Bio-organic Chemistry

Lecture 2

Overview – today

- Conformation and stereochemistry

- Textbook: Organic Chemistry With a Biological Emphasis (Chapter 3)

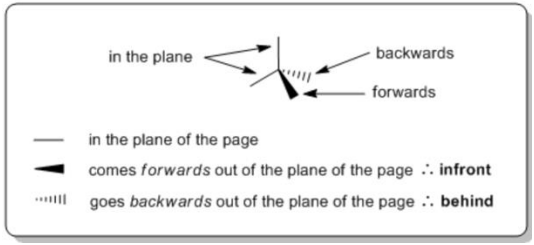
Organic Chemistry

With a Biological Emphasis

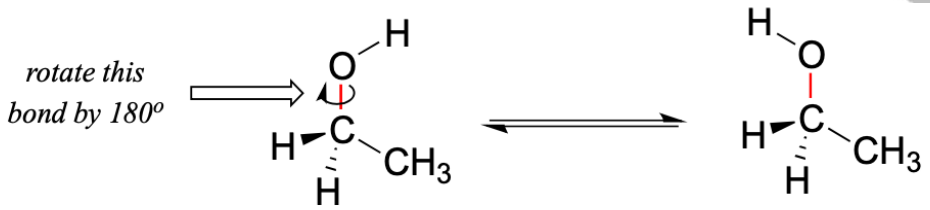
Tim Soderberg
University of Minnesota, Morris

Conformational isomerism

- Conformational isomerism is related to rotation around single bonds (a.k.a. conformers)

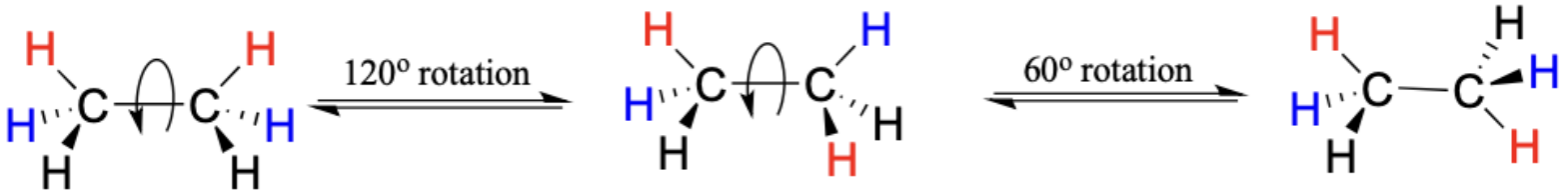


-The example on ethanol



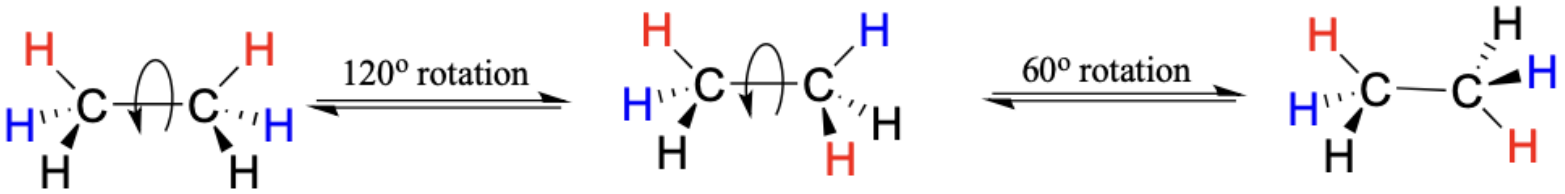
- Notice that despite the small movement this has a large impact in the shape of the molecule

-example on ethane

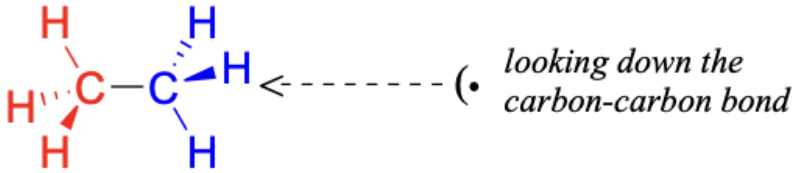


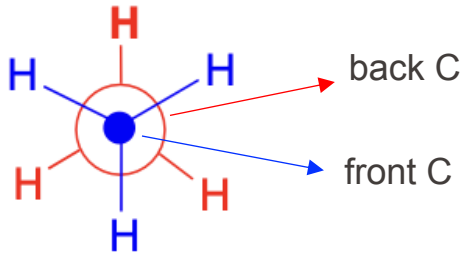
Conformational isomerism

Newman projection



Newman Projection

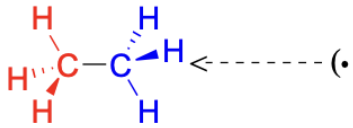




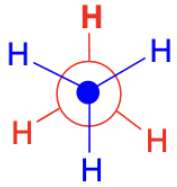
'staggered' conformation
(Newman projection)

Let's think about Energy

Dihedral angle = 90

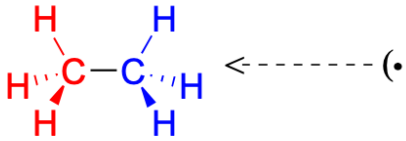


looking down the carbon-carbon bond

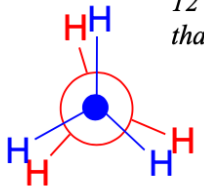


'staggered' conformation
(Newman projection)

Dihedral angle = 0

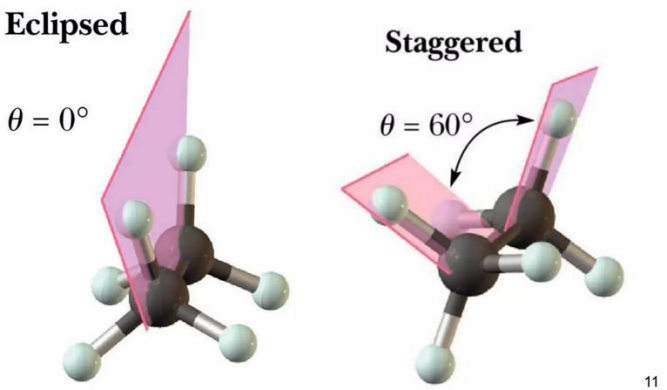


12 kJ/mol higher energy than staggered

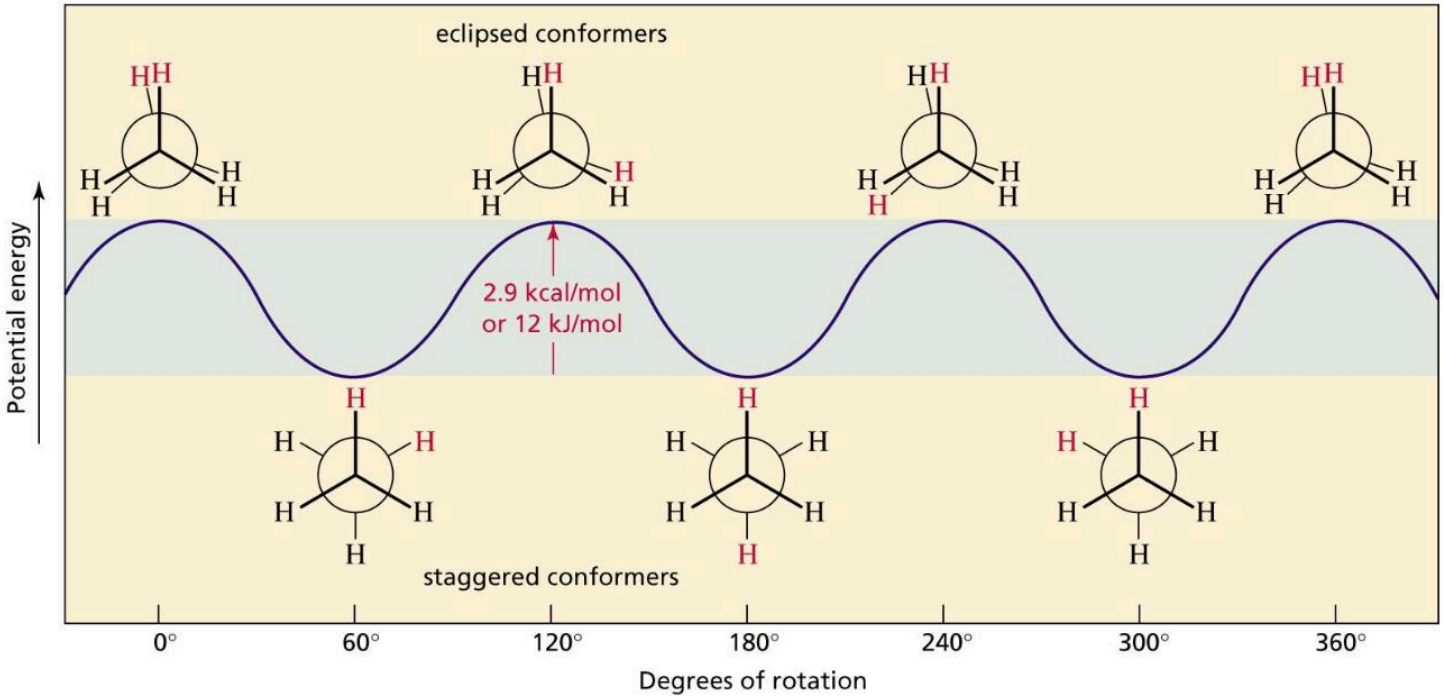


'eclipsed' conformation

Explanation of dihedral angles

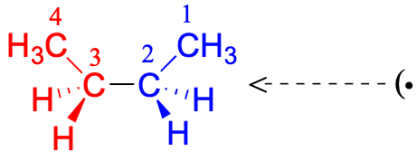


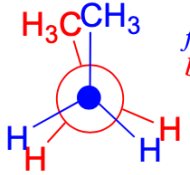
Let's think about Energy



A more complex molecule

-Looking at butane



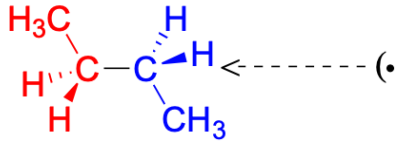


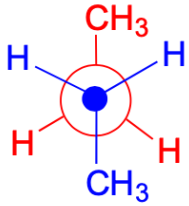
front carbon (dot): carbon 2
back carbon (circle): carbon 3

eclipsed (A)

Dihedral = 0

-three rotatable bonds – we focus on the middle bond



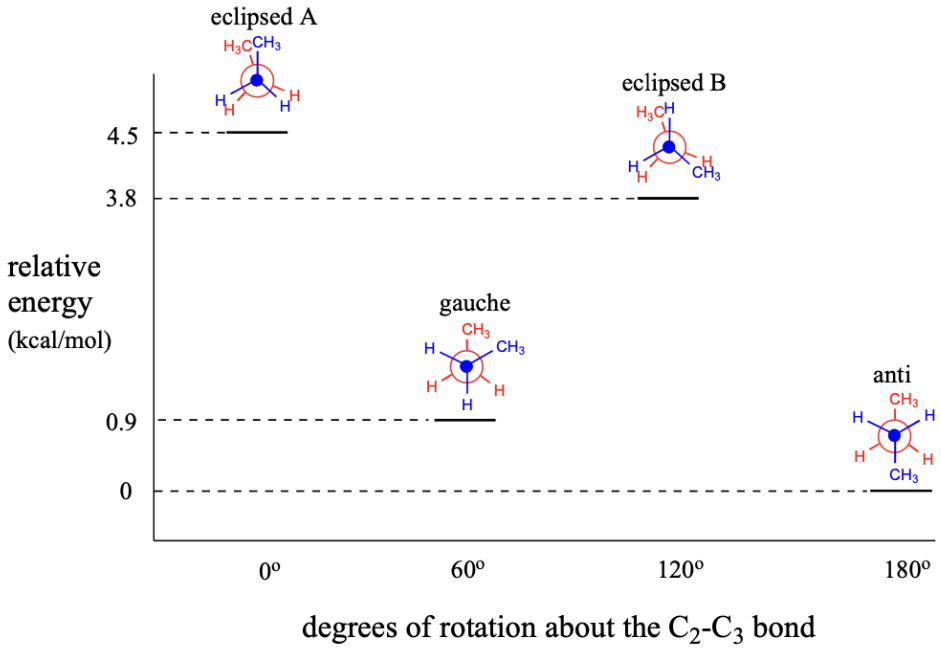


anti

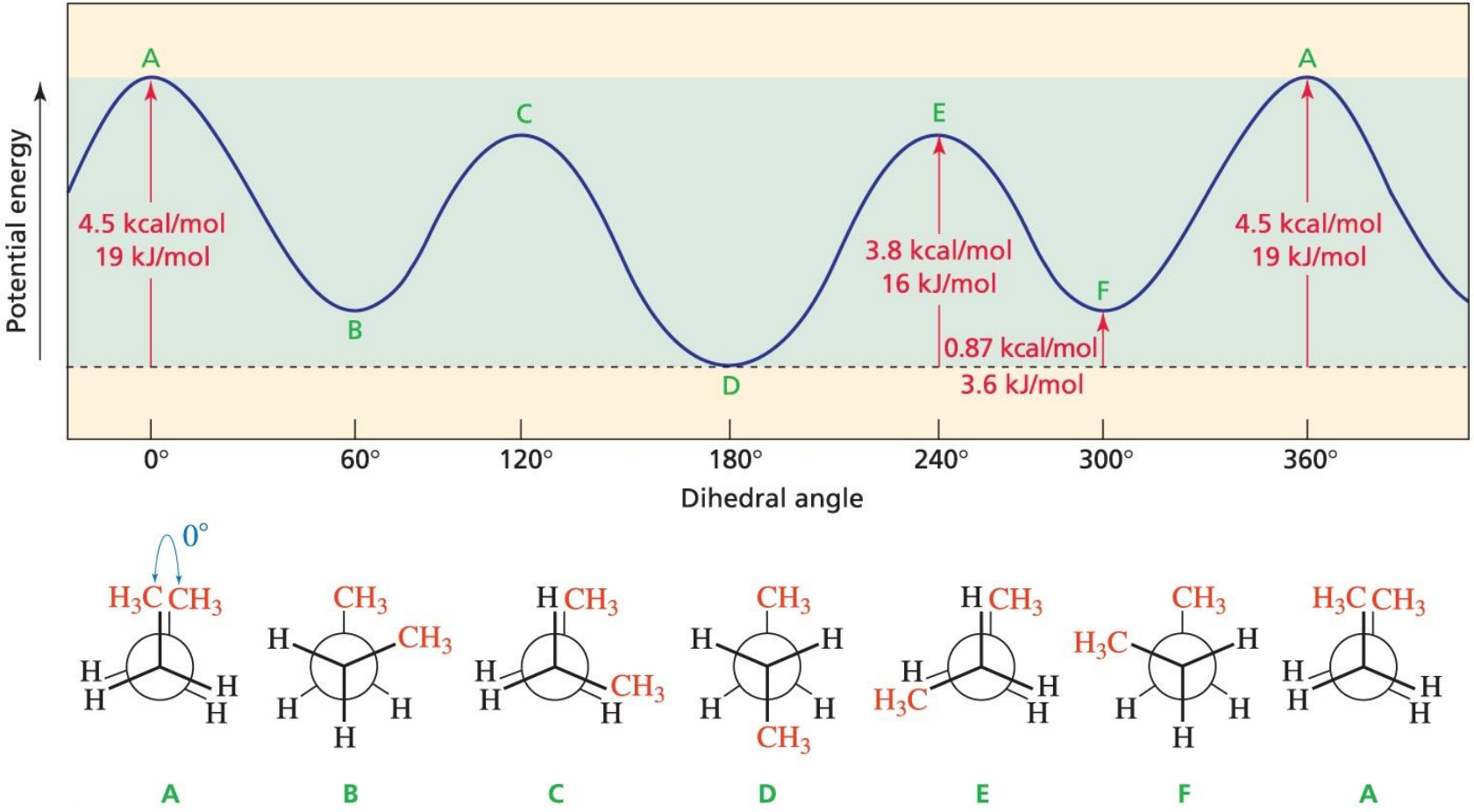
Dihedral = 180

Energy Diagram of Butane conformations

-Essentially the 2 methyl groups determine the energetic landscape base on the steric strain and the repulsion of the two bulky groups

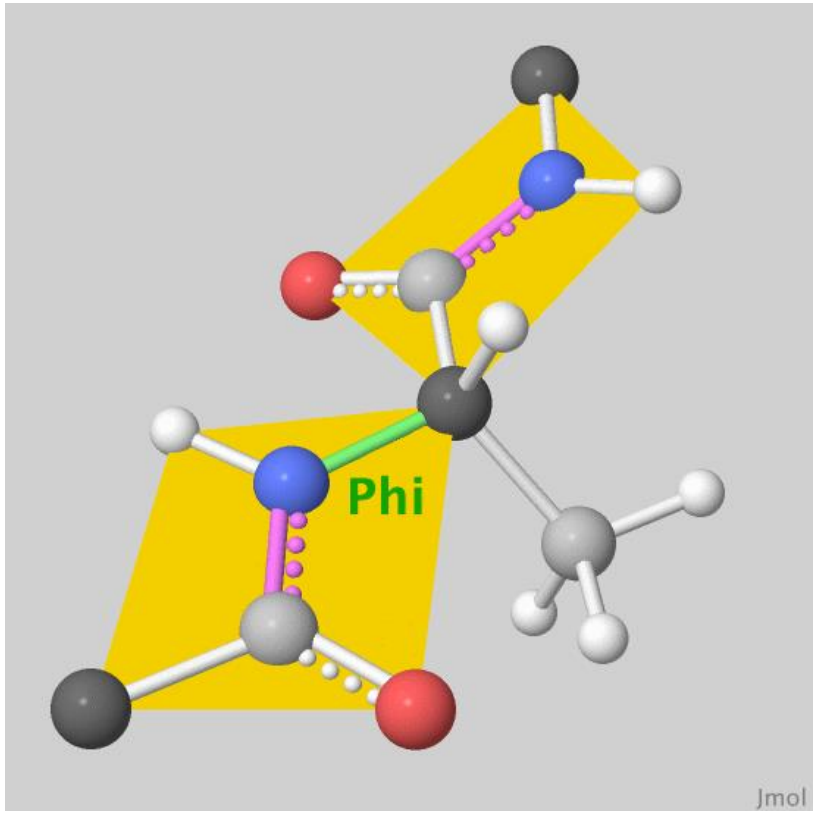


Energy Diagram of Butane conformations



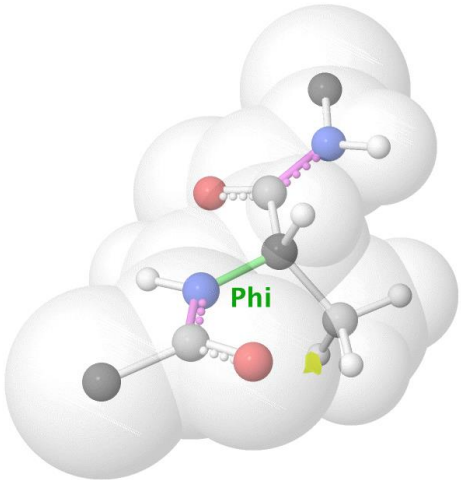
- Steric strain is repulsion between the electron clouds of atoms or groups.

Examples on how different conformers are important in biology - Peptide bonds



Because they cannot rotate, each **peptide bond** holds 6 atoms in a **plane**.

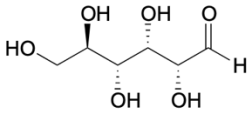
However, most possible angles of **Phi** (**φ**) and **Psi** (**ψ**) are impossible due to clashes between atoms. These balls are much smaller than the atoms they represent.



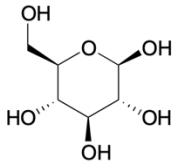
Source: https://proteopedia.org/wiki/index.php/Tutorial:Ramachandran_principle_and_phi_psi_angles, Accessed 2024/02/22

Conformations of cyclic organic molecules

-cyclic structures are frequent in biology



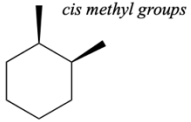
open-chain glucose

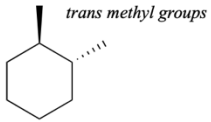


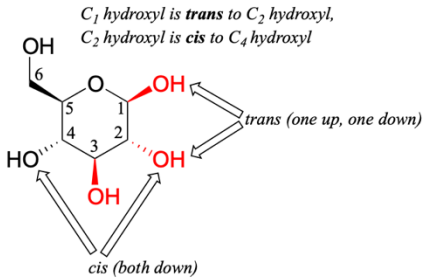
cyclic glucose (b-glucopyranose)

-Groups bound to the tetrahedral ring carbons either point up or down the plane of the page

-Substituents pointing to the same side are ***cis*** and opposite sides are ***trans*** to each other



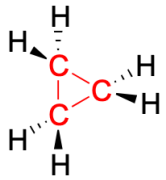




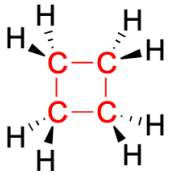
Conformations of cyclic organic molecules

-Ring structures in organic molecules are five membered or six membered

-But other structures exist



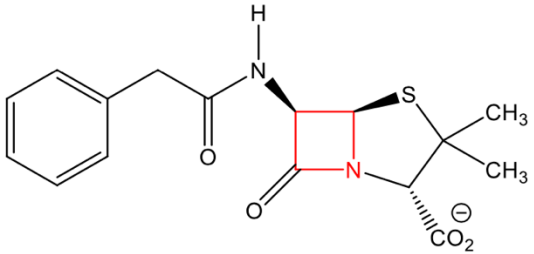
cyclopropane



cyclobutane

-Also found in antibiotics

fosfomycin



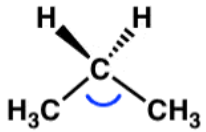
penicillin G

Why are they less common ?

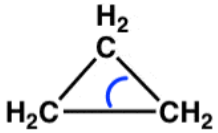
Conformations of cyclic organic molecules

- Bond angle strains make the structures energetically more unstable

Bond angles in propane, cyclopropane, and cyclobutane

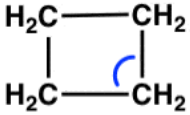


C–C–C bond angle 109.5°



interior bond angle 60°

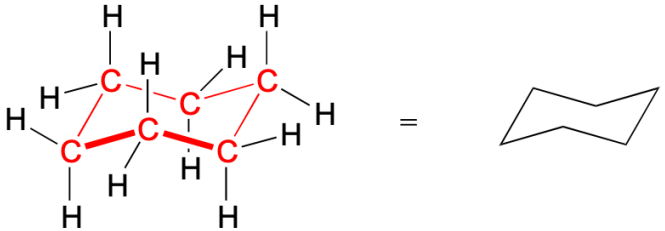
(~ 49° less than ideal of 109°) *[see note at bottom of post]*



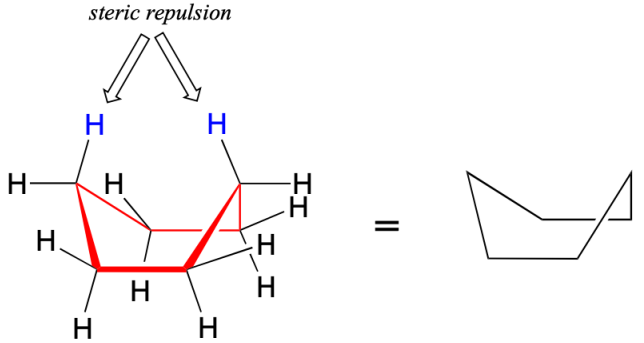
interior bond angle 90°

(~ 19° less than ideal of 109°)

Six membered rings adopt several conformations



'chair' conformation of cyclohexane

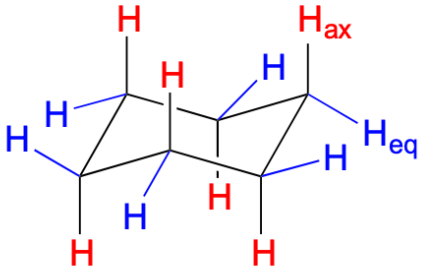


'boat' conformation of cyclohexane

-all carbons in tetrahedral conformations (very stable)

-all carbons in tetrahedral conformations (30 kJ/mol less stable)

The ring substituents are not all equivalent in conformation

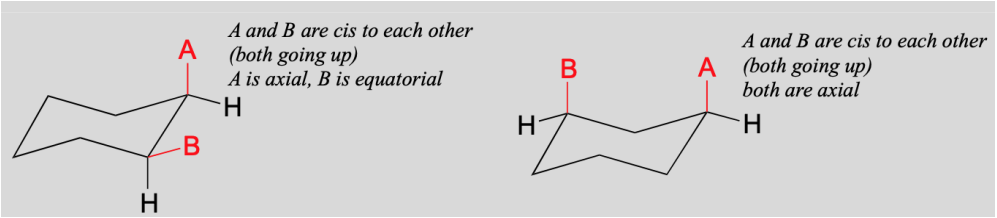


axial hydrogens red
equatorial hydrogens blue

-six hydrogens in the axial position (pointing either up or down from the plane of the ring)

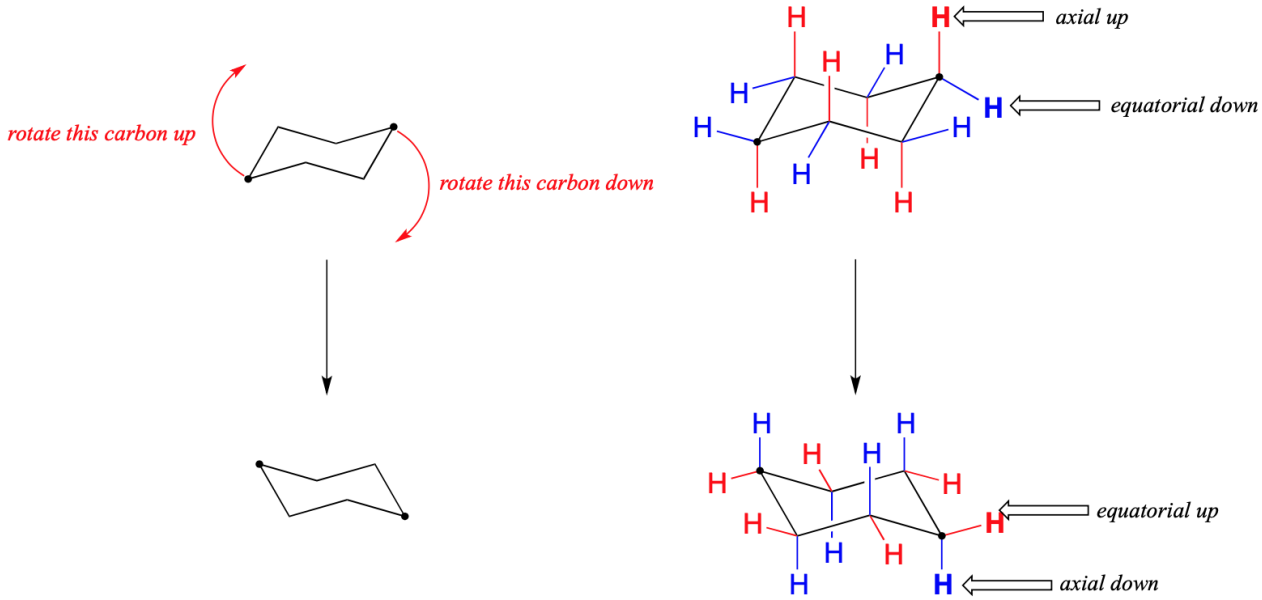
-six hydrogens in the equatorial position (pointing away from the perimeter of the ring)

Confusion alarm !!!!



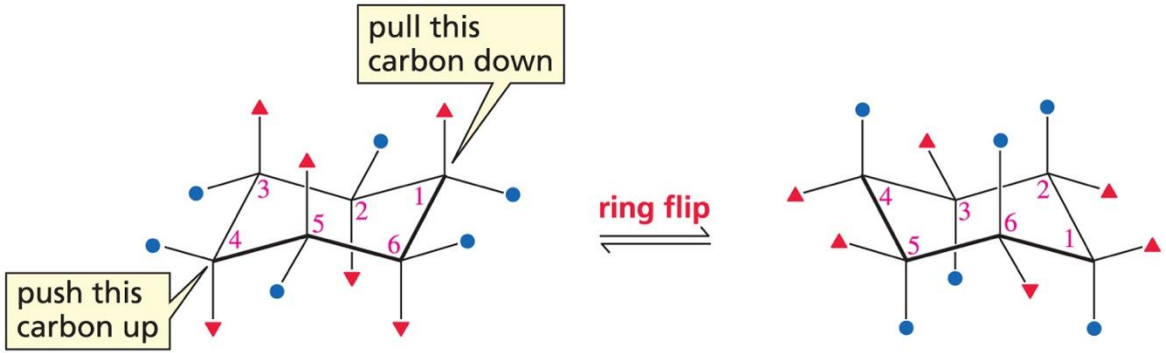
Dot not mix
equatorial and axial
with
cis and trans

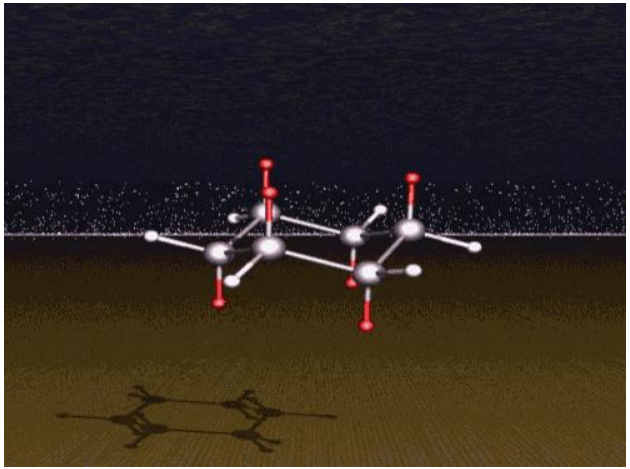
Chair configurations can have different conformations



-This process is called ring inversion
-Axial hydrogens become equatorial and vice versa
-for the cyclohexane case the 2 configurations are rapidly interchanging in solution

Chair configurations can have different conformations

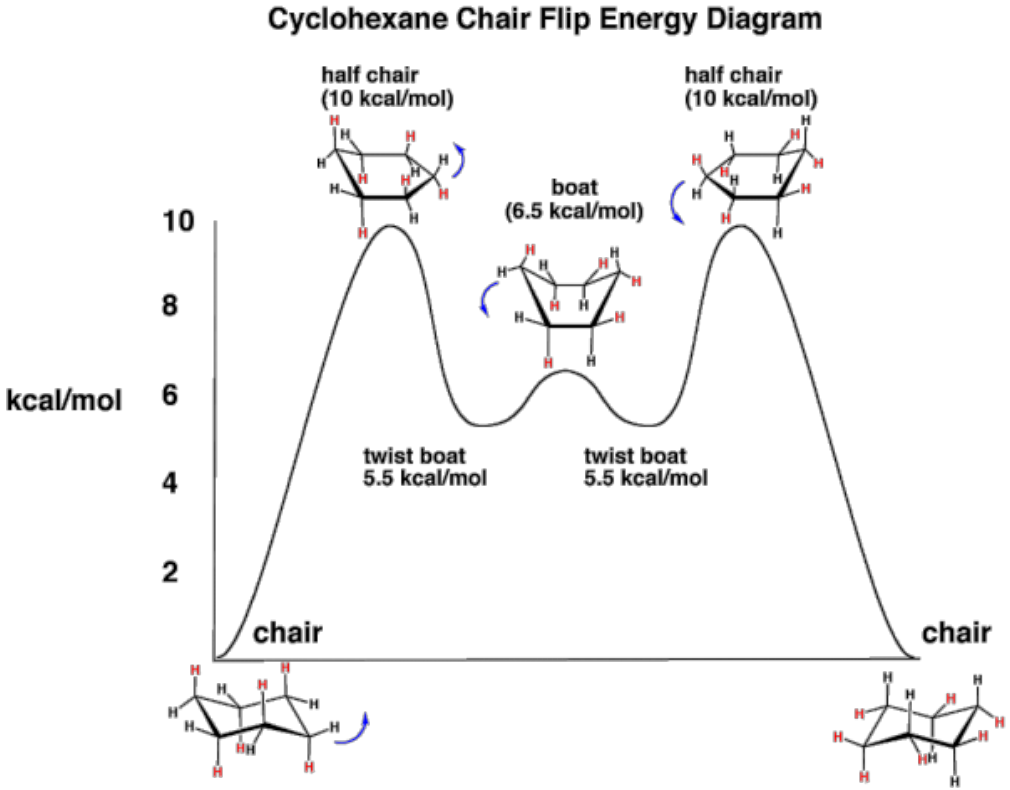




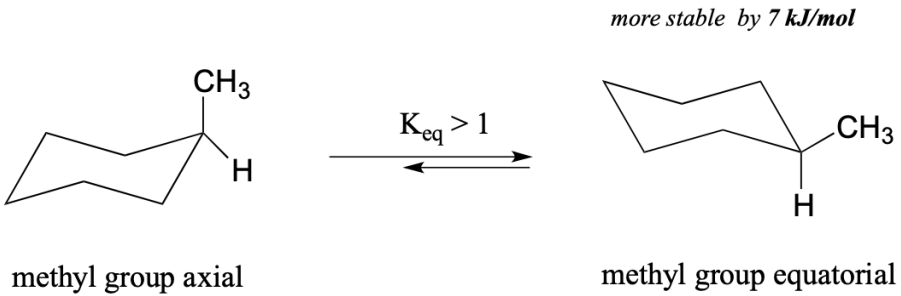
Cyclohexane interconverts between two stable chair conformers.

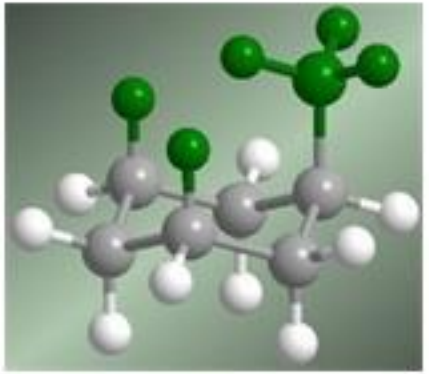
Cyclohexane

Ring-flip



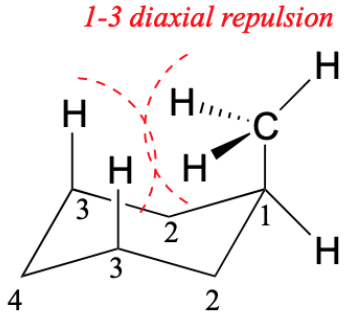
Rings with large substituents





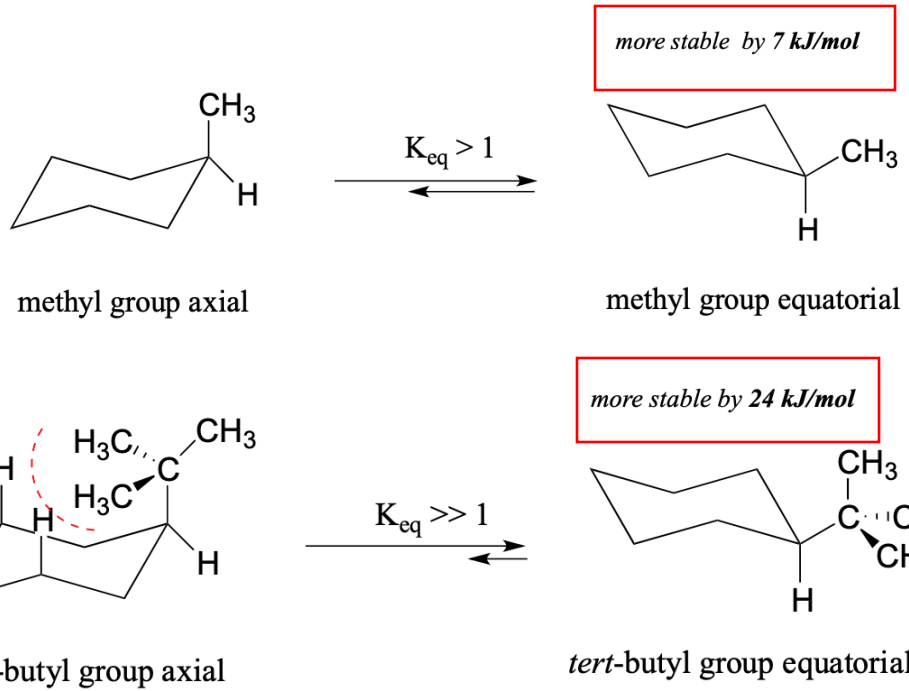
-The 2 chair conformations of methylcyclohexane are quite distinct and also their relative stability

- In equatorial position the methyl is pointing away from the rest of the ring eliminating repulsions with the rest



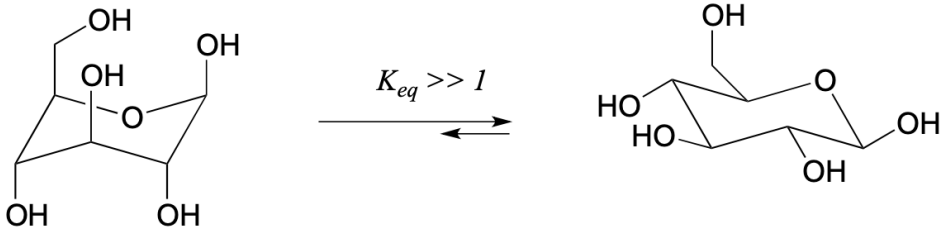
Rings with large substituents

-As you could expect the size of the substituent will have a wide impact on the energy



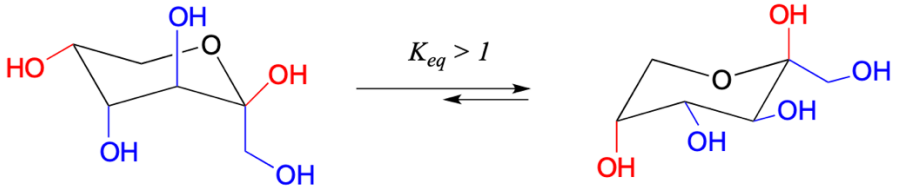
- **-The most stable chair conformation of six-membered ring will be the one which the bulkiest groups are equatorial**

Some examples in biological molecules – sugars

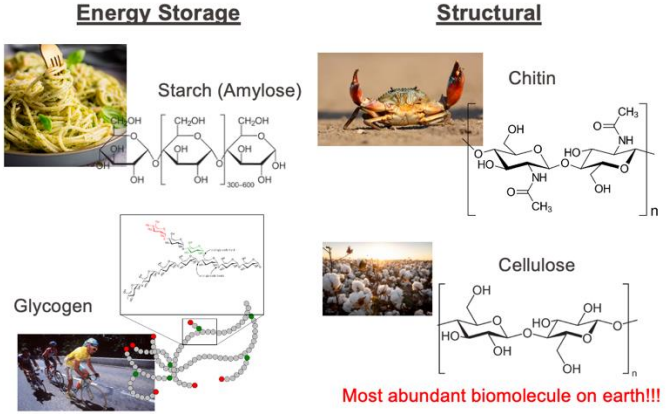


all axial *all equatorial*

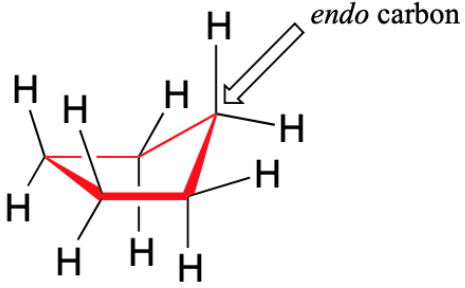
glucose
(b-glucopyranose form)



fructose
(b-fructopyranose form)



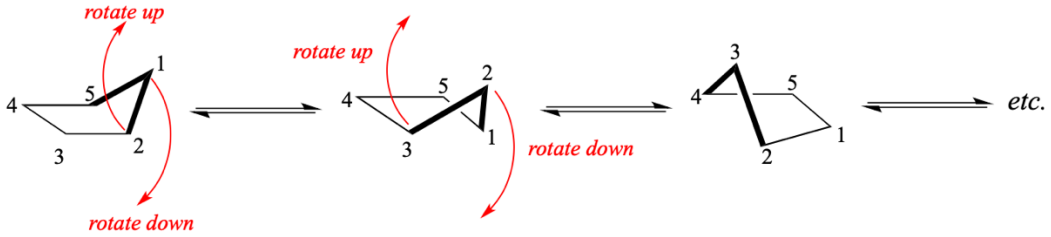
Five-membered rings



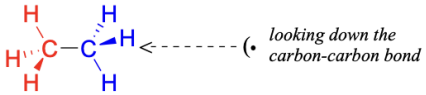
'envelope' conformation of cyclopentane

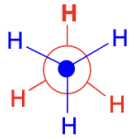
-Their conformation as called “envelope”
-The out-of-plane carbon is in the ***endo*** position
-No axial and equatorial positions

-In solution cyclopentane undergoes rapid pseudorotation where each of the carbons takes the endo poistion

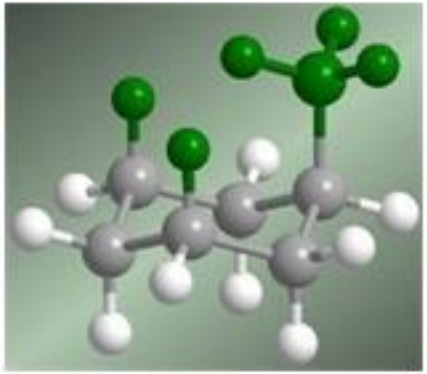


C_1 *endo* C_2 *endo* C_3 *endo*

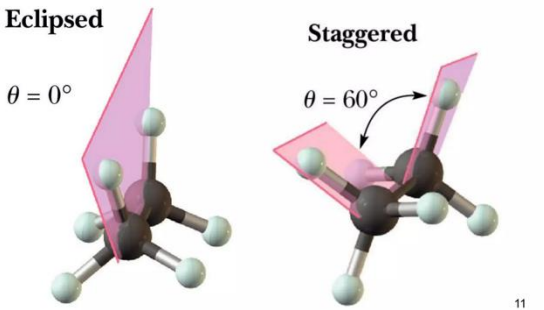


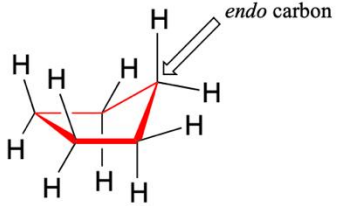


'staggered' conformation
(Newman projection)



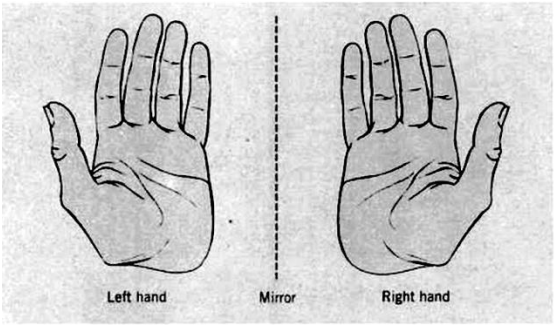
Questions ?

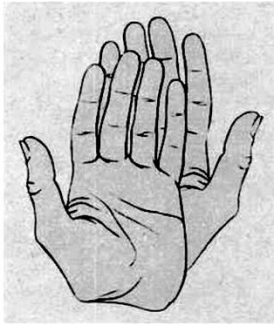




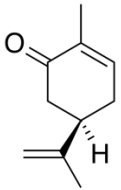
'envelope' conformation of cyclopentane

Chirality is everywhere in nature

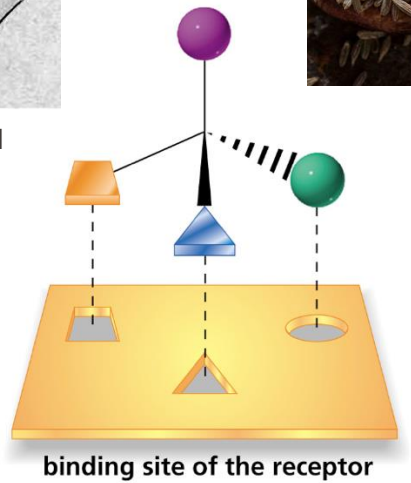


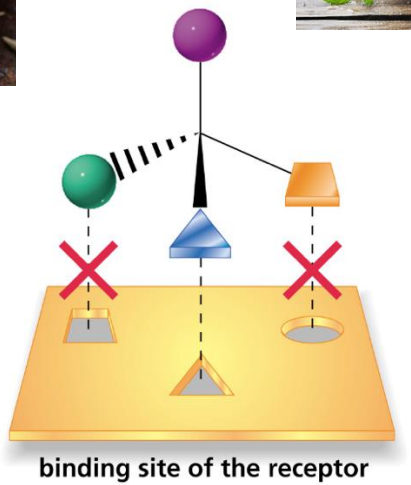


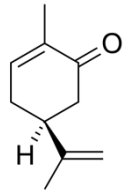
Left hand mirrors right hand but they can't be superimposed



(R)

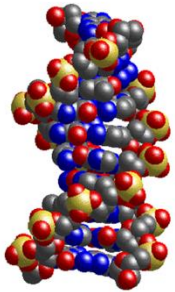






(S)

DNA–the molecule that holds our genetic information…



… is a spiral

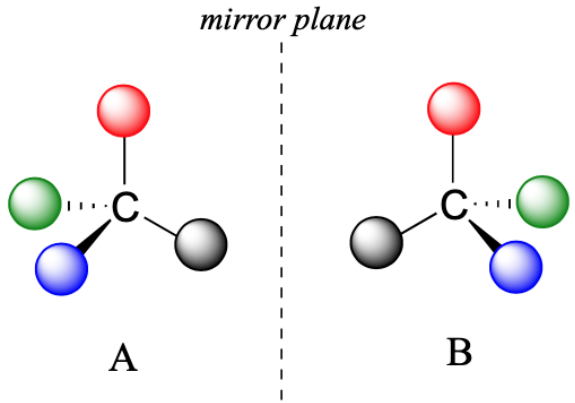
It is a right-handed spiral, there is no left-handed spiral in this context

Chirality

-Chiral refers to anything that which cannot be superimposed on its own mirror image

-**Chiral objects do not have a plane of symmetry**

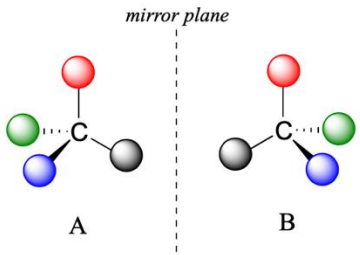
-Achiral objects have internal planes of symmetry

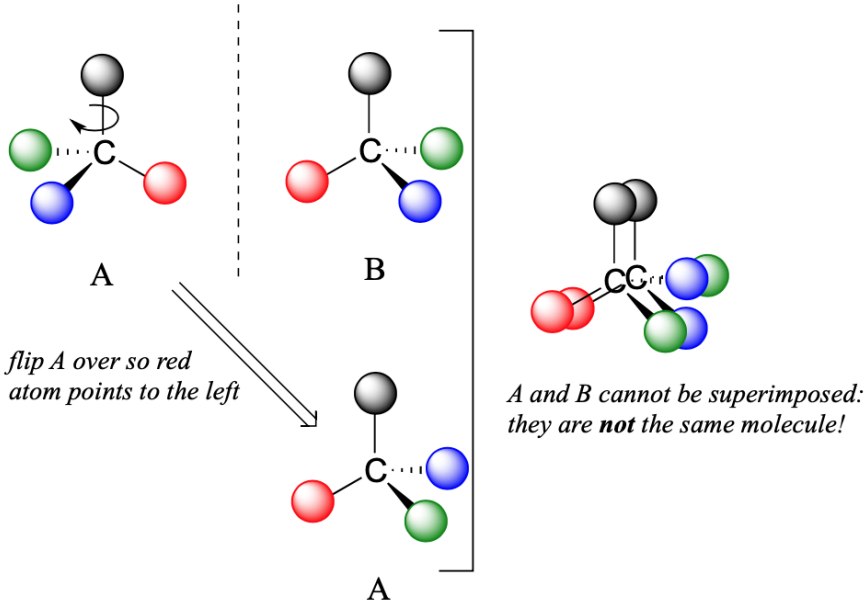


-Chiral molecules contain one or more chiral centers which are almost always tetrahedral (sp3-hybridized) with four different substituents

Chirality

- Toy example to show that mirror images are not superimposable

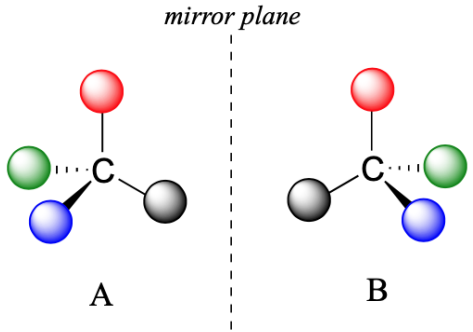




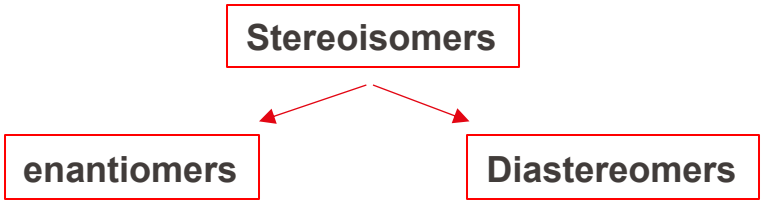
-**A is not superimposable in B(mirror image)** and by definition B is not superimposable in A
-**A and B are both chiral molecules** as they have no internal plane of symmetry

Chirality

- Toy example to show that mirror images are not superimposable

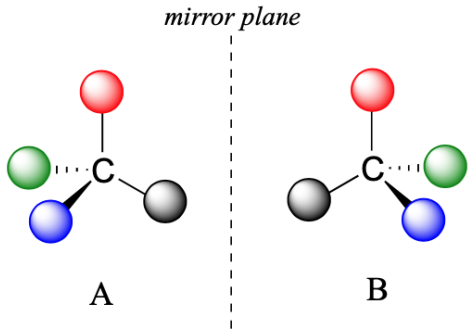


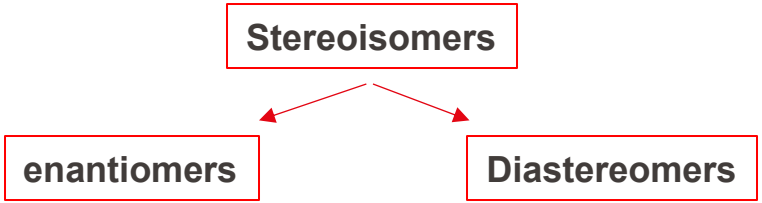
-**A and B** are **stereoisomers** – same molecular formula, same bonding arrangement, different arrangement of atoms in space



Chirality

- Toy example to show that mirror images are not superimposable





-**Enantiomers** – are pairs of stereoisomers which are mirror image of each other (like A and B)

-Identical physical properties (melting point, boiling point, density and others)

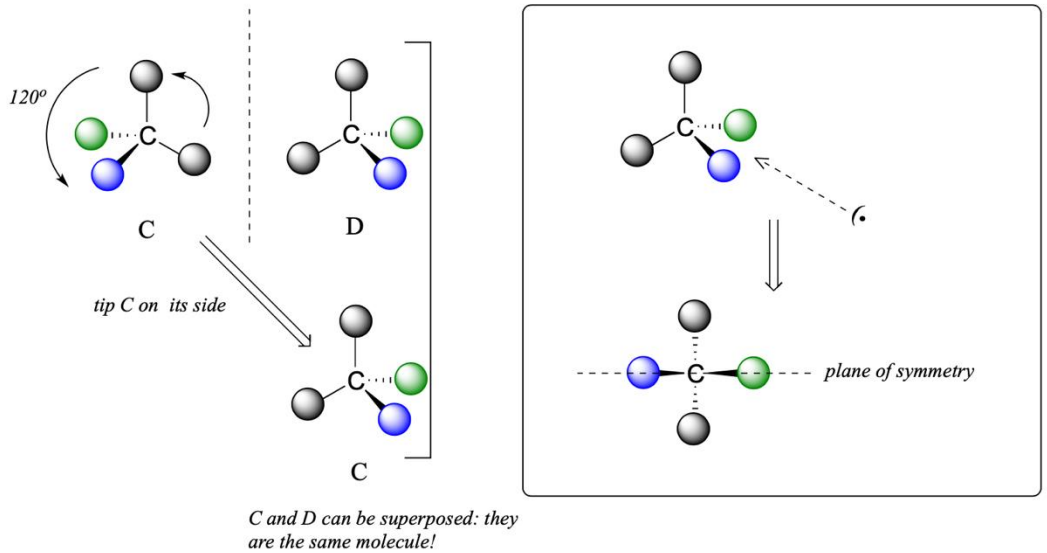
-Different interaction with polarized light (further in lecture)

-**Diastereomers** – stereoisomers that are not mirror images of each other (further in lecture)

A few achiral examples

-A tetrahedral carbon with two identical substituents – its mirror image is superimposable

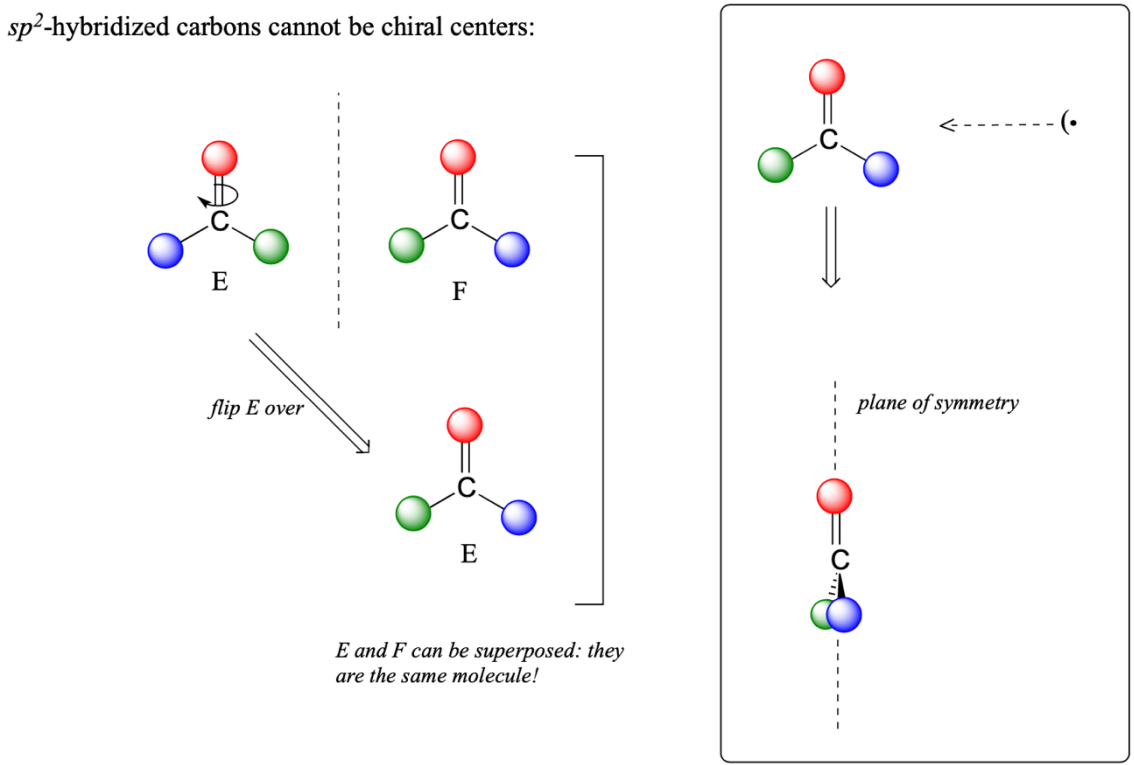
-One can find a plane of symmetry



https://youtu.be/yChPRfm4yvg

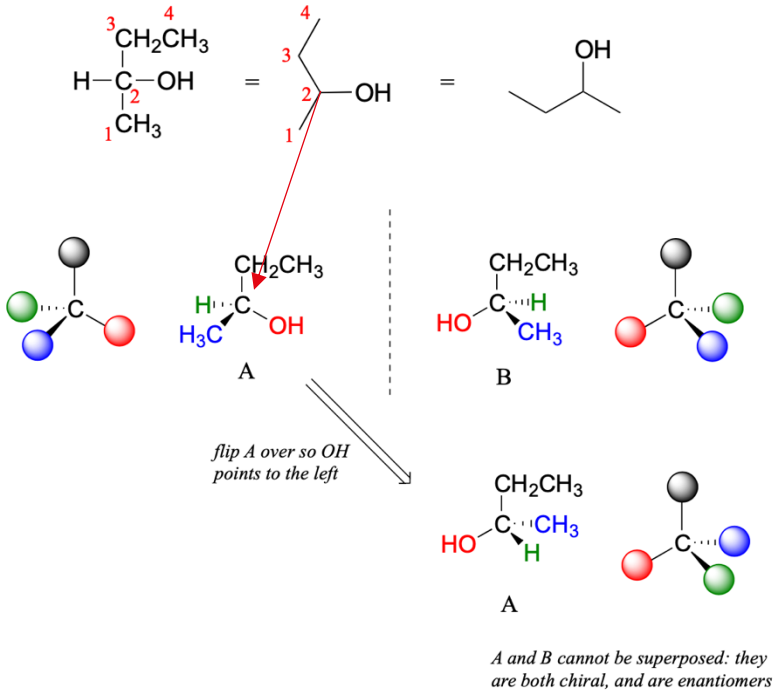
A few achiral examples

-sp2 hybridized carbons are also not chiral

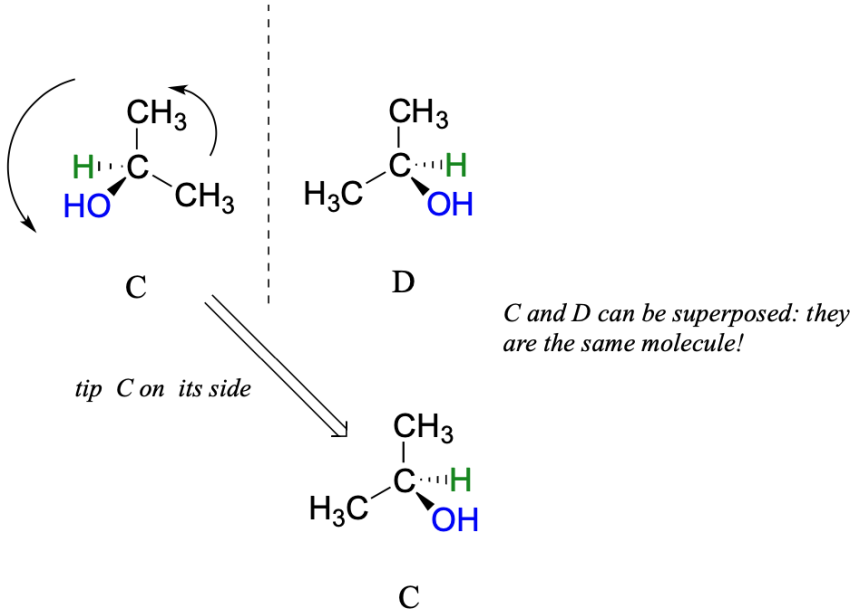


Lets look at chirality in real molecules

2-butanol (chiral)



2-propanol (achiral)

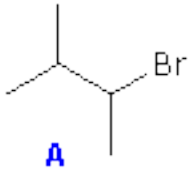


-C2 is a chiral center - sp3 hybridized with 4 different substituents

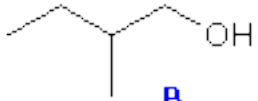
-sp3 hybridized with only 3 different substituents

Let's Discuss

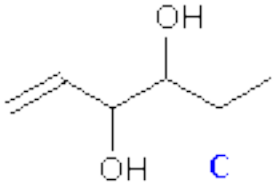
Some of these structures are chiral and some are achiral. Try to identify all chiral stereogenic centers.



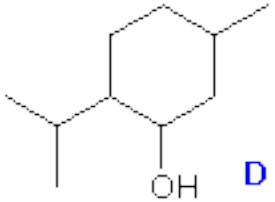
A



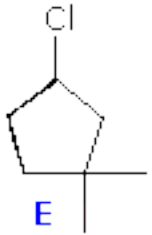
B



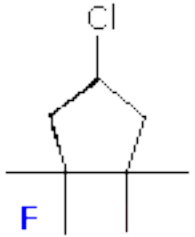
C



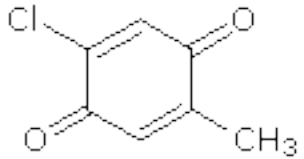
D



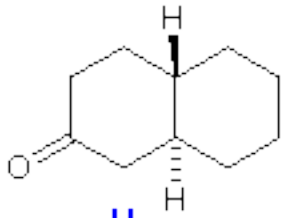
E



F



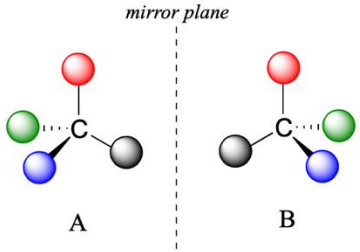
G

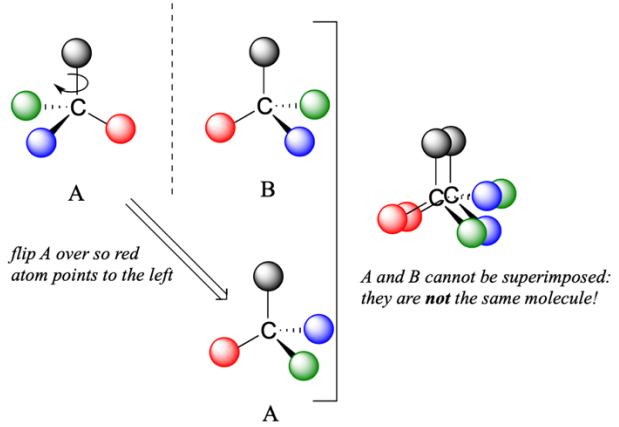


H

Chirality

- Toy example to show that mirror images are not superimposable





Can a chiral center be something other than a tetrahedral carbon with four different substituents ?

The answer is yes … but very rarely and in the context of bio-organic chemistry

Labeling chiral centers

-To distinguish different stereoisomers the Cahn-Ingold-Prelog system is used

-Isomers can be R(right-handed) or S(left-handed)

Rules for assigning R/S to a chiral center

1 – Assign priorities to the substituents: #1 highest priority to #4 lowest priority. Priorities based on the atomic number

2-Trace a circle from #1 to #2 to #3

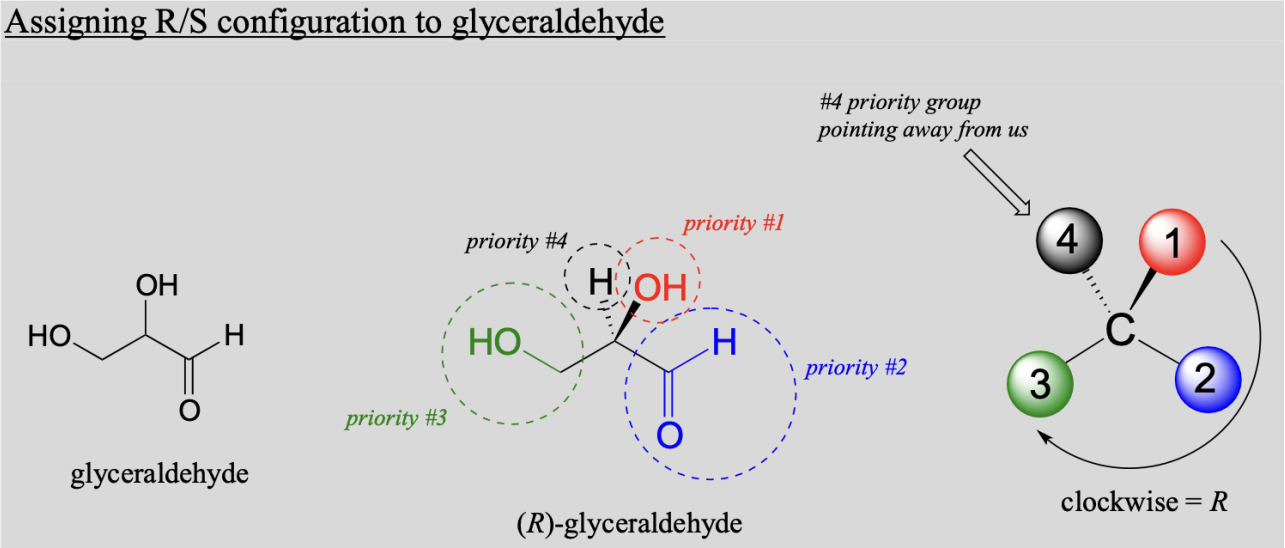
3 - Determine the orientation of #4 priority group: into the plane of the page -> 4a ; outside of the plane of the page -> 4b

4a- clockwise circle in 2 – R configuration; counterclockwise – S configuration

4b – clockwise circle in 2 – S configuration; counterclockwise – R configuration

Take your time at home to process these procedures !

Labeling chiral centers



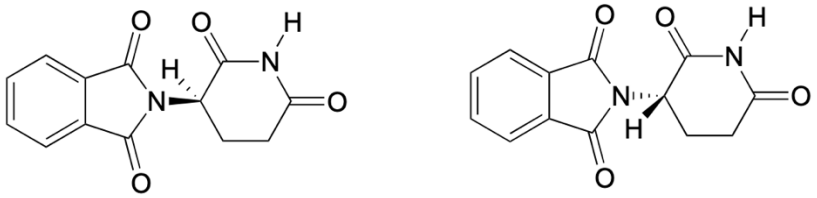
- two priorities are straightforward – H is the lowest (#4) and O is the highest(#1)

-Which 2 of C is #2? We move one more bond away from the chiral center, the atom is the same (O) but bonding is different and double bonds take priority – aldehyde group is #2 and CH_2OH is #3

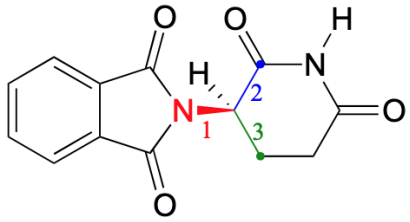
-group #4 is pointing away and thus rule 4a with clockwise circle thus an R

Enantiomers in drugs can have devastating effects

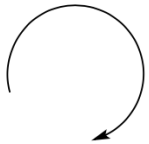
-German drug approved in the 50sfor morning sickness in pregnant women



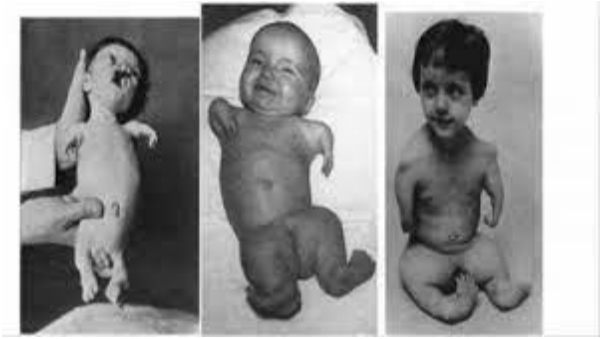
two enantiomers of thalidomide



(R)-thalidomide



clockwise: *R*

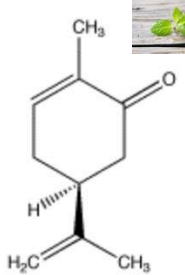


-R enantiomer had the desired medical effects
-S is responsible for birth defects

-Thalidomide became a very good drug against multiple myeloma

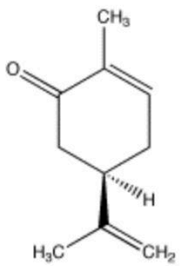
-Mixtures of S/R compounds are called racemic

Enantiomers: What's different, what's the same?



(*S*)-carvone
oil at 25°C
bp: 230-231°C
d: 0.965 g/mL
n: 1.4988
insol H2O, misc EtOH, MeOH
$[\alpha]_D = 61.2°$

Spearmint



(*R*)-carvone
oil at 25°C
bp: 230-231°C
d: 0.965 g/mL
n: 1.4988
insol H2O, misc EtOH, MeOH
$[\alpha]_D = -62.46°$

Caraway (carvi)

Identical physical properties:

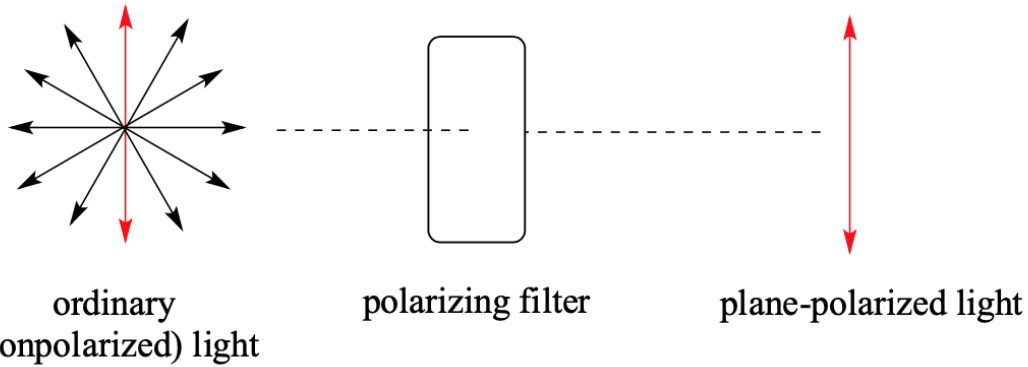
- Color
- Melting point / boiling point
- Density
- Refractive index
- …

Differences:

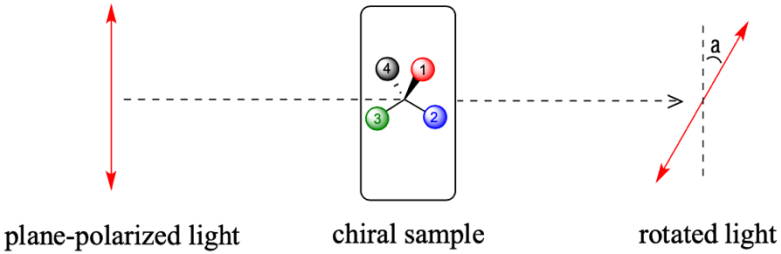
- Opposite optical rotations
- Chemical reactivity with other chiral molecules
- Biological properties (receptor specificity)

Optical activity of enantiomers

-Light waves are oscillating electric and magnetic fields
-In ordinary light the oscillation is randomly oriented

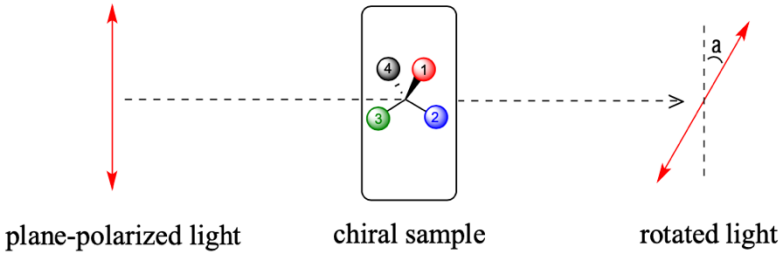


-Polarized light when passed through a sample of a chiral compound will rotate



Optical activity of enantiomers

-Polarized light when passed through a sample of a chiral compound will rotate

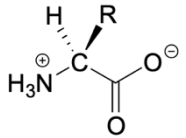


-If a compound rotates polarized light clockwise (+) direction is **dextrorotatory** if it does so in the counterclockwise (-) is **levorotatory**

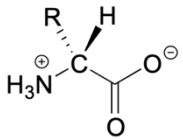
-For instance L- and D- aminoacids

-the measure specific rotations is measured as a physical property

R = *amino acid side chain*



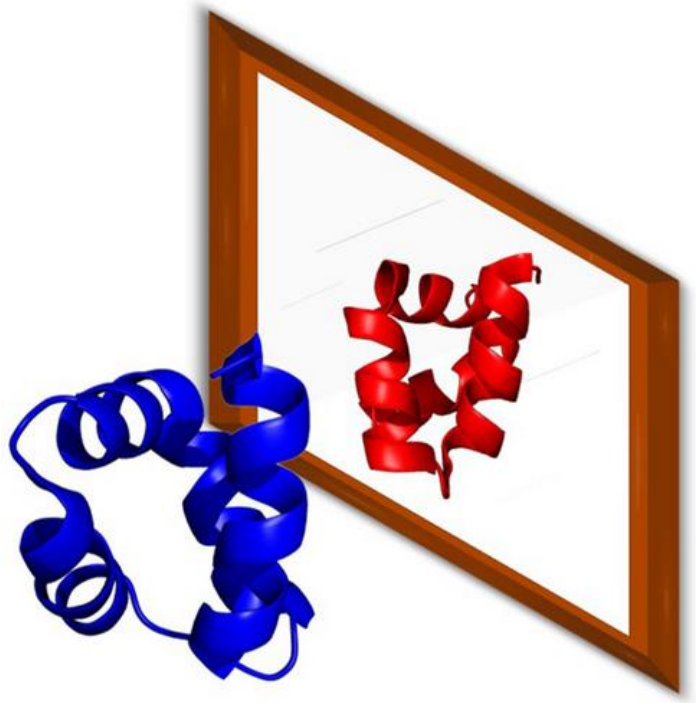
L-amino acids
(common in nature)

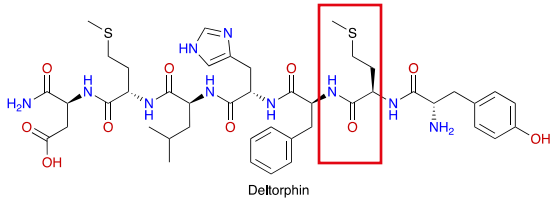


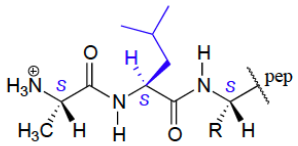
D-amino acids
(rare in nature)

There is no relationship between the chiral compound R/S designation and the direction of its specific rotation.

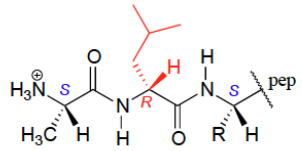
Effects on structure of an L and D protein







peptide with L-Leu at position 2

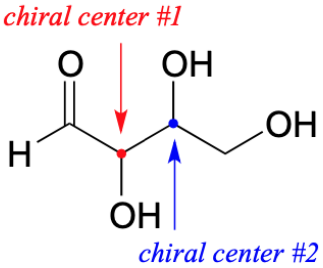


peptide with D-Leu at position 2

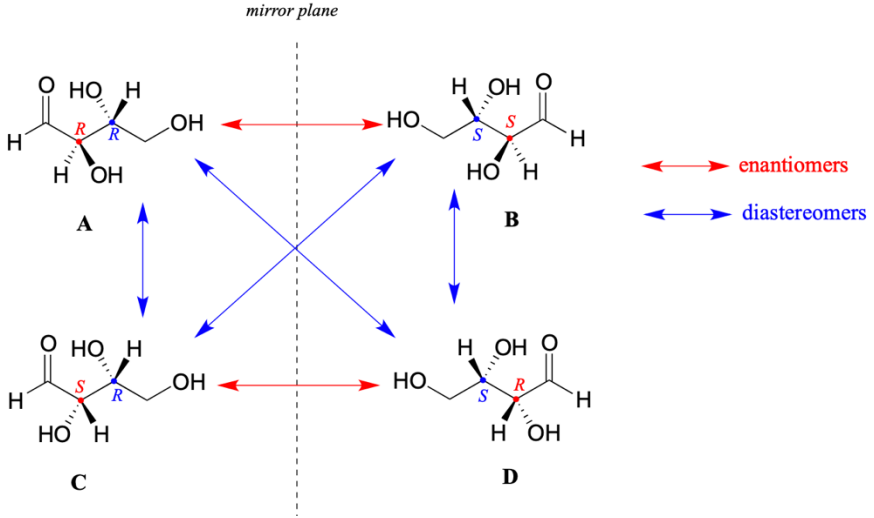
D-protein enantiomers can be accessed through total chemical synthesis and their preparation enables establishment of mirror-image life

Compounds with multiple chiral centers

-Example of a 4-carbon sugar



Different combinations of chiral centers



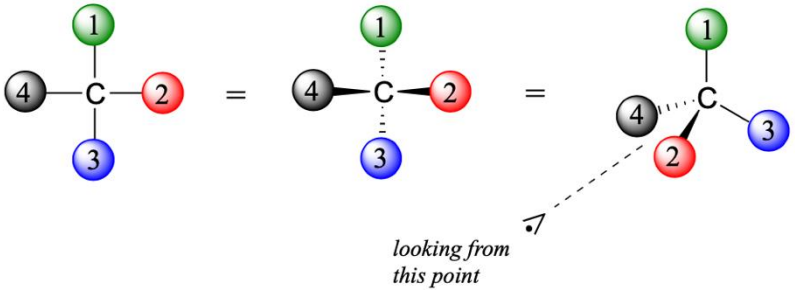
The four possible configurations:

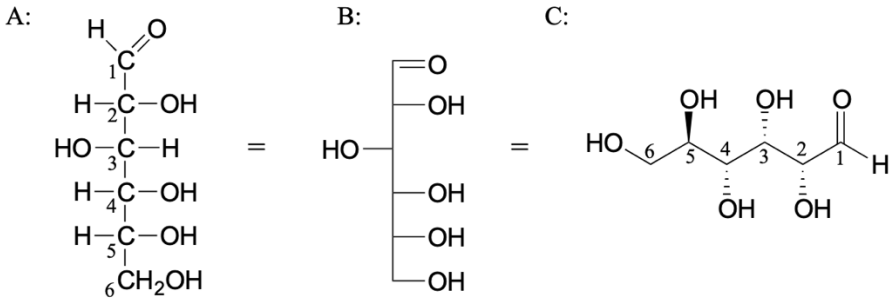
RR *RS*
SS *SR*

Enantiomers – non superimposable mirror images
Diastereomers – non superimposable non mirror images

Fischer and Haworth projections

-For Fischer projections the stereochemical information is conveyed by a simple rule where vertical bonds point into the plane of the page while horizontal bonds point out of the page





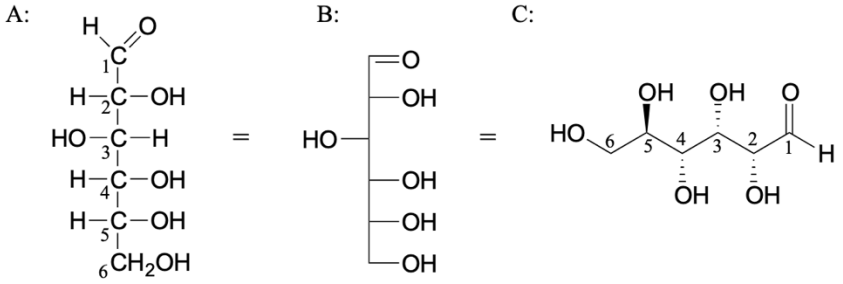
Fischer projection

Fischer projection with no carbons and hydrogens

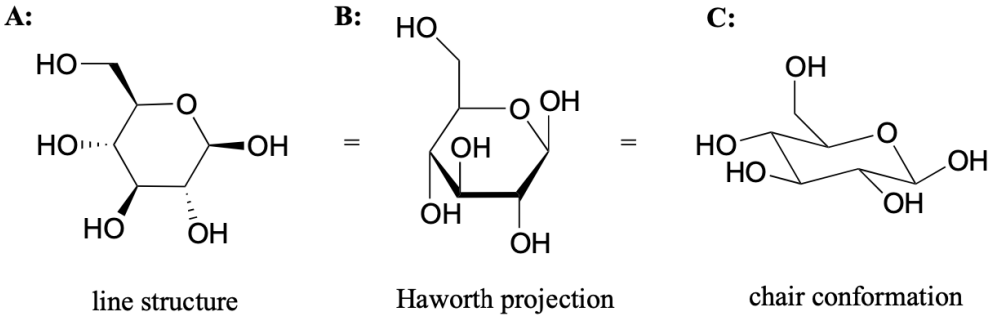
Zig-zag

Fischer and Haworth projections

Fischer projections – used for representing open-chain sugars

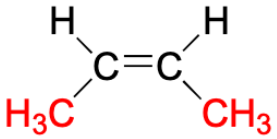


Haworth – used for representing for cyclic sugars

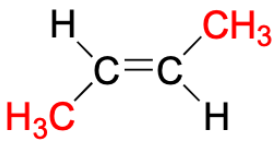


-Haworth is convenient way to show stereochemistry but not useful for conformation

Stereochemistry of alkenes

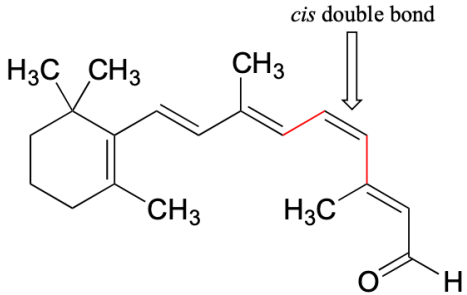


cis-2-butene

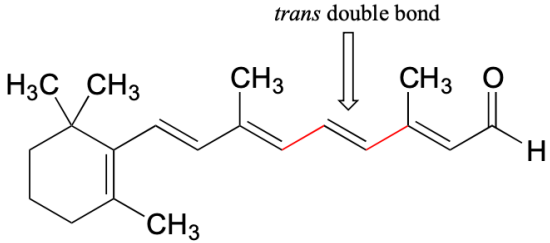


trans-2-butene

-No chiral centers
-Same molecular formula and bonding connectivity
-Stereoisomers that are not mirror images and thus diastereomers
-alkene groups that can exist in two stereoisomeric forms are referred to as **stereogenic**



11-*cis*-retinal



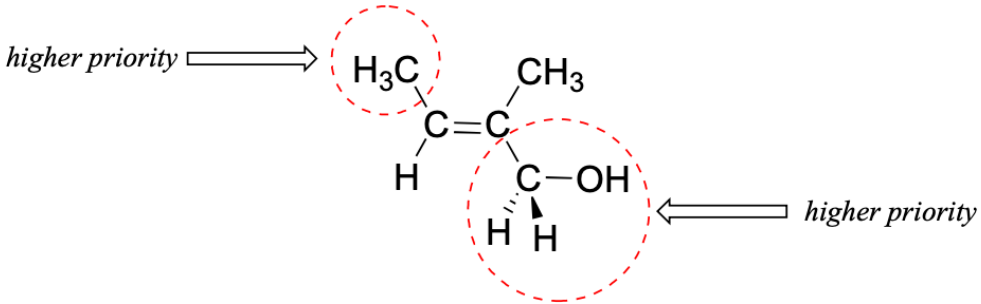
all-*trans*-retinal

-retinal is a light-sensitive molecule
-upon light irradiation a cis bond is converted to trans

Stereochemistry of alkenes

-Beyond cis and trans the ‘E’ and ‘Z’ notation can also be used

-Example of an E-alkene – the key is to decide which groups are the highest priority



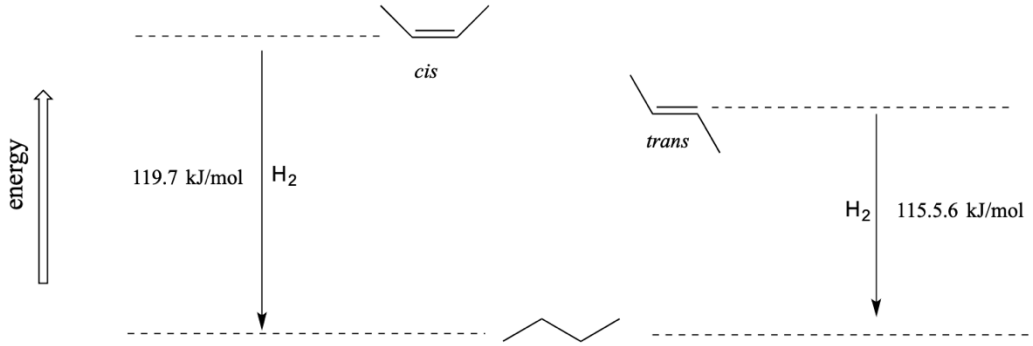
an *E*-alkene

-Not all alkenes can be labeled E/Z – if one or both of the double bond has identical substituents the alkene is not stereogenic

Stability of alkenes

-Alkenes with bulkiest groups on opposite sides are more stable due to reduced strain

-Energy is higher means that the molecule is less stable releasing more energy upon hydrogenation



- How many stereoisomers are possible for a given structure

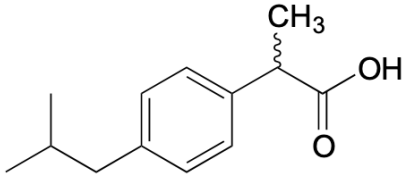
number of stereoisomeric forms = 2^n

. . . where n = the number of chiral centers ***plus*** the number of stereogenic alkene groups

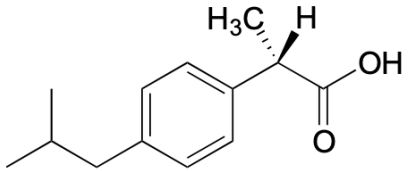
(the rare exception to this rule is when a meso *form is possible - in this case, the rule becomes* 2^n*-1)*

Chirality in biological systems

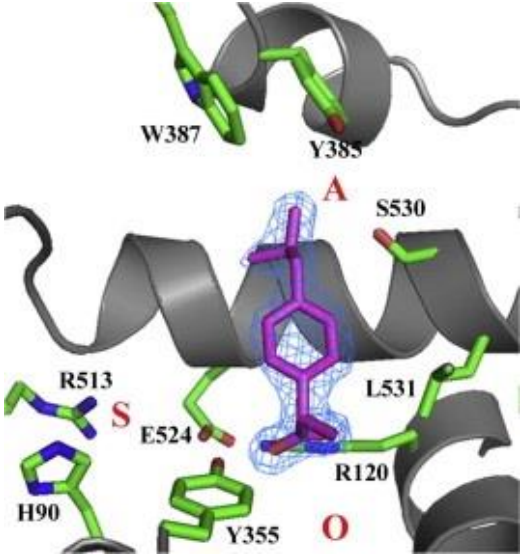
-Proteins are chiral molecules (as mentioned) as such compound chirality is critical for its activity



racemic ibuprofen



(*S*)-ibuprofen
(active enantiomer)

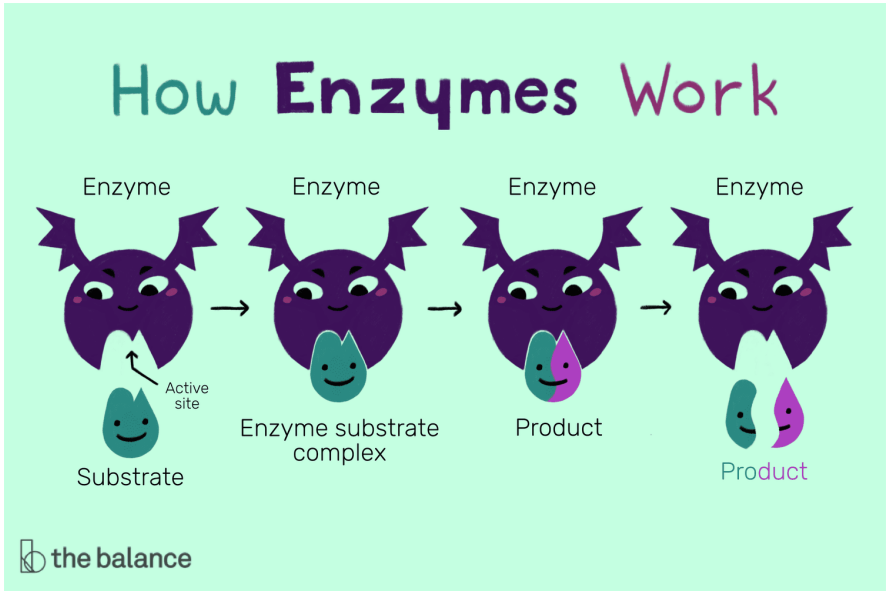


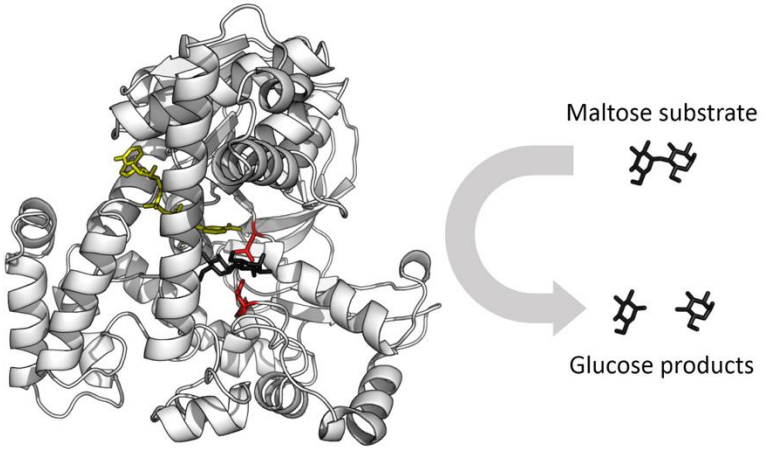
-let's take a look in 3D and

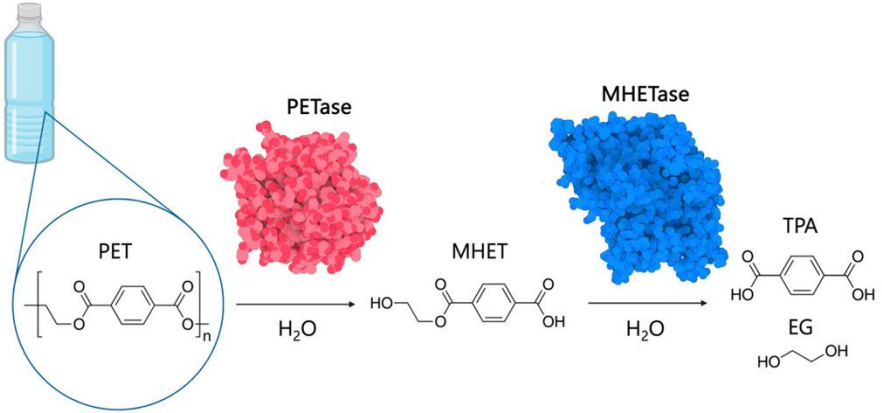
- How many chiral centers you see in this molecule ?

Chirality in biological systems

-Importance of chirality in enzyme-substrate recognition

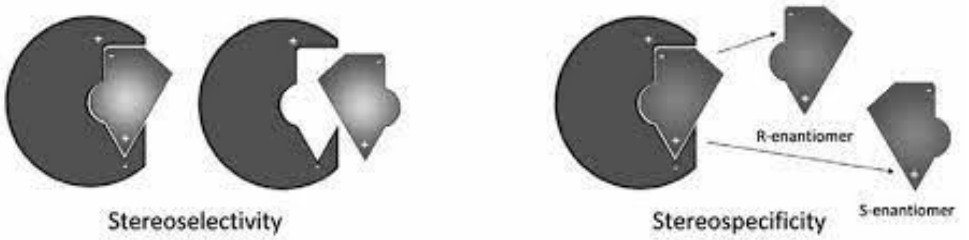


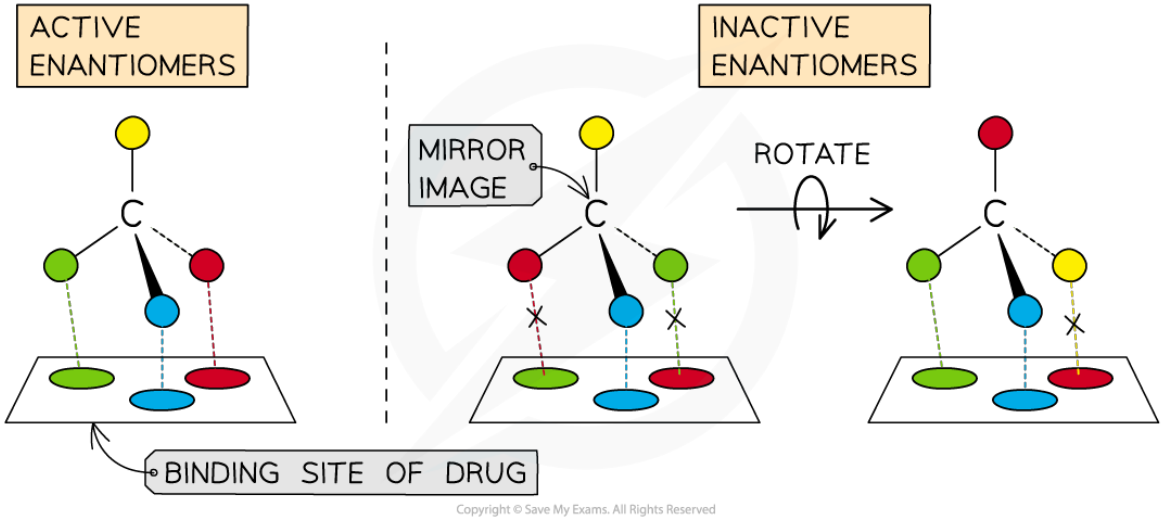




Chirality in biological systems

-Importance of chirality in enzyme-substrate recognition





Take home messages

-Eclipsed, staggered, gauche and anti conformations

-Newman projections

-Angle strain, envelope conformation, chair and boat conformation

-Equatorial and axial conformations

-Chirality

-Enantiomers and Diastereomers

-R/S and E/Z configurations

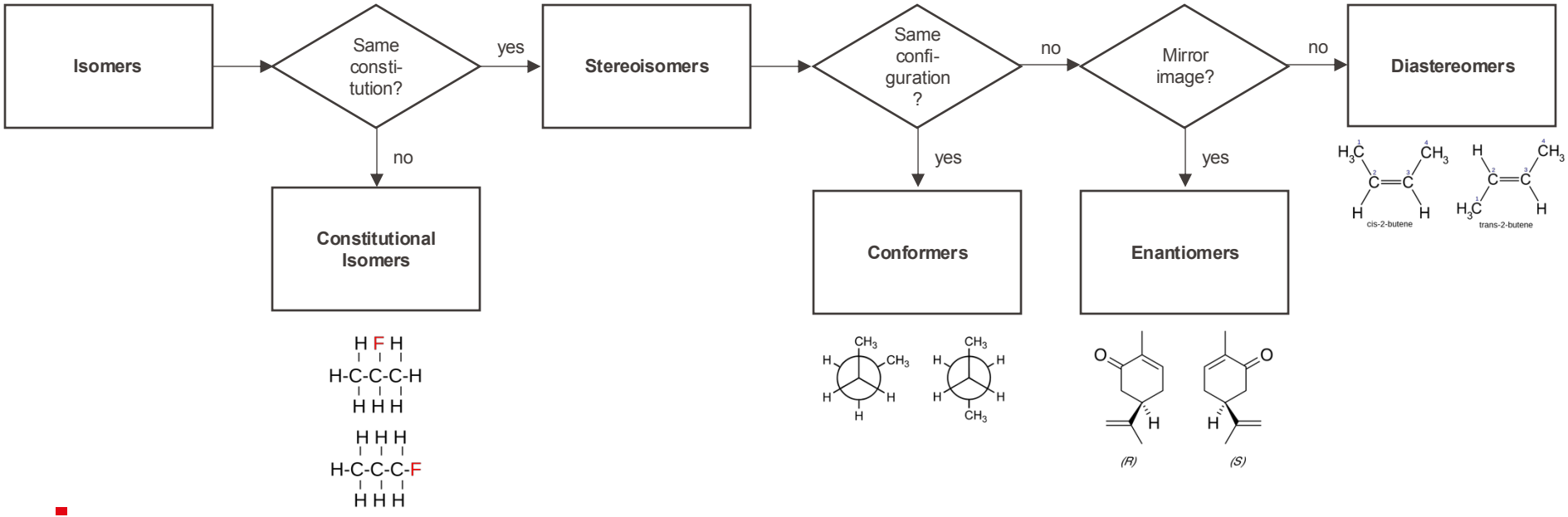
-Pro-chirality

-Capability of proteins to “read” stereochemistry

Stereochemistry

Summary

Isomers = molecules with identical molecular formula but distinct arrangements of atoms in space



Next lecture

Structure determination (Chapter 4)

Questions ?