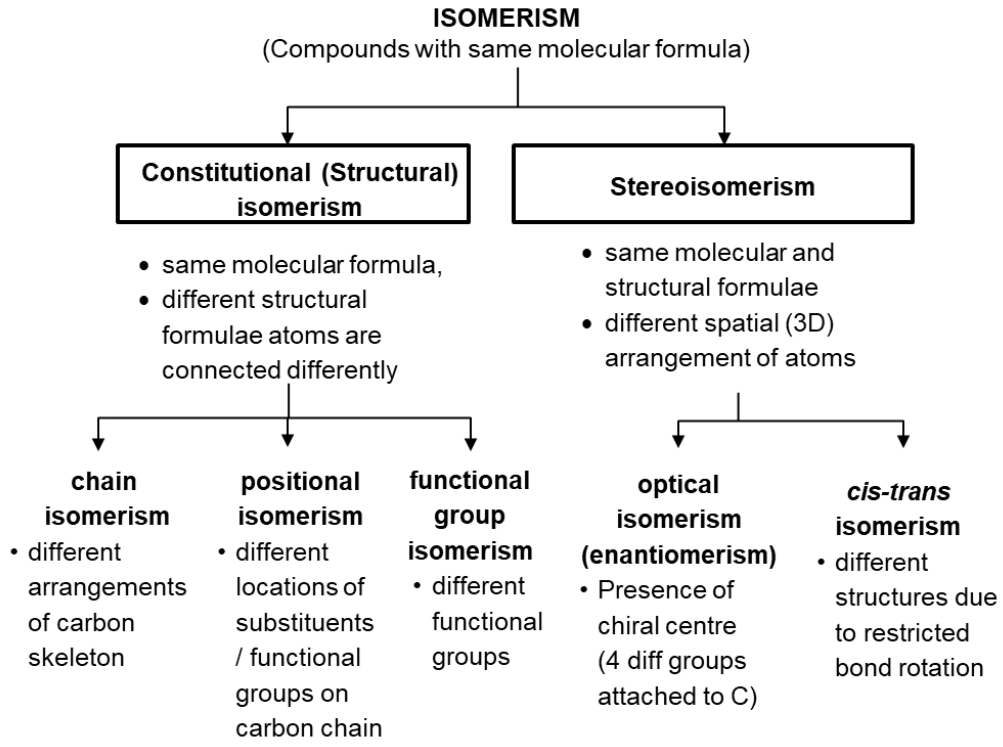
2 ISOMERISM

2.1 INTRODUCTION

Isomerism refers to the **existence of two or more stable compounds** with the **same molecular formula** but **different arrangement** of the **atoms**. These compounds are known as **isomers.**

Note: bonds have to be broken in order for isomer A to be converted to isomer B.

There are 2 **major** types of isomerism: **constitutional (structural) isomerism** and **stereoisomerism.**



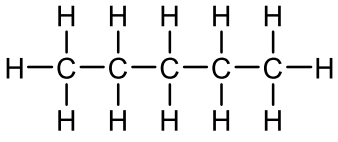
2.2 STRUCTURAL ISOMERISM (CONSTITUTIONAL ISOMERISM)

Success Criteria:
- I can describe and draw constitutional (structural) isomers

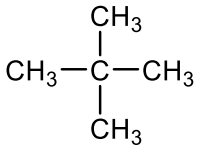
Structural isomers have the **same molecular formula** but **different structural formulae**; i.e., at least one atom is bonded to a different atom in one isomer compared to another.

(i) Chain Isomers

e.g. structural isomers of C_5H_{12}



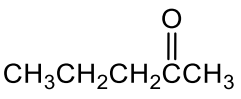
Pentane (b.p. 36 °C)
Straight Chain



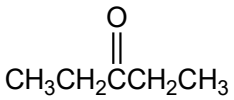
2,2-dimethylpropane (b.p. 10 °C)
Branched

Both share the same molecular formulae but differ in the longest continuous hydrocarbon chain.

(ii) Positional Isomers
e.g. pentan-3-one vs pentan-2-one



pentan-2-one



pentan-3-one

Both share the same molecular formulae but different location of C=O group on the longest continuous hydrocarbon chain.

Chain and positional isomers have **different physical properties** such as density, solubility, melting and boiling points as the **surface area of contact between molecules** are different.

These isomers have **similar chemical properties** as they have the same functional groups.

However, the shape of a molecule often determines its chemical reactivity. An easy-to-reach functional group or other side chain reacts more readily than one that experiences **steric hindrance.** (i.e., one that is "buried" in the middle of a long C chain or "protected" by bulky groups). *(Concept of steric hindrance will be covered in details in later chapter.)*

(iii) Functional group isomers

There are **4 common pairs of functional group** isomers.

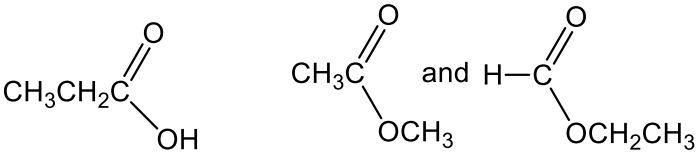
- alcohols and ethers with general formula $C_nH_{2n+2}O$
  CH_3CH_2OH, ethanol and CH_3OCH_3, dimethyl ether

- aldehydes and ketones with general formula $C_nH_{2n}O$

- alkenes and cycloalkanes with general formula C_nH_{2n}

$CH_3CH_2CH_2CH=CH_2$ 

- Carboxylic acids and esters with general formula $C_nH_{2n}O_2$



Functional group isomers have **different** physical and chemical properties.

Note:
Consider
1) chain isomerism
- vary no. of C atom in longest chain by moving C atoms to become substituent (e.g. branch)

2) positional isomerism
- vary positional number of principal functional group and substituents

3) functional group isomerism
-vary arrangement of atoms into a different functional group

Checkpoint 1

(a) Draw all the structural isomers of molecular formula C_6H_{14}.

(b) Draw all the structural isomers of an ester of molecular formula $C_4H_8O_2$.

2.3 STEREOISOMERISM

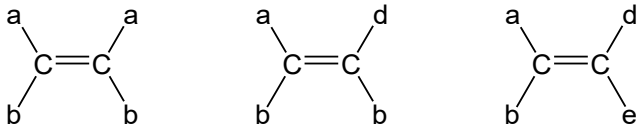
Stereoisomers have the same molecular and structural formulae. The corresponding atoms are bonded to the same atoms but differ in the spatial (3D) arrangements of their bonds. There are two types of stereoisomerisms:
cis-trans isomerism and optical isomerism (enantiomerism).

2.3.1 Cis-trans Isomerism

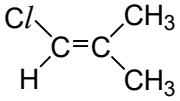
Success Criteria:
- I can identify the two structural features required for an alkene to undergo cis-trans isomerism, and explain it in terms of restricted rotation due to the presence of π bonds.
- I can name and draw cis- and trans- isomers.

Two conditions are required for cis-trans isomerism to exist:
- restricted rotation about a bond can be due to (i) C=C bonds in a straight chain) (ii) a ring structure (not in H2 syllabus)
- two different groups on **each** of the carbon atoms with restricted rotation.

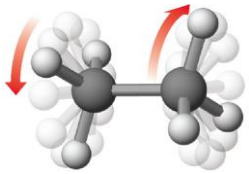
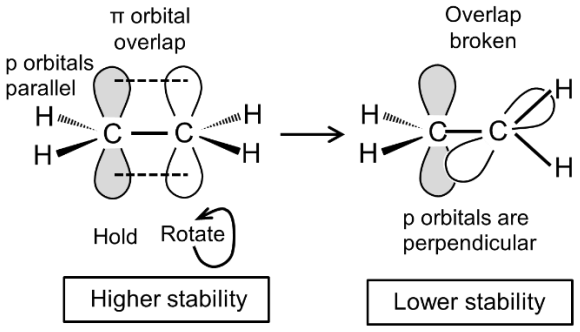
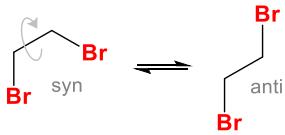
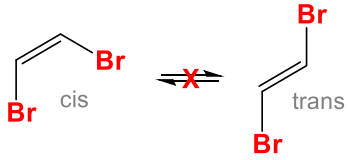
e.g.



The compound below does not exhibit cis-trans isomerism as it has two methyl groups attached to one of the C atoms in the C=C bond.

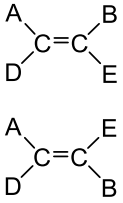


(i) Restricted rotation about single bonds versus double bonds

Single bond	Double bond
	
Free rotation is possible about σ bonds. Rotation does not cause any bond to be broken. 	Free rotation is not possible about a double bond.  Conversion of cis-isomer to trans-isomer requires the π bond to be broken

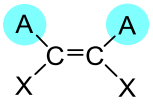
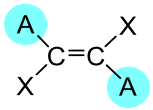
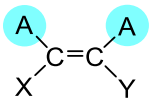
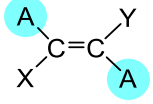
Note:
Free rotation about the single C–C bond may cause spatial arrangement of atoms across 2 C to differ but they are not isomers of each other as bond breaking process is not involved to convert 1 arrangement to the other.

Note:
Alkenes with four different substituents across C=C also exhibit cis-trans isomerism. Another naming convention (E / Z) is used instead.
**E/Z naming is not in H2 syllabus.



*Cyclic alkenes do not exhibit cis-trans isomerism despite satisfying both structural features required. (see 2.3.1.)

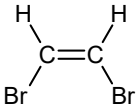
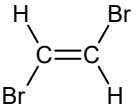
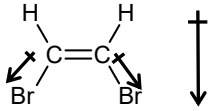
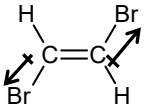
(ii) Naming of cis-trans Isomers

***cis*-isomers**	***trans*-isomers**
have identical atoms / groups of atoms on the **same** side of the double bond	have identical atoms / groups of atoms on diagonally **opposite** sides of the double bond
e.g. 	
e.g. 	

(iii) Properties of cis-trans isomers

Success Criteria:
- I can explain why cis- and trans- isomers have different boiling and melting points

Cis-trans isomers have the same chemical but different physical properties.

	cis-isomer	trans-isomer
Structural Formula		
Net Polarity	 polar molecule	 non-polar molecule
Boiling Point	has a higher boiling point as more energy is needed to overcome stronger permanent dipole-permanent dipole interactions between the molecules	has a lower boiling point as less energy is needed to overcome weaker intermolecular instantaneous dipole-induced dipole interactions
Melting Point	has lower melting point due to poorer packing efficiency (lesser number of molecules per unit volume in solid state), leading to less intermolecular forces to overcome per unit volume	has a higher melting point due to better packing efficiency of molecules (packs better in a crystalline lattice due to its more symmetrical shape), leading to more intermolecular forces to overcome per unit volume

(iv) Molecules containing two or more cis-trans C=C

In general, a molecule with **"m" cis-trans C=C** has a maximum of **2^m** stereoisomers.

For a compound with three cis-trans C=C, eight (2^3) stereoisomers are expected.

2.3.2 Optical Isomers

Success Criteria:

- I can identify a chiral centre and explain what it means.
- I can use suitable diagrams to illustrate optical isomerism and state the properties of optical isomers.
- I can explain the similarities and differences in physical and chemical properties trends of enantiomers.
- I understand the term racemic mixture and able to explain why it is optically inactive.
- I can deduce whether a molecule is chiral by checking for the (i) presence of chiral centre and (ii) plane of symmetry.

Optical isomerism exists when molecules contain at least one chiral centre causing them to lack both a point and plane symmetries.

(i) Chirality

Video on Chirality

Time: 0:38 – 2:08

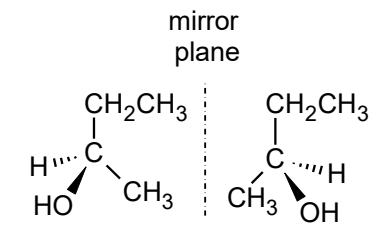
https://tinyurl.com/aasmpfj7

A molecule is described to contain a '**chiral** centre' if it has a carbon atom attached with four different atoms / groups of atoms. As a result, the mirror images of the molecules are non-superimposable.

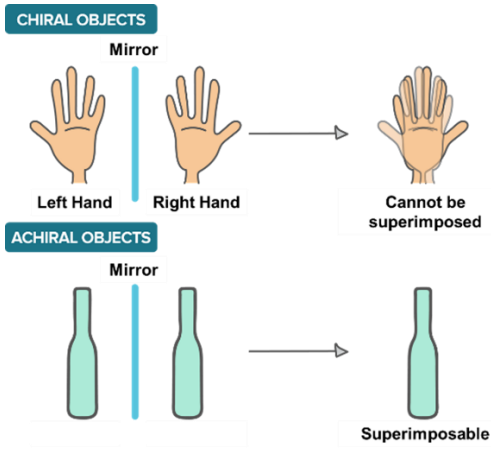
A chiral carbon is usually labelled with an asterisk (*).

Enantiomers refer to a pair of compounds with the same connectivity but opposite three-dimensional shapes. Enantiomers are non-superimposable mirror images of each other.

e.g. a molecule with a chiral centre with its enantiomer



enantiomers /
non-superimposable mirror images



Obtained from https://www.khanacademy.org/

(ii) Properties of optical isomers (enantiomers)

Enantiomers:

- rotate the plane of plane-polarised light by equal angles but in **opposite** directions when equal concentration of enantiomers are being analysed.
- have **similar chemical properties** (except in their interactions with another chiral molecule).
- have **similar physical properties** (except in the direction in which they rotate plane-polarised light).
- have different biological properties.

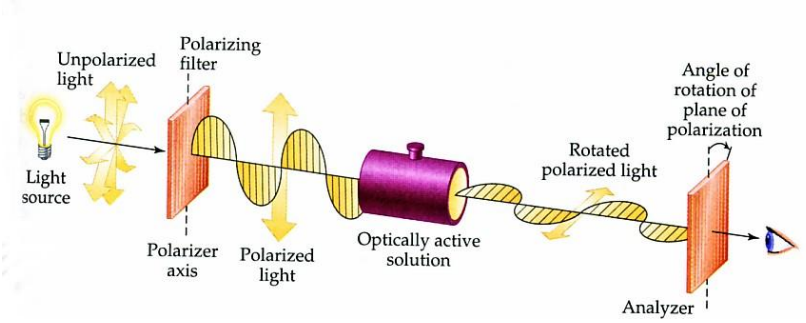
(iii) Racemic mixture

In a mixture that contains **equal concentrations of enantiomers**, the equal but opposite rotation of plane-polarised light by each enantiomer results in net zero optical activity. Such a mixture is termed a **racemic mixture (racemate)**. The mixture becomes **optically inactive** (does not rotate plane of plane-polarised light) despite having chiral molecules.

Note:
It is not possible to know which optical isomer rotates the plane polarized light clock-wise or anti-clockwise unless an experiment is carried out.

PLANE-POLARISED LIGHT (*For info only, not in H2 syllabus*)

Light is a wave vibrating in all planes at right angles to the direction of its propagation. Light vibrating in all possible planes is said to be unpolarised. Plane-polarised light, composed of waves that vibrate in only one plane, can be produced by passing unpolarised light through a polariser.



The rotation of the plane of plane-polarised light by an optically active compound can be measured by a polarimeter.

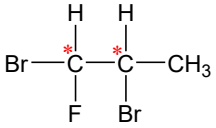
- The enantiomer which rotates polarised light to the right is termed dextrorotatory (D or (+) form).
- The enantiomer which rotates polarised light to the left is termed laevororotatory (L or (-) form).

(iv) Molecules containing two or more chiral centers

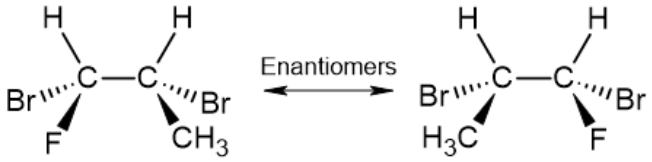
In general, a molecule with **n chiral centers** has a maximum of $\mathbf{2^n}$ stereoisomers.

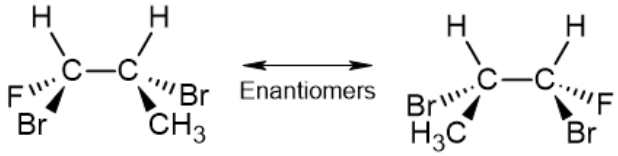
For a compound with two chiral centers, four stereoisomers are expected.
total no. of stereoisomers = $2^2 = 4$

e.g.



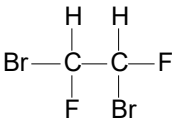
3D structures of stereoisomers:





However, there are some molecules with 2 chiral centers with less than 4 stereoisomers.

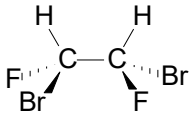
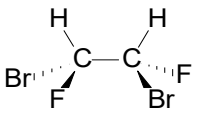
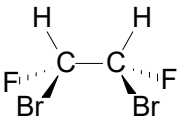
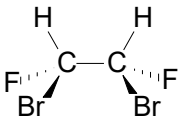
e.g.



Theoretical: total no. of stereoisomers = $2^2 = 4$
Actual: total no. of stereoisomers = 4 – 1 = 3

Video on
Meso Compound

https://tinyurl.com/
mesocompound

Isomer **A**	Isomer **B**
	
Isomer **C**	Isomer **D**
	

Isomers **A** and **B** are enantiomers (non-superimposable mirror images).

Isomers **C** and **D** are identical (superimposable mirror images). **C** or **D** is known as a meso compound.

Hence, this molecule has a total of only **<u>three</u>** stereoisomers despite having 2 chiral centres.

(v) Meso compound

A meso compound is one that contains two chiral centers but is super-imposable on its mirror image as it has an **internal plane of symmetry**.

A meso compound is optically inactive as the effect on the plane-polarised light by each half of the molecule is equal in magnitude but opposite in directions. Hence, they cancel each other to give a net zero effect on plane-polarised light.

2.3.3 Molecules that exhibit both cis-trans and optical isomerism

Success Criteria:

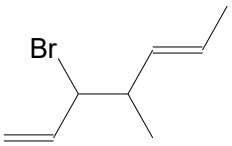
- I can identify chiral centres and/or cis-trans isomerism in a molecule of a given structural formula.
- I can deduce the maximum possible number of isomers using 2^{m+n}.

Note:
Stereoisomerism refers to BOTH cis-trans isomerism and optical isomerism

In general, a molecule with **m** C=C bonds that exhibit cis-trans isomerism and **n** chiral centers has a maximum of **2^{m+n}** stereoisomers.

Worked Example 1

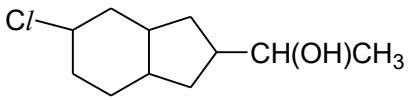
What is the total number of stereoisomers for the following compound?



2 chiral carbon and 1 cis-trans C=C
Total number of stereoisomers = $2^3 = 8$

Worked Example 2

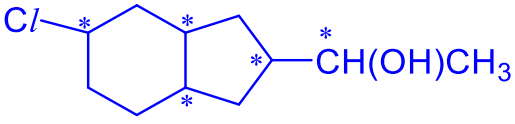
How many chiral carbons are present in the molecule below? Label each chiral C with *.



To identify chiral carbon in skeletal formula,

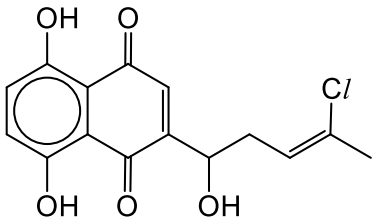
1) look out for intersections of 3 single bonds (4th bond is C−H that is not drawn) or 4 single bonds

2) Check there are 4 unique groups bonded to the carbon.



Checkpoint 2

(a) How many stereoisomers are there in the following compound?



A 2 **B** 4 **C** 6 **D** 8

(b) State and explain clearly the type of stereoisomerism shown by each compound and state the total number of stereoisomers, if any.

(i) $CH_3CH=CHCH_2CH(OH)CH_3$

(ii) $(CH_3)_2C=CHCH_2CH(OH)CH_2CH=C(CH_3)_2$

(iii) 

2.4 Biological Properties of Optical Isomers (Enantiomers)

Success Criteria:

- I can recognize different stereoisomers exhibit different biological properties, for example in drug action.

The small difference in the spatial arrangement of atoms between a pair of enantiomers may seem trivial and unimportant to you and me but to **living organisms** this difference is critical. Cells and enzymes recognise these differences and **often can use only one of the enantiomers**.

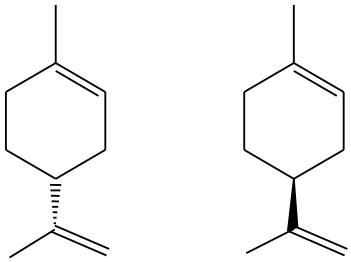
Below are some examples.

The proteins in our bodies are built from only one enantiomer of each amino acid.

Enantiomers can interact differently with the chiral receptor cells in the taste buds on our tongue, leading to different tastes. Most D-amino acids taste sweet; their enantiomeric counterparts are either tasteless or bitter.

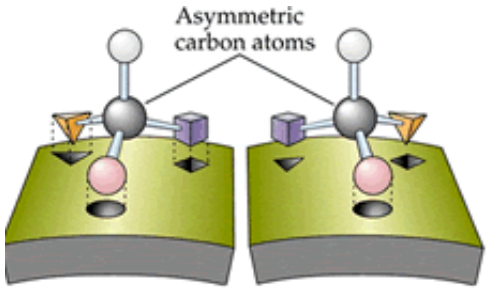
Enantiomers can interact differently with the chiral receptor cells in our nose, leading to different smells.

enantiomers of limonene



found in oranges found in lemons

Drugs work by interacting with the appropriate receptor site via intermolecular interactions. The interactions are very specific. Treating the patient with the wrong enantiomer of a drug can at best be harmless; at worst can harm the patient even further.



Hence, it is important that optically pure compounds are synthesised and administered. However, **racemic mixtures are usually obtained in normal laboratory syntheses**. Further isolation and purification are required to obtain the desired isomer.

Pharmaceutical companies devised enantioselective synthesis to prepare only the single enantiomer. It is also important to test the target compound under physiological conditions to ensure it does not undergo racemisation.

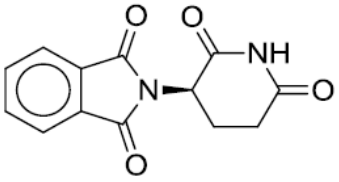
Stereoisomerism in the Real-World (For info only)

Video on Thalidomide

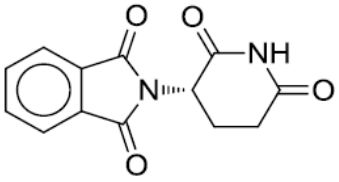
https://tinyurl.com/d9jpkb7h

Thalidomide, was released into the market in 1957 in West Germany to treat morning sickness in pregnant women. Shortly after the drug was sold, in Germany, between 5,000 and 7,000 infants were born with malformation of the limbs. Later it was found that of the two enantiomers, (+)-thalidomide has the desired sedative effect, while (–)-thalidomide possesses the undesirable teratogenic effects (caused birth defects).

However, the enantiomers can interconvert in vivo (in the human body), so if a human is given pure (+)-thalidomide or (-)-thalidomide, both isomers will be present in the body eventually. Therefore, even administering the (+) isomer will NOT prevent the teratogenic effects in humans.



(+)-thalidomide



(–)-thalidomide

Recommended website for revision and further reading

http://www.chemguide.co.uk/basicorg/isomermenu.html#top

(Good notes on the topic and many very good examples.)

CONCEPTS IN ISOMERISM			
	Success Criteria	Relevant Tutorial Question	What do you still struggle with? Write your queries here.
	I am able to:		
(a)	Describe constitutional (structural) isomerism	CP1, Tutorial Qn 1, 2 and 3	
(b)	Describe cis-trans isomerism in alkenes, and explain its origin in terms of restricted rotation due to the presence of π bonds	CP2, Tutorial Qn 4,5 and 6	
(c)	Explain what is meant by a chiral centre		
(d)	Deduce whether a given molecule is chiral based on the presence or absence of chiral centers and/or a plane of symmetry	CP2, Tutorial Qn 7,8 and 10 (c).	
(e)	Recognise that an optically active sample rotates plane-polarised light and contain chiral molecules	Tutorial Qn 12 (b), 13 (c)	
(f)	Recognise that enantiomers have identical physical properties except in the direction in which they rotate plane-polarised light	Tutorial Qn 1	
(g)	Recognise that enantiomers have identical chemical properties except in their interactions with another chiral molecule	Tutorial Qn 1	
(h)	Recognise that different stereoisomers exhibit different biological properties, for example in drug action	Tutorial Qn 9	
(i)	Deduce the possible isomers for an organic molecule of known molecular formula	Tutorial Qn 3, 10 (c), 14 (b) and (c)	
(j)	Identify chiral centres and/or cis-trans isomerism in a molecule of given structural formula.	Tutorial Qn 7,8, 10 (c), 11 (c) (d), 12 (a), 13 (a) and 14.	

Isomerism Tutorial

Properties of isomers

1 Two organic isomers are known to contain the **same** functional group. Assess the following statements about the two molecules.

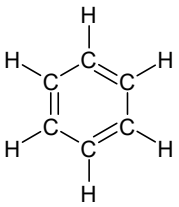
(a) They have the same empirical formula. **true / may be true / false**

(b) They have the same boiling point. **true / may be true / false**

(c) They have the same chemical properties. **true / may be true / false**

(d) They have the same solubility in water. **true / may be true / false**

Constitutional Isomerism (Structural Isomerism)

2 How many isomers of dichlorobenzene are there? (benzene: C_6H_6  )

A 2 **B** 3 **C** 4 **D** 5

3 A halogenoalkane has the molecular formula $C_3H_5Cl_3$.

Which are the possible names of the isomers of this compound?

1 1,1,1-trichloropropane
2 1,2,2-trichloropropane
3 2,2,3-trichloropropane

A **1, 2** and **3** are correct **B** **1** and **2** only are correct

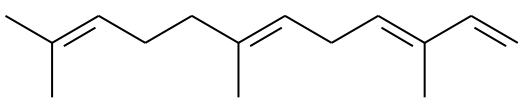
C **2** and **3** only are correct **D** **1** only is correct

Cis-trans Isomerism

4 How many structural and *cis-trans* isomers are there in dichloropropene, $C_3H_4Cl_2$?

A 3 **B** 5 **C** 6 **D** 7

5 α*–Farnesene* is a constituent of the natural wax found on apples. It is also responsible for the characteristic odour of green apples.



α*–Farnesene*

How many *cis-trans* isomers does this molecule have?

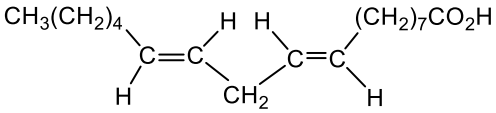
A 2 **B** 4 **C** 8 **D** 16

6 Low fat sunflower spreads which are high in polyunsaturated contain esters of linoleic acid.

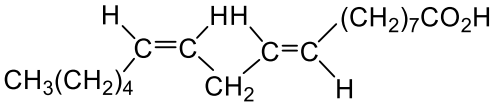
$$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H$$

On the lid of a brand of spread, it is claimed that the spread contains virtually no *trans* fatty acid. Which isomer does **not** contain a *trans* linkage that could be present in the spread?

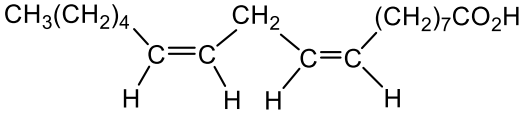
A



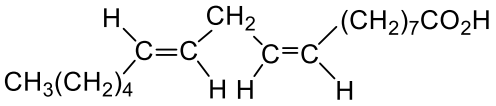
B



C

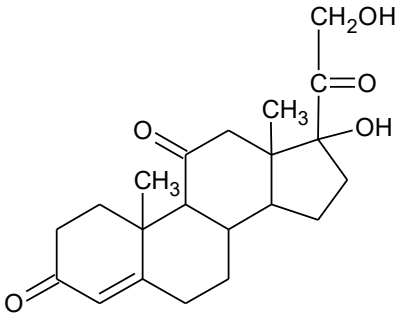


D



Optical Isomerism (enantiomerism)

7 The drug cortisone has the formula shown.

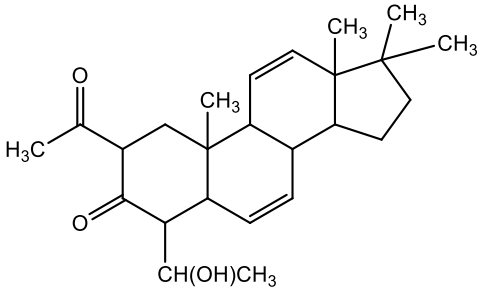


cortisone

How many chiral centers are present in each cortisone molecule?

A 3 **B** 4 **C** 5 **D** 6

8 What is the maximum number of stereoisomers for the molecule shown below?



A 2^8 **B** 2^9 **C** 2^{10} **D** 2^{11}

9 The drug ibuprofen has two enantiomers. One enantiomer has the desired pharmacological activity while the other is inactive.

Which statement gives correct reasons for this difference?

1 The biological receptors that the drugs bond with are chiral
2 The enantiomers are structural isomers with different chemical properties.
3 The enantiomers have many different physical properties.

A 1,2 and 3 **B** 1 and 2 only **C** 1 only **D** 2 and 3 only

Answer to MCQ

2	**B**	**3**	**B**	**4**	**D**	**5**	**B**	**6**	**C**	**7**	**D**	**8**	**B**	**9**	**C**

10 **(a)** What is meant by the term 'optical isomerism'?

(b) What conditions must be fulfilled for a compound to exhibit optical activity?

(c) Draw the structural formula of the alkane with the lowest M_r that can exhibit optical isomerism.

Application Questions

11 A hydrocarbon **Q** consists of 86% carbon by mass.

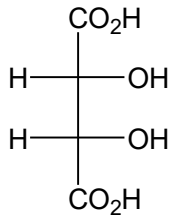
(a) Calculate the empirical formula of **Q**.

(b) 5.0 g of **Q** was found to occupy 2.0 dm^3 at 0 °C and 1 atm. Deduce the molecular formula of **Q**.

(c) **Q** exists as a pair of *cis-trans* isomers. Draw the structural formulae for the isomers.

(d) **P** is a structural isomer of **Q** and does **not** show *cis-trans* isomerism. Suggest a structure for **P**.

12 The effect of plane-polarised light on tartaric acid, $HO_2CCH(OH)CH(OH)CO_2H$, was investigated by Louis Pasteur.



tartaric acid

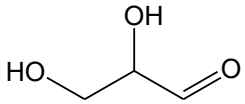
Pasteur identified three different types of tartaric acid molecule.

- molecule **A** rotated plane-polarised light to the right.
- molecule **B** rotated plane-polarised light to the left.
- molecule **C** has no effect on plane-polarised light.

(a) Label each chiral centre in tartaric acid with an asterisk (*).

(b) Suggest an explanation for the observations about molecules **A**, **B** and **C** made by Pasteur.

13 Glyceraldehyde as shown below is chiral and exists as two enantiomers, *D*-glyceraldehyde, and *L*-glyceraldehyde.



glyceraldehyde

(a) Identify the chiral centre using (*).

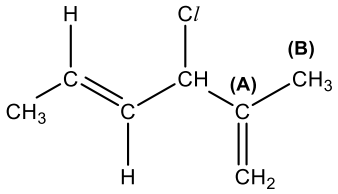
(b) Given that sample I contains only the *D*-isomer which rotates the plane of plane-polarised light in the clockwise direction. Complete the table below using the given information.

sample number	relative amount of *D*-isomer in sample	relative amount of *L*-isomer in sample	about the sample	is sample optically active?	direction of rotation of plane-polarised light
I	100	0	pure *D*-isomer	Yes	clockwise
II	75	25	excess *D*-isomer		
III	50	50			
IV	25	75			
V	0	100			

(c) The samples of glyceraldehyde were analysed for optical activity. Only one sample was found to be optically inactive.

Identify the optically inactive sample and account for its optical activity.

14 Compound **X** can exhibit stereoisomerism.



Compound **X**

(a) State the maximum number of stereoisomers that **X** can have. Explain your answer. [2]

(b) Draw all the stereoisomers of **X**. [4]

(c) Draw a structural isomer of **X** which does **not** exhibit any form of stereoisomerism. [1]

(d) Explain why the C−C bond between carbons **(A)** and **(B)** is stronger than a typical C−C bond in an alkane such as ethane. [2]