Chemistry and Introduction to Biochemistry

Isomerism

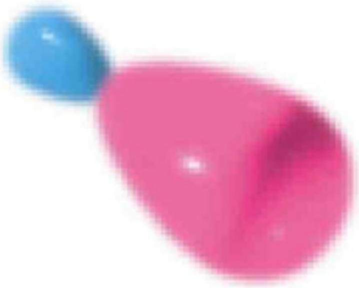
F Malatesta

Orbital hybridization (L. Pauling)

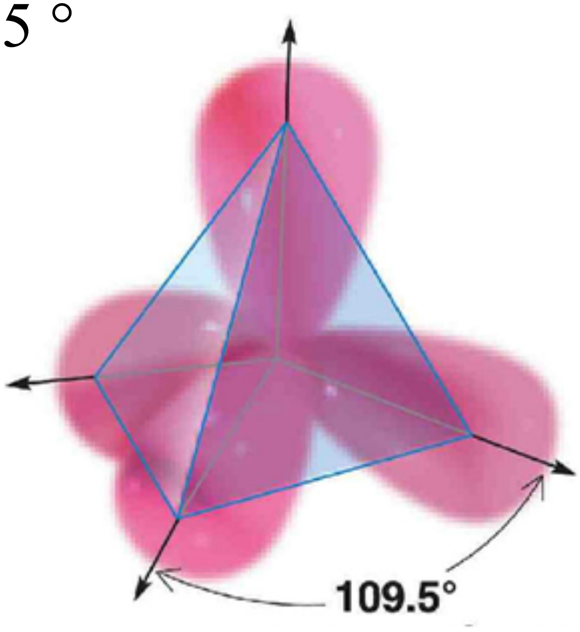
- 3 types of hybrid orbitals:
  - sp^3 (1 s orbital s + 3 p orbitali)
  - sp^2 (1 s orbital + 2 p orbitals)
  - sp (1 s orbital + 1 p orbital)
- the overlap of hybrid orbitals produces 2 types of bonds depending on the geometry of the overlap:
  - σ bonds: co-axial overlap
  - π bonds: lateral overlap

sp^3 hybrid orbitals (present in all alkanes)

- one 2s orbital and three 2p orbitals are mixed to give 4 sp^3 orbitals
- each sp^3 hybrid orbital has 2 lobes of different sizes
- the sign of the wave function is positive in one lobe, negative in the other and is null at the nucleus
- the 4 sp^3 hybrid orbitals are directed at the vertices of a regular tetrahedron with angles of 109.5 °



an sp^3 hybrid orbital

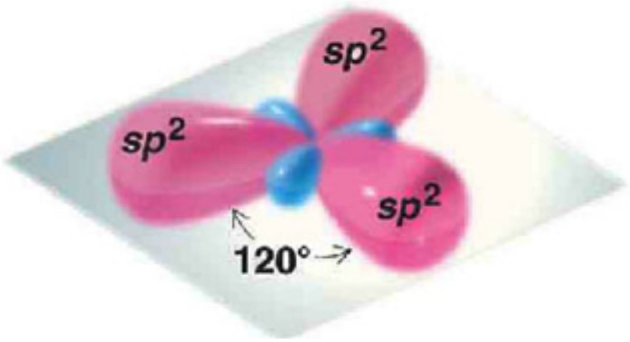


4 tetrahedral sp^3 orbitals

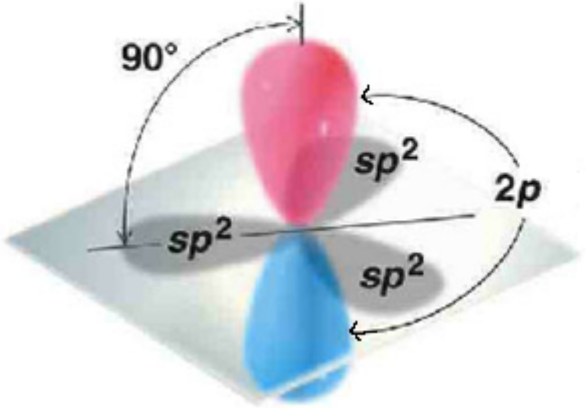
Orbitali ibridi sp^2 (presenti in tutti gli alcheni e areni)

- one 2s orbital and two 2p orbitals are mixed to give 3 sp^2 orbitals, one unhybridized 2p orbital remains
- each sp^2 hybrid orbital has 2 lobes of different sizes
- the axes of the three sp^2 hybrid orbitals lie on a plane and are directed at the vertices of an equilateral triangle with angles of 120°
- the unhybridized 2p orbital is perpendicular to the plane of the three sp^2 hybrid orbitals

a sp^2 hybrid orbital



3 trigonal planar sp^2 orbitals

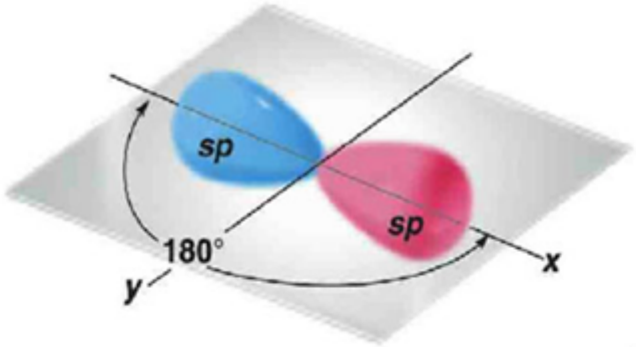


3 sp^2 orbital and 1 2p orbital not hybridized orbital

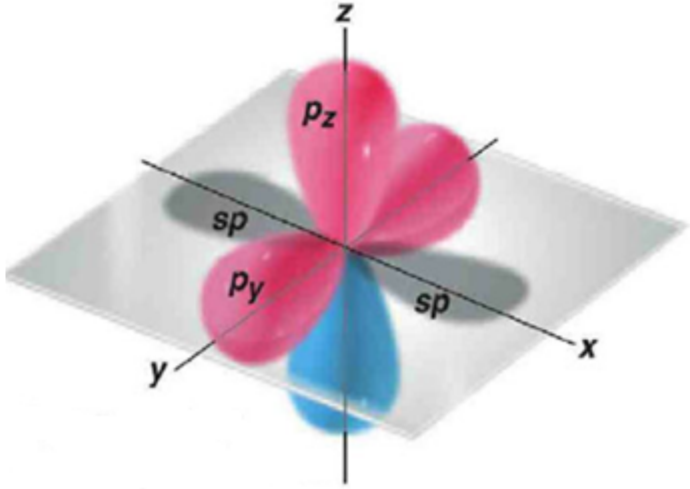
Orbitali ibridi sp (presenti in tutti gli alchini)

- 1 orbitale 2s e 1 orbitale 2p si mescolano per dare 2 orbitali sp, e rimangono 2 orbitali 2p non ibridizzati
- ogni orbitale ibrido sp ha 2 lobi di dimensione diversa
- i 2 orbitali sp sono coassiali (angolo di 180°)
- i 2 orbitali 2p non ibridizzati sono fra loro perpendicolari e perpendicolari all'asse che congiunge i 2 orbitali sp

un orbitale
ibrido sp



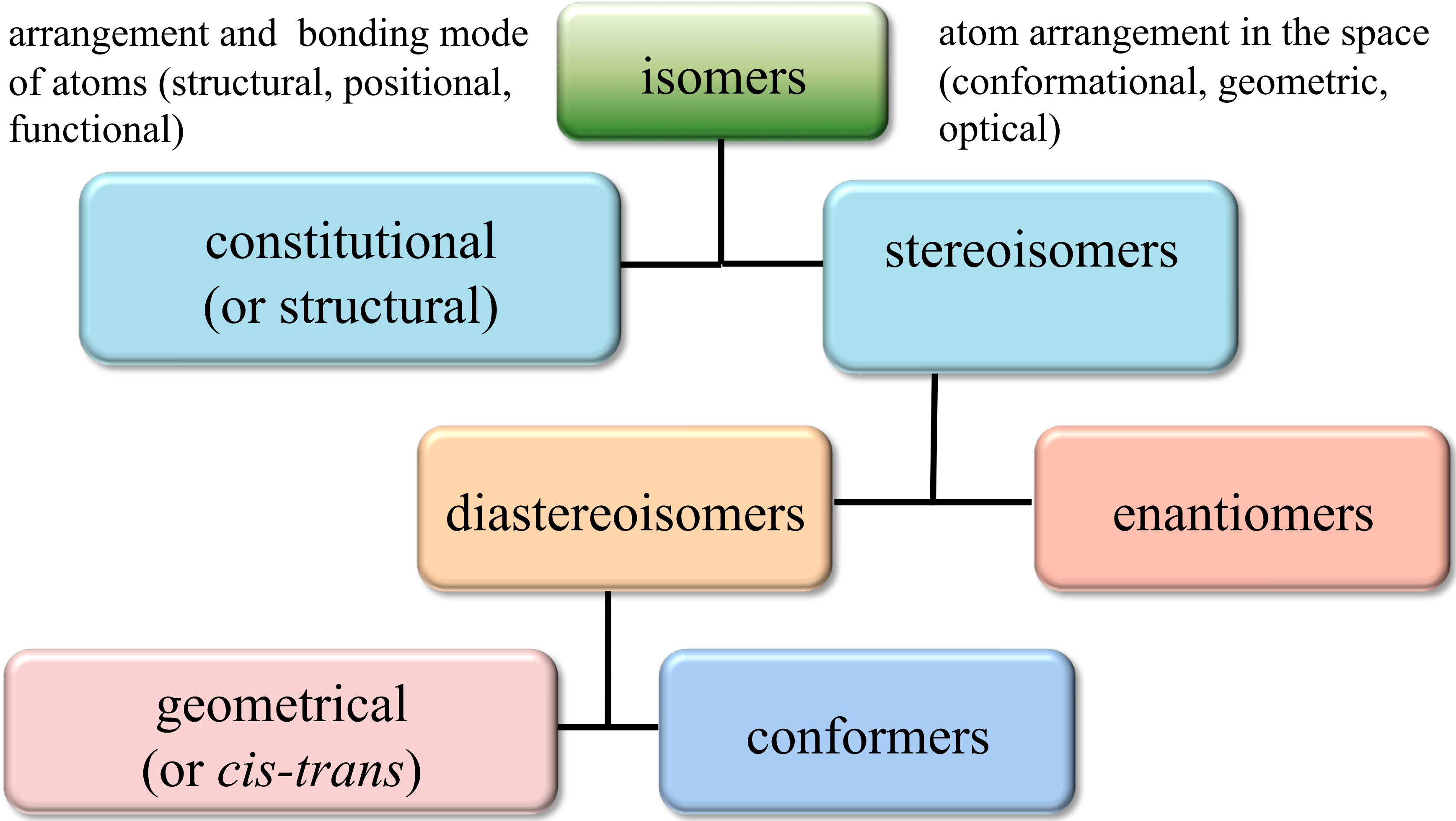
2 orbitali
ibridi sp



2 orbitali sp e 2 orbitali
2p non ibridizzati

Isomerism

The relation of two or more compounds that are composed of the same kinds and numbers of atoms but differ from each other in their structural arrangement (from Greek υσοσ = equal, μεροσ = part). Isomers do not share chemical and physical properties



arrangement and bonding mode of atoms (structural, positional, functional)

isomers

atom arrangement in the space (conformational, geometric, optical)

constitutional (or structural)

stereoisomers

diastereoisomers

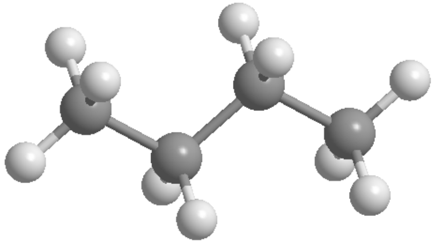
enantiomers

geometrical (or *cis-trans*)

conformers

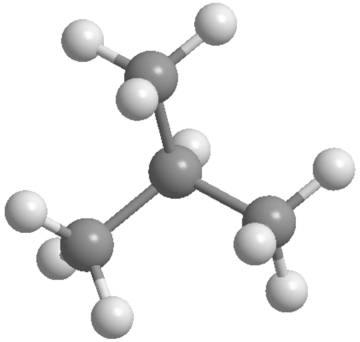
Constitutional isomers: differ in the arrangement and bonding mode of atoms

Structural: different carbon backbone C_4H_{10}



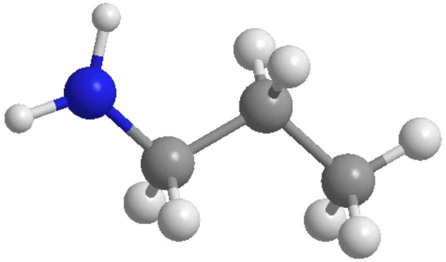
butane

C_4H_{10}



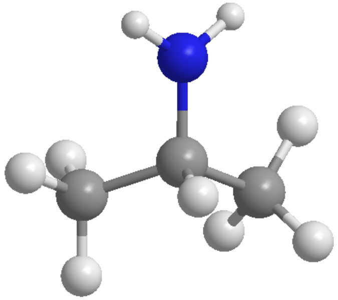
methylpropane

Positional: different position of functional groups C_3H_9N



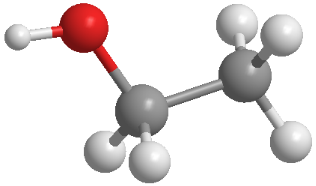
1-amino-propane

C_3H_9N



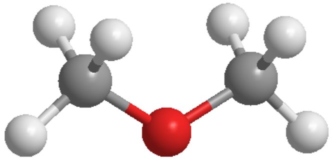
2-amino-propane

Functional: different functional groups C_4H_{10}



ethanol

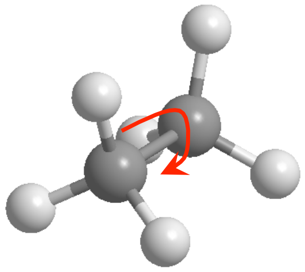
C_2H_6O



dimethy eter

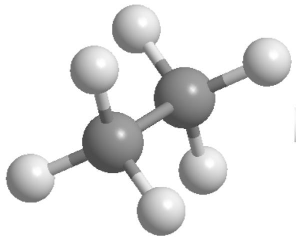
Stereoisomers: they differ in atom arrangement in space

Conformational:
rotation around a
σ bond
C_2H_6



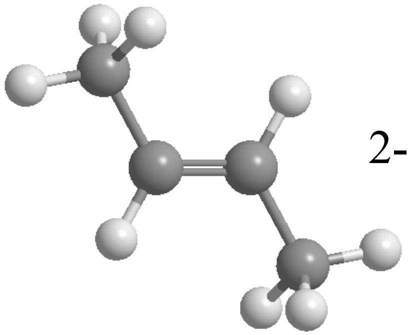
eclipsed

ethane



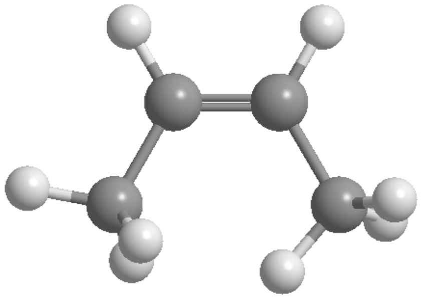
staggered

Geometrical: impediment to
rotation due to the presence
of a double bond or ring
C_4H_8



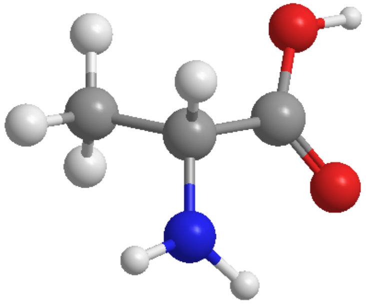
trans

2-butene



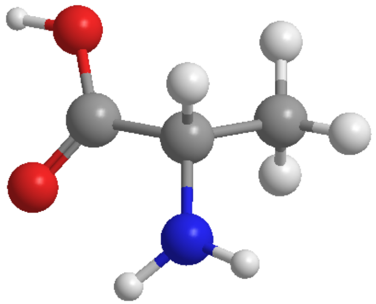
cis

Optical: presence of
chiral centers
$C_3H_7NO_2$



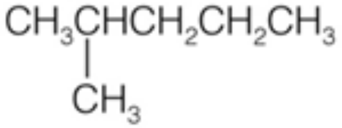
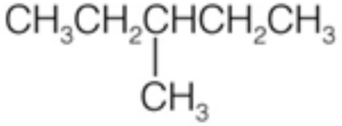
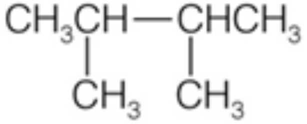
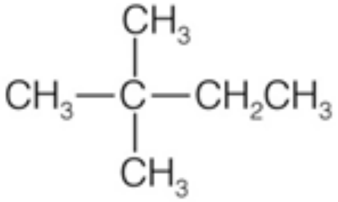
R ore D

alanine



S or L

Constitutional isomers have different physical properties

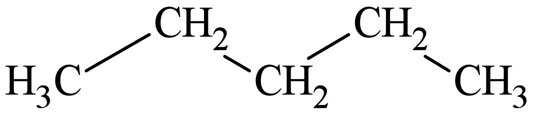
empirical formula	structural	T_{fus} (°C)	T_{eb}1atm (°C)	$\delta^{20°}$ (g/ml)
C_6H_{14}	$CH_3CH_2CH_2CH_2CH_2CH_3$	−95	68.7	0.6594
C_6H_{14}	 $CH_3\underset{CH_3}{C}HCH_2CH_2CH_3$	−153.7	60.3	0.6532
C_6H_{14}	 $CH_3CH_2\underset{CH_3}{C}HCH_2CH_3$	−118	63.3	0.6643
C_6H_{14}	 $CH_3\underset{CH_3}{C}H-\underset{CH_3}{C}HCH_3$	−128.8	58	0.6616
C_6H_{14}	 $CH_3-\overset{CH_3}{\underset{CH_3}{C}}-CH_2CH_3$	−98	49.7	0.6492

top to bottom: *n*-hexane, 2-methylpentane, 3-methylpentane, 2,3-dimethylbutane, 2,2-dimethylbuthane

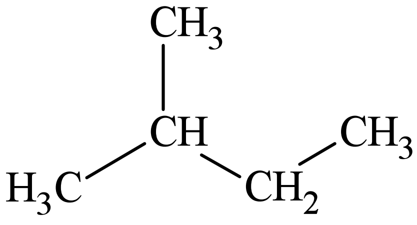
There are no constitutional isomers for methane, ethane and propane. The number of isomers increases rapidly with the number of C atoms

empirical formula	number of possible constitutional isomers
C_4H_{10}	2
C_5H_{12}	3
C_6H_{14}	5
C_7H_{16}	9
C_8H_{18}	18
C_9H_{20}	35
$C_{10}H_{22}$	75
$C_{15}H_{32}$	4347
$C_{20}H_{42}$ (icosane)	366 319
$C_{30}H_{62}$ (triacontane)	4 111 846 763
$C_{40}H_{82}$ (tetracontane)	62 481 401 147 341

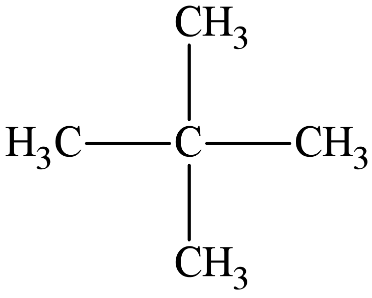
Example: how many isomers of pentane (C_5H_{12}) are possible?



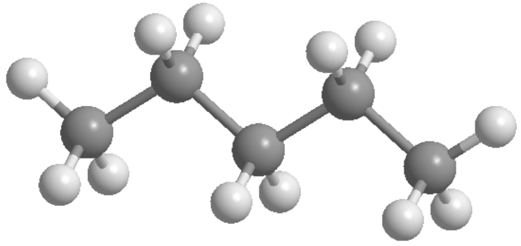
pentane

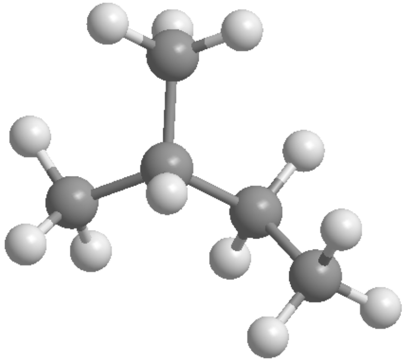


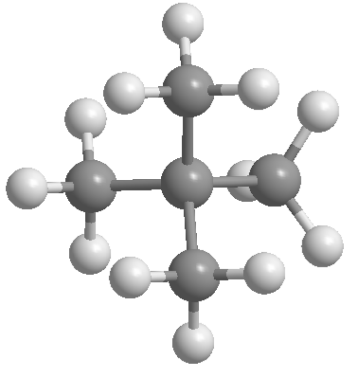
2-methylbutane



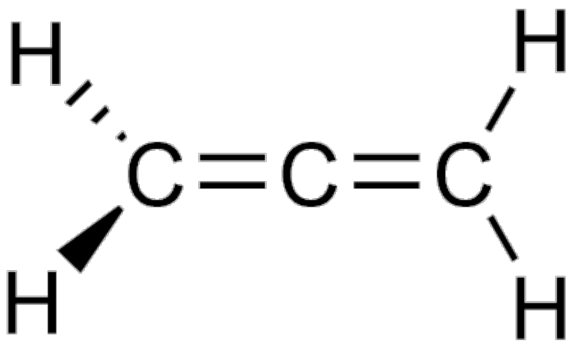
dimethylpropane



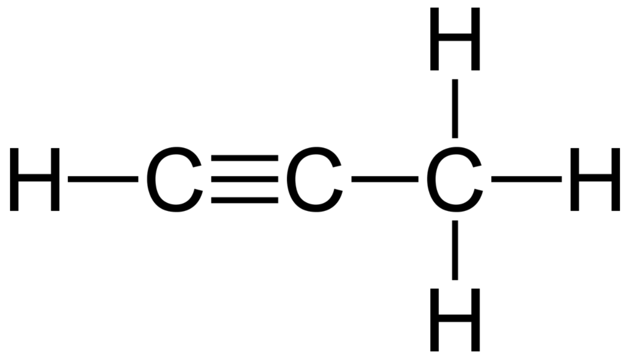




Classify these two isomers



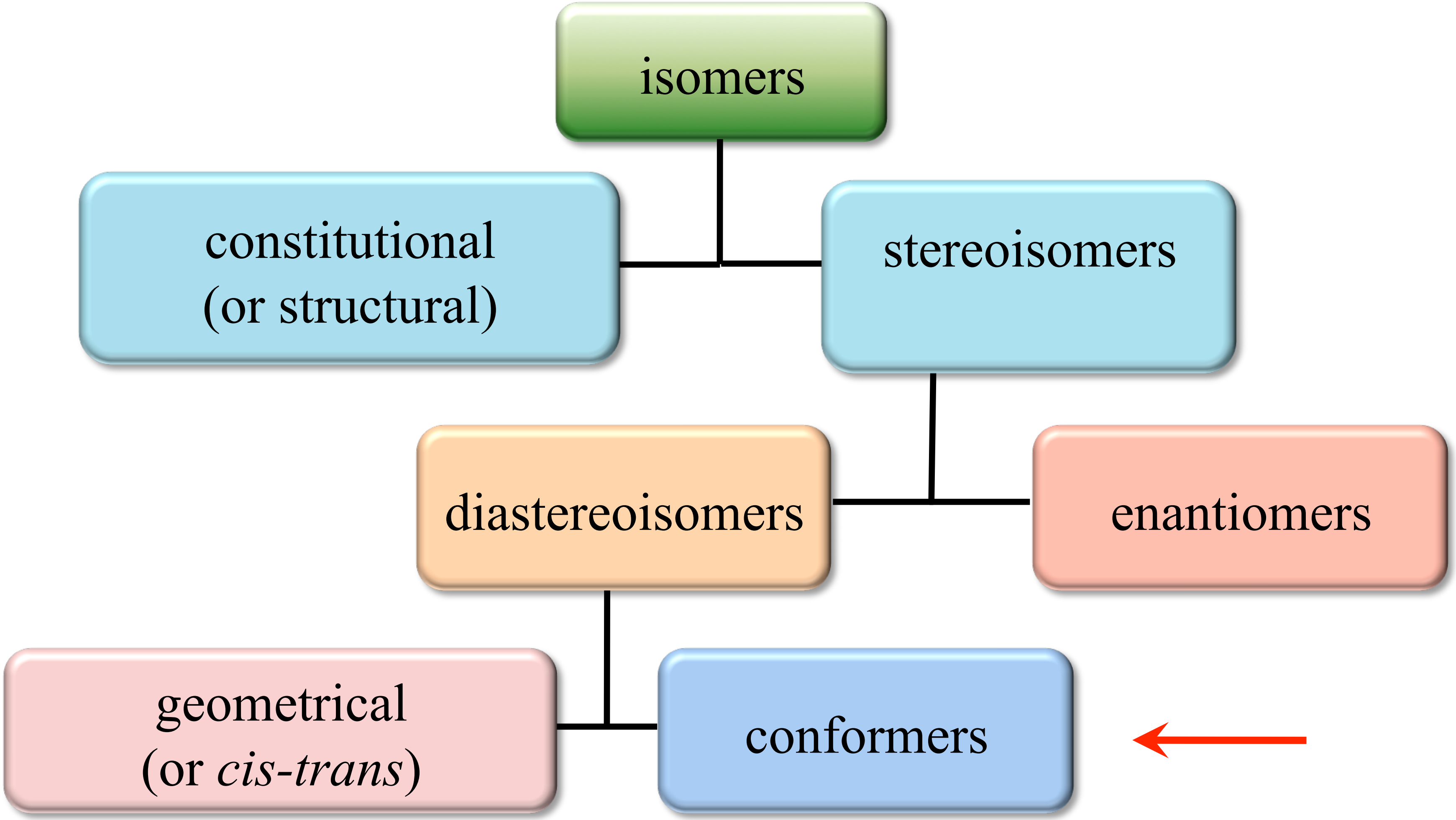
propadiene



propyne

Both are isomers since: C_3H_4

They are constitutional functional isomers



isomers

constitutional
(or structural)

stereoisomers

diastereoisomers

enantiomers

geometrical
(or *cis-trans*)

conformers

The conformation of a molecule

The conformation of a molecule is the spatial arrangement that the atoms of a molecule take by rotating around a σ bond. Each conformation is also called conformational isomer, conformer or rotamer.

In the vast majority of cases, at room temperature the conformations rapidly interconvert one into the other and it is not possible to isolate a single conformer.

There may be cases, however, in which the steric hindrance blocks the molecule in one of the possible conformations

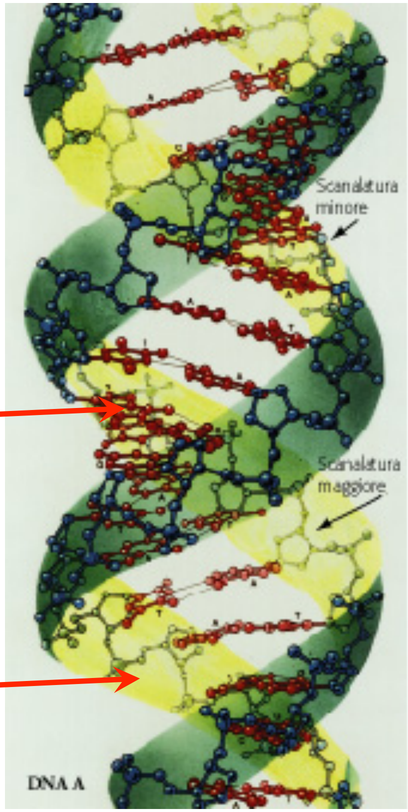
Conformational changes are of fundamental importance in biology

- protein folding is a complex conformational process
- during the catalytic cycle many enzymes necessarily change conformation
- DNA can take different shapes
- allosteric proteins (hemoglobin)

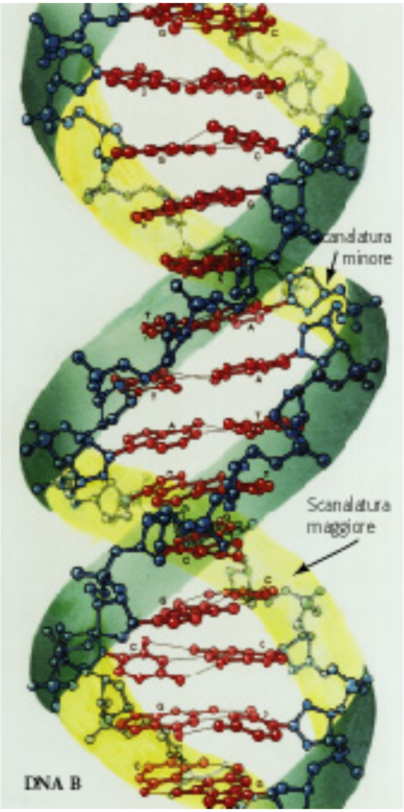
The DNA double helix can take on different conformations, which can influence DNA-protein recognition. The relative dimensions of the major and minor grooves vary with the type of conformation

minor groove

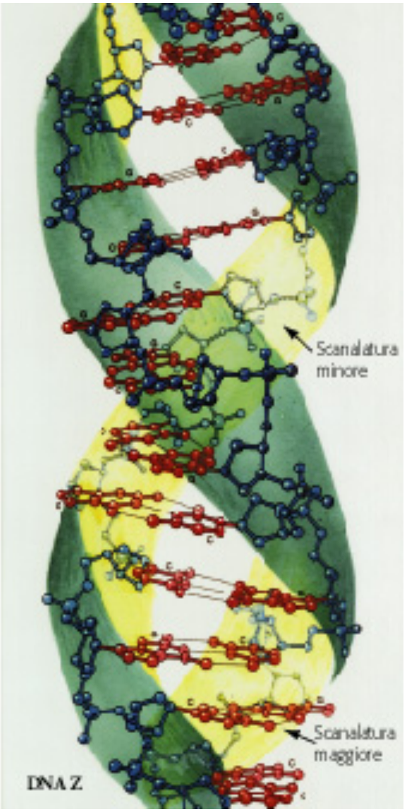
major groove



A DNA

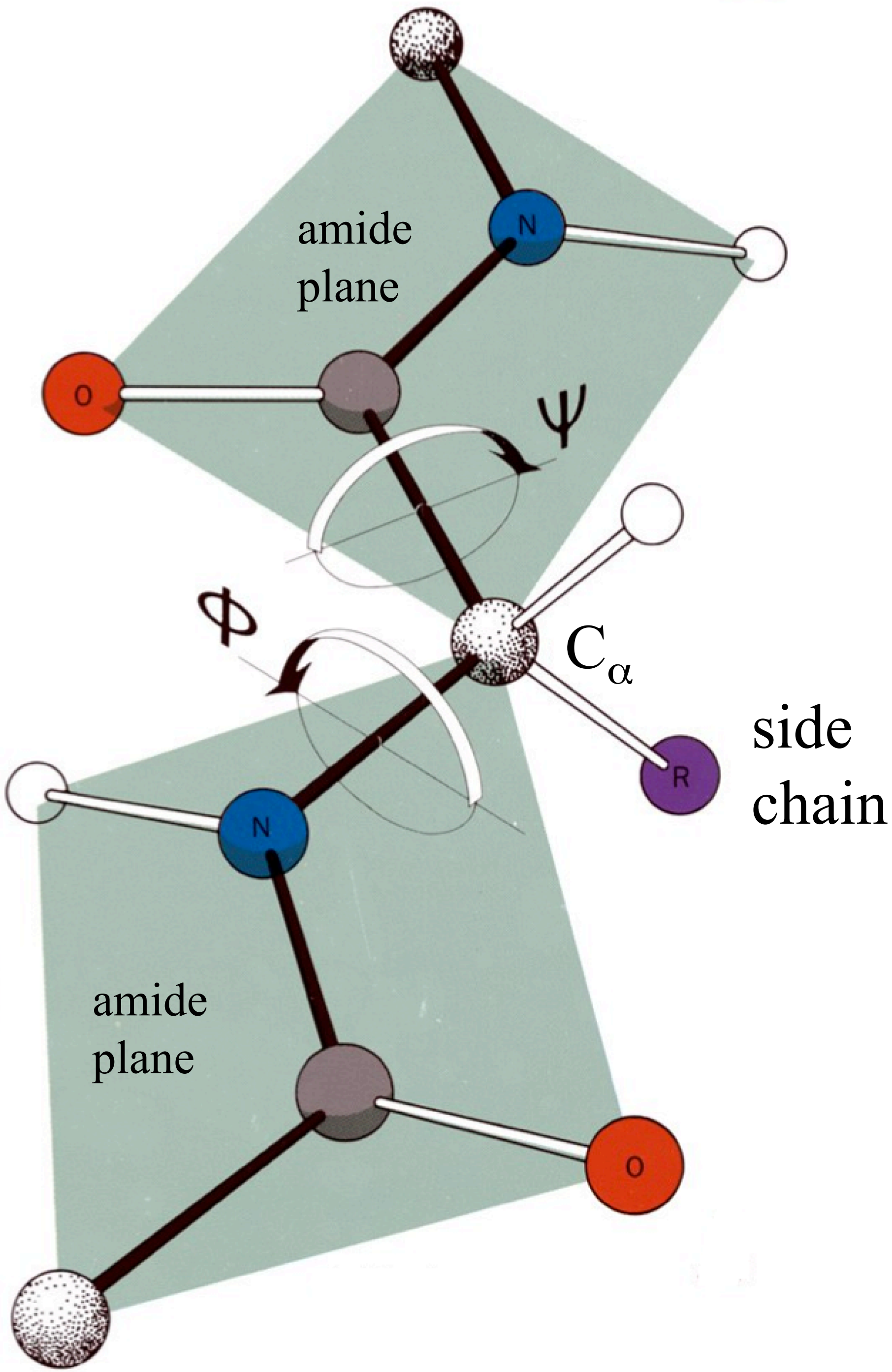


B DNA



Z DNA

A= 11 bases/turn (24.6 Å) – diameter: 26 Å – right-handed
B= 10 bases/turn (33.2 Å) – diameter: 20 Å – right-handed
Z= 12 bases/turn (45.6 Å) – diameter: 18 Å – left-handed



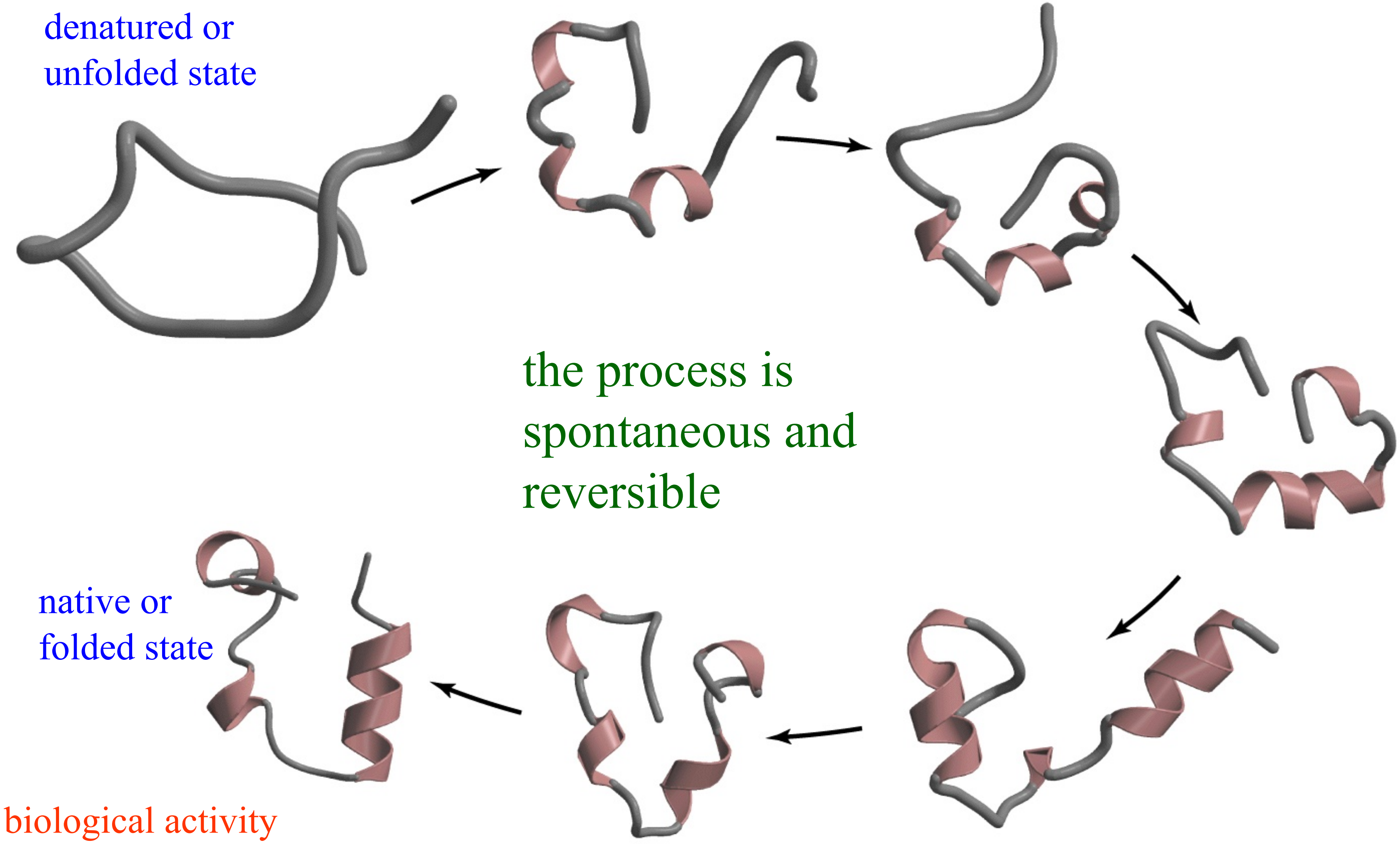
The peptide bond and the ϕ e ψ solid angles

ϕ: rotation around the amide C_α-N bond

ψ: rotation around the C_α- carbonyl C bond

The numerical values of the dihedral angles identify the conformation of the polypeptitide

Protein folding: a conformational process



denatured or
unfolded state

the process is
spontaneous and
reversible

native or
folded state

biological activity

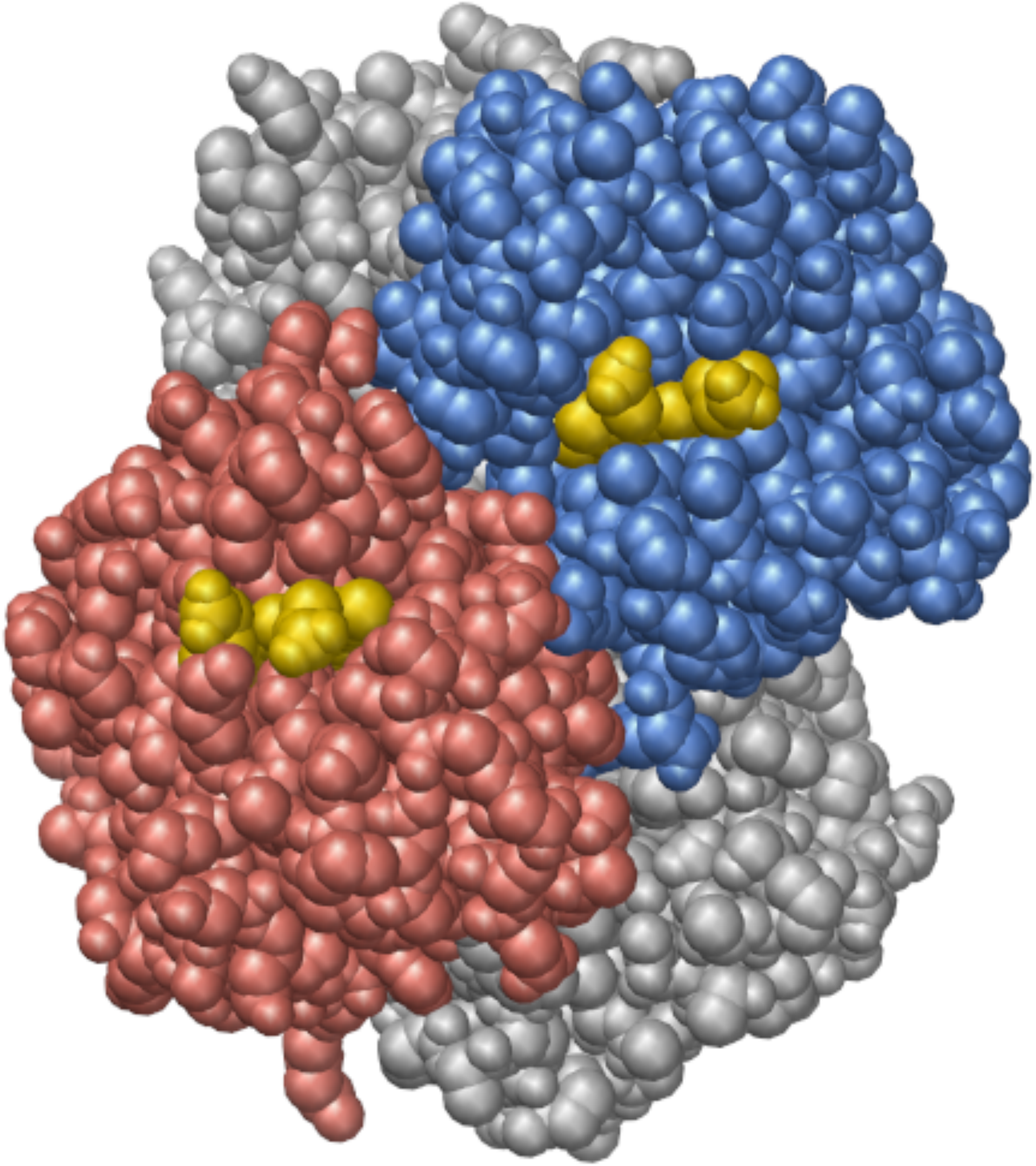
Representative protein folding diseases

disease	protein	site of folding
hypercholesterolaemia	low-density lipoprotein receptor	ER
cystic fibrosis	cystic fibrosis transmembrane regulator	ER
phenylketonuria	phenylalanine hydroxylase	cytosol
Huntington's disease	huntingtin	cytosol
Marfan syndrome	fibrillin	ER
osteogenesis imperfecta	procollagen	ER
sickle cell anaemia	haemoglobin	cytosol
α1-antitrypsin deficiency	α1-antitrypsin	ER
Tay–Sachs disease	β-hexosaminidase	ER
scurvy	collagen	ER
Alzheimer's disease	β-amyloid/presenilin	ER
Parkinson's disease	α-synuclein	cytosol
scrapie/Creutzfeldt–Jakob disease	prion protein	ER
familial amyloidoses	transthyretin/lysozyme	ER
retinitis pigmentosa	rhodopsin	ER
cataracts	crystallins	cytosol
cancer	p53	cytosol

Conformational changes in hemoglobin change O_2 affinity

Deoxy state

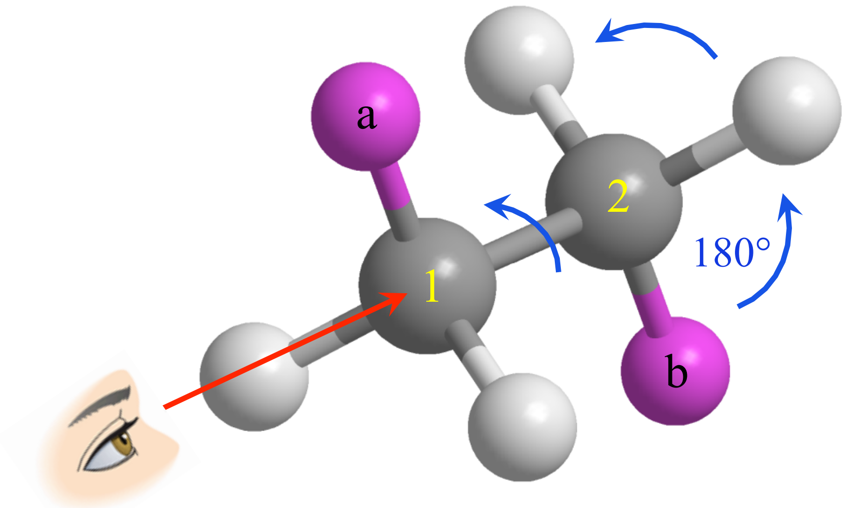
Oxy state

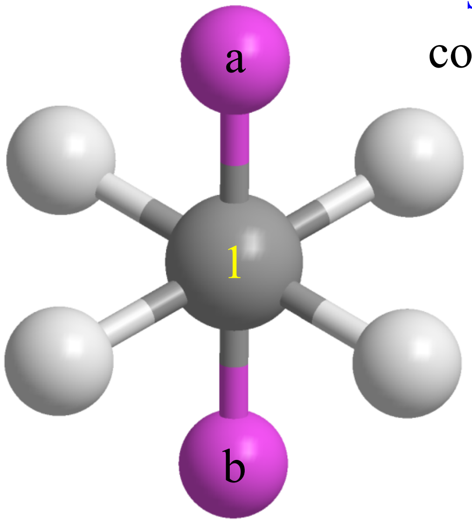


α_1

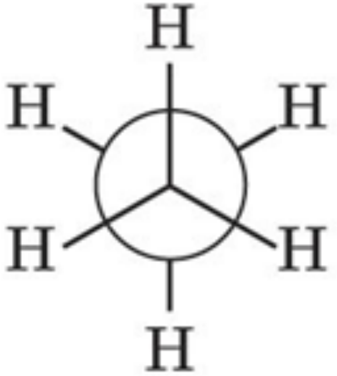
β_1

The conformations of ethane (C_2H_6)



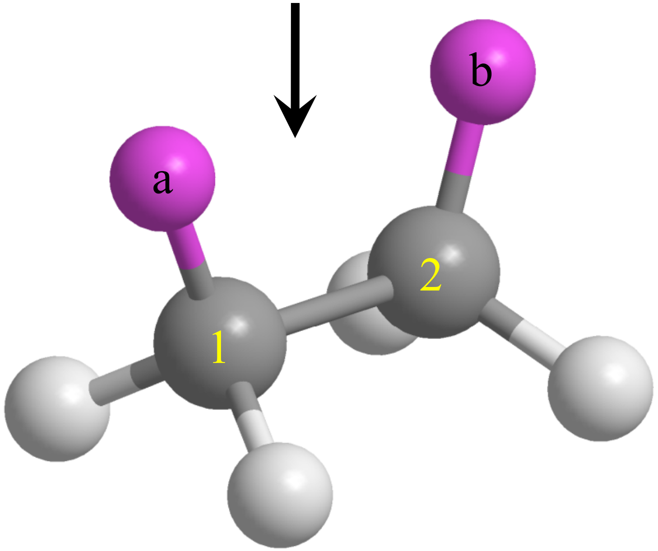


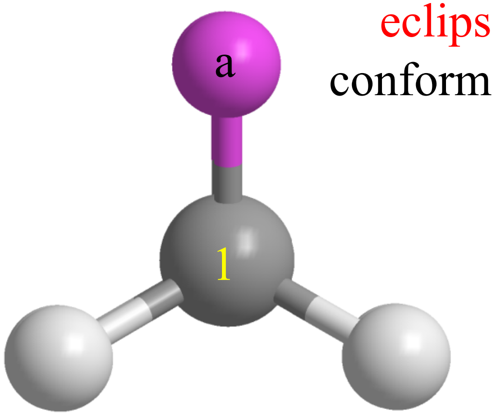
staggered
conformation

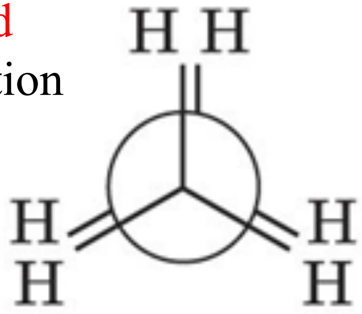


Newman
projections

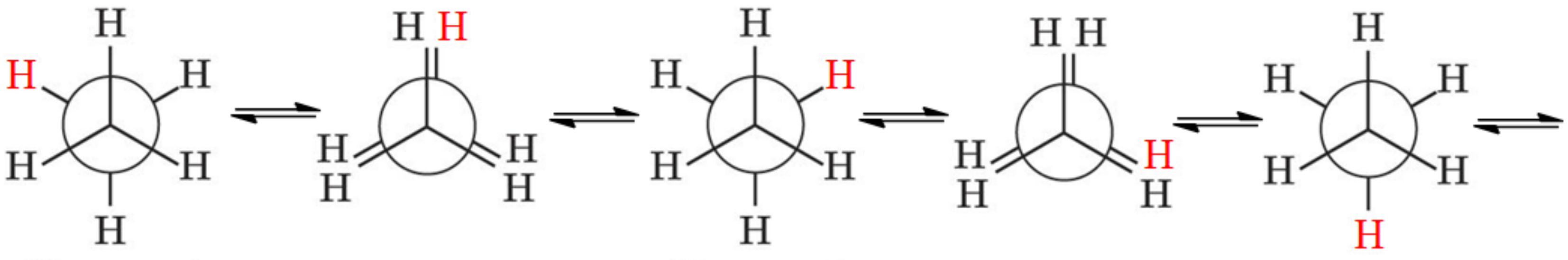
eclipsed
conformation

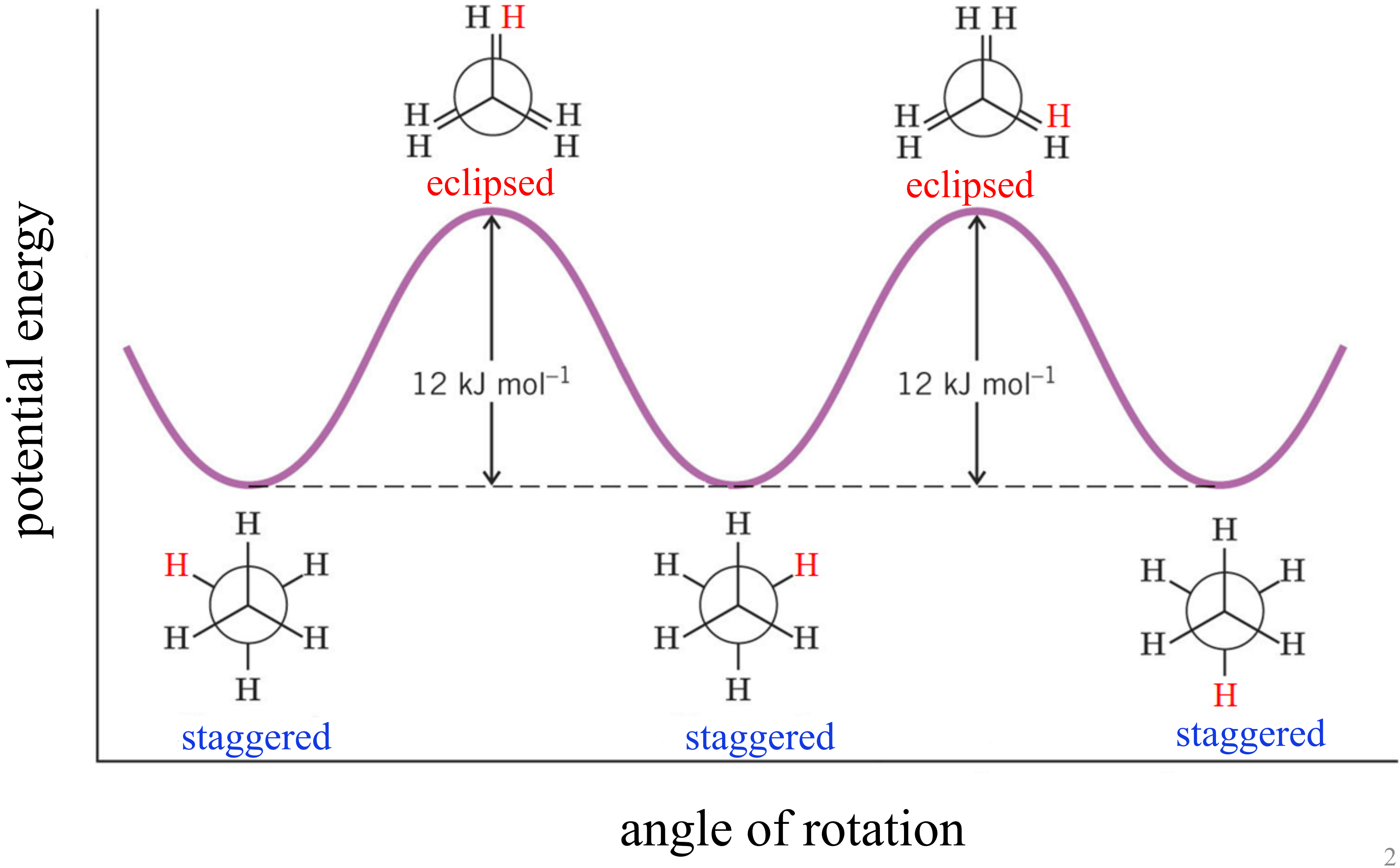






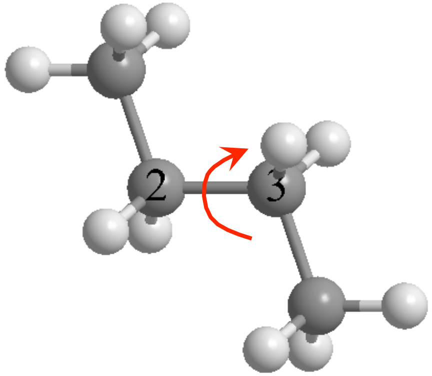
Because of the reciprocal electrostatic repulsion between the electrons, ethane tends to preferably assume a staggered conformation

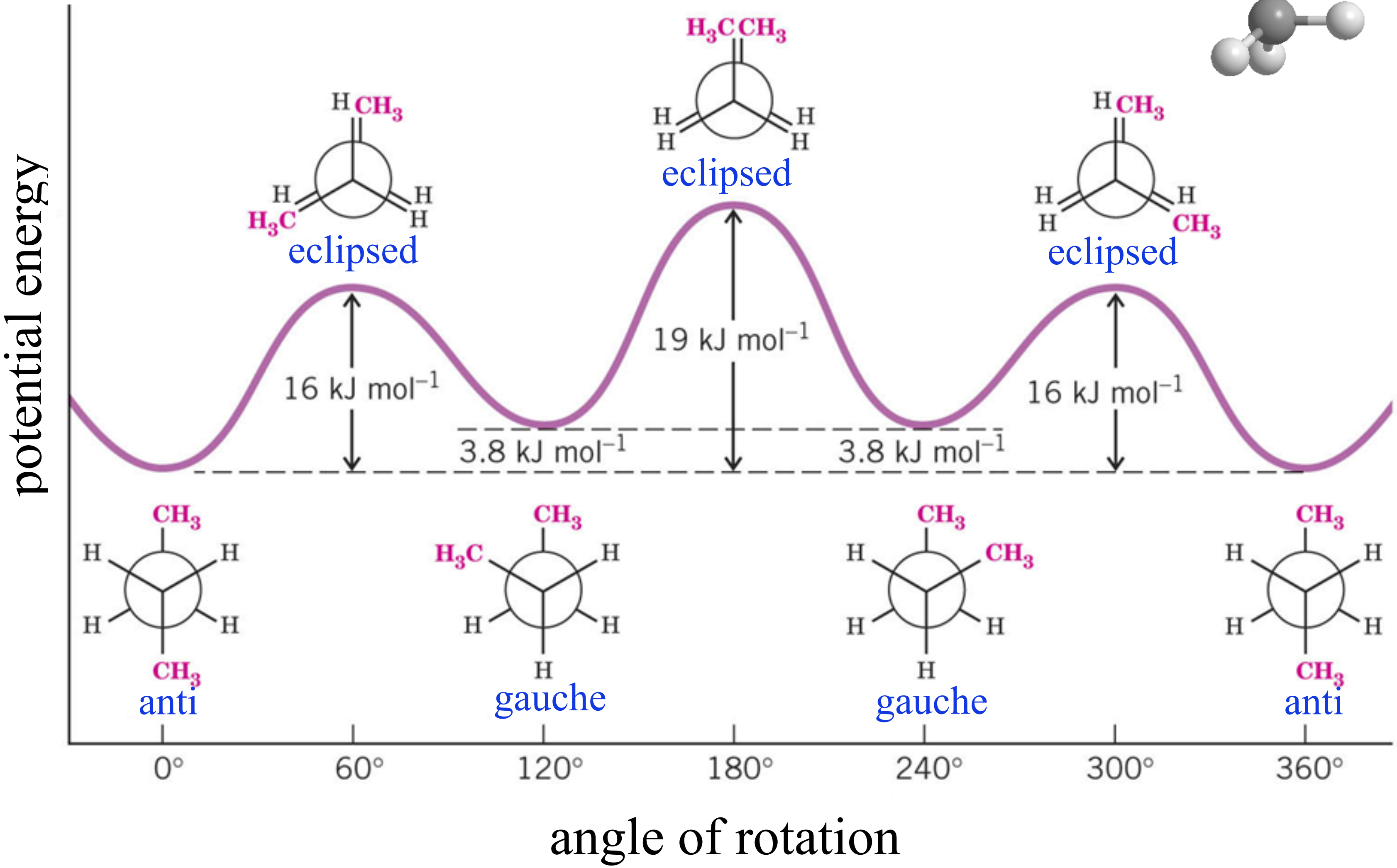



eclipsed
eclipsed
12 kJ mol^{-1}
12 kJ mol^{-1}
potential energy
staggered
staggered
staggered
angle of rotation

The conformations of butane

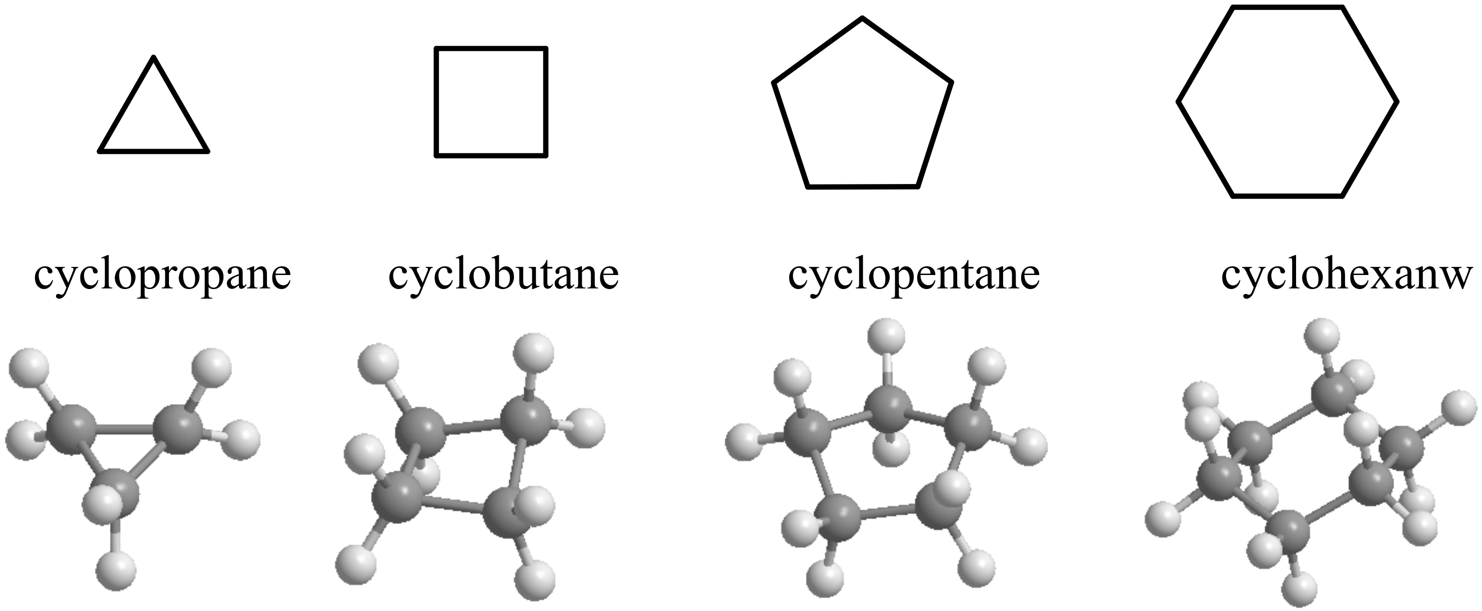
The rotation around the C_2 - C_3 generates several conformers





I cycloalkanes (C_nH_{2n})

Cycloalkanes are cyclic aliphatic hydorcarbons

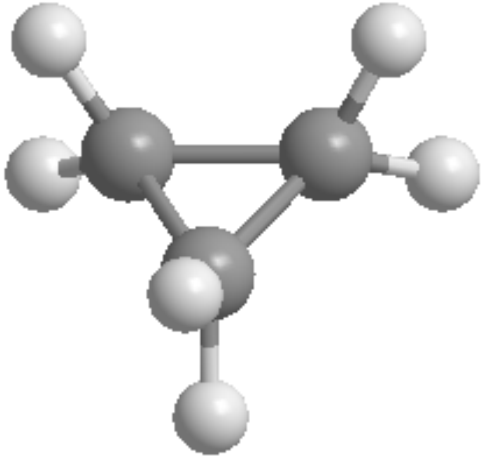


cyclopropane cyclobutane cyclopentane cyclohexanw

They can give addition reactions that cause ring rupture and the formation of open chain compounds. The unusual fact that an alkane gives addition reactions is possible because cycloalkanes have a so-called ring tension.

- In a sp^3 carbon, any deviation from the tetrahedral angle is accompanied by an angular tension.
- Each pair of sp^3 carbons tends to reach a staggered conformation: any deviation from such an arrangement results in a torsional tension.
- Due to the steric hindrance between neighboring groups a steric tension also develops

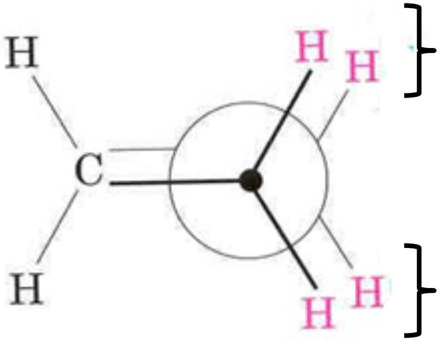
cyclopropane



one planare conformation

In cyclopropane the bond angles of 60° determine a very large angular tension

In this configuration there are 6 pairs of eclipsed C-H bond interactions



eclipsed hydrogens

eclipsed hydrogens

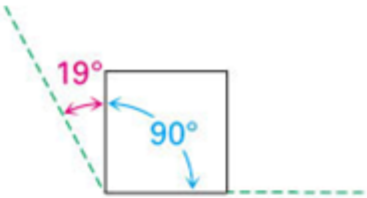
Ring or anular tension

Angular tension: the tension that originates from the expansion or compression of the bond angles.

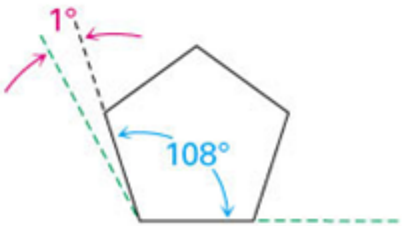
Torsional tension: the tension caused by the eclipsing of bonds on adjacent atoms.

Steric tension: the tension caused by the repulsive interactions between atoms that are too close to each other

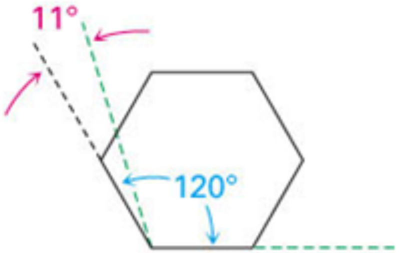
cyclopropane



cyclobutane



cyclopentane



cyclohexane

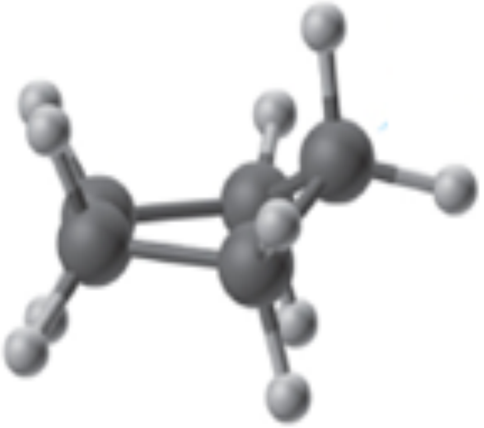
Cycloalkanes partially solve the problem of annular tension by adopting non-planar conformations

In the planar conformation of cyclopentane there are 10 pairs of eclipsed C-H bond interactions

Adpating to a non-planar conformation partially eliminates the torsional tension due eclipsing

cyclopentane

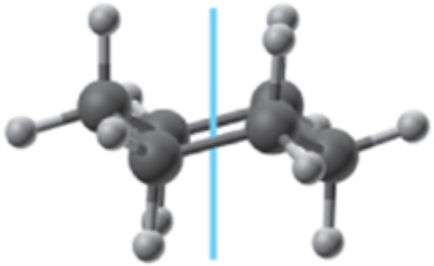
planar conformation

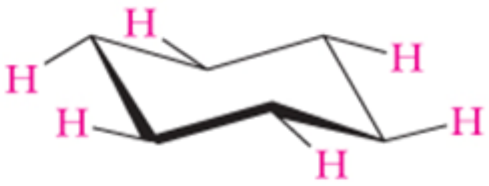


envelope conformation

In cyclohexane the ring tension is removed by adopting a chair conformation

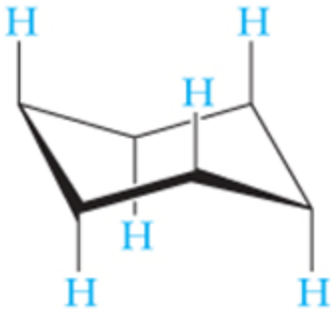
axis





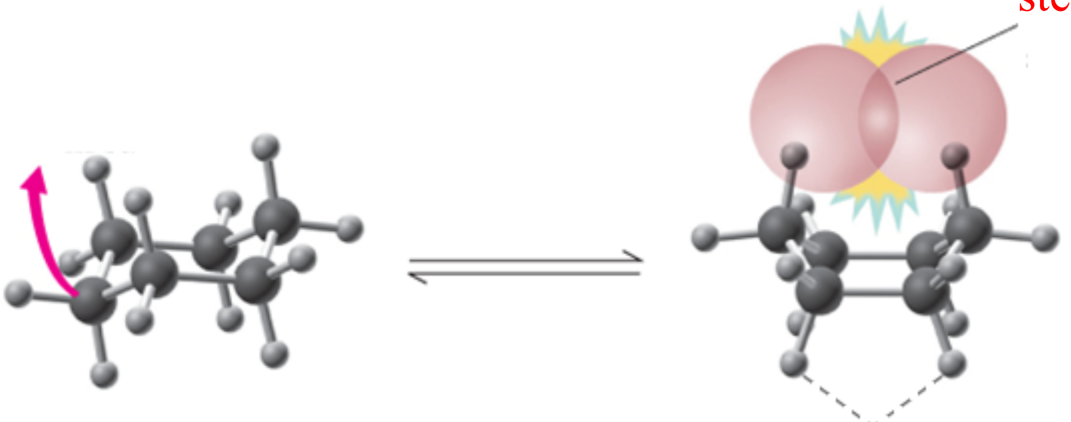
6 equatorial C-H bonds

6 axial C-H bonds



The chair conformation is the most stable because the staggered arrangement of each C-C pair is free of torsional stresses and has less steric repulsion.

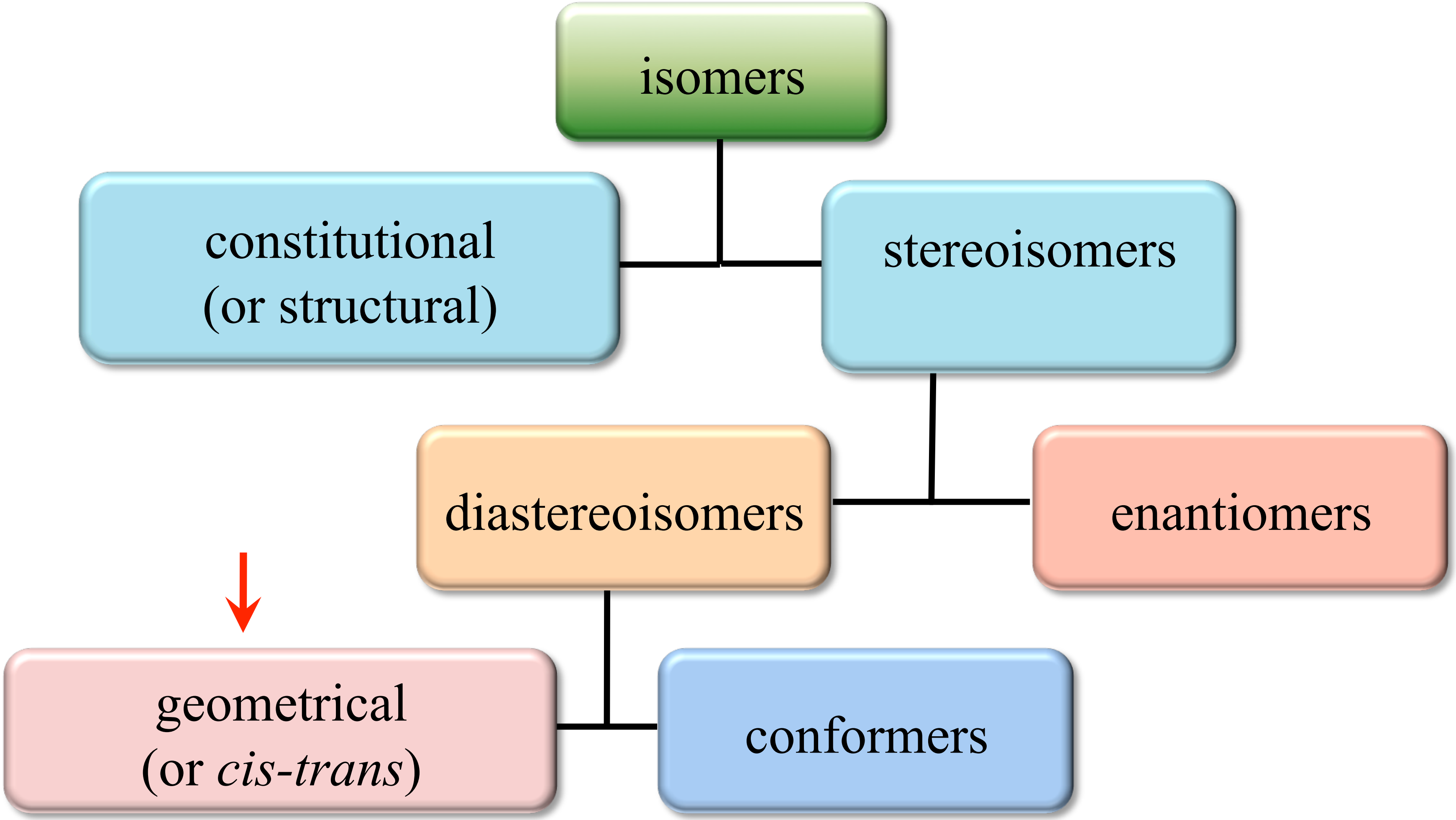
chair conformation



boat conformation

steric clash

unfavorable interaction between eclipsed hydrogens



isomers

constitutional
(or structural)

stereoisomers

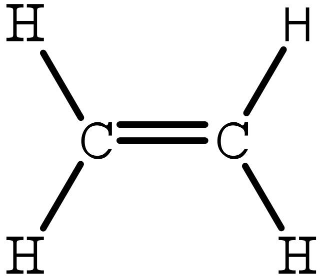
diastereoisomers

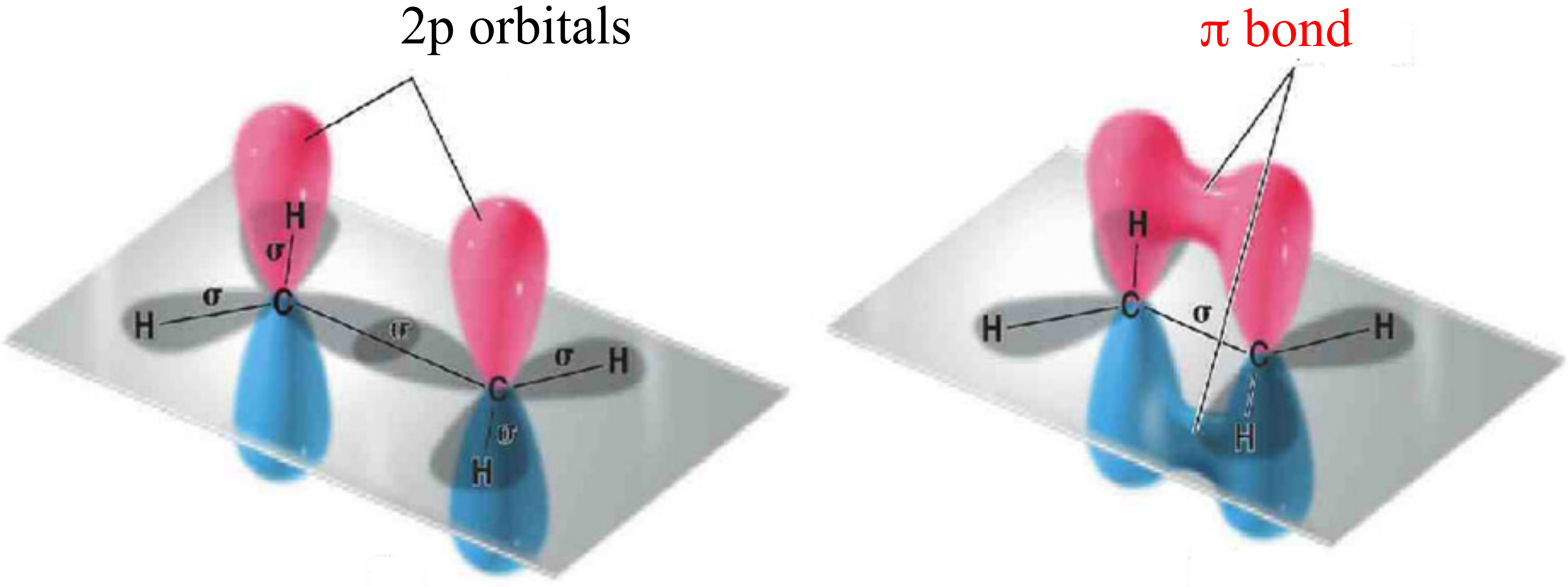
enantiomers

geometrical
(or *cis-trans*)

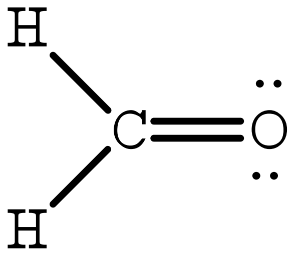
conformers

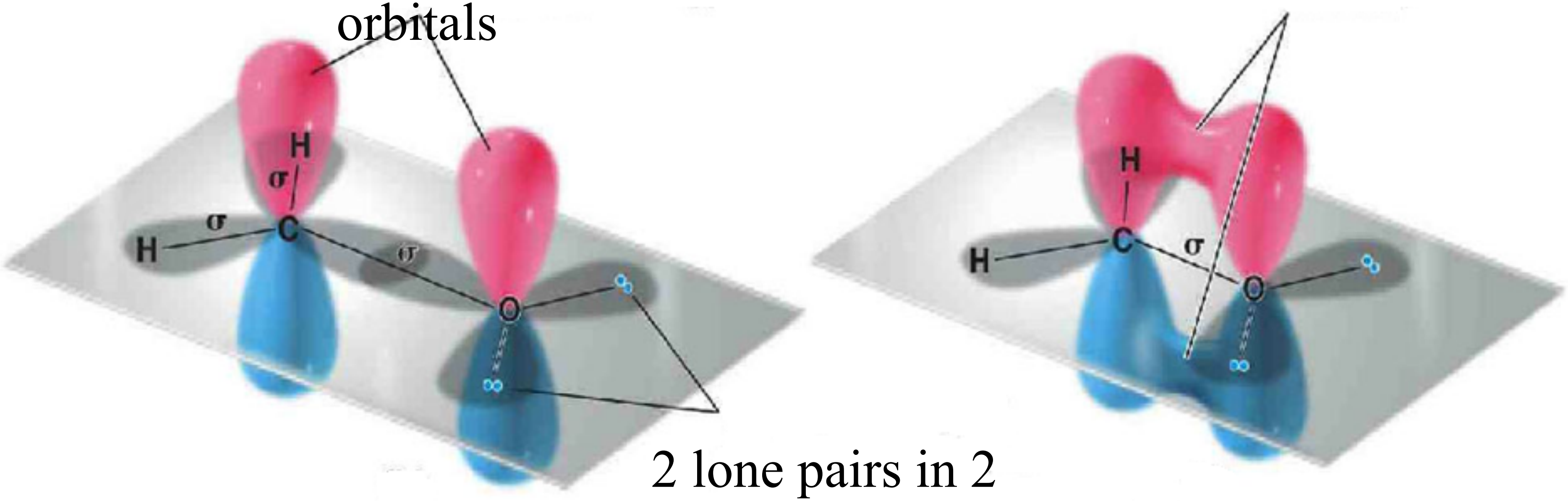
L’ethene (or ethylene)





Formaldehyde





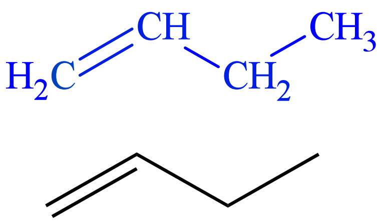
orbitali 2p
orbitals

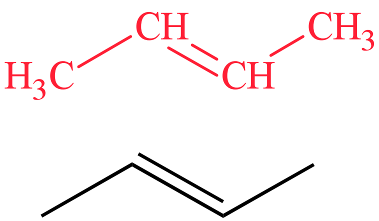
π bond

2 lone pairs in 2
hybrid sp^2 orbitals of
oxygen

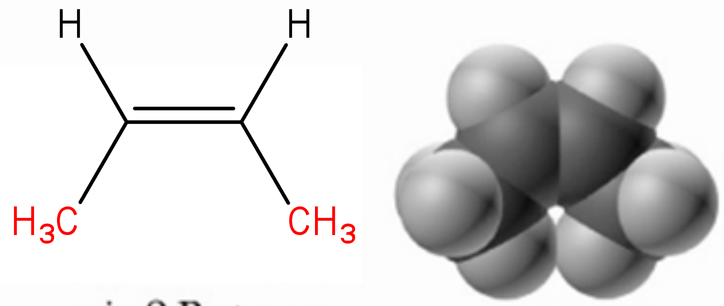
Geometric isomerism

Depending on the position of the double bond, butene may exist as 1-butene or 2-butene

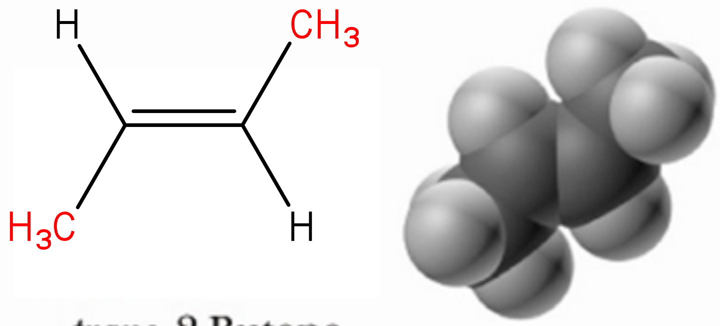




2-butene can in turn have two different structures:



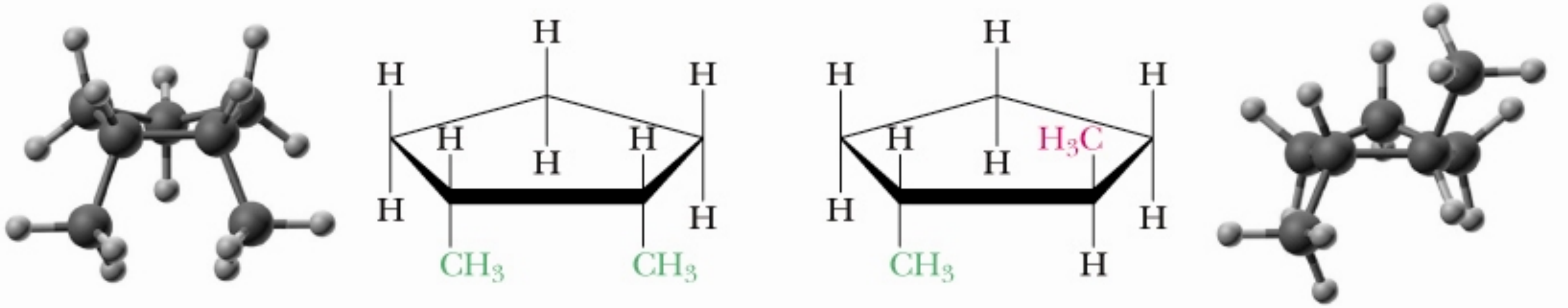
cis-2-Butene
pf – 139°C, pc 4°C



trans-2-Butene
pf – 106°C, pc 1°C

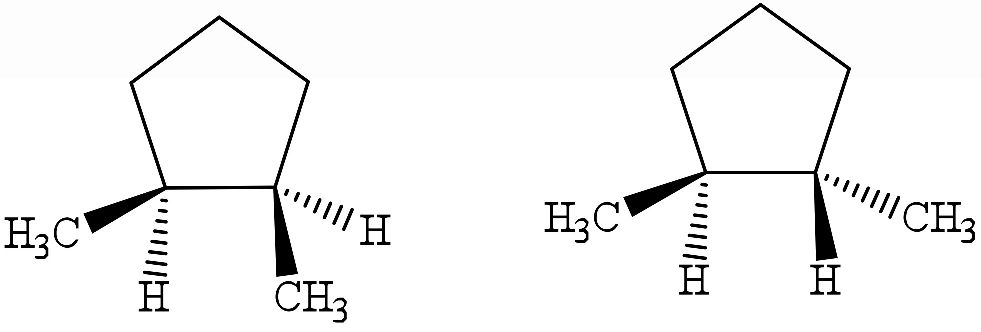
Stereoisomers: they differ only in the arrangement of atoms in space. More precisely, they are called diastereoisomers because they are not the mirror image of each other (they are not enantiomers).

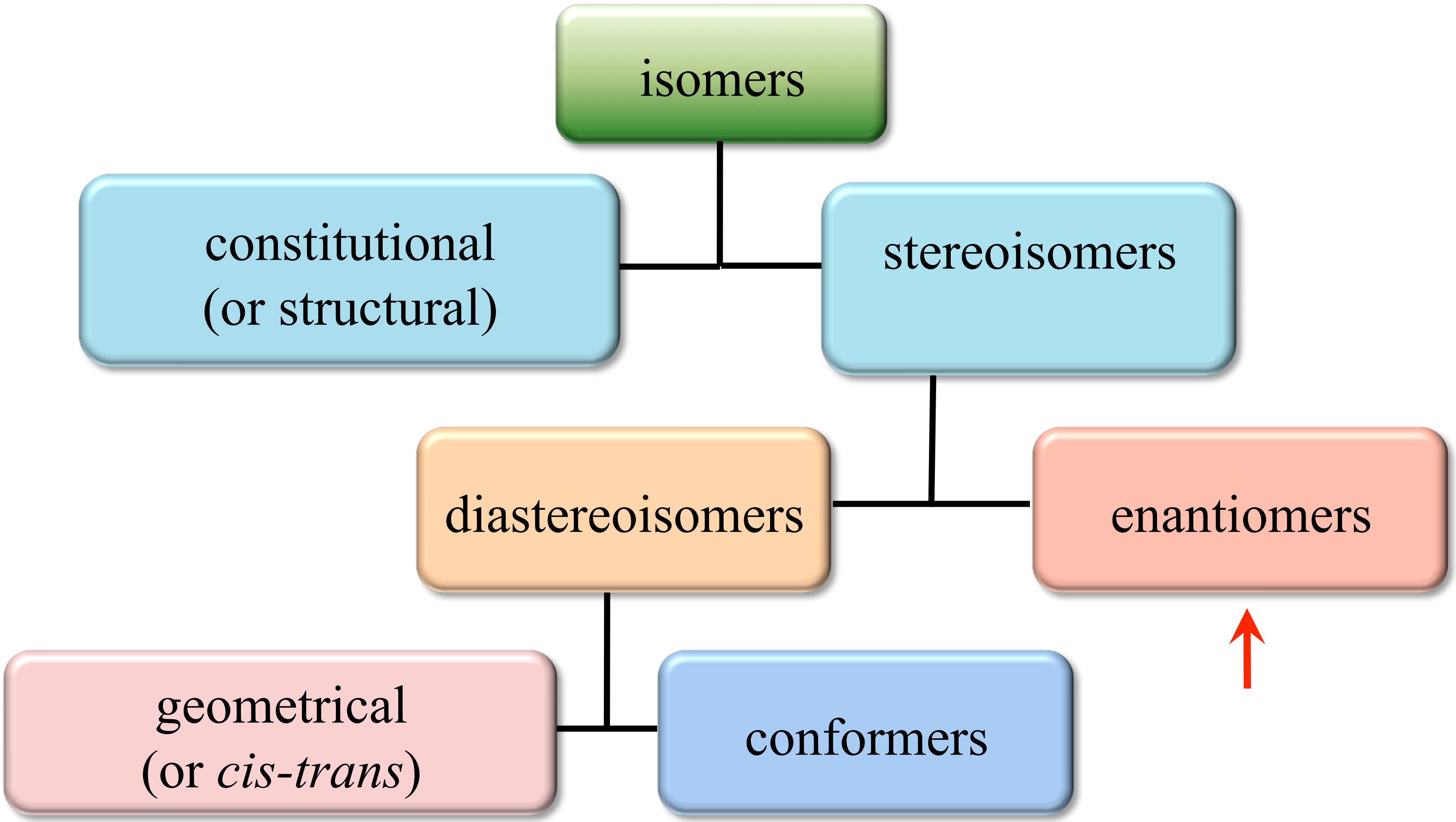
Geometric isomerism may exist if the is an impediment to rotation around a σ bond: substituted cycloalkanes



cis-1,2-dimethylcyclopentane

trans-1,2-dimethylcyclopentane





isomers

constitutional
(or structural)

stereoisomers

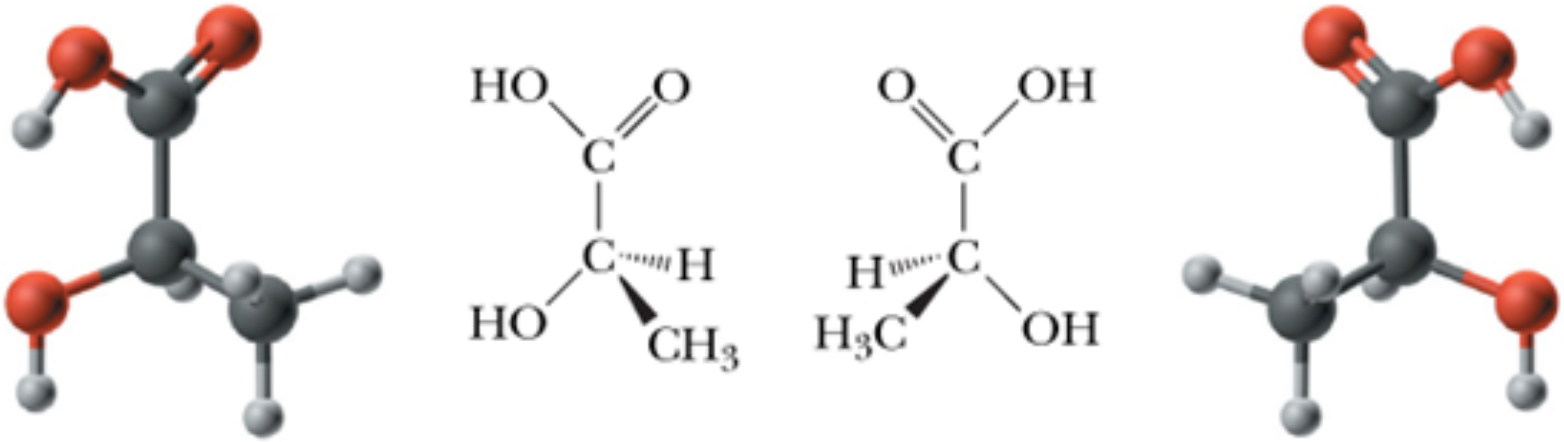
diastereoisomers

enantiomers

geometrical
(or *cis-trans*)

conformers

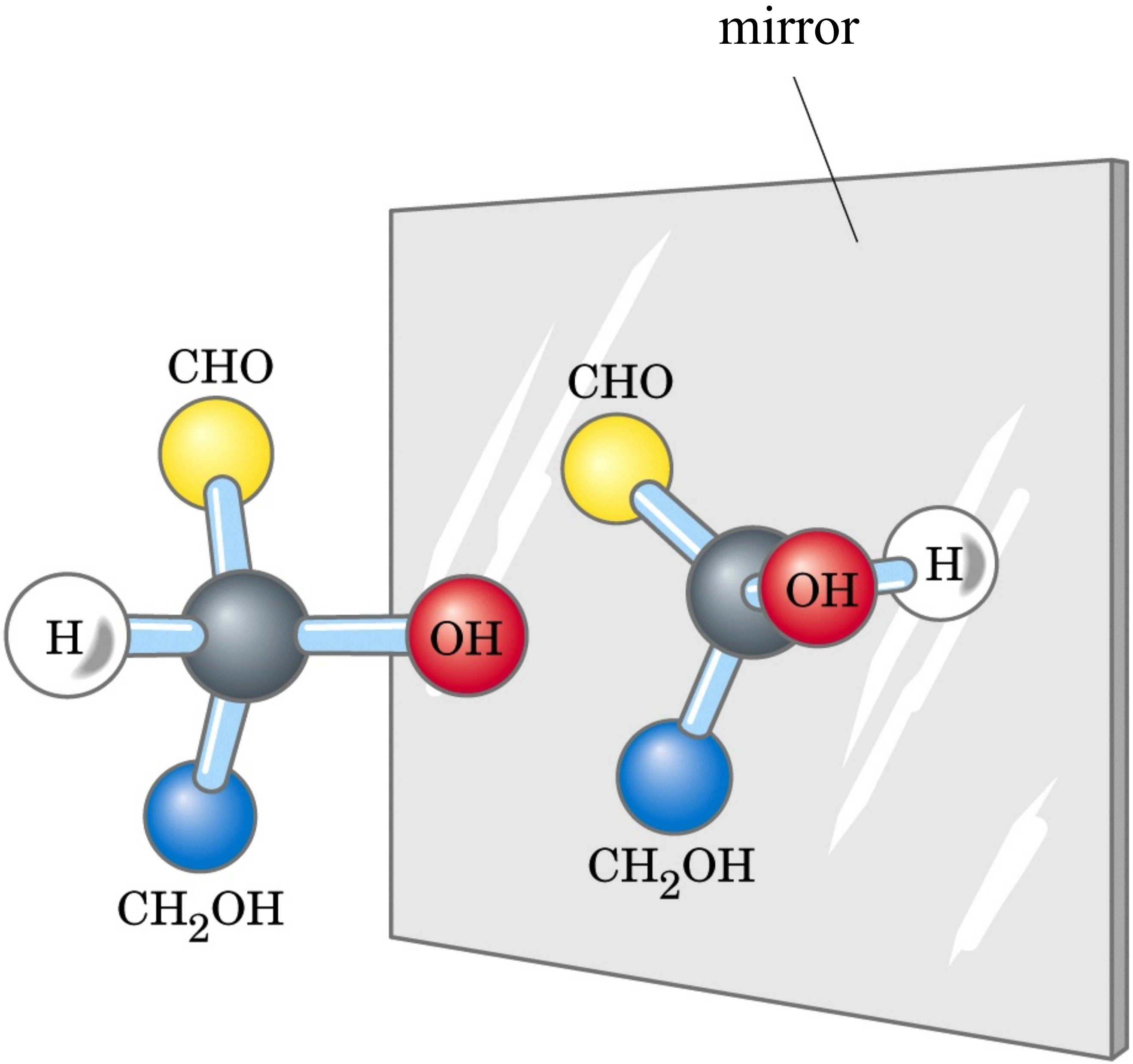
Optical isomerism and molecular chirality



lactic acid

These two molecules differ only in the fact that they are the non-superimposable mirror image of each other and called enantiomers

Enantiomers have identical physical and chemical properties except for a particular optical property: the angle of rotation of the plane of polarized light


mirror
CHO
H
OH
CH₂OH
CHO
OH
H
CH₂OH

Polarized filters in photography

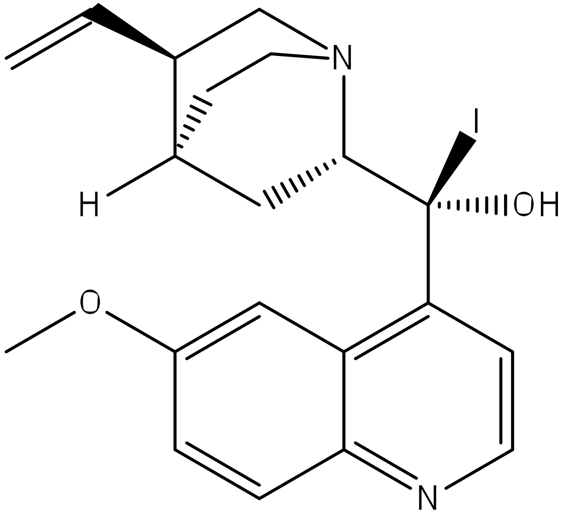
The filter mounted on the camera can be rotated until you eliminate the reflection and see inside.

Polarizers

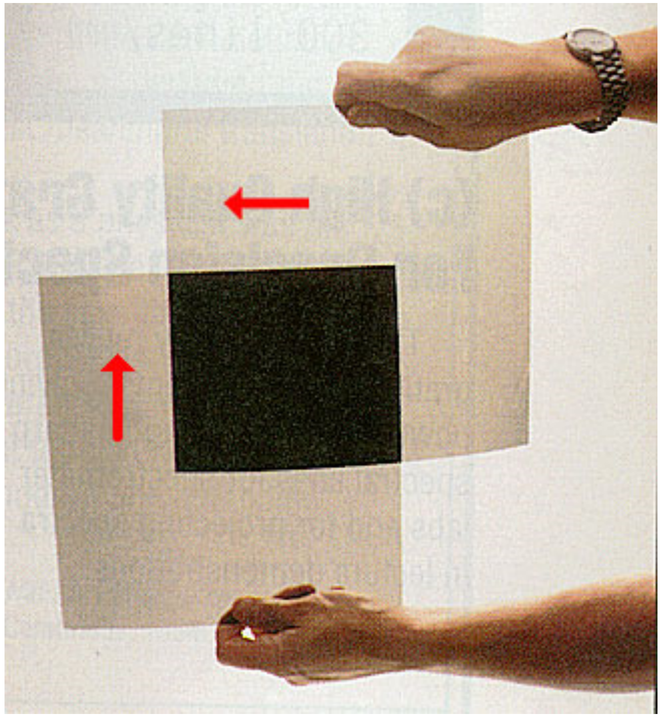
- Calcite crystals ($CaCO_3$)
- Polaroid

Series of microscopic crystals of iodiochinine sulfate layered on a transparent polymeric nitrocellulose film.

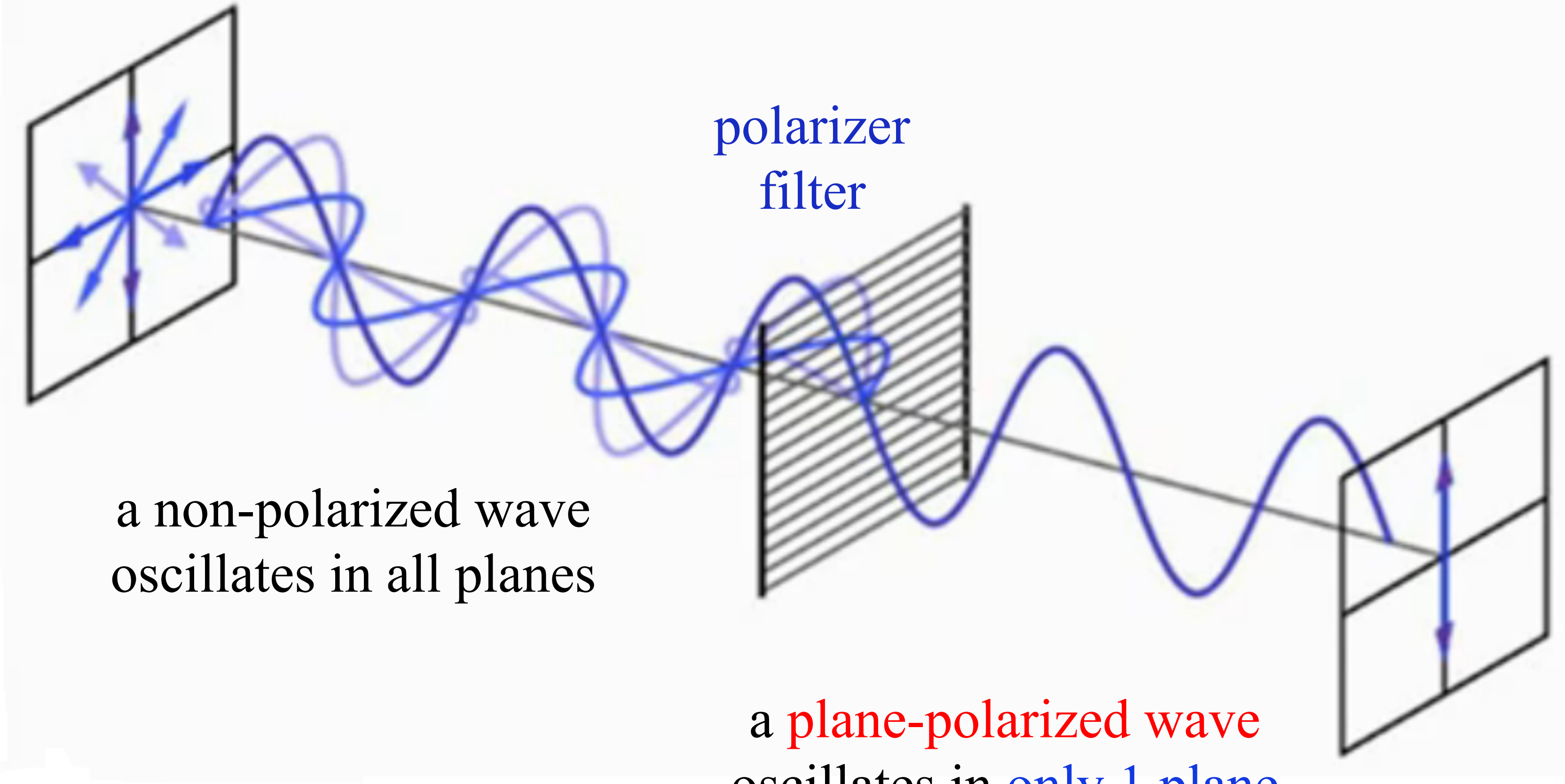
During the manufacturing process the needle-like crystals are aligned by applying a magnetic field. This sheet is dichroic: it tends to absorb the polarized light perpendicular to the alignment direction of the crystals, allowing the light to pass parallel to them.



iodiochinine sulfate



Polarized light



light source

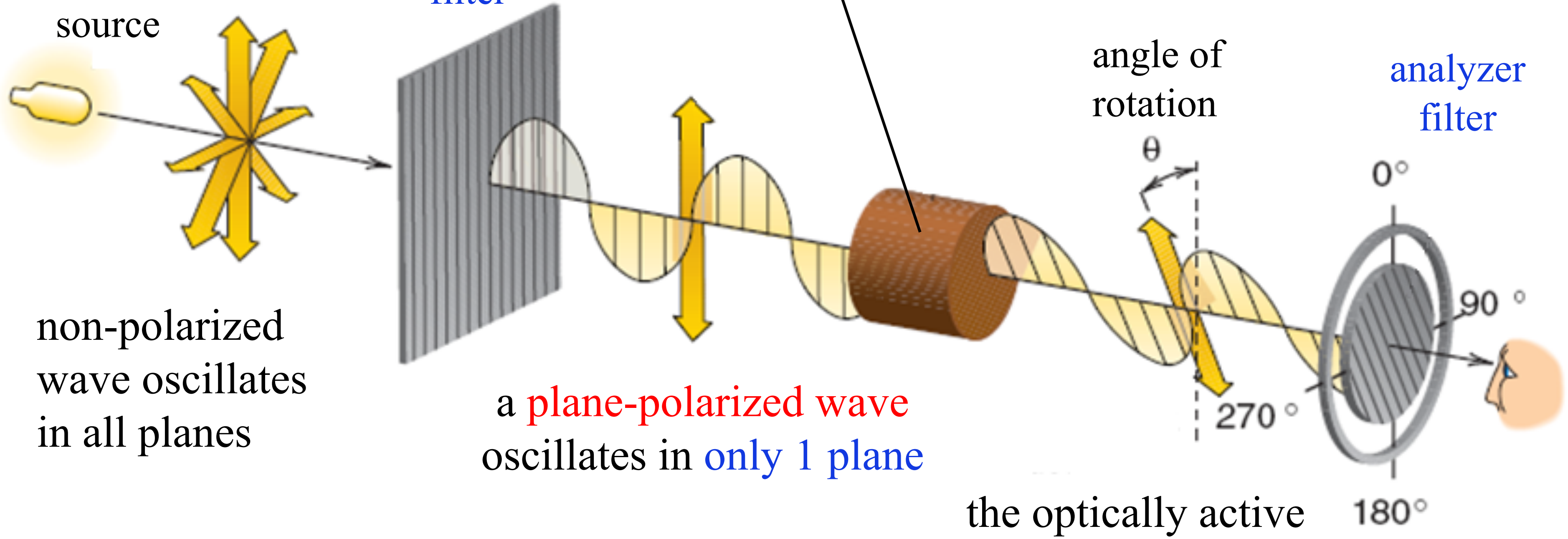
polarizer
filter

a non-polarized wave
oscillates in all planes

a plane-polarized wave
oscillates in only 1 plane

Schematic representation of a polarimeter containing a solution of an optically active compound.

Chiral compounds rotate the plane of polarized light



light source

polarizer filter

tube containing a solution of an optically active substance

angle of rotation

analyzer filter

non-polarized wave oscillates in all planes

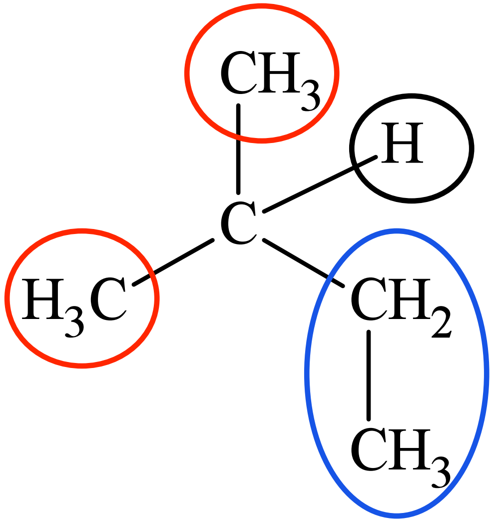
a plane-polarized wave oscillates in only 1 plane

the optically active substance rotates the plane of polarized light by an angle θ

How is an optically active substance recognized?

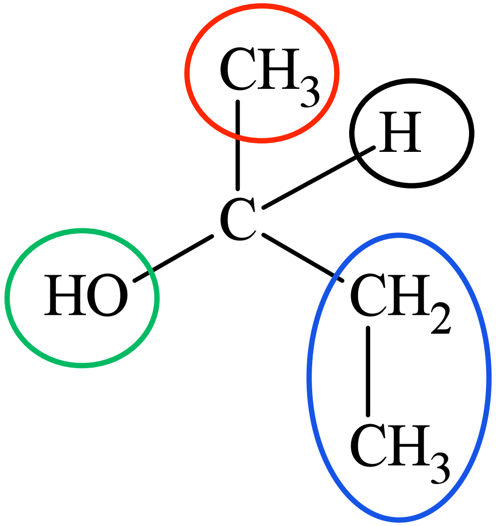
If a compound contains an sp^3 carbon atom with 4 different substituents, then the compound will be optically active. This carbon is called an **asymmetric carbon.**

Which of these two compounds is chiral?



2-methyl-butane

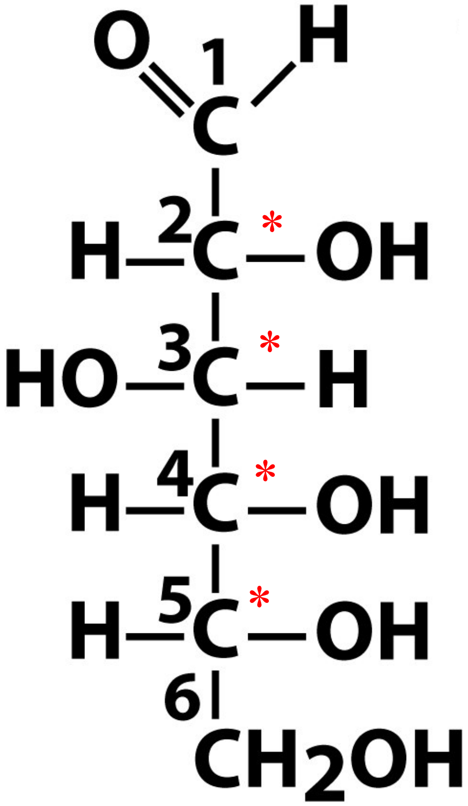
non chiral



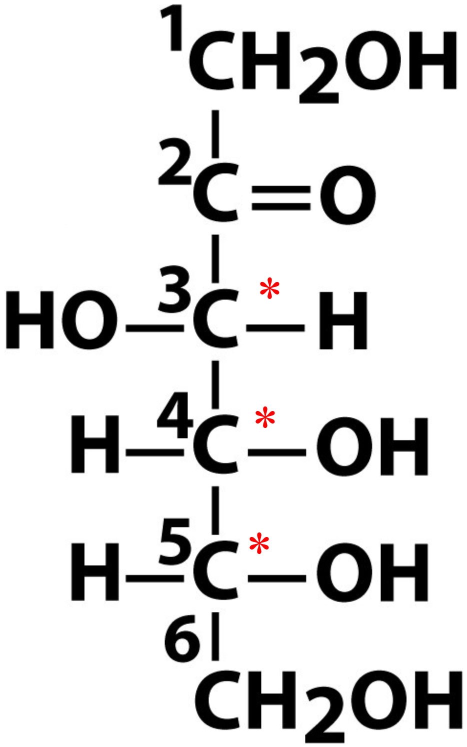
2-hydroxy-butane

chiral

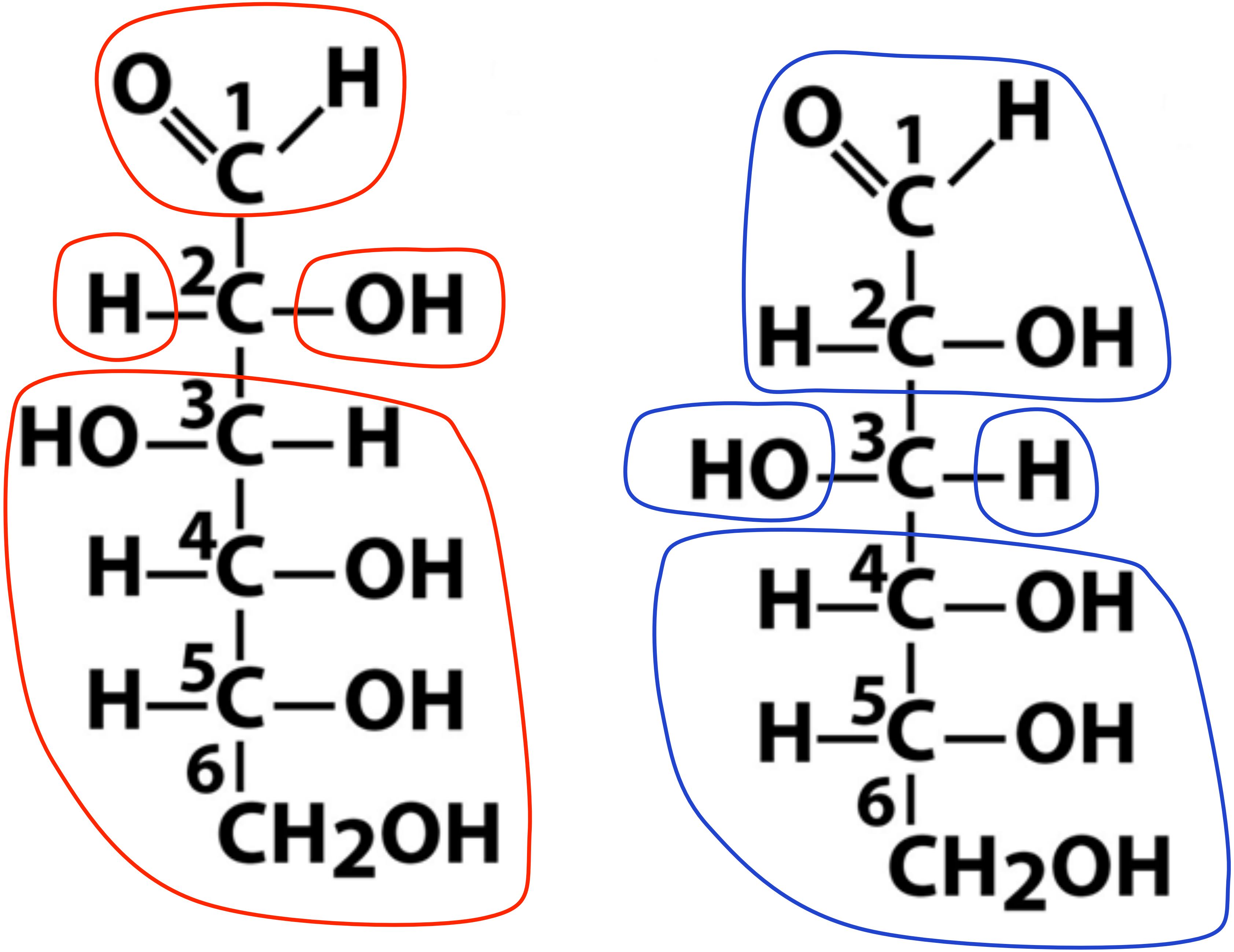
Many compounds contain more than one chiral center



D-glucose

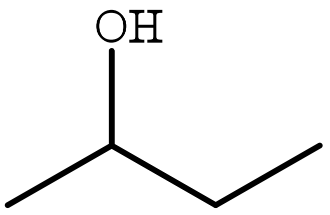


D-fructose

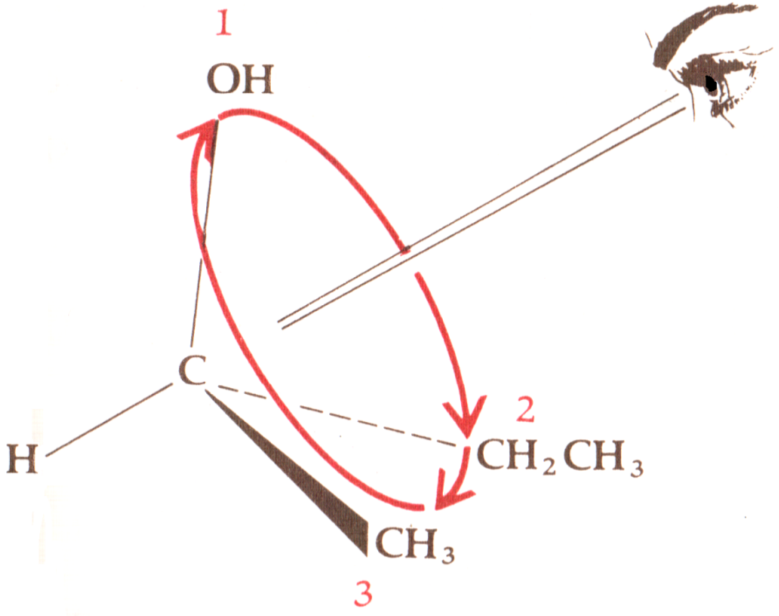

O
1
H
C
H
2
C
OH
HO
3
C
H
H
4
C
OH
H
5
C
OH
6
CH2OH
O
1
H
C
H
2
C
OH
HO
3
C
H
H
4
C
OH
H
5
C
OH
6
CH2OH

The Cahn-Ingold-Prelog system

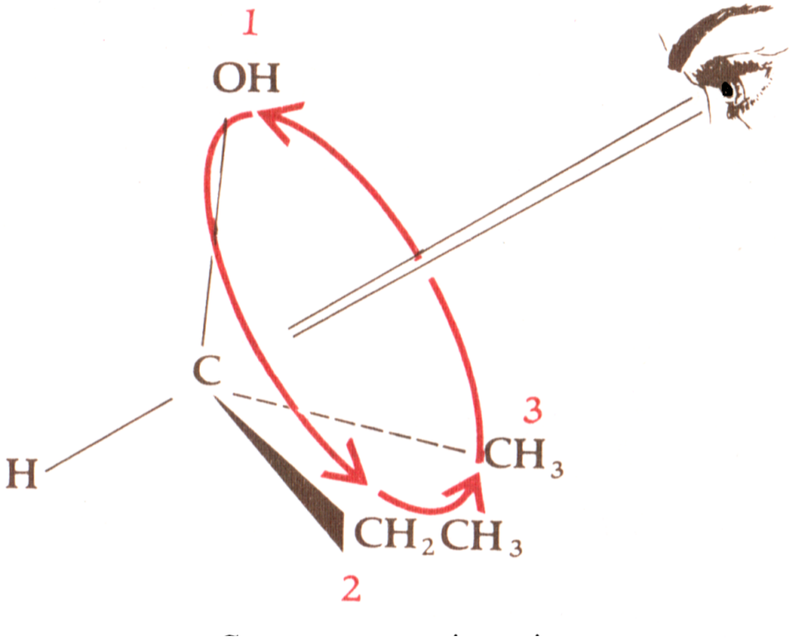
Priority: SH > OH > NH_2 > COOH > CHO > CH_2OH > C_6H_5 > ^2H > ^1H



2-butanol



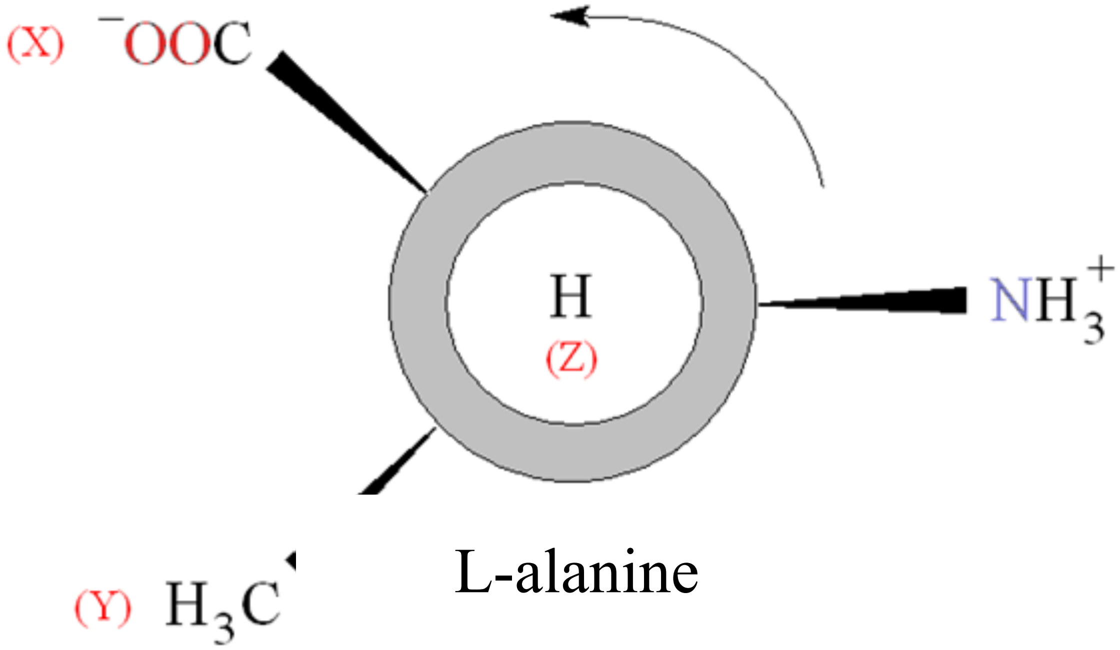
D-2-butanol



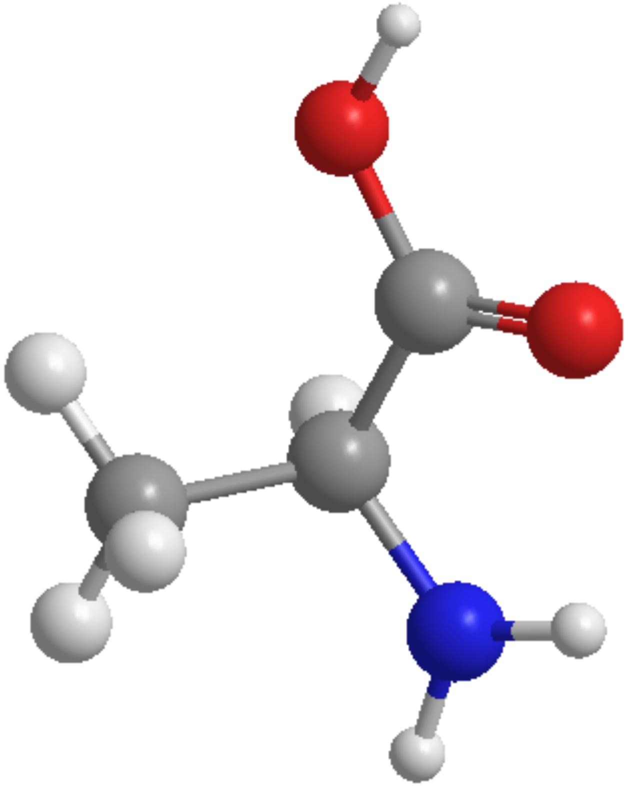
L-2-butanol

The Cahn-Ingold-Prelog system

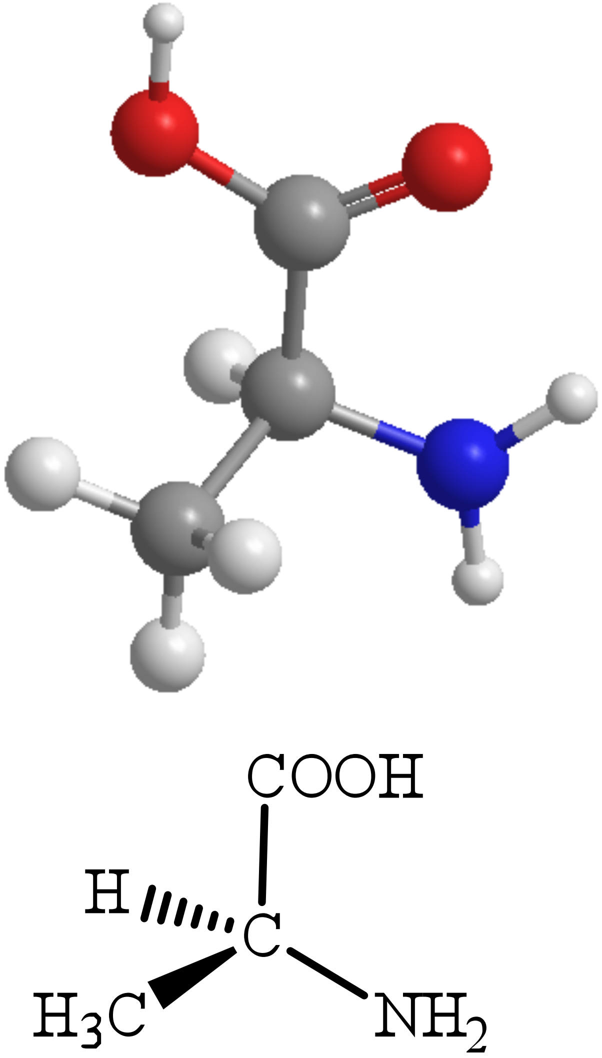
Priority: $SH > OH > NH_2 > COOH > CHO > CH_2OH > C_6H_5 > {}^2H > {}^1H$



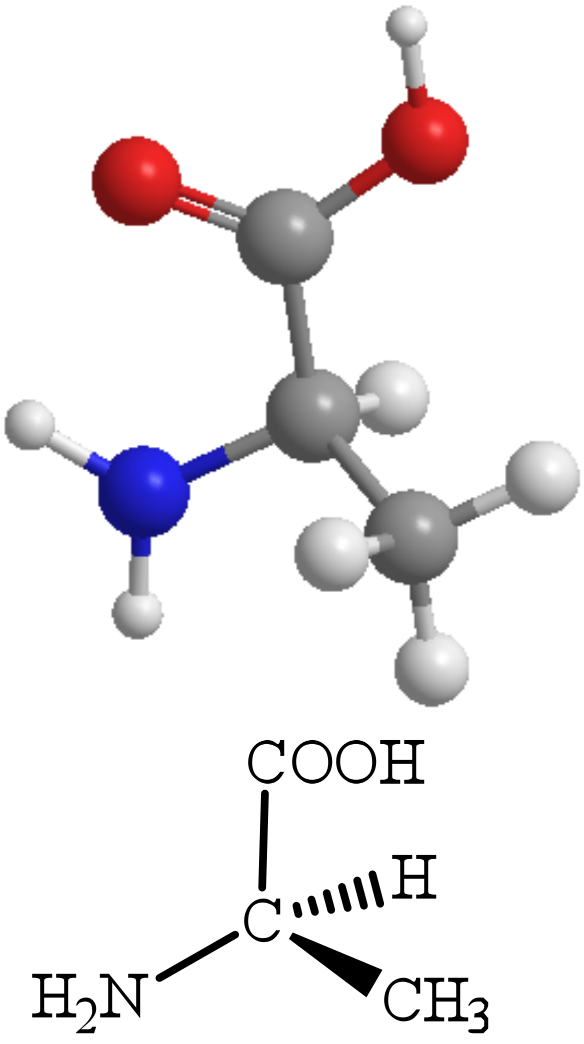
L-alanine



The stereoisomery of amino acids

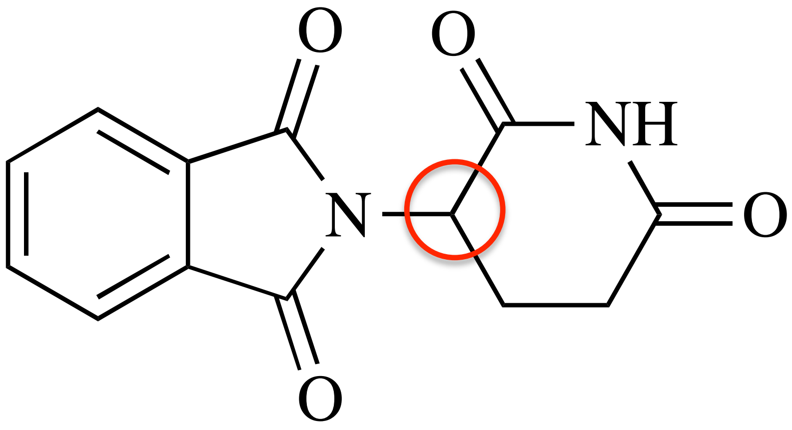


L-alanine



D-alanine

Thalidomide: where is the chiral center?



Teratogen: any agent that can disturb the development of an embryo or fetus causing a birth defect in the child.

About 20,000 children affected by phocomelia

D-thalidomide

L-thalidomide