20.1 Types of organic reactions

- Nucleophiles are electron rich and attack areas of electron deficiency. They act as Lewis bases and donate a pair of electrons in forming a new covalent bond. Typical examples include OH^-, H_2O, NH_3, and CN^-.
- Electrophiles are electron deficient and accept electron pairs from a nucleophile. They act as Lewis acids. Typical examples include H^+, Br^+, and NO_2^+.

Halogenoalkanes

- General formula is $C_nH_{2n+1}X$ (where X = halogen)
- Halogenoalkanes contain an atom of fluorine, chlorine, bromine, or iodine bonded to the carbon skeleton of the molecule.

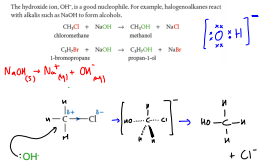
Nucleophilic substitution reactions: halogenoalkanes

The shorthand notation S_N – substitution nucleophilic – is used for this type of reaction.

The hydroxide ion, OH^-, is a good nucleophile. For example, halogenoalkanes react with alkalis such as NaOH to form alcohols.

$$CH_3Cl + NaOH \rightarrow CH_3OH + NaCl$$
chloromethane — methanol

$$C_3H_7Br + NaOH \rightarrow C_3H_7OH + NaBr$$
1-bromopropane — propan-1-ol



Primary halogenoalkanes: S_N2 mechanism

Primary halogenoalkanes have at least two hydrogen atoms attached to the carbon of the carbon–halogen bond. For example chloroethane:

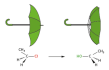
The overall reaction that occurs with NaOH is:

$$C_2H_5Cl + OH^- \rightarrow C_2H_5OH + Cl^-$$

Mechanism:

This is known as a bimolecular reaction as there are 2 molecules involved in the slow step.

We therefore describe the mechanism as a S_N2 mechanism.

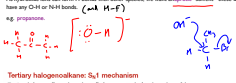


We see an inversion in this process around the central carbon which is important as it leads to stereospecific products.

We can encourage this mechanism by choosing particular solvents. In this case we want a solvent that will not interact too much with the hydroxide ions that are involved in the reaction.

As hydroxide ions can form H-bonds with other species, we want an aprotic solvent - these do not have any O-H or N-H bonds. (and H–F)

e.g. propanone.



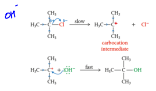
Tertiary halogenoalkanes: S_N1 mechanism

Tertiary halogenoalkanes have three alkyl groups attached to the carbon of the carbon–halogen bond. 2-chloro-2-methylpropane is an example:

The overall reaction that occurs with NaOH is:

$$(CH_3)_3CCl + OH^- \rightarrow (CH_3)_3COH + Cl^-$$
2-chloro-2-methylpropane — 2-methyl-propan-2-ol

The OH- ion cannot attack the partially positive carbon due to steric hinderance .

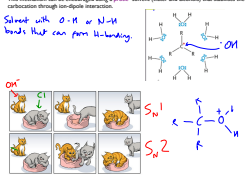


The carbocation is stabilised by the positive inductive effect from the surrounding carbons.

As the slow step only contains 1 mlecule we describe this as a unimolecular reaction, or a S_N1 reaction.

As the intermediate has a triangular planar shape , the OH- can attack from either side giving a mixture of products.

This mechanism can be encouraged using a protic solvent (water and alcohols) that stabilises the carbocation through ion-dipole interaction.



Secondary halogenoalkanes

It is not possible to be precise about the mechanism of nucleophilic substitution in secondary halogenoalkanes, as data show that they usually undergo a mixture of both S_N1 and S_N2 mechanisms.

Comparison of the rates of nucleophilic substitution reactions

1 The effect of the mechanism

Experimental data shows:

tertiary > secondary > primary

S_N1 — S_N1 and S_N2 — S_N2

Fastest — Slowest

2 The influence of the leaving group (halogen)

There are two opposing factors to consider here.

(a) The polarity of the carbon–halogen bond

Expected rate:

fluoroalkane > chloroalkane > bromoalkane > iodoalkane

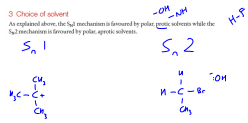
(b) The strength of the carbon–halogen bond — Most important factor

Expected rate:

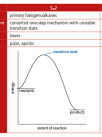
C—I > C—Br > C—Cl > C—F

3 Choice of solvent

As explained above, the S_N1 mechanism is favoured by polar, protic solvents while the S_N2 mechanism is favoured by polar, aprotic solvents.



Summary

	S_N2	S_N1
Favoured by	primary halogenoalkanes	tertiary halogenoalkanes
Nature of mechanism	concerted one-step mechanism with unstable transition state	two-step reaction via carbocation intermediate
Relative rate	lower	higher
Favoured solvent	polar, aprotic	polar, protic
Reaction profile		

The rate of reaction can be monitored by adding silver nitrate to the reaction mixture.

When the halogen (Cl, Br or I) is released, it reacts with the silver ions to form insoluble AgX.

AgCl - White

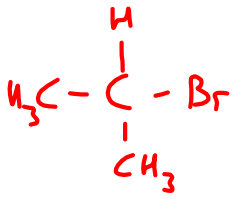
AgBr - Cream

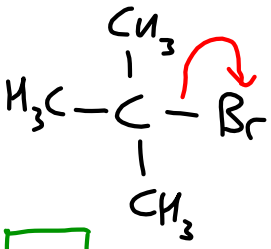
AgI - Yellow

S_n1 S = substitution, n = nucleophilic

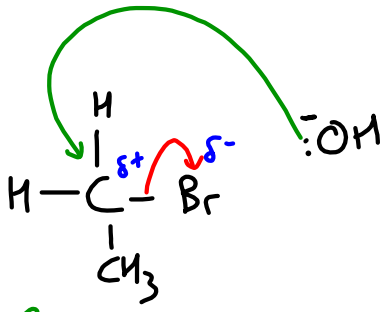
1 molecule in the RDS (slow step)

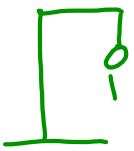
S_n2 ← 2 involved in the RDS (slow step)

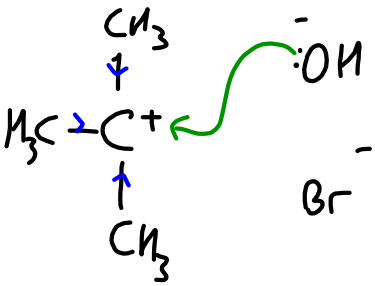


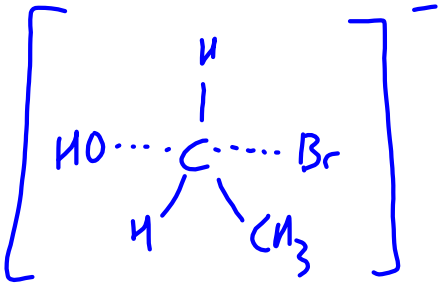


positive inductive effect



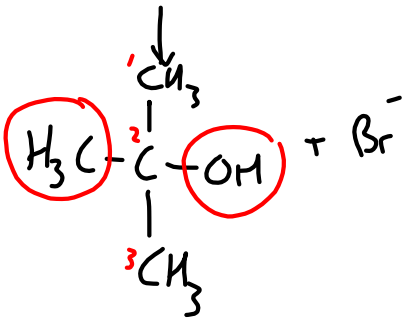


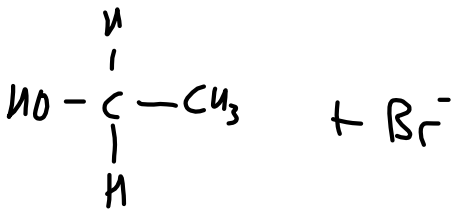




Carbocation

Transition state

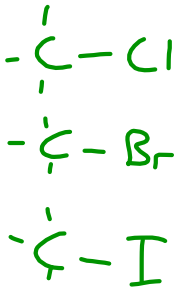




2-methylpropan-2-ol

ethanol

ethanol



Exercises

17 **(a)** Give the structural formulas of three isomers of C_4H_9Br which can be classified as primary, secondary, or tertiary.

(b) Identify which of these isomers will react with aqueous sodium hydroxide almost exclusively by an S_N1 mechanism. Explain the symbols in the term S_N1.

(c) Using the formula RBr to represent a bromoalkane, write an equation for the rate-determining step of the reaction.

18 Which compound reacts most readily by a S_N1 mechanism?

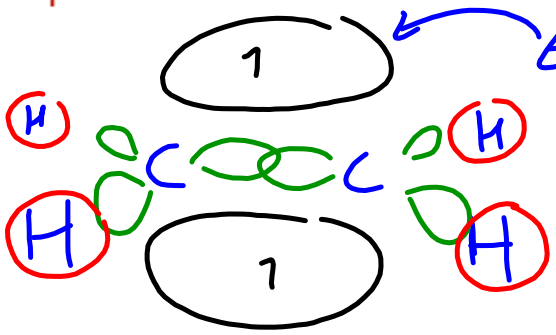
A $(CH_3)_3CCl$ **B** $CH_3CH_2CH_2CH_2Cl$
C $(CH_3)_3CI$ **D** $CH_3CH_2CH_2CH_2I$

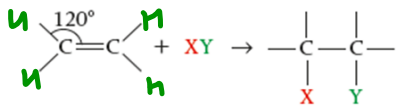
19 Suggest explanations for the following:

(a) Iodo- and bromo- compounds are more useful than chloro-compounds as intermediates in synthesis pathways.

(b) Two compounds X and Y have the same molecular formula, C_4H_9Cl. When each compound is reacted with dilute alkali and $AgNO_3(aq)$ is added, a white precipitate that darkens on exposure to air forms rapidly with X, but only slowly with Y.

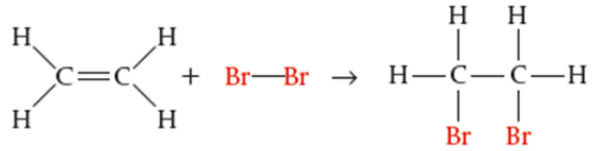
Electrophilic addition reactions: alkenes





Ethene + bromine

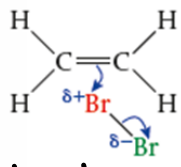
When ethene gas is bubbled through bromine at room temperature, the brown colour of the bromine fades as it reacts to form the saturated product 1,2-dibromoethane.



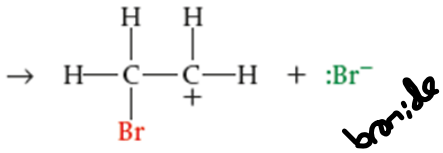
ethene | bromine (brown/orange) | 1,2-dibromoethane (colourless)

The mechanism of the reaction is as follows:

- Bromine is a non-polar molecule, but as it approaches the electron rich region of the alkene, it becomes polarized by electron repulsion.

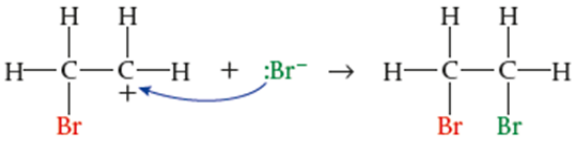


a bromine molecule is polarized by an alkene



heterolytic fission (different number e⁻ to each atom)

- This unstable species then reacts rapidly with the negative bromide ion, Br^-, forming the product 1,2-dibromoethane.



1,2-dibromoethane

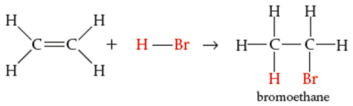
Overall the equation for the reaction is:

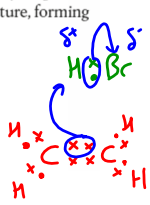
$$C_2H_4 + Br_2 \rightarrow CH_2BrCH_2Br$$

If this reaction is carried out with bromine water in place of pure bromine, predict how the product formed may be different and what colour change may be observed.

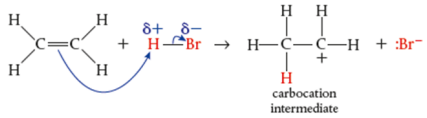
Ethene + hydrogen bromide

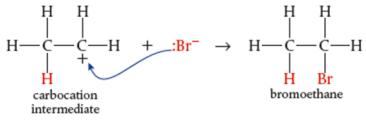
When ethene gas is bubbled through a concentrated aqueous solution of hydrogen bromide, HBr, an addition reaction occurs fairly readily at room temperature, forming bromoethane.





The mechanism is as follows:

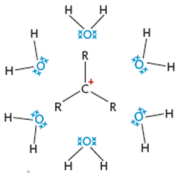




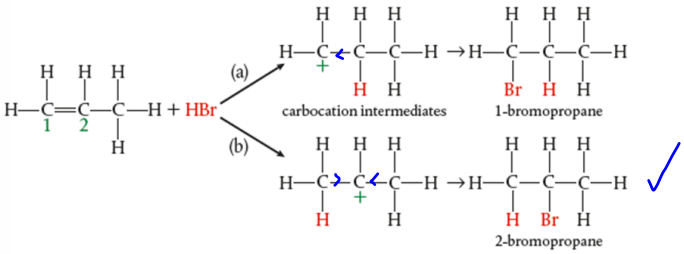
Which type of solvent would be used with this reaction?

Protic

Protic solvents are able to form hydrogen bonds as they contain an -OH or -NH group. THis means that they can stabilise the carbocation.



Propene + hydrogen bromide (unsymmetric addition)

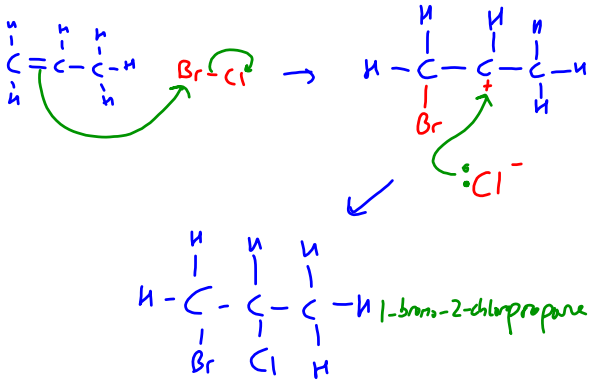


Markovnikov´s rule

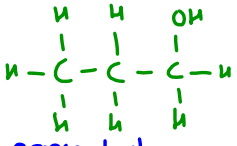
The hydrogen will bond with the carbon that has the greatest number of hydrogens already.

Worked example

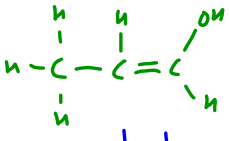
Write names and structures for the two possible products of the addition of the interhalogen compound BrCl to propene. Consider which is likely to be the major product and explain why.



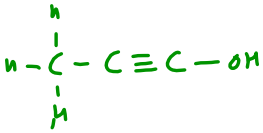
Spanish formulation



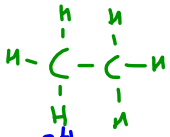
propan-1-ol
propan-1-ol



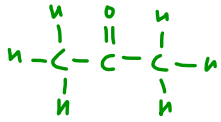
propen-1-ol
propen-1-ol



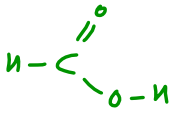
propyn-1-ol
propin-1-ol



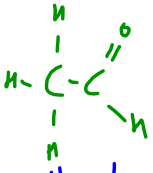
ethane
etano



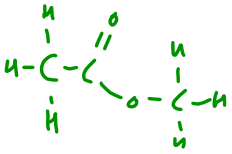
propanone
propanona



Methanoic acid
ácido metanoico

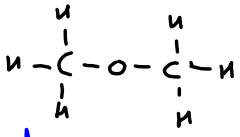


ethanal
etanal

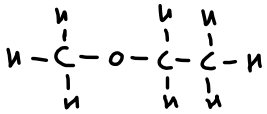


Methyl ethanoate
etanoato de metilo

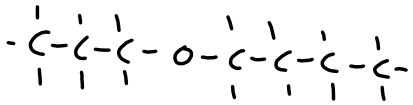
Ethers Éteres



dimetil éter

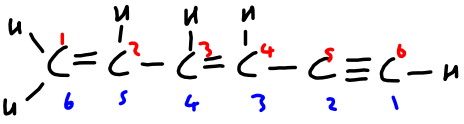


etil metil éter



butil propil éter

(Only Selectividad)



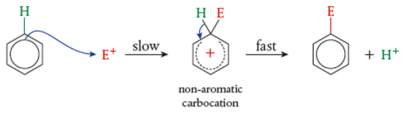
1,3-hexdien -5-yne

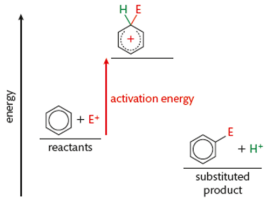
hex-1,3-dien-5-yne

hex-1,3-dien-5-...

Electrophilic substitution reactions: benzene

Using E^+ to represent an electrophile, we can show the reaction as follows.

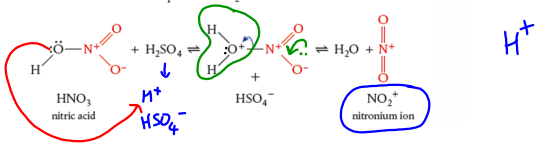




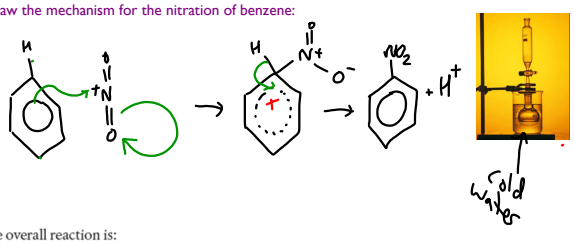
Nitration of benzene

The nitration of benzene is the substitution of —H by $—NO_2$ to form nitrobenzene, $C_6H_5NO_2$.

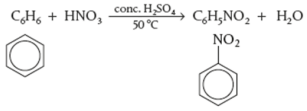
The electrophile for the reaction is NO_2^+, the nitronium ion. This is generated by using a nitrating mixture, a mixture of concentrated nitric and concentrated sulfuric acids at 50 °C. As the stronger of the two acids, sulfuric acid protonates the nitric acid, which then loses a molecule of water to produce NO_2^+.



Draw the mechanism for the nitration of benzene:

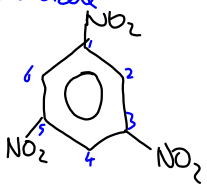


The overall reaction is:



Nitrobenzene

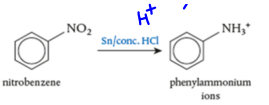
1,3,5-trinitrobenzene

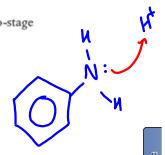


Reduction of nitrobenzene

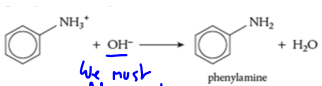
Nitrobenzene, $C_6H_5NO_2$, can be converted into phenylamine, $C_6H_5NH_2$, in a two-stage reduction process.

1.





2.



Where does the oxygen go?

We must add some base to remove the H^+ again.

NOS - Green chemistry

In many instances, organic synthesis reactions use or produce toxic/ environmentally unfriendly solvents and side-products. Such as the use of dichloromethane (a carcinogen).

In response to this the American Chemical Society developed the 12 principles of Green Chemisty that aim to develop synthetic processes to minimise negative impacts and improve sustainability.

- Use of catalysts to improve energy efficiency
- Prevent harmful waste products
- Improve atom economy

Reduction of carbonyl compounds

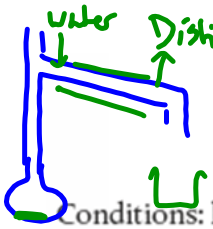
We have previously seen the oxidation of alcohols using...

[O]/H+

- primary alcohol → aldehyde → carboxylic acid
- secondary alcohol → ketone

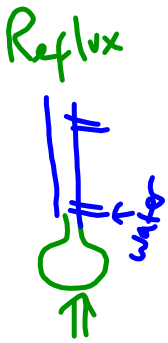
[O] → $KMnO_4$
[O] → $K_2Cr_2O_7$

We can reverse these reactions using lithium aluminium hydride ($LiAlH_4$) or sodium borohydride ($NaBH_4$). Both produce the hydride (H-) ion which acts as a nucleophile that attacks the electropositive carbon.



$CH_3COOH \xrightarrow{[+H]} CH_3CHO \xrightarrow{[+H]} CH_3CH_2OH$

ethanoic acid (carboxylic acid) → ethanal (aldehyde) → ethanol (primary alcohol)



Conditions: heat with $LiAlH_4$ in dry ether. The reaction cannot be stopped at the aldehyde as it reacts too readily with $LiAlH_4$.

$(CH_3)_2CO \xrightarrow{[+H]} (CH_3)_2CHOH$

propanone (ketone) → propan-2-ol (secondary alcohol)

Conditions: heat with $NaBH_4$(aq).

4

$LiAlH_4$ is much more reactive than the borohydride so the initial reaction must be carried ou in anhydrous condition such as...

diethyl ether $H_5C_2-O-C_2H_5$

(The final step of the reaction often involves a weak acid)

20.2 Synthetic routes

Understandings:

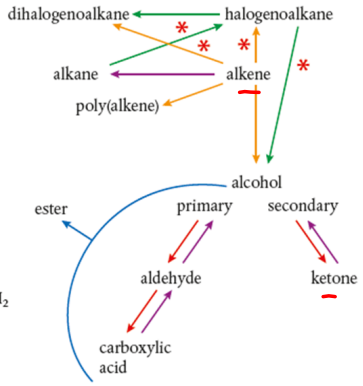
- The synthesis of an organic compound stems from a readily available starting material via a series of discrete steps. Functional group interconversions are the basis of such synthetic routes.
- Retro-synthesis of organic compounds.

Guidance
Conversions with more than four stages will not be assessed in synthetic routes.

Applications and skills:

- Deduction of multi-step synthetic routes given starting reagents and the product(s).

Guidance
Reaction types can cover any of the reactions covered in Topic 10 and Section 20.1.



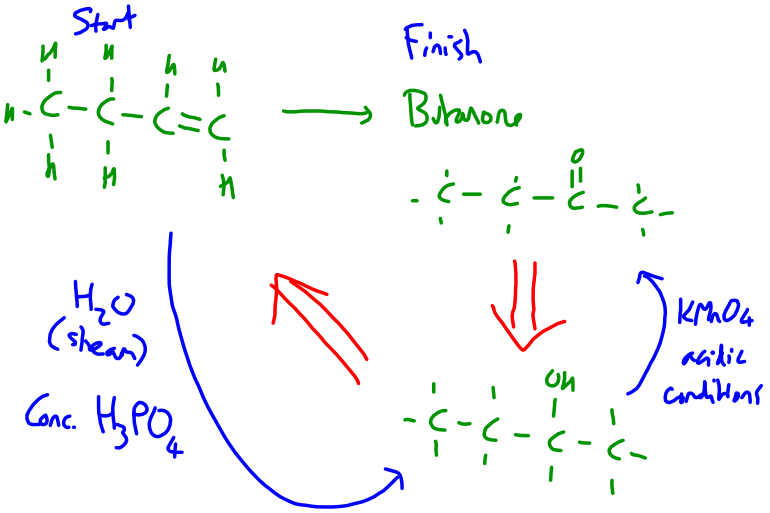
* = mechanism required
→ = oxidation
→ = reduction/addition of H_2
→ = substitution
→ = addition
→ = condensation

Retro-synthesis

Working backwards to work out how to synthesize a molecule.

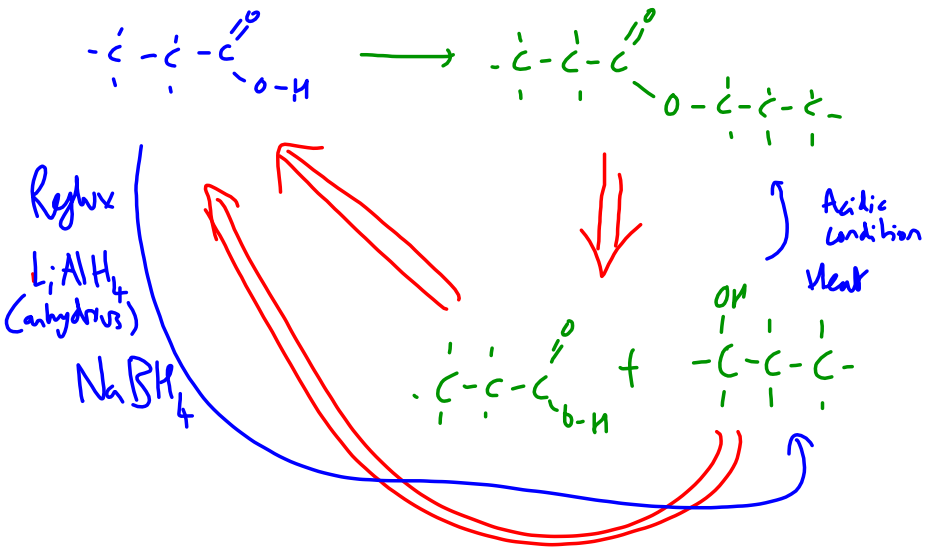
target molecule ⇒ precursor 1 ⇒ precursor 2 ⇒ starting material

the symbol '⇒' means 'can be made from'



Worked example

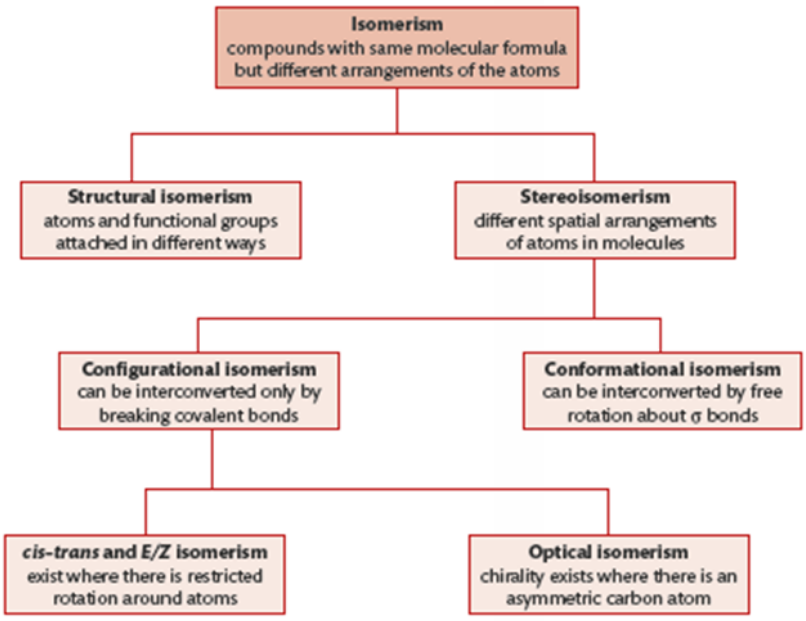
Explain how propyl propanoate can be synthesized from a single carboxylic acid. Give equations and conditions for all reactions, and state the type of reaction occurring at the functional group at each step.



20.3 Stereoisomerism

Understandings:

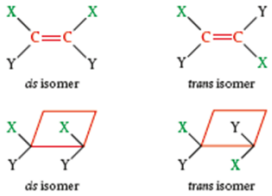
- Stereoisomers are sub-divided into two classes: conformational isomers, which interconvert by rotation about an σ bond, and configurational isomers, which interconvert only by breaking and reforming a bond.
- Configurational isomers are further sub-divided into *cis-trans* and *E/Z* isomers and optical isomers.
- *Cis-trans* isomers can occur in alkenes or cycloalkanes (or hetero-analogues) and differ in the positions of atoms (or groups) relative to a reference plane. According to IUPAC, *E/Z* isomers refer to alkenes of the form R1R2C=CR3R4 (R1 ≠ R2, R3 ≠ R4) where neither R1 nor R2 need be different from R3 or R4.
- A chiral carbon is a carbon joined to four different atoms or groups.
- An optically active compound can rotate the plane of polarized light as it passes through a solution of the compound. Optical isomers are enantiomers.
- Enantiomers are non-superimposeable mirror images of each other. Diastereomers are not mirror images of each other.

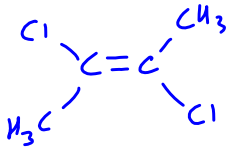


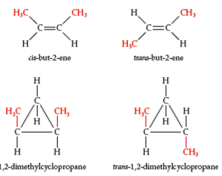
Cis-trans isomerism and E/Z isomerism

When a double bond or a cyclic structure is present in a molecule, the substituted groups become fixed in specific positions.

If there are only 2 substituted groups then we can see cis-trans isomerism:

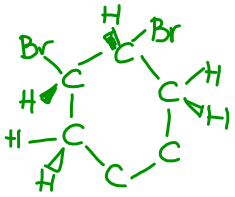


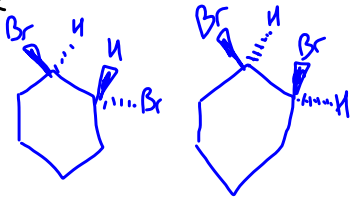




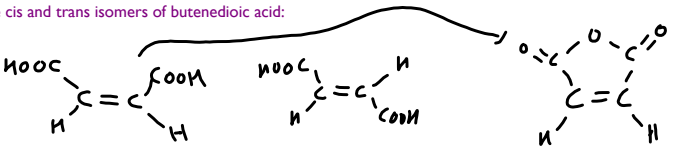
1,2-dichlorocyclobutane

Draw cis/trans isomers of 1,2-dibromocyclohexane

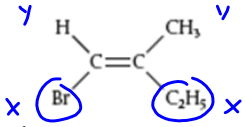




Draw the cis and trans isomers of butenedioic acid:



Is this the cis or trans isomer?



E/Z labelling requires an analysis of the groups attached to each carbon:

- Rule 1: Look at the atom bonded to the carbon of the double bond. The atom with the higher atomic number has the higher priority.
- Rule 2: If the atoms are the same, for example if they are both carbon atoms, apply the same rule to the next bonded atom. This means that longer hydrocarbon chains have higher priority.

$C_3H_7 > C_2H_5 > CH_3 > H$ and $Br > Cl > F$

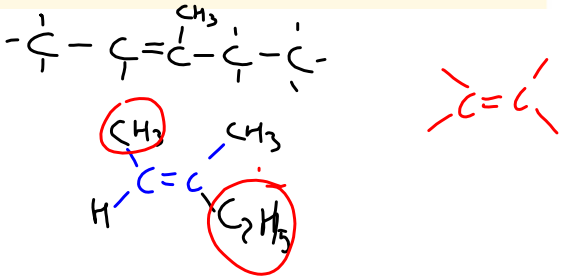
zusammen - "together"

entgegen - "opposite"

(Z)-1-bromo-2-methylbut-1-ene (E)-1-bromo-2-methylbut-1-ene

Worked example

Draw and name, using the E/Z convention, the two stereoisomers of 3-methylpent-2-ene.

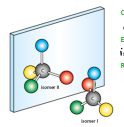


Optical isomerism / Stereoisomerism

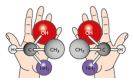
Chiral / asymmetric carbon - Any carbon with 4 different groups.

Enantiomers - Non-superimposable mirror images.

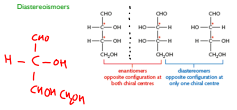
Racemic mixture - 50:50 mixture of 2 enantiomers.



If you look at your two hands you will see that they also are mirror images. When you put them on top of each other, the fingers and thumbs do not line up – we say they are non-superimposable.



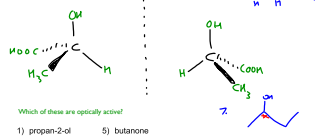
Diastereoismoers



How do we draw optical isomers?

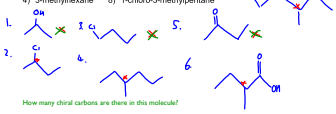
Worked example

Draw the enantiomers of 2-hydroxypropanoic acid (lactic acid). Mark the chiral carbon atom and show the plane of the mirror.

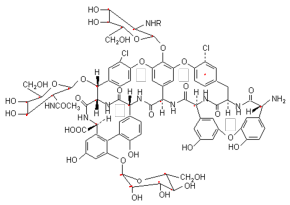


Which of these are optically active?

1) propan-2-ol
2) 2-chlorobutane
3) 1-chlorobutane
4) 3-methylhexane
5) butanone
6) 2-methylbutanoic acid
7) butan-2-ol
8) 1-chloro-3-methylpentane



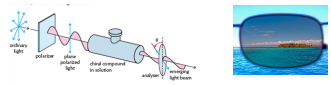
How many chiral carbons are there in this molecule?

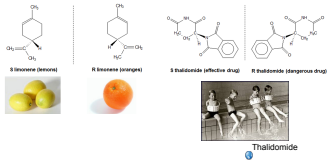


Properties of enantiomers

Diastereomers usually differ from each other in their physical and chemical properties. Enantiomers, on the other hand, have identical physical and chemical properties – with two important exceptions.

1. Optical activity





Thalidomide

2 Reactivity with other chiral molecules

When a racemic mixture is reacted with a single enantiomer we produce 2 different products that will have distinct physical and chemical properties. This means they can be separated using a process called resolution .

https://www.khanacademy.org/test-prep/mcat/chemical-processes/separations-purifications/a/resolution-of-enantiomers

Exercises

27 Which compound can exist as optical isomers?

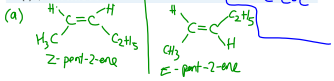
A $CH_3CHBrCH_3$
B $CH_3CH(OH)CH_2Cl$
C $CH_2CHBrCOOH$
D $CH_3CH_2CH_2OH$

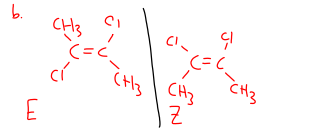
Carbon with 4 different substituents

28 Write the structure of the first alkene to show optical isomerism

29 Draw and name the isomers of the following using the E/Z convention

(a) pent-2-ene
(b) 2,3-dichlorobut-2-ene





Draw the optical isomers shown by 2-bromo-2-chlorobutane