

# IB Chemistry DP

## 20. HL Organic Chemistry

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YOUR NOTES



## 20.1 Types of Organic Reactions

### 20.1.1 Nucleophilic Substitution Reactions

#### Nucleophilic Substitution Reactions

- In nucleophilic substitution reactions involving halogenoalkanes, the halogen atom is replaced by a nucleophile
- The strength of any nucleophile depends on its ability to make its lone pair of electrons available for reaction
- The hydroxide ion,  $\text{OH}^-$ , is a stronger nucleophile than water because it has a full negative charge
  - This means that it has a readily available lone pair of electrons
- A water molecule only has partial charges,  $\delta+$  and  $\delta-$ 
  - This means that its lone pair of electrons is less available than the hydroxide ions
  - The lone pairs of electrons in a water molecule are still available to react



**Lewis structures of the hydroxide ion and water molecule - illustrating the lone pairs of electrons and charges within their structures**



#### Exam Tip

In general:

- A negatively charged ion will be a stronger nucleophile than a neutral molecule
- A conjugate base will be a stronger nucleophile than its corresponding conjugate acid
  - e.g. the hydroxide ion is a stronger nucleophile than water

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## SN1 Mechanism

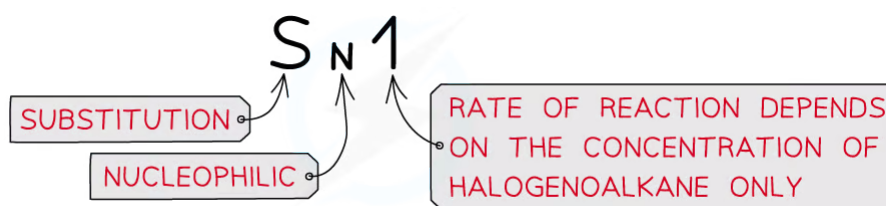
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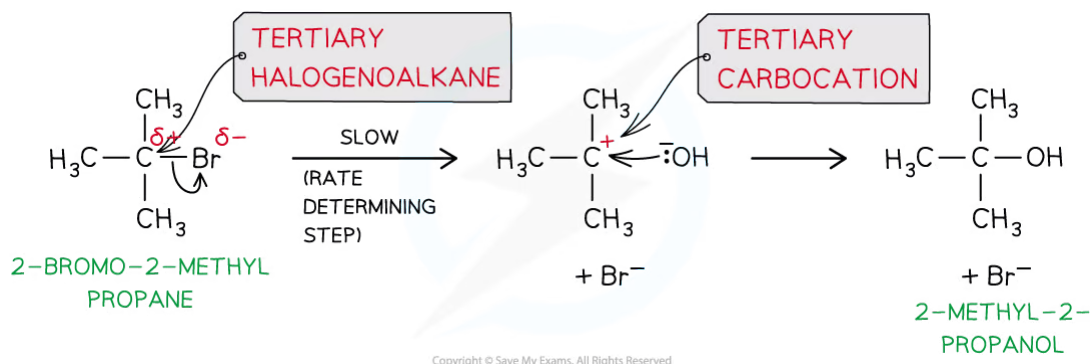
- Nucleophilic substitution reactions can occur in two different ways (known as  $S_N2$  and  $S_N1$  reactions) depending on the structure of the halogenoalkane involved

### $S_N1$ reactions

- In **tertiary** halogenoalkanes, the carbon that is attached to the halogen is also bonded to three alkyl groups
- These halogenoalkanes undergo nucleophilic substitution by an  $S_N1$  mechanism
  - 'S' stands for 'substitution'
  - 'N' stands for 'nucleophilic'
  - '1' means that the rate of the reaction (which is determined by the slowest step of the reaction) depends on the concentration of only one reagent, the halogenoalkane



- The  $S_N1$  mechanism is a **two-step** reaction
- In the first step, the C-X bond breaks heterolytically and the halogen leaves the halogenoalkane as an  $X^-$  ion (this is the **slow** and **rate-determining step**)
  - As the rate-determining step only depends on the concentration of the halogenoalkane, the rate equation for an  $S_N1$  reaction is **rate =  $k$ [halogenoalkane]**
  - In terms of molecularity, an  $S_N1$  reaction is unimolecular
  - This forms a tertiary carbocation (which is a tertiary carbon atom with a positive charge)
  - In the second step, the tertiary carbocation is attacked by the nucleophile
- For example, the nucleophilic substitution of 2-bromo-2-methylpropane by hydroxide ions to form 2-methyl-2-propanol



**The mechanism of nucleophilic substitution in 2-bromo-2-methylpropane which is a tertiary halogenoalkane**



### Exam Tip

You are expected to know the difference between the heterolytic fission that features in  $S_N1$  reactions and homolytic fission in other reactions:

- Heterolytic fission forms anions and cations and uses double headed arrows to show the movement of both electrons from the covalent bond
- Homolytic fission forms free radicals and uses single headed arrows, sometimes called fish hooks, to show the movement of a single electron as the covalent bond breaks

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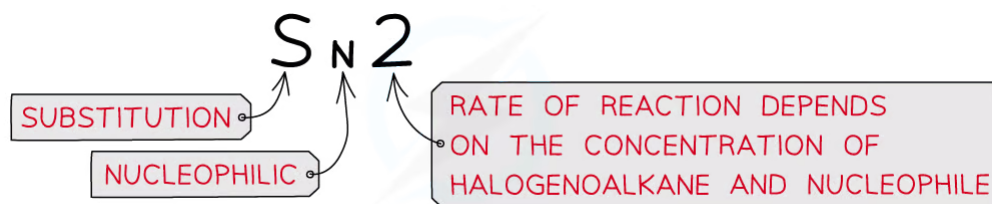
## SN2 Mechanism

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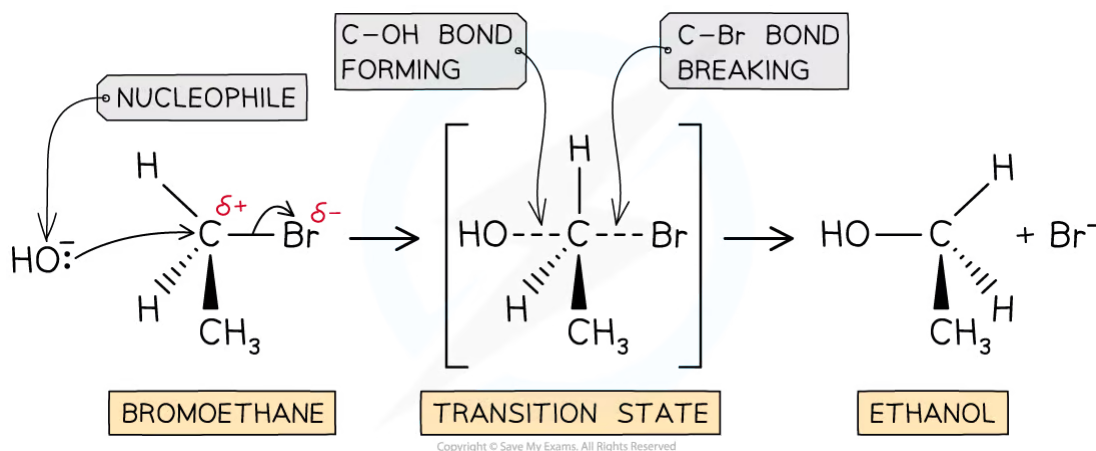


### S<sub>N</sub>2 reactions

- In **primary** halogenoalkanes, the carbon that is attached to the halogen is bonded to one alkyl group
- These halogenoalkanes undergo nucleophilic substitution by an **S<sub>N</sub>2** mechanism
  - 'S' stands for 'substitution'
  - 'N' stands for 'nucleophilic'
  - '2' means that the rate of the reaction (which is determined by the slowest step of the reaction) depends on the concentration of both the halogenoalkane and the nucleophile ions

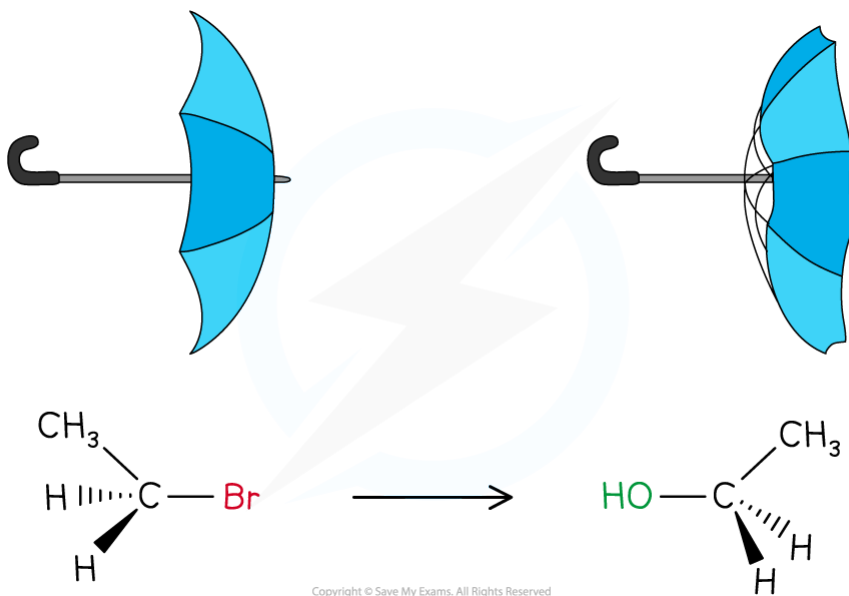


- The S<sub>N</sub>2 mechanism is a **one-step** reaction
  - The nucleophile donates a pair of electrons to the δ<sup>+</sup> carbon atom of the halogenoalkane to form a new bond
    - As this is a one-step reaction, the rate-determining step depends on the concentrations of the halogenoalkane and nucleophile, the rate equation for an S<sub>N</sub>2 reaction is **rate = k[halogenoalkane][nucleophile]**
    - In terms of molecularity, an S<sub>N</sub>2 reaction is bimolecular
  - At the same time, the C-X bond is breaking and the halogen (X) takes both electrons in the bond (heterolytic fission)
  - The halogen leaves the halogenoalkane as an X<sup>-</sup> ion
- For example, the nucleophilic substitution of bromoethane by hydroxide ions to form ethanol



**The S<sub>N</sub>2 mechanism of bromoethane with hydroxide causing an inversion of configuration**

- The bromine atom of the bromoethane molecule causes **steric hindrance**
- This means that the hydroxide ion nucleophile can only attack from the opposite side of the C-Br bond
  - Attack from the same side as the bromine atom is sometimes called frontal attack
  - While attack from the opposite side is sometimes called backside or rear-side attack
- As the C-OH bond forms, the C-Br bond breaks causing the bromine atom to leave as a bromide ion
  - As a result of this, the molecule has undergone an inversion of configuration
  - The common comparison for this is an umbrella turning inside out in the wind



***Inversion of configuration – umbrella analogy***



### Exam Tip

If you are asked to explain reaction mechanisms where there is an inversion of configuration, you will be expected to:

- Use partial charges,  $\delta+$  and  $\delta-$ , to help explain why the nucleophile attacks and the halogen leaves
- Use dotted, wedge and tapered bonds to show the change in configuration of the atoms / functional groups around the carbon that is being attacked
- Draw the transition state with the nucleophile attached to the carbon with a dotted bond and the halogen still attached to the carbon, also, with a dotted bond
- Be aware that the compound you draw is a transition state and not an intermediate

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## Factors Affecting Nucleophilic Substitution

YOUR NOTES



### Factors affecting nucleophilic substitution

- Various factors affect the rate of nucleophilic substitution, regardless of  $S_N1$  or  $S_N2$ , involving a halogenoalkane:
  1. The nature of the nucleophile
  2. The halogen involved (leaving group)
  3. The structure (class) of the halogenoalkane
  4. Protic & aprotic solvents

### 1. The nature of the nucleophile

- The most effective nucleophiles are neutral or negatively charged species that have a lone pair of electrons available to donate to the  $\delta^+$  carbon in the halogenoalkane
- The greater the electron density on the nucleophile ion or molecule; the stronger the nucleophile
  - Consequently, negative anions tend to be more reactive than their corresponding neutral species, e.g. hydroxide ions and water molecules (as previously discussed)
- When nucleophiles have the same charge, the electronegativity of the atom carrying the lone pair becomes the deciding factor
  - The less electronegative the atom carrying the lone pair; the stronger the nucleophile
  - For example:
    - Ammonia is a stronger nucleophile than water because the nitrogen atom in ammonia is less electronegative than the oxygen atom in water
  - This is because a less electronegative atom has a weaker grip on its lone pair of electrons, which means that they are more available for reaction
- The effectiveness of nucleophiles is as follows:

**Strongest**  $CN^- > OH^- > NH_3 > H_2O$  **Weakest**

### 2. The halogen involved (leaving group)

- The halogenoalkanes have different rates of substitution reactions
- Since substitution reactions involve breaking the carbon-halogen bond, the bond energies can be used to explain their different reactivities

#### Approximate Halogenoalkane Bond Energy Table



Bond	Bond Energy (kJ mol <sup>-1</sup> )
C-F	492 (strongest bond)
C-Cl	324
C-Br	285
C-I	228 (weakest bond)

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- The table above shows that the C-I bond requires the least energy to break, and is therefore the weakest carbon-halogen bond
  - During substitution reactions, the C-I bond will break heterolytically as follows:



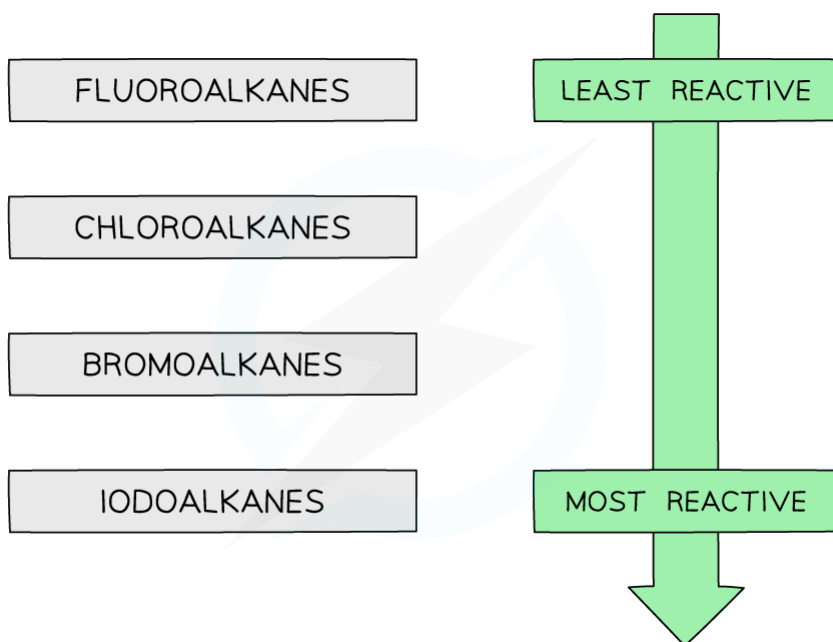
- The C-F bond, on the other hand, requires the most energy to break and is, therefore, the strongest carbon-halogen bond
  - Fluoroalkanes will therefore be less likely to undergo substitution reactions
- This idea can be confirmed by reacting the product formed by nucleophilic substitution of the halogenoalkane with aqueous silver nitrate solution
- As a halide ion is released, this results in the formation of a precipitate
- The rate of formation of these precipitates can also be used to determine the reactivity of the halogenoalkanes

**Halogenoalkane Precipitates Table**

Halogenoalkane	Precipitate
Chlorides	White (silver chloride)
Bromides	Cream (silver bromide)
Iodides	Pale yellow (silver iodide)

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- The formation of the pale yellow silver iodide is the fastest (fastest nucleophilic substitution reaction) whereas the formation of the silver fluoride is the slowest (slowest nucleophilic substitution reaction)
- This confirms that fluoroalkanes are the least reactive and iodoalkanes are the most reactive halogenoalkanes

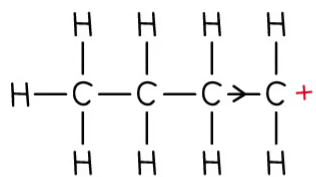


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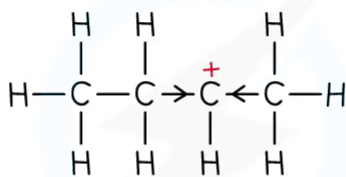
### *The trend in reactivity of halogenoalkanes*

### 3. The structure (class) of the halogenoalkane

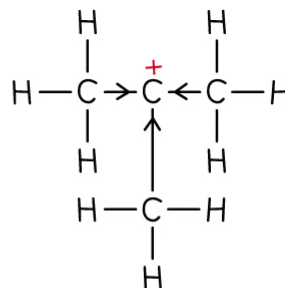
- Tertiary halogenoalkanes undergo  $S_N1$  reactions, forming stable tertiary carbocations
- Secondary halogenoalkanes undergo a mixture of both  $S_N1$  and  $S_N2$  reactions depending on their structure
- Primary halogenoalkanes undergo  $S_N2$  reactions, forming the less stable primary carbocations
- This has to do with the **positive inductive effect** of the alkyl groups attached to the carbon which is bonded to the halogen atom
  - The alkyl groups push electron density towards the positively charged carbon, reducing the charge density
  - In tertiary carbocations, there are three alkyl groups stabilising the carbocation
  - In primary carbocations, there is only one alkyl group
    - This is why tertiary carbocations are much more stable than primary ones



PRIMARY CARBOCATION  
(LEAST STABLE)



SECONDARY  
CARBOCATION



TERTIARY CARBOCATION  
(MOST STABLE)

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**The diagram shows the trend in stability of primary, secondary and tertiary carbocations**

- Overall, the structure (class) has a direct effect on the formation of the carbocation and, therefore, the rate-determining step
- Consequently, this affects the overall rate of the nucleophilic substitution reaction

YOUR NOTES



## Protic & Aprotic Solvents

YOUR NOTES



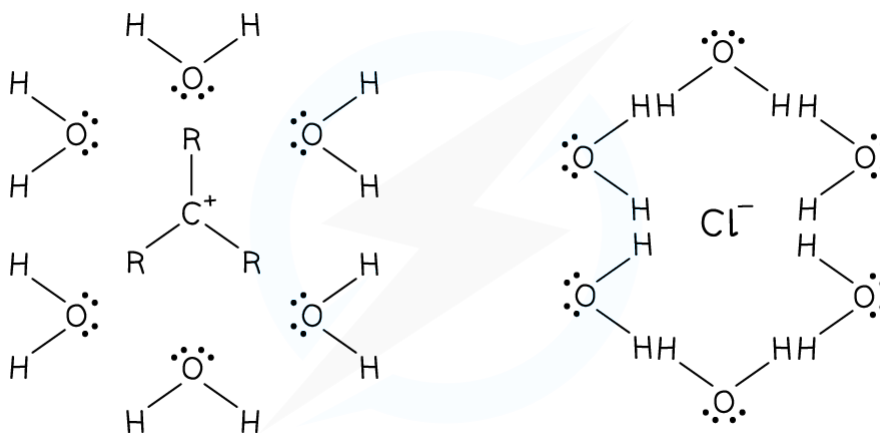
### 4. Protic & Aprotic Solvents

#### Hydrogen bonding

- Protic, polar solvents contain a hydrogen atom bonded to a very electronegative nitrogen or oxygen atom
  - This means that they are capable of hydrogen bonding
  - Examples of protic solvents include ammonia, carboxylic acids, ethanol and water
- Aprotic, polar solvents contain hydrogen atoms but they are not bonded to an electronegative atom
  - This means that they cannot participate in hydrogen bonding
  - Examples of aprotic solvents include ethanenitrile, ethyl ethanoate and propanone

#### Solvation

- Solvation is where solvent molecules surround a dissolved ion
  - In  $S_N1$  reactions, the rate-determining step is **not** the attack of the nucleophile
  - The rate-determining step is the formation of the carbocation intermediates and halide ion
  - Both ions could be stabilised by the use of a protic solvent, as shown in the following example:



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#### **Protic polar solvent stabilising carbocation intermediates and halide ions**

- In  $S_N2$  reactions, the rate-determining step is the attack of the nucleophile
  - The use of aprotic solvents does not **solvate** the nucleophile
  - This means that the nucleophile is more able to react and form the transition state
- $S_N1$  reactions are best conducted using protic, polar solvents
  - $S_N2$  reactions are best conducted using aprotic, non-polar solvents

## 20.1.2 Electrophilic Addition Reactions

YOUR NOTES

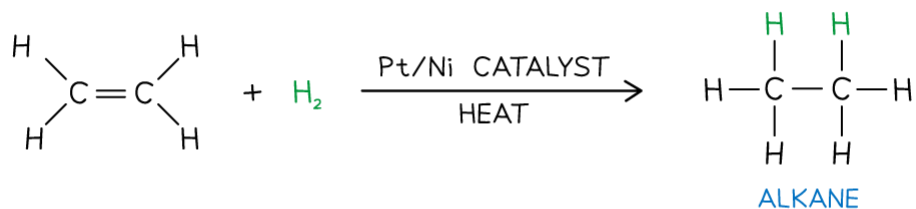
**Electrophilic Addition Mechanism****Electrophilic Addition**

- **Electrophilic addition** is the addition of an electrophile (or Lewis acid) to an alkene double bond,  $C=C$
- The alkene double bond,  $C=C$ , is an area of high electron density which makes it susceptible to attack by electrophiles
- The  $C=C$  bond breaks forming a single  $C-C$  bond and 2 new bonds from each of the two carbon atoms
- Electrophilic addition reactions include the addition of:
  - Hydrogen,  $H_2(g)$
  - Steam,  $H_2O(g)$
  - Hydrogen halides,  $HX$
  - Halogens,  $X_2$

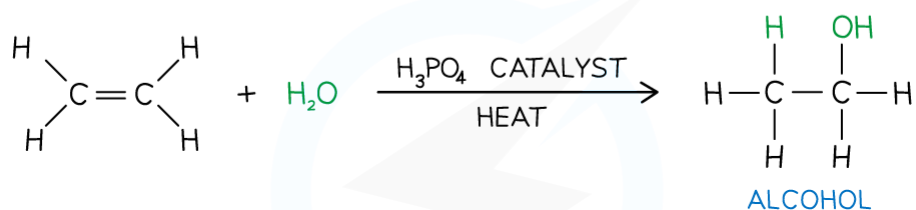


ELECTROPHILIC ADDITION

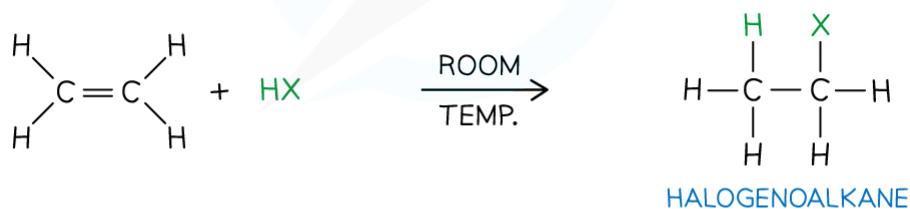
HYDROGENATION



STEAM



HYDROGEN HALIDES (HX)



HALOGENS (X<sub>2</sub>)



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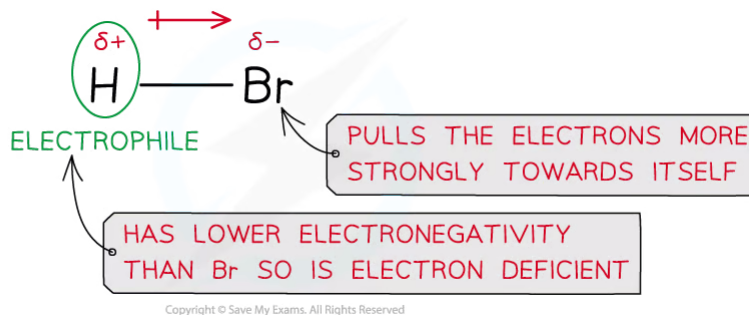
**Alkene electrophilic addition reaction overview**

**Electrophilic addition of hydrogen halides**

- A hydrogen halide molecule is polar as the hydrogen and halogen atoms have different electronegativities
  - For example, in a molecule of hydrogen bromide, HBr, the bromine atom has a stronger pull on the electrons in the H-Br bond
  - As a result of this, the Br atom has a partial negative and the H atom a partial positive charge

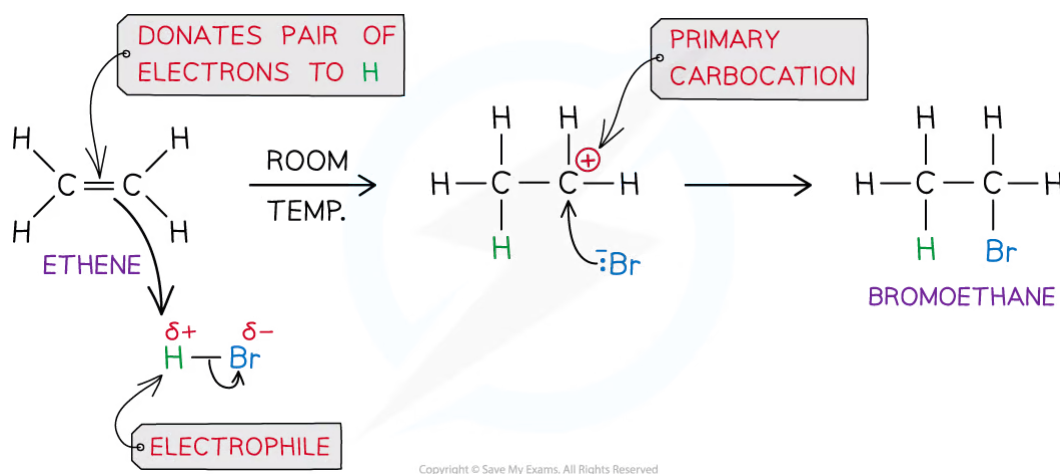
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**Due to differences in electronegativities of the hydrogen and bromine atom, HBr is a polar molecule**

- In electrophilic addition reactions with hydrogen halides, the H atom acts as an electrophile and Lewis acid by accepting a pair of electrons from the C=C bond in the alkene
  - The H-Br bond breaks heterolytically, forming a Br<sup>-</sup> ion
- This results in the formation of a highly reactive carbocation intermediate which reacts with the bromide ion, Br<sup>-</sup>
- For example, the mechanism for the electrophilic addition of hydrogen bromide and ethene is:



**Electrophilic addition reaction of HBr and ethene to form bromoethane**



### Exam Tip

For electrophilic addition mechanisms, the curly arrows must:

- Be double-headed to show the movement of a pair of electrons
- Start from a lone pair of electrons or an area of high electron density, e.g. the C=C bond
- Move towards a  $\delta+$  electrophile or the positive charge of a carbocation

Examiners often comment about the poor and incorrect use of curly arrows in organic mechanisms

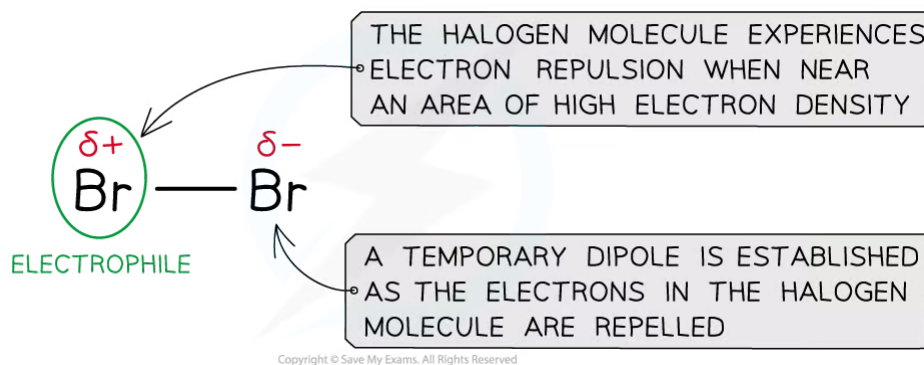
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## Electrophilic addition of halogens

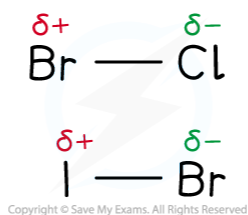
- The mechanism for the electrophilic addition of halogens (and hydrogen) is the same as the electrophilic addition of hydrogen halides with one key exception:
  - Hydrogen halide molecules have a **permanent dipole** (as shown above)
  - Halogen molecules have a **temporary (or induced) dipole** caused by the repulsion of the halogens electrons by the high electron density C=C bond



### *The temporary (or induced) dipole in a halogen molecule*

## Electrophilic addition of interhalogens

- Interhalogens** are compounds that contain two or more different type of halogens
- The mechanism for the electrophilic addition of interhalogens is the same as the electrophilic addition of hydrogen halides
- Just like hydrogen halide molecules, interhalogens have a **permanent dipole**
- Differences between the electronegativity of the halogens determine which halogen will become the  $\delta+$  electrophile
  - The electronegativity increases as you move up the halogens,  $F > Cl > Br > I$



### *The polarity of interhalogen molecules*



#### Exam Tip

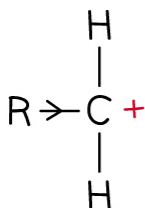
The electrophilic addition reactions of alkenes with hydrogen halides, halogens and interhalogens are the same. The difference is whether the electrophile is due to a permanent or temporary dipole

## Markovnikov's Rule

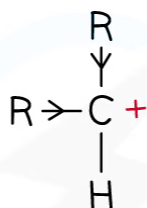
- **Carbocations** are positively charged carbon atoms with only three covalent bonds instead of four
- There are three types of carbocations: primary, secondary and tertiary

### Inductive effect

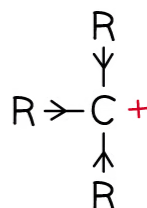
- The alkyl groups attached to the positively charged carbon atoms are 'electron donating groups'
  - This is also known as the inductive effect of alkyl groups
- The inductive effect is illustrated by the use of arrowheads on the bonds to show the alkyl groups pushing electrons towards the positively charged carbon
  - This causes the carbocation to become less positively charged
- As a result of this, the charge is spread around the carbocation which makes it energetically more stable
- This means that tertiary carbocations are the most stable as they have three electron-donating alkyl groups which energetically stabilise the carbocation
- Due to the positive charge on the carbon atom, carbocations are electrophiles



PRIMARY CARBOCATION  
(LEAST STABLE)



SECONDARY  
CARBOCATION



TERTIARY CARBOCATION  
(MOST STABLE)

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**Alkyl groups push electron density towards the carbocation making it energetically more stable; the more alkyl groups the carbocation is bonded to, the more stabilised it is**

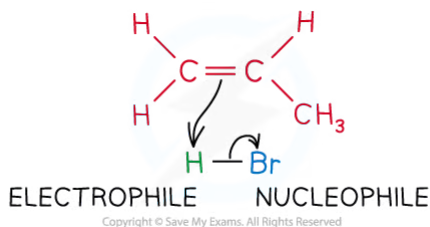
### Markovnikov's rule

- Markovnikov's rule predicts the outcome of electrophilic addition reactions and states that:
  - In an electrophilic addition reaction of a hydrogen halide (HX) to an alkene, the halogen ends up bonded to the most substituted carbon atom
  - In an electrophilic addition reaction of an interhalogen to an alkene, the most electronegative halogen ends up bonded to the most substituted carbon atom
- Markovnikov addition applies to electrophilic addition reactions with unsymmetrical alkenes, e.g. propene and but-1-ene
  - Markovnikov addition favours the formation of the major product
  - Anti-Markovnikov addition favours the formation of the minor product
- In electrophilic addition reactions, an electrophile reacts with the double bond of alkenes (as previously discussed)

YOUR NOTES



- The mechanism for electrophilic addition reactions with unsymmetrical alkenes is slightly different, e.g. propene + hydrogen bromide



**The electrophile reacts with the electron-rich C-C double bond**

- The electrophile can attach in two possible ways:
  - Breaking the C=C bond and attaching to the the least substituted carbon
    - This will give the **most** stable carbocation as an intermediate that will form the **major** product
  - Breaking the C=C bond and attaching to the the most substituted carbon
    - This will give the **least** stable carbocation as an intermediate that will form the **minor** product



MORE STABLE SECONDARY  
CARBOCATION INTERMEDIATE

LESS STABLE PRIMARY  
CARBOCATION INTERMEDIATE

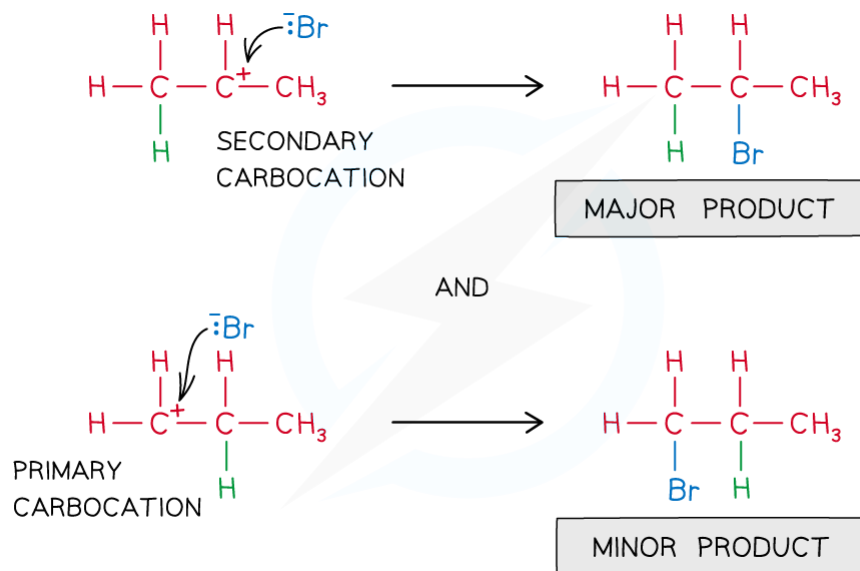
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**The major and minor carbocation intermediates formed during the reaction of propene and hydrogen bromide**

- The nucleophile will bond to the positive carbon atom of the carbocation
  - The more stable carbocation produces the major product
  - The less stable carbocation produces the minor product

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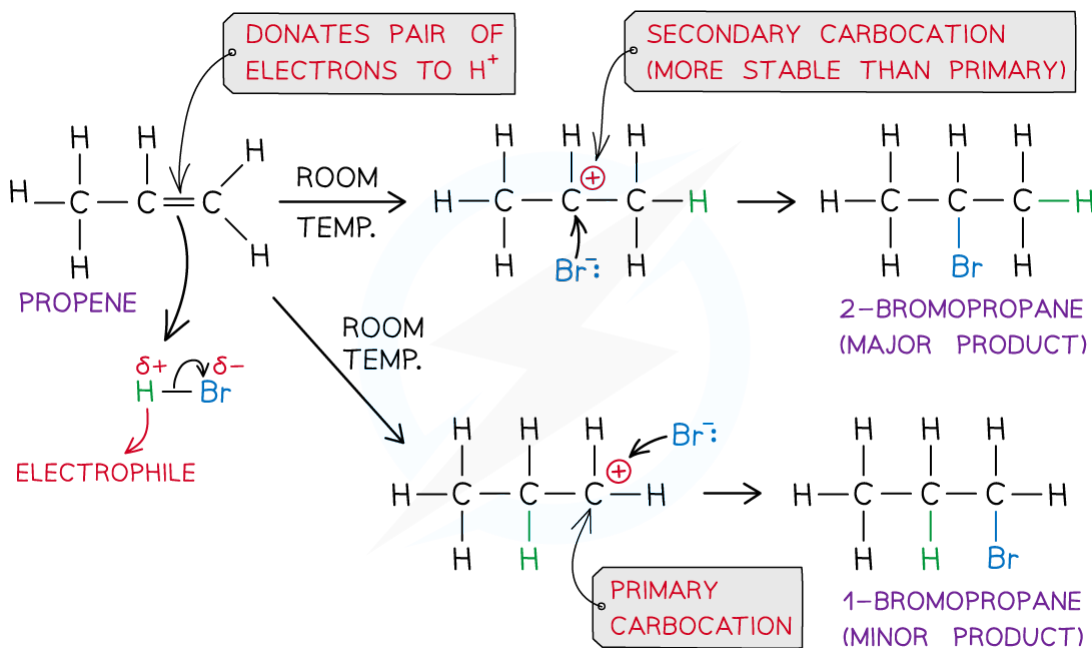




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**Formation of the major and minor products of the reaction of propene with hydrogen bromide**

- The mechanism for the electrophilic addition of hydrogen bromide to propene, showing the formation of the major and minor products can be shown as:



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**The electrophilic addition reaction mechanism of HBr and propene to form 1-bromopropane and 2-bromopropane**



### Exam Tip

The stability of the carbocation intermediate is as follows:

**tertiary > secondary > primary**

When more than one carbocation can be formed, the major product of the reaction will be the one that results from the nucleophilic attack of the most stable carbocation.

YOUR NOTES



## 20.1.3 Electrophilic Substitution Reactions

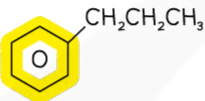
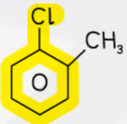
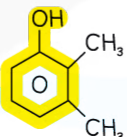
YOUR NOTES



### The Structure of Benzene

- In normal, everyday conversation the word 'aromatic' is used to refer to pleasant, fragrant smells
- However, in chemistry, it is used to describe molecules that contain one or more benzene rings, i.e. a ring with **conjugated  $\pi$  systems**
  - Conjugated  $\pi$  systems arise from alternating double and single bonds in which the electrons are delocalised
- Benzene is found in many useful pharmaceuticals, pesticides, polymers and dyes
  - The common painkillers aspirin, paracetamol, ibuprofen and morphine all contain benzene rings

#### Examples of aromatic compounds including benzene table

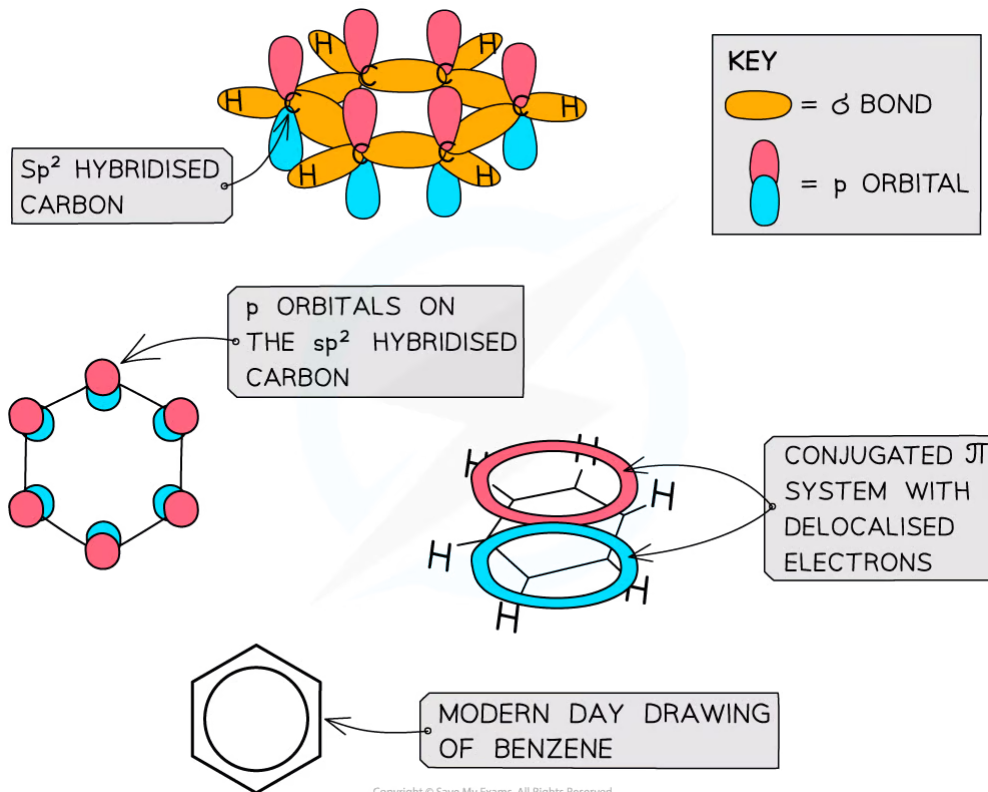
Functional Group	Example	Name
Arene		propylbenzene
Chlorobenzene		2-methylchlorobenzene
Phenol		2,3-dimethyl phenol

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### Structure of Benzene

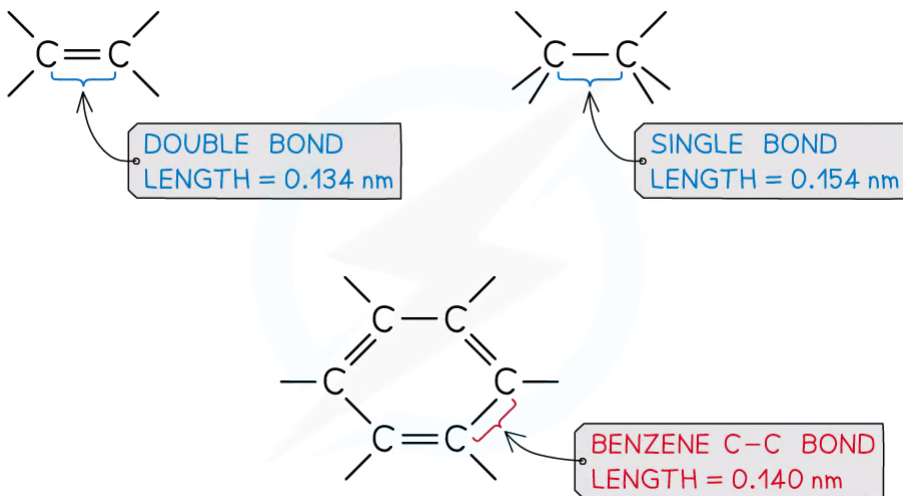
- The structure of benzene was determined many years ago, by the German chemist Friedrich August Kekulé
- The structure consists of 6 carbon atoms in a hexagonal ring, with alternating single and double carbon-carbon bonds
  - This suggests that benzene should react in the same way as an unsaturated alkene
  - However, this is not the case





**Like other aromatic compounds, benzene has a planar structure due to the  $sp^2$  hybridisation of carbon atoms and the conjugated  $\pi$  system in the ring**

- Each carbon atom in the ring forms three  $\sigma$  bonds using the  $sp^2$  orbitals
- The remaining p orbitals overlap laterally with p orbitals of neighbouring carbon atoms to form a  $\pi$  system
- This extensive sideways overlap of p orbitals results in the electrons being delocalised and able to freely spread over the entire ring causing a  $\pi$  system
  - The  $\pi$  system is made up of two ring shaped clouds of electron density - one above the plane and one below it
- Benzene and other aromatic compounds are regular and planar compounds with bond angles of  $120^\circ$
- The delocalisation of electrons, as shown below, means that all of the carbon-carbon bonds in these compounds are identical and have both single and double bond character
  - Single covalent bonds have a bond order of 1 and double covalent bonds have a bond order of 2
  - The covalent bonds within benzene have a bond order of 1.5
- The bonds all being the same length is evidence for the delocalised ring structure of benzene



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### The Delocalisation of Benzene Model

YOUR NOTES



## Electrophilic Substitution Mechanism

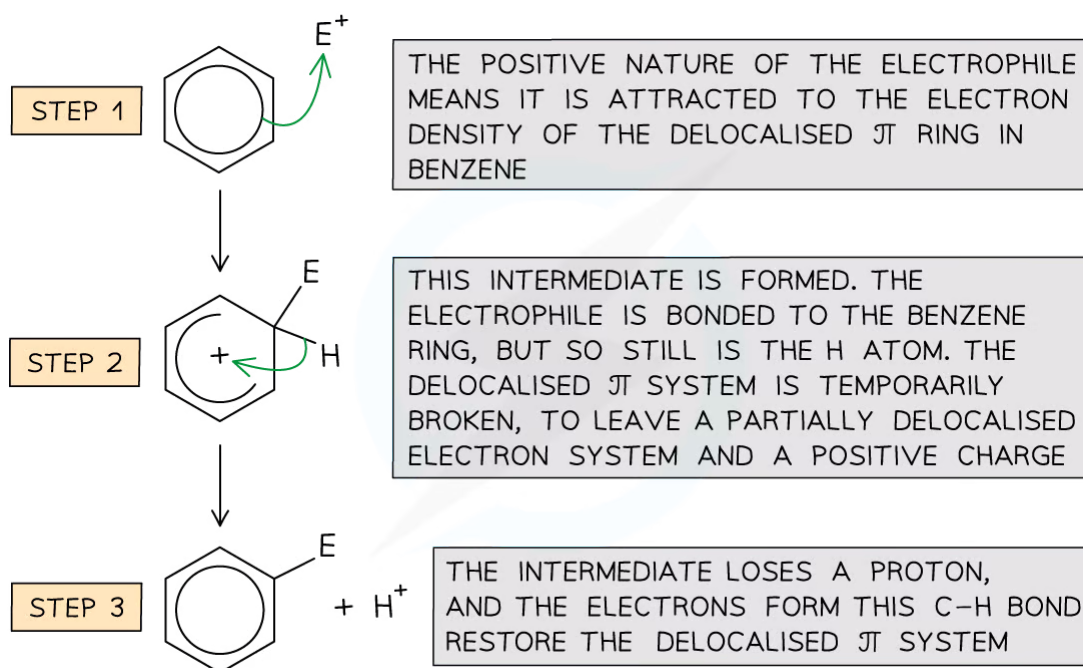
YOUR NOTES



### Reactions of Benzene

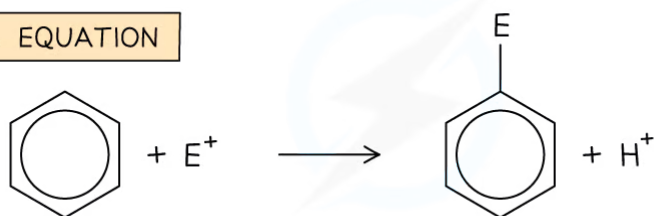
- The main reactions which benzene will undergo involve the replacement of one of the hydrogen atoms from the benzene ring
  - This is different to the reactions of unsaturated alkenes, which involve the double bond breaking and the electrophile atoms 'adding on' to the carbon atoms
- These reactions where benzene hydrogen atoms are replaced, are called **electrophilic substitution** reactions
  - The delocalised  $\pi$  system is extremely stable and is a region of high electron density
  - The hydrogen atom is substituted by an electrophile, which is either a positive ion or the positive end of a polar molecule

### General Electrophilic Substitution Mechanism:



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### OVERALL EQUATION





### Exam Tip

Make sure you understand the general steps of the electrophilic substitution mechanism and that you can explain what is happening - the same steps happen every time, the only difference is the electrophile used in the reaction!

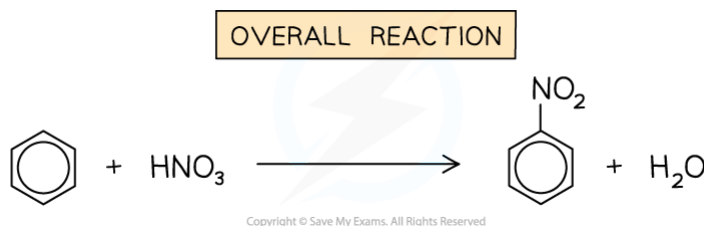
- There are numerous electrophiles which can react with benzene
  - However, they usually cannot simply be added to the reaction mixture to then react with benzene
  - The electrophile has to be produced in situ, by adding appropriate reagents to the reaction mixture

## Nitration of Benzene

- You must be able to provide the mechanism for the nitration of benzene via electrophilic substitution
- The electrophilic substitution reaction in arenes consists of three steps:
  1. Generation of an electrophile
  2. Electrophilic attack
  3. Regenerating aromaticity

## Nitration of Benzene Mechanism

- The nitration of benzene is an example of electrophilic substitution as a hydrogen atom is replaced by a nitro ( $-\text{NO}_2$ ) group



### *The overall reaction of nitration of arenes*

- Step 1: Generation of an electrophile
  - The electrophilic nitronium ion,  $\text{NO}_2^+$ , is generated by reacting **concentrated** nitric acid,  $\text{HNO}_3$ , and **concentrated** sulfuric acid,  $\text{H}_2\text{SO}_4$
  - The sulfuric acid is a catalyst
- Step 2: Electrophilic attack
  - Once the electrophile has been generated, it will carry out an electrophilic attack on the benzene ring
  - The nitrating mixture of  $\text{HNO}_3$  and  $\text{H}_2\text{SO}_4$  is **refluxed** with the arene at  $25 - 60^\circ\text{C}$
- Step 3: Regenerating aromaticity
  - The aromaticity is restored by the heterolytic cleavage of the C-H bond
- For the nitration of benzene, there is an extra step involving the regeneration of the sulfuric acid catalyst

YOUR NOTES



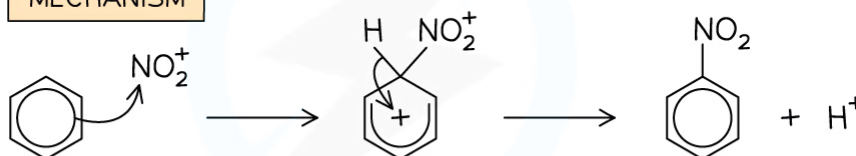


FORMATION OF ELECTROPHILE

ELECTROPHILE



MECHANISM



REFORMING THE CATALYST

CATALYST



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**The different stages in the nitration of benzene**

**Chlorination of Benzene Mechanism**

- The chlorination, or halogenation, of benzene is another example of electrophilic substitution

OVERALL REACTION



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**The overall reaction of chlorination of arenes**

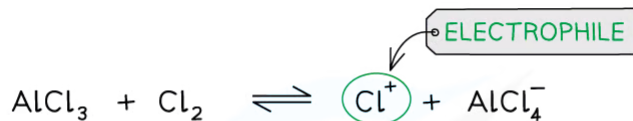
- Step 1: Generation of an electrophile
  - The electrophilic chlorine cation,  $\text{Cl}^+$ , is generated by reacting chlorine with anhydrous aluminium chloride,  $\text{AlCl}_3$ 
    - The aluminium chloride is electron deficient and acts as a Lewis acid by accepting a lone pair from one of the chlorine atoms
    - As the aluminium forms a dative covalent bond with one of the chlorine atoms, the other chlorine atom becomes a chlorine cation,  $\text{Cl}^+$
- Step 2: Electrophilic attack
  - Once the electrophile has been generated, it will carry out an electrophilic attack on the benzene ring

- Step 3: Regenerating aromaticity
  - The aromaticity is, once again, restored by the **heterolytic cleavage** of the C-H bond
- For the chlorination of benzene, there is an extra step involving the regeneration of the aluminium chloride catalyst

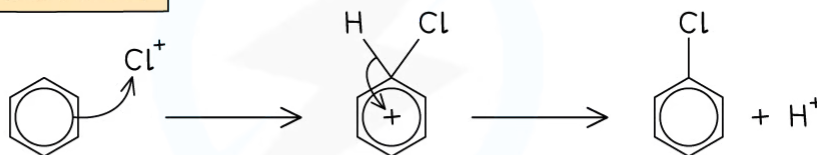
YOUR NOTES



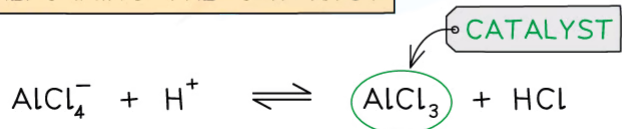
FORMATION OF ELECTROPHILE



MECHANISM



REFORMING THE CATALYST



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**The different stages in the chlorination of benzene**

## 20.1.4 Reduction Reactions

YOUR NOTES


**Reduction Reactions**
**Carbonyl compounds**

- Alcohols can be oxidised to carbonyl compounds in the presence of a suitable oxidising agent
  - Primary alcohol → aldehyde → carboxylic acid
  - Secondary alcohol → ketone
  - Tertiary alcohol - no reaction
- These reactions can be reversed in the presence of a suitable reducing agent
  - Carboxylic acid → aldehyde → primary alcohol
  - Ketone → secondary alcohol
- The two most common reducing agents for carbonyl compounds are:
  - Lithium aluminium hydride,  $\text{LiAlH}_4$ , in anhydrous conditions, commonly dry ether, followed by the addition of aqueous acid
    - This is the stronger of these reducing agents and can reduce carboxylic acids
  - Sodium borohydride,  $\text{NaBH}_4$ , in aqueous or alcoholic solutions
    - This is the less hazardous of these reducing agents but it cannot reduce carboxylic acids
- Both of these reagents produce the nucleophilic hydride ion,  $\text{H}^-$


**Exam Tip**

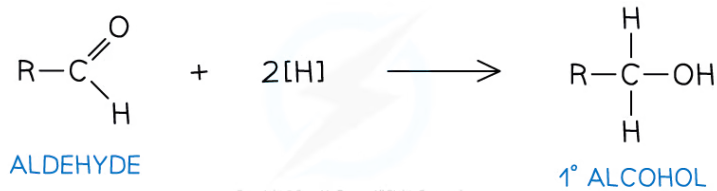
You can be expected to know typical conditions and reagents of all reactions, e.g. catalysts, reducing agents, reflux, etc. However, you do not need to know more precise details such as specific temperatures

**Reduction Reactions**

- Equations for reduction reactions can be written using  $[\text{H}]$  to represent the reducing agent
- Carboxylic acid to a primary alcohol (using  $\text{LiAlH}_4$  refluxed in dry ether, followed by dilute acid)
  - Remember that  $\text{NaBH}_4$  cannot reduce carboxylic acids

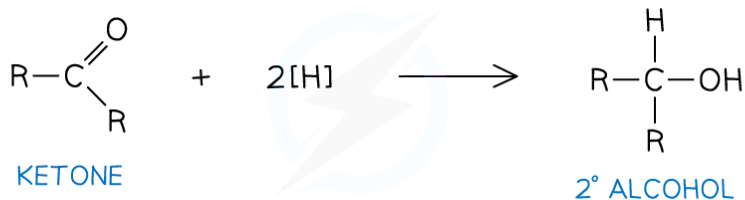


- Aldehyde to a primary alcohol (using  $\text{LiAlH}_4$  or  $\text{NaBH}_4$ )



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- Ketone to a secondary alcohol (using  $\text{LiAlH}_4$  or  $\text{NaBH}_4$ )



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### Exam Tip

Take care if you are asked about the formation of an aldehyde from a carboxylic acid. You have to use  $\text{LiAlH}_4$  refluxed in dry ether, followed by dilute acid but this reaction cannot be stopped at the aldehyde because the  $\text{LiAlH}_4$  is too powerful. To form an aldehyde from a carboxylic acid, you have to reduce the carboxylic acid down to a primary alcohol and then oxidise it back up to the aldehyde.

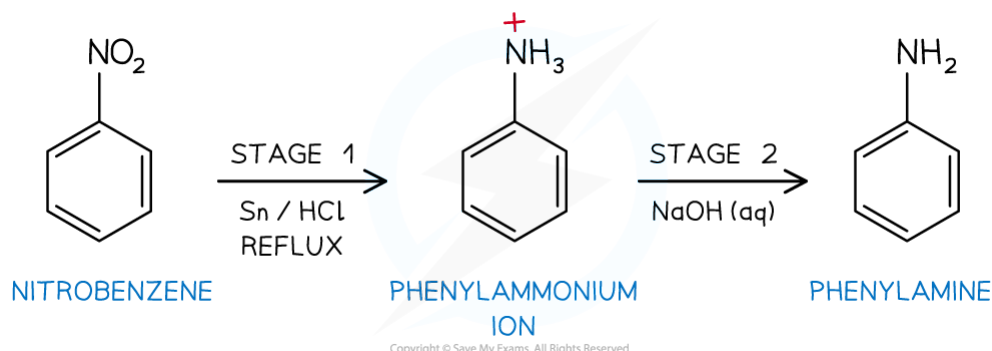
YOUR NOTES





## Reduction of nitrobenzene

- Nitrobenzene,  $C_6H_5NO_2$ , can be reduced to phenylamine,  $C_6H_5NH_2$ , according to the following two-stage reaction:



### *The two-stage reduction reaction of nitrobenzene to phenylamine*

#### Stage 1 – Reduction of nitrobenzene

- $C_6H_5NO_2(l) + 3Sn(s) + 7H^+(aq) \rightarrow C_6H_5NH_3^+(aq) + 3Sn^{2+}(aq) + 2H_2O(l)$
- Nitrobenzene,  $C_6H_5NO_2$ , is reacted with tin, Sn, and concentrated hydrochloric acid, HCl
- The reaction mixture is heated under reflux in a boiling water bath
- The phenylammonium ions,  $C_6H_5NH_3^+$ , are protonated due to the acidic conditions

#### Stage 2 – Formation of phenylamine

- $C_6H_5NH_3^+(aq) + OH^-(aq) \rightarrow C_6H_5NH_2(l) + H_2O(l)$
- The phenylammonium ions,  $C_6H_5NH_3^+$ , are deprotonated by the addition of sodium hydroxide solution, NaOH (aq)

YOUR NOTES



## 20.2 Synthetic Routes

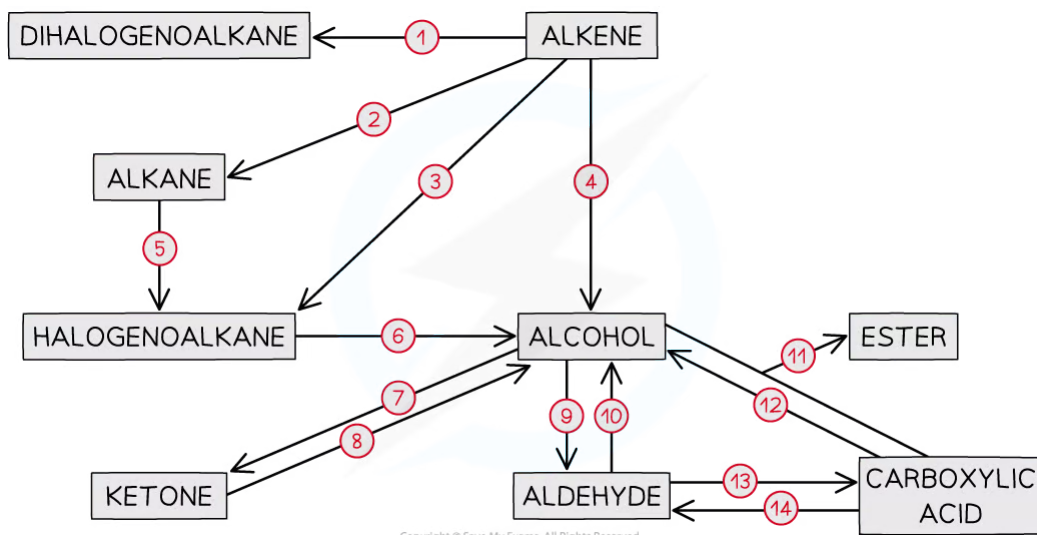
### 20.2.1 Synthesis

#### Organic Synthesis

- It is possible to make a large number of organic products from a few starting compounds and the necessary reagents and conditions
- Knowing how organic functional groups are related to each other is key to the synthesis of a given molecule
- The main functional groups you need to know are
  - Alkanes
  - Alkenes
  - Halogenoalkanes
  - Alcohols
  - Carbonyls (aldehydes & ketones)
  - Carboxylic acids and derivatives
  - Arenes

#### Aliphatic Reaction Pathways

- The key functional groups and their interconversions are summarised here:



The main reaction pathways in aliphatic chemistry

#### Aliphatic Chemistry Reactions Table

YOUR NOTES





Reaction	Reagent(s)	Conditions	Mechanism	Reaction type
1	Halogen	Room temperature	Electrophilic	Addition
2	Hydrogen	Ni catalyst 200°C / 1000 kPa	Electrophilic	Addition / Reduction
3	Hydrogen halide	Room temperature	Electrophilic	Addition
4	Steam + H <sub>2</sub> SO <sub>4</sub>	Heat	–	Hydration
5	Halogen	UV light	Free radical	Substitution
6	NaOH (aq)	Heat under reflux	Nucleophilic	Substitution
7	K <sub>2</sub> Cr <sub>2</sub> O <sub>7</sub> / H <sub>2</sub> SO <sub>4</sub>	Heat	–	Oxidation
8	NaBH <sub>4</sub> (aq)	Heat	–	Reduction
9	K <sub>2</sub> Cr <sub>2</sub> O <sub>7</sub> / H <sub>2</sub> SO <sub>4</sub>	Heat	–	Oxidation
10	NaBH <sub>4</sub> (aq)	Heat	–	Reduction
11	Alcohol + carboxylic acid, H <sub>2</sub> SO <sub>4</sub> catalyst	Heat	–	Esterification / condensation
12	LiAlH <sub>4</sub> in dry ether	Heat	–	Reduction
13	K <sub>2</sub> Cr <sub>2</sub> O <sub>7</sub> / H <sub>2</sub> SO <sub>4</sub>	Heat under reflux	–	Oxidation
14	LiAlH <sub>4</sub> in dry ether	Heat	–	Reduction

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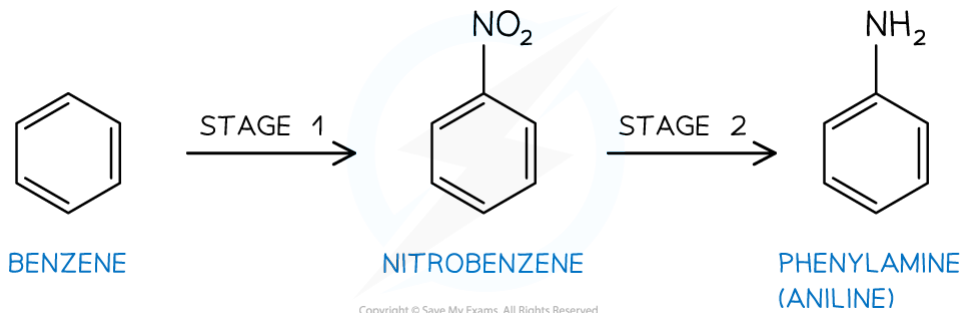


### Exam Tip

Remember, that due to the strength of the LiAlH<sub>4</sub> as a reducing agent, it is unlikely that reaction 14 can be stopped at the aldehyde. To form an aldehyde from a carboxylic acid, you reduce the carboxylic acid to a primary alcohol and then oxidise it to the aldehyde.

## Aromatic Reaction Pathways

- The key aromatic reaction for this course is:



**The nitration and reduction reactions to form phenylamine from benzene**

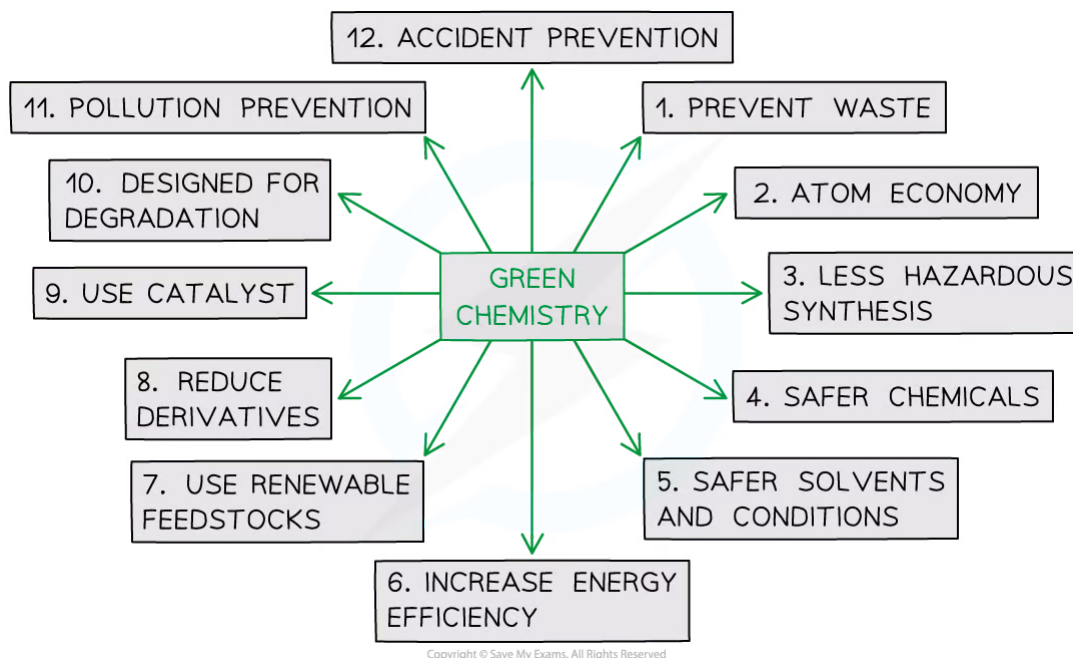
**Aromatic Nitration and Reduction Reactions Table**

Reaction	Reagent	Conditions	Mechanism	Reaction type
1	Conc. $\text{HNO}_3$ + $\text{H}_2\text{SO}_4$	$25-60^\circ\text{C}$	Electrophilic	Substitution
2	$\text{Sn}$ + Conc $\text{HCl}$ followed by $\text{NaOH}$ (aq)	Heat	–	Reduction

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**Choosing A Reaction Pathway**

- Chemists will often have several choices of reaching a target molecule and those choices need to take into the principles of green chemistry



**The twelve principles of green chemistry**

- By choosing a pathway that has fewer steps, you can prevent waste and reduce energy demands which is better for the environment
  - This also reduces production costs
- By analysing the atom economy of each step, you can select reactions that give a higher atom economy
- Choosing alternative safer solvents also follows the principles of green chemistry

YOUR NOTES



## Designing a Reaction Pathway

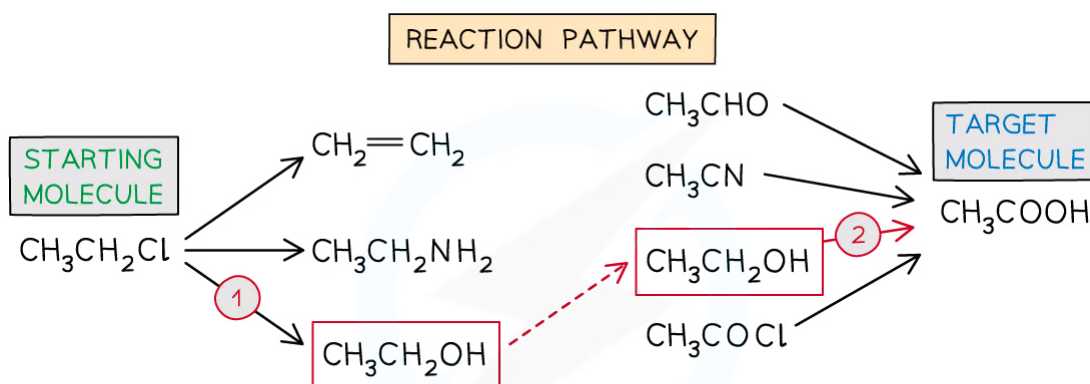
- The given molecule is usually called the **target molecule** and chemists try to design a synthesis as efficiently as possible
- Designing a reaction pathway starts by drawing the structures of the target molecule and the **starting molecule**
- Work out all the compounds that can be made from the starting molecule and all the molecules that can be made into the target molecule
  - Match the groups they have in common and work out the reagents and conditions needed



### Worked Example

Suggest how the synthesis of ethanoic acid from chloroethane could be carried out

Answer



① REACT WITH  $\text{NaOH(aq)}$  + HEAT UNDER REFLUX

② OXIDISE WITH  $\text{K}_2\text{Cr}_2\text{O}_7 + \text{H}_2\text{SO}_4 + \text{HEAT UNDER REFLUX}$

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### Exam Tip

You could be required to design a synthesis with up to four steps.

## 20.3 Stereoisomerism

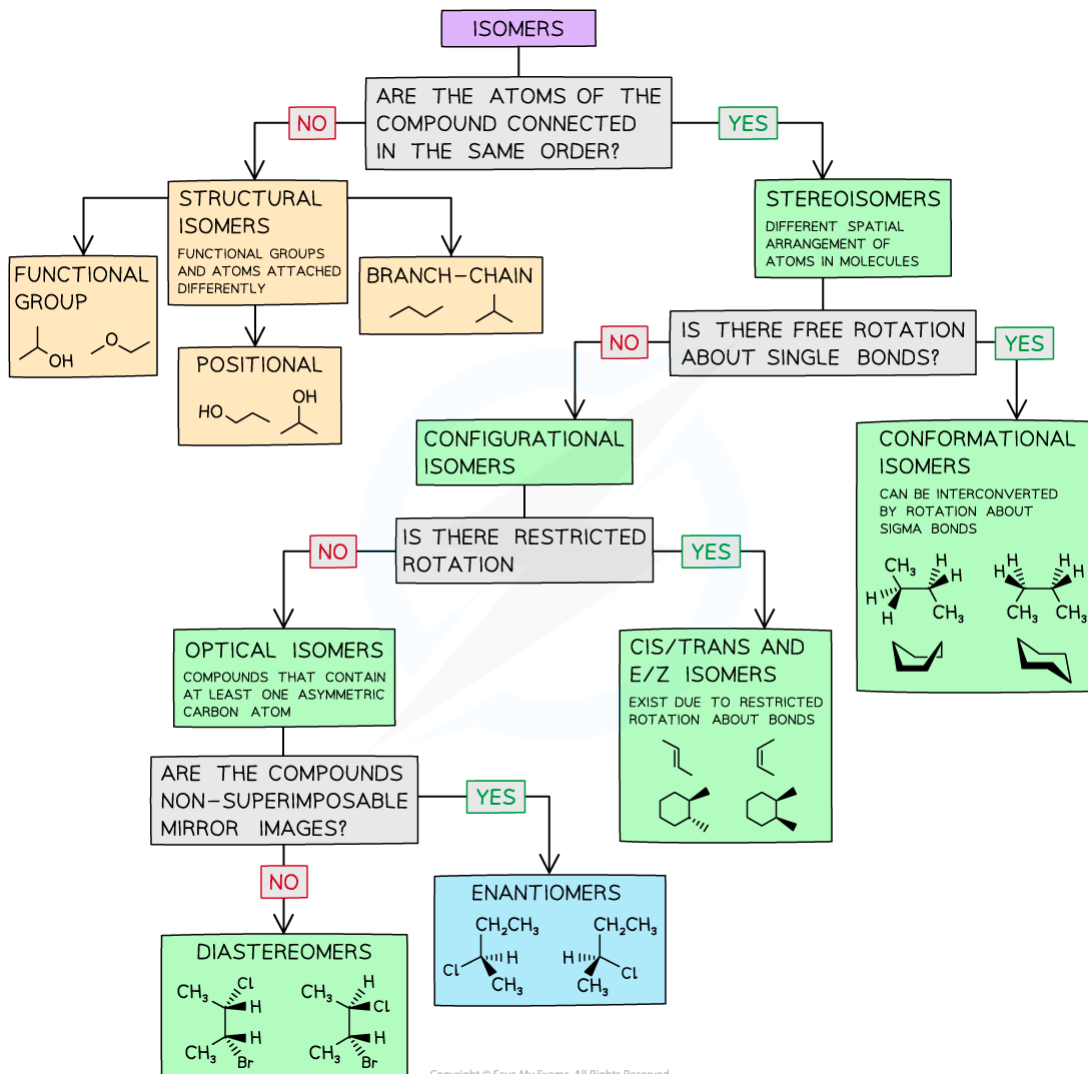
### 20.3.1 Stereoisomers

YOUR NOTES



### Conformational & Configurational Isomers

- Isomers are compounds that have the same molecular formula but a different arrangement of atoms
- Isomers can be grouped into various categories, as shown:



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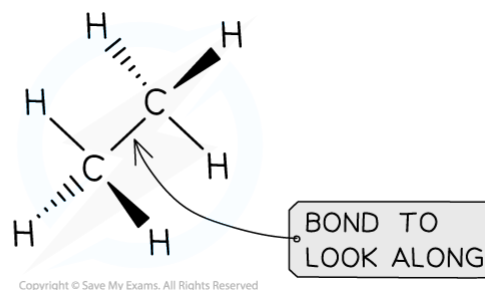
#### Flow chart of the various isomers with points to help identify them

- At Standard Level, we encountered three types of structural isomers:
  - Functional group isomers, e.g. propanal and propanone
  - Position isomers, e.g. propan-1-ol and propan-2-ol
  - Branch-chain isomers, e.g. butane and methylpropane

- If the atoms within an isomer are arranged in the same order then we are dealing with stereoisomers
  - Stereoisomers can be **conformational** or **configurational**

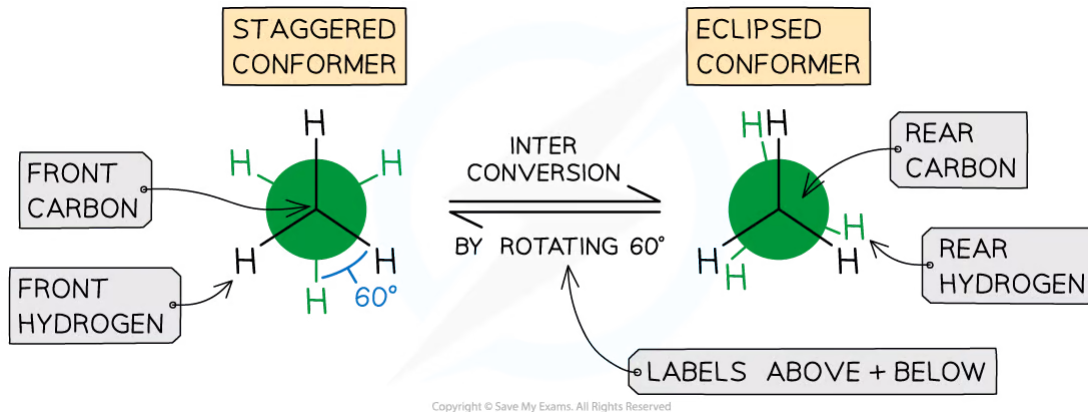
## Conformational Isomers

- Conformational isomers, or **conformers**, occur due to free rotation about a single  $\sigma$ -bond and can be described as:
  - **Staggered**
  - **Eclipsed**
- One of the simplest examples of conformational isomerism is ethane,  $\text{CH}_3\text{CH}_3$



### Three-dimensional structure of ethane identifying the bond for conformational isomerism

- By looking along the C-C bond highlighted in the diagram we can draw the two Newman projections, staggered and eclipsed



### The staggered and eclipsed conformers of ethane

- The staggered conformer has angles between hydrogen atoms on adjacent carbons of  $60^\circ$ , as shown
  - It is also more stable / lower energy than the eclipsed conformer because the C-H bonds are as far apart as possible to minimise the repulsion between the electrons in the C-H bonds
- The eclipsed conformer has angles between hydrogen atoms on adjacent carbons of  $0^\circ$ , this is not shown in the diagrams so that the conformation can be seen
  - The eclipsed conformer is less stable / higher energy due to the repulsion between the electrons in the C-H bonds that are closer together

YOUR NOTES



- The free rotation that causes these conformers means that it is easy to interconvert from one conformer to the other and back
  - This is also the reason that it is almost impossible to isolate a single conformer

### Conformational Isomerism in Cyclic Structures

- Conformational isomerism can also be seen in cyclic structures
- A common example of this is cyclohexane,  $C_6H_{12}$ 
  - Cyclohexane isomers exist in boat and chair forms:



#### **Skeletal structures showing the boat and chair forms of cyclohexane**

- The boat form is less stable / higher energy as there are four eclipsed bonds causing strain on the overall structure
  - There is also repulsion of the hydrogen atoms on the end of the boat structure
- It is possible to "flip" between the boat and chair forms which explains the difficulty in isolating just one of the forms
  - During the interconversions, it is also possible to get other structures commonly called the half chair and the twisted boat

### Configurational Isomers

- Interconversion of configurational isomers can only occur by breaking bonds or rearranging stereocentres
- Configurational isomers can be divided into:
  - *cis* / *trans* isomers and *E* / *Z* isomers
  - optical isomers

YOUR NOTES





## 20.3.2 Cis-Trans &amp; E/Z Isomers

YOUR NOTES



### Cis-Trans & E/Z Isomers

- **Configurational isomerism** can be seen in unsaturated compounds, cyclic structures or compounds that contain at least one asymmetric carbon (sometimes called a chiral centre)
  - These structures have the same molecular formula and order of atoms (the atoms are connected similarly to each other) but different shapes
- As previously discussed, these can be grouped into further types of isomers:
  - Cis / trans
  - E / Z
  - Optical



#### Exam Tip

You may still see the term geometric isomers being used when talking about some configurational isomers. This was recommended by IUPAC but it is now obsolete and being replaced with cis-trans isomers and E/Z isomers.

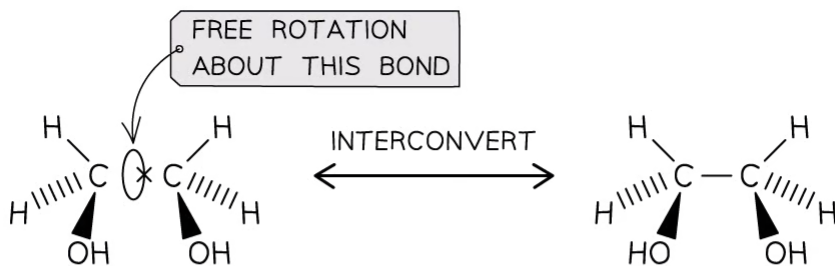
#### Cis / trans isomers

- In saturated compounds, the atoms / functional groups attached to the single,  $\sigma$ -bonded carbons are not fixed in their position due to the free rotation about the C-C  $\sigma$ -bond
  - This causes **conformational isomers**, as previously discussed
- In unsaturated compounds, the groups attached to the C=C carbons remain fixed in their position
  - This is because free rotation of the bonds about the C=C bond is not possible due to the presence of a  **$\pi$  bond**
- Cis / trans nomenclature can be used to distinguish between the isomers
  - Cis isomers have two functional groups on the same side of the double bond / carbon ring, i.e. both above the C=C bond or both below the C=C bond
  - Trans isomers have two functional groups on opposite sides of the double bond / carbon ring, i.e. one above and one below the C=C bond



1, 2 - ETHANEDIOL

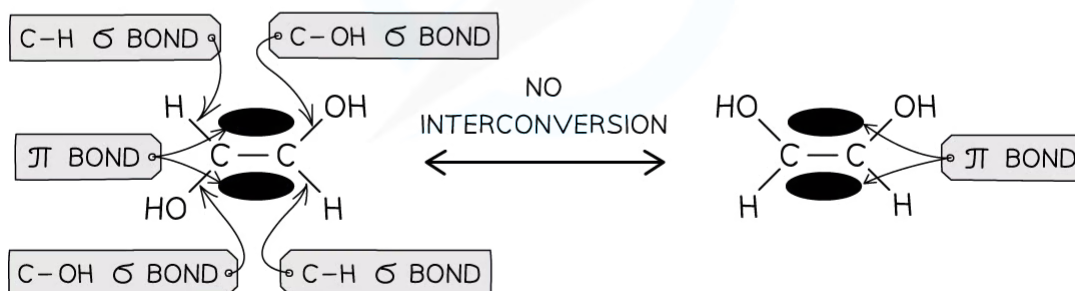
1, 2 - ETHANEDIOL



ROTATION ABOUT C-C BOND IS POSSIBLE SO THE TWO MOLECULES CAN CHANGE FROM ONE CONFORMATION INTO THE OTHER: THE 2 MOLECULES ARE IDENTICAL

TRANS-1, 2-ETHENEDIOL

CIS-1, 2-ETHENEDIOL



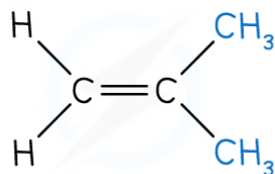
NO ROTATION AROUND C=C POSSIBLE SO THE 2 MOLECULES CAN'T CHANGE FROM ONE CONFORMATION INTO THE OTHER: EACH ISOMER HAS DIFFERENT CHEMICAL AND PHYSICAL PROPERTIES

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**The presence of a  $\pi$  bond in unsaturated compounds restricts rotation about the C=C bond forcing the groups to remain fixed in their position and giving rise to the formation of certain configurational isomers**

### Naming cis / trans isomers

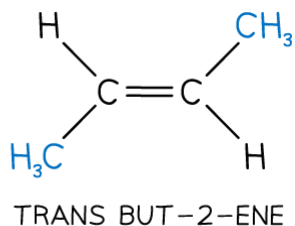
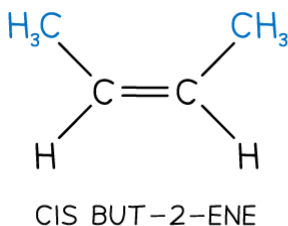
- For cis / trans isomers to exist, we need two different atoms or groups of atoms on either side of the C=C bond
  - This means that 2-methylpropene cannot have cis / trans isomers as the methyl groups are both on the same side of the C=C bond:



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**2-methylpropene molecules do not have cis / trans isomers**

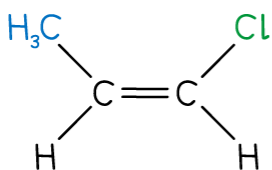
- However, moving one of the methyl groups to the other side of the C=C bond causes cis / trans isomerism:



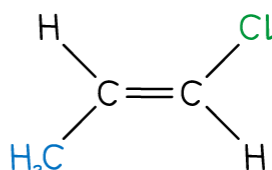
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**But-2-ene does have cis / trans isomers**

- The atoms or groups of atoms on either side of the C=C bond do not have to be the same for cis / trans isomers:



CIS 1-CHLOROPROP-1-ENE



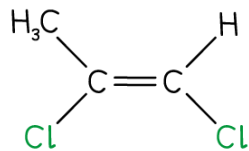
TRANS 1-CHLOROPROP-1-ENE

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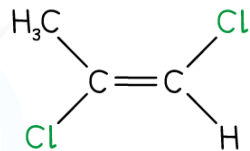
**1-chloroprop-1-ene also shows cis / trans isomerism**

- However, the cis / trans naming system starts to fail once we have more than one atom or group of atoms on either side of the C=C bond
  - The cis / trans naming system can still be used with three atoms / groups of atoms but only if:

- Two of the three atoms or groups of atoms are the same
- These two atoms or groups of atoms are on opposite sides of the double bond



CIS 1,2-DICHLOROPROPENE HAS BOTH Cl ATOMS ON THE SAME SIDE



TRANS 1,2-DICHLOROPROPENE HAS BOTH Cl ATOMS ON THE OPPOSITE SIDES

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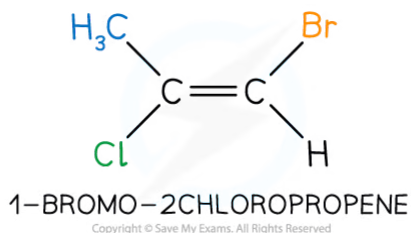
**1,2-dichloropropene can be named using cis / trans**

- The cis / trans naming system cannot be used with three atoms / groups of atoms when they are all different

YOUR NOTES



- This requires the use of the *E* / *Z* naming system



**1-bromo-2-chloropropene cannot be named using *cis* / *trans***

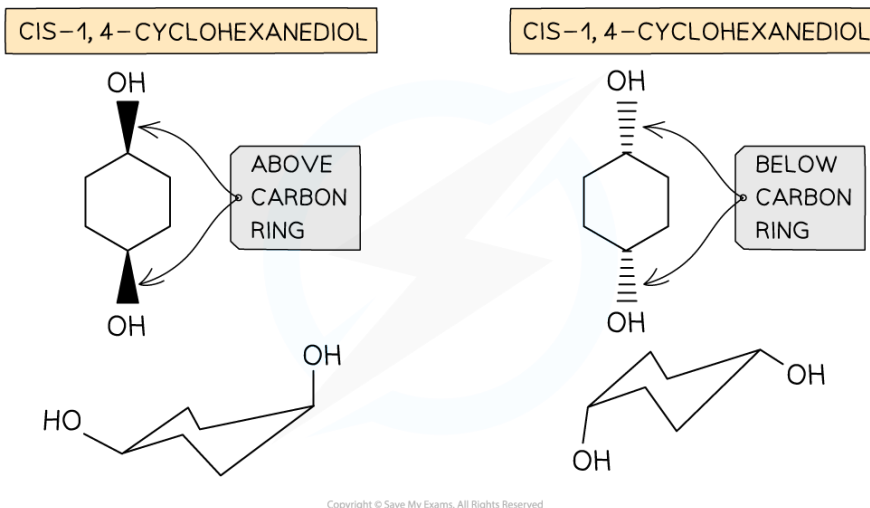


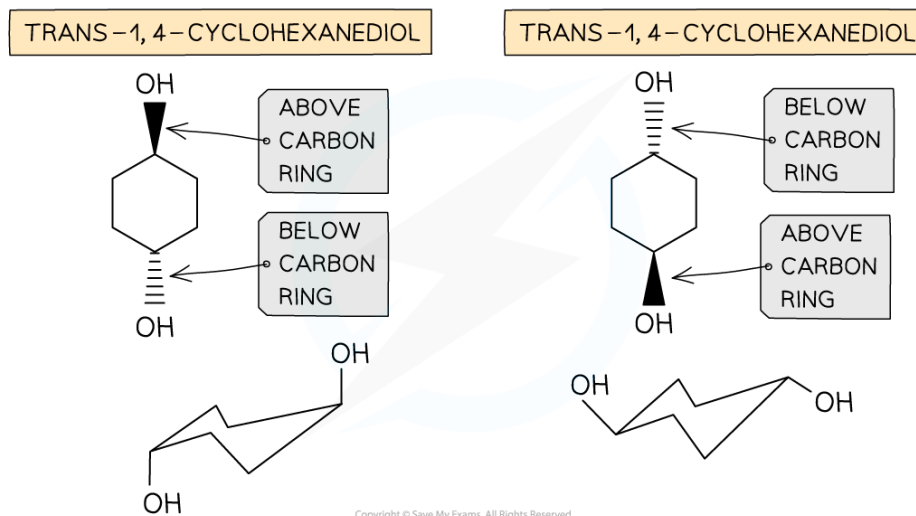
### Exam Tip

Although not part of this topic, the relationship between *cis* / *trans* isomers, their packing and melting points is applicable to the Option B: Biochemistry topic. *Cis* / *trans* isomerism affects the intermolecular forces by introducing a dipole moment between molecules, not just London dispersion forces. This will affect the packing of the molecules as well as physical properties such as melting and boiling point.

## Cyclic *cis* / *trans* isomers

- *Cis* / *trans* isomerism can also occur in cyclic structures
  - Even though cyclic alkanes contain single carbon-carbon bonds, the rigid structure of the ring system does not allow for free rotation
    - Therefore, *cis* isomers can occur when the atoms (or groups of atoms) are on the same side of the ring, i.e. both above or both below
    - While *trans* isomers can occur when the atoms (or groups of atoms) are on the opposite side of the ring, i.e. one above and one below

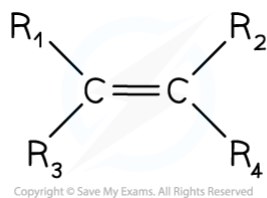




### *Cis / trans isomerism in cyclic compounds*

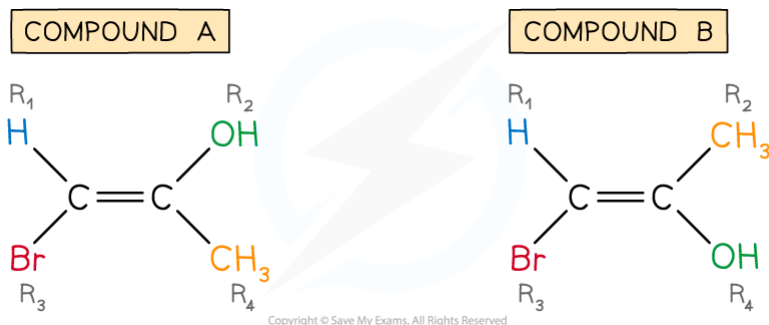
### *E / Z isomers*

- To discuss *E / Z* isomers, we will use an alkene of the general formula  $C_2R_4$ :



### *The general alkene, $C_2R_4$*

- When the groups  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  are all different (i.e.  $R_1 \neq R_2 \neq R_3 \neq R_4$ ), we have to use the *E / Z* naming system
  - This is based on Cahn-Ingold-Prelog (CIP) priority rules
- To do this, we look at the **atomic number** of the first atom attached to the carbon in question
  - The higher the atomic number; the higher the priority
- For example, 2-bromo-1-propen-1-ol has four different atoms or groups of atoms attached to the  $C=C$  bond
  - This means that it can have two different displayed formulae:



### 2-Bromo-1-propen-1-ol (compounds A and B)

#### Compound A

- **Step 1: Apply the CIP priority rules**
  - Look at  $R_1$  and  $R_3$ :
    - Bromine has a higher atomic number than hydrogen so bromine has priority
  - Look at  $R_2$  and  $R_4$ :
    - Oxygen has a higher atomic number than carbon so oxygen has priority
- **Step 2: Deduce E or Z**
  - E isomers have the highest priority groups on opposite sides of the  $C=C$  bond, i.e. one above and one below
    - The E comes from the German word "entgegen" meaning opposite
  - Z isomers have the highest priority groups on the same side of the  $C=C$  bond, i.e. both above or both below
    - The Z comes from the German word "zusammen" meaning together
  - In compound A, the two highest priority groups are on opposite sides (above and below) the  $C=C$  bond
    - Therefore, compound A is E-2-bromo-1-propen-1-ol

#### Compound B

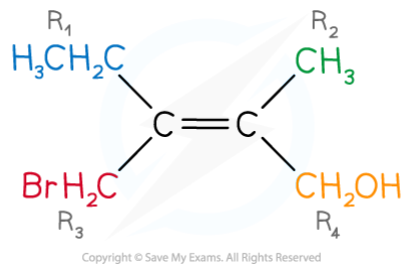
- **Step 1: Apply the CIP priority rules**
  - Look at  $R_1$  and  $R_3$ :
    - Bromine has a higher atomic number than hydrogen so bromine has priority
  - Look at  $R_2$  and  $R_4$ :
    - Oxygen has a higher atomic number than carbon so oxygen has priority
- **Step 2: Deduce E or Z**
  - In compound B, the two highest priority groups are on the same side (both below) the  $C=C$  bond
    - Therefore, compound B is Z-2-bromo-1-propen-1-ol

#### More complicated E/Z isomers

- Compound X exhibits E/Z isomerism:

YOUR NOTES





**Compound X**

YOUR NOTES



• **Step 1: Apply the CIP priority rules**

- Look at  $R_1$  and  $R_3$ :
  - Carbon is the first atom attached to the  $C=C$  bond, on the left hand side
- Look at  $R_2$  and  $R_4$ :
  - Carbon is the first atom attached to the  $C=C$  bond, on the right hand side
- This means that we cannot deduce if compound X is an *E* or *Z* isomer by applying the CIP priority rules to the first atom attached to the  $C=C$  bond
  - Therefore, we now have to look at the second atoms attached
- Look again at  $R_1$  and  $R_3$ :
  - The second atoms attached to  $R_1$  are hydrogens and another carbon
  - The second atoms attached to  $R_3$  are hydrogens and bromine
  - We can ignore the hydrogens as both R groups have hydrogens
  - Bromine has a higher atomic number than carbon, so bromine is the higher priority
    - Therefore, the  $CH_2Br$  group has priority over the  $CH_3CH_2$  group
- Look again at  $R_2$  and  $R_4$ :
  - The second atoms attached to  $R_2$  are hydrogens
  - The second atoms attached to  $R_4$  are hydrogens and an oxygen
  - Oxygen has a higher atomic number than hydrogen, so oxygen is the higher priority
    - Therefore, the  $CH_2OH$  group has priority over the  $CH_3$  group

• **Step 2: Deduce *E* or *Z***

- In compound X, the two highest priority groups are on the same side (both below) the  $C=C$  bond
  - Therefore, compound X is the *Z* isomer

20.3.3 Optical Isomers

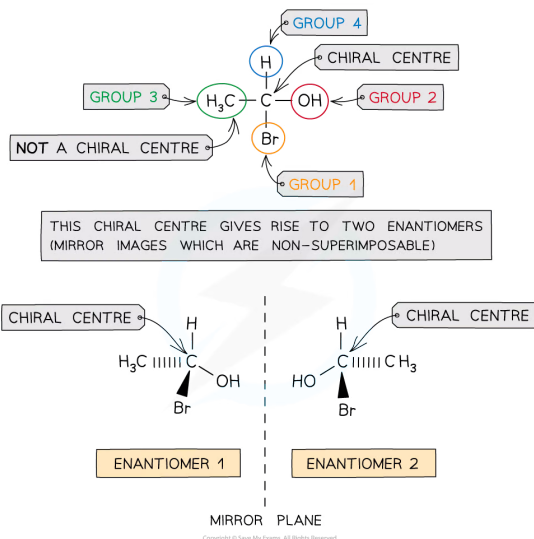
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## Optical Isomers

### Optical isomers

- A carbon atom that has four different atoms or groups of atoms attached to it is called a **chiral carbon** or **chiral centre**
  - Chira comes from a Greek word meaning hand, so we talk about these molecules having a handedness
- The carbon atom is described as being **asymmetric**, i.e. there is no plane of symmetry in the molecule
- Compounds with one chiral centre (**chiral molecules**) exist as two optical isomers, also known as **enantiomers**
- Just like the left hand cannot be superimposed on the right hand, enantiomers are **non-superimposable**
  - Enantiomers are **mirror images** of each other

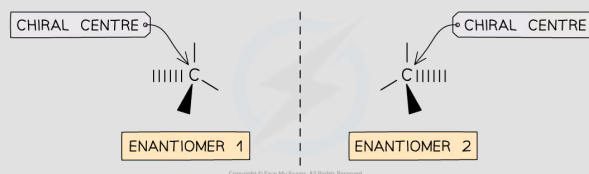


**A molecule has a chiral centre when the carbon atom is bonded to four different atoms or group of atoms; this gives rises to enantiomers**



#### Exam Tip

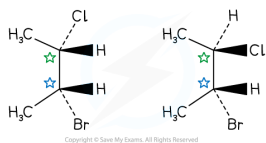
When drawing optical isomers, always draw mirror images including wedge and dashed bonds





## Diastereomers

- Diastereomers are compounds that contain more than one chiral centre
  - Diastereomers are not mirror images of each other because each chiral carbon has two isomers
  - This also means that they have different physical and chemical properties



***2-bromo-3-chlorobutane exists as a diastereomer due to 2 chiral centres***

YOUR NOTES



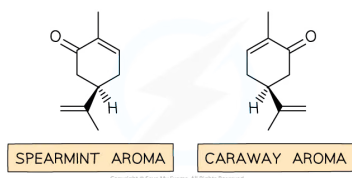
## Polarimetry

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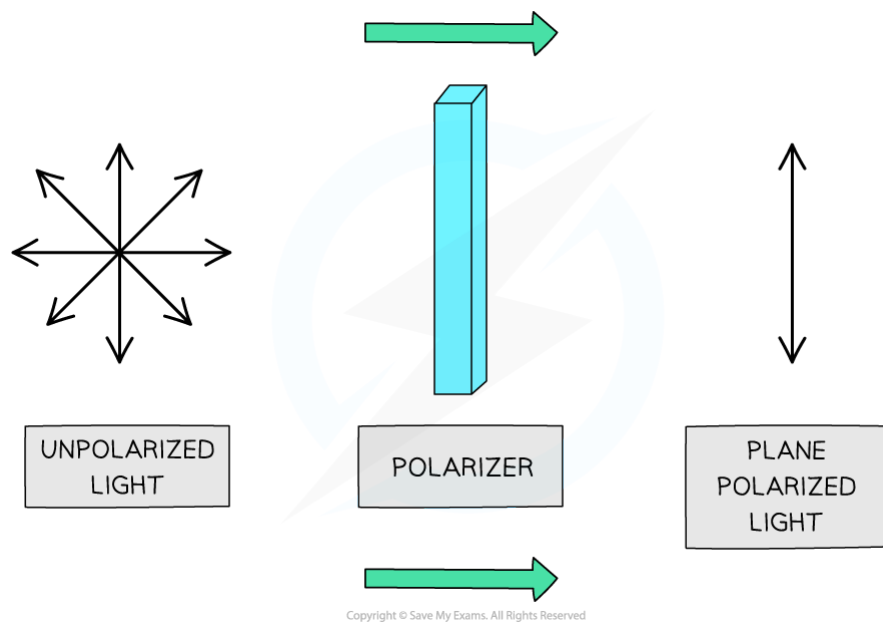
### Properties of optical isomers

- The chemical properties of optical isomers are generally identical, with one exception
  - Optical isomers interact with biological sensors in different ways
    - For example, one enantiomer of carvone smells of spearmint, while the other smells of caraway



### *Carvone optical isomers have distinctive smells*

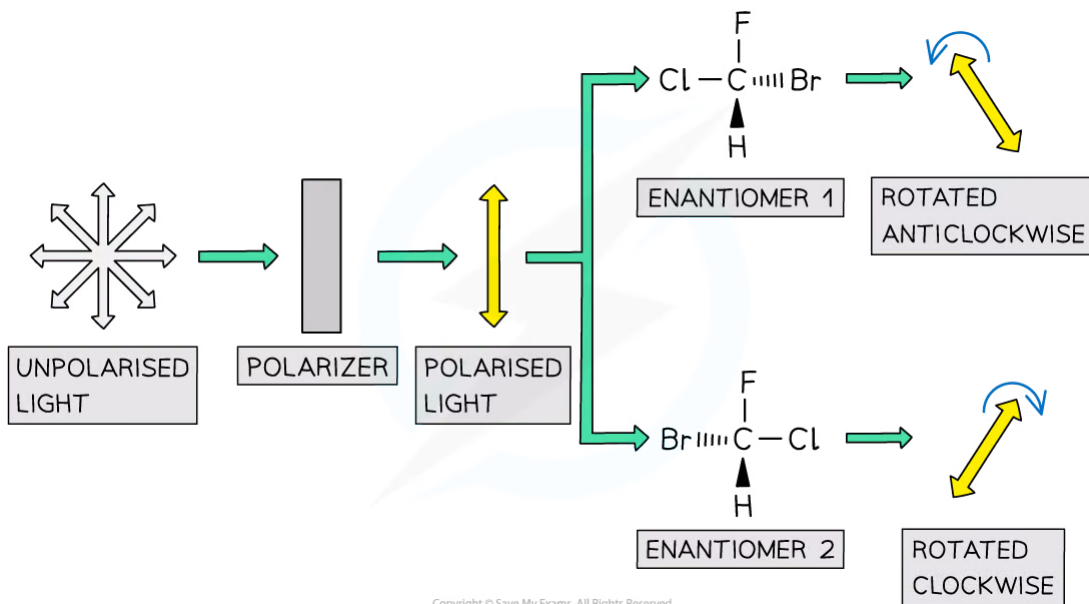
- Optical isomers have identical physical properties, with one exception
  - Isomers differ in their ability to rotate the plane of polarised light



**When unpolarised light is passed through a polariser, the light becomes polarised as the waves will vibrate in one plane only**

- The major difference between the two enantiomers is:
  - One enantiomer rotates plane polarised light in a **clockwise** manner and the other in an **anticlockwise** fashion
  - A common way to differentiate the isomers is to use (+) and (-), but there are other systems using d and l, D and L, or R and S
- The rotation of plane polarised light can be used to determine the identity of an optical isomer of a single substance

- For example, pass plane polarised light through a sample containing one of the two optical isomers of a single substance
- Depending on which isomer the sample contains, the plane of polarised light will be rotated either clockwise or anti-clockwise by a fixed number of degrees



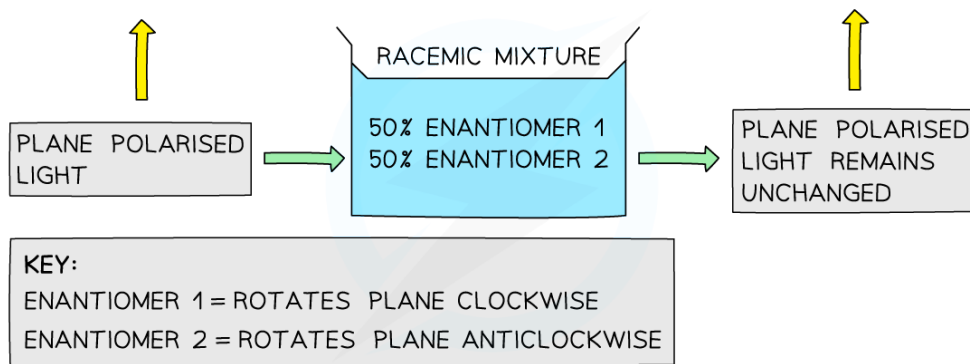
**Each enantiomer rotates the plane of polarised light in a different direction**

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## Racemic Mixtures

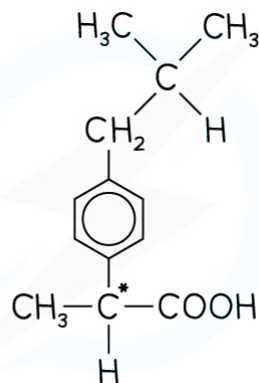
- A **racemic mixture** (or **racemate**) is a mixture containing **equal amounts** of each enantiomer
  - One enantiomer rotates light clockwise, the other rotates light anticlockwise
- A racemic mixture is **optically inactive** as the enantiomers will cancel out each others effect
  - This means that the plane of polarised light will **not change**



**Racemic mixtures are optically inactive**

### Racemic mixtures and drugs

- In the pharmaceutical industry, it is much easier to produce synthetic drugs that are racemic mixtures than producing one enantiomer of the drug
- Around 56% of all drugs in use are chiral and of those 88% are sold as racemic mixtures
- Separating the enantiomers gives a compound that is described as **enantiopure**, it contains only one enantiomer
- This separation process is very expensive and time consuming, so for many drugs it is not worthwhile, even though only half the of the drug is pharmacologically active
- For example, the pain reliever ibuprofen is sold as a racemic mixture



**The structure of ibuprofen showing the chiral carbon that is responsible for the racemic mixture produced in the synthesis of the drug**

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