ANDERSON SERANGOON JUNIOR COLLEGE
JC1 H2 CHEMISTRY
ISOMERISM

Contents

- Isomerism: *constitutional (structural)*; *cis–trans*; *enantiomerism*

Learning Outcomes (LOs)

Candidates should be able to:

(a) describe constitutional (structural) isomerism
(b) describe *cis–trans* isomerism in alkenes, and explain its origin in terms of restricted rotation due to the presence of π bonds
[use of *E*, *Z* nomenclature is **not** required]
(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 centres and/or a plane of symmetry
(e) recognise that an optically active sample rotates plane–polarised light and contains chiral molecules
(f) recognise that enantiomers have identical physical properties except in the direction in which they rotate plane–polarised light
[usage of the term diastereomers is **not** required]
(g) recognise that enantiomers have identical chemical properties except in their interactions with another chiral molecule
(h) recognise that different stereoisomers exhibit different biological properties, for example in drug action
(i) deduce the possible isomers for an organic molecule of known molecular formula
(j) identify chiral centres and/or *cis–trans* isomerism in a molecule of given structural formula

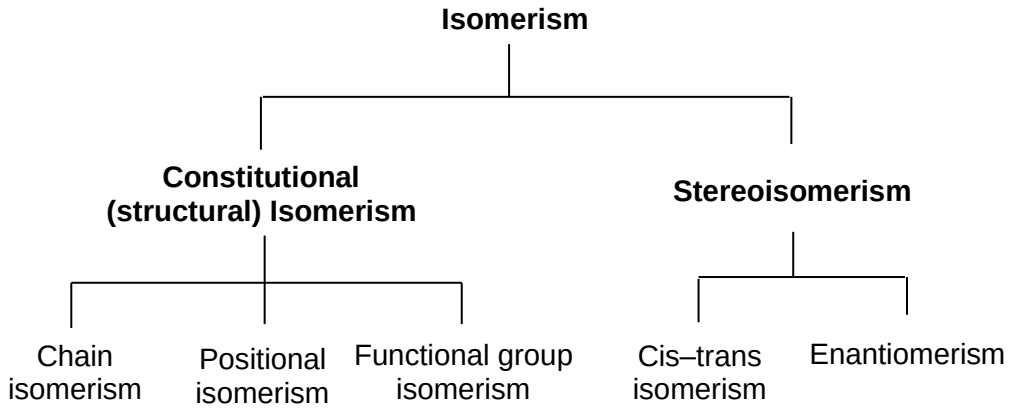
References

1. *Chemistry for Advanced Level*, Cann and Hughes, Murray
2. *Organic Chemistry*, McMurry, Brooks/ Cole
3. *Understanding Advanced Physical Inorganic Chemistry*, Jeanne Tan and Kim Seng Chan

I. INTRODUCTION

- Isomerism is the phenomenon in which two or more compounds possessing the same molecular formula exist in different forms due to different arrangements of atoms in their molecules. These compounds are known as isomers.

- Isomerism in organic compounds can be classified into 2 broad categories which in turn can further differentiate into 5 types as shown:



(A) Constitutional (structural) isomerism

- Constitutional (structural) isomers are compounds with the same molecular formula but different structural formulae.

- Structural isomers can be members of different homologous series (i.e. functional groups), or they may be members of the same series. As structural isomers have different structures, they have different properties.

- There are 3 types of structural isomerism.

1. Chain isomerism

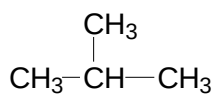
- Chain isomers have the same number of carbon atoms, but their carbon backbones are different.

- Example of chain isomers with the formula C_4H_{10}

butane

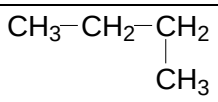
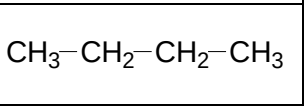
$CH_3{-}CH_2{-}CH_2{-}CH_3$

2−methylpropane



Checkpoint 1

Consider structures **A** and **B**

A	B
	

Is **A** a chain isomer of **B**? (Hint: try using the rules that you've learnt in nomenclature to suggest the names for both structures.

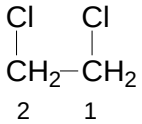
Answer: **A** is _____ 1-methylpropane! Both **A** and **B** are the _____ molecule, _____!

- When we consider the longest continuous carbon chain, both structures have 4 carbon atoms and no branching!
- There is complete free rotation about any C−C single bond, so the two diagrams are just different ways of representing butane. One can be formed from the other simply by rotating about a single bond.

2. Positional isomerism

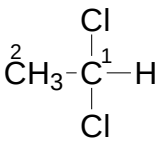
- Positional isomers have the same carbon backbone, but the positions of their functional group(s) differ.
- Examples of pairs of positional isomers

Notice the difference in positions of Cl atom.



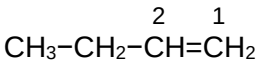
1,2−dichloroethane

vs



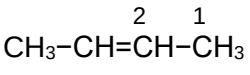
1,1−dichloroethane

Notice the difference in positions of C=C



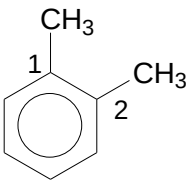
but−1−ene

vs



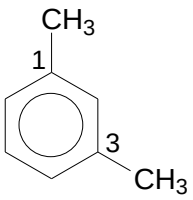
but−2−ene

Notice the difference in positions of CH_3- group



1,2−dimethylbenzene

vs



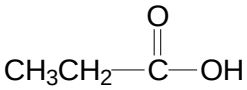
1,3−dimethylbenzene

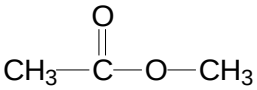
3. Functional group isomerism

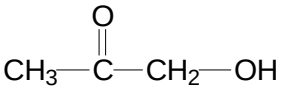
- Functional group isomers contain different functional groups. They often have very different reactions from one another.

- Example of functional group isomers with the same formula $C_3H_6O_2$.

$CH_3CH_2CO_2H$	$CH_3CO_2CH_3$	CH_3COCH_2OH
propanoic acid	methyl ethanoate	hydroxypropanone







Checkpoint 2

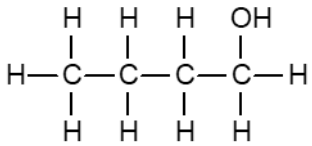
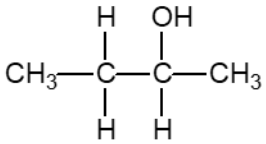
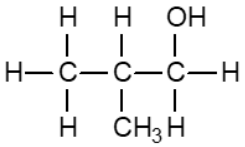
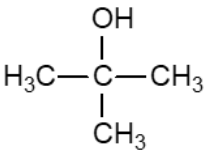
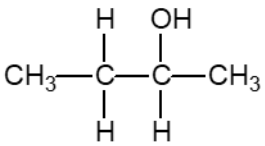
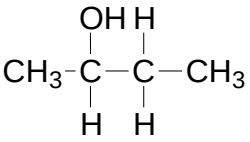
Compound **X** is a non-cyclic alkane with a molecular formula of C_5H_{12}.

Draw the structural formulae for all its constitutional isomers.

Checkpoint 3

How many alcohols, including **only** constitutional isomers, can have the molecular formula $C_4H_{10}O$?

What is a systematic way to derive the number of isomers?

Step 1: Start with the longest C chain with functional group of high priority on C1. Obtain the first isomer.	
Step 2: Continue with the longest C chain, shift the position of the functional group to adjacent C atom to get another isomer.	
Step 3: Repeat Step 2 until you don't get more isomers with the same longest C chain.	No more isomers. Putting –OH group on C3 will get the same structure as putting –OH on C2.
Step 4: Using the isomer from Step 1, shorten the C chain by shifting the last C to C2.	
Step 5: Similar to Step 2 and 3, using the isomer from Step 4 and shift the position of the functional group to adjacent C atom to get another isomer.	
Step 6: Check if Step 4 - 5 can be repeated to derive different isomers of even shorter carbon chains.	No longer possible for this molecule.
Step 7: As a final check, you can try to name all the isomers drawn. You should have different names for all the structures. If you arrive at the same name, this means that you have drawn the same molecule!	E.g.  and  are both butan-2-ol! They are identical molecules, not isomers!

You can try the steps above yourself and practice with other molecules of different molecular formula!

(B) Stereoisomerism

- Stereoisomers contain the same atoms bonded to one another, and the bonding and functional groups are identical (i.e. they have the same structural formula! They are NOT structural isomers of each other).
- Stereoisomers differ only in the way the atoms are arranged in 3−dimensional space.

- There are 2 types of stereoisomerism: *cis–trans* and enantiomerism

1. *Cis−trans* isomerism

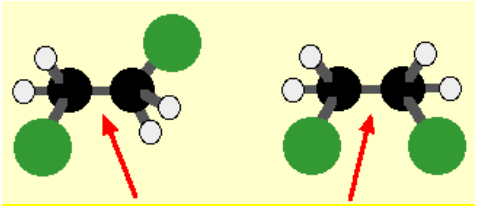
Criteria for alkenes to exhibit *cis–trans* isomerism:

(i) Presence of C=C double bond to prevent free rotation about the double bond.

(ii) Have two different groups / atoms attached to each C atom of the C=C double bond.

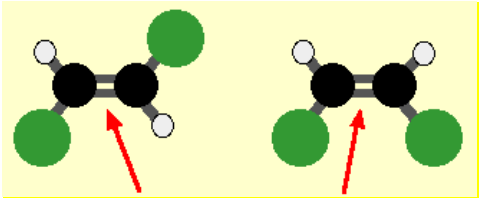
- *Cis–trans* isomerism occurs with alkenes that do not have two identical groups on both ends of the C=C double bond.

- It arises because, unlike the case of a C−C single bond, it is not possible to rotate freely about a C=C double bond. Doing so involves breaking the π bond and this requires more energy than is available at normal temperatures.



Free rotation about this single bond

Hence, structure on the right can be created from structure on the left by a simple rotation of C-C. Both structures are the same molecule.

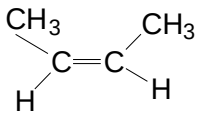


NO free rotation about this double bond

Hence, structures on the right CANNOT be created from structure on the left. The two structures are different molecules!

- The following two forms of but−2−ene are therefore distinct and separate isomers where the atoms are arranged differently in the 3D space.

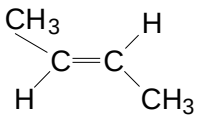
cis−but−2−ene



*–CH_3 on **same side** of C=C*

*OR H on **same side** of C=C*

trans−but−2−ene

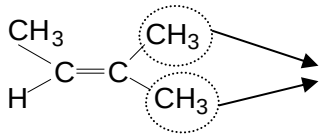


*–CH_3 on **different sides** of C=C*

*OR H on **different sides** of C=C*

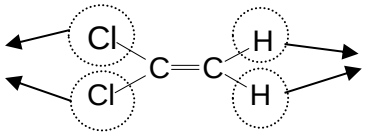
- *Cis−trans* isomers differ in their physical properties but have similar chemical properties.

- The following compounds do not exhibit *cis–trans* isomerism because one end, or both ends, of the double bond have 2 identical atoms / groups attached.



2 identical –CH_3 groups at one end of the double bond

2 identical –C*l* groups at one end of the double bond



2 identical –H groups at one end of the double bond

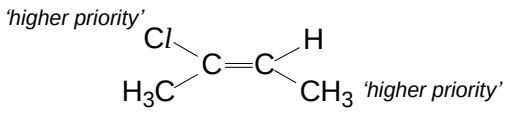
Counting total number of *cis–trans* isomers:

Total number of <u>*cis*−*trans* isomers</u> possible = 2^n
(where n = no. of C=C with *2 different groups attached to each C of C=C*)

<u>FYI (not in syllabus)</u>
A more general method for describing double–bond geometry is provided by the *E–Z* system of nomenclature. It uses a series of sequence rules to assign priorities to the substituent groups on the doubly bonded carbons. A simplified step is given below.

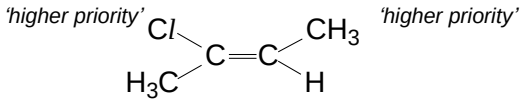
<u>Naming *E/Z* isomers</u>

- Consider the 2 doubly bonded carbons separately.
- Atoms directly attached to each doubly bonded carbon with a <u>higher atomic mass</u> receive higher priority. If a decision cannot be reached based on the first atoms, look along the chain of atoms until the first difference is found.
- The prefix *Z* indicates that atoms or groups of higher priority are on the <u>same side</u> of the double bond while the prefix *E* shows that they are on <u>opposite</u> sides.



E–2–chlorobut–2–ene

"trans"



Z–2–chlorobut–2–ene

"cis"

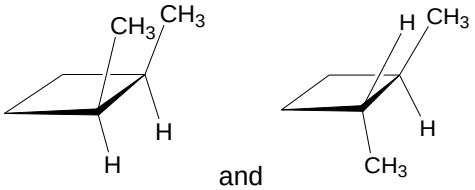
Note

1) *Cis–trans* isomerism is not limited to compounds with C=C double bonds. It can arise wherever rotation about a bond is restricted. Hence *cis–trans* isomerism also occurs in ring systems, where rotation around a **single** bond is prevented by linkage in a ring.

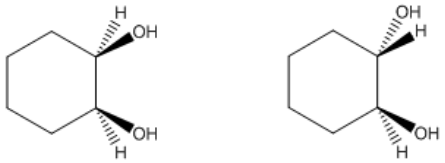
   e.g.

cis−1,3−dimethylcyclobutane

trans−1,3−dimethylcyclobutane

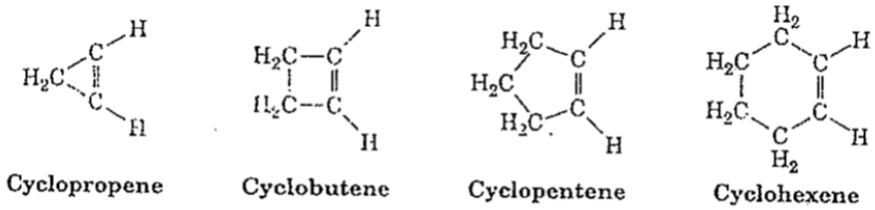


and



cis–1,2–dimethylcyclobutane *trans*–1,2–dimethylcyclobutane cyclohexane–1,2–diol

2) **There is no cis-trans isomerism for cycloalkenes with 7C or less.** In **small cycloalkenes**, the ring is not large enough to accommodate the geometry required by a *trans* double bond and still be stable at room temperature. The introduction of a *trans* double bond into such small rings would introduce more strain than the bonds of the ring atoms could accommodate.

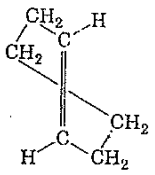


Cyclopropene Cyclobutene Cyclopentene Cyclohexene

Figure 7.3 *cis*-Cycloalkenes.

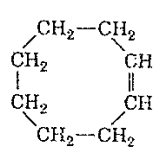
Trans–cycloheptene (7-C compound) has a short lifetime and cannot be isolated. *Trans*–cyclooctene (8-C compound) has been isolated. The C–8 membered ring is large enough to accommodate the geometry required by a *trans* double bond and still be stable at room temperature.

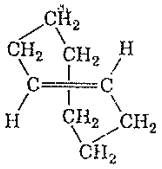
Notice that one of the C–C bond in the hypothetical trans isomer has to be very long to accommodate the trans arrangement. Too weak and unstable to exist.



Hypothetical *trans*-cyclohexene. This molecule is apparently too highly strained to exist at room temperature.

(6-C compound)





cis-Cyclooctene *trans*-Cyclooctene

Figure 7.5 The *cis* and *trans* forms of cyclooctene.

(8-C compound)

2. Enantiomerism

- Enantiomerism arises from the *inherent asymmetry* of the **non–superimposable mirror image molecules**, known as enantiomers. Enantiomers are said to be **optically active**, which means that they are able to rotate plane–polarised light.

Criteria for molecules to exhibit enantiomerism:

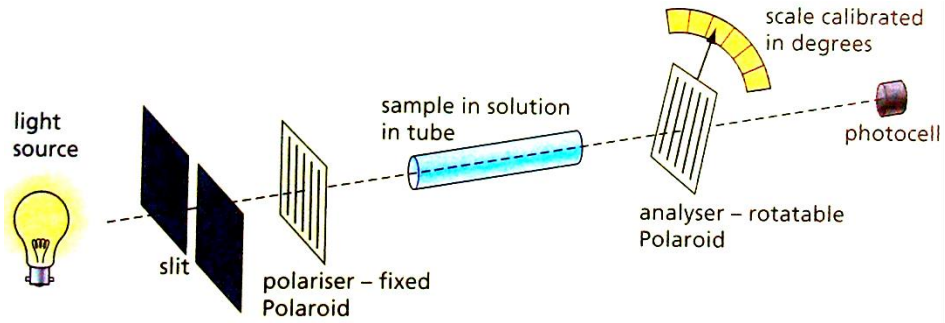
(i) Has a chiral carbon.

(ii) Has no internal plane of symmetry.

(a) Optical activity

- **Optical Activity is** the ability of a substance to rotate the plane of a *plane-polarised* light. (*Note: A ray of light has waves that vibrate in many directions at right angles to the direction of travel of the ray. Some materials can act as a polariser to remove from light all waves, except those vibrating in a single plane, making light plane−polarised.*)

- Such substances that can rotate the plane of a plane-polarised light are said to be **optically active.** When plane-polarised light is shone through a solution of the optically active substance in a suitable solvent, the *plane* in which the polarised light vibrates will be *rotated clockwise* or *anti–clockwise*.



(b) Enantiomers

- **Enantiomers** – Two molecules that are non–superimposable mirror images of each other.
- Such molecules have a **chiral centre** and **no internal plane of symmetry** within the molecule. They are also called **chiral molecules**. Although they are mirror images of each other, they are NOT identical! They are **not superimposable** on each other (it is impossible to arrange them so that all the groups correspond in position).

- The relationship between chiral molecules is similar to the relationship between your left and right hand. Your hands are mirror images of each other and cannot be superimposed on each other (try putting your right hand on your left hand). Your left hand and right hand are NOT identical!

Similarities and differences between enantiomers

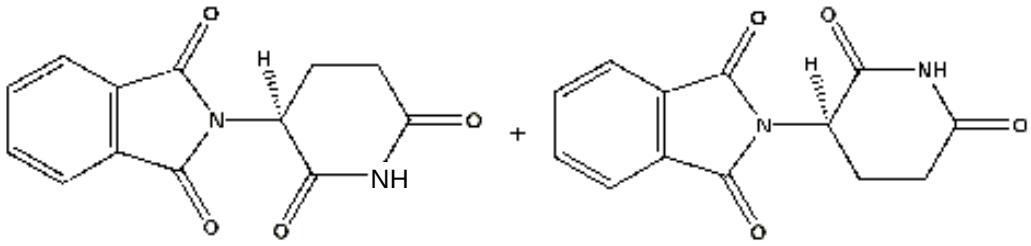
- Enantiomers have identical physical properties, but rotate plane–polarised light to the same extent in opposite direction – one clockwise and the other anti−clockwise. (i.e. different optical activity). The direction of rotation is determined experimentally, not simply from the arrangements of the atoms in the 3-dimensional space.

- Enantiomers have identical chemical properties, except in their interactions with another chiral molecule. For example, when (+)–lactate is added to a mixture of (+)–alanine and (–)–alanine, the (+)–lactate/(+)–alanine salt crystallises while the (+)–lactate/(–)–alanine salt is soluble in water.

Biological properties of stereoisomers (Refer to page 15 for more details)

- Stereoisomers exhibit different biological properties, for example in drug action.

- For example, one enantiomer [(+)isomer] of thalidomide is a very successful, non–toxic sedative that can be used for the treatment of morning sickness. The other enantiomer [(–)isomer], however, can damage the foetus and result in badly deformed babies.



(+) isomer of thalidomide (–) isomer of thalidomide

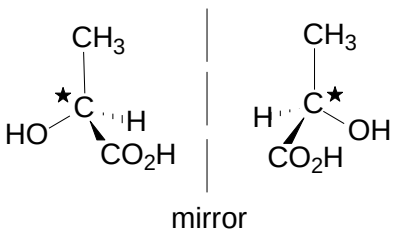
Simplest case of chirality in syllabus

- Many optically active samples contain complex structures and it can be difficult to tell whether or not their molecules are chiral.

- The **simplest case of chirality** occurs when a molecule contains a tetrahedral carbon atom attached to **4 different** atoms or **groups** of atoms with an **absence of a plane of symmetry**. Such atoms are termed **chiral carbon** atoms, or **chiral centres**.

- There are **2 ways** of arranging the 4 groups around a *chiral tetrahedral carbon atom*, and these 2 arrangements produce molecules that are *mirror images of each other*.

- When drawing a pair of enantiomers, it is important to show the *3–dimensional* structures clearly using **wedged** and **dashed** bonds according to the convention used in the example below.

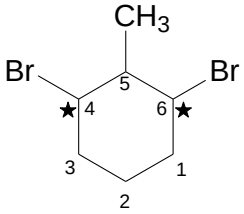


chiral carbon atoms are usually labelled with *

You can identify chiral carbon atoms by identifying carbon atoms that are attached to **4 different groups** of atoms

- A carbon atom that is part of a ring can be a chiral centre as well if it is attached to 4 different atoms or different groups of atoms.

e.g.



- Each of C1, C2 and C3 are attached to 2 H atoms, and are thus <u>not</u> chiral carbons.

- C4 is a chiral centre as it is attached to 4 'different groups':

  ✓ 1 Br atom
  ✓ 1 H atom
  ✓ (going clockwise in the ring) $CH(CH_3)$ followed by CHBr, CH_2, CH_2 and CH_2
  ✓ (going anti–clockwise in the ring) CH_2 followed by CH_2, CH_2, CHBr and $CH(CH_3)$

  The last 2 'groups' are considered different as the sequence of the groups of atoms are different.

- Similar to C4, C6 is a chiral centre.

- C5 is not a chiral centre as it is attached to:

  ✓ 1 CH_3 group
  ✓ 1 H atom
  ✓ (going clockwise in the ring) CHBr, CH_2, CH_2, CH_2, CHBr
  ✓ (going anti–clockwise in the ring) CHBr, CH_2, CH_2, CH_2, CHBr

  of which the last 2 'groups' have the same sequence and thus are considered the same.

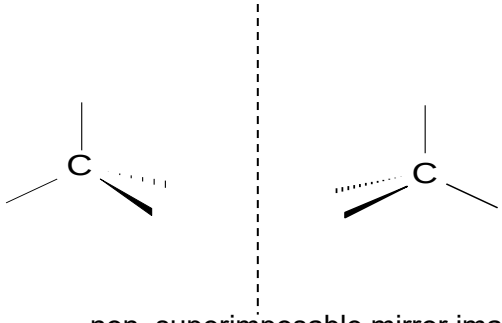
<u>Counting total number of enantiomers</u>

Total number of <u>enantiomers</u> possible = 2^n
(where n = no. of chiral carbon)

<u>Counting total number of stereoisomers (*cis–trans* isomers + enantiomers)</u>

Total number of stereoisomers possible = 2^n
(where n = no. of chiral carbon + no. of C=C with *2 different groups attached to each C*)

<u>Checkpoint 4</u>
Draw the possible enantiomers for $CH_3CH_2CH(OH)CH_3$.

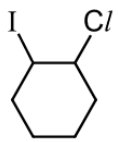


non–superimposable mirror images

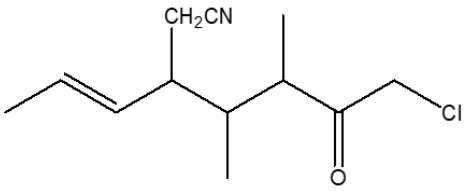
Checkpoint 5

For each of the following compounds, circle the chiral carbons and state the total number of stereoisomers present.

(i)



(ii)



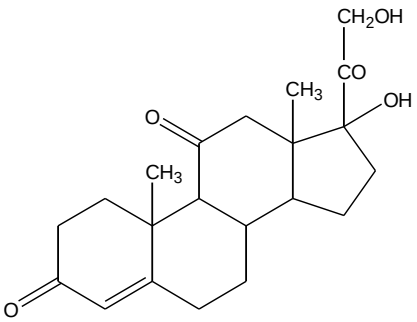
Solution:

total number of stereoisomers =

total number of stereoisomers =

Checkpoint 6

The drug cortisone has the formula shown.



How many chiral centres are present in the molecule?

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

Hint: Count the no. of carbon atoms that have <u>4 different</u> atoms/ groups of atoms attached to it.

(c) Racemic mixture (or racemate)

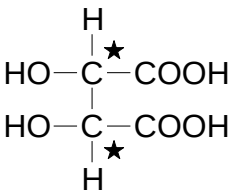
- Since the angles through which a pair of enantiomers rotate the plane–polarised light are *equal*, but in *opposite directions*, a 50:50 mixture of the two isomers has no net effect on the passage of plane–polarised light. The clockwise rotation caused by one isomer is exactly cancelled by the anti–clockwise rotation of the other isomer.

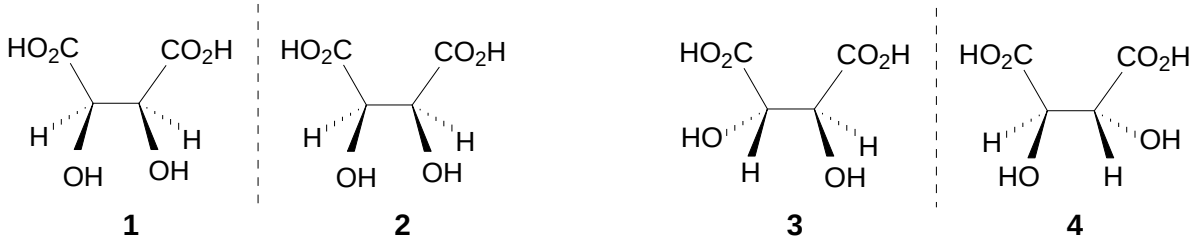
- This mixture with equal amounts of the two enantiomers is called a **racemic mixture**, or **racemate**.

(d) Meso compound

- Compounds that are achiral but yet contain chiral centres are known as meso compounds. The plane of symmetry makes one half of the molecule a mirror image of the other half.

  Example: tartaric acid

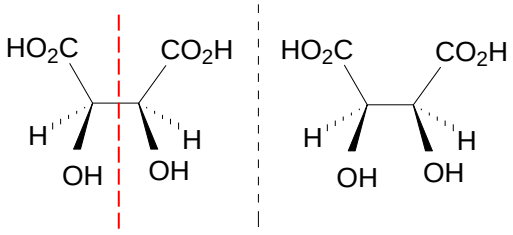




1 **2** **3** **4**

- Since tartaric acid has 2 chiral carbons, it exhibits enantiomerism. However, as it has a plane of symmetry, 2 of the enantiomers are identical (molecule **1** and **2**) and hence only 3 ($2^n - 1$) stereoisomers are possible (2 enantiomers and 1 meso form).

- It appears that "molecules" **1** and **2** are enantiomers but upon closer inspection, you will notice that there is a plane of symmetry within each molecule. Hence the two so called "mirror image molecules" are actually identical (i.e. superimposable on one another).

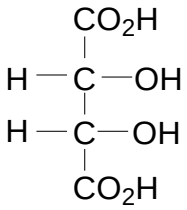


1 **2**

- This plane of symmetry is not present in molecule **3** or **4**. Hence molecules **3** and **4** are enantiomers (molecules that are non–superimposable mirror images of each other). They can be distinguished by the direction to which each isomer rotates plane polarised light.
- IF molecule **3** rotates plane polarised light clockwise by 10^o, molecule **4** will rotate anti–clockwise by the same magnitude.
- Diastereomers are stereoisomers that are not enantiomers and the meso compound illustrated above (molecule **1** or **2**) is a diastereomer of molecules **3** and **4**.

Example: N12/P2/Q5(c)

The effect of planed polarised light on tartaric acid (2,3-dihydroxybutanedioic acid), $HO_2CCH(OH)CH(OH)CO_2H$ was investigated by Louis Pasteur.



tartaric acid

Pasteur identified three different types of tartartic acid molecule.

molecule **A** rotated plane polarised light to the right

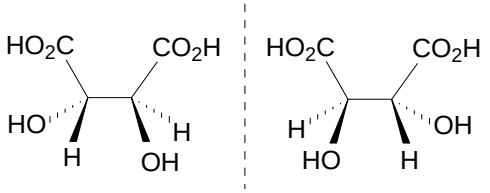
molecule **B** rotated plane polarised light to the left

molecule **C** had no effect on planed polarised light

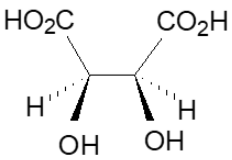
Suggest an explanation for these observations. [3]

Answers

molecule	explanation
A	The 2 chiral centers on molecule **A** with no plane of symmetry both rotate the plane polarised light to the right. Hence, overall, it is observed that the plane polarised light is rotated to the right.
B	Molecule **B** is the enantiomer of molecule **A** and hence the 2 chiral centers on molecule **B** both rotate the plane polarised light to the left. Hence, overall, it is observed that the plane polarised light is rotated to the left.
C	Molecule **C** is a meso compound that has an internal plane of symmetry. The 2 chiral centers on the tartaric acid molecule rotates plane polarised light in different directions by the same extent and their optical activity are cancelled out. Hence, there is overall no effect on the plane polarised light.



molecules **A** and **B**



molecule **C**

II. Additional Readings

Drugs effects of the enantiomers of Thalidomide

Thalidomide first appeared in Germany on 1st October 1957. It was marketed as a sedative with apparently remarkably few side effects. It was believed the drug was safe and even suitable for prescription to pregnant women to manage symptoms of morning sickness.

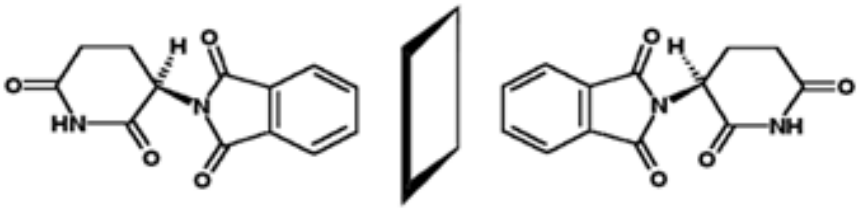
It was quickly prescribed to thousands of women and spread to most corners of the globe. No one knew what was to follow. Drug testing procedures were far more relaxed at this time, and although tests had taken place on thalidomide, they didn't reveal any of its tetragenic (causes abnormalities in foetus after exposure during pregnancy) properties. The tests on thalidomide were conducted on rodents which metabolised the drug in a different way from humans.

Towards the end of the fifties, children began to be born with shocking disabilities, such as flipper–like limbs. Babies affected by this tragedy were thus given the name *'Thalidomide Babies'*.

Pictured right are some of children born with the flipper–like limbs. Remarkably, many of the children involved have gone on to lead successful and fulfilling lives.

The chemistry behind the incident

Thalidomide has one chiral atom and exists as two enantiomers. The diagram below shows the enantiomers of this drug.



R-Thalidomide
(sleep-inducing)

S-Thalidomide
(teratogenic)

Laboratory tests after the thalidomide disaster showed that only one isomer of thalidomide ('R' isomer) was an effective sedative while the 'S' isomer is a teratogen.

However, it is now known that even when a stereo selective sample of thalidomide (only one of the enantiomers) is created, the isomers interconvert under biological conditions. This means that both enantiomers will exist in the blood. So, even if a drug of only the 'R' isomer is administered, the disaster would not have been averted.

Sources:
www.chm.bris.ac.uk/motm/thalidomide/first.html
https://www.acs.org/molecule-of-the-week/archive/t/thalidomide.html#:~:text=Thalidomide%20exists%20in%20two%20mirror,isomers%20before%20use%20is%20ineffective.