

Topic II

Stereochemistry of Organic Molecules

Lecture slides are courtesy of:

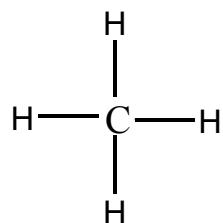
Prof. Pradeepkumar P. I. , IIT Bombay

Prof. Peter Volhardt, UC Berkeley

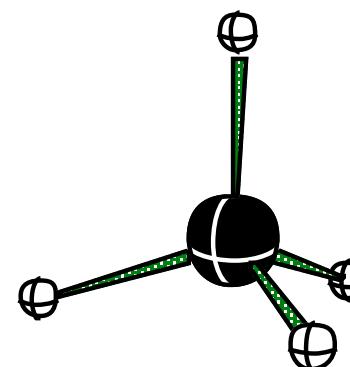
Prof. J. M McBride, Yale University

Oxford University Press

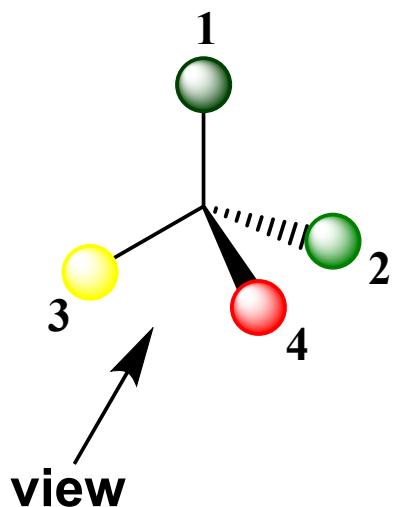
Representation of three dimensional structures-METHANE



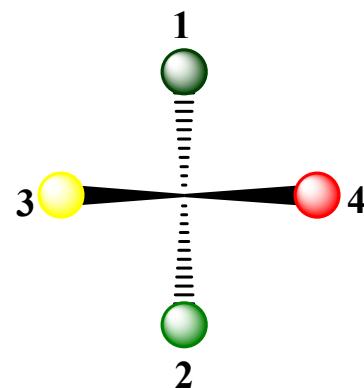
2D drawing



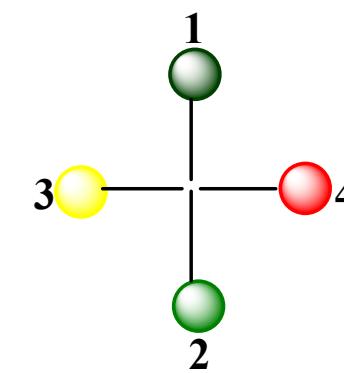
3D drawing



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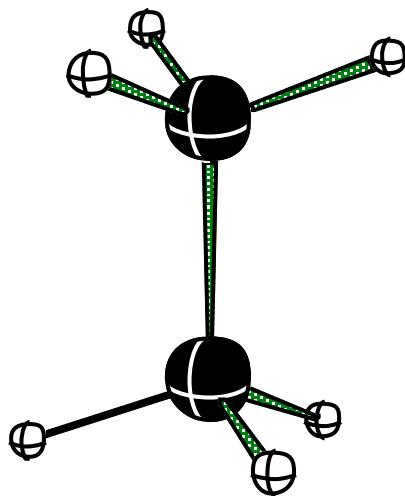


Fischer Projection

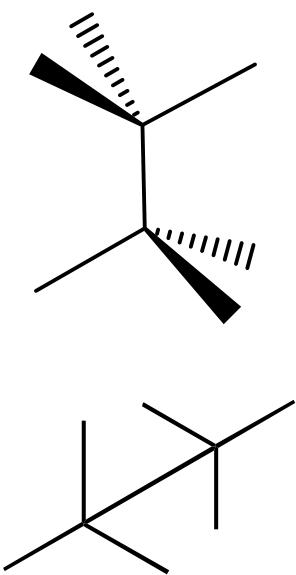
Perspective drawing

Or Flying-wedge formula

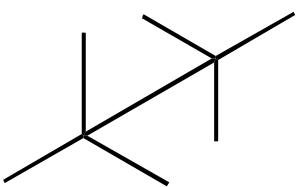
Representation of three dimensional structures-ETHANE



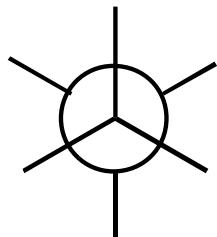
3D Image



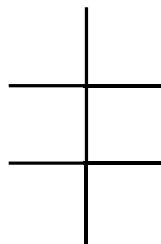
Flying-wedge formula



Sawhorse formula

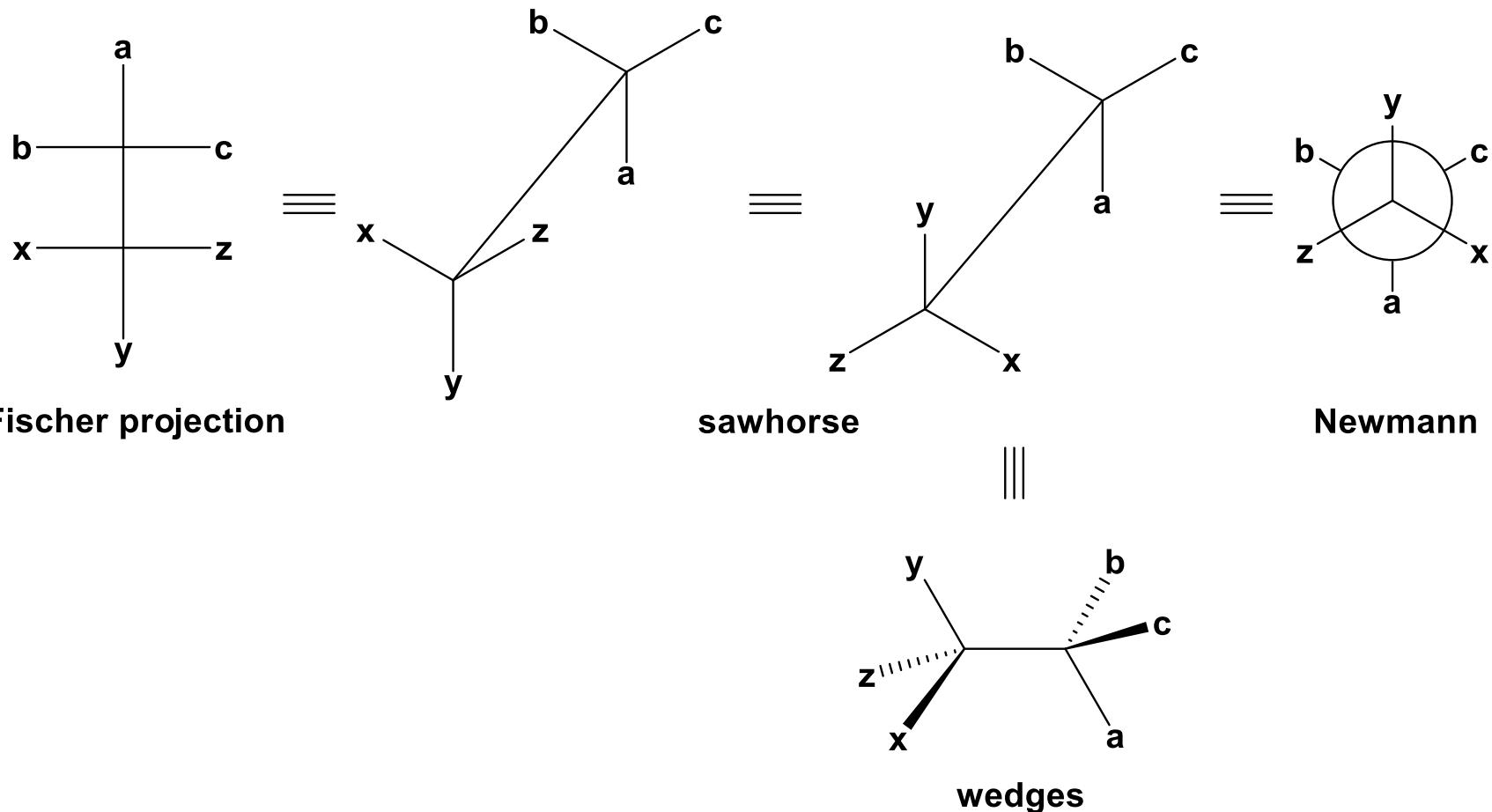


Newman Projection



Fischer Projection

Inter-converting molecular representations



Isomers

Isomers are different compounds with the same molecular formula

Isomers can differ in,

(1) Constitution: connectivity between atoms are different

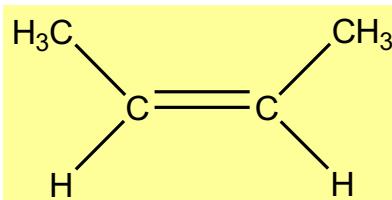
Constitutional isomers (Structural isomers)

(2) Orientation (configuration) of atoms in space:

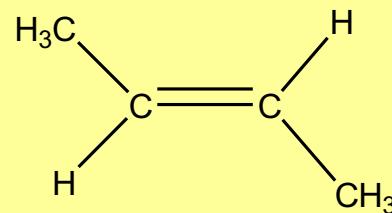
Stereoisomers

Isomers

E.g., C₄H₈



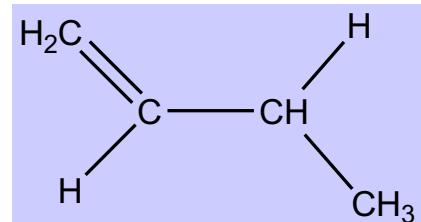
cis-2-butene



trans-2-butene

Stereo

Constitutional

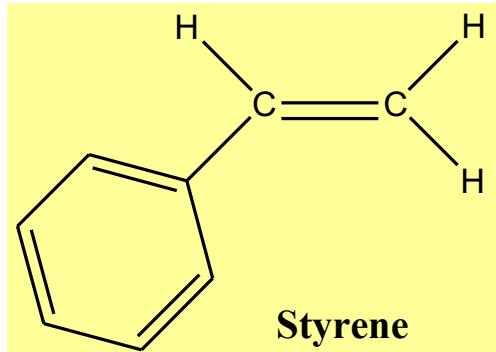


1-butene

Isomers

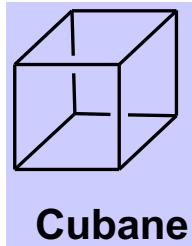
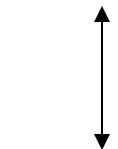
CH103
R. B. Sunoj

E.g., C₈H₈



Used for making polymers

Constitutional

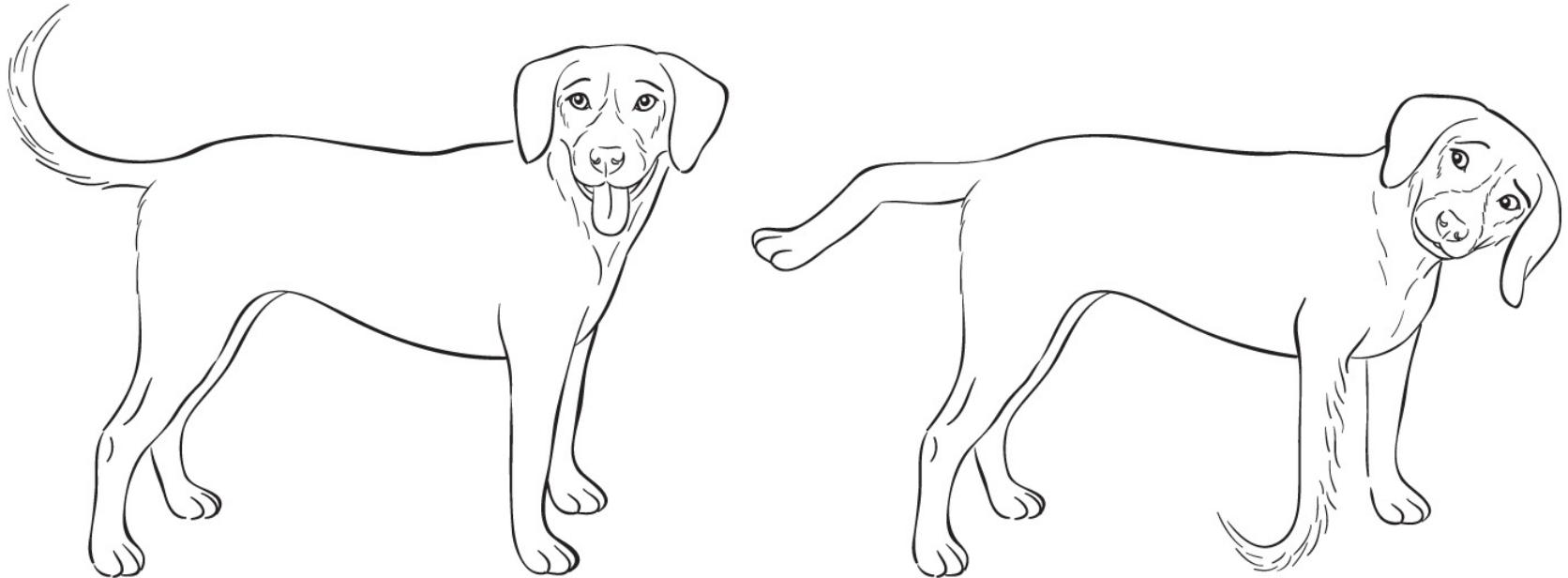


Used as solid propellants (strain energy of 166 kcal/mol)

Poly**nitro** cubane is an explosive!

Different Configurations

Different Configurations



Compounds with different configurations can be separated.

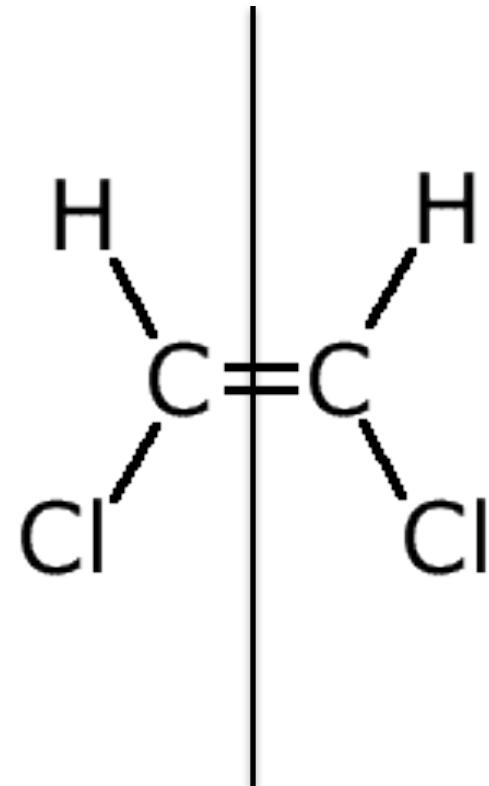
Cis–trans isomers have different configurations.

Symmetry in Organic Molecules

- The symmetry of a molecule is determined by the existence of **symmetry operations** performed with respect to **symmetry elements**.
 - **symmetry element** is a line, a plane or a point in or through an object, about which a rotation or reflection leaves the object in an orientation indistinguishable from the original.
1. Plane of symmetry (σ)
 2. Rotational axis of symmetry (C_n)
 3. Center or point of symmetry (i)
 4. Rotation reflection or improper rotation axis of symmetry(S_n)

Symmetry in Organic Molecules

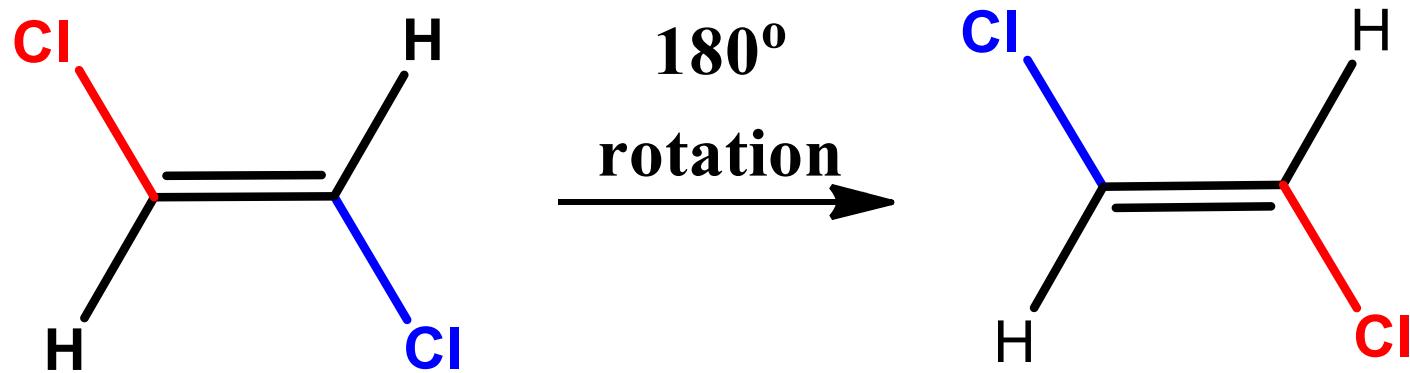
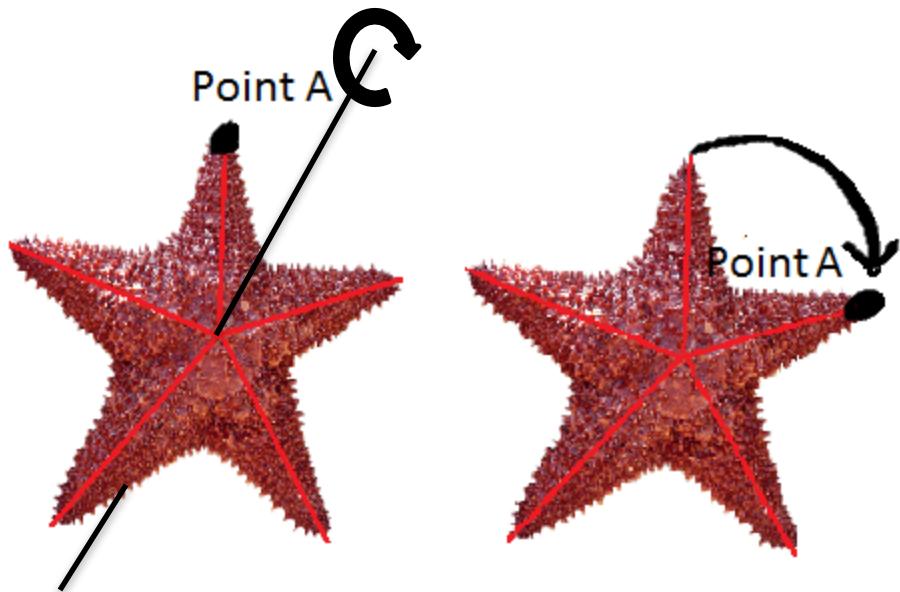
Plane of symmetry



Cis-1,2-dichloroethane

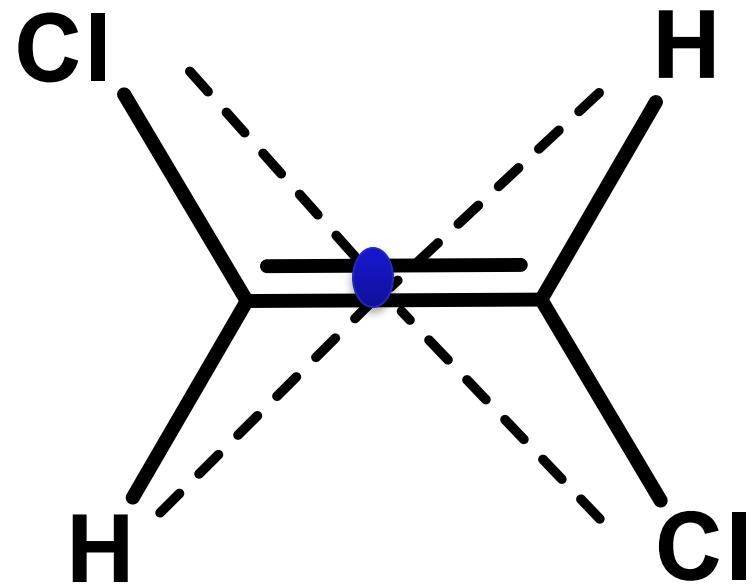
Symmetry in Organic Molecules

Rotational axis of symmetry



Symmetry in Organic Molecules

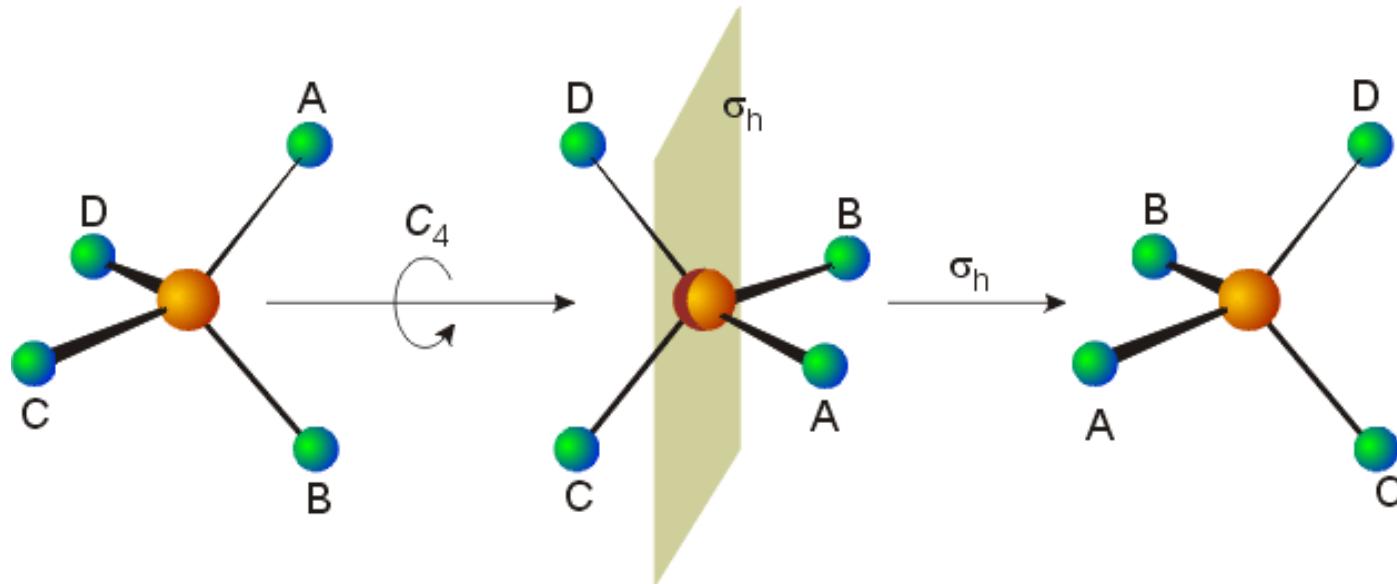
Center or point of symmetry



Symmetry in Organic Molecules

Improper Rotation

An improper rotation is rotation, followed by reflection in the plane perpendicular to the axis of rotation.

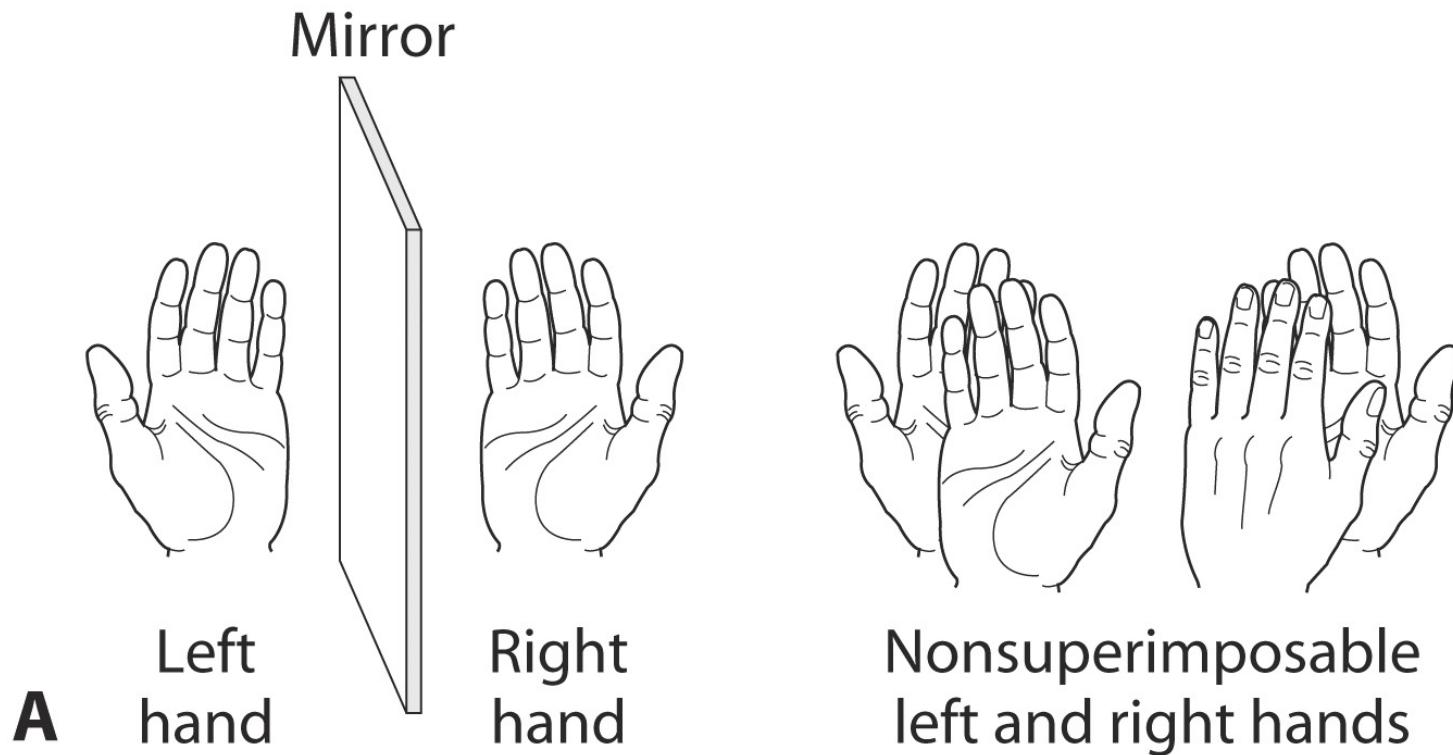


Chirality

The word ‘chiral’ is derived from Greek word

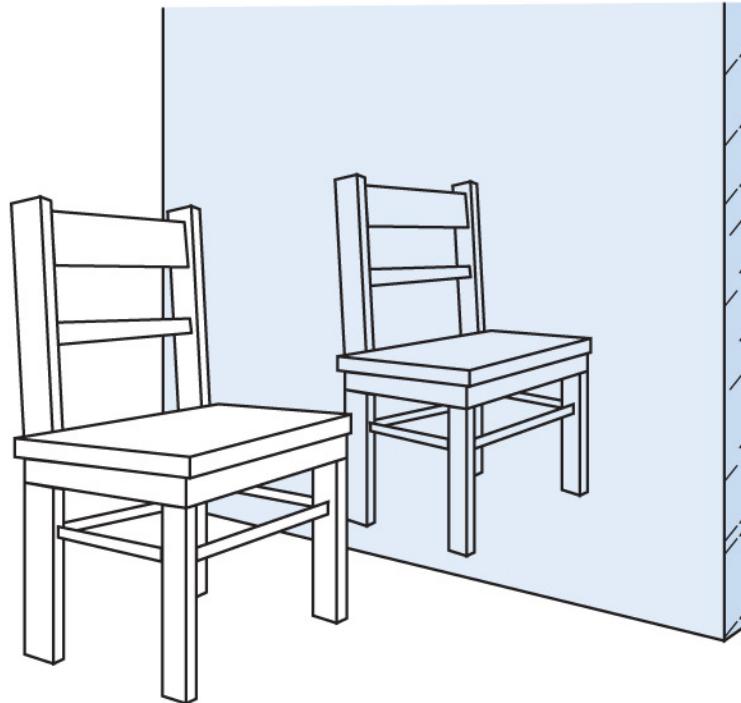
‘cheir = handed’

Human hands have **OBJECT** and **MIRROR IMAGE** relationship and they are **NON SUPERIMPOSABLE**



Chirality

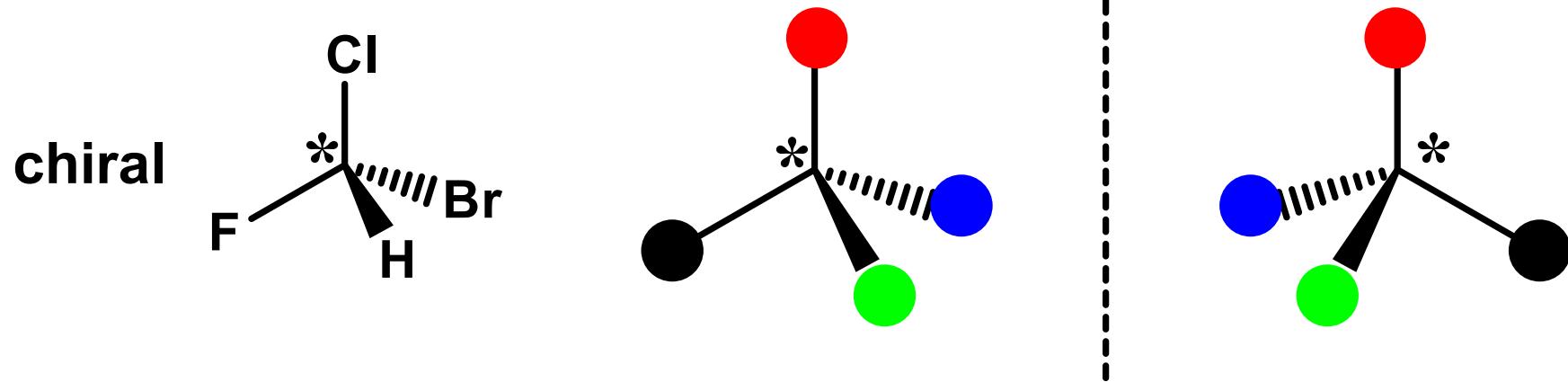
Mirror images that can be superposed are *achiral* (not chiral).



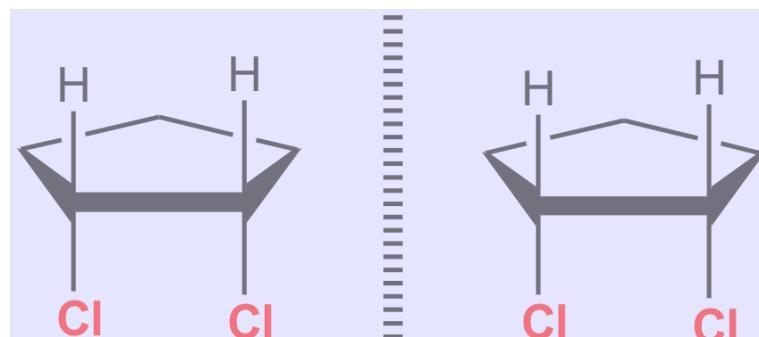
Chirality

- Presence of a **stereocenter (chiral center)** is neither necessary nor sufficient requirement for molecular chirality
- An molecule having no **symmetry elements** is called asymmetric. Such an object is necessarily **chiral**.
- the presence of **Plane or Point of symmetry element** makes a molecule **achiral**
- One or more **rotational axes of symmetry** may exist in both **chiral, dissymmetric, and achiral molecule**.

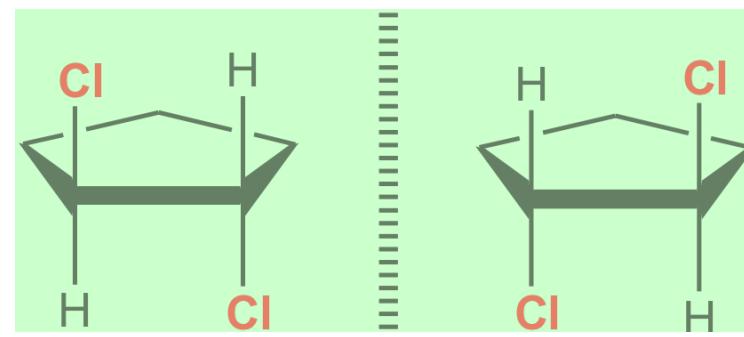
Chiral Molecules-Enantiomers



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



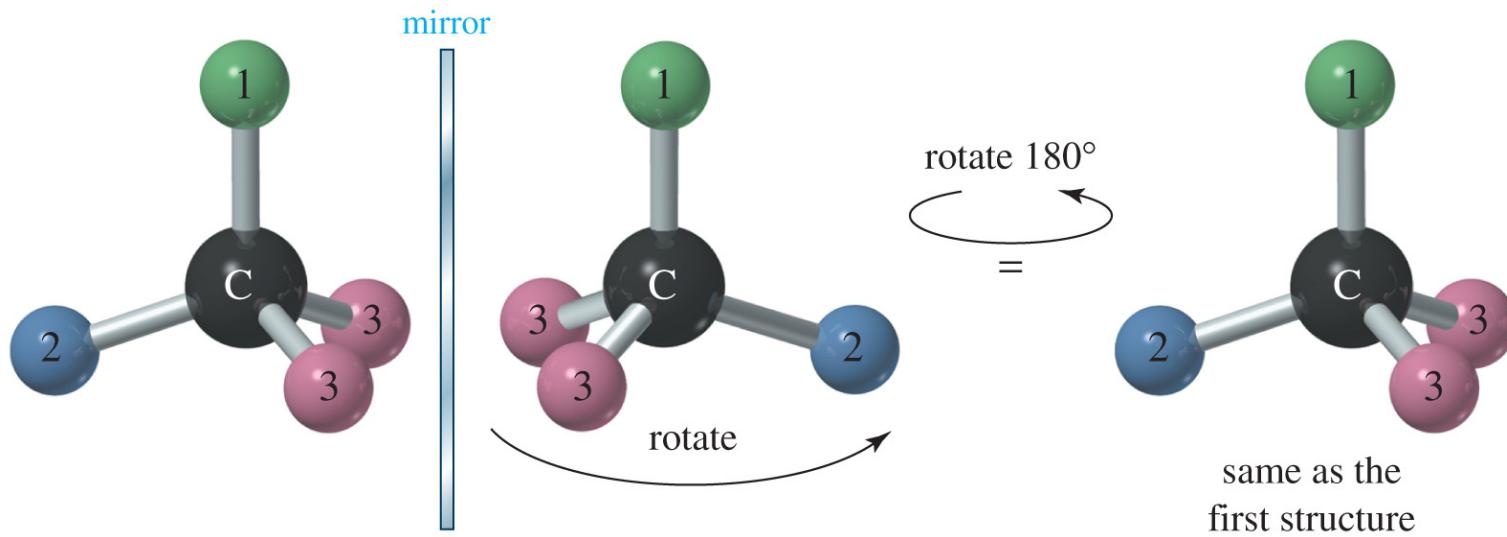
Identical



Enantiomers

Same physical and chemical properties

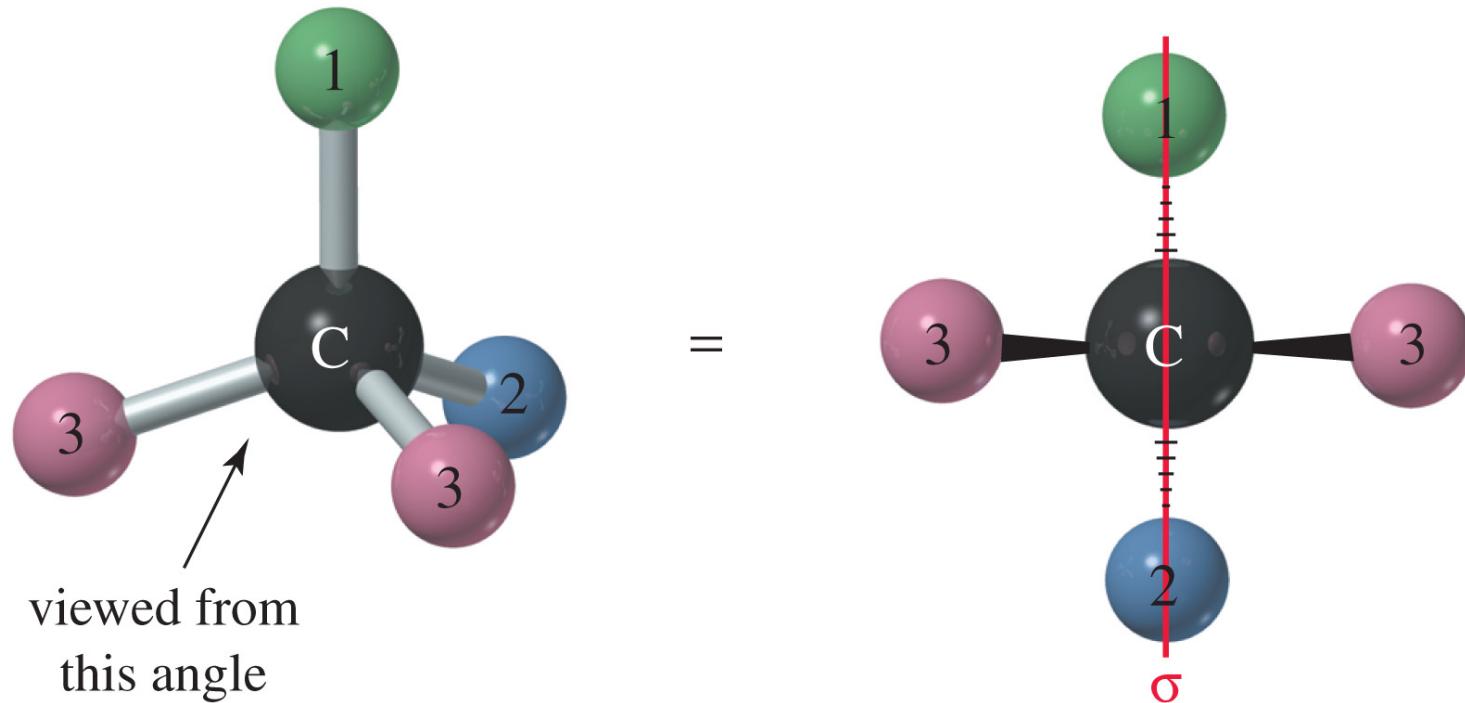
Achiral Compounds



Take this mirror image and try to superimpose it on the one to the left matching all the atoms. Everything will match.

When the images can be superposed the compound is ***achiral***.

Planes of Symmetry



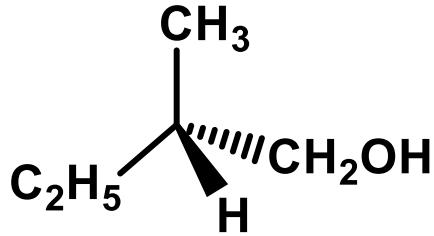
- A molecule that has a plane/centre of symmetry is *achiral*.

Properties of Enantiomers

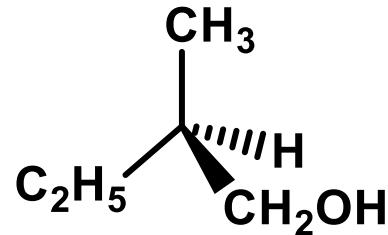
1. Enantiomers are chiral
2. Pure sample of single enantiomer is optically active
3. Enantiomers have identical physical and chemical properties in an achiral environment
4. Different biological properties

Example

(+) or dextro



(-) or laevo



[α]

+5.9

-5.9

BP

128.9

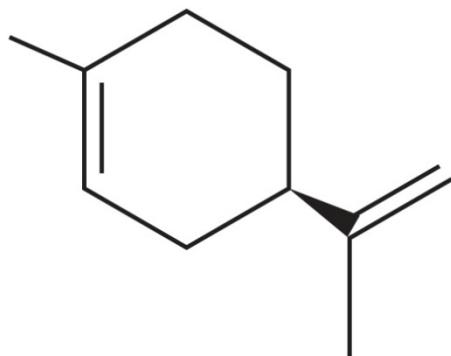
128.9

μ

1.4107

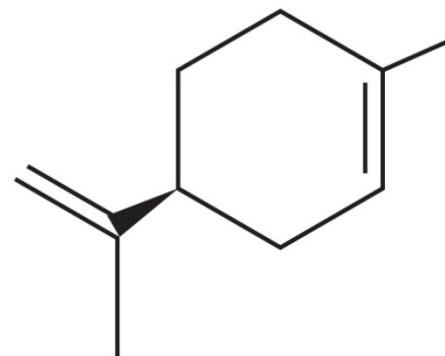
1.4107

Oranges and Lemons



(+)-limonene

found in oranges



(-)-limonene

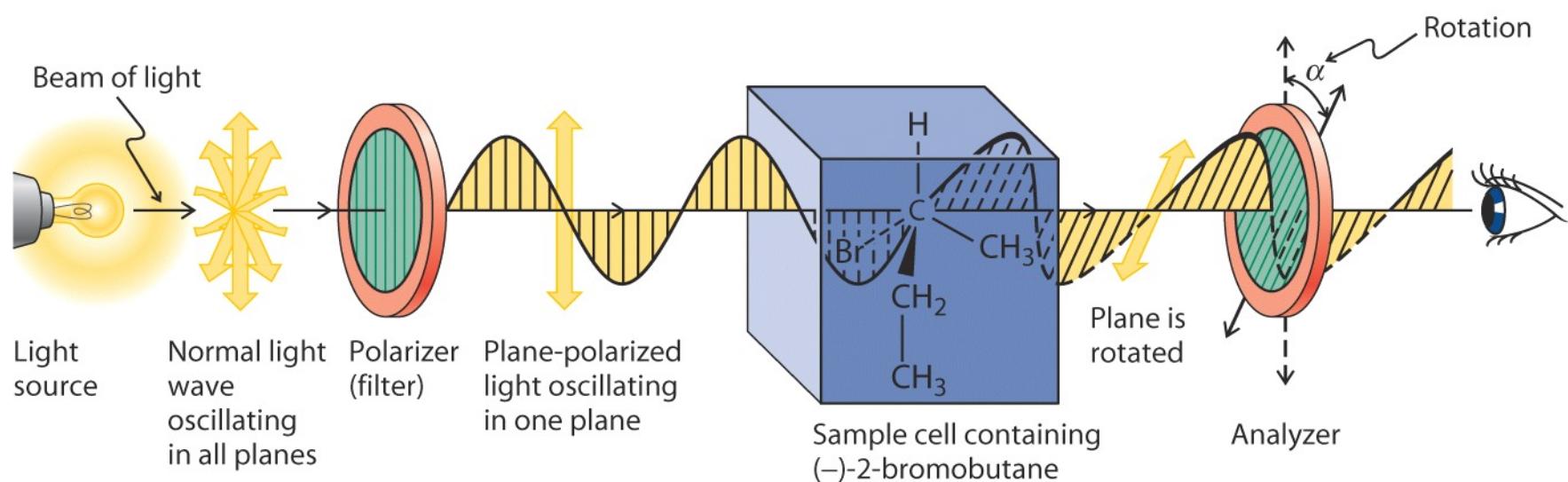
found in lemons

Stereoisomerism & Optical Activity

Enantiomers: Which is which? **Absolute configuration.**

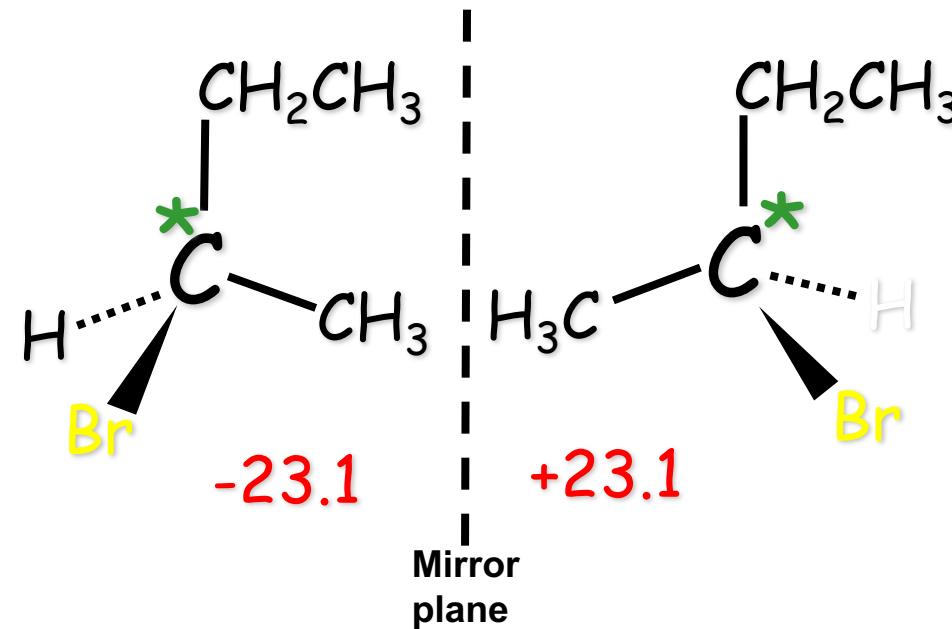
1. X-ray crystal structure. “Photo.”
2. Polarimeter: Optical rotation of plane polarized light:
Image → **dextrorotatory (clockwise), (+)-enantiomer**

Mirror image → **levorotatory (counter-clockwise), (-)-enantiomer.**



Enantiomers are optically active

Optical rotation:



$$[\alpha]_{\lambda}^{+}(^{\circ}\text{C}) = \frac{a}{l c}$$

Measured rotation

Length of vessel (in dm usually)

Concentration (g ml⁻¹)

$[\alpha]$ is called *specific rotation*.

Note: Sign of rotation does not tell you absolute configuration

Optical Purity

- Optical purity (o.p.) is sometimes called enantiomeric excess (e.e.).
- One enantiomer is present in greater amounts.

$$\text{o.p.} = \frac{\text{observed rotation}}{\text{rotation of pure enantiomer}} \times 100$$

Calculate % Composition

The specific rotation of (S)-2-iodobutane is +15.90°.
Determine the % composition of a mixture of (R)- and (S)-2-iodobutane if the specific rotation of the mixture is -3.18°.

Sign is from the enantiomer in excess: levorotatory.

$$\text{o.p.} = \frac{3.18}{15.90} \times 100 = 20\%$$

$$2l = 120\% \quad l = 60\% \quad d = 40\%$$

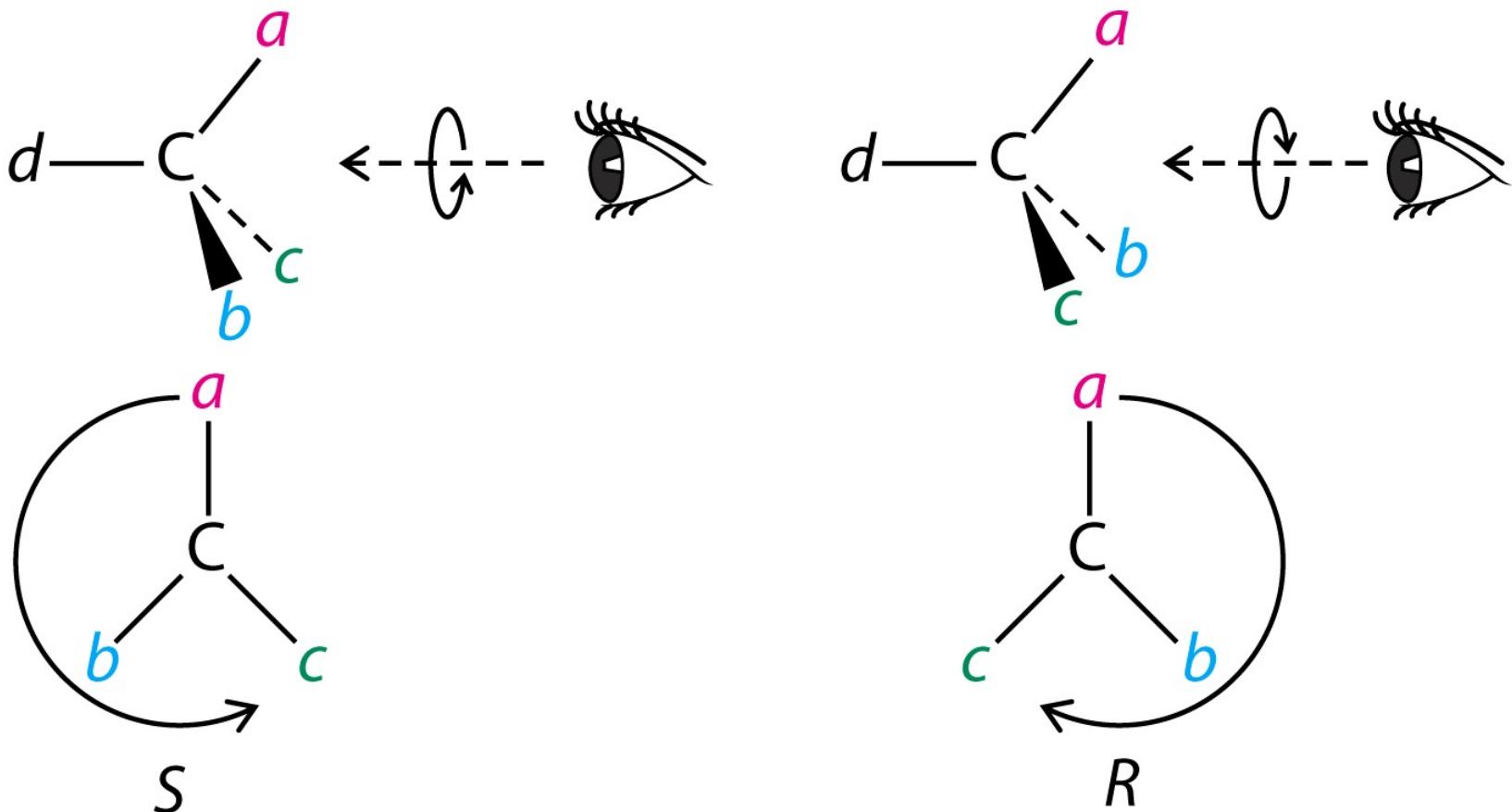
Naming Enantiomers (Absolute Configuration)

- A self consistent and unambiguous system of configurational nomenclature based on 3-D structure
- Introduced by Cahn-Ingold-Prelog (hence CIP rules!)
- R (rectus – right) and S (sinister – left) describe topography and have no correlation with the sign of rotation
- Two rules are used to assign configuration
 - (i) The sequence Rule
 - (ii) Chirality rule

CIP rule

- Arrange the four ligands of a chiral centre (Cabcd) in a priority sequence e.g. a>b>c>d or the ligands are numbered 1>2>3>4. (Sequence rule)
- The chiral centre is then viewed from the side remote from the lowest ranking group (d or 4).
- If from this point of view, the arrangement a → b → c (or 1 → 2 → 3) appears in the clockwise direction, the configuration is **R** and if the arrangement appears in the anticlockwise direction, the configuration is **S** (Chirality Rule)

Procedure for Assignment of R , S



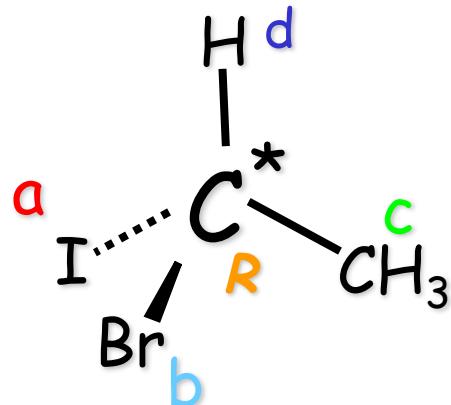
The sequence rule for deciding priority

- (0) Near end of an axis or a plane precedes the farther end (proximity rule)
- (1) Higher atomic number precedes lower e.g. S > F > O > N > C > H
- (2) Higher atomic mass no. precedes lower e.g. T > D > H
- (3) ‘Cis’ precedes ‘trans’ and Z precedes E
- (4) Like pair R,R or S,S precedes unlike pair R,S or S,R
- (5) R precedes S; M precedes P

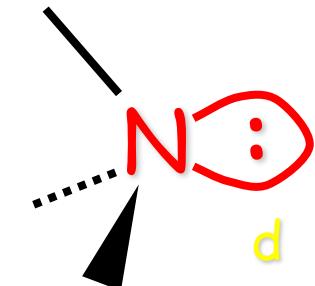
NOTE: For most cases only rule (1) and (2) are important
Subrule (0) is applicable to axial and planar chirality
There are subrules of rule (1) and use rule (2) after exhausting rule (1)!

Sequence Rules

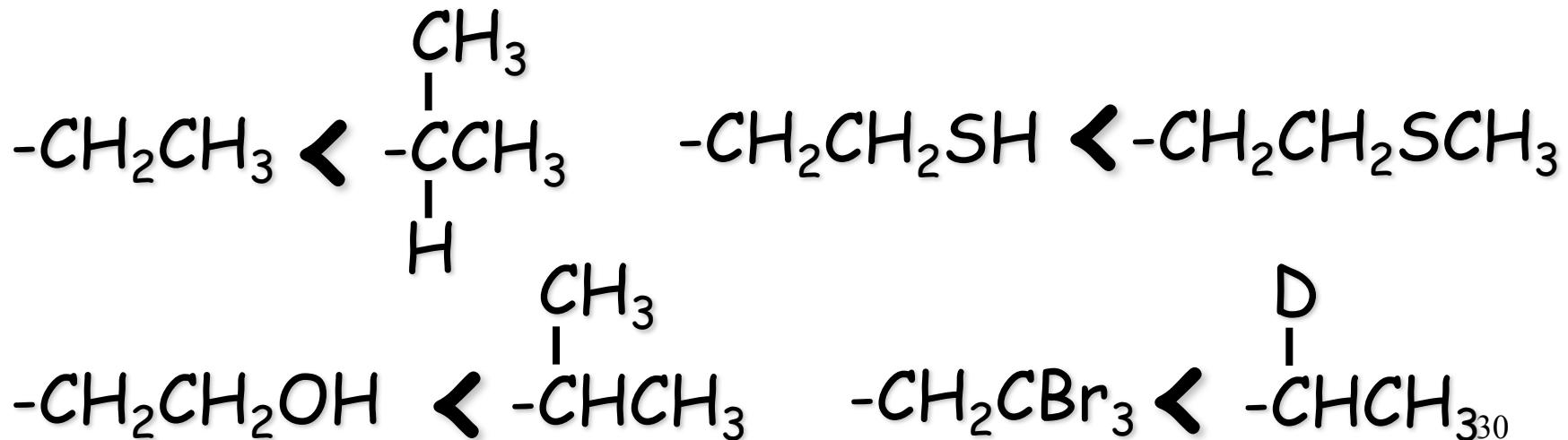
1. Order by **atomic number**, i.e. H = 1, lowest.



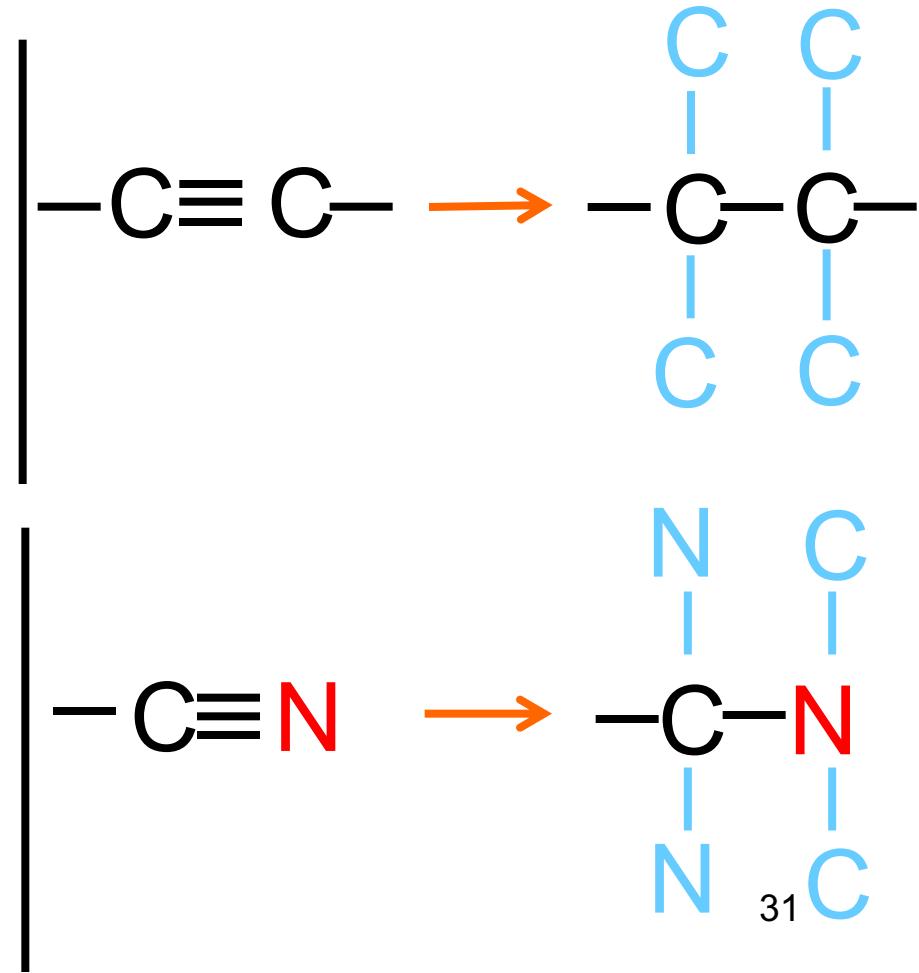
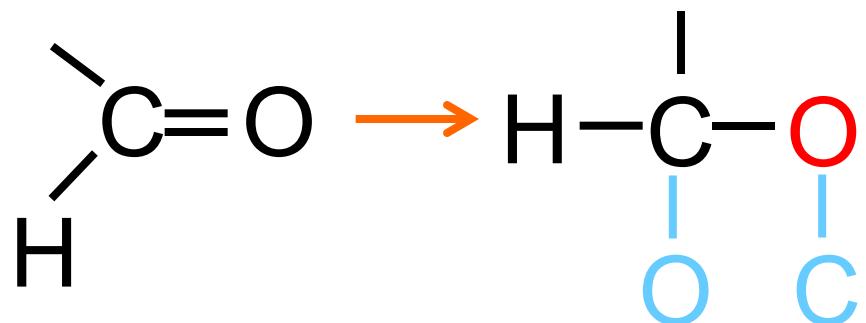
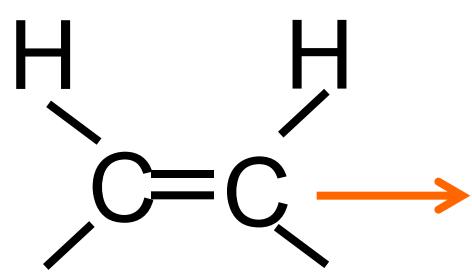
Exception: lone pair,
“zero”. E.g., amines:



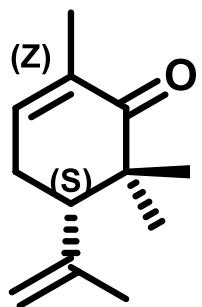
2. If same priority at first atom: Go to **first point of difference**.



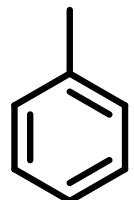
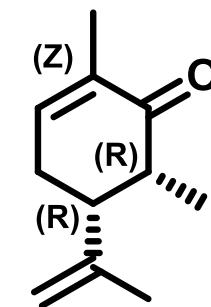
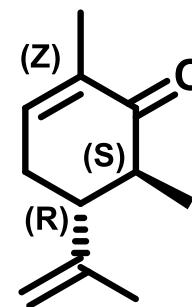
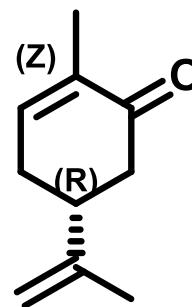
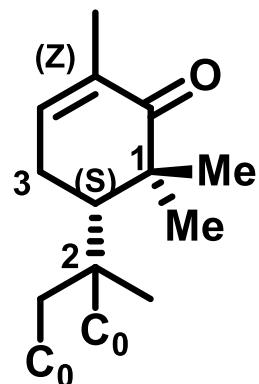
3. **Multiple bonds:** Add double or triple representations of atoms at the respective other end of the multiple bond.



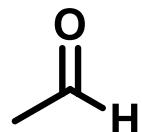
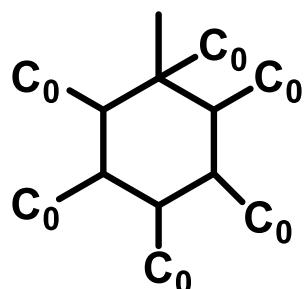
Some examples



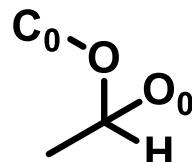
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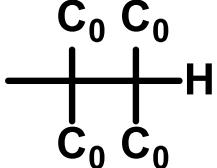
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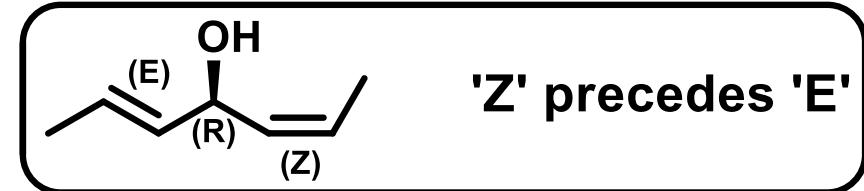
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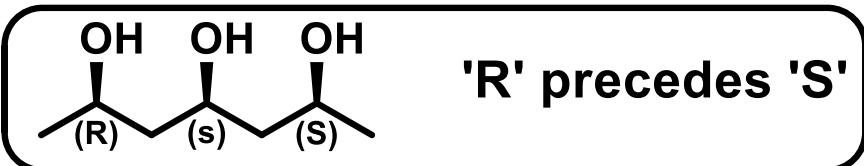
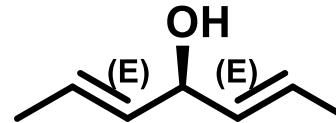
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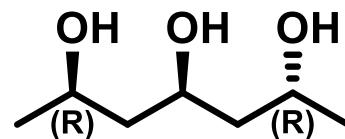
C₀ = 'Phantom' atom



'Z' precedes 'E'



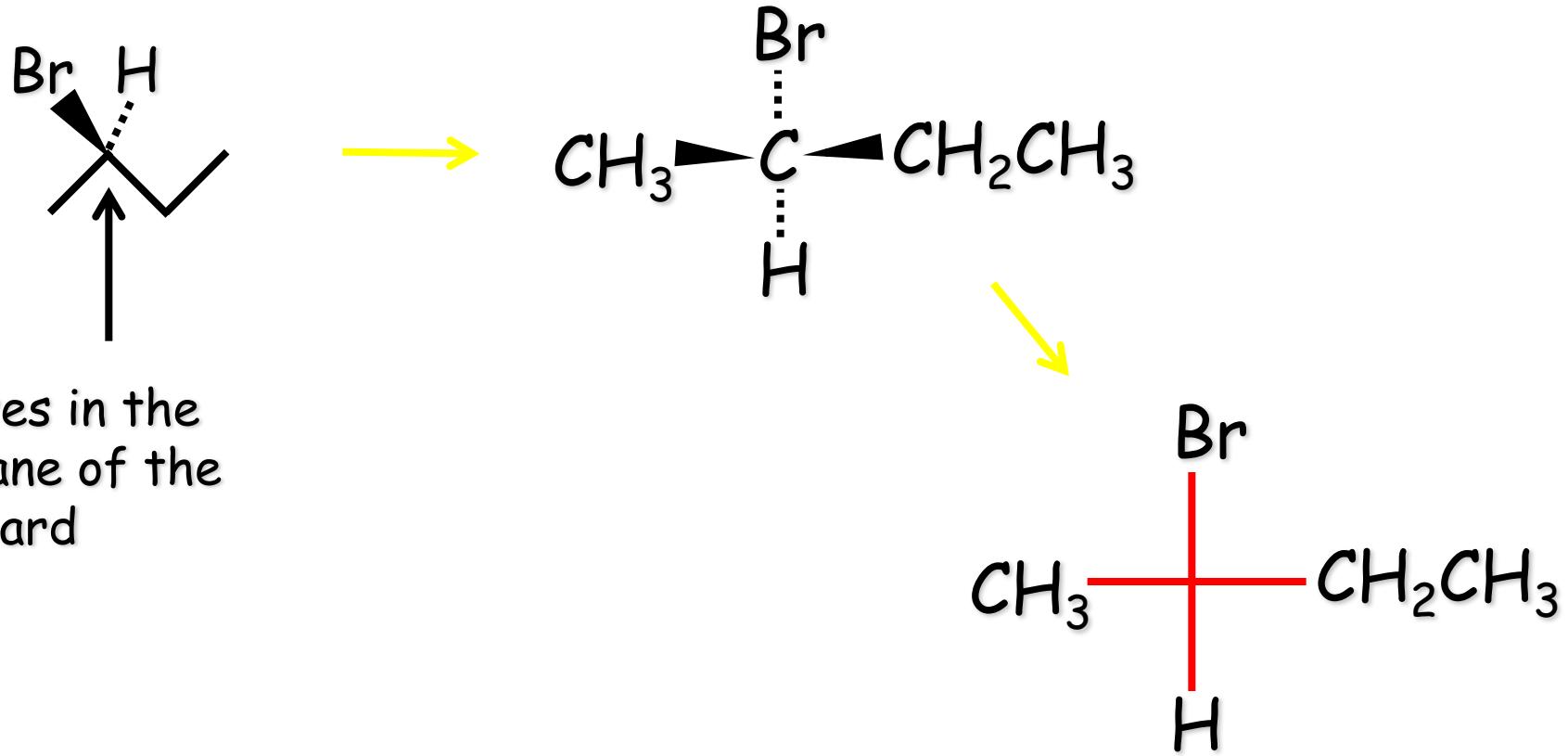
'R' precedes 'S'



HINT

If the lowest-priority atom (usually H) is oriented toward you, you don't need to turn the structure around. You can leave it as it is with the H toward you and apply the *R/S rule backward*.

Fischer Projection: A flat stencil

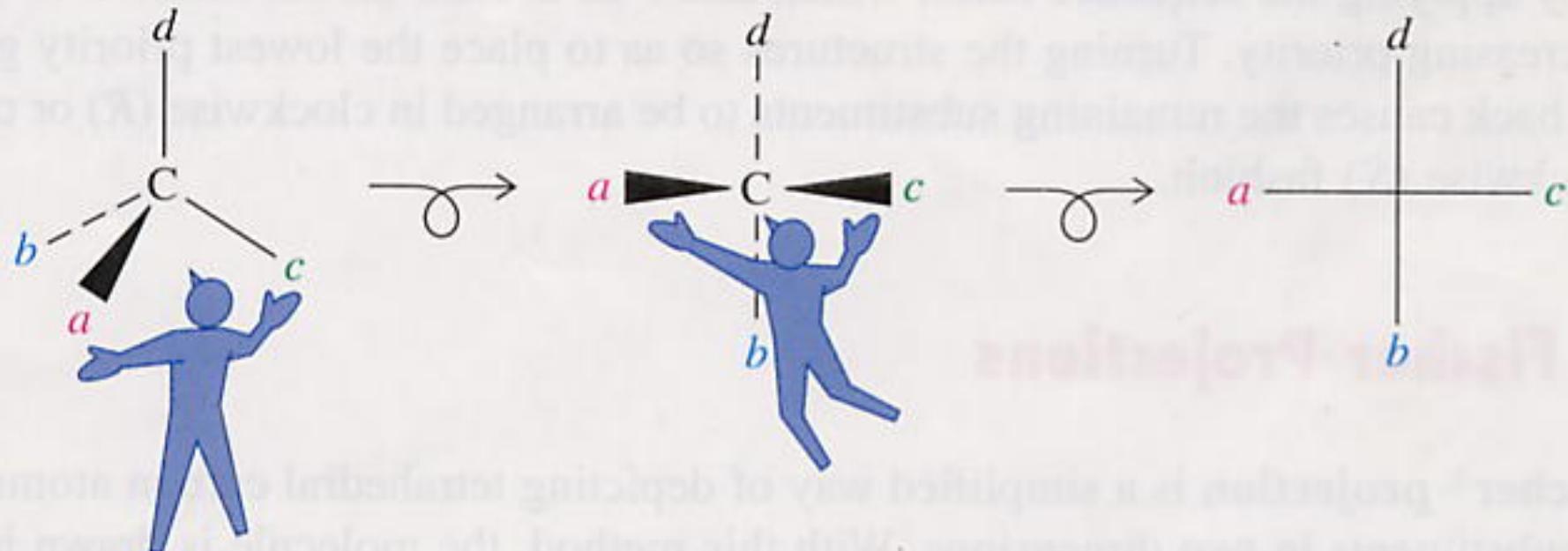


Eyes in the
plane of the
board

Depending on your starting dashed-wedged line structure, **several** Fischer projections are possible for the **same** molecule.

Fischer Projections

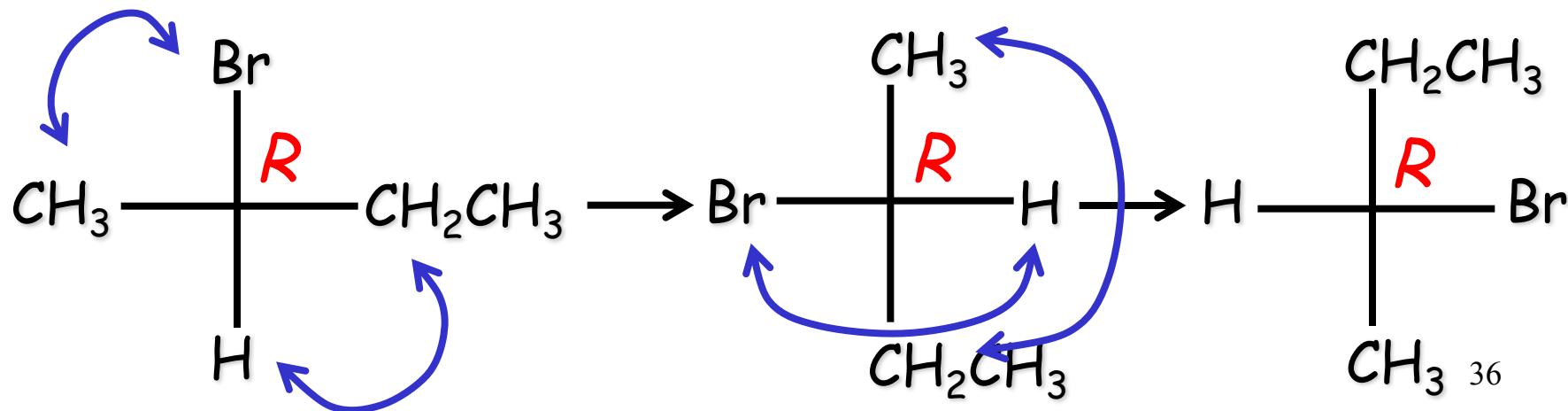
A Simple Mental Exercise:
Conversion of Dashed-Wedge Line Structures into Fischer Projections



Rules for handling Fischer projections:

1. Don't rotate.
2. The mutual exchange of any pair gives the other enantiomer

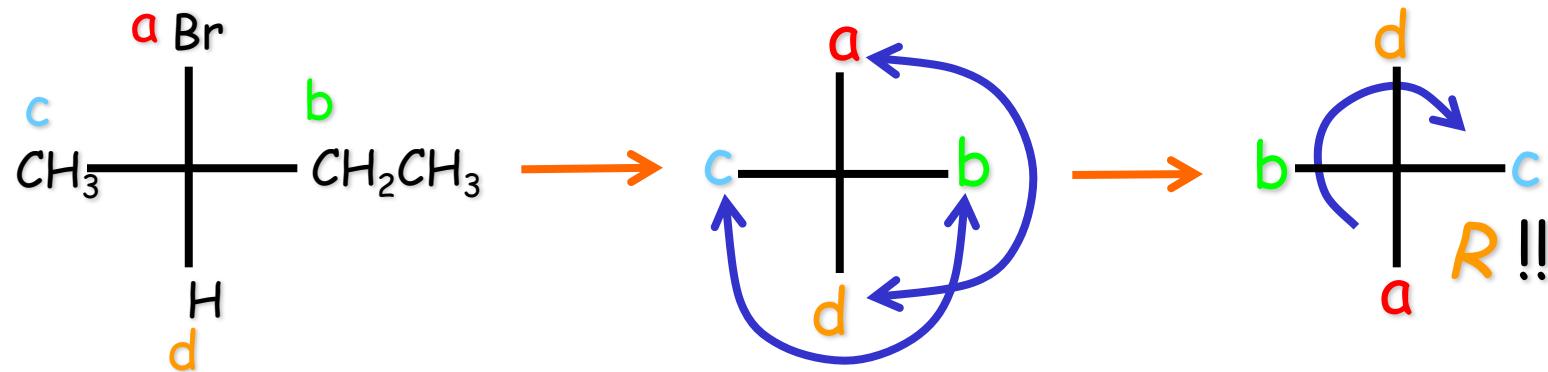
Therefore: Two exchanges leave absolute configuration. Example: (2R)-Bromobutane



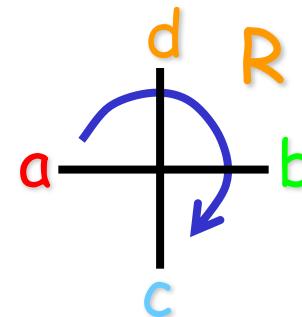
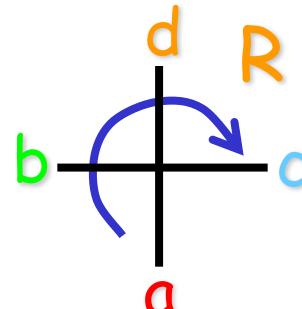
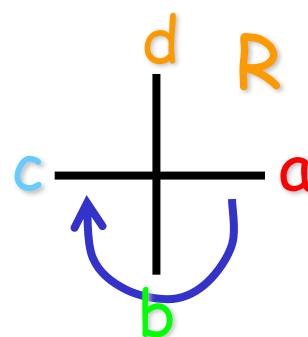
This procedure can be used to readily assign R,S :

Do double exchanges to place d on top.

Example:



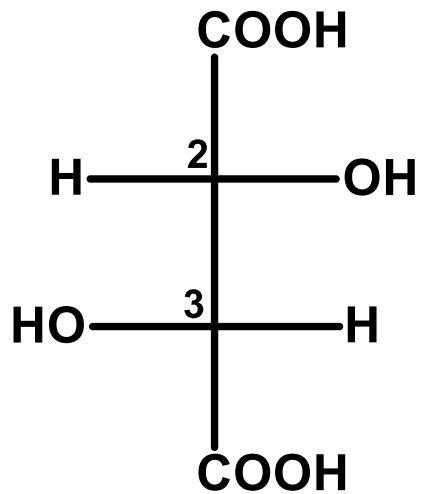
Note: There are three possible arrangements for each, R or S, e.g., R :



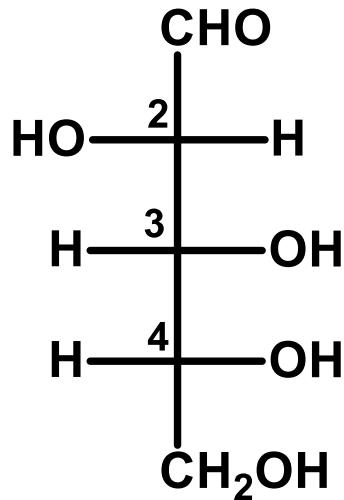
R/S in Fischer Projection

- Remember “Very Good” = “Vertical is Good”!
- Assign priority 1-4.
- Don’t worry about no. 4
- Find direction from 1-3
- If substituent 4 is on vertical line, it’s correct R/S nomenclature
- If no. 4 substituent is not on vertical line, the answer is wrong and you write opposite!

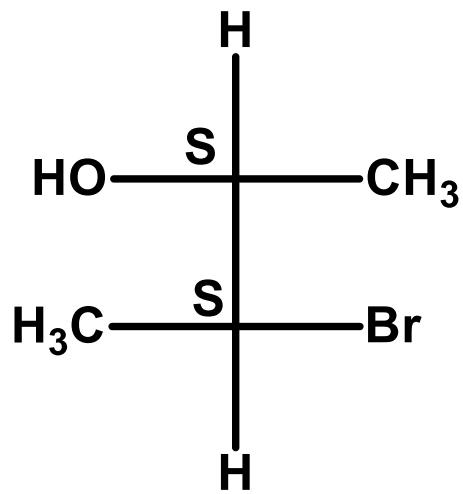
Some examples



2R, 3R



2S, 3R, 4R

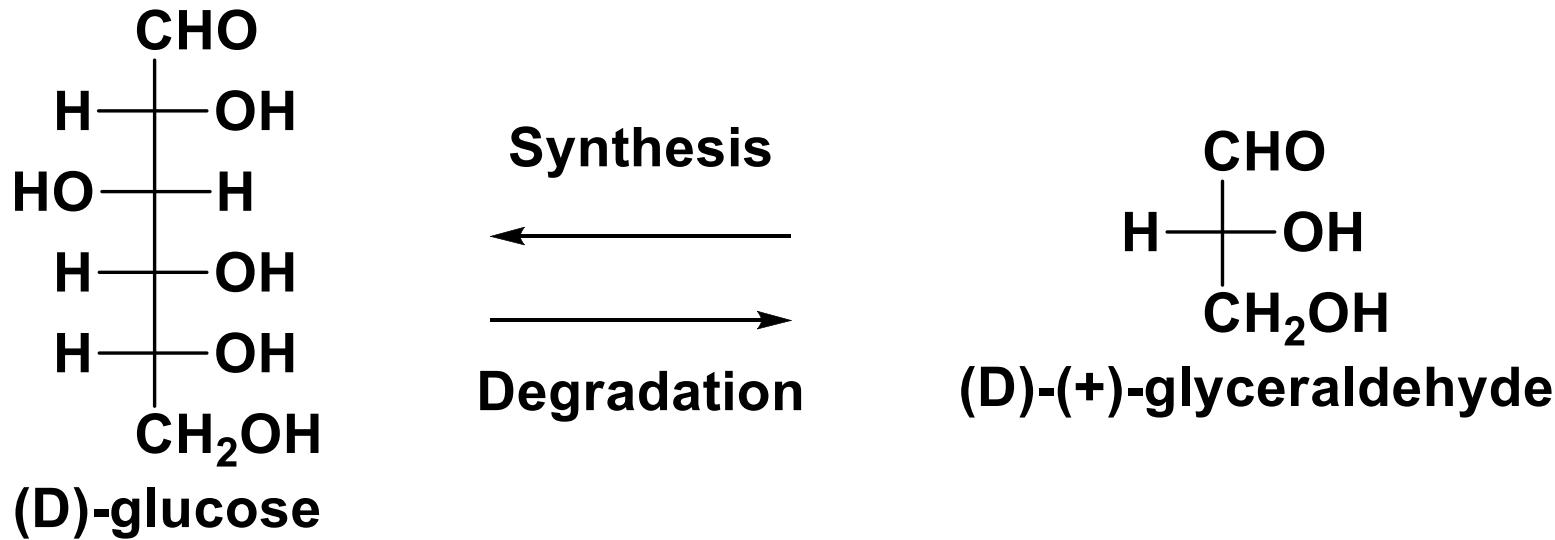


Assign absolute configuration for all stereocentres of

1. (D)-glucose
2. All natural amino acids

Fischer's D and L nomenclature

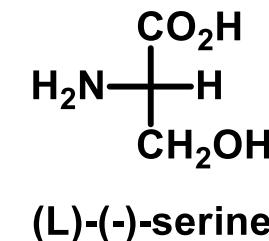
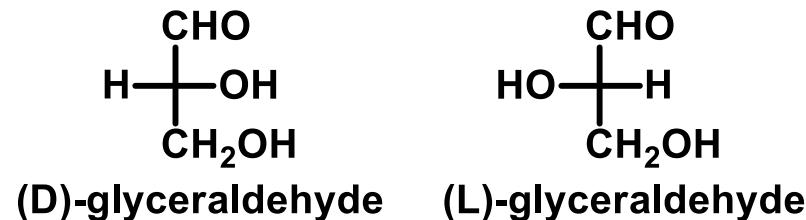
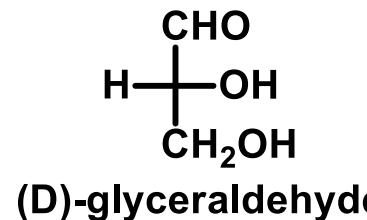
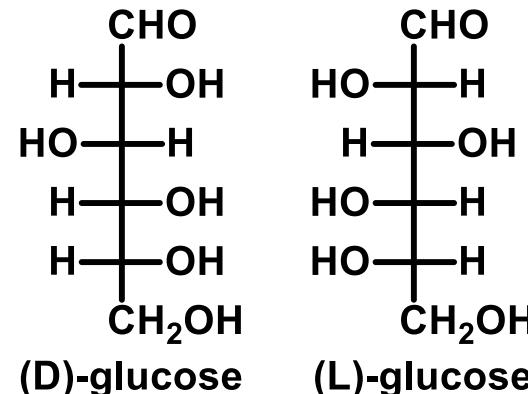
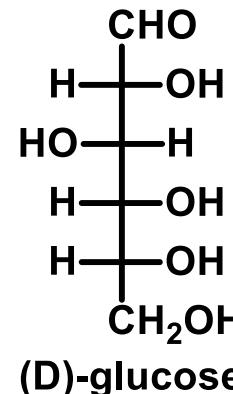
- Fischer established the relative configuration of (+)-glucose and arbitrarily represented it by the structure – He called it (D)-(+)-glucose



Structures which can be correlated chemically to these compounds are (D) – opposite isomers called (L)

Conventions used for Fischer's configurations

- The molecule written with largest carbon chain placed vertically
- The most highly oxidised end of the chain is placed at the top (as CHO in glucose)
- If in the projected structure, the OH group (or any electronegative group X) at the bottom most chiral centre is on the right hand side, the molecule is given D-configuration – if it is on left, the molecule is given L-configuration

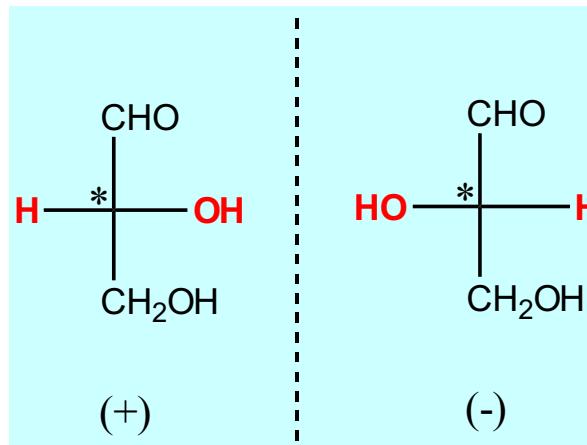


Chemical correlation fails sometime – Hence an alternative

Relative Configuration

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

D-(+)-glyceraldehyde



L-(-)-glyceraldehyde

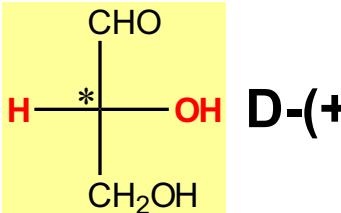
Glyceraldehyde is used as a standard for assigning *relative configurations*

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

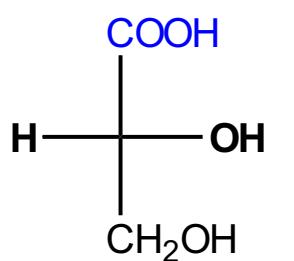
Relationship with Glyceraldehyde



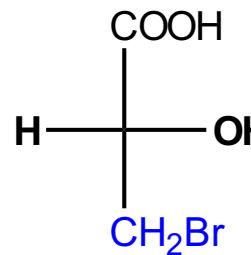
D-(+)-glyceraldehyde



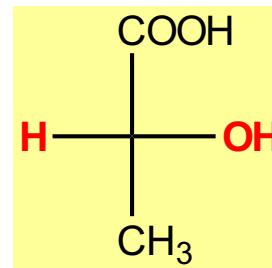
Br₂ / H₂O



PBr₃



Zn / H⁺



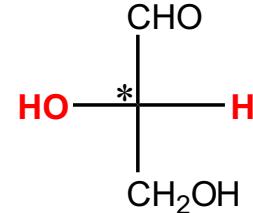
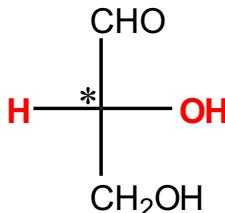
Maintaining the basic connectivity, D-lactic acid is related to D-glyceraldehyde

D-Lactic acid

D-optical family

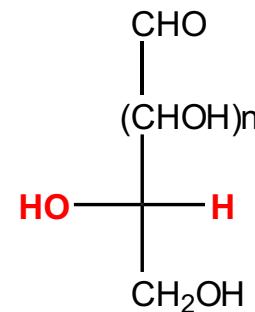
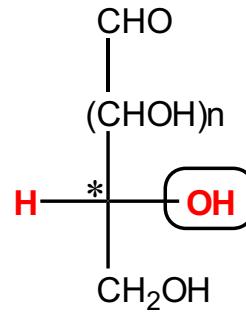
Optical Families

D-(+)-glyceraldehyde



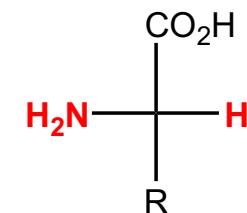
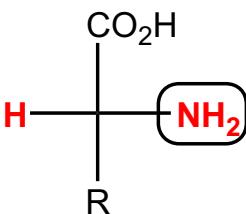
L-(-)-glyceraldehyde

D-sugars



L-sugars

D-amino acids



L-amino acids

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

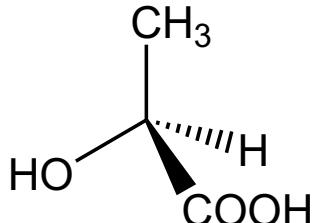
There is NO direct relationship between the configurational descriptors R/S or D/L

and

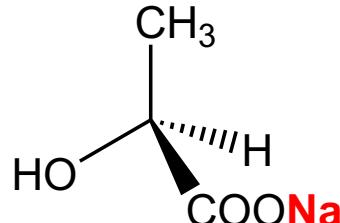
The sign of rotation

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

Lactic acid



(S)-(+)- Lactic acid



Sodium lactate

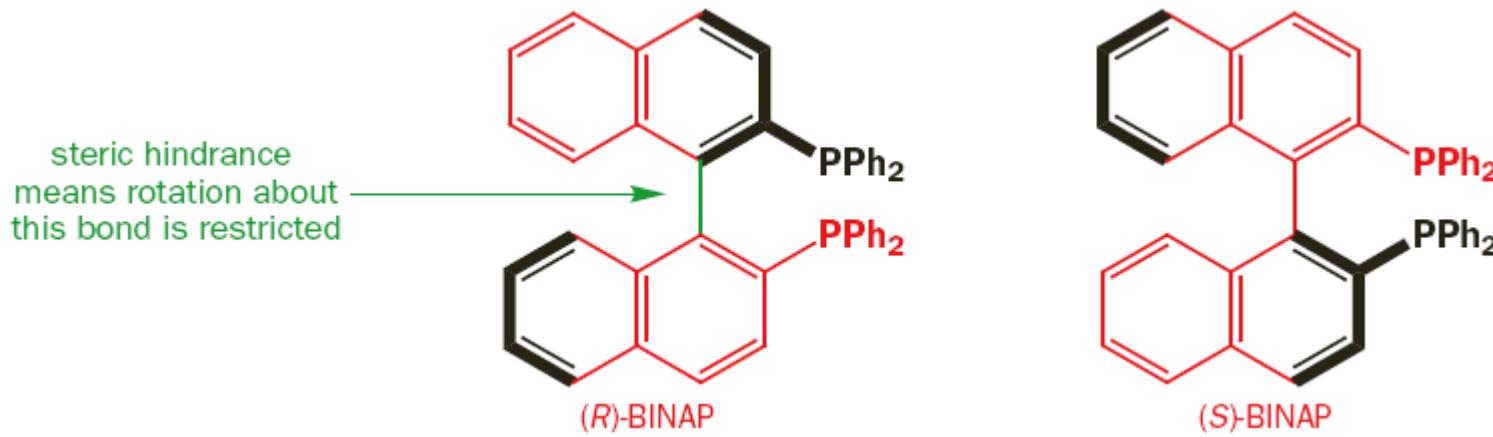
(S)-(-)- Sodium lactate

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)

Example 1:



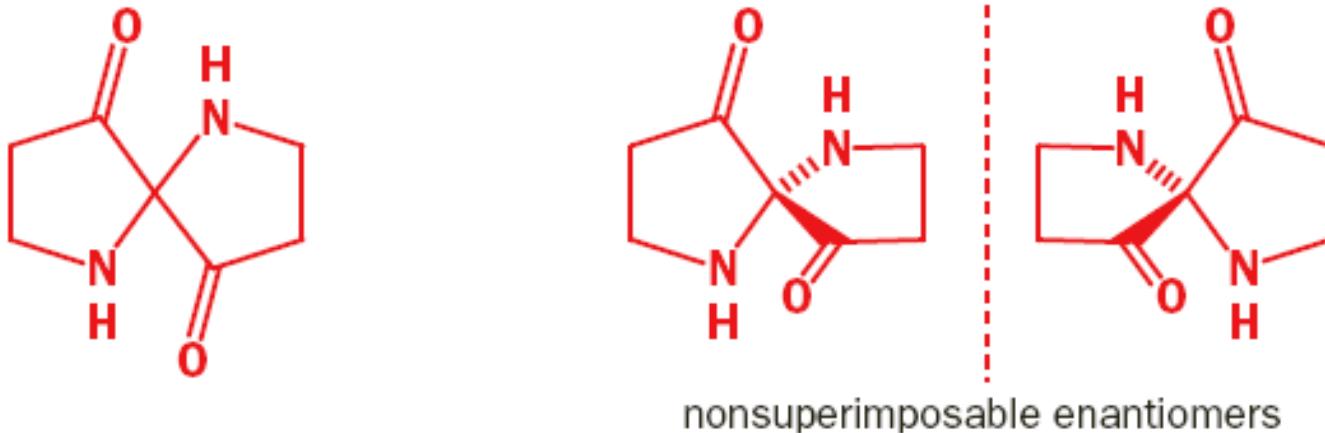
These molecules are **axially chiral** (axial asymmetry) arises due to restricted rotation around the C-C bond

Chiral Molecules-with no chiral centers

Example 2:

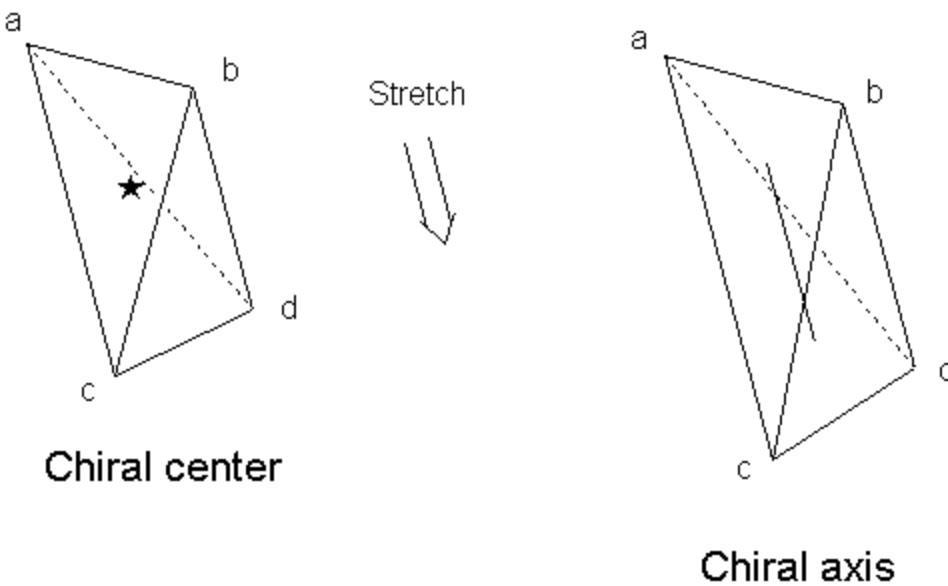


Example 3:

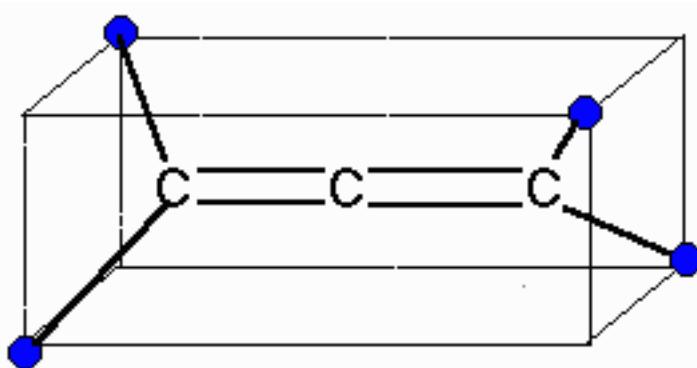


Axial Chirality

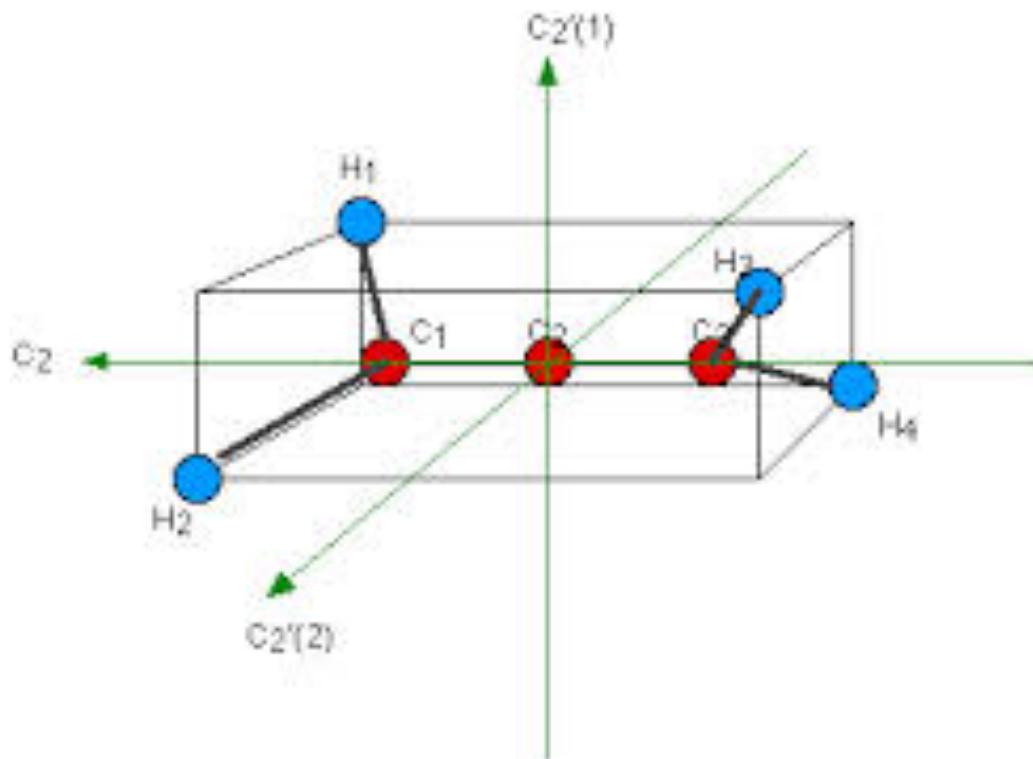
- Consider the tetrahedral arrangement of ligands around a chiral center
- If we grasp opposite edges of the tetrahedron and stretch, the chiral center is extended into a *chiral axis*.



Allene in a rectangular box!

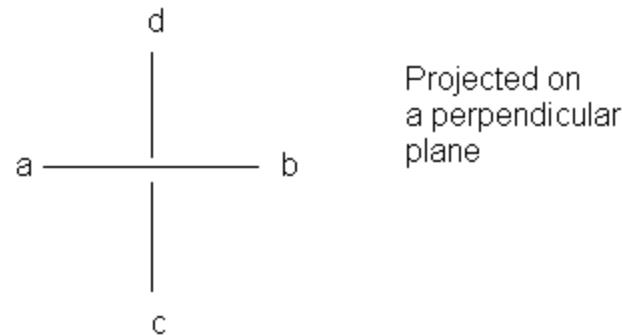


Axis of symmetry in allene



Allene - C_2 - Before

- The structure remains dissymmetric, lacking a plane of symmetry, so long as (a) \neq (b) and (c) \neq (d).
- Structures with (a) and (b) the same as (c) and (d) remain chiral.
- Note: Caabb is achiral for tetrahedral arrangement but Caabb is chiral in elongated tetrahedron!

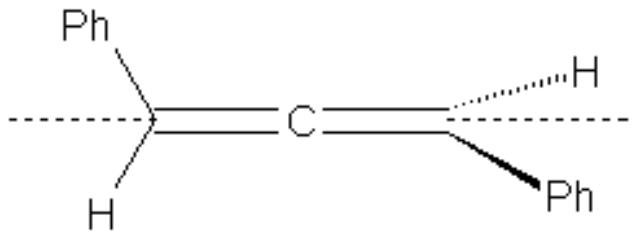


CIP rules for axially chiral compounds

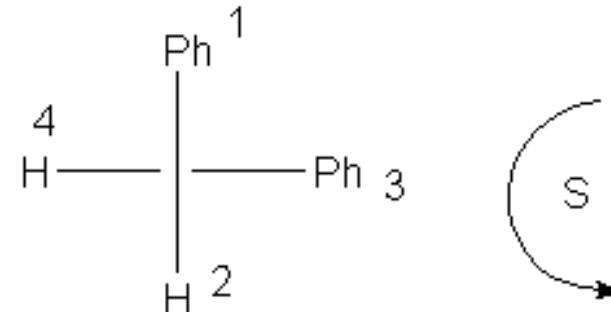
- The molecule is viewed along the chiral axis;
 - Near ligands take precedence over far;
 - The ligand of lowest priority is ignored.
-
- Examples: allenes, biphenyls, spiranes, alkylidene cycloalkanes, adamantoids

R/S for allenes

- Allenes in which the substituents on each terminus are different (the same condition as for stereoisomerism in alkenes) are chiral; the long axis of the molecule is a chiral axis. Here we assign a configuration of S.

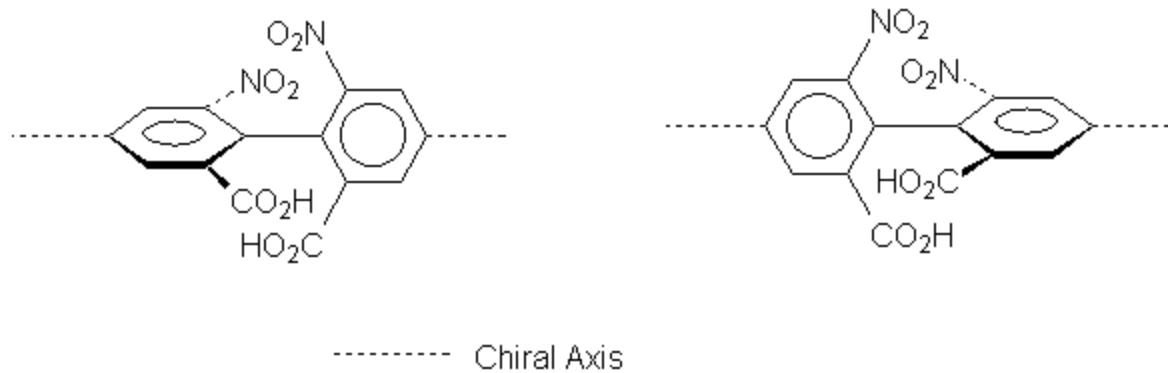


View
from
left:

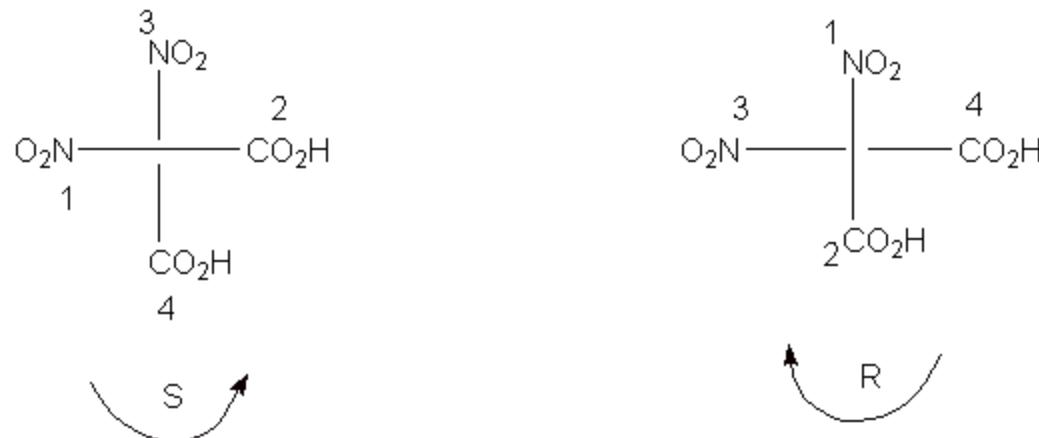


R/S for biphenyls

Chirality due to restricted rotation around the bond connecting the two phenyl rings – also referred to as Atropisomerism
Here is an example, a biphenyl and its enantiomer.

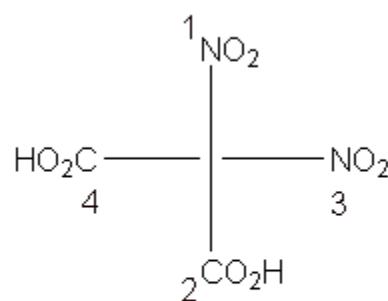


If we view the structures from the left, and project them onto a perpendicular plane, we obtain:

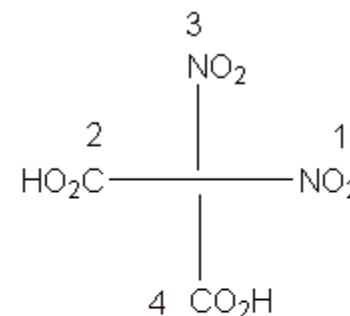


R/S for biphenyls

- Note that the application of the near > far rule means that the CO_2H on the front ring takes precedence over the NO_2 on the rear ring. Thus, the left hand structure is S, and the right hand, R.
- It may seem that this result could be related to our choosing to view the molecules from the left; not so. Here are the projections obtained if each is viewed from the right.



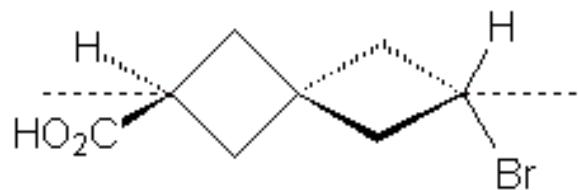
S



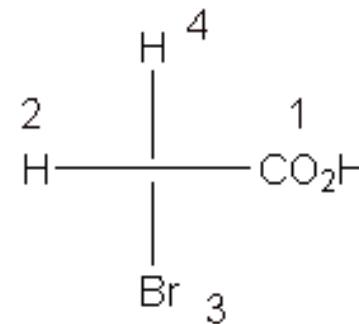
R

The assigned configurations are unchanged.

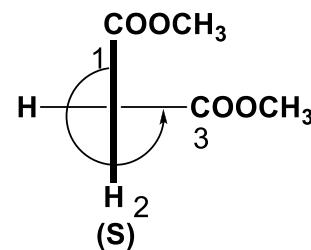
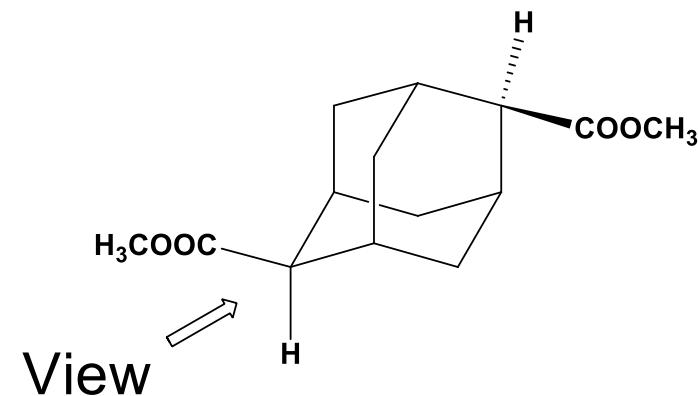
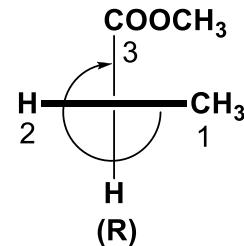
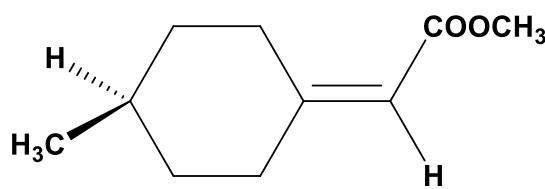
Spiro compounds, Alkylidene cycloalkane, adamantoids



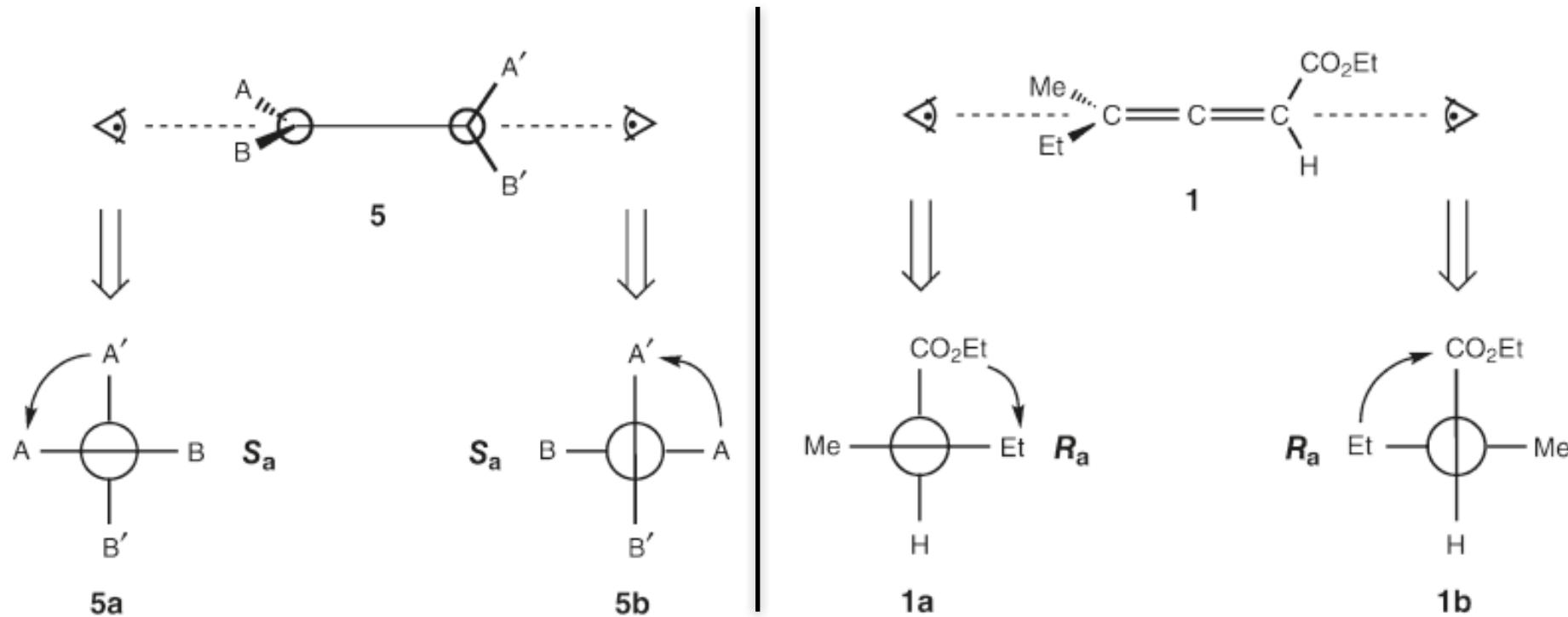
View from
left; lines
represent
bonds, not
ring planes



View \Rightarrow



Absolute configuration of molecules with an axis of chirality



Diastereomers

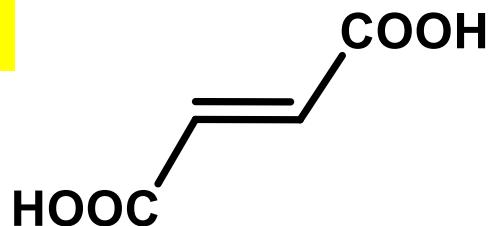
Diastereomers are stereoisomers that are not enantiomers

They are chemically (and physically) different

OR

Stereoisomers that are not mirror images

E.g., 1



Fumaric Acid

MP: 299-300 °C



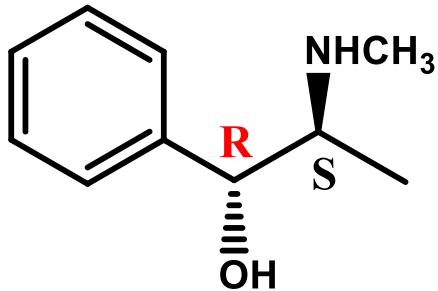
Maleic Acid

MP: 140-142 °C

Forms anhydride upon heating

Diastereomers

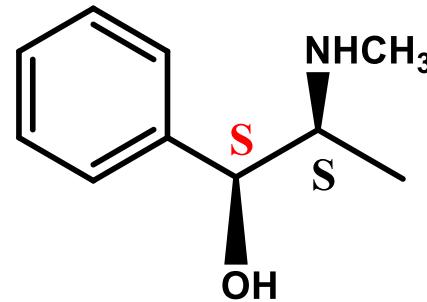
Example 1:



Ephedrine

(+)-ephedrine is used
in traditional medicine

(as a nasal
decongestant)



pseudoephedrine

Diastereomers can be chiral or achiral

E.g., cis-trans geometrical isomers

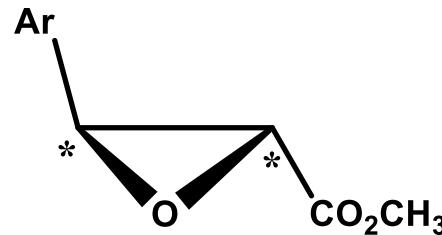
Diastereomers

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.,2

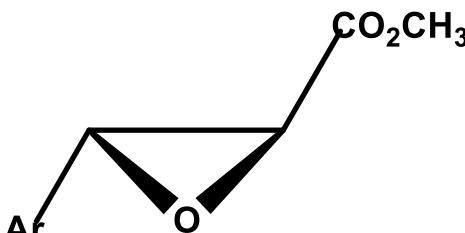
SR



ss

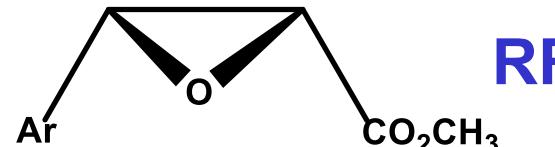
Enantio

RS



Enantio

RR

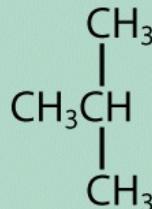
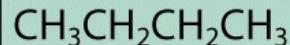


Isomers

Have the same molecular formula, but different structures

Constitutional Isomers

Differ in the order of attachment of atoms (connectivity); Section 1-9

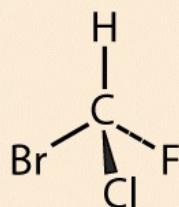


Stereoisomers

Atoms are connected in the same order, but differ in spatial orientation

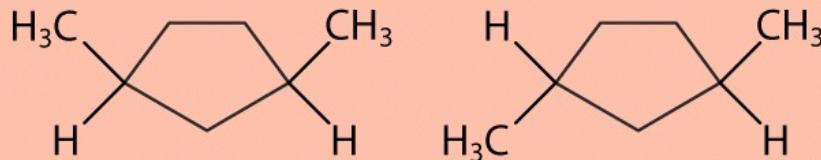
Enantiomers

Image and mirror image are not superimposable; Section 5-1



Diastereomers

Not related as image and mirror image; Section 5-5



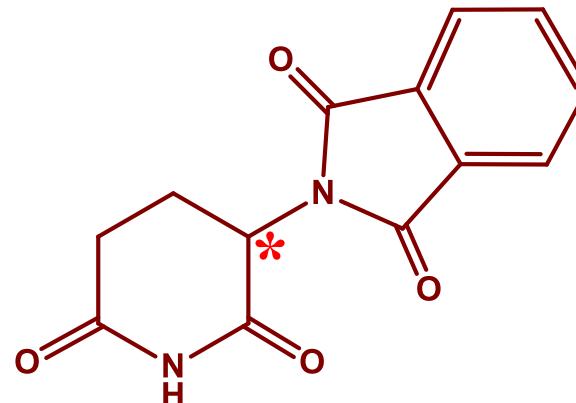
Two or More Chiral Carbons

- When compounds have two or more chiral centers they have **enantiomers, diastereomers, or meso isomers.**
- **Enantiomers** have opposite configurations at each corresponding chiral carbon.
- **Diastereomers** have some matching, some opposite configurations.
- **Meso compounds** have internal mirror planes.
- Maximum number of isomers is **2^n** , where **n** = the number of chiral carbons.

Properties of Enantiomers differ in Chiral medium

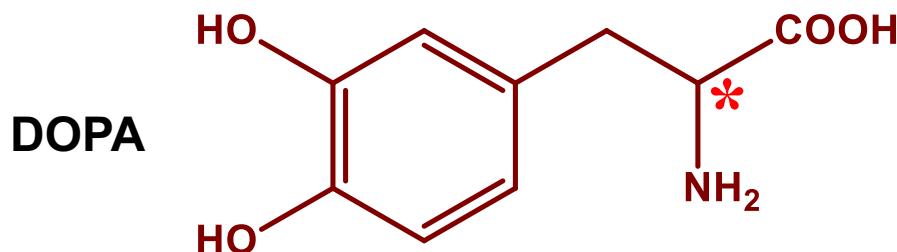
Biological properties of enantiomers are different, as the receptor sites are chiral

E.g., 1 Thalidomide



- R against nausea
- S cause fetal damage

E.g., 2

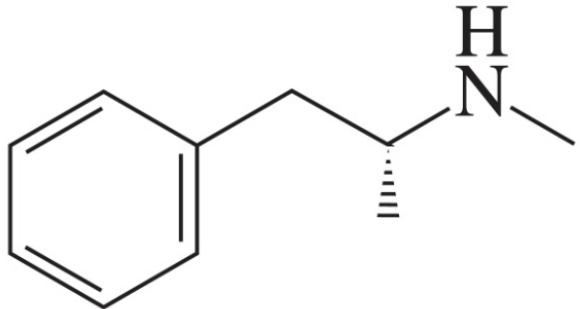


- L treatment of Parkinson's disease
- D biologically inactive !

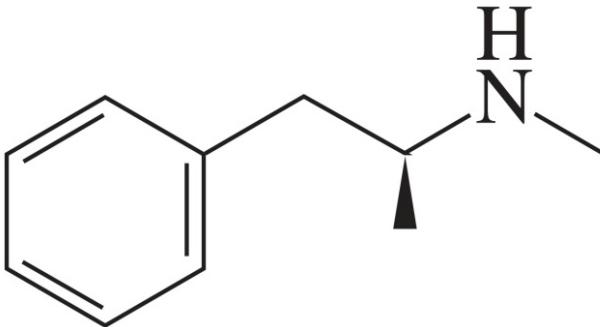
E.g., 3

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

Physiological Properties of Enantiomers



the active ingredient
in Vicks Vapor Inhaler®

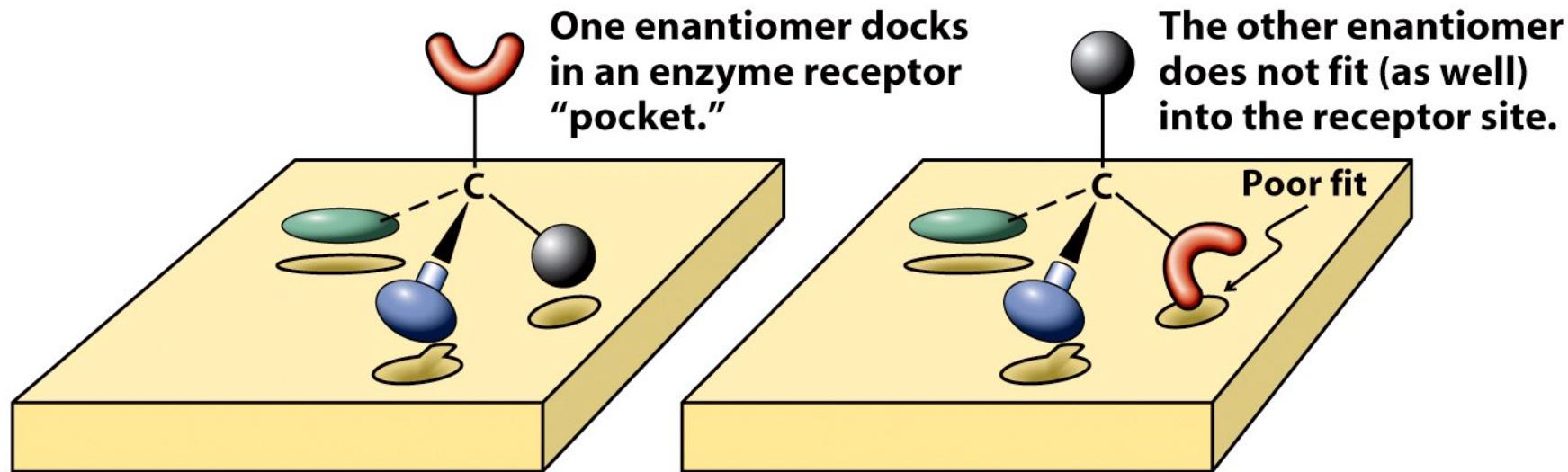


methamphetamine
“speed”

Enantiomers can have very different physiological properties.

Biological Targets are Chiral!

Schematized Enantiomer Recognition in the Receptor Site of an Enzyme



Unnumbered figure pg 198b

Organic Chemistry, Fifth Edition

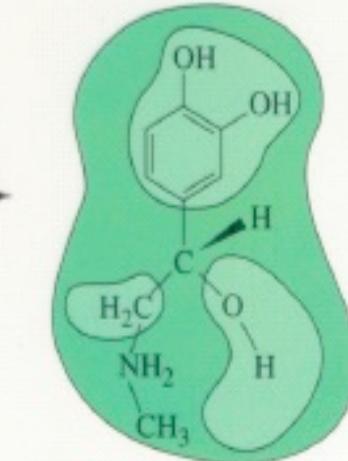
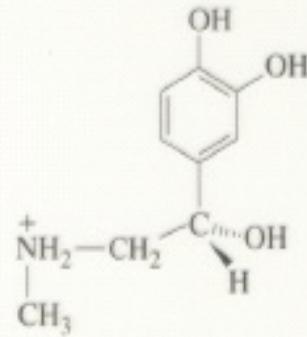
© 2007 W.H. Freeman and Company

Biological Targets are Chiral!

Substrate specific binding is key to drug action

active

R-isomer
of ephinephrine

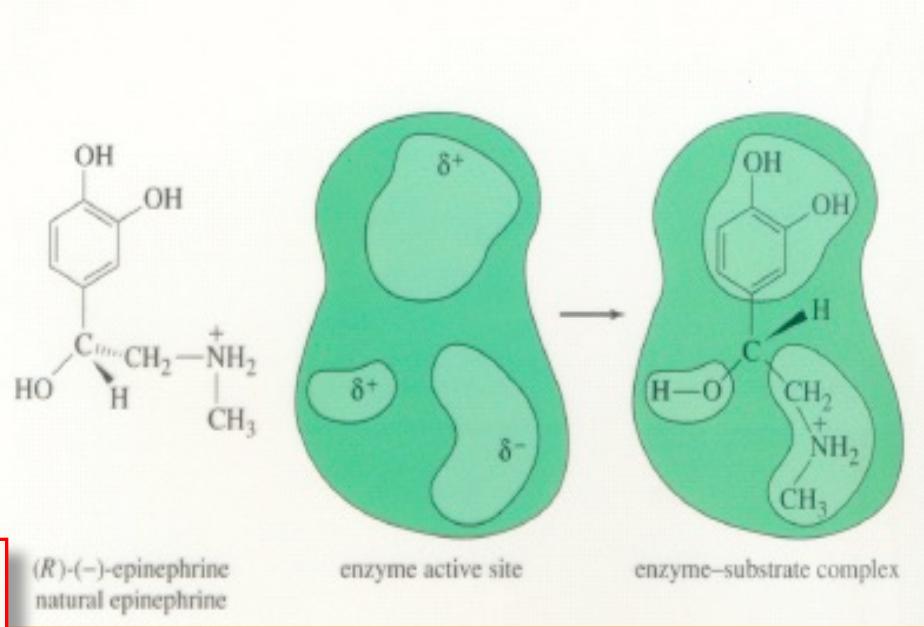


(*R*)-(-)-epinephrine
natural epinephrine

does not fit the enzyme's active site

S-isomer

inactive



Resolution of Enantiomers

(R)- and (S)-2-butanol

plus

(R,R)-tartaric acid



(R)-2-butyl
(R,R)-tartrate

+

(S)-2-butyl
(R,R)-tartrate

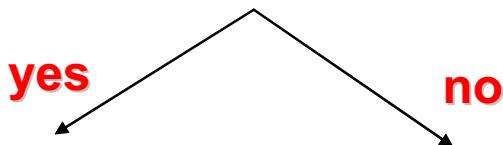
diastereomers, *not* mirror images

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React the racemic mixture with a pure chiral compound, such as tartaric acid, to form diastereomers, then separate them.

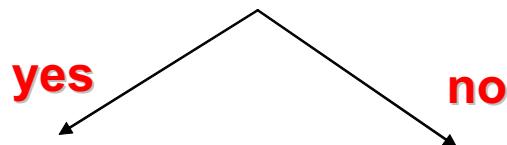
Comparing Structures

Are the structures connected the same?



Are they mirror images?

Constitutional Isomers



Enantiomers

*All chiral centers will
be opposite between them.*

Is there a plane of symmetry?



Meso

superimposable

Diastereomers