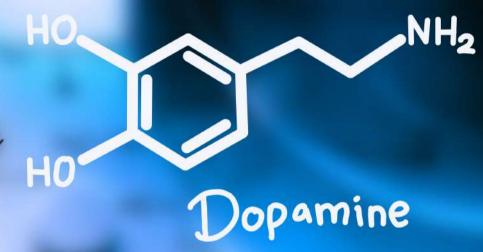
Dryanic 1





Subject: Sterochemistry



Pharmaceutical Organic Chemistry-1

Chapter-5: Stereoisomerism

Isomers: molecular formula 11 viei les ciuso
2 (connectivity) Structural/constitutional isomers Connectivity Structural/constitutional isomers Connectivity Structural/constitutional isomers Connectivity Structural/constitutional isomers
Cz Hz O miecular CMzCHz OH, CMzOM, : Sho 2 - (społiw arrangment) Ejvil & wij is wis wind arrangment Stereais omerism OH A Jho The
Isomers
Constitutional Isomers Stereoisomerism
s rieletal functional positional
reman Conformationale
configurationala
d
geometrical optical

معدمة كيف بيجي السؤال في الامتحال وكيف طريقة الحل بشكل عام:

- what is the relation between the following compounds;

a) same

b) different

C) constitutional isomers

d) stereoisomers

: ple slû jest -

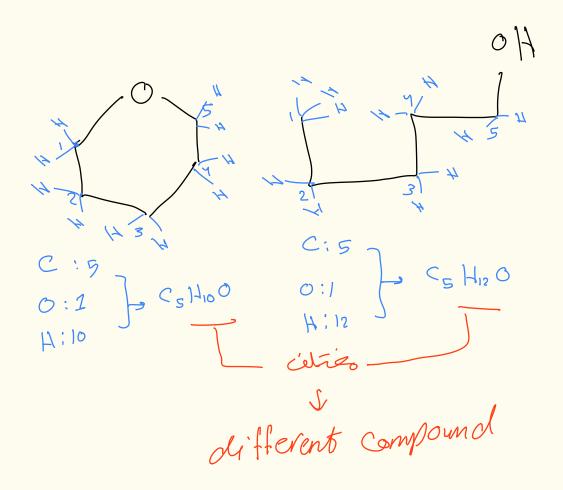
1- نقوم نبد انوام الذرات وعدد كل نوع لمعرف الصيفة الجزيدية [في حال كان المركبان يختلفان في الصيفة فعي محتلفان (لمحالك المحالك المحالة الكانبة على العضوة الكانبة على الإنتقال العضوة الكانبة على المحالة المحالفة الم

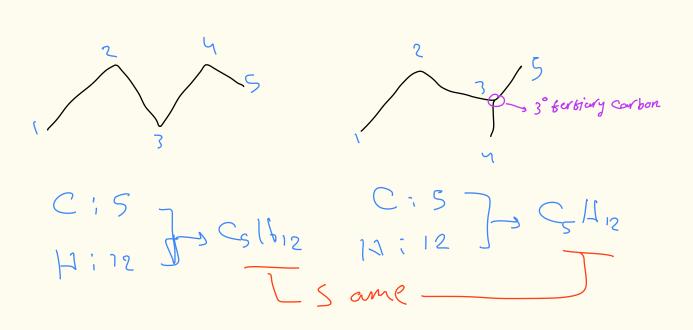
" lieen - 1 Los Stul pois - 2

(C-cons bitubional isomers) له و ما المركبان معتقلاً في الرينقال المحظوة و على المان مثبت بيال يتم الإنتقال المحظوة و على حال كان مثبت بيال يتم الإنتقال المحظوة و

euis "spatial arrangment" 3- نقوم بالتأكد مك النرات في الفراغ (d-stereoisomers) أو في حال كان المركب في الغرافي في الغرافي في حال كان المركب في الغرافي في حال كان المركب في الترتيب في الترتيب في الغرافي في حال كان متشابيين في الترتيب في الغرافي في حال كان المركب في حال كان المركب في الترتيب في الغرافي في حال كان المركب في الترتيب في الغرافي في حال كان المركب في الترتيب في الغرافي في حال كان المركب في الترتيب في المركب في المركب

: Jho





not the same connectivity -> structural

Answer -> 1'somers

what is the relation between ex:
A. Cy Hio Jame A. B. B. Same C. Cy His

Cy His

Cy His

Constitutional isome for A and C

A and C are the same -> there is no different in molecular formula, Connectivity and Spallal orrengment 5x: positional constitutional isomer some ex: \bigwedge , 1 $\frac{1}{3}$ $\frac{4}{5}$ the same A anel B 13.5 with are Constitutional Isomers

Chirality & Stereochemistry

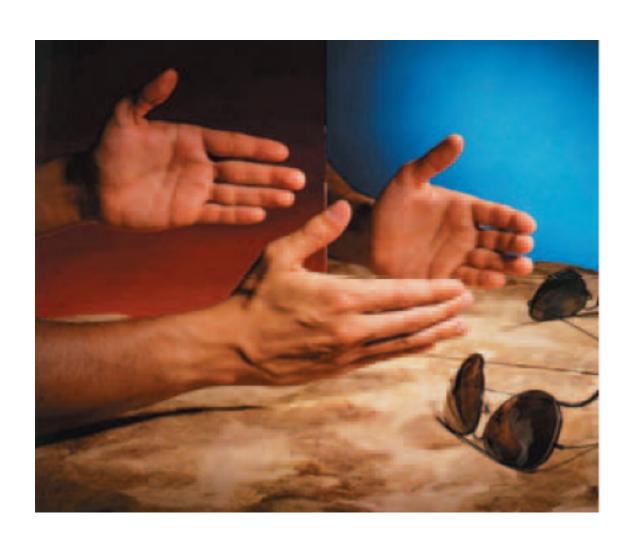
An object is achiral (not chiral) if the object and its mirror image are identical

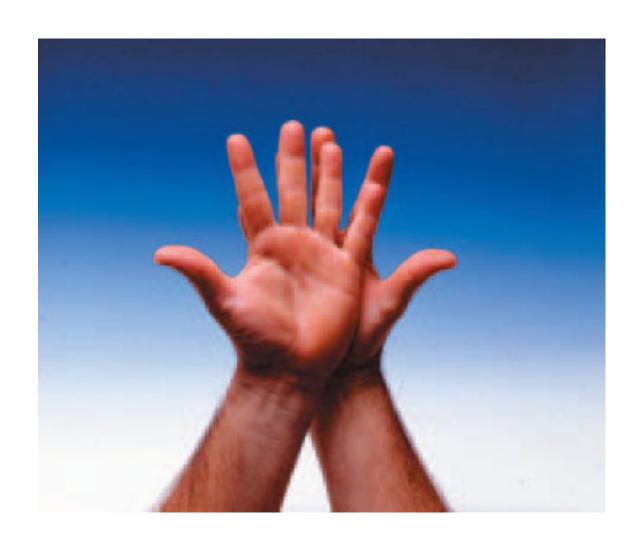


وادا رسمت خط و قسمت المركب على قسمين متماثلين فحيكون مفايق لمورته باعراة على مدلناكي مداناتها على المركب المر

A chiral object is one that cannot be superposed on its mirror image

(منطيق)





chiralisation of your leve c si

1. Isomerism: Constitutional Isomers & Stereoisomers

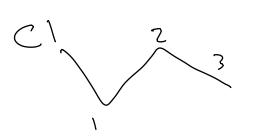
1A. Constitutional Isomers

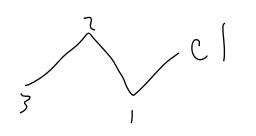
- Isomers: different compounds that have the same molecular formula
 - Constitutional isomers: isomers
 that have the same molecular
 formula but different connectivity
 –their atoms are connected in a
 different order

Examples

Molecular Formula

 C_4H_{10}



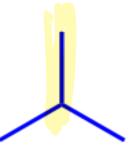


Constitutional

Isomers

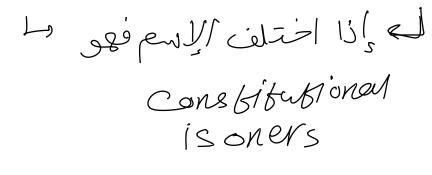


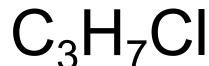
and



Butane

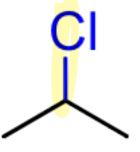
2-Methylpropane







and



1-Chloropropane

2-Chloropropane

Examples

Molecular Formula

 C_2H_6O

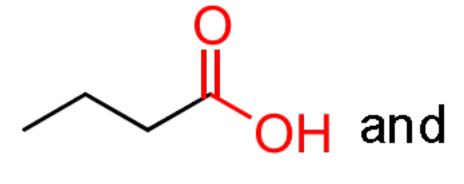
Constitutional Isomers

OH and Ethanol

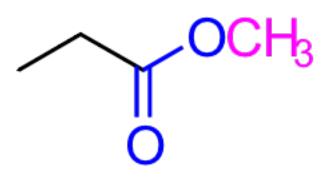
CH3-O-CH3

Methoxymethane

$$C_4H_8O_2$$



Butanoic acid



Methyl propanoate

Functional Constitutional isomers; - في حال المركبين اختلفوا بار functional groub z mekhory mekhane Ethones positional constitutional isomers: عي حال اختلاف موقع ال functional growt CI)
-: Jho 2-chloro propune 1 - chloro propone

Skeletal Constitutional isomers:

(19:511 (166 G Uis) Joge
-: Jan

butene 2-me thyl butane

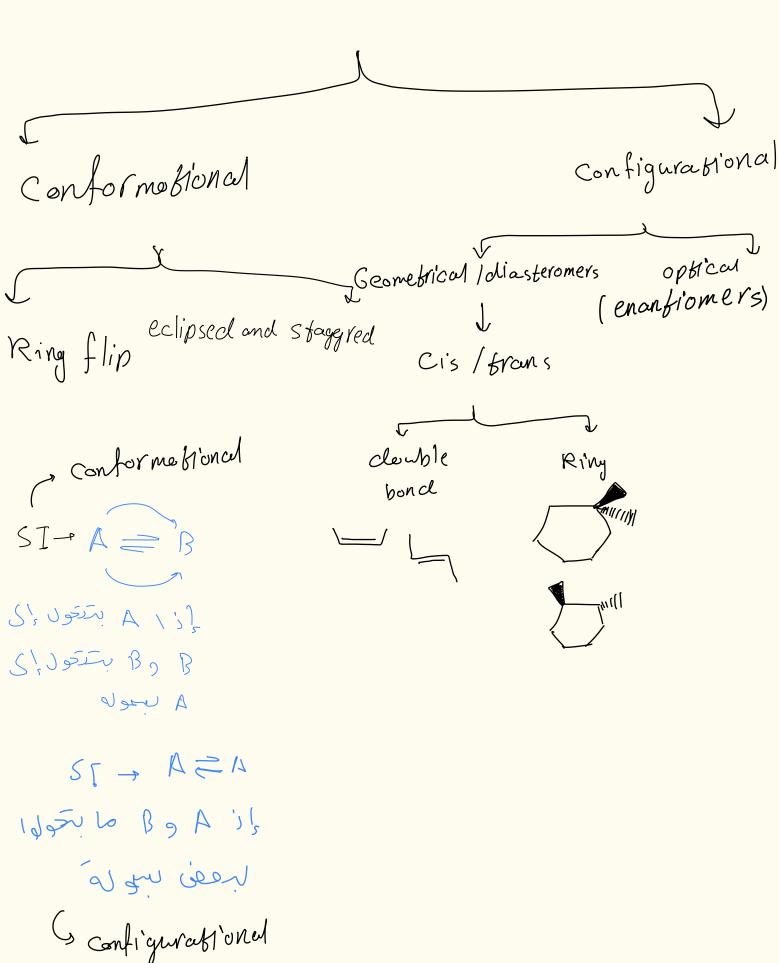
[Zuland Fiolial Coloo)

1B. Stereoisomers

Stereoisomers are NOT constitutional isomers

Stereoisomers have their atoms connected in the same sequence but they differ in the arrangement of their atoms in space. The consideration of such spatial aspects of molecular structure is called stereochemistry

Steven Somers (S.T)

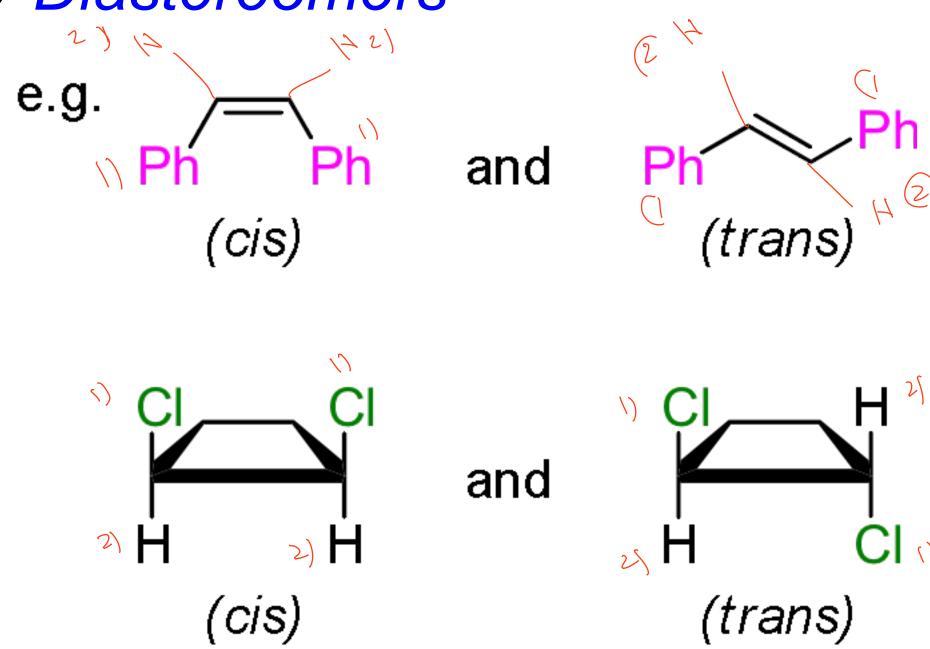


1C. Enantiomers & Diastereomers

- Stereoisomers can be subdivided into two general categories:
 - enantiomers & diasteromers
 - Enantiomers stereoisomers
 whose molecules are
 nonsuperposable mirror images of
 each other
 - Diastereomers stereoisomers whose molecules are not mirror images of each other

Geometrical isomers (cis & trans isomers) are:

Diastereomers



Subdivision of Isomers

Isomers

(different compounds with same molecular formula)

Constitutional Isomers

(isomers whose atoms have a different connectivity)

Stereoisomers

(isomers that have the same connectivity but differ in spatial arrangement of their atoms)

Enantiomers

(stereoisomers that are nonsuperposable mirror images of each other)

Diastereomers

(stereoisomers that are NOT mirror images of each other)

2. Enantiomers and Chiral Molecules

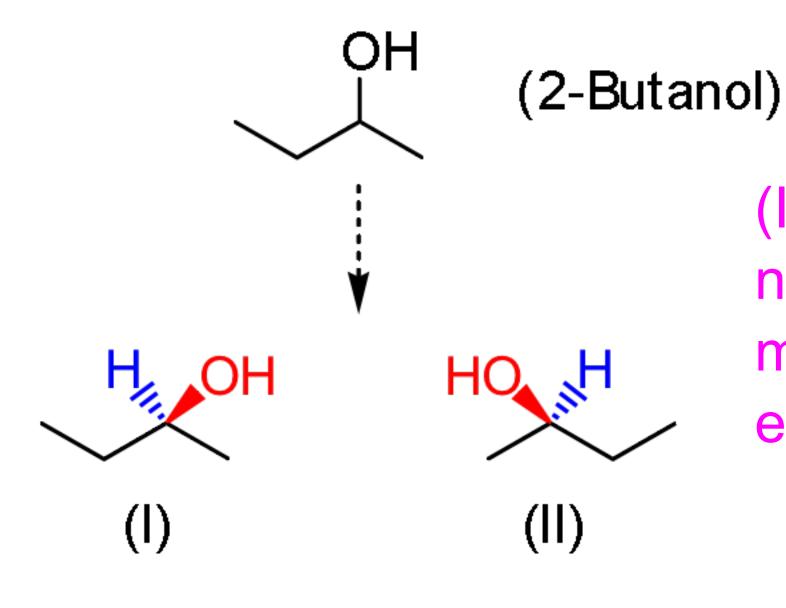
- Enantiomers occur only with compounds whose molecules are chiral
- A chiral molecule is one that is NOT superposable on its mirror image
- The relationship between a chiral molecule and its mirror image is one that is enantiomeric. A chiral molecule and its mirror image are said to be enantiomers of each other

Solid-Jash

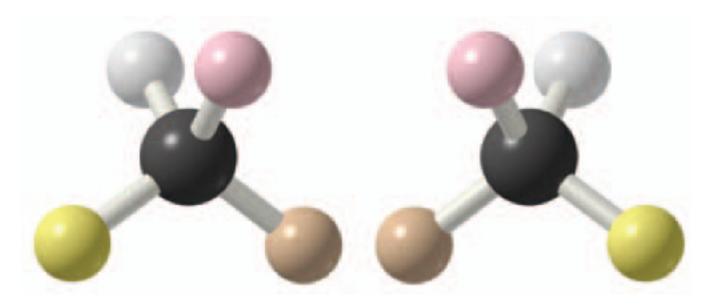
تَبين هذه الحَطوط الجاهات الذرات في الغرام

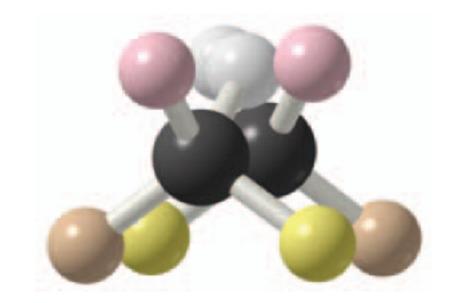
العن المعان في العالق المعادية بين المعادية والمعادية المعادية ال

لوجود - Cis واذا في عاطسه أو Ring في حال عدم وجودها نبجم في كونة achiral في حال كان متطابق ال يعتبر المحمد في حال كان متطابق لا يعتبر enantiomers دفي حال كان متطابق لا يعتبر enantiomers وإذا كال عنم منطبق يعتبر enantiomers وإذا كال عنم منطبق يعتبر enantiomers



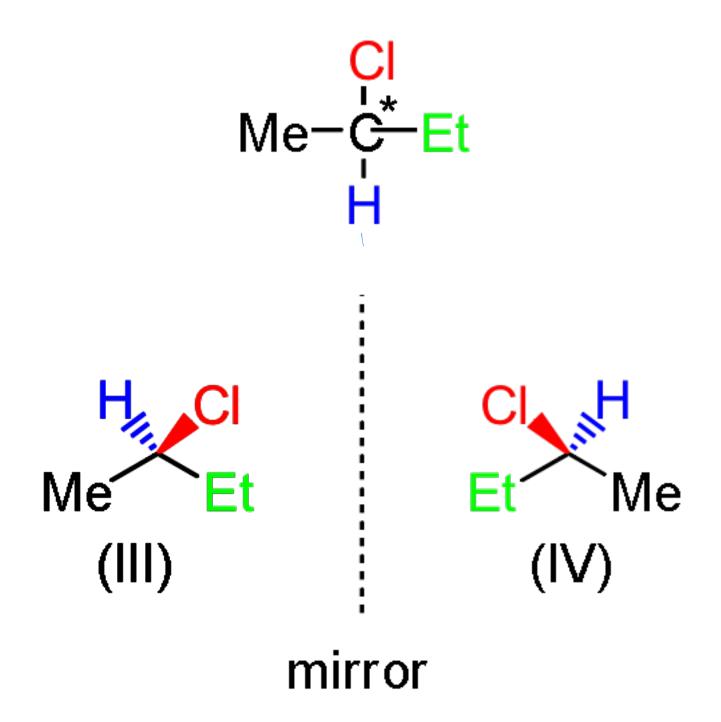
(I) and (II) are nonsuperposable mirror images of each other



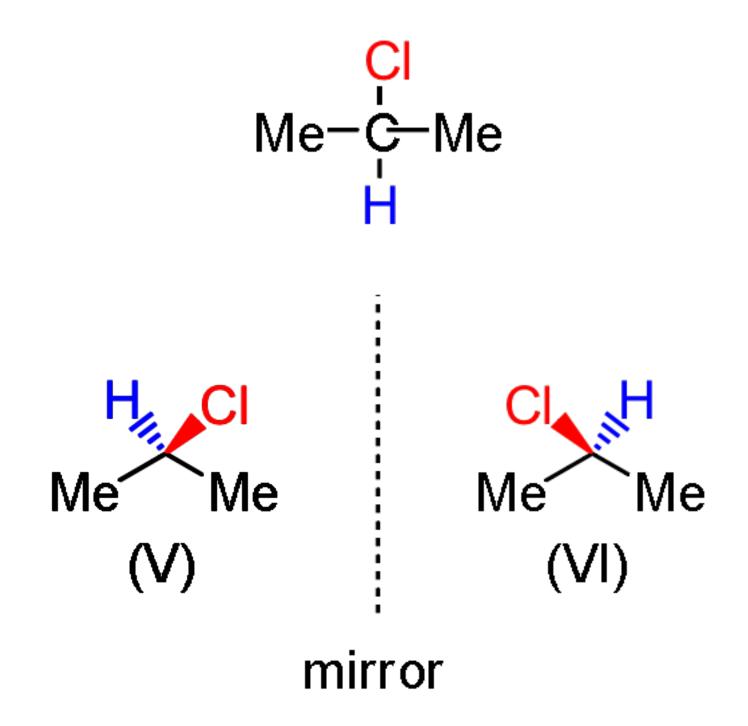


3. A Single Chirality Center Causes a Molecule to Be Chiral

The most common type of chiral compounds that we encounter are molecules that contain a carbon atom bonded to four different groups. Such a carbon atom is called an asymmetric carbon or a chiral center and is usually designated with an asterisk (*)



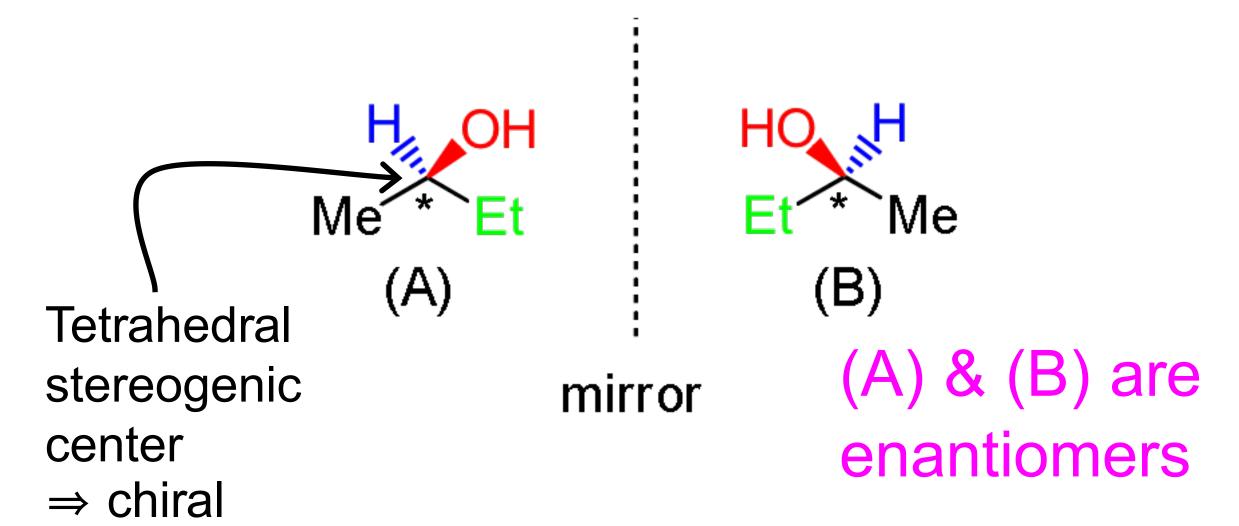
(III) and (IV) are nonsuperposable mirror images of each other



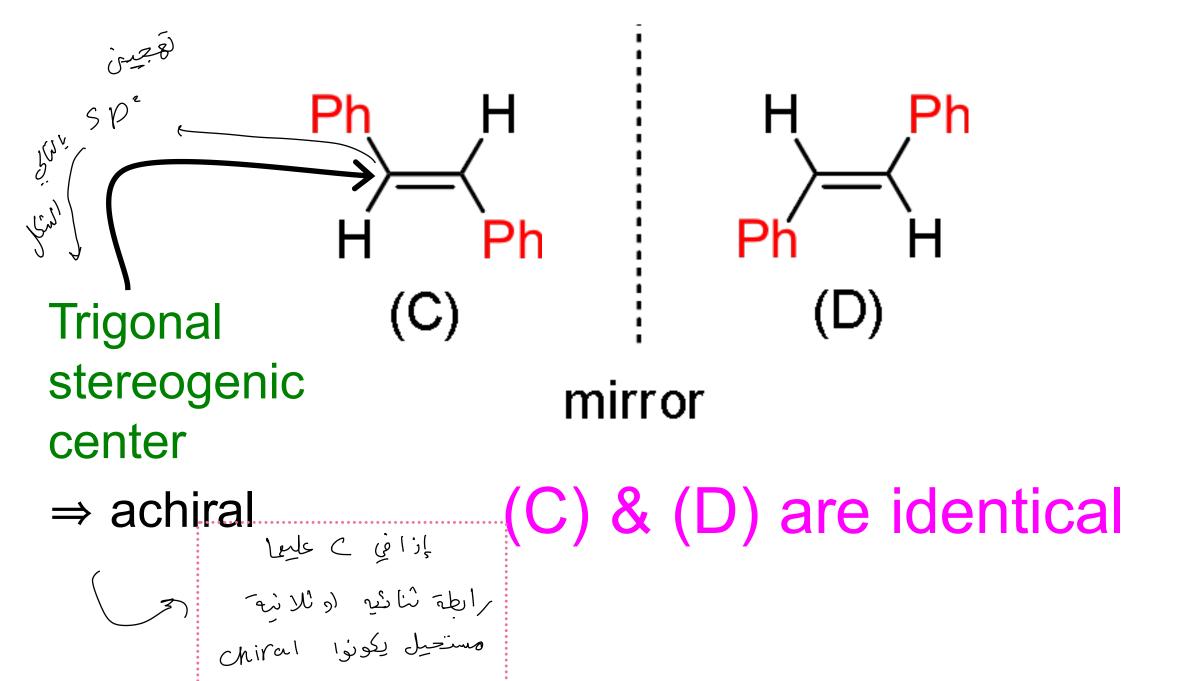
(V) and (VI) are superposable⇒ not enantiomers ⇒ achiral

3A. Tetrahedral vs. Trigonal Stereogenic Centers

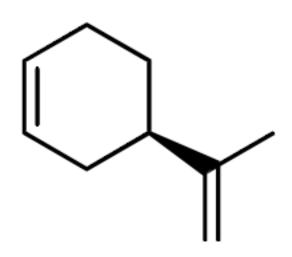
Chirality centers are tetrahedral stereogenic centers



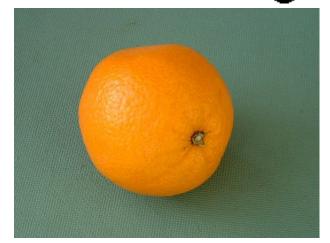
Cis and trans alkene isomers contain trigonal stereogenic centers

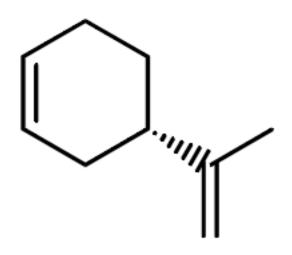


4. More about the Biological Importance of Chirality



(+)-Limonene (limonene enantiomer found in oranges)





(-)-Limonene (limonene enantiomer found in lemons)



Thalidomide

The activity of drugs containing chirality centers can vary between enantiomers, sometimes with serious or even tragic consequences

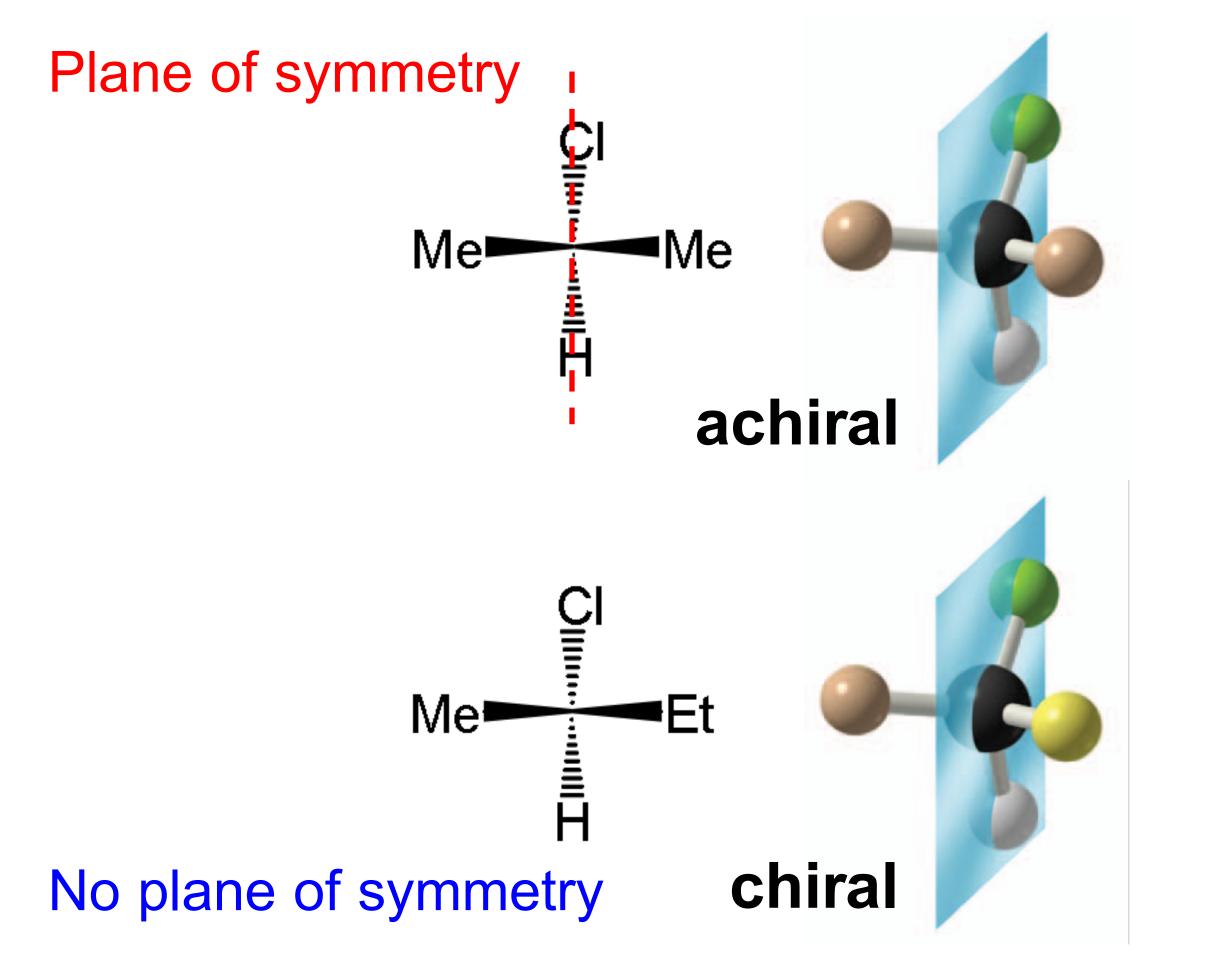
For several years before 1963 thalidomide was used to alleviate the symptoms of morning sickness in pregnant women In 1963 it was discovered that thalidomide (sold as a mixture of both enantiomers) was the cause of horrible birth defects in many children born subsequent to the use of the drug

Thalidomide (cures morning sickness)

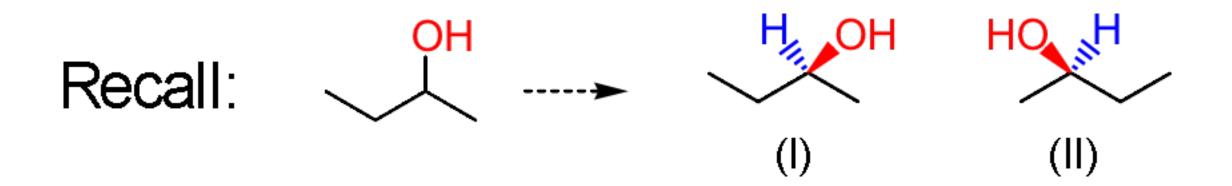
enantiomer of
Thalidomide
(causes birth defects)

5. How to Test for Chirality: Planes of Symmetry

- A molecule will not be chiral if it possesses a plane of symmetry
- A plane of symmetry (mirror plane) is an imaginary plane that bisects a molecule such that the two halves of the molecule are mirror images of each other
- All molecules with a plane of symmetry in their most symmetric conformation are achiral



6. Naming Enantiomers: R,S-System



- Using only the IUPAC naming that we have learned so far, these two enantiomers will have the same name:
 - 2-Butanol
- This is undesirable because each compound must have its own distinct name

6A. How to Assign (R) and (S) Configurations

Rule 1

 Assign priorities to the four different groups on the stereocenter from highest to lowest (priority bases on atomic number, the higher the atomic number, the higher the priority)

Increasing the abomic number

I > Br > Cl > S > P > F 70 > N > C > H

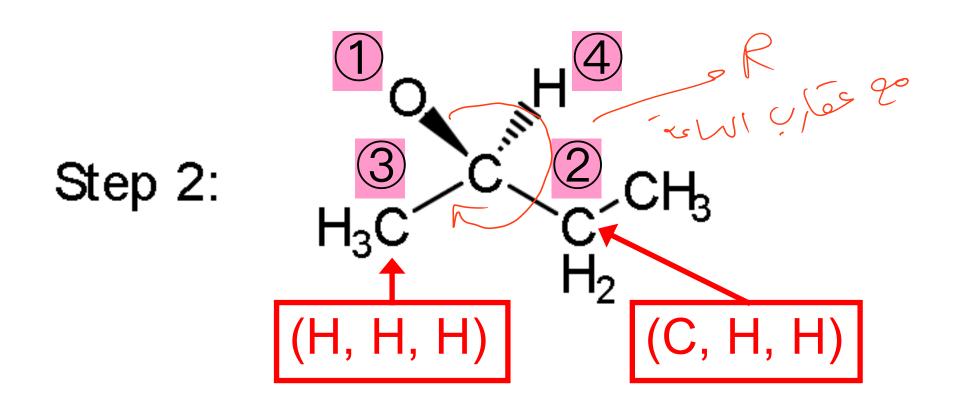
Rule 2

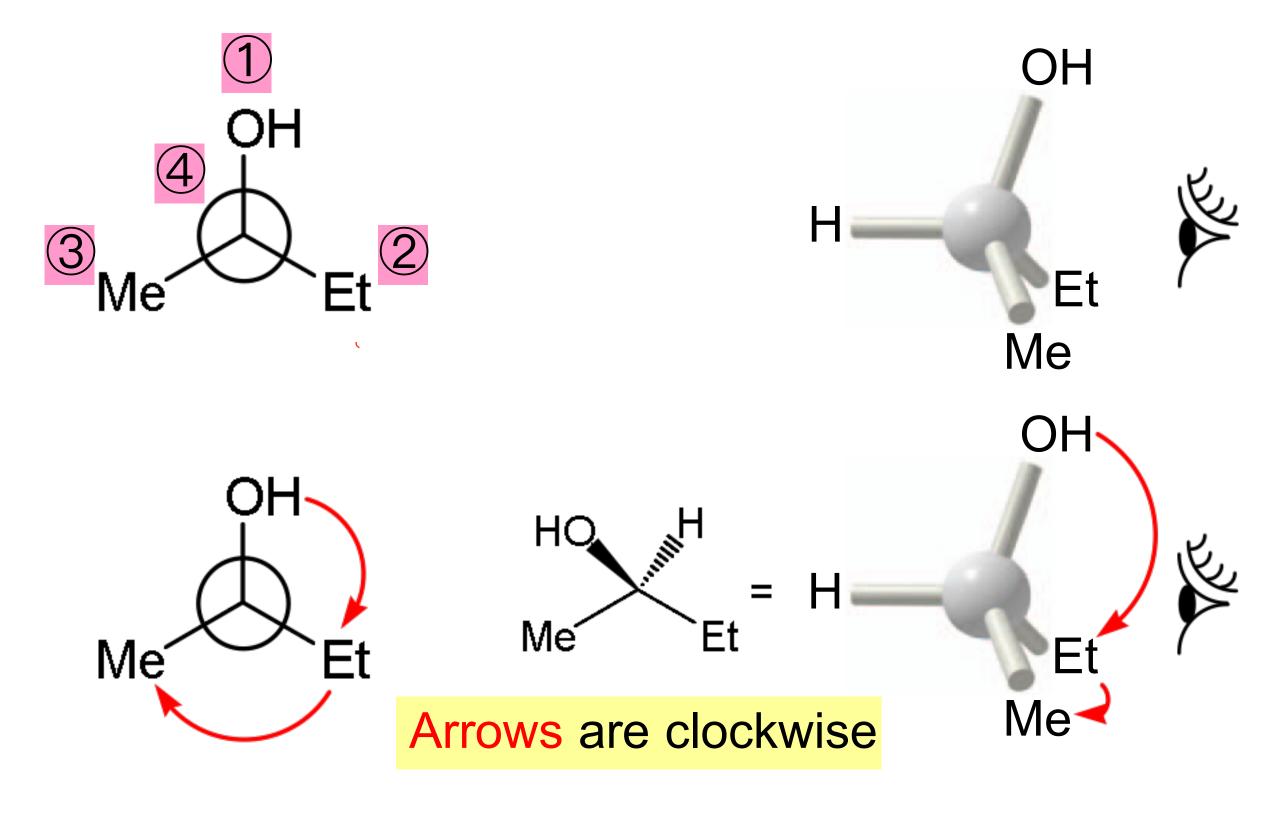
 When a priority cannot be assigned on the basis of the atomic number of the atoms that are directly attached to the chirality center, then the next set of atoms in the unassigned groups is examined. This process is continued until a decision can be made.

Re Delm) colès es Se delm) colès en de

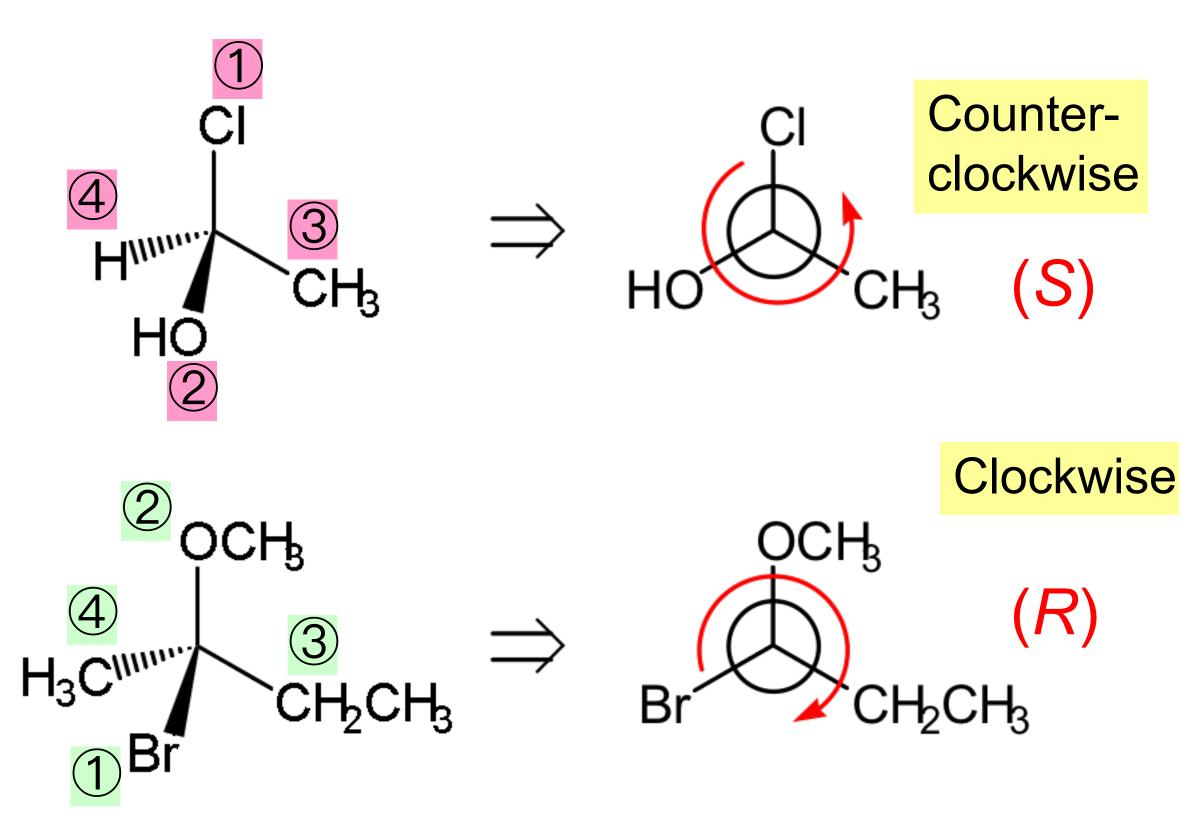
* Rule 3

 Visualize the molecule so that the lowest priority group is directed away from you, then trace a path from highest to lowest priority. If the path is a clockwise motion, then the configuration at the asymmetric carbon is (R). If the path is a counter-clockwise motion, then the configuration is (S)

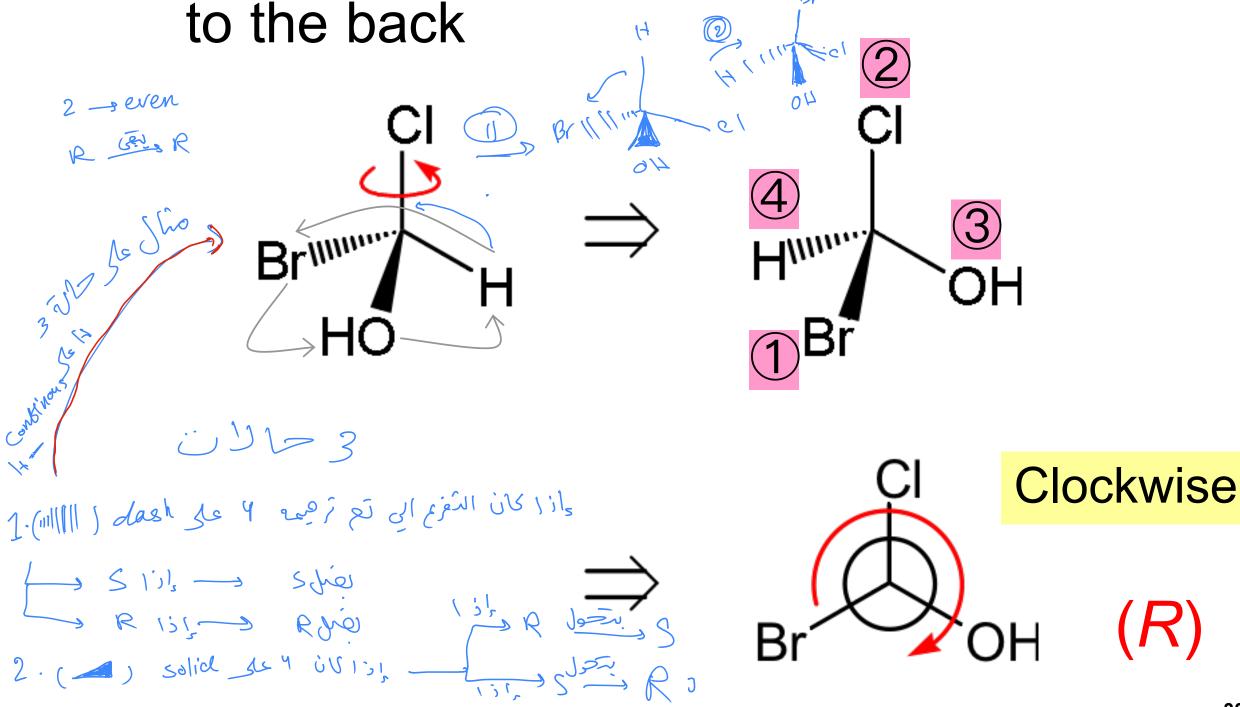




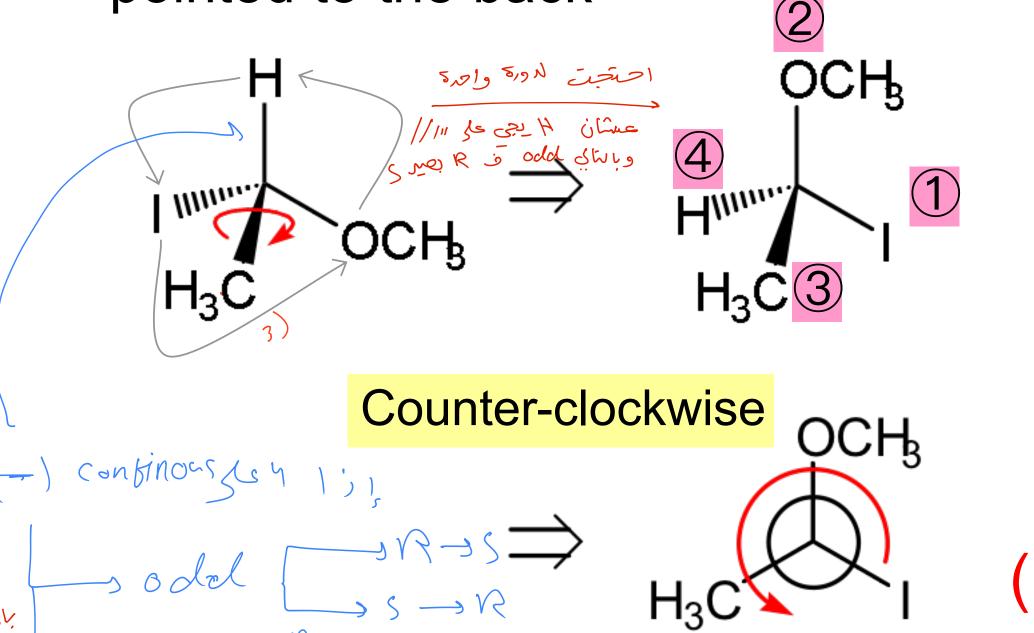
(R)-2-Butanol



Rotate C–Cl bond such that H is pointed



 Rotate C–CH₃ bond such that H is pointed to the back



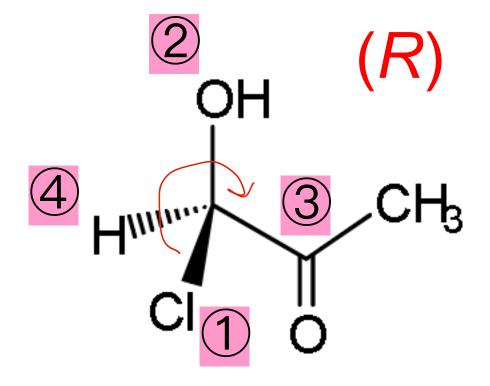
Rule 4

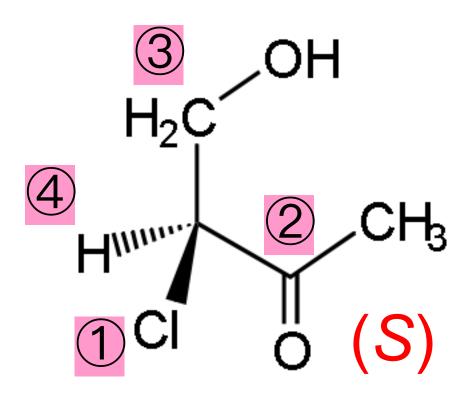
 For groups containing double or triple bonds, assign priorities as if both atoms were duplicated or triplicated

Example

Thus,
$$-CH_3 \Rightarrow (H, H, H)$$

$$-CH=CH_2 \Rightarrow (C, C, H)$$

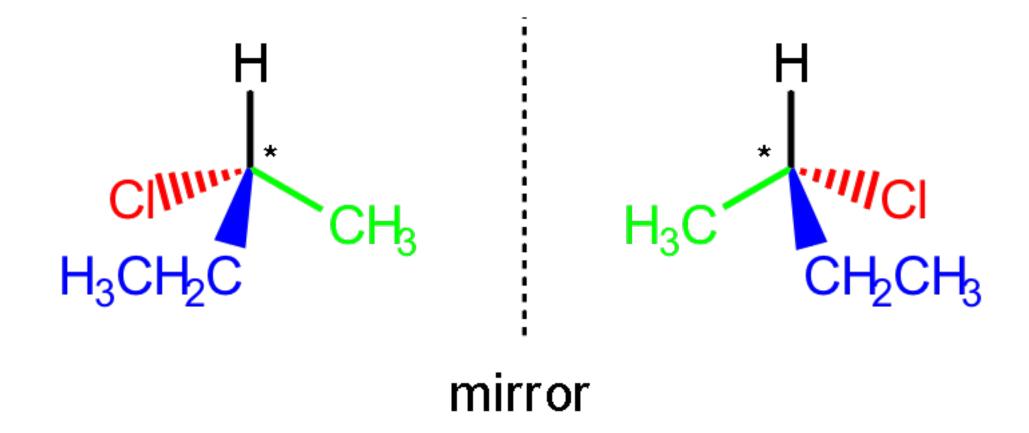




$$\bigcirc$$
 C \Rightarrow (O, O, C)

7. Properties of Enantiomers: Optical Activity

- Enantiomers
 - Mirror images that are not superposable



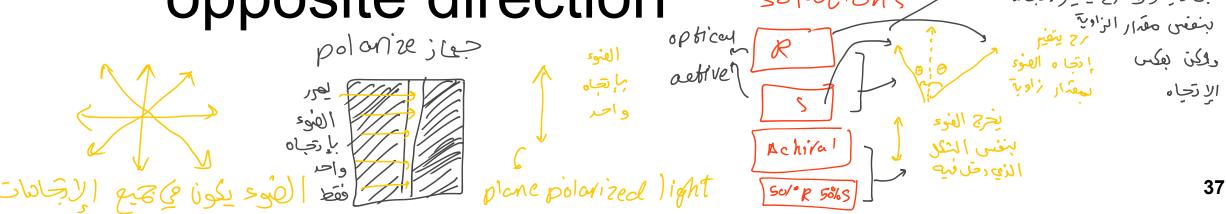
* Enantiomers have identical physical properties (e.g. melting point, boiling point, refractive index, solubility etc.)

Compound	bp (°C)	mp (°C)
(R)-2-Butanol	99.5	> enontioner
(S)-2-Butanol	99.5	عل جم لازم رهيم على
(+)-(R,R)-Tartaric Acid	R R Janua klome	168 – 170
(-)-(S,S)-Tartaric Acid	S September 1	168 – 170
(+/–)-Tartaric Acid	enantioners جدال المناب عنه عنه منه منه منه منه منه منه منه منه منه م	210 – 212

reactivity se sor celisis chairal eo Jelis chiral la

Enantiomers

- Have the same chemical properties (except reaction/interactions with chiral substances)
- Show different behavior only when they interact with other chiral substances
- Turn plane-polarized light on opposite direction

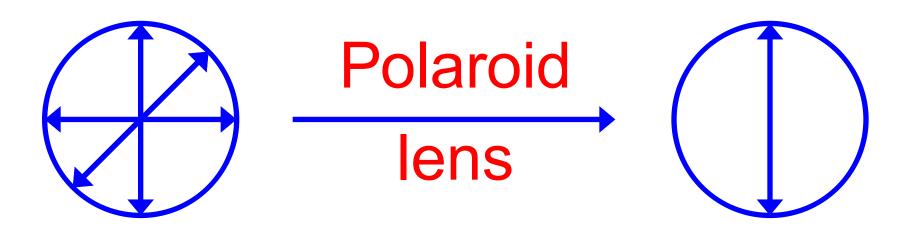


Optical activity

 The property possessed by chiral substances of rotating the plane of polarization of plane-polarized light

7A. Plane-Polarized Light

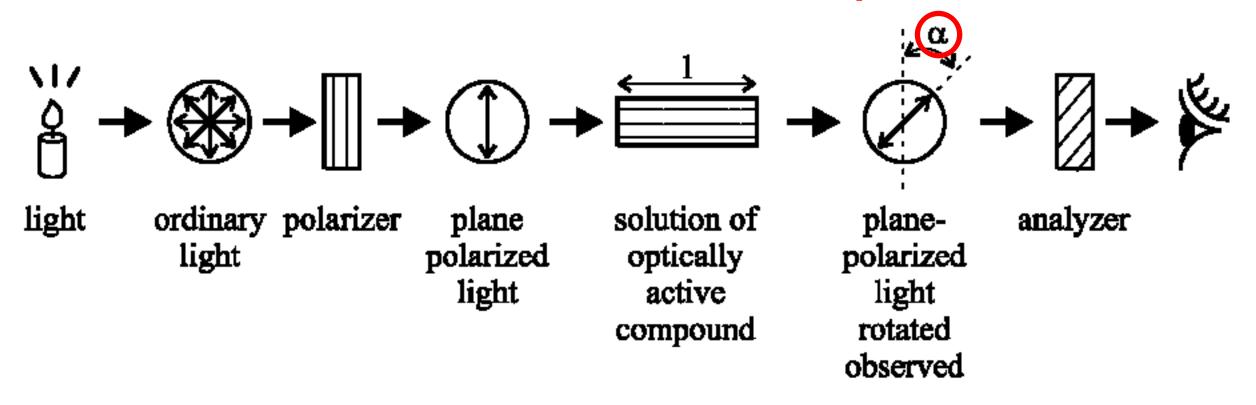
- The electric field (like the magnetic field) of light is oscillating in all possible planes
- When this light passes through a polarizer (Polaroid lens), we get planepolarized light (oscillating in only one plane)



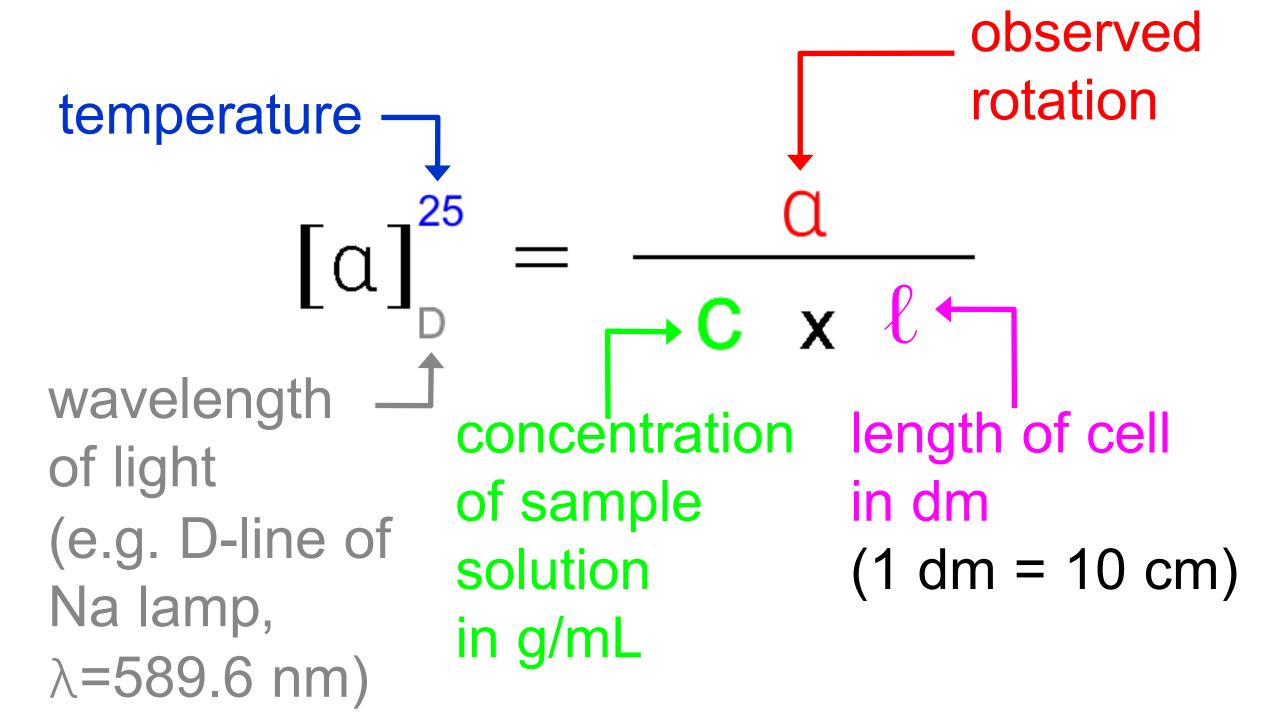
7B. The Polarimeter

A device for measuring the optical activity of a chiral compound

a = observed optical rotation



7C. Specific Rotation

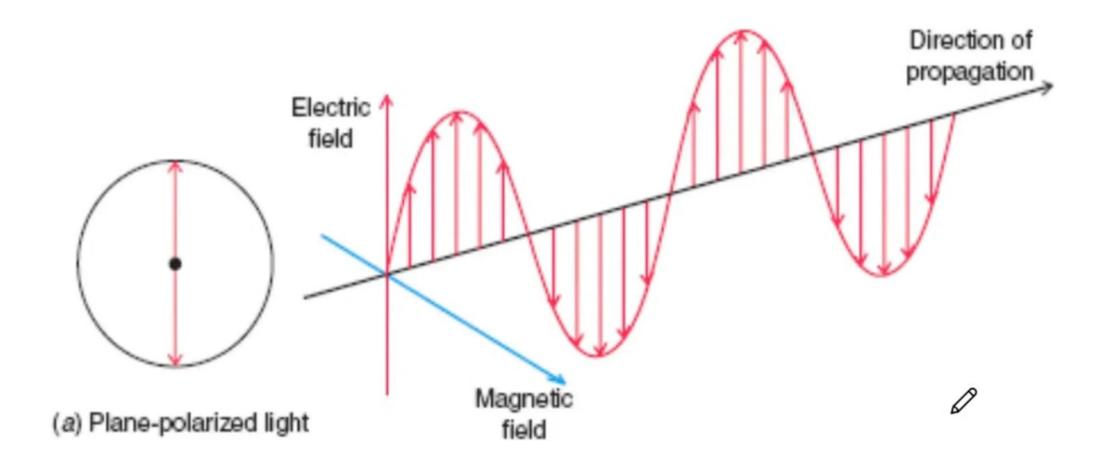


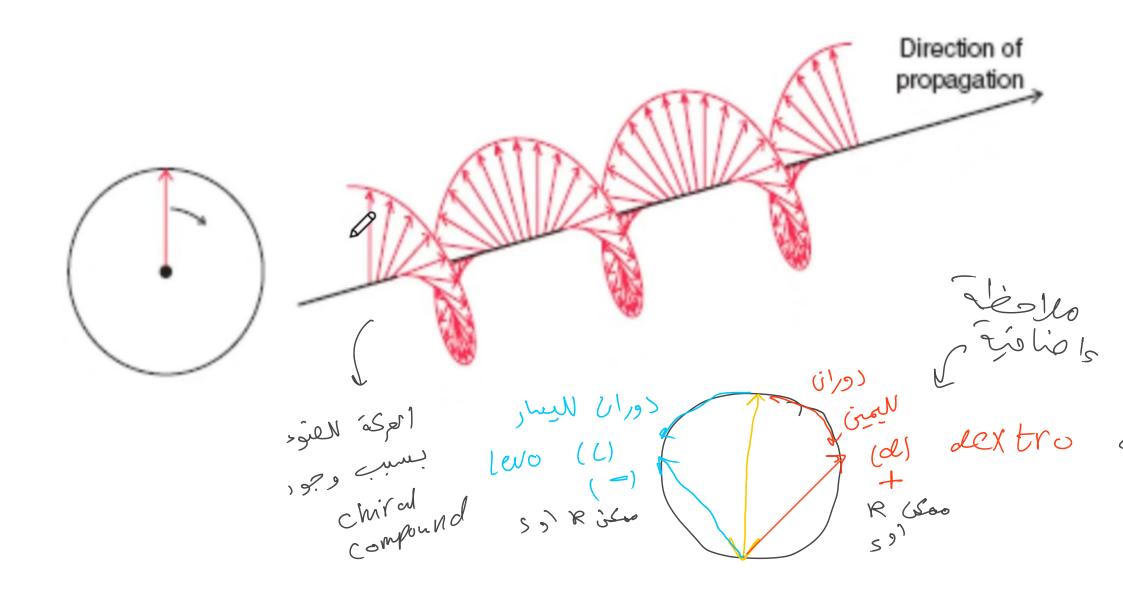
- The value of α depends on the particular experiment (since there are different concentrations with each run)
 - But specific rotation [a] should be the same regardless of the concentration

Two enantiomers should have the same value of specific rotation, but the signs are opposite

$$H_{0}$$
 H_{0}
 H

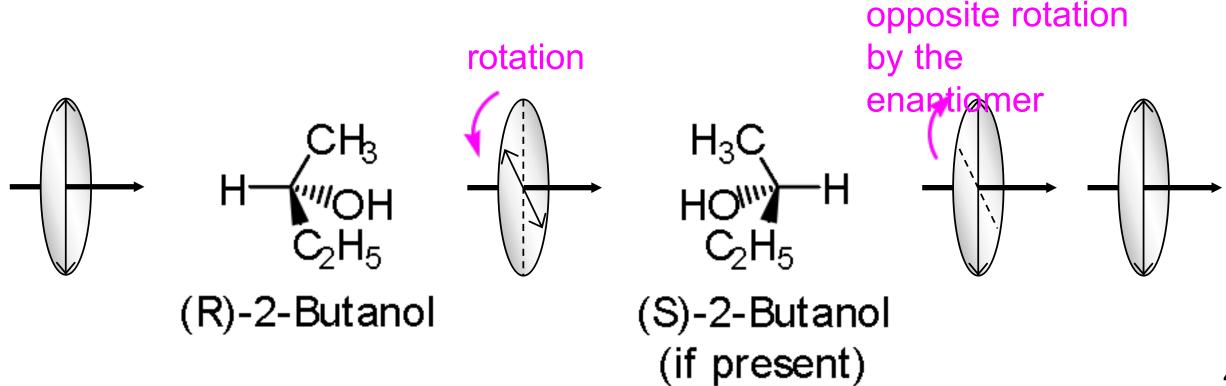
8. The Origin of Optical Activity





8A. Racemic Forms

- An equimolar mixture of two enantiomers is called a racemic mixture (or racemate or racemic form)
- A racemic mixture causes no net rotation of plane-polarized light



equal &

8B. Racemic Forms and Enantiomeric Excess

❖ A sample of an optically active substance that consists of a single enantiomer is said to be enantiomerically pure or to have an enantiomeric excess of 100% An enantiomerically pure sample of (S)-(+)-2-butanol shows a specific rotation of +13.52

- ❖ A sample of (S)-(+)-2-butanol that contains less than an equimolar amount of (R)-(−)-2butanol will show a specific rotation that is less than 13.52 but greater than zero
- Such a sample is said to have an enantiomeric excess less than 100%

Enantiomeric excess (ee)

Also known as the optical purity

$$\frac{\text{mole of one }}{\text{excess}} = \frac{\left(\begin{array}{c} \text{mole of one } \\ \text{enantiomer} \end{array}\right) - \left(\begin{array}{c} \text{moles of other } \\ \text{enantiomer} \end{array}\right)}{\text{total moles of both enantiomers}} \times 100$$

Can be calculated from optical rotations

Example

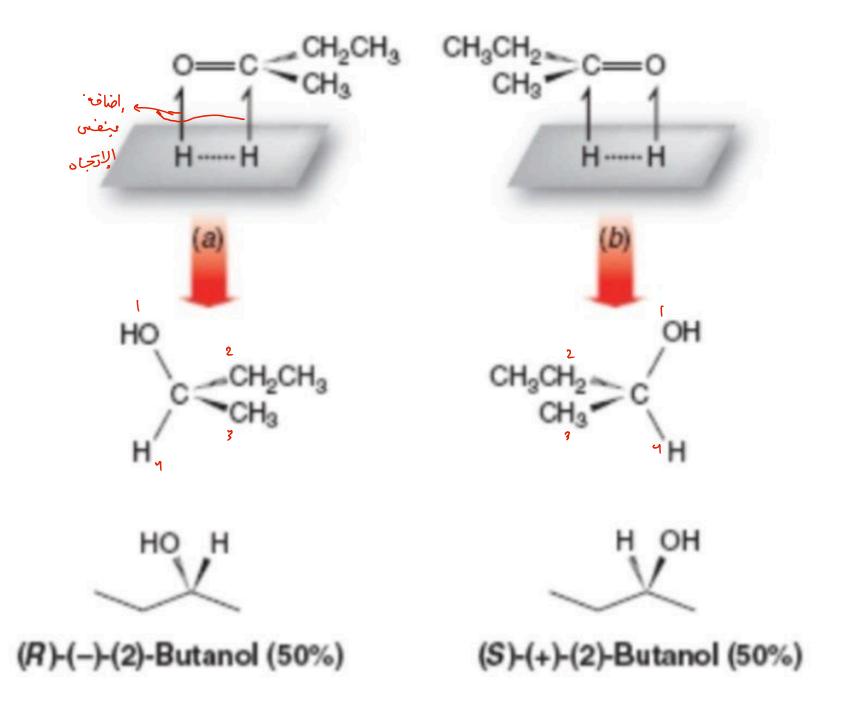
 A mixture of the 2-butanol enantiomers showed a specific rotation of +6.76. The enantiomeric excess of the (S)-(+)-2-butanol is 50%

$$\frac{\text{% enantiomeric}}{\text{excess *}} = \frac{+6.76}{+13.52} \times 100 = 50\%$$

9. The Synthesis of Chiral Molecules

9A. Racemic Forms

Butanone (achiral molecules) Hydrogen (achiral molecules) (±)-2-Butanol (chiral molecules; but 50:50 mixture (R) & (S))



9B. Stereoselective Syntheses

- * Stereoselective reactions are reactions that lead to a preferential formation of one stereoisomer over other stereoisomers that could possibly be formed
 - enantioselective if a reaction من الثانية produces preferentially one enantiomer والعلاقة over its mirror image
 - diastereoselective if a reaction leads preferentially to one diastereomer over others that are possible

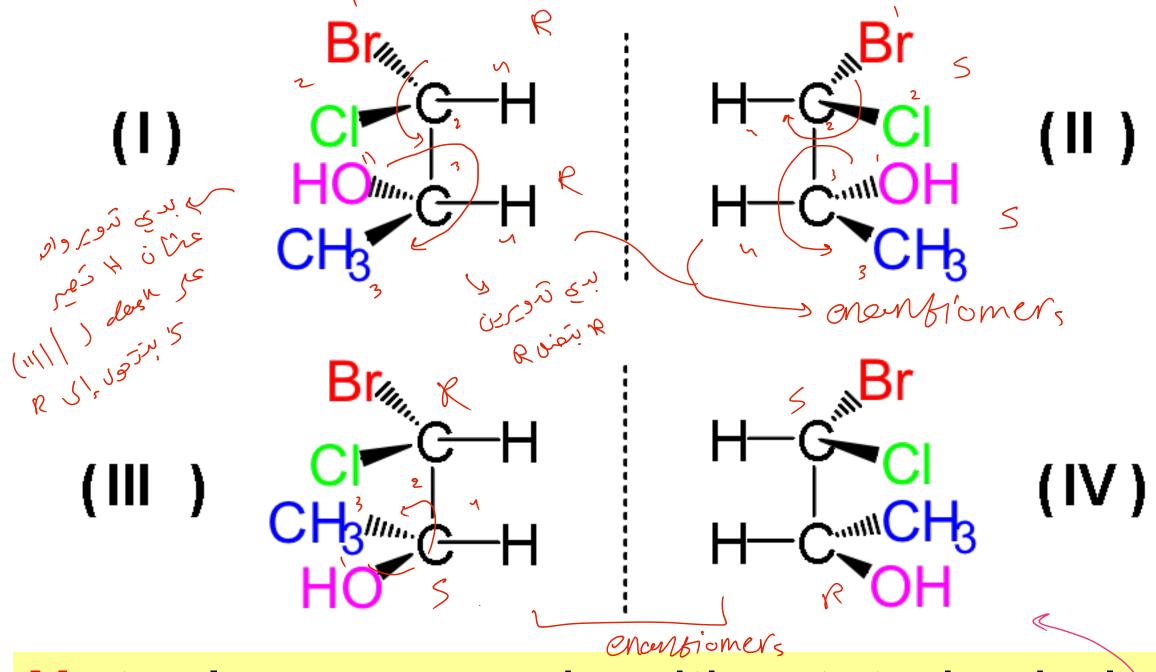
10. Molecules with More than One Chirality Center

- Diastereomers
 - Stereoisomers that are not enantiomers

 Unlike enantiomers, diastereomers usually have substantially different chemical and physical properties

oill Viceing

(2R, 3s)-3-floro-2 (25,3R)-3-Floro-2-butanol the relation is diasteroner Chiral & Elicon enantioners S 5 John R Richos

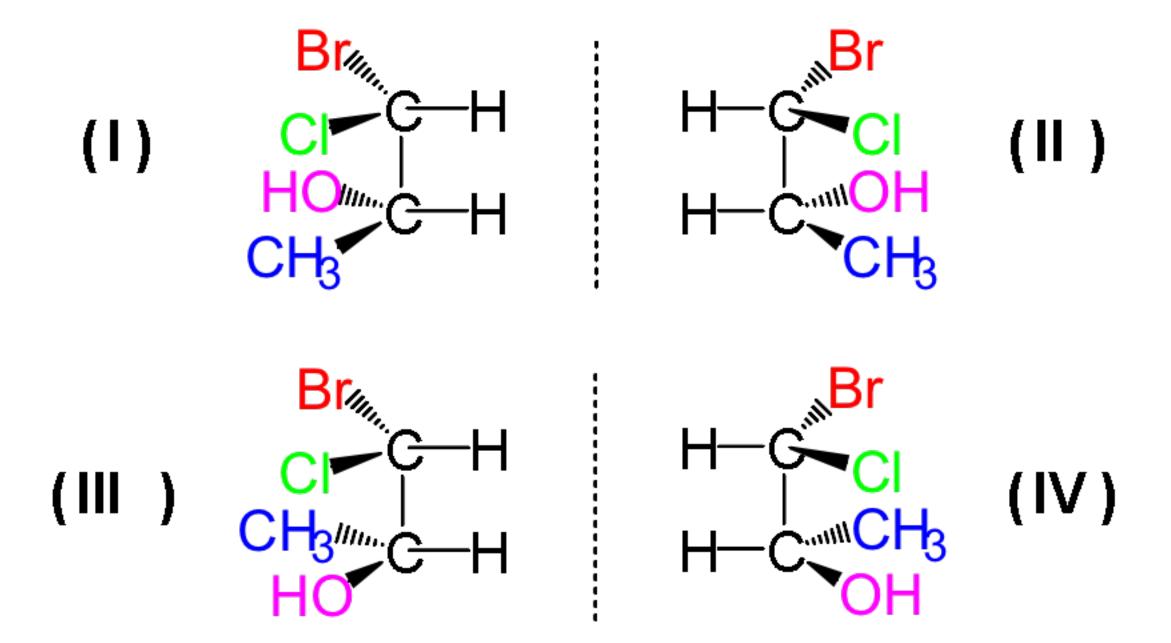


Note: In compounds with n tetrahedral stereocenters, the maximum number of stereoisomers is 2^n .

4 ste reoisomergie isse 4 = 2°

2 confer

وحسب القانور



(I) & (II) are enantiomers to each other(III) & (IV) are enantiomers to each other

- Diastereomers to each other:
 - (I) & (III), (I) & (IV), (II) & (III), (II) &(IV)

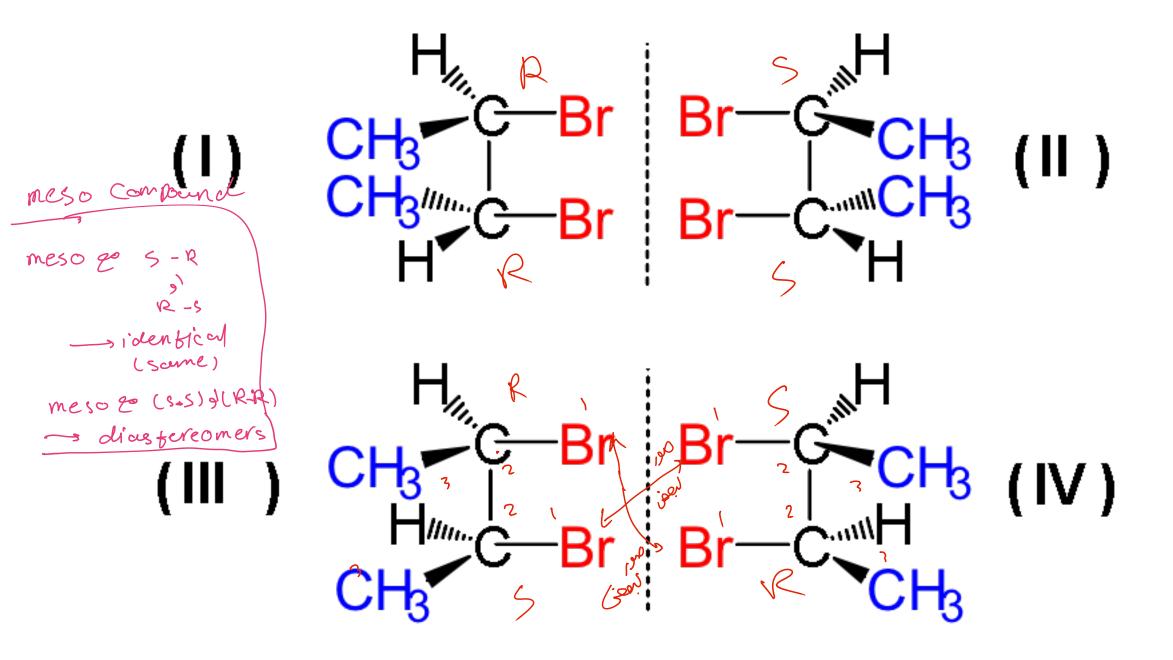
10A. Meso Compounds

- For example, 2,3-dichlorobutane has two stereocenters, but only has 3 stereoisomers (not 4)

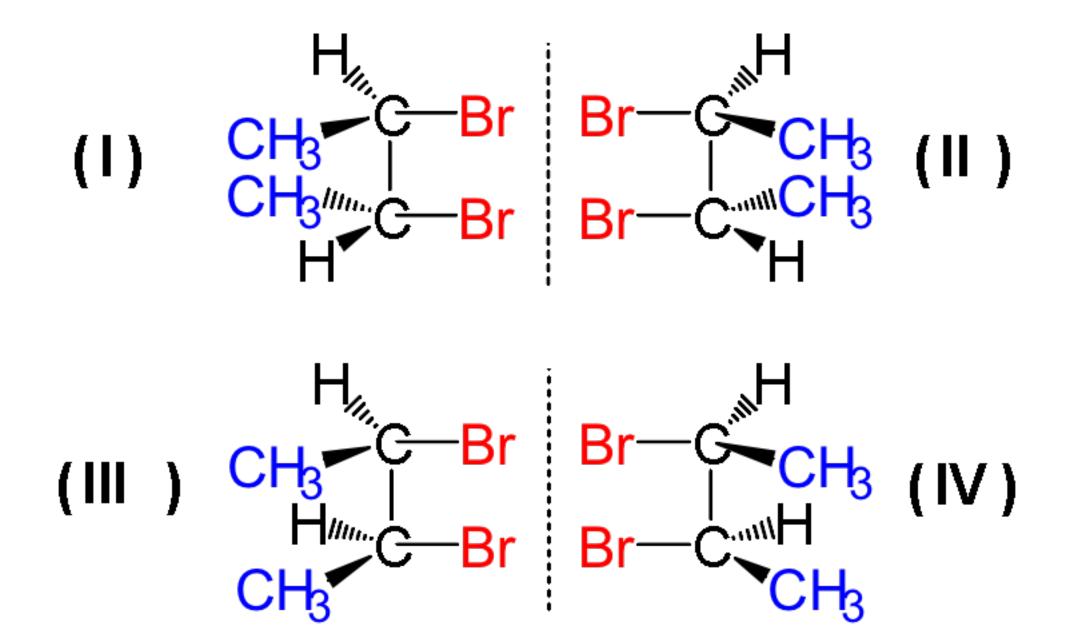
Meso Compound journels just 1

Je VISte 2 chairal center es just sight sights phically achairal compounding in Uls

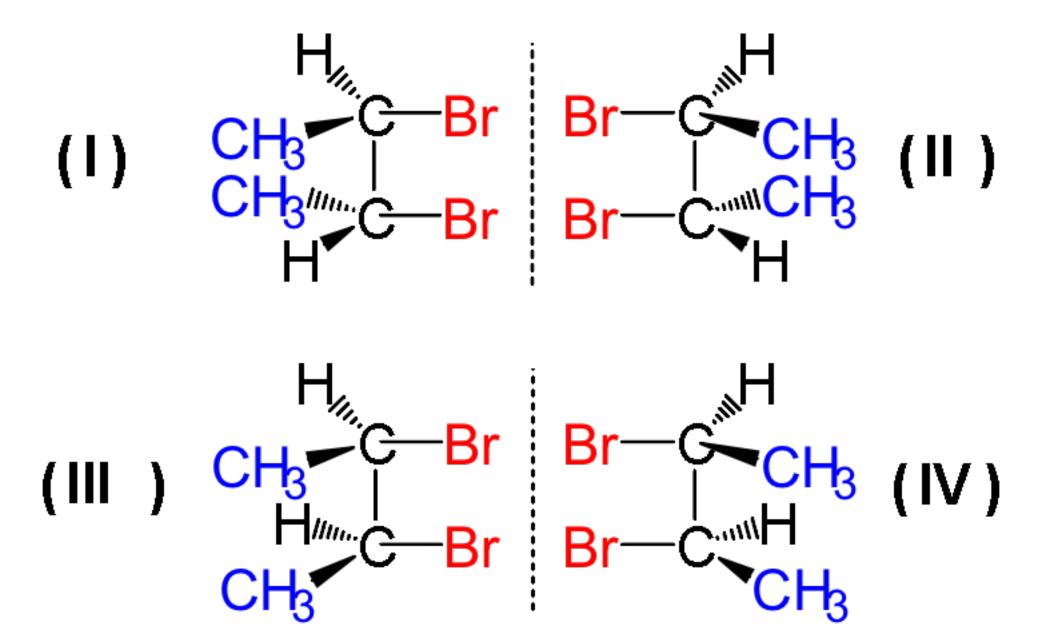
machine



Note: (III) contains a plane of symmetry, is a meso compound, and is achiral ($[\alpha] = 0^{\circ}$).



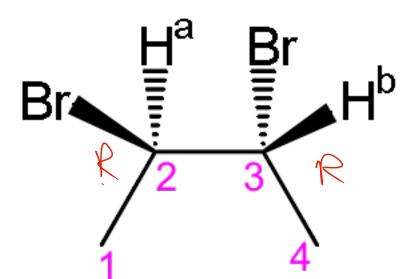
- (I) & (II) are enantiomers to each other and chiral
- (III) & (IV) are identical and achiral



- * (I) & (III), (II) & (III) are diastereomers
- Only 3 stereoisomers:
 - (I) & (II) {enantiomers}, (III) {meso}

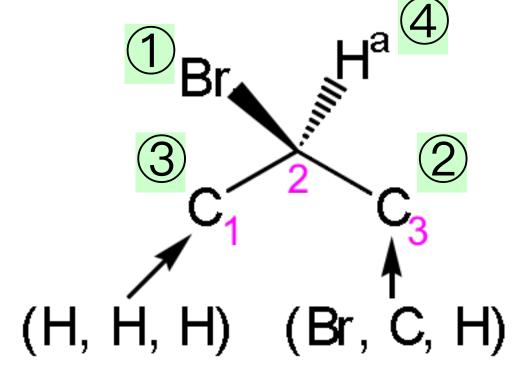
10B. How to Name Compounds with More than One Chirality Center

2,3-Dibromobutane

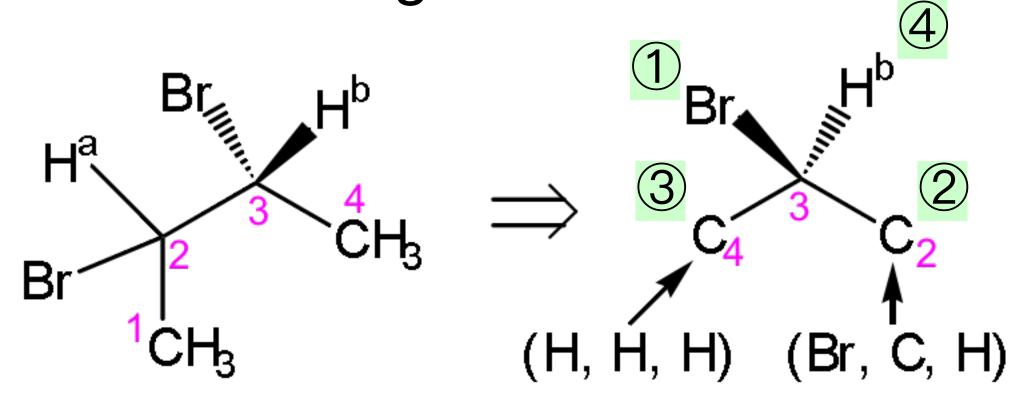


Look through C2–Ha bond

C2: (R) configuration



Look through C3–Hb bond



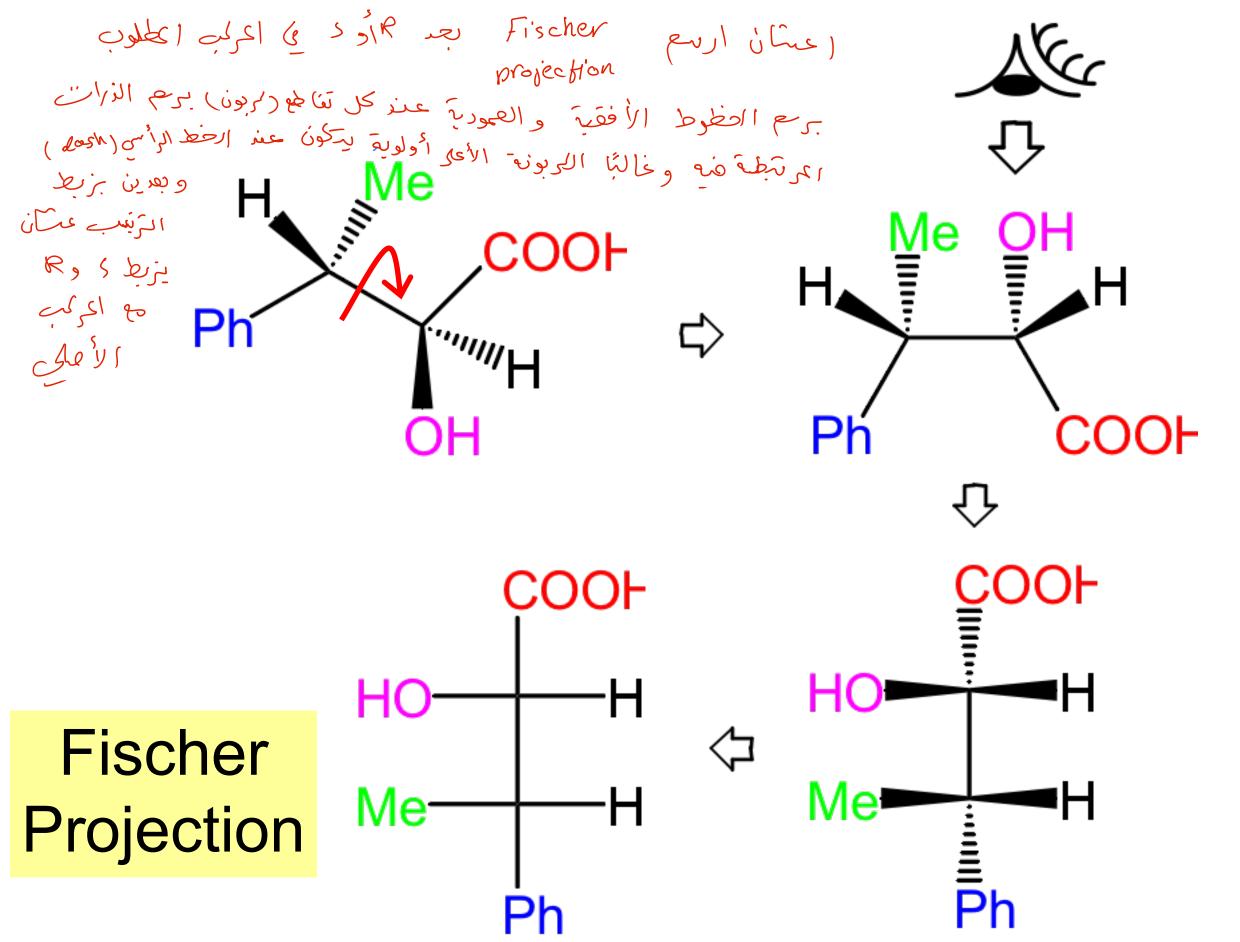
C3: (R) configuration

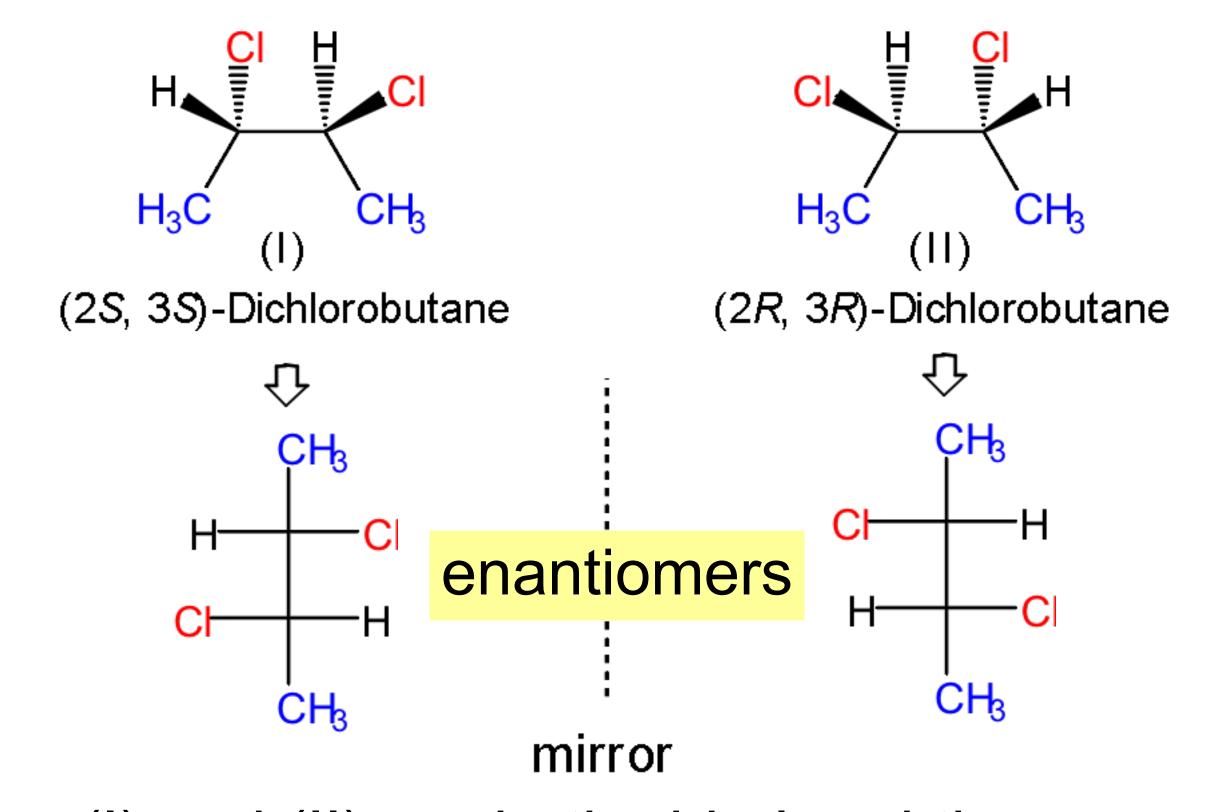
- Full name:
 - ♦ (2R, 3R)-2,3-Dibromobutane

11. Fischer Projection Formulas

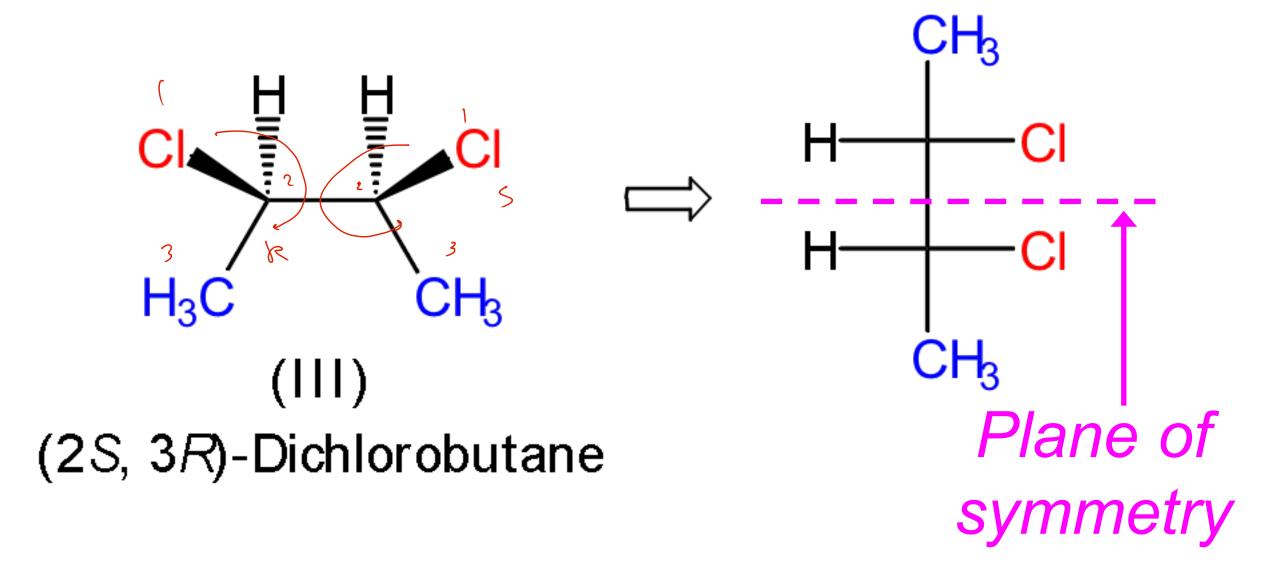
11A. How To Draw and Use Fischer

Projections Fischer Projection



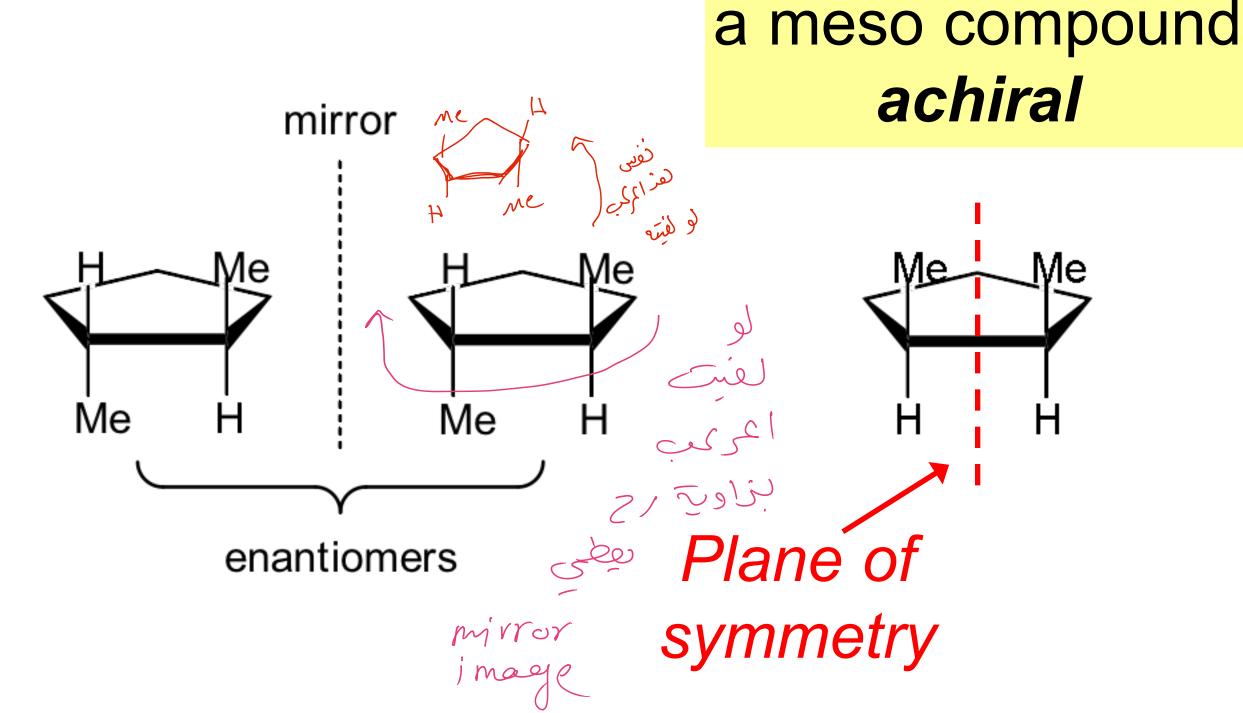


(I) and (II) are both chiral and they are enantiomers with each other



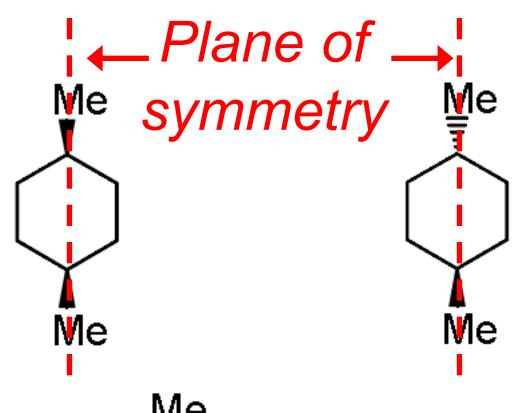
- (III) is achiral (a meso compound)
- (III) and (I) are diastereomers to each other

12. Stereoisomerism of Cyclic Compounds

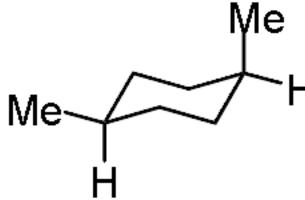


12A. Cyclohexane Derivatives

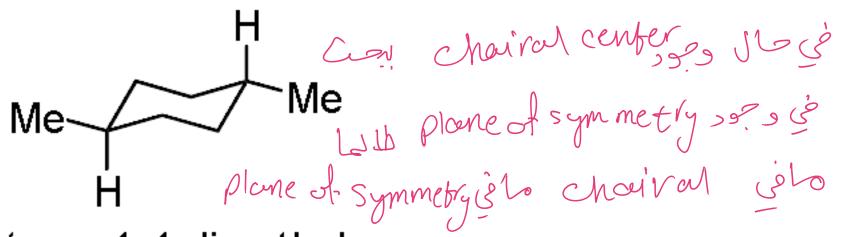
* 1,4-Dimethylcyclohexane



 Both cis- & trans-1,4-dimethylcyclohexanes are achiral and optically inactive

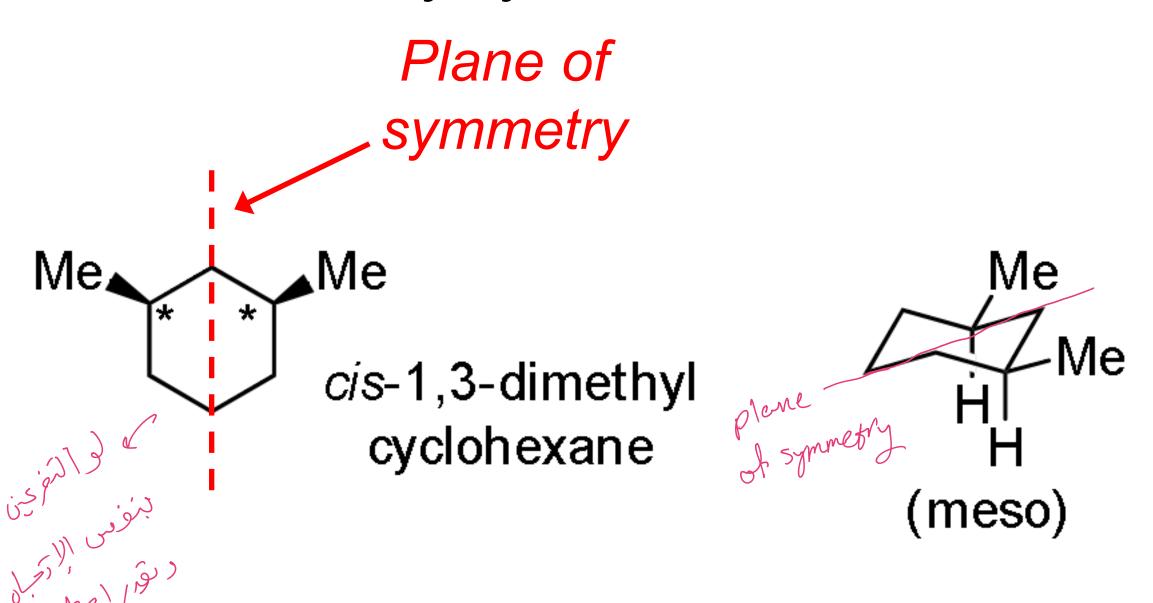


cis-1,4-dimethyl cyclohexane



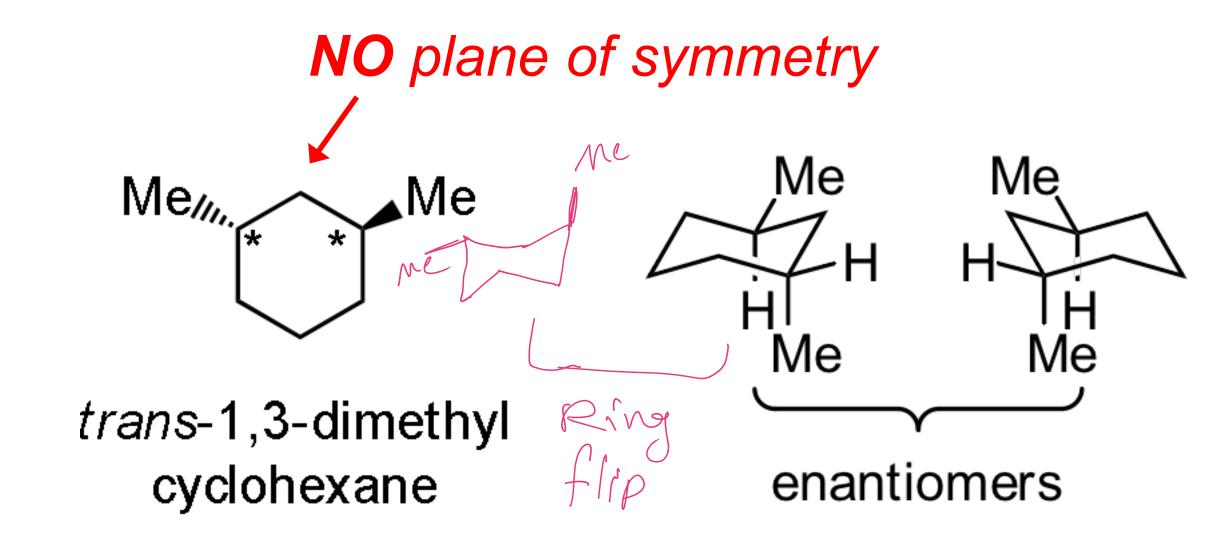
trans-1,4-dimethyl cyclohexane

* 1,3-Dimethylcyclohexane



 cis-1,3-Dimethylcyclohexane has a plane of symmetry and is a meso compound

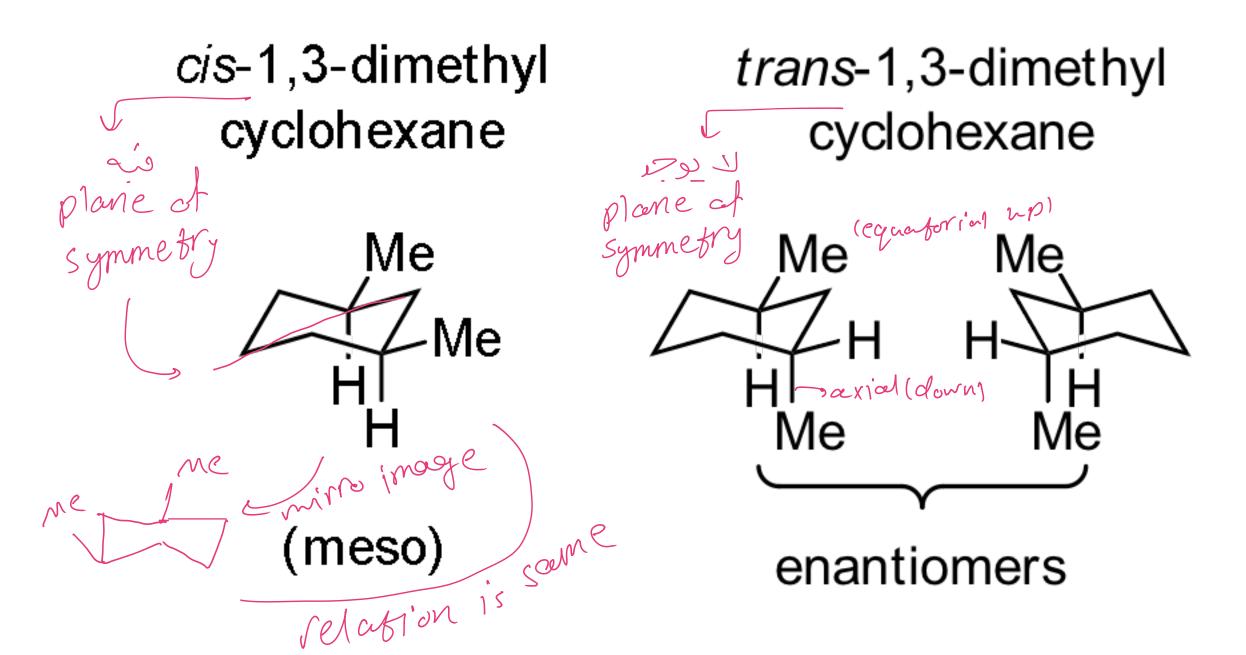
* 1,3-Dimethylcyclohexane



 trans-1,3-Dimethylcyclohexane exists as a pair of enantiomers

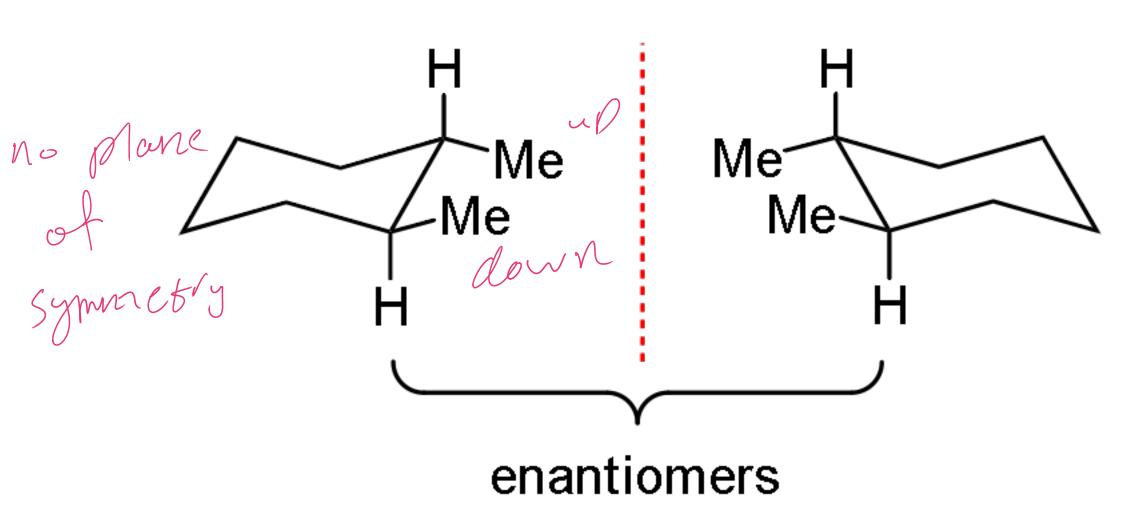
* 1,3-Dimethylcyclohexane

 Has two chirality centers but only three stereoisomers



* 1,2-Dimethylcyclohexane

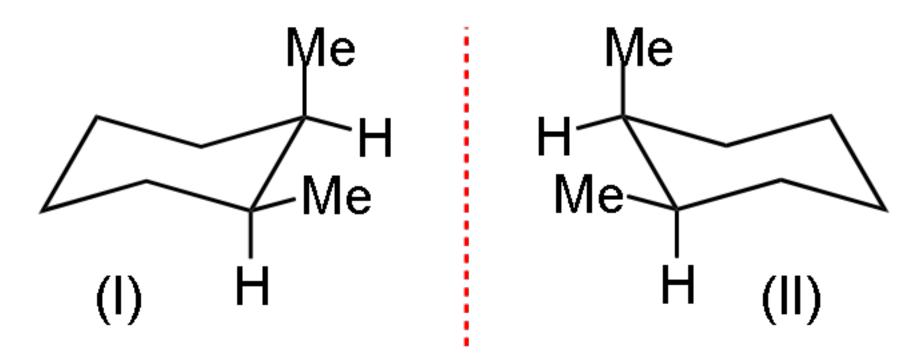
mirror



 trans-1,2-Dimethylcyclohexane exists as a pair of enantiomers

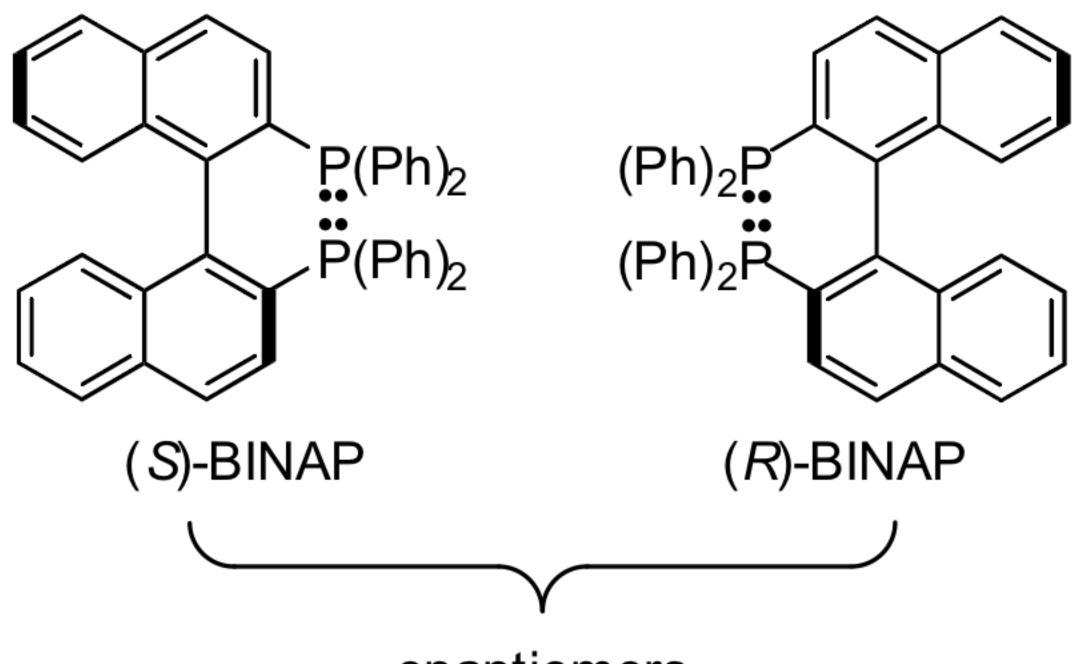
- * 1,2-Dimethylcyclohexane
 - With cis-1,2-dimethylcyclohexane the situation is quite complicated

mirror



 (I) and (II) are enantiomers to each other

13. Chiral Molecules That Do Not Possess a Chirality Center



enantiomers

