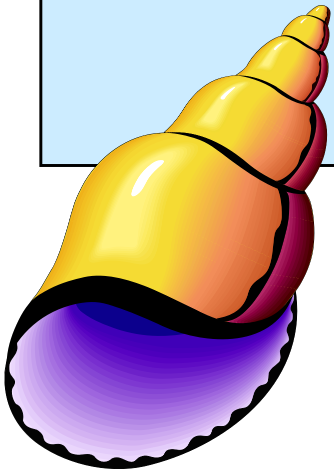
CHIRALITY, SYMMETRY PLANES AND ENANTIOMERS



Craig Wheelock

October 17th, 2008

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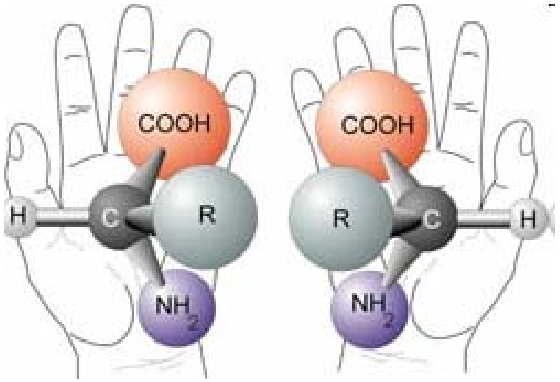
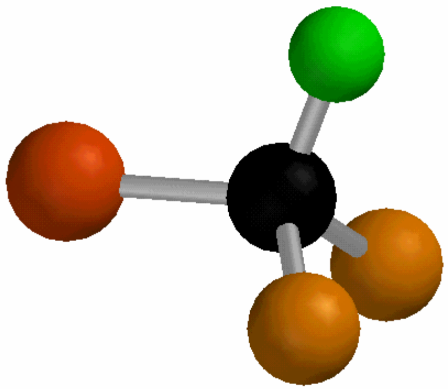
http://www.metabolomics.se/

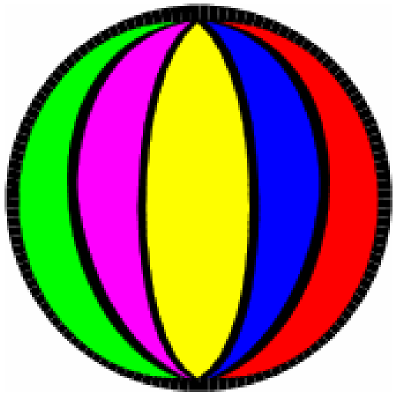
(copies of slides can be downloaded from my homepage)



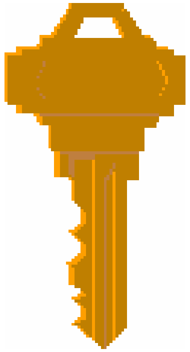


WHICH OBJECTS ARE SYMMETRIC ?

(mirror image is identical)

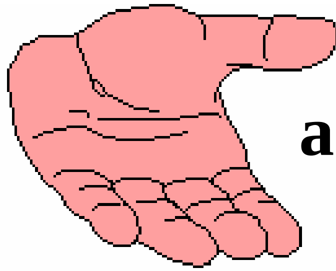


sym

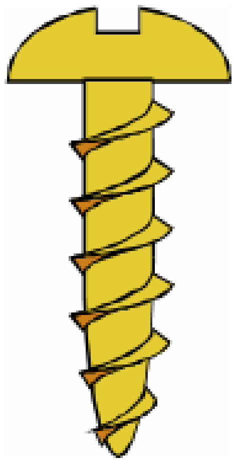


asym

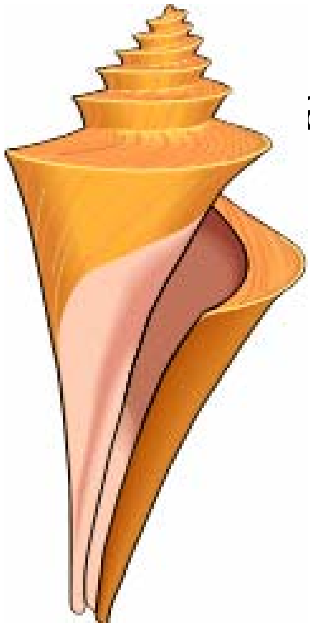
sym (outside)



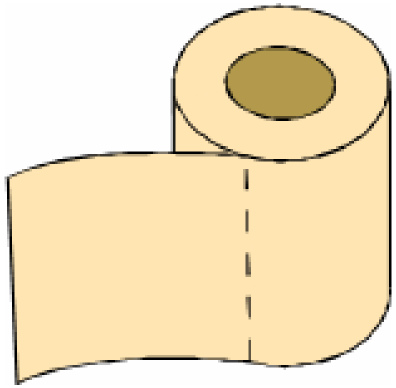
asym



asym



asym

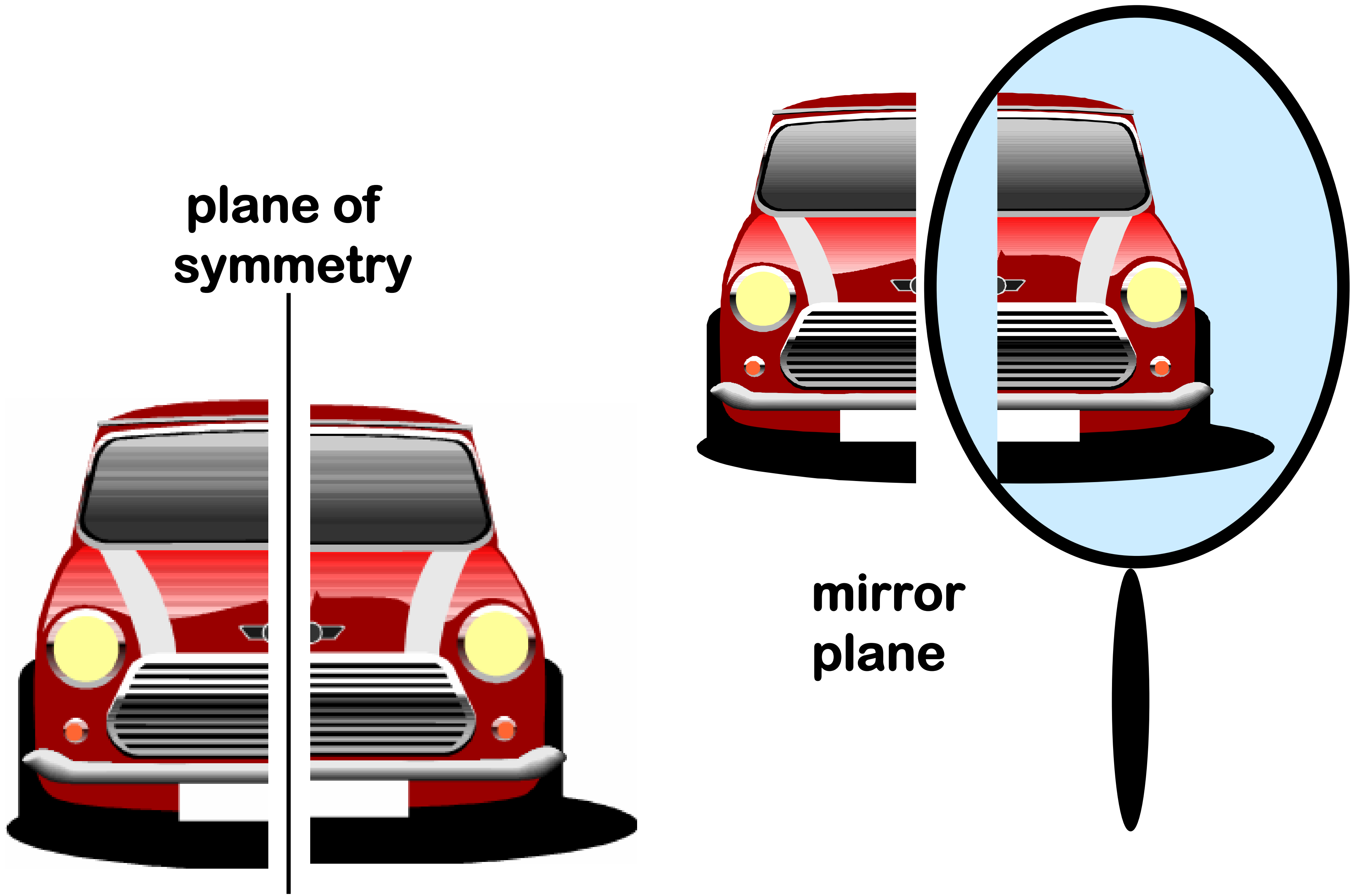


sym

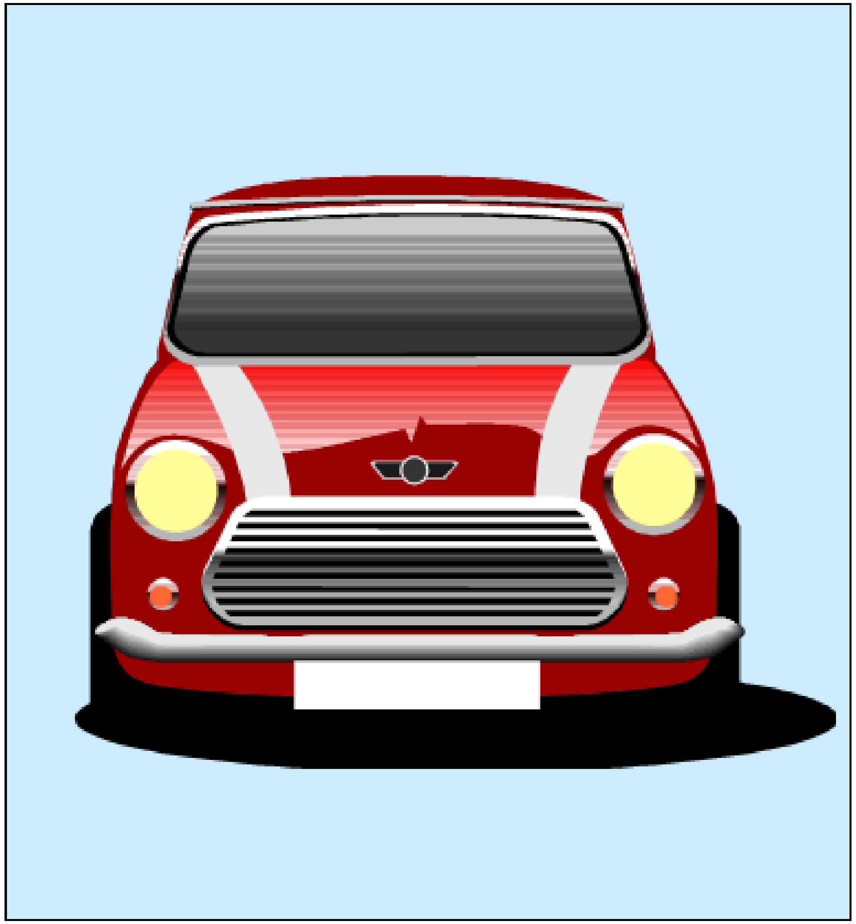
sym

PLANES OF SYMMETRY

A SYMMETRIC OBJECT HAS A PLANE OF SYMMETRY
- ALSO CALLED A MIRROR PLANE



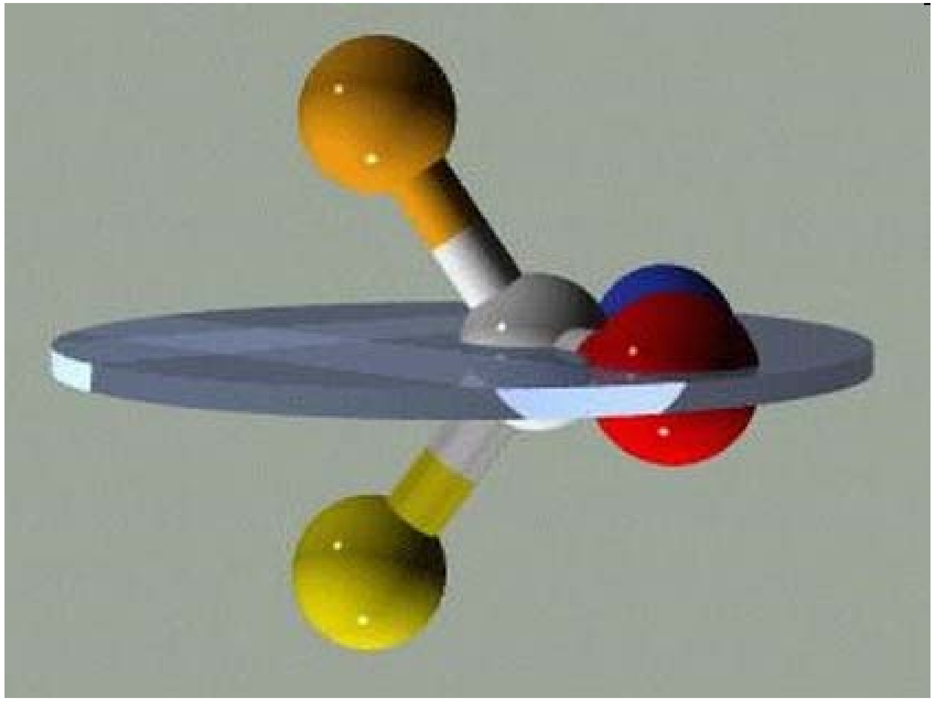
IF AN OBJECT HAS A PLANE OF SYMMETRY, ITS MIRROR IMAGE WILL BE IDENTICAL



IDENTICAL MIRROR IMAGES WILL SUPERIMPOSE

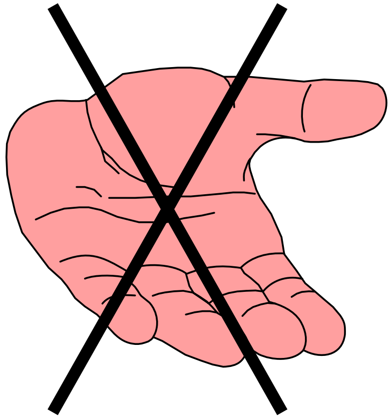
(MATCH EXACTLY WHEN PLACED ON TOP OF EACH OTHER)

CHIRALITY

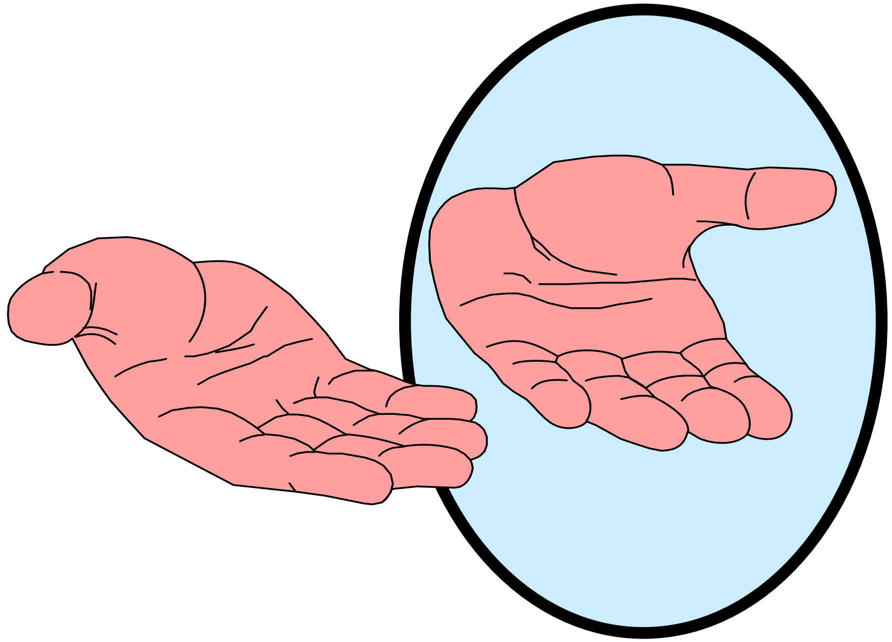


An object without symmetry is **CHIRAL**

no symmetry



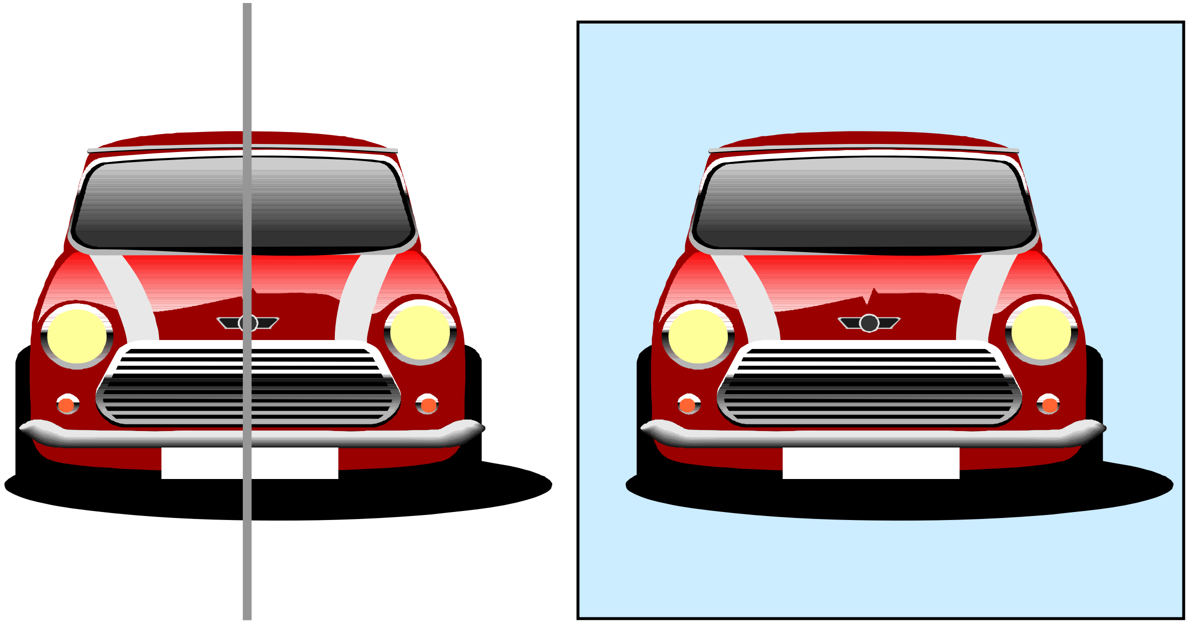
The mirror image of a chiral object is different and will not superimpose on the original object.



OBJECTS WHICH ARE CHIRAL HAVE A SENSE OF “HANDEDNESS” AND EXIST IN TWO FORMS

An object with symmetry is ACHIRAL (not chiral)

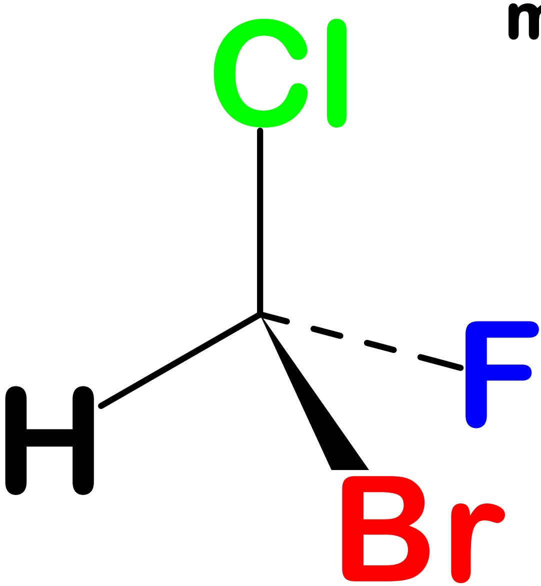
The mirror image of an achiral object is identical and will superimpose on the original object.

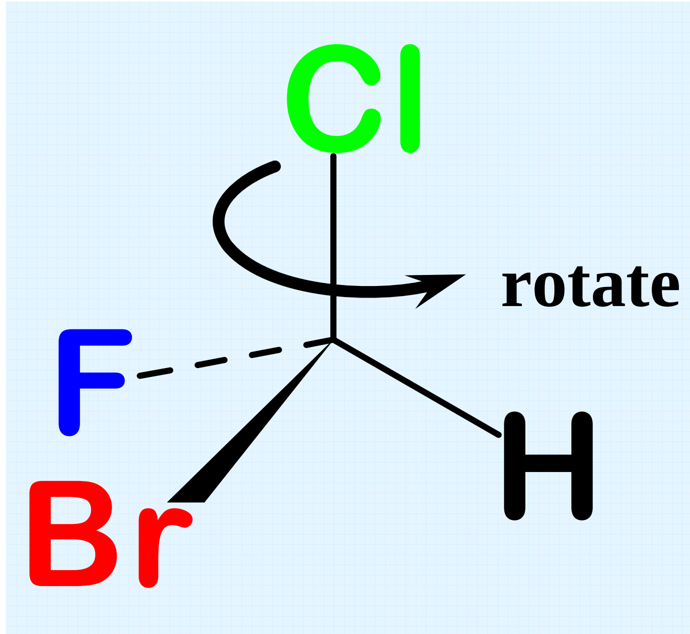


plane of symmetry

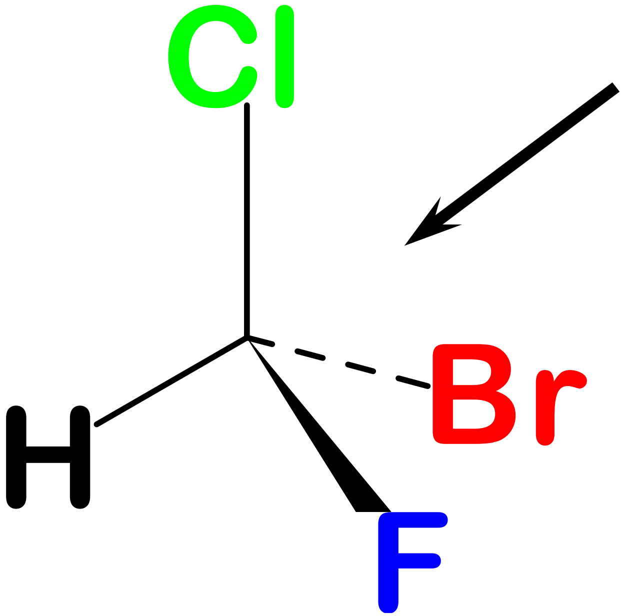
ENANTIOMERS

non-superimposable
mirror images

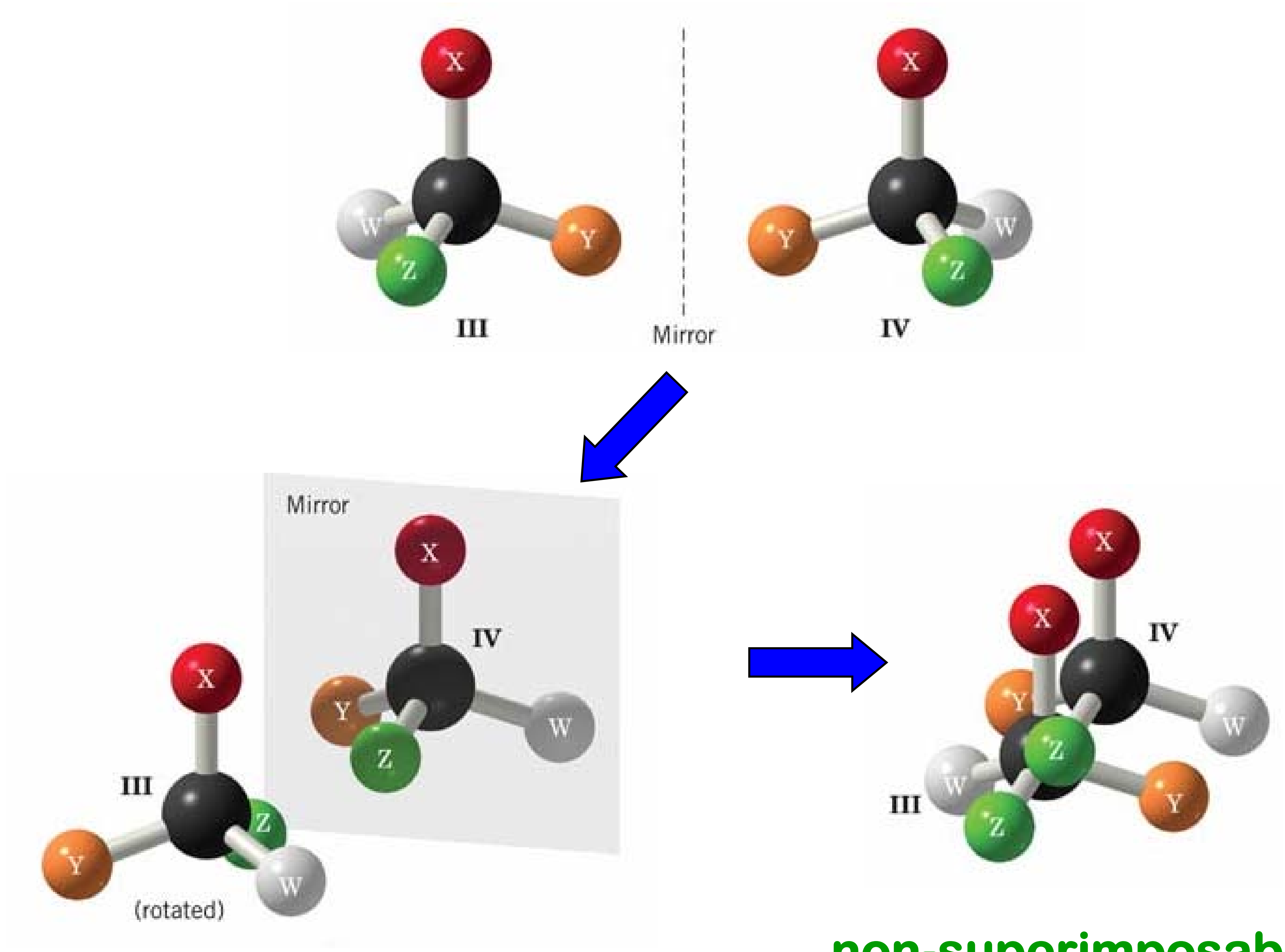




this molecule
is chiral



note that the fluorine
and bromine have been
interchanged in the
enantiomer

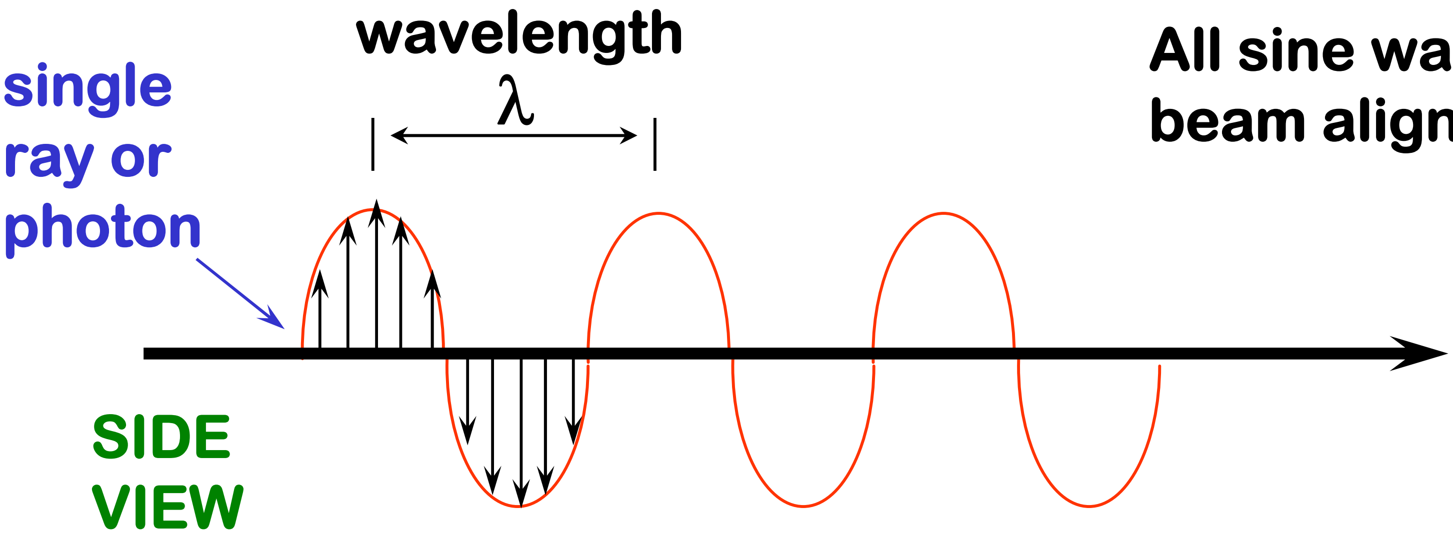


non-superimposable

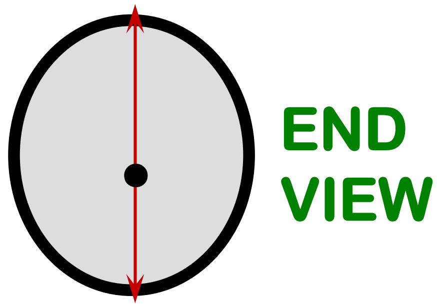
OPTICAL ACTIVITY

PLANE-POLARIZED LIGHT

PLANE-POLARIZED LIGHT BEAM



All sine waves (rays) in the beam aligned in same plane.



polarized beam

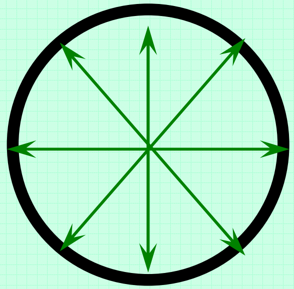
A beam is a collection of these rays.

frequency (ν)

$$\nu = \frac{c}{\lambda}$$

c = speed of light

NOT PLANE-POLARIZED



Sine waves are not aligned in the same plane.

unpolarized beam

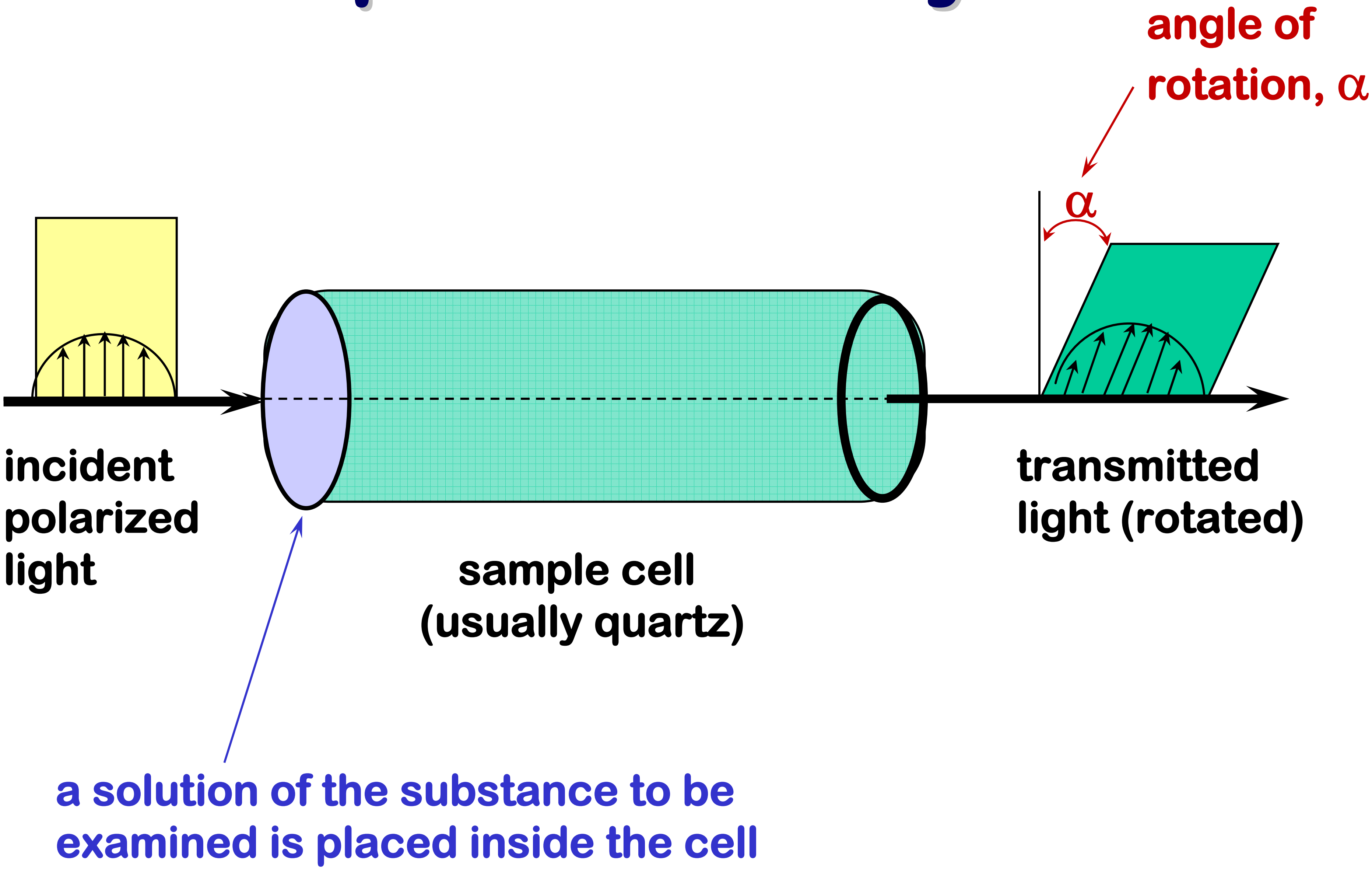
Optically Active

- **Refers to molecules that interact with plane-polarized light**

Jean Baptiste Biot
French Physicist - 1815

He discovered that some natural substances (glucose, nicotine, sucrose) rotate the plane of plane-polarized light and that others did not.

Optical Activity



TYPES OF OPTICAL ACTIVITY

Dextrorotatory

new	older
(+)-	d-

Rotates the plane of plane-polarized light to the right.

Levorotatory

new	older
(-)-	l-

Rotates the plane of plane-polarized light to the left.

Specific Rotation $[\alpha]_D$

$$[\alpha]_D^t = \frac{\alpha}{cl}$$

This equation corrects for differences in cell length and concentration.

Specific rotation calculated in this way is a <u>physical property</u> of an optically active substance.

You always get the same value of $[\alpha]_D^t$

α = observed rotation

c = concentration (g/mL)

l = length of cell (dm)

D = yellow light from sodium lamp

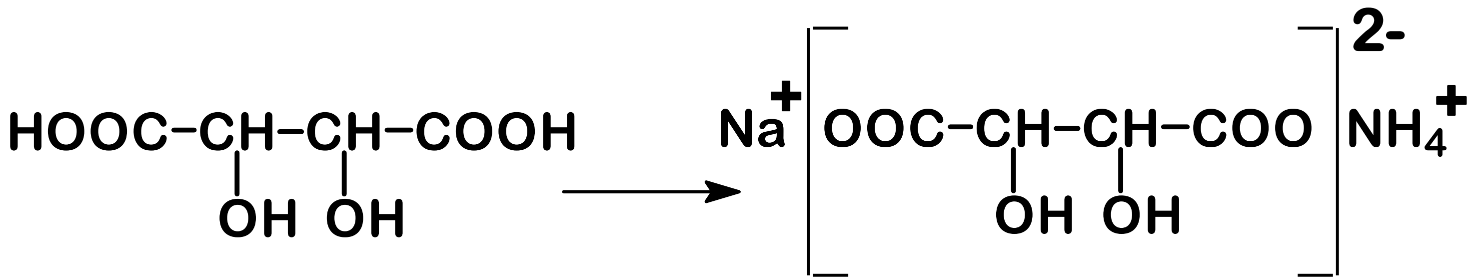
t = temperature (Celsius)

SPECIFIC ROTATIONS OF BIOACTIVE COMPOUNDS

COMPOUND	$[\alpha]_D$
cholesterol	-31.5
cocaine	-16
morphine	-132
codeine	-136
heroin	-107
epinephrine	-5.0
progesterone	+172
testosterone	+109
sucrose	+66.5
β-D-glucose	+18.7
α-D-glucose	+112
oxacillin	+201

PASTEUR'S DISCOVERY

Louis Pasteur 1848
Sorbonne, Paris



tartaric acid
(found in wine must)

sodium ammonium tartrate

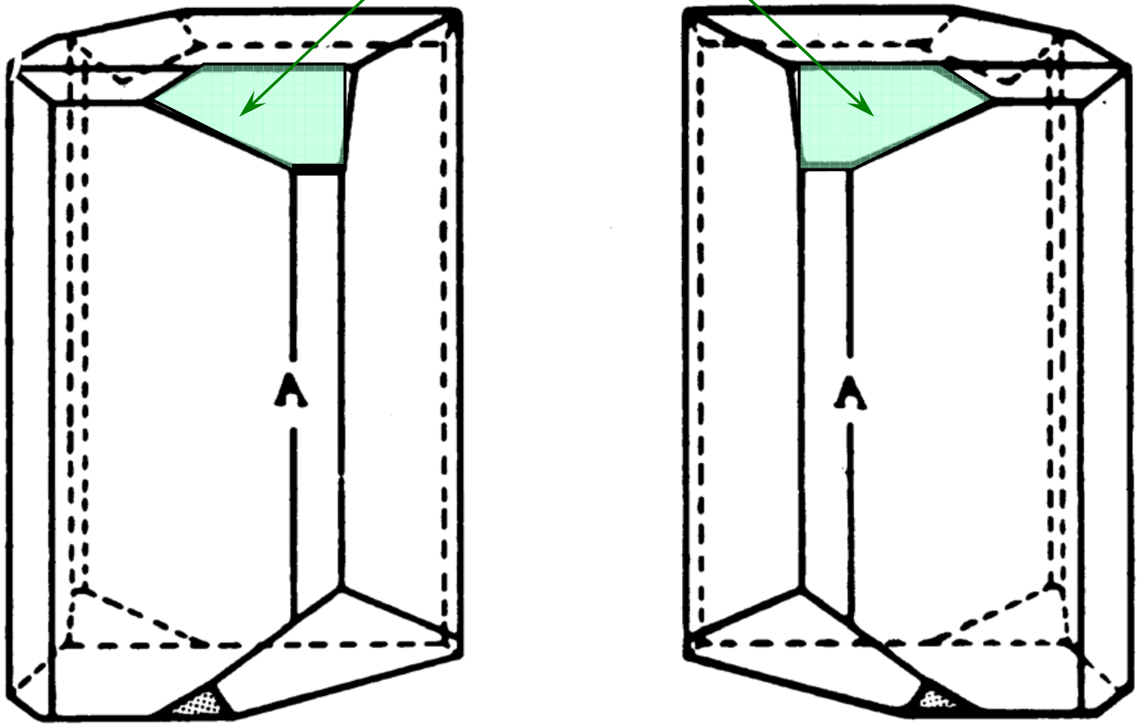
Pasteur crystallized this substance on a cold day

Crystals of Sodium Ammonium Tartrate

Pasteur found two different crystals.

hemihedral faces

mirror images



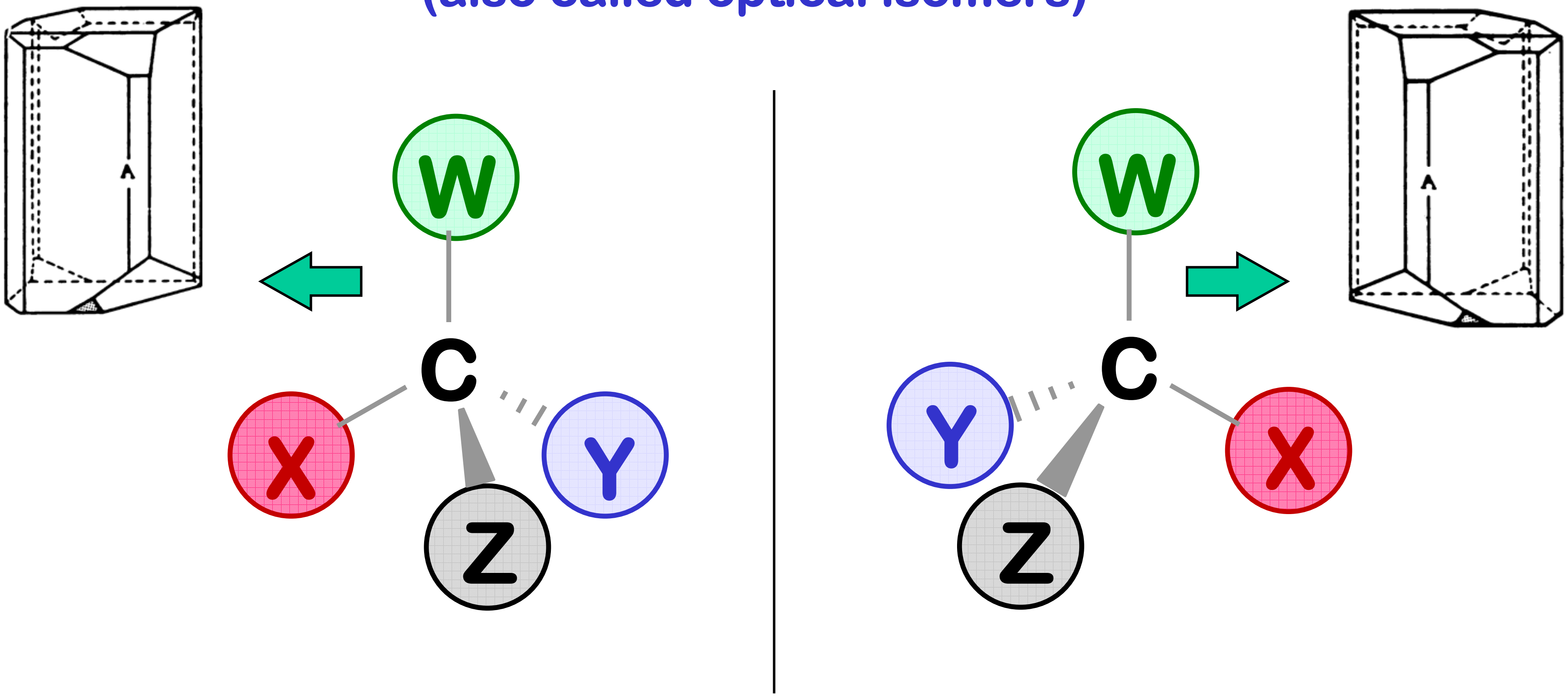
Biot's results : (+) (-)

Louis Pasteur separated these and gave them to Biot to measure.

Enantiomers

non-superimposable mirror images

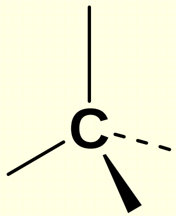
(also called optical isomers)



Pasteur decided that the molecules that made the crystals, just as the crystals themselves, must be mirror images. Each crystal must contain a single type of enantiomer.

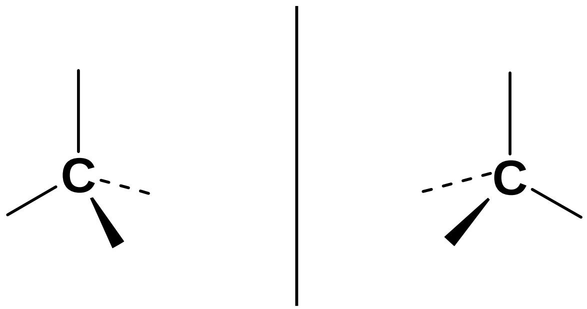
Pasteur's hypothesis eventually led to the discovery that tetravalent carbon atoms are tetrahedral.

Van't Hoff and LeBel (1874)

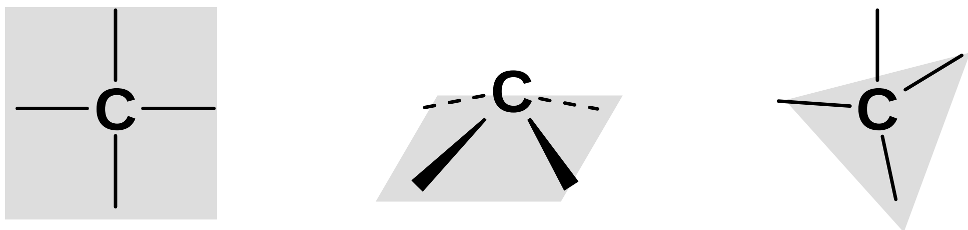


tetrahedral carbon

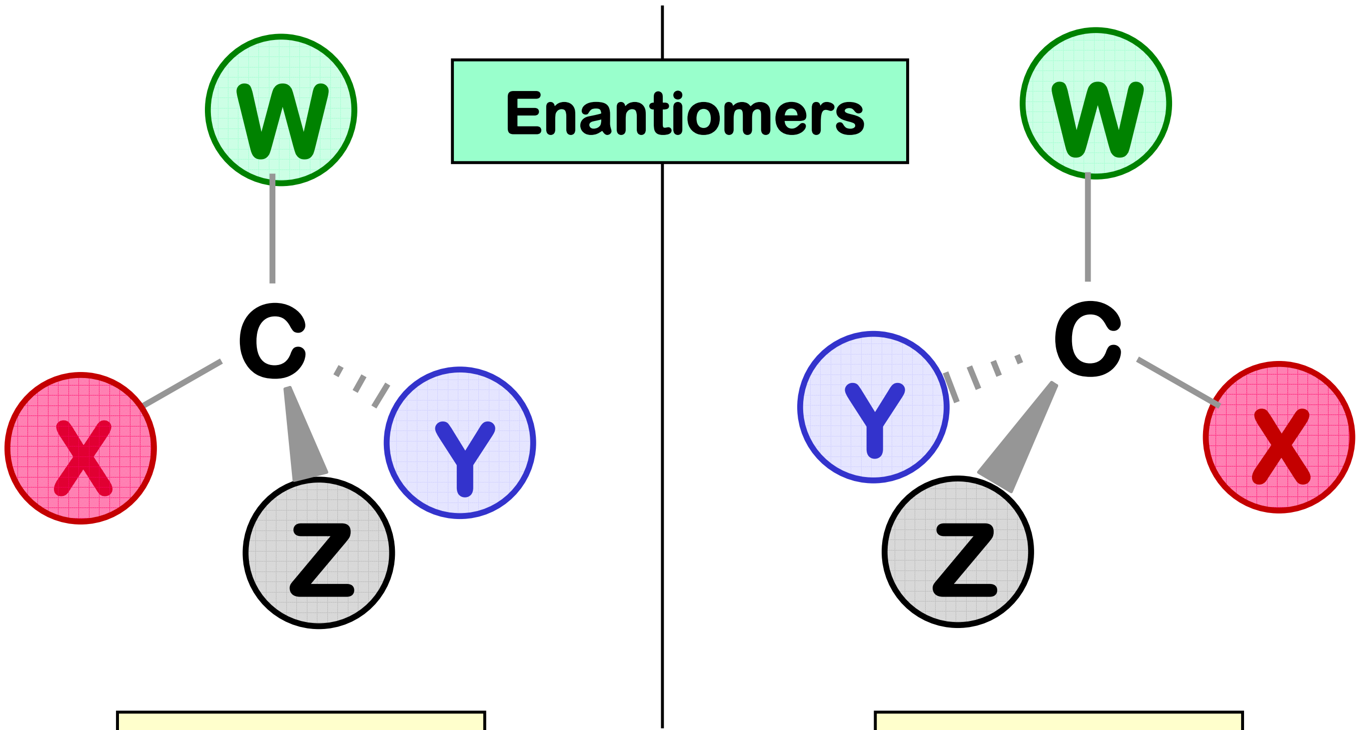
Only tetrahedral geometry can lead to mirror image molecules:



Square planar, square pyrimidal or trigonal pyramid will not work:



ENANTIOMERS HAVE EQUAL AND OPPOSITE ROTATIONS



(+)-nn°

dextrorotatory

(-)-nn°

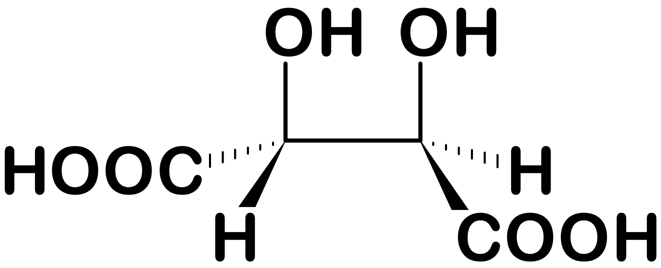
levorotatory

ALL OTHER PHYSICAL PROPERTIES ARE THE SAME

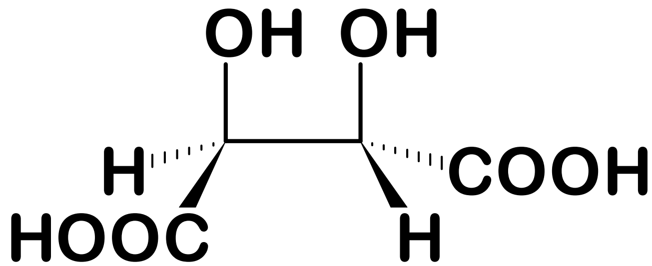
TARTARIC ACID

from fermentation of wine

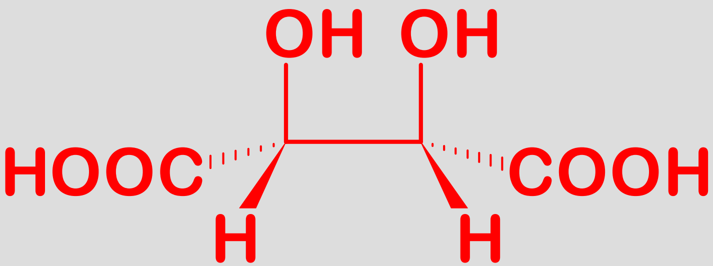
Enantiomers



(+)-tartaric acid



(-)-tartaric acid



***meso*-tartaric acid**

ALSO FOUND

(as a minor component)

$[\alpha]_D = 0$

more about this compound later

TARTARIC ACID

(-) - tartaric acid

$[\alpha]_D$ = -12.0°

mp 168 - 170°
solubility of 1 g
- 0.75 mL H_2O
- 1.7 mL methanol
- 250 mL ether

insoluble $CHCl_3$
d = 1.758 g/mL

(+) - tartaric acid

$[\alpha]_D$ = +12.0°

mp 168 - 170°
solubility of 1 g
- 0.75 mL H_2O
- 1.7 mL methanol
- 250 mL ether

insoluble $CHCl_3$
d = 1.758 g/mL

meso - tartaric acid

$[\alpha]_D$ = 0°

mp 140°
d = 1.666 g/mL

solubility of 1 g
- 0.94 mL H_2O

insoluble $CHCl_3$

RACEMIC MIXTURE

an equimolar (50/50) mixture of enantiomers

$$[\alpha]_D = 0^o$$

the effect of each molecule is cancelled out by its enantiomer

STEREOISOMERS

ENANTIOMERS are a type of STEREOISOMER

Stereoisomers are the same constitutional isomer, but differ in the way they are arranged in 3-D space at one or more of their atoms.

STEREOCENTERS

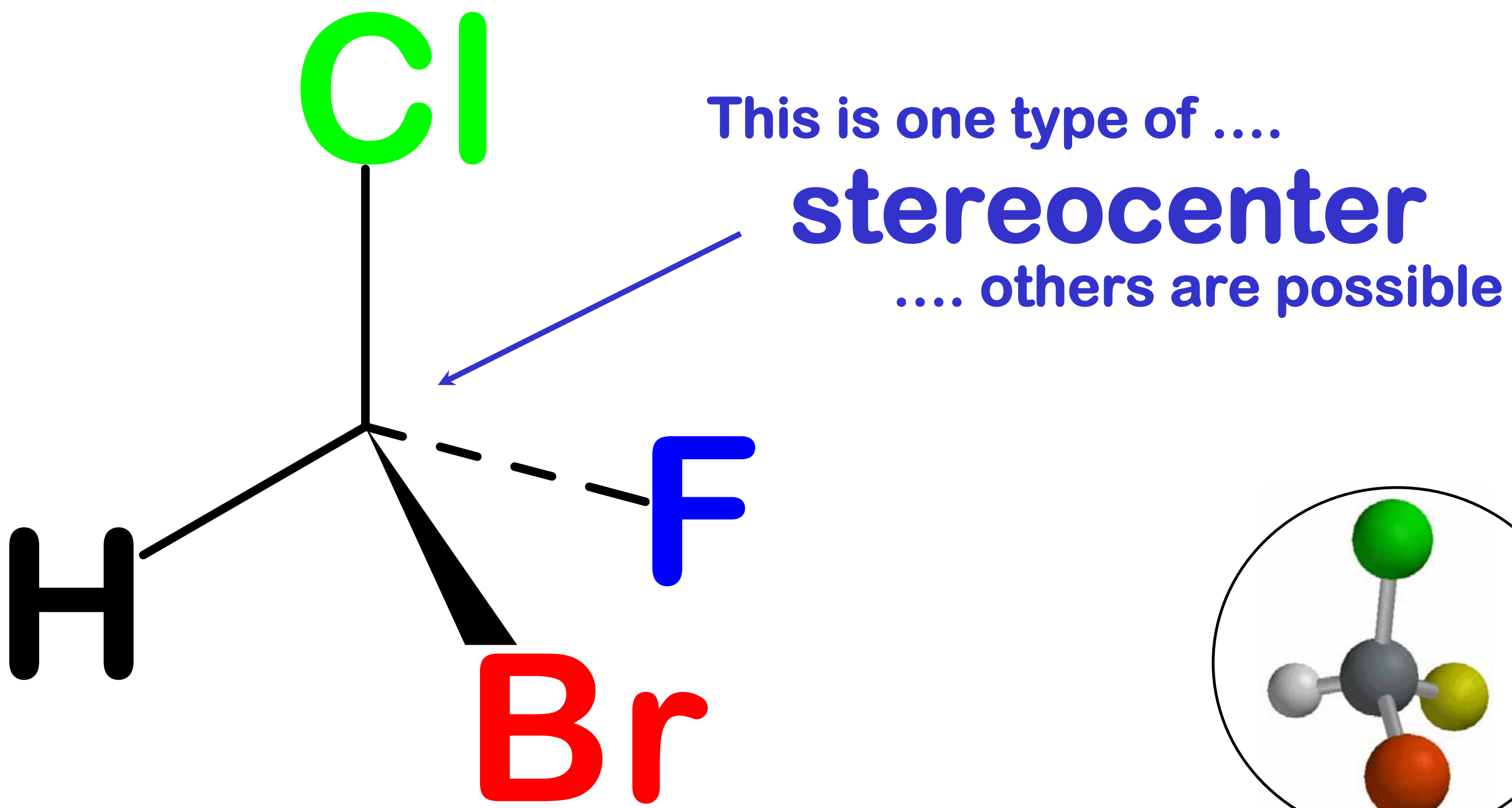
One of the ways a molecule can be chiral is to have a stereocenter

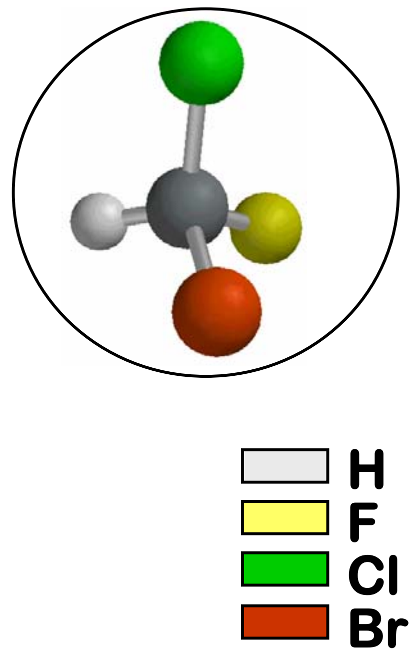
A stereocenter is an atom, or a group of atoms, that can potentially cause a molecule to be chiral

stereocenters - can give rise to chirality

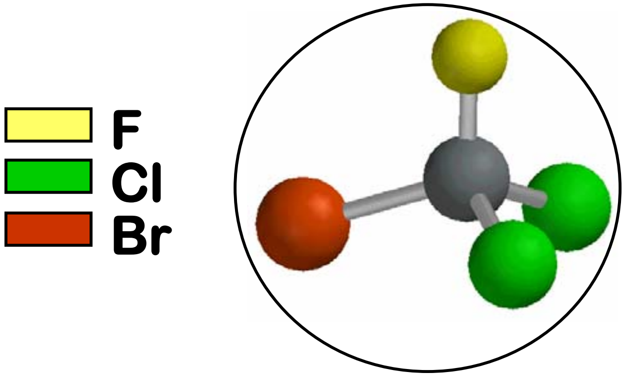
STEREOGENIC CARBONS

(called "chiral carbons" in older literature)



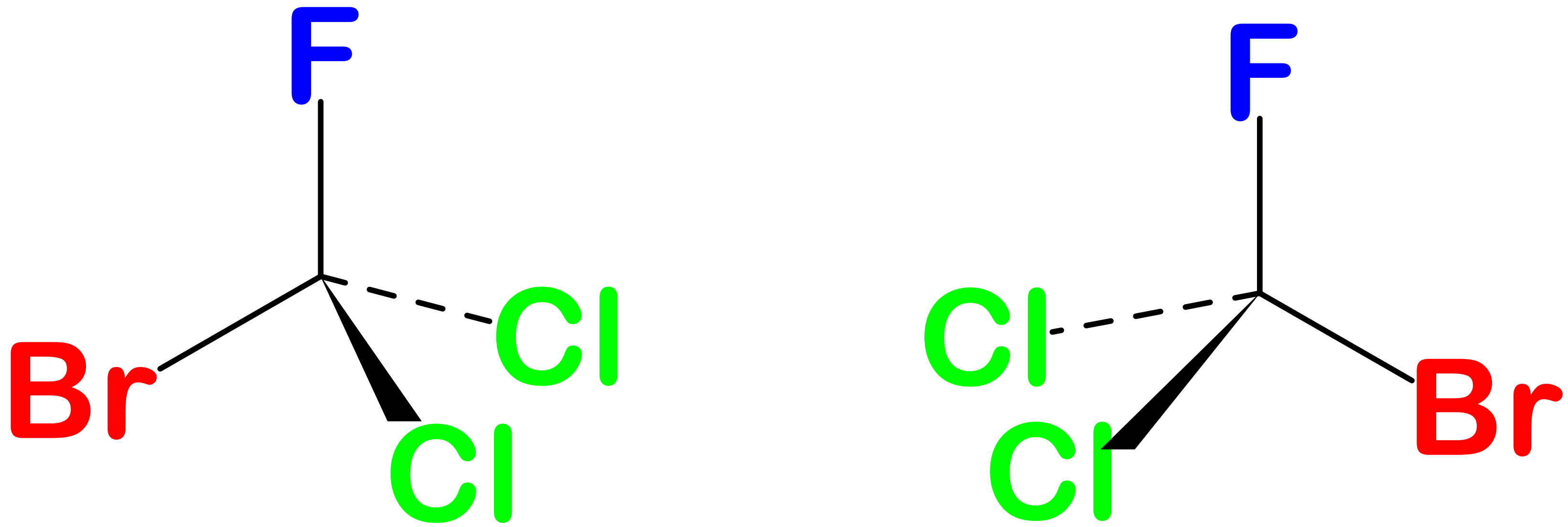


A **stereogenic carbon** is tetrahedral and has four different groups attached.



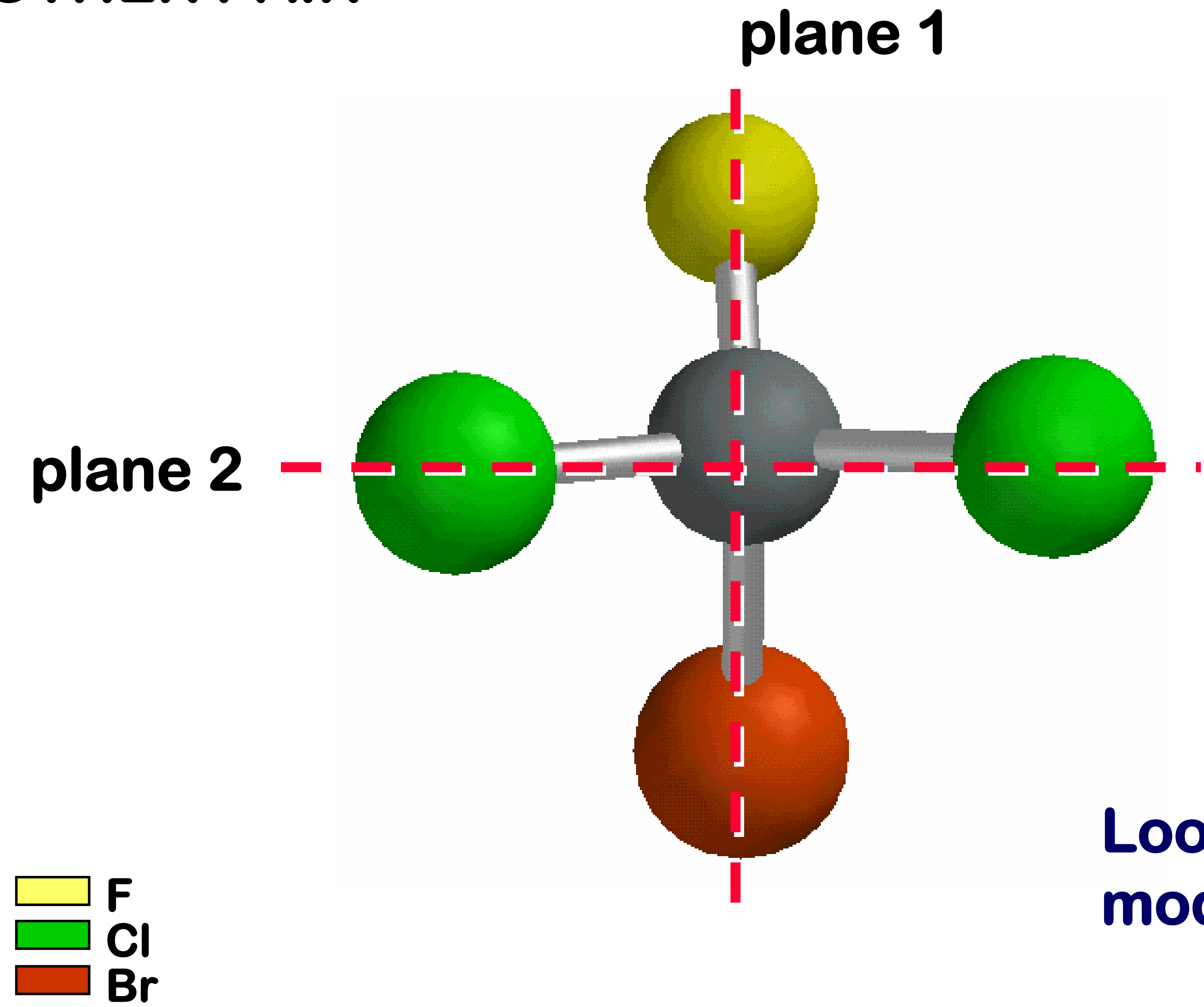
ACHIRAL

The plane of the paper is a plane of symmetry



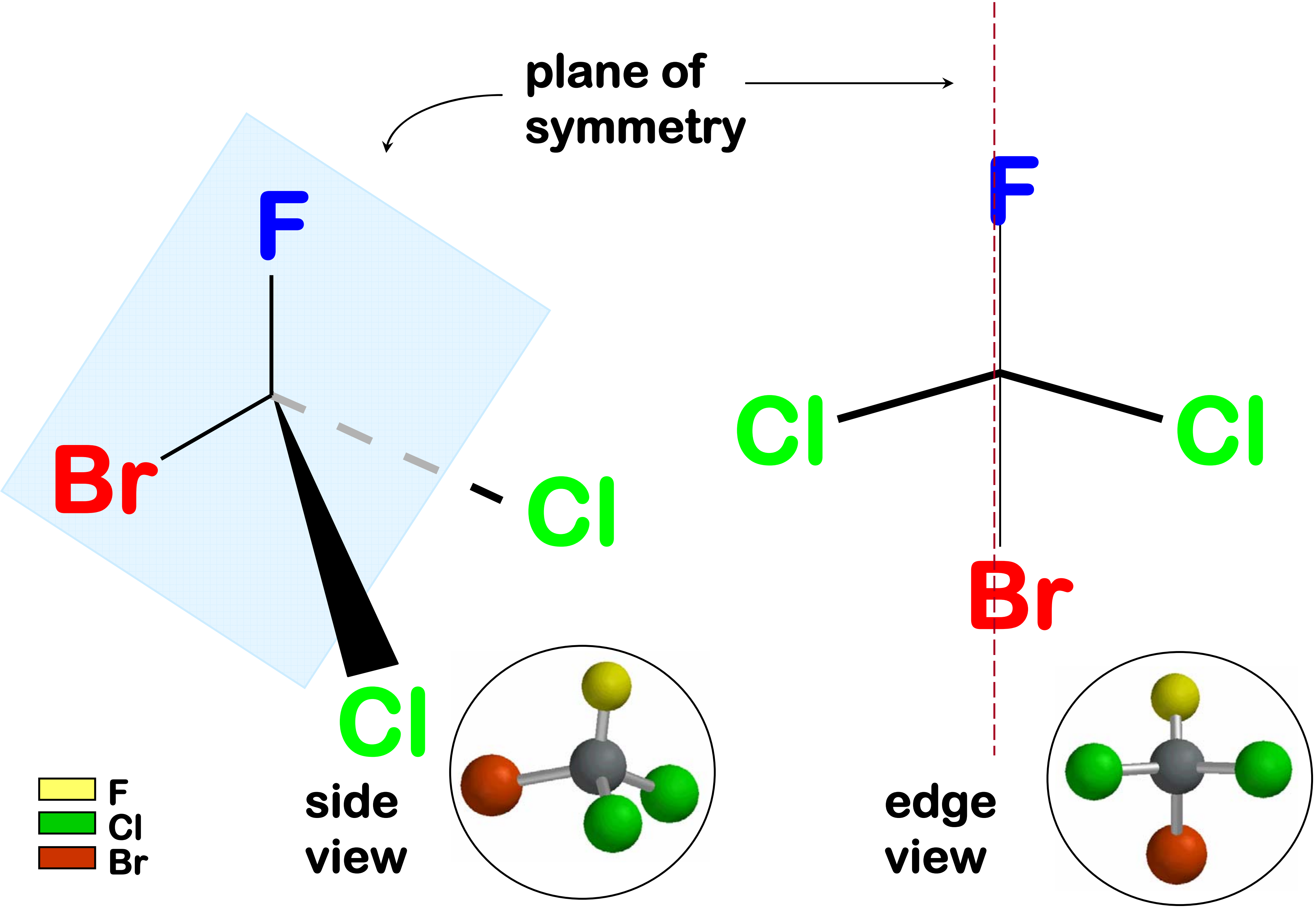
TWO IDENTICAL GROUPS RENDERS A TETRAHEDRAL CARBON ACHIRAL

ONE PAIR OF ATOMS ATTACHED TO A TETRAHEDRAL CARBON IS IN A PLANE PERPENDICULAR TO THE OTHER PAIR



Look at your model set !!!!

TWO VIEWS OF THE PLANE OF SYMMETRY



CONFIGURATION

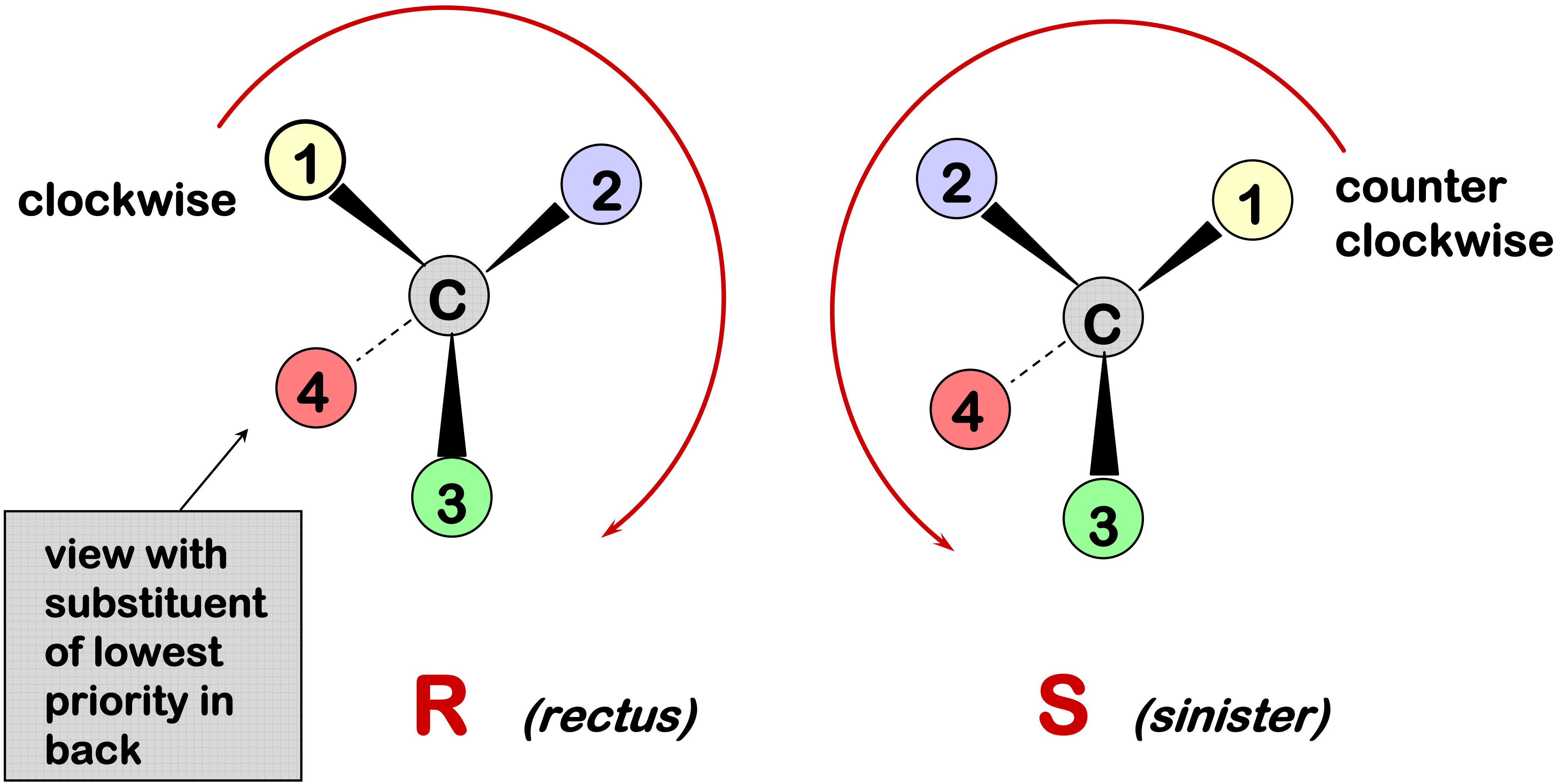
ABSOLUTE CONFIGURATION (R / S)

CONFIGURATION

The three dimensional arrangement of the groups attached to an atom

Stereoisomers differ in the configuration at one or more of their atoms.

CONFIGURATION - relates to the three dimensional sense of attachment for groups attached to a chiral atom or group of atoms (i.e., attached to a stereocenter).



SPECIFICATION OF CONFIGURATION

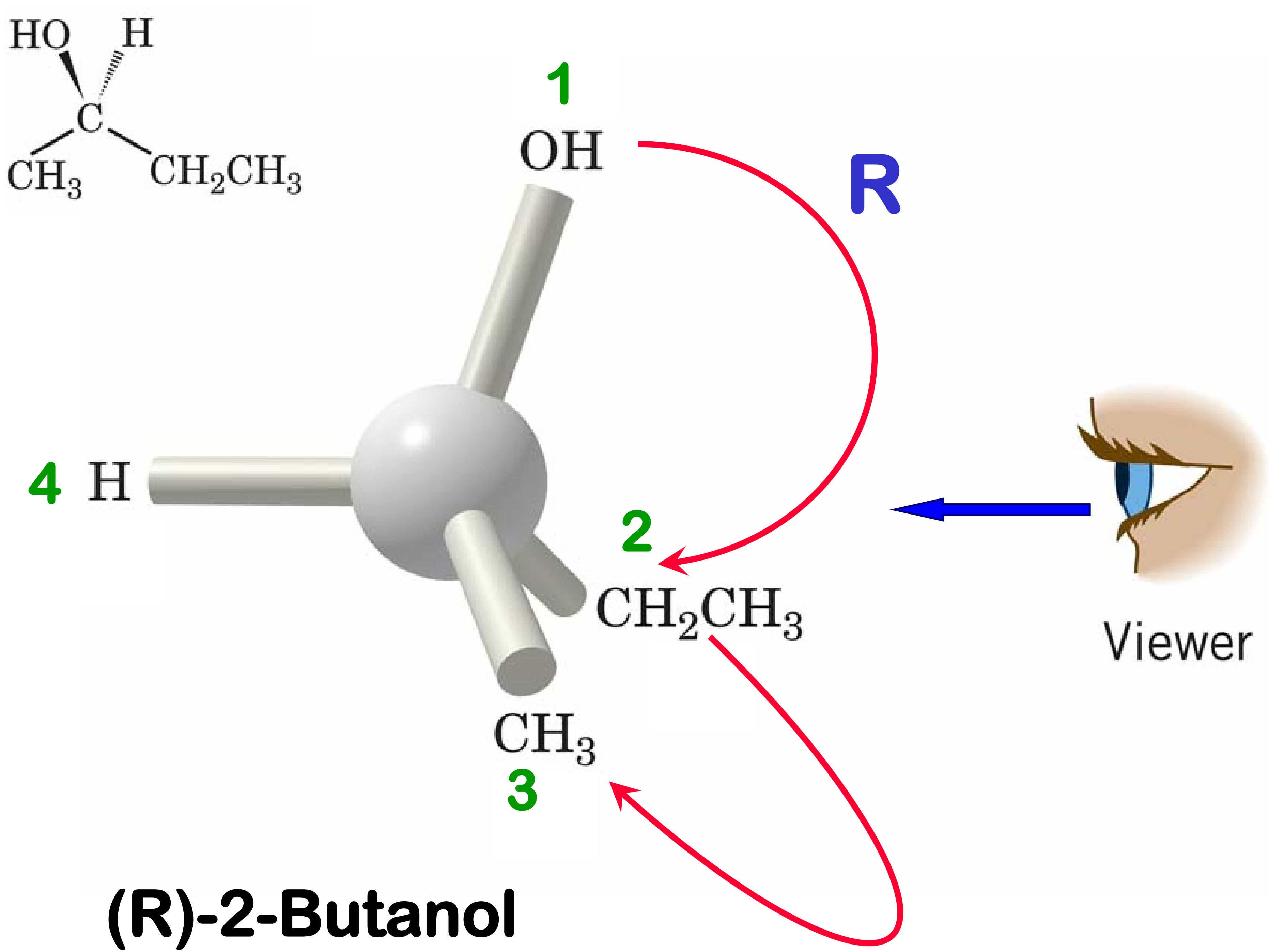
Enantiomers are assigned a **CONFIGURATION** using the same priority rules we developed for *E* / *Z* stereoisomers.

1. Higher atomic number has higher priority.

2. If priority cannot be decided based on the first atom attached move to the next atom, following the path having the highest prioity atom.

3. Expand multiple bonds by replicating the atoms attached to each end of the bond.

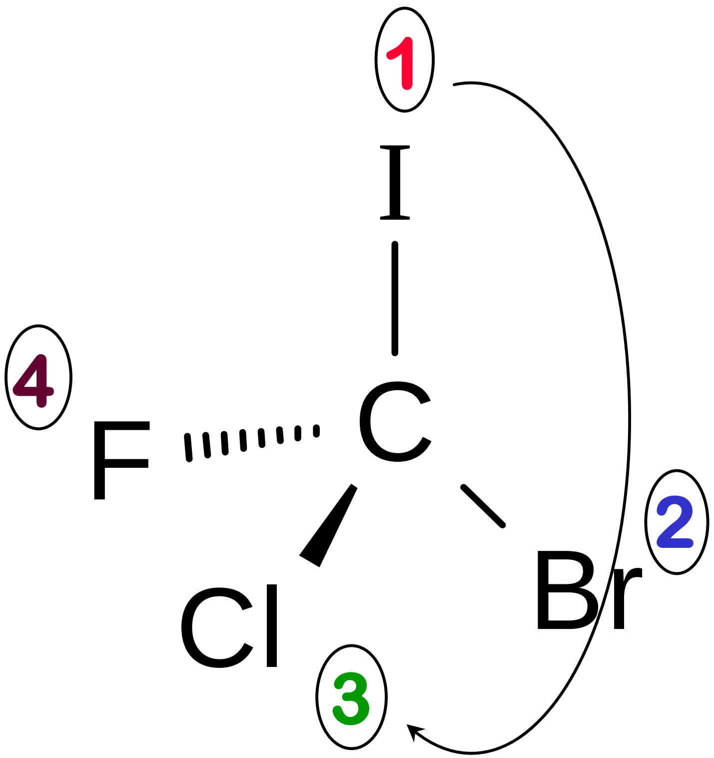
CAHN-INGOLD-PRELOG
SEQUENCE RULES



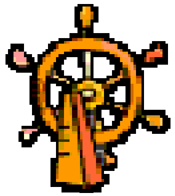
(R)-2-Butanol

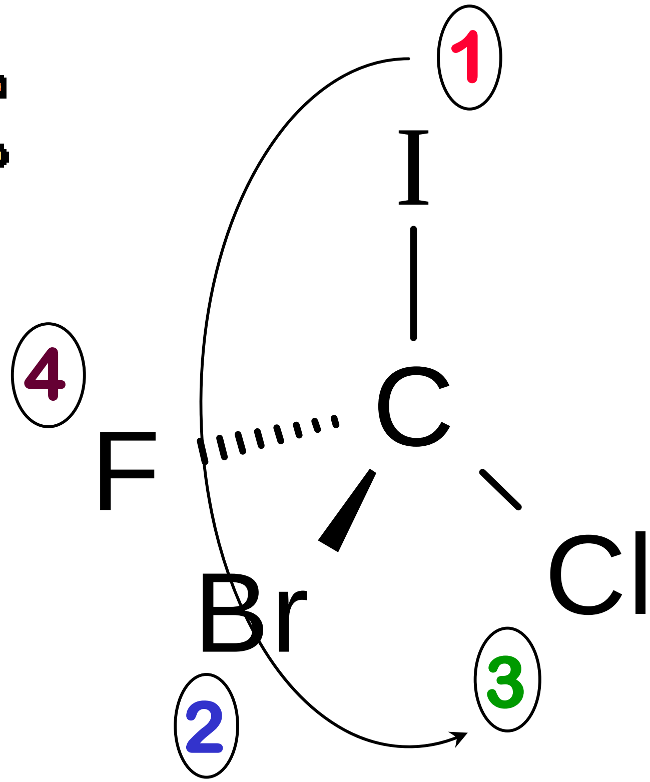
Bromochlorofluoroiodomethane

atomic number →	1	9	17	35	53
	H	F	Cl	Br	I



R





S

Enantiomers

NUMBER OF STEREOISOMERS POSSIBLE

How Many Stereoisomers Are Possible?

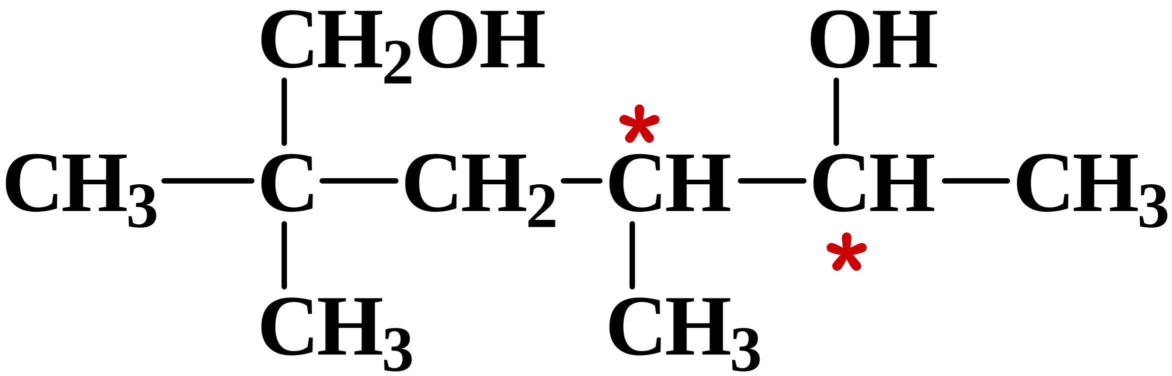
maximum number of stereoisomers

sometimes fewer than this number will exist

$= 2^n$,

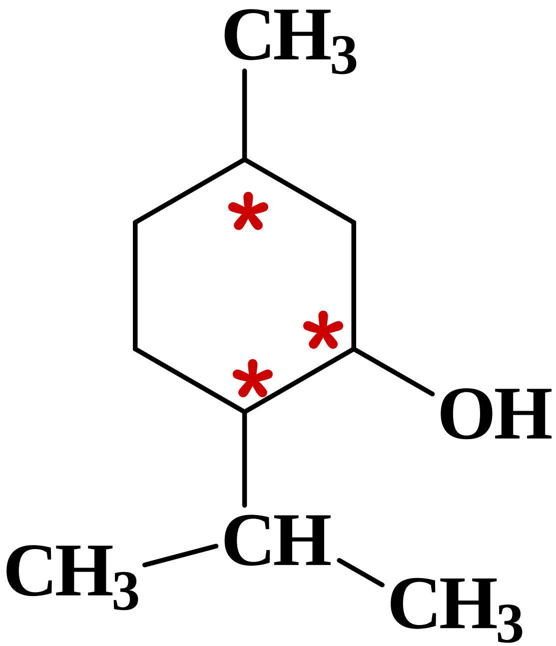
where n = number of stereocenters

(sterogenic carbons)



R R
R S
S R
S S

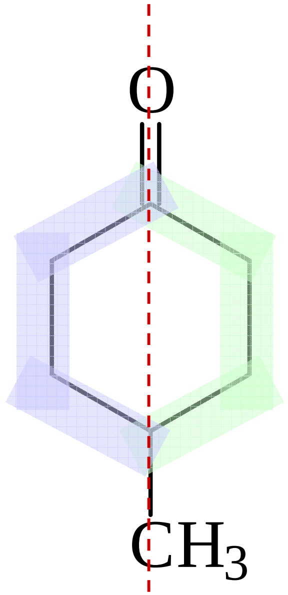
$2^2 = 4$ **stereoisomers**

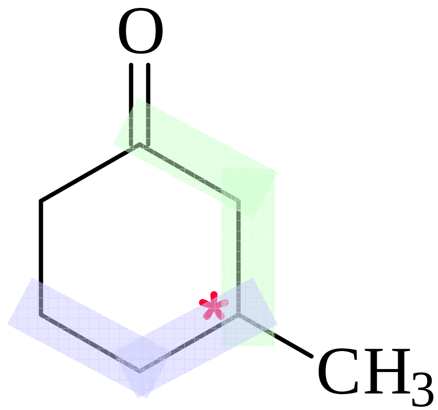


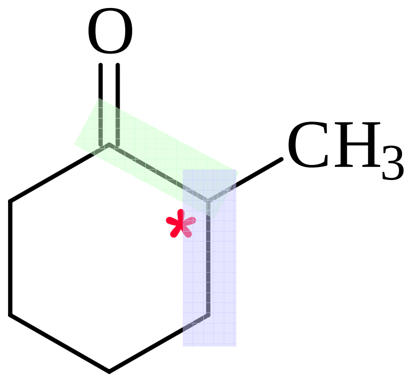
R R R	R S S
R R S	S R S
R S R	S S R
S R R	S S S

$2^3 = 8$ **stereoisomers**

FINDING STEREOCENTERS
(STEREOGENIC CARBONS)







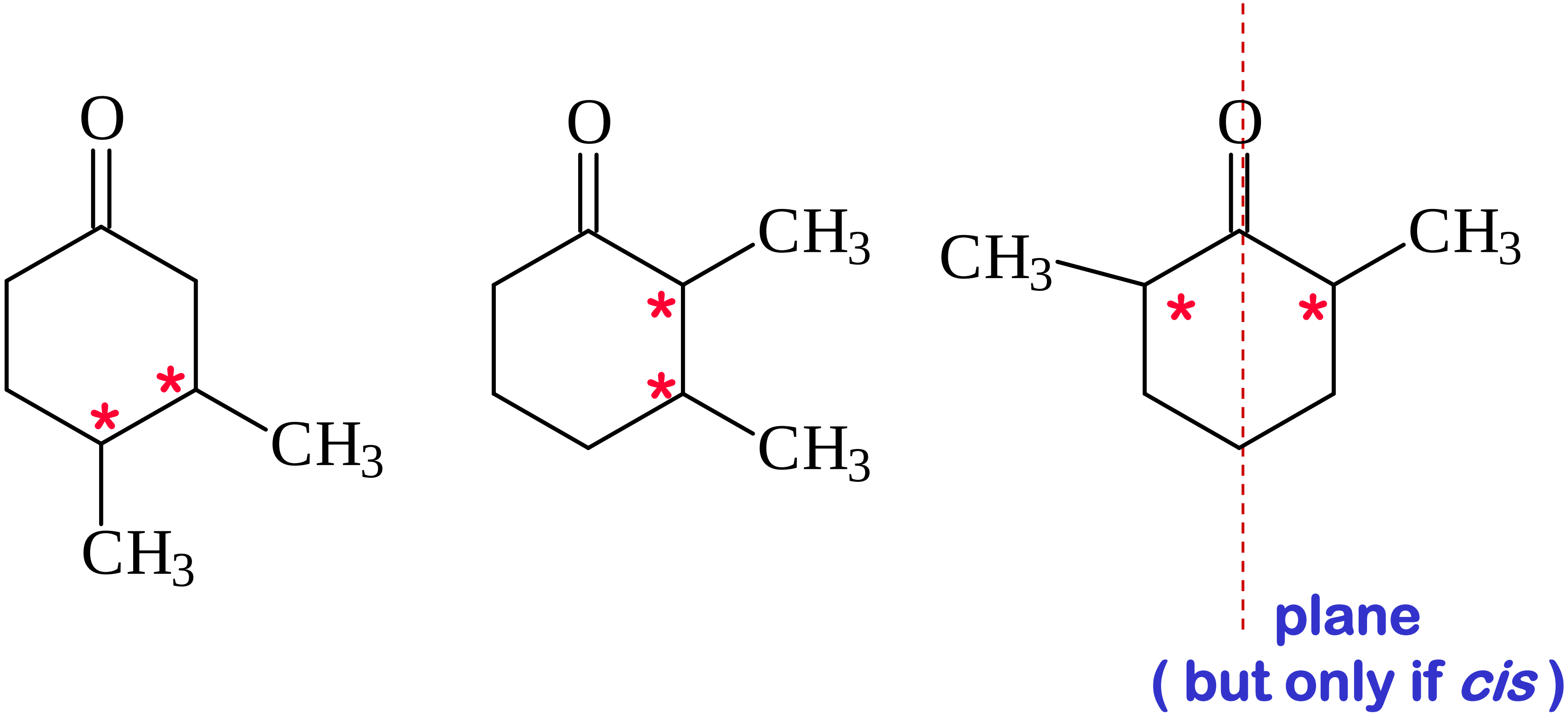
plane

(indicates no stereoisomers)

stereoisomers (max) :

$2^0 = 1$ $2^1 = 2$ $2^1 = 2$

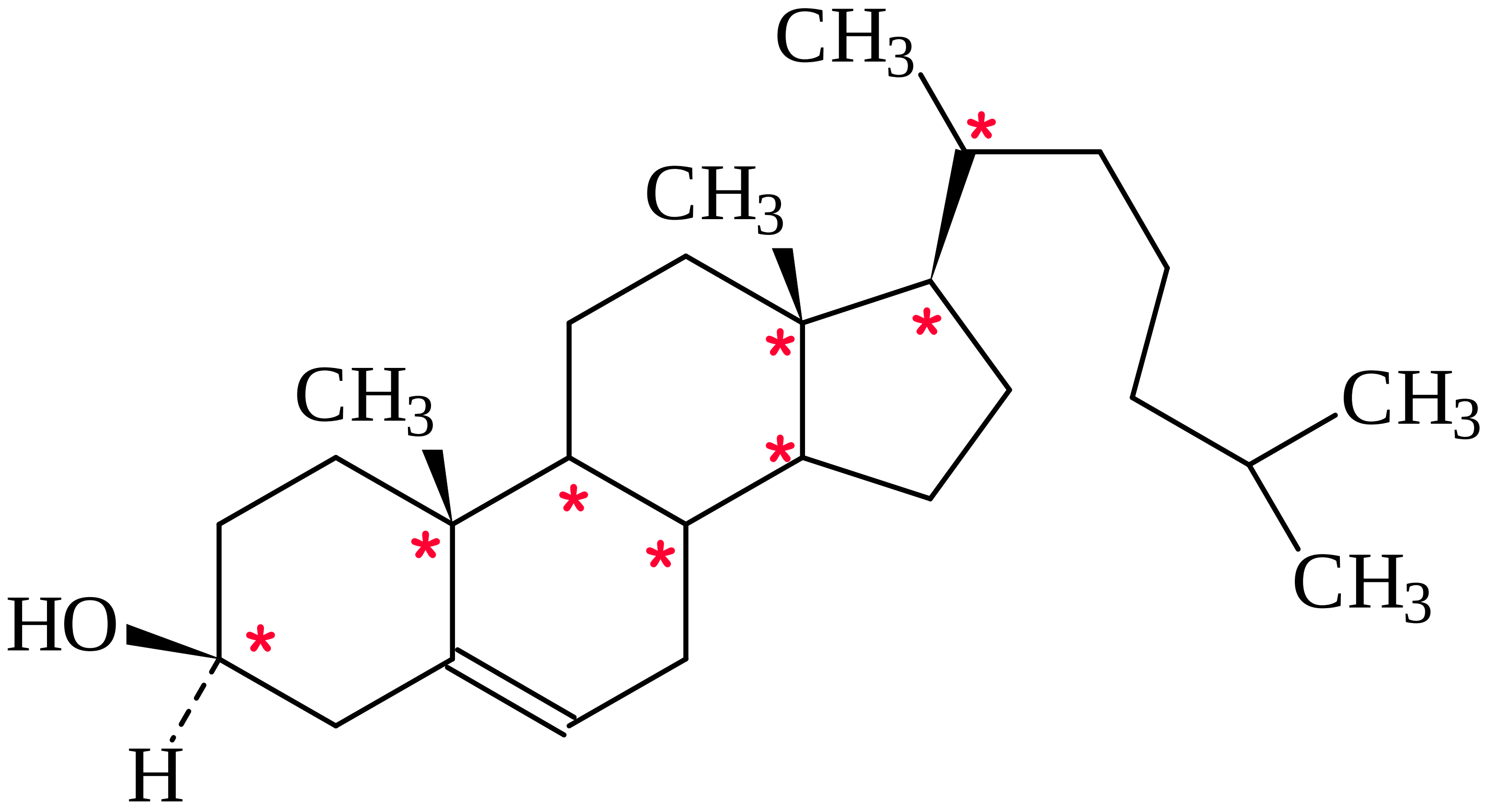
FINDING STEREOCENTERS (STEREOGENIC CARBONS)



stereoisomers (max) :

$2^2 = 4$ $\quad$ $2^2 = 4$ $\quad$ $2^2 = 4$

FINDING STEREOCENTERS (CHIRAL CARBONS)



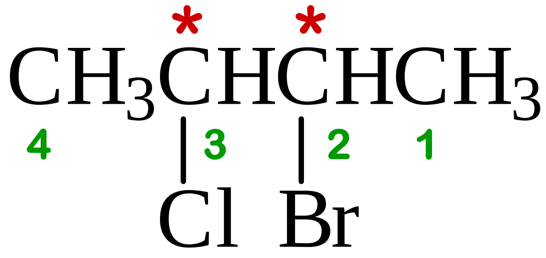
n = 8

$2^8 = 256$

MOLECULES WITH TWO STEREOCENTERS

DIASTEREOMERS / MESO

2-Bromo-3-chlorobutane



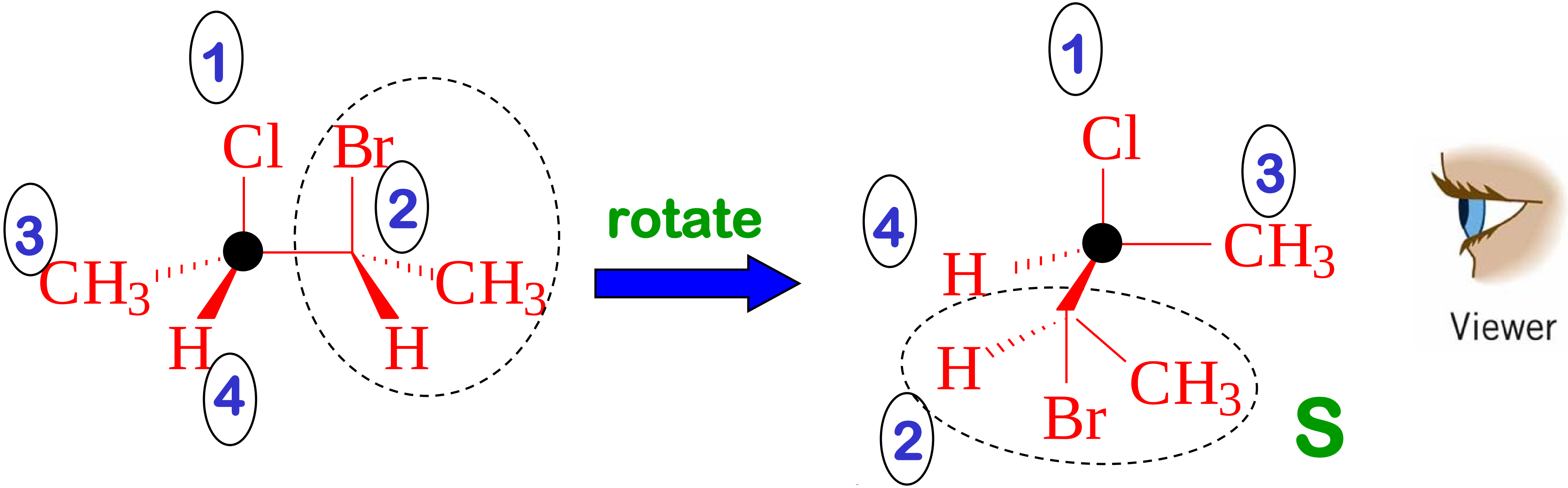
$2^2 = 4$ stereoisomers possible

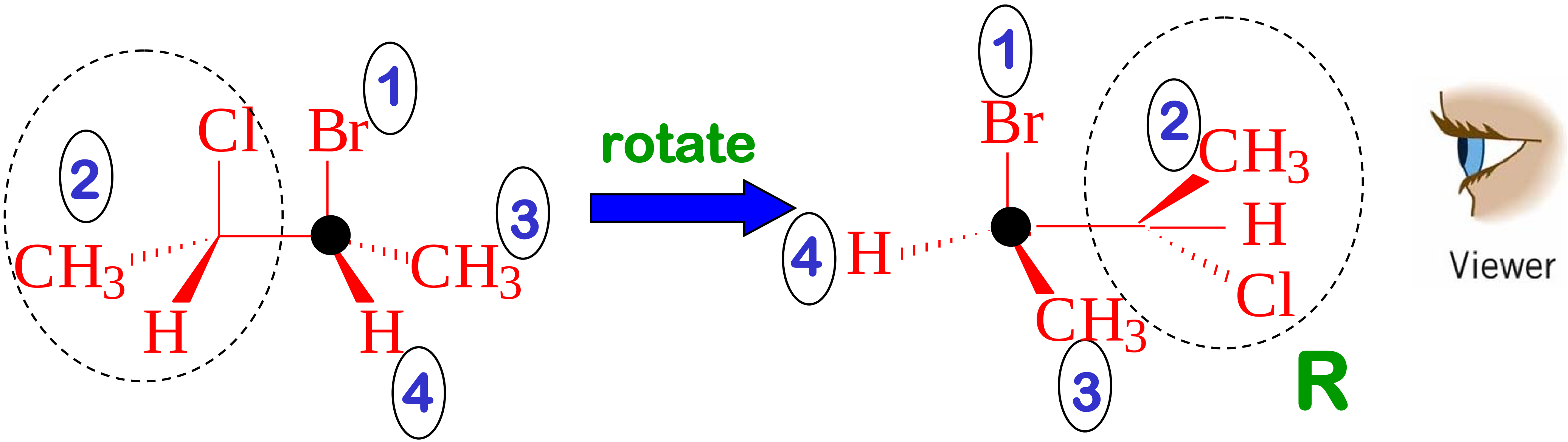
SR RS	SS RR

When comparing butanes, the comparisons are done best using the eclipsed conformation.

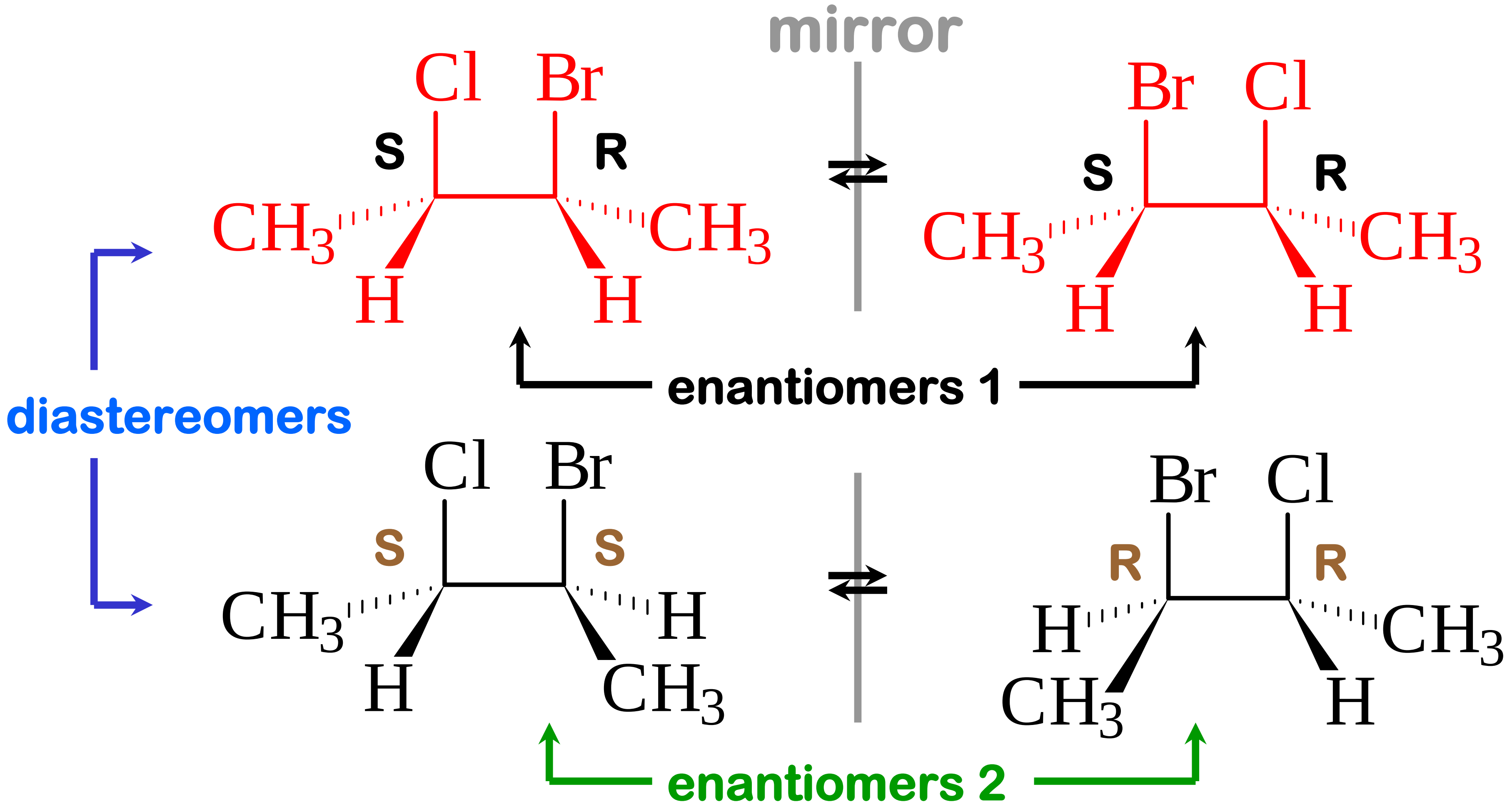
The relationships and planes of symmetry are not easily seen in other conformations.

PRIORITIES AND DETERMINING R and S



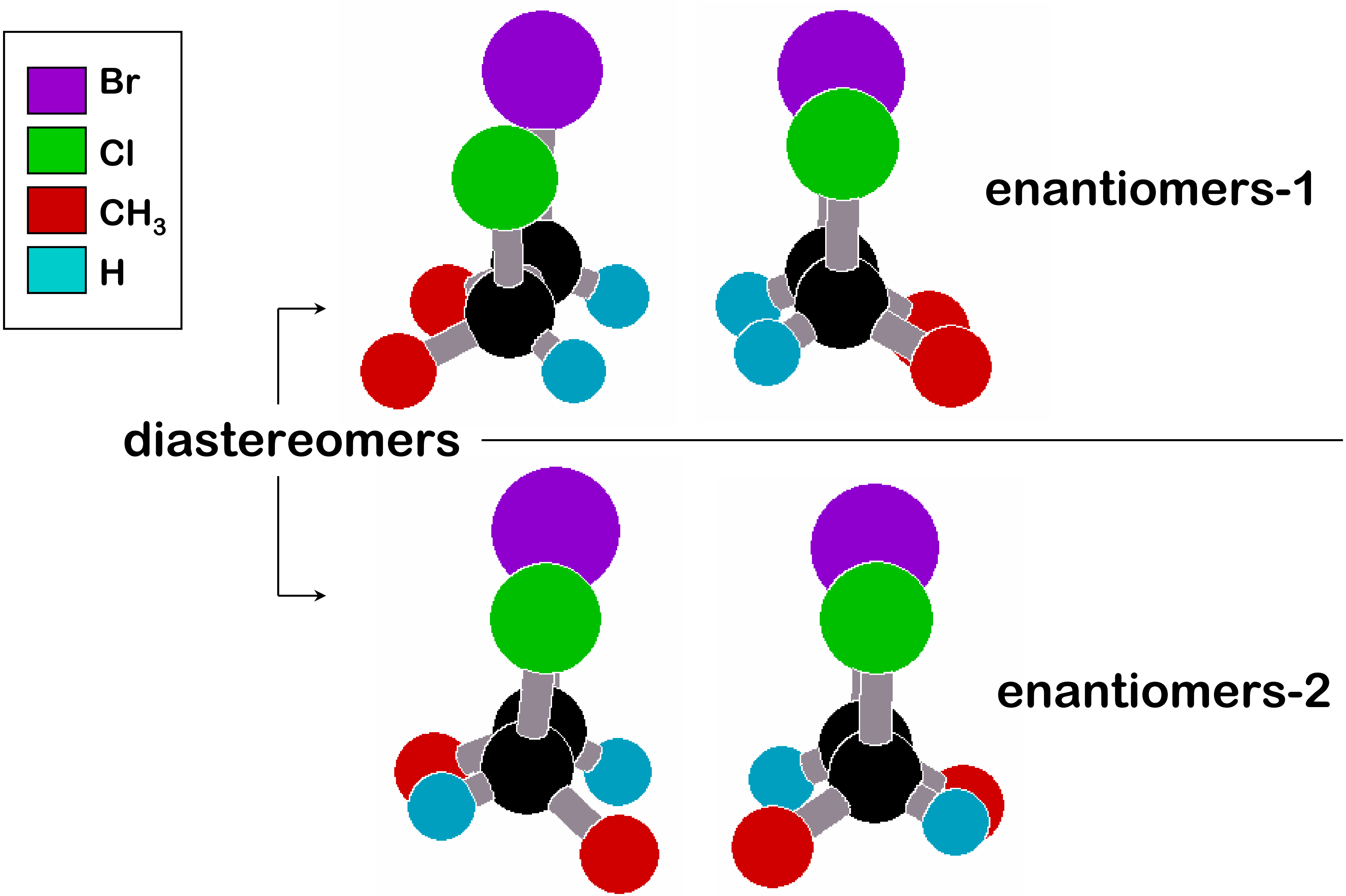


2-Bromo-3-chlorobutane

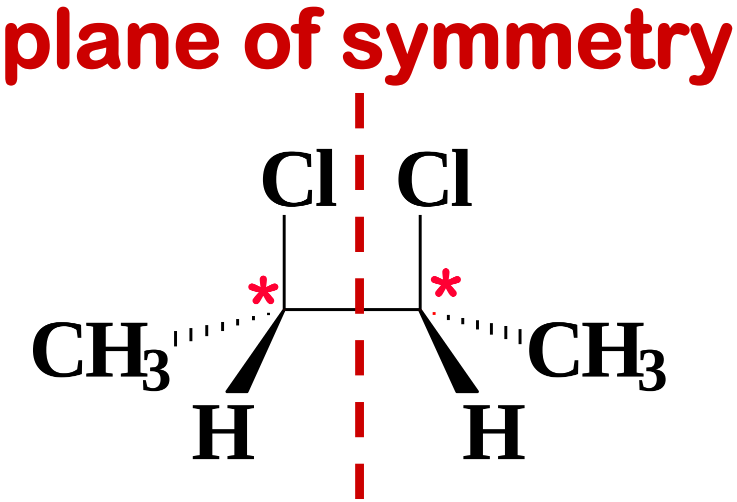


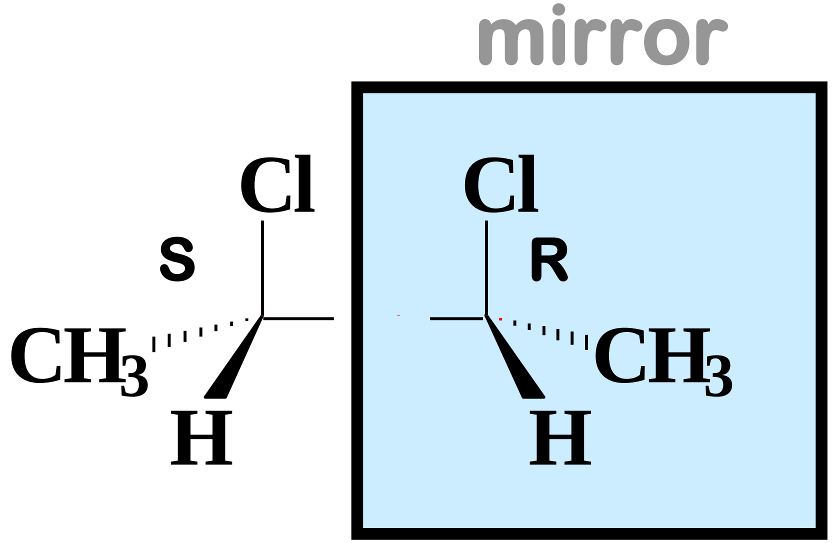
Models of the Isomers of 2-Bromo-3-chlorobutane

(methyl groups are reduced to a single red atom)



MESO ISOMER



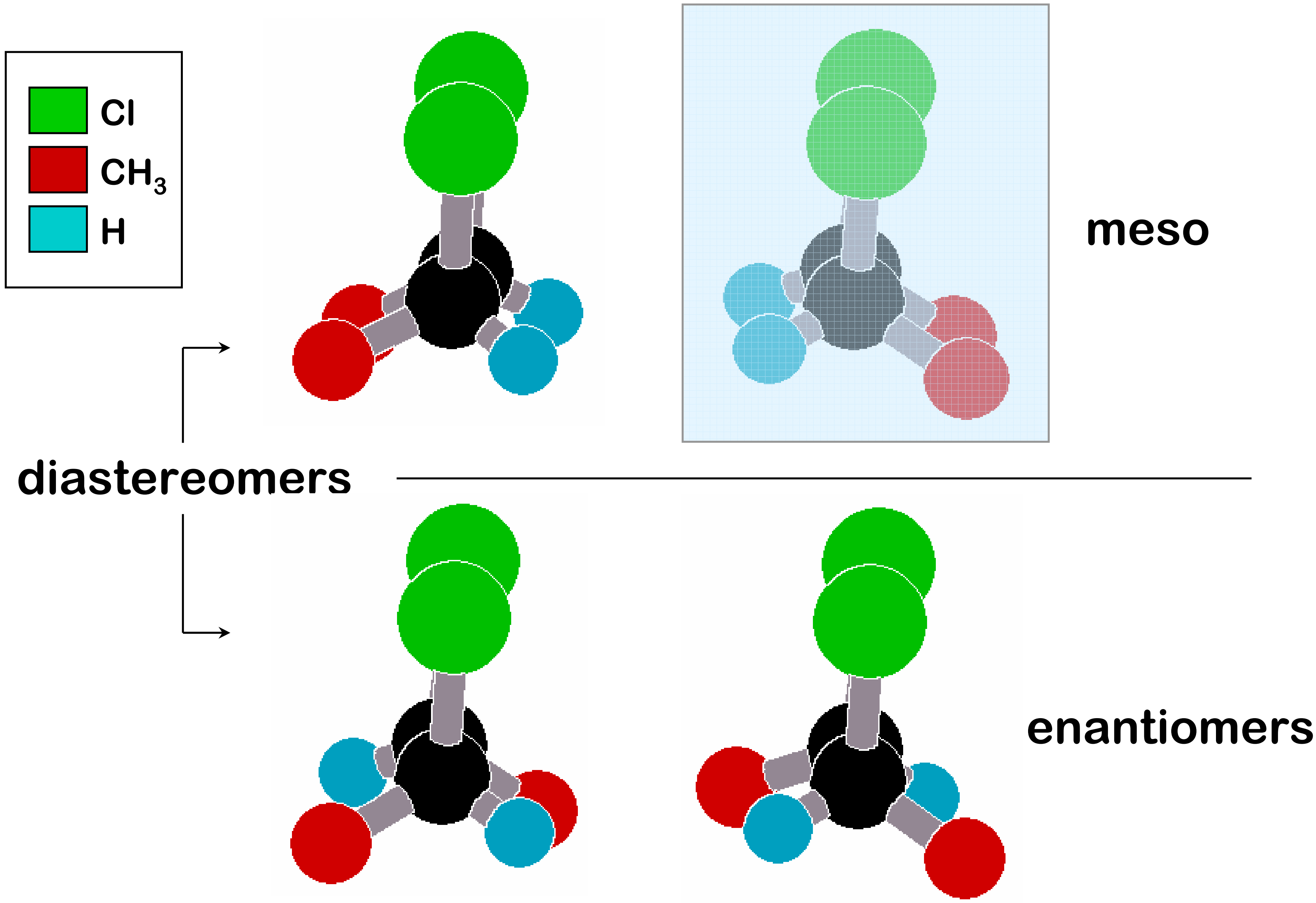


Meso isomer - has a plane of symmetry and the mirror image is identical to the original molecule.

- must have ≥ 2 stereocenters

Models of the Isomers of 2,3-Dichlorobutane

(methyl groups are reduced to a single red atom)

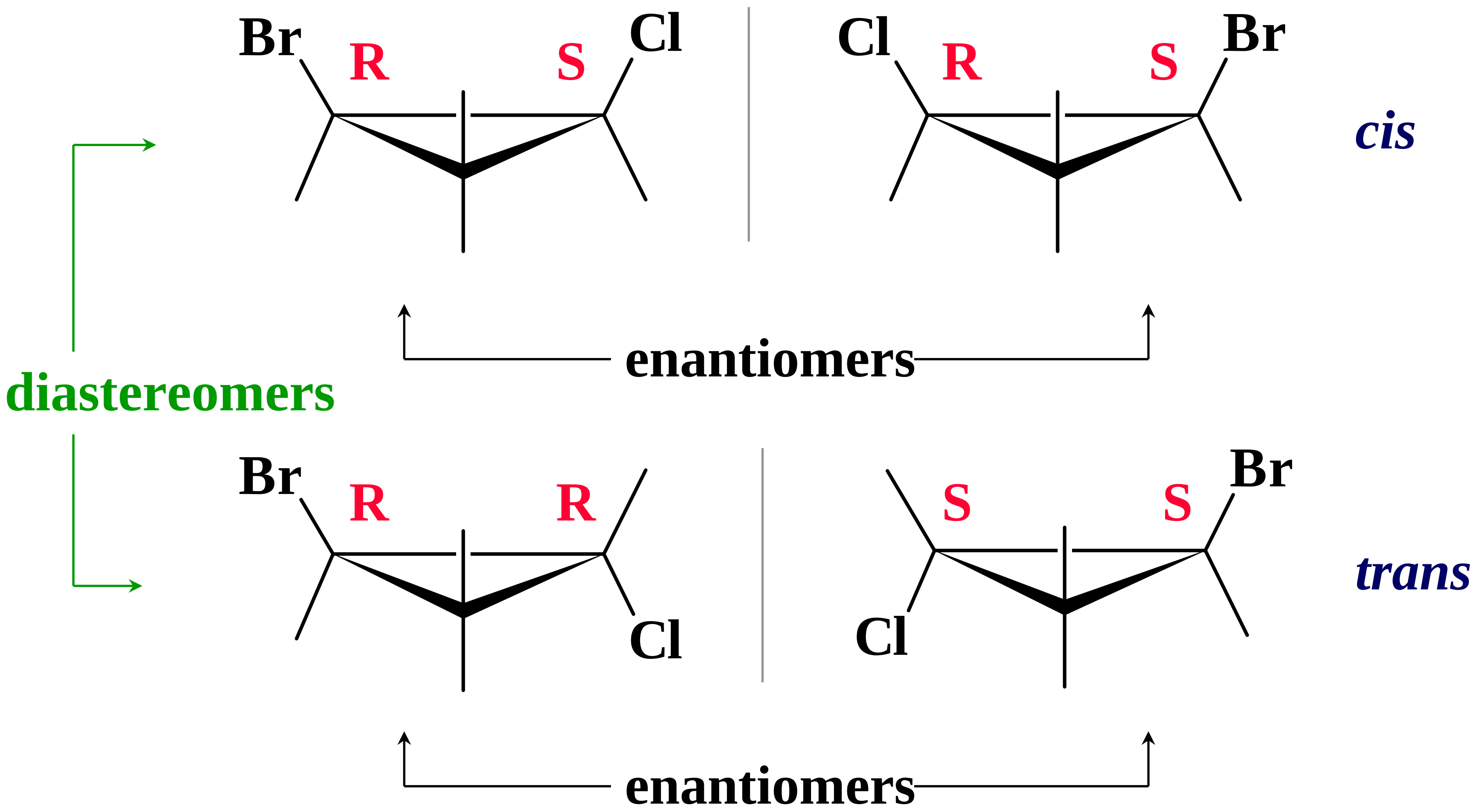


CIS/ TRANS RINGS

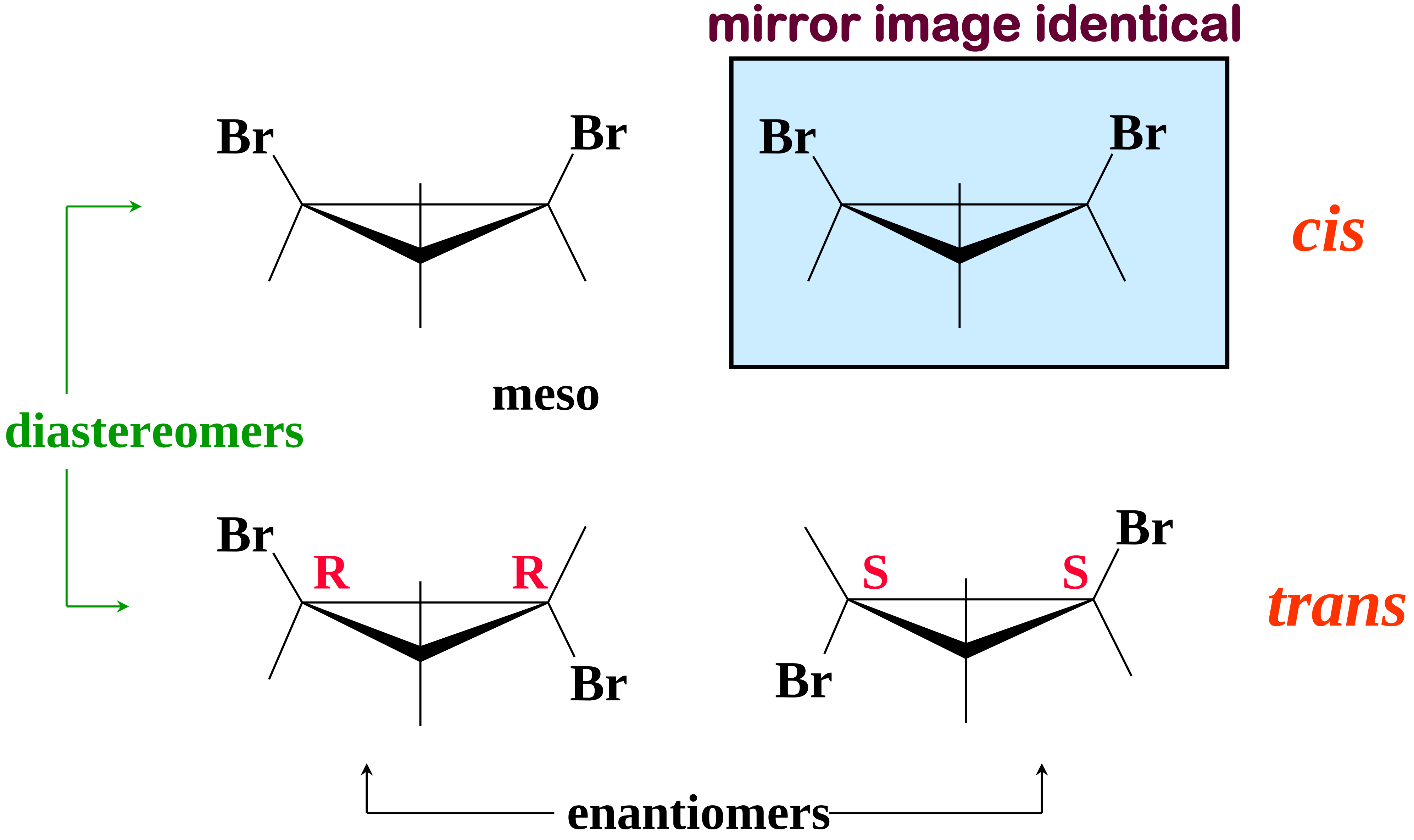
DIASTEREOMERS

1-Bromo-2-chlorocyclopropane

note that the *cis* / *trans* isomers are also diastereomers



1,2-Dibromocyclopropane

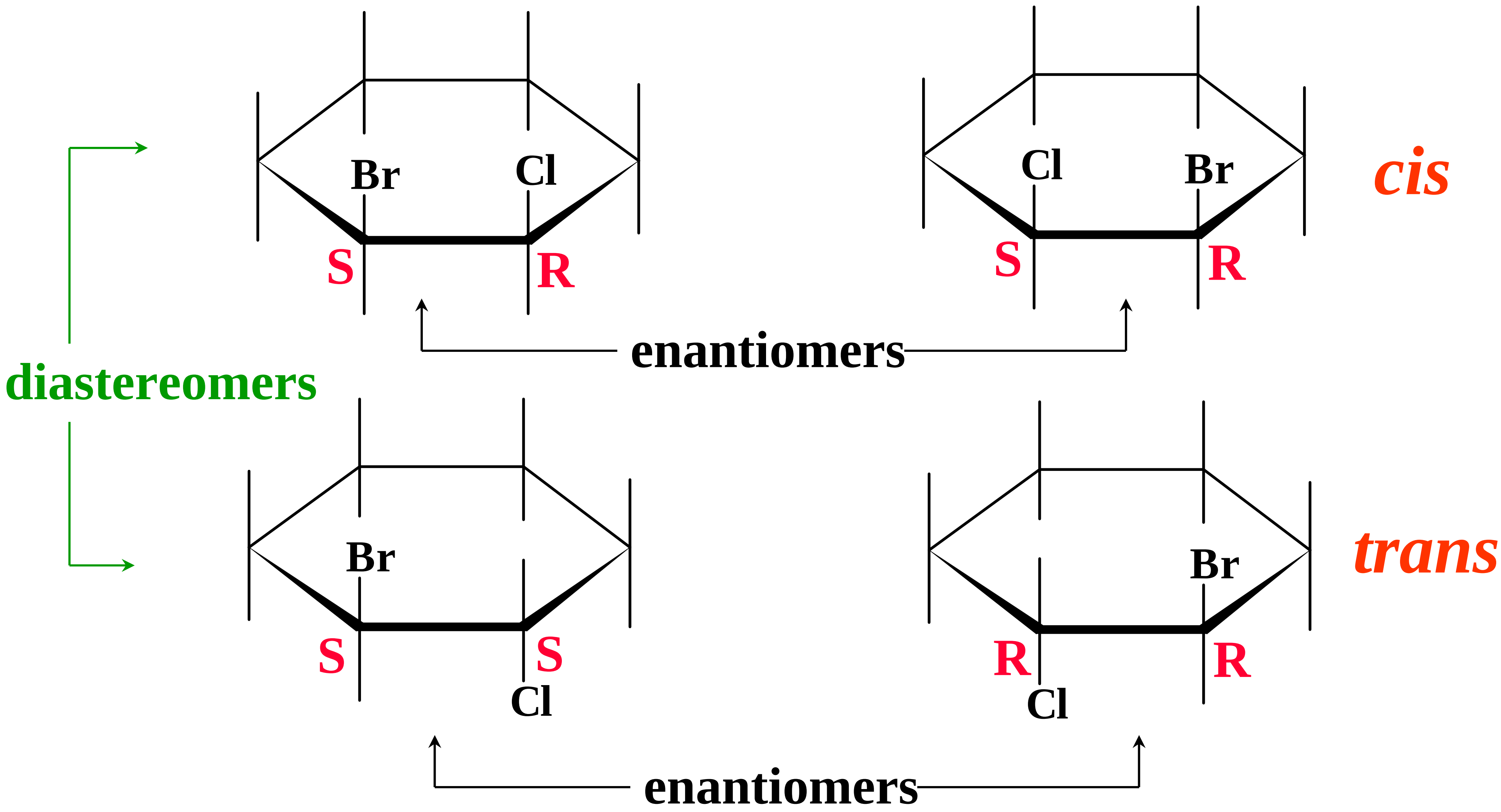


DISUBSTITUTED CYCLOHEXANES

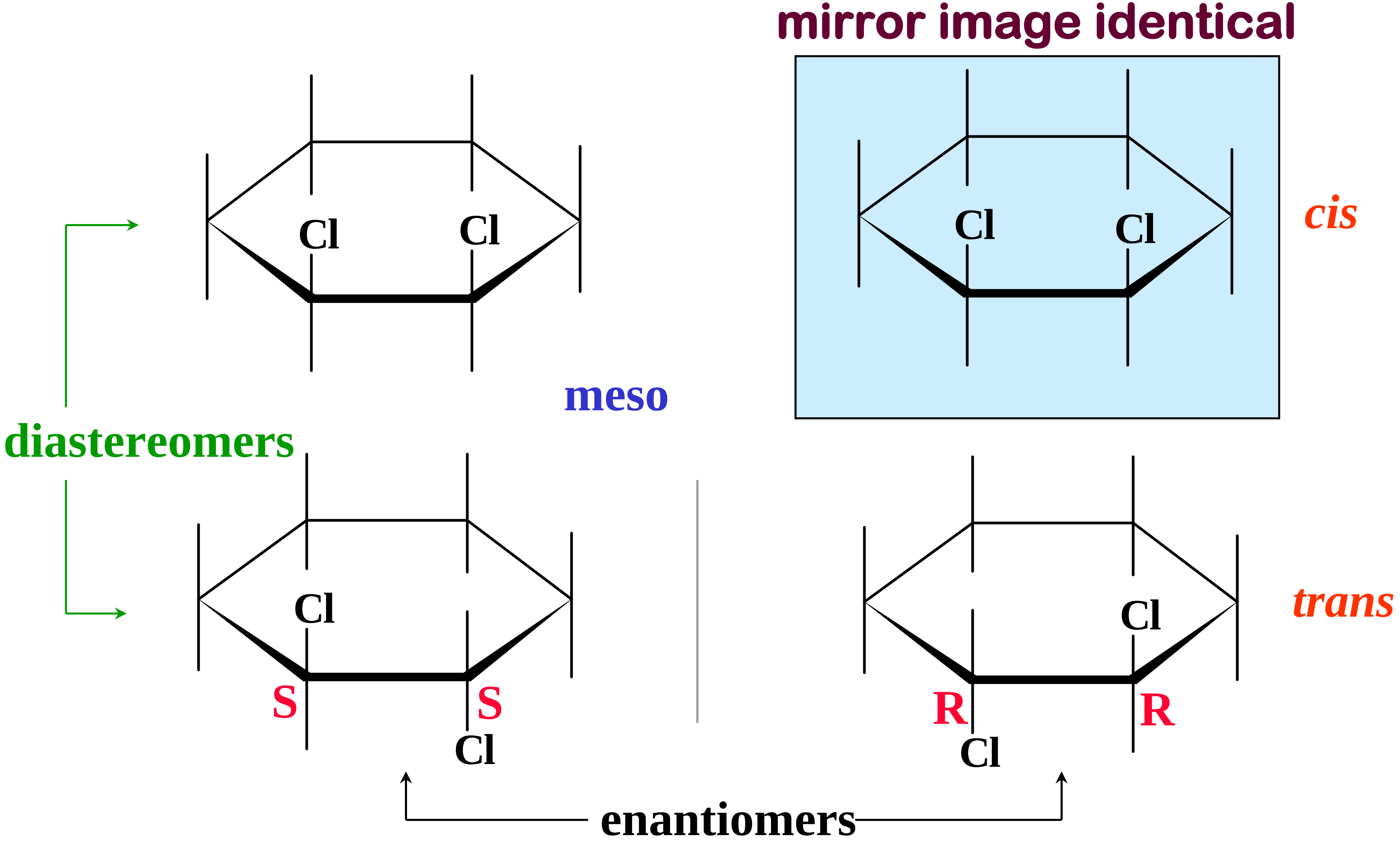
USING PLANAR RINGS FOR STEREOCHEMICAL ANALYSIS

1-Bromo-2-chlorocyclohexane

cyclohexanes may be analyzed using planar rings



1,2-dichlorocyclohexane



CONCLUSION

2^n = the maximum number

When a molecule has

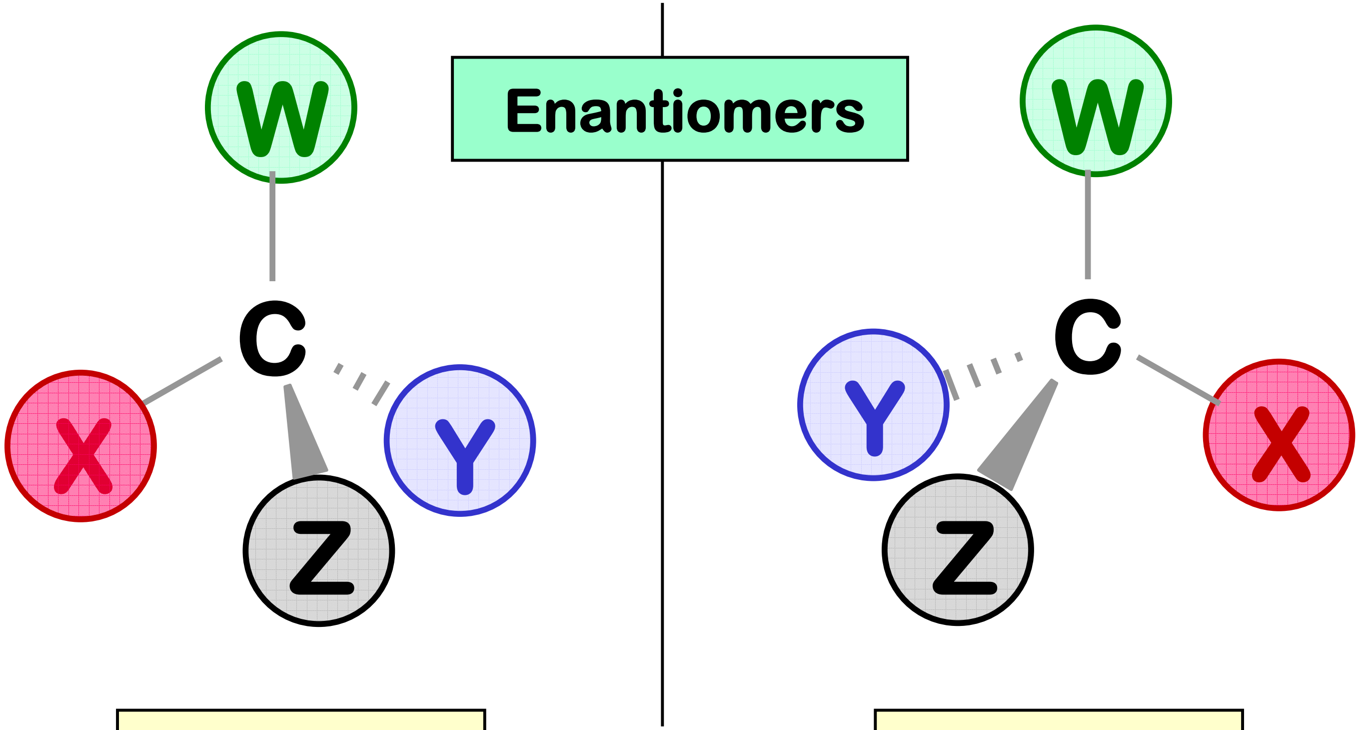
1. multiple stereocenters and
2. there is a possibility of an arrangement with a plane of symmetry

you will not always find all of the 2^n stereoisomers that are possible.

Some of the stereoisomers may be ***meso*** isomers, and their mirror images will be superimposable (identical) - this will eliminate at least one of the possible stereoisomers, and sometimes more.

PHYSICAL PROPERTIES OF ENANTIOMERS, DIASTEREOMERS AND MESO COMPOUNDS

REMEMBER : ENANTIOMERS HAVE EQUAL AND OPPOSITE ROTATIONS



(+)-nn°	(-)-nn°
dextrorotatory	levorotatory

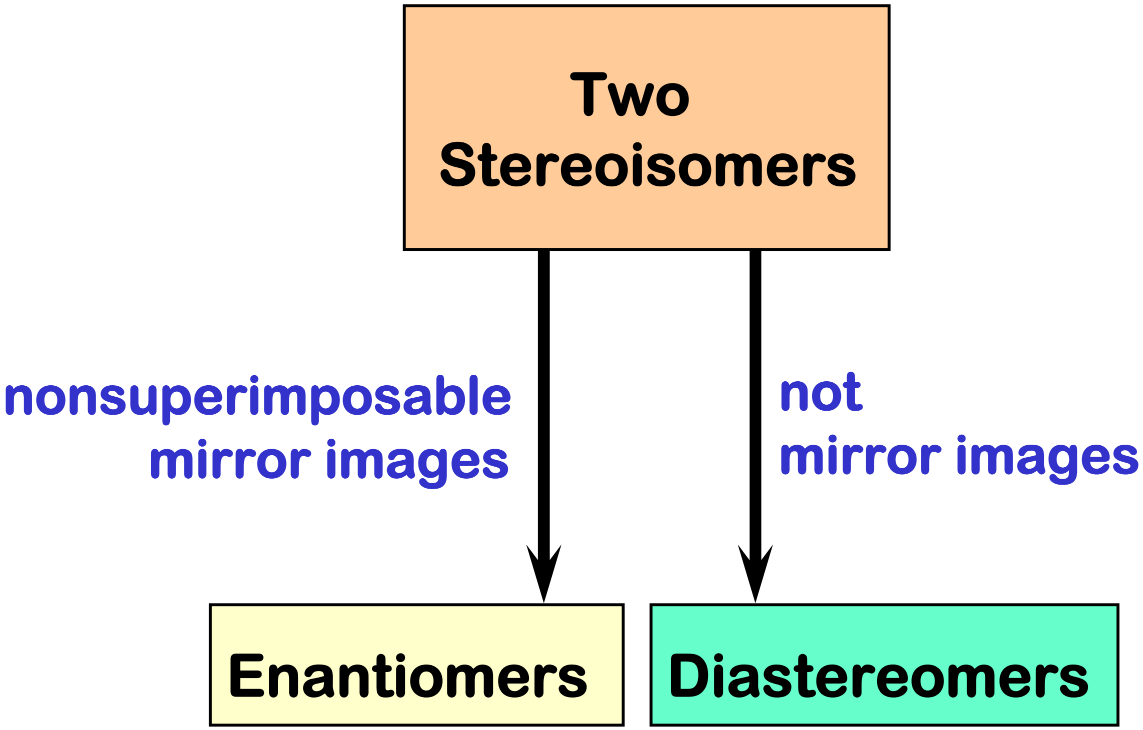
ALL OTHER PHYSICAL PROPERTIES ARE THE SAME

IN CONTRAST : **DIASTEREOMERS MAY HAVE DIFFERENT ROTATIONS**

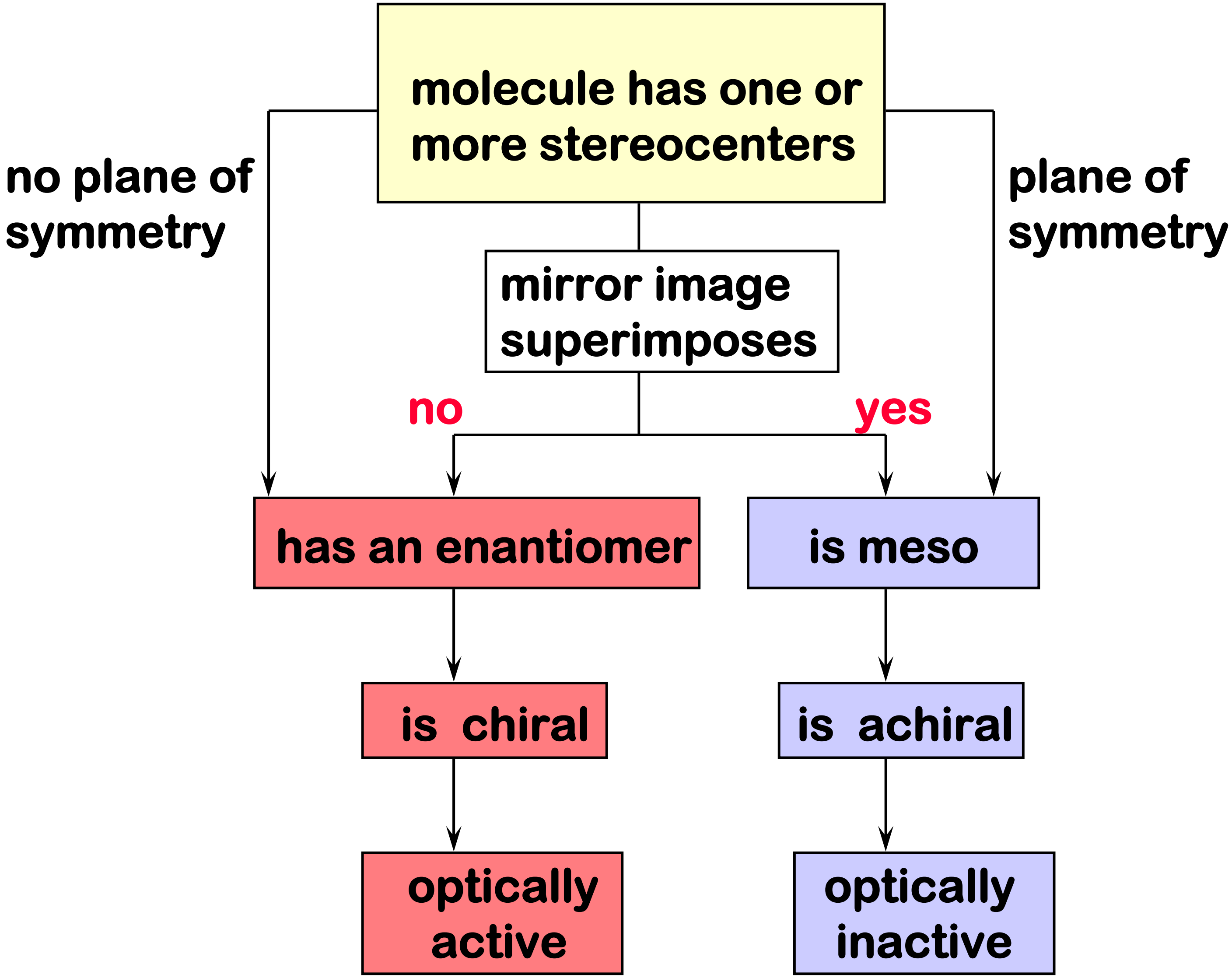
AND ALSO <u>DIFFERENT</u> PHYSICAL PROPERTIES

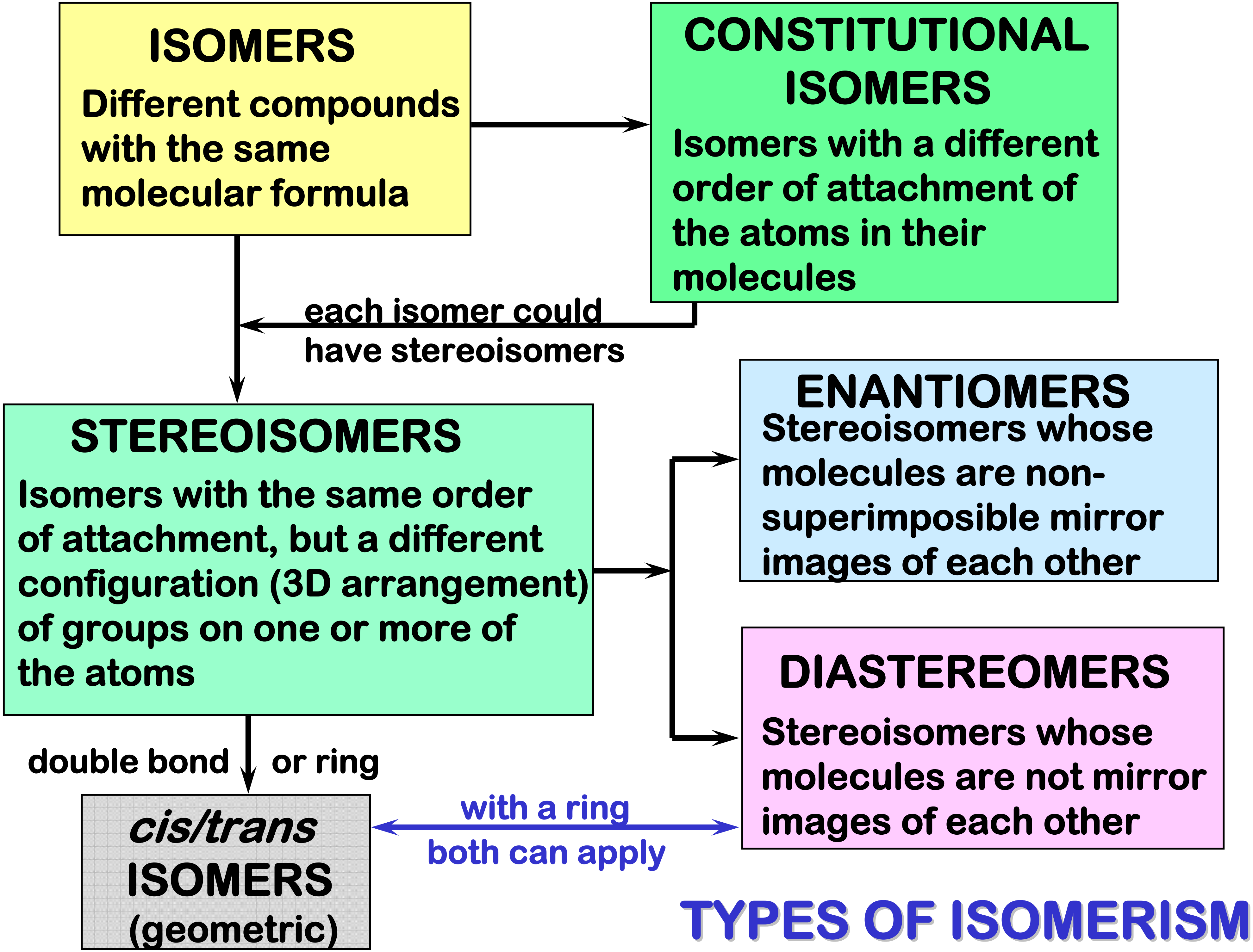
RELATIONSHIPS AMONG STEREOISOMERS

COMPARING TWO STEREOISOMERS

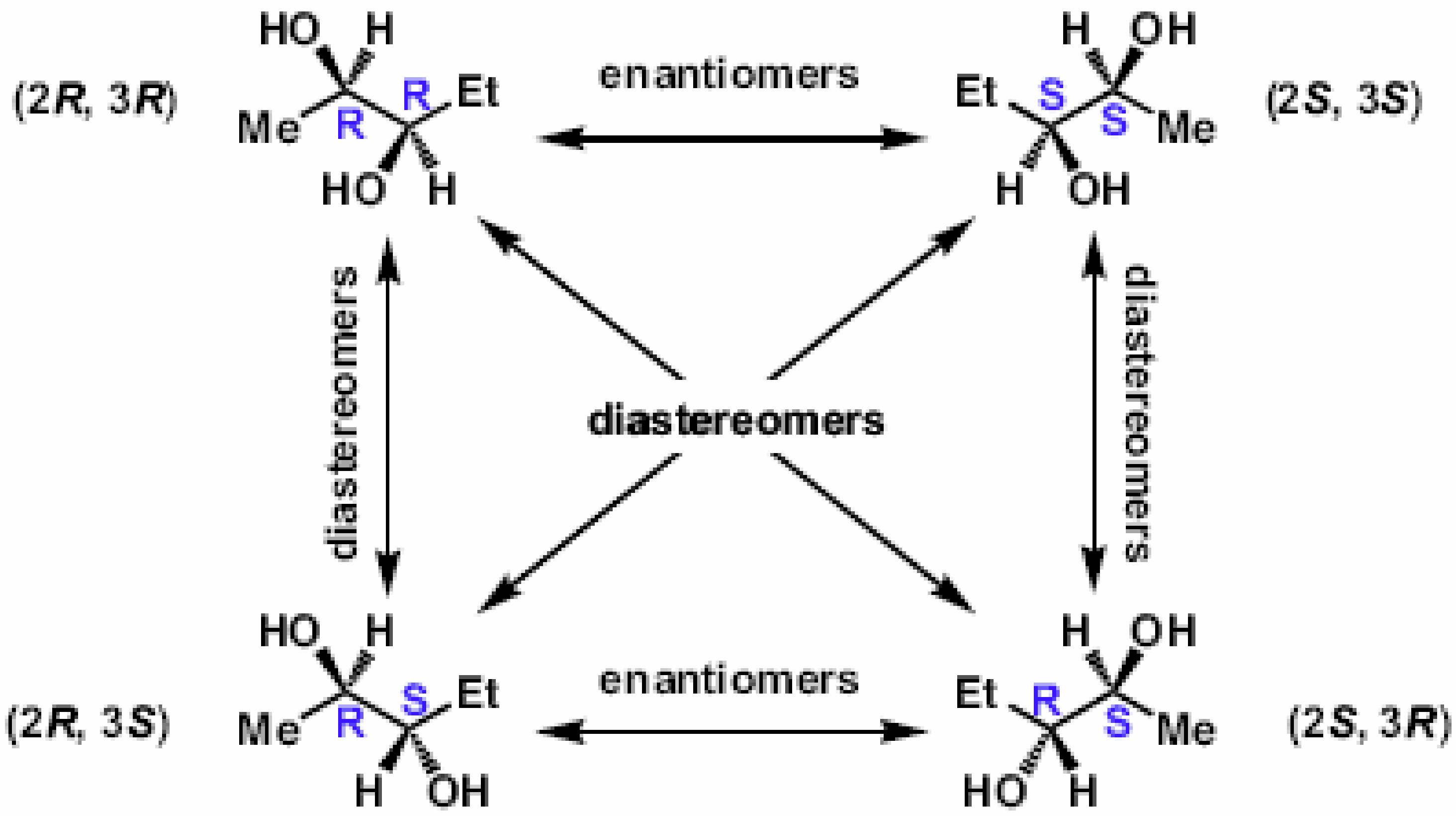


DETERMINING CHIRALITY / OPTICAL ACTIVITY

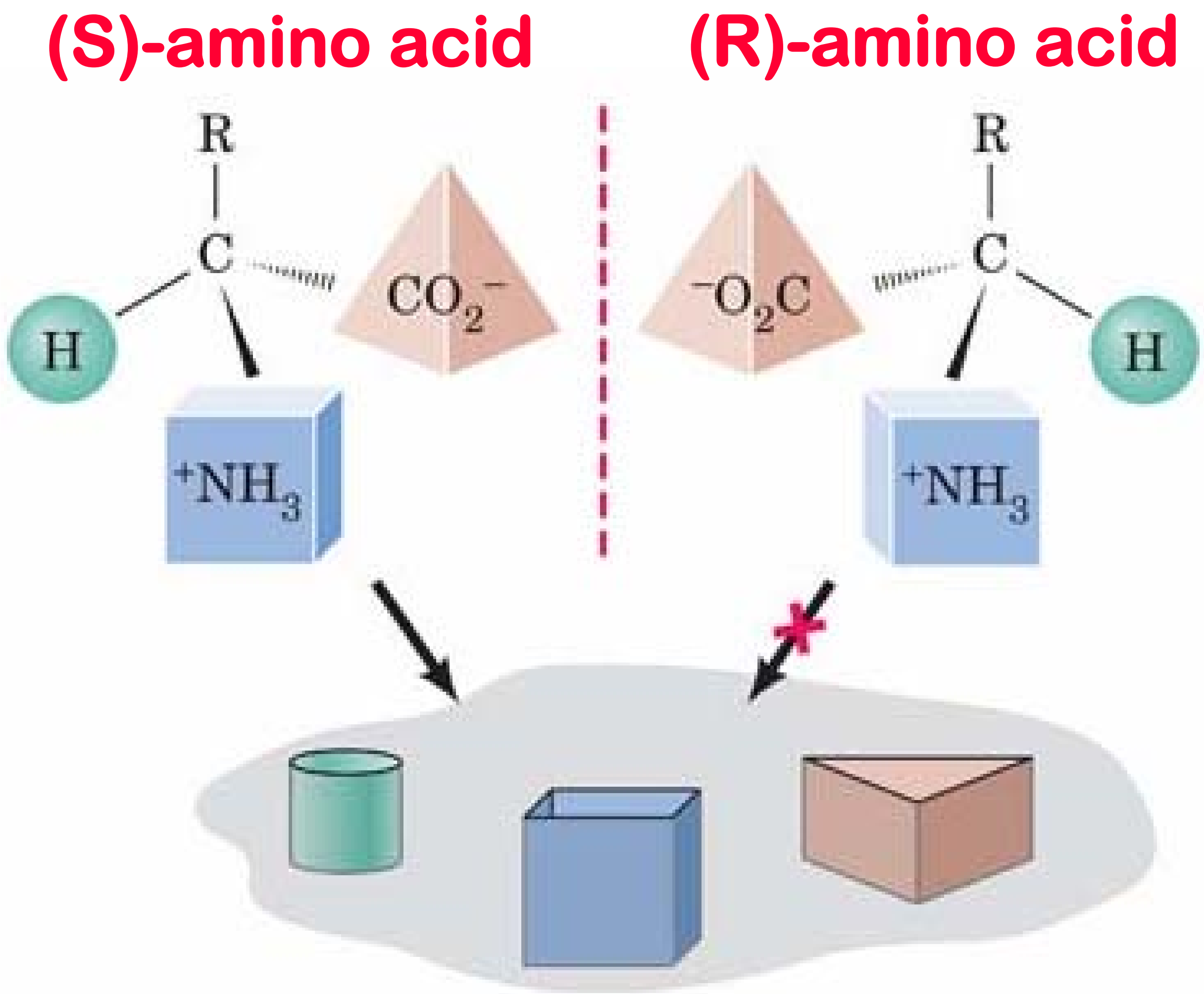



ISOMERS
Different compounds with the same molecular formula
CONSTITUTIONAL ISOMERS
Isomers with a different order of attachment of the atoms in their molecules
each isomer could have stereoisomers
STEREOISOMERS
Isomers with the same order of attachment, but a different configuration (3D arrangement) of groups on one or more of the atoms
ENANTIOMERS
Stereoisomers whose molecules are non-superimposible mirror images of each other
DIASTEREOMERS
Stereoisomers whose molecules are not mirror images of each other
double bond
or ring
cis/trans ISOMERS (geometric)
with a ring both can apply
TYPES OF ISOMERISM

Enantiomers and Diastereomers



Biological role of stereochemistry



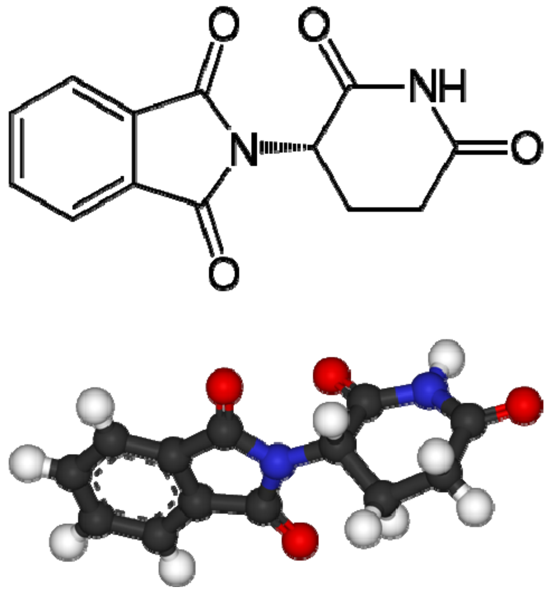
Only one of the 2 amino acid enantiomers can achieve 3-point binding with the enzyme binding site

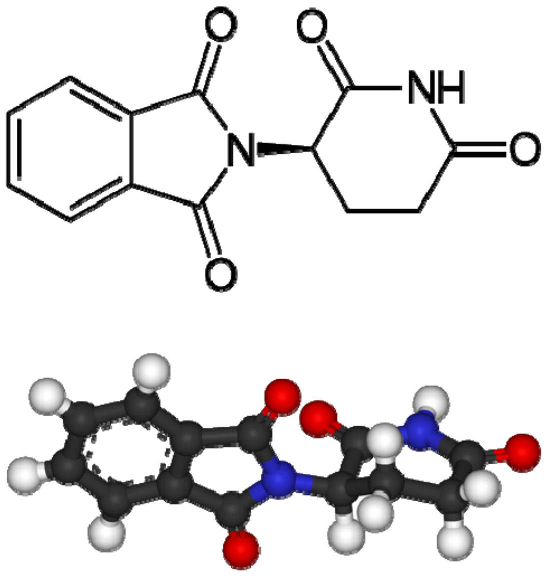
Importance of stereochemistry

- **Thalidomide (Neurosedyn)**

S

teratogenic and causes birth defects





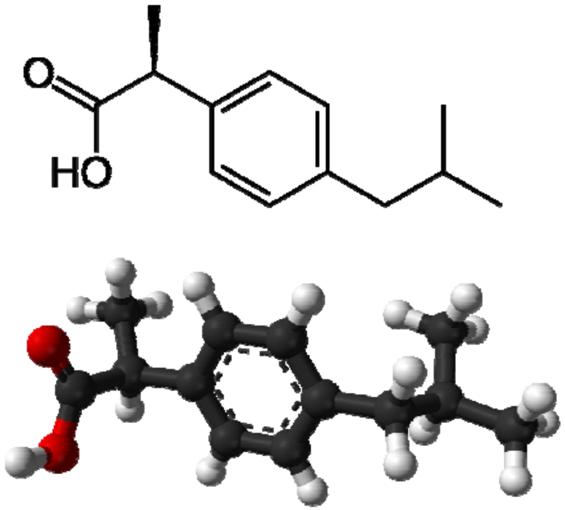
R

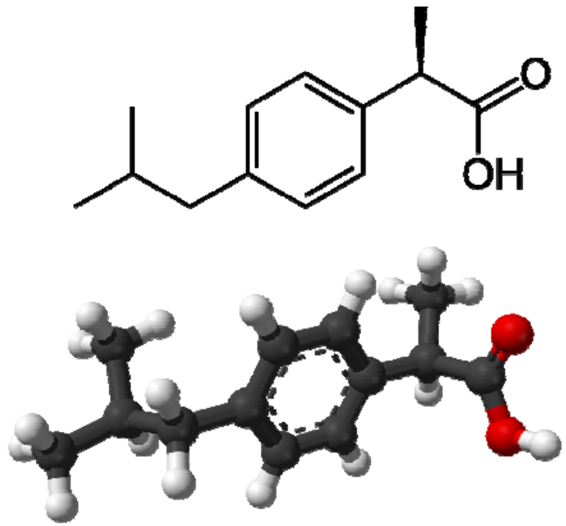
effective against morning sickness

- **Ibuprofen (Ipren)**

S

active form





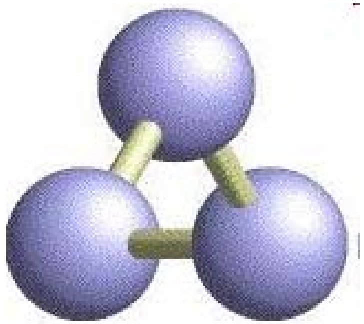
R

inactive

To recapitulate . . .

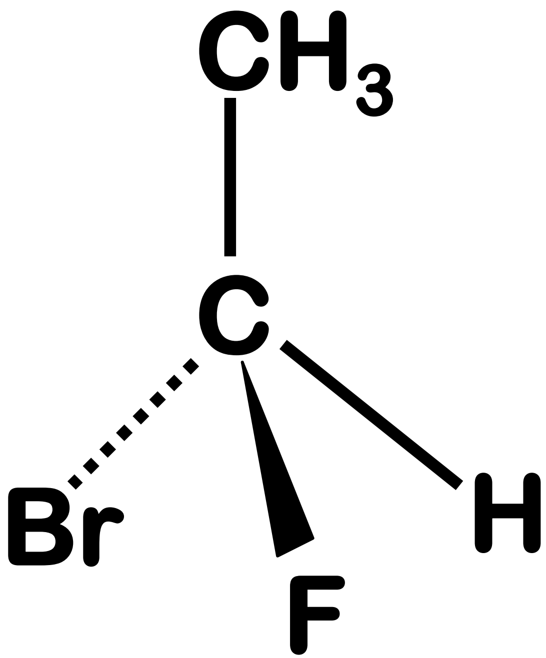
- chirality and optical activity
  - plane of symmetry
- enantiomers and diastereomers
  - *R* and *S*
- use Cahn-Ingold-Prelog priority rules
- meso compounds
  - contain stereocenters, but are achiral
- stereoisomers can have significant biological effects

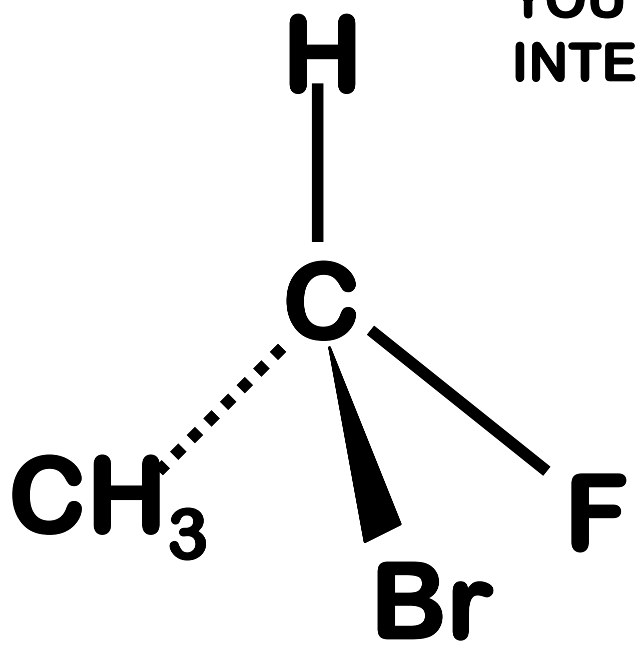
Web resources



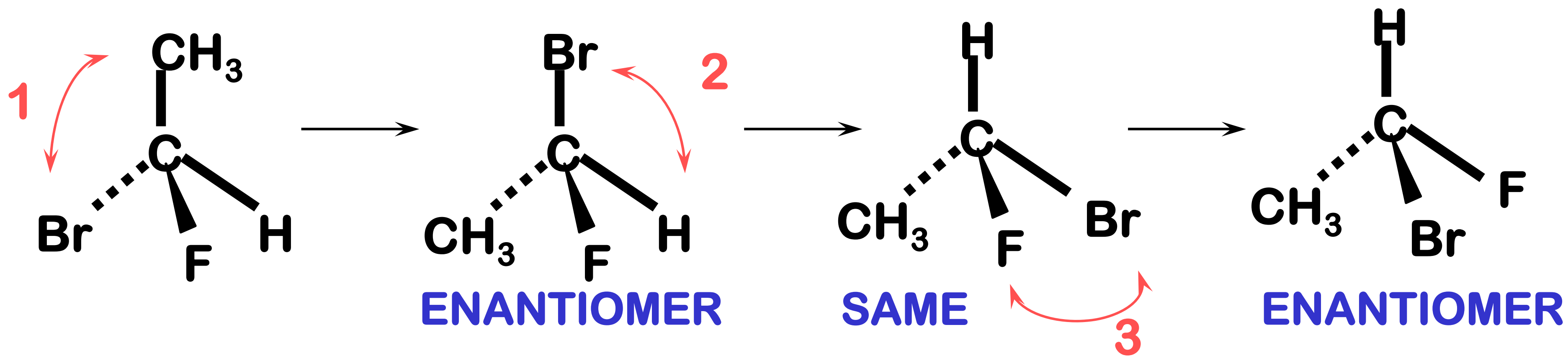
- ISIS Draw Structure Drawing Software
  - http://www.mdli.com/
- Chime Molecular Display
  - http://www.mdli.com/
- RasMol Molecular Display Software
  - http://rasmol.org/
- Jmol Java viewer for 3D chemical structures
  - http://jmol.sourceforge.net/
- General resource for organic chemistry
  - http://www.organicworldwide.net/
- Spartan computational chemistry
  - http://www.wavefun.com/

PROBLEM: ARE THESE IDENTICAL OR ARE THEY ENANTIOMERS?



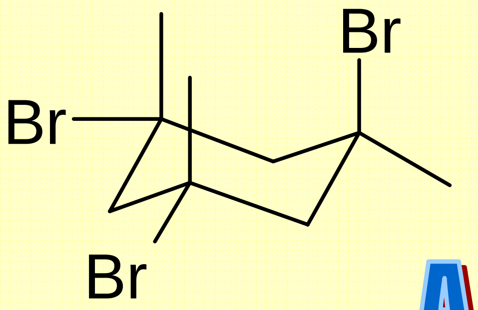


YOU CAN USE INTERCHANGES



What is the <u>best term</u> to describe the relationship between A and each of the other molecules?

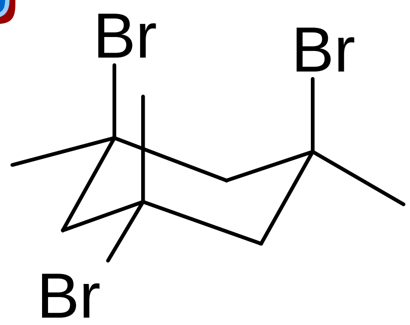
Constitutional isomers?
Conformations?
Enantiomers?
Diastereomers?
Identical?



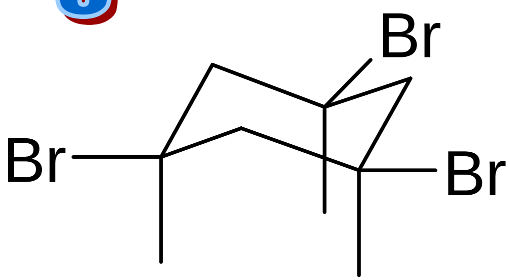
A

Are any of these molecules optically active?

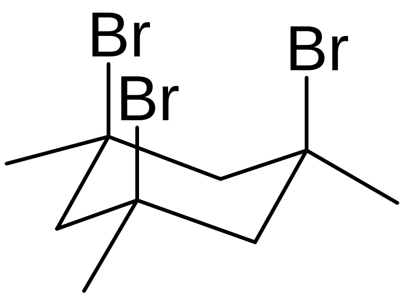
B



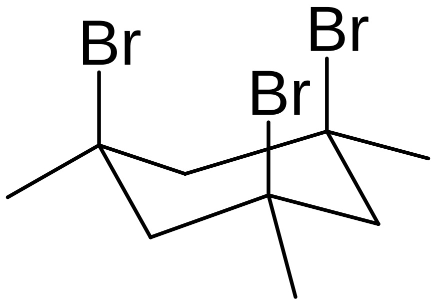
C



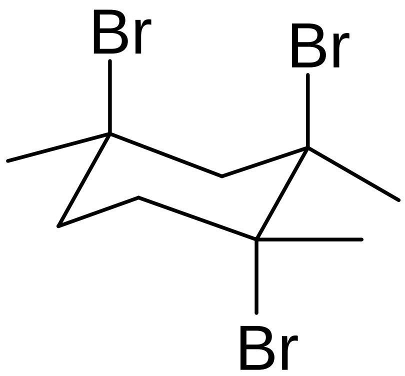
D



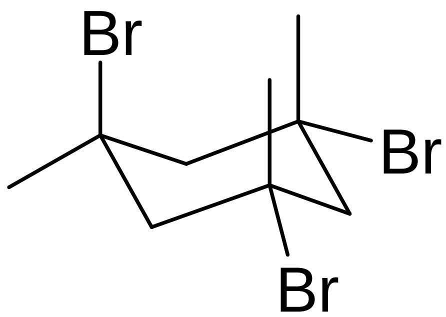
E



F



G



ANSWERS

A-C and E are all the same constitutional isomer, 1,3,5-trichloro- , but F is 1,2,4-trichloro-

- F is a <u>constitutional isomer</u> to A and to any of the others.
- A (e,e,a) and B (a,a,e) are <u>conformations</u>
- A (e,e,a) and C (e,e,e) are <u>diastereomers</u>
- A and D are <u>diastereomers</u> (D is a conformation of C)
- A and E are <u>diastereomers</u> (E is identical to D, turned left-to-right)
- A and G are <u>identical</u> (G is the same as A turned left-to-right)

Only F is optically active, all the rest are <u>meso</u> molecules!

$[\alpha]_D \neq 0$ $[\alpha]_D = 0$