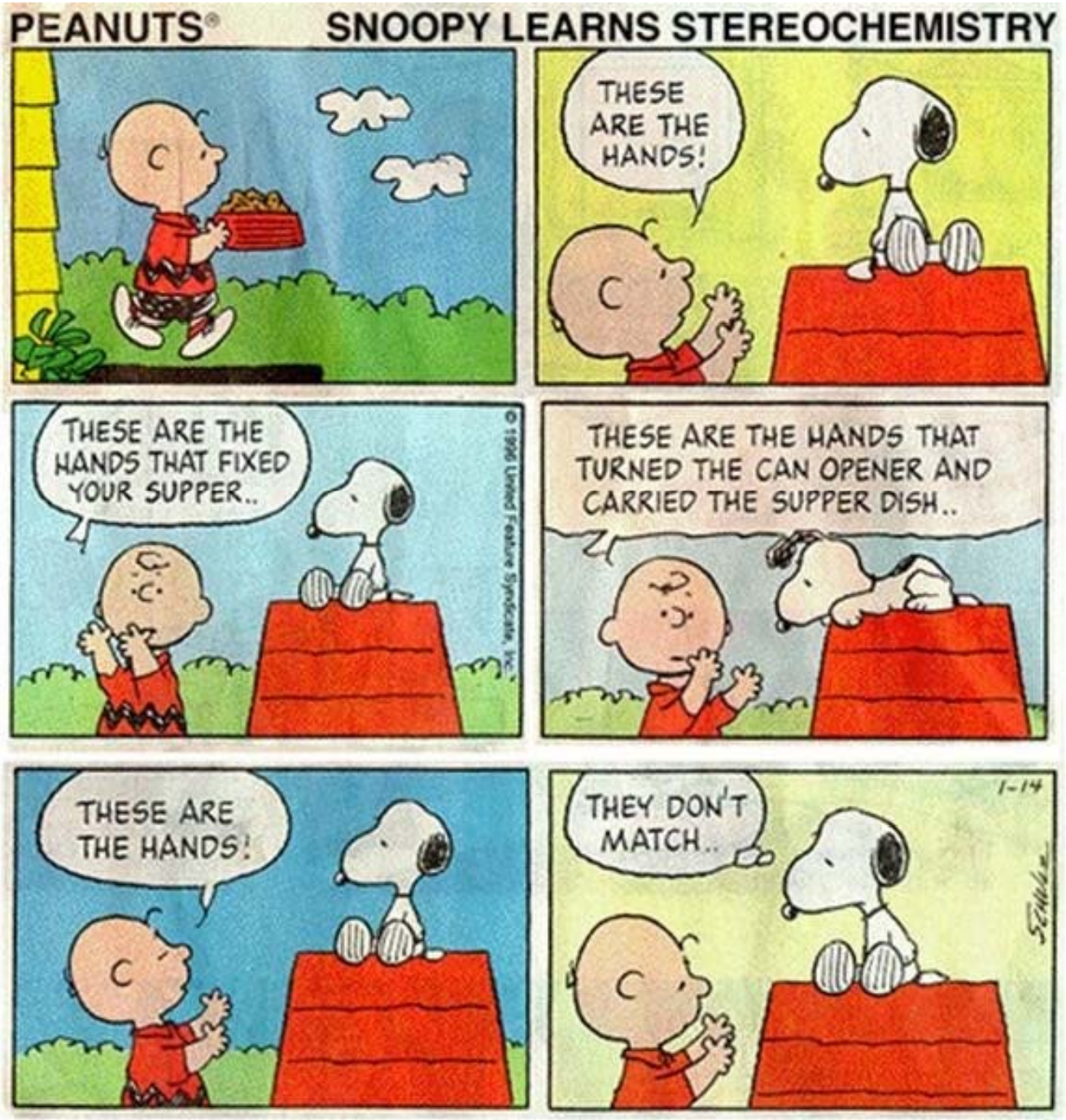
Chapter 7
Stereochemistry

Chirality

- A molecule is *chiral* if its two mirror image forms ***are not*** superimposable upon one another.

- A molecule is *achiral* if its two mirror image forms ***are*** superimposable.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SNOOPY LEARNS STEREOCHEMISTRY
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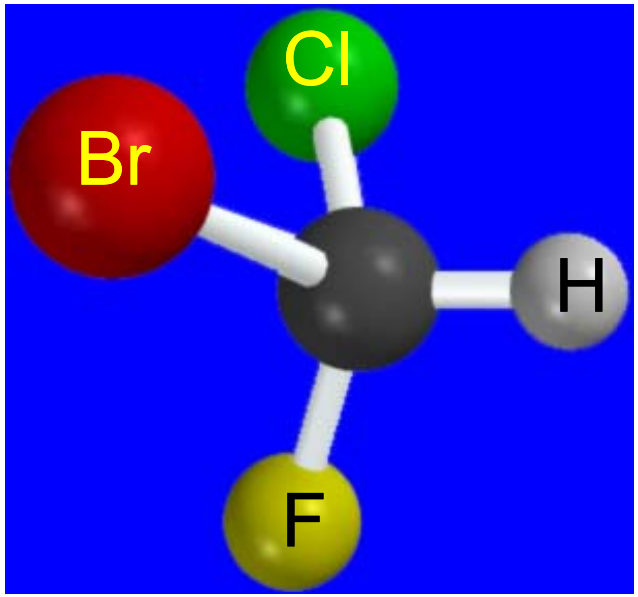
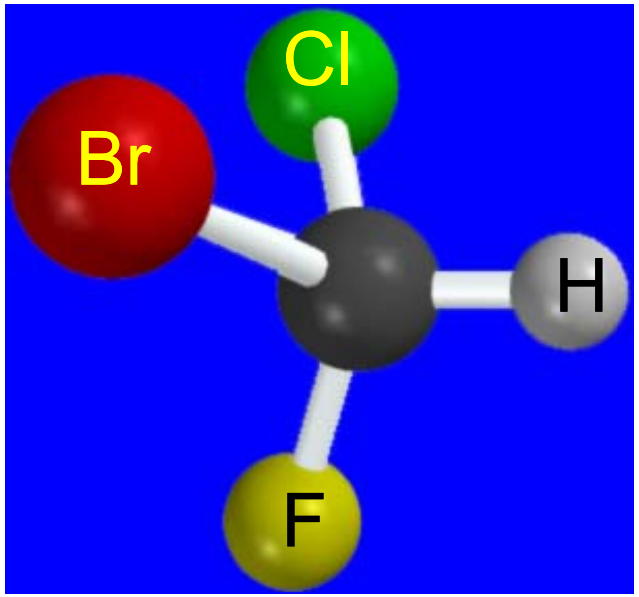
THESE ARE THE HANDS THAT TURNED THE CAN OPENER AND CARRIED THE SUPPER DISH..
THESE ARE THE HANDS!
THEY DON'T MATCH..
1-14

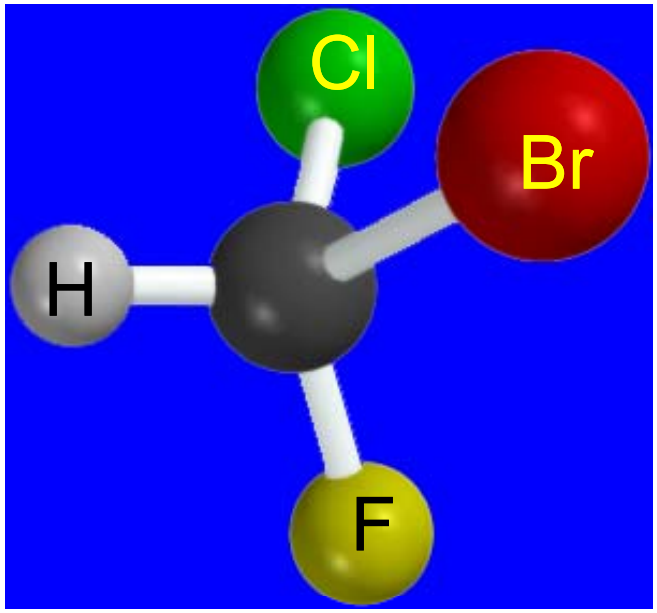
Bromochlorofluoromethane is chiral



- It cannot be superimposed point for point on its mirror image.

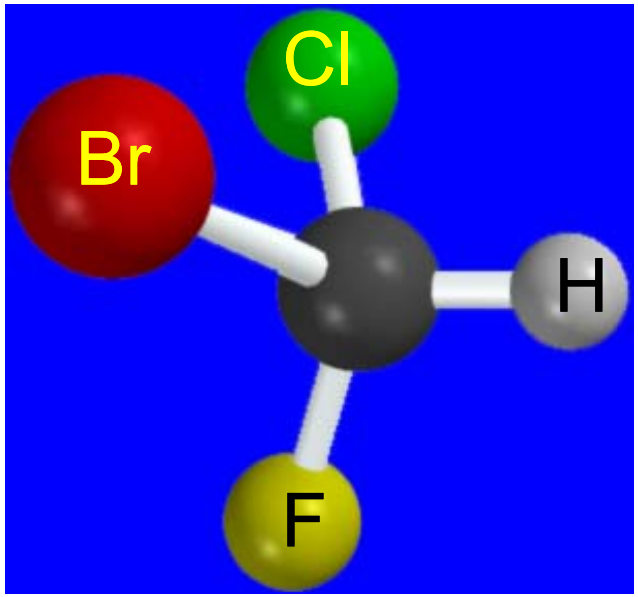
Bromochlorofluoromethane is chiral

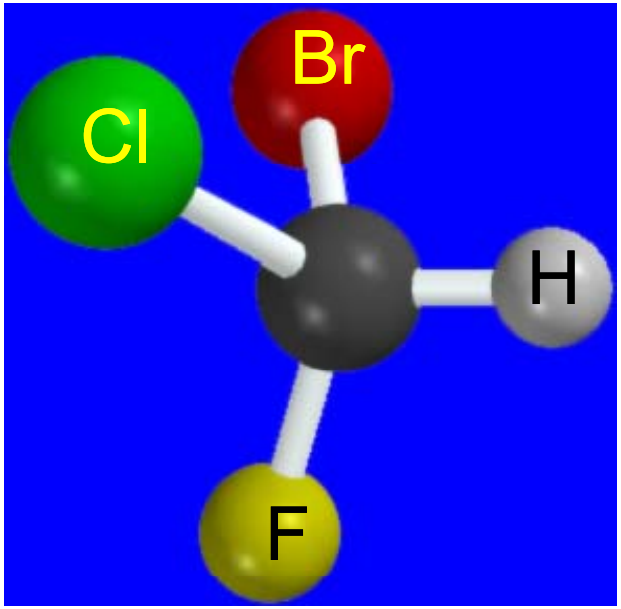




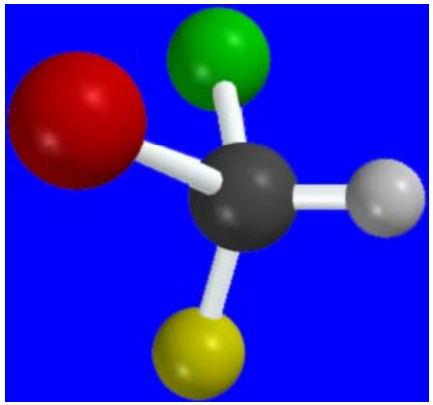
➢ To show nonsuperimposability, rotate this model 180° around a vertical axis.

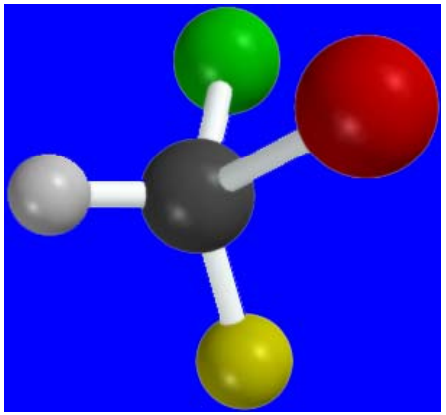
Bromochlorofluoromethane is chiral

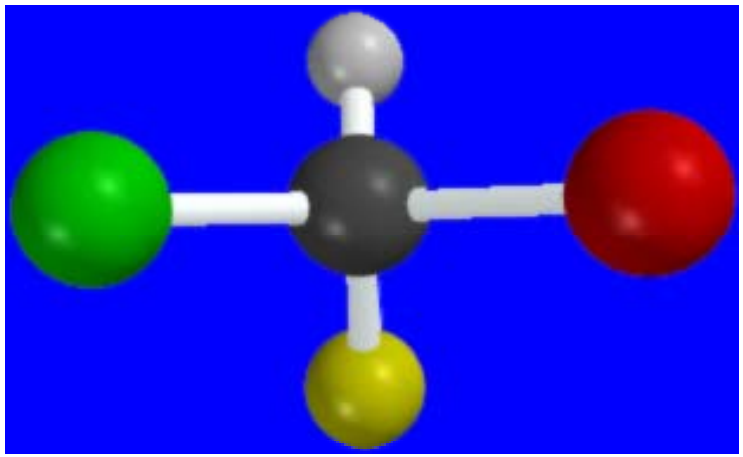


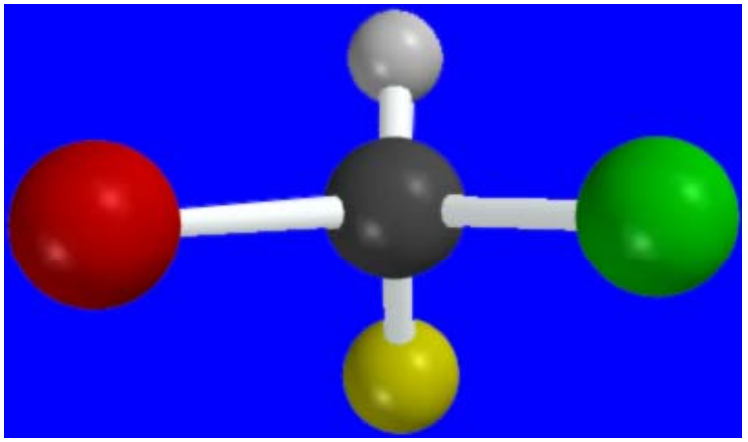


Another look



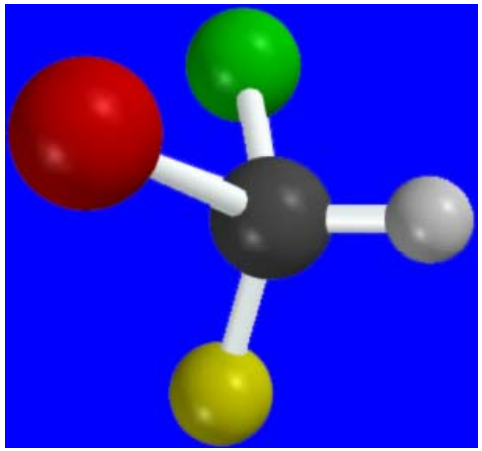




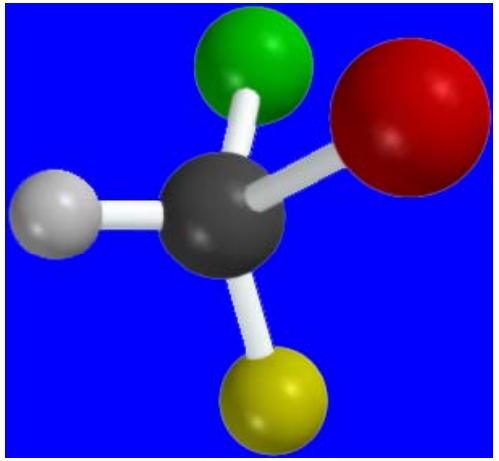


Enantiomers

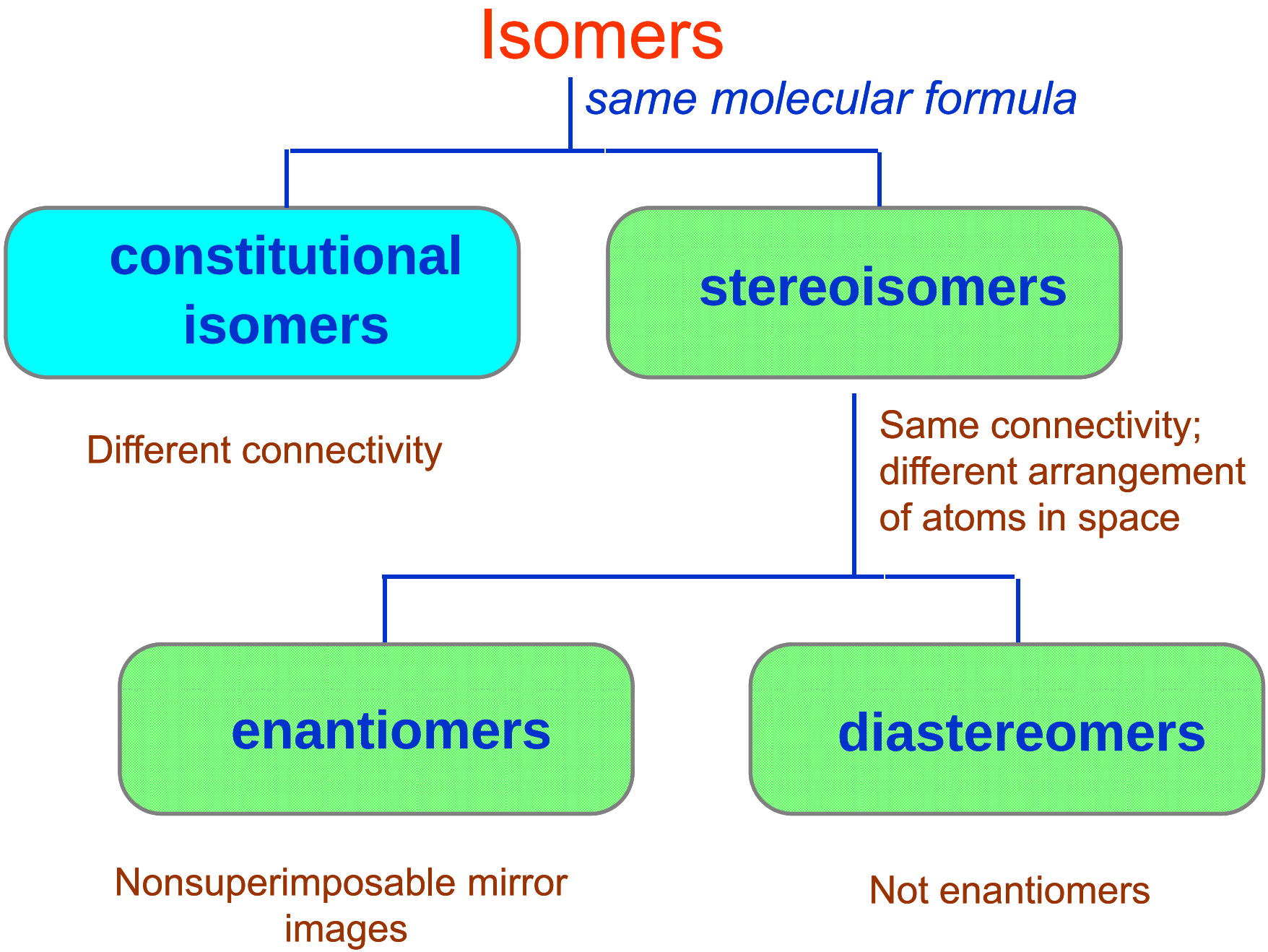
nonsuperimposable mirror images are called enantiomers

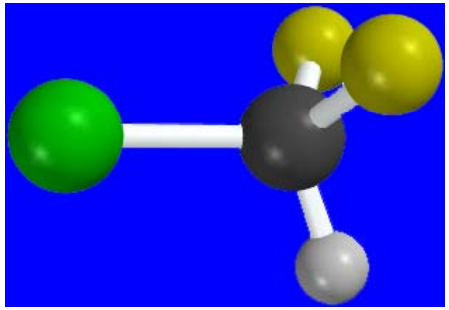


and

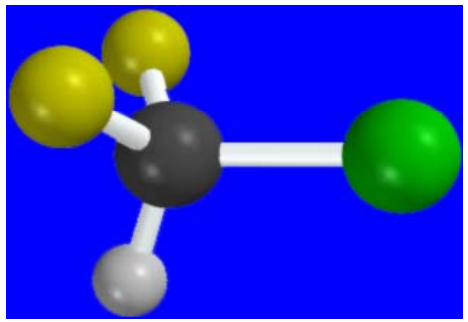


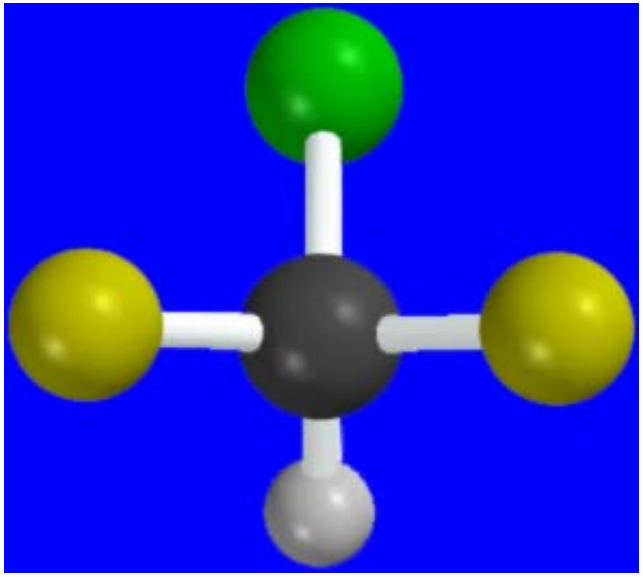
are enantiomers with respect to each other!

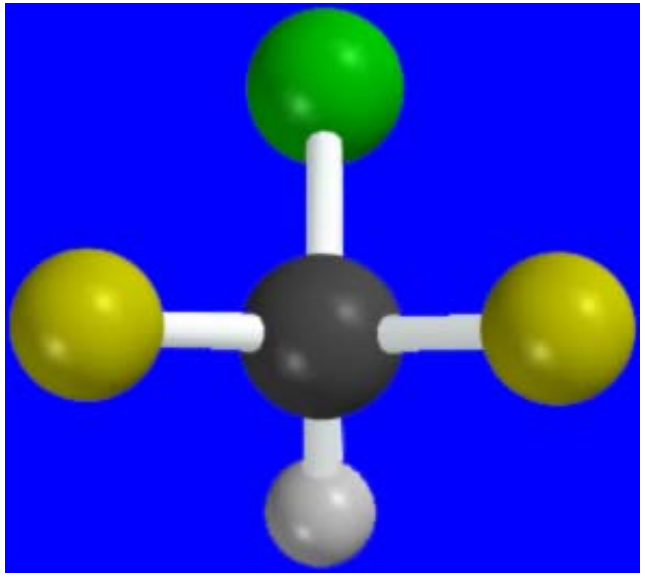

Isomers
same molecular formula
constitutional isomers
stereoisomers
Different connectivity
Same connectivity; different arrangement of atoms in space
enantiomers
diastereomers
Nonsuperimposable mirror images
Not enantiomers

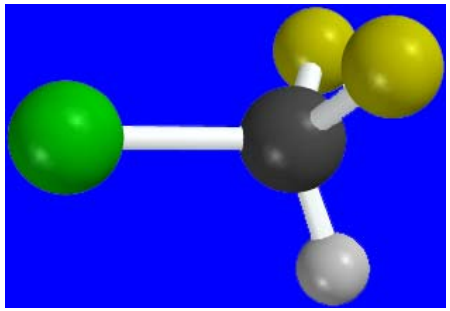


Chlorodifluoromethane is achiral

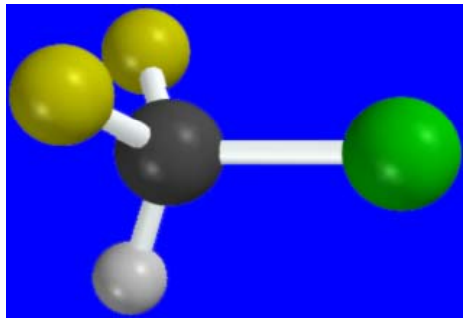


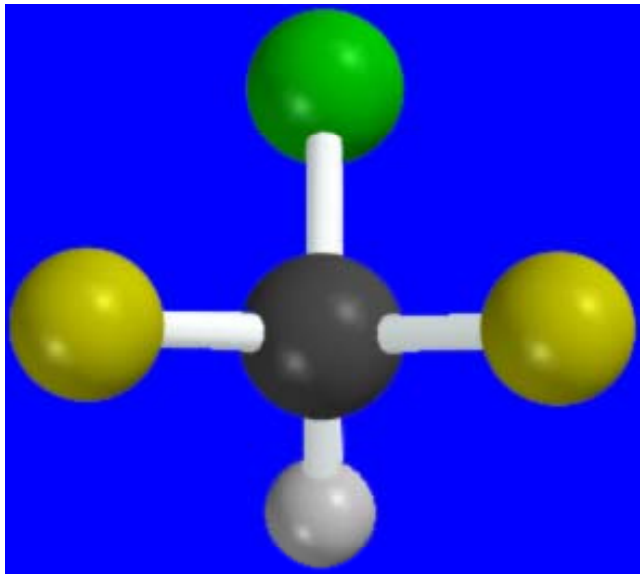






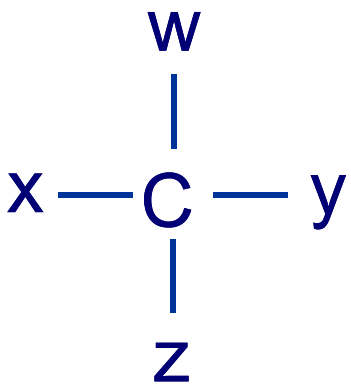
Chlorodifluoromethane is achiral





- The two structures are mirror images, but are not enantiomers, because they can be superimposed on each other.

7.2. The Chirality Center

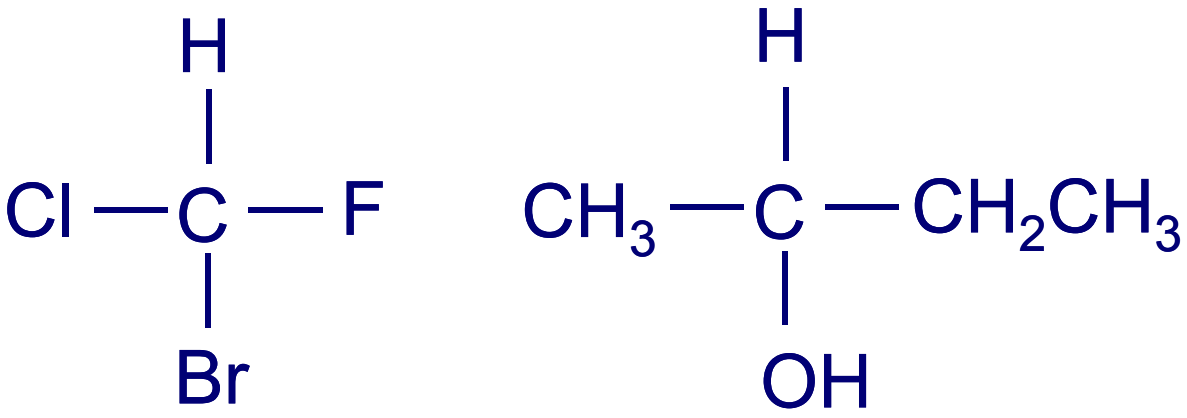


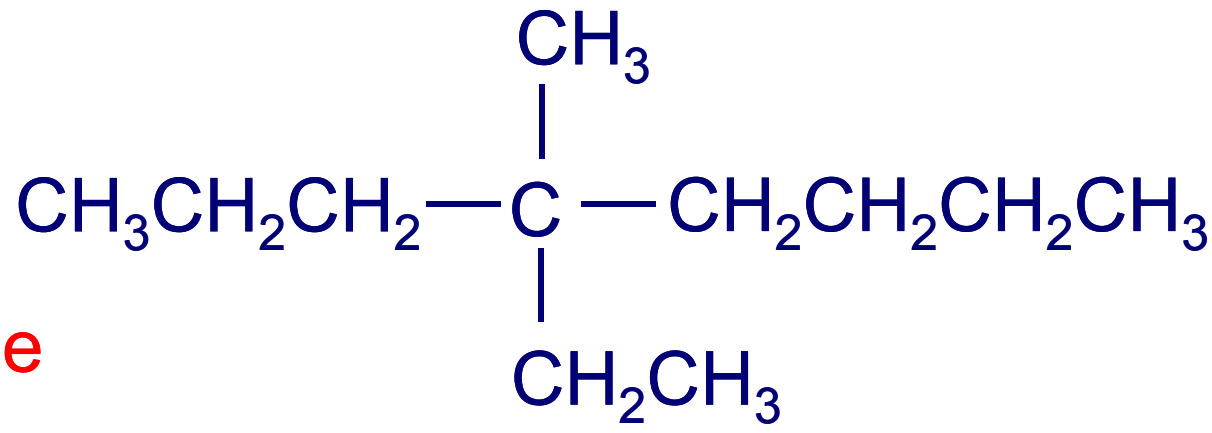
- A carbon atom with four different groups attached to it

- Also called:
  - Chiral center
  - Asymmetric center
  - Stereocenter
  - Stereogenic center

Chirality and Chirality Centers

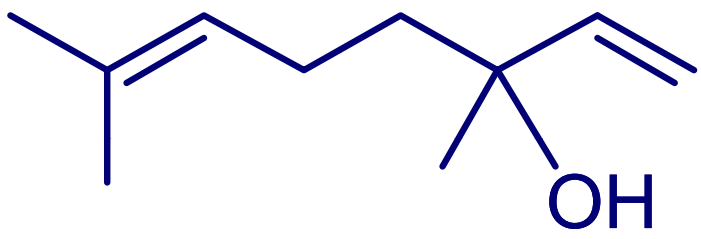
- A molecule with a single chirality center is *chiral*.
- Bromochlorofluoromethane & 2-butanol are examples.





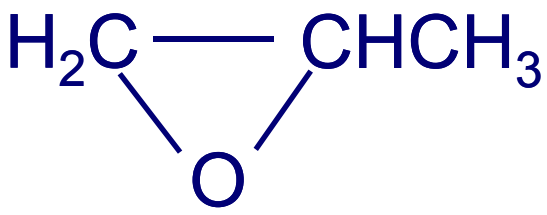
Chiral alkane

Examples of Molecules With 1 Chirality Center



Linalool, a naturally occurring chiral alcohol

Examples of Molecules With 1 Chirality Center



1,2-Epoxypropane: chirality center can be part of a *ring.*

Attached to the chirality center are:

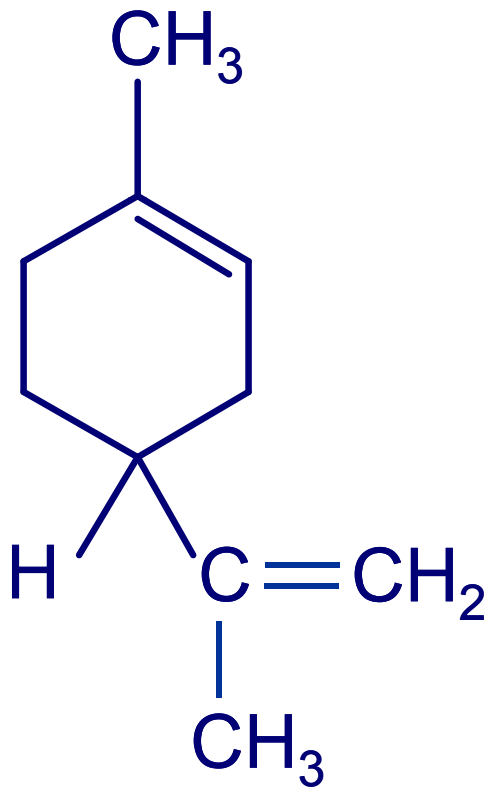
—H

—CH_3

—OCH_2

—CH_2O

Examples of Molecules With 1 Chirality Center



- Limonene: a chirality center can be part of a ring.

Attached to the chirality center are:

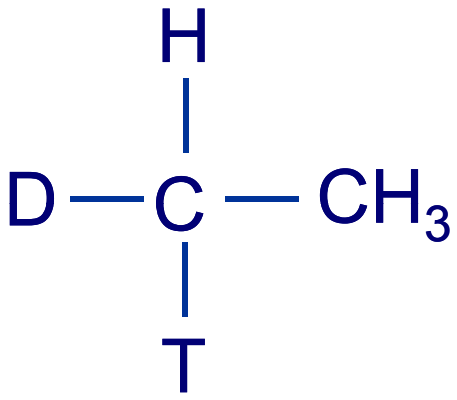
—H

—CH_2CH_2

—CH_2CH=

—C=

Examples of Molecules With 1 Chirality Center



D: Deuterium (^2H)

T: Tritium (^3H)

Chiral as a result of isotopic substitution.

7.3. Symmetry in Achiral Structures

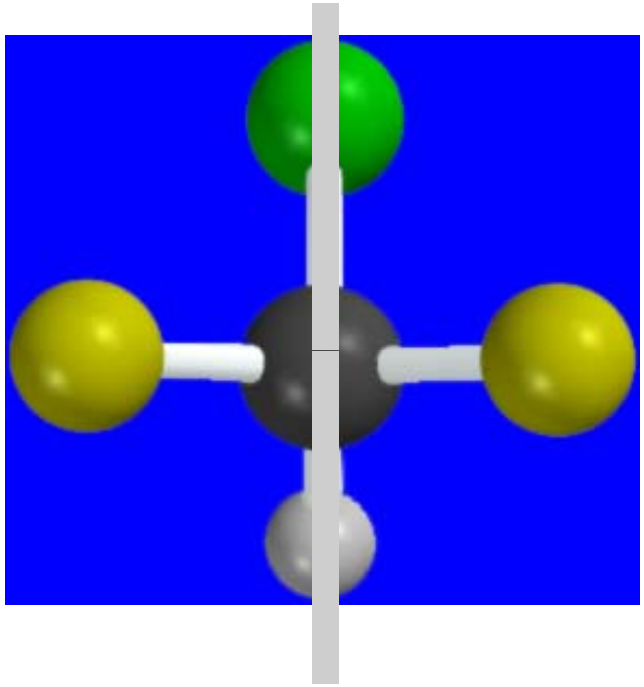
A molecule with a single chirality center must be chiral.

But, a molecule with two or more chirality centers may be chiral or it may not (Sections 7.11-7.13).

Symmetry tests for achiral structures

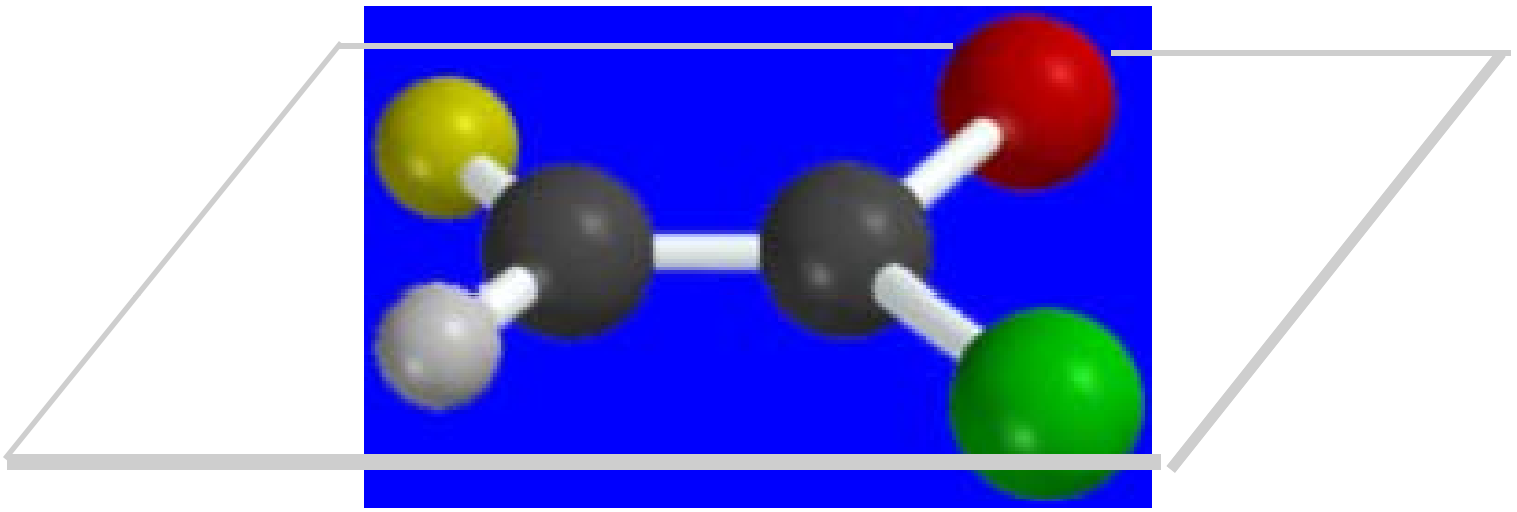
Any molecule with a plane of symmetry or a center of symmetry must be *achiral*.

Plane of Symmetry



A plane of symmetry bisects a molecule into two mirror image halves. Chlorodifluoromethane has a plane of symmetry.

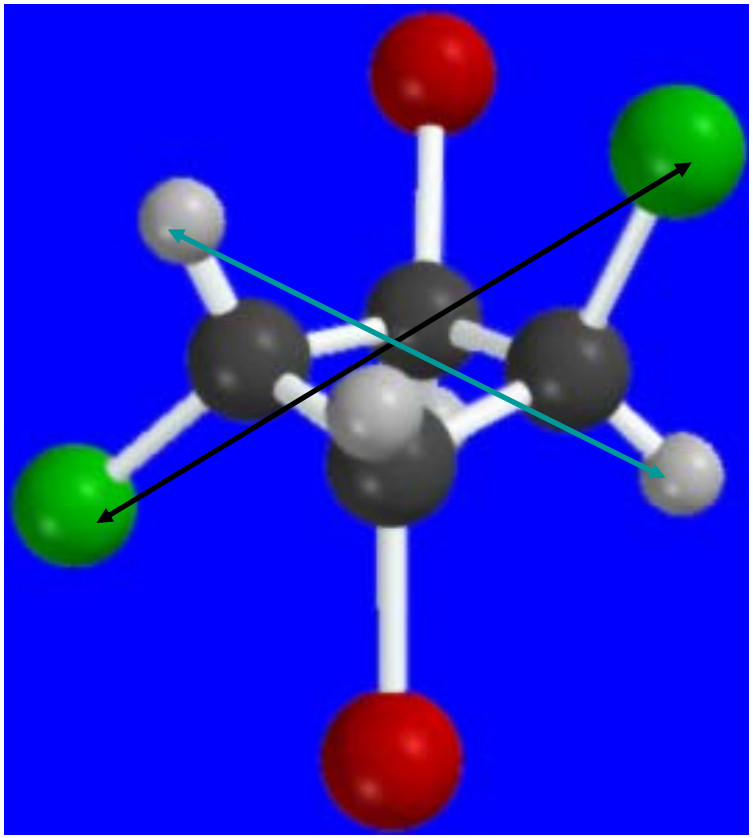
Plane of Symmetry



A plane of symmetry bisects a molecule into two mirror image halves.

1-Bromo-1-chloro-2-fluoroethene has a plane of symmetry.

Center of Symmetry



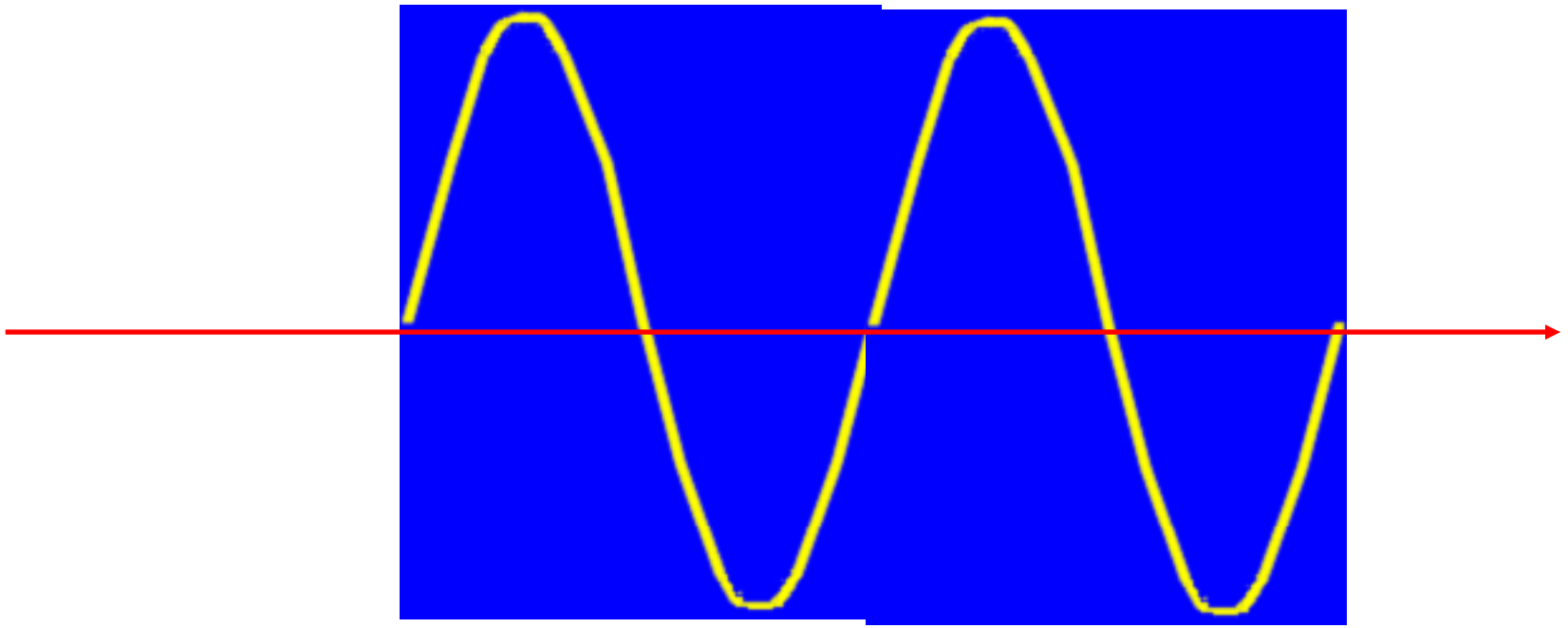
- A point in the center of the molecule is a center of symmetry if a line drawn from it to any element, when extended an equal distance in the opposite direction, encounters an identical element.

7.4. Properties of Chiral Molecules: Optical Activity

- A substance is optically active if it rotates the plane of polarized light.

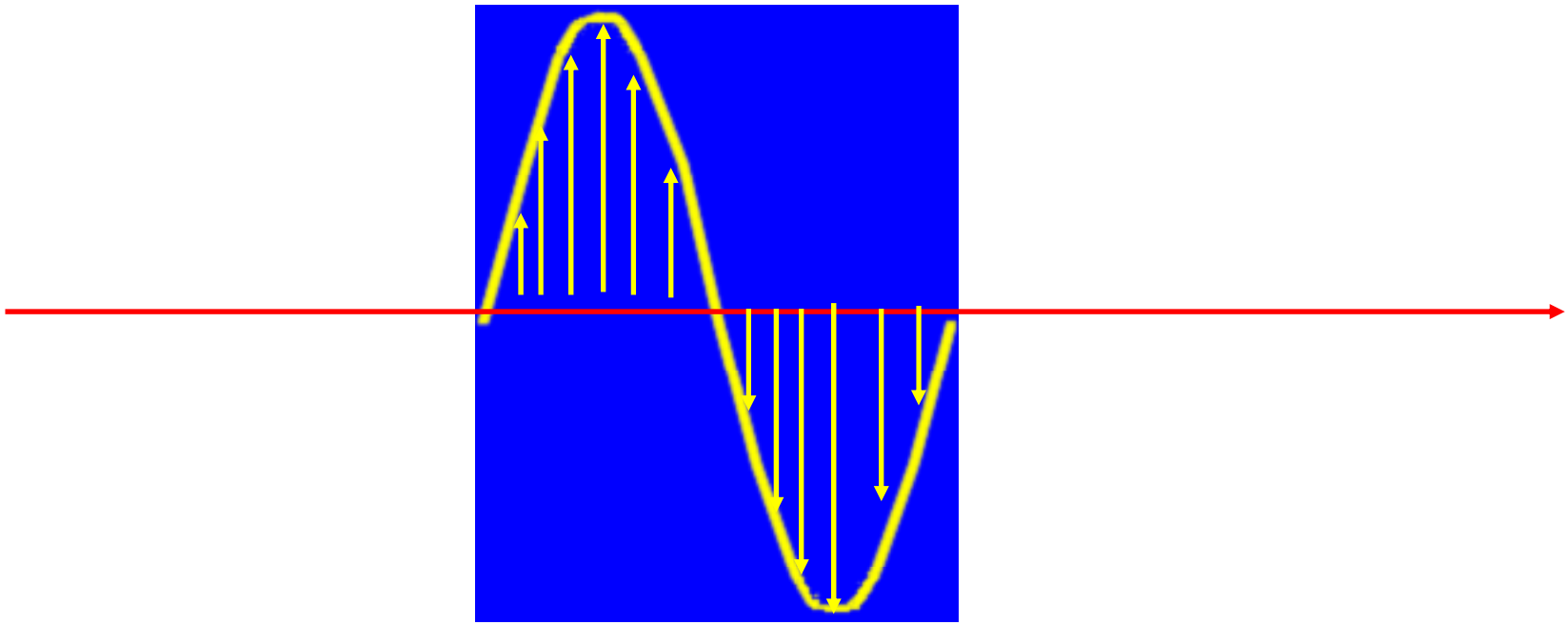
- In order for a substance to exhibit optical activity, it must be *chiral* and one enantiomer must be present in excess of the other.

Light



- Has wave properties.
- Periodic increase and decrease in amplitude of wave.

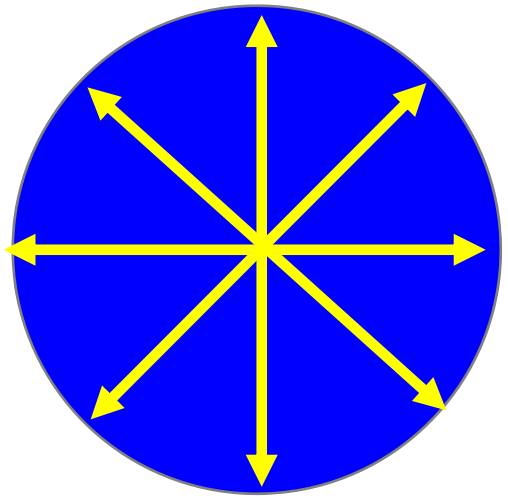
Light



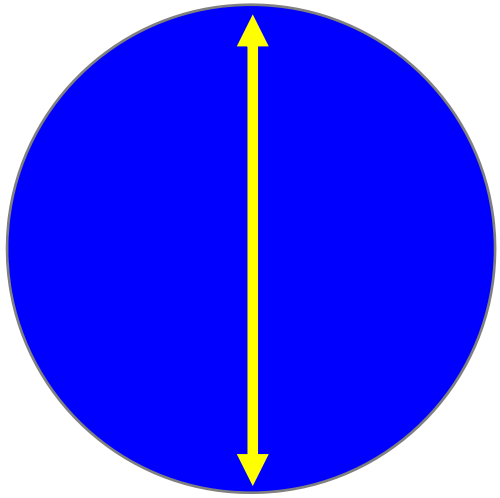
- Optical activity is usually measured using light having a wavelength of 589 nm.
- This is the wavelength of the yellow light from a sodium lamp and is called the D line of sodium.

Polarized light

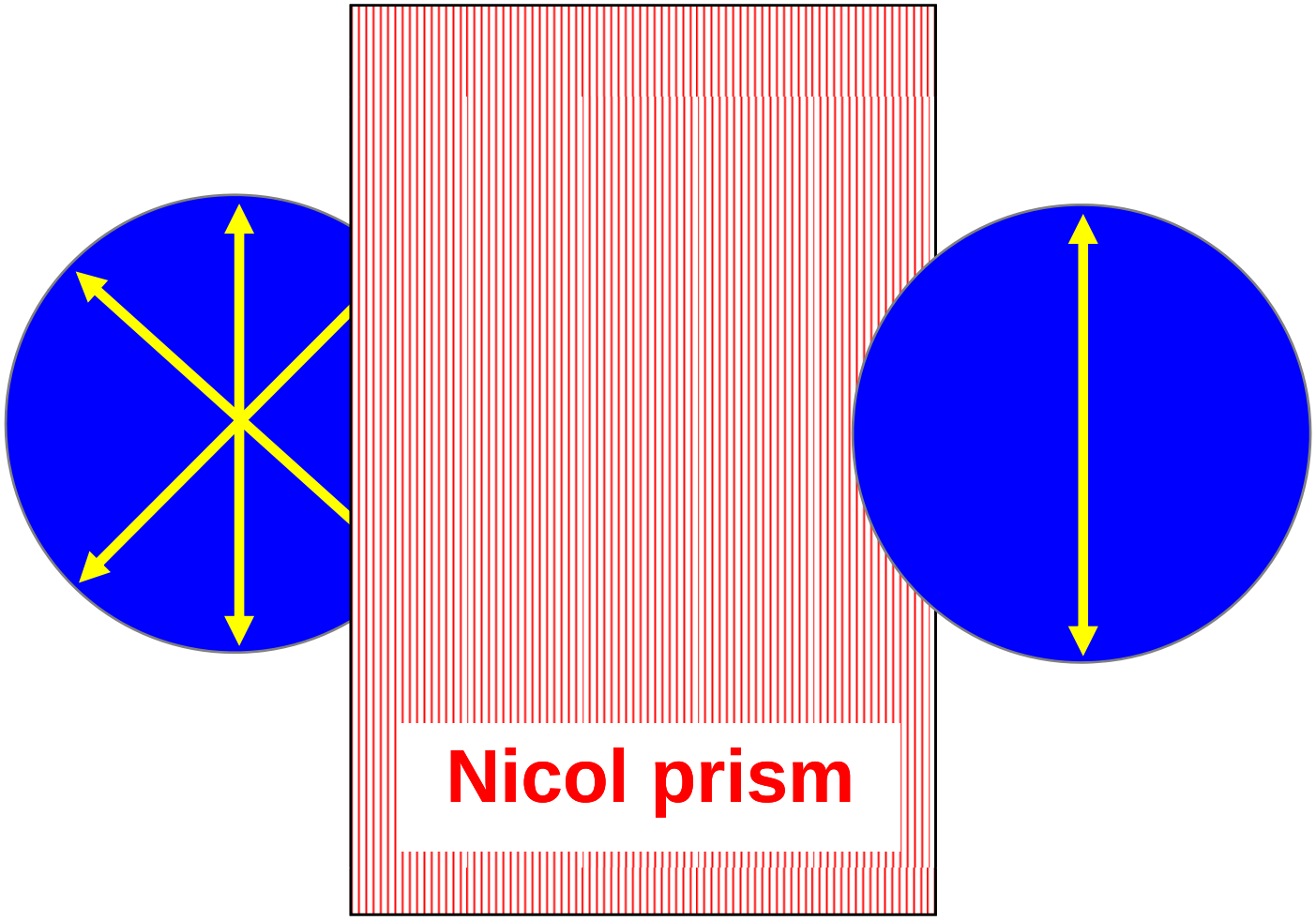
- Ordinary (nonpolarized) light consists of many beams vibrating in different planes.



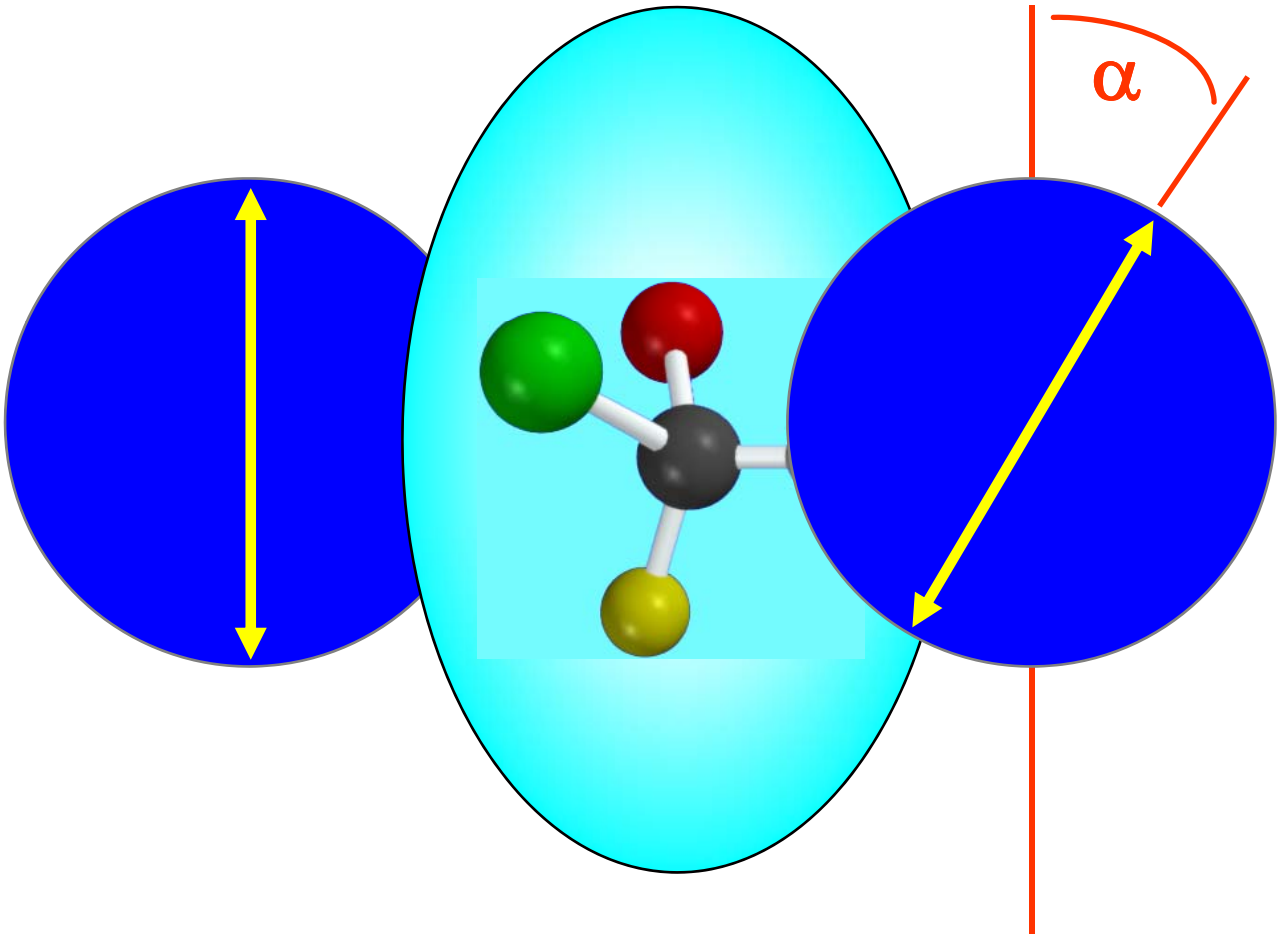
- Plane-polarized light consists of only those beams that vibrate in the same plane.



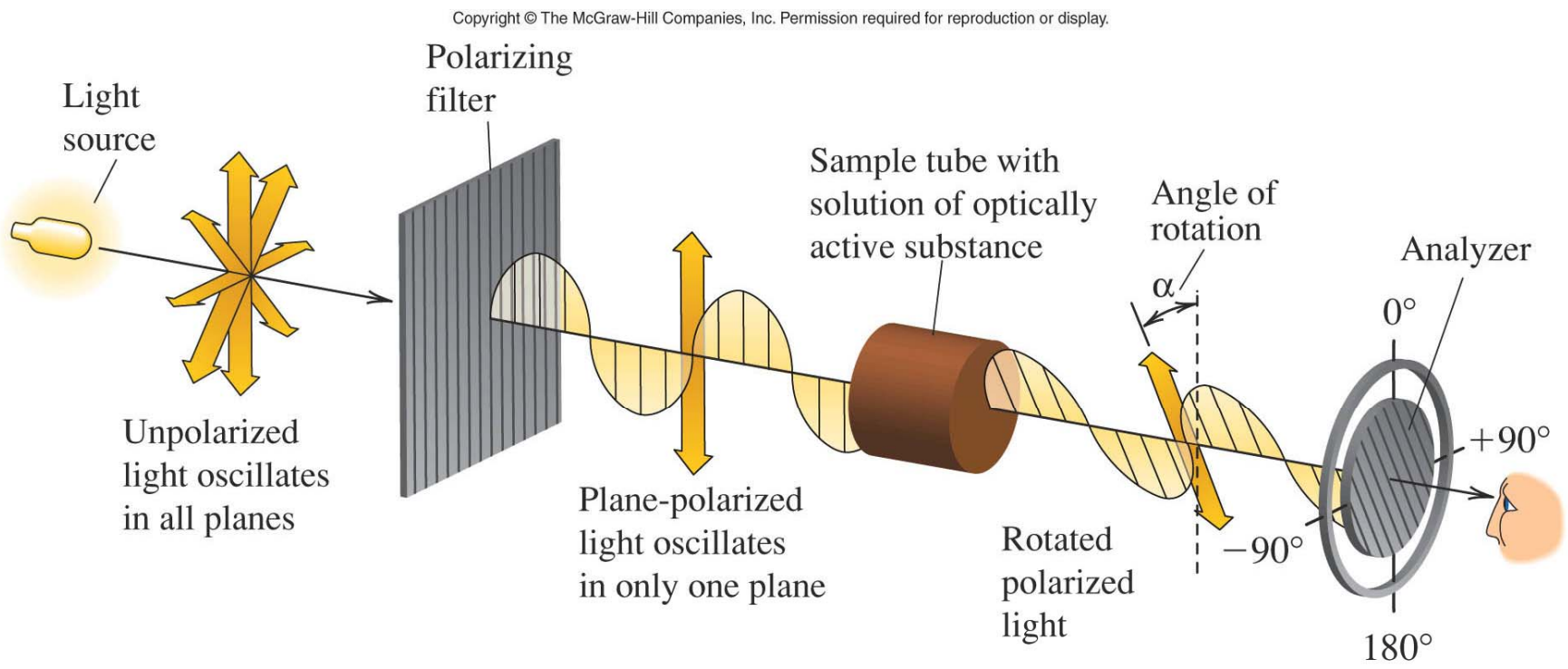
Polarization of Light



Rotation of Plane-Polarized Light



Polarimeter



Specific Rotation [α]

- Observed rotation (α) depends on the number of molecules encountered and is proportional to:

Path length (*l*), and concentration (*c*)

Therefore, define specific rotation [α] as:

$$[\alpha] = \frac{100\ \alpha}{cl}$$

concentration = g/100 mL

length in decimeters

Racemic Mixture

- A mixture containing equal quantities of enantiomers is called a *racemic mixture.*

- A racemic mixture is *optically inactive* ($\alpha = 0$).

- A sample that is optically inactive can be either achiral substance or a racemic mixture.

Optical Purity

- An optically pure substance consists exclusively of a single enantiomer.

Enantiomeric excess =

% one enantiomer – % other enantiomer

% Optical purity = enantiomeric excess

7.5. Absolute and Relative Configuration

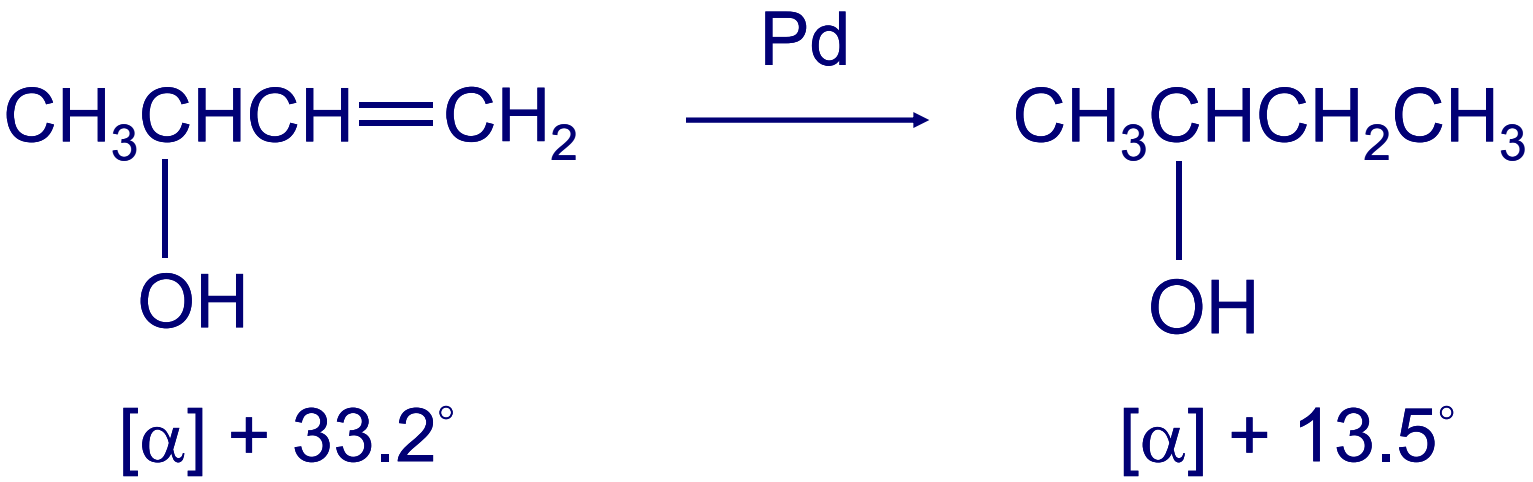
- *Relative configuration* compares the arrangement of atoms in space of one compound with those of another.

until the 1950s, all configurations were relative.

- *Absolute configuration* is the precise arrangement of atoms in space.

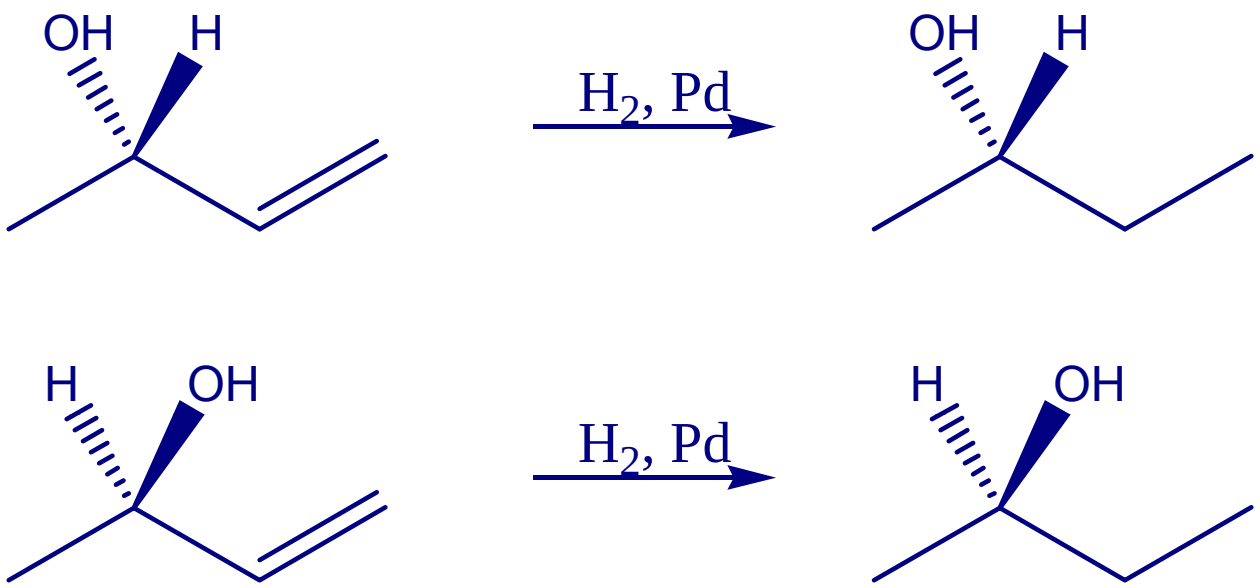
We can now determine the absolute configuration of almost any compound!

Relative configuration



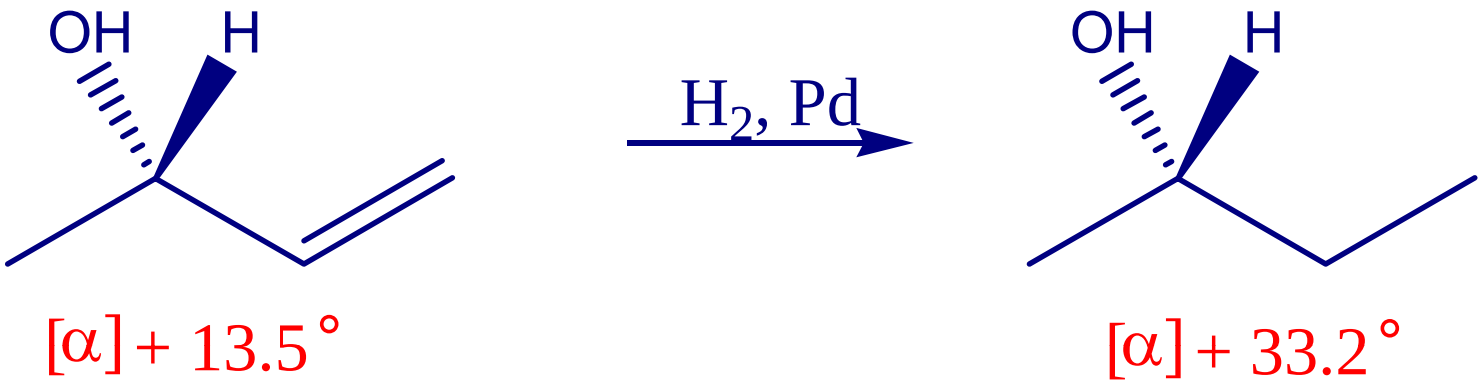
- No bonds are made or broken at the chirality center in this experiment. Therefore, when (+)-3-buten-2-ol and (+)-2-butanol have the same sign of rotation, the arrangement of atoms in space is analogous. The two have the same relative configuration.

Two possibilities

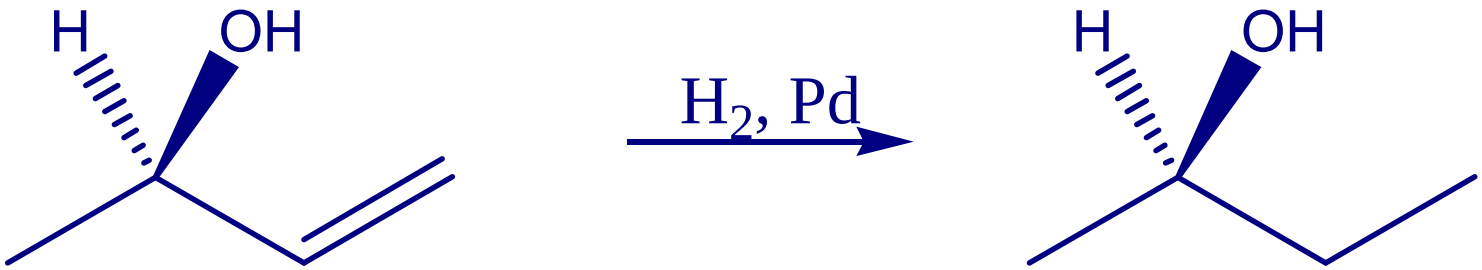


- But in the absence of additional information, we can't tell which structure corresponds to (+)-3-buten-2-ol, and which one to (–)-3-buten-2-ol.
- Nor can we tell which structure corresponds to (+)-2-butanol, and which one to (–)-2-butanol.

Absolute configurations

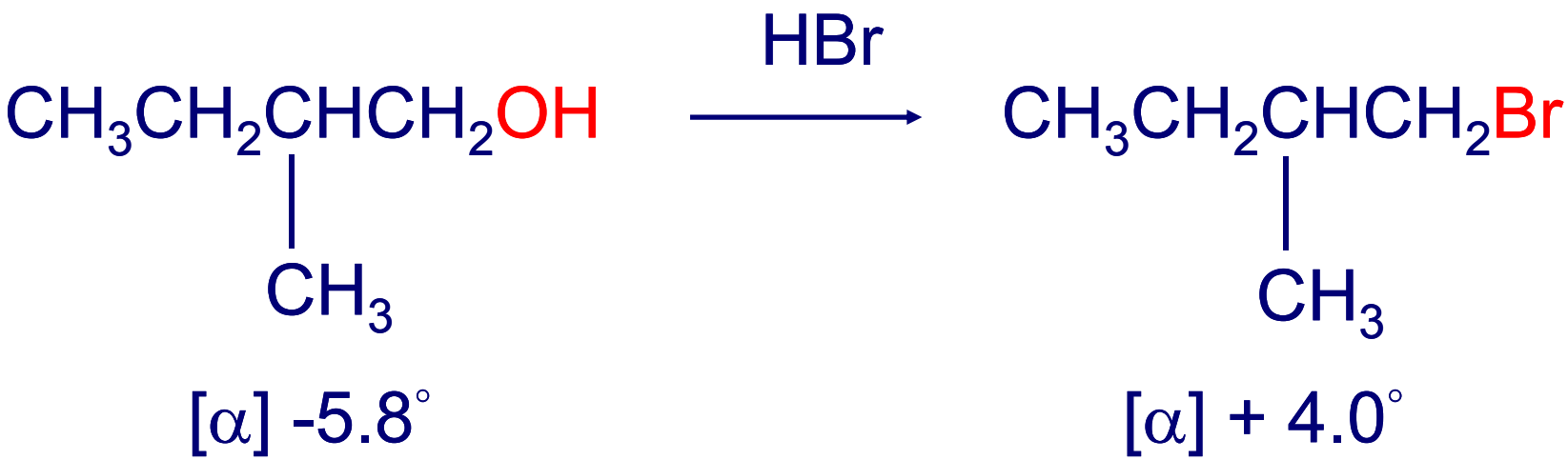


$[\alpha] + 13.5^\circ$ $[\alpha] + 33.2^\circ$



$[\alpha] - 13.5^\circ$ $[\alpha] - 33.2^\circ$

Relative configuration



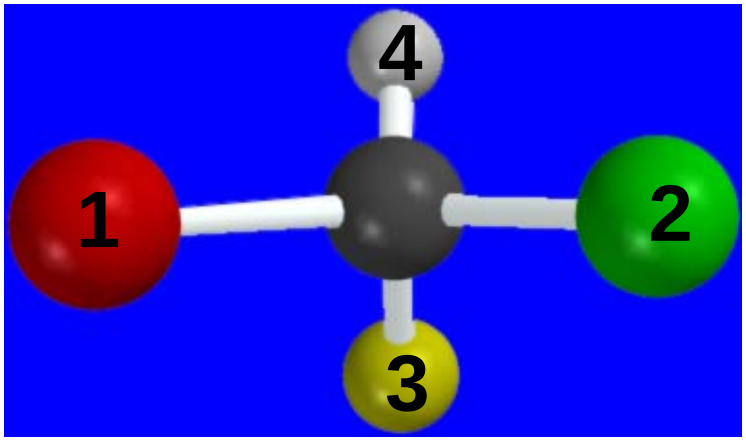
➢ Not all compounds that have the same relative configuration have the same sign of rotation. No bonds are made or broken at the chirality center in the reaction shown, so the relative positions of the atoms are the same. Yet the sign of rotation changes.

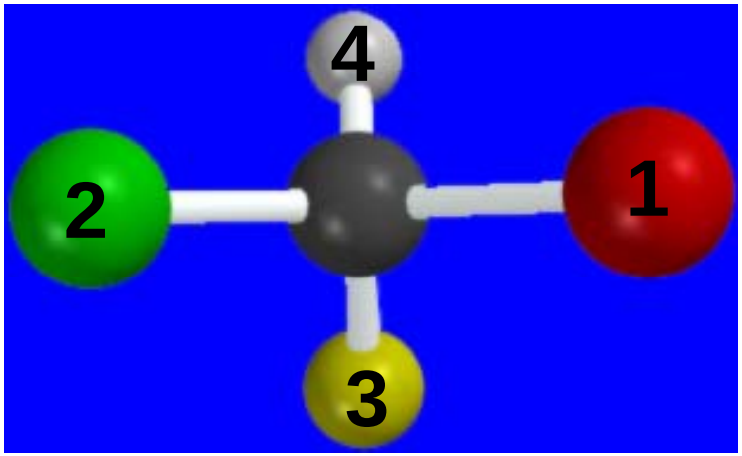
7.6. The Cahn Ingold Prelog *R-S* Notational System

The Cahn-Ingold-Prelog (CIP) Rules

1. Rank the substituents at the chirality center.
2. Orient the molecule so that lowest-ranked substituent points away from you.
3. If the order of decreasing precedence traces a clockwise path, the absolute configuration is *R*. If the path is counterclockwise, the configuration is *S*.

Example

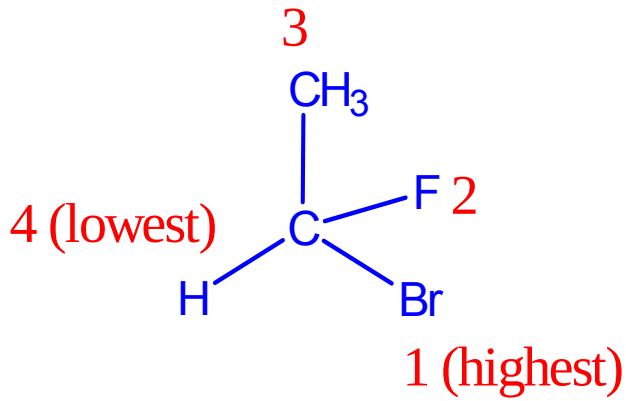




Order of decreasing rank:
1 > 2 > 3 > 4

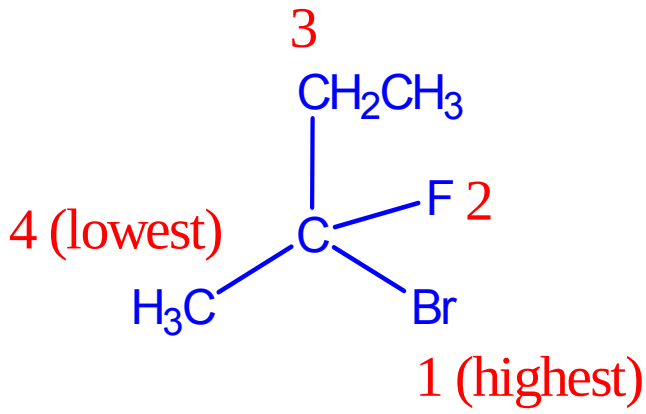
CIP Rules

(1) Higher atomic number outranks lower atomic number



(2) When two atoms are identical, compare the atoms attached to them on the basis of their atomic numbers. Precedence is established at the first point of difference.

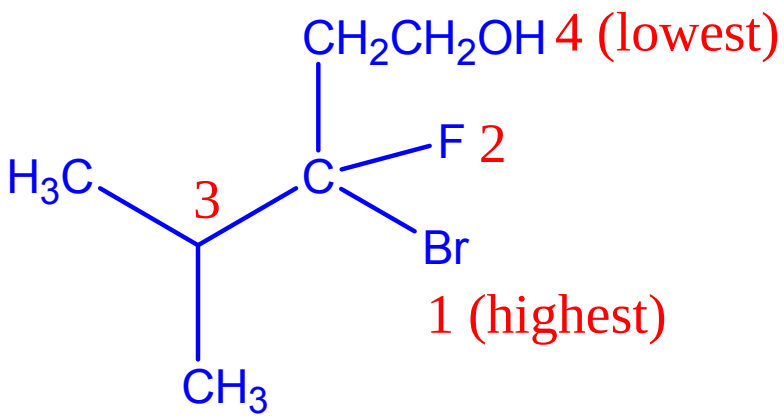
—CH_2CH_3 outranks —CH_3



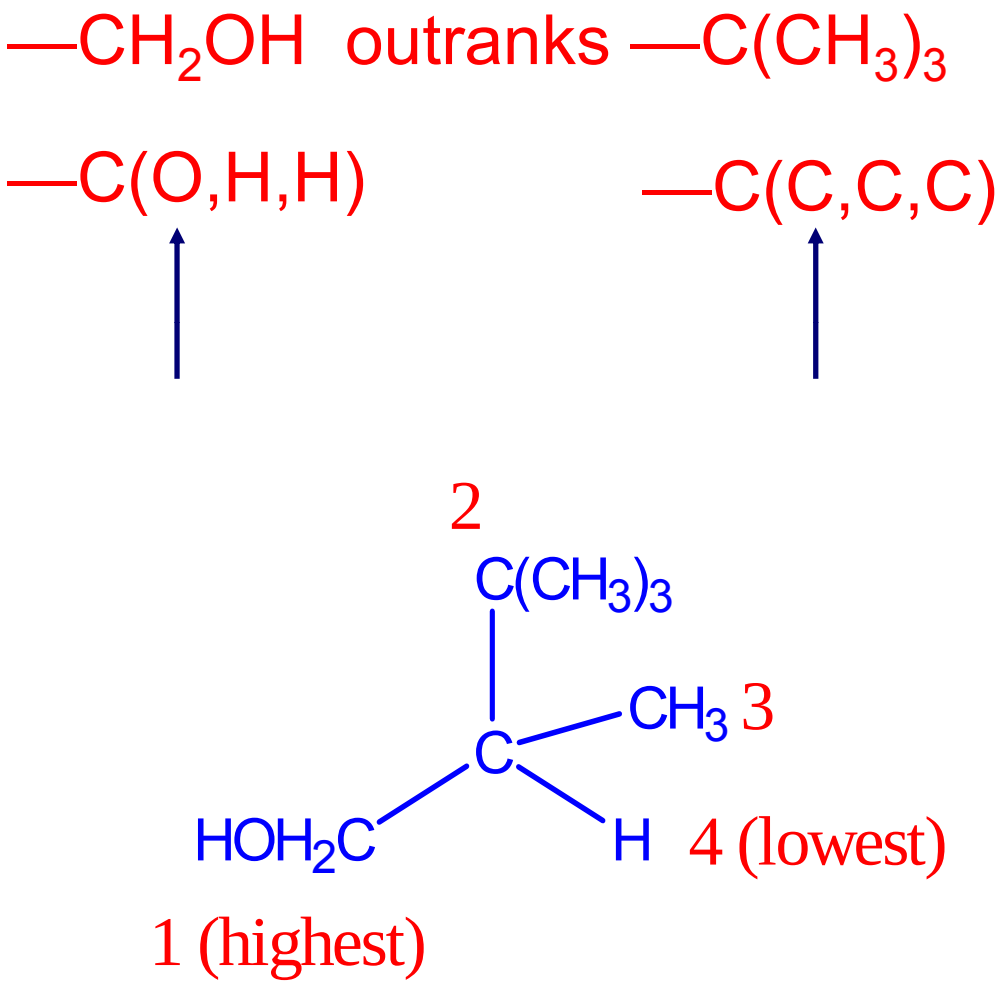
(3) Work outward from the point of attachment, comparing all the atoms attached to a particular atom before proceeding further along the chain.

—$CH(CH_3)_2$ outranks —CH_2CH_2OH

—C(C,C,H) —C(C,H,H)



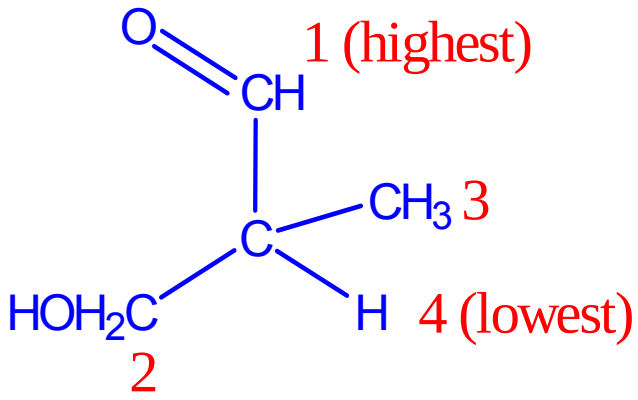
(4) Evaluate substituents one by one. Don't add atomic numbers within groups.



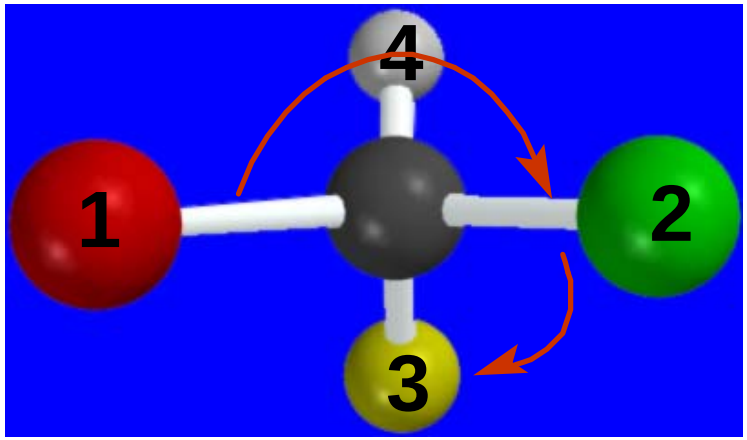
(5) An atom that is multiply bonded to another atom is considered to be replicated as a substituent on that atom.

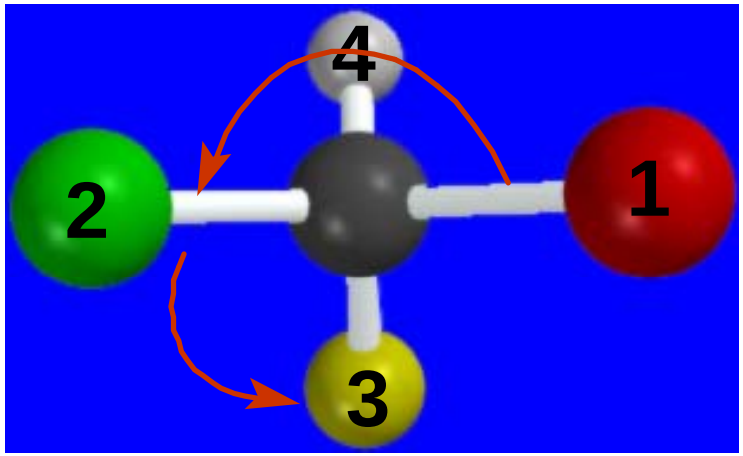
—CH=O outranks —CH_2OH

—C(O,O,H) —C(O,H,H)



Example





Order of decreasing rank:

$1 \rightarrow 2 \rightarrow 3$

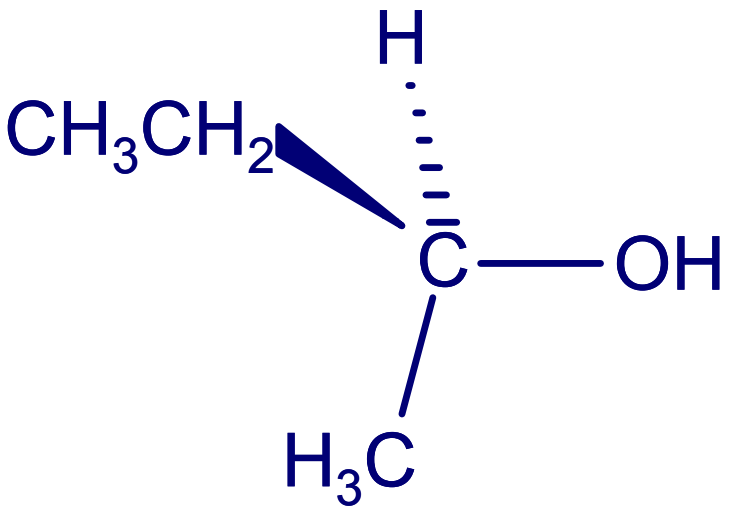
clockwise

R

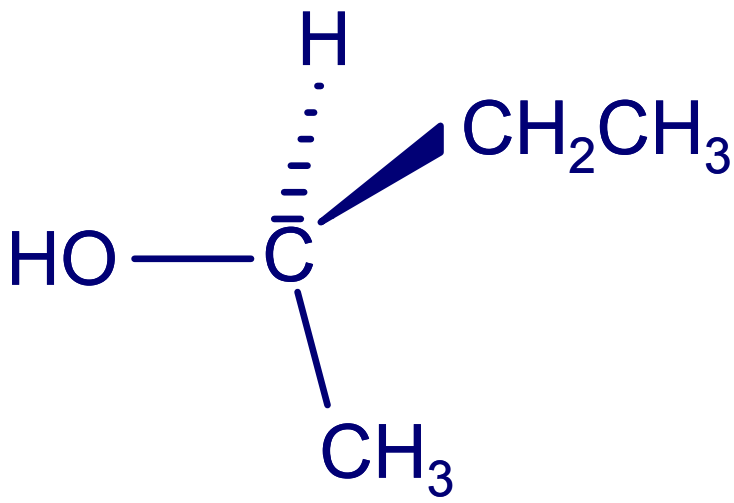
counterclockwise

S

Enantiomers of 2-butanol



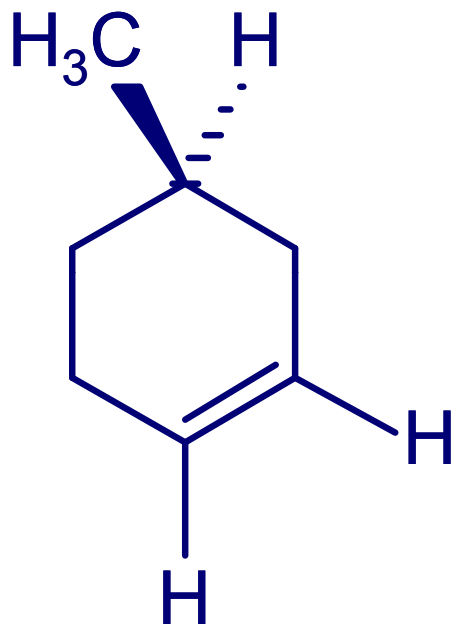
(*S*)-2-Butanol



(*R*)-2-Butanol

Very important! Two different compounds with the same sign of rotation need not have the same configuration.

Chirality center in a ring



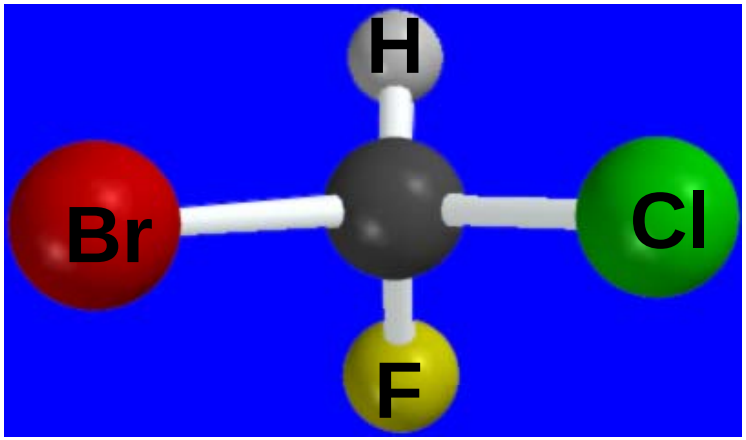
R

—$CH_2C{=}C$ > —CH_2CH_2 > —CH_3 > —H

7.7. Fischer Projections

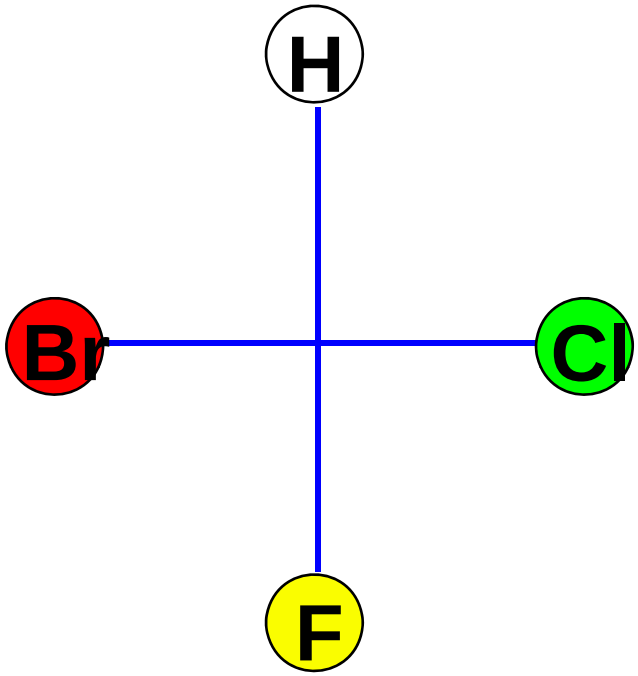
➢ Purpose of Fischer projections is to show configuration at chirality center without necessity of drawing wedges and dashes or using models.

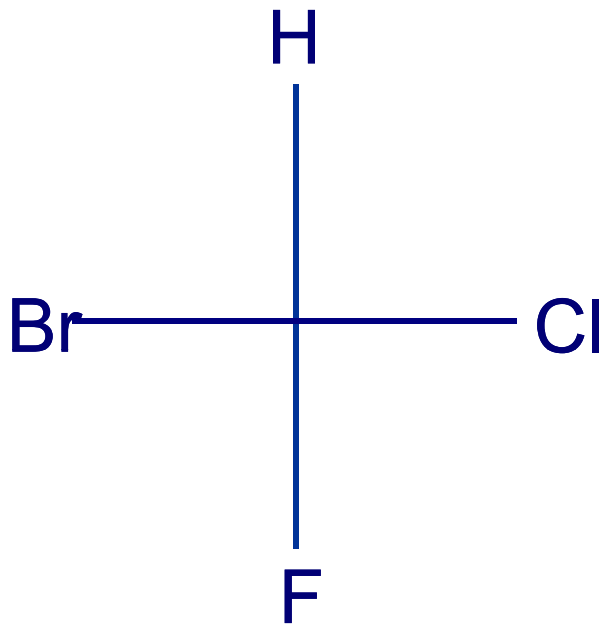
Rules for Fischer projections



➢ Arrange the molecule so that horizontal bonds at chirality center point toward you and vertical bonds point away from you.

Rules for Fischer Projections





- Projection of molecule on page is a cross. When represented this way it is understood that horizontal bonds project outward, vertical bonds are back.

7.8. Properties of Enantiomers

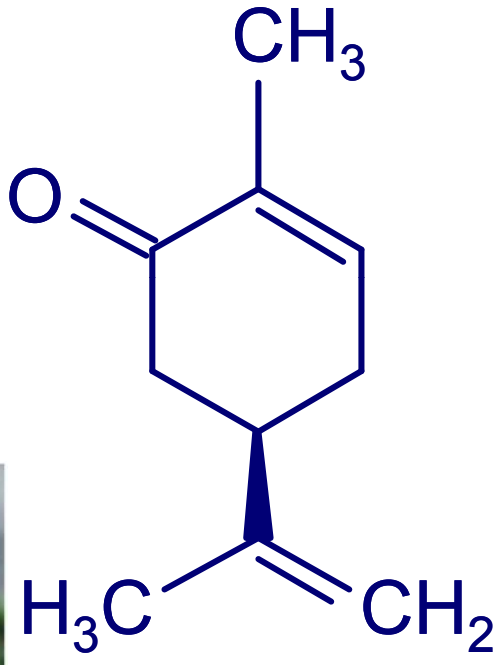
- Same:

  Melting point, boiling point, density, etc.

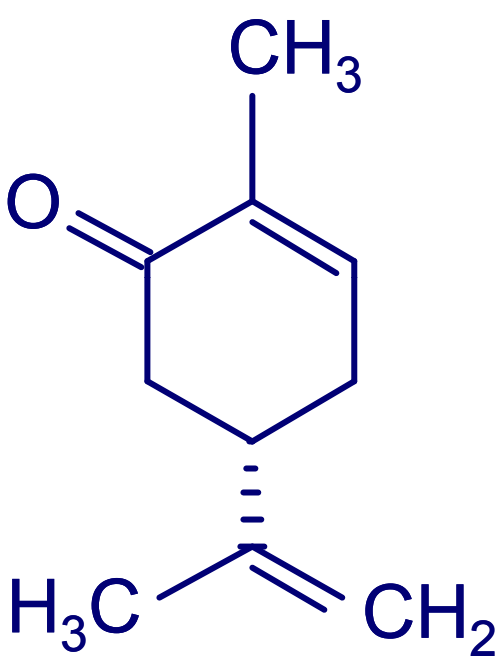
- Different:

  Properties that depend on shape of molecule (biological-physiological properties) can be different.

Odor



(–)-Carvone
spearmint oil

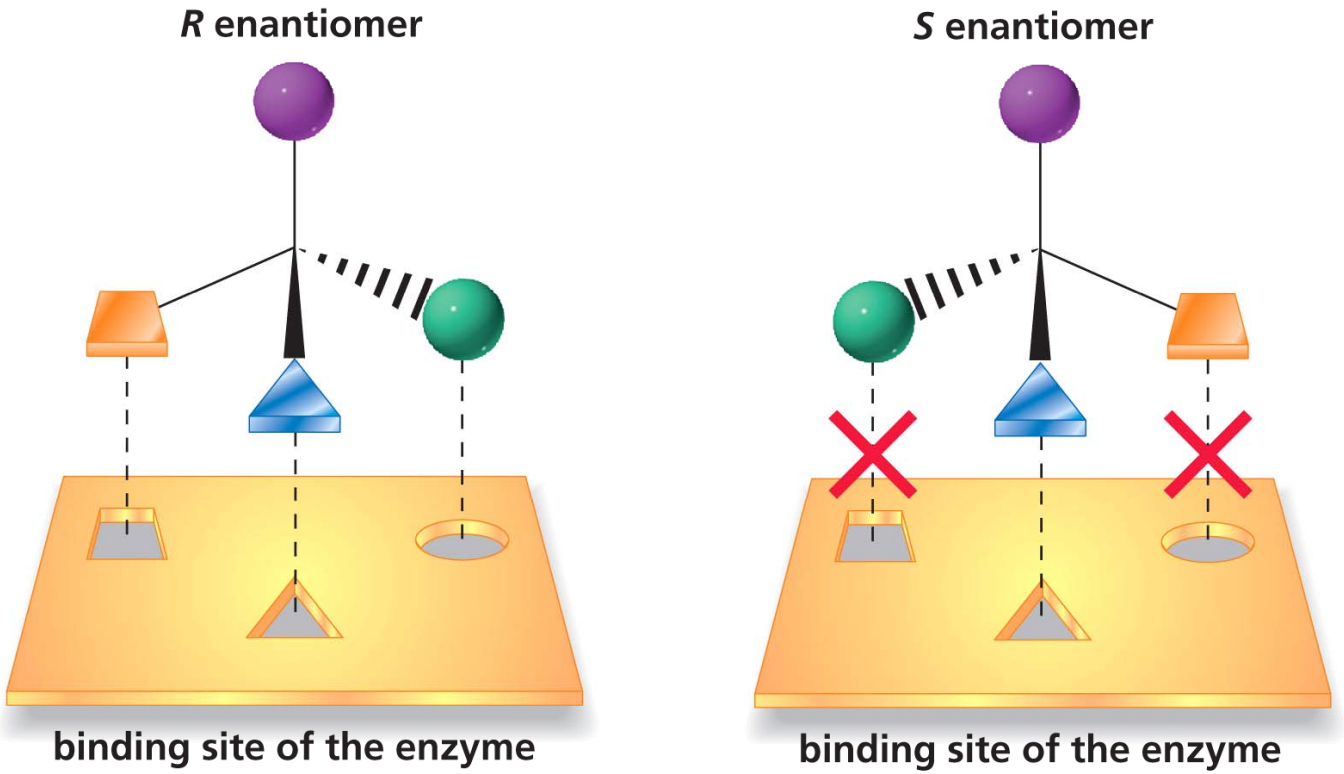


(+)-Carvone
caraway seed oil

Spearmint leaves

Caraway seeds

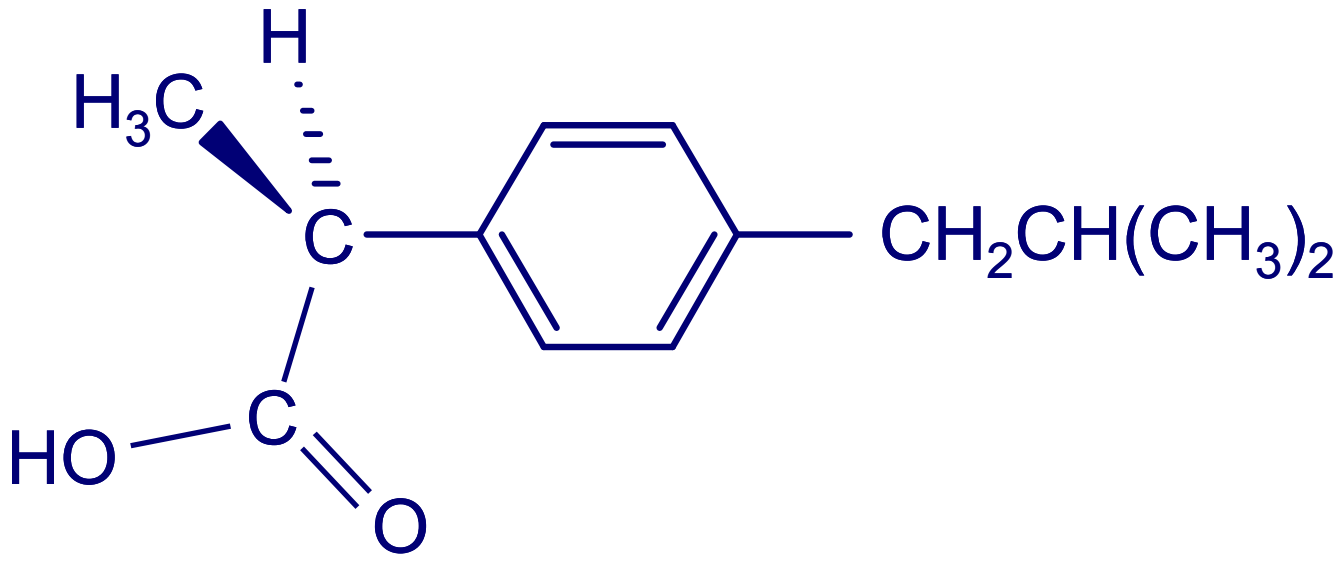
Chiral Receptor



Chiral receptor sites: chiral recognition

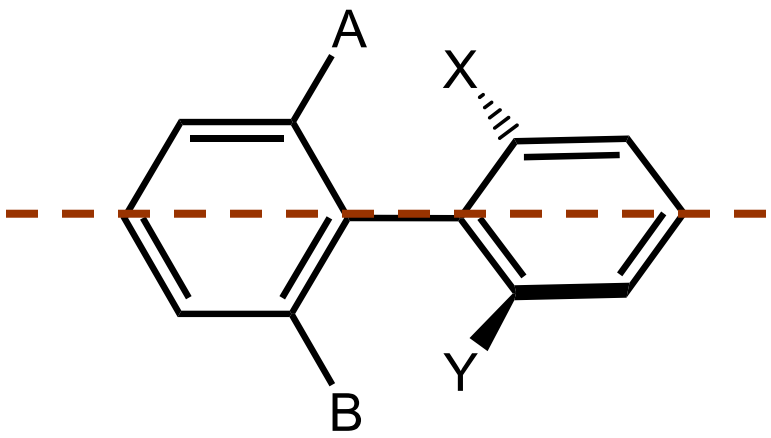
Chiral Drugs

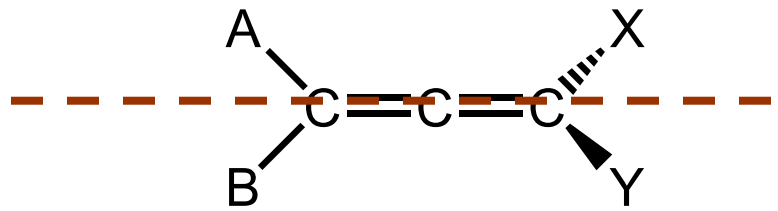
➢ *Ibuprofen* is chiral, but normally sold as racemic mixture. The *S* enantiomer is the one responsible for its analgesic and antiinflammatory properties.



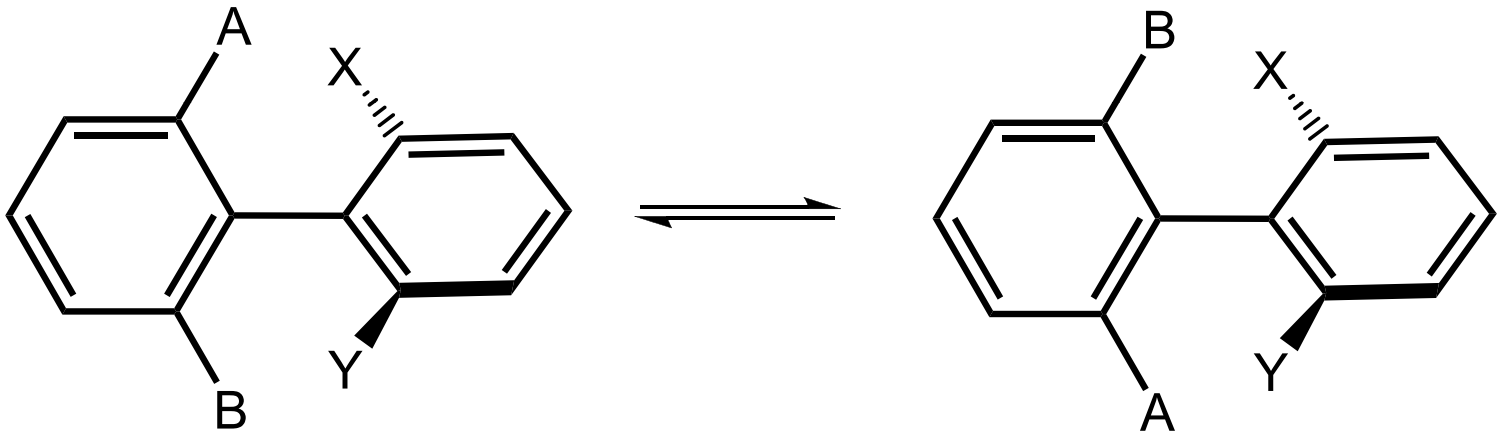
7.9.The Chirality Axis

- A diverse group of molecules are chiral but do not contain a chirality center.
- Some of these contain a **chirality axis**-an axis about which groups are arranged so that the spatial arrangement is not superimposable on its mirror image.
- Examples include substituted biphenyls and allenes:



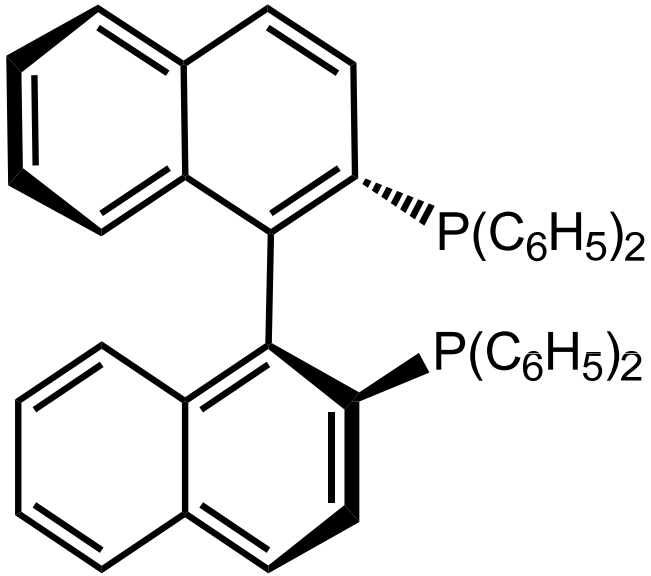


- In the appropriately substituted biphenyls, rotation around the bond joining the rings is slowed and the enantiomers can be isolated:



- Conformational isomers that are stable, isolable compounds are called atropisomers.

- Substituted 1,1'-binaphthyl derivatives exhibit atropisomerism due to hindered rotation about the single bond that connects the two naphthalene rings.
- An example is (S)-(-)-BINAP shown below and discussed further in Chapter 14.



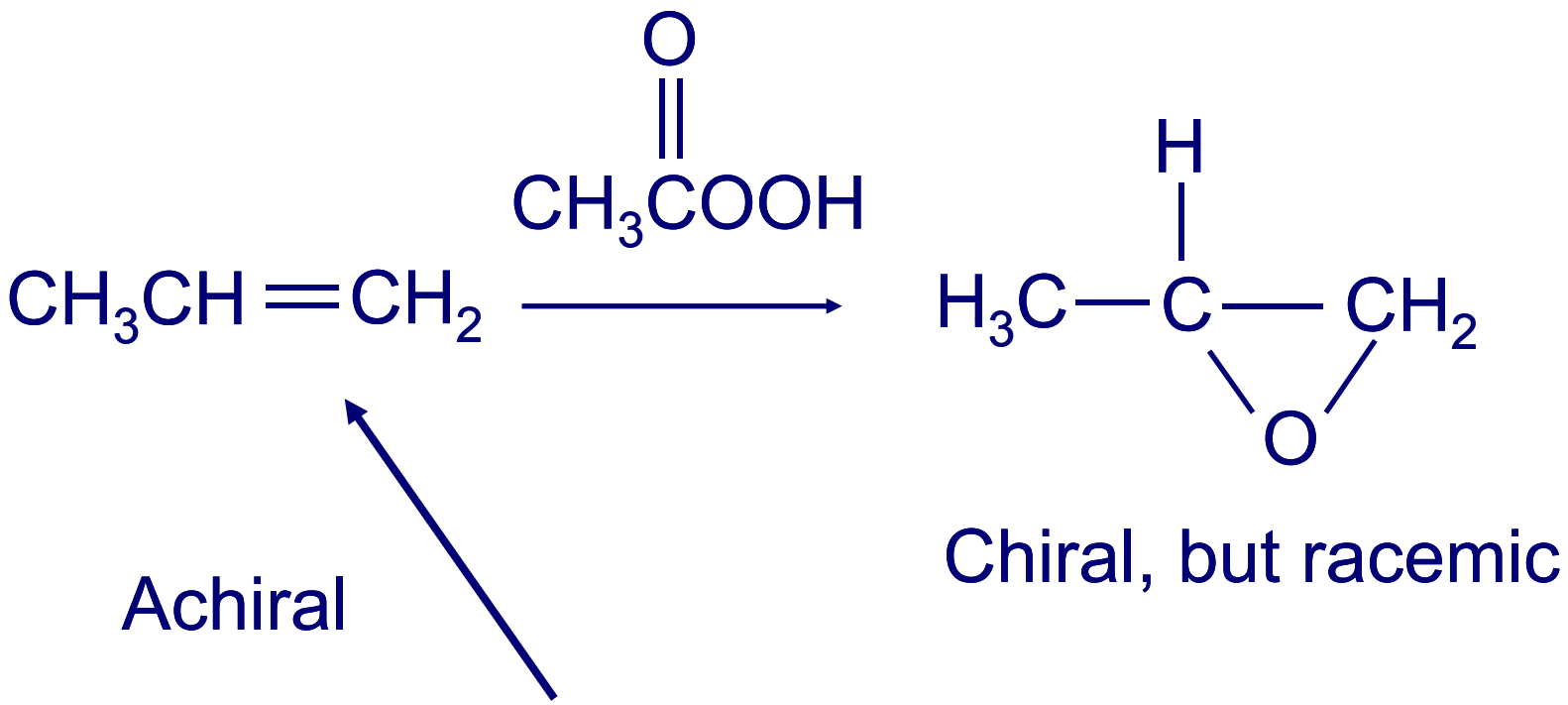
BINAP is an abbreviation for 2,2'-bis(diphenylphosphino)-1,1'-binapthyl

7.10. Reactions That Create a Chirality Center

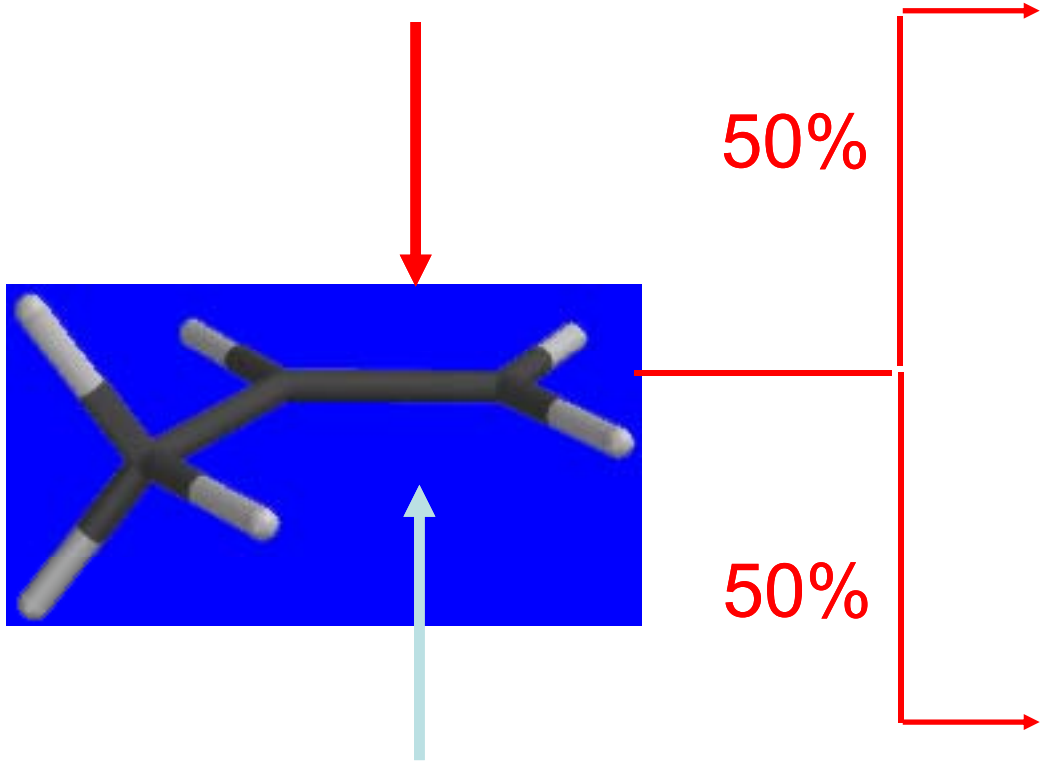
- It is important to recognize, however, that if all of the components of the starting state (reactants, catalysts, solvents, etc.) are achiral, any chiral product will be formed as a racemic mixture.

- This generalization can be more simply stated as "Optically inactive starting materials can't give optically active products" (Remember: In order for a substance to be optically active, it must be chiral and one enantiomer must be present in greater amounts than the other.)

Example

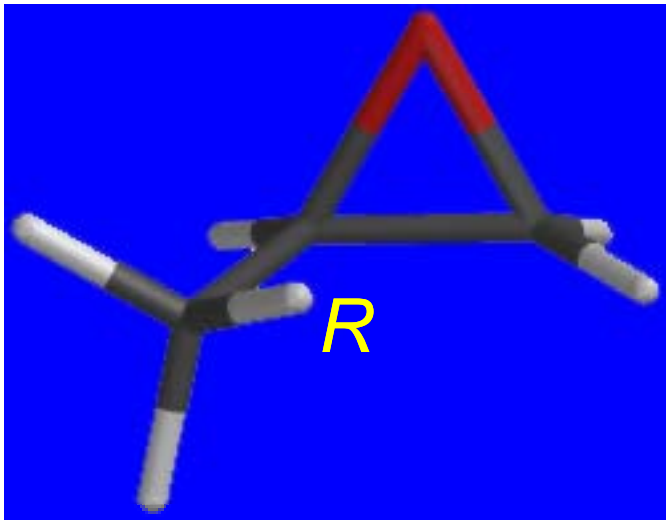

O
CH3COOH
CH3CH=CH2
H
H3C—C—CH2
O
Achiral
Chiral, but racemic
Prochiral structural unit

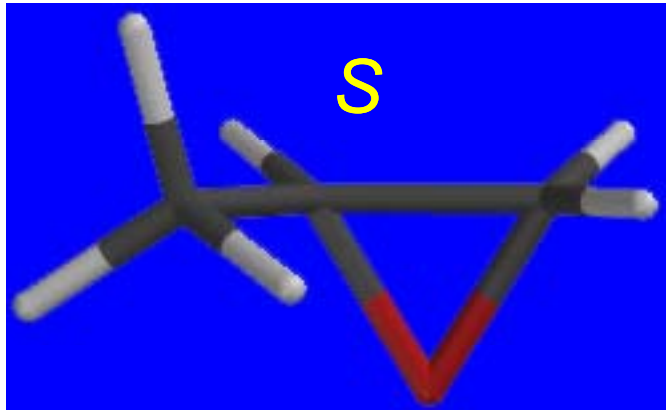
Epoxidation from this direction gives *R* epoxide



50%

50%

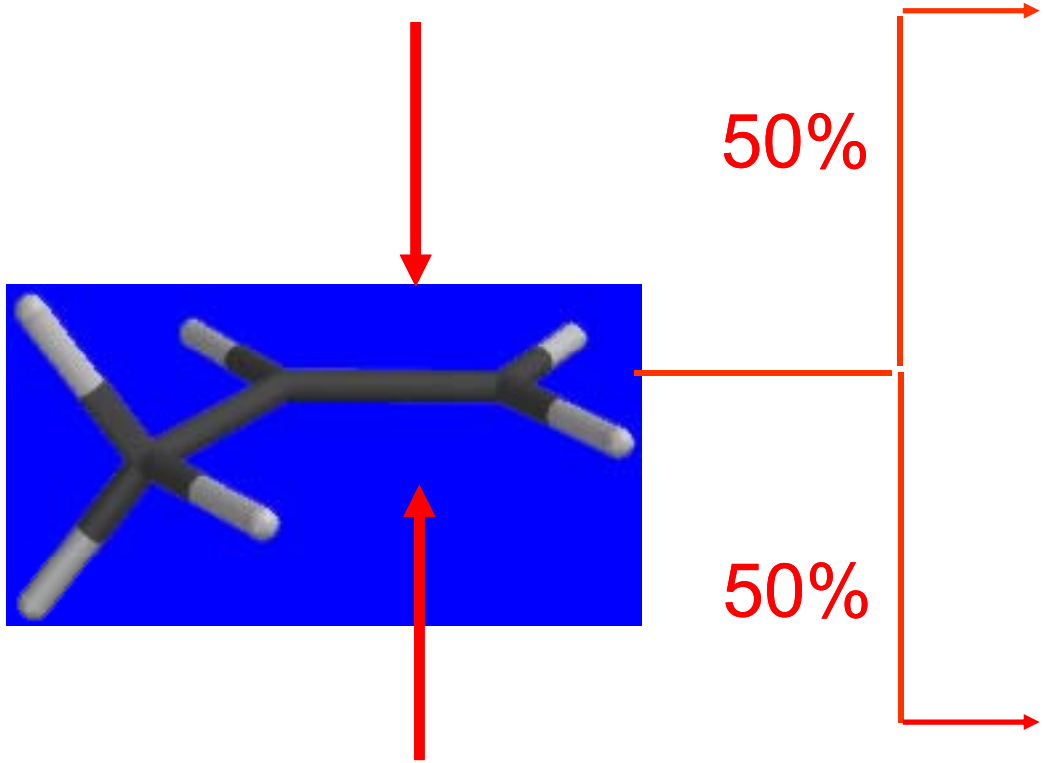




Epoxidation from this direction gives *S* epoxide

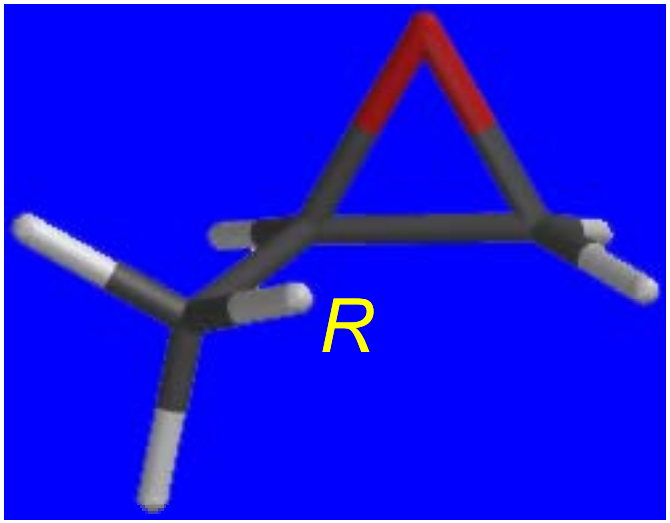
Top and bottom faces:

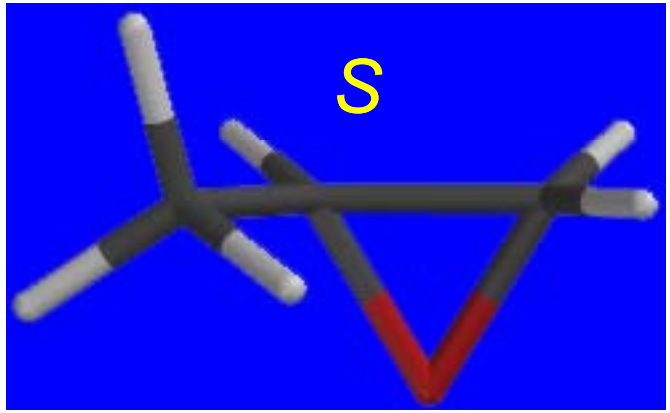
Prochiral faces



50%

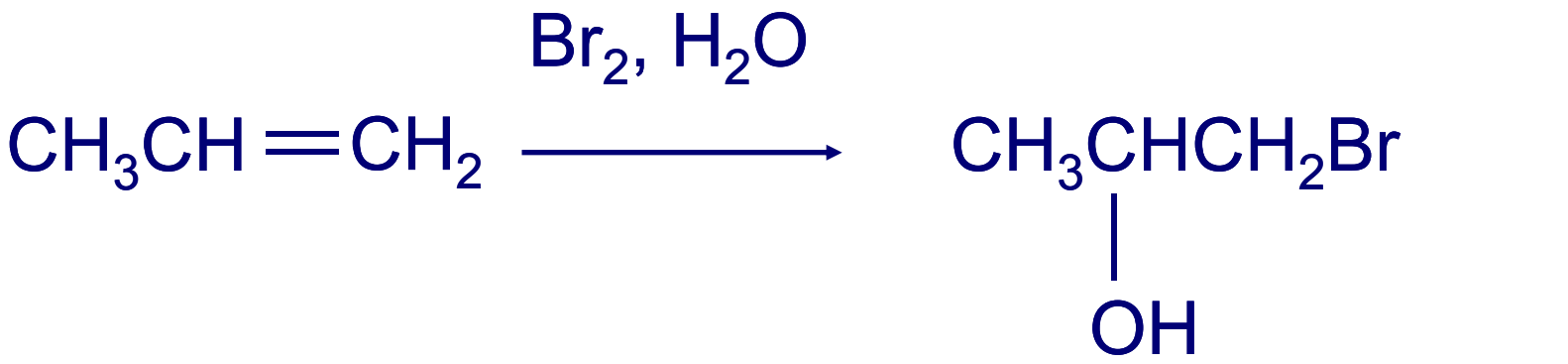
50%





Relationship between the two faces: *Enantiotopic*

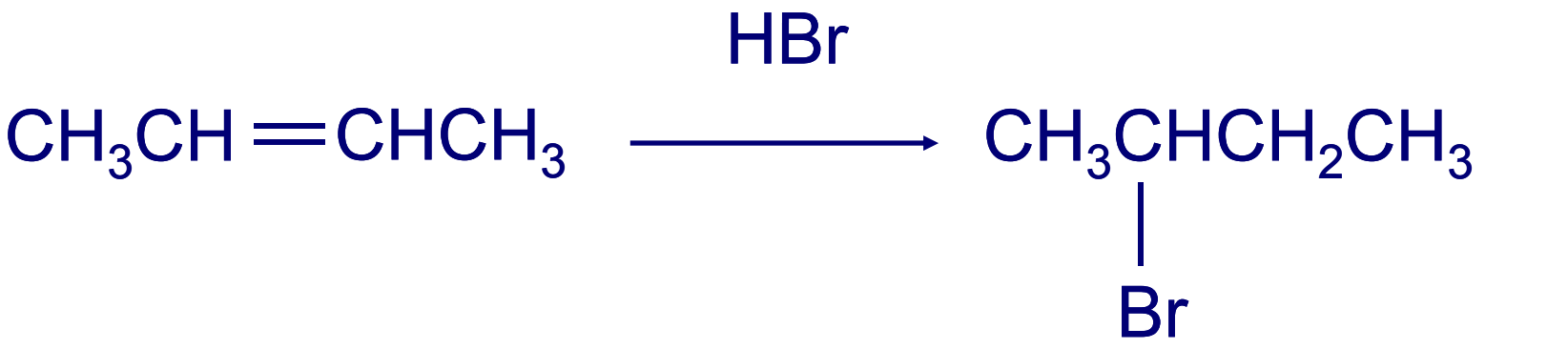
Example



Achiral

Chiral, but racemic

Example



Achiral

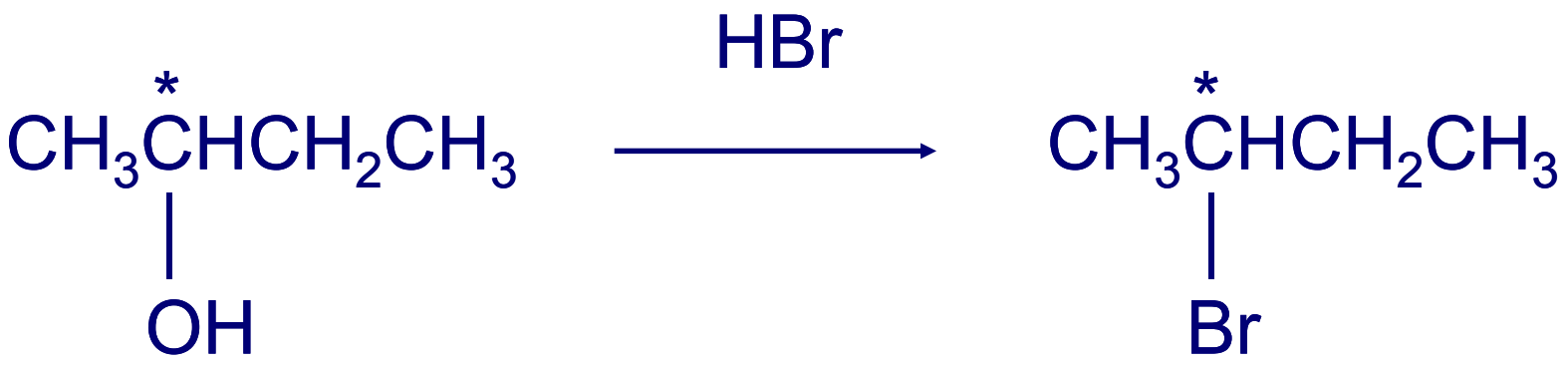
Chiral, but racemic

Many reactions convert chiral reactants to chiral products

- However, if the reactant is racemic, the product will be racemic also.

- Remember: "Optically inactive starting materials can't give optically active products."

Example



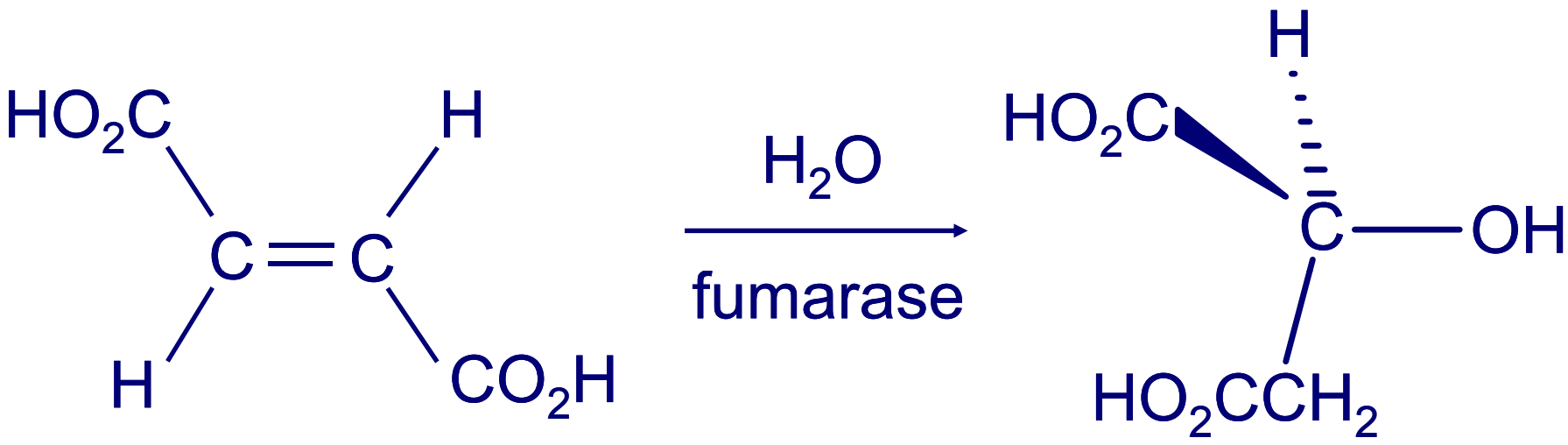
Chiral, but racemic

Chiral, but racemic

Many biochemical reactions convert an achiral reactant to a single enantiomer of a chiral product

- The enzyme (catalyst) is part of the reacting system, so such reactions don't violate the generalization that "Optically inactive starting materials can't give optically active products".

Example



Fumaric acid

Achiral

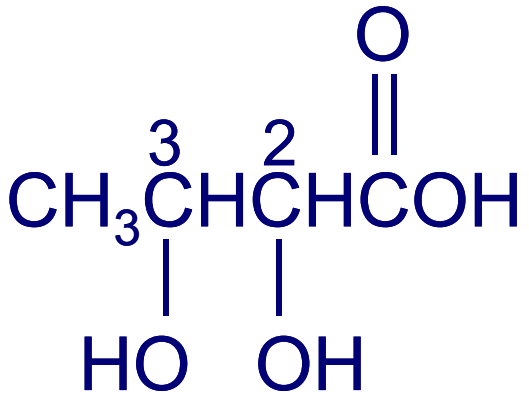
(*S*)-(–)-Malic acid

Single enantiomer

7.11. Chiral Molecules with Two Chirality Centers

How many stereoisomers when a particular molecule contains two chirality centers?

2,3-Dihydroxybutanoic acid

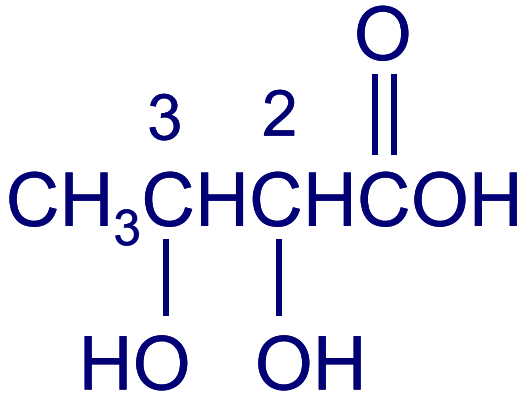


What are all the possible *R* and *S* combinations of the two chirality centers in this molecule?

Carbon-2	*R*	*R*	*S*	*S*	4 Combinations =
Carbon-3	*R*	*S*	*R*	*S*	4 Stereoisomers

What is the relationship between these stereoisomers?

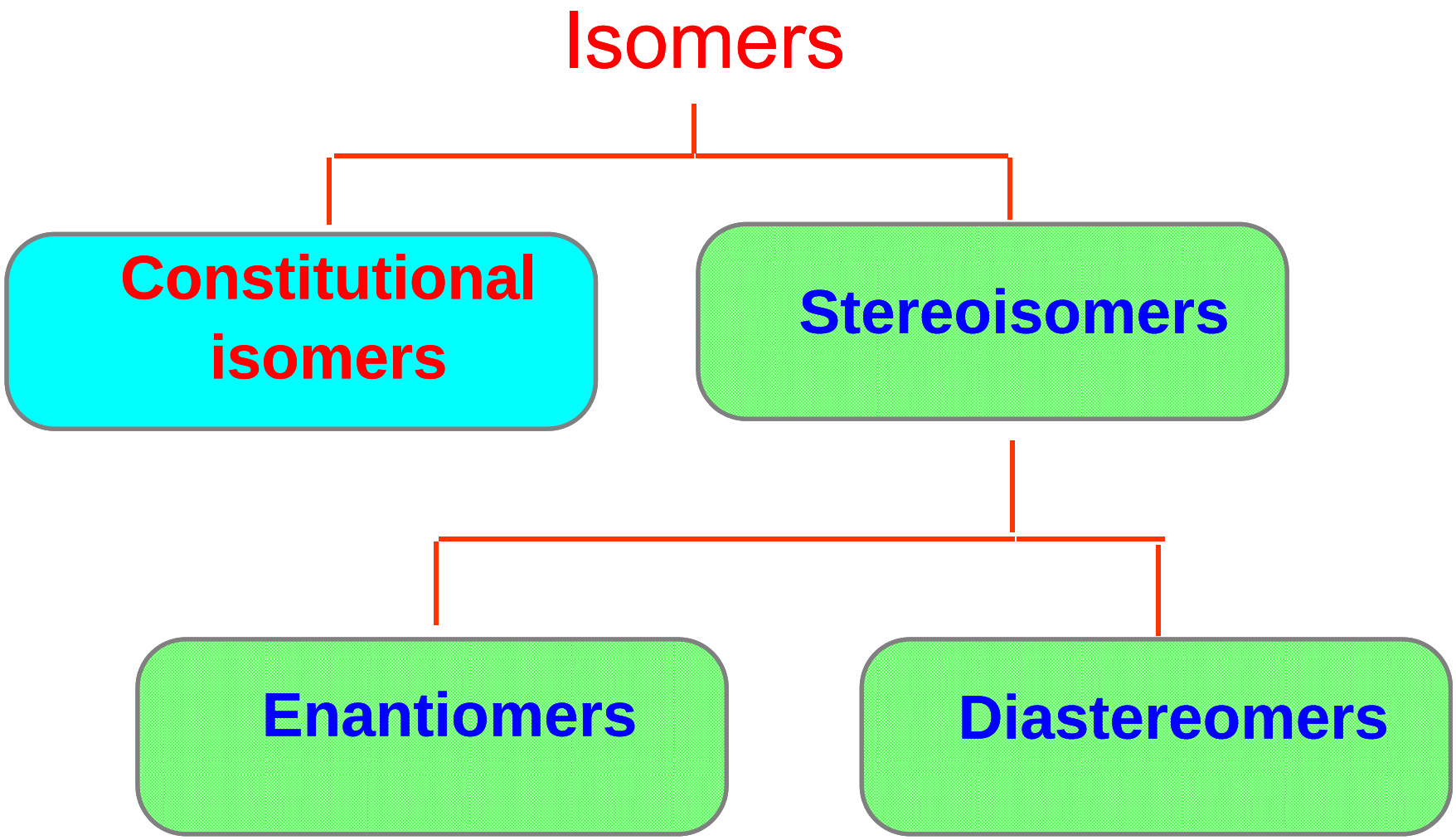
2,3-Dihydroxybutanoic acid

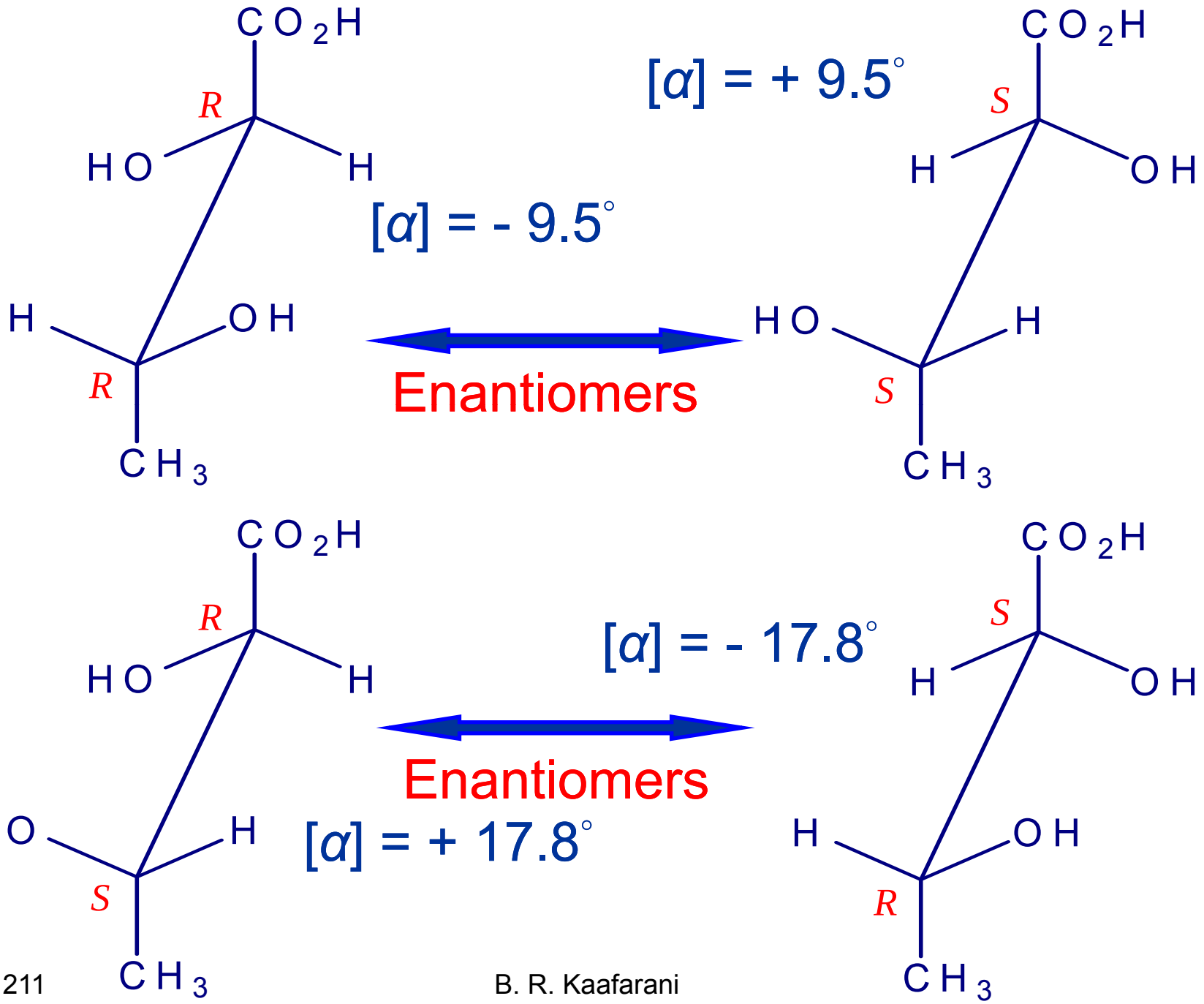


Enantiomers: 2*R*,3*R* and 2*S*,3*S*

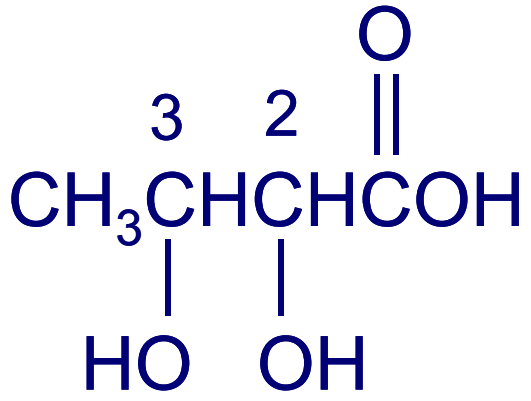
2*R*,3*S* and 2*S*,3*R*

Carbon-2	*R*	*R*	*S*	*S*
Carbon-3	*R*	*S*	*R*	*S*


Isomers
Constitutional isomers
Stereoisomers
Enantiomers
Diastereomers

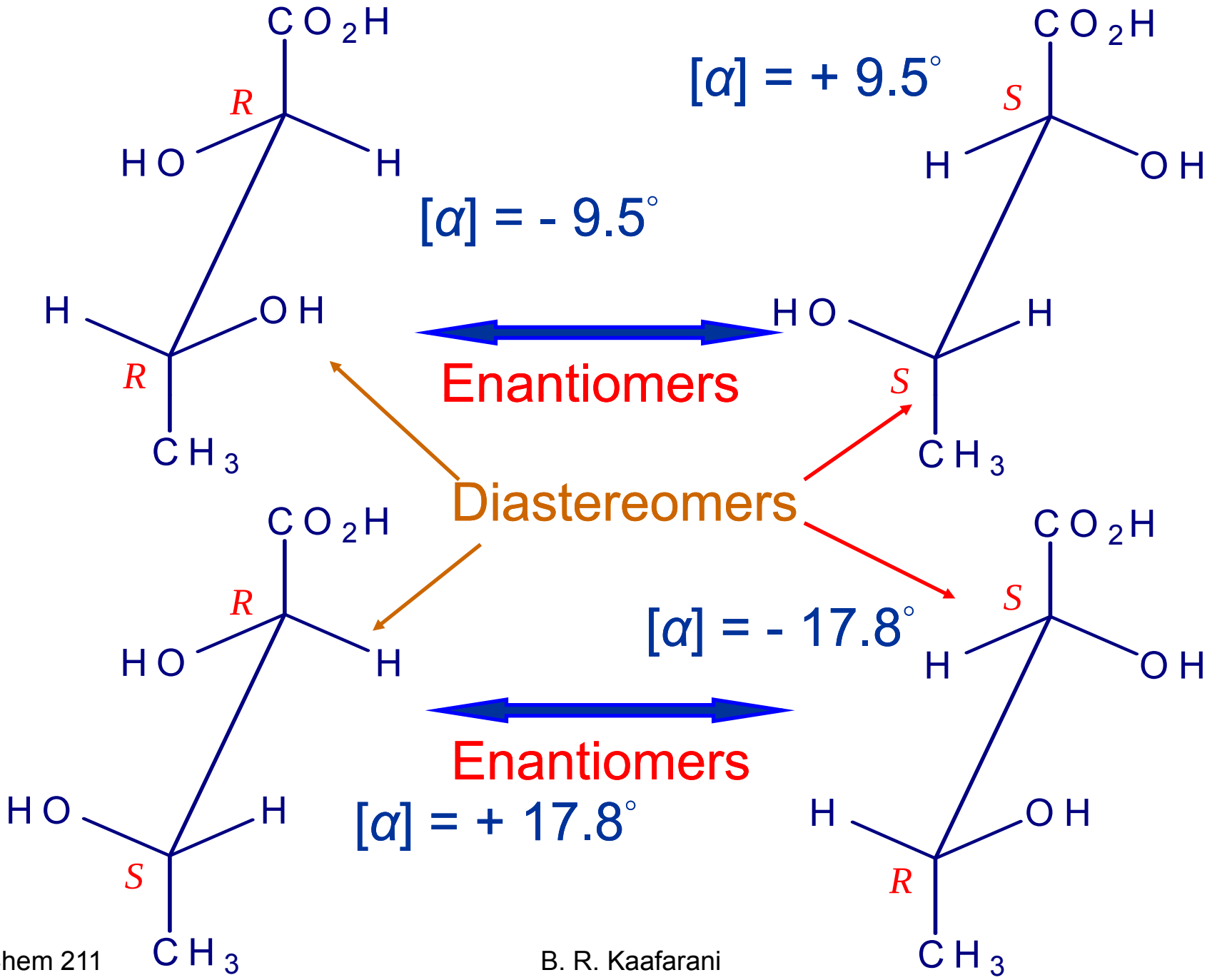

C O 2 H
R
H O
H
H
O H
R
C H 3
[α] = + 9.5°
[α] = - 9.5°
Enantiomers
C O 2 H
S
H
O H
H O
H
S
C H 3
C O 2 H
R
H O
H
H O
H
S
C H 3
[α] = - 17.8°
[α] = + 17.8°
Enantiomers
C O 2 H
S
H
O H
H
O H
R
C H 3

2,3-Dihydroxybutanoic acid

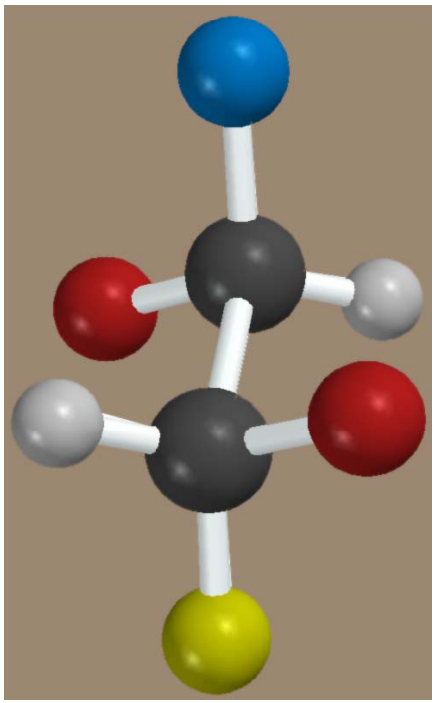


- But not all relationships are enantiomeric.
- Stereoisomers that are not enantiomers are diastereomers.

Carbon-2	*R*	*R*	*S*	*S*
Carbon-3	*R*	*S*	*R*	*S*

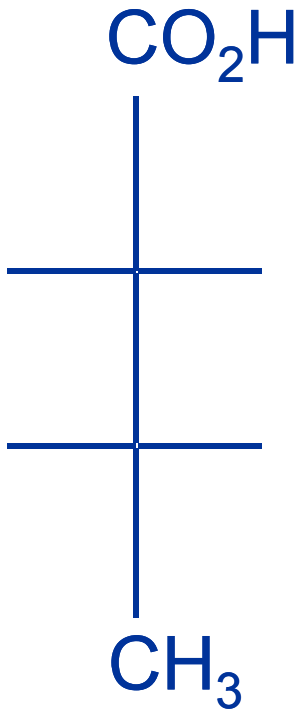

CO2H
R
HO
H
H
OH
R
CH3
[α] = - 9.5°
[α] = + 9.5°
CO2H
S
H
OH
HO
H
S
CH3
Enantiomers
Diastereomers
CO2H
R
HO
H
[α] = - 17.8°
CO2H
S
H
OH
Enantiomers
[α] = + 17.8°
HO
H
S
CH3
H
OH
R
CH3

Fischer Projections

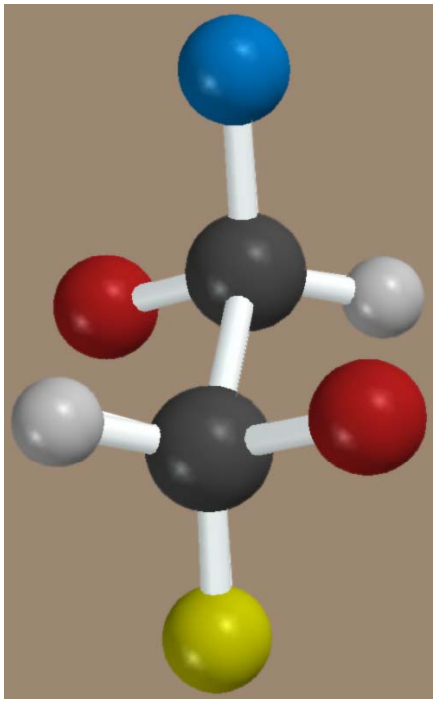


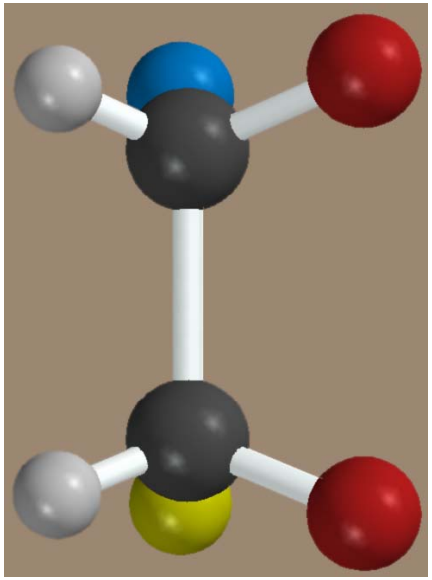
- Recall for Fischer projection: horizontal bonds point toward you; vertical bonds point away.

- Staggered conformation does not have correct orientation of bonds for Fischer projection.



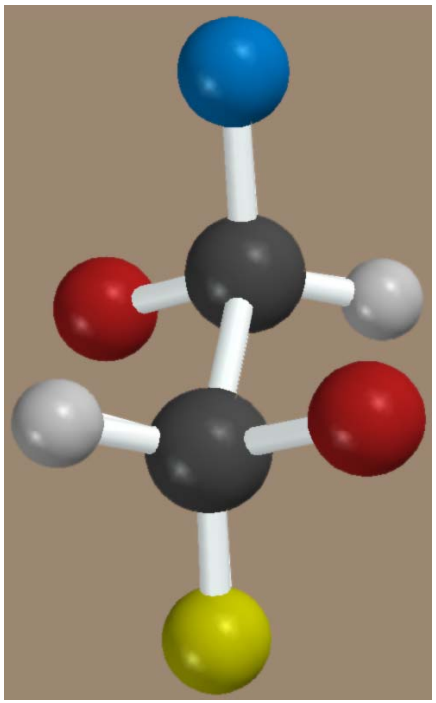
Fischer projections

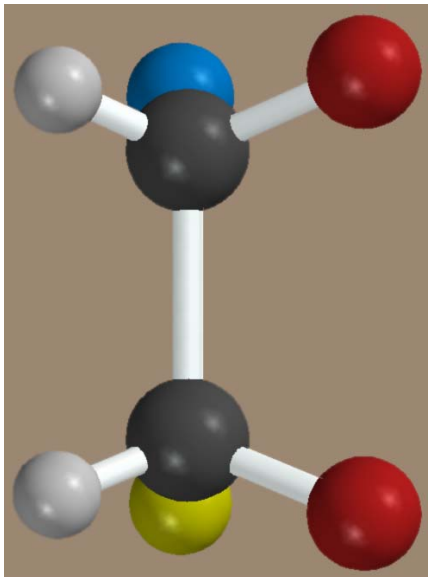


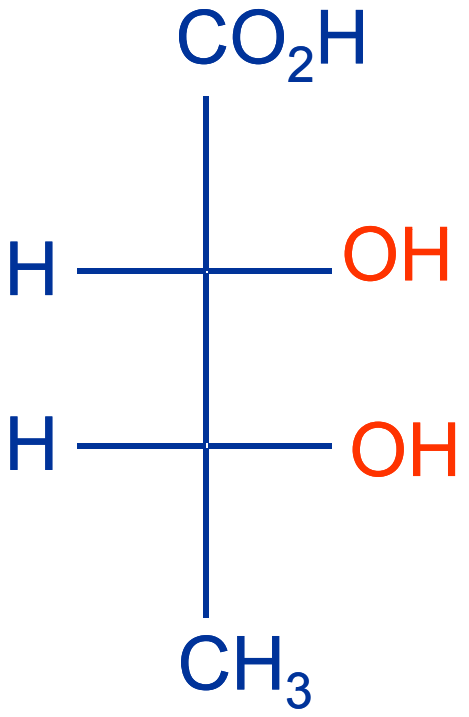


- Transform molecule to eclipsed conformation in order to construct Fischer projection

Fischer projections







Erythro and Threo

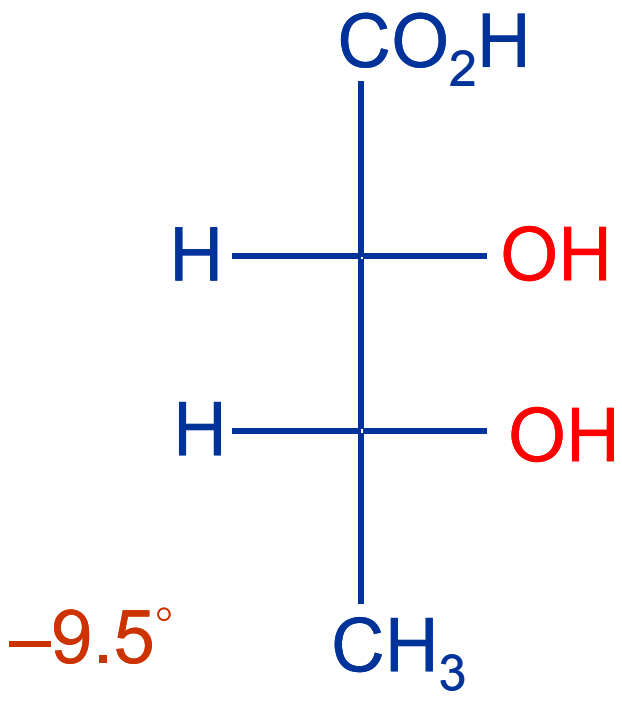
- Stereochemical prefixes used to specify relative configuration in molecules with two chirality centers.

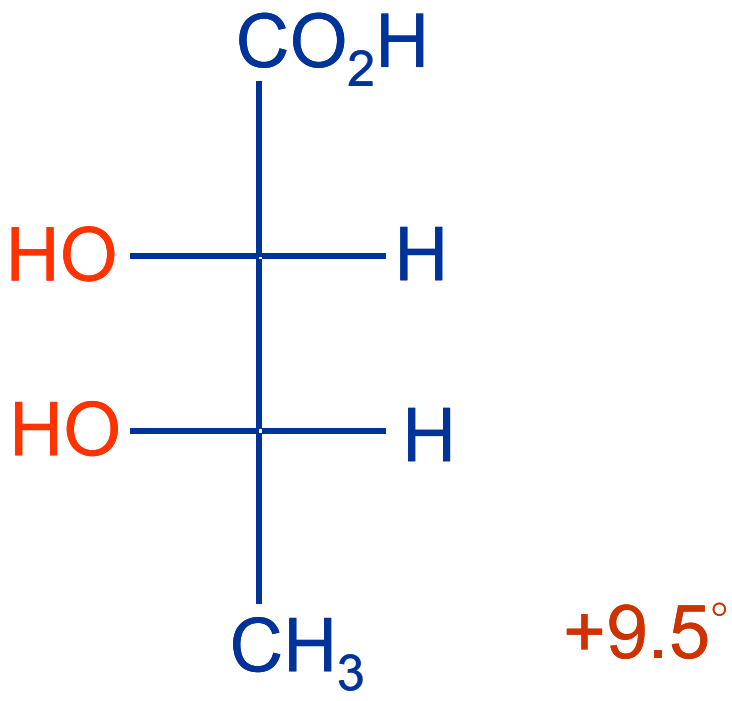
- Easiest to apply using Fischer projections.

- Orientation: vertical carbon chain.

Erythro

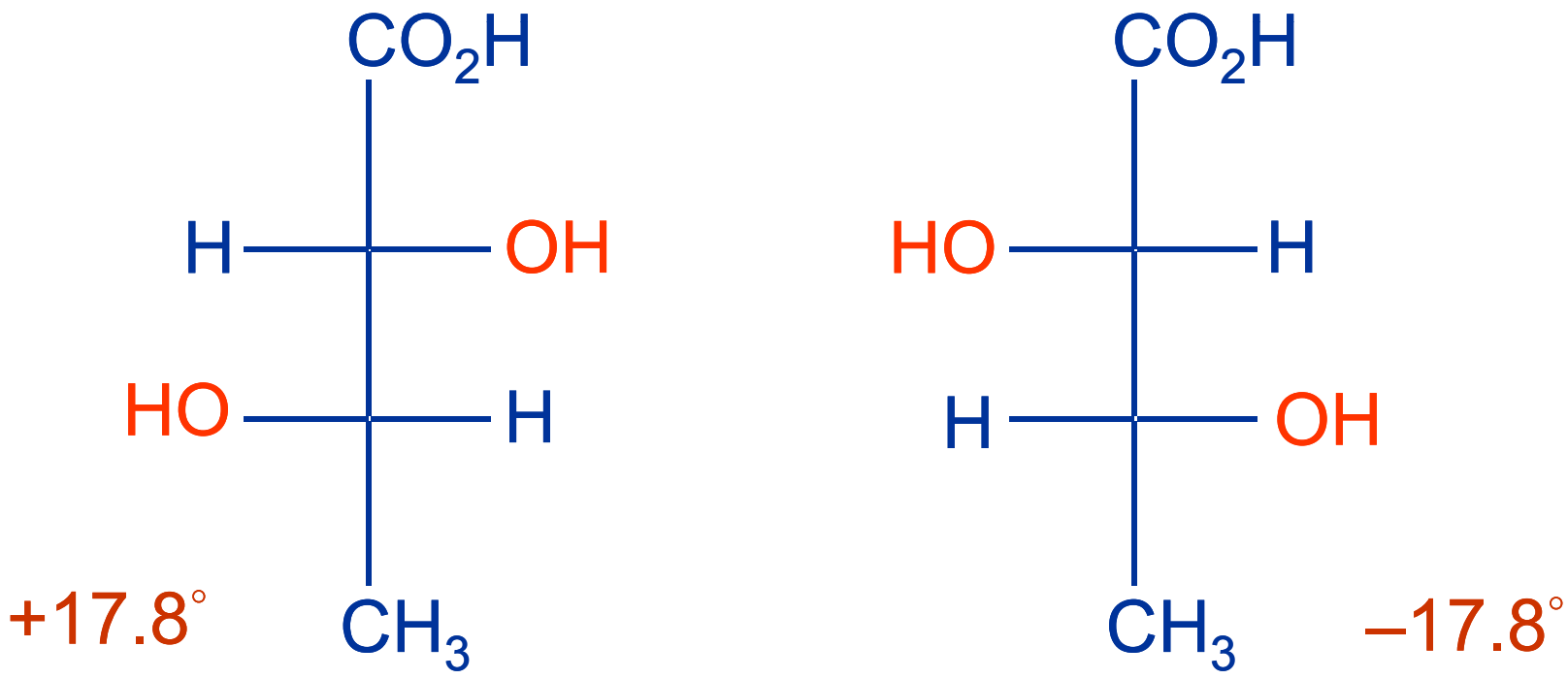
➢ When carbon chain is vertical, same (or analogous) substituents on same side of Fischer projection

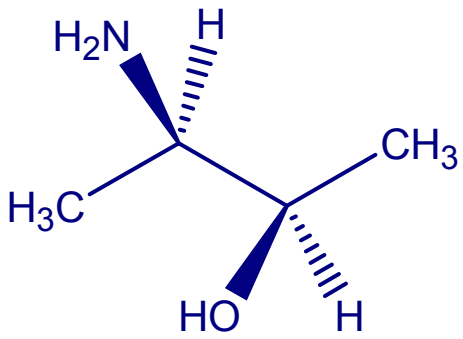




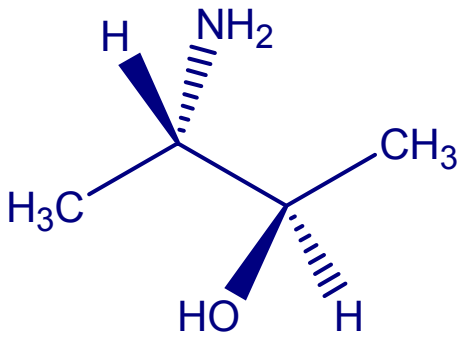
Threo

- When carbon chain is vertical, same (or analogous) substituents on opposite sides of Fischer projection.



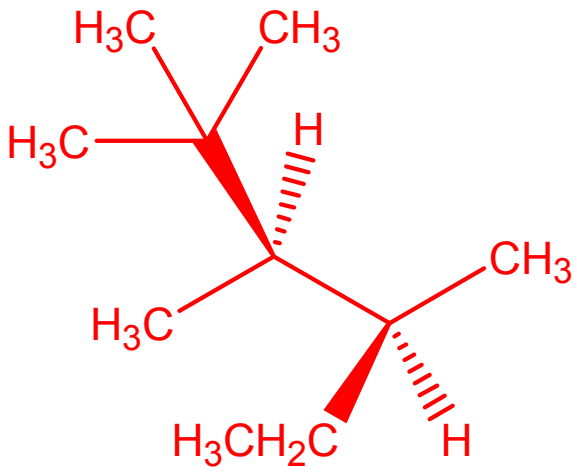


(2*R*,3*R*)-3-Amino-2-butanol
Liquid

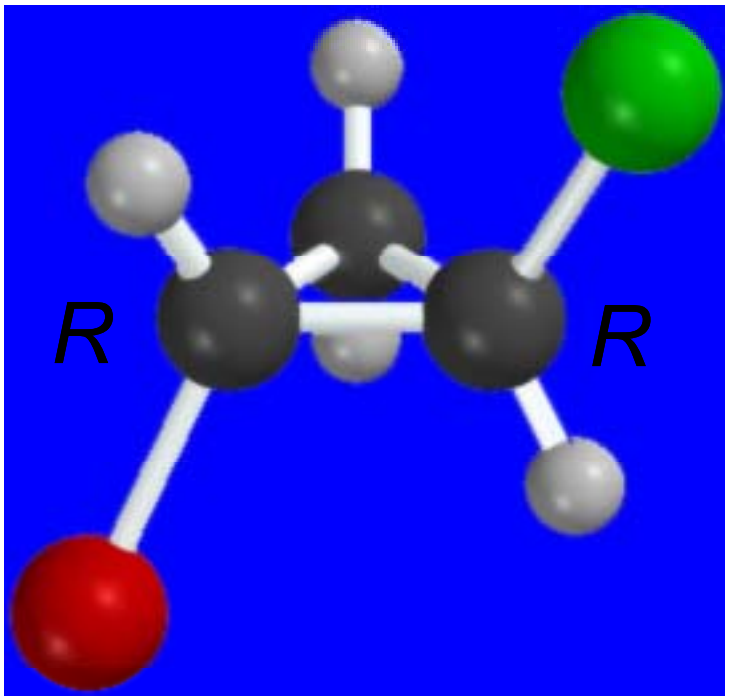


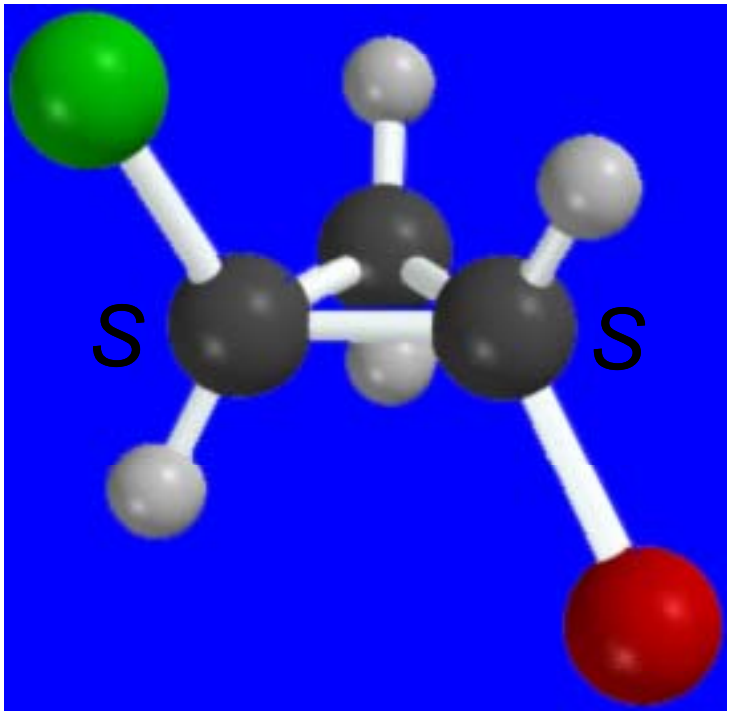
(2*R*,3*S*)-3-Amino-2-butanol
Solid, mp = 49 ℃

Name the following:



Two chirality centers in a ring

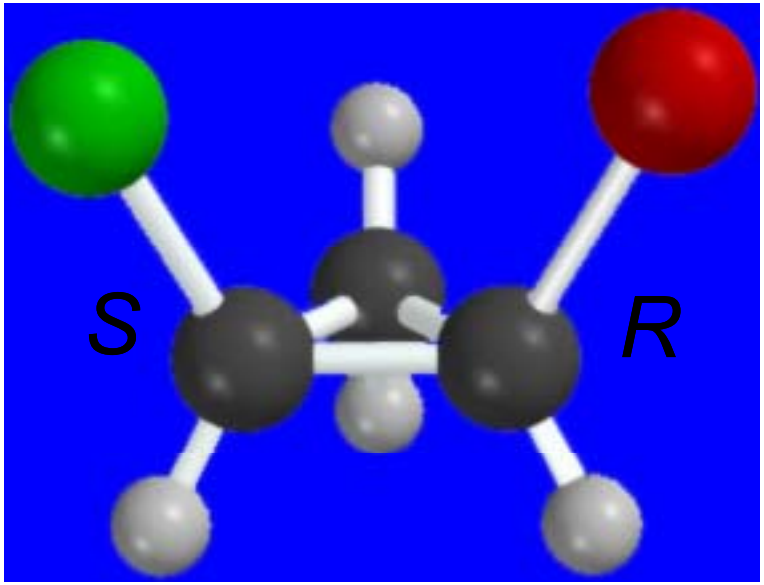


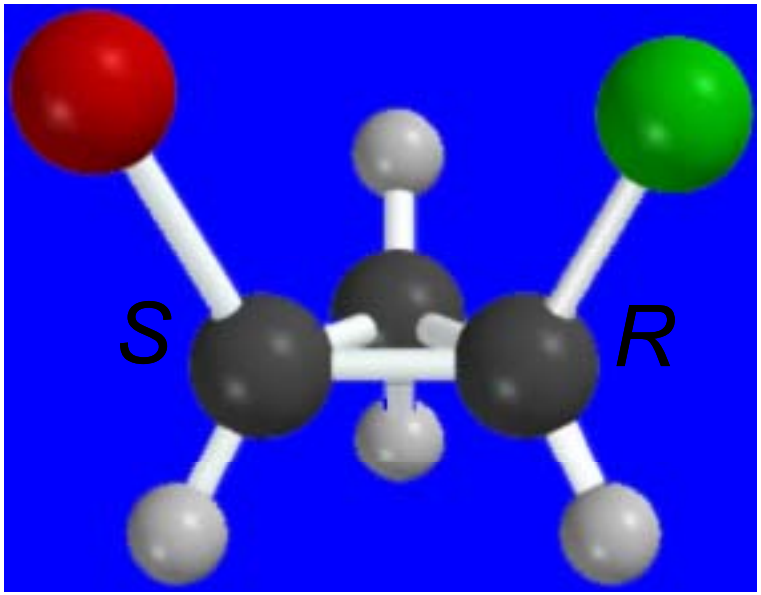


trans-1-Bromo-1-chlorocyclopropane

Nonsuperimposable mirror images; enantiomers.

Two chirality centers in a ring

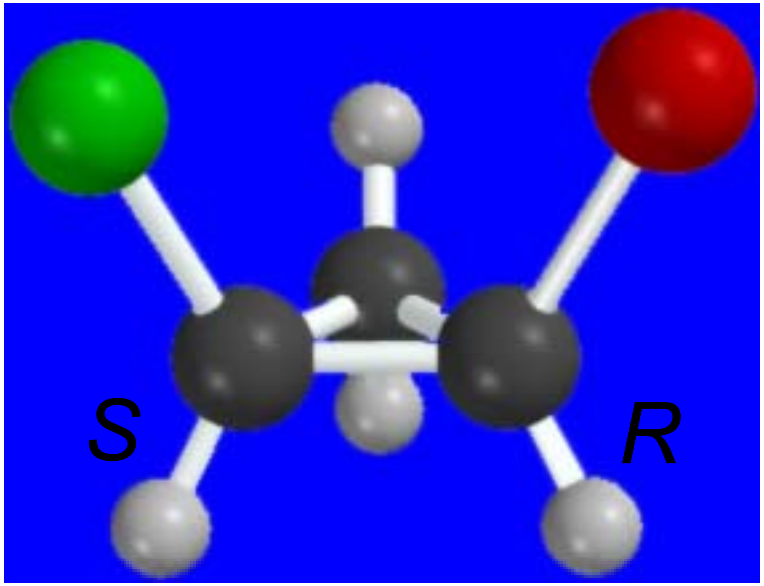




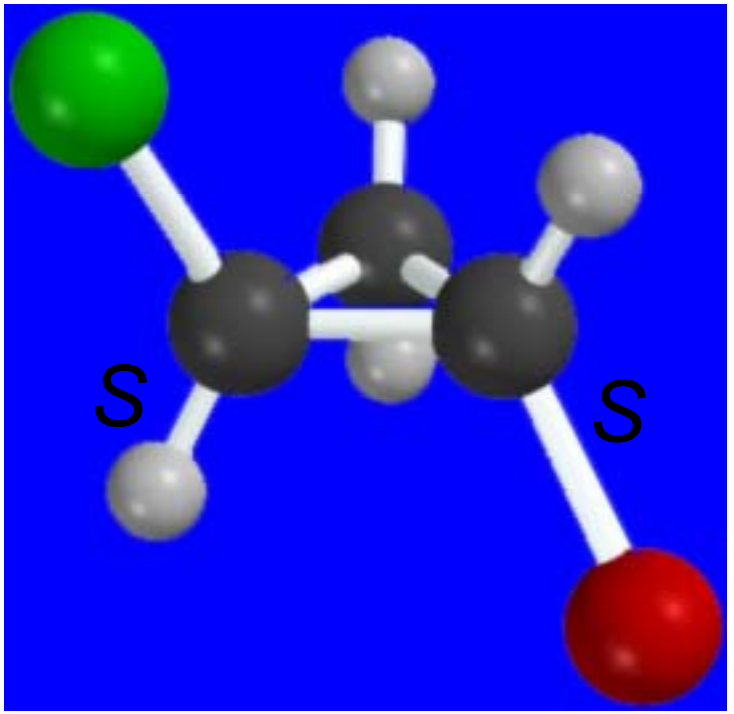
cis-1-Bromo-2-chlorocyclopropane

Nonsuperimposable mirror images; enantiomers.

Two chirality centers in a ring



cis-1-Bromo-2-chloro-cyclopropane



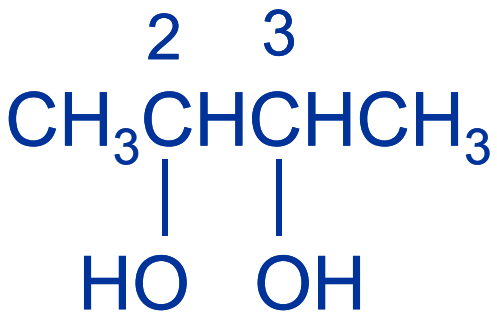
trans-1-Bromo-2-chloro-cyclopropane

Stereoisomers that are not enantiomers; diastereomers

7.12. Achiral Molecules with Two Chirality Centers

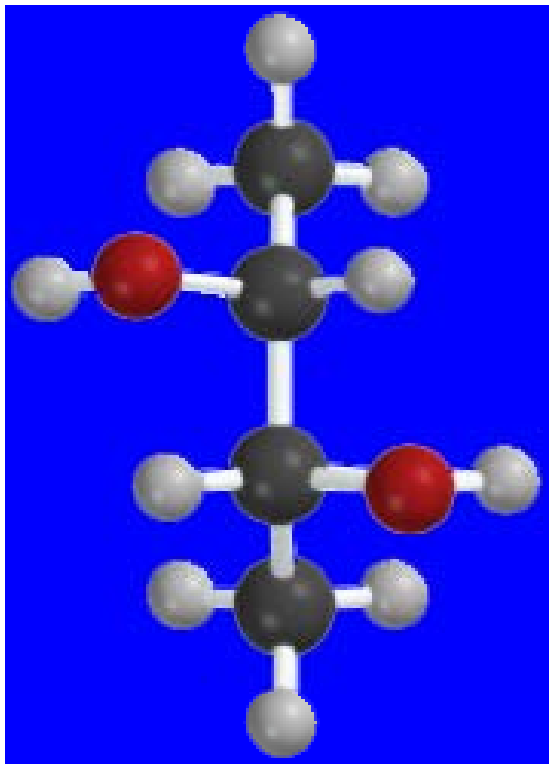
It is possible for a molecule to have chirality centers yet be achiral!?

2,3-Butanediol



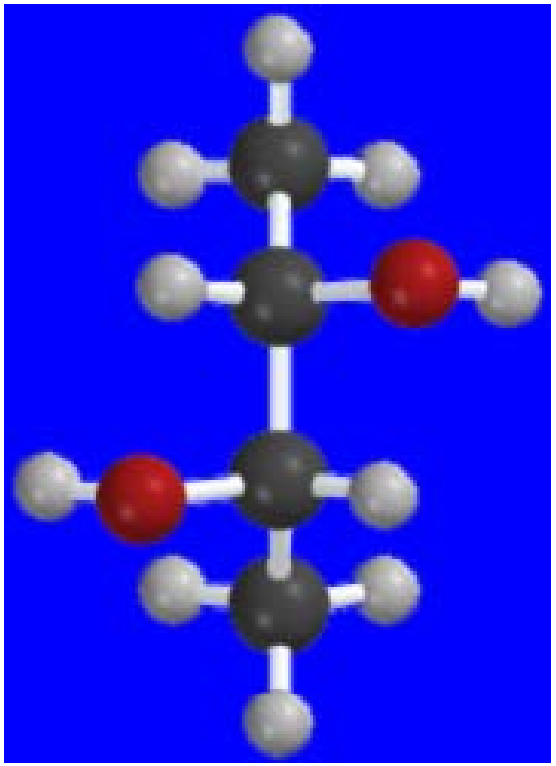
➢ Consider a molecule with two equivalently substituted chirality centers such as 2,3-butanediol.

Three stereoisomers of 2,3-butanediol



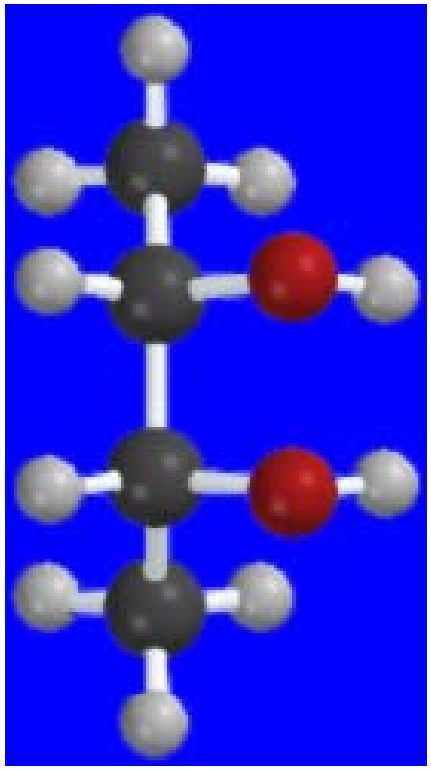
2R,3*R*

chiral



2*S*,3*S*

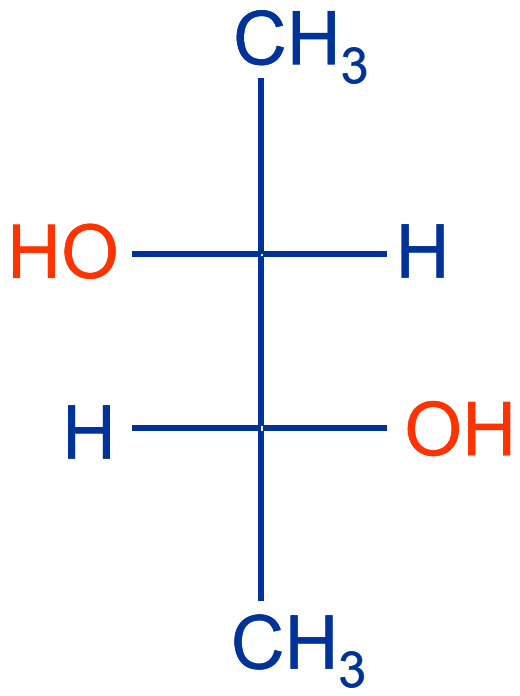
chiral



2*R*,3*S*

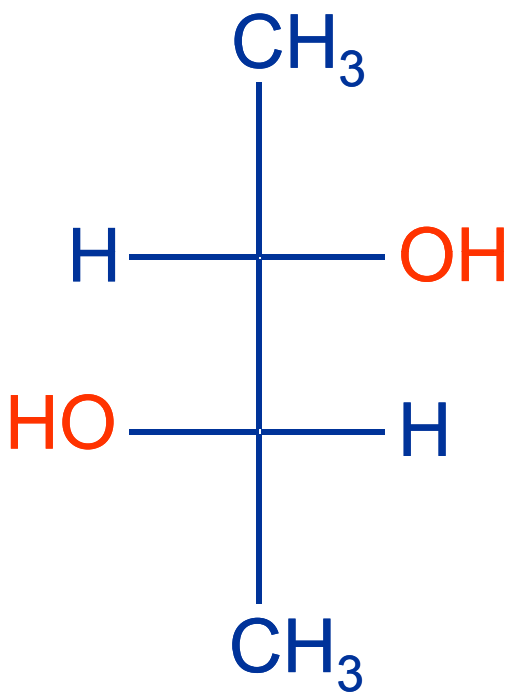
achiral

Three stereoisomers of 2,3-butanediol



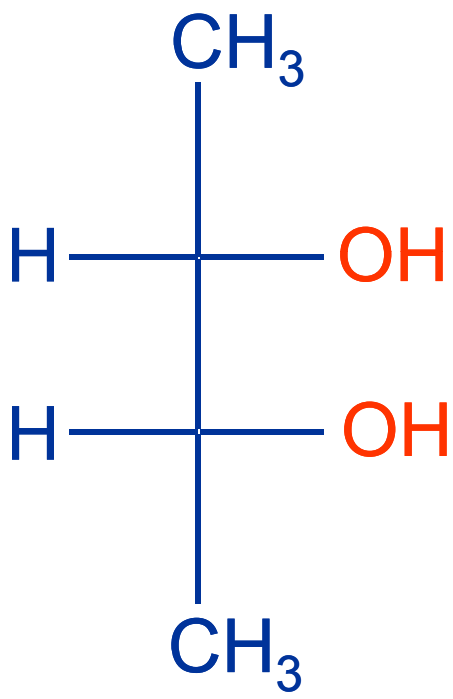
2*R*,3*R*

chiral



2*S*,3*S*

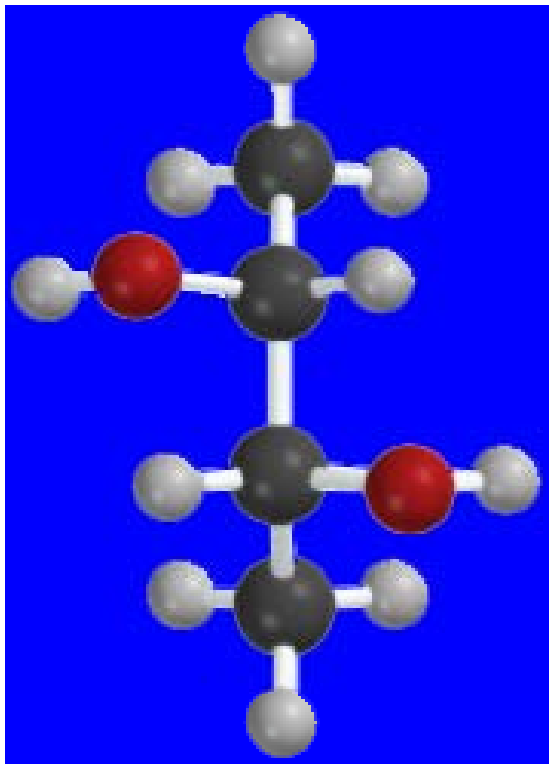
chiral



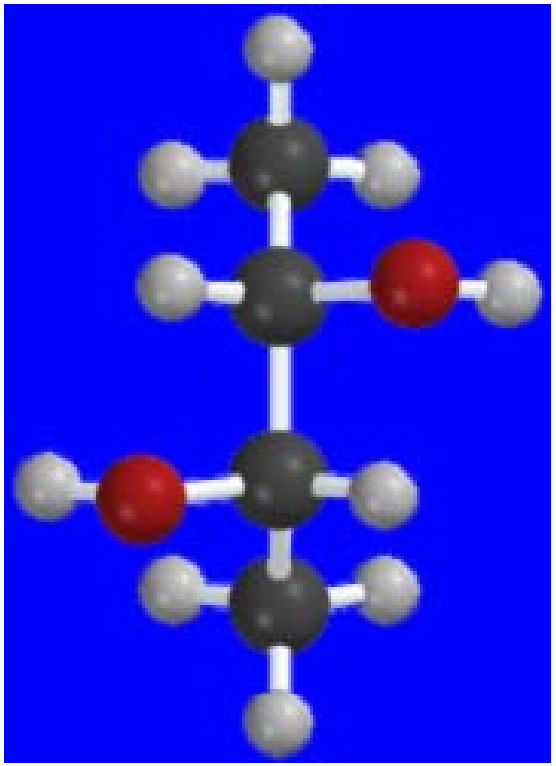
2*R*,3*S*

achiral

Three stereoisomers of 2,3-butanediol



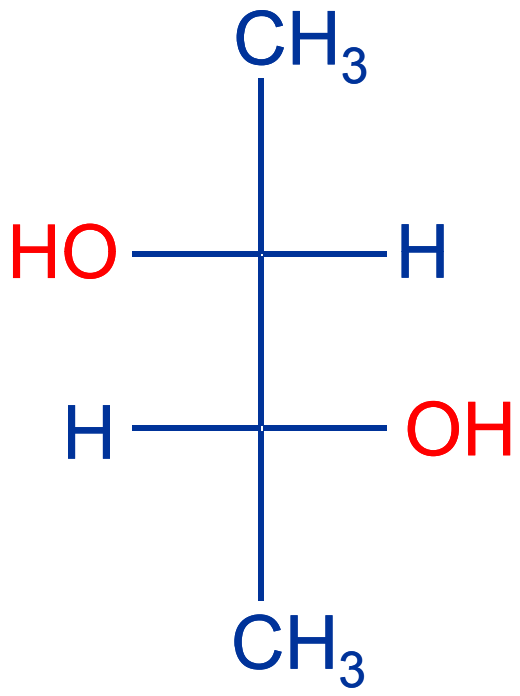
2*R*,3*R*
chiral



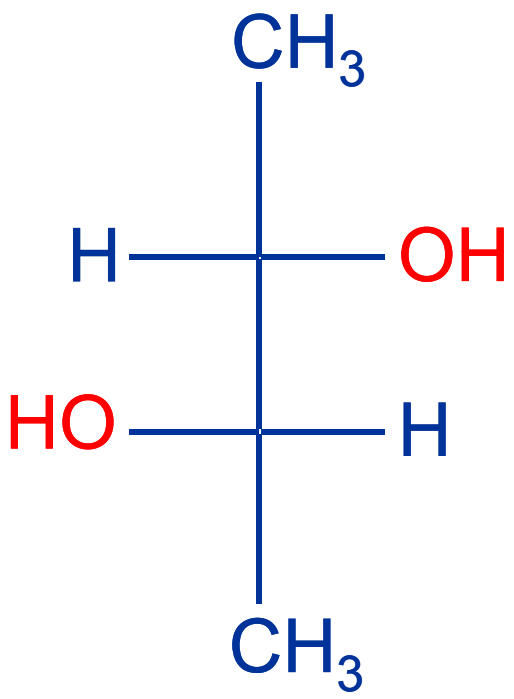
2*S*,3*S*
chiral

These two are enantiomers

Three stereoisomers of 2,3-butanediol



2R,3R
chiral

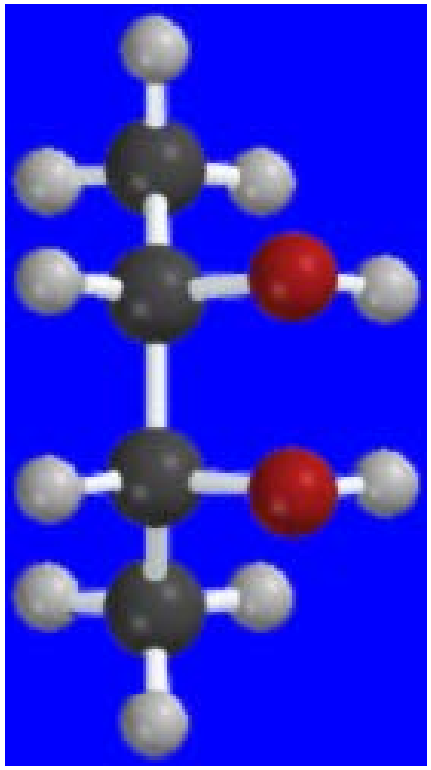


2S,3S
chiral

These two are enantiomers

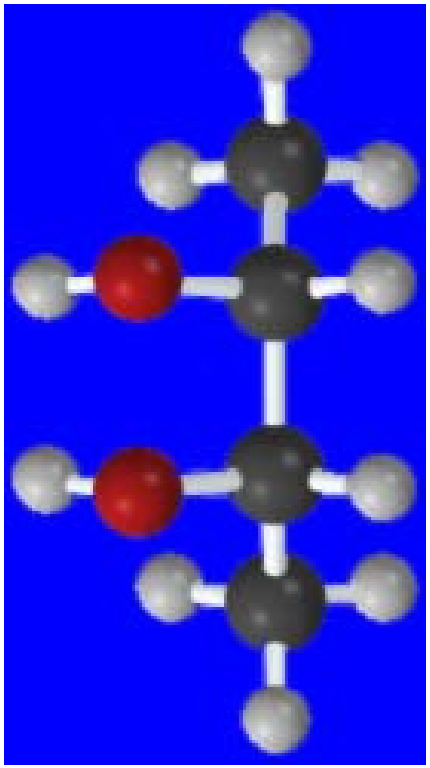
Three stereoisomers of 2,3-butanediol

- The third structure is superimposable on its mirror image.

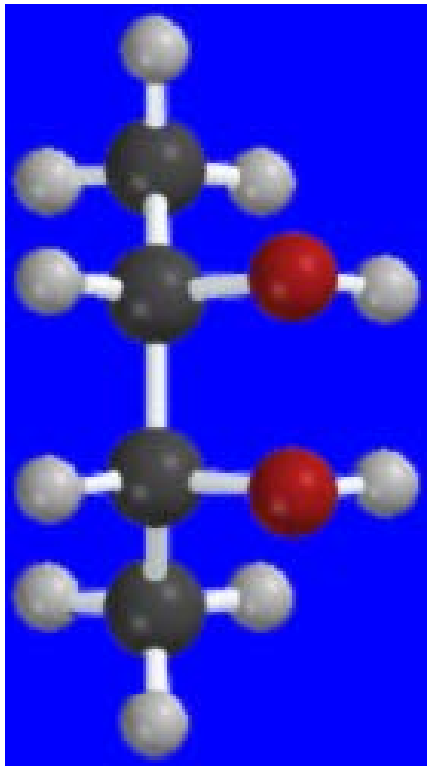


2*R*,3*S*
achiral

Three stereoisomers of 2,3-butanediol



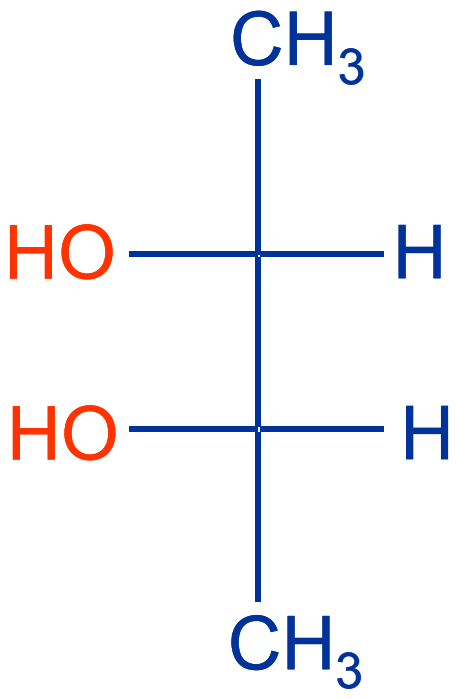
- Therefore, this structure and its mirror image are the same.
- It is called a *meso* form.
- A *meso* form is *achiral* molecule that has chirality centers.



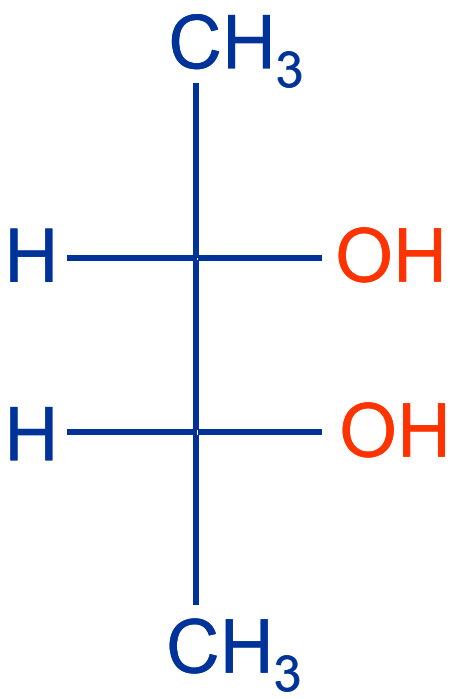
2*R*,3*S*

achiral

Three stereoisomers of 2,3-butanediol



- Therefore, this structure and its mirror image are the same.
- It is called a *meso* form.
- A *meso* form is *achiral* molecule that has chirality centers.

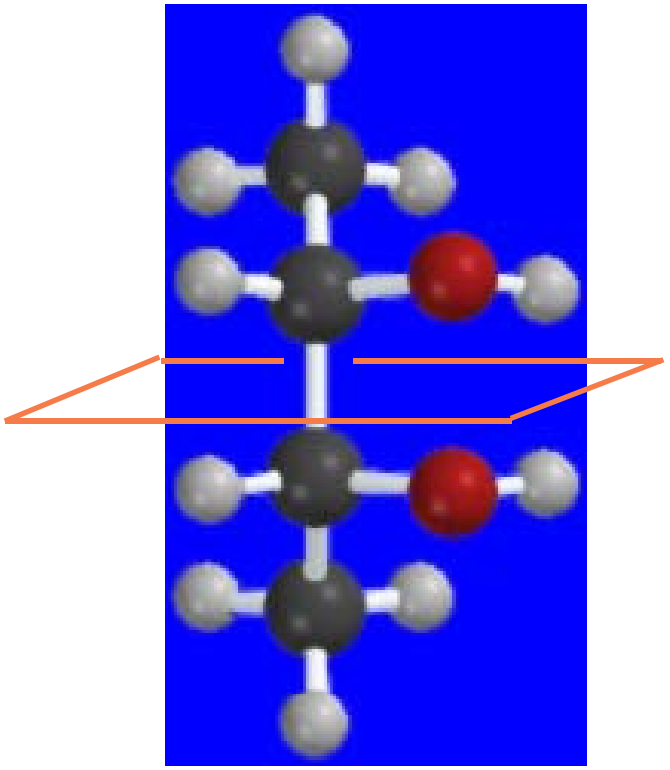


2*R*,3*S*

achiral

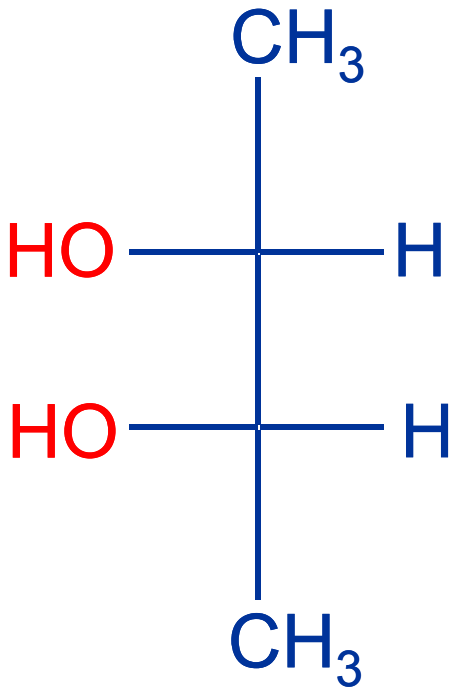
Three stereoisomers of 2,3-butanediol

- *Meso* forms have a plane of symmetry and/or a center of symmetry.
- Plane of symmetry is most common case.
- Top half of molecule is mirror image of bottom half.

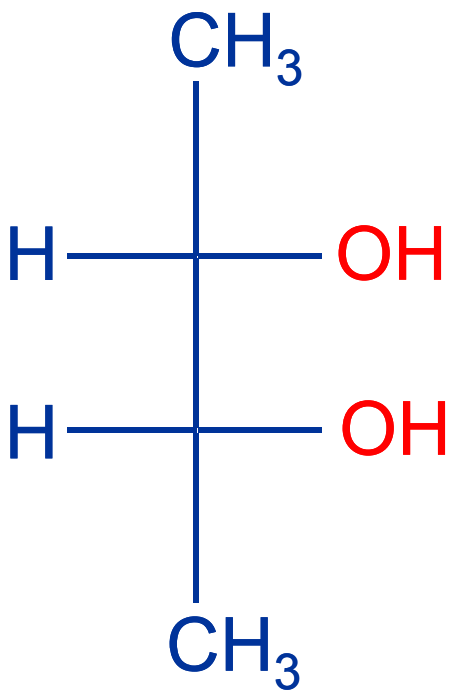


2*R*,3*S*
achiral

Three stereoisomers of 2,3-butanediol



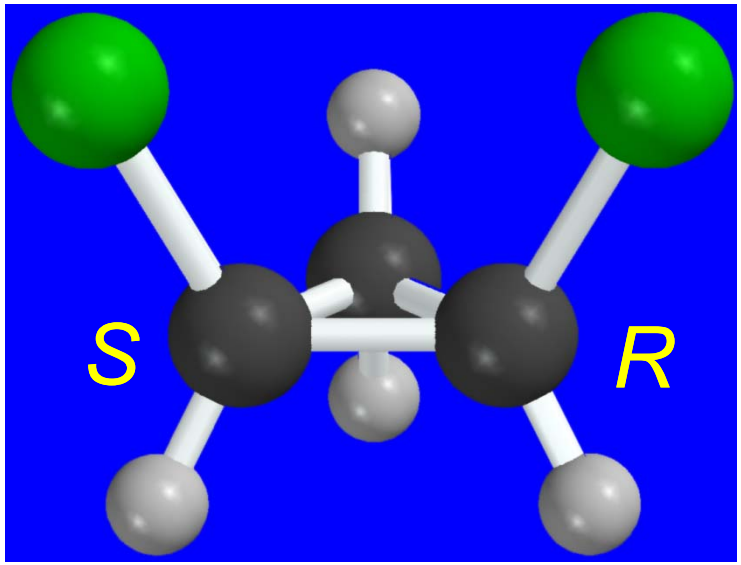
- A line drawn in the center of the Fischer projection of a *meso* form bisects it into two mirror-image halves.



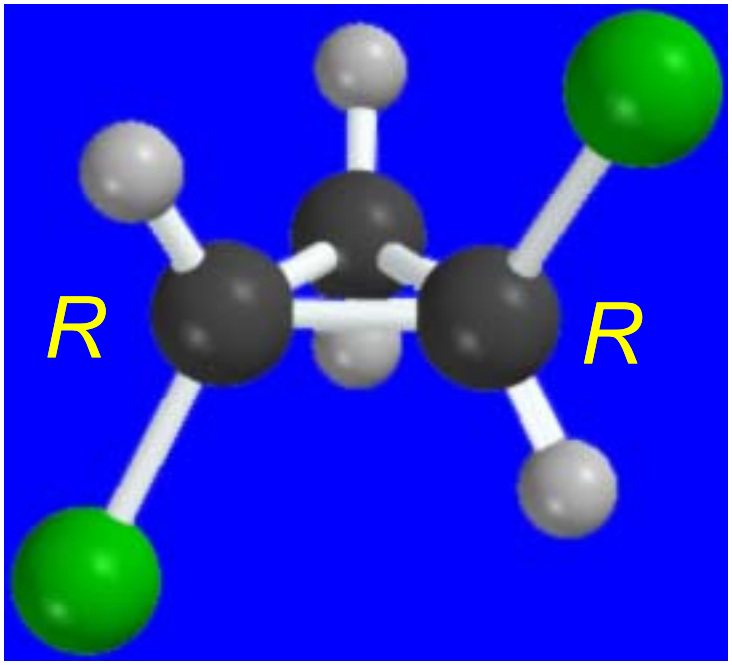
2*R*,3*S*

achiral

Cyclic compounds



meso



chiral

➢ There are three stereoisomers of 1,2-dichloro-cyclopropane; the achiral (*meso*) *cis* isomer and two enantiomers of the *trans* isomer.

7.13. Molecules with Multiple Chirality Centers

How many stereoisomers?

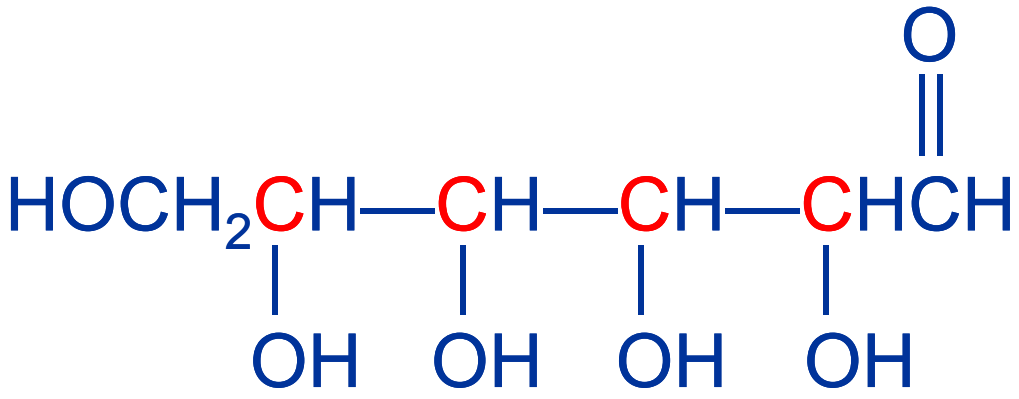
- Maximum number of stereoisomers = 2^n.

where n = number of structural units capable of stereochemical variation.

- Structural units include chirality centers and *cis* and/or *trans* double bonds.

- Number is reduced to less than 2^n if *meso* forms are possible.

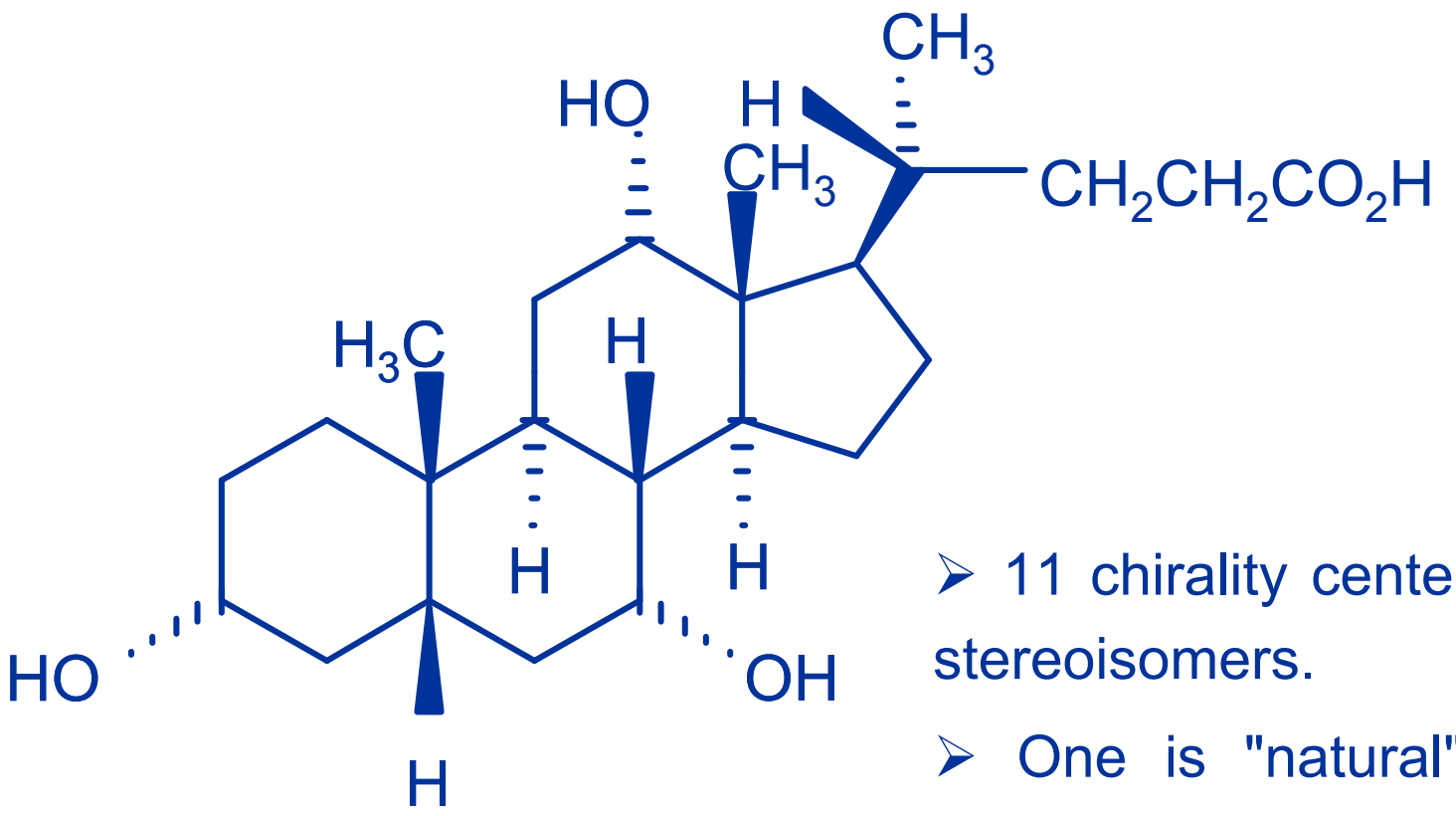
Example



4 chirality centers

16 stereoisomers

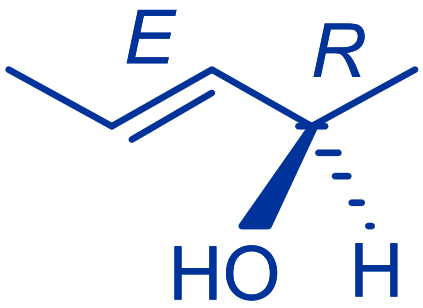
Cholic acid (Figure 7.11)

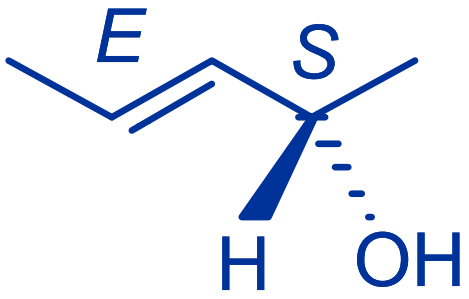


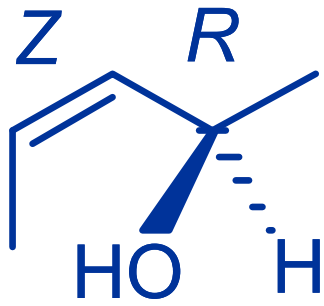
- 11 chirality centers 2^{11} = 2048 stereoisomers.
- One is "natural" cholic acid; another is the enantiomer of natural cholic acid.
- 2046 are diastereomers of cholic acid.

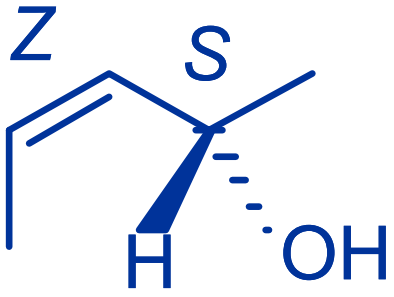
How many stereoisomers?

3-Penten-2-ol



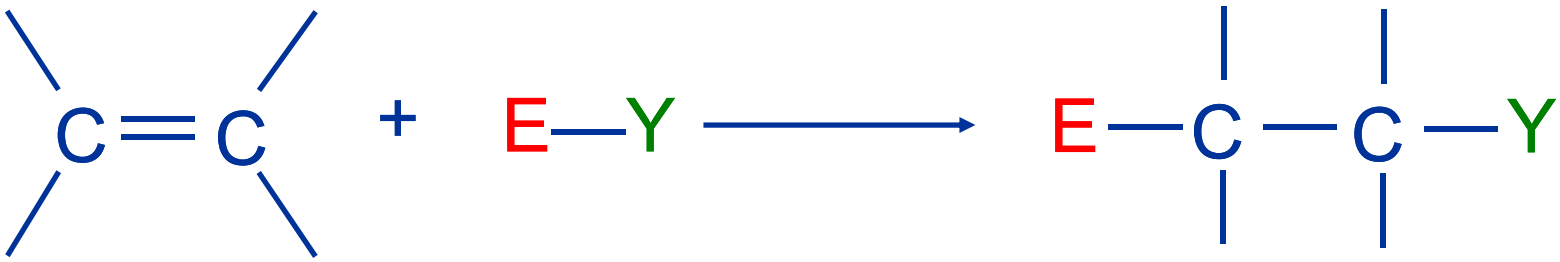






7.14
Reactions That Produce Diastereomers

Stereochemistry of Addition to Alkenes

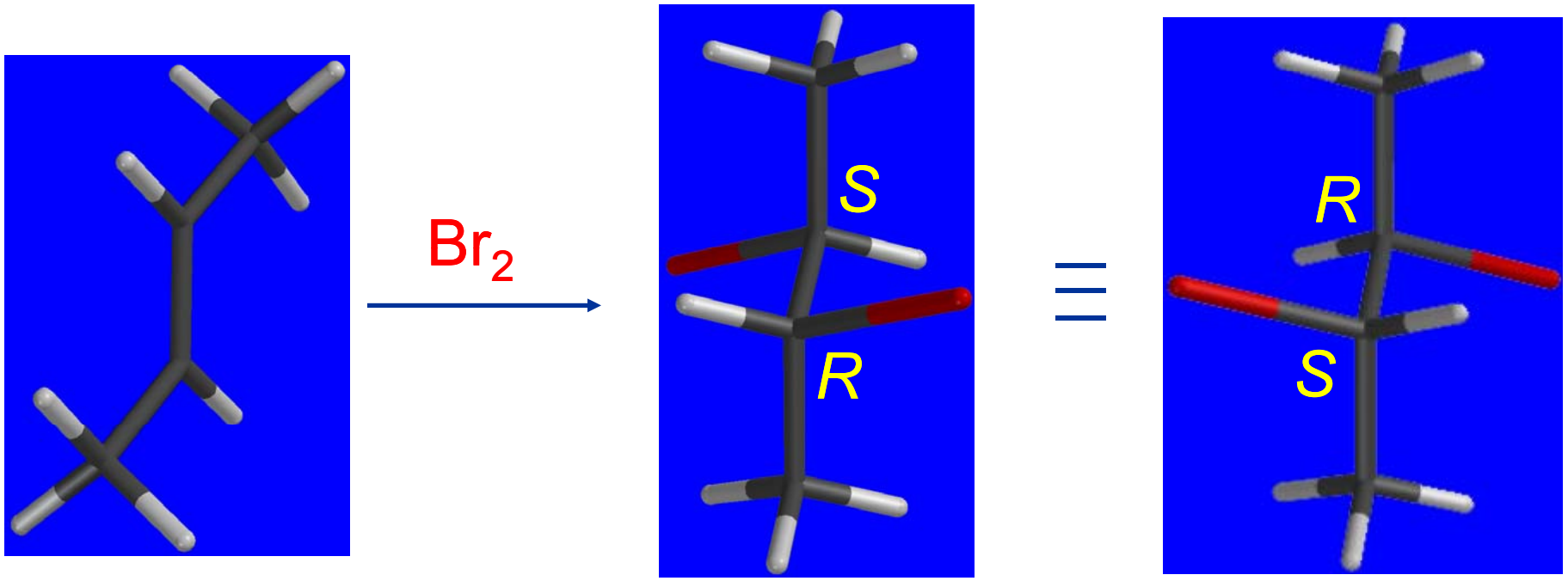


➢ *In order to understand stereochemistry of product, you need to know two things:*

(1) stereochemistry of alkene (*cis* or *trans*; *Z* or *E*).

(2) stereochemistry of mechanism (*syn* or *anti*).

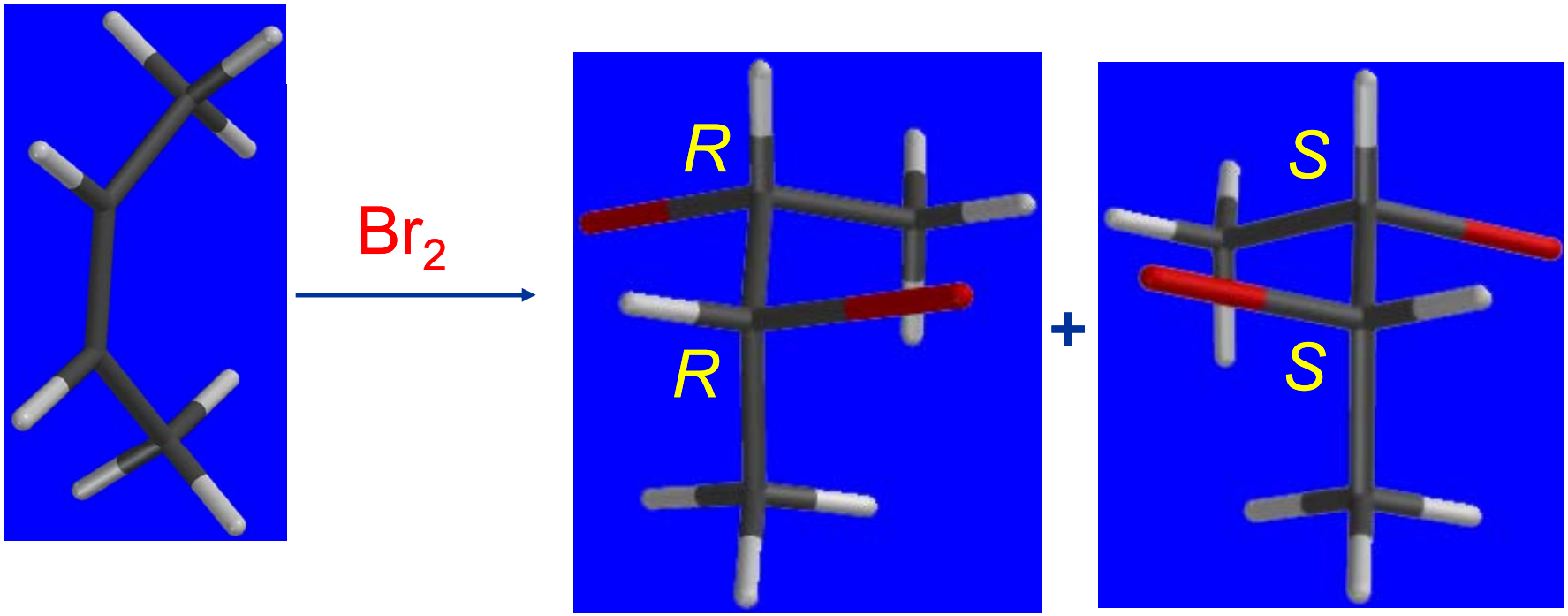
Bromine Addition to *trans*-2-Butene



meso

Anti addition to *trans*-2-butene gives a *meso* form.

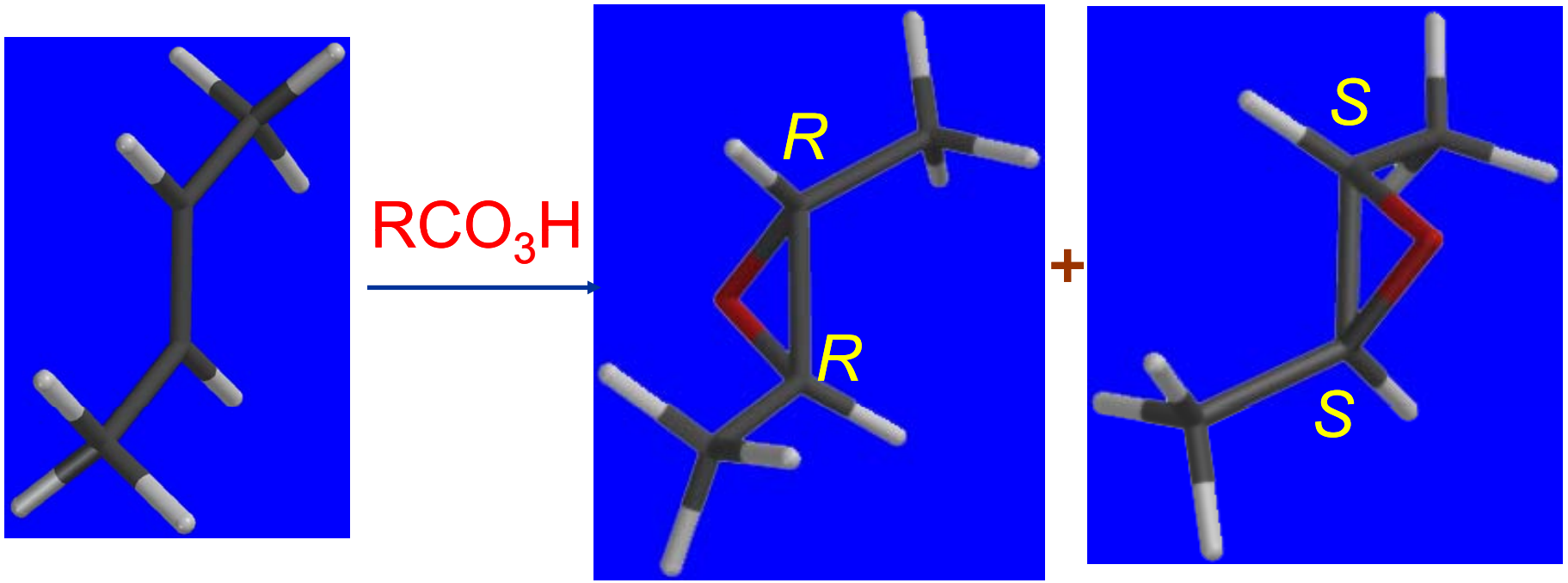
Bromine Addition to *cis*-2-Butene



50% 50%

➢ *Anti* addition to *cis*-2-butene gives racemic mixture of chiral enantiomers.

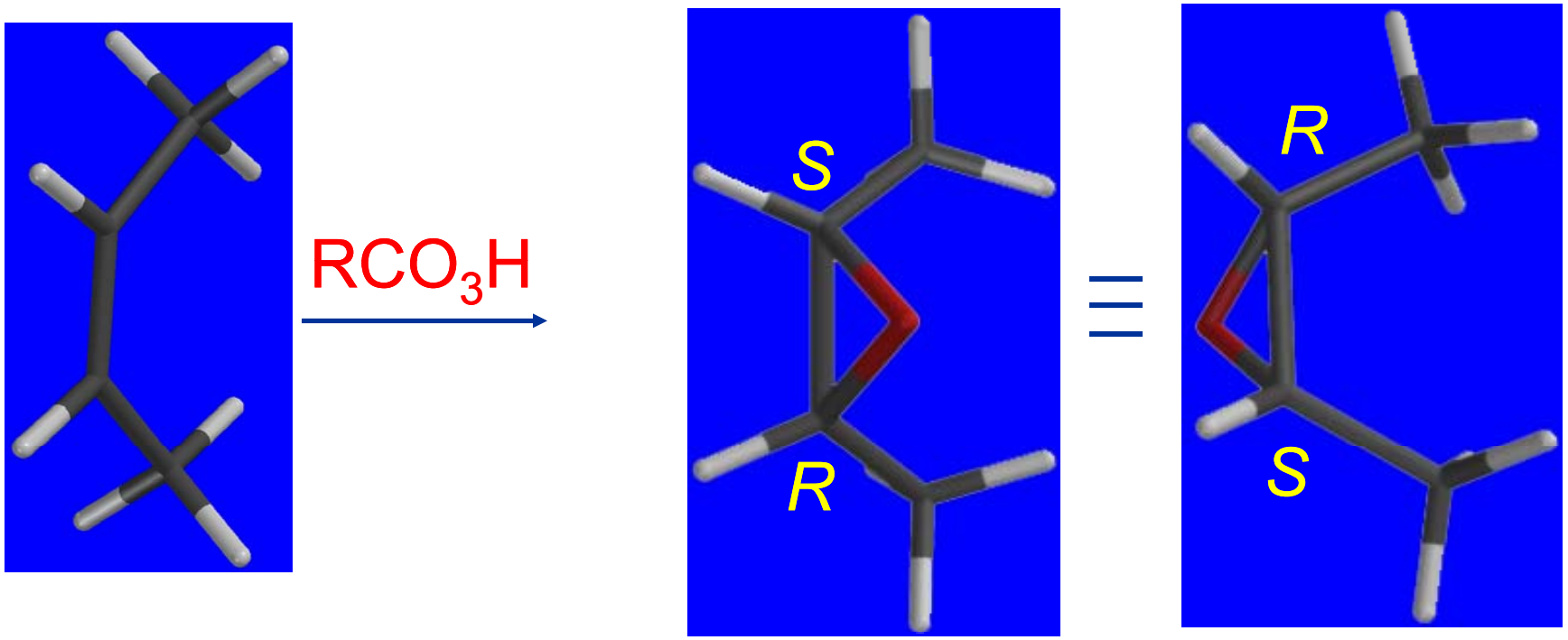
Epoxidation of trans-2-Butene
Problem 7.20



50% 50%

- *syn* addition to *trans*-2-butene gives racemic mixture of chiral enantiomers.

Epoxidation of cis-2-Butene
Problem 7.20



meso

- *syn* addition to *cis*-2-butene gives a *meso* form.

Stereospecific Reaction

- Of two stereoisomers of a particular starting material, each one gives different stereoisomeric forms of the product.

- Related to mechanism: terms such as *syn* addition and *anti* addition refer to *stereospecificity.*

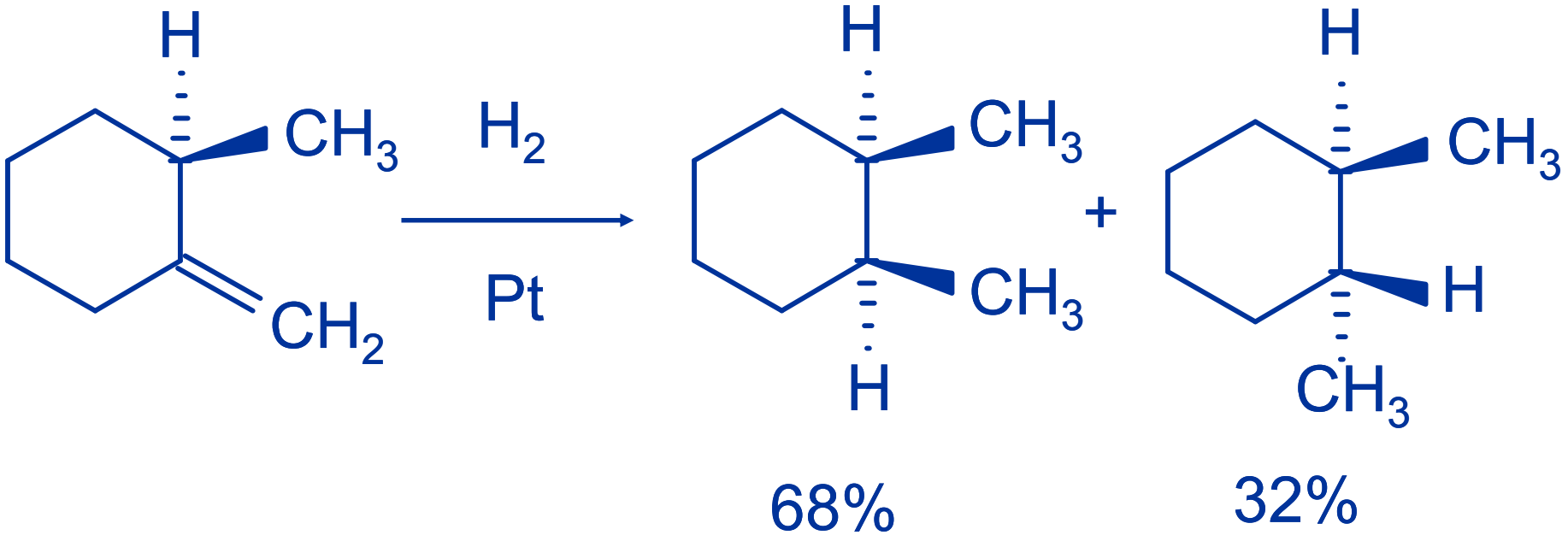
cis-2-butene	bromination	*anti*	2*R*,3*R* + 2*S*,3*S*
trans-2-butene	bromination	*anti*	*meso*

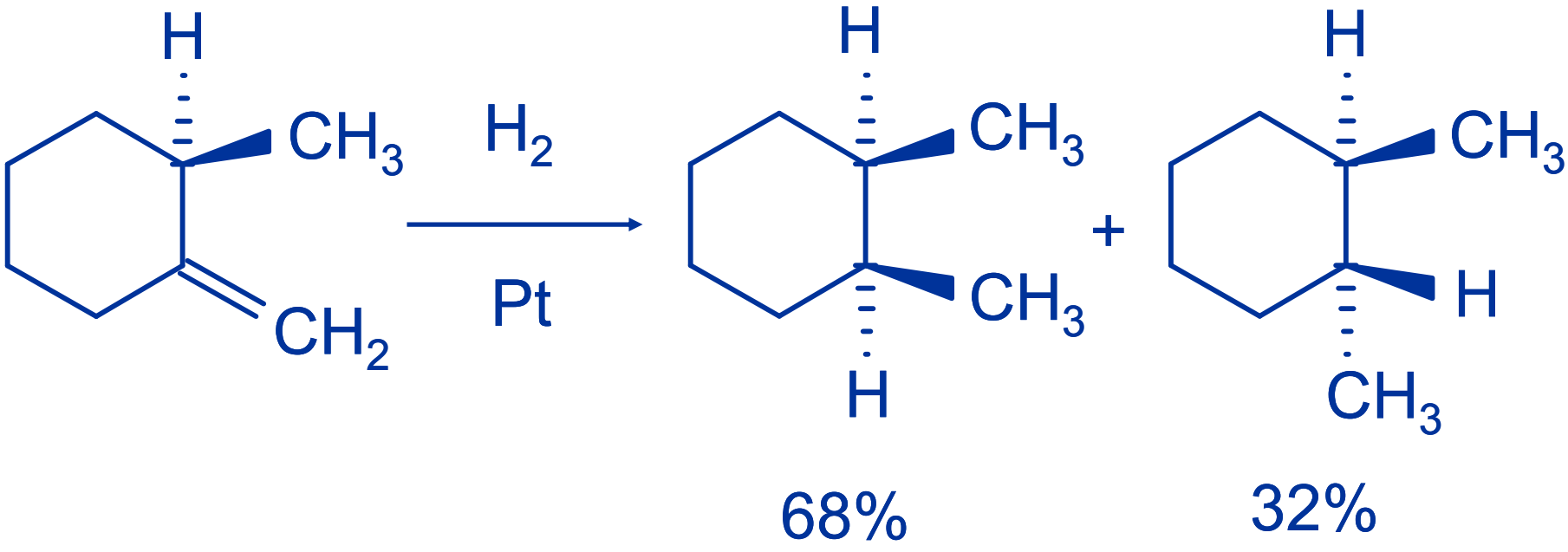
Stereospecific reaction

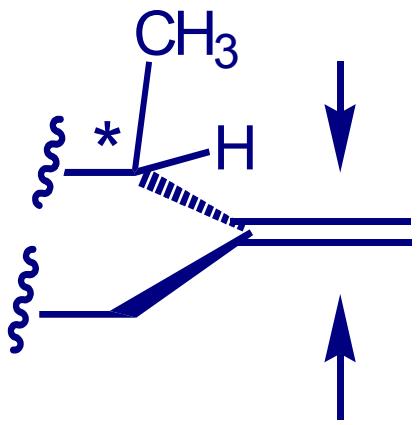
cis-2-butene	epoxidation	*syn*	*meso*
trans-2-butene	epoxidation	*syn*	2*R*,3*R* + 2*S*,3*S*

Stereoselective Reaction

➢ A single starting material can give two or more stereoisomeric products, but gives one of them in greater amounts than any other.







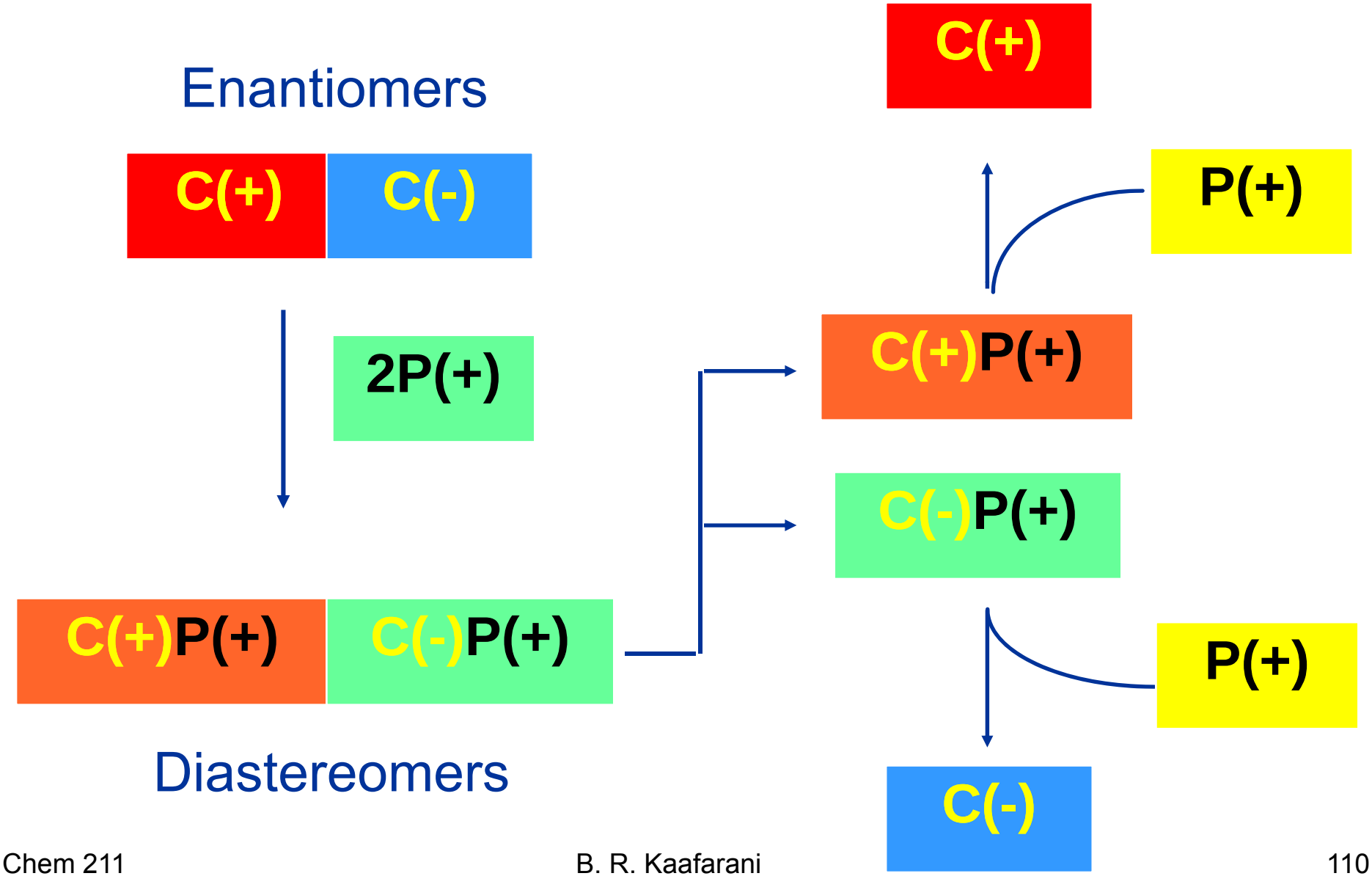
Prochiral faces

Diastereotopic

7.15
Resolution of Enantiomers

- Separation of a racemic mixture into its two enantiomeric forms.

Strategy



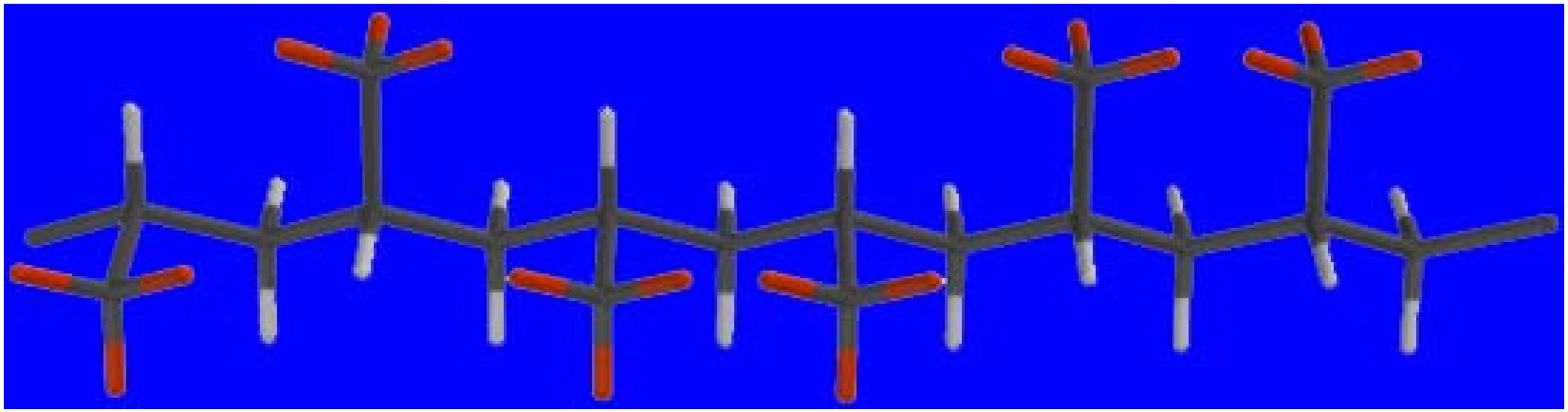
7.16
Stereoregular Polymers

Atactic

Isotactic

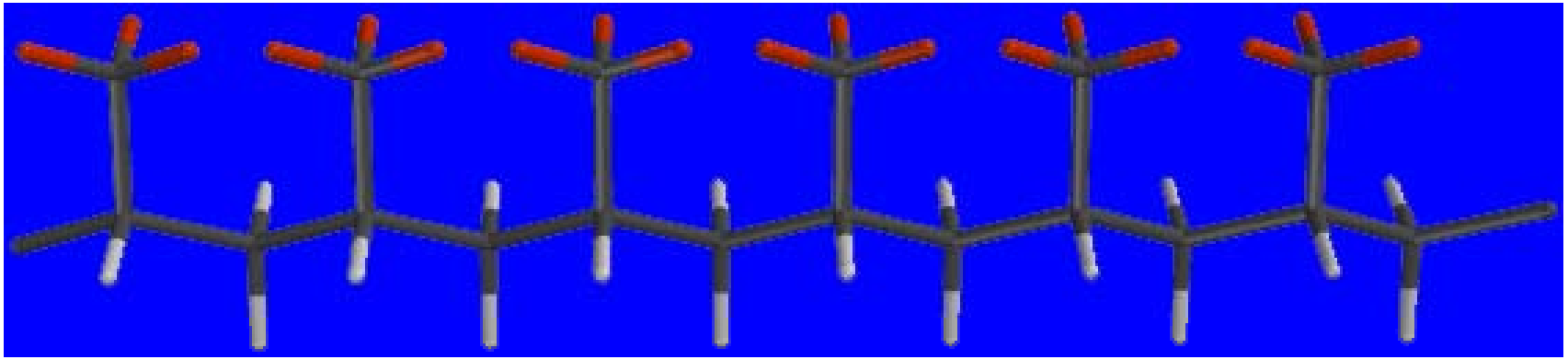
Syndiotactic

Atactic Polypropylene



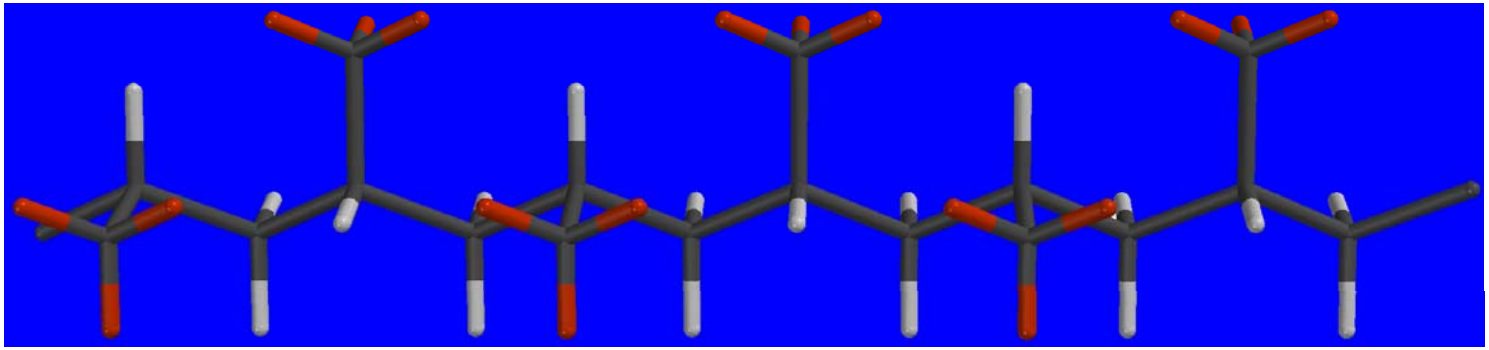
- Random stereochemistry of methyl groups attached to main chain (stereorandom).
- Properties not very useful for fibers etc.
- Formed by free-radical polymerization.

Isotactic Polypropylene



- Stereoregular polymer; all methyl groups on same side of main chain.
- Useful properties.
- Prepared by coordination polymerization under Ziegler-Natta conditions.

Syndiotactic Polypropylene



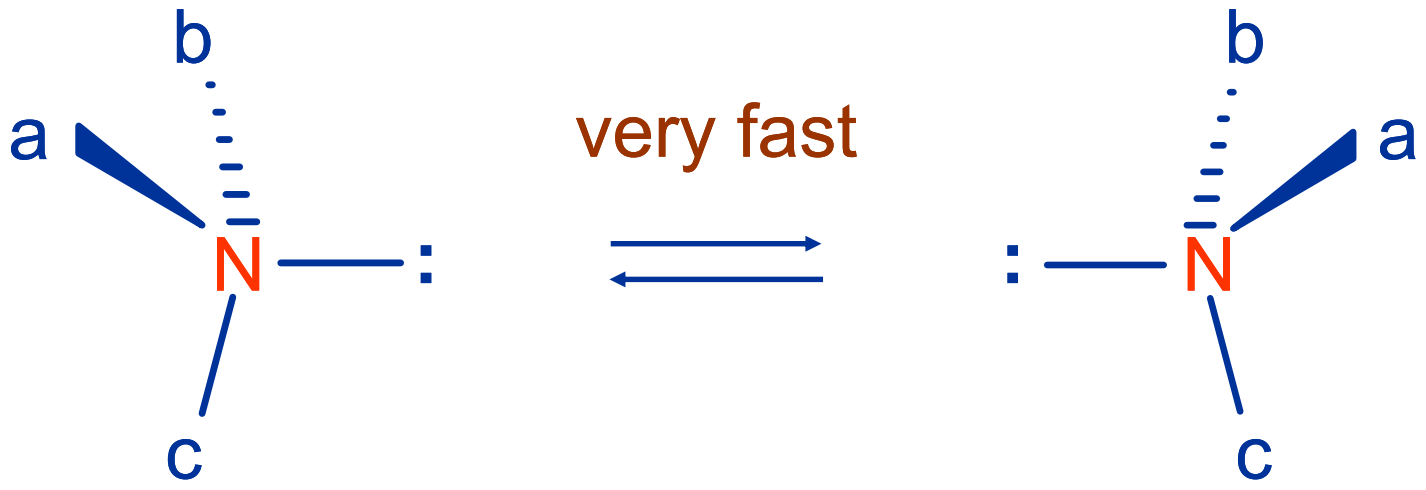
- Stereoregular polymer; methyl groups alternate side-to-side on main chain.
- Useful properties.
- Prepared by coordination polymerization under Ziegler-Natta conditions.

7.17. Stereogenic Centers Other Than Carbon

Silicon

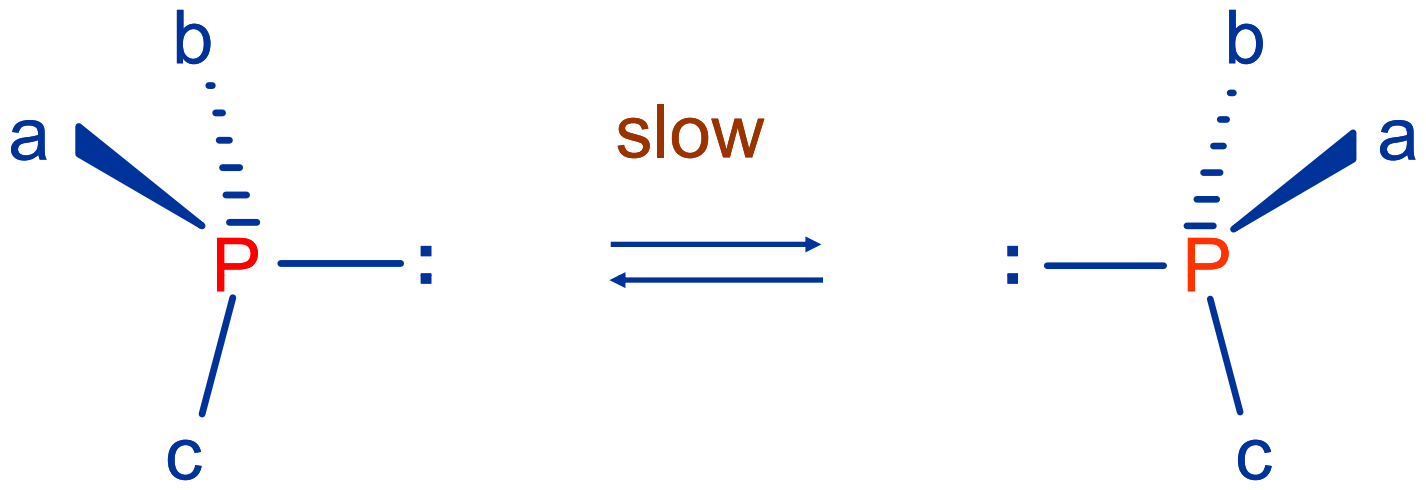
- Silicon, like carbon, forms four bonds in its stable compounds and many chiral silicon compounds have been resolved.

Nitrogen in Amines



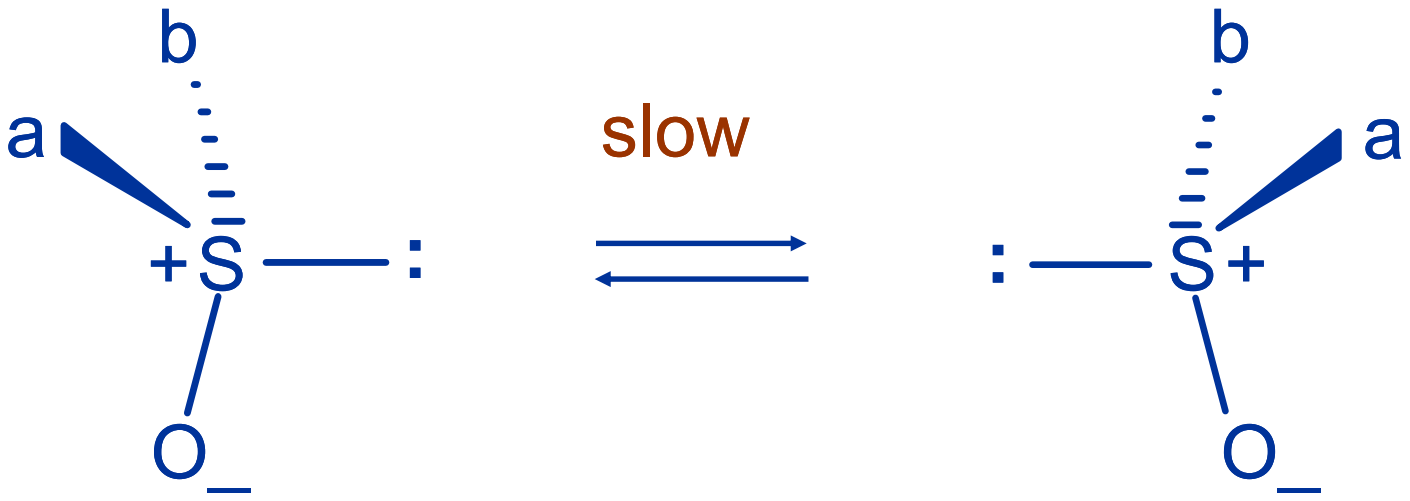
- Pyramidal geometry at nitrogen can produce a chiral structure, but enantiomers equilibrate too rapidly to be resolved.

Phosphorus in phosphines



➢ Pyramidal geometry at phosphorus can produce a chiral structure; pyramidal inversion slower than for amines and compounds of the type shown have been resolved.

Sulfur in Sulfoxides



➢ Pyramidal geometry at sulfur can produce a chiral structure; pyramidal inversion is slow and compounds of the type shown have been resolved.

Assigned Problems

7.26-7.35, 7.40-7.42