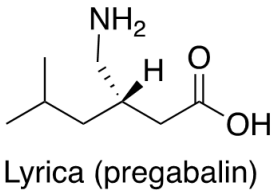
6.3: Computational Instructions

In this computational exercise, we will seek to accomplish two different objectives. First, we will use the molecular visualization capabilities of Avogadro to help us assign the absolute configuration of chiral centers of pharmaceuticals. Secondly, we will examine the energy values of a set of diastereomers and a set of enantiomers to illustrate their difference in properties.

Part 1: Using Avogadro to examine the chiral centers of pharmaceuticals.

Start by creating a folder on your PC's desktop and naming it Stereochemistry Exercise. Next you should download the supporting files for this exercise and save them to the Stereochemistry Exercise file that you just created. While you have likely learned to assign absolute configurations, let's work through the determination of the chiral center in the pharmaceutical pregabalin together. This will allow us to both review this important skill and learn how Avogadro can help us visualize molecules in three dimensions. Pregabalin, sold under the brand name Lyrica, is a pharmaceutical used in the treatment of pain caused by nerve damage.[7] As shown in Figure 3, pregabalin has a single chiral center in the middle of the molecule.



Lyrica (pregabalin)

Figure 3. Structure of pregabalin, which is sold under the brand name of Lyrica.

As shown in Figure 4, we start by determining the location of the chiral center. A chiral center is an atom, often carbon, that is bound to four unique groups. This carbon is identified with a red circle.

Figure 4. Finding the chiral center of pregabalin

Next, we need to rank the priorities of the groups bound to the chiral center using the Cahn-Ingold-Prelog priorities. These priorities rank groups based upon atomic number. A group with highest priority will be 1 while the group with the lowest priority will be 4. As shown in Figure 5, hydrogen has the lowest priority as it has the lowest atomic number and is assigned priority 4. The other three groups begin with carbon, so we examine atoms bound to these carbons. The presence of a nitrogen (atomic number 7) breaks the tie allowing us to assign 1st priority to that group. The last two groups are still tied so we move outward and see that the group on the left is bound to two carbons and a hydrogen while the group on the right is making three bonds to oxygen. Because oxygen has a higher atomic number than carbon the tie is broken, and we assign the group on the right 2nd priority. The remaining group is assigned priority 3.

Step 2. Rank Groups According to CIP Priority.

- Atoms attached to a chiral center are ranked by atomic number.
- If two atoms have the same atomic number we examine what else is attached to the atom to look for a difference in atomic number.
- If there is still at tie we move outwards and repeat the process until a difference is found.

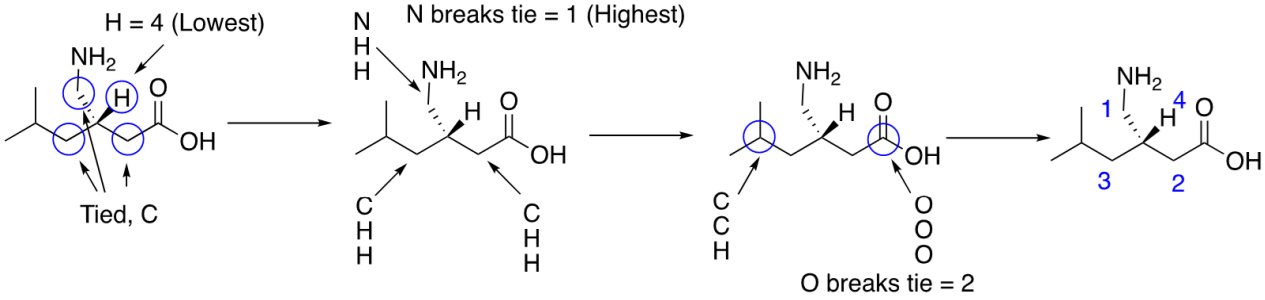


Figure 5. Assigning priorities using the Cahn-Ingold-Prelog system for pregabalin.

After assigning priorities, we need to rotate the molecule such that the lowest priority group is pointed to the back (dashed bond), into the plane of the paper. To do this, envision taking the $C-C$ bond between the chiral center and the group whose priority we assigned 2 and spinning it like you would an umbrella. This will place the hydrogen atom, which has the lowest priority, to the back.

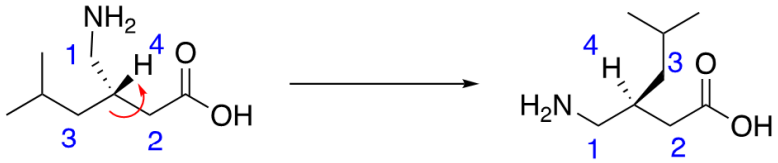


Figure 6. Rotating the molecule so that the lowest priority group is pointing into the plane of the paper.

Finally, we draw an arrow connecting priorities 1-2-3 in order. If this arrow is rotating clockwise the configuration of the chiral center is R, while if the arrow is rotating counterclockwise the configuration is S.

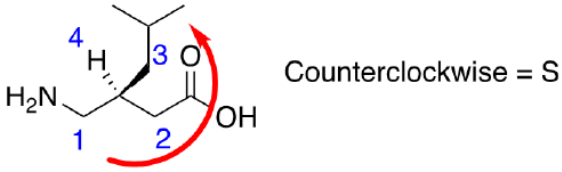


Figure 7. Determining whether the chiral center is R or S.

We will now use Avogadro to make this process of manipulating the molecule to determine its chirality much easier. In the Pharmaceutical Structures folder that you downloaded in the supporting files, open Pregabalin.xyz in Avogadro. As shown in Figure 8, the structure of pregabalin is shown in three dimensions. By clicking on the navigation button, which looks like a compass rose, you can rotate the molecule in three dimensions. Try to rotate the molecule such that the lowest priority of the chiral center is pointing into the screen. With this completed you can easily determine R or S.

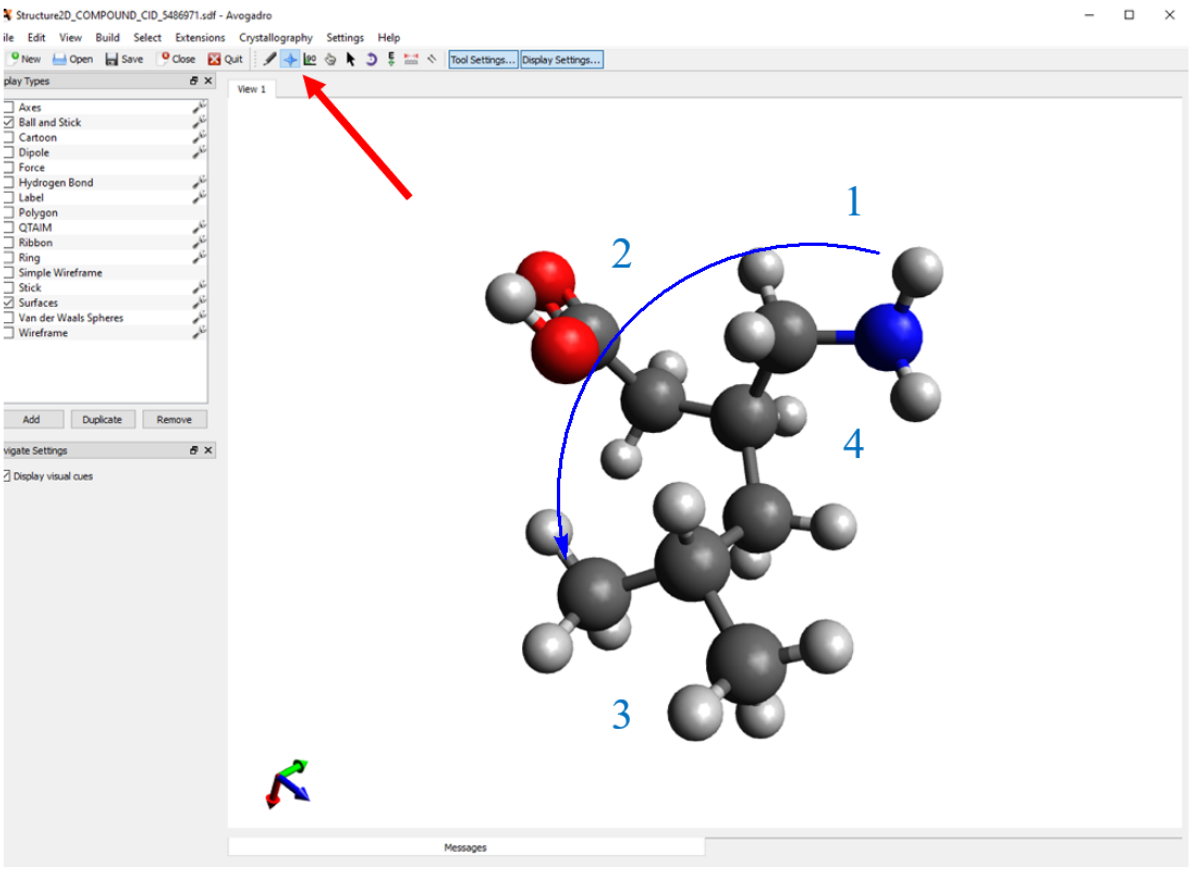


Figure 8.

The structure of pregabalin rotated such that the lowest priority group is pointed away from you into the screen. The navigation button is indicated by a red arrow.

One additional feature of Avogadro is that it makes creating an enantiomer of the structure that you have drawn easy and convenient. To create the enantiomer of the pregabalin molecule on your screen click on Build → Invert Chirality.

Please complete the questions for part 1 at the end of the assignment.

Part 2: Examining the energies of enantiomers versus diastereomers.

As described above, enantiomers of a compound have remarkably similar chemical properties. They will melt at the same temperature, have the same IR spectra, and react the same. One of the only places where enantiomers will differ is their interaction with plane polarized light. Specifically, enantiomers of a compound will rotate plane polarized light in opposite directions. This similarity does not extend to diastereomers. Unlike enantiomers, diastereomers will have different chemical properties and will often display unique melting points, different IR spectra, and they may react differently. In the second part of the computational exercise that follows we will examine the chemical properties of the amino acid threonine which has two chiral centers.

As shown in Figure 9, the amino acid threonine has two chiral centers. One set of enantiomers has historically been known as threonine while the other set of enantiomers is referred to as allothreonine, but these compounds have the same molecular connectivity. Given what we know about enantiomers and diastereomers, we would expect these L and D-threonine (enantiomers) to have identical energy values. L-Threonine and L-Allothreonine, however, would be expected to have different energy values because they are diastereomers.

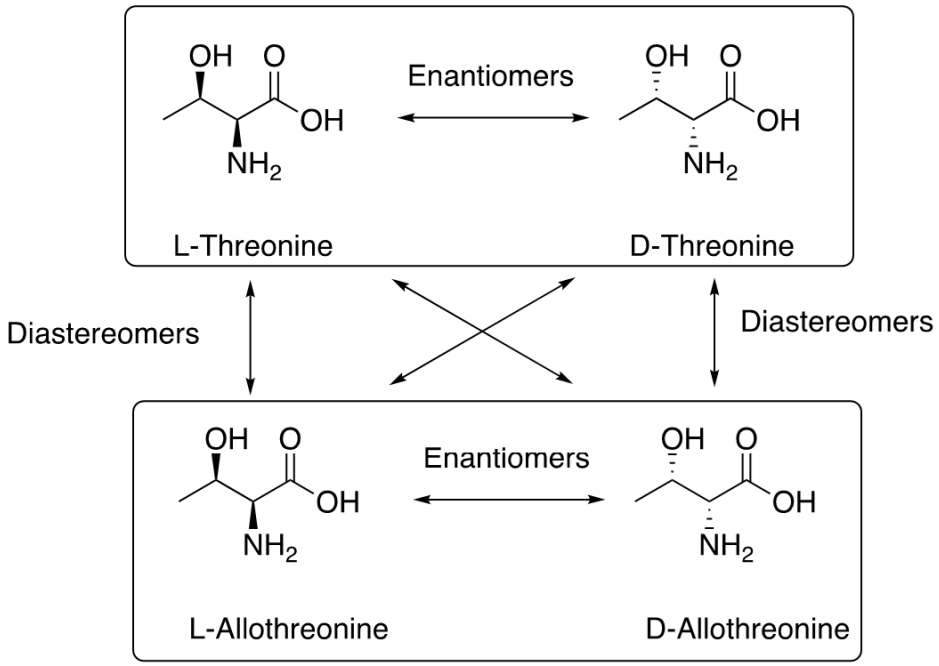


Figure 9. The diagrammed relationship between enantiomers of threonine and allothreonine.

The geometry of all four stereoisomers of threonine were optimized in the gas phase and an energy calculation performed on the optimized geometry using a B3LYP functional and DEF2-SVP basis set using Orca.[4–6] The Gibbs free energy values are summarized in the table below and the optimized structures are available in the supporting files. Please use these data and your knowledge of stereochemistry to complete the questions associated with part 2 of this exercise.

Table 1. Summary of ground state Gibbs free energy values for threonine and allothreonine.

Species	Gibbs Free Energy, Eh
L-Threonine	-437.599724
D-Threonine	-437.599618
L-Allothreonine	-437.609162
D-Allothreonine	-437.609163

References

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