Isomerism

- **Isomers** are molecules with the same molecular formula but different chemical structures.
  - That is, isomers contain the same number of atoms of each element, but have different arrangements of their atoms in space
- There are two main forms of isomerism:
  - Structural isomerism
  - Stereoisomerism
- Isomers do not necessarily share similar properties, unless they also have the same functional groups.
- There are many different classes of isomers, like positional isomers, *cis-trans* isomers and enantiomers, etc.

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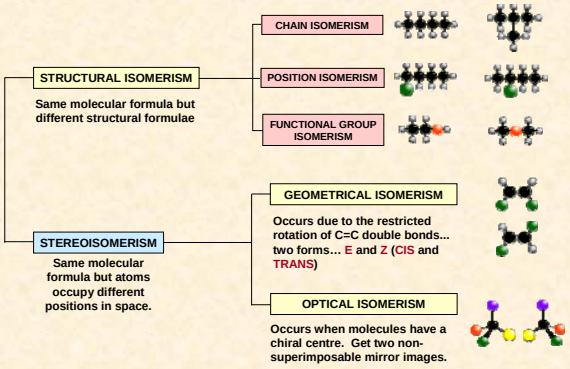
TYPES OF ISOMERISM



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GEOMETRICAL ISOMERISM

RESTRICTED ROTATION OF C=C BONDS

C=C bonds have restricted rotation so the groups on either end of the bond are 'frozen' in one position; it isn't easy to flip between the two.

This produces two possibilities. The two structures cannot interchange easily so the atoms in the two molecules occupy different positions in space.

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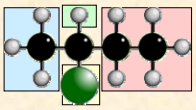
OPTICAL ISOMERISM

- Occurrence
  - another form of stereoisomerism
  - occurs when compounds have non-superimposable mirror images
- Isomers
  - the two different forms are known as optical isomers or enantiomers
  - they occur when molecules have a chiral centre
  - a chiral centre contains an asymmetric carbon atom
  - an asymmetric carbon has four different atoms (or groups) arranged tetrahedrally around it.

CHIRAL CENTRES

There are four different colours arranged tetrahedrally about the carbon atom



2-chlorobutane exhibits optical isomerism because the second carbon atom has four different atoms/groups attached

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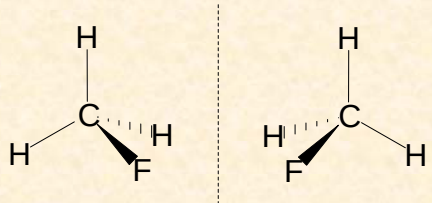
OPTICAL ISOMERISM

- All molecules have a mirror image – but for most molecules it is the same molecule.



fluoromethane

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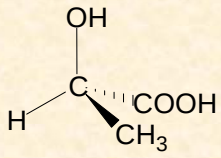
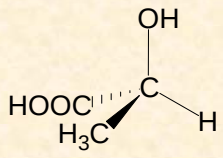
OPTICAL ISOMERISM

- For some molecules the mirror image is a different molecule (the mirror image is non-superimposable).



(-) lactic acid in sour milk



(+) lactic acid in muscles

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OPTICAL ISOMERISM

- Left and right hands are an example of non-superimposable mirror images.

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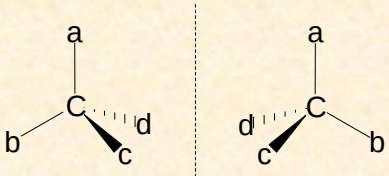
OPTICAL ISOMERISM

- This usually happens when a molecule contains a C atom with four different groups attached (chiral / asymmetric C).
- Such molecules are said to be chiral or optically active.



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OPTICAL ISOMERISM

Chiral Carbons

- Tetrahedral carbons with 4 different attached groups are chiral.
- Its mirror image will be a different compound (enantiomer).

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OPTICAL ISOMERISM

SPOTTING CHIRAL CENTRES

Look at each carbon atom in the chain and see what is attached to it. For a chiral centre you need an asymmetric carbon with four different atoms/groups) arranged tetrahedrally around it.

IF A CARBON HAS MORE THAN ONE OF ANY ATOM/GROUP ATTACHED, IT CAN'T BE CHIRAL

$CH_3CH_2CH_2CH_2Cl$ 1-chlorobutane	C	3 H's around it	NOT chiral	✗
	C	2 H's around it	NOT chiral	
	C	2 H's around it	NOT chiral	
	C	2 H's around it	NOT chiral	

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	C	2 H's around it	NOT chiral	
	C	2 H's around it	NOT chiral	
	C	2 H's around it	NOT chiral	
$CH_3CH_2CHClCH_3$ 2-chlorobutane	C	3 H's around it	NOT chiral	✓
	C	2 H's around it	NOT chiral	
	C	H, CH_3, Cl,C_2H_5 around it	CHIRAL	
	C	3 H's around it	NOT chiral	

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OPTICAL ISOMERISM

SPOTTING CHIRAL CENTRES

Look at each carbon atom in the chain and see what is attached to it. For a chiral centre you need an asymmetric carbon with four different atoms/groups) arranged tetrahedrally around it.

IF A CARBON HAS MORE THAN ONE OF ANY ATOM/GROUP ATTACHED, IT CAN'T BE CHIRAL

$CH_3CH_2CH_2CH_2Cl$ 1-chlorobutane	C	3 H's around it	NOT chiral	✗
	C	2 H's around it	NOT chiral	
	C	2 H's around it	NOT chiral	
	C	2 H's around it	NOT chiral	
$CH_3CH_2CHClCH_3$ 2-chlorobutane	C	3 H's around it	NOT chiral	✓
	C	2 H's around it	NOT chiral	
	C	H, CH_3, Cl,C_2H_5 around it	CHIRAL	
	C	3 H's around it	NOT chiral	
$(CH_3)_2CHCH_2Cl$ 1-chloro-2-methylpropanane	C	3 H's around it	NOT chiral	✗
	C	2 CH_3's around it	NOT chiral	
	C	2 H's around it	NOT chiral	
$(CH_3)_3CCl$ 2-chloro-2-methylpropanane	C	3 H's around it	NOT chiral	✗
	C	3 CH_3's around it	NOT chiral	

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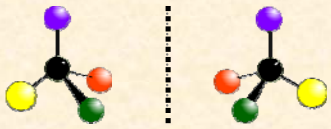
OPTICAL ISOMERISM

Spatial differences between isomers

- two forms exist which are NON-SUPERIMPOSABLE MIRROR IMAGES of each other
- non-superimposable means you you can't stack one form exactly on top of the other



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OPTICAL ISOMERISM

Spatial differences between isomers

- two forms exist which are NON-SUPERIMPOSABLE MIRROR IMAGES of each other
- non-superimposable means you you can't stack one form exactly on top of the other

Some common objects are	mirror images and superimposable	spoons
	superimposable but not mirror images	books
	non-superimposable mirror images	hands

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OPTICAL ISOMERISM

Spatial differences between isomers

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Some common objects are	mirror images and superimposable	spoons
	superimposable but not mirror images	books
	non-superimposable mirror images	hands

NB For optical isomerism in molecules, both conditions must apply... they must be mirror images AND be non-superimposable

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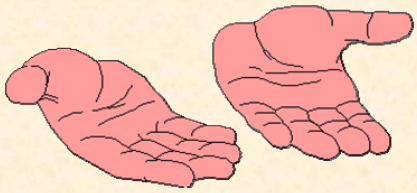
OPTICAL ISOMERISM

Spatial differences between isomers

- Left and right hands are an example of non-superimposable mirror images.



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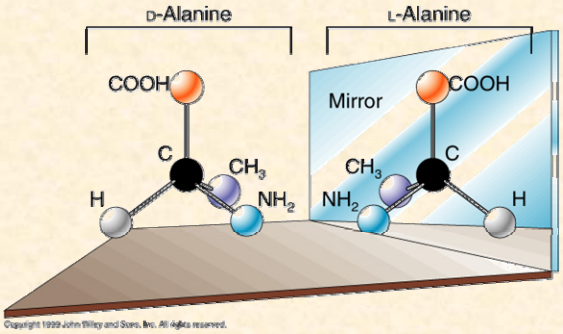
OPTICAL ISOMERISM

Spatial differences between isomers



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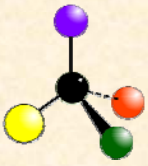
OPTICAL ISOMERISM

What is a non-superimposable mirror image?



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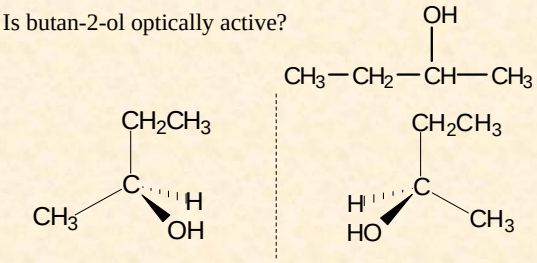
OPTICAL ISOMERISM

Is butan-2-ol optically active?



OPTICALLY ACTIVE

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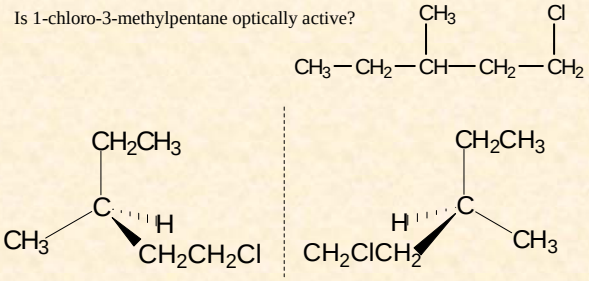
OPTICAL ISOMERISM

Is 1-chloro-3-methylpentane optically active?



OPTICALLY ACTIVE

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OPTICAL ISOMERS - DIFFERENCE

- isomers differ in their reaction to plane-polarised light
- plane polarised light vibrates in one direction only
- one isomer rotates light to the right, the other to the left
- rotation of light is measured using a polarimeter
- rotation is measured by observing the polarised light coming out towards the observer

• If the light appears to have	turned to the right DEXTROROTATORY d or + form	turned to the left LAEVOROTATORY l or - form

Racemate — a 50-50 mixture of the two enantiomers (dl) or (±) is a racemic mixture. The opposite optical effects of each isomer cancel each other out

Examples — Optical activity is common in biochemistry and pharmaceuticals
- Most amino acids exhibit optical activity
- many drugs must be made of one optical isomer to be effective
  - need smaller doses (safer and cost effective)
  - get reduced side effects
  - improved pharmacological activity

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Symmetry Tests for Chirality

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

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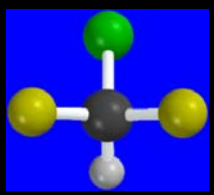
Plane of symmetry



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

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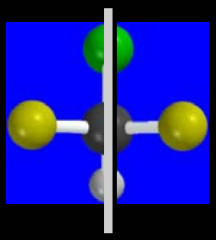
Plane of symmetry



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

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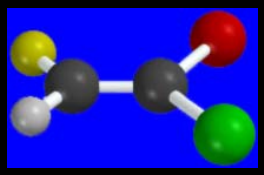
Plane of symmetry



A plane of symmetry bisects a molecule into two mirror image halves.
1-Bromo-1-chloro-2-fluoroethene has a plane of symmetry.

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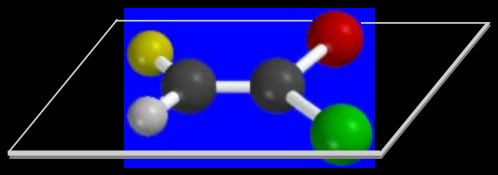
Plane of symmetry



A plane of symmetry bisects a molecule into two mirror image halves.
1-Bromo-1-chloro-2-fluoroethene has a plane of symmetry.

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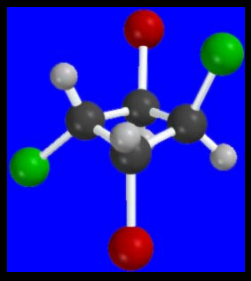
Center of symmetry



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

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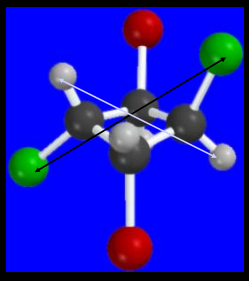
Center of symmetry



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.

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Cahn - Ingold - Prelog RS Notational System

- Because enantiomers are different configurations of the same compound, a notational system had to be developed that would indicate the three - dimensional arrangement of atoms at specific stereogenic centers.
- Such a system was devised by the chemists Cahn, Ingold, and Prelog.

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Cahn - Ingold - Prelog RS Notational System

- In this system, the substituents of a stereogenic center are ranked by atomic weight as dictated by a series of **priority rules.**
- A projection of the molecule is then viewed so that the group or atom of lowest priority is eclipsed by the stereogenic center.
- The ranking of the three remaining groups is then determined.
  - If their rank from highest to lowest is in a clockwise direction, the configuration is ***R***.
  - If the rank declines in a counterclockwise direction, the configuration is ***S***.

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Cahn - Ingold - Prelog RS Notational System

- The labels *R* and *S* come from the Latin words *rectus*, which means "right," and *sinister*, meaning "left."
- The right and left designations refer only to the order of atoms or groups about a stereogenic center. They do not refer to the direction in which plane - polarized light is rotated by the molecule.

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Cahn-Ingold-Prelog Rules

- Assign a priority number to each group attached to the chiral carbon.
- Atom with highest atomic number assigned the highest priority #1.
- In case of ties, look at the next atoms along the chain.
- Double and triple bonds are treated like bonds to duplicate atoms.

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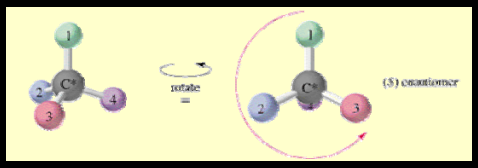
Assign (*R*) or (*S*)

- Working in 3D, rotate molecule so that lowest priority group is in back.
- Draw an arrow from highest to lowest priority group.
- Clockwise = (*R*), Counterclockwise = (*S*)



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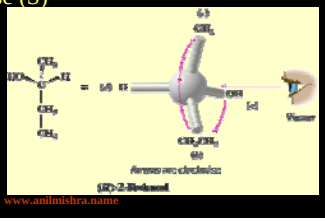
Assign (*R*) or (*S*)

Orient the molecule so that lowest-ranked (lightest) substituent points away from you. Trace the path from highest to lowest. Clockwise (R), Counter Clockwise (S)



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Molecules with more than One Chiral Carbon

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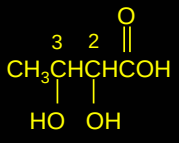
2,3-Dihydroxybutanoic acid



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

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

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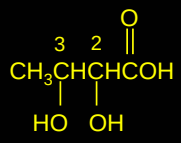
2,3-Dihydroxybutanoic acid



4 Combinations = 4 Stereoisomers

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

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2,3-Dihydroxybutanoic acid

4 Combinations = 4 Stereoisomers

What is the relationship between these stereoisomers?

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

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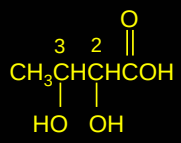
2,3-Dihydroxybutanoic acid



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

They have the same physical properties.

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

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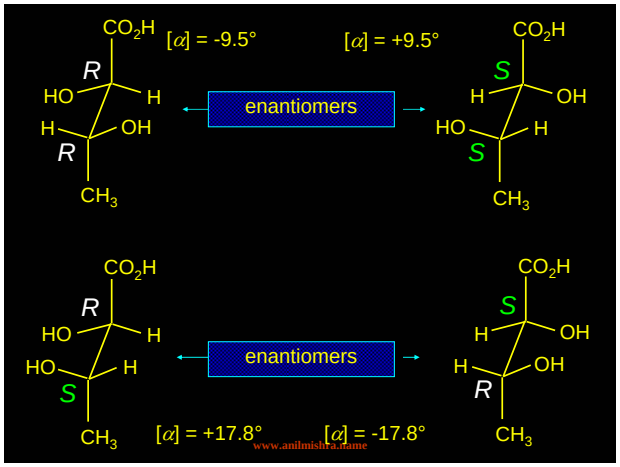

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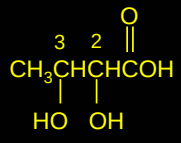
2,3-Dihydroxybutanoic acid



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*

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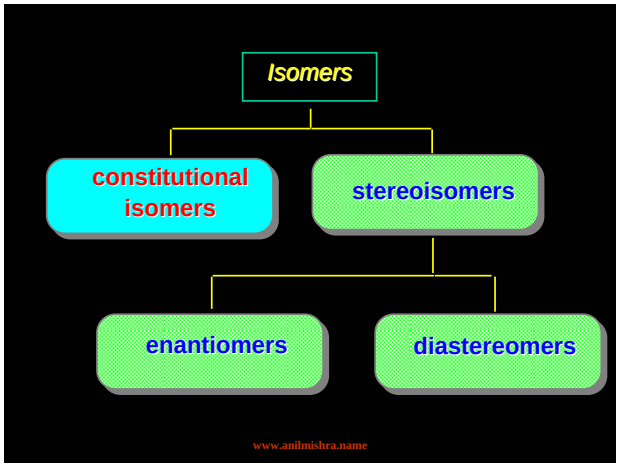

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Enantiomers

- Molecules that are optical isomers are called enantiomers.
- Enantiomers have identical chemical and physical properties, except:
  - Their effect on plane polarised light;
  - Their reaction with other chiral molecules
- Optical isomers are said to be chiral, and the isomers are called a pair of enantiomers.

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Diastereomers

- **Diastereomers** are stereoisomers that are not enantiomers
- They are distinct molecules with the same structural arrangement of atoms that are non-superimposible, non-mirror images of each other.

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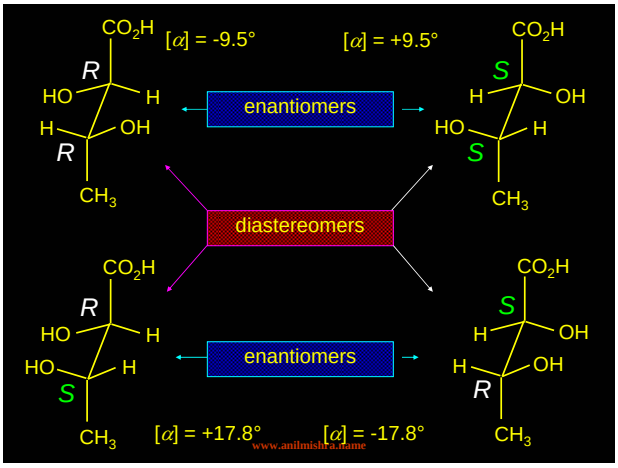

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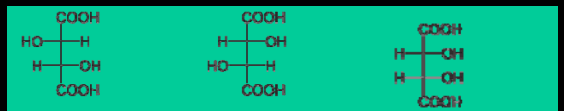
Diastereomers

- In tartaric acid, both of the central carbon atoms are stereogenic centers. Thus, they both must be assigned R or S configurations according to the Cahn–Ingold–Prelog system.
- The first two molecules (2S,3S)-tartaric acid and (2R,3R)-tartaric acid, are clearly enantiomers of each other since they are mirror images.



(2S,3S)-tartaric acid (2R,3R)-tartaric acid (2R,3S)-tartaric acid

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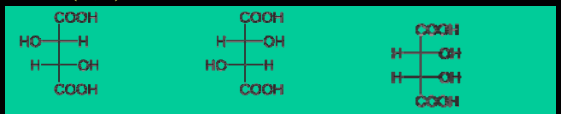
Diastereomers

- But what about the third molecule, (2R,3S)-tartaric acid? It is clearly distinct from the first two, yet the same atoms are bonded to each other.
- It is also very clearly not a mirror image of either of the first two. Thus, as a non-superimposible, non-mirror image with the same arrangement of atoms,
  - (2R,3S)-tartaric acid is a **diastereomer** of the first two molecules.



(2S,3S)-tartaric acid (2R,3R)-tartaric acid (2R,3S)-tartaric acid

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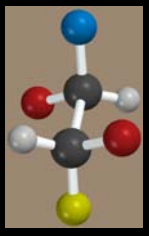
Fischer Projections



For Fischer projection: horizontal bonds point toward you; vertical bonds point away

staggered conformation does not have correct orientation of bonds for Fischer projection

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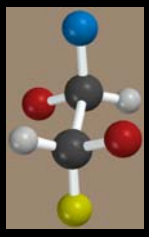
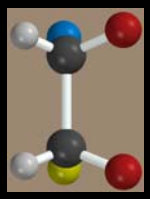
Fischer projections





transform molecule to eclipsed conformation in order to construct Fischer projection

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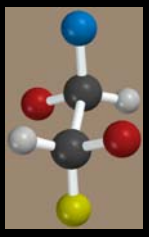
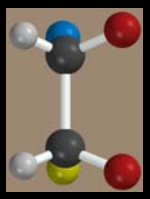
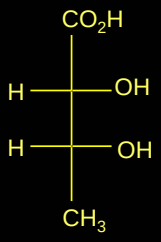
Fischer projections







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Erythro and Threo

stereochemical prefixes used to specify relative configuration in molecules with two chiral carbons

easiest to apply using Fischer projections

orientation: vertical carbon chain

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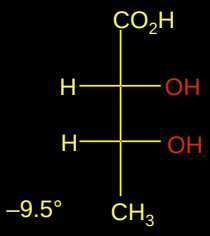
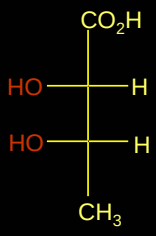
Erythro

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



–9.5°



+9.5°

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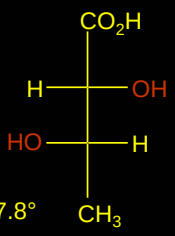
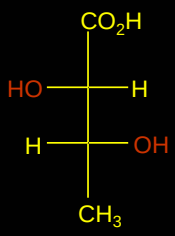
Threo

when carbon chain is vertical, same (or analogous) substituents on **opposite sides** of Fischer projection



+17.8°



–17.8°

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Achiral Molecules
with
Two Chiral Centers

It is possible for a molecule to have chiral carbons yet be achiral.

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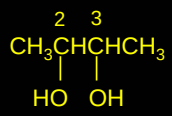
2,3-Butanediol



Consider a molecule with two equivalently substituted chiral carbons such as 2,3-butanediol.

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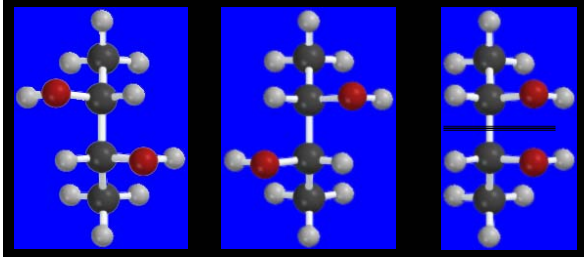
Three stereoisomers of 2,3-butanediol



2R,3*R* chiral

2S,3*S* chiral

2R,3*S* achiral

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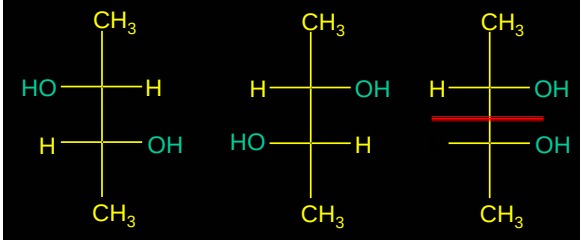
Three stereoisomers of 2,3-butanediol



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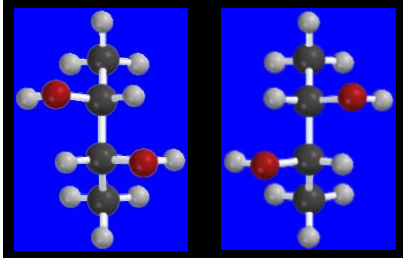
Three stereoisomers of 2,3-butanediol



these two are enantiomers

2R,3*R* chiral

2S,3*S* chiral

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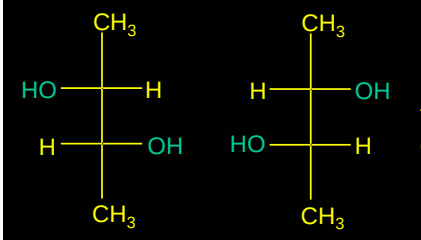
Three stereoisomers of 2,3-butanediol



these two are enantiomers

2R,3*R* chiral

2S,3*S* chiral

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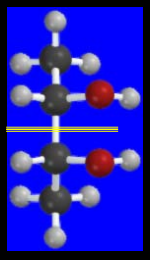
Three stereoisomers of 2,3-butanediol

the third structure is superposable on its mirror image



2R,3*S* achiral

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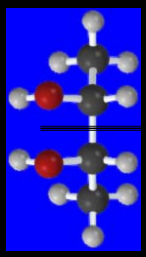
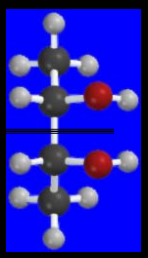
Three stereoisomers of 2,3-butanediol



therefore, this structure and its mirror image are the same

it is called a meso form

a meso form is an achiral molecule that has chiral carbons



2R,3S

achiral

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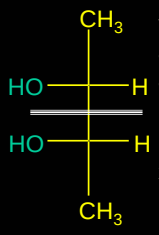
Three stereoisomers of 2,3-butanediol



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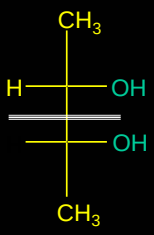

2R,3S

achiral

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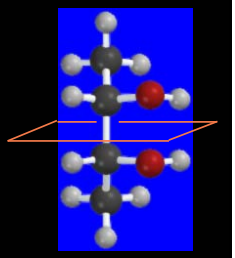
Three stereoisomers of 2,3-butanediol

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



2R,3S

achiral

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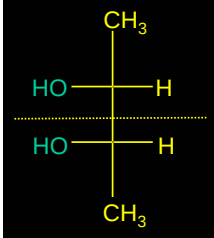
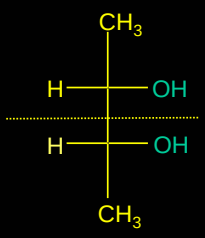
Three stereoisomers of 2,3-butanediol



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



2R,3S

achiral

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