

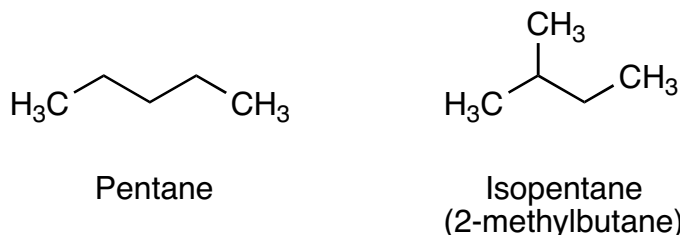
Cahn-Ingold-Prelog Notation Tutorial

Introduction

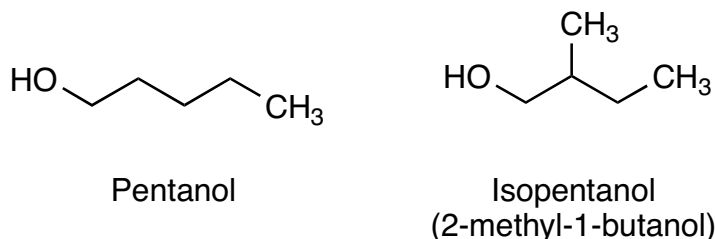
The topics in this tutorial are covered in the textbook: Stryer, page 17, 43 & Ch. 11.1; Bruice, 4.5, 4.8 to 4.10, 20.1, 20.2, 20.10.

The purpose of this tutorial is to help you master the method of assigning Cahn-Ingold-Prelog notation for stereocentres that you will encounter in biological molecules. It is not an exhaustive review of the subject.

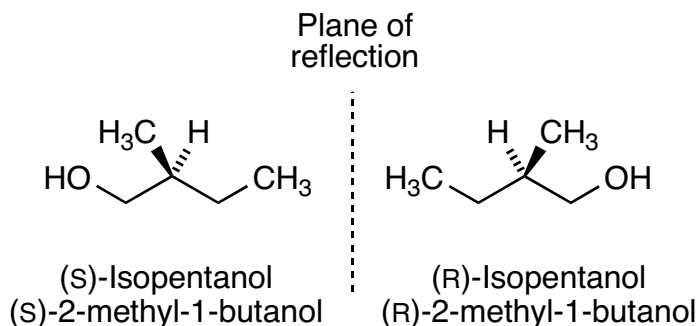
In organic chemistry there are molecules that can have exactly the same connections between atoms and yet still be different molecules. An example of this is a pair of enantiomers, two molecules that are mirror images of each other. In regular isomers we can easily designate different atomic connections in the name of the chemical, e.g. butane and isobutene are two different isomers where they have the same atoms but different bonding arrangements.



Now let us consider pentanol. We might have isomers like *n*-pentanol and isopentanol (2-methyl-1-butanol).



But the isopentanol shown above has two possible isomers. These isomers are the result of one of the carbon atoms having 4 different groups in a tetrahedral arrangement. There are actually two different ways that we can arrange these groups in 3-dimensions without changing the chemical bonding arrangements. These two compounds are called **stereoisomers**. The carbon atom with four different groups is called the **stereocentre** or **chiral centre**. In the case that 2 stereoisomers are also exact mirror images of each other (and this is always the case if there is only one stereocentre) then we call the two stereoisomers a pair of **enantiomers**. Below are the two stereoisomers of 2-methyl-1-butanol, note that they are enantiomers.



Assumed Knowledge

This tutorial assumes the following...

1. You know how to depict organic molecules. (Bruice, chapters 1 & 2, especially 1.4, 2.1 to 2.6, 2.10 and also 4.3, 4.10; Stryer, pages 16-17, 43)
2. You know what sugars and amino acids are. (Bruice, chapter 21.1 to 20.2; Stryer, chapters 3.1, 11.1)
3. You know how to number and label carbons in sugars and amino acids. . (Bruice, chapters 20.1 to 20.4 & 21.1 to 21.2; Stryer, chapters 3.1, 11.1)
4. You are familiar with the concept of chiral molecules and stereocentres in chiral molecules. . (Bruice, chapter 4.1 to 4.11; Stryer, chapters 3.1, 11.1)

If you are unfamiliar with any of the above concepts you will be better able to benefit from this tutorial if you review them before proceeding. The references for each subject are from Bruice, 3rd edition and Stryer, 5th edition. Bruice was the textbook used in chemistry 241.242 and Stryer is the textbook used in this course.

Cahn-Ingold-Prelog Notation

It is easy to denote structural isomers by using a chemical naming convention, but how can we express the exact arrangement of groups around a stereocentre? This exact arrangement is called the **absolute configuration**. We can describe the absolute configuration using the system developed by the scientists for which it was named. Cahn-Ingold-Prelog notation (hereafter called CIP notation) provides an unambiguous description of a stereoisomer of a compound.

There are two possible absolute configurations around any single stereocentre and each configuration will be labeled either R or S in the CIP notation system.

To decide which notation fits a given stereocentre we will take a tetrahedral stereocentre (sp^3 carbon is the most common example of a tetrahedral system in biochemistry) and examine the exact orientation of the groups relative to each other. We will apply the set of rules and determine the absolute configuration to be either R or S.

This will require an ability to rotate molecules in your head. Practice will be necessary.

Assigning Absolute Configuration

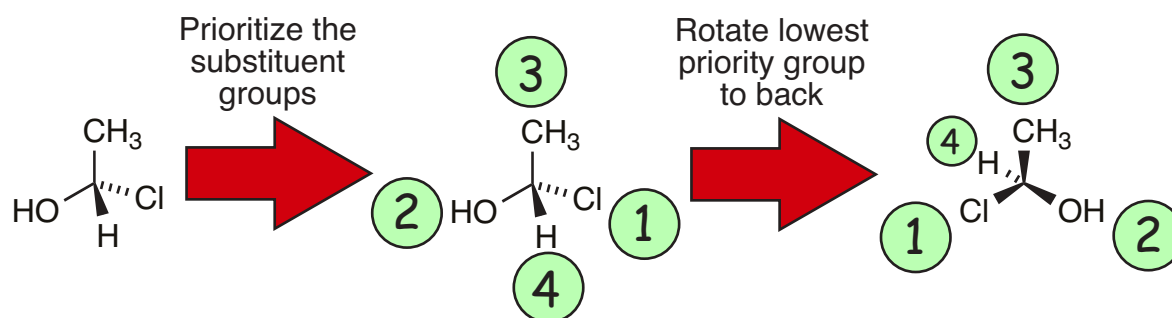
Step 1: Take a single stereocentre in the molecule and number the groups in order of “priority”.

We will discuss how to determine priority shortly. Priority is most simply describes by saying that the atom with the higher mass has the higher priority. Things will become more complicated when the atoms directly attached are the same and we have to look at what is attached to each of those two atoms to order them in priority.

Let us consider 1-chloro-1-ethanol. The atoms attached to the stereocentre are; a hydrogen (mass =1 AMU), a carbon (in the CH₃ group, C has a mass of 12 AMU), an oxygen (in the OH group, O has a mass of 16 AMU), and a chlorine (mass = 36 AMU). So the order of priority is Cl, O, C, H. Let us assign Cl a priority of 1 and assign H the lowest priority of 4.

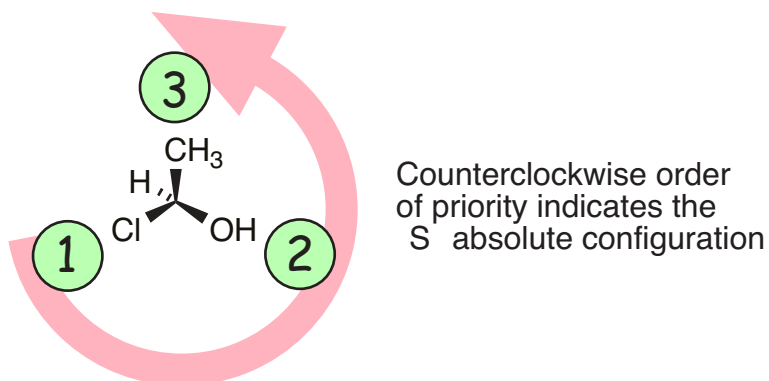
Step 2: Rotate the molecule so that the lowest priority group is pointing away from the reader.

Figure 1. 1-chloro-1-ethanol with priorities assigned and then rotated to that the lowest priority group is placed at the rear



Step 3: Trace your finger around the three highest priority groups in order of the priority. If the circle is moving counterclockwise the CIP designation is “S”. If the circle is moving clockwise the CIP designation is “R”.

Figure 2. Assigning absolute configuration based on group priority.



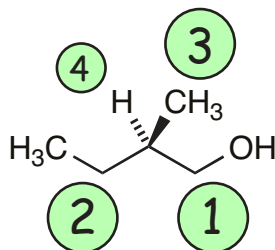
That's all there is to it. You must develop the skills for rotating molecules correctly on paper or in your head. Practice!

Assigning Priorities to Groups

Group Priorities

Let us return to the example of 2-methyl-1-butanol and develop the rules for assigning priority.

Figure 3. An enantiomer of 2-methyl-1-butanol with priorities assigned.



Three of the atoms attached to the stereocentre are carbon and we will have to consider each group in more detail to order these three carbons in priority. The fourth group is hydrogen. It is lower in priority than any carbon atom (1 AMU vs. 12 AMU) and so is assigned the lowest priority of 4.

We must consider the atoms attached to each of the carbon groups so that we can prioritize them. Two identical atoms are further prioritized in rank of the highest priority substituent on each. Let's go through the three carbon atoms in question.

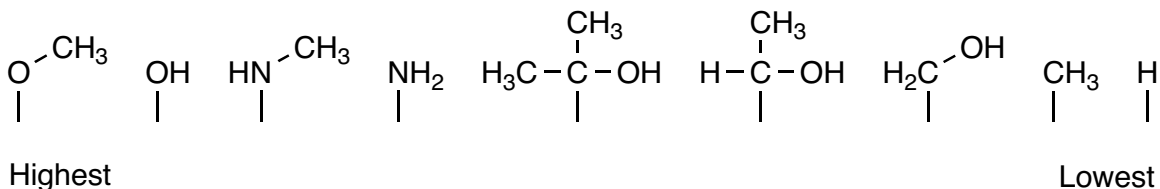
Atom #3: 3 hydrogen substituents

Atom #2: 2 hydrogen and 1 carbon substituent

Atom #1: 2 hydrogen and 1 oxygen substituent

Atom #1 has the highest priority oxygen substituent (mass of O is 16 AMU), atom #2 is next in priority with the carbon substituent (mass is 12 AMU), and atom #3 is last in priority with only low priority hydrogen as its highest substituent.

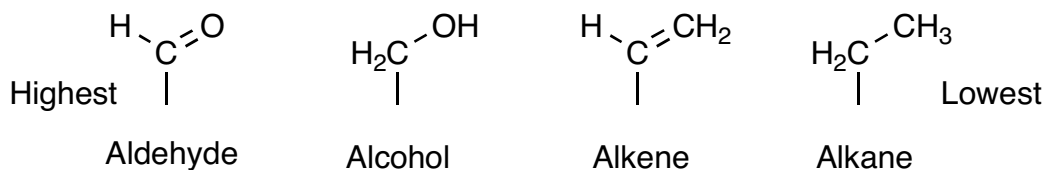
Figure 4. Some example groups in order of priority (highest to lowest).



Double and Triple Bonds

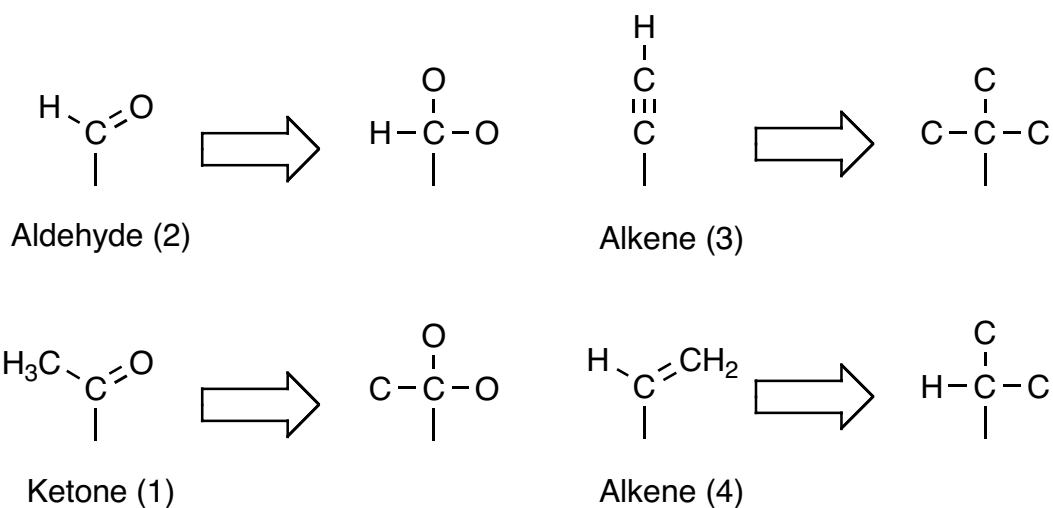
What about double bonds? An aldehyde group has an oxygen and a hydrogen attached to the carbon atom while an alcohol group has an oxygen and two hydrogens attached to the carbon. Which is higher in priority?

Figure 5. Some groups with double bonds



We count each bond as a separate connection. So an aldehyde has two bonds to an oxygen atom and the alcohol has only one. Therefore the aldehyde is higher in priority. Similarly, an alkene carbon is higher in priority than an alkane carbon. Triple bonds are treated analogously

Figure 6. Groups with double and triple bonds. Relative priorities are in parentheses.



Complex Molecules

If two or more groups are the same element, then we examine the attached atoms. If they are also the same, we must examine the atoms attached to those atoms until we have a winner.

In biochemistry we will encounter this situation in the sugars. So let us now examine the case of glucose.

Assigning Stereocenters in Sugars

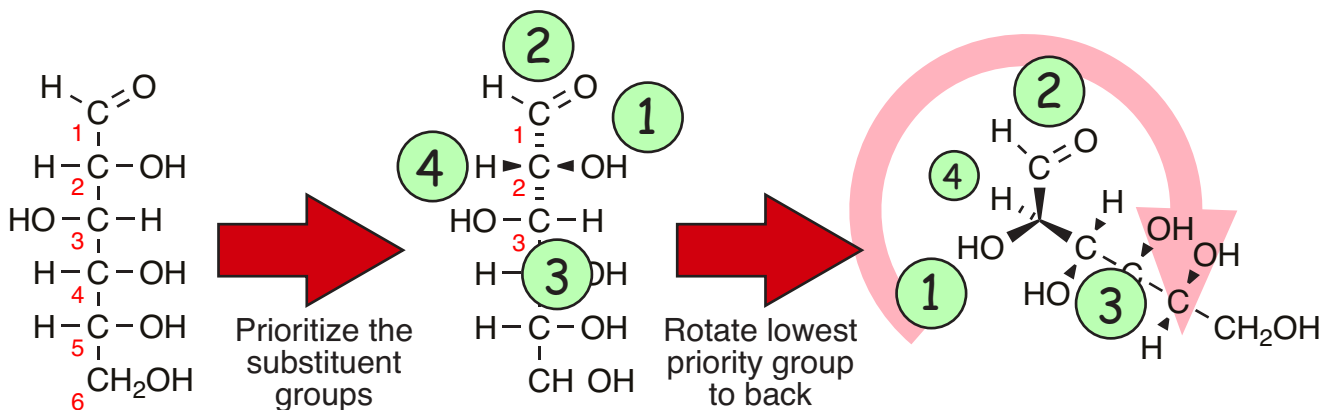
In the case of glucose, the 1-carbon of glucose is in a planar SP_2 aldehyde group and cannot be chiral as it has a mirror plane (in the plane containing the atoms). But the 2-carbon is a tetrahedral SP_3 carbon with four different substituents.

Let us examine the four groups. The first we will consider is the hydrogen group, it is obviously of the lowest priority. Let us now look at the hydroxyl group. The oxygen atom will be the highest priority of the four groups. The two remaining groups are both carbon atoms so we must consider the atoms attached to those carbons to break the tie.

The 1-carbon (aldehyde group) can be considered to be attached to a hydrogen atom and two oxygen atoms (two bonds to an oxygen atom) and the 3-carbon group has one oxygen, one carbon and one hydrogen atom attached. The 1-carbon has two oxygen connections and the 3-carbon has one oxygen connection so the aldehyde group is higher in priority.

So we can order the groups in order of priority: hydroxyl group, 1-carbon, 3-carbon, hydrogen.

Figure 7. Assigning the stereochemistry of the 2-carbon of glucose.



As seen in figure 7, the 2-carbon is in the R-configuration.

You should practice the exercise of rotating a stereocentre in a Fischer projection to various points of view. This is a valuable skill.

Assigning Stereocentres Using Fischer projections

We can determine the CIP designation (R or S) directly from Fischer projection using the following rules (adapted from Bruice, ch. 4.5).

After assigning the group priorities we will have three cases:

1. The two highest priority groups are **adjacent** to each other in the Fischer projection and the lowest priority group is on a **vertical** bond.
2. The two highest priority groups are **adjacent** to each other in the Fischer projection and the lowest priority group is on a **horizontal** bond.
3. The two highest priority groups are **opposite** to each other in the Fischer projection and the lowest priority group is on a **vertical** bond.
4. The two highest priority groups are **opposite** to each other in the Fischer projection and the lowest priority group is on a **horizontal** bond.

Case 1. The lowest priority group is on a vertical bond and is thus pointing away from you. We can therefore use standard CIP ordering. Move your finger in a circular motion around the stereocentre from the highest priority group to the next highest. If you moved clockwise it is R and if you moved counterclockwise it is S

Case 2. **This case applies to sugars.** The lowest priority group is on a horizontal bond and is thus pointing toward you. We must therefore use opposite CIP ordering (we are looking from the reverse direction that CIP ordering utilizes). Move your finger in a circular motion around the stereocentre from the highest priority group to the next highest. If you moved counterclockwise it is R and if you moved clockwise it is S.

Case 3. The lowest priority group is on a vertical bond and is thus pointing away from you. We can therefore use standard CIP ordering. Move your finger in a circular motion from the highest priority group to the next to the next (1 to 2 to 3). If you moved clockwise it is R and if you moved counterclockwise it is S

Case 4. The lowest priority group is on a horizontal bond and is thus pointing toward you. We must therefore use opposite CIP ordering (we are looking from the reverse direction that CIP ordering utilizes). Move your finger in a circular motion from the highest priority group to the next to the next (1 to 2 to 3). If you moved counterclockwise it is R and if you moved clockwise it is S.

Rule of Thumb: If the rotation of the circle formed by the three highest priority groups is clockwise then the assignment is R if the lowest priority group is vertical. Think of Vertical, Clockwise, R or VCR.

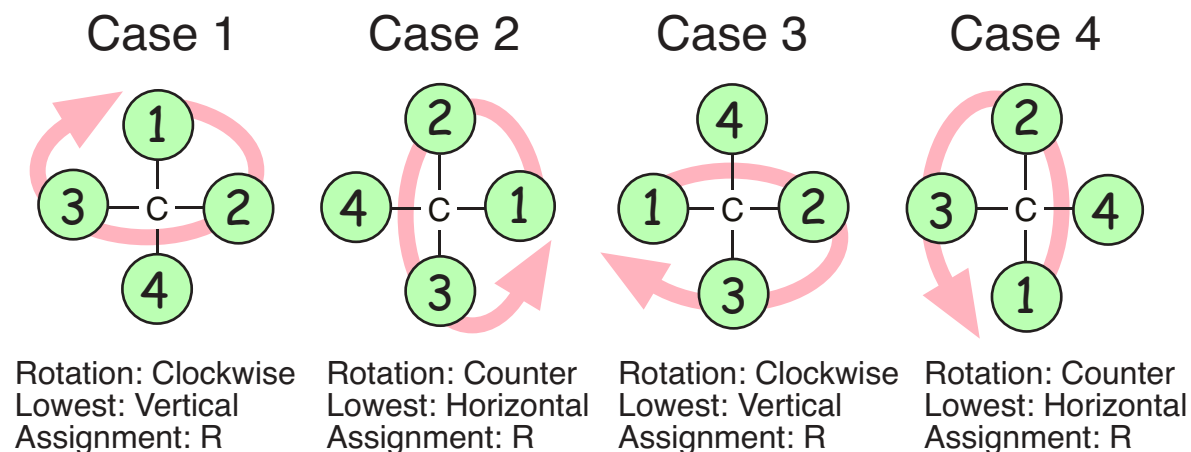
Vertical, Clockwise = R (VCR)

Horizontal, Clockwise = S (HCS, HiCkupS)

Vertical, Counterclockwise = S

Horizontal, Counterclockwise = R

If any one of the first two elements of VCR is opposite then the R is opposite as well and is an S. If both are opposite (horizontal, counterclockwise) then the opposite of the opposite is the same and the R remains R.

Figure 8. Assigning CIP designations to Fischer projections. All of the below are R.

The Stereocentres of Glucose

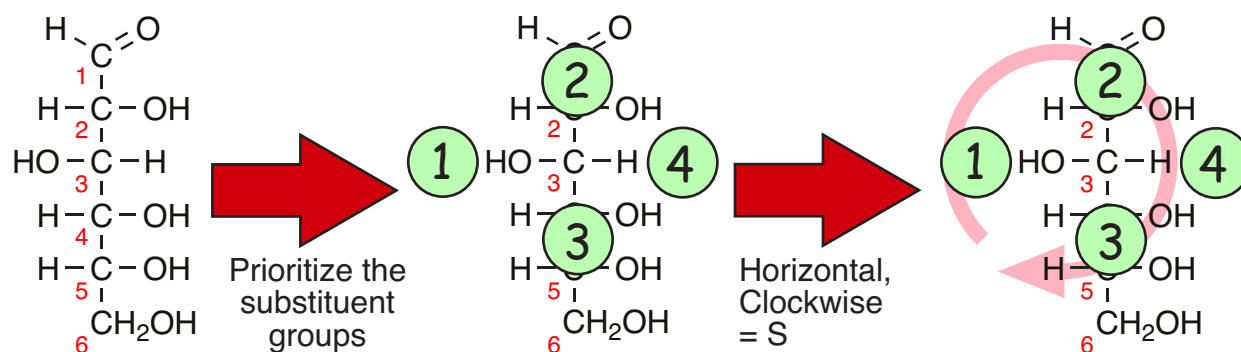
We have seen that the 2-carbon in glucose is in the R configuration. Let us now consider the 3-carbon. In the Fischer projection we will order the groups attached to the 3-carbon. The hydroxyl group is again the highest priority and the hydrogen group is again the lowest. Again, we have two carbon groups to prioritize based on their substituents.

The 2-carbon has a carbon, a hydrogen and an oxygen attached. the 4-carbon has a carbon, a hydrogen and an oxygen attached. We still have a tie.

In this complex situation we then consider what is attached to the groups attached to each carbon. Both hydrogens are identical, and both oxygens have a hydrogen attached and are also therefore identical. The tiebreaker will be what is attached to the carbon atom.

The 5-carbon is attached to the 4-carbon. It has a hydrogen, an oxygen and a carbon. The 1-carbon is attached to the 2-carbon. It is an aldehyde group and has two connections to an oxygen (double bond) and one connection to a hydrogen. The 1-carbon with C(O)(O)(H) is higher in priority than the 5-carbon C(C)(O)(H). So that means that the 2-carbon has higher priority groups attached to it than the 4-carbon. Therefore the 2-carbon is higher in priority than the 4-carbon.

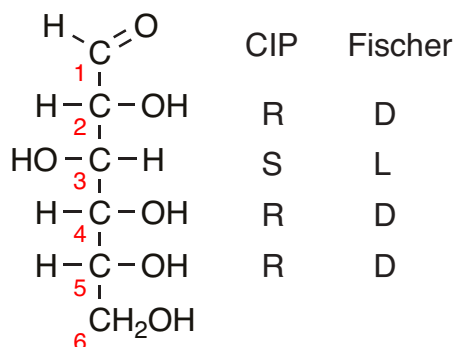
So we will order them in priority as the oxygen, 2-carbon, 4-carbon and hydrogen.

Figure 9. Assigning the stereochemistry of the 3-carbon of glucose.

We can repeat this exercise for all four chiral carbons and we will observe the following stereochemical CIP assignments shown in figure 10. The Fischer convention assignments (D or L) are also included. You will remember that in the Fischer convention for sugars (and only sugars) a carbon is designated as D in configuration if the hydroxyl group is on the right hand side and L if it is on the left.

You will observe from figure 10 that in the case of sugars presented in the Fischer projection (and this is not necessarily true of any other kind of molecule) we see that D and R are equivalent and L and S are equivalent.

Figure 10. The stereocentres of D-glucose



Determine the CIP assignment for the 4-carbon and 5-carbon for yourself and convince yourself that the above assignments are correct.

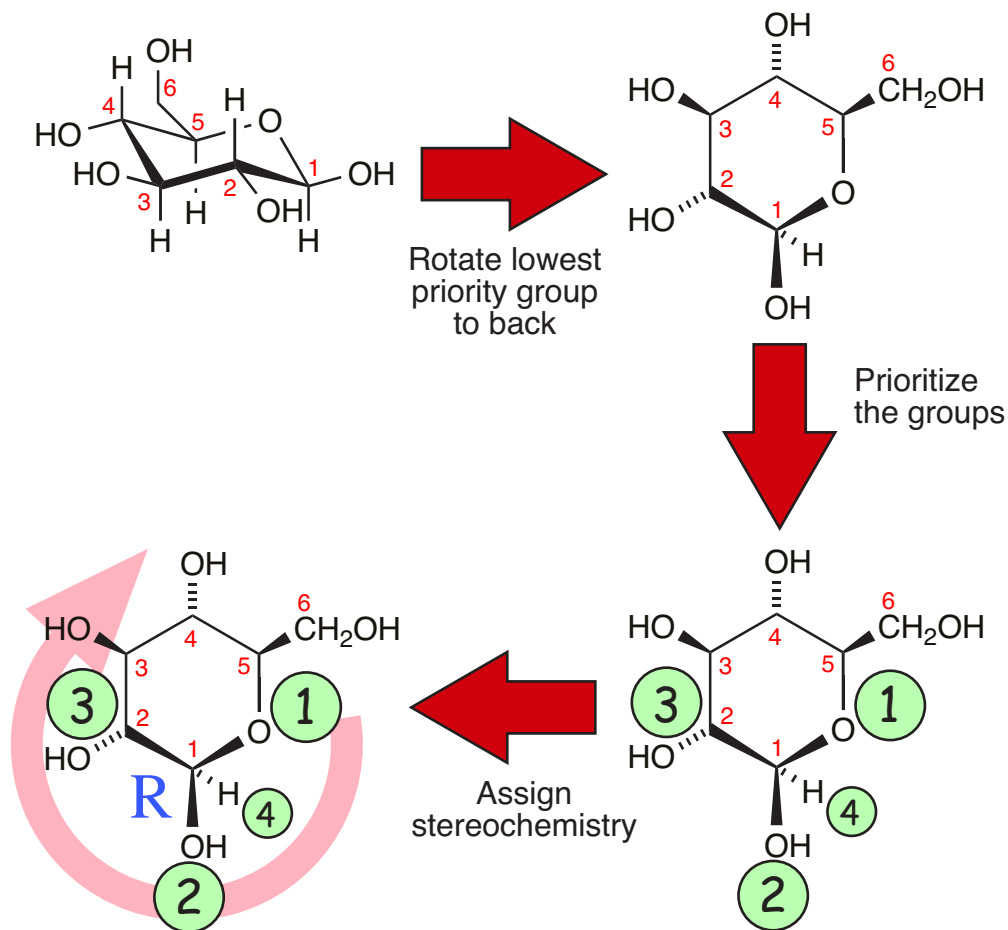
Rules of Thumb: It may have come to your notice that for a given stereocentre in a sugar, the carbon group close to the most oxidized carbon group is the carbon group with the higher priority. Another way of saying this is that the lower numbered carbon is of higher priority than the other.

Assigning Stereocentres For Cyclic Sugars

Cyclic sugars are no different than linear sugars for assigning priorities. The oxygen (hydroxyl) group is the highest priority and the hydrogen is the lowest. Of the two carbon groups we can apply the CIP rules to determine priority or use the rule of thumb that the lower numbered carbon is of higher priority than the other.

In the case of a cyclic glucose let us consider the β anomer. The anomeric carbon is a new stereocentre formed when the 5-carbon hydroxyl group adds to the planar SP_2 aldehyde group to give a new tetrahedral SP_3 acetal group.

The new tetrahedral carbon has a hydrogen group (lowest priority) a carbon group (next lowest) and 2 oxygen groups (tied for highest). The 5-carbon oxygen group has a carbon group attached and is higher in priority than the hydroxyl group. So we prioritize the groups as shown in figure 11 and determine the stereochemistry to be R.

Figure 11. Assigning the anomeric stereocentre in β -D-glucopyranose.**Figure 12. The Haworth projection of β -D-glucopyranose and assigned stereochemistry.**

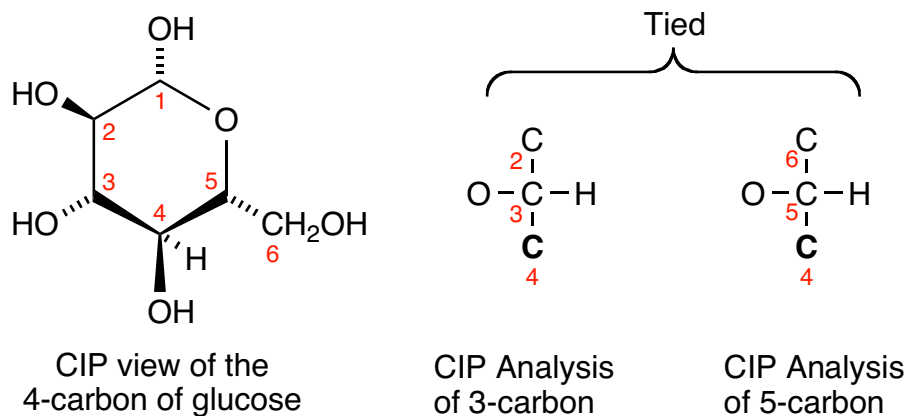
β -D-glucopyranose	Carbon	Assignment	
	1 (anomeric)	R (β)	
	2	R	(D)
	3	S	(L)
	4	S	(D)
	5	R	(D)

The acetal group will cause some confusion in assigning priorities for carbon groups near the acetal. Priorities will be clear using the established rules for the 1,2,3 and 5-carbons. The 4-carbon has some confusing issues.

In linear glucose we observe that the 3-carbon attached to the 4-carbon has a higher priority than the 5-carbon that is also attached to the 4-carbon. *Work it out for yourself and convince yourself that this is true.* However, the cyclic form now has an alkyl group attached to the oxygen group of the 5-carbon (it is now part of an acetal group) instead of the hydrogen (when it was a hydroxyl group). Does this change our priorities?

It does. Examine the two carbon groups in the cyclic molecule. Both groups start with a carbon atom and each carbon atom is attached to another carbon, a hydrogen and an oxygen group. So we are tied.

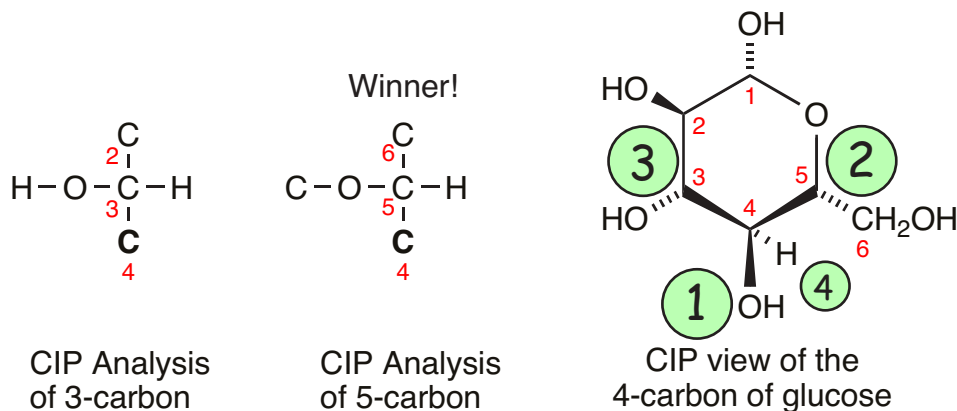
Figure 13. Analysis of the carbon groups for the 3-carbon and the 5-carbon. Both have the same priority so far.



Now we will examine each of the attached groups in order of priority (oxygen first, then carbon) to see if any are higher in priority in a “sudden death” playoff. The moment we get a higher priority we declare a winner. So we will see if one of the oxygen groups is higher in priority. We will trace the molecular chain out from these higher priority groups until one of the oxygens wins or we see that both oxygens are identical. If they are identical then we will turn our attention to the next highest priority group, the carbon.

The oxygen on the 3-carbon is a hydroxyl group and has a hydrogen substituent. The oxygen on the 5-carbon now has a carbon substituent (because we formed an acetal when we closed the ring) and is higher in priority. We now can prioritize all 4 substituents and determine the CIP designation.

Figure 14. Analysis of the higher priority oxygen groups on the 3-carbon and the 5-carbon. The oxygen group on the 5-carbon is higher in priority. The 5-carbon wins!



We now see that the 4-carbon of D-glucose is S in the cyclic pyranose form but is R in the linear form. The absolute configuration has not changed! Only the designation has changed due to the rules used. In the Fischer convention it is still designated D (down in Haworth projection, right in Fischer projection).

Rules of Thumb: As you may already have realized, hydroxyl groups that were to the right (D) in the Fischer projection are below the ring plane in cyclic sugars and are the lower groups in Haworth projection. See the Haworth projection tutorial for more. So groups that point down in the Haworth projection are assigned D in the Fischer convention and, correspondingly, R in CIP designation (except in some special cases as seen above).

However, at the anomeric carbon, the priorities of groups is different because of the fact that the hydroxyl group is the second highest in priority instead of being the highest. This is an artifact produced by the fact that the ring oxygen came with an alkyl group attached to it. As a result the CIP designation with respect to Fischer convention is reversed for the anomeric carbon. For similar reasons the R:D relationship is also reversed for the 4-carbon in the case of glucose.

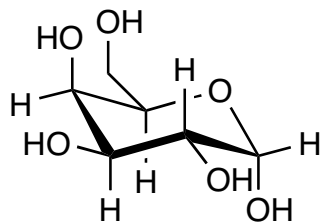
At the anomeric carbon we see that a configuration that is D in the Fischer convention (α -anomer) is S in CIP designation. A configuration that is L in the Fischer convention (β -anomer) is R in CIP designation.

By practicing choosing CIP and Fischer convention designations of stereocentres you will start to observe these patterns and exceptions to these patterns. Practice!

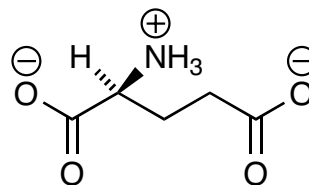
Exercises

1. Identify and correctly assign the CIP designation for all the stereocentres in the following molecules. All of the molecules are sugars, nucleosides or amino acids. Correctly identify each molecule.

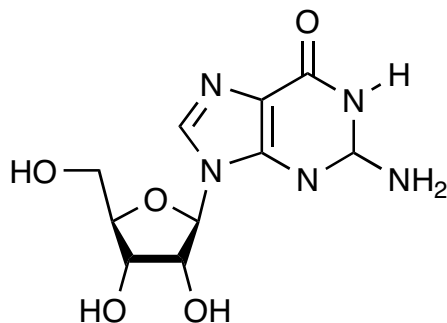
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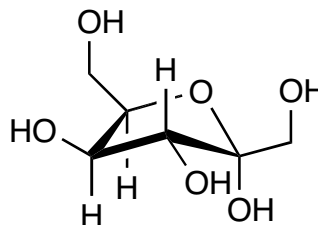
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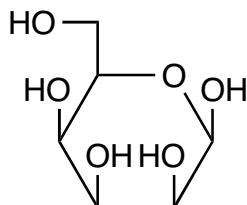
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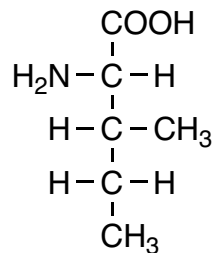
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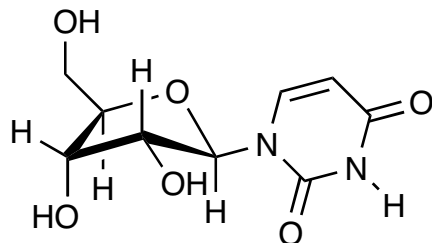
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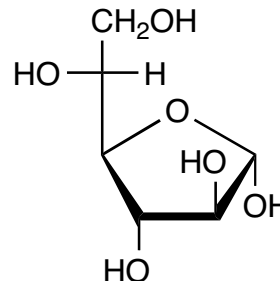
f)



g)



h)



2. Glucose can be called a 2,3,4,5,6-pentahydroxyhexanal (hexanal for the aldehyde group. It would be hexanol if the 1-carbon were an alcohol). Correctly draw the Fischer projection of the following sugars. Identify the sugars.
- 2-(S)-3-(S)-4-(R)-5-(R)-6-pentahydroxyhexanal
 - 2-(R)-3-(S)-4-(R)-5-tetrahydroxypentanal