MCAT STEREOCHEMISTRY

INTRODUCTION AND OUTLINE

This section will definitely increase your MCAT Stereochemistry knowledge and skills. Stereochemistry and isomerization are important in medicine and are notoriously tested on the MCAT. Formally, these topics are listed under content Category 5B: "Nature of molecules and intermolecular interactions". A discussion of each topic is accompanied by a series of rigorous MCAT style questions.

Content Category 5B examines the majority of content that focuses on isomers. In Content Category 5D, carbohydrate stereochemistry is listed. We have integrated carbohydrates as part of the discussion of diastereomers.

The MCAT tests, often in integrated fashion, multiple facets of isomers, including their chemistry, physics, and of course, their biological significance. You will be expected to recognize various types of isomers, understand their physical and chemical properties and appreciate their biological functioning that nicely illustrates the structure-function paradigm of biomolecules. As enzymes recognize one type of stereoisomer (i.e. L amino acids vs D amino acids), expect for their biological relevance and applications to also be tested despite the fact that the topic of isomers are formally listed in the physical sciences section. Expect to see some biological application questions in the physical sciences section.

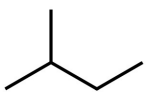
Below is the list for Stereochemistry in the AAMC MCAT[2015] Content Outline. This section will examine each topic, but will be presented in a slightly different order. Each entry should be considered as a learning objective/goal that will be tested at the end.

Stereochemistry of covalently bonded molecules

- **Isomers**
- **Structural isomers**
- **Stereoisomers (diastereomers, enantiomers, cis/trans isomers)**
- **Conformational isomers**
- **Polarization of light, specific rotation**
- **Absolute and relative configuration**
- **Convention for writing R and S forms**
- **Anomers and epimers**

Isomers. Isomers are molecules that possess identical molecular formulas and masses, yet their three-dimensional structures vary due to differences in the spatial orientation of their constituent atoms. Several various classes and properties of isomers relevant to the MCAT will be examined here.

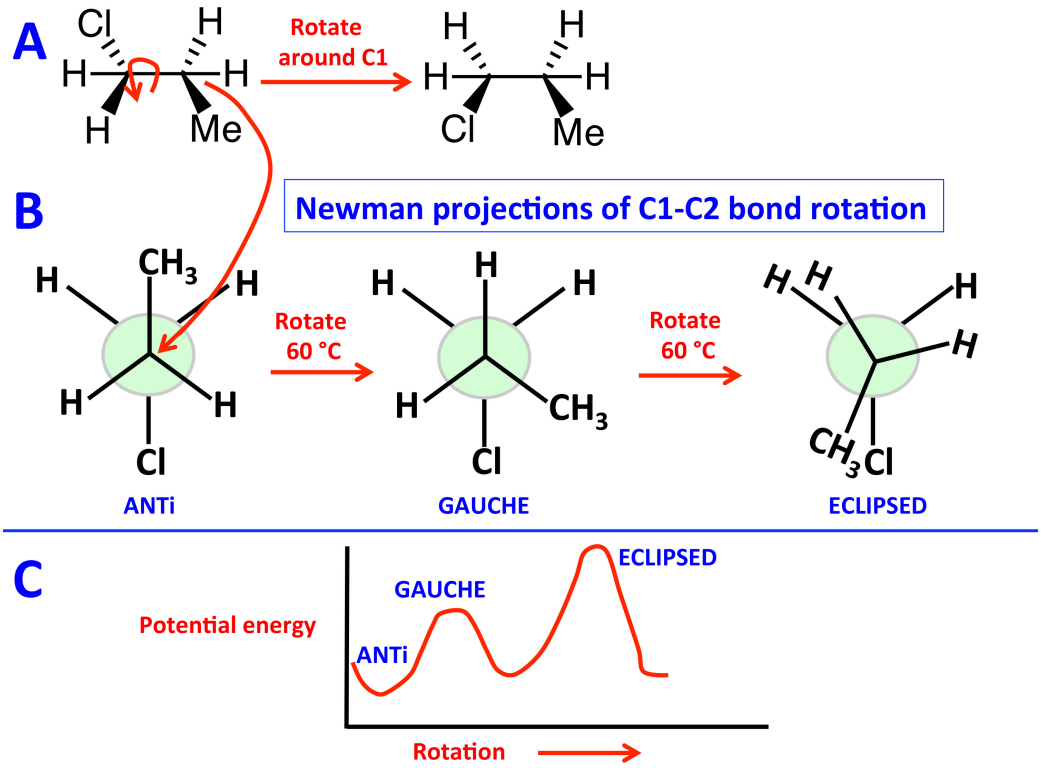
Structural isomers. Also called constitutional isomers, structural isomers of molecules (such as pentane; see Table) possess different bond connections, while maintaining identical molecular formulas (C_5H_{12}), and molecular masses (72.15 g/mole). However, structural isomers have different physical and chemical properties. For example, the three structural isomers of pentane have different boiling and melting points. Significantly, both n-pentane and isopentane (IUPAC name 2-methylbutane) are liquids at room temperature, but neopentane (IUPAC: 2, 2-dimethylpropane) is a gas at room temperature. The difference can be explained through the understanding that boiling point is dependent on intermolecular forces. The variations in physical properties between isopentane and

C_5H_{12} 72.15 g/mol	N-pentane 	Isopentane 	Neopentane 
Melting point	-129 °C	-160 °C	-160 °C
Boiling point	36 °C	27.8 °C	9.5 °C

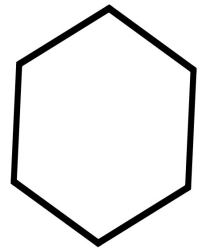
neopentane clearly illustrate the distinct physical properties that exist between molecules with identical molecular formula.

Conformational isomers. Due to free rotation around sigma (σ) bonds, molecules can exist in various rotational states. Such conformational isomers have the exact bond connections, yet differ in their rotational states. This is illustrated below with 1-chloropropane. Panel A shows the perspective diagram focusing on the orientation of the groups on carbon atoms C_1-C_2. Note that the two largest groups are orientated on opposite sides of the carbon backbone, but after rotation around C_1, the two groups are facing outwards. These two rotational outcomes are considered conformational isomers, or conformers.

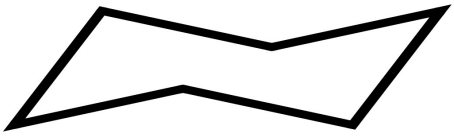
In many cases, conformational isomers are represented by Newman projections that examine the molecule through a view of the longitudinal axis of the carbon skeleton. Newman projections examine the rotational states around carbon-carbon σ bonds. Through examination of Panel B, we learn that these projections are drawn by starting with the initially viewed carbon as a point in a vertex. This vertex is bound to four separate constituents, including the second longitudinal carbon that is represented by a sphere (**Panel B).** Stable carbon atoms are bonded to up to four constituent atoms. Remember that the valence of carbon is 4 (electron configuration: $1s^2 2p^4$). As shown, the *anti-conformation* has the two largest groups bonded to C_1 and C_2 as they are lying 180 ° apart. After rotating 60°, the two groups lie closer together in the guache conformation. Both the anti and gauche are considered as "staggered" forms. A further 60° rotation produces the eclipsed form. This is the conformation where both groups lie closest together. Such steric hindrance creates electron repulsion, making the eclipsed form the least energetically favorable of the conformational isomers (**Panel C**).



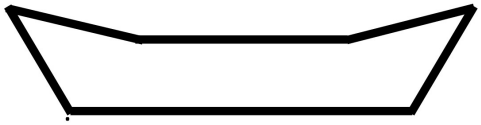
Ring structures often exist in multiple conformations. In the example of cyclohexane, the six-membered ring structure is often presented as a flat, planar structure. However, if this depiction were accurate, the bond angles would be 120 °C. As the bonds in cyclohexane are sp^3 hybridized, the most stable structure would have angles of 109.5 °C. Thus, being planar is not favorable for cyclohexane. To accommodate optimal bond angles cyclohexane exists in the chair and boat conformational isomers (conformers) as shown below.



Cyclohexane



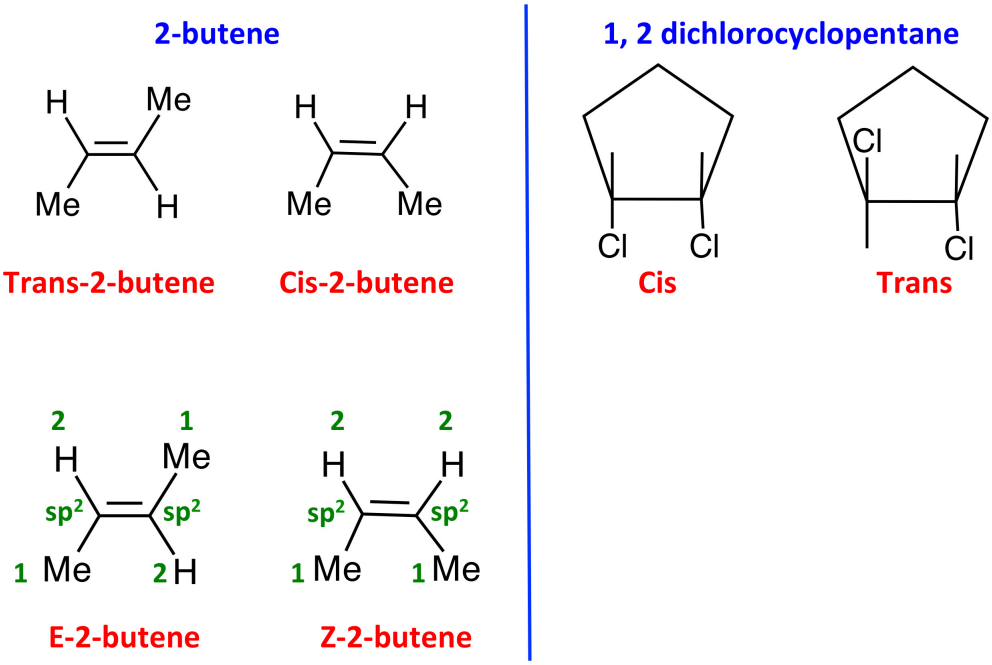
CHAIR



BOAT

Geometric (cis/trans) isomers. Unlike conformational isomers that arise through rotation around σ bonds, geometric isomers arise as a result of the consequence of the failure to rotate around bonds. Geometric isomerization is listed on the MCAT checklist as "cis/trans isomers". Cis refers to groups on the same side and trans indicates groups on opposite sides of carbon bonds.

The common feature of geometric isomers is that they all possess structures that have some form of restricted rotation around a bond. As rotational restriction around double bonds is prohibited, geometric isomers are often seen in molecules with π bonds (sp^2 carbon-carbon double bonds). Geometric isomerization is also found in ring structures. Note as shown below that the cis and trans-1, 2 dichlorocyclopentane geometric isomers are also diastereomers. This class of stereoisomers will be discussed below.



Two geometric isomers exist for 2-butene: the cis and trans forms. The cis isomer is the form that has the two hydrogen atoms bonded to the sp^2 carbon on the same side of the double bond; trans is when they lie on opposite sides. The boiling points (cis = -139 °C and trans = -105 °C) and melting points (cis = 4.0 °C and trans = 1.0 °C) for the two isomers are different.

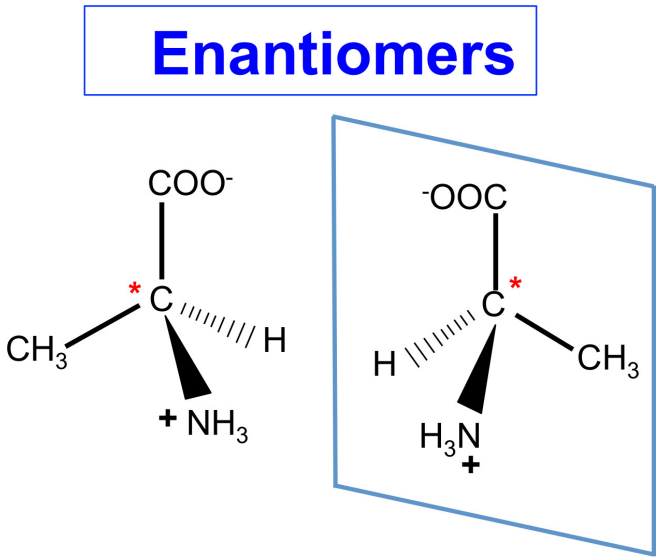
Geometric isomers for alkenes are formally designated with the E/Z system. Here are the rules for assignments. To each of the two carbon atoms participating in the double bond, group priority numbers are assigned based upon atomic number. As the atomic number of carbon is greater than hydrogen (C > H), the CH_3 methyl group has a priority of 1 and the hydrogen has a priority of 2. By definition, E isomers have each of the two number 1 assignments on opposite sides of the double bond. If the two 1 assignments are on the same side, then the isomer is classified as "Z". In most, but not all, cases, the E isomer represents trans.

Stereoisomers (diastereomers, enantiomers, cis/trans isomers)

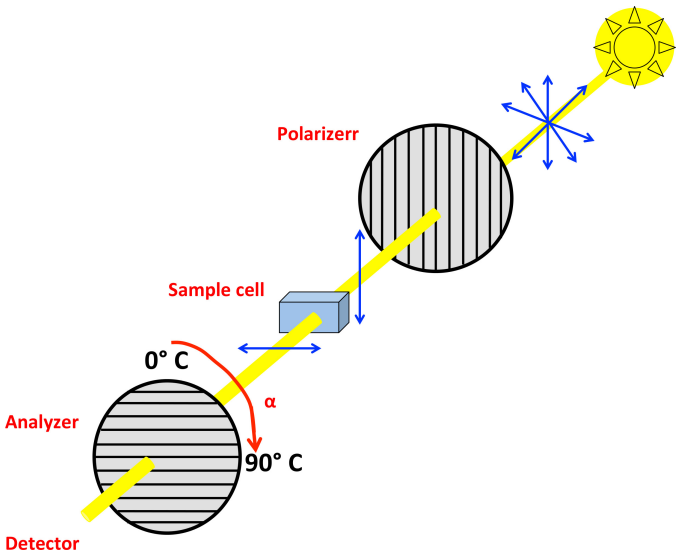
Isomers that differ in their 3D-spatial arrangement of atoms are termed **stereoisomers**. Any molecule that cannot be superimposed on its mirror image exhibits **chirality**. The simplest way to envision chirality

is to note that your left hand cannot be superimposed on your right hand: they are mirror images of each other. Chirality refers to "handedness" and exists throughout nature. Helices in nucleic acids and proteins have handedness. Thus, chirality is a term referring to handedness or symmetry, and is an intrinsic property of stereoisomers.

A molecule and its non-superimposable mirror image are called **enantiomers**. The two enantiomers of the amino acid alanine are shown. The red asterisk designates the chiral carbon stereocenter. The two molecules are non-superimposable mirror images. Enantiomers possess identical physical properties (i.e. boiling and melting points) with the exception of how they interact with light (discussed below). A 1:1 mixture of enantiomers is called a **racemic** mixture. Any ratio of enantiomers deviating from 1:1 is called a **scalemic** mixture.



Stereoisomers possess one or more stereogenic atoms or **stereocenters**. According to Mislow and Siegel, a stereocenter represents a position in a molecule where the exchange of two groups generates a stereoisomer. Stereocenters are often referred to as chiral or asymmetric centers. Although many atoms can exhibit chirality, the MCAT will largely, if no exclusively, focus on carbon.



Chiral molecules were first observed to interact with light and exhibit optical activity in the 1800s. Monochromatic light passing through a filter (Think of light passing through a picket fence.) is polarized, or is able to pass through in one plane (See image). When passing through a sample with optical activity (i.e. chiral molecule), the plane of polarized light rotates either clockwise (CW) or counter clockwise (CCW) at an angle α through its interaction with a chiral center. CW rotation is noted as (+) or dextrorotatory and CCW rotation is called (-) or levorotatory. Dextrorotatory and levorotatory are often abbreviated with a small case d and l, respectively. Enantiomers will rotate the plane of polarized light in opposite directions, but with equal magnitude. A racemic mixture will therefore not rotate the plane of polarized light. The direction and magnitude of rotation of a chiral molecule must be experimentally measured by polarimetry. It cannot be determined by visual inspection of the molecule.

The specific rotation [α] is the change in orientation of a chiral molecule when examined through a monochromatic source of polarized light as illustrated. α depends on the concentration of the sample, the length of the sample cell, temperature, as well as the wavelength of the light source. The formula for specific rotation is given by:

$[\alpha] = \alpha / (c)(l)$

[α] = specific rotation, α = observed rotation, c = concentration of molecule (g/ml), and l = path length of tube in decimeters.

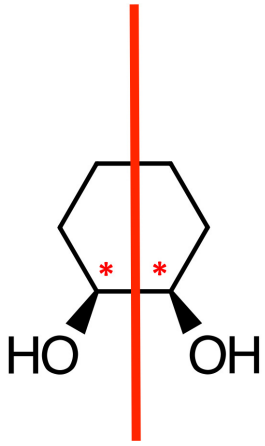
Identifying chiral centers and chiral molecules

sp^3 tetrahedral carbon atoms (109.5° bond angles) that have four different substituent groups are identified as chiral centers. For example, one chiral center is found in alanine as shown in Panel A. The chiral center is indicated with an asterisk. Observe that the chiral α carbon is tetrahedral and bound to four different substituents. Its mirror image is also shown.

For a molecule with one chiral center, two enantiomers exist and possess identical physical properties except for how they rotate the plane of polarized light. In general, there are 2^N stereoisomers where N = the number of chiral centers. The two exceptions concern molecules with bridged structures ($2^N/2$ isomers) and the meso compounds (2^N - 1).

Shown below is the meso compound, 1,2 dihydroxycyclohexane. The molecule has two chiral carbons (asterisks) but exhibits no optical activity. This is because the meso compound has an internal plane of symmetry.

MESO COMPOUND



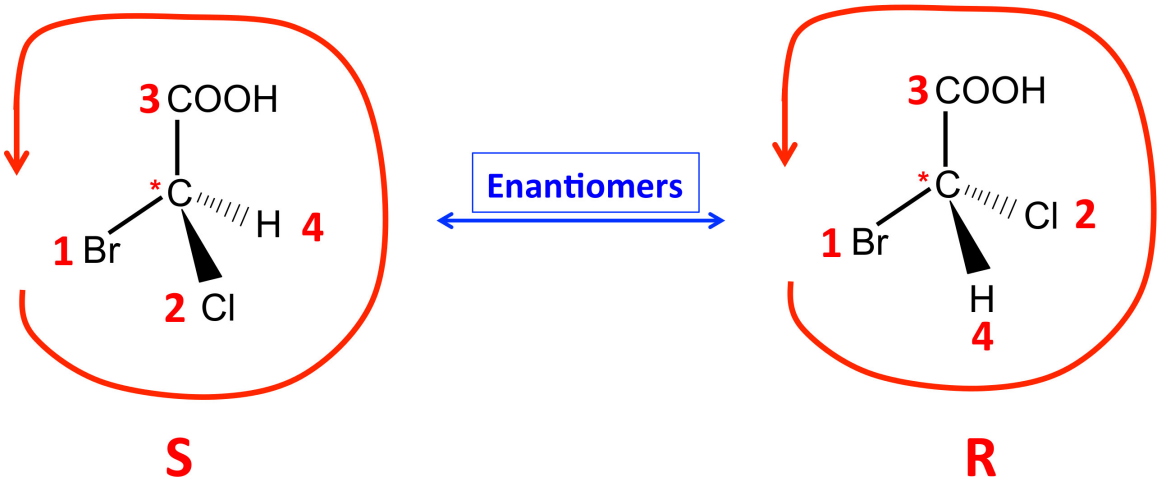
Molecules that have internal planes of symmetry are achiral. Meso compounds possess at least two chiral centers yet have no optical activity due to the internal plane of symmetry. Meso compounds are therefore achiral. Therefore, the presence of chiral centers does not automatically make a molecule chiral and this is because of symmetry.

Remember: Any molecule that has a plane of symmetry that can divide the molecule into two identical mirror images is achiral, even if there are chiral carbon centers.

Absolute configuration. As enantiomers possess differing spatial arrangements of atoms, the R and S system for nomenclature has been adopted and to differentiate between them. This system is also applied to other stereoisomers including diastereomers and meso compounds. The R and S system is formally called Cahn-Ingold-Prelog system and the rules are described and implemented below for 2, bromo, 2 chloroethanoic acid, a molecule that has one chiral center and two enantiomers. The R and S isomers are shown below.

Cahn-Ingold-Prelog Rules (Absolute configuration)

1. Assign priorities 1-4 where the highest priority is the largest atom (or mass number for isotopes) attached to the chiral center.
2. If the smallest priority is pointed "in the back" with a hatched line, then draw an arrow from 1-3: if CW then it is "R" and if CCW, it is an "S".
3. If the smallest group is not in the back (as is the case for the 3' carbon, then draw an arrow from 1-3, but reverse the "apparent" configuration to arrive at the absolute configuration.

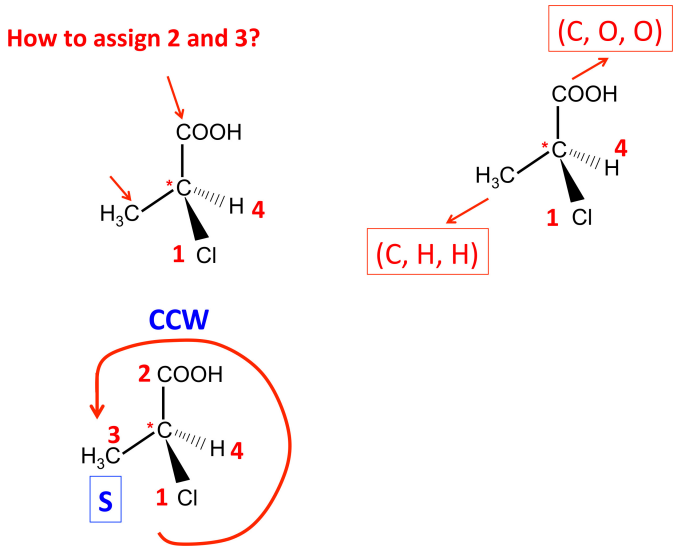


Note that for the S isomer, drawing an arrow from 1-3 generates a CCW direction. For the R isomer, the drawn arrow from priorities 1-3, is also CCW. However, because the #4 priority H atom is NOT in the back

(wedge vs hedged line), the direction is changed to a CW arrow. This gives the assignment as an "R".

Although not applicable in this specific case, the 4th rule for assigning absolute configuration applies to chiral compounds with isotopes. When isotopes are bonded to a carbon stereocenter, the rules for assigning priorities state that the highest mass number receives the highest priority. For example in the case of hydrogen, Tritium (^{3}H, mass number 3 from 1 proton and 2 neutrons) would have a higher priority than deuterium (^{2}H, mass number 2 from 1 proton and 1 neutron), and hydrogen (^{1}H) that has one proton and zero neutrons.

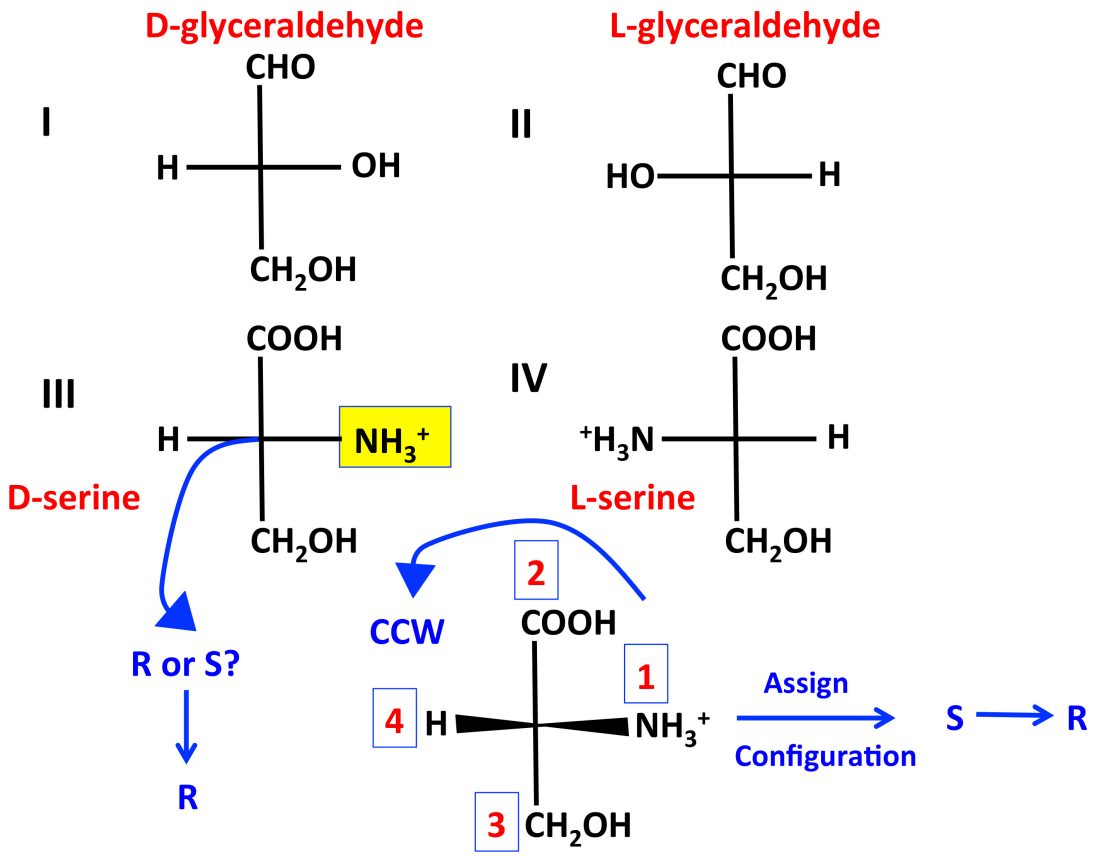
In some cases, assigning an absolute configuration to molecules is not as straight forward as determining priority numbers. Take the case of 2-chloro propionic acid as shown below. The chiral carbon is shown with an asterisk. Although it is easy to assign the #1 and #4 priorities as Cl and H, respectively, the #2 and #3 priority assignments is less clear as both atoms appear to be carbon. As shown, in these situations, determine the "next" three bound atoms. In this case, this is the difference between a carbon and two hydrogen atoms (C, H, H) and a carbon and two oxygen atoms (C, O, O). Although the carbons are equal in atomic number, since O > H, the #2 priority is defined and assigned as shown.



Relationship between R/S and, + and –, and d/l system. We have seen that chiral molecules rotate the plane of polarized light in either a clockwise (+) or counterclockwise (-) manner, which is linked to the d (dextrorotatory) and l (levorotatory) nomenclature. This is used to distinguish how a chiral molecule rotates the plane of polarized light. The (+)-d and (-)-l system describes how an entire molecule interacts with polarized light. In contrast, the R and S system defines the absolute configuration of individual chiral centers within a molecule. There is no relationship between the two systems of nomenclature, meaning that a chiral molecule with a single stereocenter assigned R does not indicate how this molecule will rotate the plane of polarized light (+ or -).

Further, when considering the d and l system, it is necessary to distinguish the meaning of the lower case nomenclature (direction of rotation in response to polarized light) to the upper case D and L nomenclature.

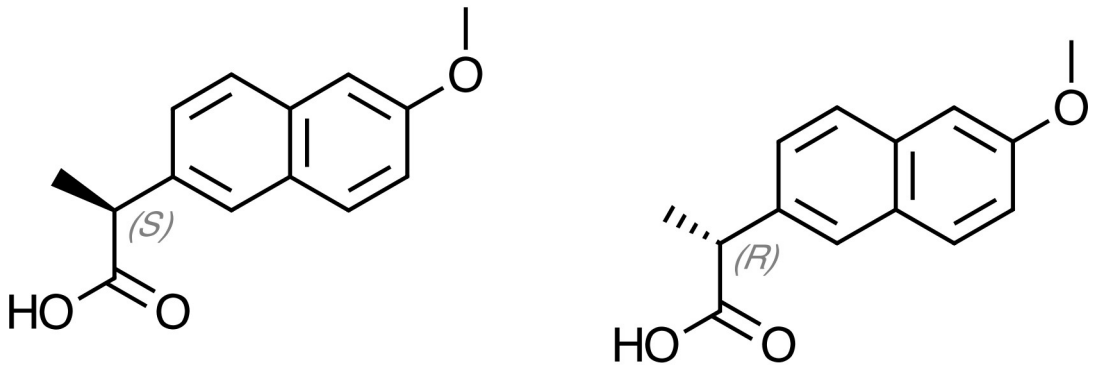
Upper case D and L nomenclature refers to an alternative system for designating absolute configuration for amino acids and sugars. Therefore, D and L isomers can also be assigned through the R and S system by application of the Cahn-Ingold-Prelog rules. These points are illustrated in the figure with serine as the example. Historically, when glyceraldehyde is drawn in a Fischer projection, if the OH group is drawn on the right then the molecule is the D isomer. If the OH is on the left, then this represents the L enantiomer. If the chiral carbons in D and L glyceraldehyde were assigned an absolute configuration based upon the Cahn-Ingold-Prelog rules , then the D isomer represents the R configuration and the L enantiomer represents the L configuration. However, you cannot always assume that D and L configurations will not equate to R and S assignments. The convention for amino acids such as serine is slightly different (see image). If the α-NH_3^+ group is on the right in the Fischer projection, then the D configuration is assigned. The conversion into the R and S system is shown through the priority assignments.



Biological significance. It is common for various enantiomers to be biologically active in one form, but not another. This is naturally seen with the L-amino acids as they are incorporated into proteins, but the D isomer is not. This is further seen with carbohydrates as they all exist in the D configuration in the human body. Thus, pharmaceutical drug design and synthesis is highly relevant for the study of stereochemistry. Understanding stereochemistry is a prerequisite the development of pharmaceuticals.

One example of the significance of stereochemistry concerns the two enantiomers of naproxen, an over the counter anti-inflammatory drug. Immediately spot that the opposite orientation of the methyl groups bonded to the sp^3 chiral center. One molecule will be in the S configuration and the other will necessarily be in the R configuration as shown. Enantiomers have opposite configuration at EACH stereocenter. However, only the S isomer isomer acts as a therapeutically beneficial drug by inhibiting cyclooxygenase-dependent synthesis of prostaglandins; the R isomer causes liver damage.

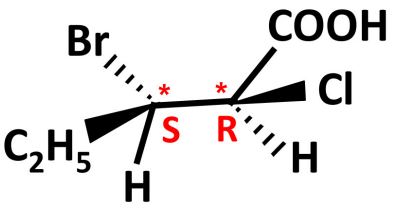
NAPROXEN STEREOISOMERS



S **R**

Diastereomers and epimers possess at least two chiral carbon centers, yet are molecules that differ in absolute chiral configuration in at least one stereocenter. Diastereomers are shown below (Panel B) in 2-chloro 3-bromopentanoic acid, a molecule with two chiral carbon centers. In this case there are 2^N or 4 different stereoisomers. Only one is shown. Enantiomers have opposite configuration at each chiral center (i.e. R vs. S or RR vs SS). In contrasts diastereomers have opposite configurations in at least one stereocenter (i.e. RRR vs RRS). Those diastereomers that differ in absolute configuration around one chiral center are termed epimers. Therefore, all epimers are diastereomers, but not all diastereomers are epimers. Note the differences in absolute configuration between enantiomers and diastereomers as shown in Panel D).

DIASTEREOMERS



Configuration at each carbon

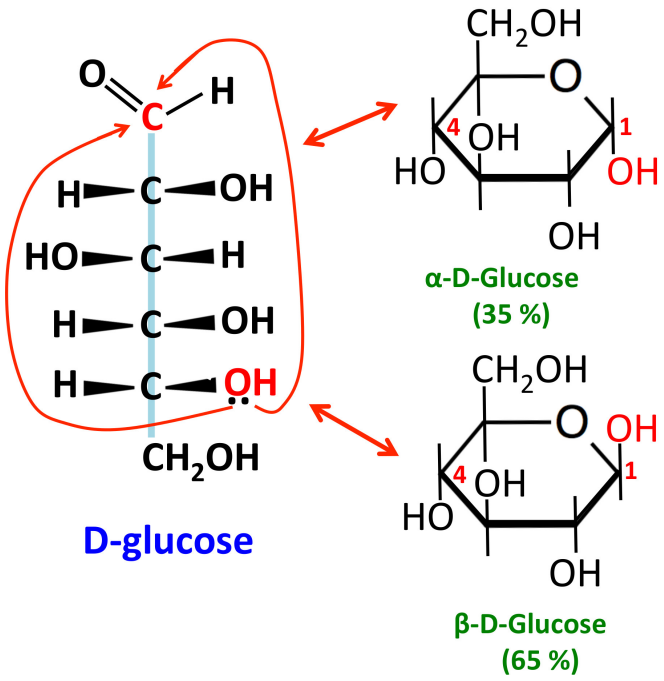
R R
R S
S R
S S

$$2^N = 2^2 = 4$$

Anomers. Anomers are a type of epimer. Their formation is illustrated with the classic sample of D-glucose as shown in the image. Glucose molecules are in equilibrium between the linear form and their closed circular structures. In the linear form, the hydroxyl group bound to carbon #5 (red in the image) serves as a nucleophile. A lone pair of electrons in the oxygen atom attacks the sp^2 carbon present in glucose. Because of the planar nature of the carbonyl carbon, the nucleophile can attack from either of two positions (above or below the plane) as shown. This reaction introduces a new chiral center in the closed glucose molecules.

In the mechanism, the hydroxyl group performs a nucleophilic attack at carbon #1. As this electrophilic center lies in a planar structure due to the sp^2 hybridization status of carbon (120° bond angles), the hydroxyl group can attack from either the top or the bottom. As a consequence, two isomers α (hydroxyl is down) and β (hydroxyl is up) are formed. Note that the combined reaction of an alcohol (R-OH) with an aldehyde (CHO) generates a hemiacetal linkage. Because this newly formed hemiacetal bond is reversible (in contrast to an acetal), anomers can interconvert in solution. The glucose molecule in solution exists in equilibrium between the open (1%) and closed forms (99%). As per the figure, the β anomer is predominant (65%) because, as seen in the chair structure, the hydroxyl at C_1 is in the more stable equatorial position.

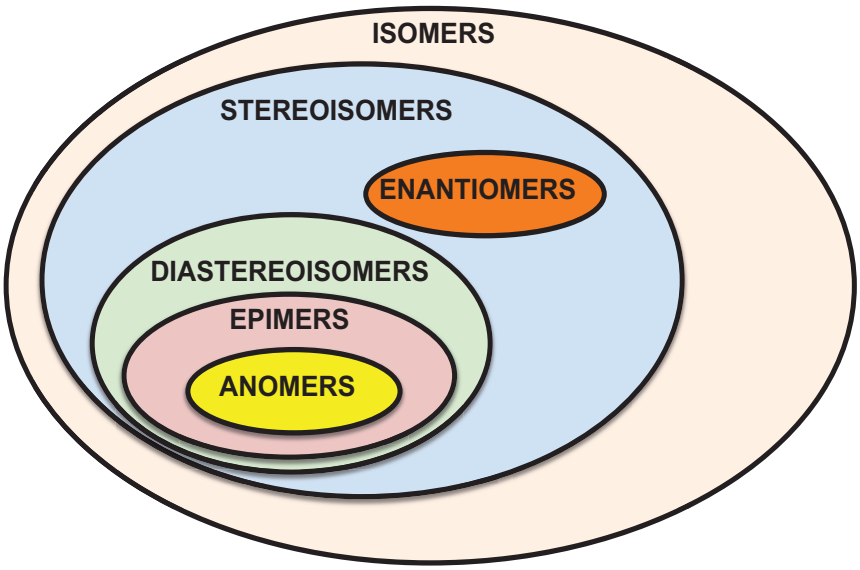
ANOMERS AND EPIMERS: THE CASE OF GLUCOSE



Upon further inspection of the structures of closed circular α-D and β-D glucose molecules, it is clear that the newly formed bond at carbon #1 is in a hemiacetal linkage. Unlike acetal linkages, hemiacetal linkages are unstable. Thus, the circularization of glucose is freely reversible. As a consequence, glucose molecules are always opening and closing and opening back up again. At equilibrium, there is more α-D glucose present in solution.

The nomenclature and mechanism of the formation of the α and β anomers of D-glucose can also be discerned from the Figure. Note that Glucose exists in both a linear and a circularized closed form (represented by the Haworth and chair structures). In the linear Fischer projection, if the hydroxyl group on the penultimate carbon (red) is on the right, then this represents the D-isomer. (The L isomer has the hydroxyl group attached to the penultimate carbon depicted on the left side in a Fischer projection.)

The relationships between stereoisomers (i.e. structural and conformational isomers is missing) is shown in the following Venn diagram.



Relationship between isomers.