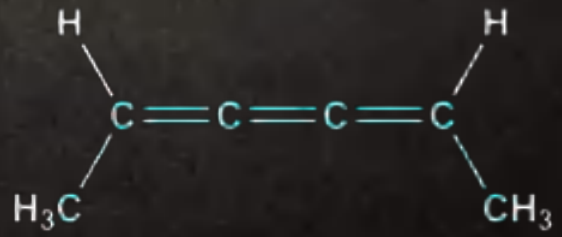
Example



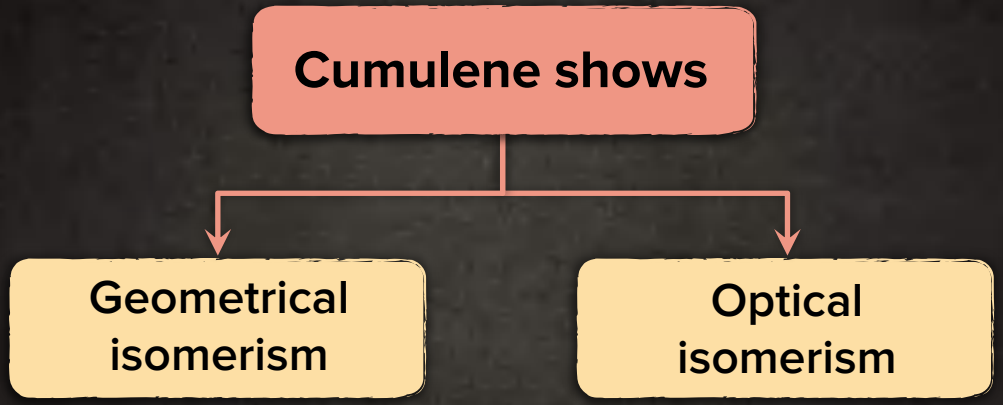
Cumulenes

Even-cumulene	Odd-cumulene
Cumulene with **even** number of **adjacent double bonds**	Cumulene with **odd** number of **adjacent double bonds**





Configurational Isomerism in Cumulenes



Geometrical Isomerism in Even-Cumulenes

In even-cumulenes, groups on the terminal carbons exist in a perpendicular plane.

↓

Generally, for compounds to exhibit geometrical isomerism, groups on the terminal carbons must be in the same plane.

↓

Hence, even-cumulenes do not show geometrical isomerism.

Geometrical Isomerism in Odd-Cumulenes

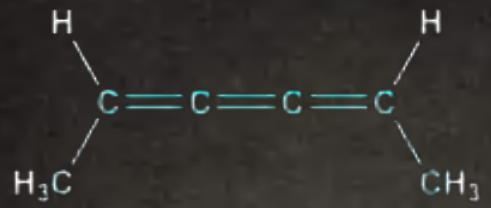
In odd-cumulenes, the **terminal groups** exist in the **same plane.**

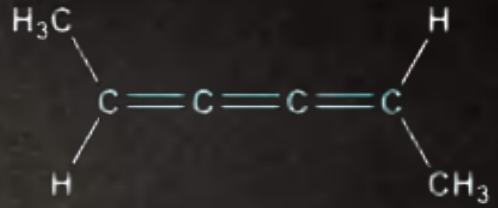
↓

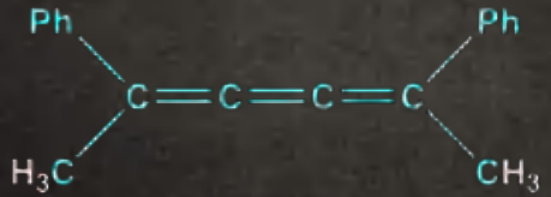
Hence, they may exhibit **geometrical isomerism.**

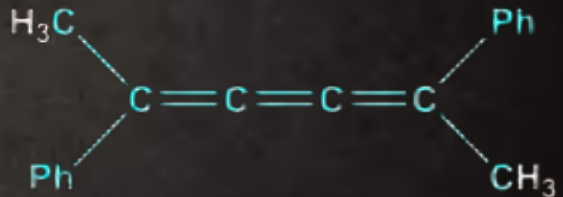
Geometrical Isomerism in Odd-Cumulenes

Examples





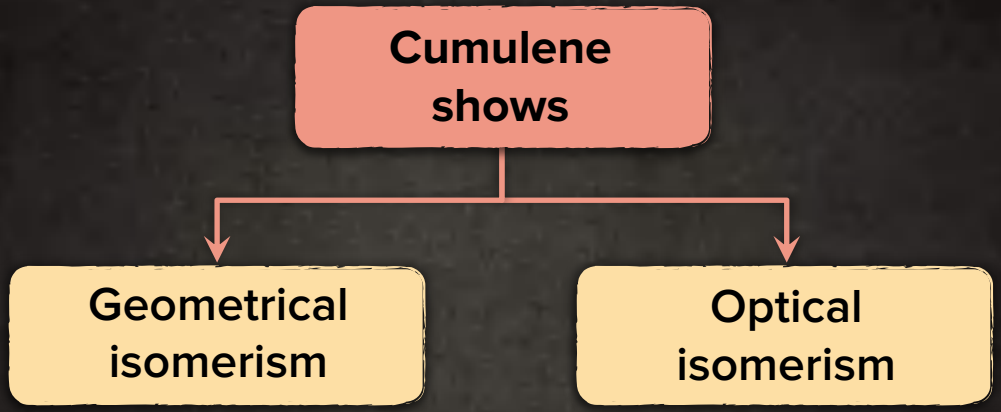




cis-form

trans-form

Configurational Isomerism in Cumulenes



Optical Isomerism in Even-Cumulenes

In even-cumulenes, two **mutually perpendicular π bonds** are formed.

Hence, the **atoms/groups** attached to the terminal sp^2 carbons are in **different planes.**

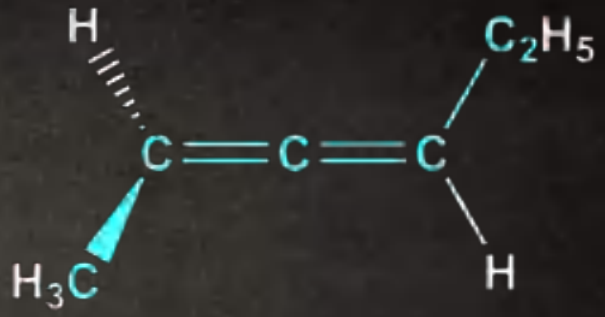
If the atoms/groups attached to terminal sp^2 carbons are **different**

So, the elements of symmetry **(i.e., POS, COS)** are **absent.**

Hence, even-cumulenes are **optically active.**

Optical Isomerism in Even-Cumulenes

Examples



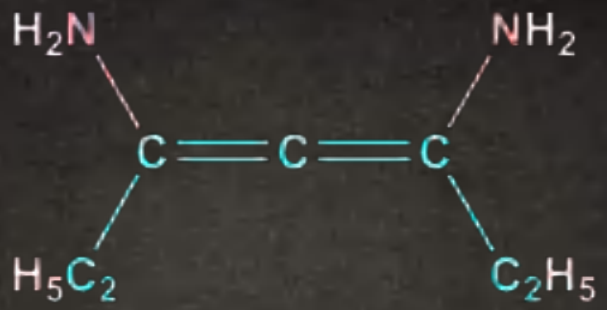
POS X

COS X

Optically active

Optical Isomerism in Even-Cumulenes

Examples



POS X

COS X

Optically active

Note!

In general

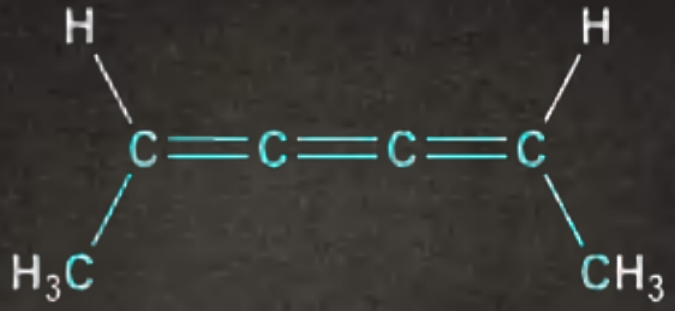
In odd-cumulenes, **terminal atoms/groups** remain in the **same plane.** Whether **terminal groups** are **different** or **same.**

POS present

Optically inactive

Optical Isomerism in Odd-Cumulenes

Examples



POS ✓

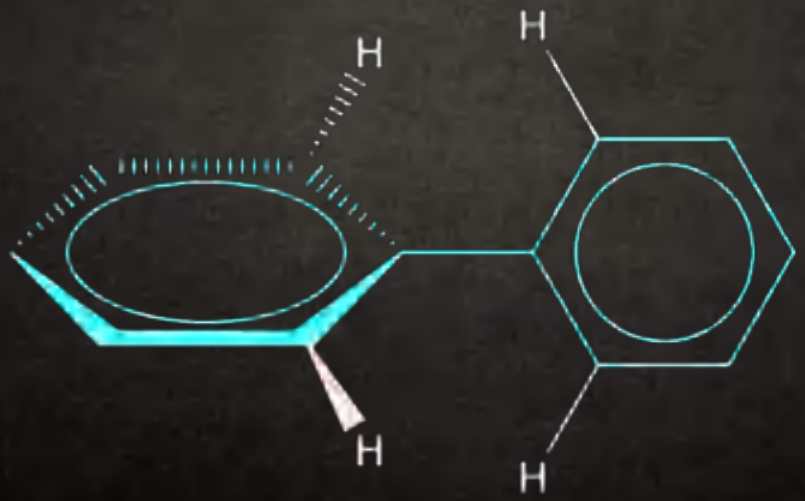
COS ✗

Optically inactive

Biphenyl System

A biphenyl system consists of **two phenyl rings** attached by a **sigma bond.**

Examples



Biphenyl System

Biphenyls containing four large groups in the ortho-positions **cannot freely rotate** about the central bond because of steric hindrance.

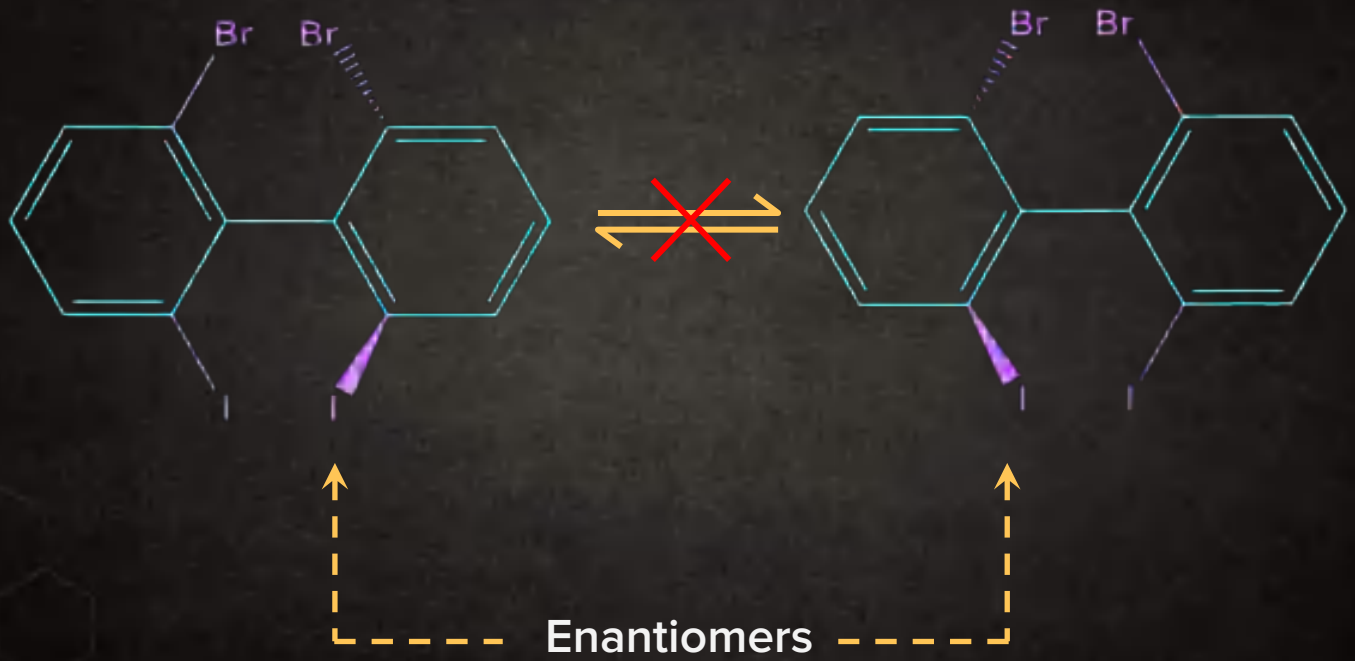
In such compounds, the two rings are in **perpendicular** planes.

Biphenyl System

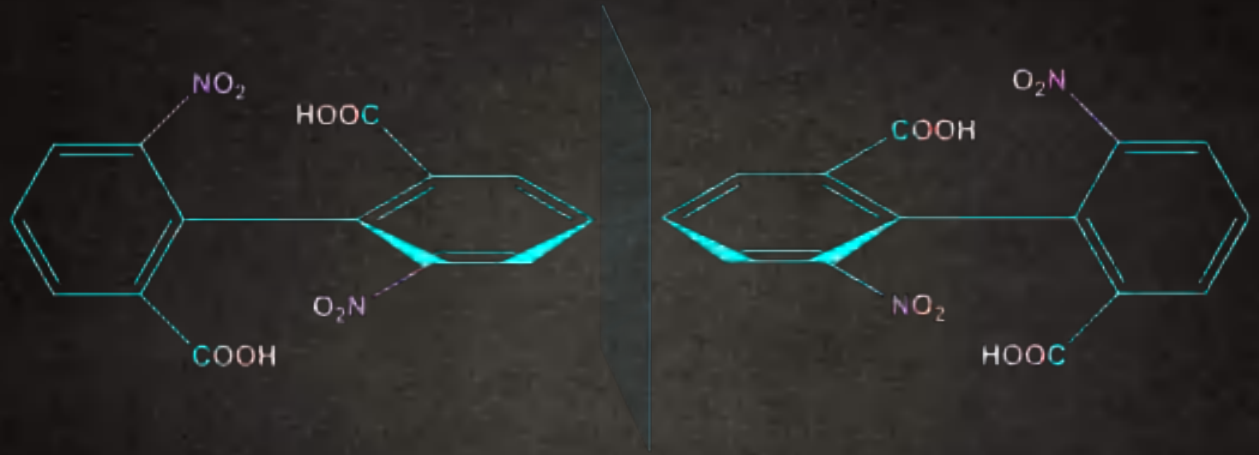
o-o′-tetrasubstituted biphenyls become **non-planar** in order to have minimum electronic repulsion among the substituents.

In this orientation (phenyl planes perpendicular to each other), the **free rotation** of C–C single bond is **restricted,** and molecule shows optical activity.

Biphenyl System



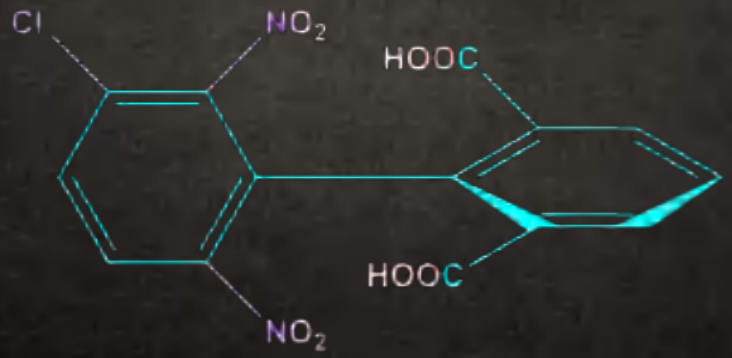
Biphenyl System



There is no plane of symmetry and hence, the molecule is **chiral**.

Biphenyl System

If either ring is **symmetrically substituted**, the molecule has a plane of symmetry. Hence, **optically inactive**.



Note!

Generally, groups in the **para** position **cannot** cause the lack of symmetry.

Atropisomers

Isomers that can be separated only because **rotation** about single bonds is **prevented**.

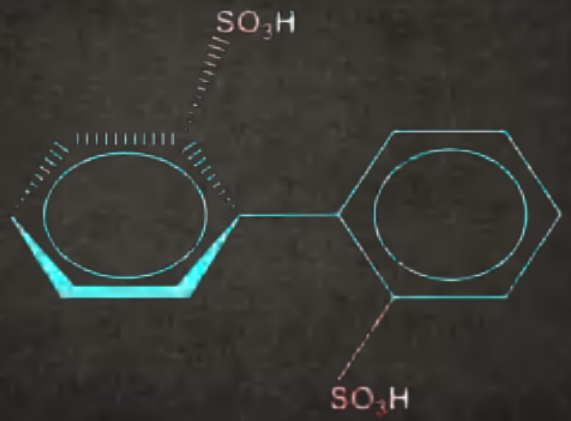
Atropisomers

It is **not always necessary** for four large ortho groups to be present for the rotation to be prevented.

Compounds with three and even two groups, if **large enough** and suitably substituted, can have hindered rotation.

Example

Biphenyl-2,2′-bis-sulphonic acid



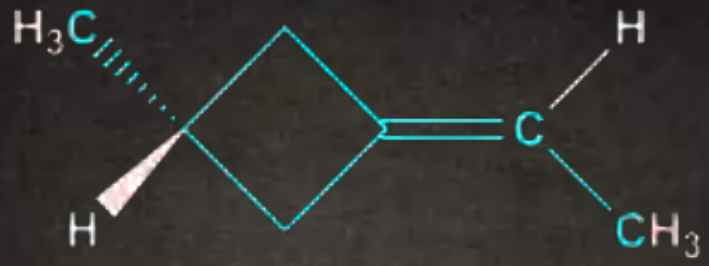
Optically active.

Cycloalkylidenes

One of the **double bonds in allenes** is **replaced** by one **cycloalkane ring.**

Example

Cycloalkylidenes

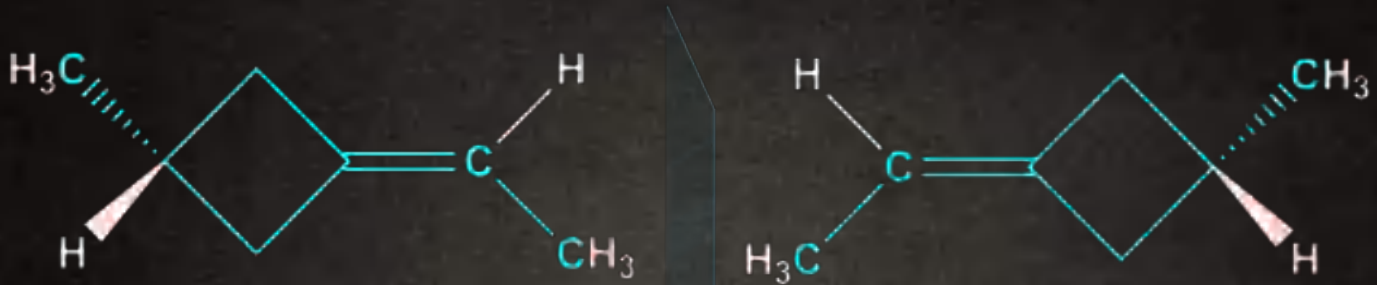


POS X

COS X

Optically active.

Cycloalkylidenes



Enantiomeric pairs

Note!

Presence of a chiral carbon is **neither a necessary nor a sufficient** condition for optical activity.

Optical activity may be present in molecules with **no chiral atom**.

Some molecules with two or more chiral carbon atoms are **superimposable** on their mirror images and hence, **optically inactive**.

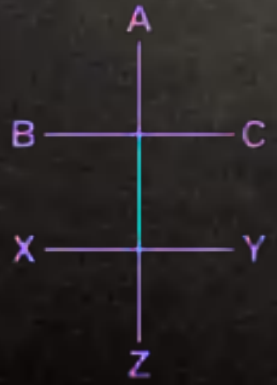
Prediction of Optical Rotation

Relation between compounds	Optical rotation
Identical	+ x°
Enantiomer	- x°

$[\alpha] = +x°$

Prediction of Optical Rotation

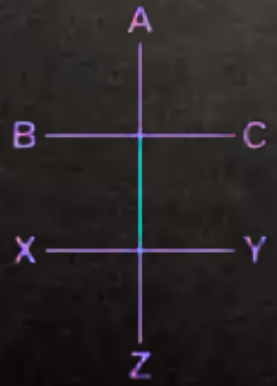
Relation between compounds		Rotation
Diastereomers	Achiral	Zero
	Chiral	Cannot be predicted



$[\alpha] = +x°$

Prediction of Optical Rotation

Relation between compounds		Rotation
Structural isomer	Achiral	Zero
	Chiral	Can not be predicted



$[\alpha] = +x°$

Note!

Optical rotation of a mixture can also be predicted if the mixture is a **racemic mixture.**

Optical rotation would be 0°

Optical Purity

Sometimes we may deal with a mixture that is **not a racemic mixture**. In these cases, we specify the optical purity of the mixture.

It is defined as the **ratio** of observed rotation to the rotation of pure enantiomer.

$$\text{Optical purity} = \frac{\text{Observed optical rotation}}{\text{Optical rotation of pure enantiomer}} \times 100$$

Example

If we have some 2-Butanol with observed rotation of **+9.72**, we compare this rotation with **+13.5** rotation of the pure (+) enantiomer.

$$\text{Optical purity} = \frac{9.72}{13.5} \times 100 = 72\%$$

That means **72%** is pure (+) 2-Butanol and **28%** is racemic mixture.

Example

Total (+) isomer = 72 + 14 = 86%

Total (-) isomer = 14%

Enantiomeric Excess

Enantiomeric Excess

To compute the enantiomeric excess of a mixture, we calculate the **excess of predominant enantiomer** as a percentage of the entire mixture.

The calculation of enantiomeric excess gives the **same result** as the calculation of **optical purity**.

Enantiomeric Excess

Optical purity = Enantiomeric excess

$$= \frac{|d - \ell|}{d + \ell} \times 100$$

$$= \frac{\text{Excess of one enantiomer over other}}{\text{Entire mixture}} \times 100$$

Example

If we have some 2-Butanol with observed rotation of +9.72, we compare this rotation with +13.5 rotation of the pure (+) enantiomer.

Optical purity = Enantiomeric excess

= d – ℓ = 72%

d + ℓ = 100%

Example

$2d = 172$

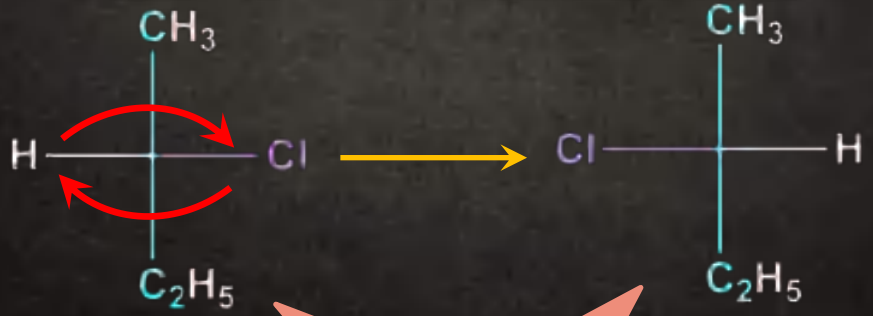
Composition of mixture

$d = 86\%$

$\ell = 14\%$

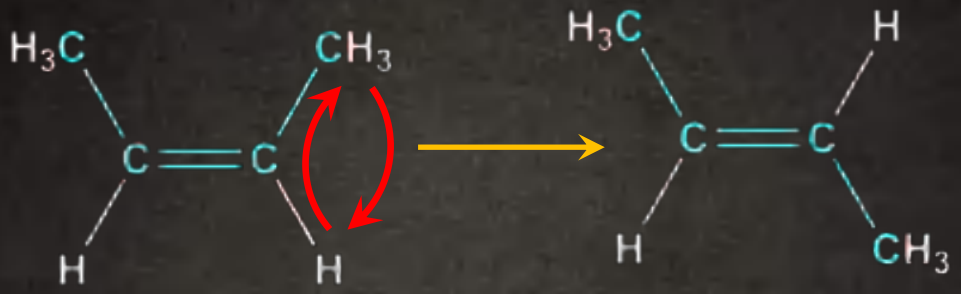
Stereo Centre

An atom or bond bearing groups such that the **interchange of any two groups** produces a stereoisomer.



Stereoisomers

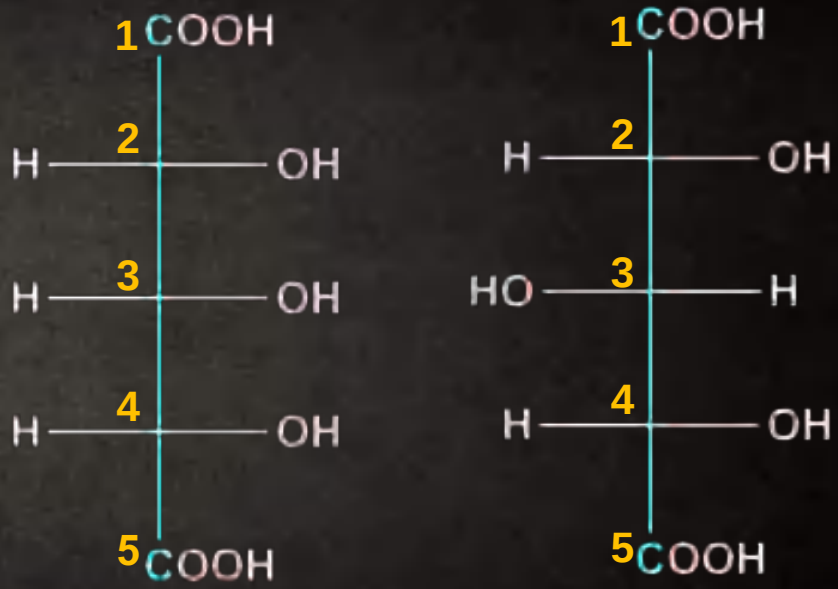
Stereo Centre



Stereoisomers

Pseudo Chiral Centre

An atom that is attached to **two constitutionally like chiral groups and two other distinct atoms**/ groups.



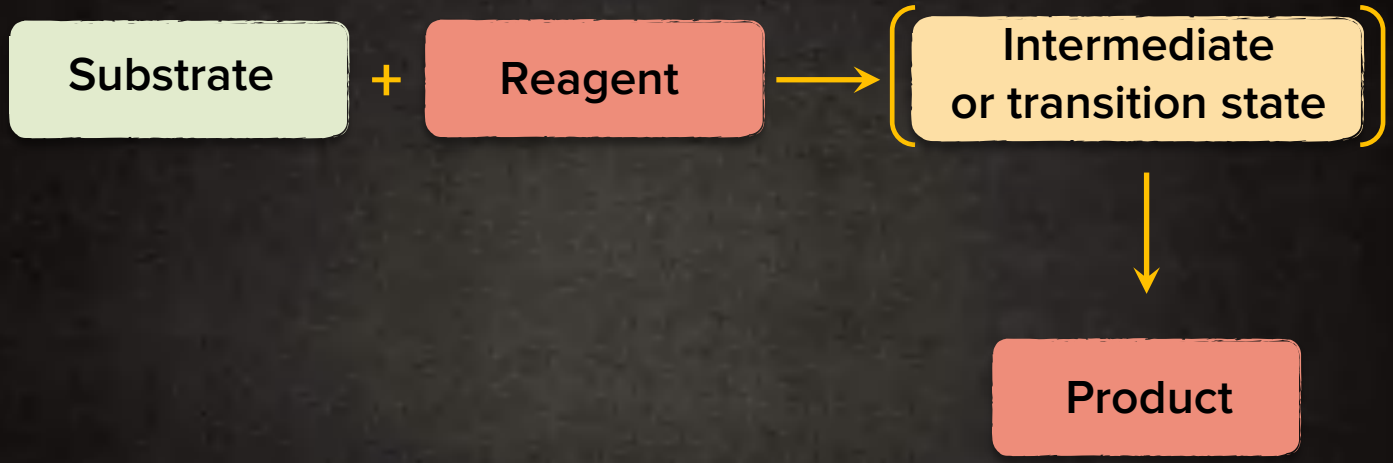
C-3 is a pseudo chiral centre.

Calculation of Number of Stereoisomers

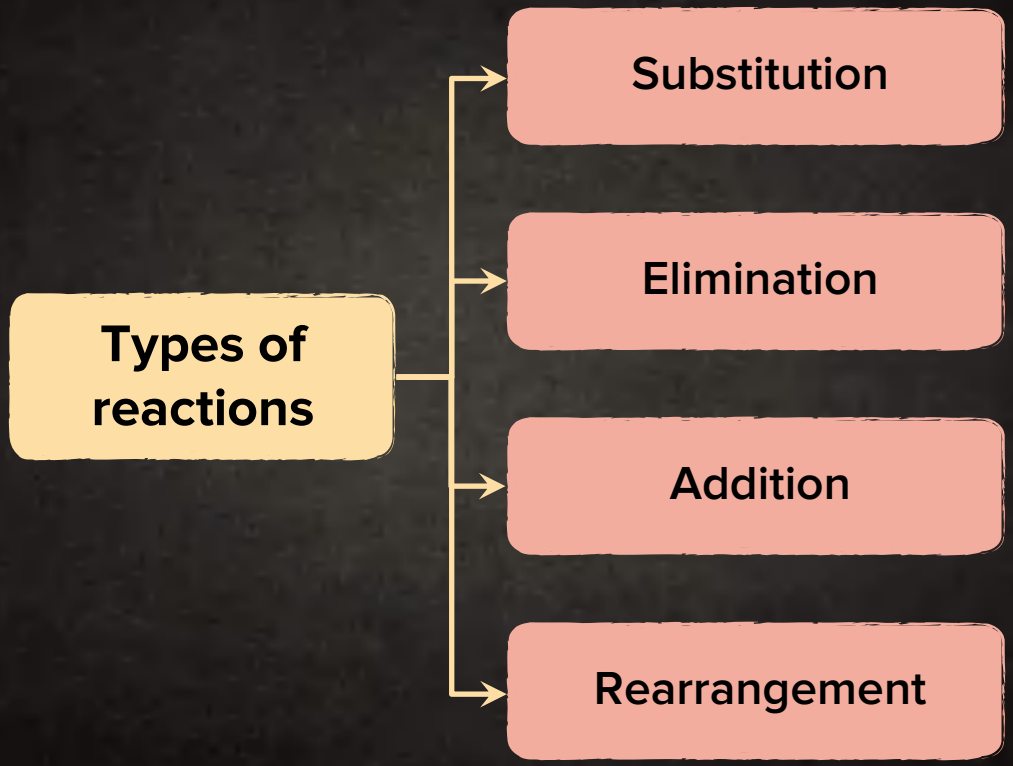
Maximum number of stereoisomers = 2^n

Where ‘n’ is the number of stereo centres

General Reaction in Organic Chemistry



Types of Reactions



Substitution Reaction

Replacement of an atom or group **by any other atom or group** in a molecule is known as **substitution reaction**.

Nucleophilic Substitution Reaction

If substitution reaction is brought about by a **nucleophile**, then it is known as **nucleophilic substitution reaction.**

Nu Nucleophile

lg Leaving group

Nucleophile (Nu)

Electron rich species having **at least one unshared** pair of electron.

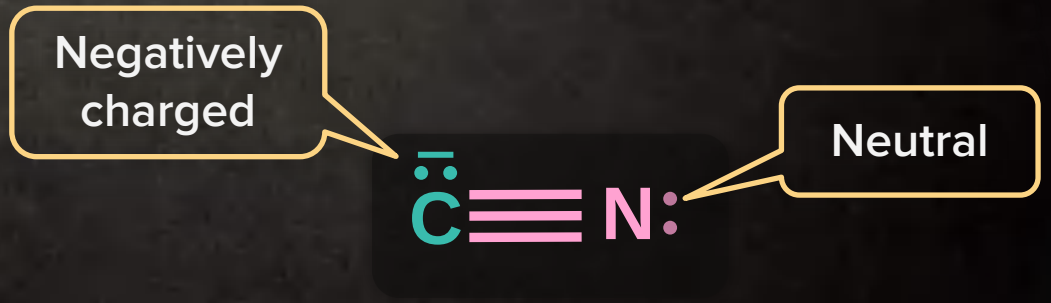
- Neutral or negatively charged
- Always a Lewis base

Examples: CN^-, OH^-, Br^-, I^-, NH_3, H_2O, etc.

Ambident Nucleophiles

Some nucleophiles have a pair of electrons on each of **two or more atoms,** or canonical forms can be drawn in which two or more atoms bear an unshared pair of electrons.

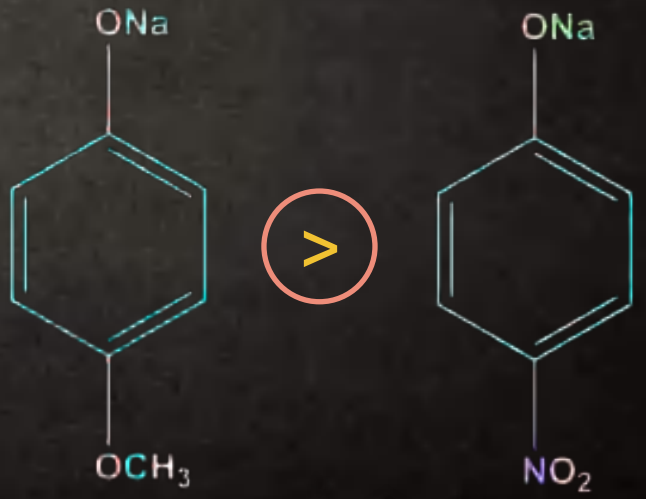
Nucleophiles which have **two attacking sites,** one **negatively charged and one neutral** site, are known as ambident nucleophiles.



Criteria for Nucleophilicity

Tendency to **give electron pair** to an electron deficient atom is called **Nucleophilicity**.

01 Factors that **increase electron density** at donor atom, increases nucleophilicity.



Criteria for Nucleophilicity

02

The more polarisable donor atom is the better nucleophile.

Periodicity

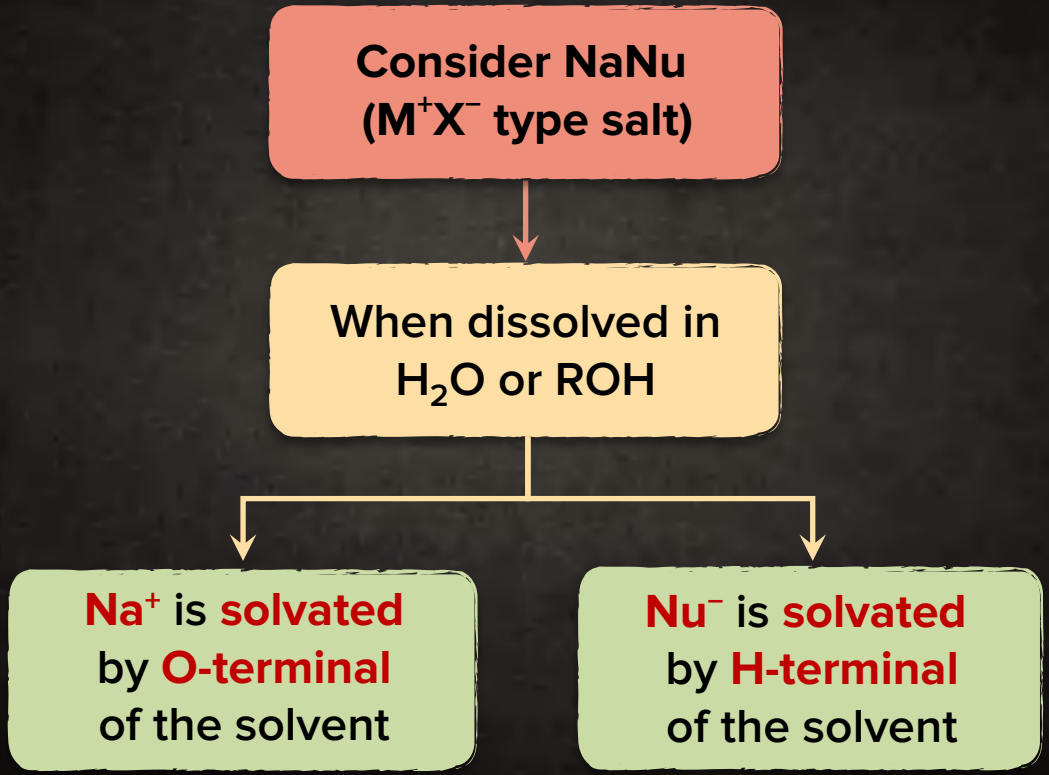
Along the period → Nucleophilicity ↓

CH_3^- > NH_2^- > OH^- > F^-

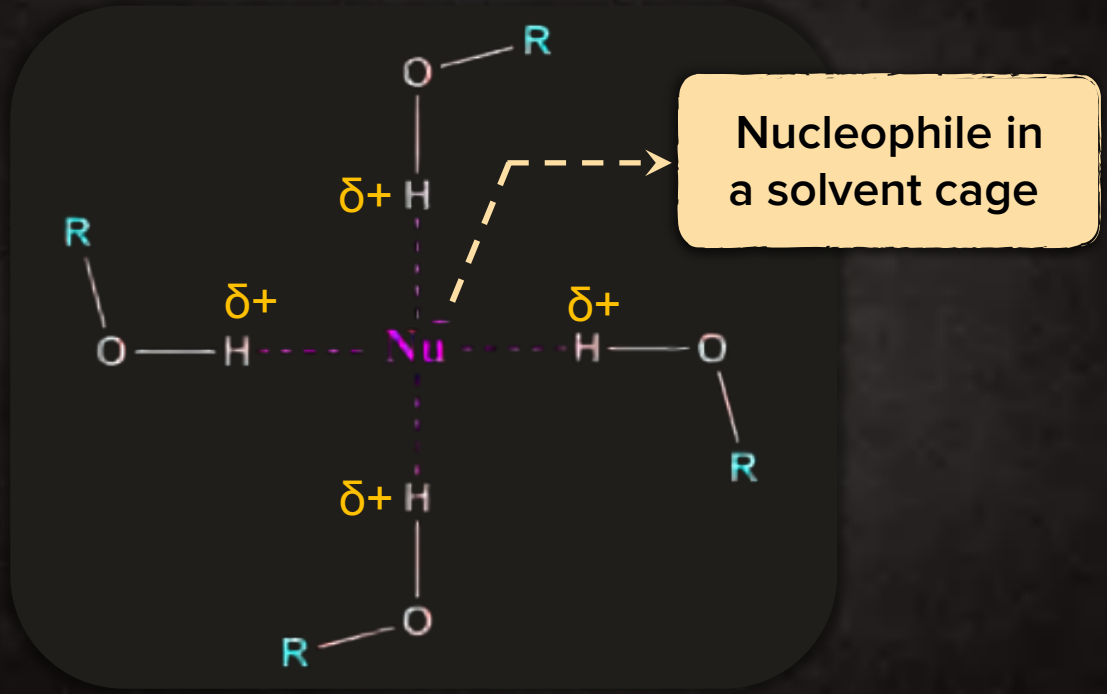
In polar protic solvent → Down the group → Nucleophilicity ↑

F^- < Cl^- < Br^- < I^-

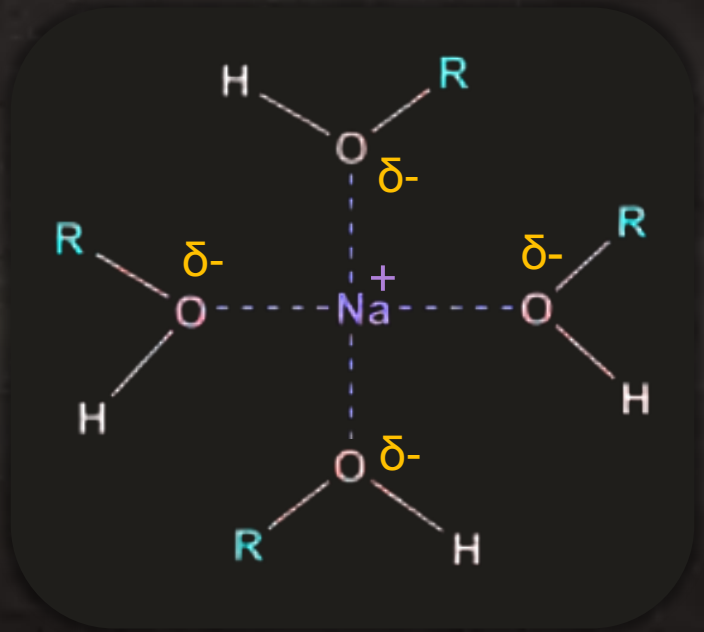
Nucleophilicity in Polar Protic Solvents



Nucleophilicity in Polar Protic Solvents



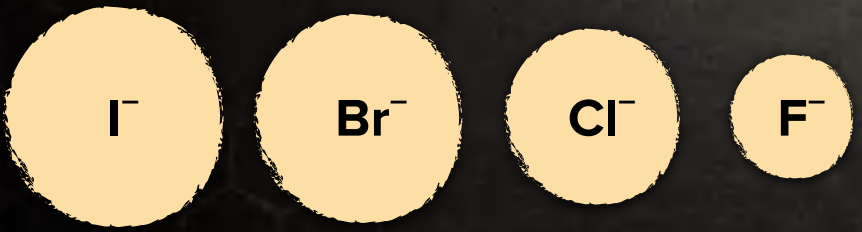
Nucleophilicity in Polar Protic Solvents



Nucleophilicity in Polar Protic Solvents

The degree of solvation of anions increases with the decrease in the size of the anions.

Example



Degree of solvation increases

Size of solvated ion increases

Nucleophilicity decreases

Nucleophilicity in Polar Protic Solvents

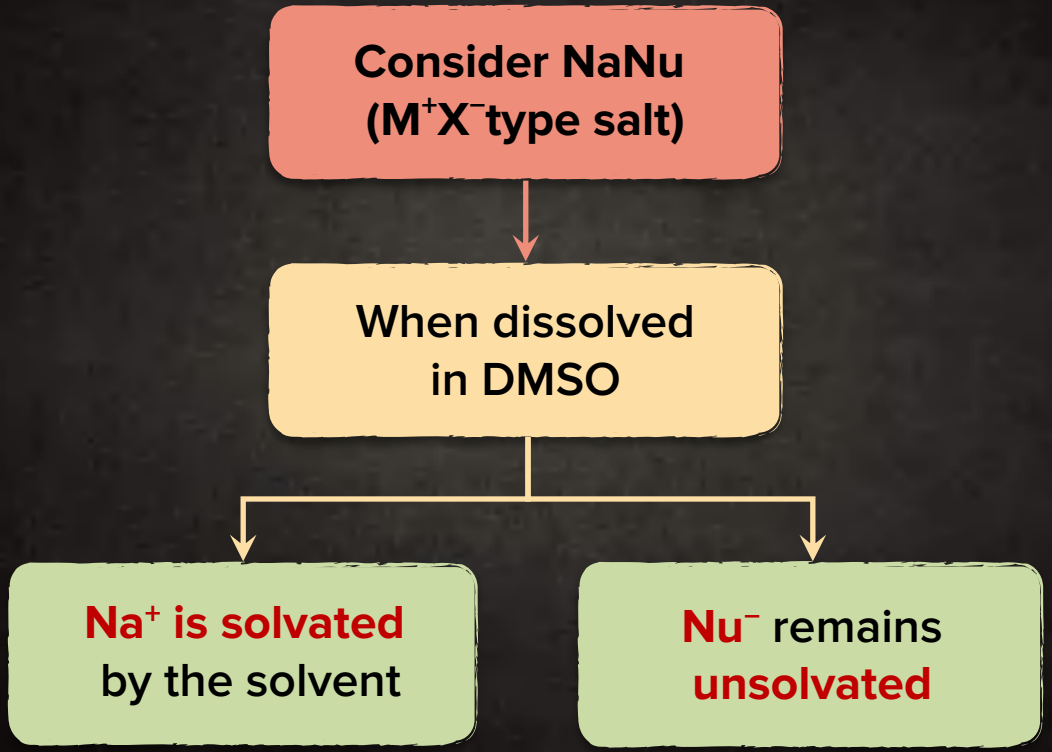
Bigger the solvated ion, **lesser** the nucleophilicity.

In polar protic solvents, **nucleophilicity increases down the group.**

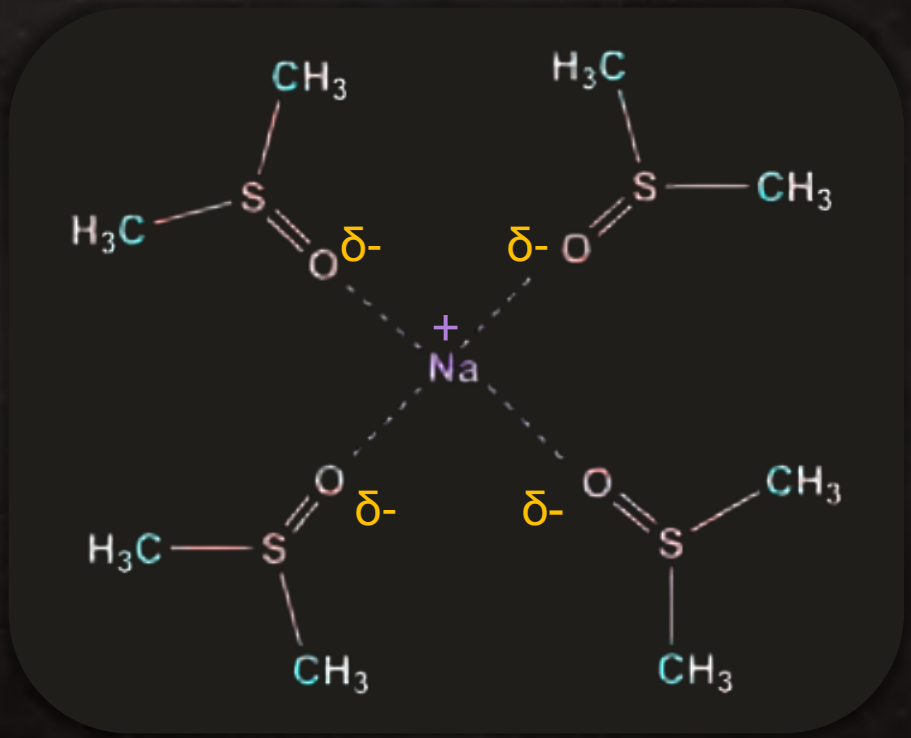
In polar aprotic solvent → Down the group → Nucleophilicity ↓

$F^- > Cl^- > Br^- > I^-$

Nucleophilicity in Polar Aprotic Solvents



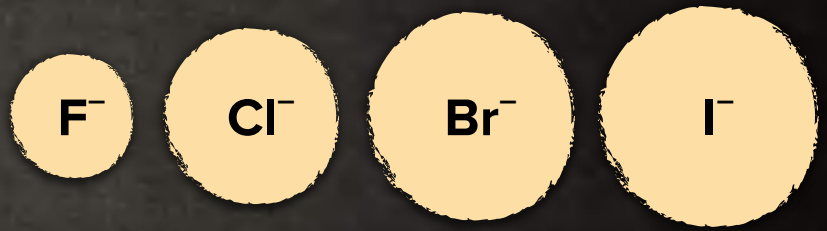
Nucleophilicity in Polar Aprotic Solvents



Nucleophilicity in Polar Aprotic Solvents

Example

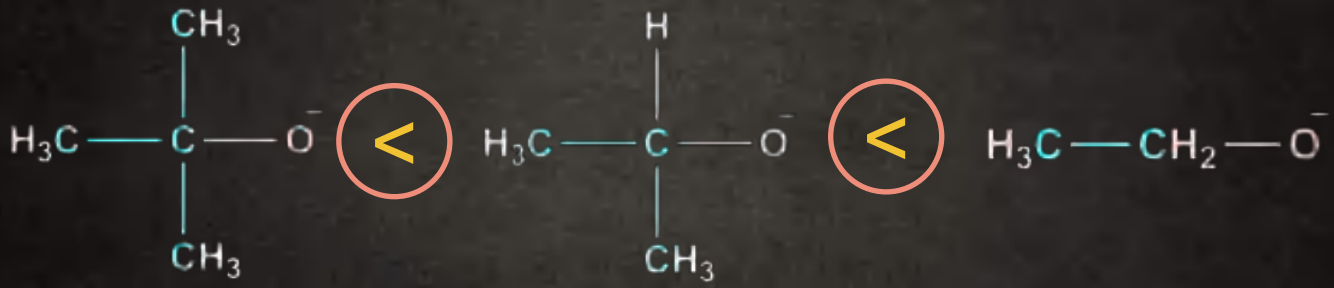
Size increases



Nucleophilicity decreases

Steric Hindrance

Nucleophilicity $\propto \frac{1}{\text{Steric hindrance}}$



(a) (b) (c)

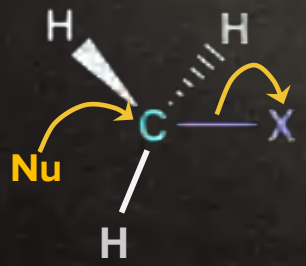
Nucleophile (a) **cannot approach electrophile easily.**

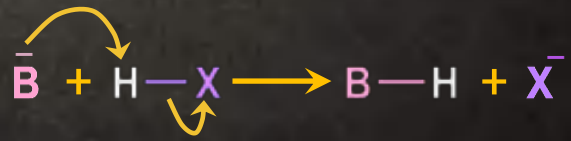
Nucleophilicity

Measure of how readily a species is able to **attack** an electron-deficient atom.

Basicity

Measure of how well, a species **abstracts** a proton.





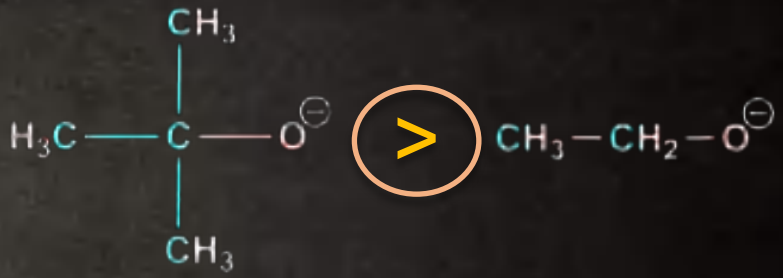
Nucleophilicity	Basicity
Kinetic property	Thermodynamic property
Determined by rate constant	Determined by equilibrium constant
Strong nucleophiles are strong bases	Strong bases are not necessarily be strong nucleophiles

Note:

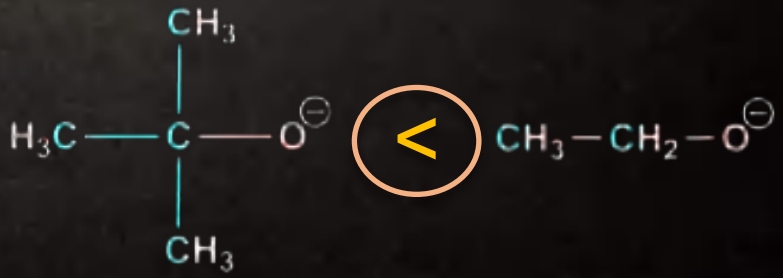
Mostly, nucleophilicity and basicity runs in parallel. But there are **exceptions**.

Sterically crowded bases are poor nucleophiles

Order of basicity



Order of nucleophilicity



Leaving Group

In a reaction in which the substrate molecule becomes **cleaved**, part of it (the part **not containing the carbon**) is usually called the leaving group.

Nucleofuge

Leaving group that **carries away** an electron pair.

Electrofuge

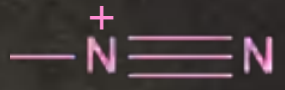
Leaving group that comes away **without** an electron pair.

Leaving Group Ability

Generally, **leaving group** carries away an electron pair

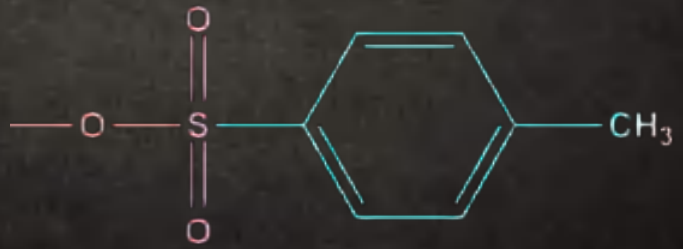
For nucleofuge, **weaker bases** are good leaving groups.

Examples

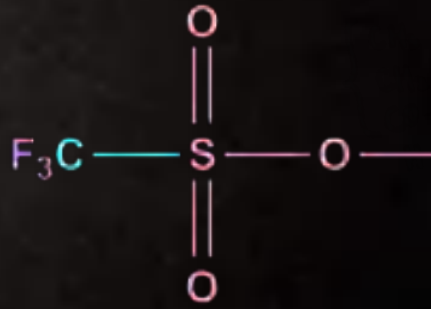


Dinitrogen

Halide



Tosylate



Triflate

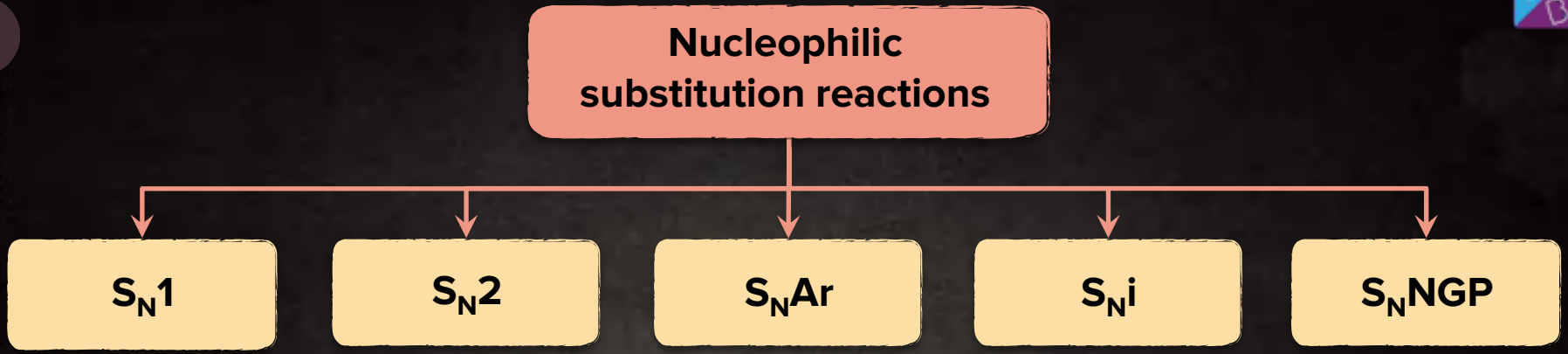
Examples

$F^- < Cl^- < Br^- < I^-$

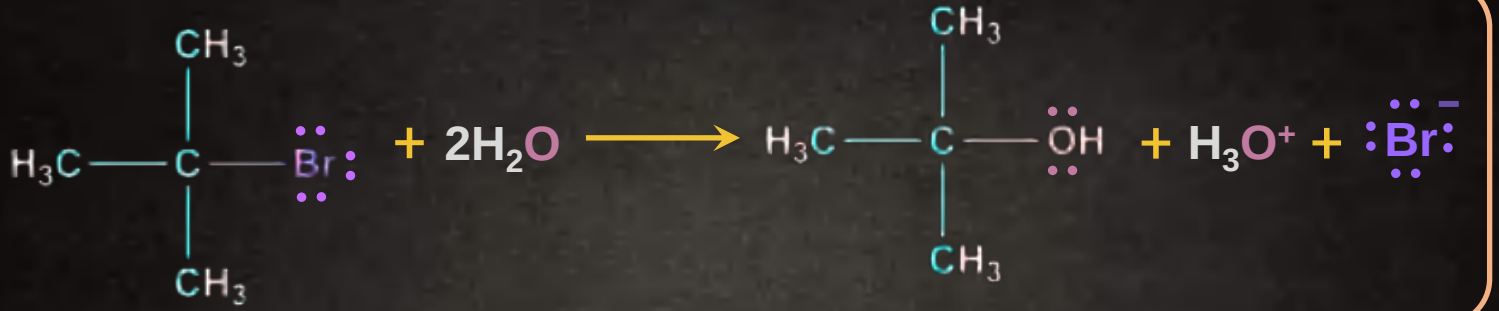
$CH_3^- < NH_2^- < OH^- < F^-$

$R\text{-}COO^- > PhO^- > HO^-$

Different Kind of Mechanisms for Nucleophilic Substitution Reaction


Nucleophilic substitution reactions
S_N1
S_N2
S_NAr
S_Ni
S_NNGP

S_N1 Reaction

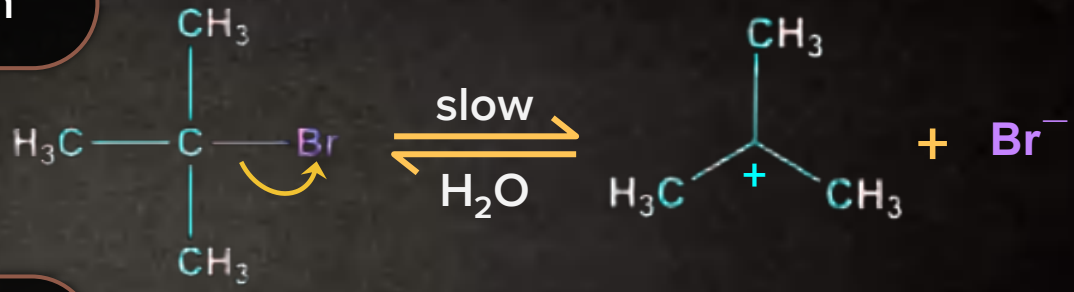


Step 1 Formation of carbocation

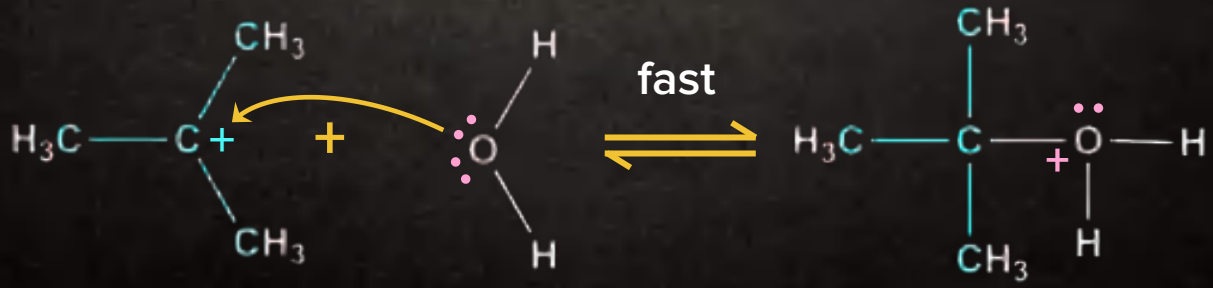
Step 2 Attack of nucleophile

Steps involved in S_N1 Reaction

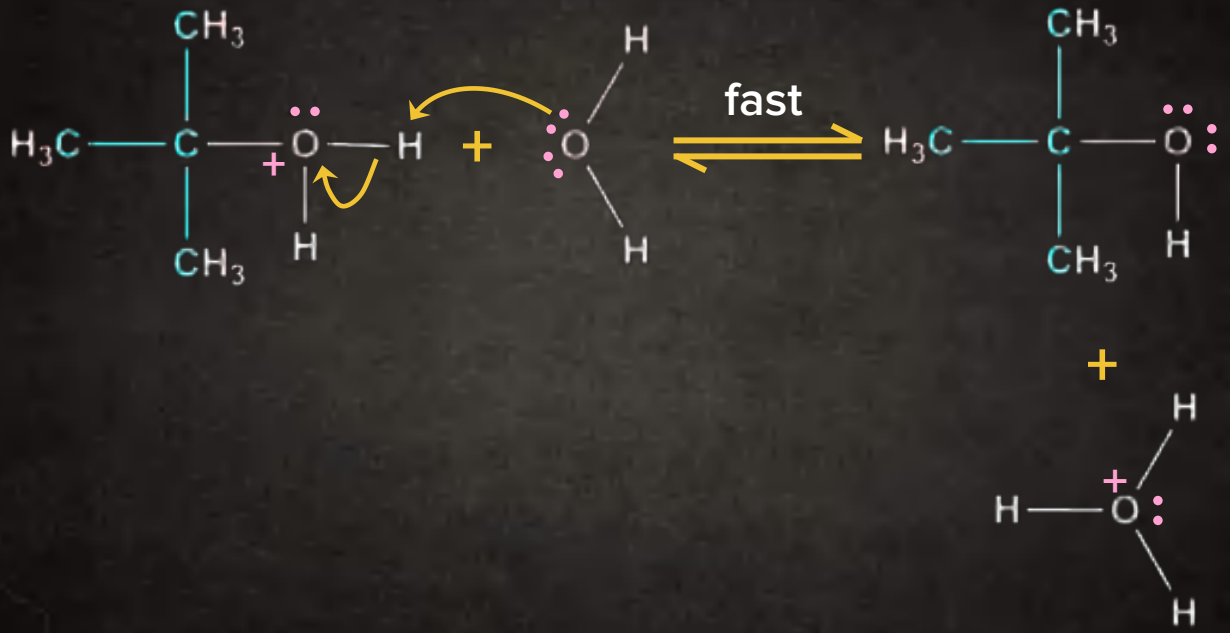
Step 1 Formation of carbocation



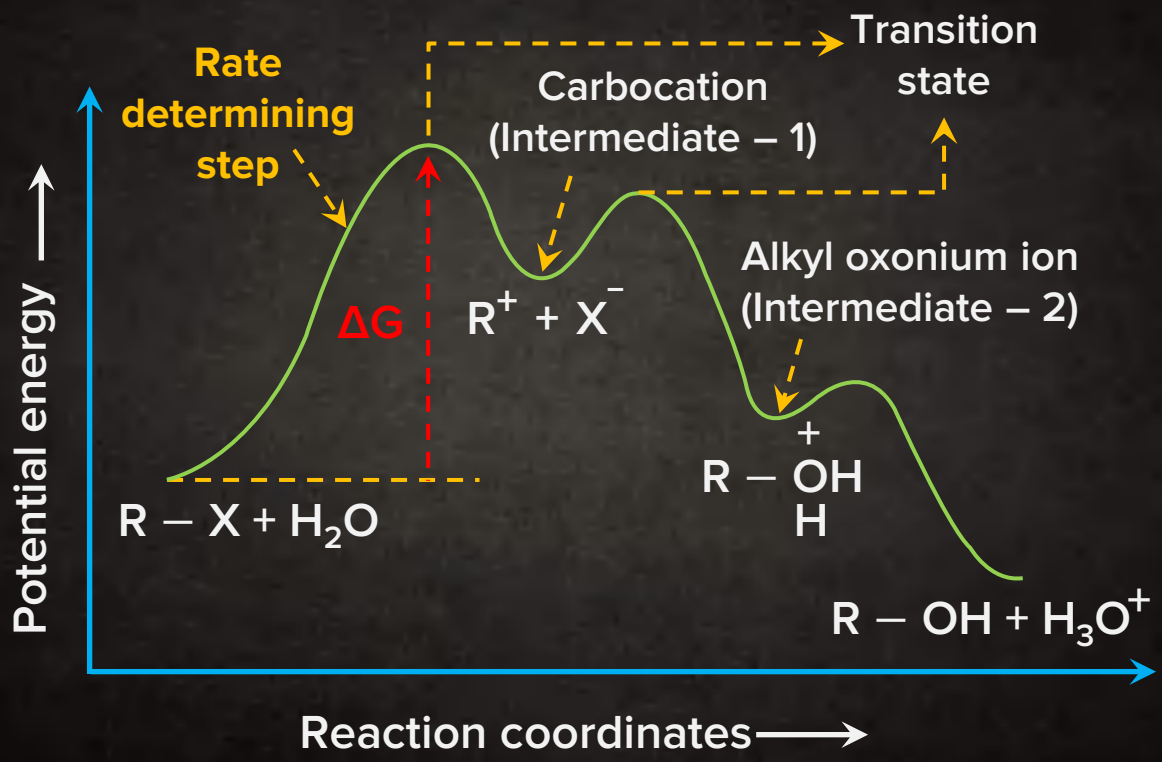
Step 2 Attack of nucleophile



Deprotonation



Energy Profile Diagram of S_N1 Reaction



Characteristics of S_N1 Reactions

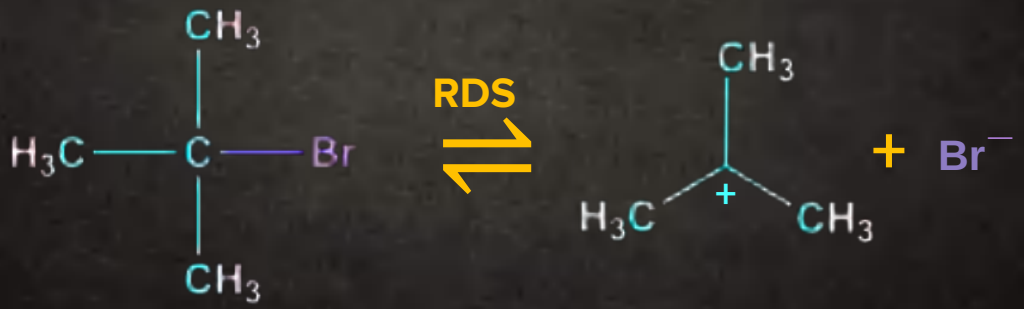
1. It is a **unimolecular, two step** process.

2. **A carbocation** intermediate is formed, so **rearrangement** is possible in S_N1 reaction.

The rate of S_N1 reaction is **independent** of the concentration and nature of the **nucleophile.**

Characteristics of S_N1 Reactions

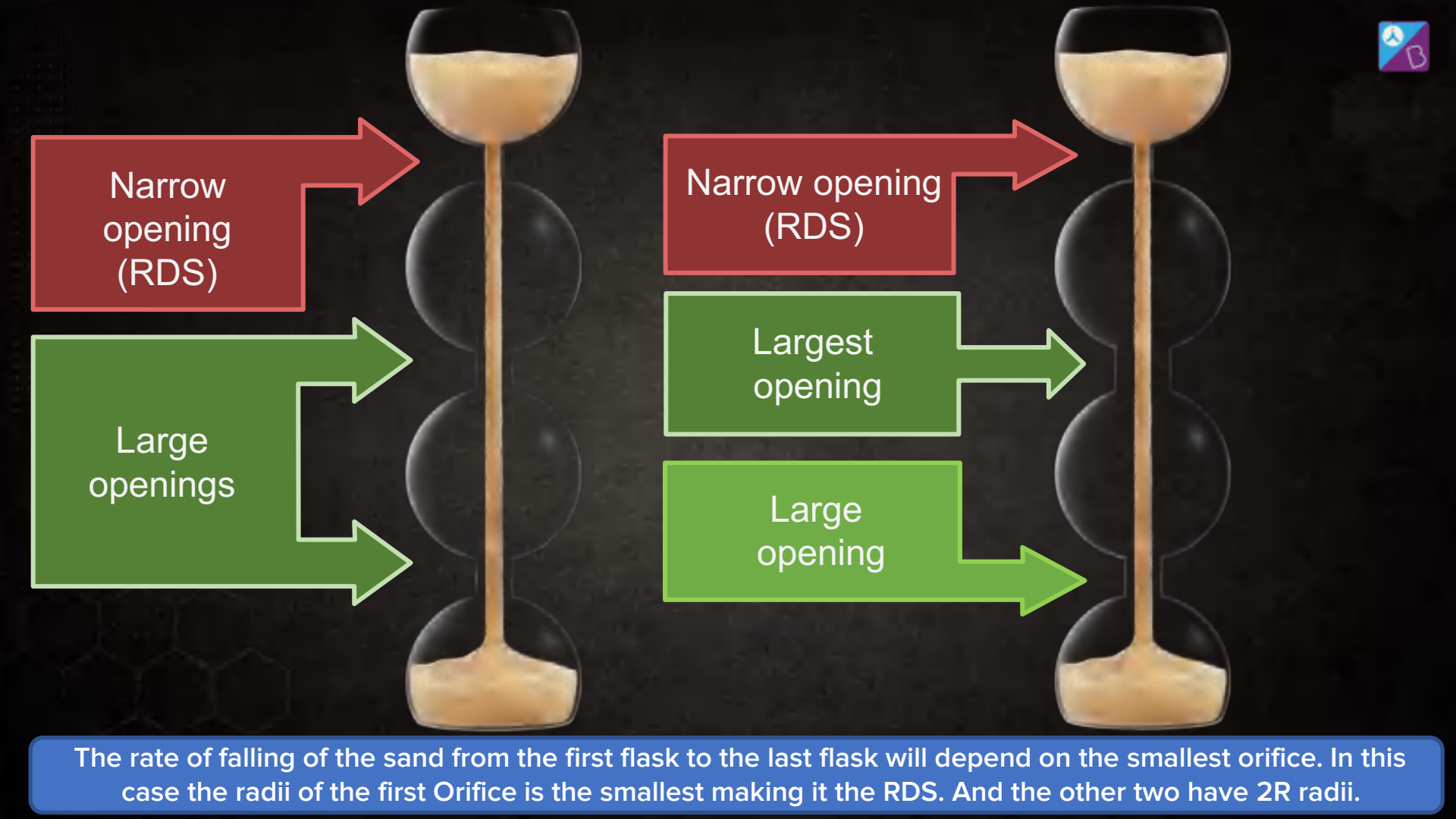
Rate ∝ [Alkyl halide] → First step must be the slow and rate-determining step.



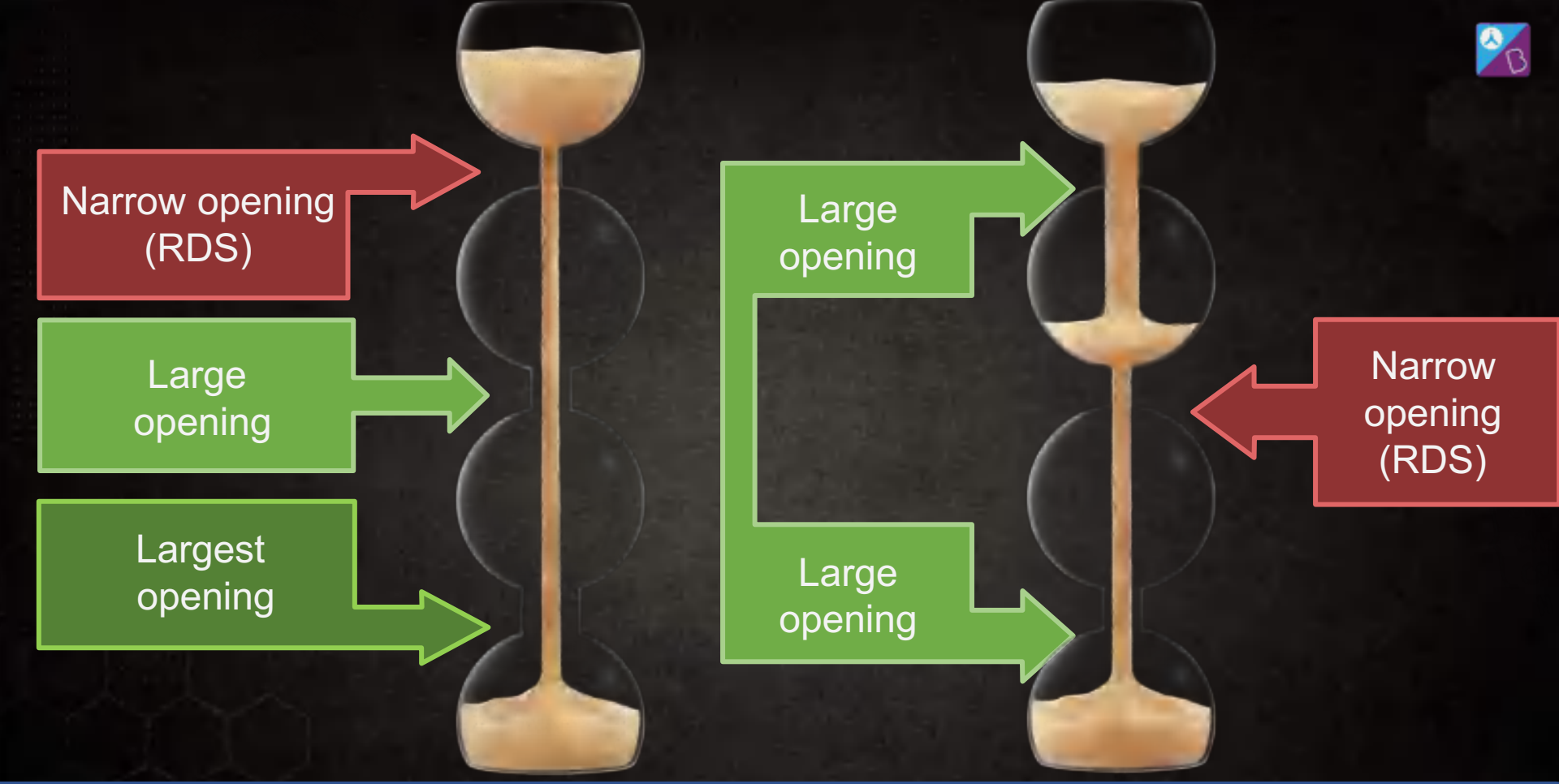
Rate-Determining Step (RDS)

If one step in a multistep reaction is **intrinsically slower** than all the others, then the rate of the overall reaction will be essentially the same as the rate of this slowest step.

This slowest step is known as the **rate-limiting** step or the **rate-determining step.**



The rate of falling of the sand from the first flask to the last flask will depend on the smallest orifice. In this case the radii of the first Orifice is the smallest making it the RDS. And the other two have 2R radii.



The rate of falling of the sand from the first flask to the last flask will depend on the smallest orifice. In this case the radii of the first Orifice is the smallest making it the RDS. And the other two have 3R and 2R respectively.

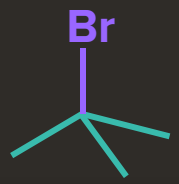
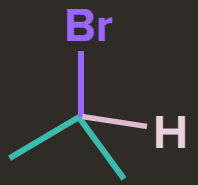
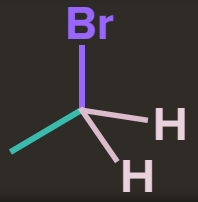
Nature of Alkyl Halide

Rate of S_N1 Reaction Depends on Carbocation Stability

S_N1 reactivity

$CH_3–X$ < 1° Alkyl halide < 2° Alkyl halide < 3° Alkyl halide

Rates of S_N1 Reactions with H_2O

Alkyl bromide	Class of alkyl bromide	Relative rate
	Tertiary	12,00,000
	Secondary	11.6
	Primary	≃ 0

Regioselective Reaction

When a reaction that can potentially yield **two or more** constitutional isomers

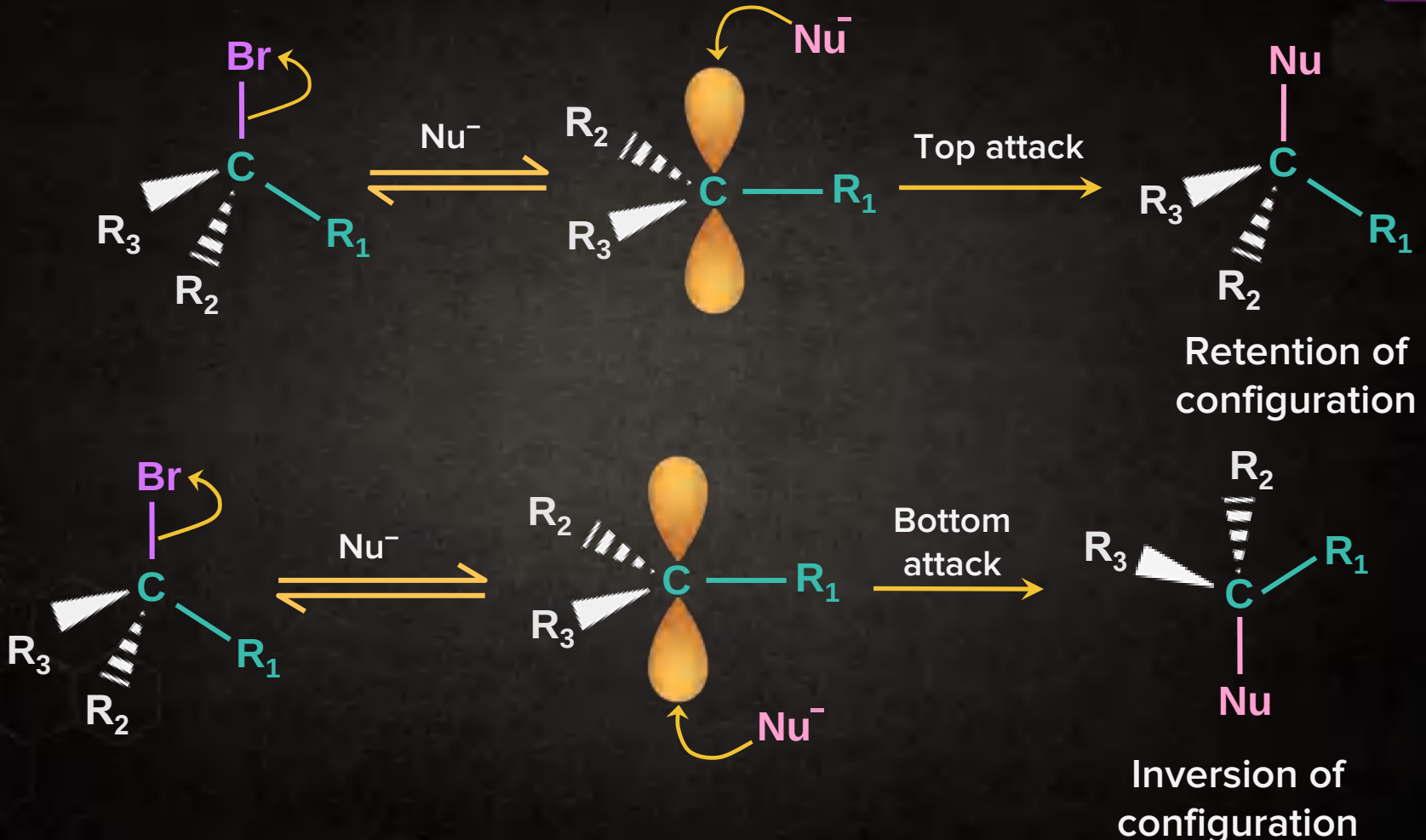
Actually, produces **only one** (or a predominance of one), the reaction is said to be **regioselective**.

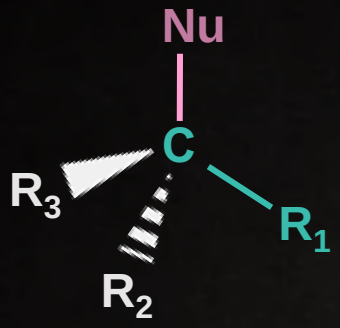
It is a **regioselective** reaction, where the most stable carbocation gives the major product.

Stereochemistry of S_N1 Reaction

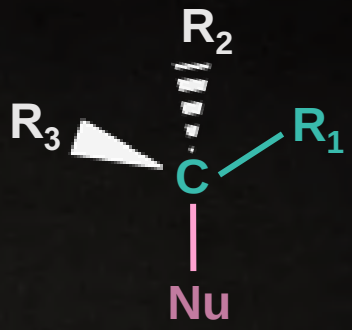
In the S_N1 mechanism, the carbocation intermediate is sp^2 hybridised and planar.

A nucleophile can attack on the carbocation from either face. If the reactant is chiral, then the attack of the nucleophile from both faces gives enantiomers as the product, which is known as racemisation.


Br
C
R3
R2
R1
Nu⁻
Nu⁻
R2
C
R1
R3
Top attack
Nu
C
R3
R1
R2
Retention of configuration
Br
C
R3
R2
R1
Nu⁻
R2
C
R1
R3
Nu⁻
Bottom attack
R2
R3
C
R1
Nu
Inversion of configuration



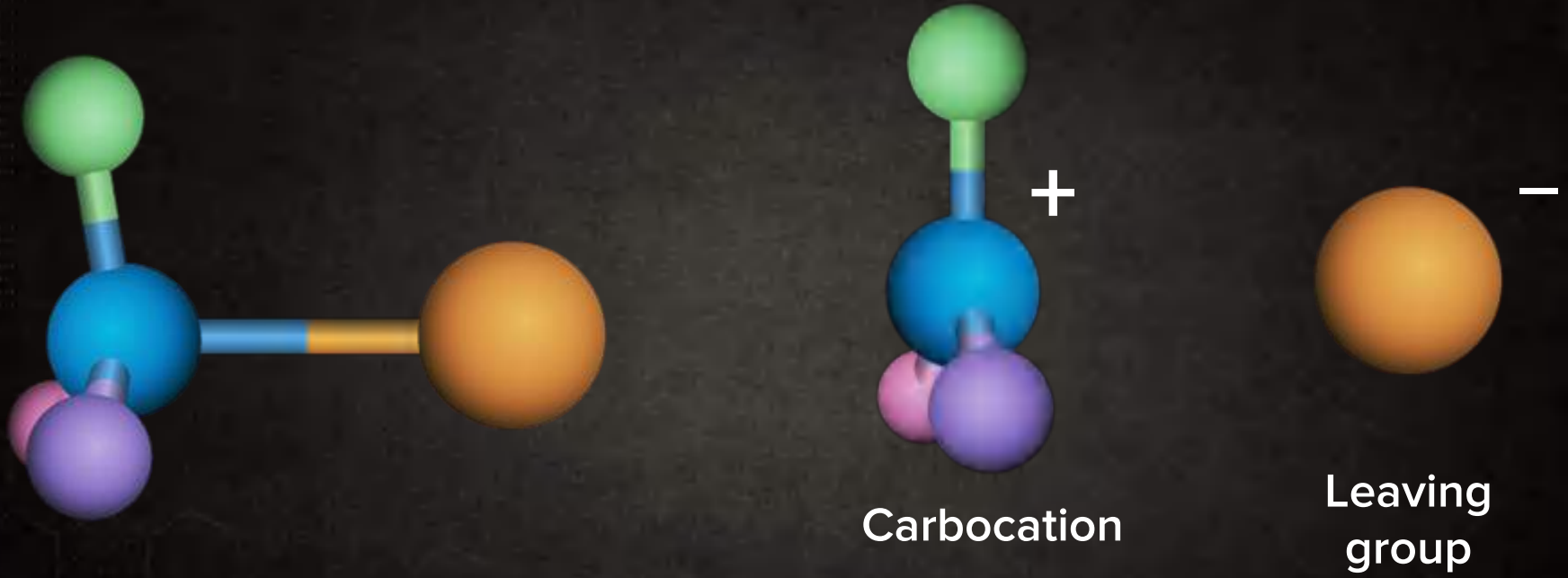
Retention of configuration

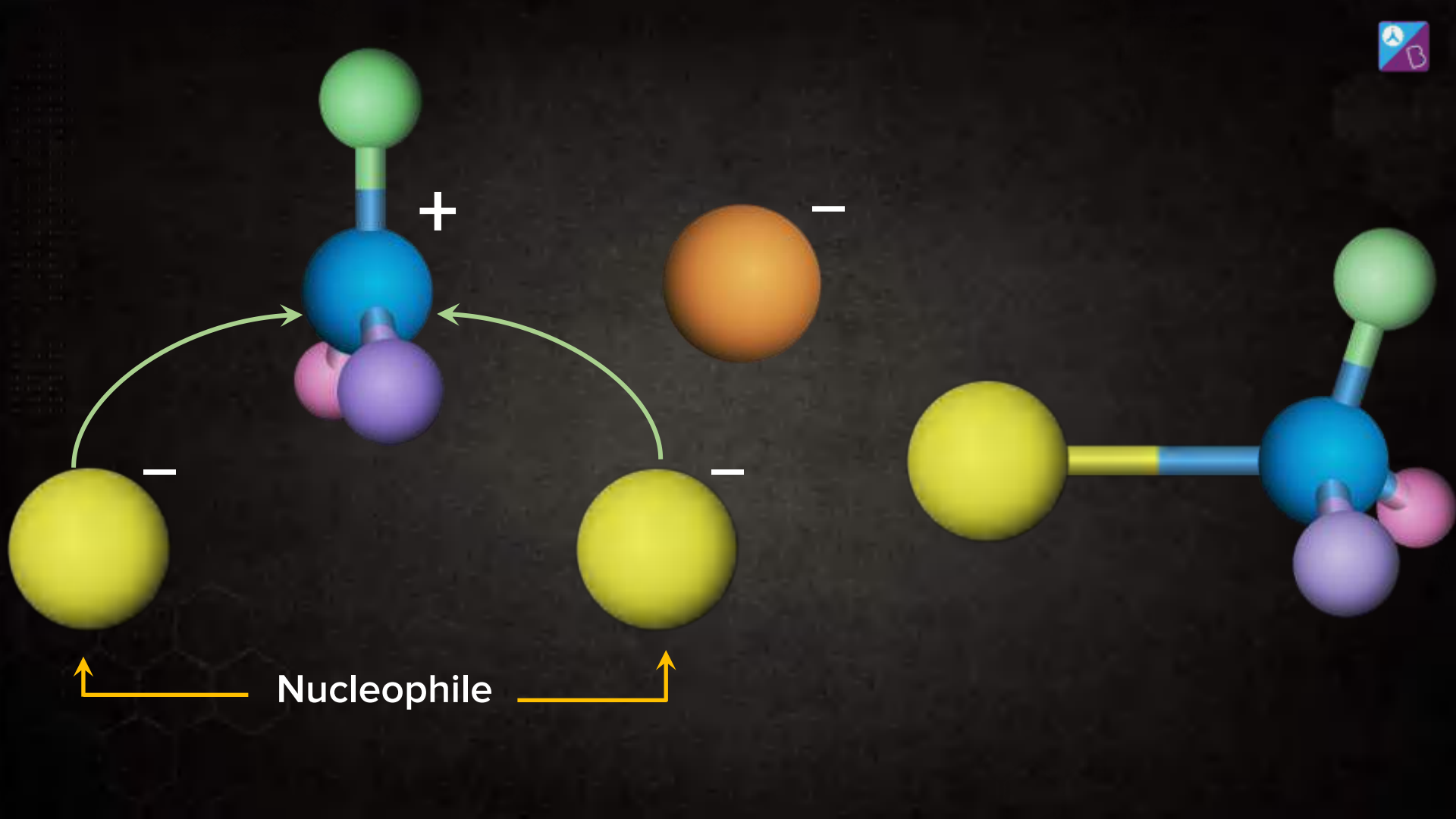


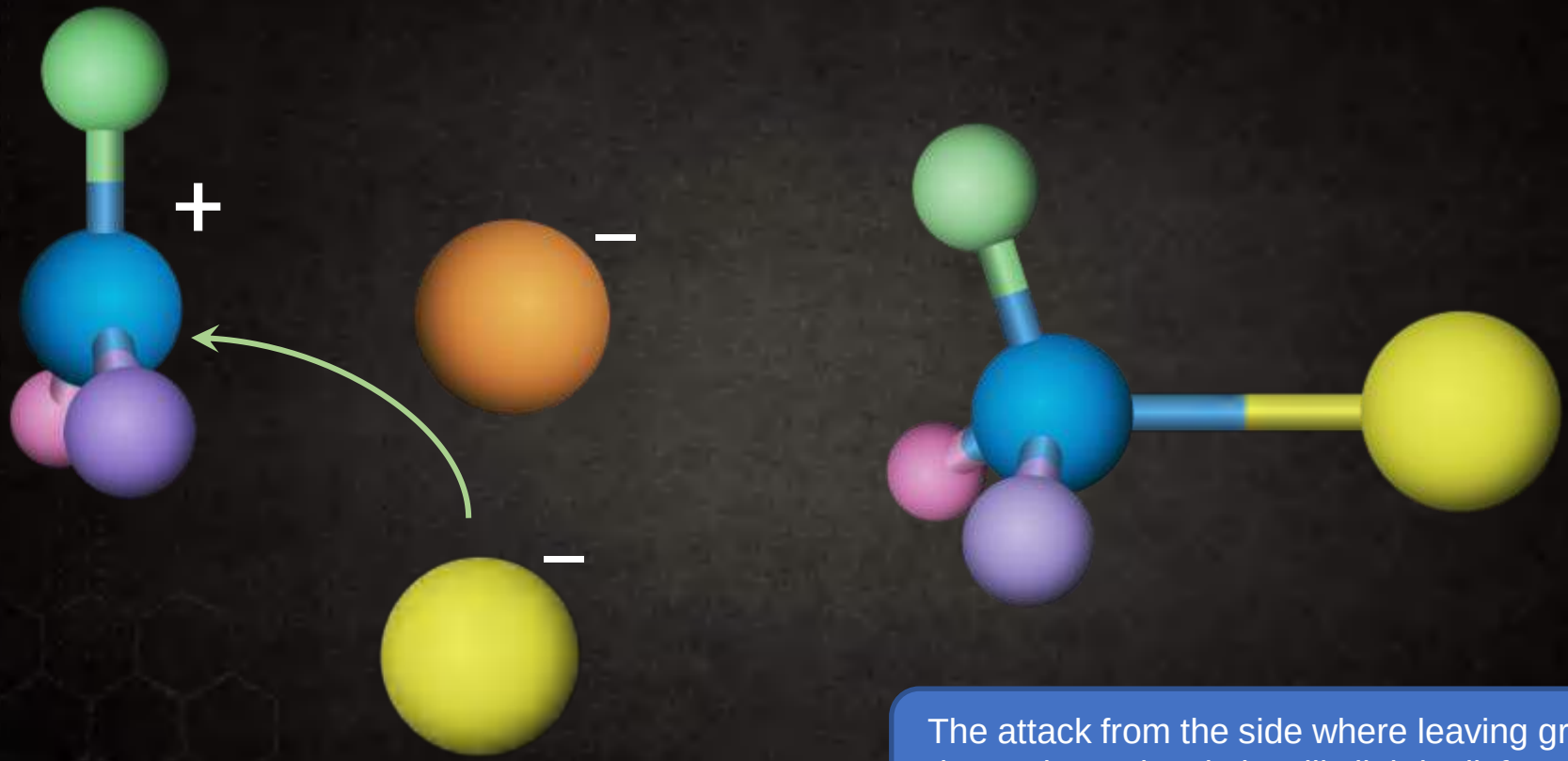
Inversion of configuration

Racemic mixture

Practically, we get a slightly higher proportion of inverted product in S_N1 reaction.

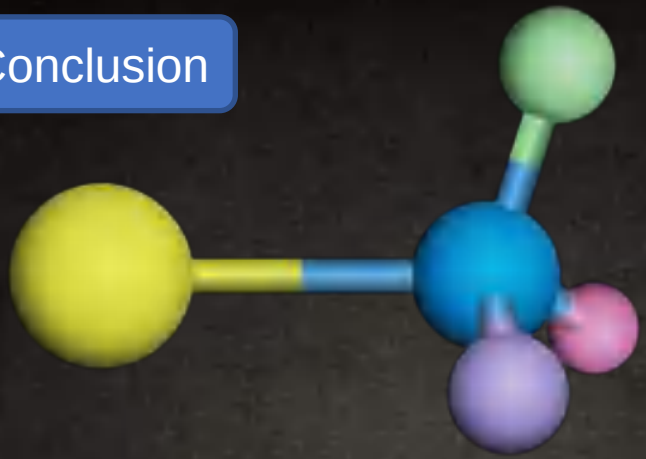

Intimate ion pair
+
−
Carbocation
Leaving group


+
−
−
−
Nucleophile

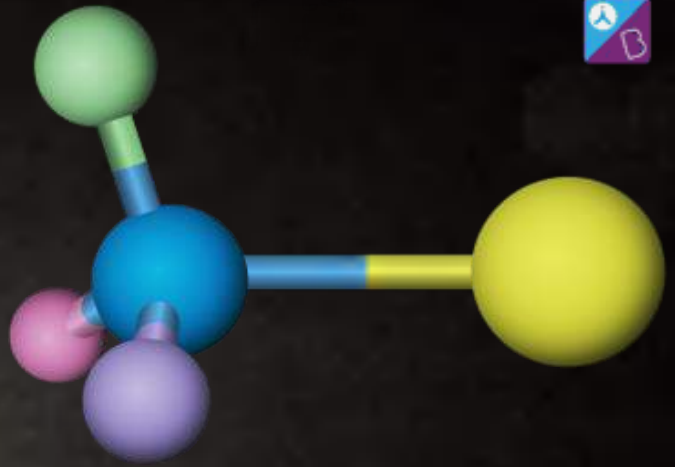


The attack from the side where leaving group leave the molecule is still slightly disfavored due to crowding.

Conclusion

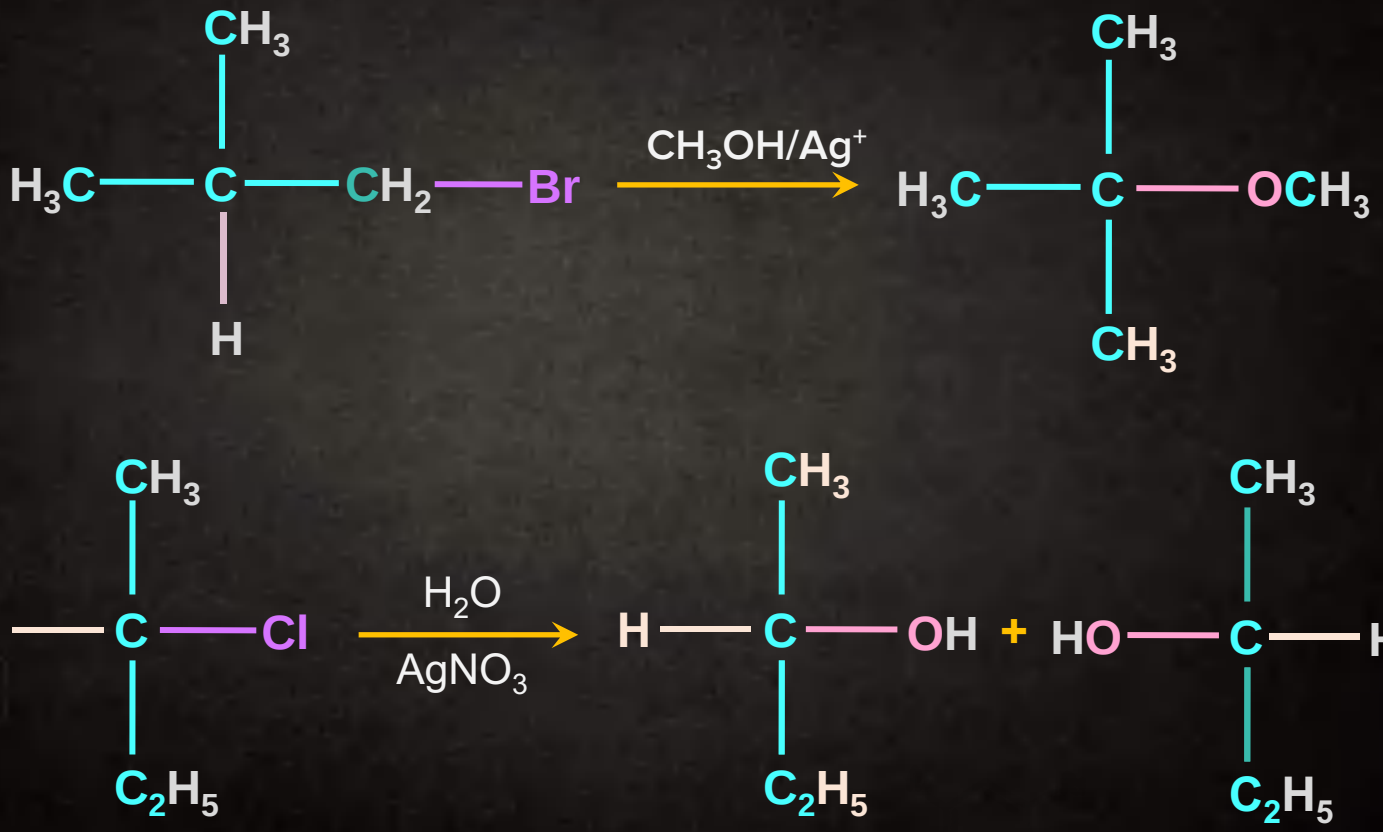


Inversion of configuration
> 50%



Retention of configuration
< 50%

Example of S_N1 Reaction



Reactions that Follow S_N1 Mechanism

Ex-1

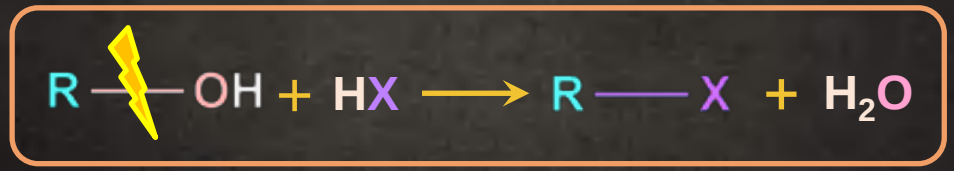
Reaction of alcohol with hydrogen halide

Ex-2

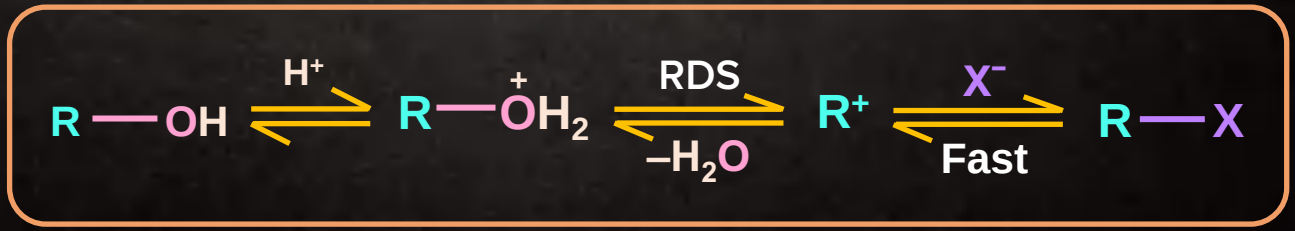
Reaction of diazonium salt with water

Reaction with Hydrogen Halide

When alcohols react with a hydrogen halide, a **substitution** takes place, producing an alkyl halide and water.

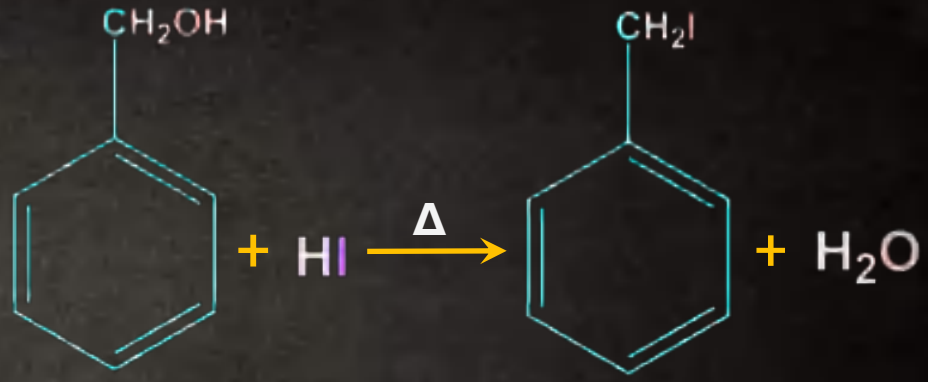


Mechanism



Reaction of Alcohol with HI

Example



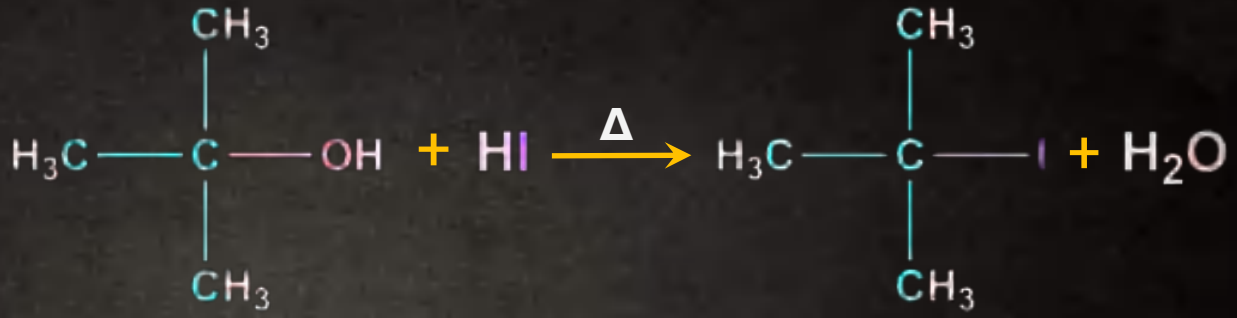
Benzyl alcohol

Benzyl iodide

Reaction occurs by **S_N1 mechanism**

Reaction of Alcohol with HI

Example



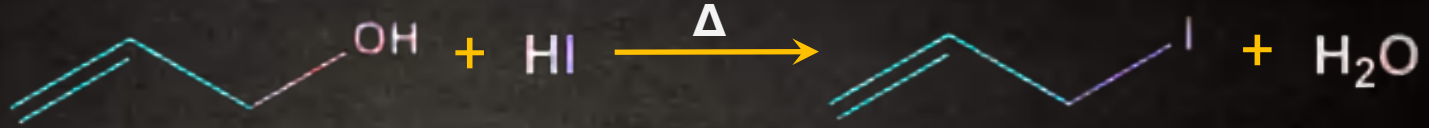
tert-butyl alcohol

tert-butyl iodide

Reaction occurs by
S_N1 mechanism

Reaction of Alcohol with HI

Example



Prop-2-en-1-ol

3-Iodoprop-1-ene

Reaction occurs by
S_N1 mechanism

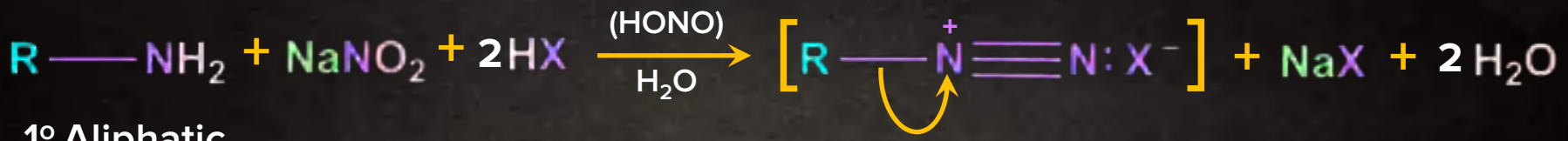
Reaction with Hydrogen Halide

Order of reactivity of HX

HI > HBr > HCl

HF is generally **unreactive**.

Reaction of Diazonium Salt



1° Aliphatic amine

Aliphatic diazonium salt (highly unstable)

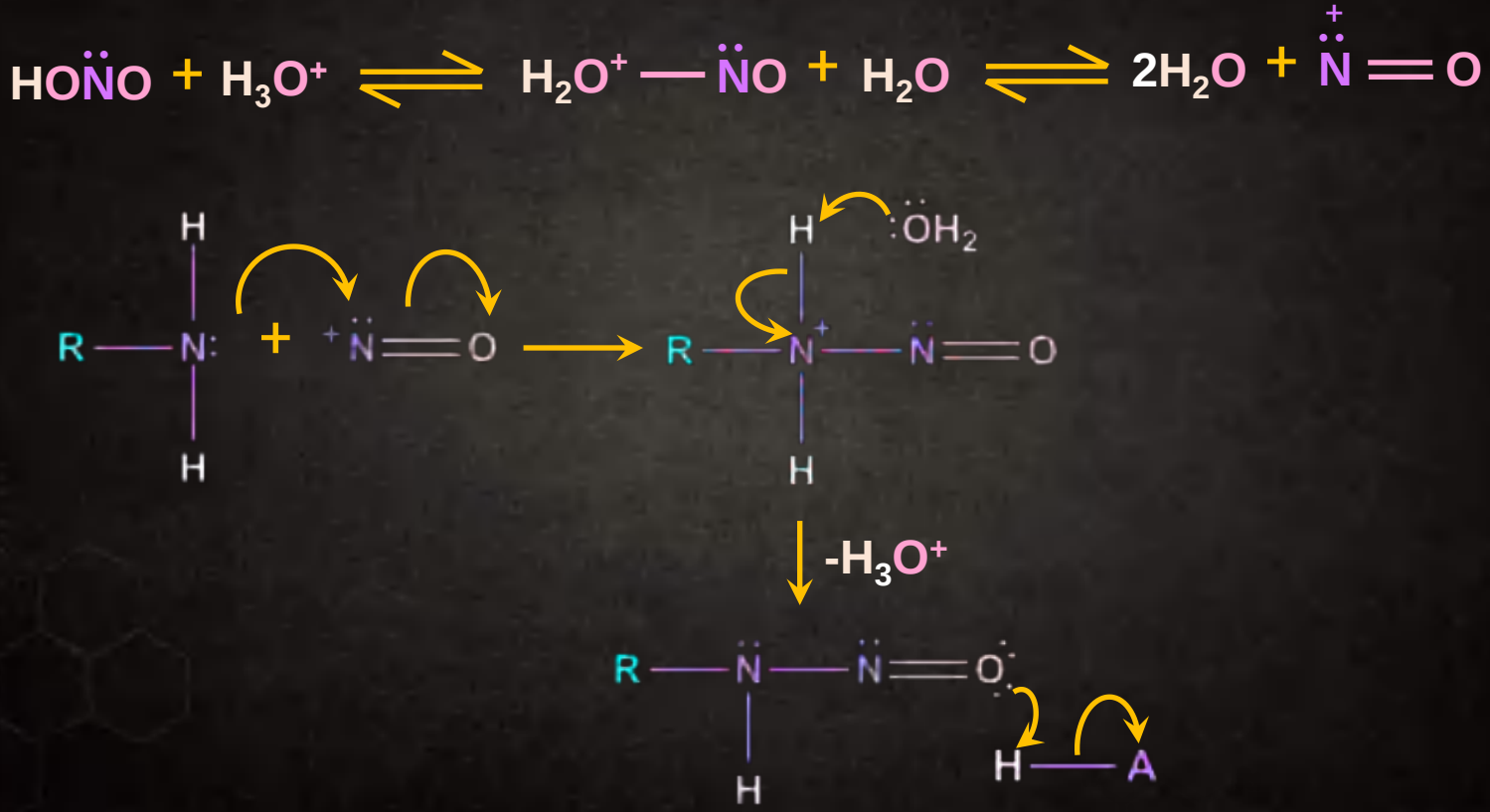
$-N_2$

$R^+ + X^-$

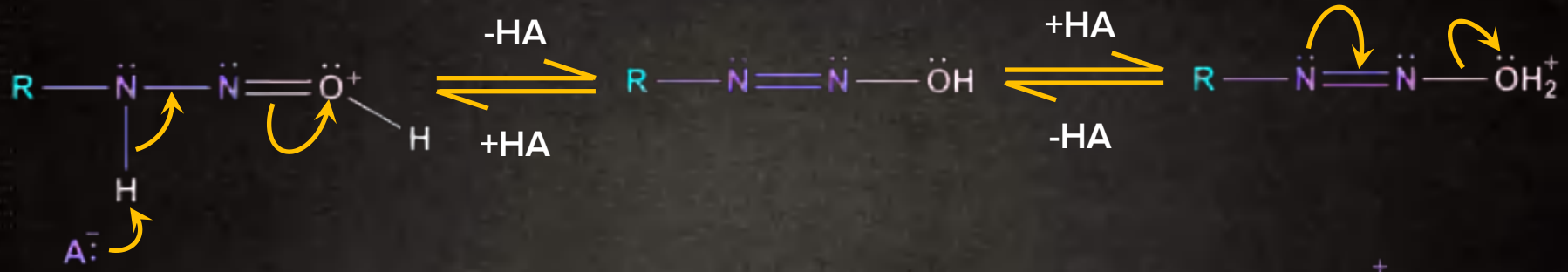
H_2O

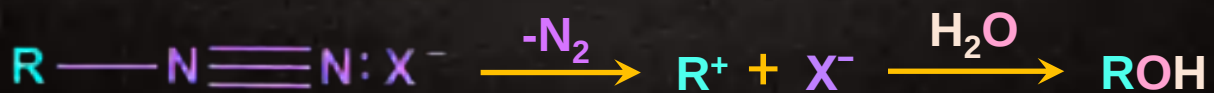
Alcohol

Mechanism



Mechanism





Reaction of Diazonium Salt with Water

General reaction

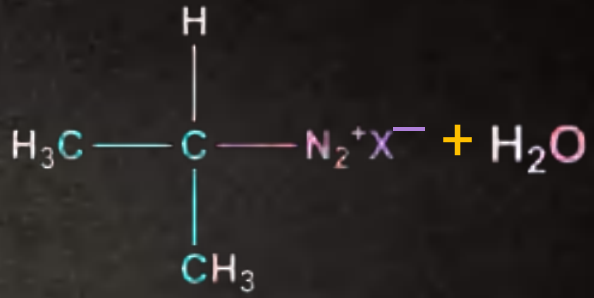
Diazonium salt

Alkyl alcohol

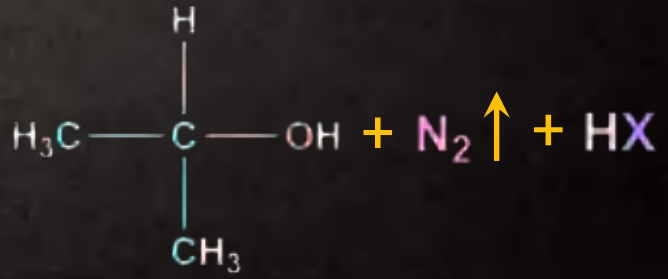
Displacement of diazo group by -OH

Reaction of Diazonium Salt with Water

Example



1-Methylethane diazonium halide



1-Methylethanol

S_N2 Reaction

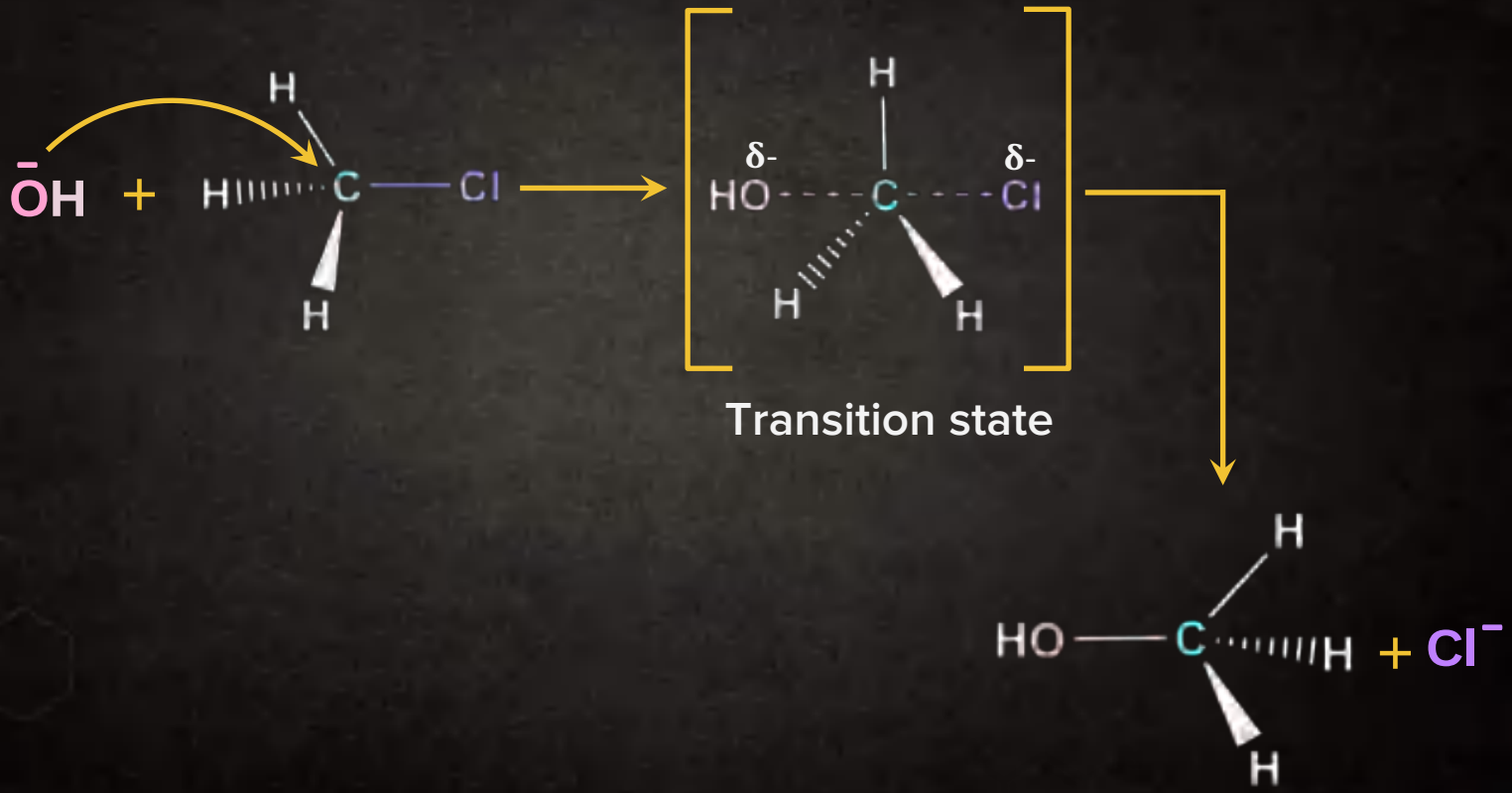
S_N2 reaction occurs in a **single step.**

It is a **concerted reaction.**

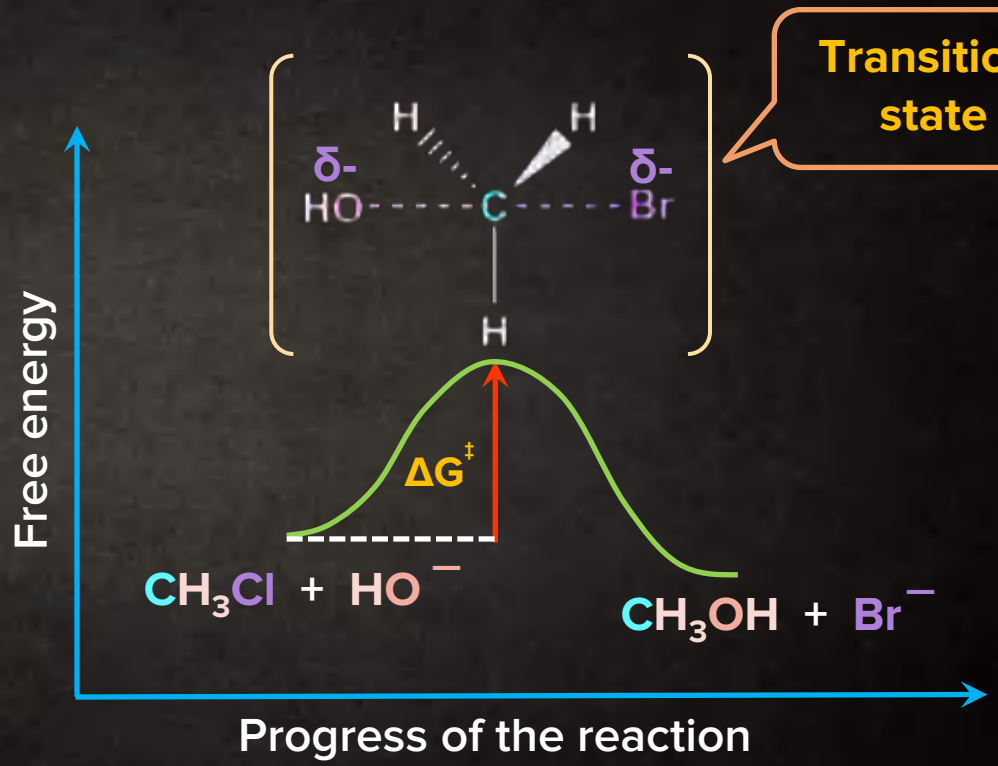
Concerted Reaction

A reaction where bond-forming and bond-breaking occur **simultaneously** (in concert) through a **single transition state.**

Mechanism

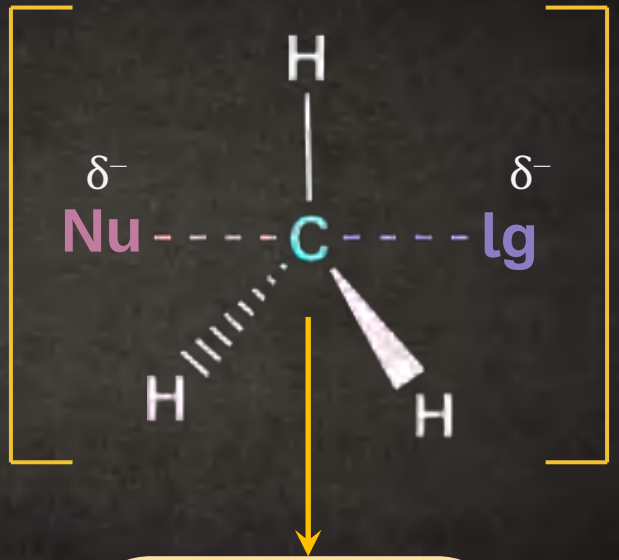


Energy Profile Diagram of S_N2 Reaction Mechanism



Transition State (T.S.)

In the **transition state,** a bond is **partially formed** between the nucleophile and the carbon, and the bond between the carbon and the leaving group is **partially broken**.



Pentavalent T.S. → Unstable

Cannot be isolated

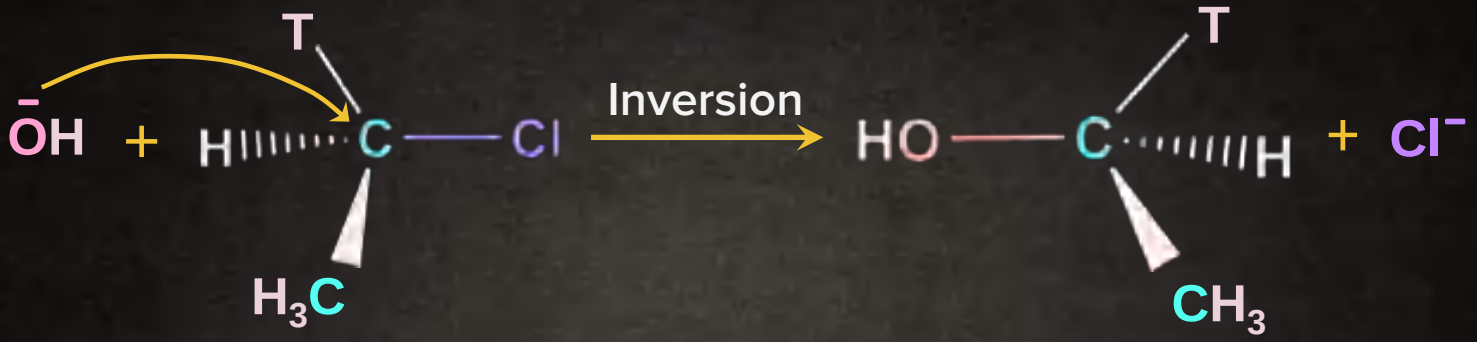
Stereochemistry of S_N2 Reaction

In an S_N2 mechanism, the nucleophile attacks from the **back side**, that is from the side directly opposite to the leaving group.

This causes an **inversion of configuration** at the chiral carbon atom.

Also known as **Walden inversion**

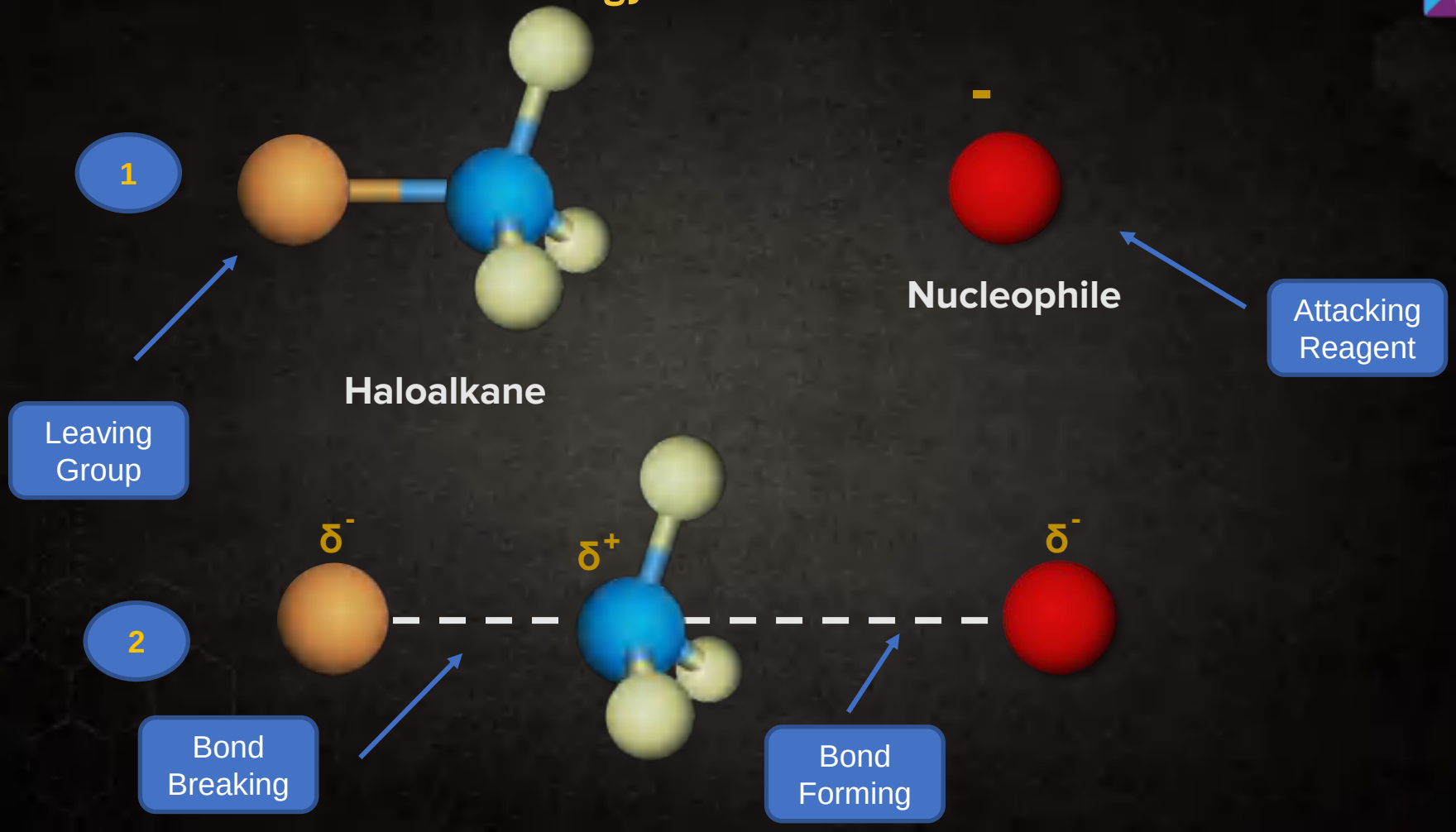
Stereochemistry of S_N2 Reaction

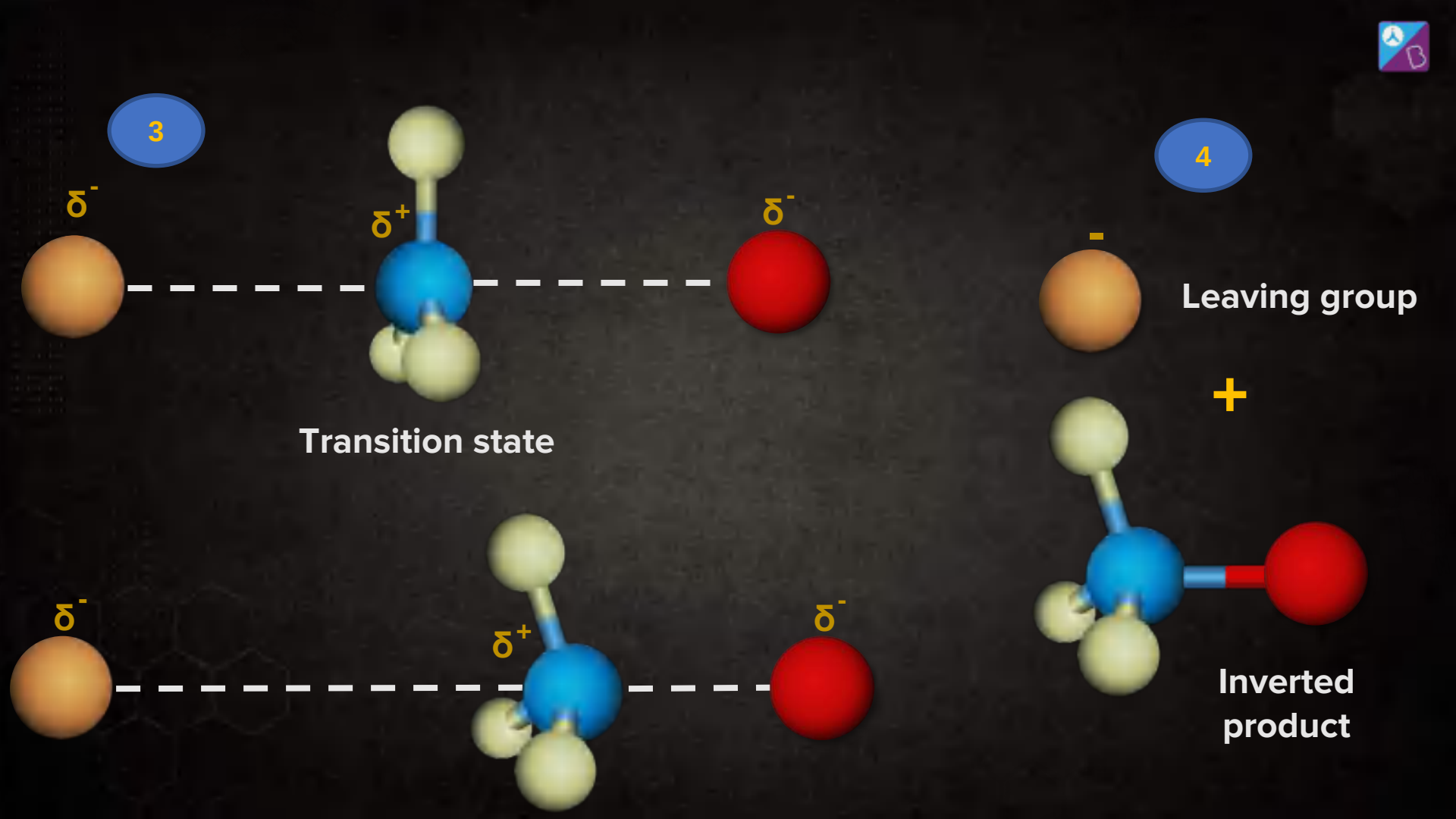


S_N2 is a **stereospecific** reaction.

A reaction in which a particular stereoisomeric form of the reactant reacts in such a way that it leads to a **specific stereoisomeric form** of the product.

Let's Understand with an Analogy




3
δ-
δ+
δ-
Transition state
4
-
Leaving group
+
δ-
δ+
δ-
Inverted
product

Characteristic of S_N2 Reaction

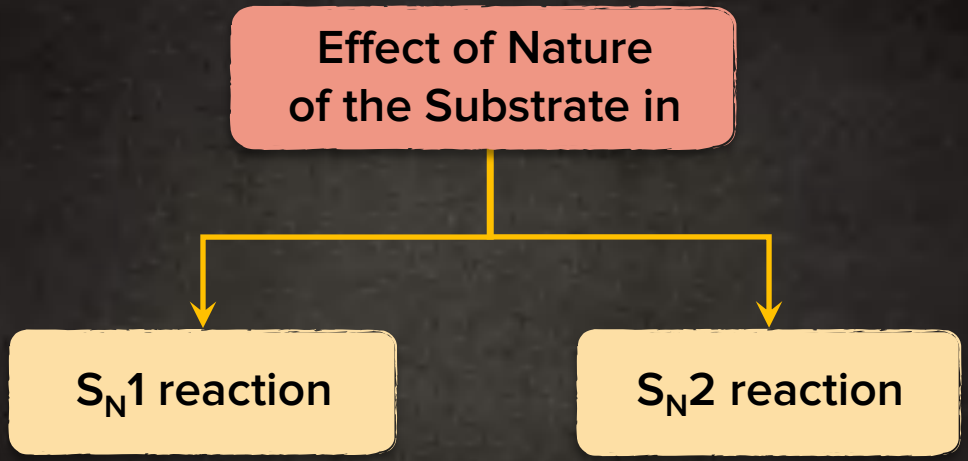
1. It is a **bimolecular, one-step** process.

2. **The rate of S_N2** reaction depends on the **concentration** of both alkyl halide and the nucleophile.

Rate ∝ [Alkyl halide][Nucleophile]

Factors Affecting S_N1 and S_N2 Reaction

- Nature of the substrate
- Nature of the nucleophile
- Nature of the solvent
- Leaving group ability

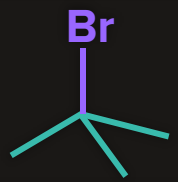
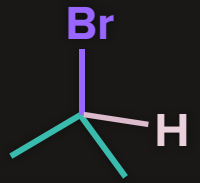
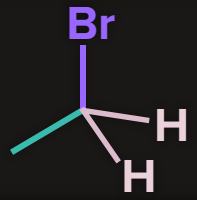

Effect of Nature of the Substrate in
S_N1 reaction
S_N2 reaction

Nature of Alkyl Halide

S_N1 reactivity

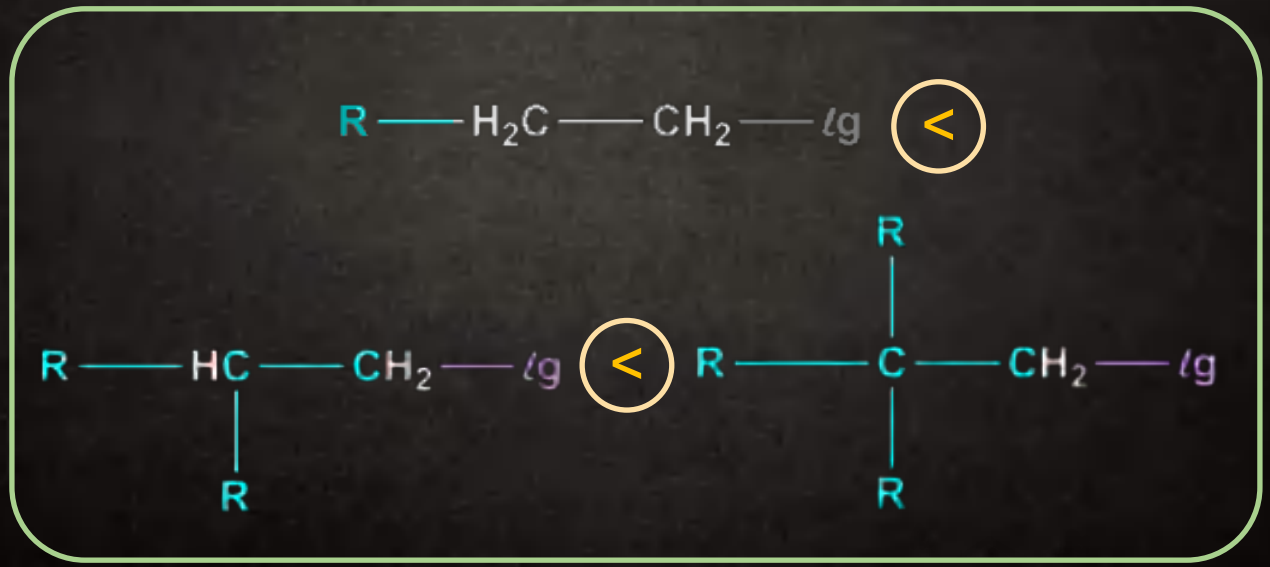
$CH_3 - X$ < 1° alkyl halide < 2° alkyl halide < 3° alkyl halide

Rates of S_N1 Reactions with H_2O

Alkyl bromide	Class of alkyl bromide	Relative rate
	Tertiary	12,00,000
	Secondary	11.6
	Primary	≃ 0

Rates of S_N1 Reactions

β -branching ↑ → Rate of reaction ↑



Nature of the Substrate

The important reason behind this order of reactivity is **steric effect**.

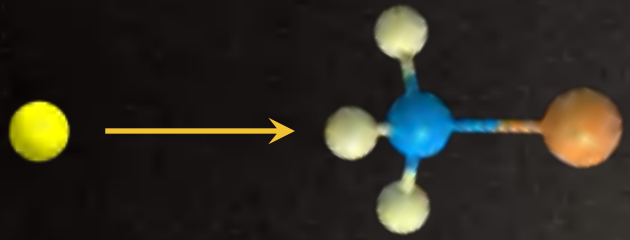
Very **large and bulky groups** can often **hinder** the formation of the required transition state. The crowding **raises the energy** of the transition state and **slows down the rate** of reaction.

Nature of Alkyl Halides

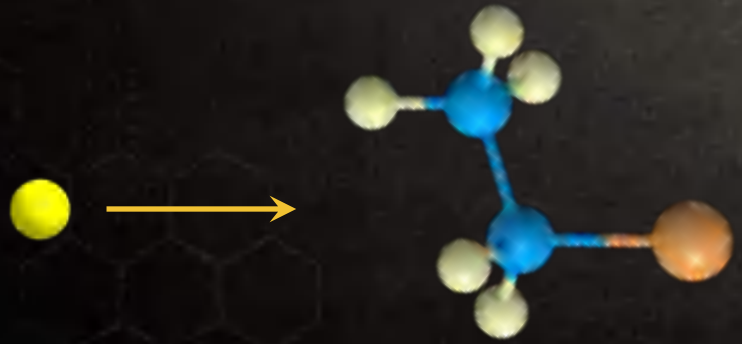
S_N2 reactivity

$CH_3–X$ > 1° alkyl halide > 2° alkyl halide > 3° alkyl halide

Nature of R-X

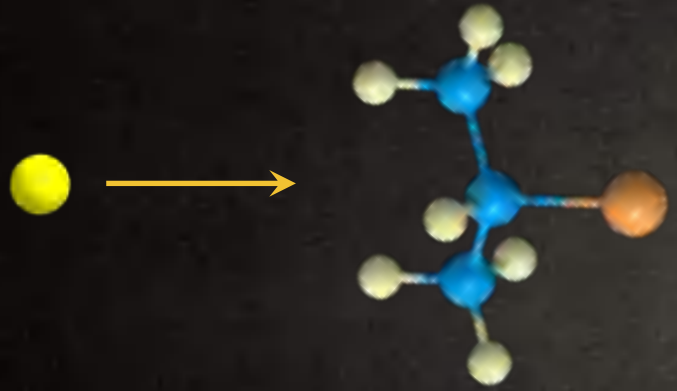


Nucleophile approaching
a methyl alkyl halide

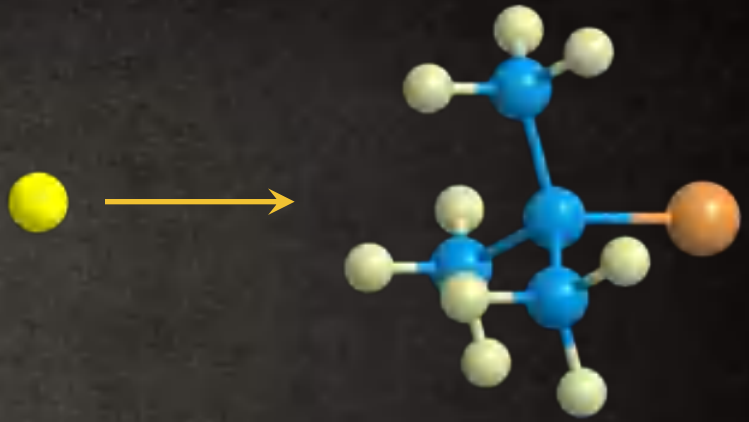


Nucleophile approaching
1° alkyl halide

Nature of R-X



Nucleophile approaching
2° alkyl halide



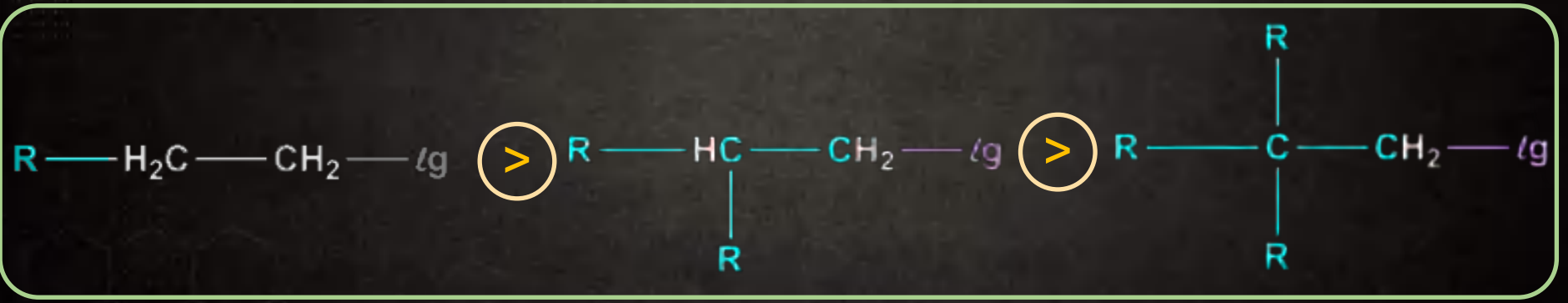
Nucleophile approaching
3° alkyl halide

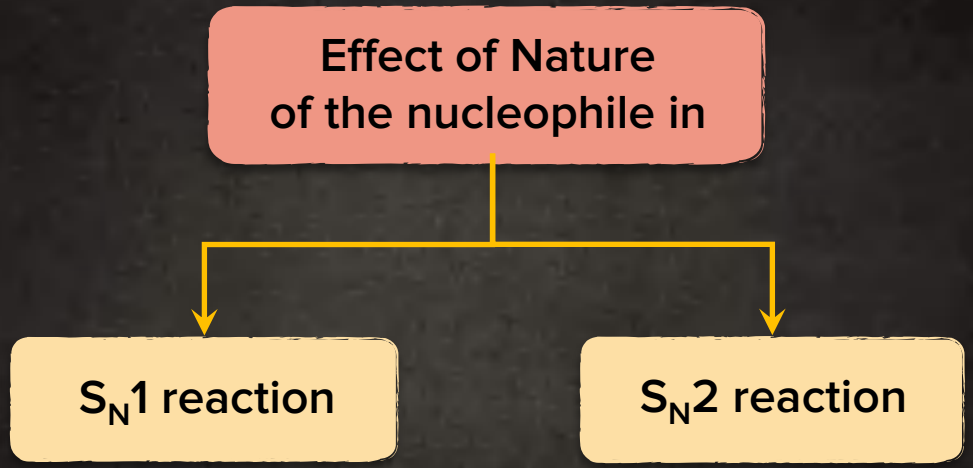
Relative Rate of Reaction of Alkyl Halides by S_N2 Mechanism

Substituent	Compound	Relative rate
Methyl	CH_3X	30
1°	CH_3CH_2X	1
2°	$(CH_3)_2CHX$	0.02
3°		~0

Rates of S_N2 Reactions

β-branching ↑ → Rate of reaction ↓




Effect of Nature
of the nucleophile in
S_N1 reaction
S_N2 reaction

Concentration & Reactivity of the Nucleophile

The rate of S_N1 reaction is **unaffected** by the **concentration** of the nucleophile.

Weak and neutral nucleophiles favour S_N1 reaction.

Concentration & Reactivity of the Nucleophile

Mostly, solvents (protic) function as nucleophiles themselves in an S_N1 reaction. So, an S_N1 reaction is termed as a **solvolysis reaction**.

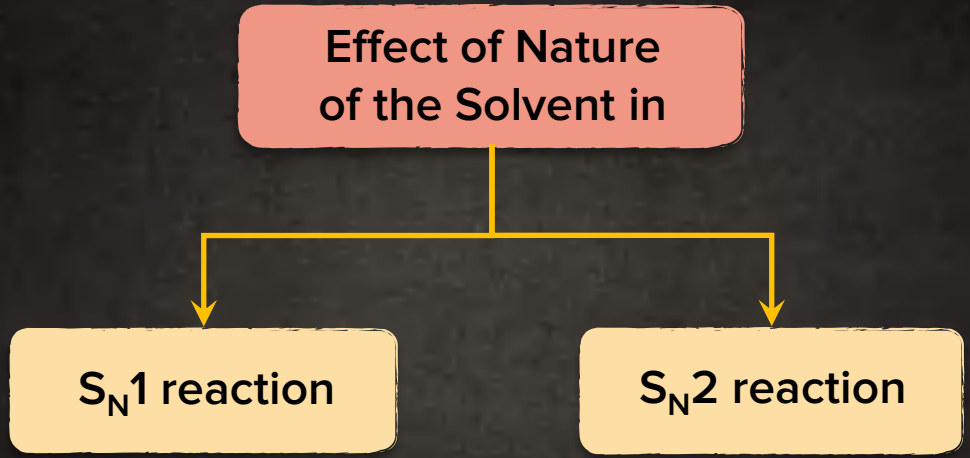
Water	Hydrolysis
Ethanol	Ethanolysis

Concentration & Reactivity of the Nucleophile

Concentration of nucleophile ↑ → Rate of S_N2 ↑

Nucleophilicity ↑ → Rate of S_N2 ↑

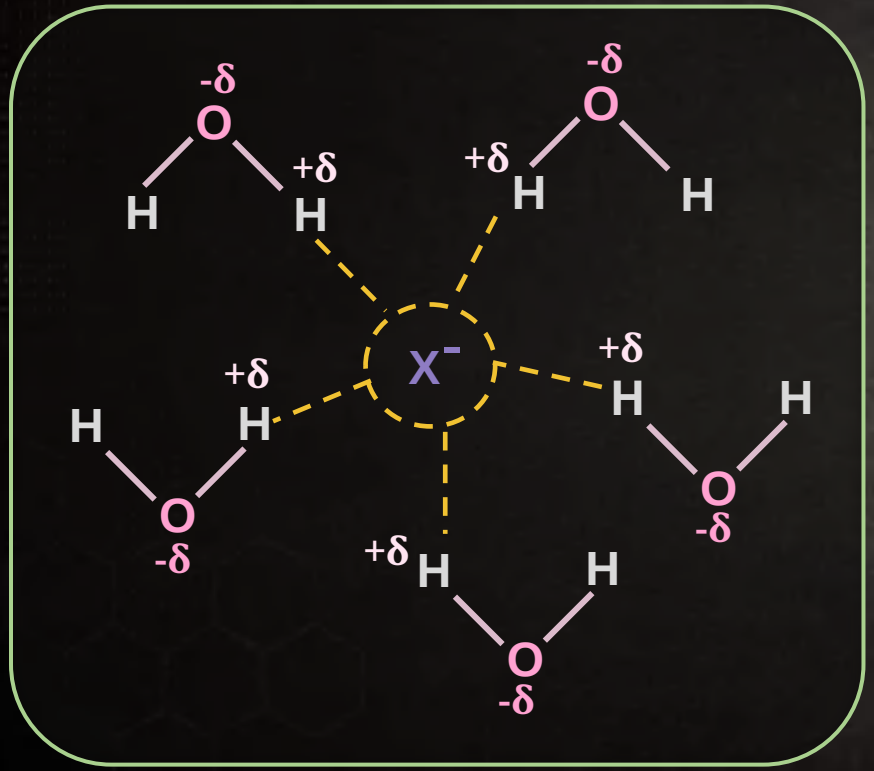
Anionic nucleophiles mostly give S_N2 reaction.

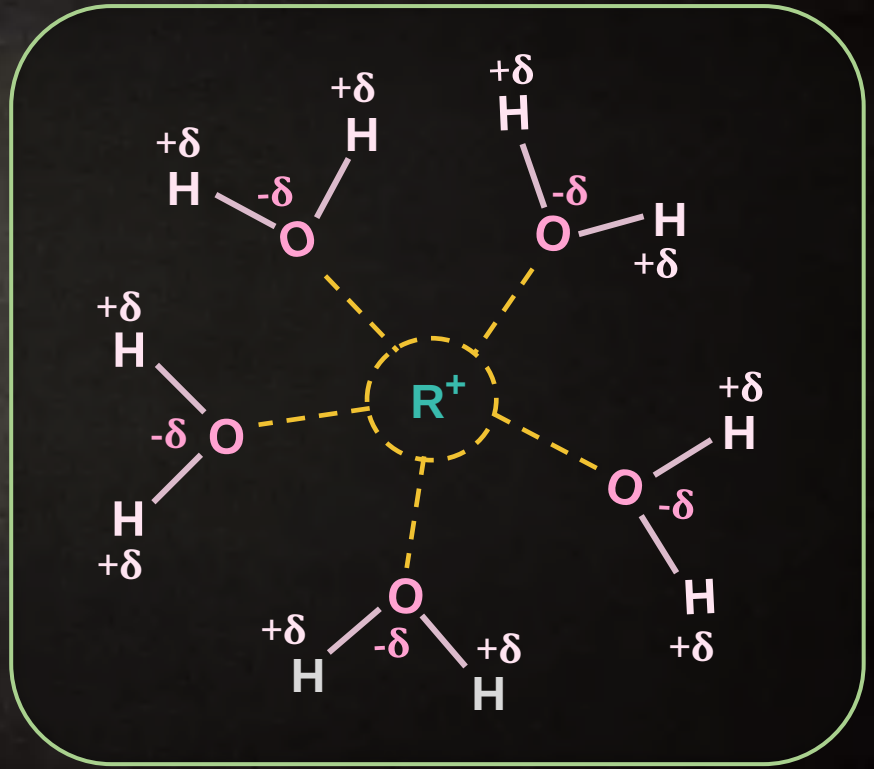

Effect of Nature of the Solvent in
S_N1 reaction
S_N2 reaction

Nature of Solvent

Using a **polar protic solvent** will greatly **increase** the rate of carbocation formation of an alkyl halide in any S_N1 reaction because of its ability to **solvate cations and anions** effectively.

Solvated Ions



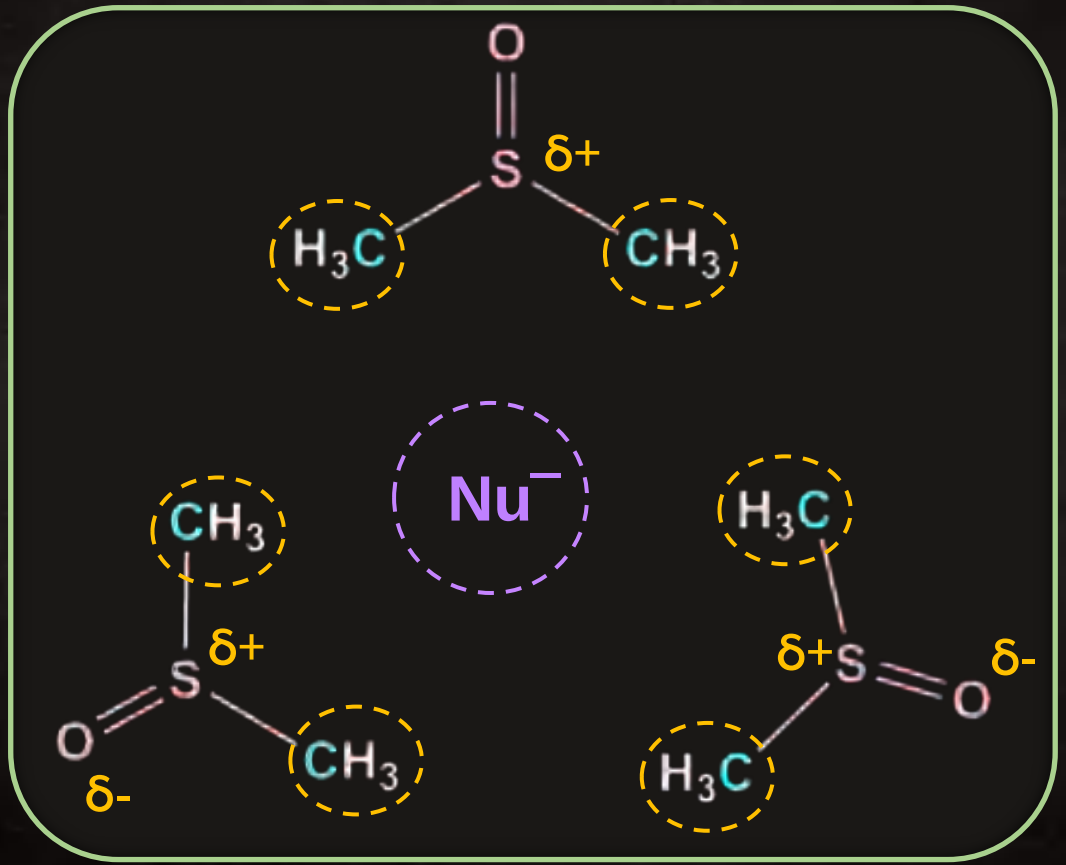


Nature of Solvent

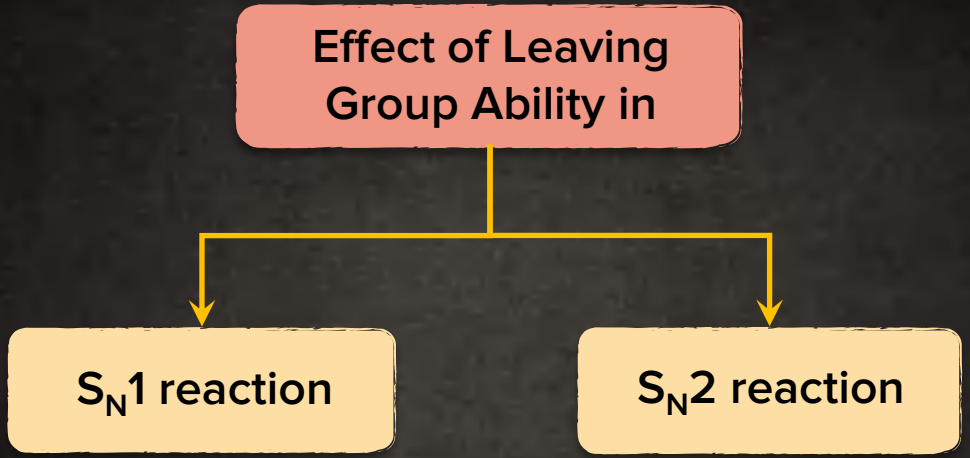
Polar aprotic solvents have a crowded **positive centre**, so they do not solvate the anion appreciably.

Hence, the rate of S_N2 reactions **increases** when they are carried out in a polar aprotic solvent.

Polar Aprotic Solvents



As we can see here, there is a repulsion between the methyls of DMSO and nu-methyl; so, nu remains unsolvated.


Effect of Leaving Group Ability in
S_N1 reaction
S_N2 reaction

Leaving Group Ability

In the S_N1 reaction, the leaving group begins to acquire a **negative charge**.

Stabilisation of this developing negative charge on the leaving group **increases** the rate of reaction.

Relative reactivities of alkyl halides

RF < RCl < RBr < RI

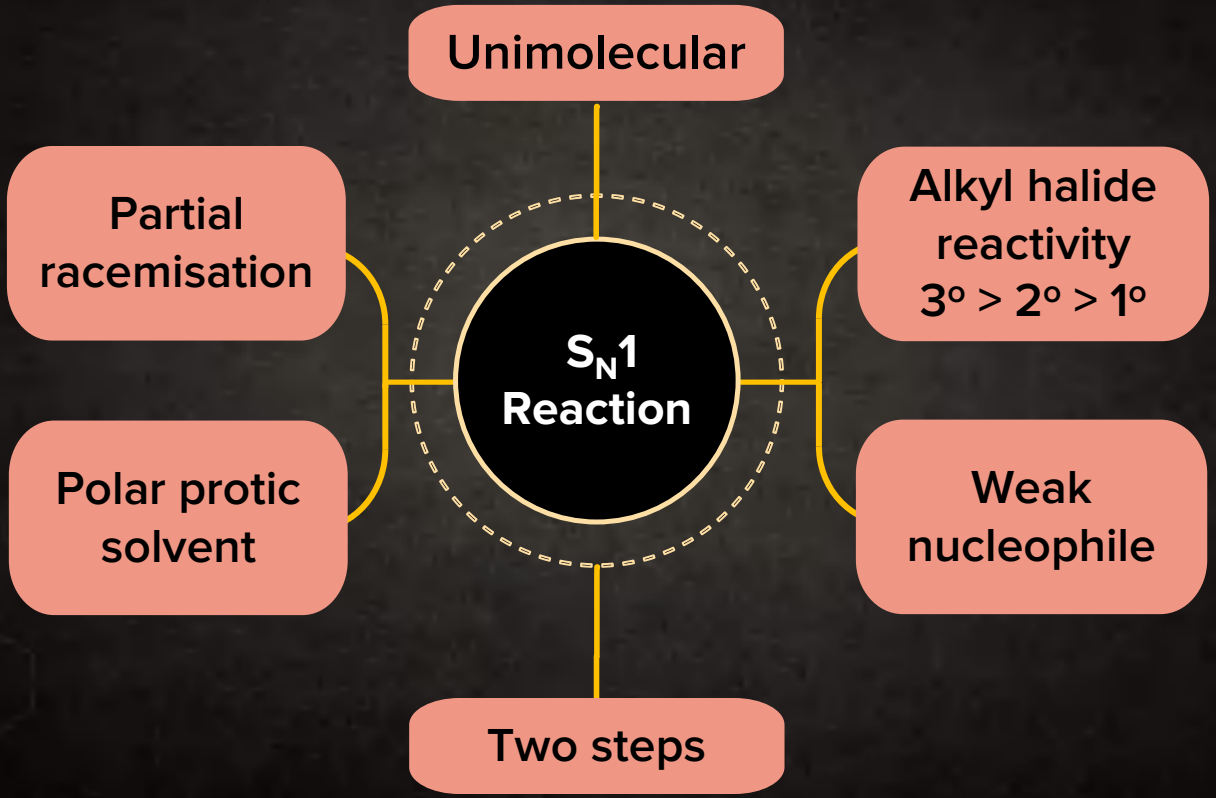
Leaving Group Ability

A good leaving group **stabilises the transition state** and thereby increases the rate of the reaction.

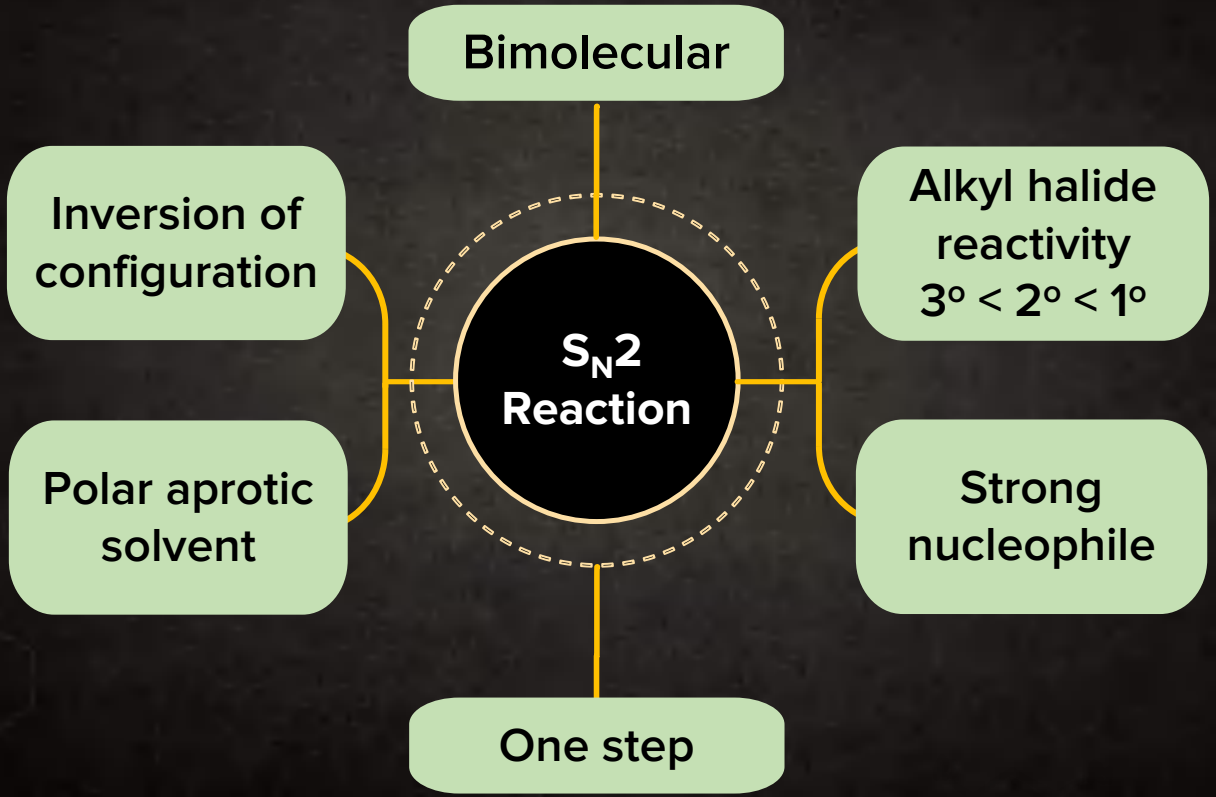
Relative reactivities of alkyl halides

RF < RCl < RBr < RI

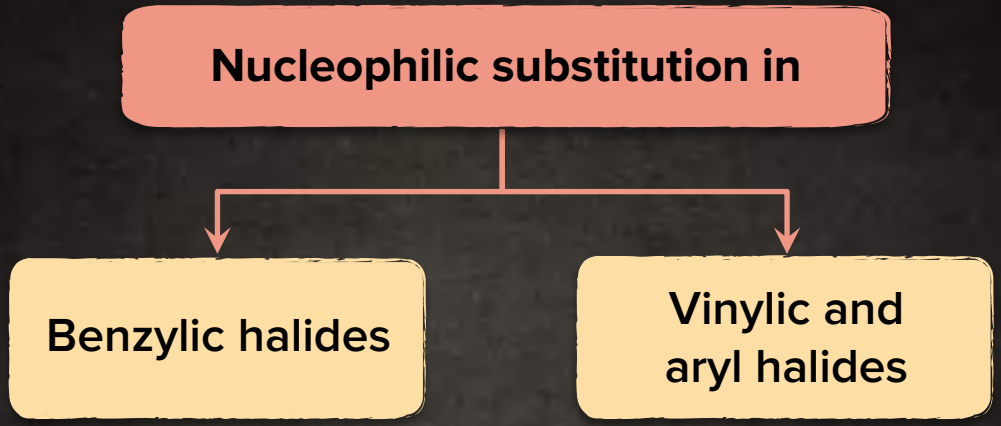
Quick Recap of S_N1 Reaction



Quick Recap of S_N2 Reaction

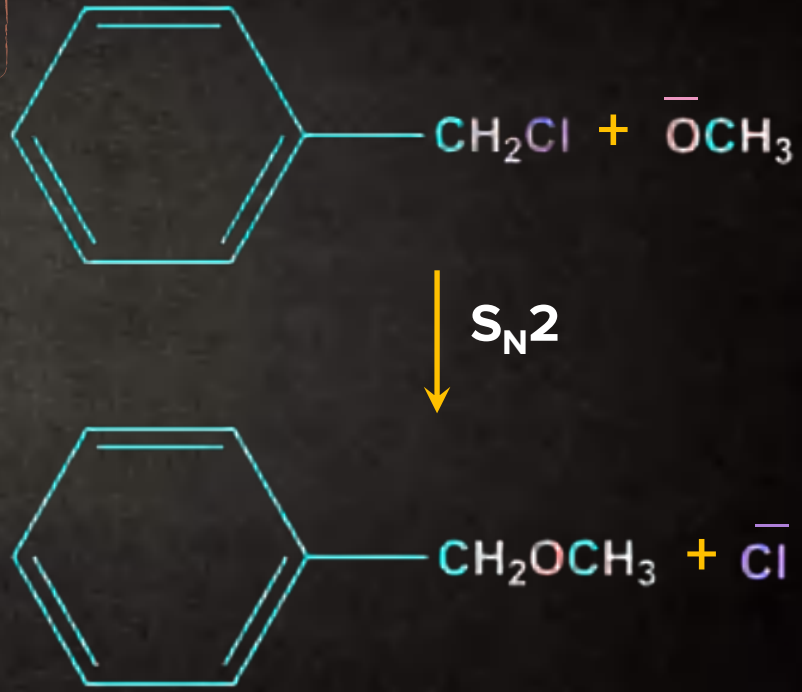


Nucleophilic Substitution Reaction in Benzylic, Vinylic, and Aryl Halides


Nucleophilic substitution in
Benzylic halides
Vinylic and
aryl halides

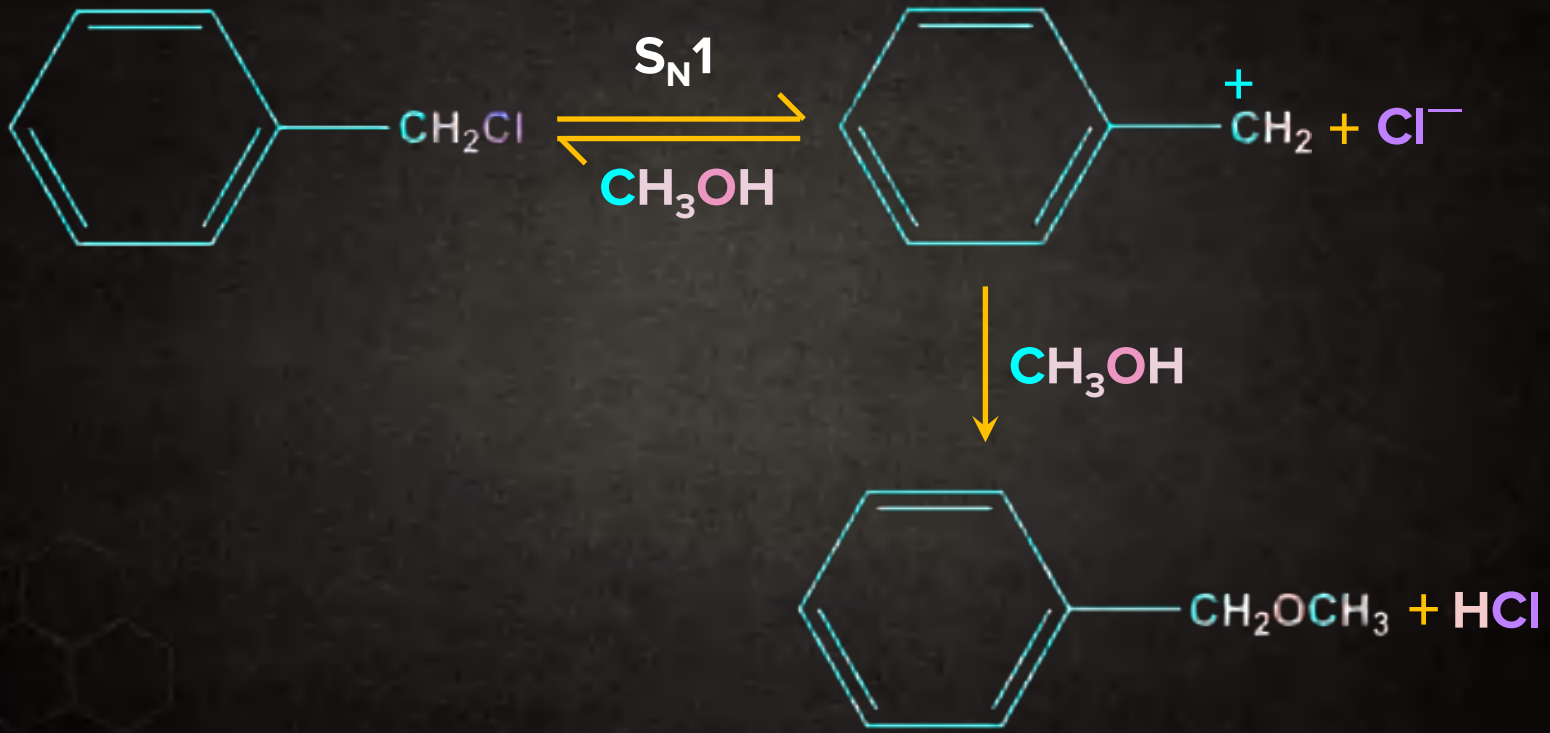
S_N2 Reaction in a Benzylic Halide

Example



Benzylic halides **may undergo** both **S_N1** and **S_N2 reactions**.

S_N1 Reaction in a Benzylic Halide



Vinylic & aryl halides generally **do not undergo** S_N1 and S_N2 reactions.

- Unstable carbocation
  - Reason why S_N1 **does not** occur
- Repulsion by π-electron cloud
  - Reason why S_N2 **does not** occur.
- Partial double bond character

Unstable Carbocation

Example

Highly unstable
to be formed

sp carbons are more electronegative than **sp²** carbons that carry the positive charge of alkyl carbocations.
This is the reason why S_N1 cannot take place because these carbocations are highly unstable.

Unstable Carbocation

Example

Aryl cation

↓

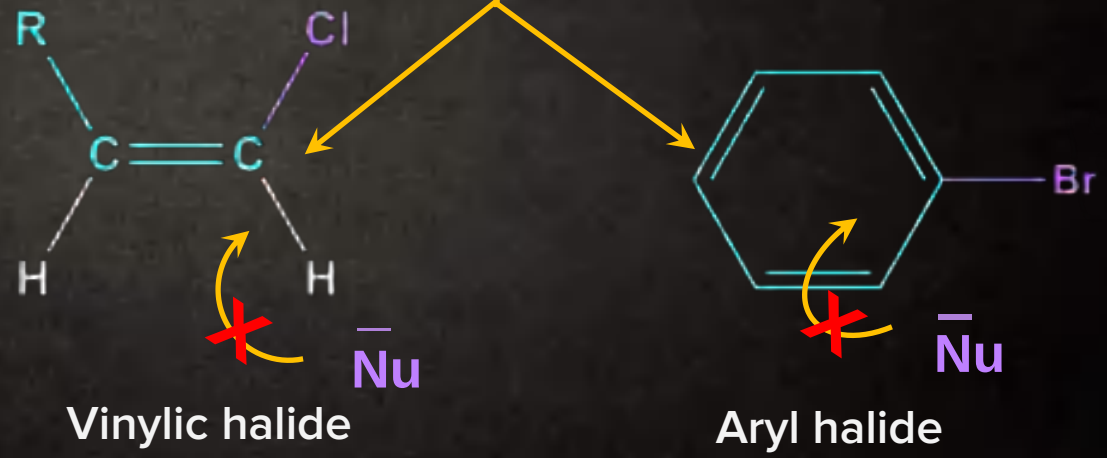
Highly unstable to be formed

sp carbons are more electronegative than **sp^2** carbons that carry the positive charge of alkyl carbocations.
An **sp^2** hybridised C atom forms a stronger bond than an **sp^3** hybridised C atom. As a result, it is hard to break the **C-X** bond when halogen is bonded to a **sp^2** C atom.

Repulsion by π-Electron Cloud

Example

Nucleophile is **repelled** by the π-electron cloud.

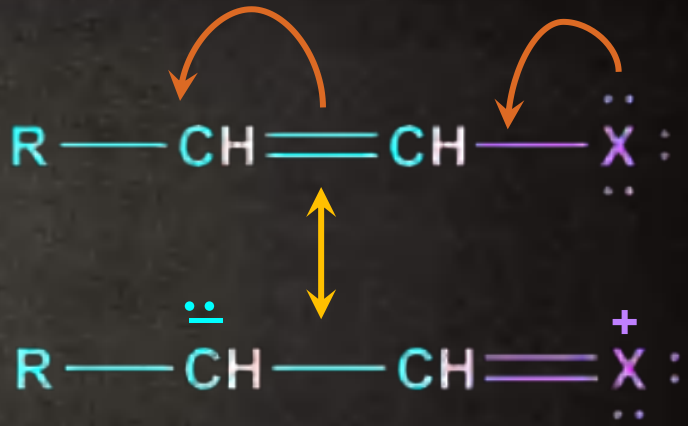


Vinylic halide

Aryl halide

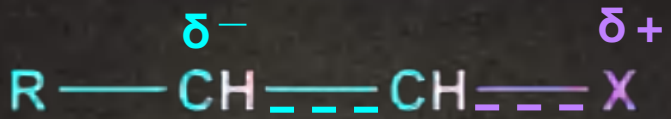
Partial Double Bond Character

Example



Vinylic halide

Partial Double Bond Character

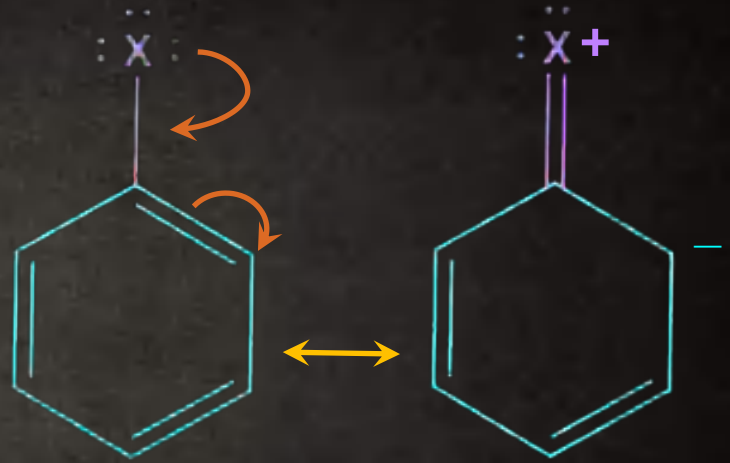


Resonance hybrid
of vinylic halide

Due to the presence of **partial double bond character**, it is **difficult to break** the C-X bond

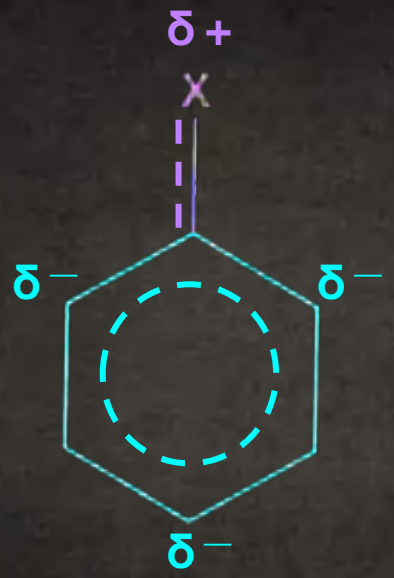
Partial Double Bond Character

Example



Aryl halide

Partial Double Bond Character



Resonance hybrid of aryl halide

Due to the presence of **partial double bond character**, it is **difficult to break** the C-X bond.

Examples of S_N2 Reaction

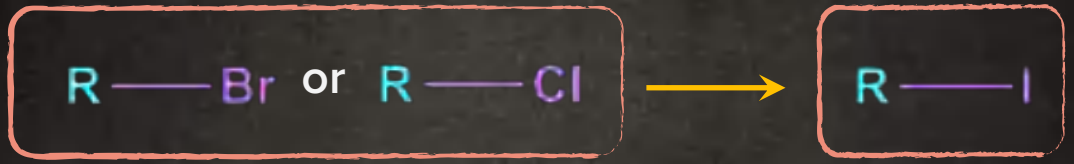
- Finkelstein reaction
- Reaction of ether with HI
- Swarts reaction
- Reaction of alcohol with PBr_3
- Williamson ether synthesis
- Alkylation of ammonia

Preparation of Alkyl Halides

Halide exchange is an **equilibrium process.**

Preparation of Alkyl Iodides

Finkelstein reaction



Reagents used: **NaI** in dry acetone

Preparation of Alkyl Iodides

General reaction

Where X = Cl, Br

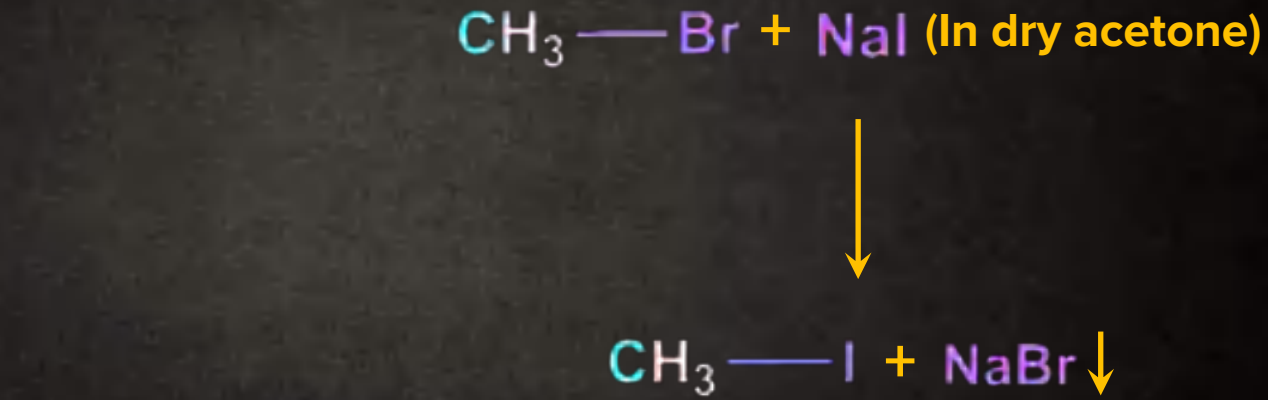
In dry acetone, **NaI** is **soluble** whereas **NaBr** and **NaCl** are **precipitated out.**

Le Chatelier's principle

This difference in **solubility** facilitates the reaction in the **forward direction.**

Preparation of Alkyl Iodides

Example



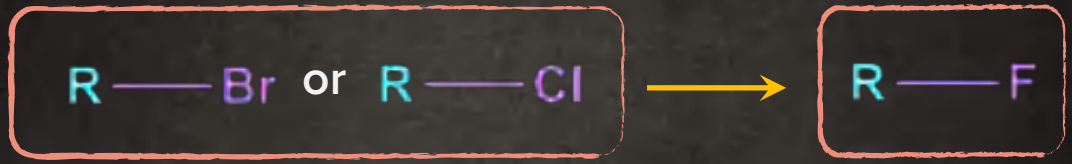
Preparation of Alkyl Iodides

Sodium iodide in dry acetone can be used as a test for **primary bromides or chlorides**.

Since the mechanism is **S_N2**, the reaction is much more successful **for primary halides** than for **secondary** or **tertiary halides**.

Preparation of Alkyl Fluorides

Swarts reaction



Reagents used: AgF, SbF_3, CoF_2, Hg_2F_2

Example

Preparation of Ethers

Williamson ether Synthesis

Laboratory Process

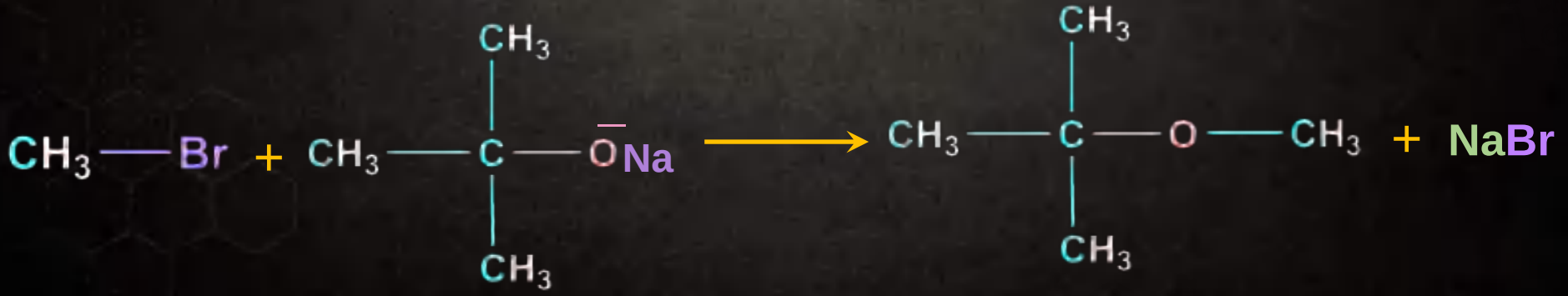
Alkyl halide → Ether

Reagents → Sodium alkoxide

Williamson Synthesis

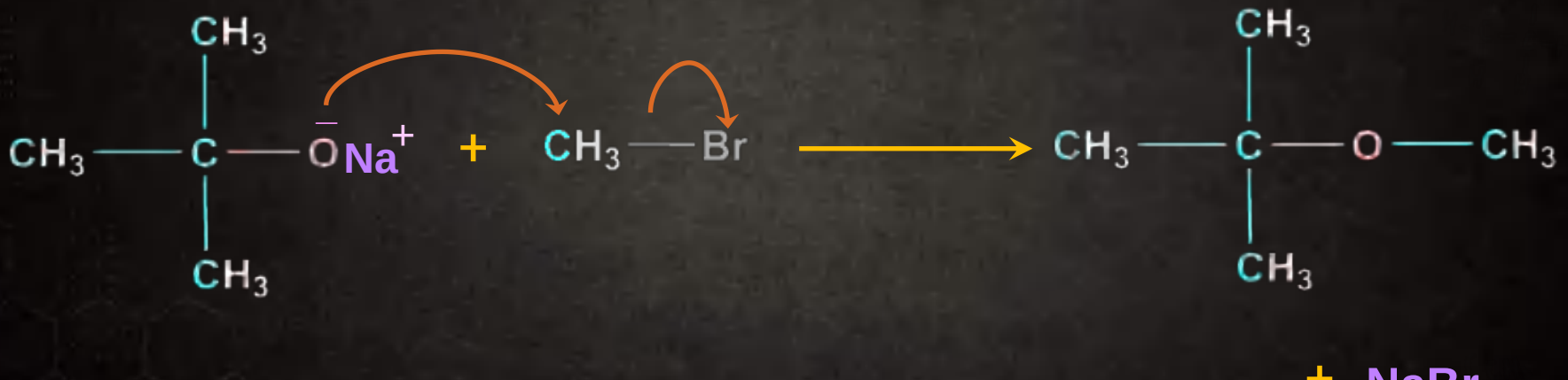
General reaction

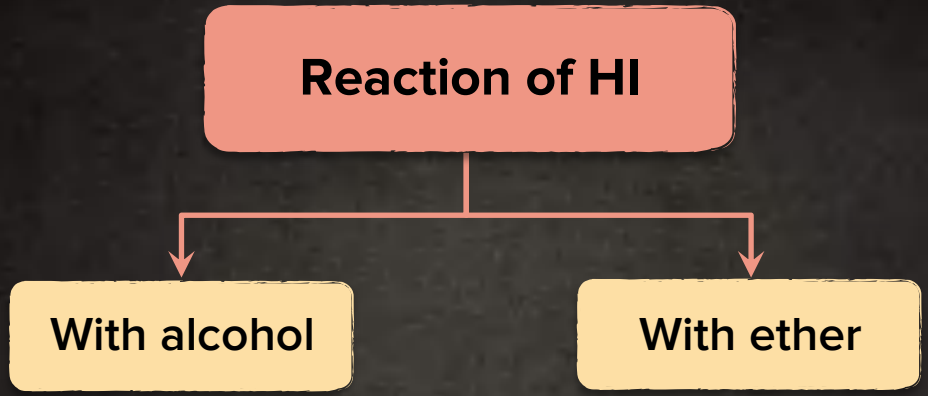
Example



Generally, the reaction follows S_N2 mechanism.

Williamson reaction occurs in a single step.




Reaction of HI
With alcohol
With ether

Reaction of HI with Alcohol

Propyl alcohol

Propyl iodide

Generally, primary alcohols and methanol react to form alkyl halides under acidic conditions by an S_N2 mechanism.

Chemical Properties of Ethers

Ethers → Alkyl halide

Reagents → HX (excess), high temperature

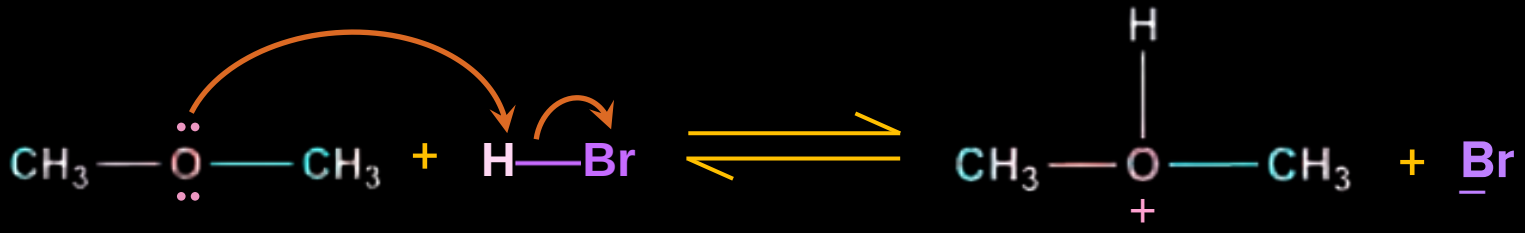
General reaction

Excess

Steps involved in O-O bond cleavage of ethers

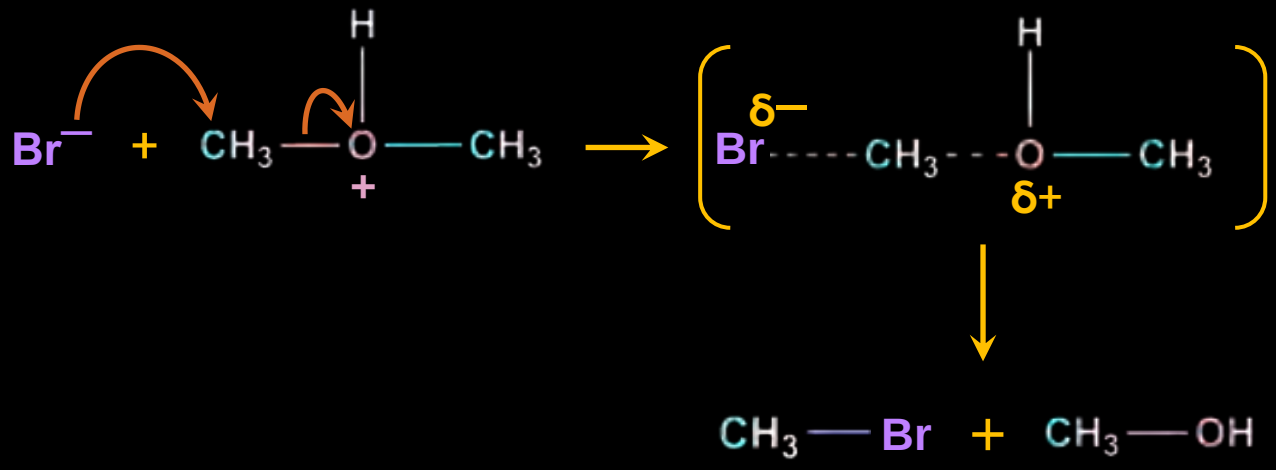
Step 1	Protonation of the ether
Step 2	Attack of the nucleophile
Step 3	Reaction of alcohol with HBr

Protonation of the Ether



Oxonium ion

Attack of the Nucleophile

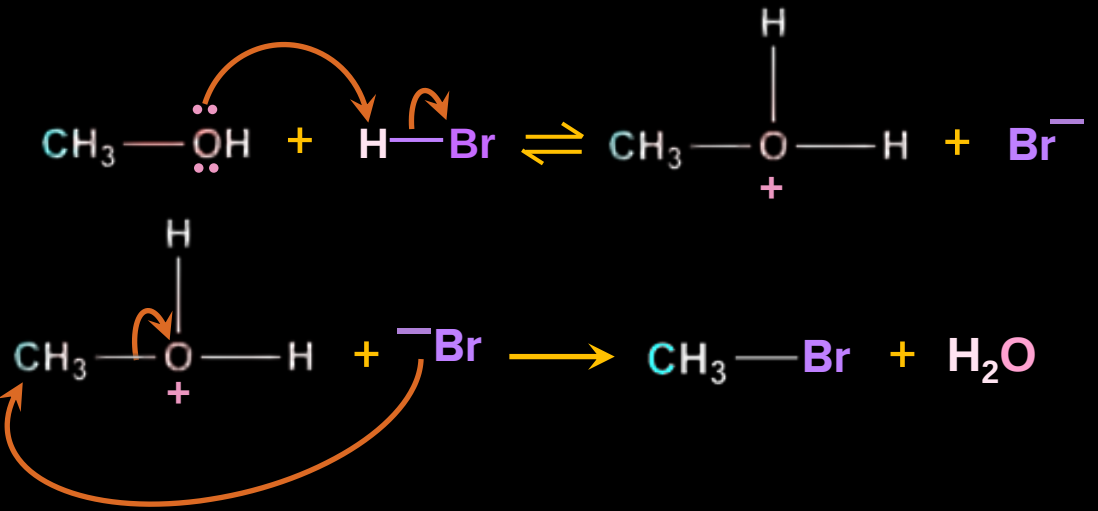


This step follows the S_N2 mechanism.

Since this is an S_N2 step, Br^- attacks the less bulky alkyl group.

Reaction of Alcohol with HBr

HBr is in **excess** (at high temperature).



Reaction of Alcohol with HI

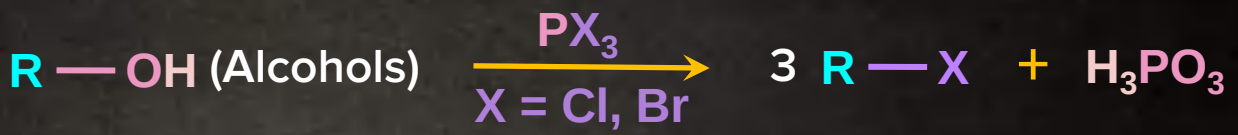
The reagent **HI** is usually used for alkyl iodides. The use of HI sometimes results in reduction of the **alkyl iodide to the alkane**.

Examples of S_N2 Reaction

- Finkelstein reaction
- Reaction of ether with HI
- Swarts reaction
- Reaction of alcohol with PX_3
- Williamson ether synthesis
- Ammonolysis of R-X

Reaction of Alcohol with PX_3

General reaction

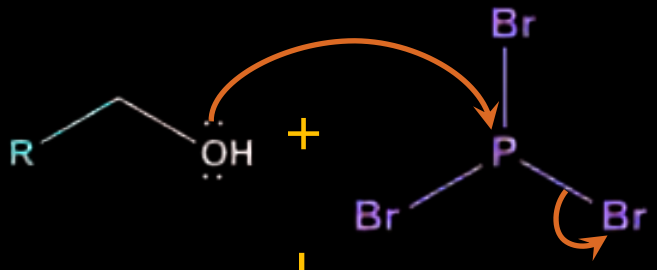


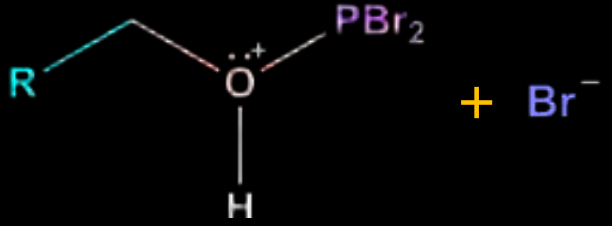
Mechanism

Step 1 Reaction of alcohol with PBr_3

Step 2 Formation of alkyl bromide

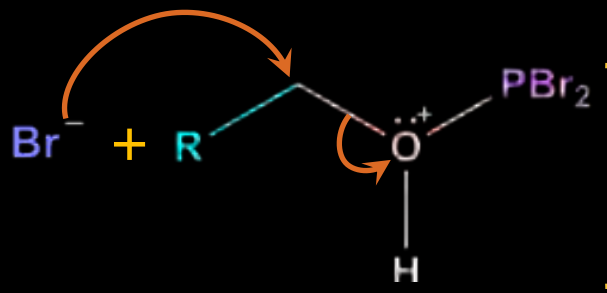
Mechanism





+ Br^-

Protonated alkyl dibromophosphite



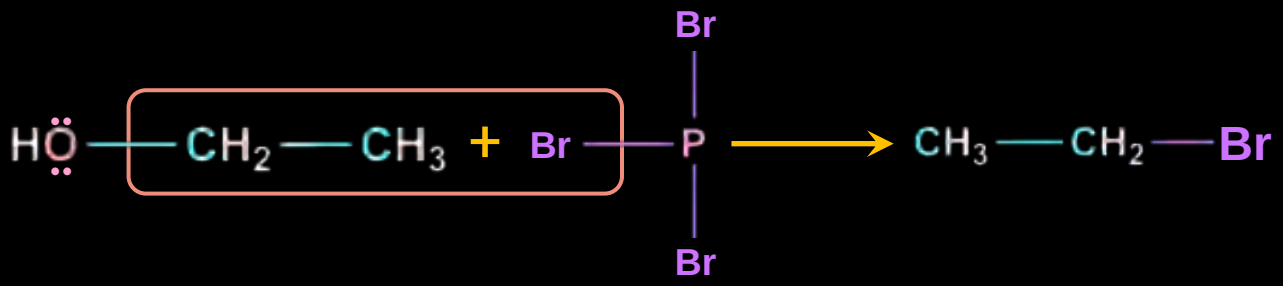
A good leaving group

+ $HOPBr_2$

Reaction of Alcohol with PBr_3

$HOPBr_2$ can react with 2 more moles of alcohol, so the net result is the conversion of 3 mol of alcohol to alkyl bromide by 1 mol of phosphorus tribromide.

Short trick



Preparation of Amines

Alkyl/benzyl halide → Amines

Ammonolysis

Ammonolysis of R — X

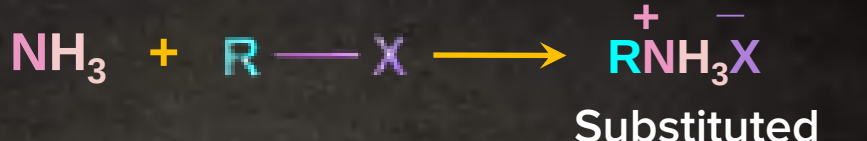
S_N2 reaction

Reagent used

Ammonia in ethanol at 373 K → In sealed tube

Ammonolysis of R-X

General reaction



Example

Ammonolysis of R-X

By the treatment with a **strong base**

General reaction

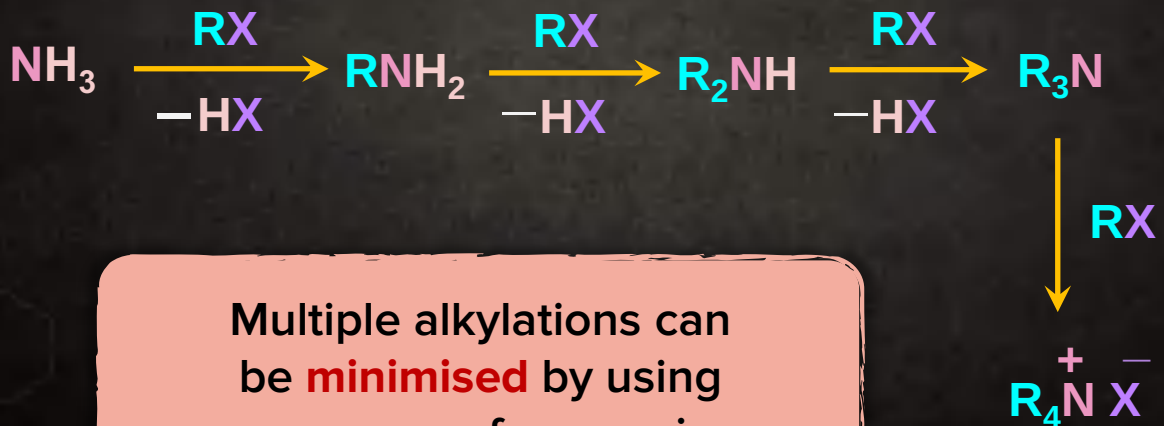
Limitation of Ammonolysis of Alkyl halides

A mixture of **1°, 2°, 3° amines** is formed.

Ammonolysis of R-X

The primary amine obtained in the first step behaves as a nucleophile.

It again reacts with alkyl halide to form secondary and tertiary amines, and finally quaternary ammonium salt.



Multiple alkylations can be minimised by using an excess of ammonia.

Ammonolysis of R-X

Ammonolysis of R — X

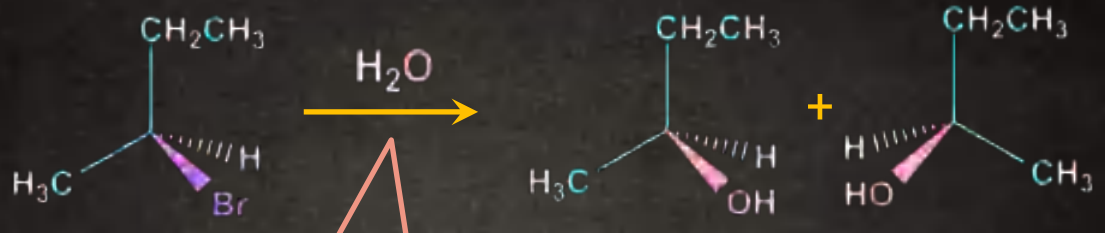
Reactivity order

RI > RBr > RCl

Factor	S_N1	S_N2
Substrate	3° (requires formation of a relatively **stable carbocation**)	Methyl > 1° > 2° (requires **unhindered substrate**)
Nucleophile	**Weak Lewis base**, neutral molecule, nucleophile may be the solvent (solvolysis)	**Strong Lewis base**, rate increased by high concentration of nucleophile

Factor	S_N1	S_N2
Solvent	**Polar protic** (Examples: Alcohols, water)	**Polar aprotic** (Examples: DMF, DMSO)
Leaving group	I > Br > Cl > F for **both S_N1 and S_N2**	

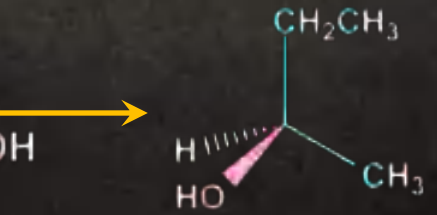
S_N1 vs S_N2

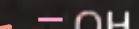


Poor nucleophile

Undergoes S_N1 reaction

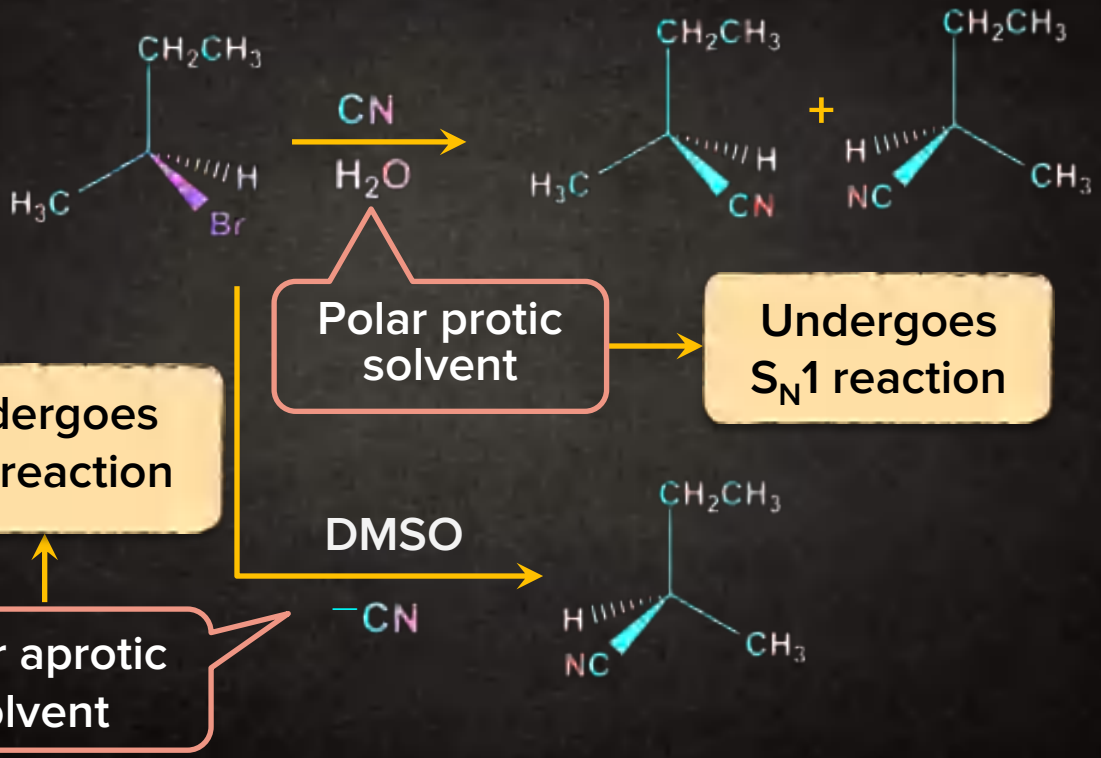
Undergoes S_N2 reaction



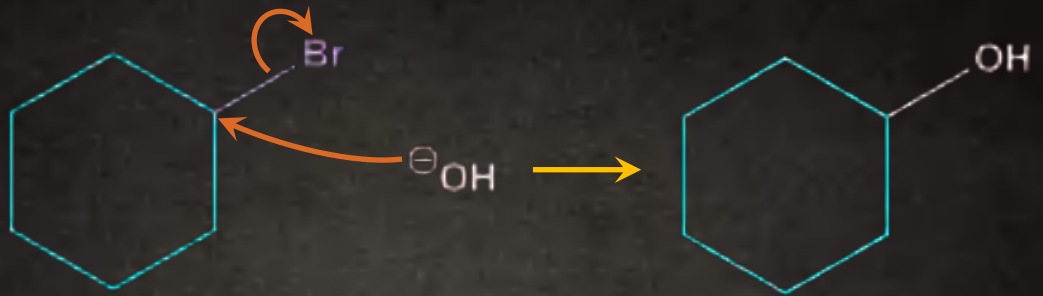


Strong nucleophile

S_N1 vs S_N2

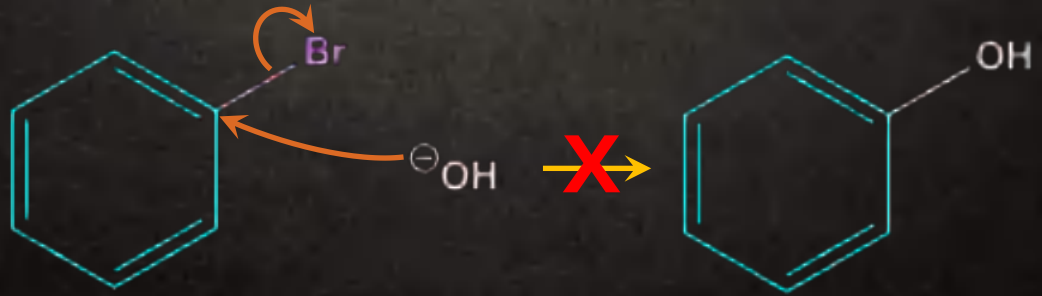

CH2CH3
H3C
H
Br
CN
H2O
CH2CH3
H3C
H
CN
+
CH2CH3
H
NC
CH3
Polar protic solvent
Undergoes SN1 reaction
Undergoes SN2 reaction
DMSO
−CN
CH2CH3
H
NC
CH3
Polar aprotic solvent

S_NAr : Nucleophilic Aromatic Substitution



Reaction **does** happen

Due to partial double bond character in aryl halides, S_N2 will not take place.



Reaction **does not** happen

Nucleophilic Aromatic Substitution

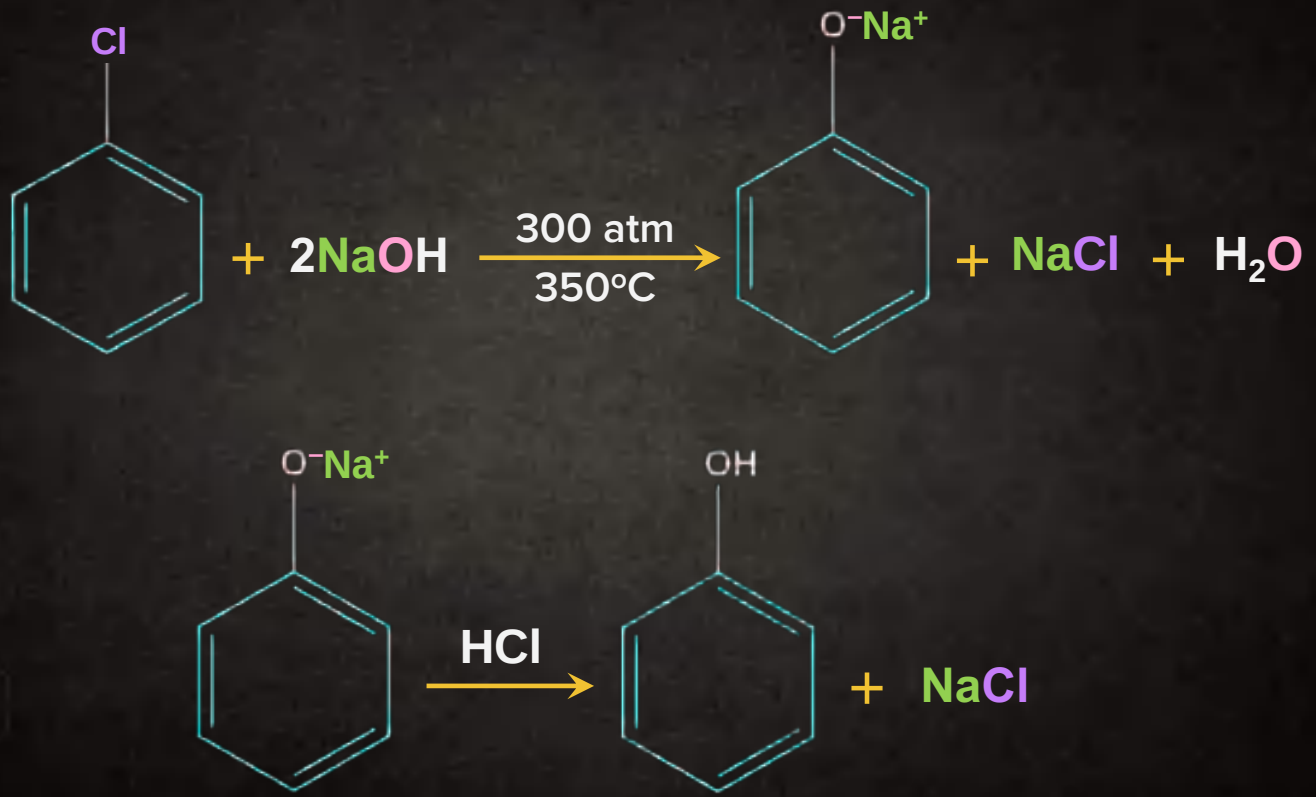
Aryl halides can be **remarkably reactive** towards nucleophiles if

- They react under the **proper conditions**
- They bear **certain substituents**.

Dow's Process

Chlorobenzene is heated at **350°C** (under high pressure) with aqueous sodium hydroxide. The reaction produces **sodium phenoxide**, which on acidification yields phenol.

Dow's Process

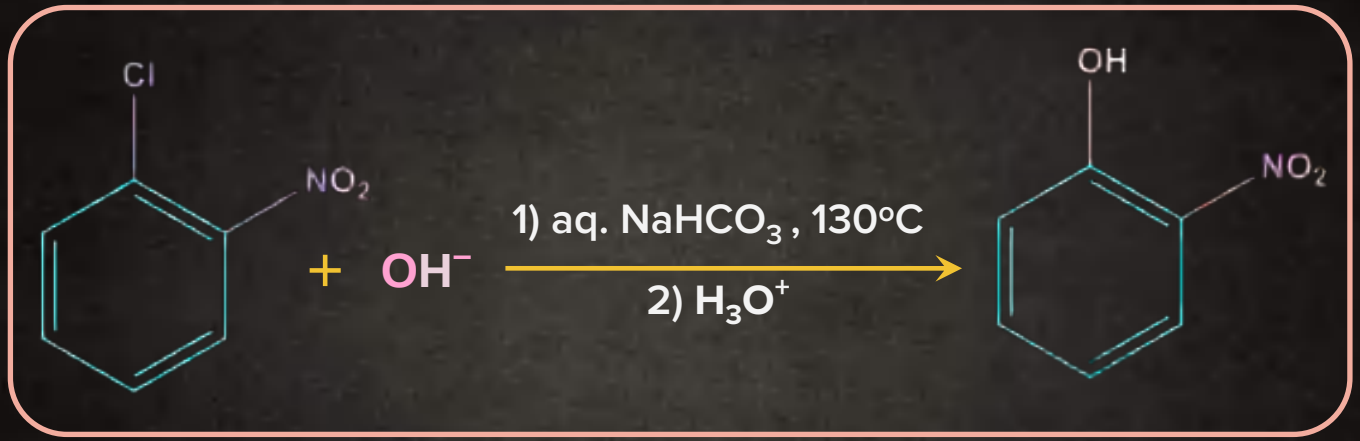


Nucleophilic Aromatic Substitution

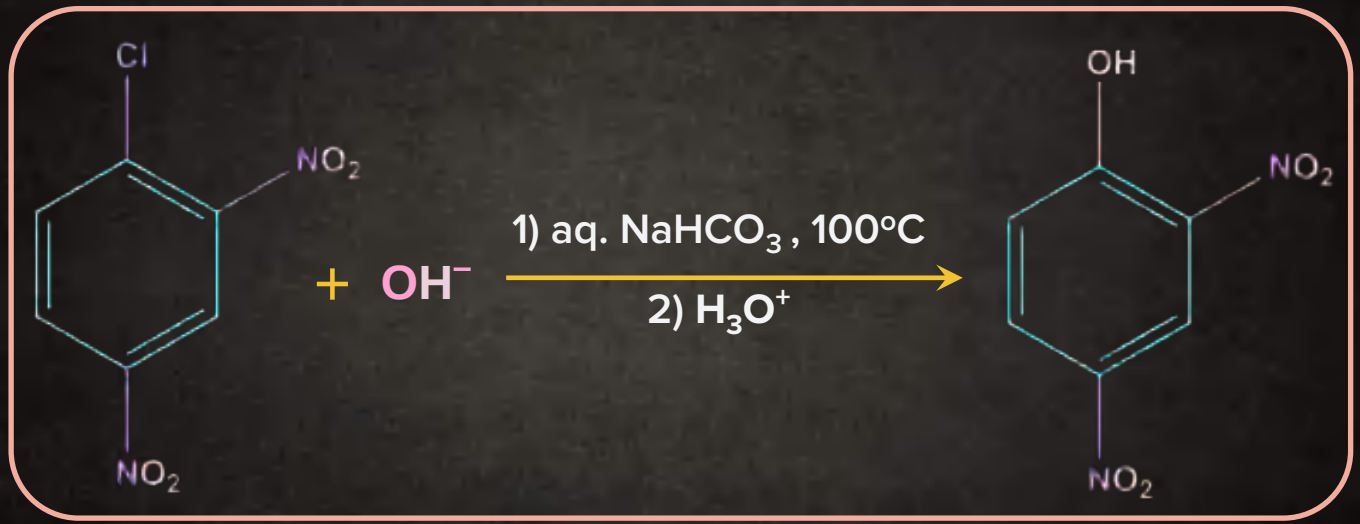
Nucleophilic substitution reactions of aryl halides do **occur readily** when an electronic factor makes the aryl carbon bonded to the halogen **susceptible to a nucleophilic attack.**

A nucleophilic aromatic substitution reaction can occur when **strong electron-withdrawing** groups are **ortho or para** to the halogen atom.

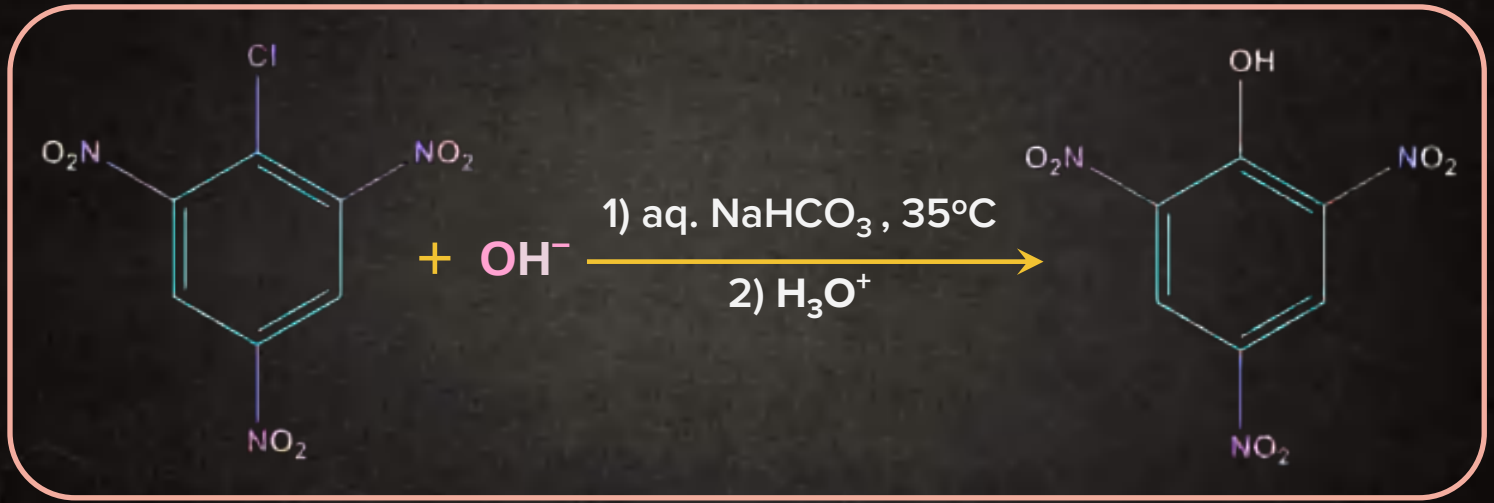
Nucleophilic Aromatic Substitution



Nucleophilic Aromatic Substitution



Nucleophilic Aromatic Substitution



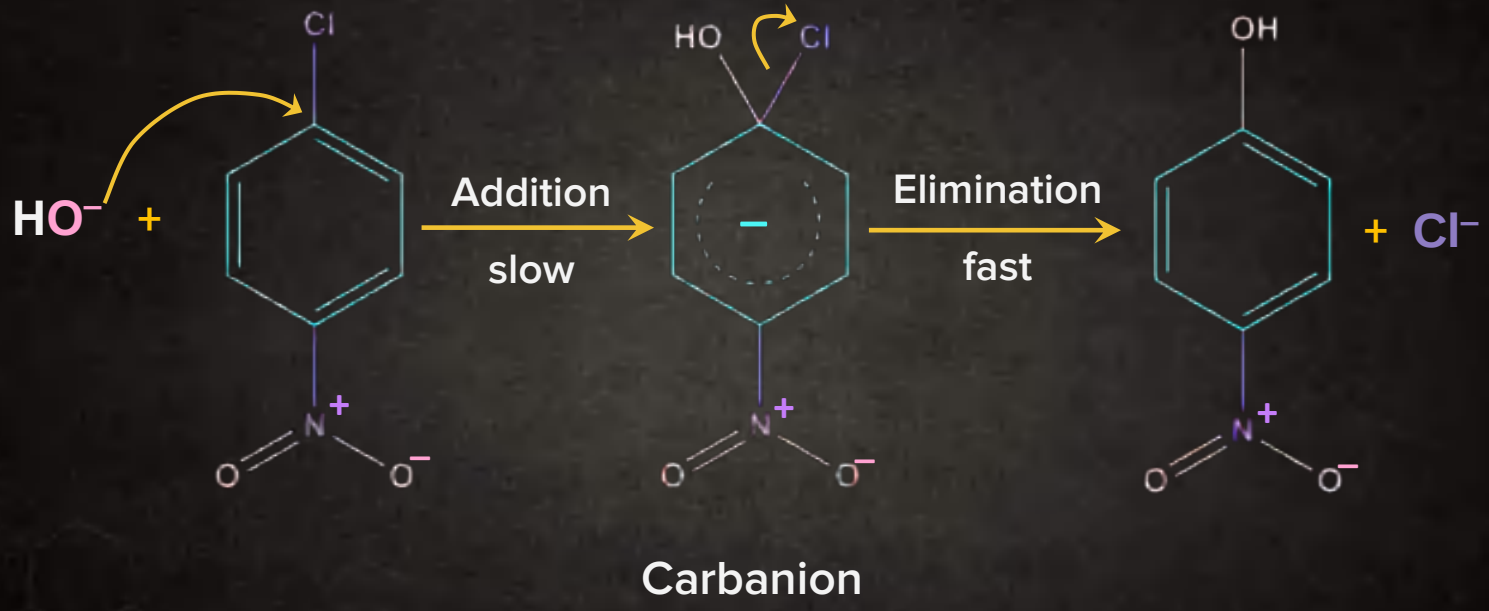
Nucleophilic Aromatic Substitution

A meta-nitro group **does not** produce a similar activating effect as that of ortho and para.

For example, m-Nitrochlorobenzene gives **no corresponding reaction**.

The process is called nucleophilic aromatic substitution (S_NAr).

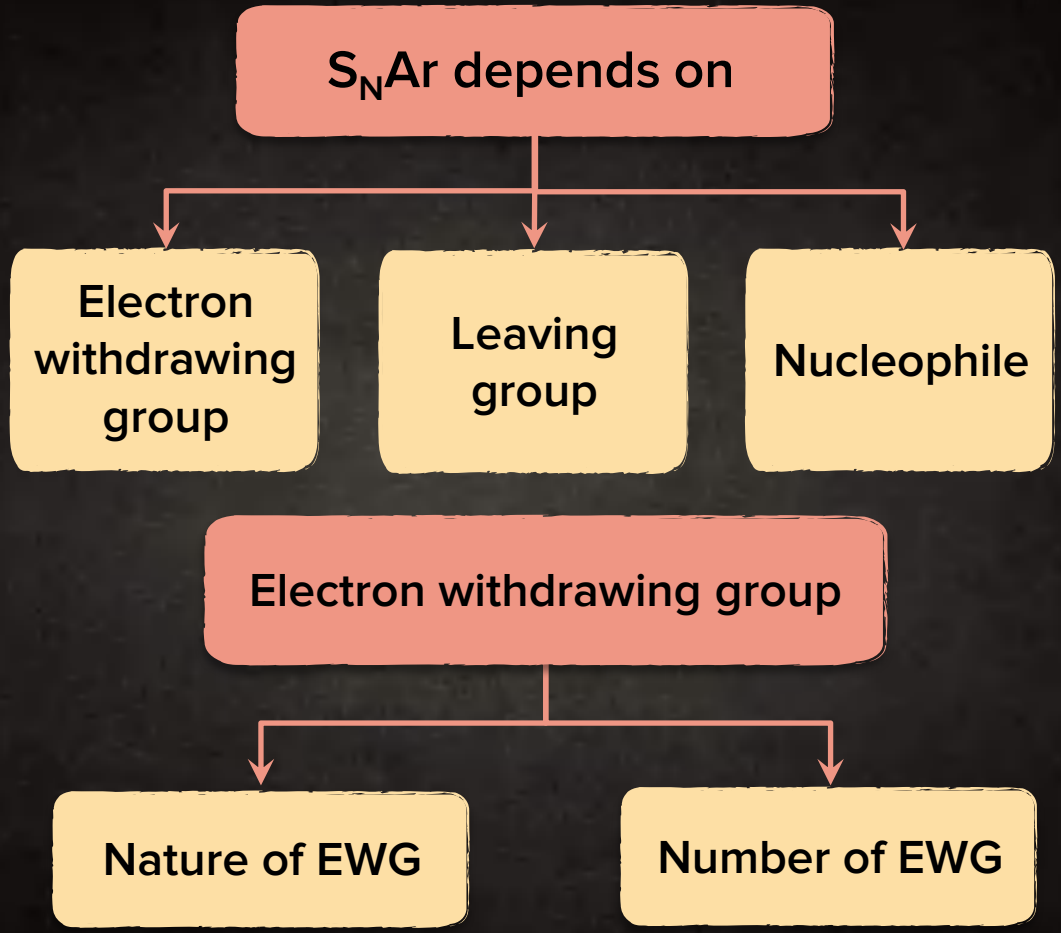
S_NAr



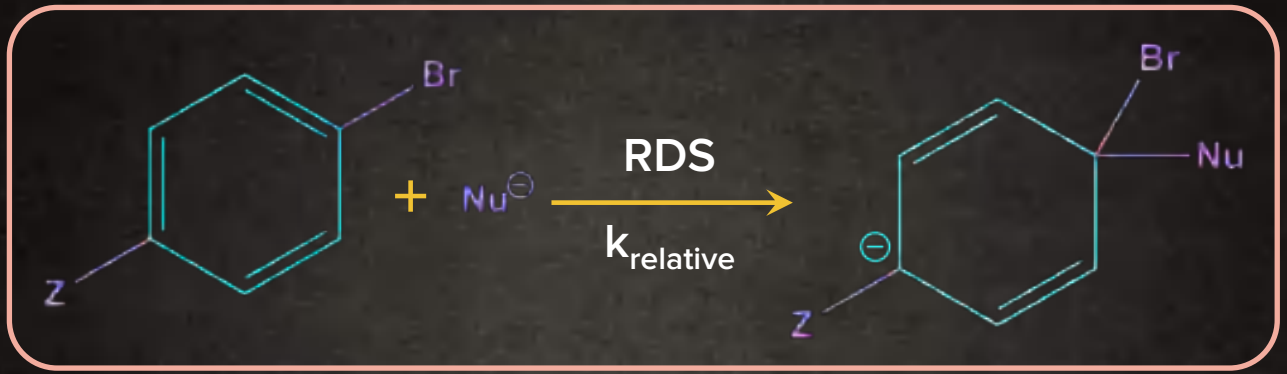
Carbanion

Nucleophilic Aromatic Substitution

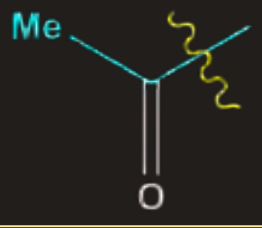
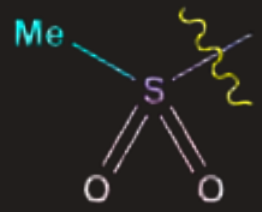
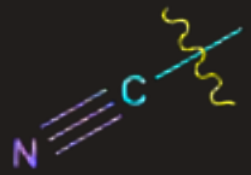
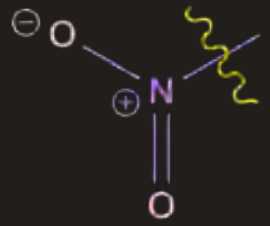
The carbanion is stabilised by **electron-withdrawing groups** in the positions **ortho and para** to the halogen atom.


S_NAr depends on
Electron withdrawing group
Leaving group
Nucleophile
Electron withdrawing group
Nature of EWG
Number of EWG

Effect of EWG on S_NAr



Stronger the EWG,
faster is the reaction.

Z	k_{rel}	Z	k_{rel}
	0.013		0.053
	0.031		1.0

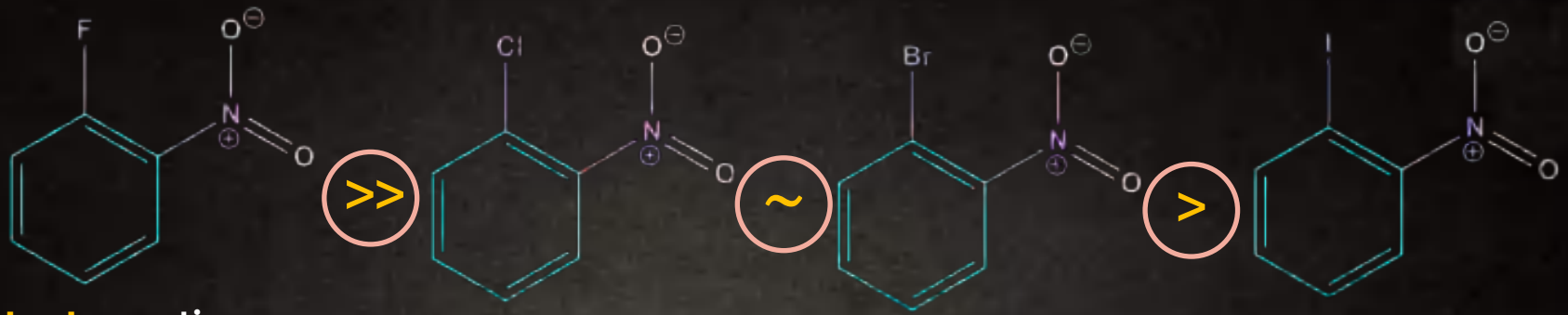
Effect of EWG on S_NAr

More the number of EWG,
faster is the reaction.

Nucleophilic Aromatic Substitution

o-Nitrochlorobenzene requires the **highest temperature** (p-Nitrochlorobenzene reacts at 130°C as well).

2,4,6-Trinitrochlorobenzene requires the **lowest temperature**.

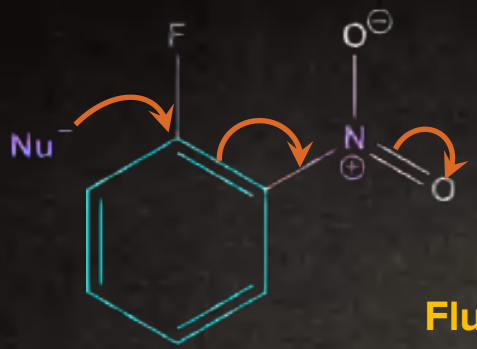


Fastest reaction

Slowest reaction

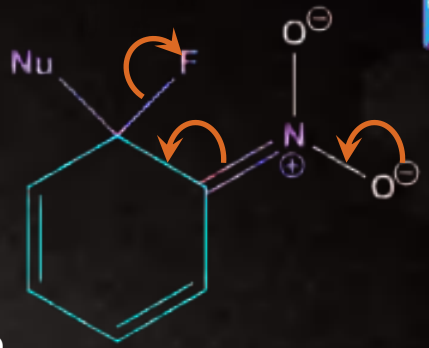
Fluoride is **never used as a leaving group** at nucleophilic substitutions at saturated carbon.

The **C–F bond is very strong**, the strongest of all the single bonds to carbon and it is difficult to break



Addition step

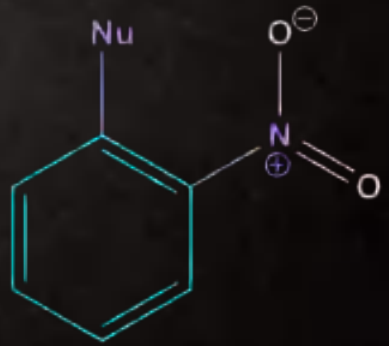
RDS



Fluoride accelerates this step because it is very electronegative

Intermediate

Elimination step | fast



Mechanism

Nucleophilic aromatic substitution

Step 1

It is slower because it **disturbs the aromaticity**.

Step 2

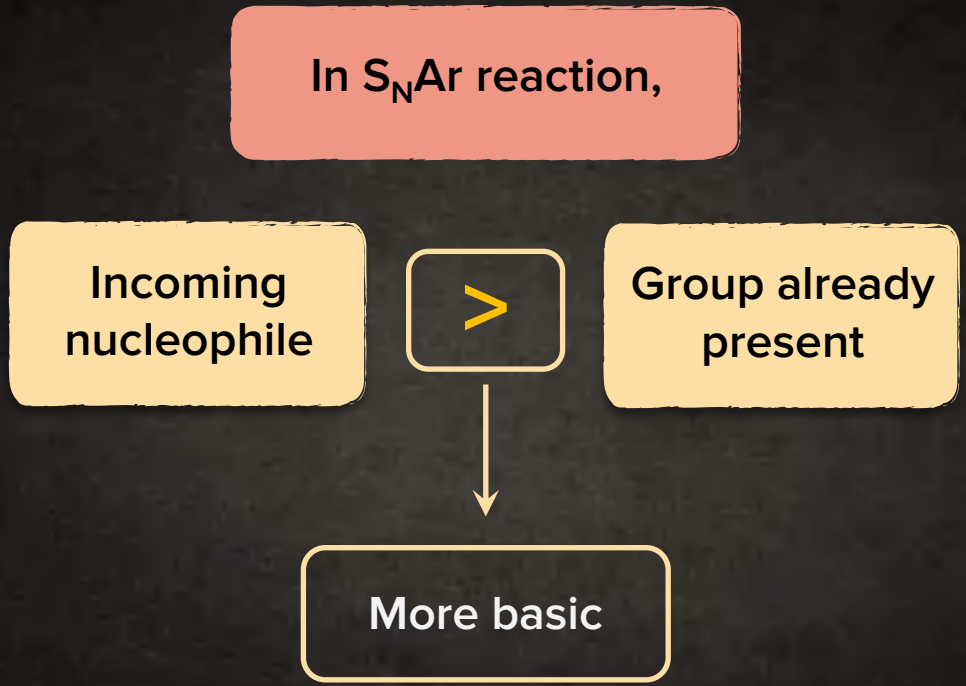
It **restores the aromaticity** and is faster.

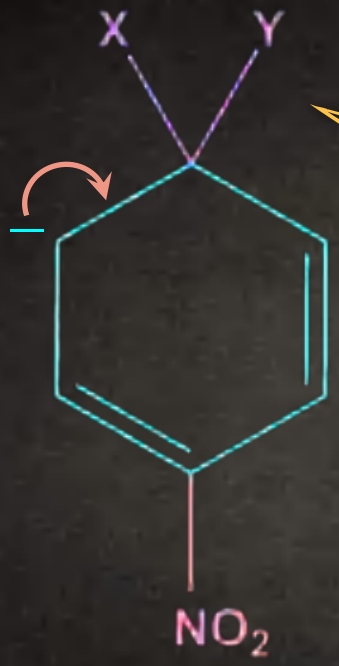
Effect of Leaving Group on S_NAr

Fluoride **accelerates the first step** simply by its enormous inductive effect.

The **effect of fluoride** or any other leaving group, can only come from its effect on the **first step.**

It is the most electronegative element of all and it **stabilises the anionic intermediate**, assisting the acceptance of electrons by the benzene ring.

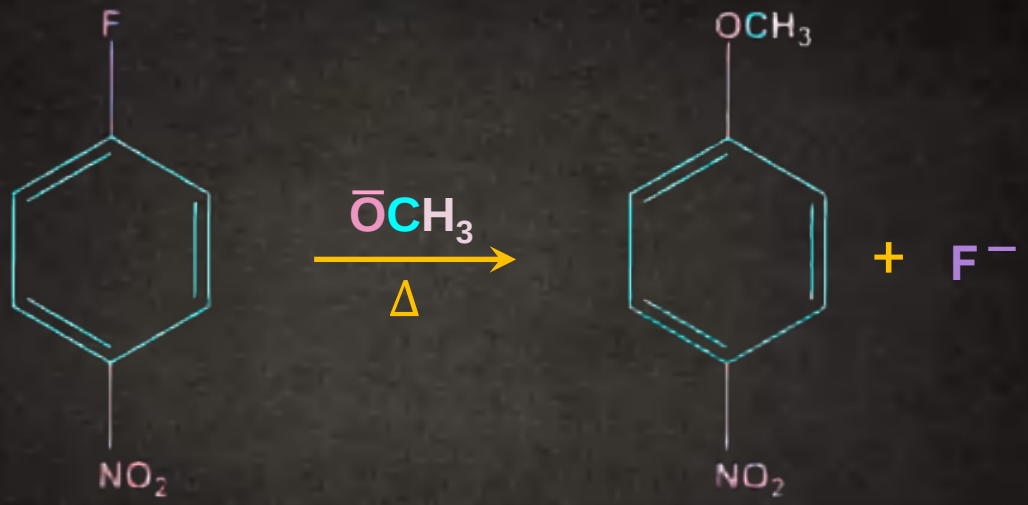

In S_NAr reaction,
Incoming nucleophile
>
Group already present
More basic



The weaker base out of the two will be eliminated.

Intermediate

Example



p-Fluoronitrobenzene

p-nitroanisole

S_Ni Reaction

In the S_Ni mechanism (substitution nucleophilic internal), a part of the leaving group must be **able to attack the substrate**

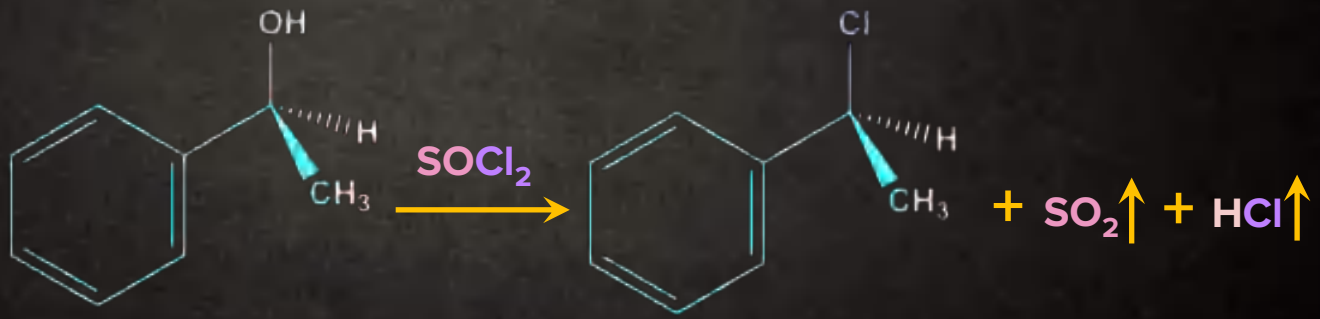
Detaching itself from the rest of the leaving group in the process.

In the S_Ni reaction, the mechanism proceeds with the **retention of configuration**.

Reaction of Alcohol with $SOCl_2$

Thionyl chloride ($SOCl_2$) converts primary and secondary alcohols to **alkyl chlorides** with the **retention of configuration**.

Reaction



Retention of configuration

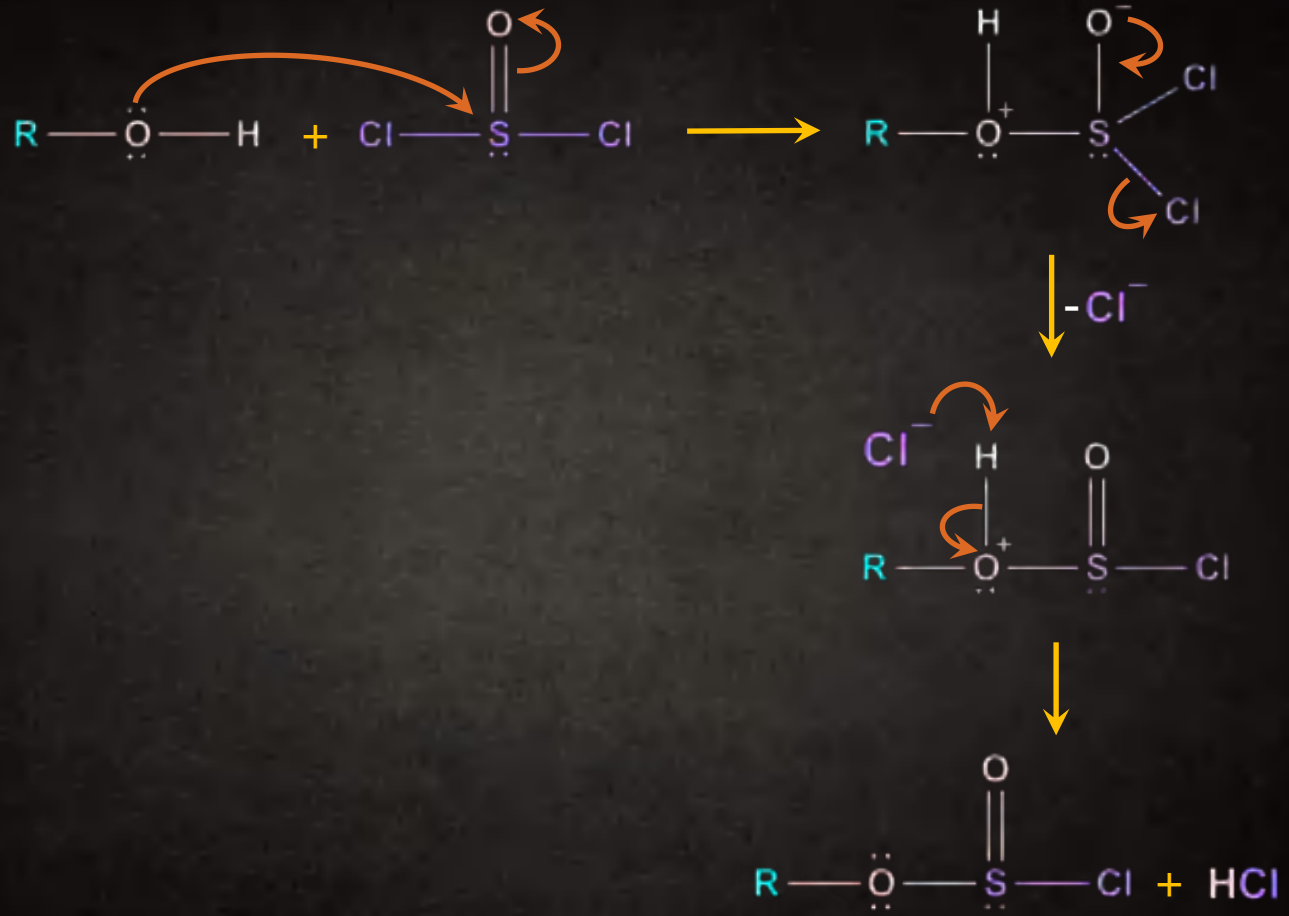
Mechanism

Step 1 Reaction of alcohol with $SOCl_2$

Step 2 Dissociation of alkylchlorosulphite.

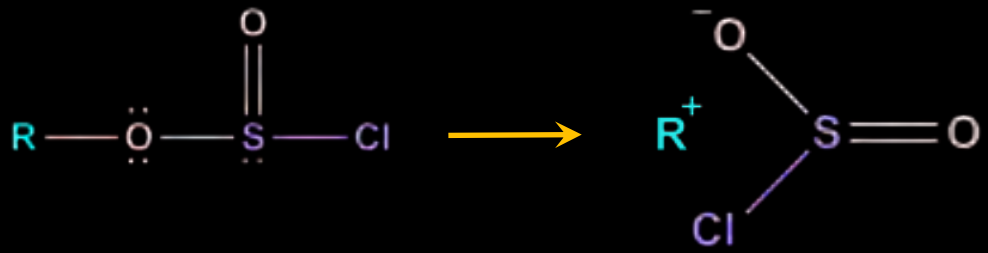
Step 3 Attack by leaving group

Alcohol reacts with thionyl chloride result is an **alkylchlorosulphite**.


R
O
H
+
Cl
S
Cl
O
H
O
Cl
Cl
-Cl⁻
Cl⁻
H
O
R
O
S
Cl
O
R
O
S
Cl
+
HCl

Mechanism

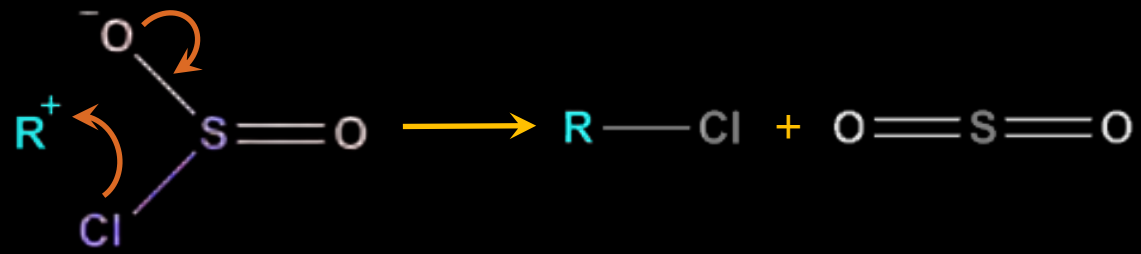
Second step is the same as the very first step of the S_N1 mechanism i.e., **dissociation into an intimate ion pair**.



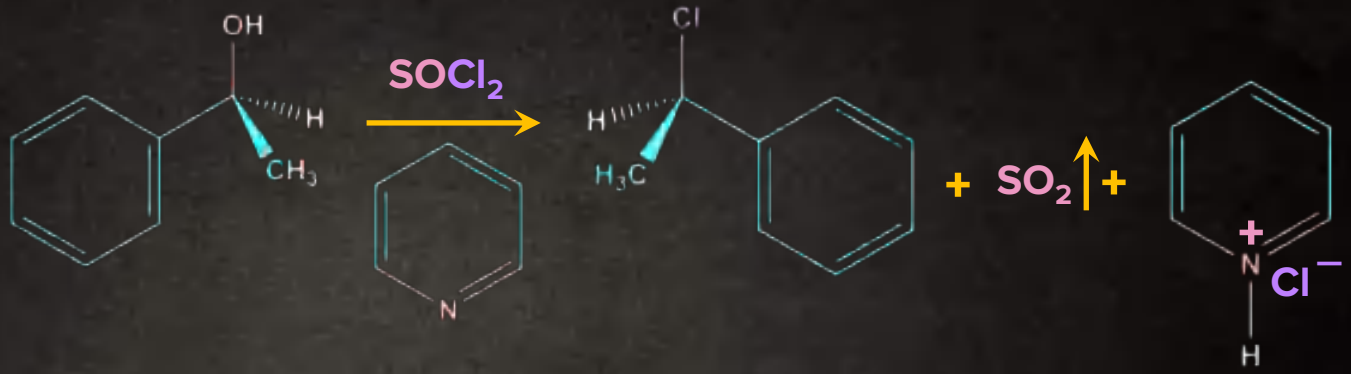
Mechanism

Part of the **leaving group attacks**, necessarily from the front since it is unable to get to the rear.

It results in **retention** of configuration.



Reaction of Alcohol with $SOCl_2$



Inversion of configuration

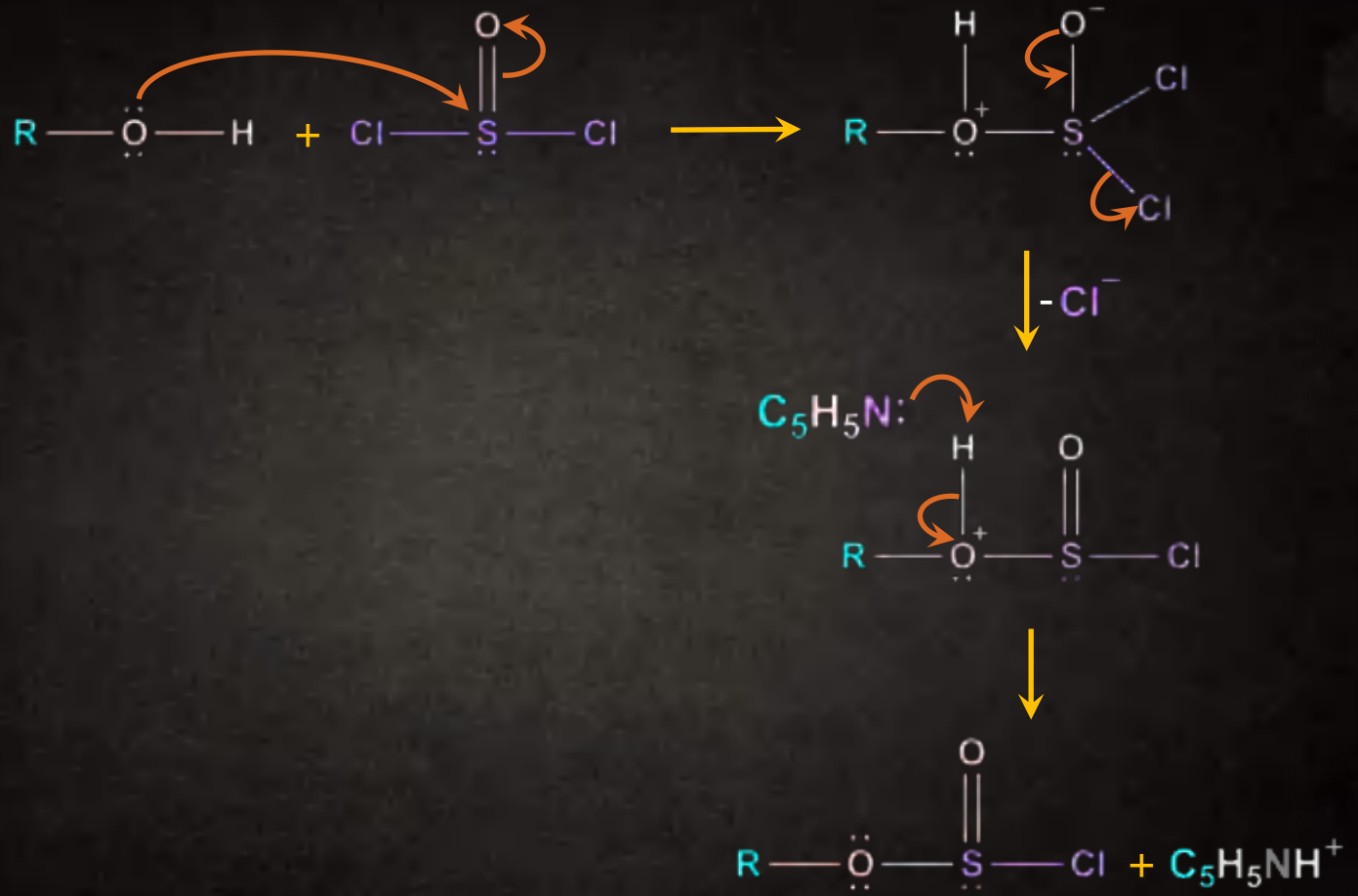
Pyridine (C_5H_5N) is often included to **promote** the reaction.

Mechanism

Step 1 Reaction of alcohol with $SOCl_2$

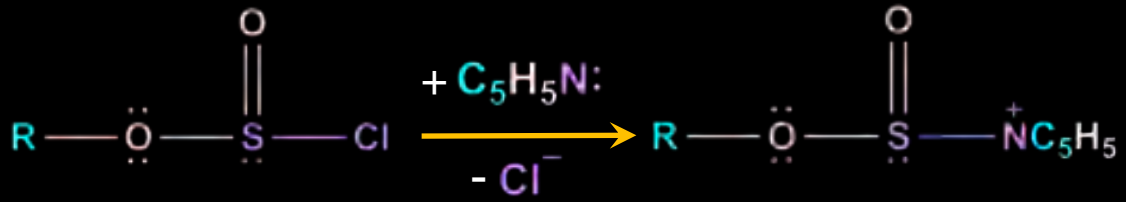
Step 2 Formation of pyridinium-alkylsulphite intermediate

Step 3 Attack by chloride anion


R — O — H + Cl — S — Cl
O
H
O⁻
Cl
Cl
- Cl⁻
C5H5N:
R — O — S — Cl + C5H5NH+

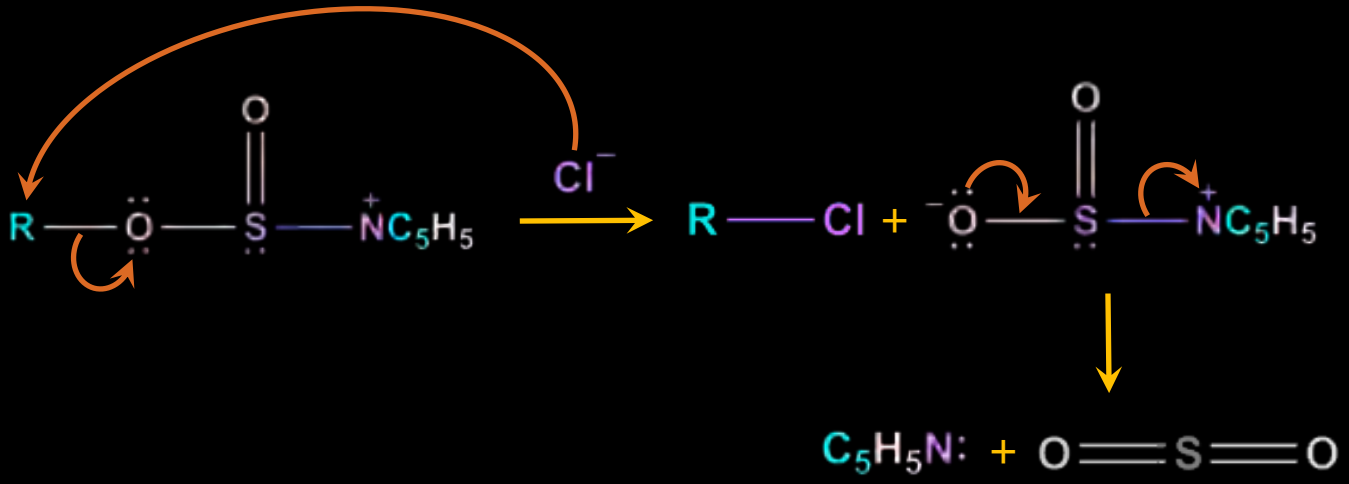
Mechanism

Alkylchlorosulphite intermediate then reacts rapidly with another molecule of pyridine, to give a **pyridinium alkylsulphite intermediate**.



Mechanism

A chloride anion then attacks the substrate carbon, displacing the sulphite leaving group.



Mechanism

Inversion results because the pyridine reacts with ROSOCl to give $ROSONC_5H_5$ before anything further can take place.

The Cl freed in this process now **attacks from the rear**.

S_NNGP Reaction

By S_NNGP

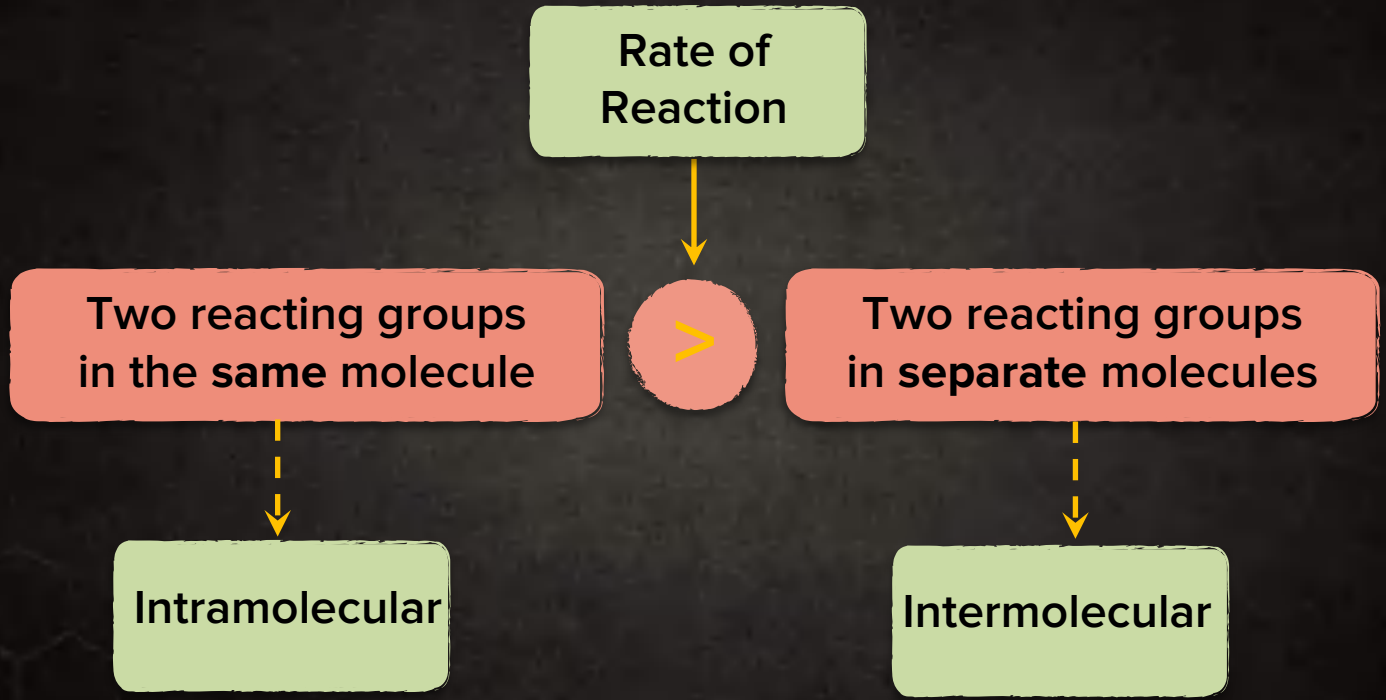
- Substitution reaction
- Nucleophilic
- Neighboring group participation

S_NNGP

Also known as **anchimeric assistance**

In Greek, Anchimeric assistance means "**Adjacent part**"

Remember!


Rate of Reaction
Two reacting groups in the same molecule
>
Two reacting groups in separate molecules
Intramolecular
Intermolecular

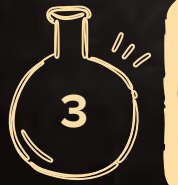
Characteristics of S_NNGP Reaction

1. The rate of reaction is **greater** than expected.
2. The configuration at a chiral carbon is **retained**.
3. The configuration at a chiral carbon is **not inverted or racemised**.

Intramolecular S_NNGP

Nucleophile should be present within the molecule/ internally.

Generally, nucleophile and leaving group should be present anti to each other at 1,2 position.



Concentration of nucleophile (external) should be less.

Mechanism

Reactions, in which there is usually a group with an **unshared pair of electrons, β** to the leaving group (or sometimes farther away).

The mechanism operating in such cases is called the **neighbouring-group mechanism**.

It consists essentially of **two S_N2** substitutions.

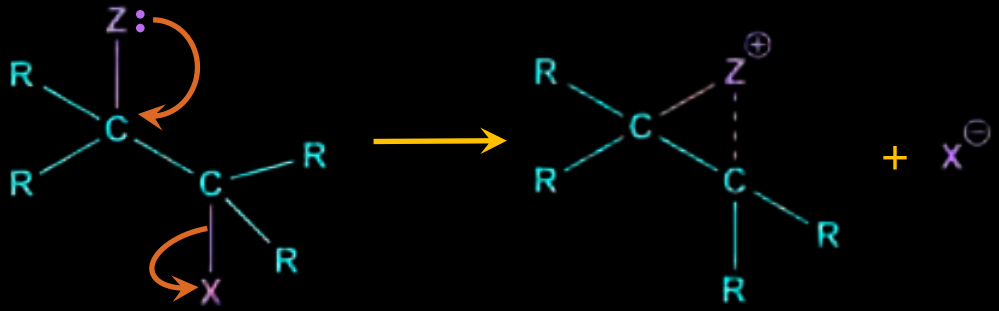
Each causing an inversion so the net result is **retention of configuration**.

Mechanism

Step 1	Intramolecular nucleophilic reaction
Step 2	External nucleophilic reaction

Mechanism

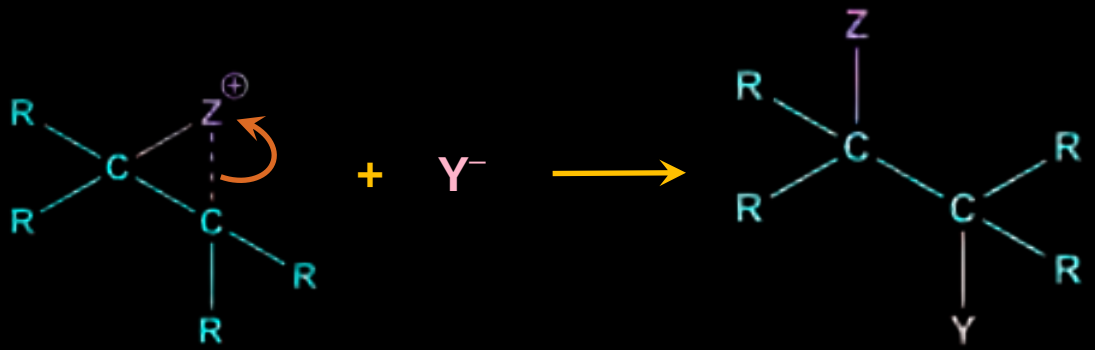
The **neighbouring group acts as a nucleophile**, pushing out the leaving group but still retaining attachment to the molecule.



Z: A neighbouring group
X: A leaving group

Mechanism

The external nucleophile displaces the neighbouring group by a backside attack.



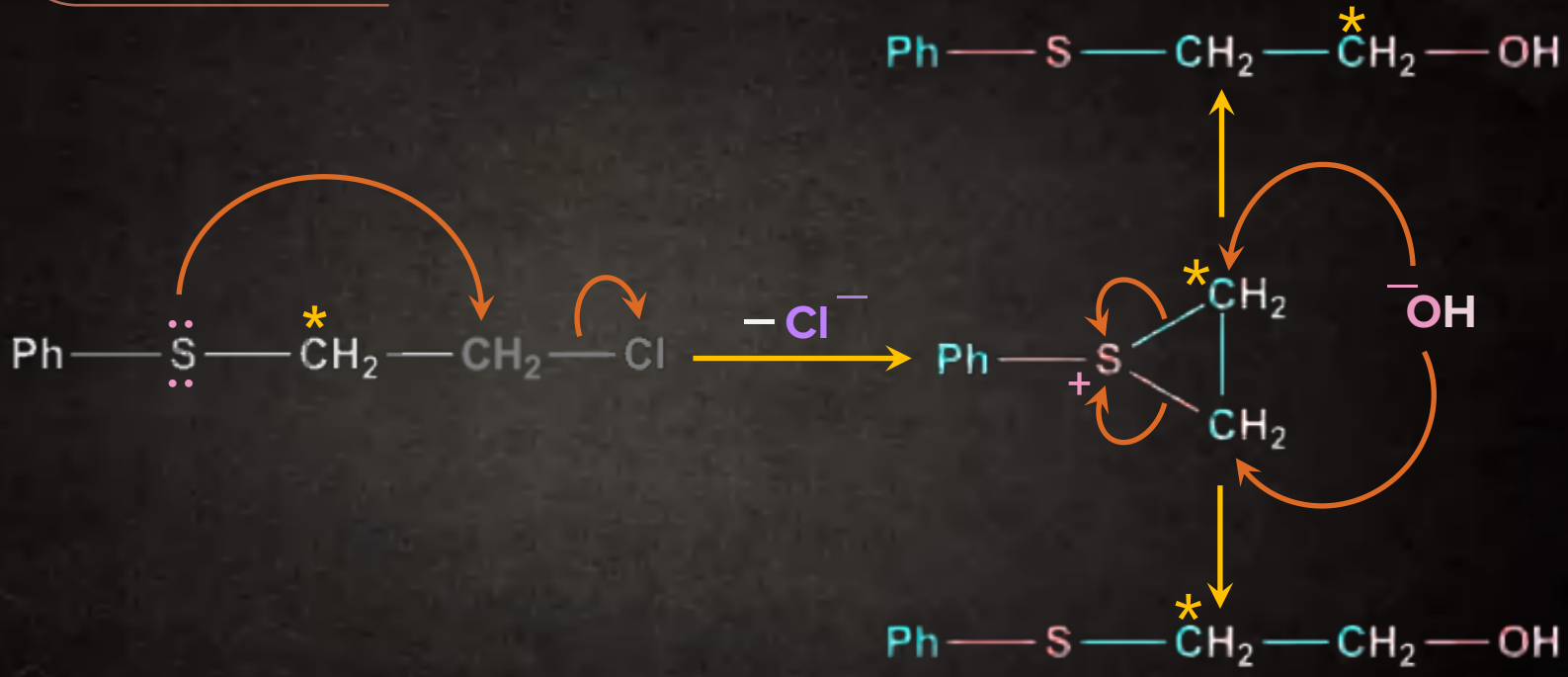
Groups Behaving as Neighboring Groups

Sulphur	-SH, -SR, $-S^-$
Carboxylic acid derivatives	$-COO^-$, -COOR, -OCOR
Oxygen	-OR, -OH, $-O^-$
Nitrogen	$-NH_2$, -NHR, $-NR_2$
Halides	-I, -Br, -Cl

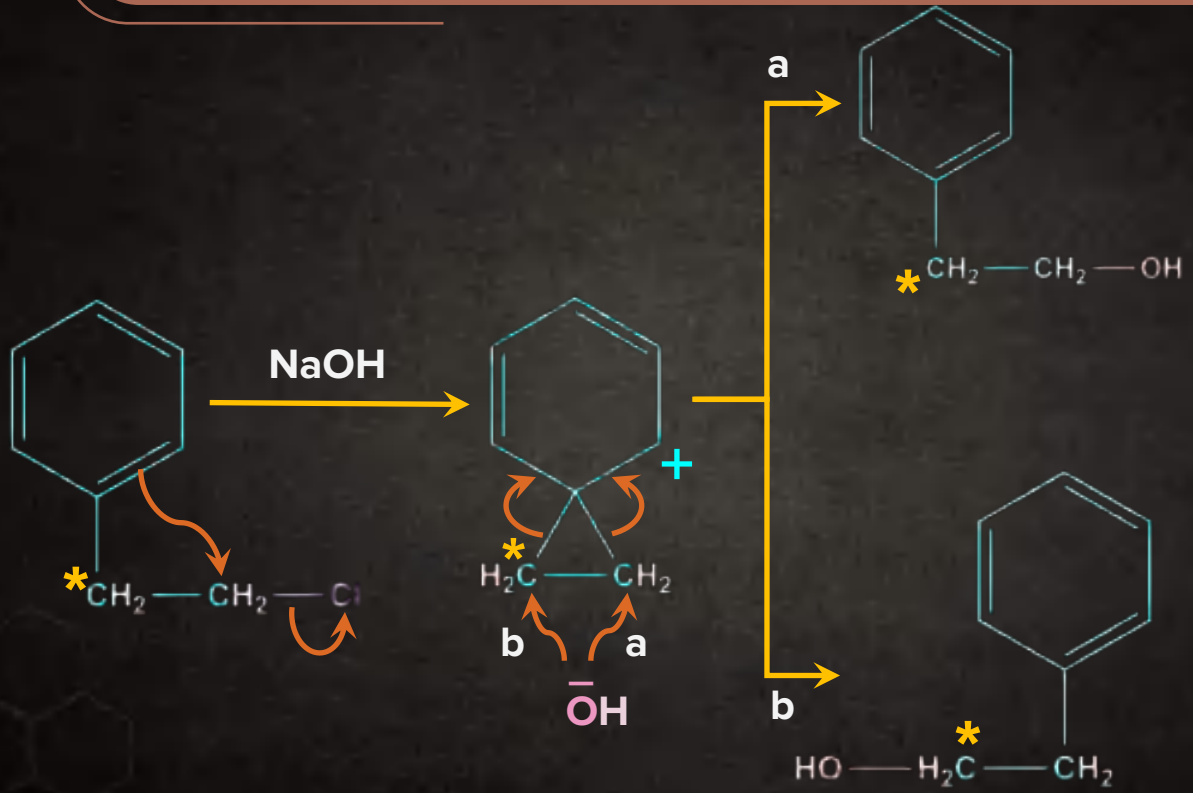
Examples of S_NNGP Reaction


Neighbouring Group Participation by
Involving species having lone pair
Aromatic rings as neighbouring groups
Cyclopropyl methyl system

Reaction that follows S_NNGP Mechanism



Reaction that follows S_NNGP Mechanism



Reaction that follows S_NNGP Mechanism

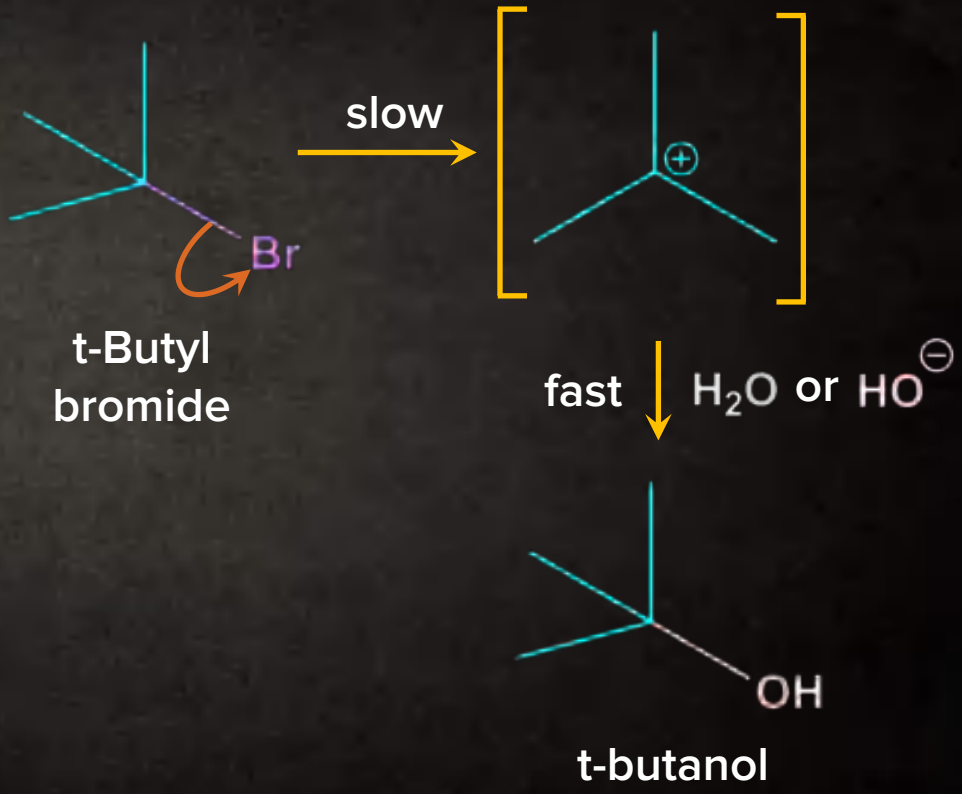
Cyclopropyl methyl substrates solvolyze with **abnormally high rates**.

The products often include not only unrearranged cyclopropyl-methyl, but also **cyclobutyl and homoallylic compounds**.

Elimination Reactions

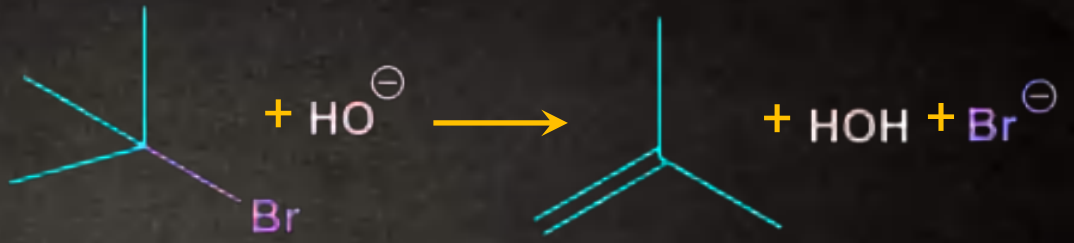
Substitution and Elimination Reaction

Reaction of *t*-BuBr with dil. NaOH



Substitution and Elimination Reaction

Reaction of *t*-BuBr with conc. NaOH



t-Butyl bromide

Isobutene (2-Methylpropene)

Substitution and Elimination Reaction

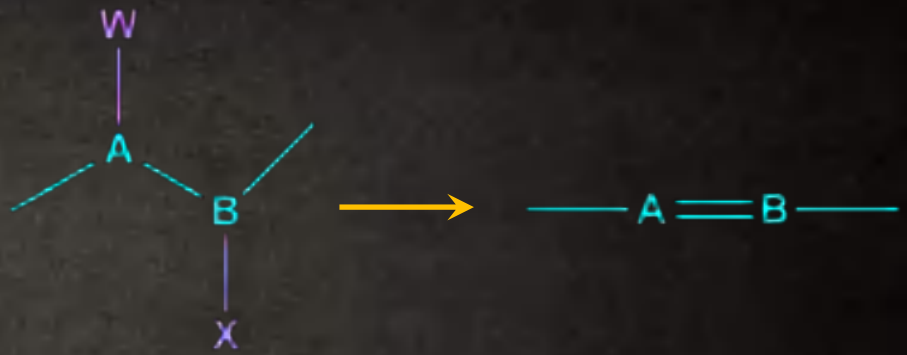
The reaction **stops being a substitution** and an alkene is formed instead.

Overall, HBr is lost from the alkyl halide, and the reaction is known as an **elimination**.

It is an organic reaction in which two groups/substituents/atoms are **removed from a molecule** so that a new double bond is formed.

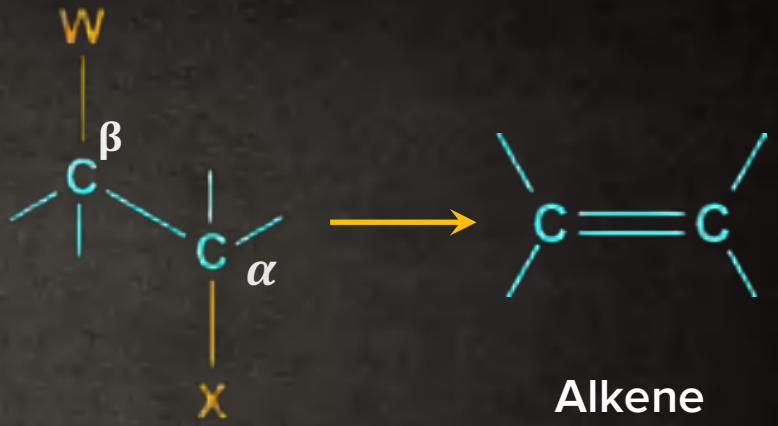
Elimination Reaction

General reaction



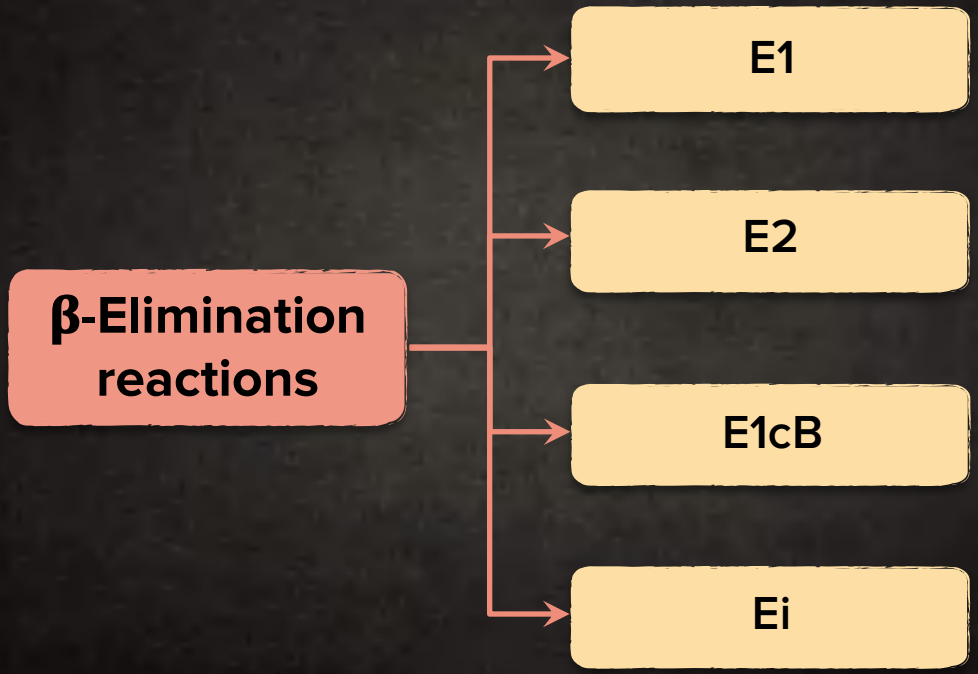
β - Elimination Reaction

When two atoms/substituents are removed from the **adjacent atoms** (α and β positions) to form a **new multiple bond**.



Also known as **1,2-elimination**

β-Elimination Reactions



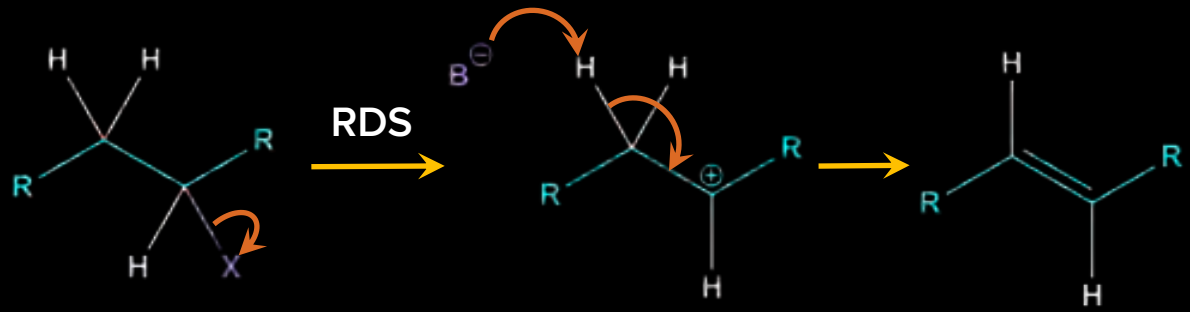
E1 Reaction

E1 describes an elimination reaction (E) in which RDS is **unimolecular (1).**

The **rate-determining step (RDS)** refers to the ionisation of the substrate to give a **carbocation** and it does not involve the base.

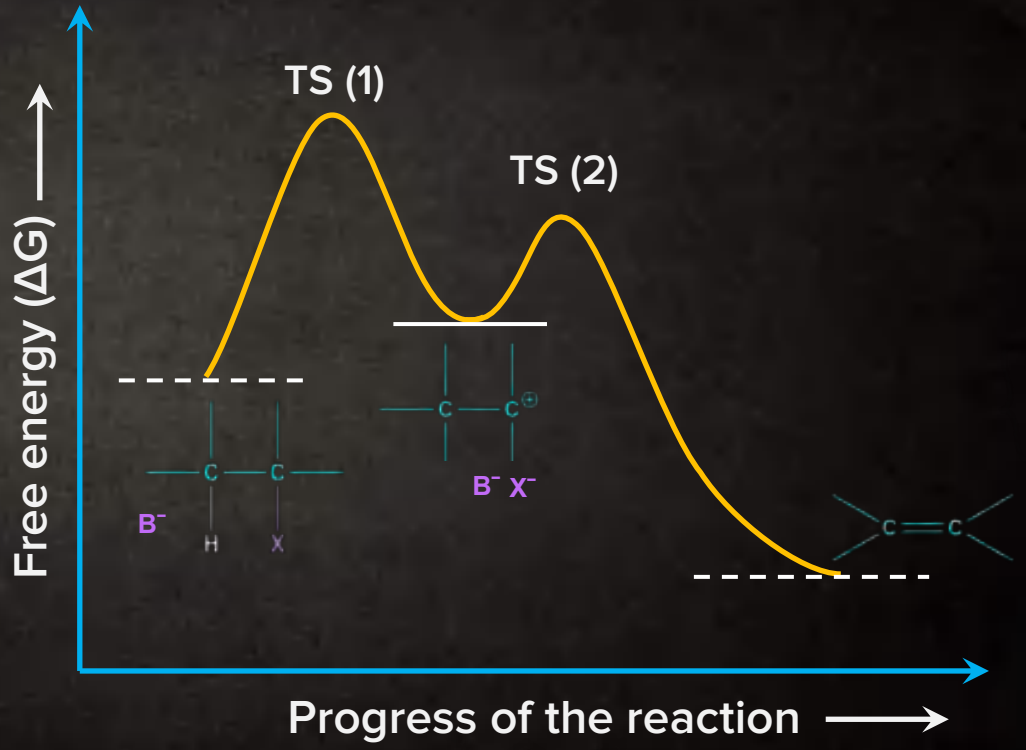
Mechanism

Rate = k[Alkyl halide]



E1 Reaction

The first step is rate determining step and hence the slowest step. So, it needs highest activation energy



E1 Reaction

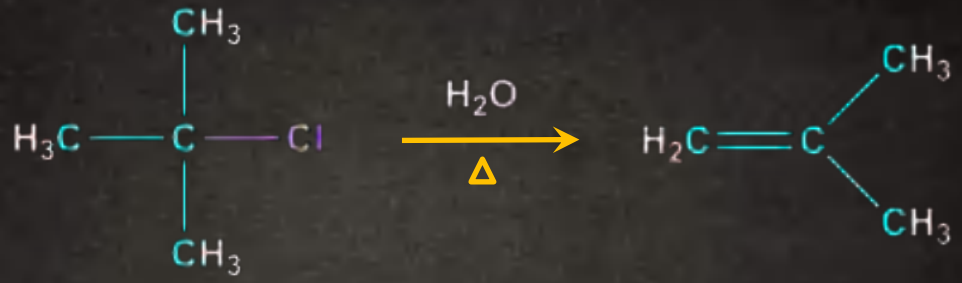
1. It is a **unimolecular, two-step** process.

2. The reaction intermediate is a carbocation. Hence, **rearrangement** is possible.

Examples

- Dehydrohalogenation of alkyl halide
- Dehydration of alcohol

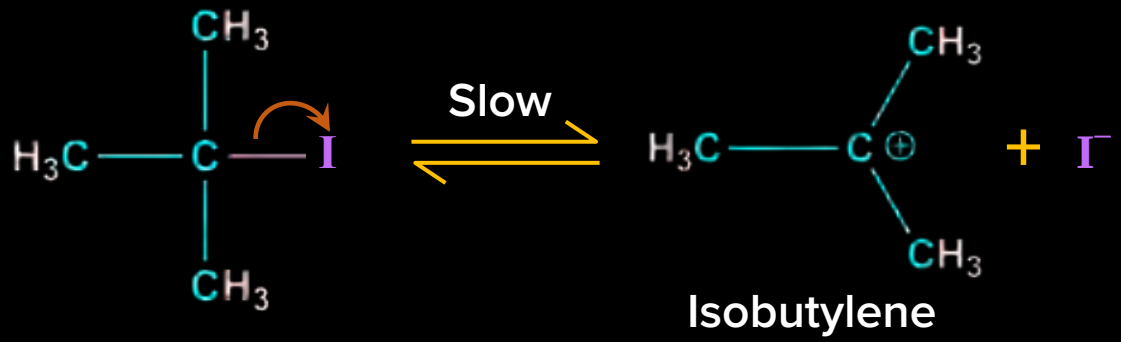
Dehydrohalogenation of Alkyl Halide



Step 1 Formation of carbocation

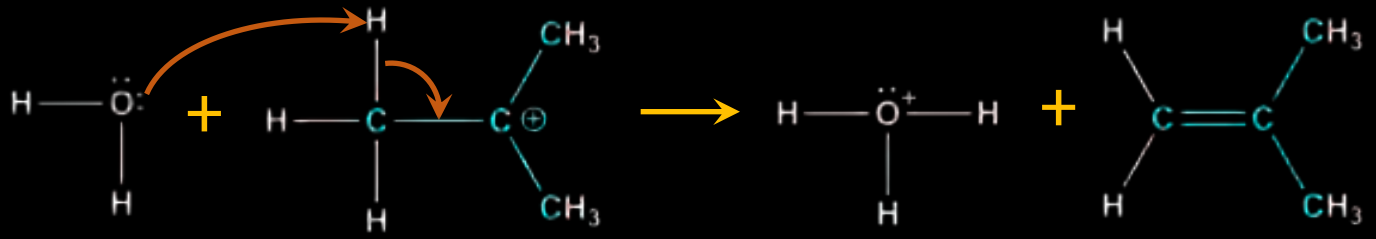
Step 2 Attack of base

Formation of Carbocation

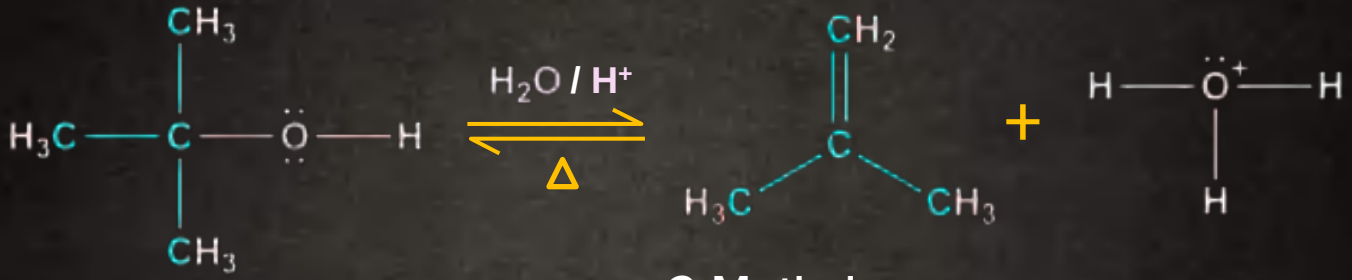


Isobutylene

Attack of Base



Dehydration of Alcohol

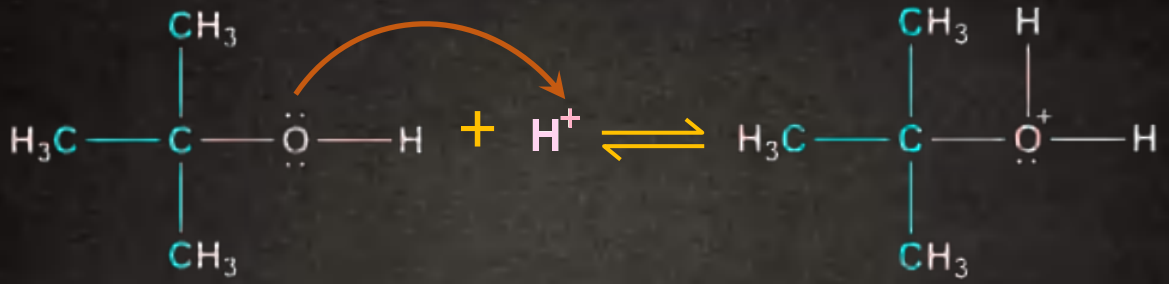


2-Methylpropene

Dehydration of Alcohol

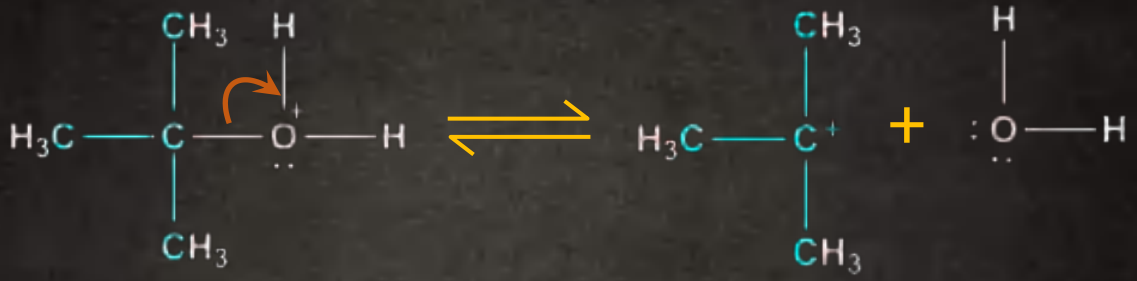
Step 1	Protonation of alcohol
Step 2	Loss of leaving group (H_2O molecule)
Step 3	Deprotonation to form alkene

Protonation of Alcohol



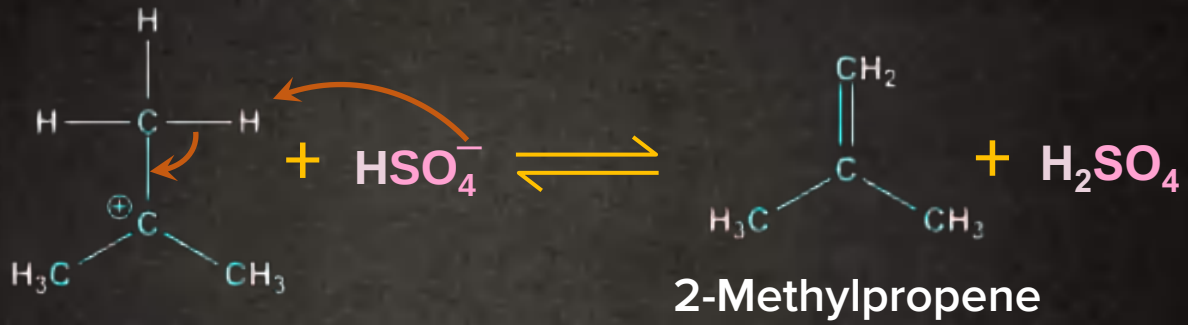
Protonated alcohol

Loss of leaving group (H_2O) molecule

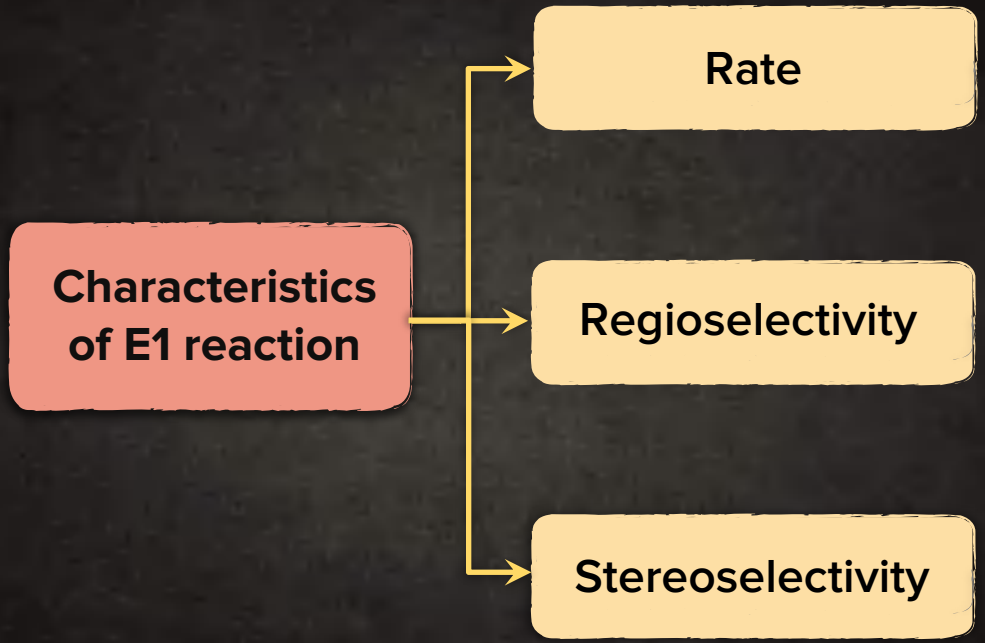


A carbocation

Deprotonation to from Alkene



2-Methylpropene


Characteristics of E1 reaction
Rate
Regioselectivity
Stereoselectivity

Rate of E1 Reaction

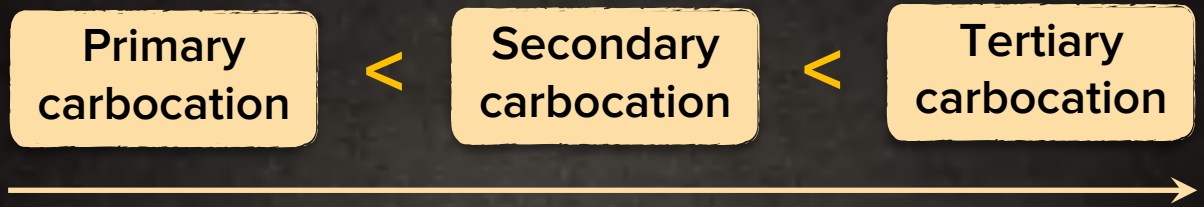
In E1 reaction, the **rate-determining step** is the formation of carbocation.

Stability of carbocation governs the rate of E1 reaction.

1. Rate of reaction $\propto$ Stability of **carbocation**

2. Rate $\propto$ [Alkyl halide]

Stability of Carbocation



Stability increases

Rate of the reaction increases

Elimination Reaction

In some eliminations **only one product** is possible.

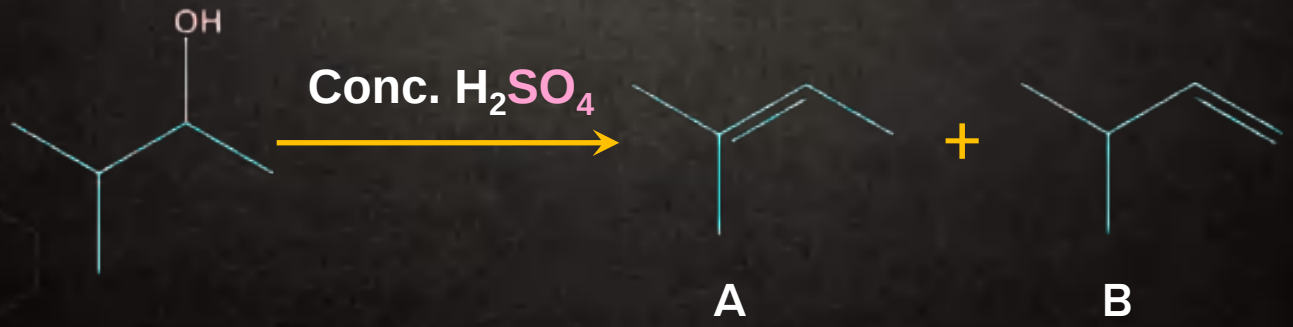
For others, there **may be a choice of two (or more)** alkene products that differ in the **location** of the double bond.

Regioselective Reaction

When a reaction that can potentially yield **two or more** constitutional isomers

→

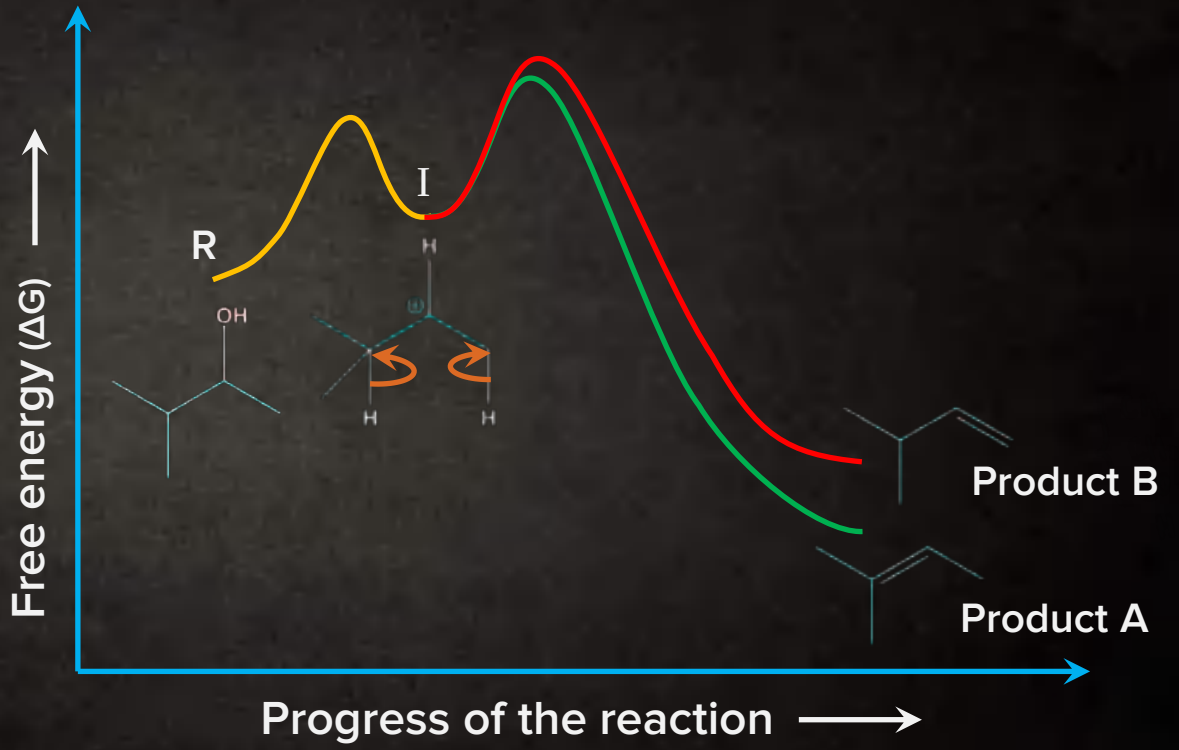
actually produces **only one** (or a predominance of one), the reaction is said to be **regioselective**.



Dehydration of Alcohols

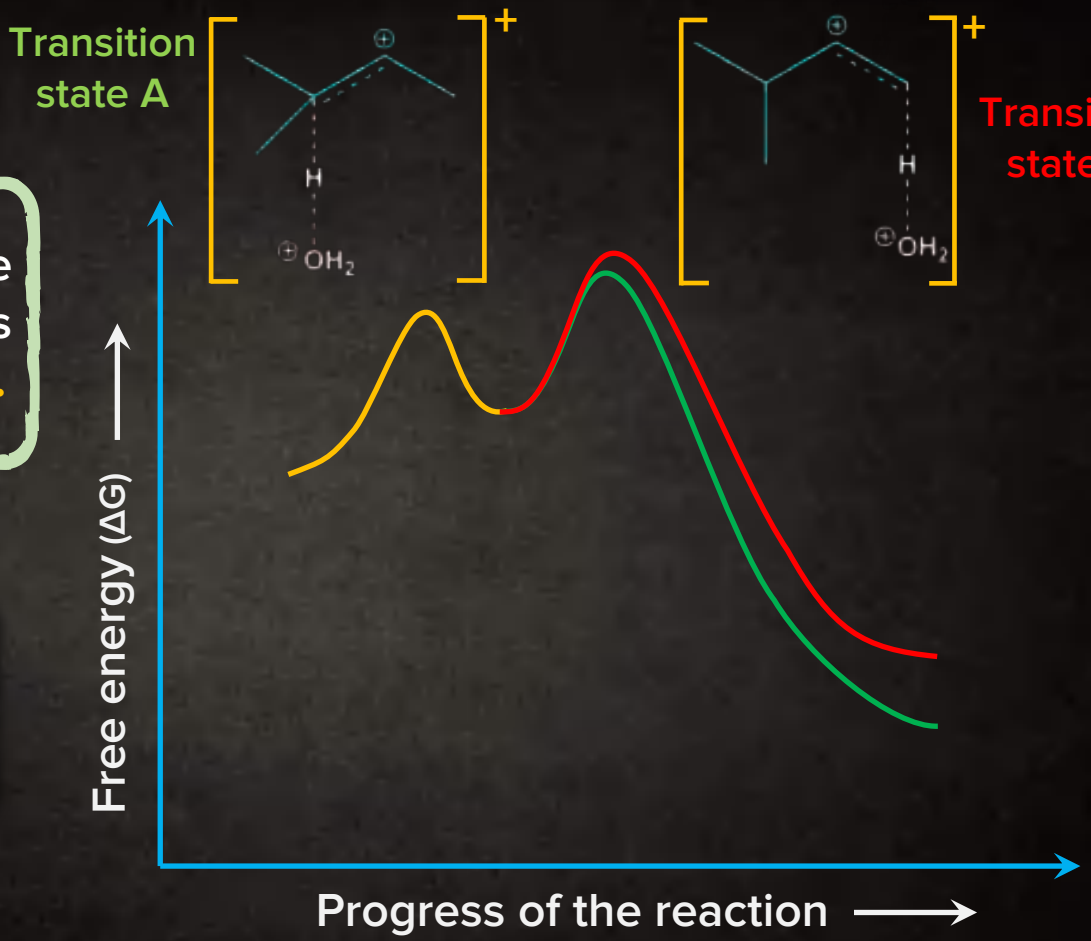
Reaction can result in two products

- A
- B



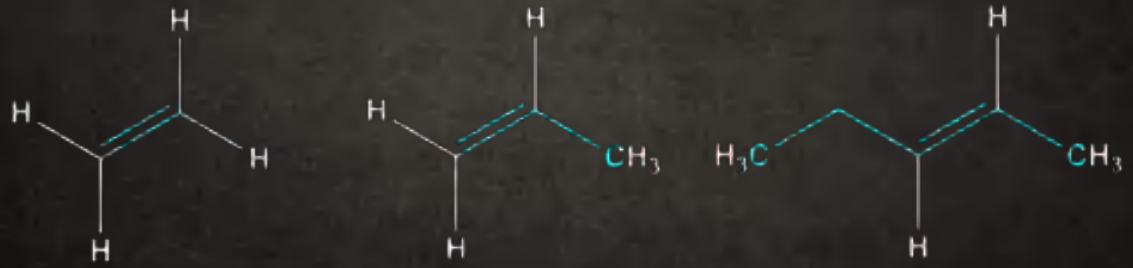
In the second step i.e., in the formation of product there is formation of alkene **like T.S.**

More stable the alkene like T.S, more stable the product (major)



Saytzeff Rule

The **more substituted alkene** product is obtained when a proton is removed from the **β-carbon** that is bonded to the **fewest hydrogens**.



Increasing substitution increases the stability of alkene

Characteristics of E1 Reaction

Stereoselectivity

In some eliminations, **only one product** is possible.

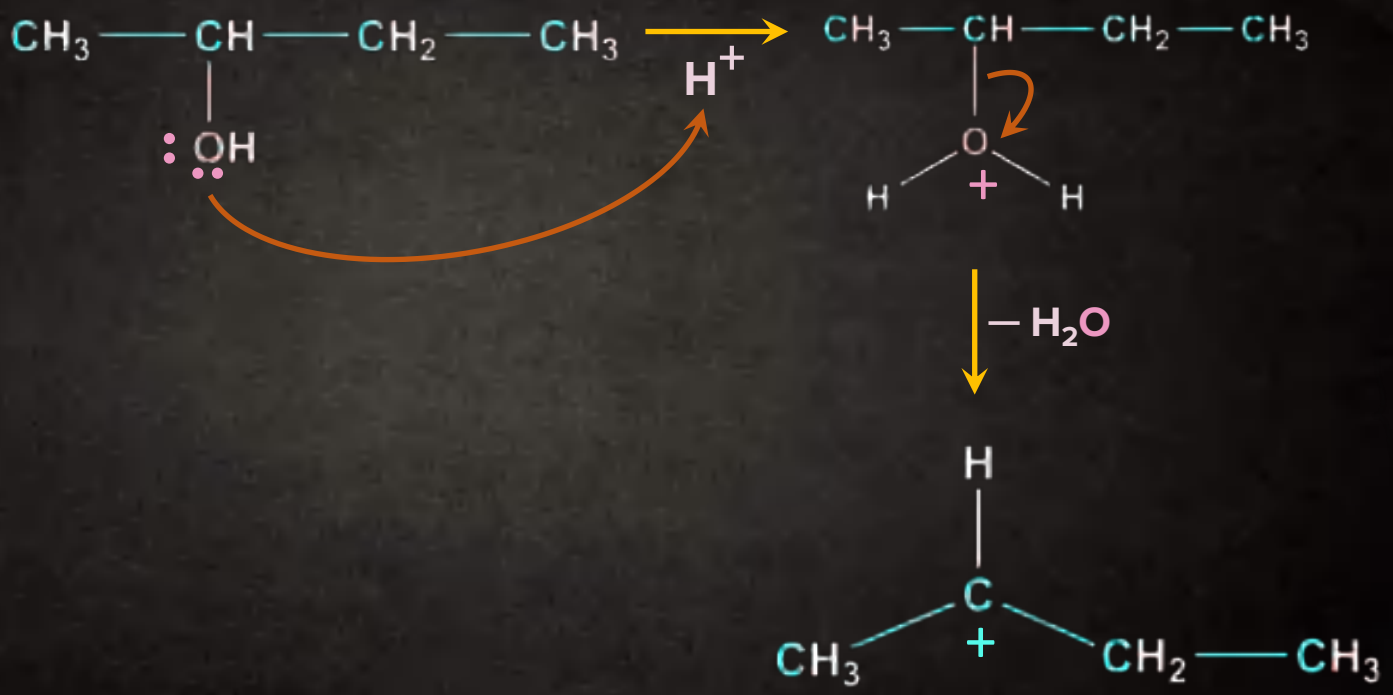
The reaction in which reactant chooses to form **predominantly** one of two possible stereoisomeric products.

For others, there **may be a choice of two (or more)** alkene products that differ in the **stereochemistry** of the double bond.

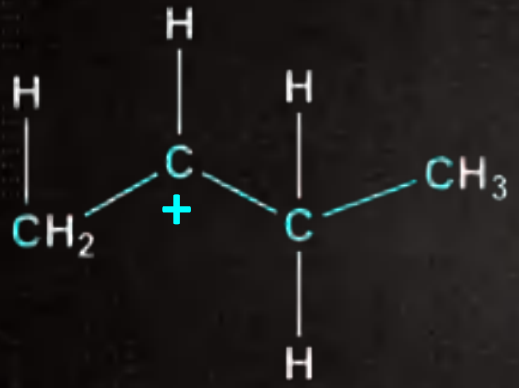
In case of eliminations, the choice of pathway is for **geometry of the double bond** in the alkene.

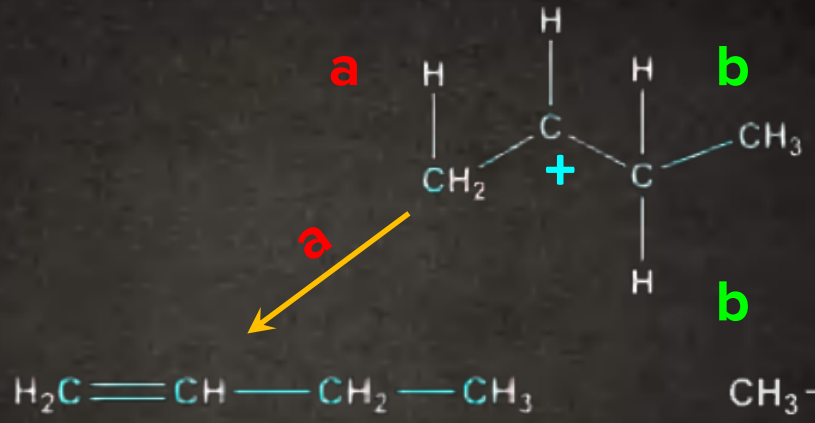
Stereochemistry of E1 Mechanism

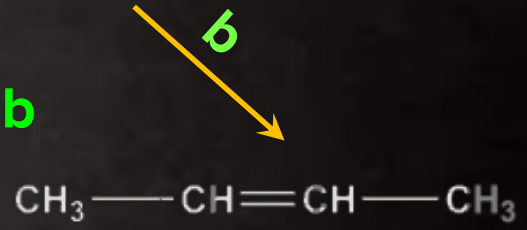
Example



Stereochemistry of E1 Mechanism



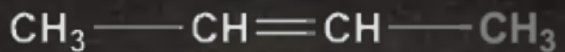


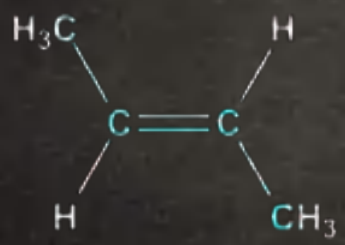


Minor

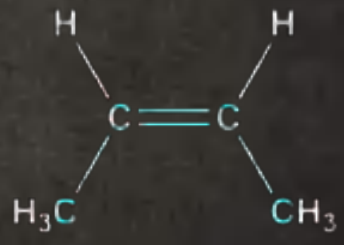
Major

Stereochemistry of E1 Mechanism



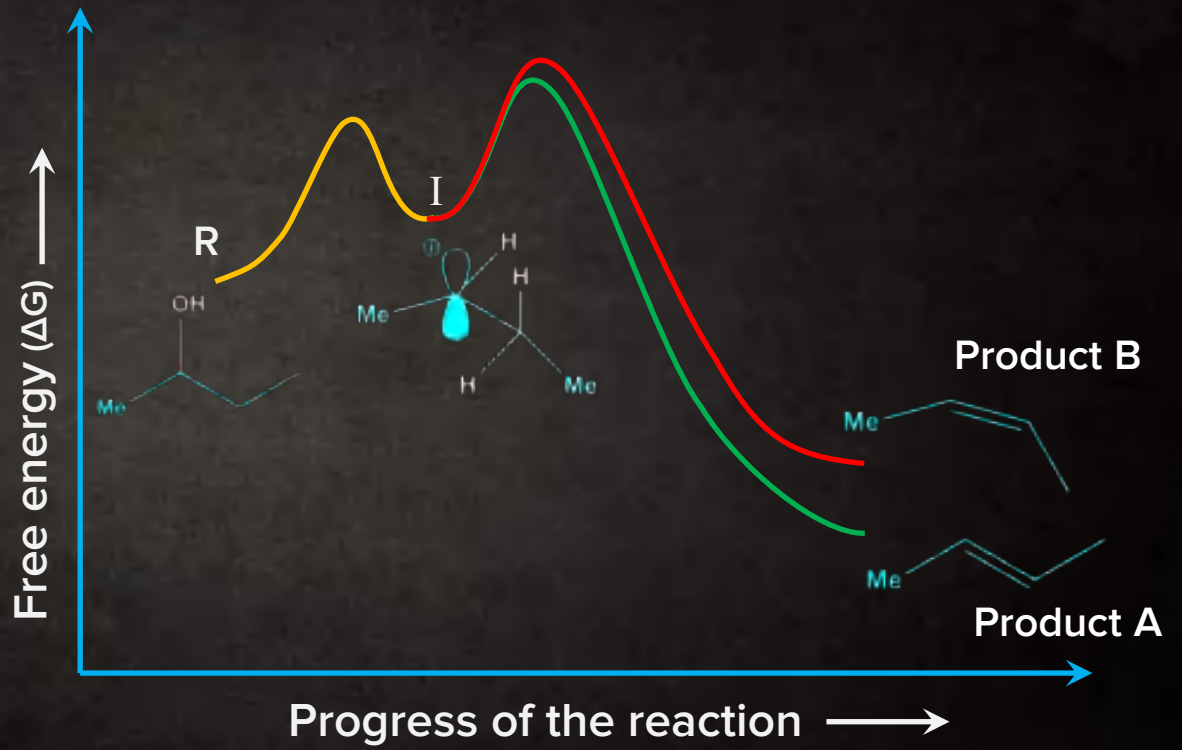


trans-but-2-ene
(A)

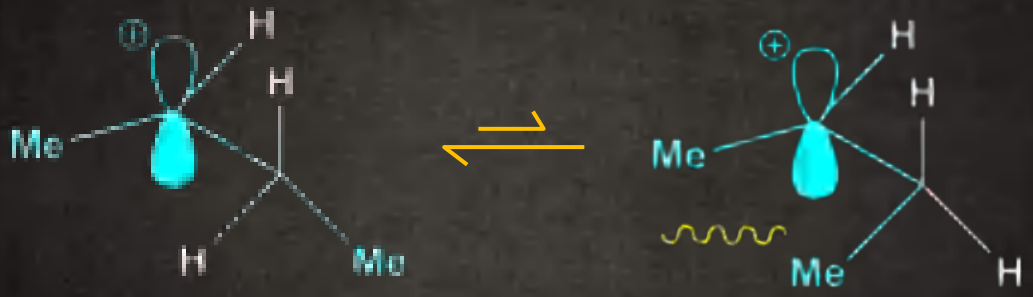


cis-but-2-ene
(B)

Generally, trans products are more stable. Hence, product A is the major product.

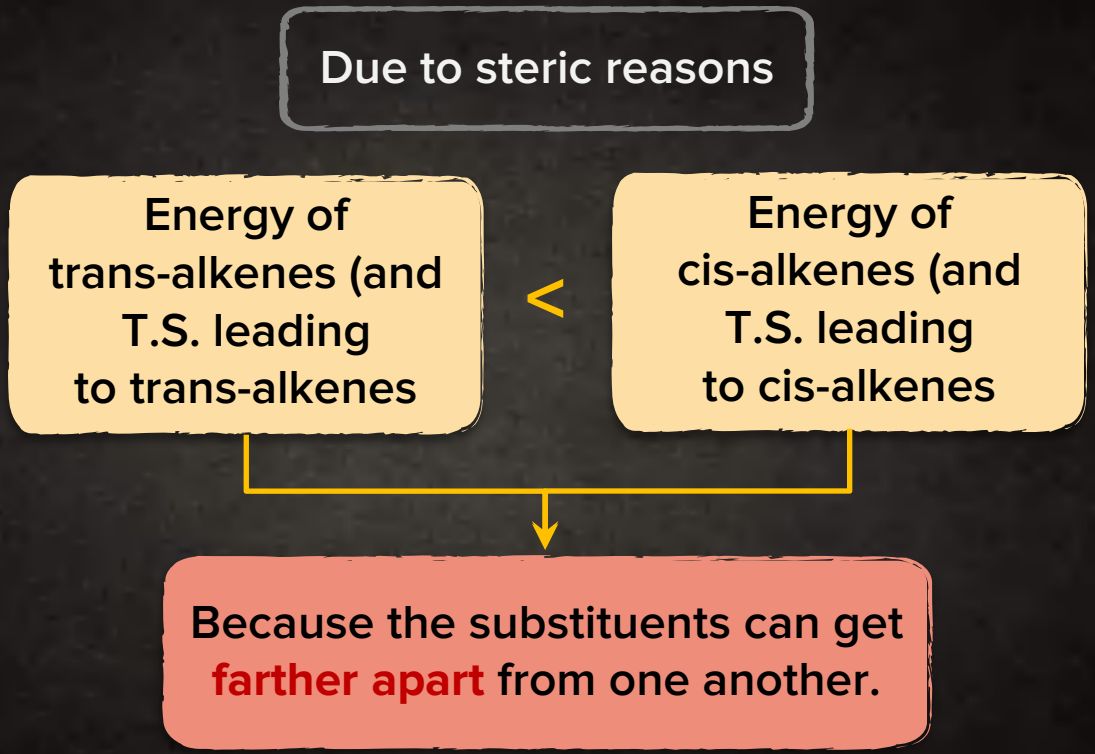


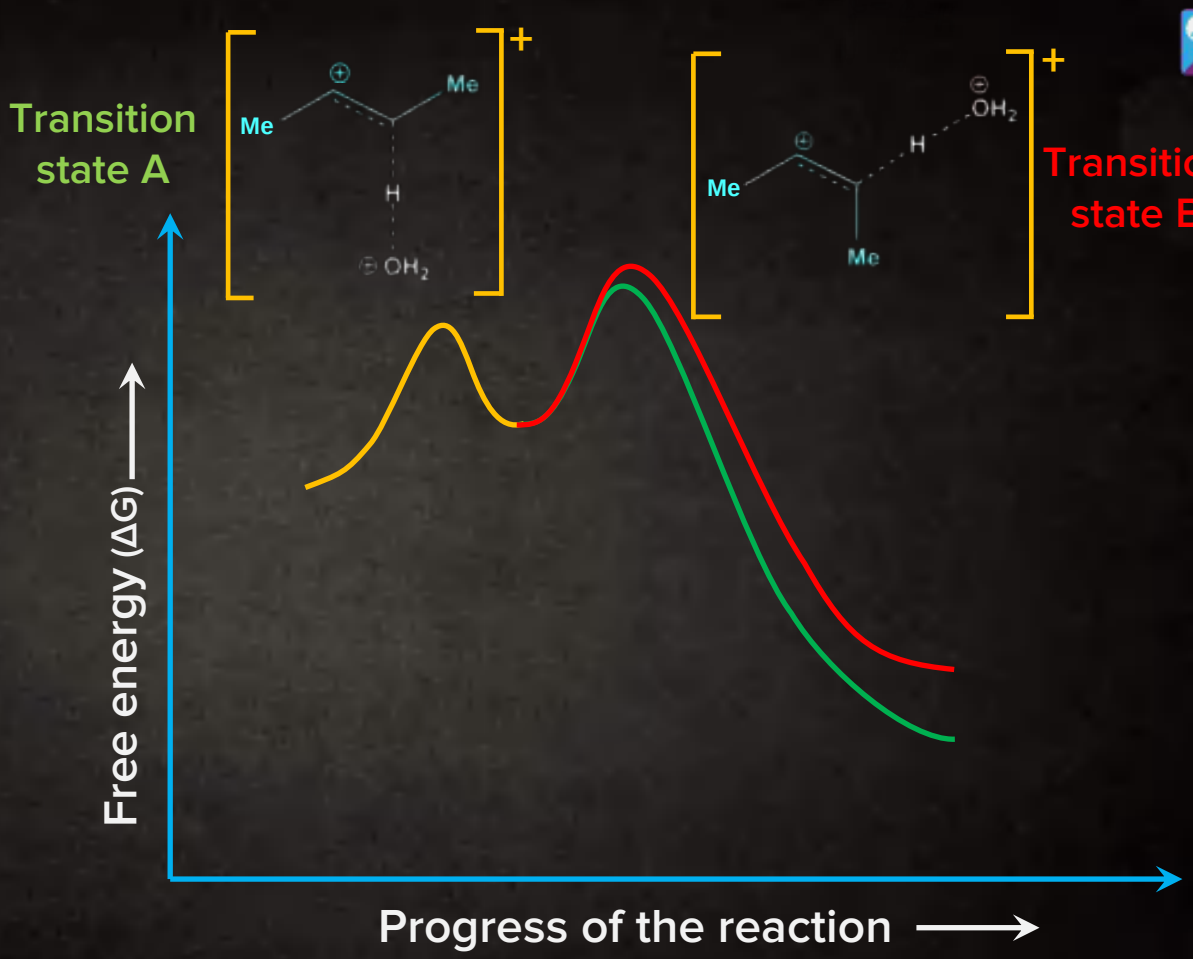
Conformations of the intermediate cation with **C-H** and **vacant p-orbital** aligned



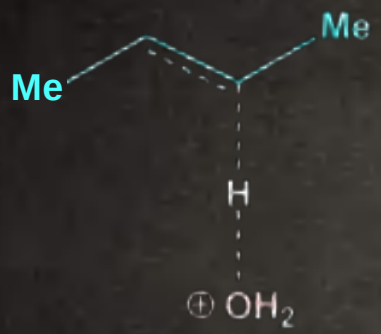
Low energy intermediate

High energy intermediate (**steric hindrance**)

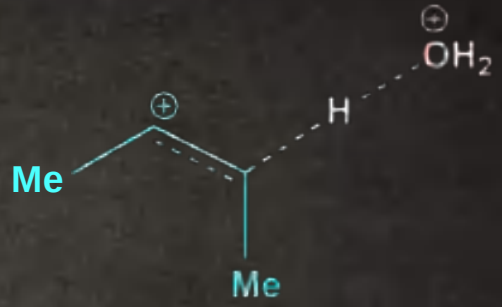

Due to steric reasons
Energy of trans-alkenes (and T.S. leading to trans-alkenes
<
Energy of cis-alkenes (and T.S. leading to cis-alkenes
Because the substituents can get farther apart from one another.


Transition state A
Me
Me
H
OH2
+
Transition state B
OH2
H
Me
Me
+
Free energy (ΔG)
Progress of the reaction

Transition State



Transition state A
More stable



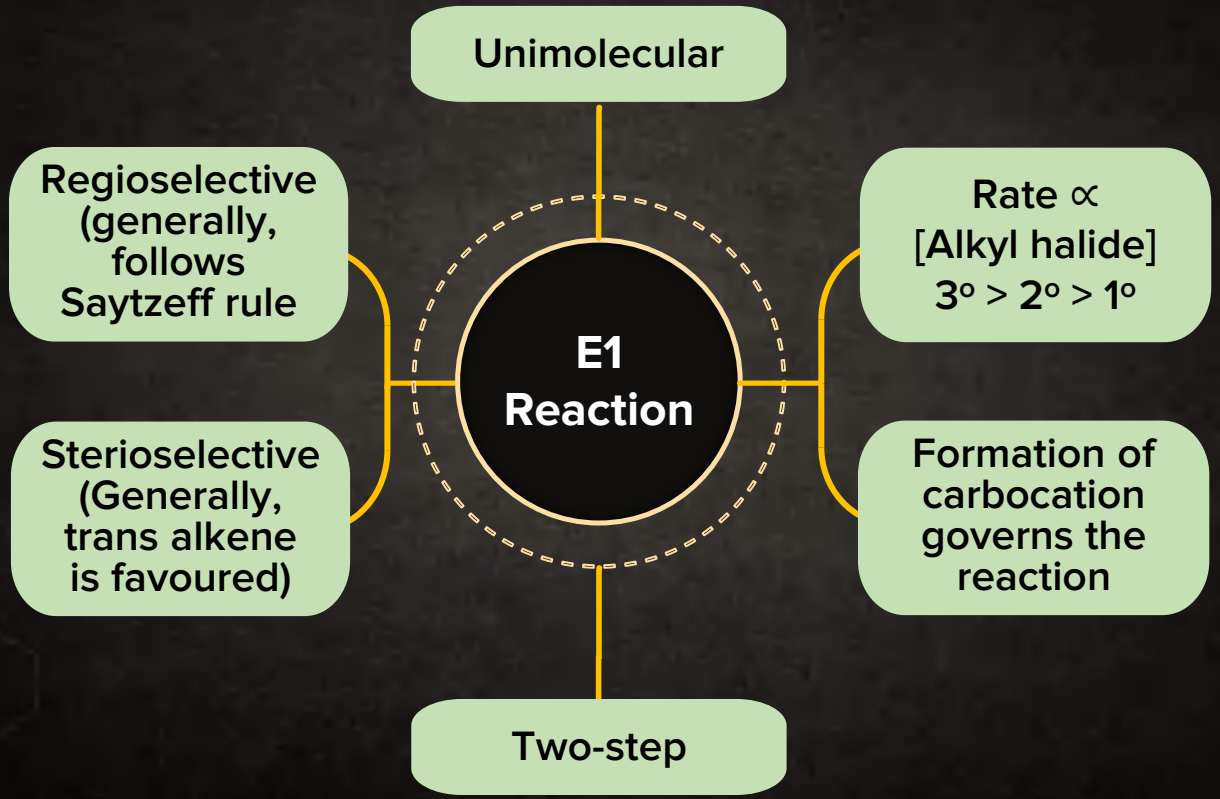
Transition state B
Less stable due to
steric hindrance

Stereoselectivity in E1 Reaction

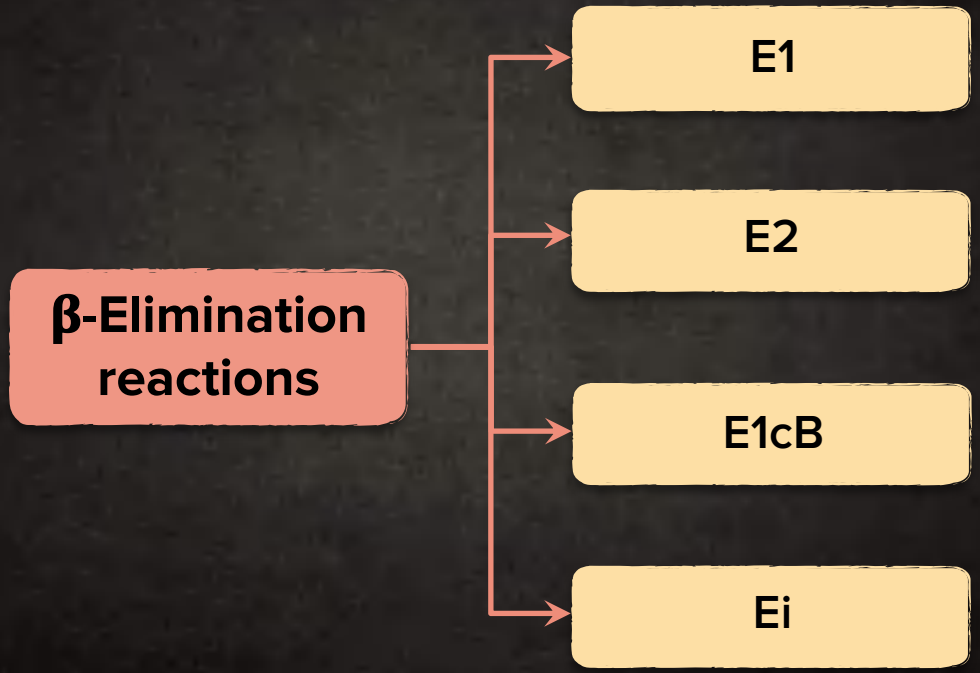
trans-isomer would be **more stable** than cis isomer.

Formation of trans-**alkene is favoured** in **E1 elimination.**

Quick Recap of E1 Reaction



β-Elimination Reactions



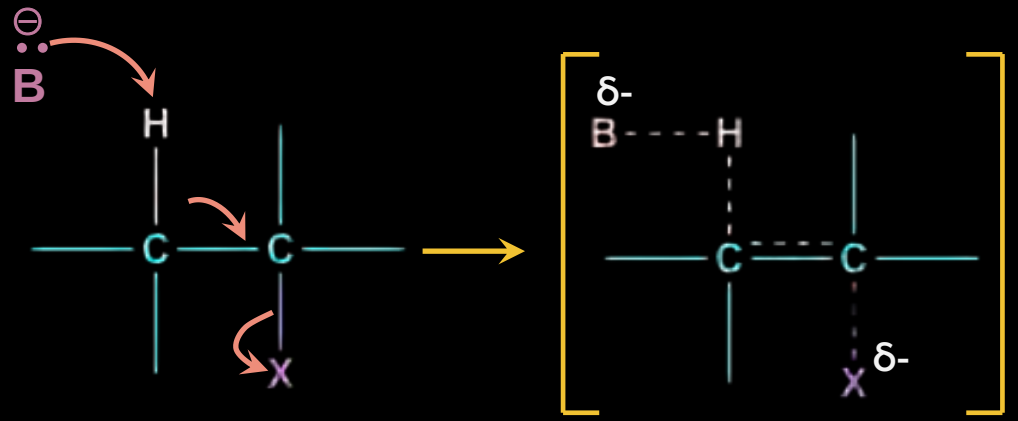
E2 Reaction

E2 describes an elimination reaction (E) in which RDS is **bimolecular(2).**

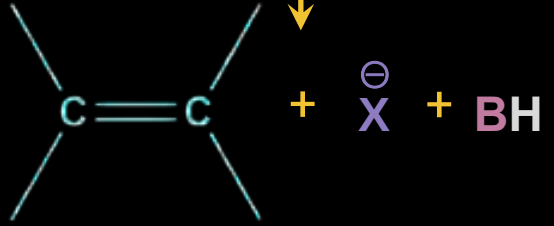
The **rate-determining step (RDS)** involves the base in which loss of the leaving group with removal of the proton by the base occurs **simultaneously**.

Mechanism

Rate = k[B⁻][alkyl halide]



Transition state



E2 Reaction

E2 reaction occurs in one step/single step.

It is a concerted reaction.

E2 reaction occurs in one step through a **transition state.**

Transition State in E2 Mechanism

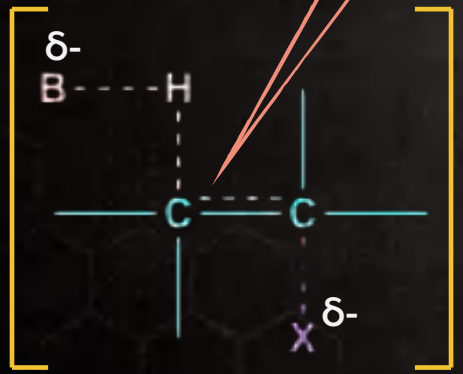
The proton is abstracted by the base.

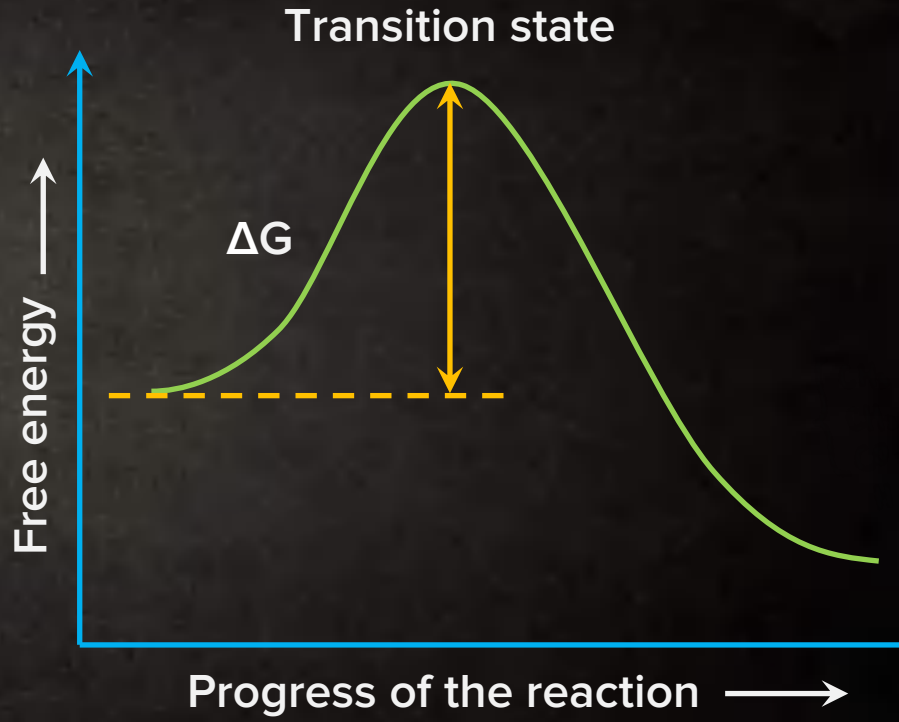
The leaving group leaves the substrate

A **partial double bond** character is developed.

Transition State in E2 Mechanism

Partial double bond character is observed in the transition state.

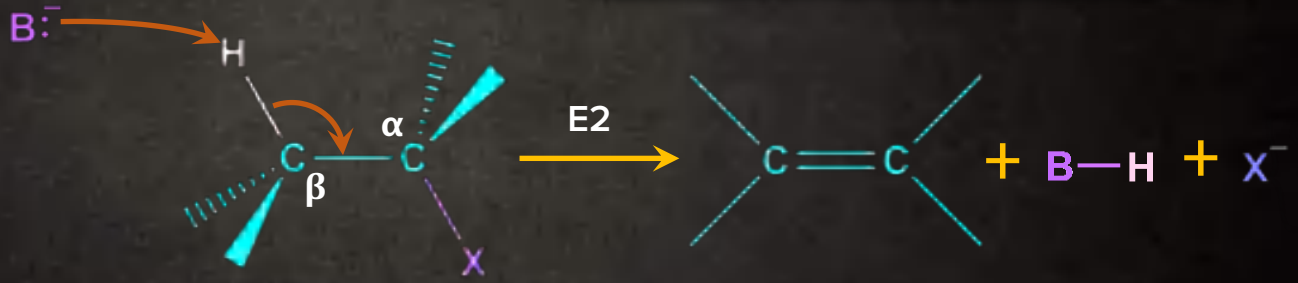




E2 Reaction of Alkyl Halide

Dehydrohalogenation → Elimination of a **hydrogen and halogen** from an alkyl halide to form an alkene

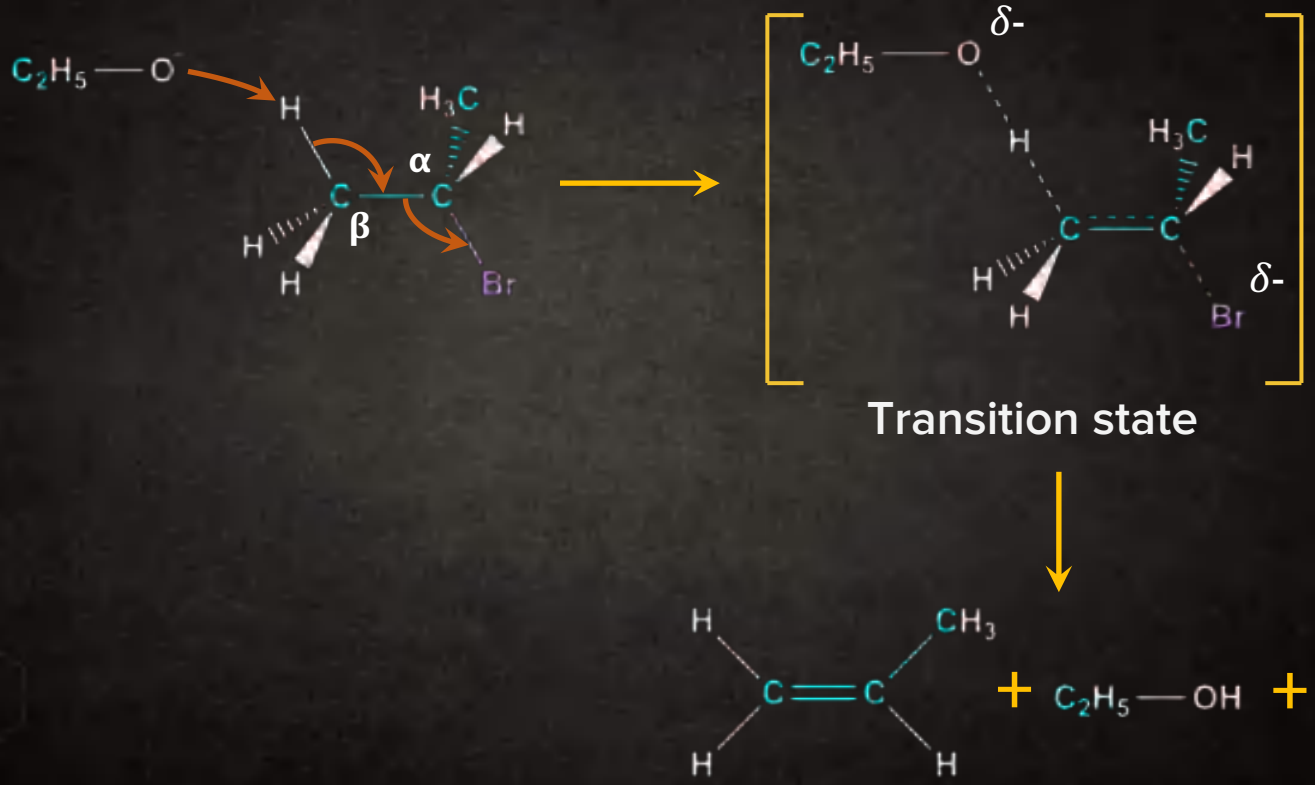
General reaction

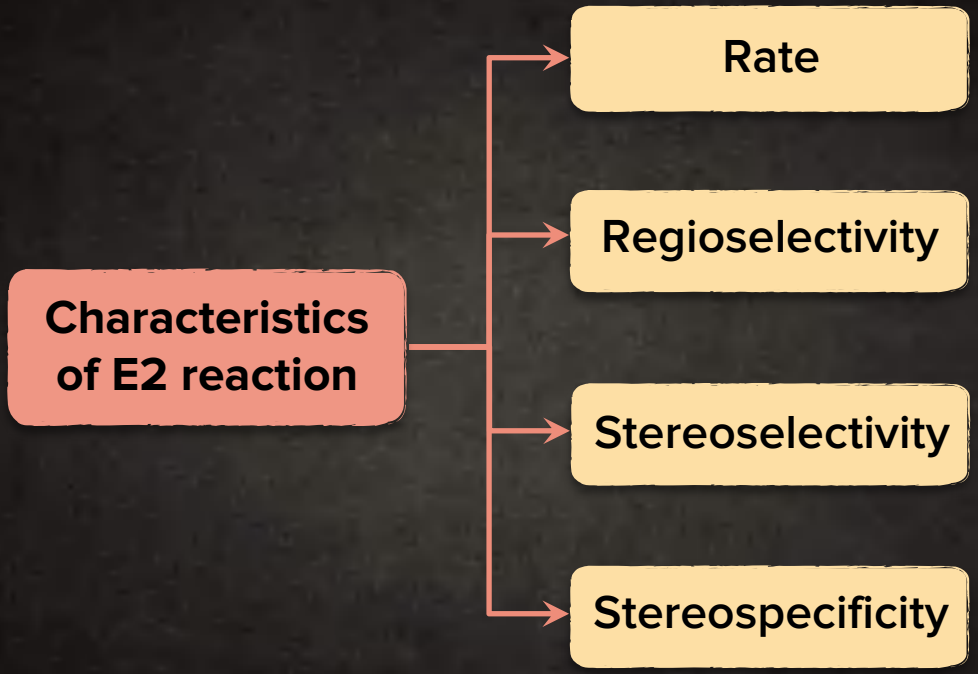


Example

$$C_2H_5O^- + CH_3CHBrCH_3 \xrightarrow{\Delta} CH_2{=}CH{-}CH_3 + C_2H_5OH + Br^-$$

Mechanism of Dehydrohalogenation




Characteristics of E2 reaction
Rate
Regioselectivity
Stereoselectivity
Stereospecificity

Rate of Reaction in E2 Mechanism

Rate of the reaction $\propto$ $[R\text{-}X]^1\,[Base]^1$

The rate of the reaction depends on the concentration of both the molecules involved.

Rate of E2 reaction depends upon

- Alkyl halides
- Base
- Leaving group

Rate of E2 Reaction

In E2, **RDS** is **formation of Alkene-**like transition state.

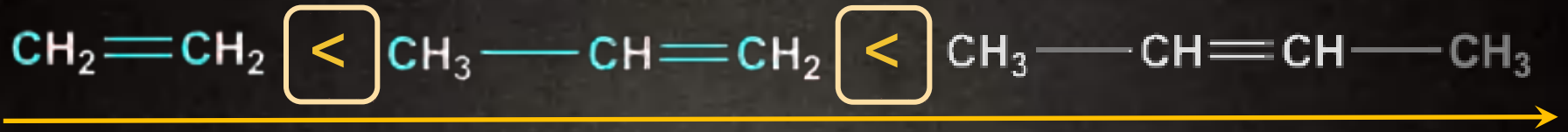
Alkyl halide, which gives more stable alkene, leads to a **faster E2 reaction.**

Rate of E2 reaction

3° Alkyl halide > **2°** Alkyl halide > **1°** Alkyl halide

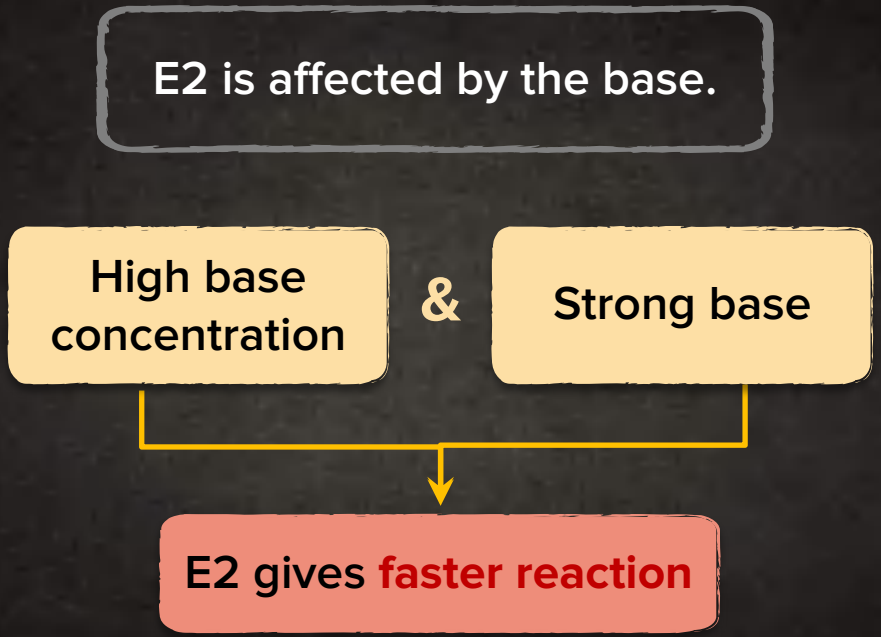
Stability of Alkene

Example



Stability **increases**

Rate of the reaction **increases**


E2 is affected by the base.
High base concentration
&
Strong base
E2 gives faster reaction

Characteristics of E2 Reaction

Reactivity towards E2

R–I > R–Br > R–Cl > R–F

Better the leaving group, faster the rate

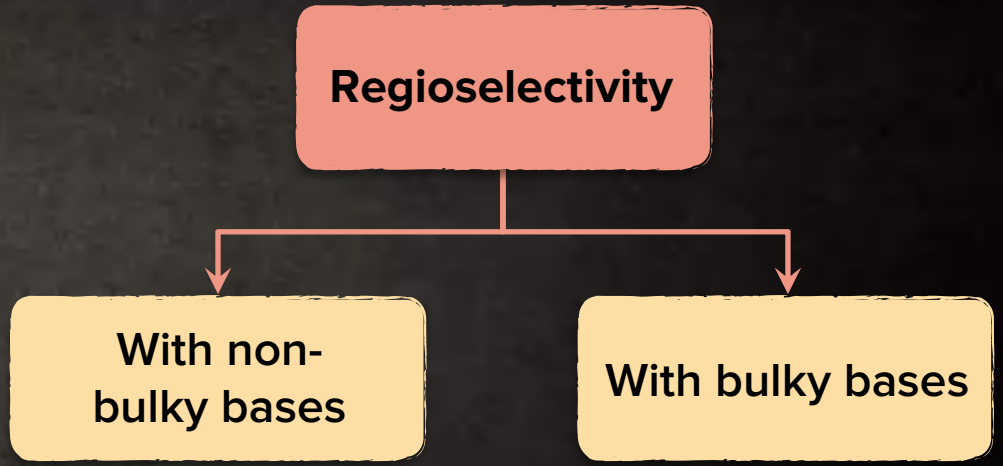
Leaving Group Ability

E2 elimination reaction	Relative Rate
$PhCH_2CH_2F + \bar{O}Et \rightarrow PhCH{=}CH_2 + F^-$	1
$PhCH_2CH_2Cl + \bar{O}Et \rightarrow PhCH{=}CH_2 + Cl^-$	70
$PhCH_2CH_2Br + \bar{O}Et \rightarrow PhCH{=}CH_2 + Br^-$	4.2×10^3
$PhCH_2CH_2I + \bar{O}Et \rightarrow PhCH{=}CH_2 + I^-$	2.7×10^4

Regioselectivity

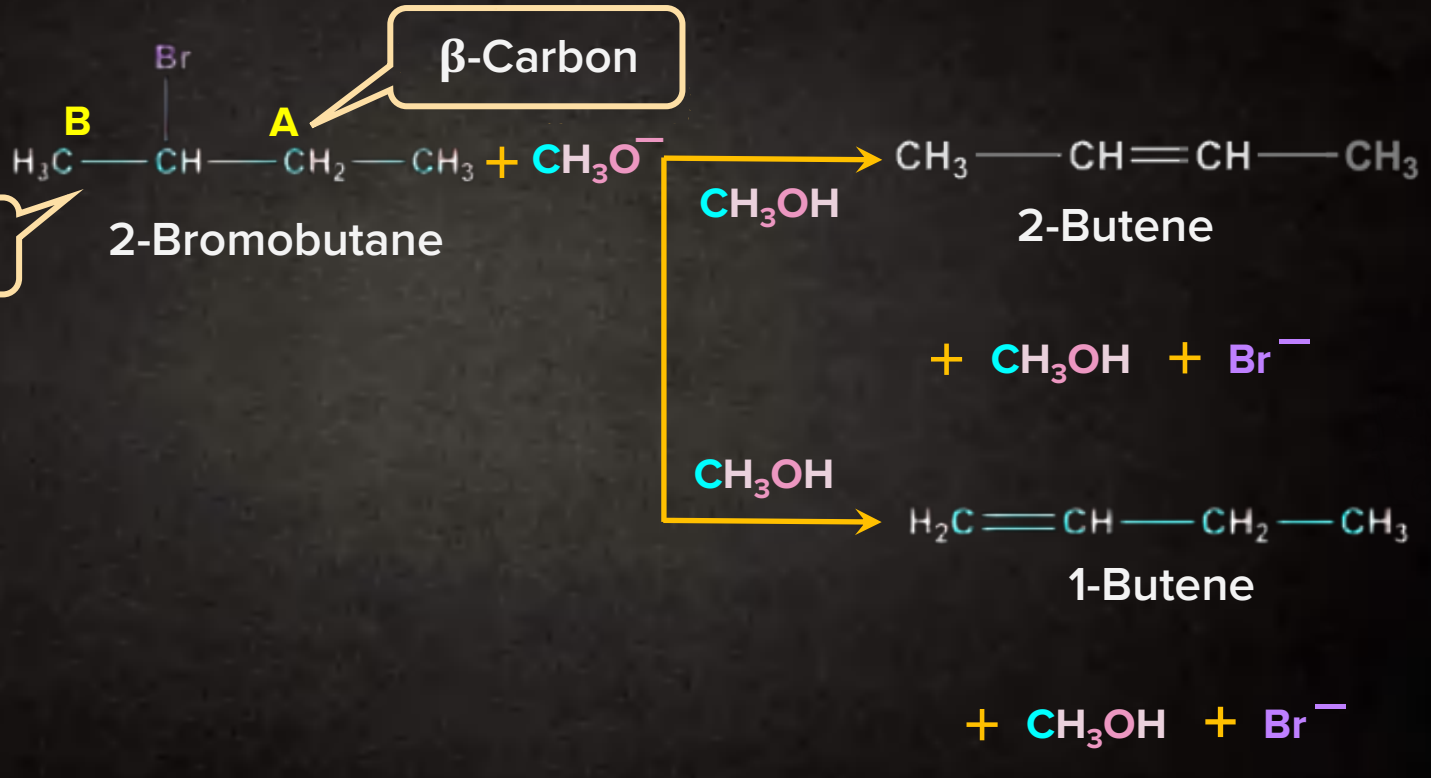
In some eliminations, **only one product** is possible.

For others, there **may be a choice of two (or more)** alkene products that differ in the **location** of the double bond.



E2 Reaction

Reaction

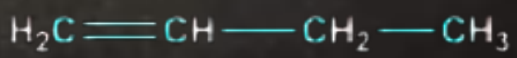


Dehydrohalogenation

The reaction can result in **two products**

- 2-Butene

- 1-Butene



E2 Mechanism

In the formation of product, an alkene-like T.S. is formed.

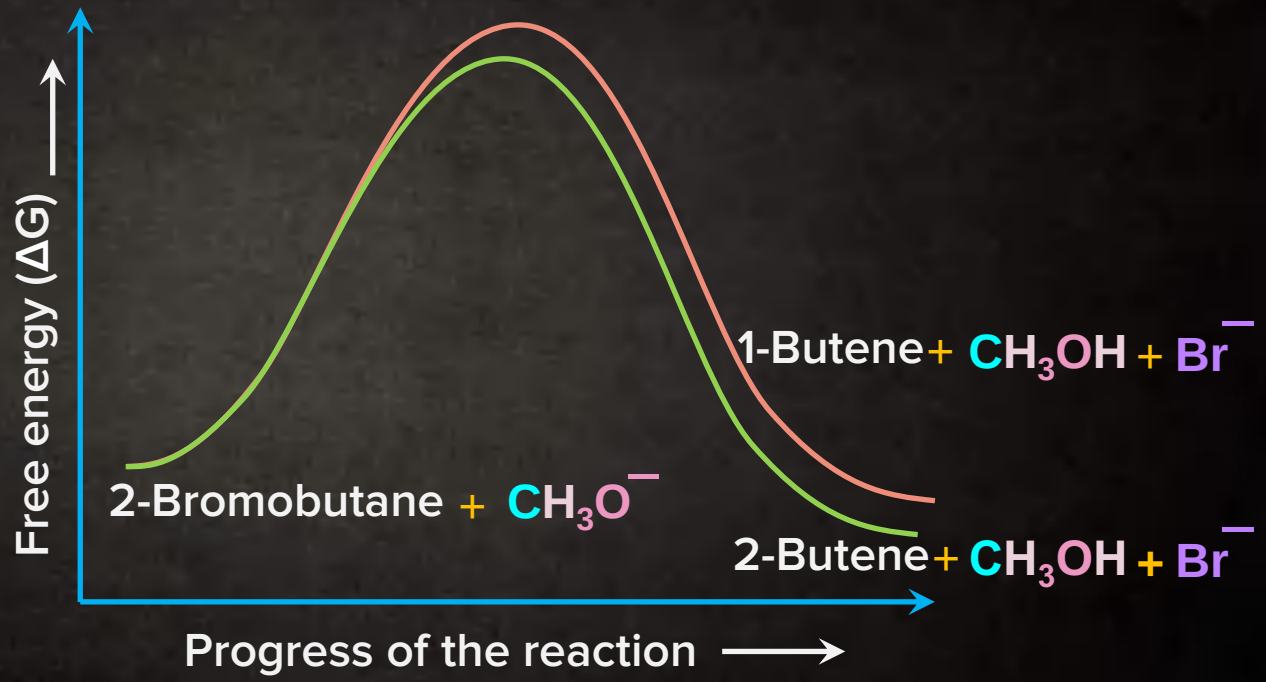
More stable the **alkene-like T.S.**

More stable the product (major)

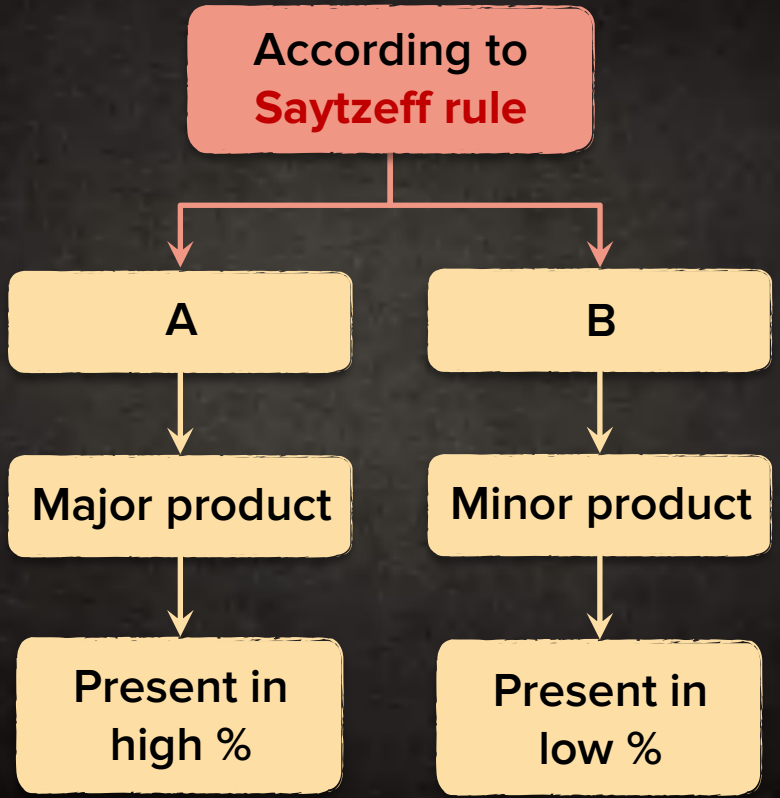
Saytzeff's Rule

The more substituted alkene product is obtained when a proton is removed from the β-carbon that is bonded to the fewest hydrogens.

Thermodynamics of E2 Reaction



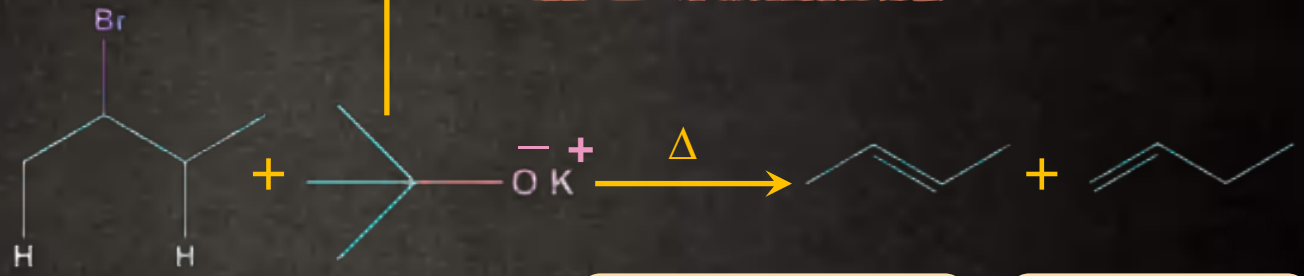
Dehydrohalogenation



Hofmann Product

Reaction

Sterically hindered bulky base

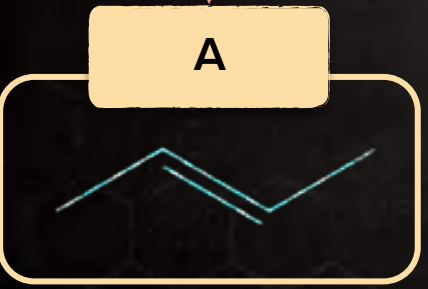


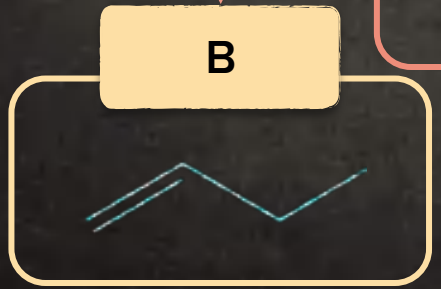
Minor product

Major product

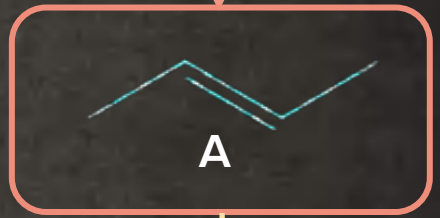
Elimination Reaction

Reaction can result in two products



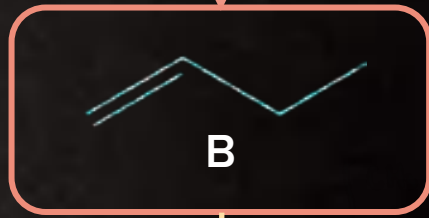


Contradicting Saytzeff Rule



Minor product

Present in low %



Major product

Present in high %

Hofmann Rule

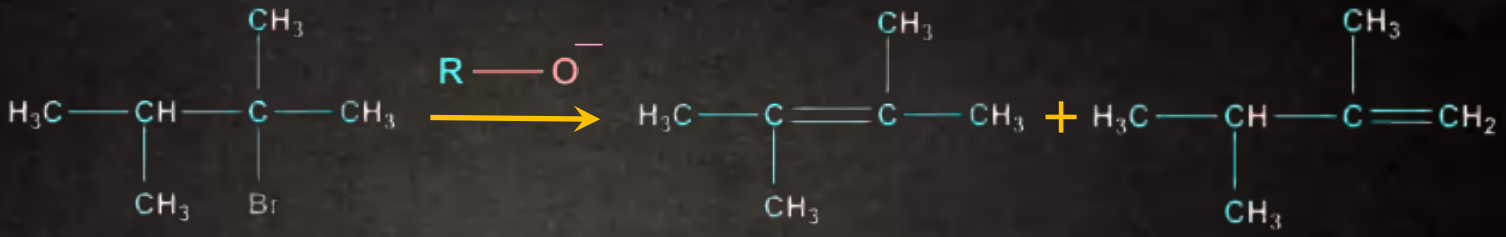
The preferred product is the alkene that has the **lesser number** of alkyl groups attached to the doubly bonded carbon atoms.

Reaction Leading to Hofmann Elimination Product

- When the base is bulkier
- If the leaving group in E2 is poor

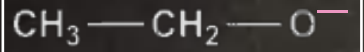
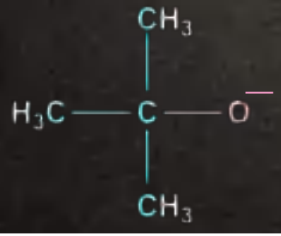
Hofmann Elimination Product

Reaction



Saytzeff product

Hofmann product

Base	More substituted alkene (Saytzeff product)	Less substituted alkene (Hofmann product)
	79%	21%
	21%	73%

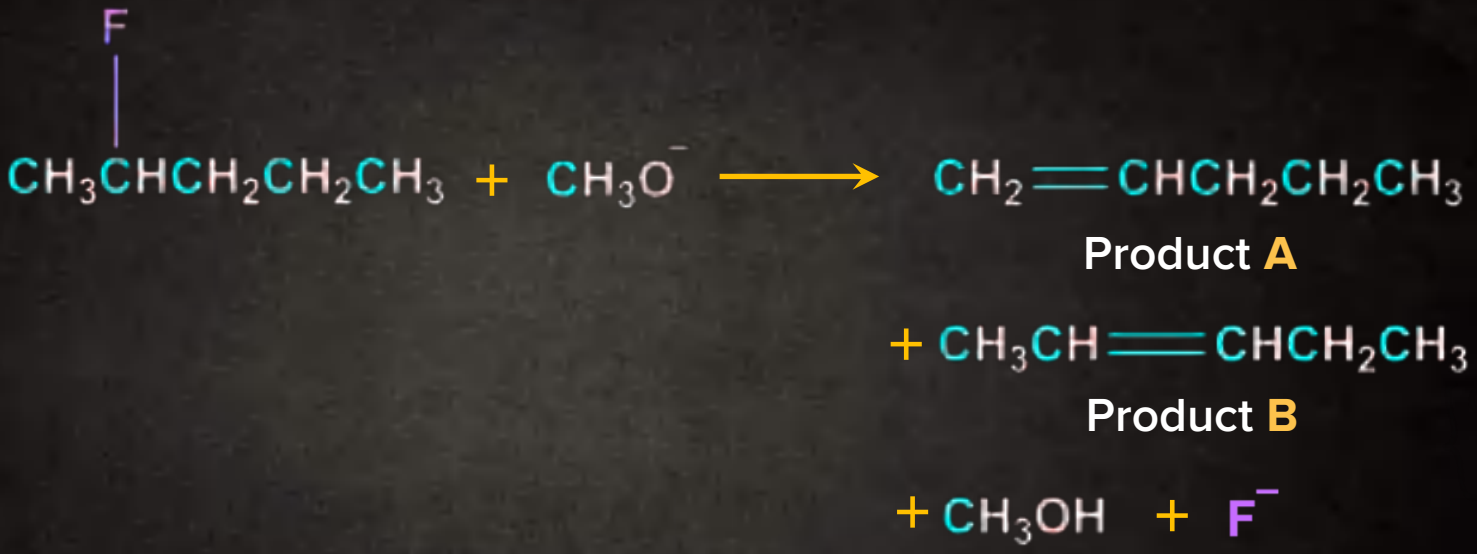
Hofmann Elimination Product

The large tert-butoxide ion appears to have **difficulty in removing** one of the internal **(2°)** hydrogen atoms

because of **greater crowding** at that site in the transition state.

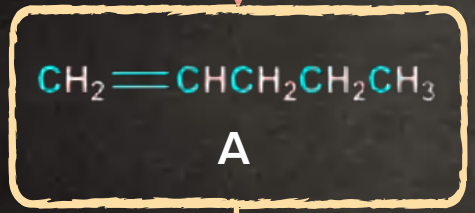
Instead the tert-butoxide ion **removes** one of the more exposed **(1°)** hydrogen atoms of the methyl group

Hofmann Elimination Product

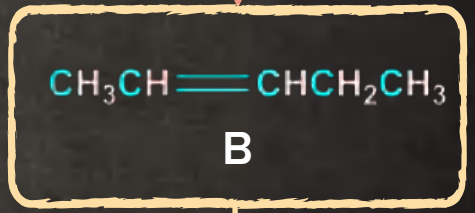


Hofmann Elimination Product

Hofmann product will be major



A



B

Major product

Present in high %

Minor product

Present in low %

Hofmann Elimination Product

When a hydrogen and a **chlorine, bromine, or iodine** are eliminated from an alkyl halide,

the **halogen starts to leave** as soon as the base begins to remove the proton.

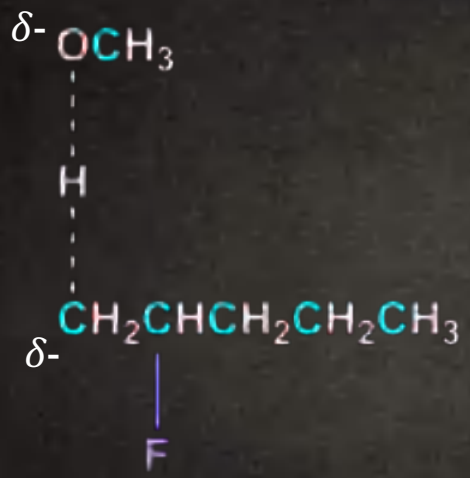
Consequently, the transition state **resembles an alkene (Saytzeff's product)**

The **fluoride ion** is the **poorest leaving group**.

As a result, a **negative charge** develops on the carbon that is losing the proton.

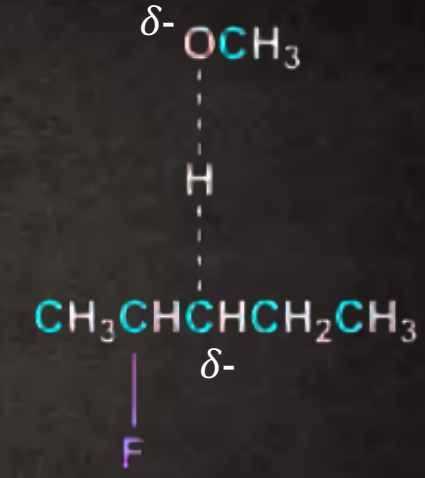
This causes the transition state to **resemble a carbanion** rather than an alkene (**Hofmann product**).

Transition State



Transition state leading to 1-pentene

More stable



Transition state leading to 2-pentene

Less stable

E2 Mechanism

Stereochemistry of E2

The **five atoms** involved in the transition state of an **E2 reaction** (including the base) must lie in the **same plane**.

The requirement for **coplanarity** of the **H–C–C–X** unit arises

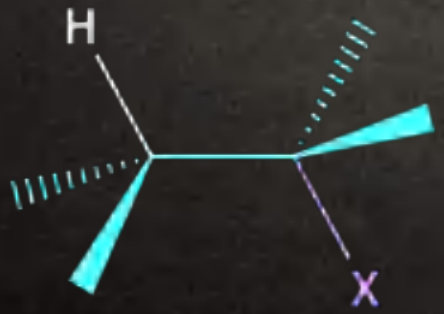
for proper overlap of orbitals in the developing **π-bond** of the alkene

The alignment can be of two types

- Anti-periplanar
- Syn-periplanar

Anti-periplanar

The H and X atoms are oriented on the **opposite sides** in the plane of the molecule.

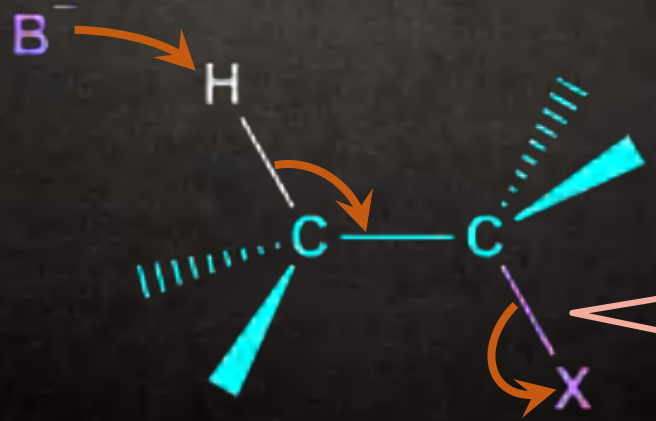


Anti-periplanar

Anti-Elimination

If the substituents are removed from the **opposite sides** of the C-C bond, the reaction is known as **anti-elimination**.

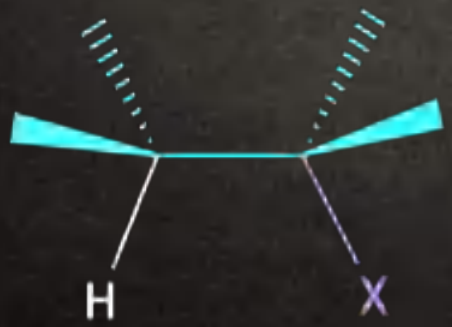
Example



H and X are anti. Hence, E2 is also known as **anti-elimination**.

Syn-periplanar

The H and X atoms are oriented on the **same side** on the plane of the molecule.

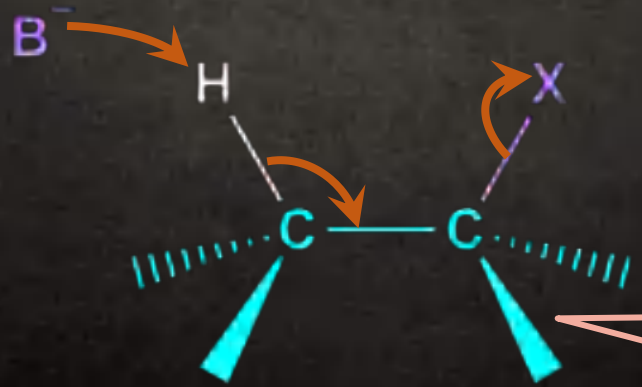


Syn-periplaner

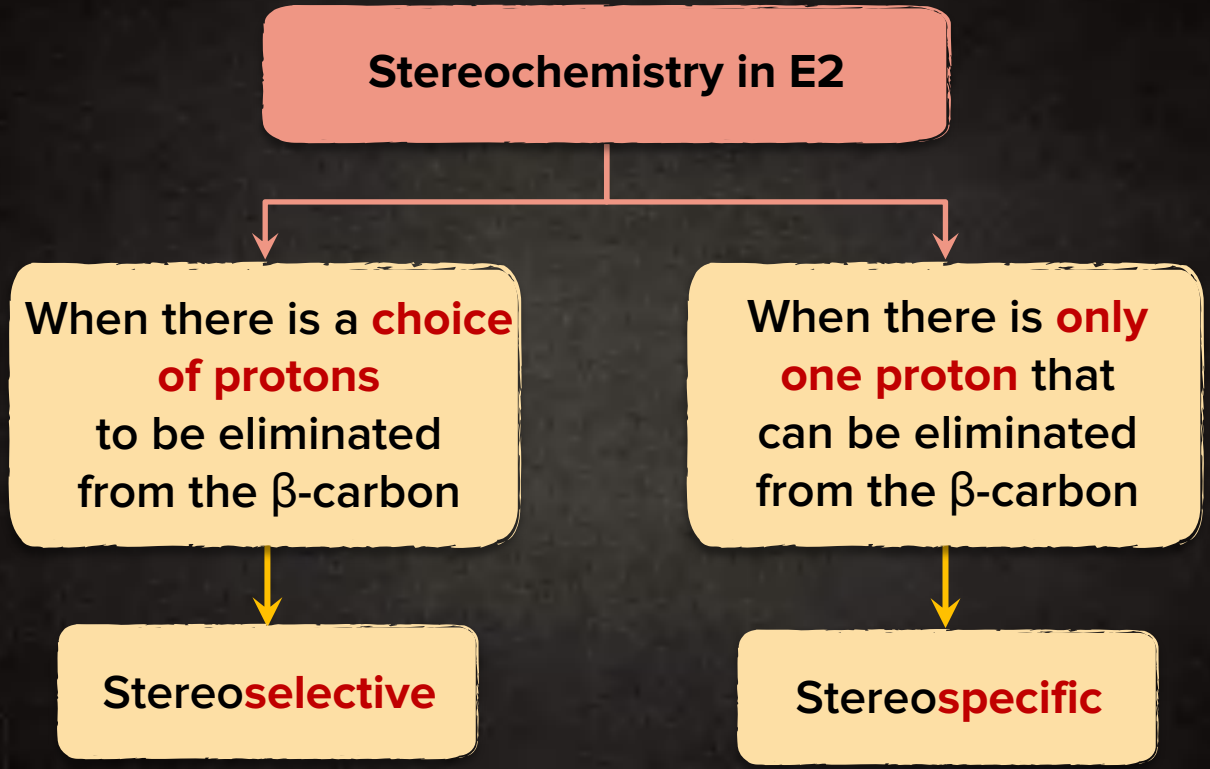
Syn-Elimination

If the substituents are removed from the **same side** of the C-C bond, the reaction is known as **syn elimination**.

Example



H and X are syn. Hence, E2 is also known as **syn-elimination**.


Stereochemistry in E2
When there is a choice of protons to be eliminated from the β-carbon
When there is only one proton that can be eliminated from the β-carbon
Stereoselective
Stereospecific

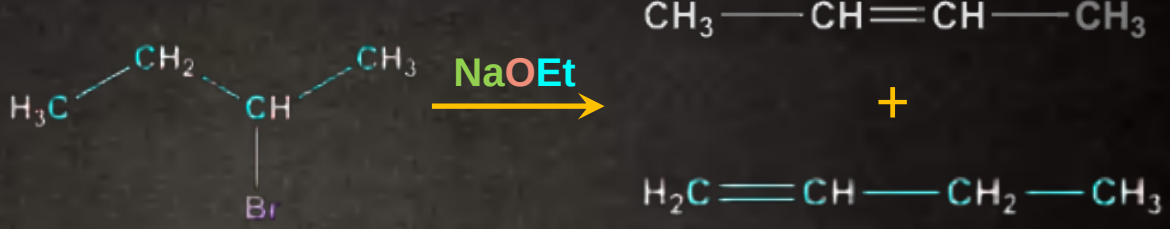
Stereoselectivity

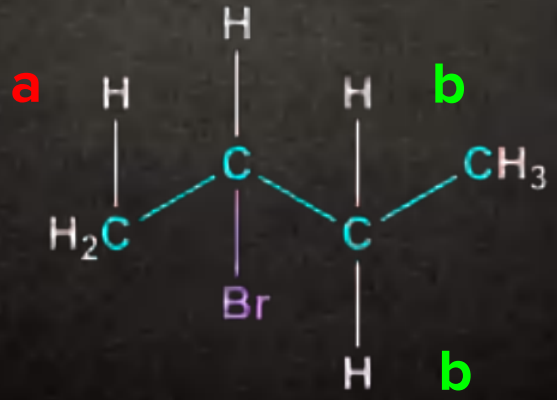
In some eliminations, only **one product** is possible.

In others, there may be a choice of **two (or more) alkene** products that differ in the **stereochemistry double bond**.

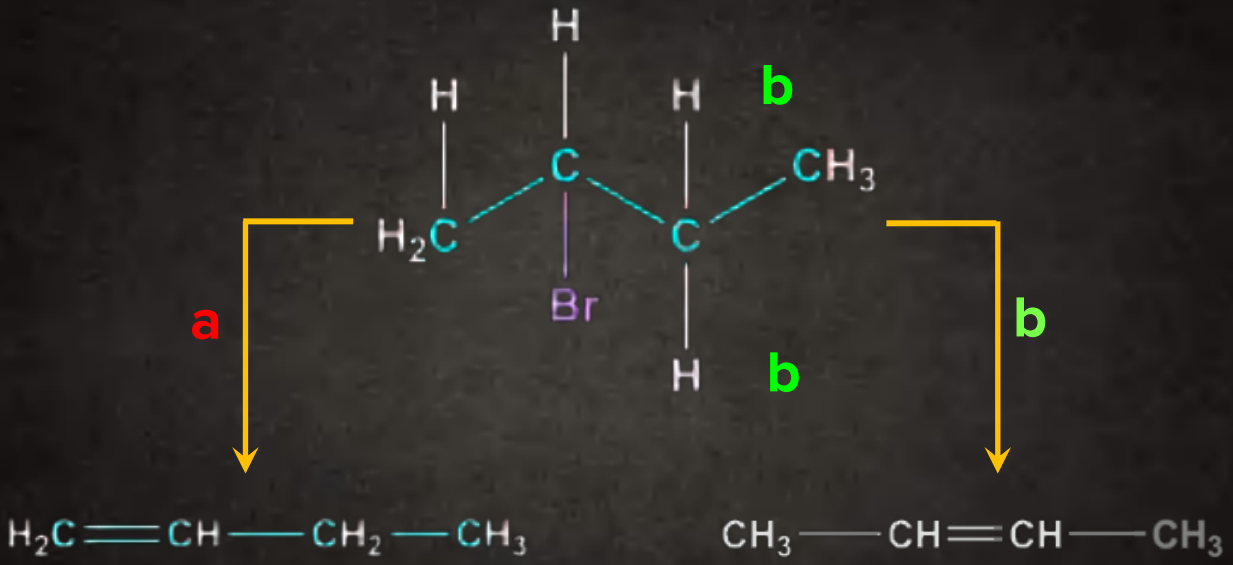
E2 Reaction

Example

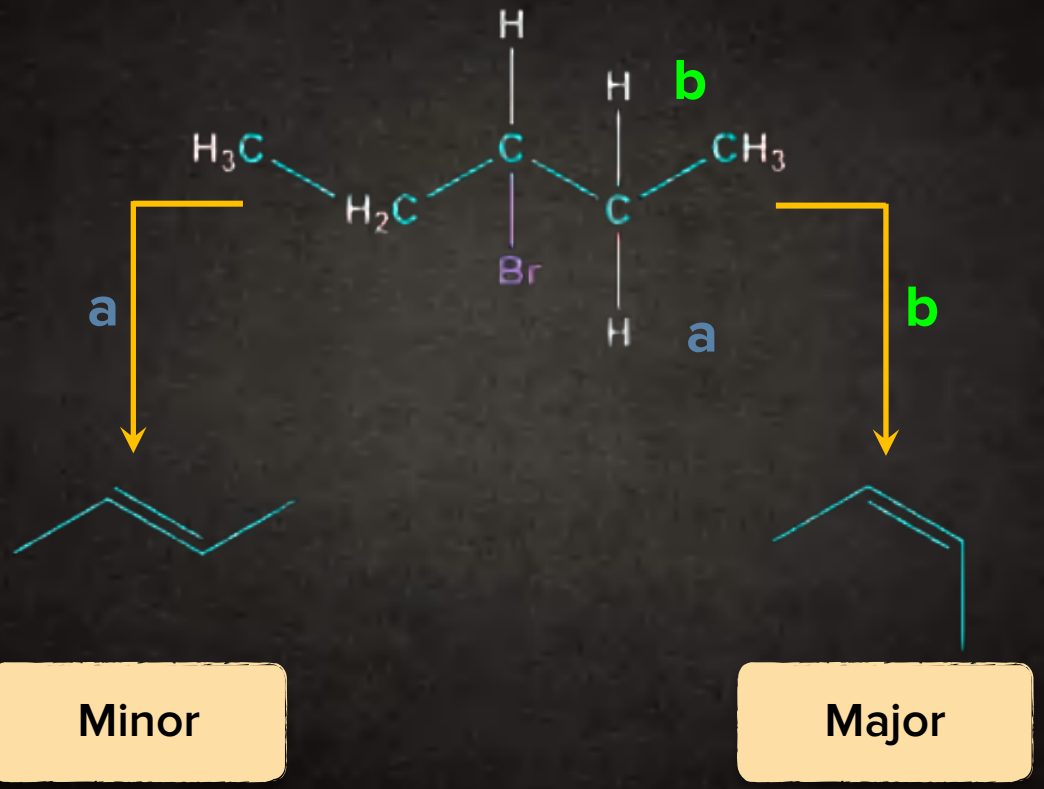




Stereochemistry of E2 Mechanism



Stereochemistry of E1 Mechanism



E2 Reaction

There is a **choice** of protons to be eliminated

Stereochemistry of the **major product** results from the proton that is **anti-periplanar** to the leaving group

E2 reaction is **stereoselective.**

Stability of **anti**-periplanar configuration > **Stability** of **syn**-periplanar configuration

Staggered | **Eclipsed**

The **anti-periplanar** conformation is the **preferred T.S. geometry**.

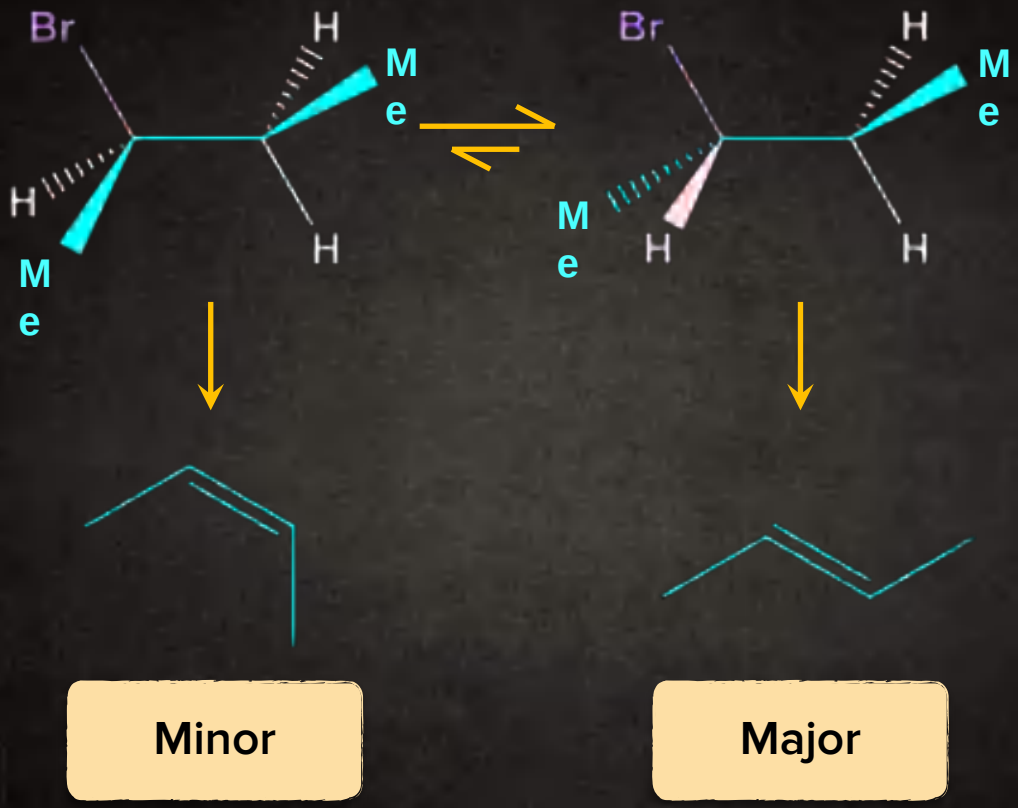
The syn-periplanar transition state occurs only with rigid molecules that are unable to assume the anti-arrangement.

Two methyl group syn-coplanar

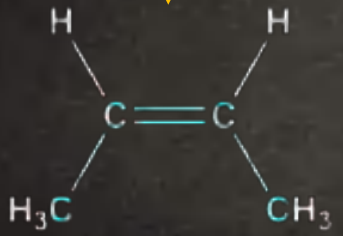
More hindered

Two methyl group anit-periplanar

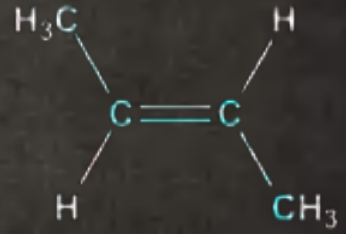
Less hindered


Br
H
Me
H
H
Me
Br
H
Me
Me
H
H
Minor
Major

Stereochemistry of E1 Mechanism



cis-but-2-ene



trans-but-2-ene

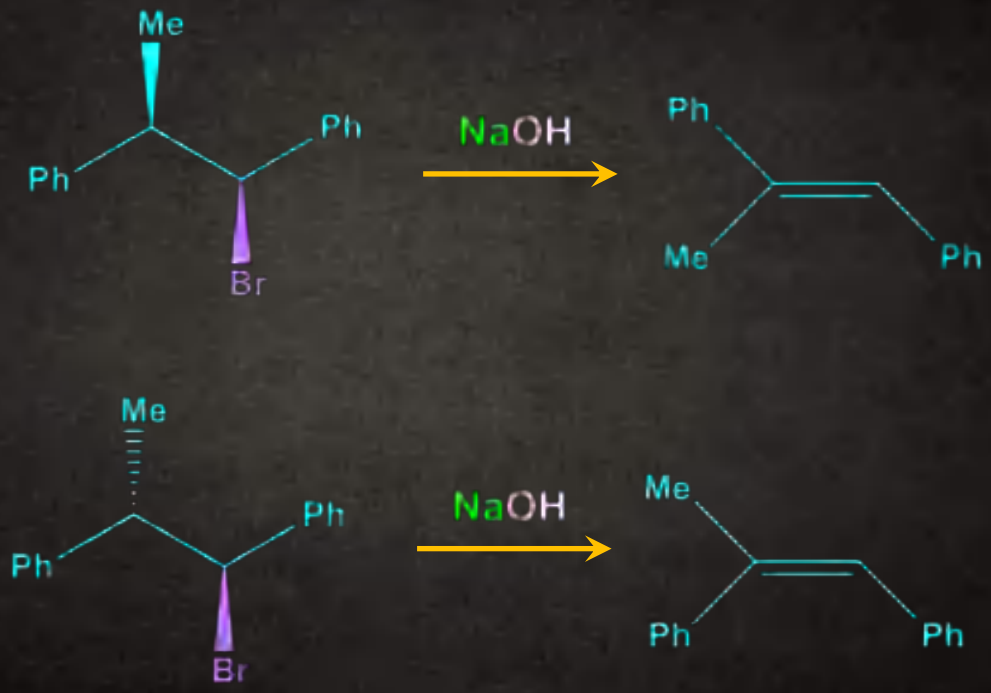
Minor

Major

Stereospecific Reaction

Reactions in which the stereochemistry of the product is determined by the **stereochemistry** of the **starting material** are called **stereospecific.**

Stereospecific Reaction

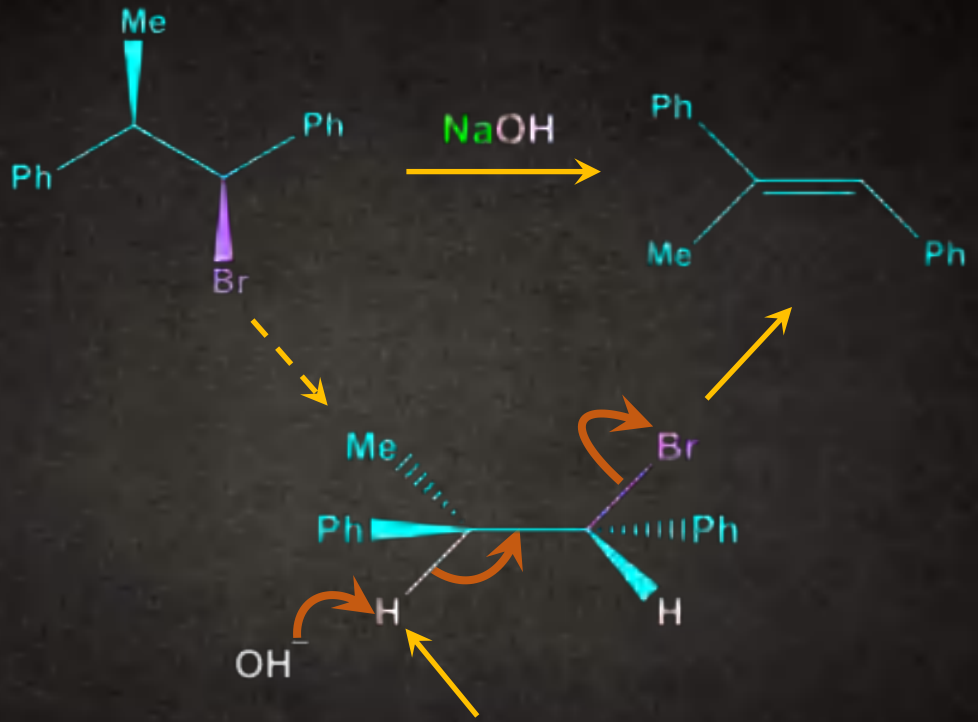


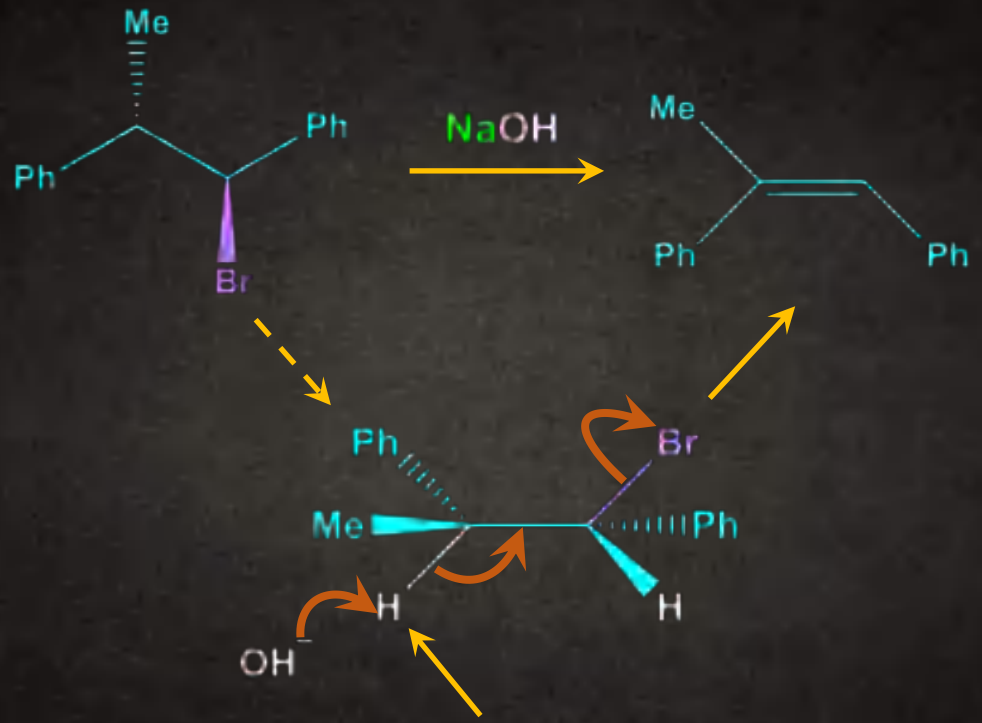
Stereospecific Reaction

When there is only **one proton** that can take part in the **elimination**, there is no option of **anti-periplanar transition states.**

Whether the product is cis **or trans**, the **E2 reaction** has only one course to follow.

The outcome depends on the **starting material** used.


Me
Ph
Ph
Br
NaOH
Ph
Me
Ph
Me
Br
Ph
Ph
H
H
OH⁻
Only this proton can
be attacked by OH⁻


Me
Ph
Ph
Br
NaOH
Me
Ph
Ph
Ph
Br
Me
Ph
H
H
OH
Only this proton can
be attacked by OH⁻

Stereoselective vs Stereospecific

Stereoselective reactions give **one predominant isomer product** because the reaction pathway has a choice.

Stereospecific reactions lead to the production of a **single isomer** as the reaction pathway has no choice.

E2 In a Nutshell!

1. Concerted, **bimolecular**

2. Rate ∝ Alkyl halide
   (**3° > 2° > 1°**)
   ∝ conc. of strong base
   ∝ Leaving group

3. Regioselectivity

Non-bulky base → **Saytzeff** rule

Bulky base → **Hofmann** rule

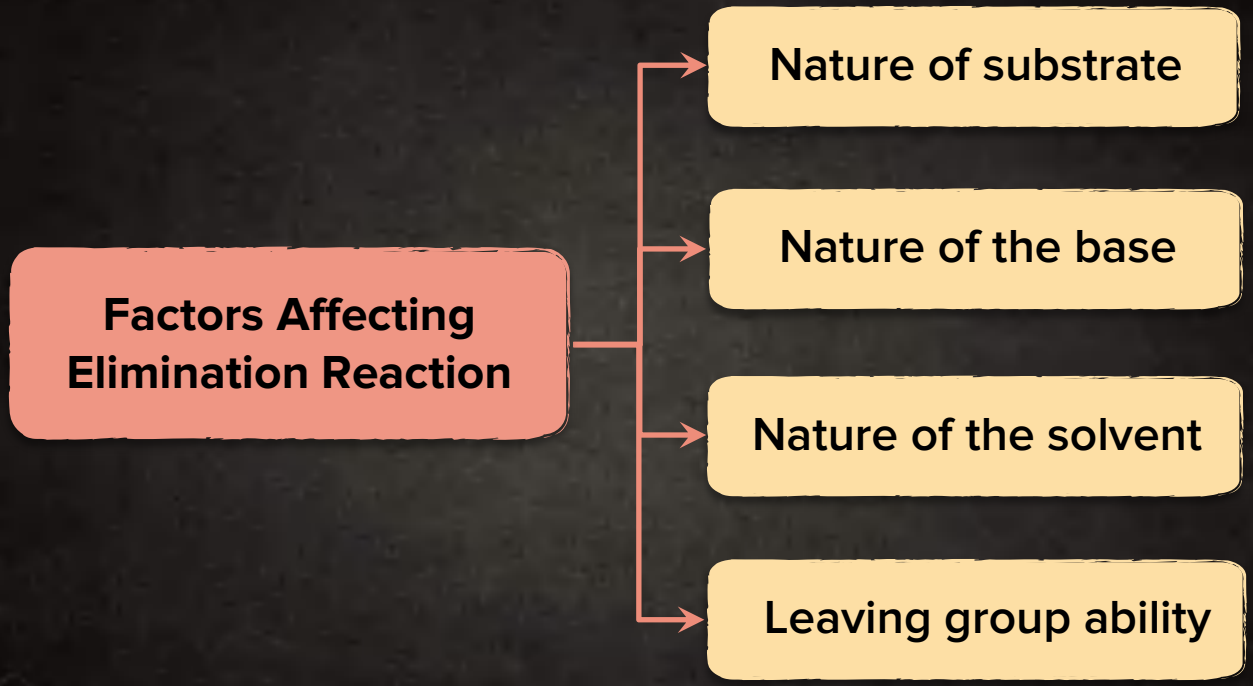
E2 In a Nutshell!

4 Stereochemistry (generally favours **anti-periplanar T.S.**)

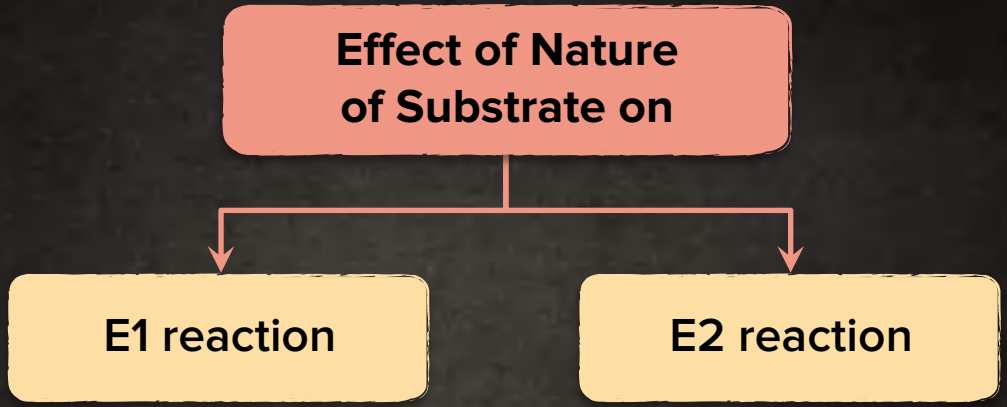
Two β-hydrogen → **Stereoselective**

One β-hydrogen → **Stereospecific**

E1 vs E2 Reaction


Factors Affecting Elimination Reaction
Nature of substrate
Nature of the base
Nature of the solvent
Leaving group ability

Effect of Nature of Substrate



Effect of Nature of Substrate on E1 Reaction

Rate of E1 reaction $\propto$ Stability of carbocation formed from alkyl halide

Primary alkyl halide < Secondary alkyl halide < Tertiary alkyl halide

Increasing order of rate of reaction for E1

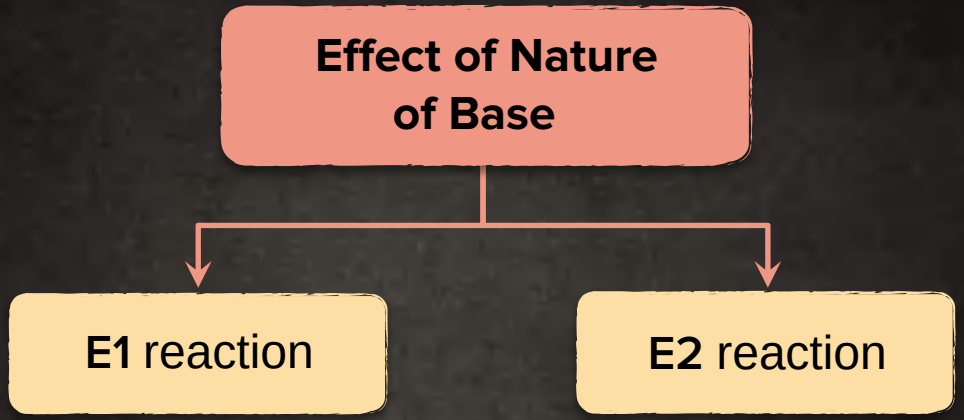
Effect of Nature of Substrate on E2 Reaction

Rate of E2 reaction $\propto$ Stability of alkene formed from alkyl halide

Primary alkyl halide < Secondary alkyl halide < Tertiary alkyl halide

Increasing order of rate of reaction for E2

Effect of Nature of Base



Effect of Nature of Base on E1 Reaction

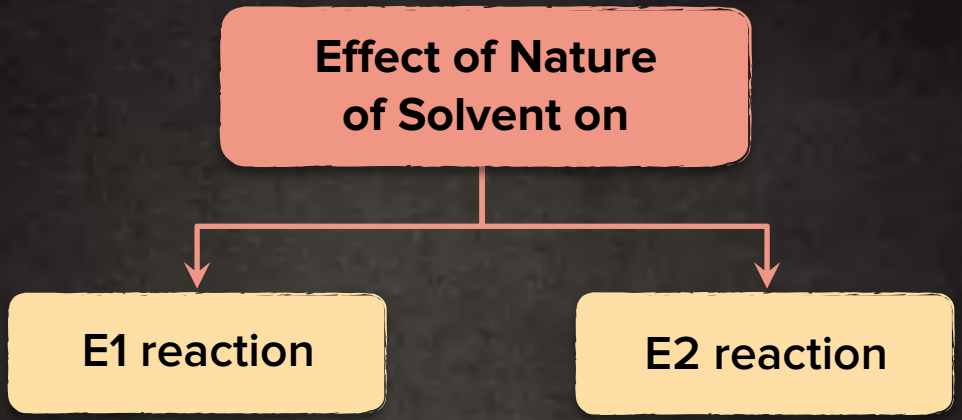
An E1 reaction is favoured by the **low concentration** of a **weak base**.

For example: H_2O, ROH etc.

An E2 reaction is favoured by the **high concentration** of a **strong base**.

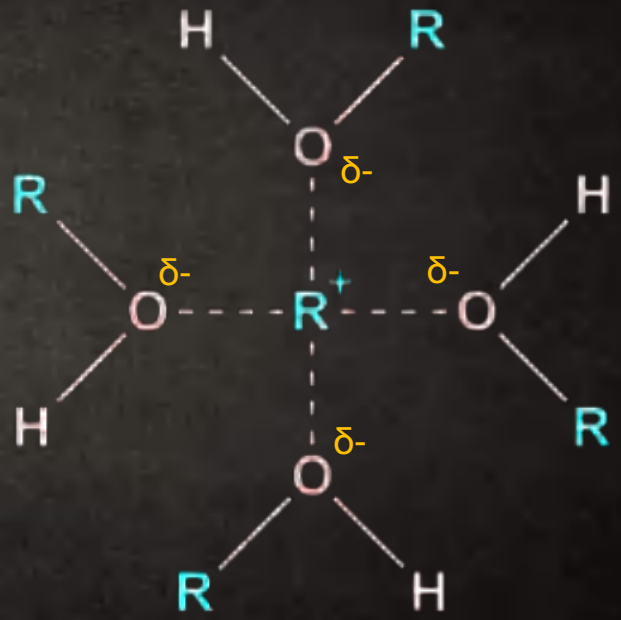
Examples: RO^-, NH_2^- etc.

Effect of Nature of Solvent



Effect of Nature of Solvent on E1 Reaction

Polar protic solvents **favour E1 reactions** because they stabilise the intermediate **carbocation.**



Effect of Nature of Solvent on E2 Reaction

E2 elimination is favoured by **polar aprotic solvents.**

Examples: **DMSO, Acetone,** etc.

Solvation of **base does not** take place because

- They **cannot** form **H-bonds**
- Their **positive centres** are well **shielded** by steric effects

Effect of Nature of Solvent on E2 Reaction

No solvation of anion increases the reactivity of anion as base

↓

It can readily attack the proton. Hence, **favours E2.**

Effect of Leaving Group Ability on Elimination Reaction

A good leaving group favours both E1 and E2 elimination reactions.

$F^- < Cl^- < Br^- < I^-$

Increasing order of leaving group ability.

E1 vs E2 Reaction

	E1	E2
Alkyl halide	$3^o > 2^o > 1^o$	$3^o > 2^o > 1^o$
Base	**Low** concentration of a weak/moderate base	**High** concentration of a strong base
Solvent	**Polar protic** solvent	**Polar aprotic** solvent
Leaving group	Good leaving group **favours** E1	Good leaving group **favours** E2

Degree of C	Type of reaction	
1°	E2 only	
2°	Mainly E2	
3°	In solvolysis (Example: H_2O/ROH)	E1
	When strong base (Example: RO^-)	E2

Elimination Reactions in Benzylic Halides

Elimination Reaction in Benzylic Halides

Benzylic halides that have β-hydrogens undergo:

- **E1** reactions
- **E2** reactions

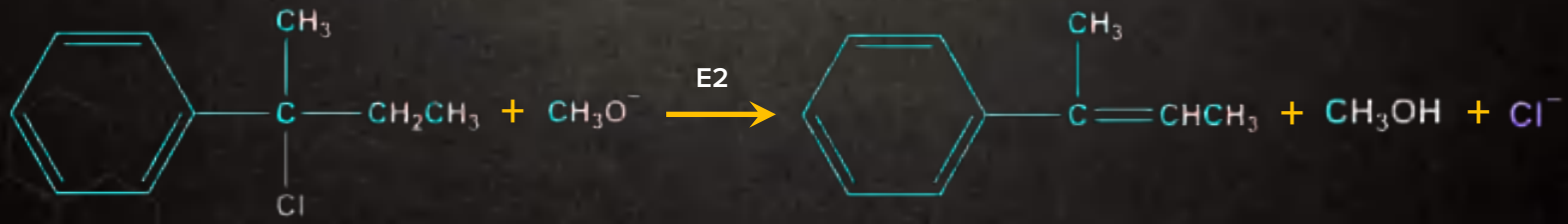
They undergo E1 reaction because they form relatively **stable carbocations.**

E2 Reaction in Benzylic Halides

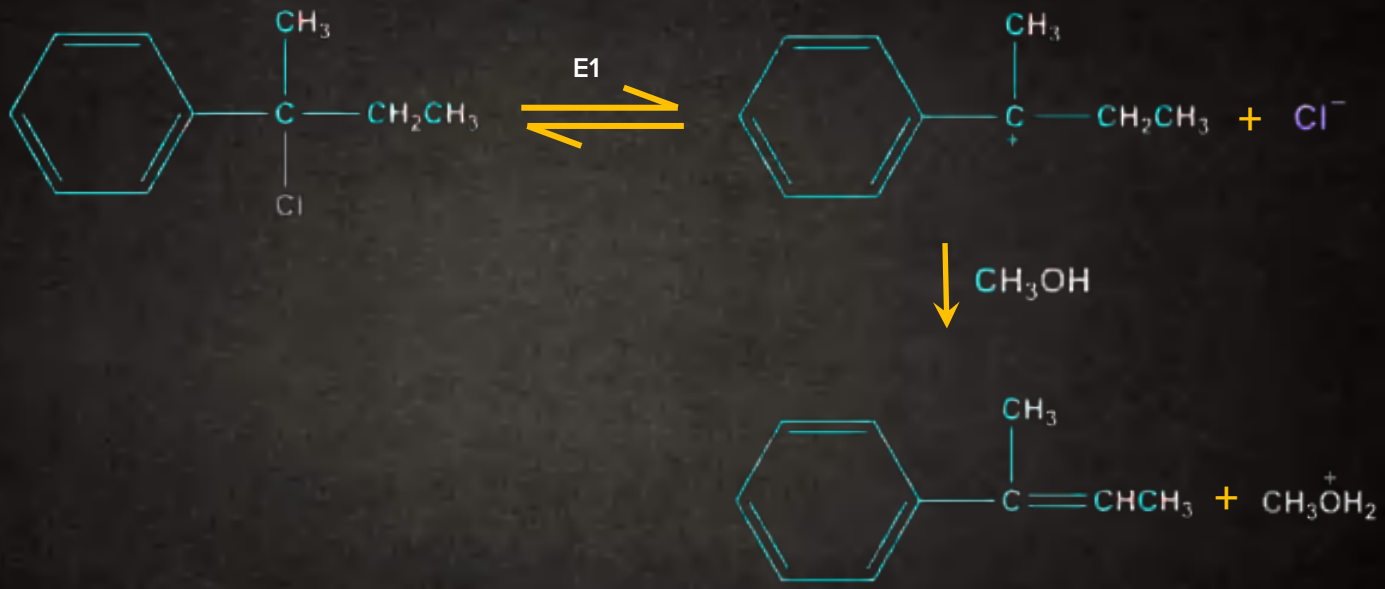
They undergo E2 reactions because the **new double bond** in the product is **relatively stable.**

→

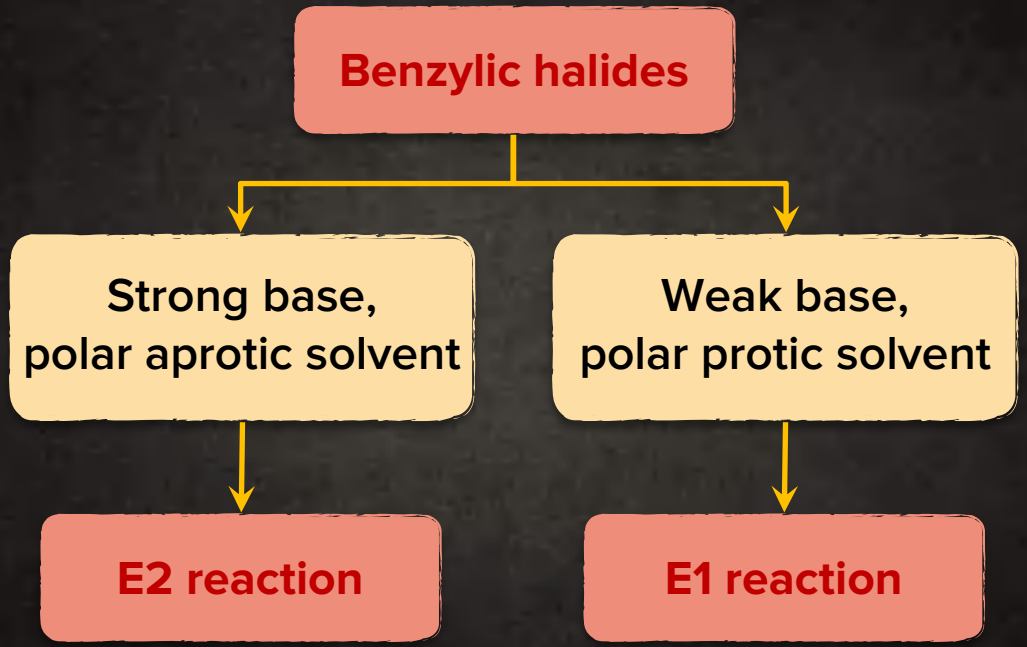
It is **conjugated** with a benzene ring



Elimination Reaction in Benzylic Halides



Elimination Reaction in Benzylic Halides



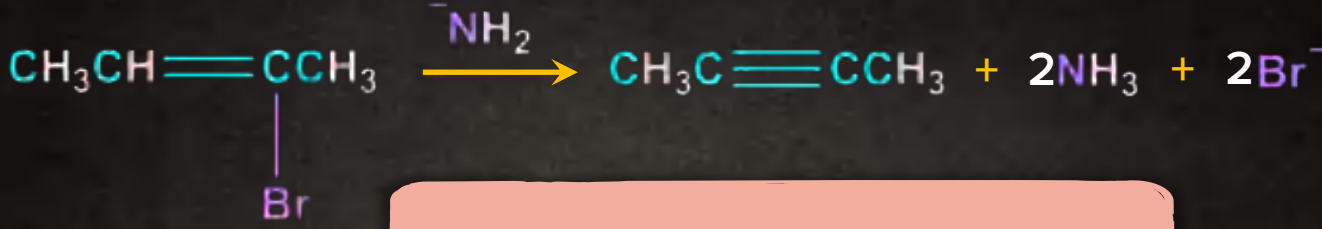
Elimination Reaction in Vinylic and Aryl Halides

Vinylic and aryl halides that have **β-hydrogens** **cannot undergo** **E1** reactions.

Vinylic halides that have **β-hydrogens** are relatively **unreactive** towards E2 reaction.

However, they can **undergo** **E2 reactions** when **a very strong base** ($-NH_2$) is reacted.

Elimination Reaction in Vinylic and Aryl Halides

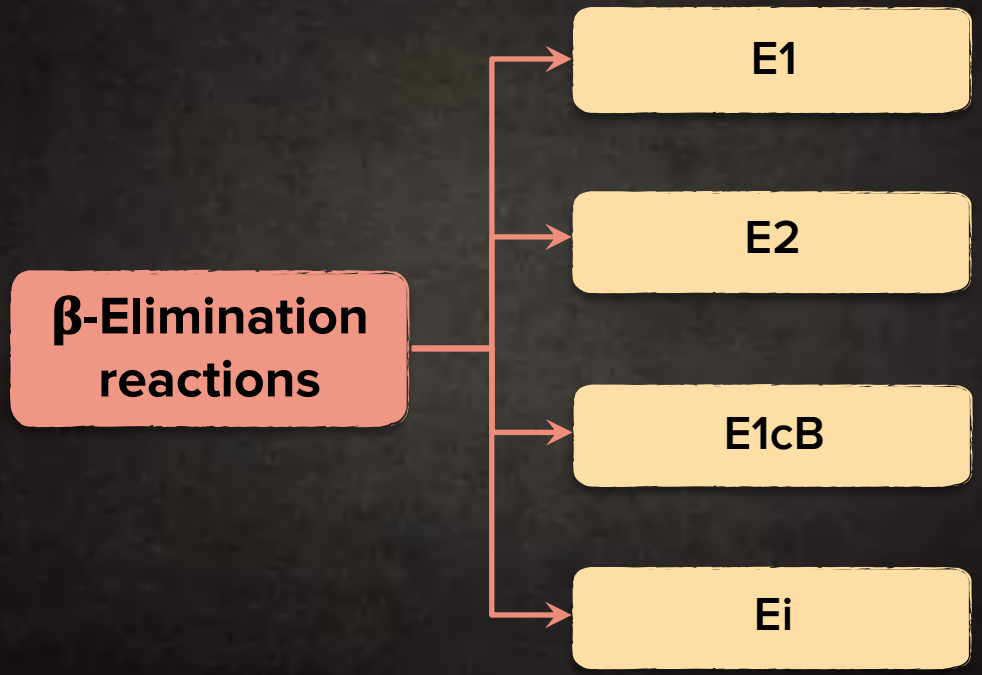


Aryl halides that have **β-hydrogens** are relatively **unreactive** towards E2 reaction.

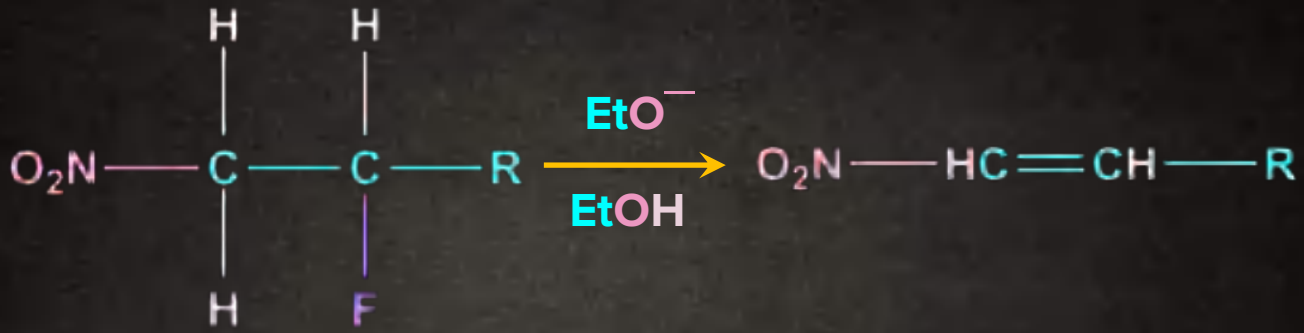
However, when a **very strong base** ($-NH_2$) is used, reaction does not take place through elimination mechanism.

Elimination Reaction

β-Elimination Reactions



E1cB Elimination



First, the **proton is abstracted** to form the **conjugate base.**

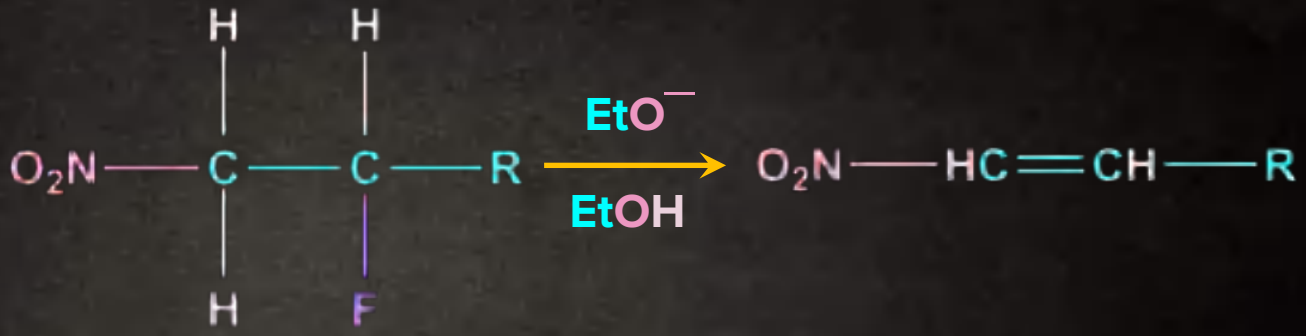
E1cB Elimination

The anion that results is stable enough to exist because it can be delocalised on to the EWG.

Although the anion is stabilised by the EWG, it still prefers to lose a leaving group and become an alkene.

E1cB Elimination

General reaction

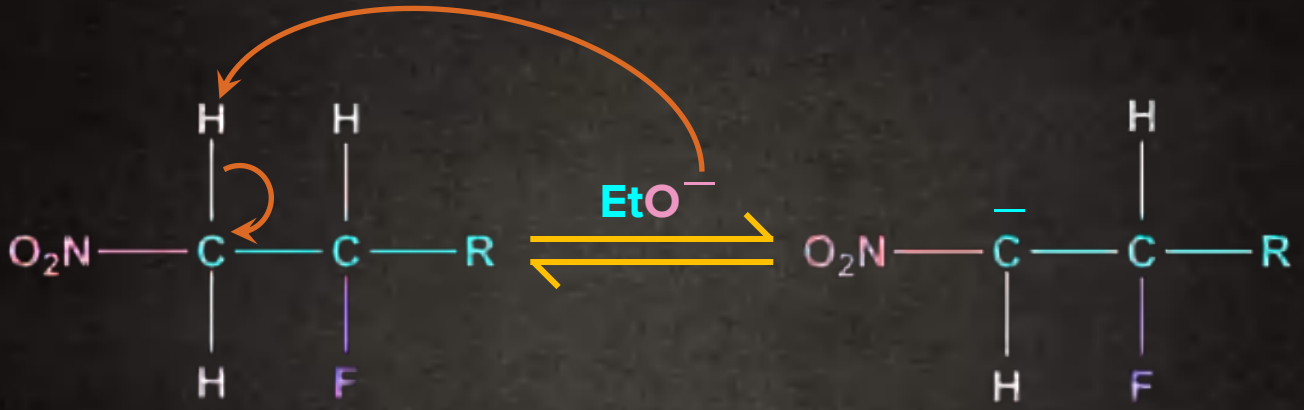


Steps Involved in E1cB Reaction

The mechanism of E1cB reaction is a **two-step** process.

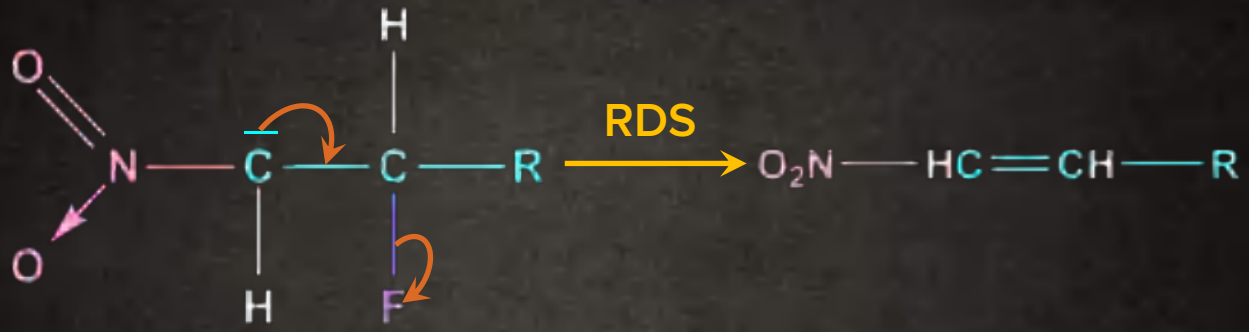
Step 1	Abstraction of proton to form carbanion
Step 2	Removal of leaving group to give an alkene

Abstraction of Proton to Form Carbanion



Carbanion

Removal of Leaving Group to Give an Alkene



E1cB Elimination

This step is also the **rate-determining step** of the elimination

The elimination is **unimolecular**, and so is some kind of **E1** reaction.

E1cB Elimination

The **leaving group** is not lost from the starting molecule, but from the **conjugate base** of the starting molecule

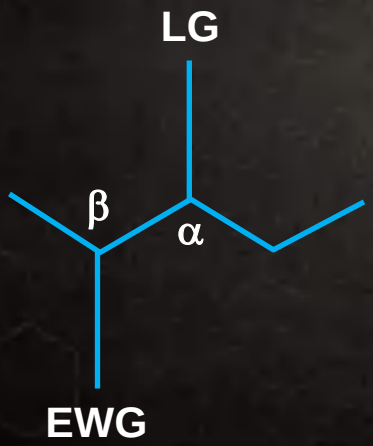
This sort of elimination, which starts with a **deprotonation**, is called **E1cB** (cB for conjugate Base).

Conditions for E1cB

- Substrate
- Leaving group

Substrate

A **good electron withdrawing** group must be present at the β-position to the leaving group.



E.g. $-NO_2$, $-COOR$, $-Ph$, $-COR$, etc.

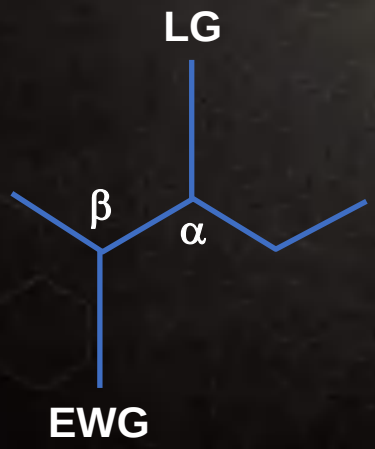
A **good electron withdrawing** group must be present at the β-position to the leaving group.

Leaving Group

Generally, **poor leaving group** shows E1cB reaction.

E.g.: —F, —OH, etc.

Generally, **poor leaving group** shows E1cB reaction.

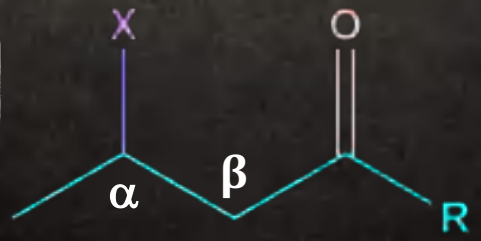


Note

It is **not necessary** that there is always a poor leaving group.

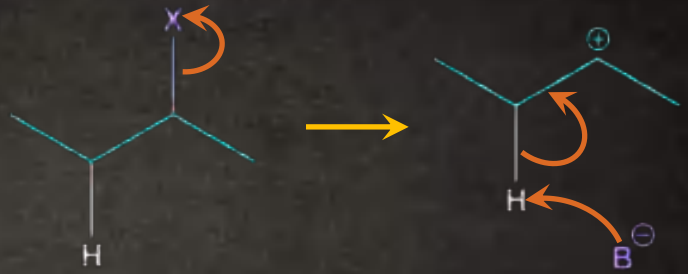
Good leaving group (like halogen) also shows **E1cB** reaction.

Example



Summary

E1 elimination
leaving group first
deprotonation second



Elimination Reaction

Several types of compound **undergo elimination** on heating, with no other reagent present.

The mechanisms are **different** from those already discussed,

Since all those require a **base** (which may be the solvent) in one of the steps.

Ei Elimination

Unimolecular, concerted mechanism

Two groups leave at about the **same time** and **bond** to each other simultaneously.

Involves a **cyclic transition** state, which may be four, five, or six membered.

Ei also known as

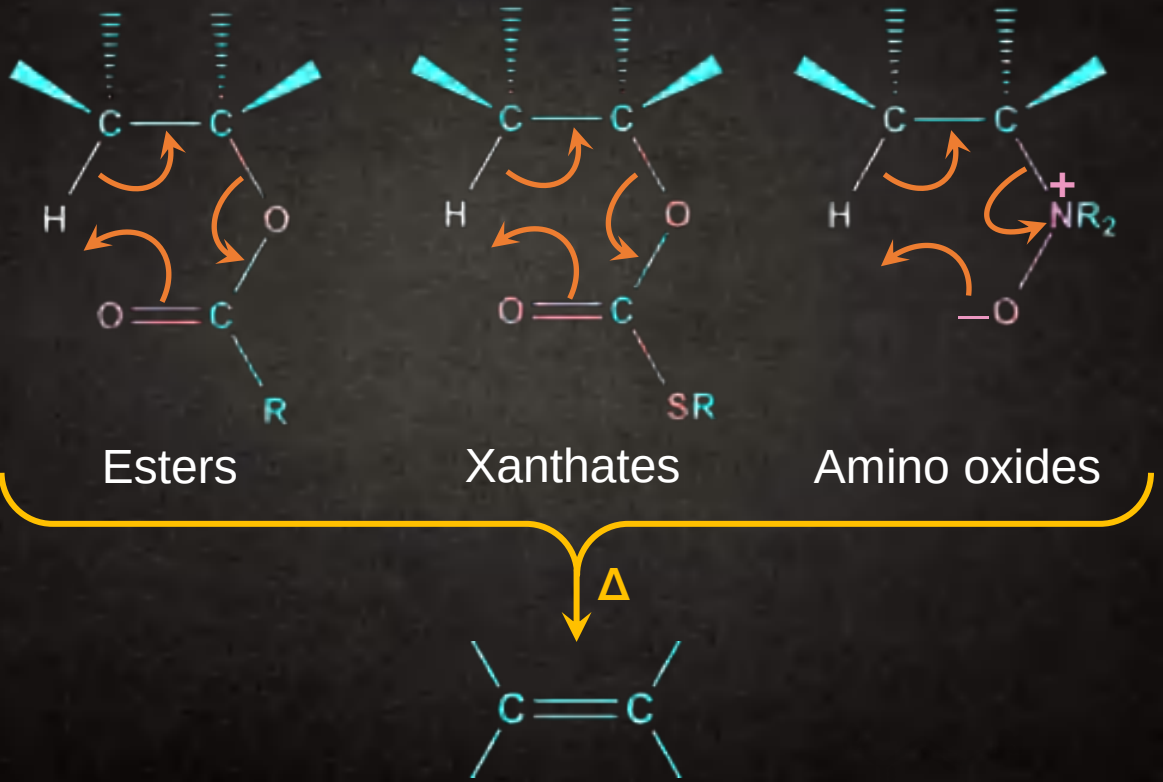
Syn elimination

The two groups leave and **bond to each other** simultaneously when they are **syn to each other**

Pyrolytic elimination

Elimination occurs under **thermal condition**

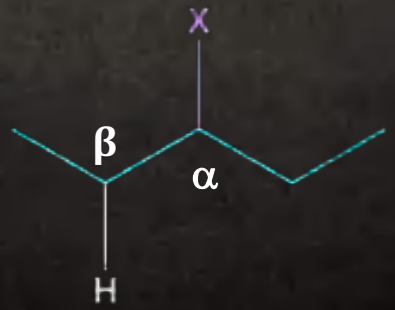
Ei Reactions



Condition for Ei Elimination

Esters, xanthate esters, 3° amine oxide

Which contains at least one β-hydrogen atom



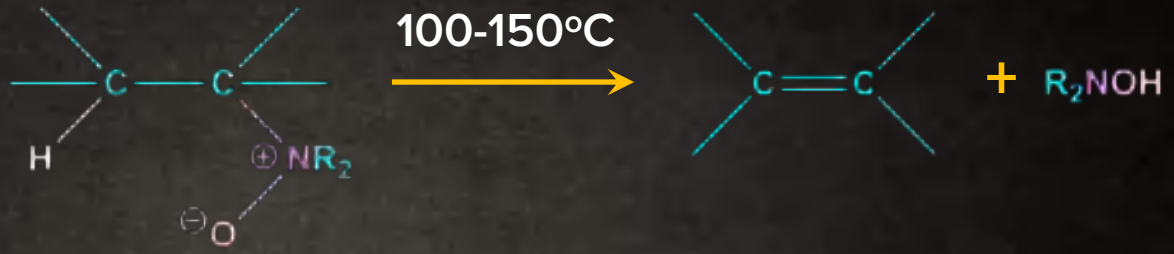
Cope Elimination

Must have at least one **β-hydrogen**

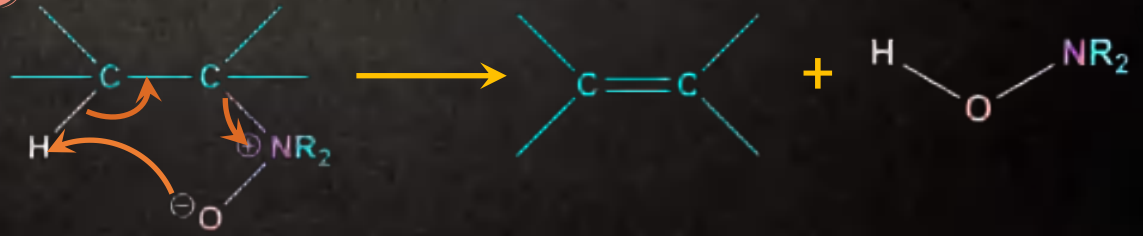
Reaction is very useful for the preparation of **alkenes**

Cope Elimination

General reaction

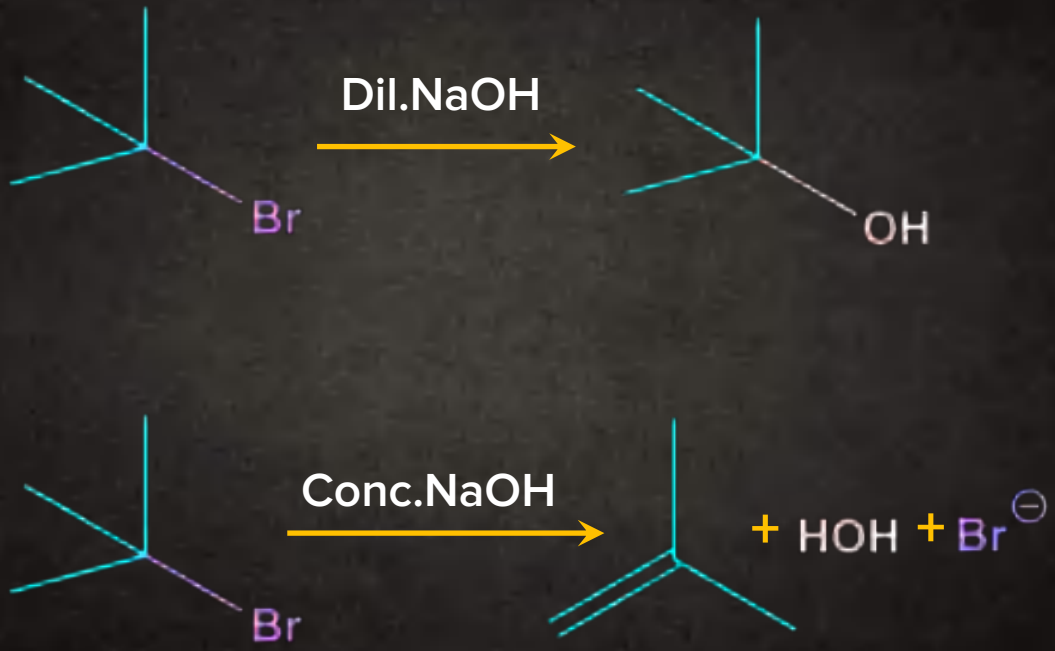


Concerted mechanism through a cyclic transition state.

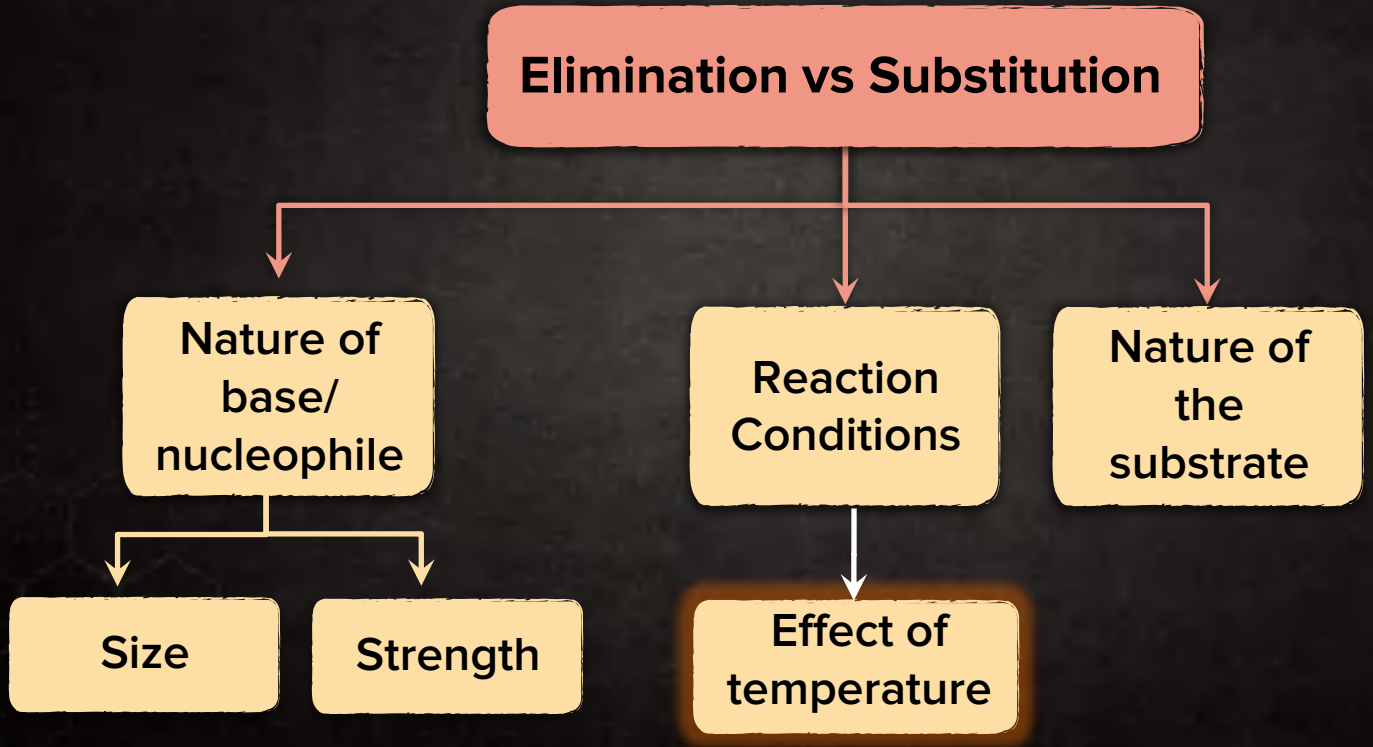


Elimination vs Substitution

Substitution and Elimination Reaction



Elimination vs Substitution



Effect of Size of the Base/Nucleophile

When the nucleophile/base is **small**

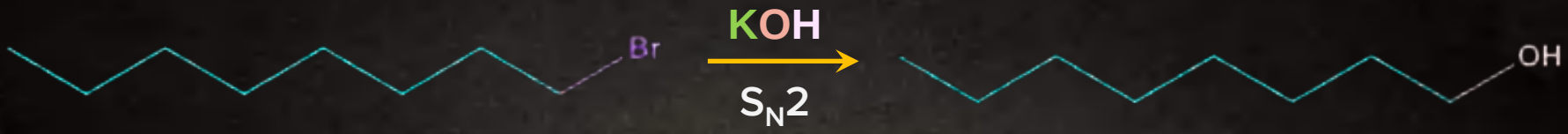
↓

It has **no difficulty** in getting to the reactive centre.

↓

Generally, it substitutes the leaving group and gives a **substitution product**.

Effect of Size of the Base/Nucleophile



When the nucleophile/base is **bulky**

It has **difficulty** getting to the reactive centre whereas getting at a **more exposed hydrogen** atom is **much easier**

Generally, it gives an **elimination product.**

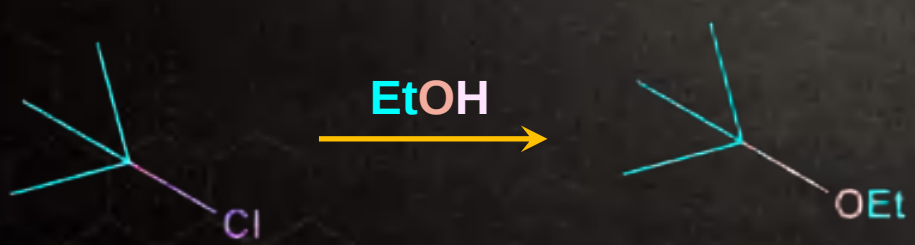
Effect of Size of the Base/Nucleophile

Size		Product
Nucleophile or base	Small	**Substitution** product
	Bulky	**Elimination** product

Effect of Strength of the Base/Nucleophile

Weak base → **Substitution**

Strong base → **Elimination**



Effect of Temperature

In general, **elimination** reactions require **higher temperature** than substitution.

If, the temperature **increases**

↓

Then, rate of both substitution and elimination **increases**

↓

But increase in rate of elimination is **more**.

Summary

Factor		Effect
Nucleophile	**Strong** base	**Favours elimination** over substitution
	Bulky	**Favours elimination** over substitution
High temperature		**Favours elimination** over substitution

Effect of Substrate

Conditions are alike for

- E2/S_N2
- E1/S_N1

S_N2 and E2 reactions are both **favoured by a high concentration** of a strong nucleophile or base.

When the nucleophile (base) attacks a **β hydrogen** atom → **Elimination**

When the nucleophile (base) attacks a **carbon** bearing the leaving group → **Substitution**

Effect of Substrate

S_N1 and E1 reactions both proceed through the formation of **carbocation**

Usually, difficult to influence the **relative partition** between **S_N1 and E1**

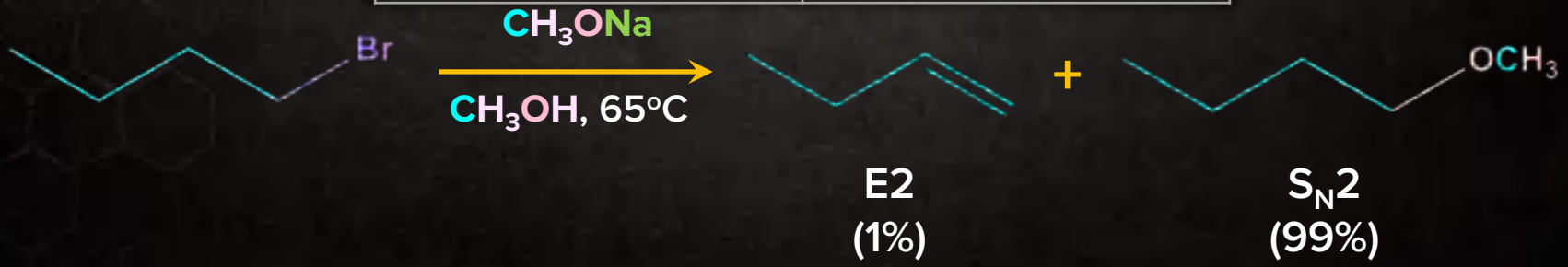
Effect of Nature of Substrate

In primary alkyl halide, carbocation is too unstable.

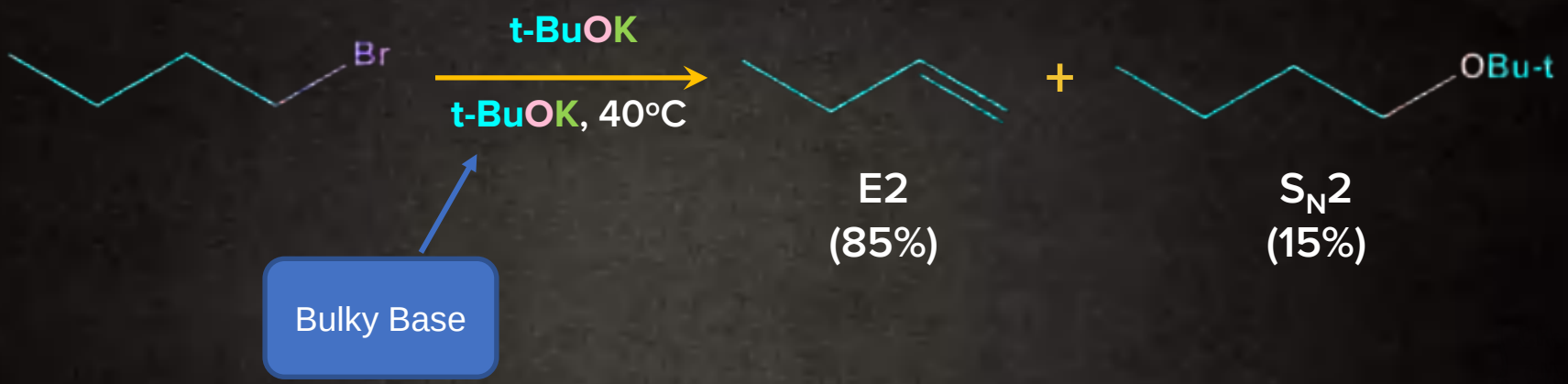
$E1/S_N1$	✗
$E2/S_N2$	✓

Elimination vs Substitution

Primary substrate	
Substitution (S_N2)	Elimination (E2)
Base is strong and unhindered	Base is strong and hindered
	High temperature favoured more for elimination



Elimination vs Substitution



Effect of Nature of Substrate

Generally,

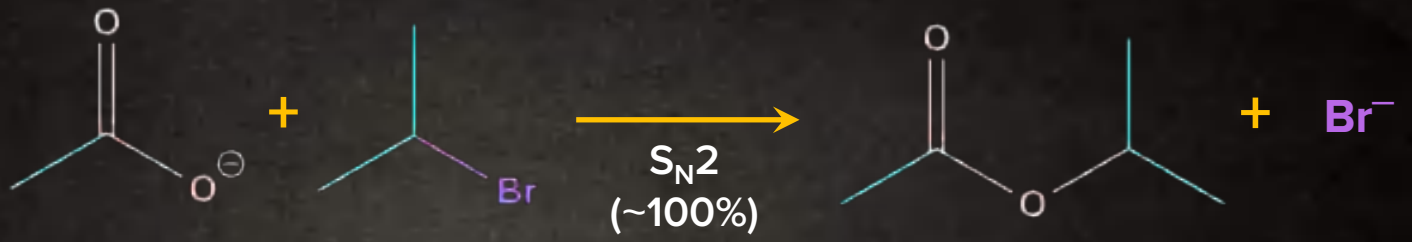
In secondary alkyl halide, carbocation is unstable.

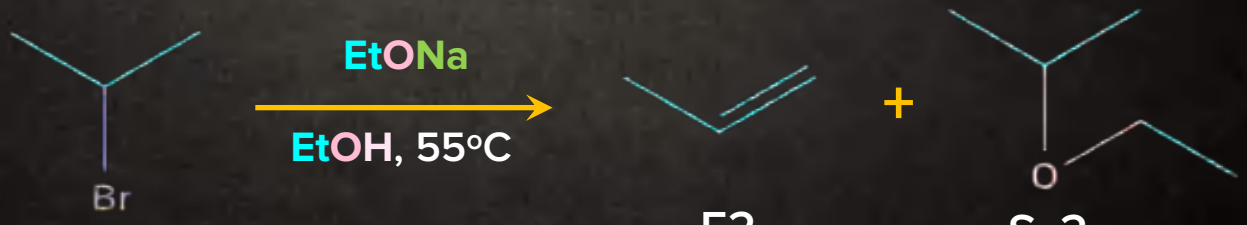
$E1/S_N1$	✗
$E2/S_N2$	✓

Effect of Nature of Substrate

Secondary substrate	
Substitution (S_N2)	Elimination (E2)
Use of a **weakly basic ion,** e.g., Cl^- or CH_3COO^- or a weakly basic and **highly polarisable** one, e.g., Br^-, I^-, or RS^-	Use of a **strong, slightly polarisable base,** e.g., OH^-, NH_2^-, or OR^- (especially a hindered one)
	High temperature

Elimination vs Substitution

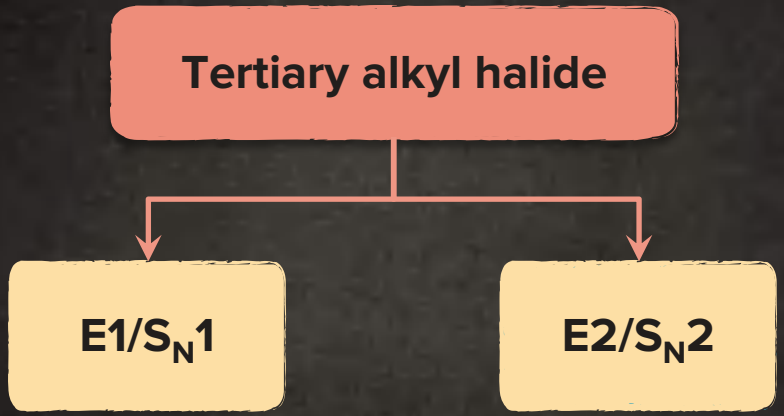




E2
(79%)

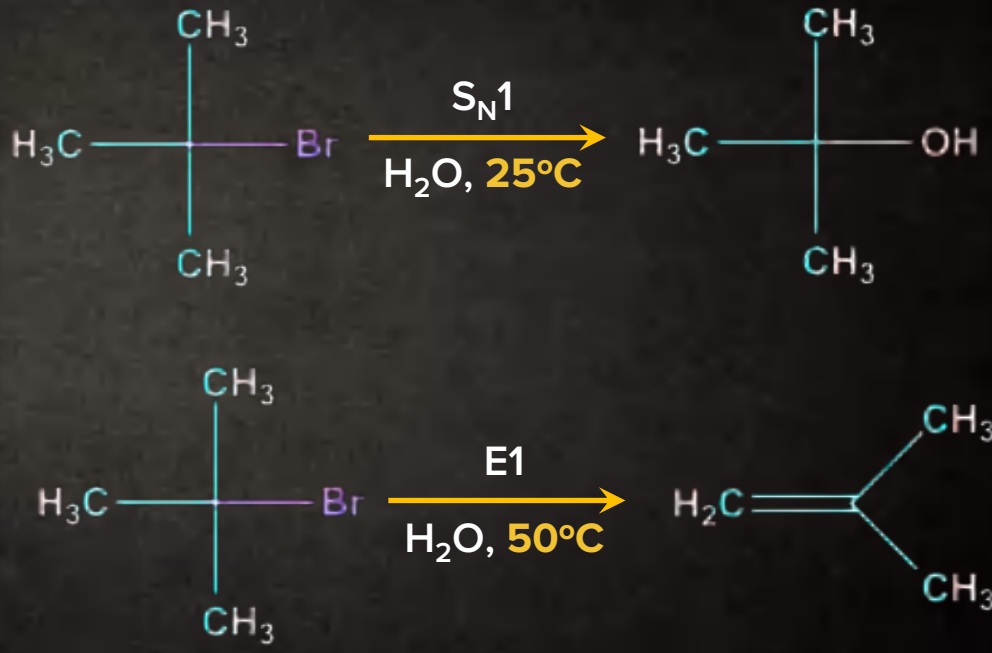
S_N2
(21%)

Elimination vs Substitution



Elimination vs Substitution

Tertiary substrate	
Substitution (S_N1)	Elimination (E1)
Favoured at lower temperatures.	Favoured at higher temperatures.

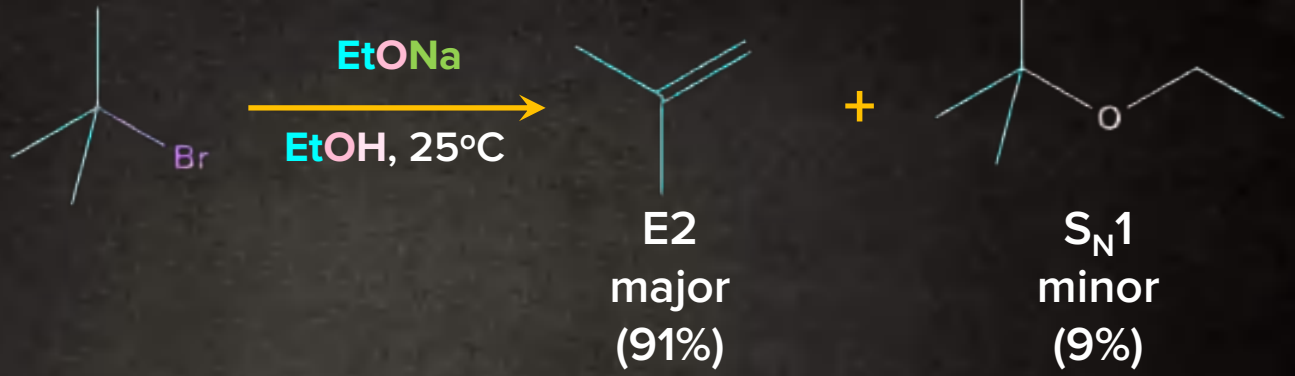


Elimination vs Substitution

Tertiary substrate	
Substitution (S_N2)	Elimination (E2)
Steric hindrance in the substrate is severe and an S_N2 reaction **cannot take place**	Highly favoured, especially when the reaction is carried out at **higher temperatures.**

Elimination vs Substitution

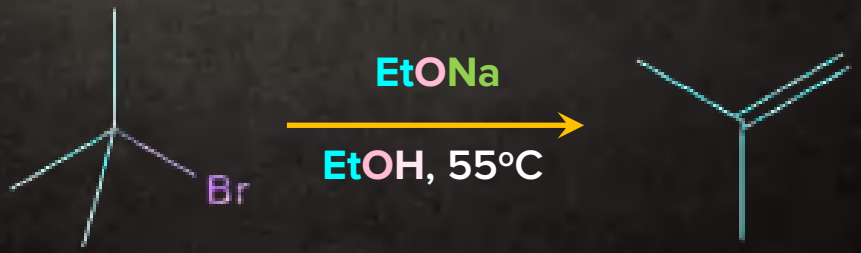
Without heating;



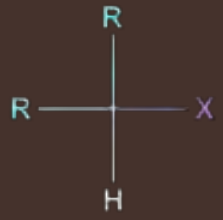
E2
major
(91%)

S_N1
minor
(9%)

Heating;



E2 + E1
only (100%)

CH_3X			
Gives S_N2 reaction	**Biomolecular (S_N2 /E2) reaction only**		**(S_N1 /E1) or E2**
	Gives mainly S_N2 except with a hindered strong base [e.g.: $(CH_3)CO^-$] and then mainly E2	Gives mainly S_N2 with a weak base (e.g. I^-, CN^-, RCO_2^- and mainly E2 with strong bases (e.g.: RO^-)	No S_N2 reaction. In solvolysis gives S_N1/E1, and at lower temperature S_N1 is favoured. When a strong base (e.g., RO^-) is used, E2 predominates