Basic Stereochemical Considerations

Key words: chirality, chiral carbon, enantiomers, diastereomers, absolute configuration, relative configuration, optical activity

Key Concepts

Basics of projection formulae

chiral carbon

chiral molecules

optical activity

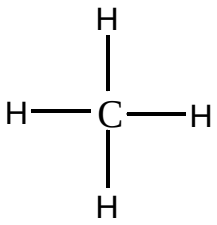
Stereoisomers (Diastereomers, Enantiomers)

Introduction

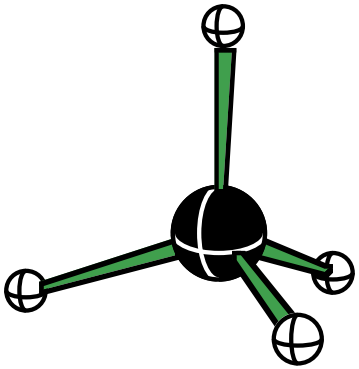
In this module, some of the key stereochemical concepts are introduced. These concepts appear in many places in this course. The most important concepts such as projection formulae, chirality are introduced in detail. The students are encouraged to refer to specialized book on stereochemistry for additional details.

The concept of stereochemistry and its proper understanding is very much required for several other chapters in this course as well as other courses in organic chemistry. In particular, the stereochemical concepts are widely used in asymmetric synthesis. Similarly, pericyclic and photochemical reactions use significant amount of stereochemical details.

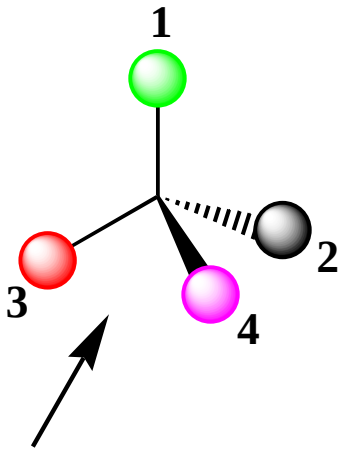
Representation of three dimensional structures-METHANE



2D drawing



3D drawing



view

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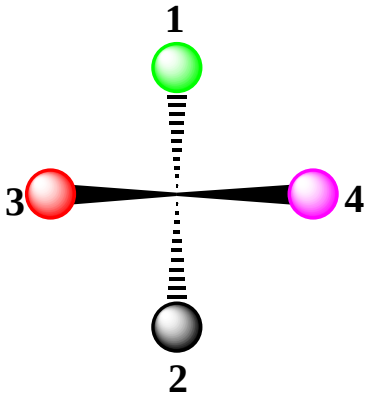

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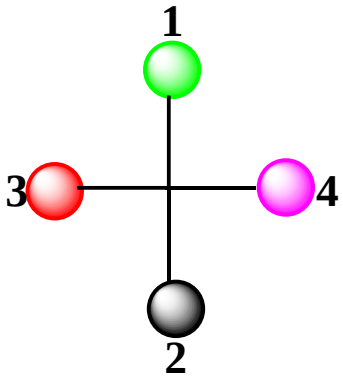
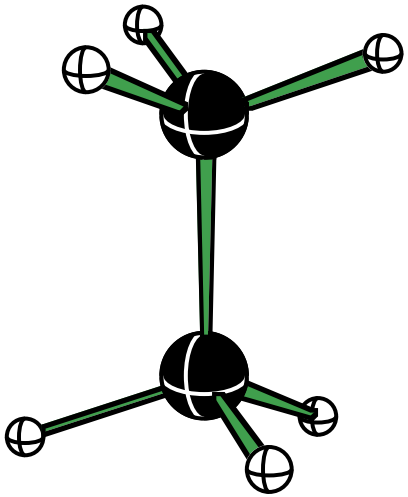


Fischer Projection

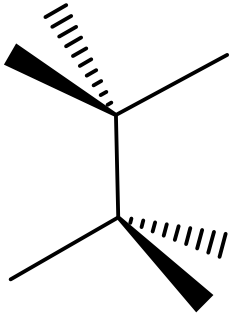
Perspective drawing

Or **Flying-wedge** formula

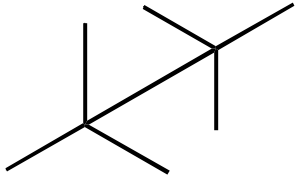
Representation of three dimensional structures-ETHANE



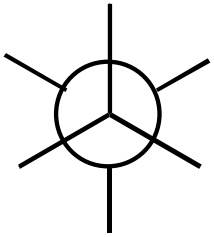
3D Image



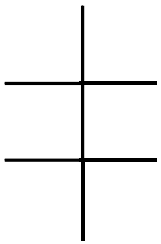
Flying-wedge formula



Sawhorse formula



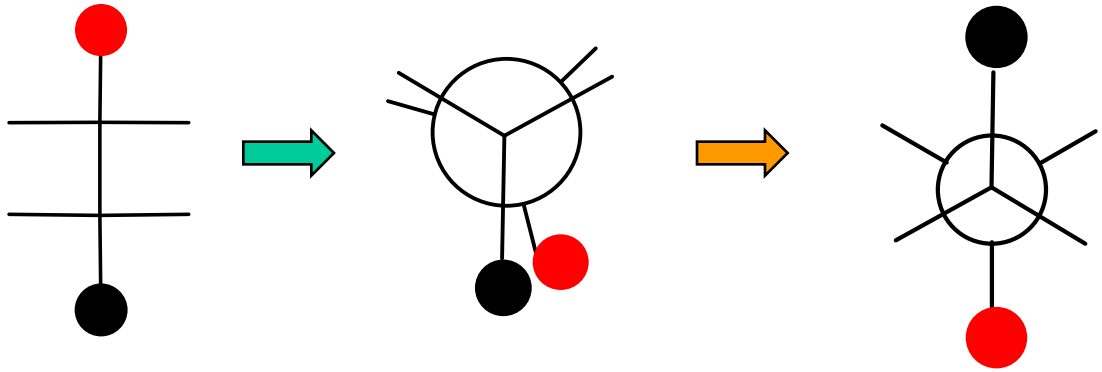
Newman Projection



Fischer Projection

Projection Formulae Inter-conversion

Fischer Projection ⇌ Newman Projection



Fischer projection refers to eclipsed conformation

Isomers

Isomers are different compounds with the same molecular formula

Isomers can differ in,

(1) Constitution: connectivity between atoms are different

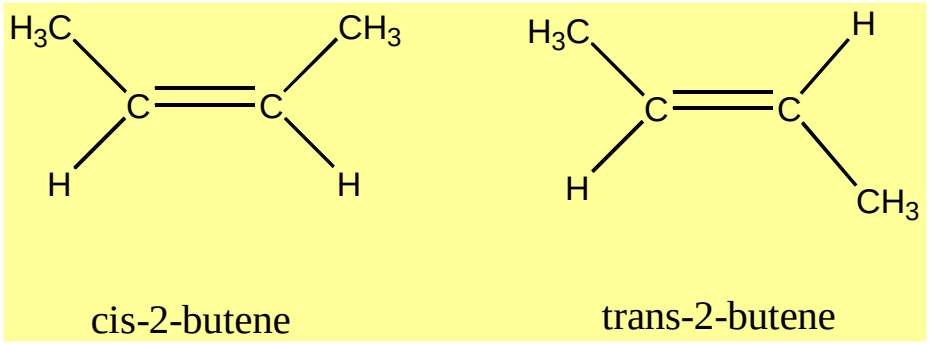
----Constitutional isomers (Structural isomers)

(2) Orientation of atoms in space:

----Stereoisomers

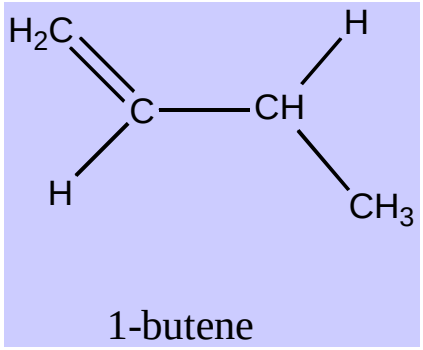
Isomers

E.g., C_4H_8



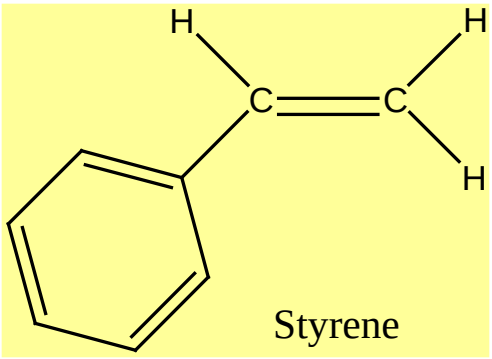
Stereo

Constitutional



Isomers

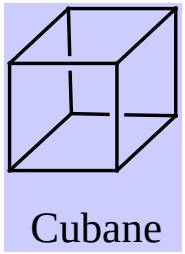
E.g., C_8H_8



Styrene

Used for making polymers

Constitutional



Cubane

Used as solid propellants
(strain energy of 166 kcal/mol)

Polynitro cubane is an explosive!

Important Terms to know

conformer

- Conformation of molecule arise due to free rotations around single bond.
- Stereoisomers which can interconvert at low temperature separated by a low energy barrier of [E < 60 kJ mol^{-1}]are called conformers.
- For spectroscopic analysis of conformers they should be subjected to a lower temperature which can freeze or slow down the rapid flipping between two conformers to elucidate data of particular conformer.

configuration

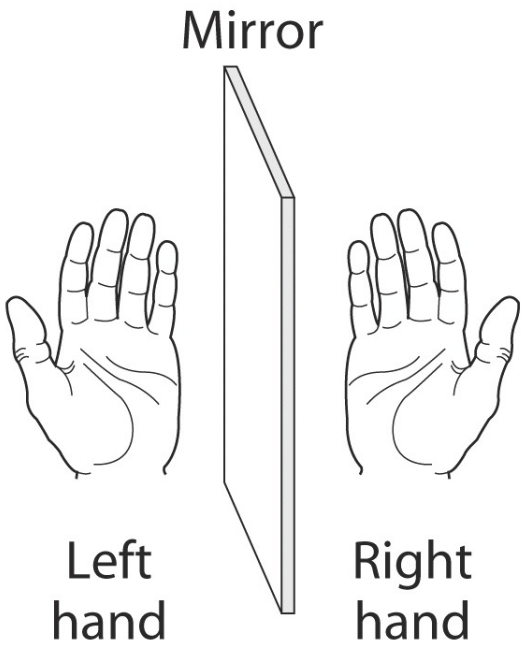
- It is a permanent spatial arrangement of molecule which can only be changed by bond breaking and reforming (such as a double bond)
- Stereoisomers having high energy barrier [E >100 kJ mol^{-1}] and stable at room temperature are called conformers.
- A configurational isomer is relatively stable and can be well elucidated at ambient temperature.

Chirality

The word ‘chiral’ is derived from Greek word ‘cheir = handed

Human hands have OBJECT and MIRRO IMAGE relationship and they are NON SUPERIMPOSABLE

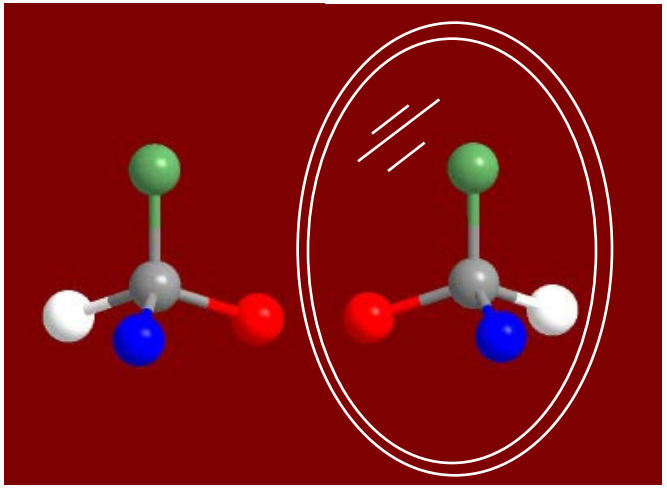
Examples: Shoe, scissors, screw



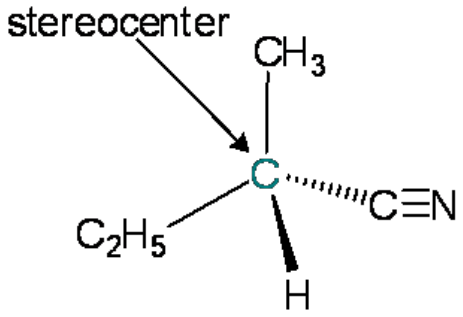
Asymmetric Center

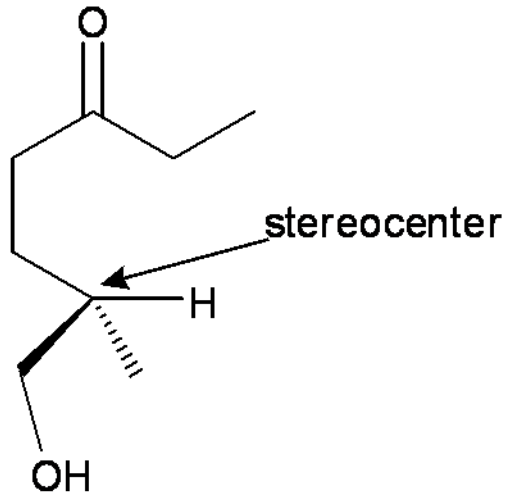
Chiral Molecules

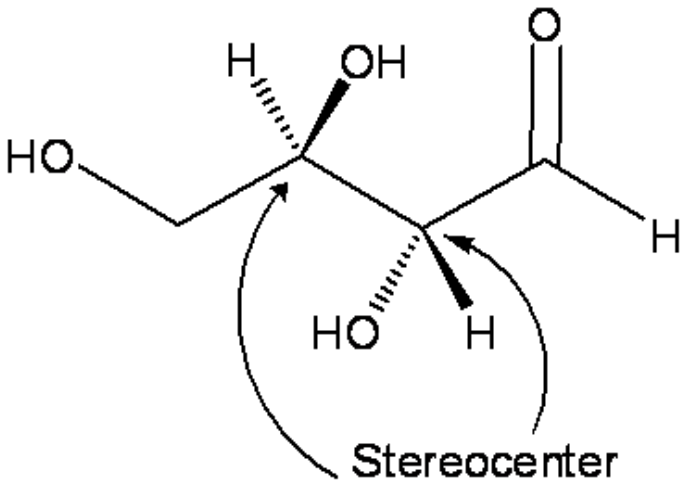
Chiral carbon has four different groups attached to a tetrahedral center



- Examples for chiral molecules



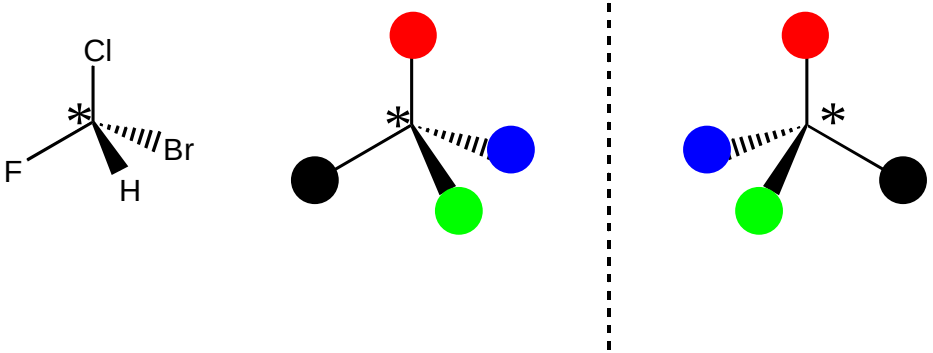




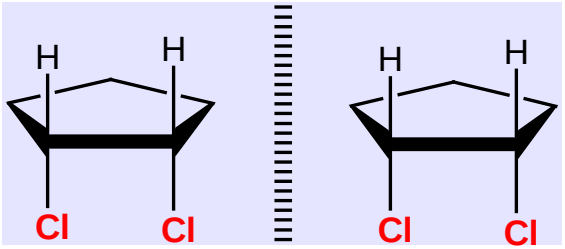
Chiral Molecules-Enantiomers

Presence of a stereocenter (chiral center) is neither necessary nor sufficient requirement for molecular chirality

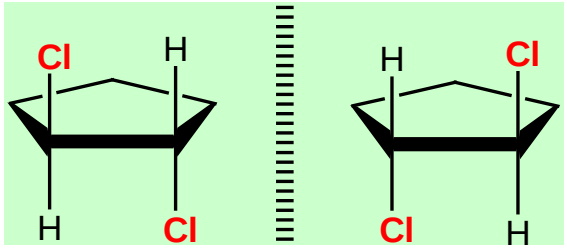
chiral



Isomers that are non-superimposable mirror images are called **ENANTIOMERS**



Identical



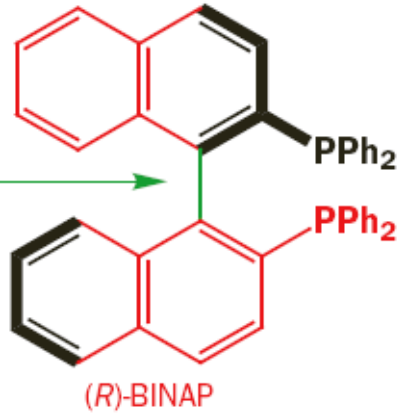
Enantiomers

Chiral Molecules-with no chiral centers

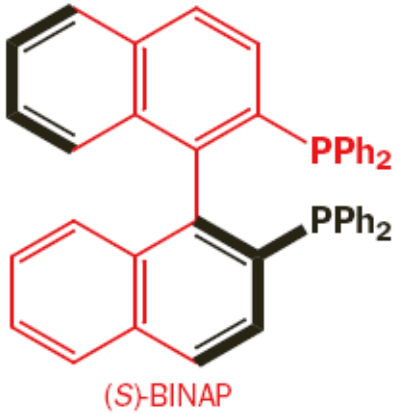
The property of chirality is determined by **overall molecular topology**

There are many molecules that are chiral even though they do not possess a chiral center (asymmetric carbon)

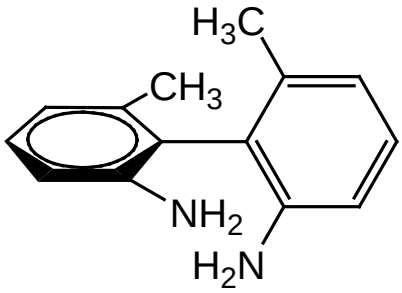
steric hindrance means rotation about this bond is restricted



(*R*)-BINAP



(*S*)-BINAP



Rot. Barrier of more than 22 kcal/mol

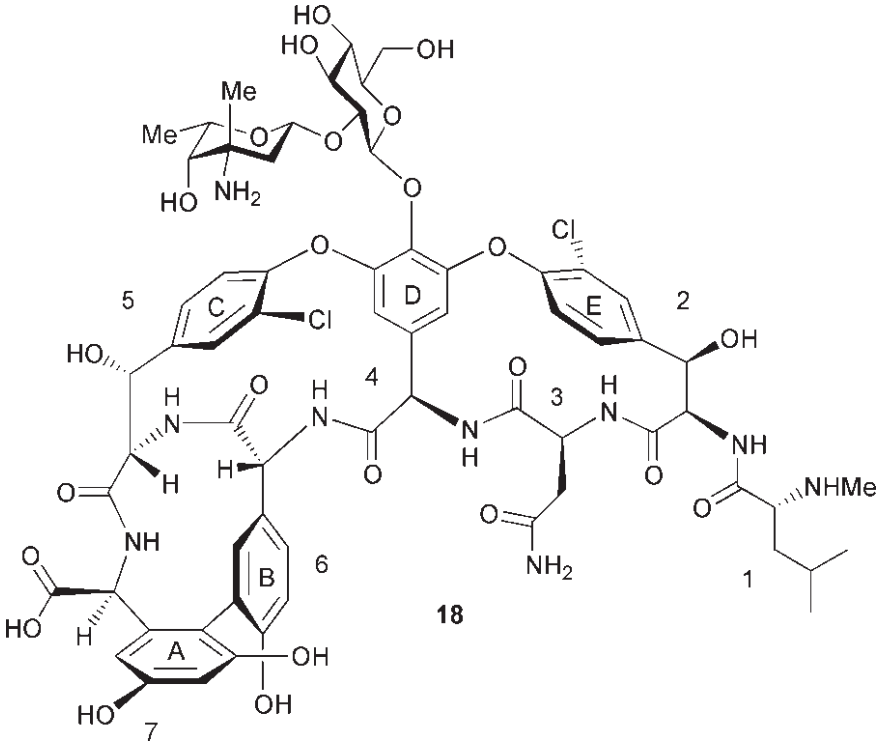
(*R*)-2,2’-Diamino-6,6’-dimethylbiphenyl

These molecules are **axially chiral** (axial asymmetry) arises due to restricted rotation around the C-C bond

Atropisomers

Stereoisomers resulting from hindered rotation about single bonds (due to high steric strain to rotation)

Vancomycin is a naturally occurring atropisomer



Used against bacterial infections

(also known as drug of last resort)

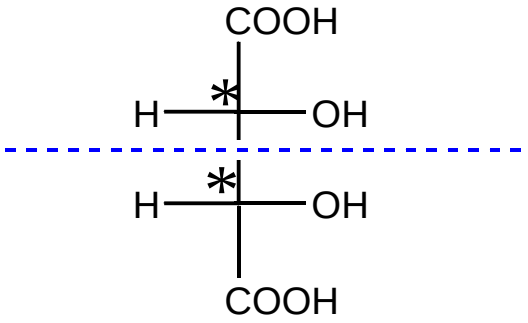
Optically Inactive!

Presence of a stereo center is not a <u>sufficient requirement</u> for molecular chirality

Though the following stereoisomer of tartaric acid possesses two chiral centers, a pure sample of this compound is optically inactive: **MESO**

Internal Compensation OR presence of plane of symmetry!

achiral

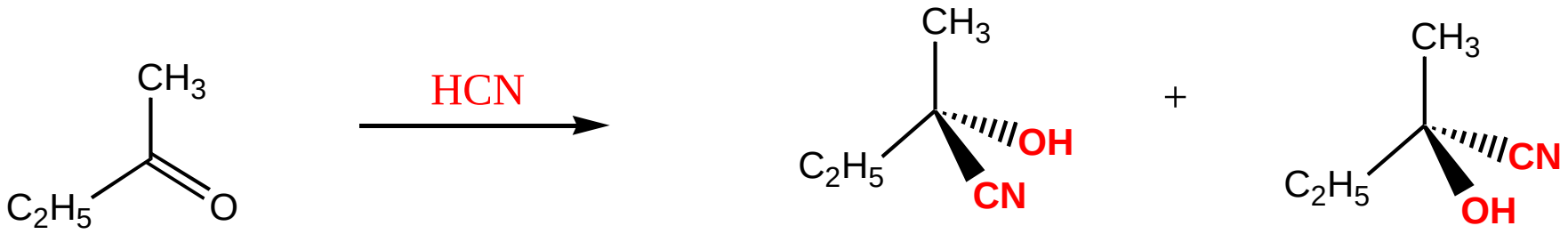


meso

Chiral Molecules-Optically Inactive

When there is equal composition (1:1) of enantiomers in the mixture, the resulting solution is optically inactive

External compensation OR cancellation due to opposite optical rotations: RACEMIC MIXTURE

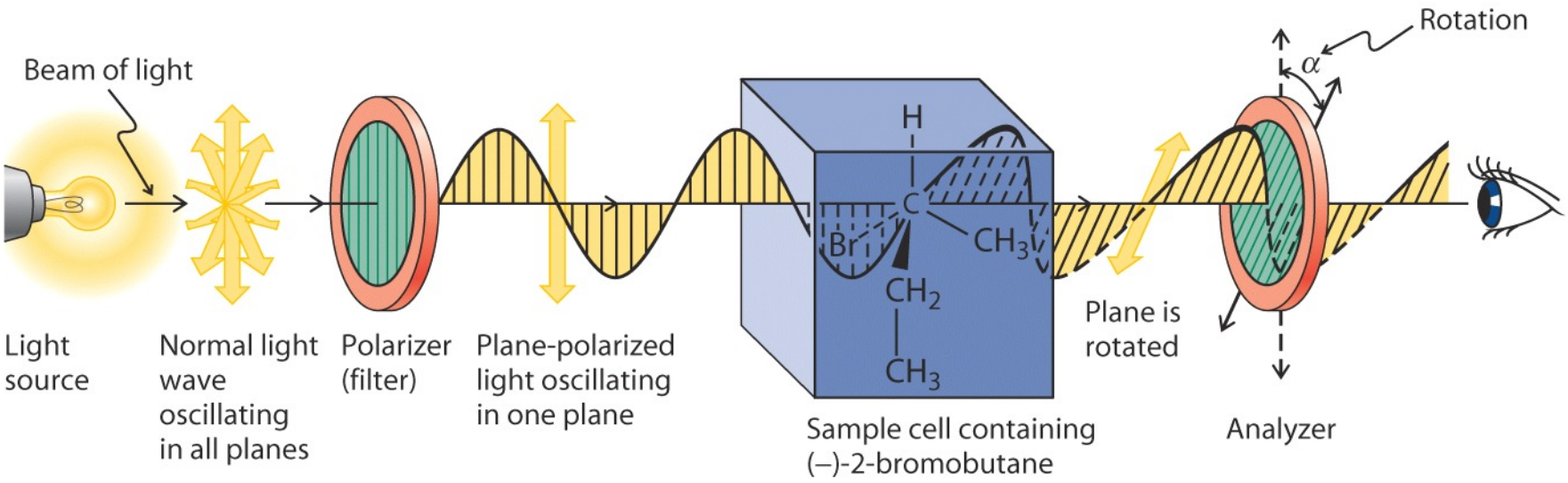


1 (50%) **1'** (50%)

Achiral chiral chiral

Optical Activity

Chiral molecules interact with plane polarized light



Enantiomer that rotate the plane polarized light to the right (clockwise) is called **dextrorotatory**. Represented as "***d***" or (+)

Other enantiomer that rotates plane polarized light to the left (counter-clockwise) is called **laevorotatory** or "***l***" or (-)

Optical Rotation

Optical rotations are measured by polarimeter

Optical rotation depends on
a) concentration of the sample
b) length of the sample cell
c) wavelength of the incident light
d) solvent
e) temperature

Specific rotation (α) of a sample at 20 ° C is given by,

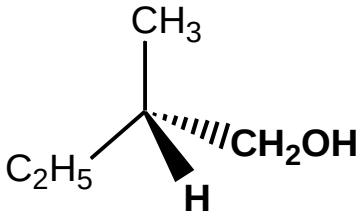
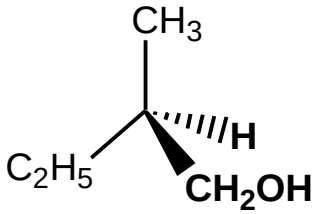
$$[\alpha]_{\lambda} = \alpha / lc$$

α – optical rotation (°), l – path length (dm), c- concentration (g/mL)

Properties of Enantiomers

1. Enantiomers are chiral
2. Pure sample of a single enantiomer is optically active
3. Enantiomers have identical physical and chemical properties in an achiral environment
4. Different biological properties

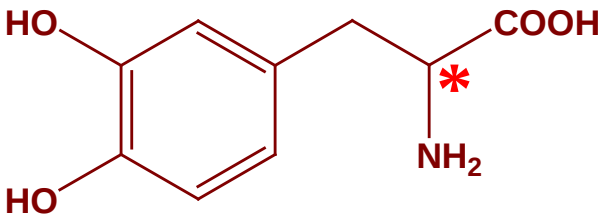
Example

	(+) or dextro	(-) or laevo
		
[α]	+5.9	-5.9
BP	128.9	128.9
μ	1.4107	1.4107

Properties of Enantiomers differ in Chiral medium

Biological properties of enantiomers are different, as the receptor sites are chiral

E.g., 1



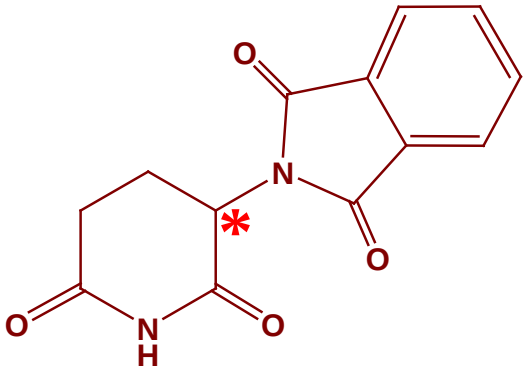
DOPA

Dihydr**O**xy**P**henyl**A**lanine

- L treatment of Parkinson's disease
- D biologically inactive !

E.g., 2

Thalidomide



- R against nausea
- S cause fetal damage

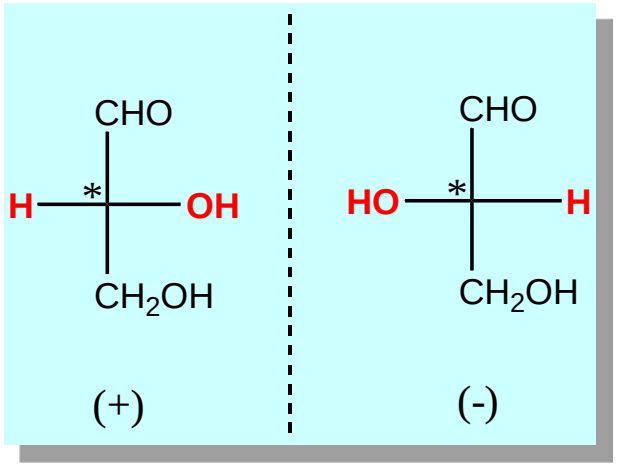
E.g., 3

(+)-glucose is metabolized by animals but NOT (-) glucose!

Relative Configuration

Glyceraldehyde is one of the simplest chiral molecule– sugar (carbohydrate)

D-(+)-glyceraldehyde



L-(-)-glyceraldehyde

Glyceraldehyde is used as a **standard** for assigning ***relative configurations***

Any enantiomerically pure compound that could be related to the configuration of

D-(+)-glyceraldehyde is labeled as D

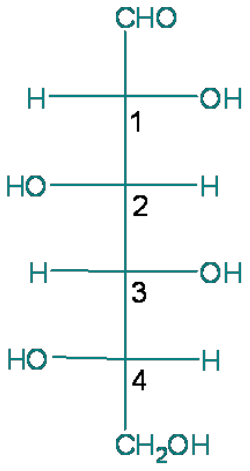
and

L-(-)-glyceraldehyde is labeled as L

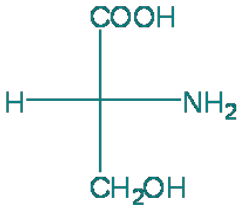
Important: note the use of capital letters

Fischer D and L projection nomenclature.

- Hermann Emil Fischer established configurational nomenclature for sugars & amino acids by first studying it on D-Glucose.
- For descriptions according to the nomenclature the molecule is placed vertically on a straight chain with most oxidised end placed at the top.
- The bottom most carbon far away from the oxidised end is then taken into consideration. If –OH (or $–NR_2$) group on that carbon is present on the **right**(dextro) the molecule is assigned D configuration and if present on the **left** (laevo) then L configuration.
- In the examples below the 4^{th} assymetric carbon is the highest numbered carbon from most oxidised carbon with –OH group on left side hence named L-Glucose.

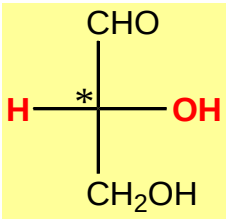


L-Glucose

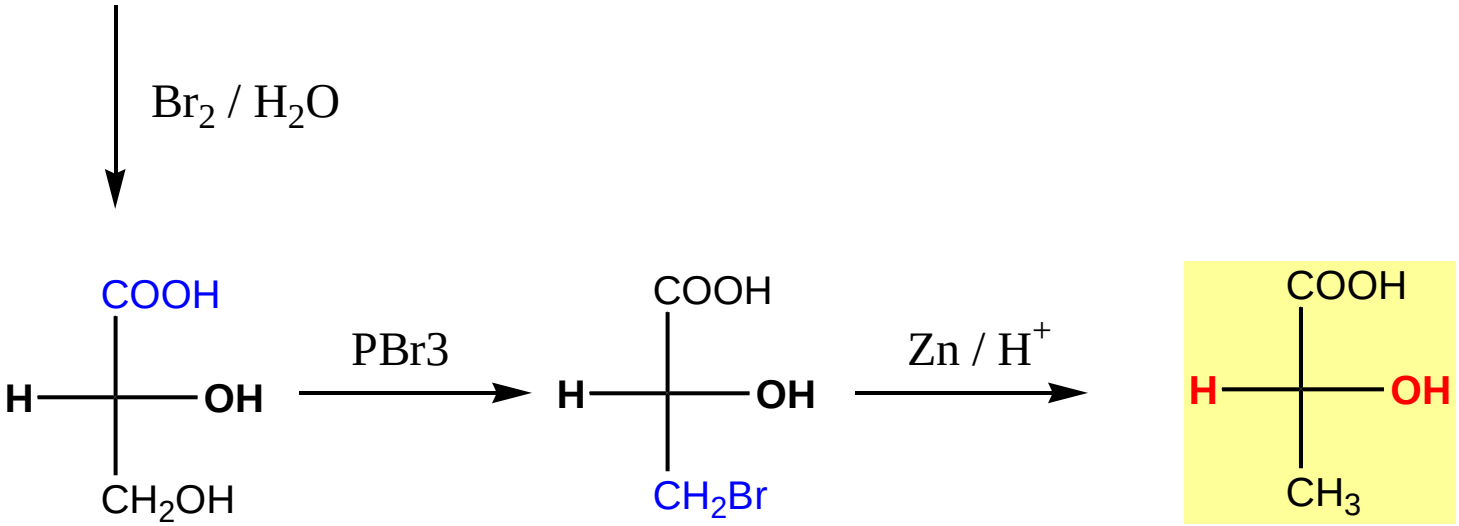


D-serine

Relationship with Glyceraldehyde



D-(+)-glyceraldehyde



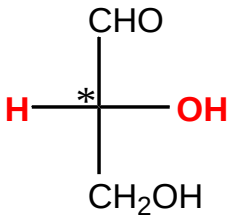
D-Lactic acid

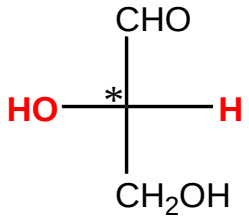
Maintaining the basic connectivity, D-lactic acid is related to D-glyceraldehyde

D-optical family

Optical Families

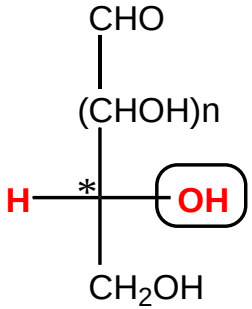
D-(+)-glyceraldehyde

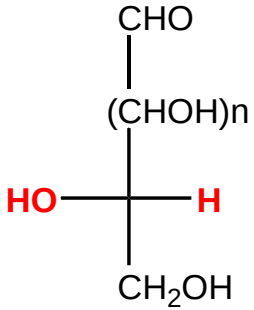




L-(-)-glyceraldehyde

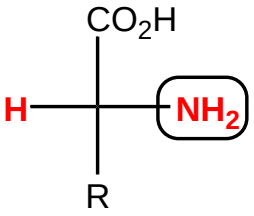
D-sugars

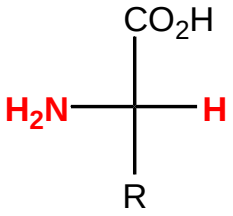




L-sugars

D-amino acids





L-amino acids

R/S (absolute) versus D/L (relative)

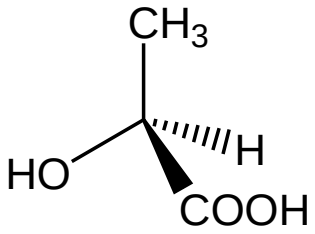
There is NO direct relationship between the configurational descriptors R/S or D/L

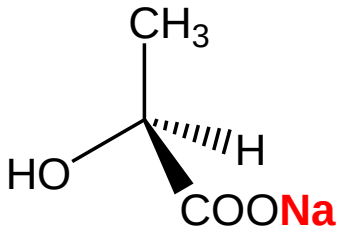
and

The sign of rotation

Sign of rotation of a sample should be measured using a polarimeter.

Lactic acid





Sodium lactate

(*S*)-(+)- Lactic acid

(*S*)-(-)- Sodium lactate

Absolute Configuration

3D structure can be specified without the help of formulae

Using stereochemical descriptors "*R*" and "*S*"

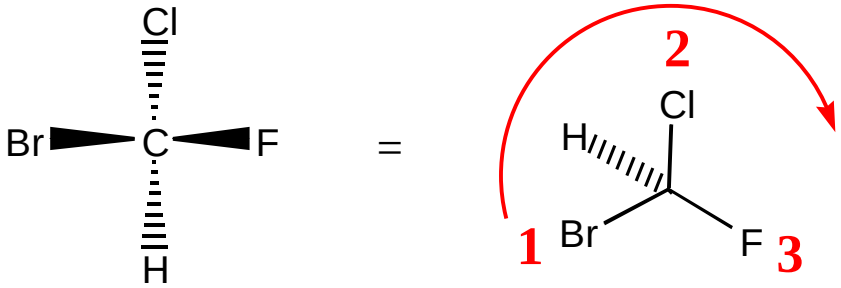
R = Rectus, S = Sinister [Latin word for clockwise and counter clockwise]

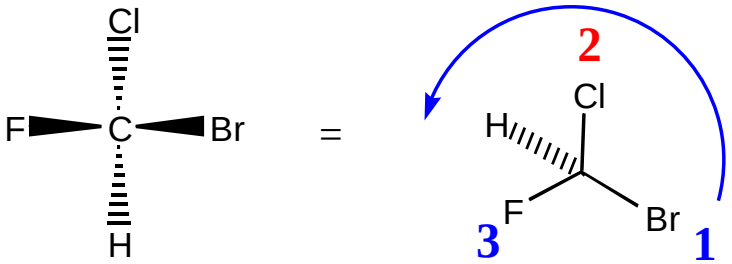
R-S notations are based on Cahn, Ingold and Prelog's **sequence rules**

CIP-Sequence Rules

Two step process: (1) First assign priorities for four substituents (ligands) (2) assign the name based on the positions of these substituents

1. Ligands of higher atomic number get higher priority than ligands of lower atomic numbers





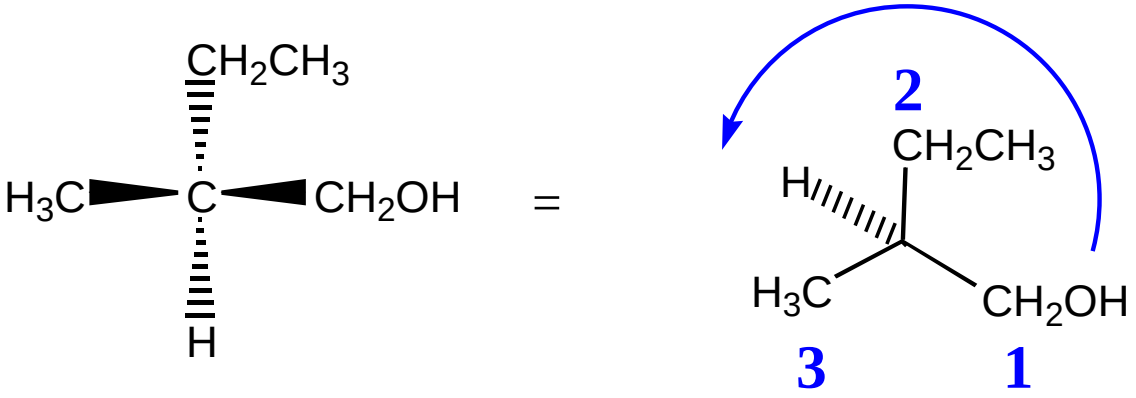
1-2-3: clockwise : **R**

counterclockwise : **S**

One interchange!

CIP-Sequence Rules

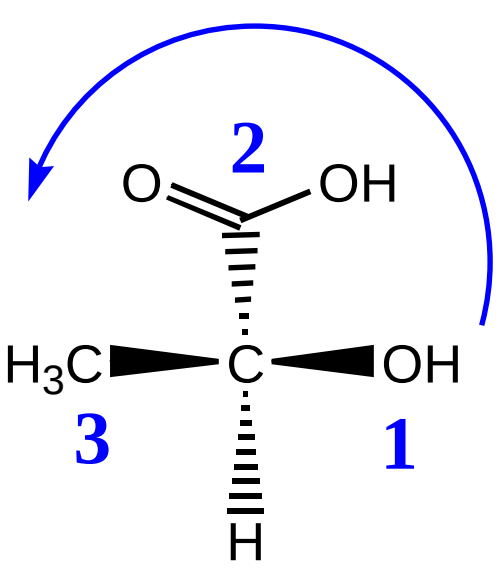
2. In case of ties, use the next atom along the chain and use rule no. 1 (as before)

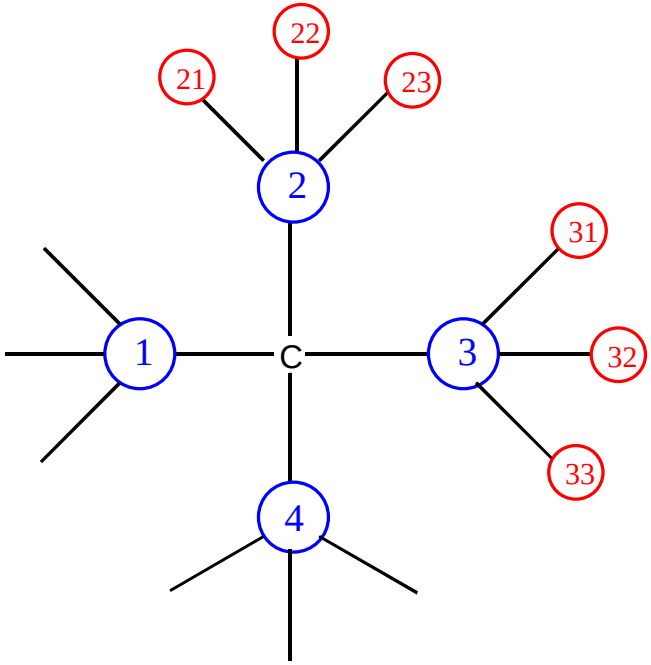


counterclockwise : **S**

CIP-Sequence Rules

3. All ligands in a given sphere must be explored before proceeding to the next (principle of outward exploration)

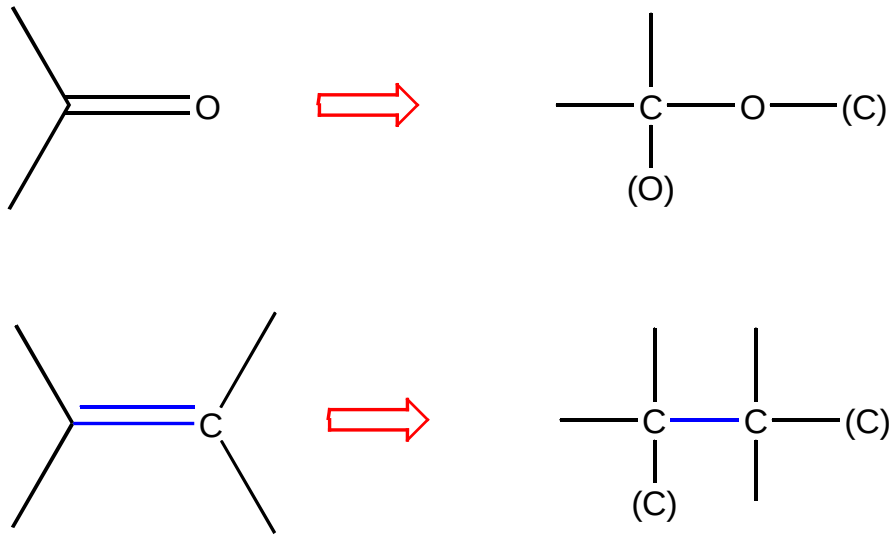




Absolute configuration is ***S***

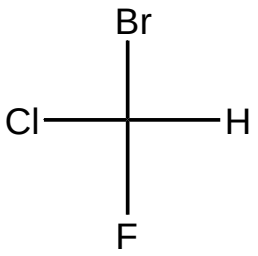
CIP-Sequence Rules

4. Each atom at a multiple bond is associated with a phantom (duplicate/triplicate) atom of the species at the other end of the multiple bond

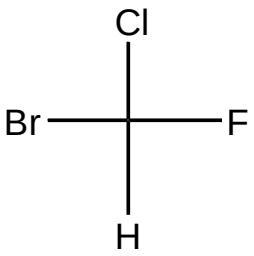


Permitted Changes in CIP Rules

Double exchanges OR **two successive exchanges** of two ligands in a Fischer projection will retain the configuration



is same as



R-enantiomer

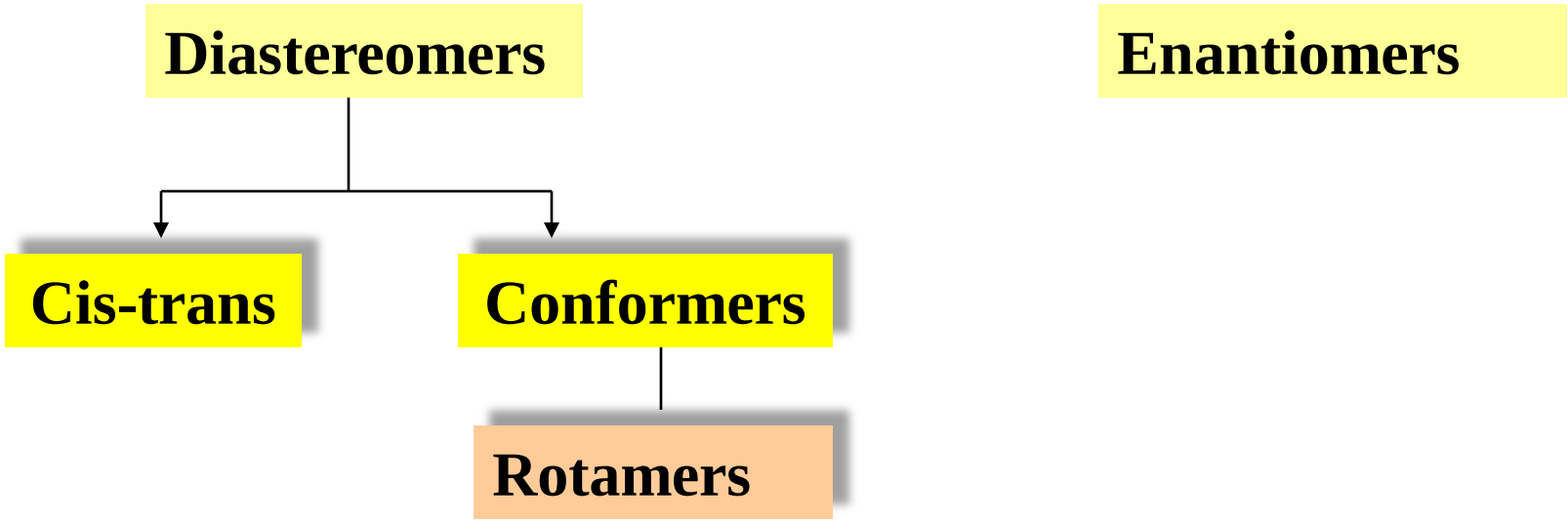
Interchange of one set of ligands in a Fischer projection will lead to opposite enantiomer

Stereoisomers

Orientation of atoms in space is different in stereoisomers

(Spatial isomers)

They are



Diastereomers

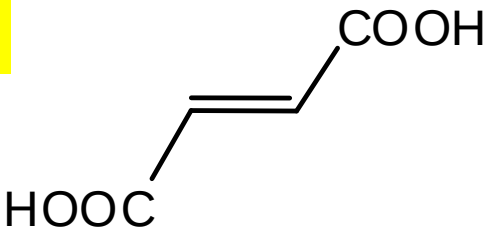
Diastereomers are stereoisomers that are not enantiomers

They are chemically (and physically) different

OR

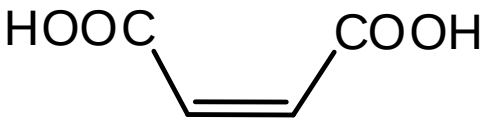
Stereoisomers that are <u>not mirror images</u>

E.g.,1



Fumaric Acid

MP: 299-300 ºC



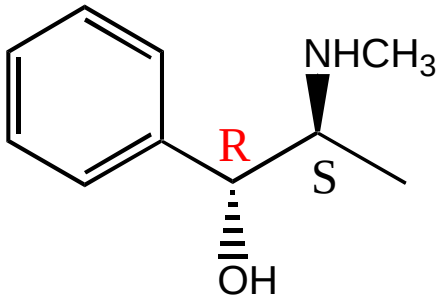
Maleic Acid

MP: 140-142 ºC

Forms anhydride upon heating

Diastereomers

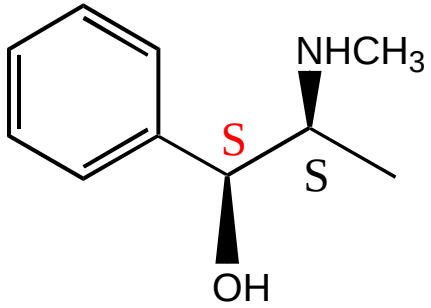
Example 1:



Ephedrine

(+)-ephedrine is used in traditional medicine

(as a nasal decongestant)



pseudoephedrine

Diastereomers can be chiral or achiral

E.g., *cis*-*trans* geometrical isomers

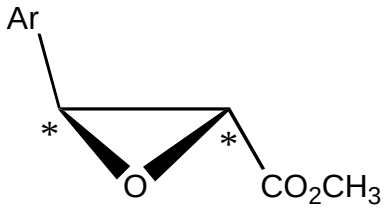
Diastereomers

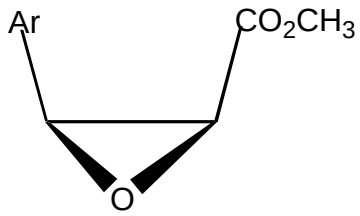
Diastereomers can be chiral or achiral

Large number of diastereomers are available which are compounds containing two or more chiral centers (usually asymmetric carbon atoms)

E.g.,1

SR

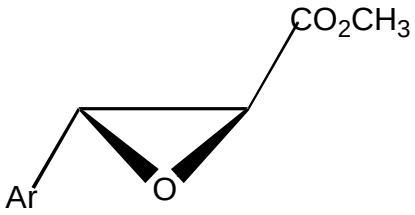




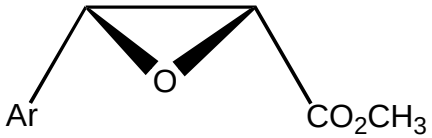
SS

Enantio

Enantio



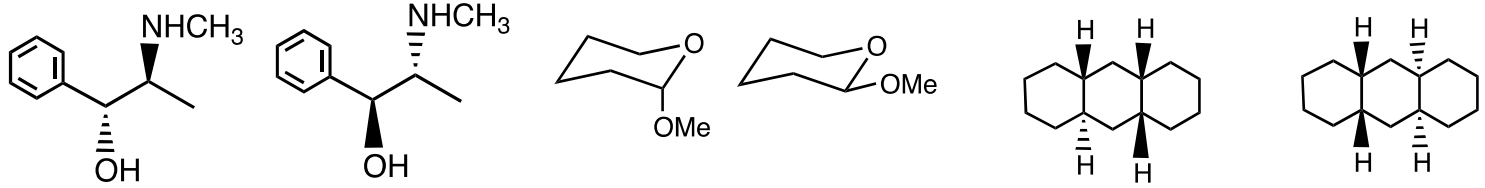
RS



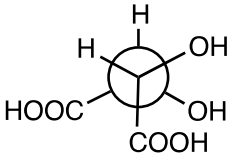
RR

Practice Problems

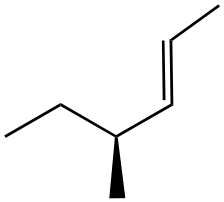
(1) Identify the stereochemical relationship between the given pair of compounds



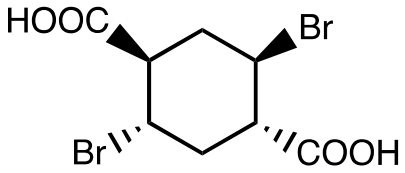
(2) Draw the Fischer projection for the following compound



(3) Name the following compound with stereochemical description

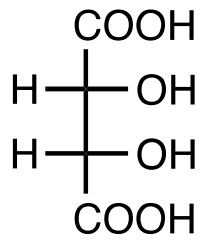


(4) Comment whether the following compound is chiral and achiral. Explain



Answers

(1) Enantiomers, Diastereomers,
Diastereomers

(2) 

(3) (*S*,*E*)-4-methylhex-2-ene

(4) Achiral, the molecule has a center of inversion