

Stereochemistry and Projections:

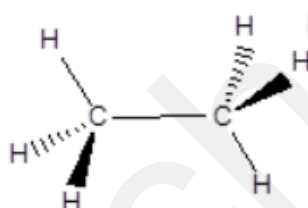
1. Conformations

Conformations are different spatial arrangements of a molecule that are generated by rotation about single bonds. Note that only atoms joined by a single bond are free to rotate. Those with double or triple bonds have a fixed orientation. There are two main conformations:

- Staggered conformation which is the most stable
- Eclipsed conformation which is the least stable

The staggered and eclipsed conformations interconvert by rotation around a C-C single bond. The decreased stability of the eclipsed form is due to the eclipsing of bonds on adjacent carbons; this is called torsional strain.

Dash and wedge: where black wedges indicate a bond coming out of the page and the dash indicates a bond going out of the page.



Newman projections: where the back C is represented by a circle and the front C by a point. The bonds to the front C are represented as lines going to the centre while bonds to the rear C are shown as lines going to the centre edge.

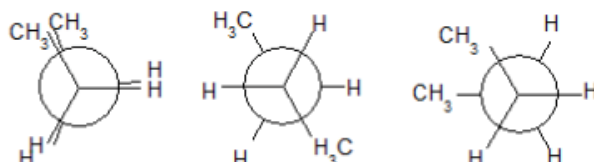


The terms anti and gauche apply only to bonds (or groups) on adjacent carbons, and only to staggered conformations. Two bonds are gauche when the angle between them is 60°. Two bonds are anti when the angle between them is 180°.

Butane C₄H₁₀ has two constitutional isomers:

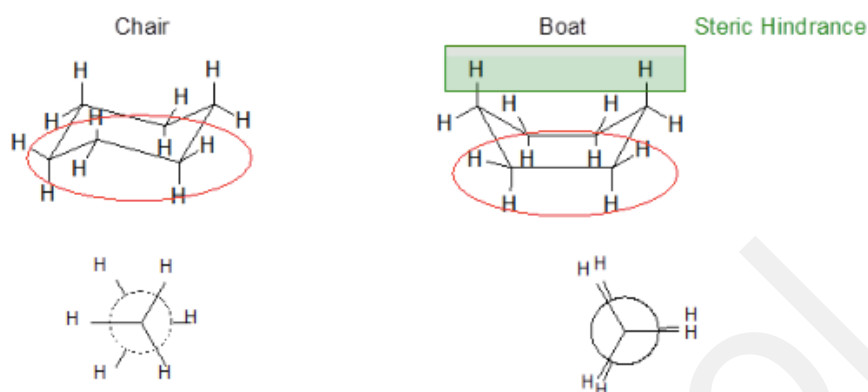
1. n-Butane which is an unbranched carbon chain
2. Isobutane which is a branched carbon chain. The conformation of butane in which the two methyl groups are eclipsed with each other is the least stable of all the conformations. It is destabilized by both torsional strain (eclipsed bonds) and van der Waals or steric strain (**steric hindrance**)
3. The gauche conformation is less stable than the anti. The gauche conformation is destabilized by van der Waals strain

Newman projections of the eclipsed, anti, and gauche isomers of butane:



Cycloalkanes:

There are two conformations for cyclohexane: chair and boat and are shown below respectively:

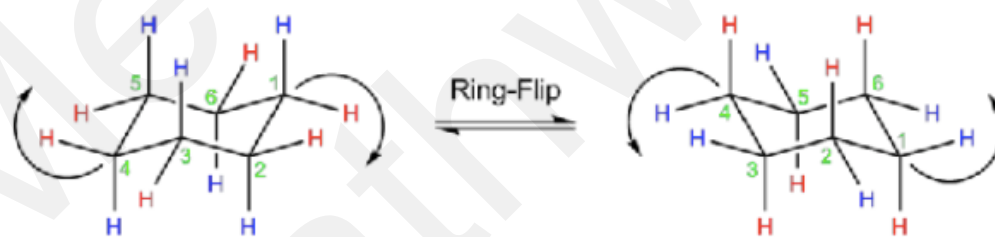


In the chair conformation, all of the bonds are staggered and the bond angles at carbon are close to tetrahedral. Chair is the most stable conformation of cyclohexane. In the boat conformation, all of the bond angles are close to tetrahedral but close contact between flagpole hydrogens causes van der Waals strain in boat, making it less stable than the chair conformation.

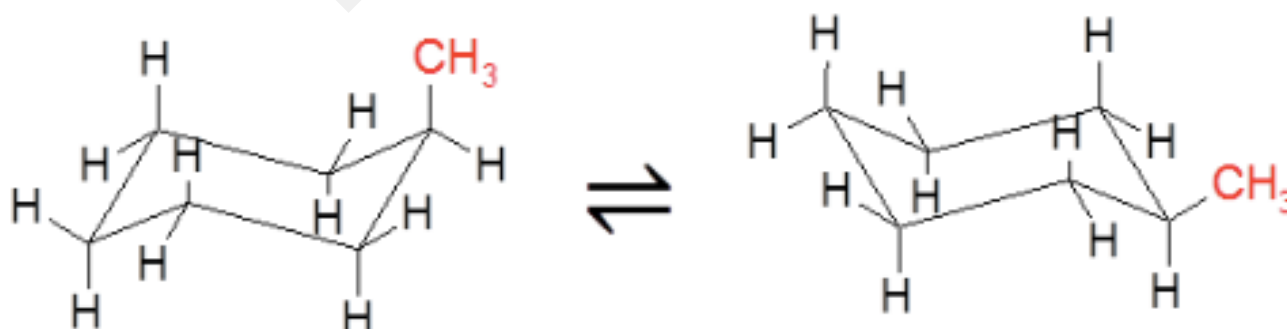
The chair conformation has two groups of H atoms 6 axial hydrogens, the bonds are parallel to a vertical axis that passes through the ring's centre, 3 up and 3 down. There are 6 equatorial hydrogen atoms and the bonds are located along the equator of the molecule; 3 up and 3 down.

One chair conformation can be converted into another chair conformation; this process is called ring inversion or flipping.

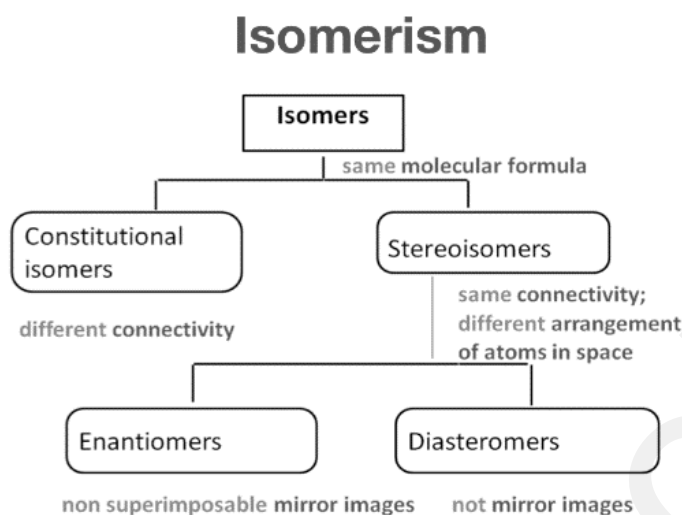
Upon ring flipping, any substituent that is axial in the original chair conformation will become equatorial in the ring flipped form and vice versa. The orientation of the bond does not change; axial up becomes equatorial up; axial down becomes equatorial down and vice versa.



In monosubstituted cycloalkanes the two chair conformations are not equivalent. A methyl group in the equatorial position is more stable because of less van der Waals. Large and bulky (highly branched) groups are more stable on the equatorial position.



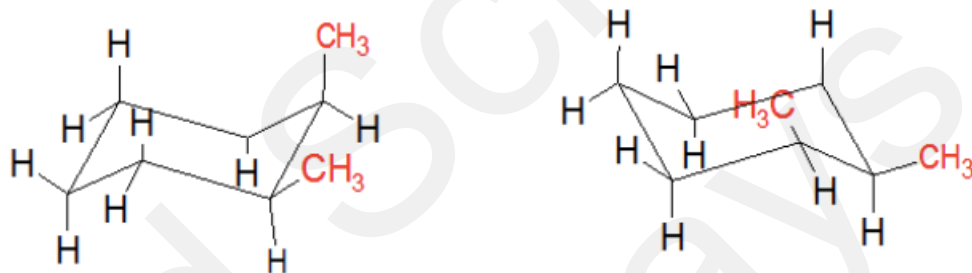
Stereoisomers:



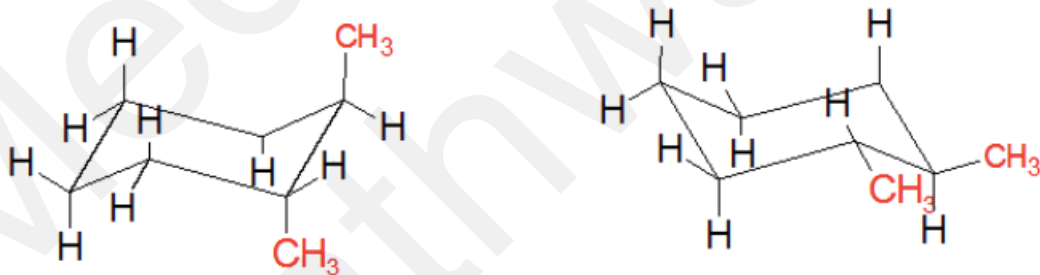
Chirality

Disubstituted cycloalkanes have 2 stereoisomers:

Cis isomers - the two substituents are on the same side of the equatorial plane of the ring:



Trans isomers - the two substituents are on opposite sides of the equatorial plane of the ring:



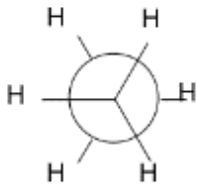
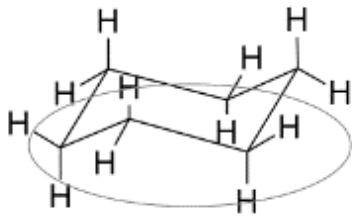
For cyclohexane, the cis stereoisomer has two equivalent conformations; each has one axial methyl group and one equatorial methyl group. In the trans stereoisomer the two conformations are not equivalent; in one both methyl groups are axial while in the other both methyl groups are equatorial making that the more stable conformation. As a result, trans isomers are more stable than cis isomers.

When the groups on the cycloalkane aren't equivalent, the most stable conformation is when the larger and bulkier group is in the equatorial position.

Conformations of Cyclohexane

2 main conformations:

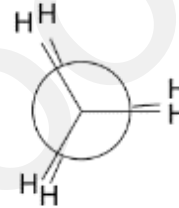
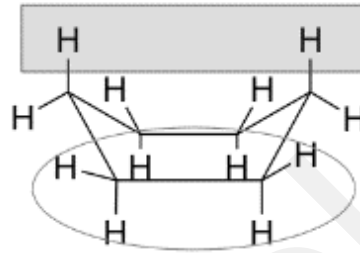
Chair



all of the bonds are staggered and the bond angles at carbon are close to tetrahedral.

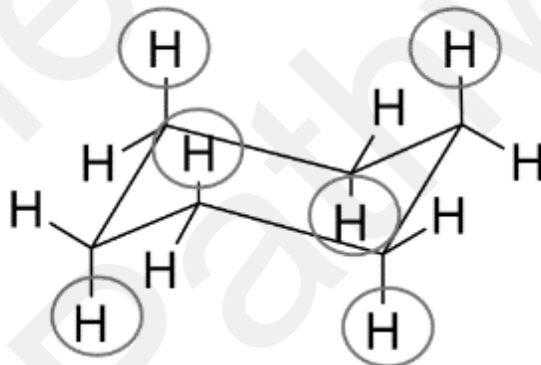
Boat

Steric Hindrance



all of the bond angles are close to tetrahedral but close contact between flagpole hydrogens causes van der Waals strain

Chair conformation

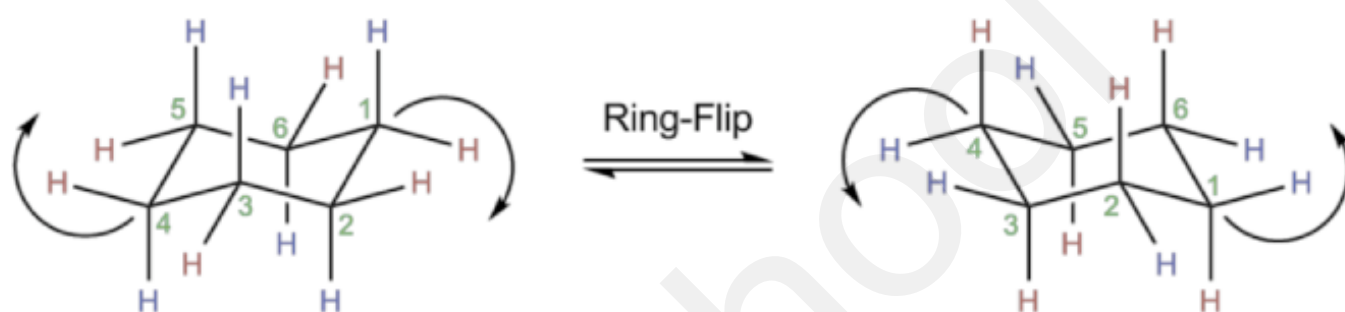


Vertical bonds:
Axial bonds

Other bonds lie on
equator of
molecule:
Equatorial bonds

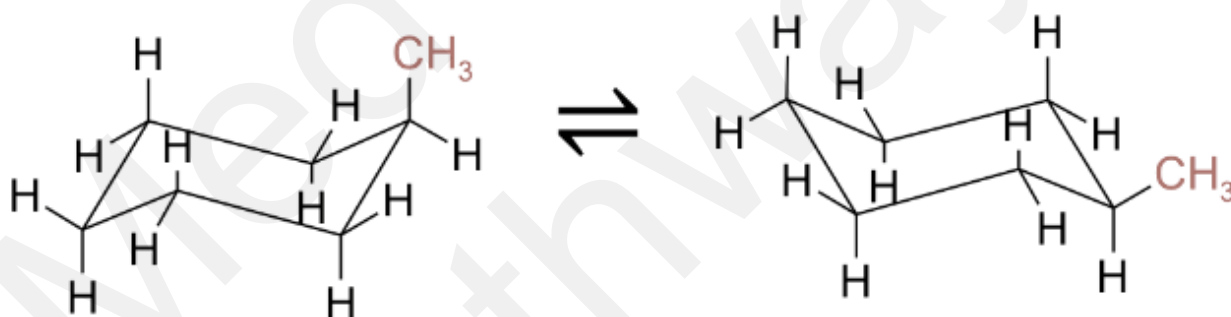
Ring Flipping

Upon ring flipping, any substituent that is axial in the original chair conformation will become equatorial in the ring flipped form and vice versa



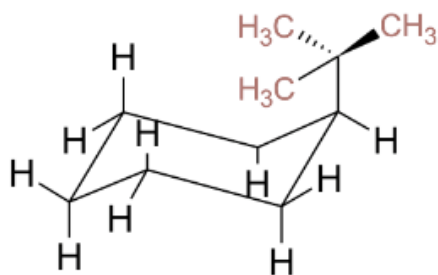
Monosubstituted cycloalkanes

In monosubstituted cycloalkanes the two chair conformations are **not** equivalent

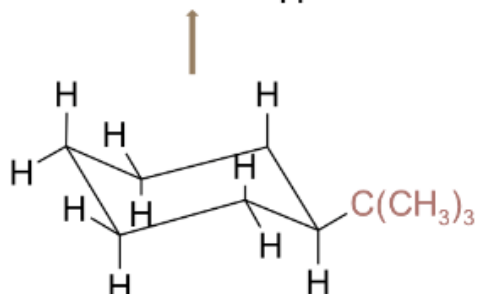


A methyl group in the equatorial position is more stable because of less van der Waals strain and axial repulsion

Monosubstituted Cycloalkanes



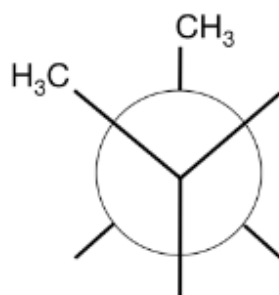
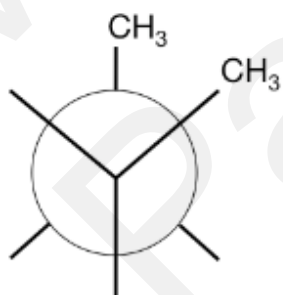
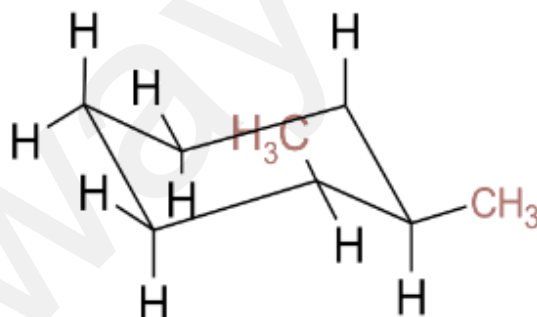
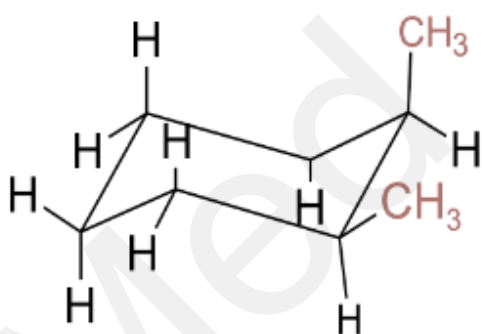
Unstable: repulsion between CH_3 and H on neighbouring atoms:



More stable in equatorial position

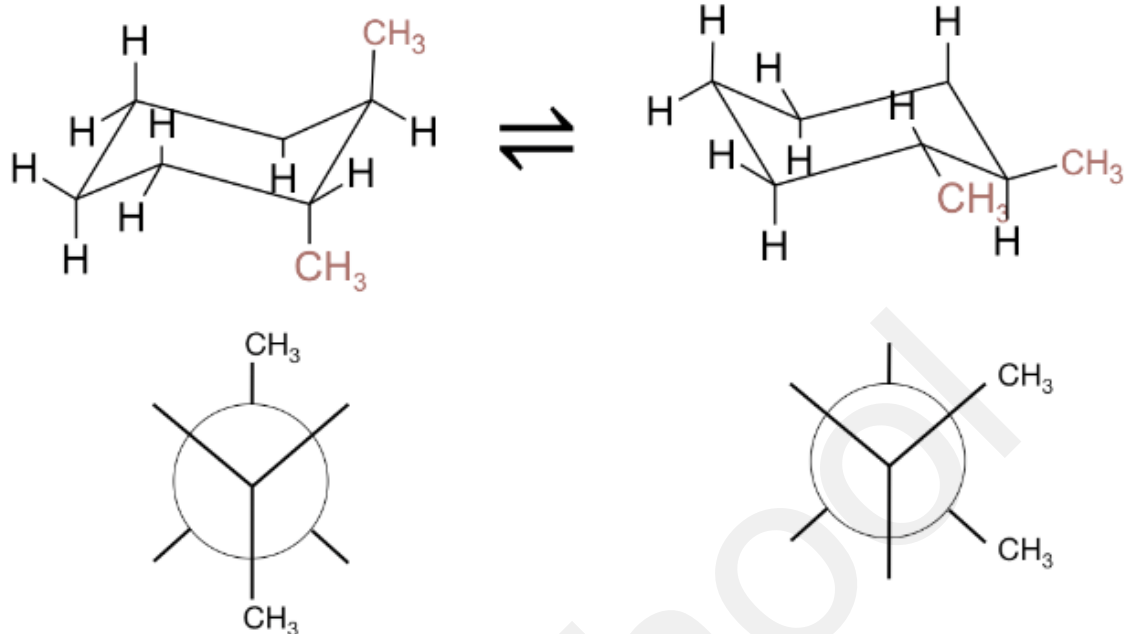
Large and bulky (highly branched) groups are more stable on the equatorial position

Cis stereoisomer



two **equivalent** conformations; each has one axial methyl group and one equatorial methyl group

Trans stereoisomer



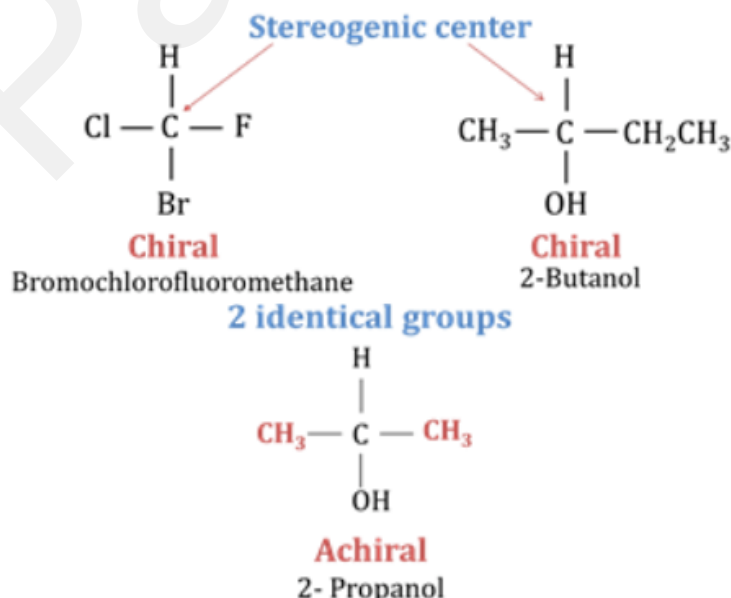
When the groups on the cycloalkane aren't equivalent, the most stable conformation is when the larger and bulkier group is in the equatorial position

Chirality:



Figure 10.1 A pair of stereoisomers

A molecule is **chiral** if it cannot be superimposed on its mirror image and **achiral** if its mirror image is the same. Chiral molecules have one or more **stereogenic centres** (aka stereocentre). Generally in organic chemistry, the stereogenic centre is a carbon with four different groups attached; if any two identical groups are attached, then the molecule is achiral.



Cyclic molecules can also be chiral; consider the example of limonene (Figure 10.3). Although at the stereogenic centre it has two bonds to the ring, one bond leads to $-\text{CH}_2\text{CH}_2-$, where the other leads to $-\text{CH}_2\text{CH}_2=$ (i.e. reaches the alkene group faster). This means that the centre does not have any two identical groups and so it is chiral.

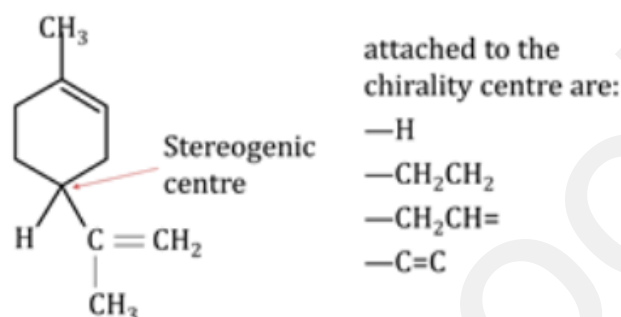
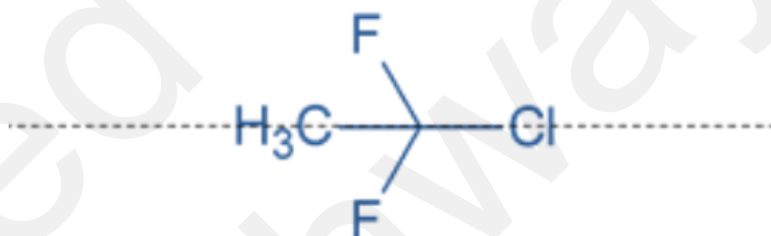


Figure 10.3 Chirality in cyclic molecules

Another way to determine whether a molecule is chiral or achiral is to check if the molecule has a plane of symmetry. A plane of symmetry bisects a molecule into two mirror image halves, and any molecule with a plane of symmetry must be achiral (Figure 10.4).



Chlorodifluoromethane has a plane of symmetry.

Figure 10.4. Planes of symmetry in chirality

A molecule with one stereogenic centre has no plane of symmetry, is chiral and is not superimposable with its mirror image. It can be represented by two distinct structures called **enantiomers**.

Chirality Notation:

Enantiomers are designated as the R-enantiomer or S-enantiomer using the Cahn-Ingold-Prelog system. This system uses three rules:

1. Rank substituents at the stereogenic centre according to the same rules used in E-Z notation.
2. Orientate the molecule so that the lowest-ranked substituent points away from you.
3. If the order of decreasing precedence in the remaining three substituents traces a clockwise path, the absolute configuration is denoted as R. If the path is counterclockwise, the configuration is denoted as S.

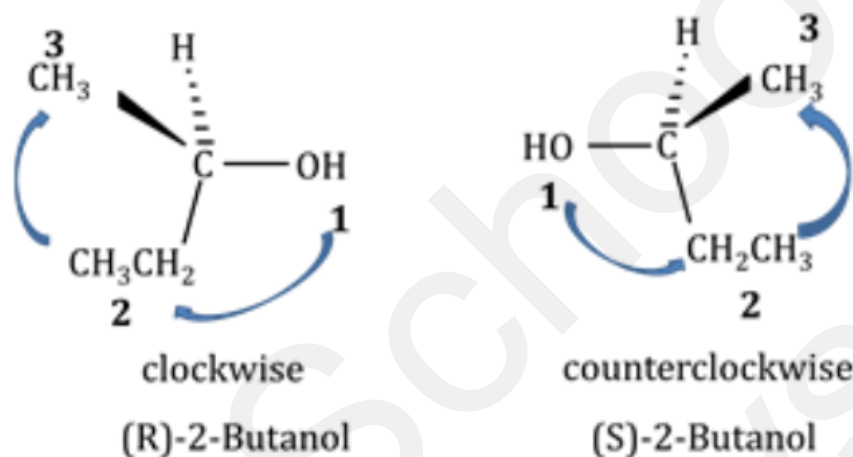


Figure 10.5. Cahn-Ingold-Prelog Rules

Fischer projections are an alternative way of representing chiral molecules where horizontal bonds in the projection represent bonds coming out of the page and vertical bonds in the projection represent bonds going into the page (Figure 10.6).

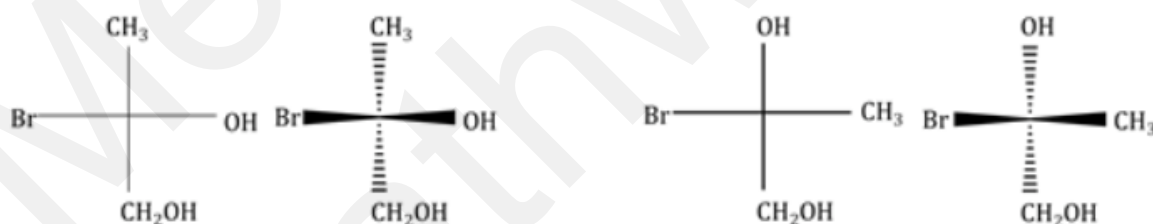


Figure 10.6. Fischer projections and their 3-dimensional representations

Fischer projections also offer an alternative method for determining chirality:

1. Rank the substituents
2. Draw a path for substituents ranked 1 – 3.
3. According to the path, give each enantiomer a 'conditional notation'
4. Is the lowest ranked group facing away?

If yes, conditional notation is the true notation

If not, reverse the conditional notation to obtain the true notation

The lowest group is pointing away if it is on the vertical plane and it is pointing towards if it is on the horizontal plane.

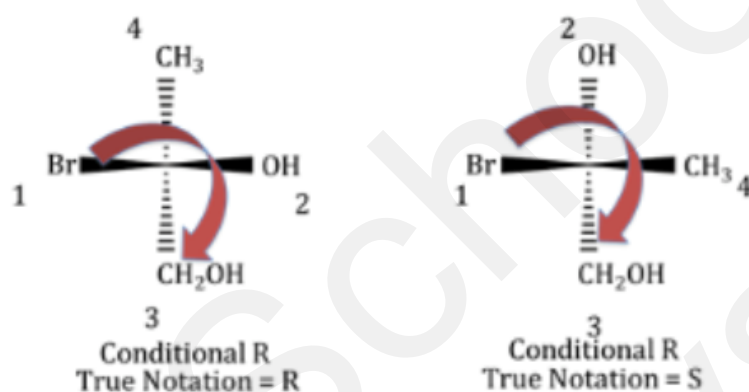


Figure 10.7 Determining chirality from Fischer projections

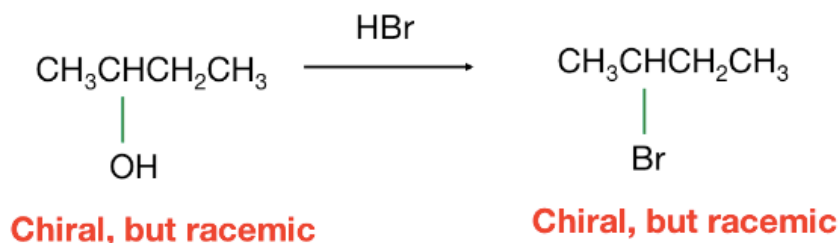
Chirality and Reaction in Biology:

Many reactions convert achiral reactants to chiral products. If all of the components of the starting state (reactants, catalysts, solvents, etc.) are achiral, then any chiral product that may be formed will be a **racemic** mixture, equal amounts of both enantiomers. Optically inactive starting materials cannot give optically active products. Many reactions convert chiral reactants to chiral products, but again, if the reactant is racemic, the product will also be racemic.

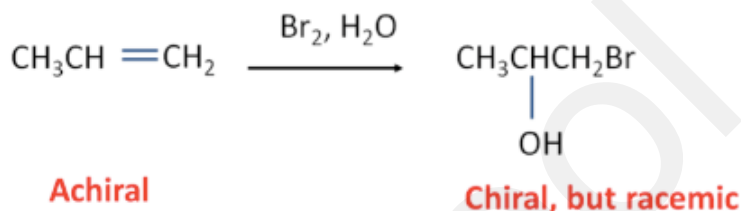
Reactions in living systems are catalyzed by enzymes, which are enantiomerically homogeneous. The enzyme (catalyst) is part of the reacting system, so such reactions don't violate the generalization that "optically inactive starting materials can't give optically active products". Enzymes can thus convert achiral molecules to a single enantiomer of product rather than a racemic mixture (Figure 10.8).



Figure 10.8. Enzymes can convert achiral molecules to enantiomerically pure products



For example:



Optical Activity:

Enantiomers are chemically and physically identical except for their optical activity. **Optical activity** is the ability to rotate plane polarized light (Figure 10.10). Each enantiomer of a chiral molecule has equal and opposite optical rotation. This can be measured using **polarimetry**. In order for a substance to exhibit optical activity, it must be chiral and one enantiomer must be present in excess of the other. A sample that is optically inactive ($\alpha = 0$) can be either an achiral substance or a racemic mixture; a mixture containing equal amounts of the two enantiomers of a chiral substance.

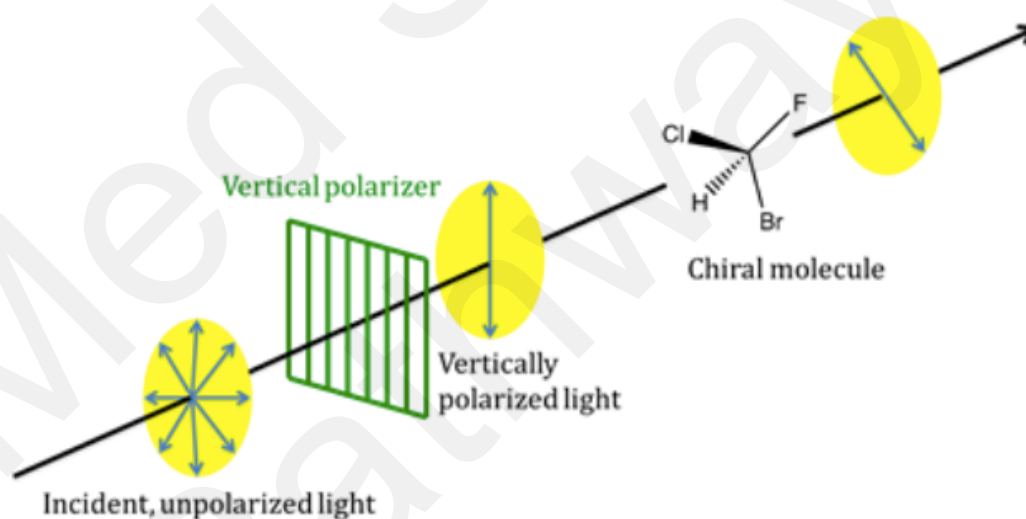


Figure 10.10. Optical activity of a chiral molecule

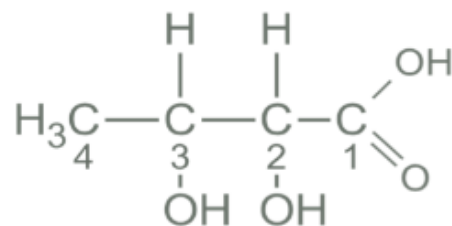
Optically inactive starting materials cant give optically active products

Diastereomers and Meso compounds:

Many molecules have multiple chiral centres, each of which was individually be assigned an R or S notation. If a pair of stereoisomers differ at all chiral centres, they are considered enantiomers. If they differ at some, but not all chiral centres, then they are termed **diastereomers**.

Another type of compound with multiple chiral centres is a **meso compound**. A molecule is considered to be a meso compound if there is a plane of symmetry within the molecule and all the chiral centres on one side of the plane are reversed on the other.

Two stereogenic centres

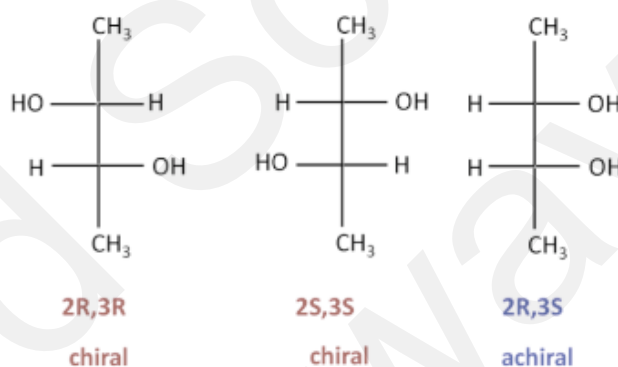


2,3-dihydroxy butanoic acid, has 2 chiral centres: C₂ and C₃.

Possible stereoisomers: (2R, 3R) (2S, 3S) (2S, 3R) (2R, 3S)
 Enantiomers Enantiomers

The stereoisomers that are not enantiomers are diastereomers.
 Diastereomers are stereoisomers that are not mirror images of each

Two stereogenic centres

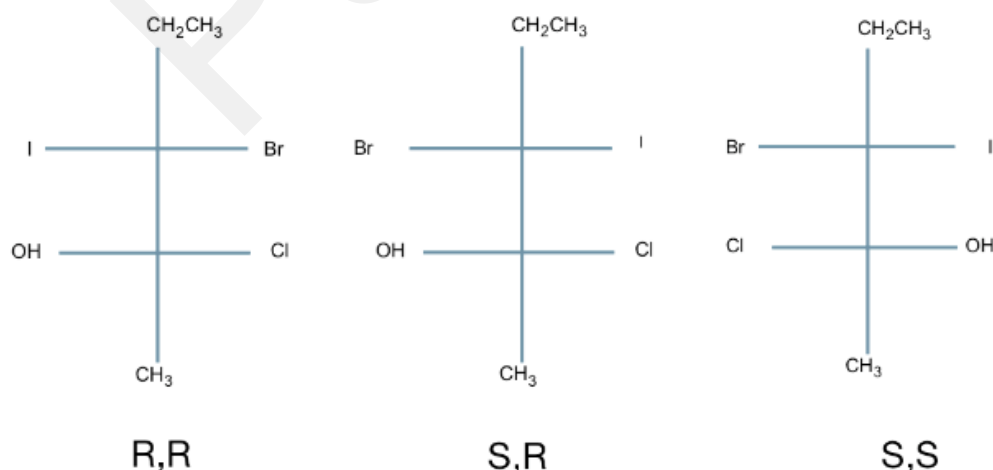


(2R, 3R) and (2S, 3S) are enantiomers, (2R, 3S) is achiral.

It is superimposable on its mirror image and is called a **meso** form.

Meso forms have a plane and/or centre of symmetry.

Examples



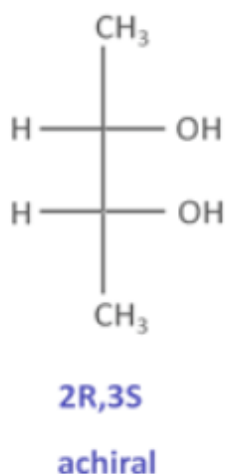


Figure 10.9. An example of a meso compound with a horizontal plane of symmetry

Molecules with Multiple Stereogenic Centres

How many stereoisomers?

maximum number of stereoisomers = 2^n

- where n = number of structural units capable of stereochemical variation
- structural units include chirality centers and cis and/or trans double bonds
- number is reduced to less than 2^n if meso forms are possible

Dienes:

Molecules with two double bonds are called dienes. There are three distinct classes of diene:

1. Isolated: the double bonds are separated by more than one bond
2. Conjugated: there is one single bond between the two double bonds
3. Cumulated: both double bonds are to the same carbon

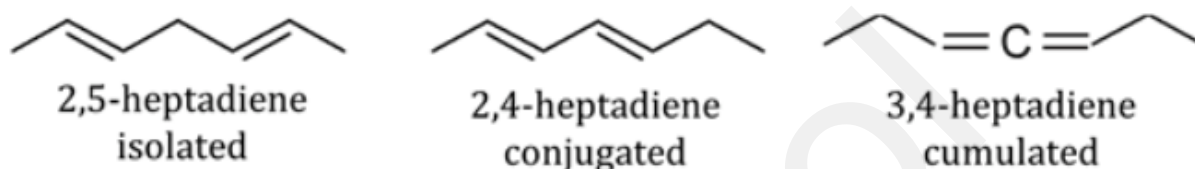


Figure 10.11 Different classes of dienes

E-Z isomers:

When the substituents on the double bond are different we use **E-Z notation**. When the higher ranked substituents are on the opposite side of the double bond, we denote it as E, where if they are on the same side of the double bond we denote it as Z (Figure 10.12).

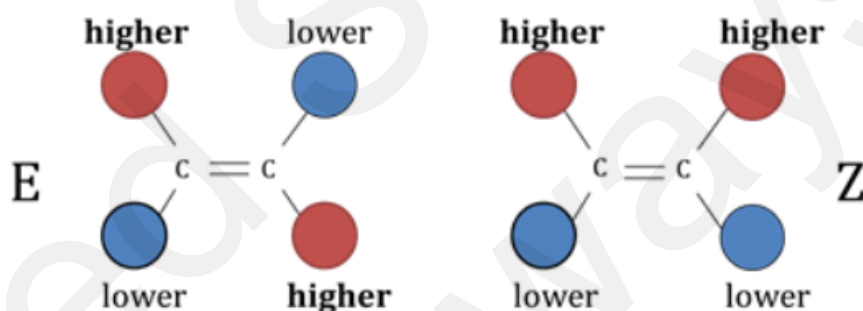
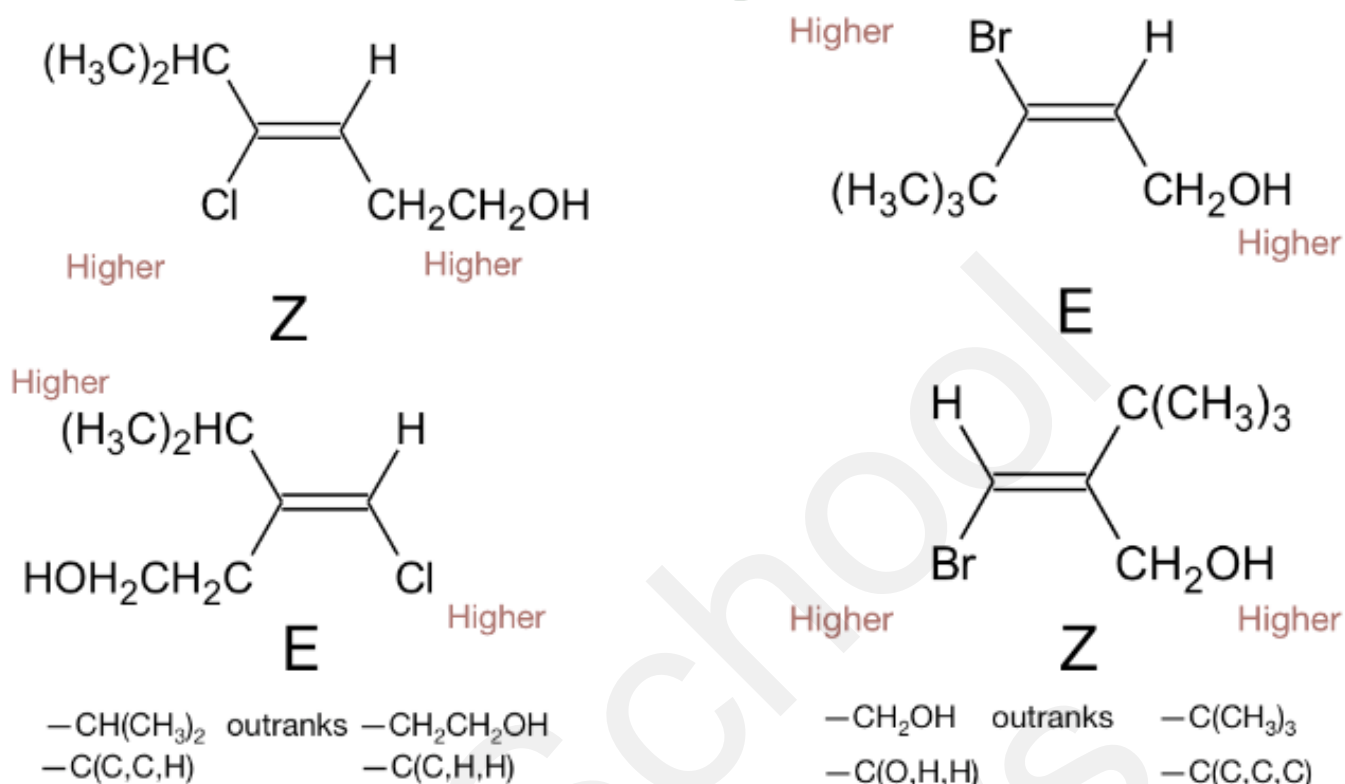


Figure 10.12. Assignment of E-Z stereochemistry in alkenes

Recall that ranking is by atomic number, and then if atomic number is the same you proceed to the next atom in each substituent and compare atomic numbers again (Figure 10.13).

Examples



Alkynes are linear and do not have stereochemistry about the triple bond

Stability of alkenes

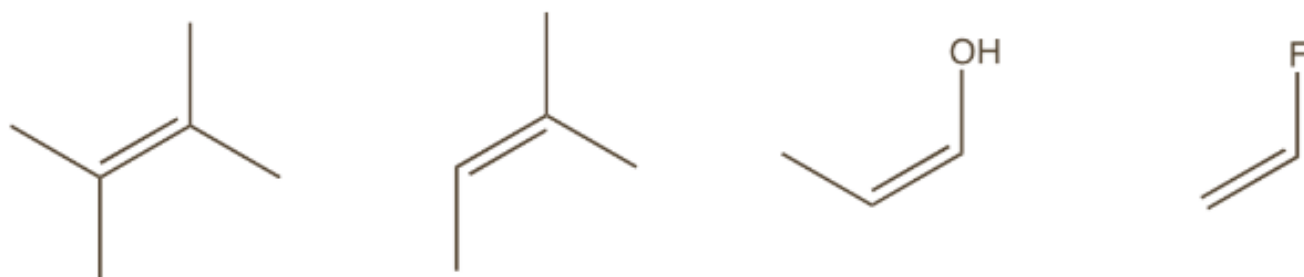
Two factors affect the stability

1. Degree of substitution:

- Alkenes are stabilized by electron-releasing groups. Alkyl groups stabilize double bonds through an **electronic effect**.
- Tetrasubstituted > trisubstituted > disubstituted > monosubstituted

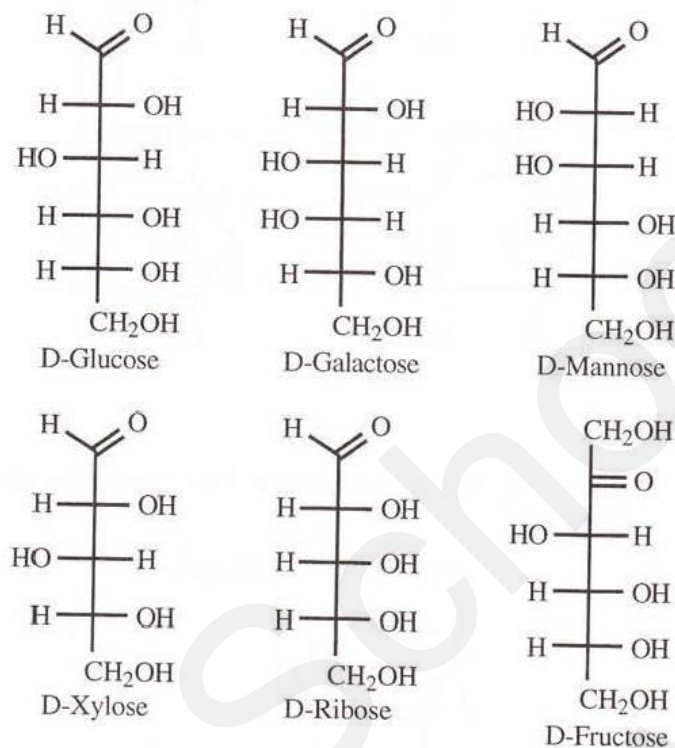
2. van der Waals strain:

- Alkenes are more stable when large substituents are *trans* to each other than when they are *cis*.



1.0:

Sugars, when metabolized by animals, generate a substantial amount of energy. Many naturally occurring monosaccharides and disaccharides can be extracted from the fruits of plants. Among the most common naturally occurring sugars are fructose, sucrose, and glucose. The figure below shows six common biological monosaccharides.



1. What is the stereo-configuration for D-Ribose?

- A. 2R, 3R, 4R
- B. 2S, 3S, 4R
- C. 2S, 3S, 4S
- D. 2R, 3R, 4S

2. What is the stereo-configuration for D-galactose?

- A. 2S, 3R, 4R, 5S
- B. 2R, 3S, 4S, 5R
- C. 2S, 3S, 4S, 5R
- D. 2R, 3R, 4S, 5R

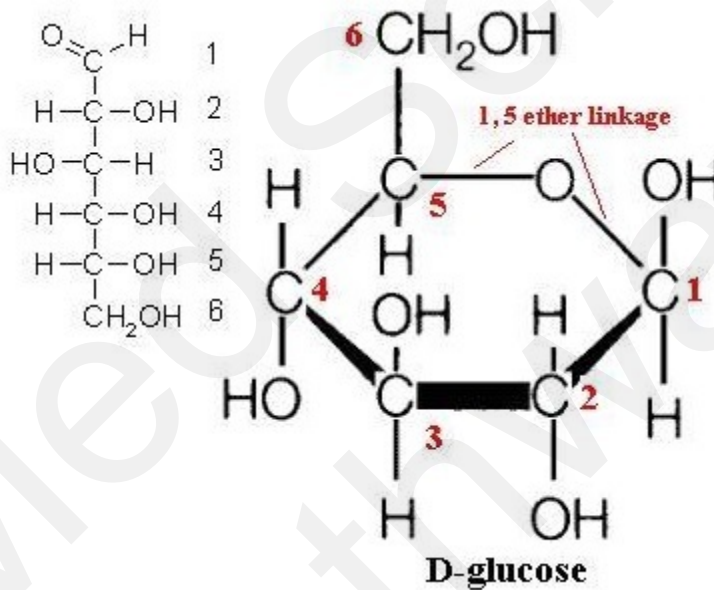
3. How many meso compounds could be identified from the list of the above monosaccharides?

A. 0
B. 1
C. 2
D. 3

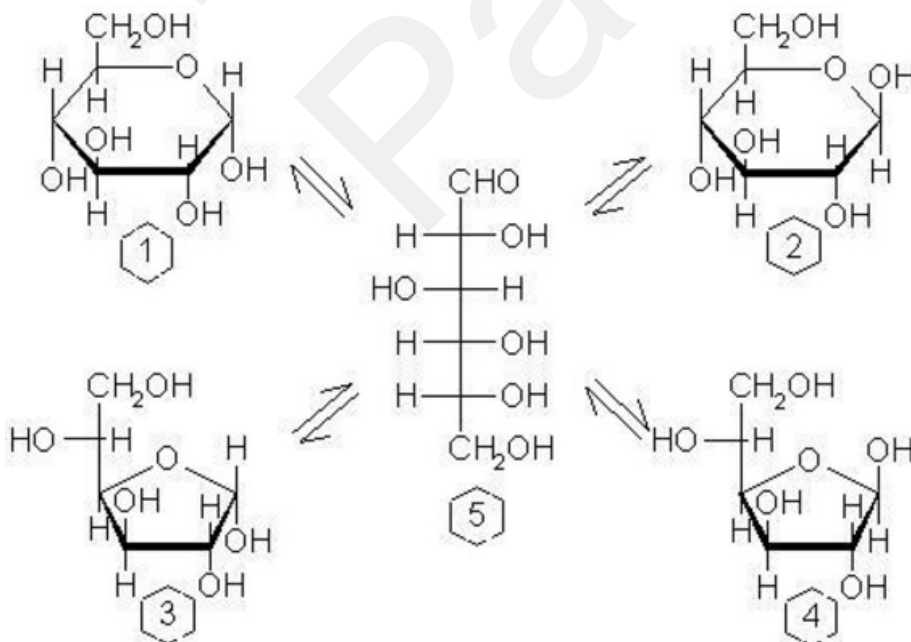
4. Questions 4-5 are related to the following additional information:

The carbon atoms with the aldehyde (or keto) group reversibly binds to one of the other carbons by "sharing" a hydroxyl oxygen, forming a C-O-C linkage. This is known as an hemiacetal linkage, and typically, the result is an n-member ring.

Below is an example of D-glucose forming a 6-membered ring

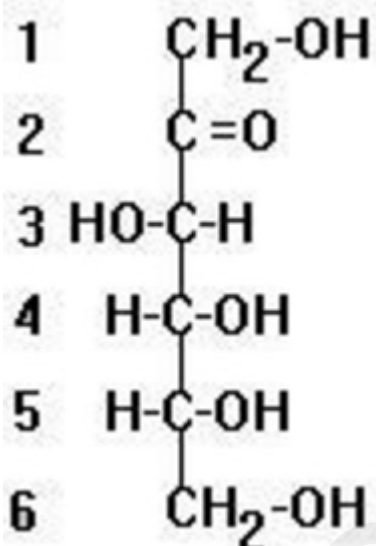


Which of the following structures are possible for glucose?

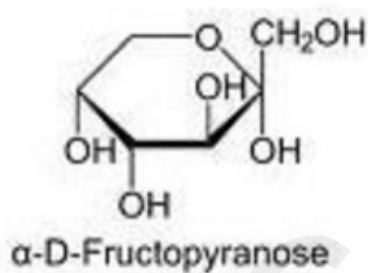


A. 2 only
B. 1 and 2 only
C. 1 and 2 and 4 only
D. 1 and 2 and 3 and 4

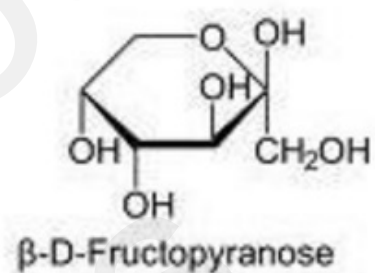
5. Which of the following rings best represent D-fructose?



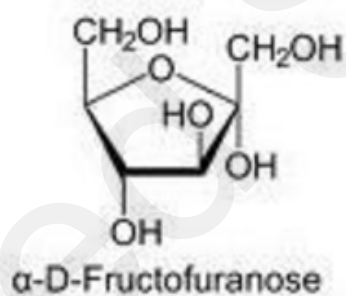
A



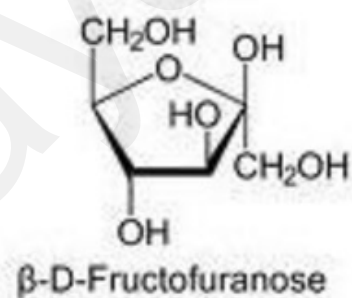
B



C



D



A. A and B

B. C and D

C. A and C

D. A, B, C and D

1.1:

Consider the following chemicals:

A: 2-chloro-2-bromobutane

B: 2-chloropropane

C: 2,3-dichlorobutane

D: 2-chloropropene

1. Which of the chemicals are chiral compounds?

A. A, B, C and D

B. A, C and D

C. A and D

D. A and C

2. Which of the following statements is correct?

A. Compound A has a single chiral center and two possible stereoisomers.

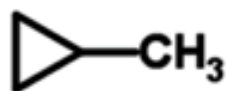
B. Compound A has two chiral centers and four possible stereoisomers.

C. Compound A has single chiral center and four possible stereoisomers due to the presence of two different halogenic groups.

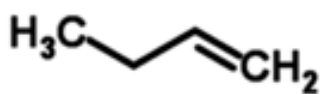
D. Compound A has two chiral centers and two possible stereoisomers.

1.2:

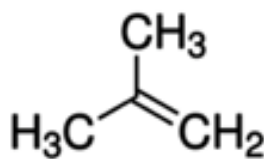
Consider the four compounds below:



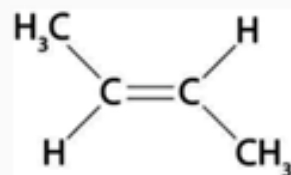
1



2



3



4

1. Which of the four compounds is not a structural isomer of the others?

- A. 1
- B. They are all structural isomers
- C. 3
- D. 4

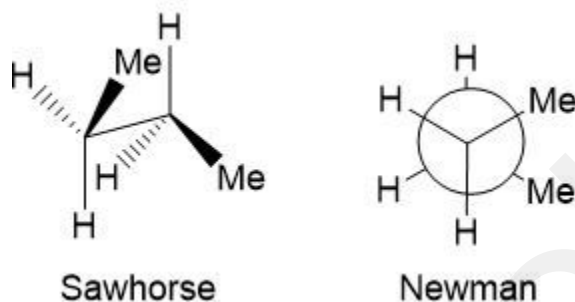
2. Which of the following is a structural isomer of at least three of the above compounds?

- A. Cyclobutane
- B. Cyclopentane
- C. 2-methyl propane
- D. 2-methyl butane

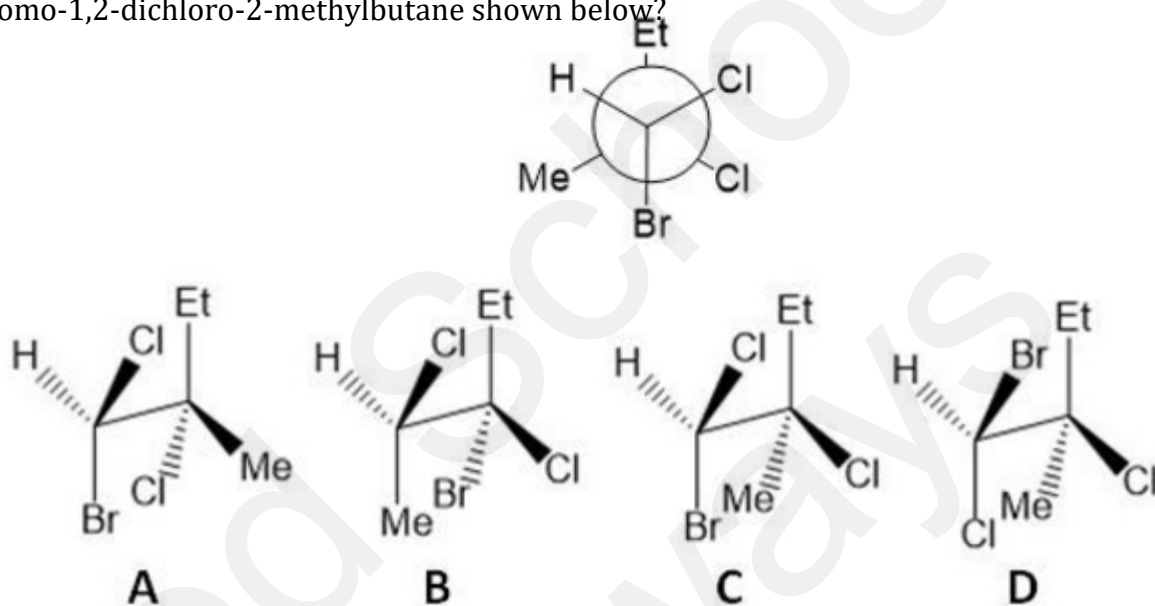
3. Which of the four compounds can exist as more than one stereoisomer?

- A. 2
- B. 3
- C. 4
- D. 2 and 4

1.3:
 There are many methods of representing organic molecules. Two such methods are shown below with the molecule butane; the sawhorse projection, which considers a 3D view of the molecule, and the Newman projection, which looks down the axis of the molecule.

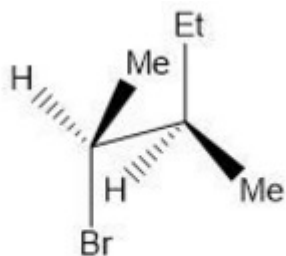


1. Which of the following sawhorse projections corresponds to the Newman projection of 1-bromo-1,2-dichloro-2-methylbutane shown below?



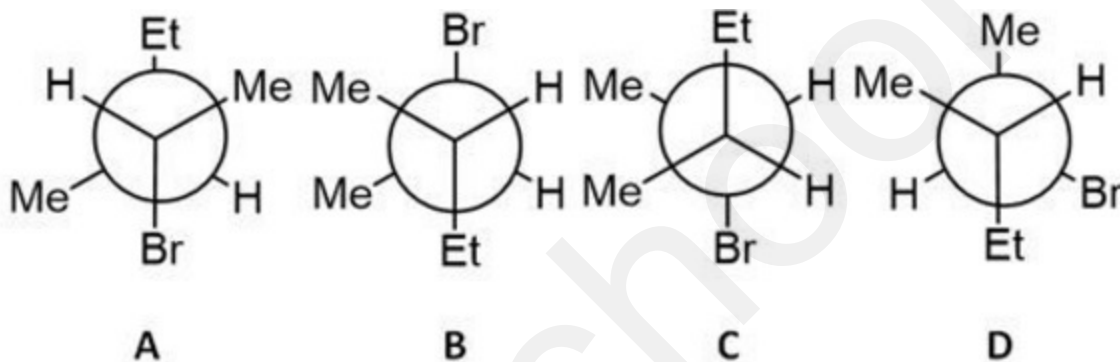
- | |
|------|
| A. A |
| B. B |
| C. C |
| D. D |

2.



(2*S*,3*R*)-2-bromo-3-methylpentane

Which of the following Newman projections represents the sawhorse projection of (2*S*,3*R*)-2-bromo-3-methylpentane shown above?



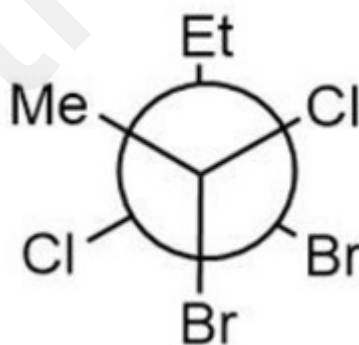
A. A

B. B

C. C

D. D

3. What is the name of the molecule below?



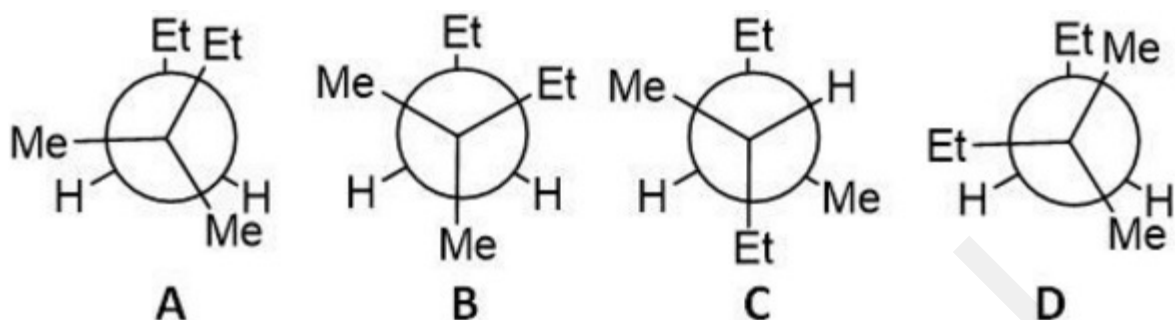
A. (2*R*,3*R*)-2,3-dibromo-2,3-dichloropentane

B. (2*S*,3*S*)-2,3-dibromo-2,3-dichloropentane

C. (2*R*,3*S*)-2,3-dibromo-2,3-dichloropentane

D. (2*S*,3*R*)-2,3-dibromo-2,3-dichloropentane

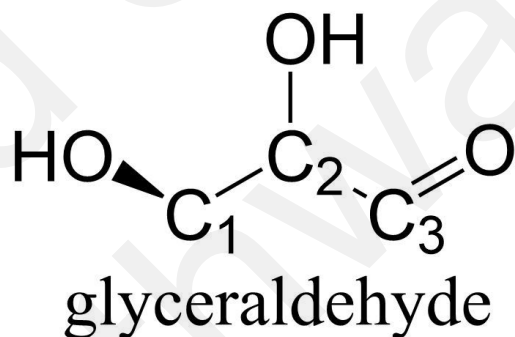
4. The most stable conformational isomer of a molecule is the one with minimal steric clashes between large groups. Which of the conformations below would be the most stable for 3,3-dimethylhexane?



- | |
|------|
| A. A |
| B. B |
| C. C |
| D. D |

1.4:

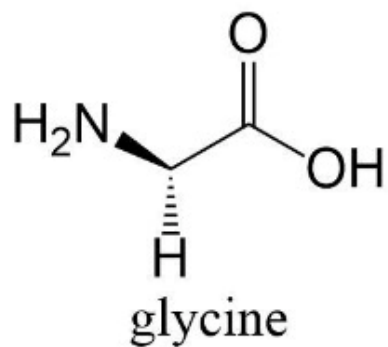
One of the older systems for assigning stereochemistry is the L/D-system, which relates chiral molecules to the two stereoisomers of glyceraldehyde, shown below.



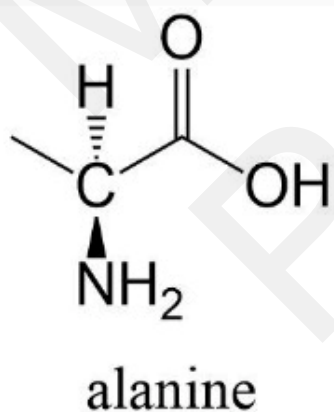
1. Where is the stereocentre in glyceraldehyde?

- | |
|-----------------------------|
| A. C1 |
| B. C2 |
| C. C3 |
| D. There is no stereocentre |

2. The L/D-notation is most commonly used with amino acids, where there exists a simplified method for assigning chirality. The groups COOH, R, NH₂ and H (where R is the side-chain) are arranged around the chiral centre carbon atom. With the hydrogen atom away from the viewer, if the arrangement of the CO→R→N groups around the carbon atom as centre is counter-clockwise, then it is the L form. If the arrangement is clockwise, it is the D form. Below is shown an isomer of glycine, the most basic proteinogenic amino acid. What isomer is shown?



- A. The D-isomer
- B. The L-isomer
- C. Not enough information is provided
- D. Glycine does not have L or D isomers
3. Another amino acid is alanine, an isomer of which is shown below. What is the R/S and L/D stereochemistry of this isomer?



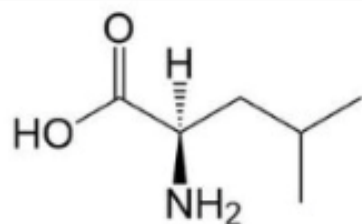
A. R/L

B. R/D

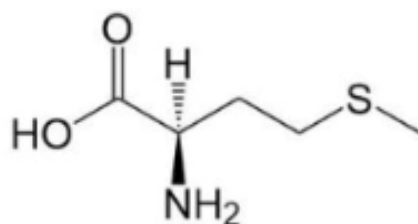
C. S/L

D. S/D

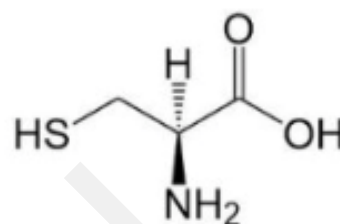
4. Below are shown three R-isomers of various amino acids. Looking at these molecules, and those in the previous questions, what is the relationship between R/S and L/D stereochemistry?



R-leucine



R-methionine



R-cysteine

- A. R-isomers are the same as L-isomers
- B. S-isomers are the same as L-isomers
- C. S-isomers are the same as D-isomers
- D. There is no clear relationship between R/S and L/D isomers