

## 6.3: ABSOLUTE CONFIGURATION AND THE (R) AND (S) SYSTEM

### Learning Objective

- name chiral compounds using (R) & (S) nomenclature

**USE YOUR MODELING KIT:** Models assist in visualizing the structure. When using a model, make sure the lowest priority is pointing away from you. Then determine the direction from the highest priority substituent to the lowest: clockwise (R) or counterclockwise (S).

**IF YOU DO NOT HAVE A MODELING KIT:** remember that the dashes mean the bond is going into the screen and the wedges means that bond is coming out of the screen. If the lowest priority bond is not pointing to the back, mentally rotate it so that it is. However, it is very useful when learning organic chemistry to use models.

*If you have a modeling kit use it as you read through this section and work the practice problems.*

### INTRODUCTION AND THE CAHN-INGOLD-PRELOG RULES OF PRIORITY

To name the enantiomers of a compound unambiguously, their names must include the "handedness" of the molecule. The letters "R" and "S" are determined by applying the Cahn-Ingold-Prelog (CIP) rules. The optical activity (+/-) can also be communicated in the name, but must be empirically derived. There are also biochemical conventions for carbohydrates (sugars) and amino acids (the building blocks of proteins).

The method of unambiguously assigning the handedness of molecules was originated by three chemists: R.S. Cahn, C. Ingold, and V. Prelog and, as such, is also often called the Cahn-Ingold-Prelog rules. In addition to the CIP system, there are two ways of experimentally determining the absolute configuration of an enantiomer:

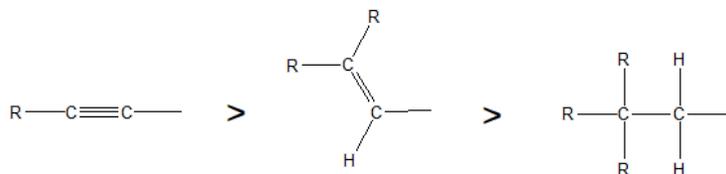
- X-ray diffraction analysis. Note that there is no correlation between the sign of rotation and the structure of a particular enantiomer.
- Chemical correlation with a molecule whose structure has already been determined via X-ray diffraction.

However, for non-laboratory purposes, it is beneficial to focus on the R/S system. The sign of optical rotation, although different for the two enantiomers of a chiral molecule, at the same temperature, **cannot** be used to establish the absolute configuration of an enantiomer; this is because the sign of optical rotation for a particular enantiomer may change when the temperature changes.

The **Cahn-Ingold-Prelog** rules of priority are based on the atomic numbers of the atoms of interest. For chirality, the atoms of interest are the atoms bonded to the chiral carbon.

- The atom with higher atomic number has higher priority ( $I > Br > Cl > S > P > F > O > N > C > H$ ).
- When comparing isotopes, the atom with the higher mass number has higher priority [ $^{18}O > ^{16}O$  or  $^{15}N > ^{14}N$  or  $^{13}C > ^{12}C$  or  $T (^3H) > D (^2H) > H$ ].
- When there is a tie in (2) above, establish relative priority by proceeding to the next atom(s) along the chain until the first difference is observed.

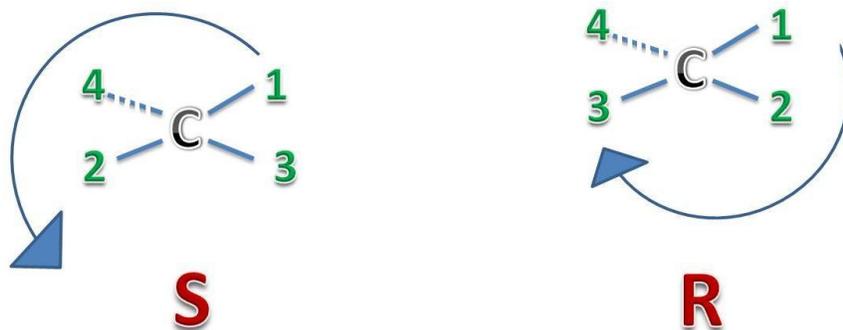
Multiple bonds are treated as if each bond of the multiple bond is bonded to a unique atom. For example, the ethenyl group ( $CH_2=CH$ ) has higher priority than the ethyl group ( $CH_3CH_2$ ). The ethenyl carbon priority is "two" bonds to carbon atoms and one bond to a hydrogen atom compared with the ethyl carbon that has only one bond to a carbon atom and two bonds to two hydrogen atoms. Similarly, the carbon-carbon triple bond of acetylene would give it higher CIP priority than the ethenyl group as summarized below.



Relative Priority according to the Cahn-Ingold-Prelog Rules

### STEREOCENTERS ARE LABELED R OR S

The "right hand" and "left hand" nomenclature is used to name the enantiomers of a chiral compound. The stereocenters are labeled as R or S.



Consider the diagram above on the left: a curved arrow is drawn counter-clockwise (c-cw) from the highest priority substituent (1) to the lowest priority substituent (4) in the **S-configuration** ("Sinister" → Latin= "left"). The counterclockwise direction can be recognized by the movement left when leaving the 12 o' clock position. Now consider the diagram above on the right where a curved arrow is drawn clockwise (cw) from the highest priority substituent (1) to the lowest priority substituent (4) in the R configuration ("Rectus" → Latin= "right"). The **R** or **S** is then added as a prefix, in parenthesis, to the name of the enantiomer of interest. A locator number is required if there is more than one chiral center. Otherwise, the person reading the name is expected to recognize the chiral center.

### Example 1

The two chiral compounds below are drawn to emphasize the chiral carbon with the full chemical name below each structure.



### ABSOLUTE CONFIGURATIONS OF PERSPECTIVE FORMULAS

Chemists need a convenient way to distinguish one stereoisomer from another. The **Cahn-Ingold-Prelog system** is a set of rules that allows us to unambiguously define the stereochemical configuration of any stereocenter, using the designations '**R**' (from the Latin *rectus*, meaning right-handed) or '**S**' (from the Latin *sinister*, meaning left-handed).

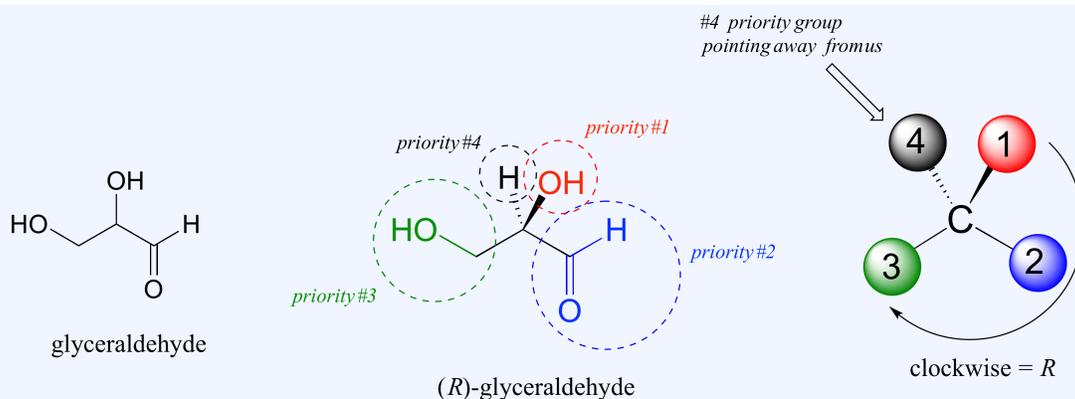
The rules for this system of stereochemical nomenclature are, on the surface, fairly simple.

#### Rules for assigning an R/S designation to a chiral center

- 1: Assign priorities to the four substituents, with #1 being the highest priority and #4 the lowest. Priorities are based on the atomic number.
- 2: Trace a circle from #1 to #2 to #3.
- 3: Determine the orientation of the #4 priority group. If it is oriented into the plane of the page (away from you), go to step 4a. If it is oriented out of the plane of the page (toward you) go to step 4b.
- 4a: (*#4 group pointing away from you*): a clockwise circle in part 2 corresponds to the *R* configuration, while a counterclockwise circle corresponds to the *S* configuration.
- 4b: (*#4 group pointing toward you*): a clockwise circle in part 2 corresponds to the *S* configuration, while a counterclockwise circle corresponds to the *R* configuration.

We'll use the 3-carbon sugar glyceraldehyde as our first example. The first thing that we must do is to assign a **priority** to each of the four substituents bound to the chiral center. We first look at the atoms that are directly bonded to the chiral center: these are H, O (in the hydroxyl), C (in the aldehyde), and C (in the CH<sub>2</sub>OH group).

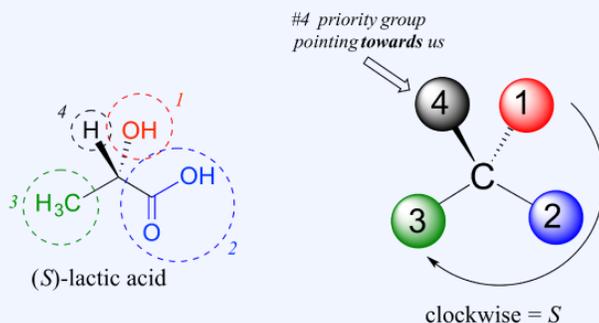
#### Assigning R/S configuration to glyceraldehyde:



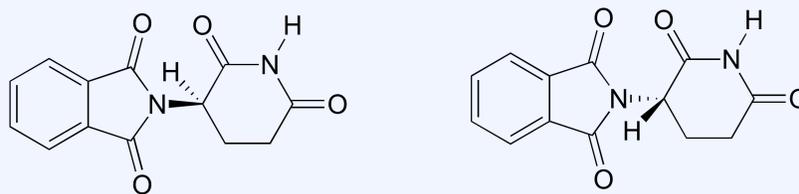
Two priorities are easy: hydrogen, with an atomic number of 1, is the lowest (#4) priority, and the hydroxyl oxygen, with atomic number 8, is priority #1. Carbon has an atomic number of 6. Which of the two 'C' groups is priority #2, the aldehyde or the CH<sub>2</sub>OH? To determine this, we move one more bond away from the chiral center: for the aldehyde we have a *double* bond to an oxygen, while on the CH<sub>2</sub>OH group we have a *single* bond to an oxygen. If the atom is the same, double bonds have a higher priority than single bonds. Therefore, the aldehyde group is assigned #2 priority and the CH<sub>2</sub>OH group the #3 priority.

With our priorities assigned, we look next at the #4 priority group (the hydrogen) and see that it is pointed back away from us, into the plane of the page - thus step 4a from the procedure above applies. Then, we trace a circle defined by the #1, #2, and #3 priority groups, in increasing order. The circle is clockwise, which by step 4a tells us that this carbon has the '*R*' configuration, and that this molecule is (*R*)-glyceraldehyde. Its enantiomer, by definition, must be (*S*)-glyceraldehyde.

Next, let's look at one of the enantiomers of lactic acid and determine the configuration of the chiral center. Clearly, H is the #4 substituent and OH is #1. Owing to its three bonds to oxygen, the carbon on the acid group takes priority #2, and the methyl group takes #3. The #4 group, hydrogen, happens to be drawn pointing *toward* us (out of the plane of the page) in this figure, so we use step 4b: The circle traced from #1 to #2 to #3 is clockwise, which means that the chiral center has the *S* configuration.

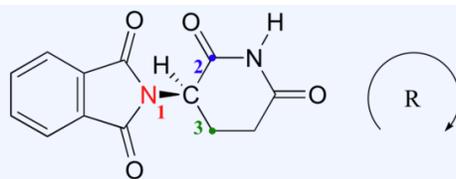


The drug thalidomide is an interesting - but tragic - case study in the importance of stereochemistry in drug design. First manufactured by a German drug company and prescribed widely in Europe and Australia in the late 1950's as a sedative and remedy for morning sickness in pregnant women, thalidomide was soon implicated as the cause of devastating birth defects in babies born to women who had taken it. Thalidomide contains a chiral center, and thus exists in two enantiomeric forms. It was marketed as a **racemic mixture**: in other words, a 50:50 mixture of both enantiomers.



two enantiomers of thalidomide

Let's try to determine the stereochemical configuration of the enantiomer on the left. Of the four bonds to the chiral center, the #4 priority is hydrogen. The nitrogen group is #1, the carbonyl side of the ring is #2, and the -CH<sub>2</sub> side of the ring is #3.



(R)-thalidomide

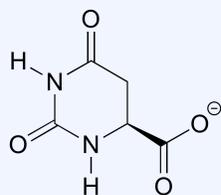
The hydrogen is shown pointing away from us, and the prioritized substituents trace a clockwise circle: this is the *R* enantiomer of thalidomide. The other enantiomer, of course, must have the *S* configuration.

Although scientists are still unsure today how thalidomide works, experimental evidence suggests that it was actually the *R* enantiomer that had the desired medical effects, while the *S* enantiomer caused the birth defects. Even with this knowledge, however, pure (*R*)-thalidomide is not safe, because enzymes in the body rapidly convert between the two enantiomers - we will see how that happens in chapter 12.

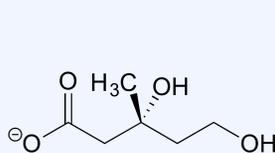
As a historical note, thalidomide was never approved for use in the United States. This was thanks in large part to the efforts of Dr. Frances Kelsey, a Food and Drug officer who, at peril to her career, blocked its approval due to her concerns about the lack of adequate safety studies, particularly with regard to the drug's ability to enter the bloodstream of a developing fetus. Unfortunately, though, at that time clinical trials for new drugs involved widespread and unregulated distribution to doctors and their patients across the country, so families in the U.S. were not spared from the damage caused.

Very recently a close derivative of thalidomide has become legal to prescribe again in the United States, with strict safety measures enforced, for the treatment of a form of blood cancer called multiple myeloma. In Brazil, thalidomide is used in the treatment of leprosy - but despite safety measures, children are still being born with thalidomide-related defects.

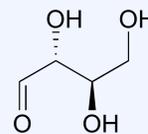
**Exercise 1.:** Determine the stereochemical configurations of the chiral centers in the biomolecules shown below.



dihydroorotate



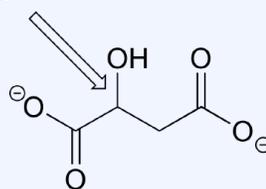
mevalonate



(D)-erythrose

**Exercise 2.:** Should the (*R*) enantiomer of malate have a solid or dashed wedge for the C-O bond in the figure below?

Draw this bond as or to get *R* configuration



(*R*)-malate

**Exercise 3.:** Using solid or dashed wedges to show stereochemistry, draw the (*R*) enantiomer of ibuprofen and the (*S*) enantiomer of 2-methylerythritol-4-phosphate (structures are shown earlier in this chapter without stereochemistry).

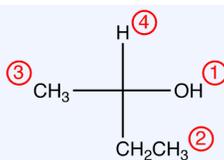
[Solutions to exercises](#)

## ABSOLUTE CONFIGURATIONS OF FISCHER PROJECTIONS

To determine the absolute configuration of a chiral center in a Fischer projection, use the following two-step procedure.

Step 1

Assign priority numbers to the four ligands (groups) bonded to the chiral center using the CIP priority system.



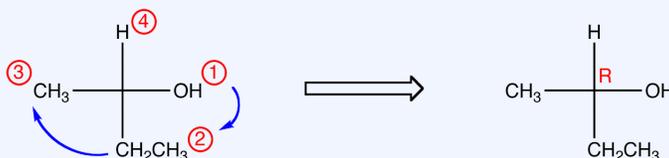
### Step 2 - vertical option

If the lowest priority ligand is on a Vertical bond, then it is pointing away from the viewer.

Trace the three highest-priority ligands starting at the highest-priority ligand (① → ② → ③) in the direction that will give a Very correct answer.

direction of ① → ② → ③	absolute configuration
clockwise	R
counterclockwise	S

In the compound below, the movement is clockwise indicating an R-configuration. The complete IUPAC name for this compound is (R)-butan-2-ol.



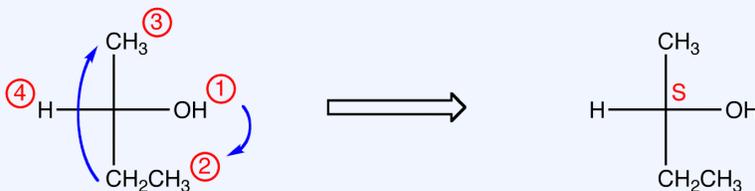
### Step 2 - horizontal option

If the lowest-priority ligand is on a Horizontal bond, then it is pointing toward the viewer.

Trace the three highest-priority ligands starting at the highest-priority ligand (① → ② → ③) in the direction that will give a Horribly wrong answer. Note in the table below that the configurations are reversed from the first example.

direction of ① → ② → ③	absolute configuration
clockwise	S
counterclockwise	R

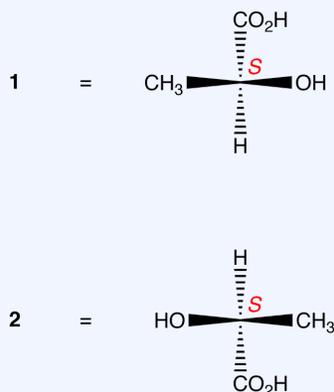
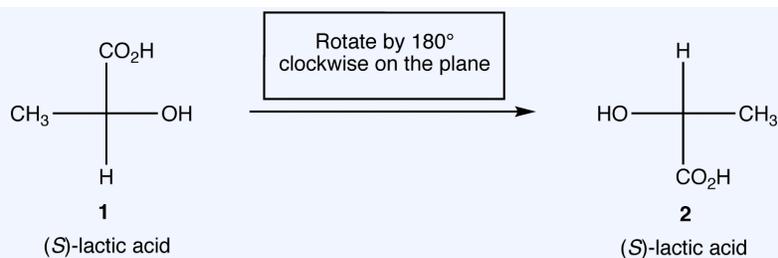
In the compound below, the movement is clockwise (R) which is Horribly wrong, so the actual configuration is S. The complete IUPAC name for this compound is (S)-butan-2-ol.



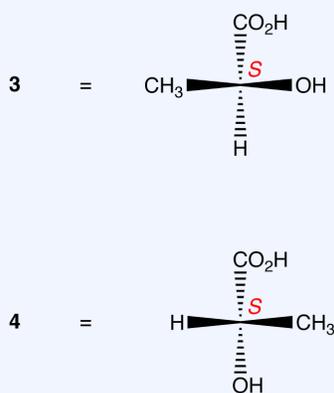
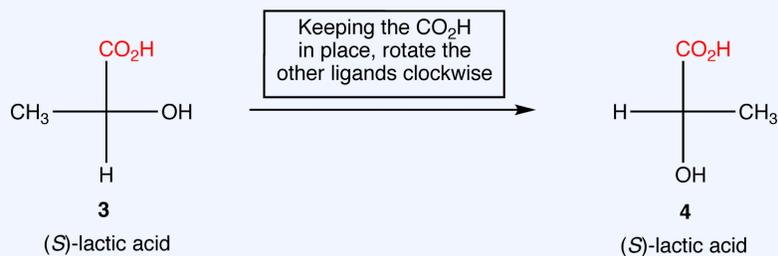
## MANIPULATING FISCHER PROJECTIONS WITH NO CHANGE TO CONFIGURATION

A Fischer projection restricts a three-dimensional molecule into two dimensions. Consequently, there are limitations as to the operations that can be performed on a Fischer projection without changing the absolute configuration at chiral centers. The operations that do not change the absolute configuration at a chiral center in a Fischer projections can be summarized as two rules.

Rule 1: Rotation of the Fischer projection by 180° in either direction without lifting it off the plane of the paper does not change the absolute configuration at the chiral center.



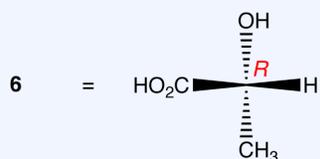
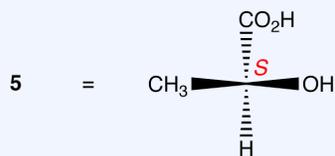
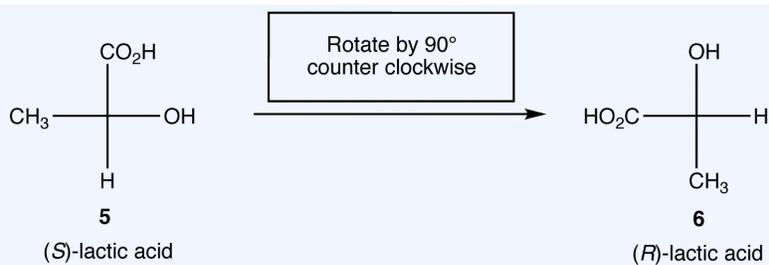
Rule 2: Rotation of three ligands on the chiral center in either direction, keeping the remaining ligand in place, does not change the absolute configuration at the chiral center.



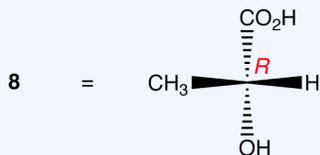
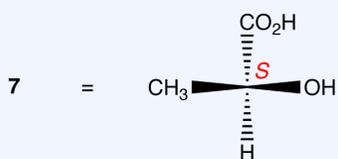
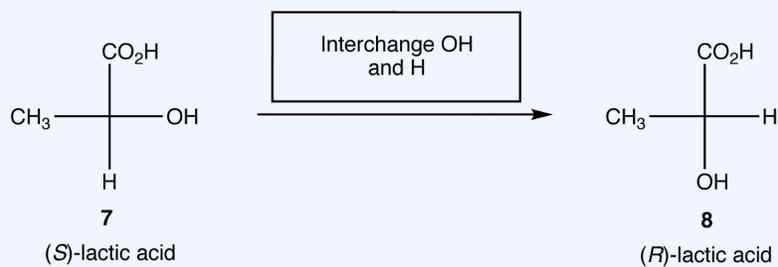
#### Manipulating Fischer Projections with Change to Configuration

The operations that do change the absolute configuration at a chiral center in a Fischer projection can be summarized as two rules.

Rule 1: Rotation of the Fischer projection by 90° in either direction changes the absolute configuration at the chiral center.



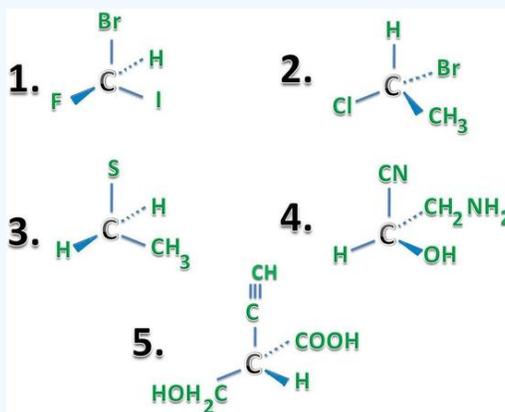
Rule 2: Interchanging any two ligands on the chiral center changes the absolute configuration at the chiral center.



The above rules assume that the Fischer projection under consideration contains only one chiral center. However, with care, they can be applied to Fischer projections containing any number of chiral centers.

### Exercise 1

Classify the following compounds as R or S?

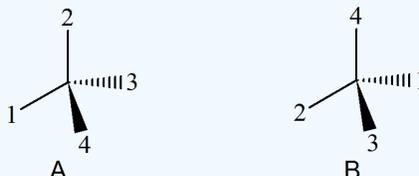


#### Solution

- S:**  $I > Br > F > H$ . The lowest priority substituent, H, is already going towards the back. It turns left going from I to Br to F, so it's a S.
- R:**  $Br > Cl > CH_3 > H$ . You have to switch the H and Br in order to place the H, the lowest priority, in the back. Then, going from Br to Cl,  $CH_3$  is turning to the right, giving you a R.
- Neither R or S:** This molecule is achiral. Only chiral molecules can be named R or S.
- R:**  $OH > CN > CH_2NH_2 > H$ . The H, the lowest priority, has to be switched to the back. Then, going from OH to CN to  $CH_2NH_2$ , you are turning right, giving you a R.
- (5) S:**  $-COOH > -CH_2OH > C\equiv CH > H$ . Then, going from  $-COOH$  to  $-CH_2OH$  to  $-C\equiv CH$  you are turning left, giving you a S configuration.

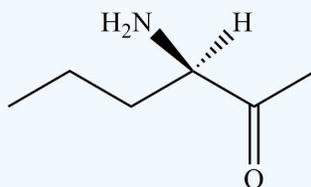
### Exercises

6. Orient the following so that the least priority (4) atom is placed behind, then assign stereochemistry (R or S).



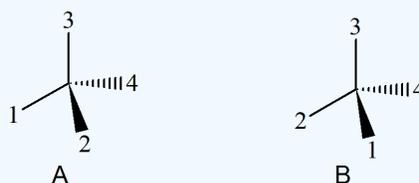
7. Draw (R)-2-bromobutan-2-ol.

8. Assign R/S to the following molecule.



#### SOLUTIONS

6.



A = S; B = R

7.

8. The stereo center is *R*.

#### OTHER RESOURCES

#### KAHN ACADEMY VIDEO TUTORIAL ON THE R-S NAMING SYSTEM

#### REFERENCES

1. Schore and Vollhardt. *Organic Chemistry Structure and Function*. New York:W.H. Freeman and Company, 2007.
2. McMurry, John and Simanek, Eric. *Fundamentals of Organic Chemistry*. 6th Ed. Brooks Cole, 2006.

#### CONTRIBUTORS AND ATTRIBUTIONS

- Ekta Patel (UCD), Ifemayowa Aworanti (University of Maryland Baltimore County)
- [Organic Chemistry With a Biological Emphasis](#) by [Tim Soderberg](#) (University of Minnesota, Morris)

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