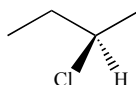


Stereochemistry Tutorials: Assigning *R/S* and *E/Z*

Definitions for vocabulary words can be found in the *Illustrated Glossary of Organic Chemistry*, available at the course web site.

Discussion: Every organic compound needs an unambiguous name that clearly delineates all structural features of the molecule. The same is true for stereocenters. Because a stereocenter can exist in only two absolute configurations, IUPAC nomenclature is easily modified to name stereocenters. To name a stereocenter, we assign priority to the groups attached to the stereocenter, and then apply a label based upon the direction in which priorities decrease. Priorities are determined based on atomic number. The system was devised by Robert S. Cahn (Royal Institute of Chemistry, London), Christopher K. Ingold (University College, London), and Vladimir Prelog (Swiss Federal Institute of Technology, Zurich) in the 1950's, and is thus called the Cahn-Ingold-Prelog convention. (Vladimir Prelog was awarded the 1975 Nobel Prize in chemistry for his work on organic stereochemistry.)

The procedure for using the Cahn-Ingold-Prelog convention for a given stereocenter is illustrated using one enantiomer of 2-chlorobutane shown below. *It is extremely useful to use molecular models for this process.*

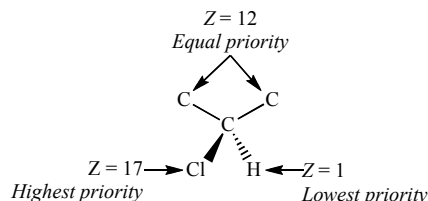


2-Chlorobutane

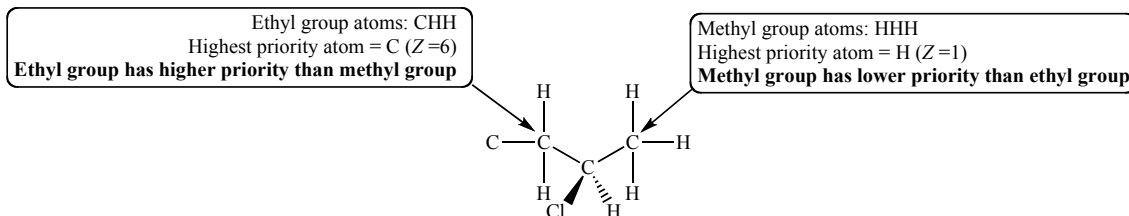
Procedure:

Step 1: Build a model! This process is much easier if you use a model.

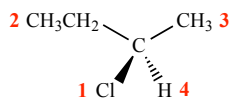
Step 2: All groups attached to the stereocenter are assigned a priority. Identify the atoms attached to the stereocenter, and arrange these atoms in order of increasing atomic number (*Z*).



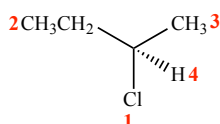
When atoms have the same priority, move one atom further out from the stereocenter until you find a difference. In this case, the two carbon atoms have the same priority, so we move further out. The methyl carbon is attached to three hydrogens, whereas the ethyl carbon is attached to two hydrogens and a carbon. Select the highest priority atom in each set and compare their priorities. The highest priority group has the highest priority atom. In this case we compare HHH on the CH₃ versus CHH on the ethyl. Hydrogen is lower atomic number and therefore lower priority than carbon, so the methyl group has lower priority than the ethyl group.



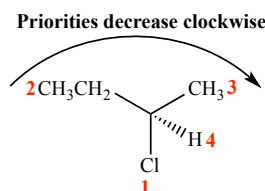
Thus the order of priorities is: Cl (1; highest priority) > C–C > C–H > H (4; lowest priority). **There is no fixed convention or general agreement how you indicate highest or lowest priority. You can label highest priority as 4 and lowest as 1, or highest as 1 or lowest as 4, or even highest as cat and lowest as dog.** In this case we use increasing numbers for decreasing priority, so the highest priority attachment (the chlorine atom) is **1**, and the lowest priority attachment (H) is **4**.



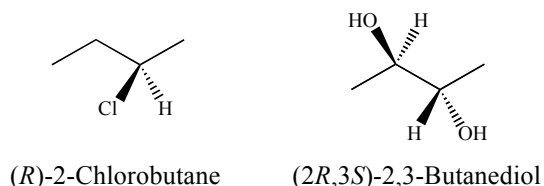
Step 3: Change your view of the molecule so that you are looking along the bond between the stereocenter and the lowest priority group, with the lowest priority group facing away from you. If you are using molecular models, use the bond between the stereocenter and the lowest priority group as a handle to hold the molecule. From this perspective, the molecule looks like this:



Step 4: Note the direction in which the priorities decrease. When the priorities decrease in a clockwise manner, we label the stereocenter as *R* (Latin: rectus, right). When the priorities decrease in a counterclockwise manner, we label the stereocenter as *S* (Latin: sinister, left). (A useful mnemonic: At the top of the molecule, draw a curved arrow showing the direction in which priorities decrease. If that arrow points to the right (clockwise), then the stereocenter is *R*.) In the example, the priorities decrease in a clockwise manner (as shown by the curved arrow), so the stereocenter has the *R* configuration.

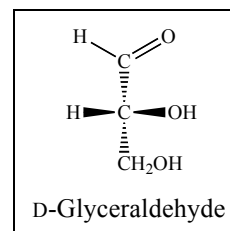


To provide the full name for the molecule, *R* or *S* is added in parenthesis in front of the name. Thus, this molecule is (*R*)-2-chlorobutane. If there is more than one stereocenter, each *R* or *S* is numbered with its position on the molecular skeleton. Example: (*2R,3S*)-2,3-butanediol.



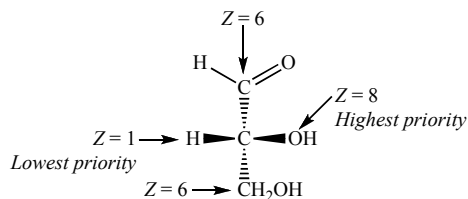
There are ways to assign absolute configuration without using models, but it's too easy to make mistakes. It's worth investing the time to build the model in order to get the right (exam) answer.

Let's learn how we handle priority assignments for double and triple bonds by working another example. Determine the absolute stereochemistry for the stereocenter of D-glyceraldehyde.

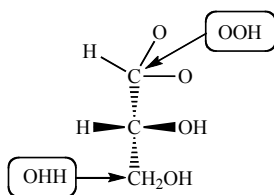


Solution:

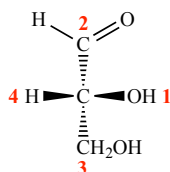
Assign priorities to the groups attached to the stereocenter. The four atoms directly attached to the stereocenter are hydrogen, carbon, carbon, and oxygen. Oxygen ($Z = 8$) has highest priority and hydrogen ($Z = 1$) has lowest priority. The two carbons ($Z = 6$) are tied in priority, so we move out to the next set of atoms attached to these carbons.



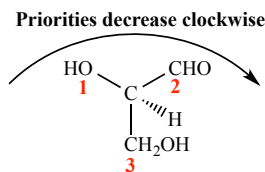
The C=O is treated as if the carbon is attached to two oxygens, by adding 'phantom atoms.'



With the phantom atoms in place, we use the usual procedure, and compare the OOH atom set (from the aldehyde) with the OHH atom set from the alcohol. OOH has priority over OHH (the oxygens cancel), so the aldehyde has priority over the alcohol.



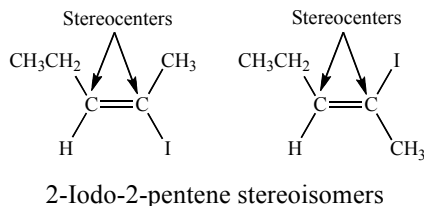
With all four priorities determined, we change the perspective to put the lowest priority group in the back (use a model!). The priorities decrease in a clockwise order so the stereocenter has the *R* absolute configuration.



Caution! From this one example you have concluded that double bonds always get priority over single bonds. This is not true! Consider the case of a carboxylic acid (–COOH) versus a thiol (–CH₂SH). The thiol gets priority because sulfur has a higher atomic number than oxygen, despite the fact that there are three oxygen atoms (including phantoms) but only one sulfur atom.

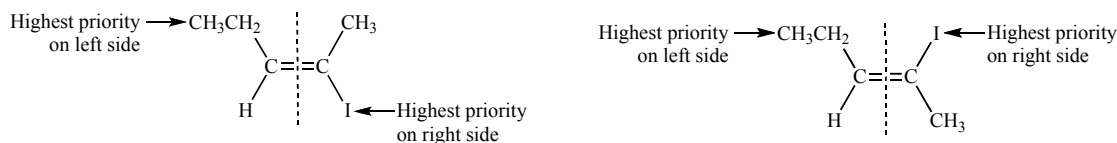
Labeling Alkene Stereochemistry

Tetrahedral carbons are not the only atoms that can be stereocenters. Alkene carbons are stereocenters when each alkene carbon has three different attachments. Convince yourself that the two isomers of 2-iodo-2-pentene show below are, in fact, stereoisomers.



We label the alkene stereochemistry by comparing the relative positions of the highest priority groups on the alkene carbons.

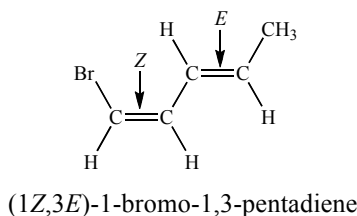
Step 1: Determine the Cahn-Ingold-Prelog priorities for the two groups attached to each alkene carbon. On the left, ethyl has higher priority than hydrogen. On the right, iodine has higher priority than methyl.



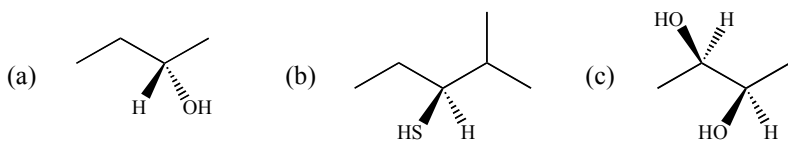
Step 2: When the highest priority groups are on the opposite alkene faces, the alkene is *E* (from German entgagen; opposite). When the highest priority groups are on the same face, the alkene is *Z* (from German zusammen; together).

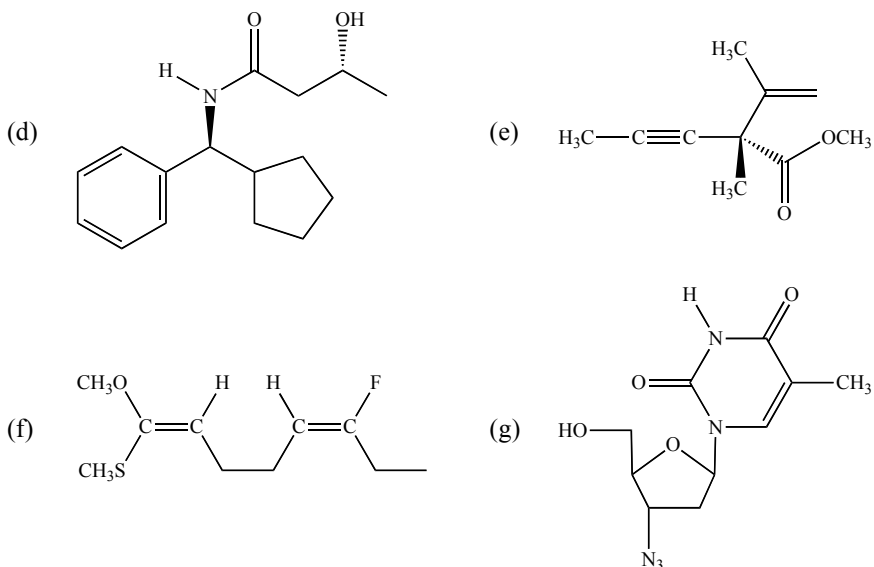


When more than one alkene is present, each alkene is labeled as *E* or *Z*.



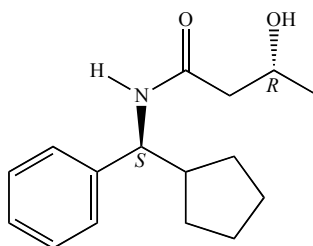
Exercises: Label each sp^3 stereocenter as *R* or *S*, and each alkene as *E* or *Z*.



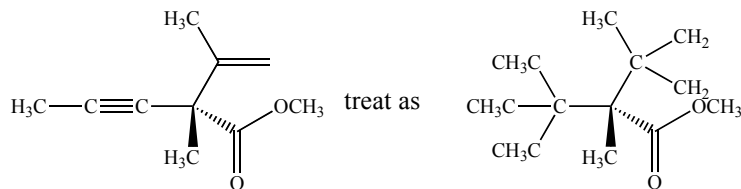


Exercise Solutions

- (a) Priority of groups at stereocenter: $\text{HO} > \text{CH}_3\text{CH}_2 > \text{CH}_3 > \text{H}$. This stereocenter is *S*.
- (b) Priority of groups at stereocenter: $\text{HS} > \text{CH}(\text{CH}_3)_2 > \text{CH}_2\text{CH}_3 > \text{H}$. This stereocenter is *S*.
- (c) Priority of groups at stereocenters: $\text{HO} > \text{CHOH} > \text{CH}_3 > \text{H}$. Both stereocenters are *R*.
- (d) Priority of groups at amine stereocenter: $\text{NH} > \text{HC}=\text{C} > \text{CH}(\text{CH}_2)_2 > \text{H}$. This stereocenter is *S*. Priority of groups at alcohol stereocenter: $\text{HO} > \text{CH}_2\text{C}=\text{O} > \text{CH}_3 > \text{H}$. This stereocenter is *R*.

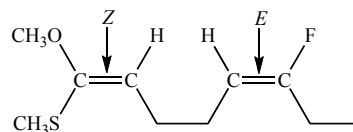


- (e) Recall that an alkene carbon is treated as being attached to two carbons, and an alkyne carbon is treated as being attached to three carbons. In this case the sp^2 and sp carbons bonded to the stereocenter carbon both count as having three carbons attached, so we must move out one carbon further. The far carbon of the alkyne has four carbons attached (one for the methyl and three for the alkyne). The far carbon of the alkene two hydrogens and two carbons (from the alkene) attached. Thus the alkyne has higher priority than the alkene.



Priority of groups at stereocenter: Ester > alkyne > alkene > methyl. This stereocenter is *S*. The alkene does not have stereoisomers, so it cannot be labeled as *E* or *Z*.

- (f) Left alkene: $\text{CH}_3\text{S} > \text{CH}_3\text{O}$ and $\text{CH}_2\text{CH}_2 > \text{H}$. This alkene is *Z*. Right alkene: $\text{CH}_2\text{CH}_2 > \text{H}$ and $\text{F} > \text{CH}_2\text{CH}_3$. This alkene is *E*.



- (g) **Assigning absolute configuration for stereocenters in a molecule of this complexity is best attempted with a molecular model.** Remember to view the molecule with the lowest priority group in the back when assigning *R* or *S* for each stereocenter. C=C within rings are usually not assigned as *E* or *Z* because the stereoisomer not shown usually has very high strain and probably cannot exist.

