1 Introductory Reading

1.0.1 Objective of the lab

The goal of this lab is to learn how to perform a simple calculation known as a potential energy scan (PES) using the technologies, techniques, and tools of computational chemistry. In this lab, you will determine the best conformer for a well known drug - Zantac (proprietary name: ranitidine).

1.0.2 Background Reading:

If there is a ”take home” message in this course, it is this: molecular structure is everything. An understanding of molecular structure allows the medicinal chemist to begin to be able to determine whether or not a drug will do what we need it to do, that being to cure some disease. Your success in this course is absolutely dependent on your ability to do a complete and significant analysis of the molecular structure of a drug. This means an understanding of organic chemistry, a topic that will be addressed at the very start of this course.

The compound in Figure 1 is a drug that you know well: acetylsalicylic acid, otherwise known as "ASA", otherwise known as "aspirin". It is acidic because of the carboxylic acid functional group, consisting of a carbon atom with a double bonded oxygen and an OH "group" attached. You should immediately identify the carboxylic acid portion of this compound. In this graphic, the carbon atoms are grayish, oxygen atoms are red, hydrogens are white. In other compounds, nitrogen atoms are typically blue.

Notice that this compound has another C=O structure, separated from the ring structure (a "benzene" ring) by an oxygen "bridge". Sometimes we call these oxygen bridge structures "oxo" compounds, a name that is not used for this particular molecule.

Molecules have energy. When you change the shape of a molecule, you change the energy. If you add something to the molecule, the energy changes. If you take something
away, the energy changes. If you bend the molecule, twist it, squish it, the energy changes. One of the things we do in drug chemistry is to rotate bonds. Take a look at the aspirin molecule. If you look at atoms 2 and 3, there is a bond between those two atoms. This is a rotatable bond. We can rotate this bond, and in doing so the energy changes. Every different rotation produces a molecule known as a conformer, which just means a different shape. When we do a conformational analysis, we change something in the molecule – we rotate a bond, we lengthen a bond, we change a bond angle, etc. – and that produces a different energy value. The question becomes: which conformer provides the most stable structure? In chemistry, stability is defined by the lowest energy value. As such, the most stable conformer is that structure that has the lowest energy value.

There are, by the way, four other rotatable bonds in this structure: between 10 and 12, 9 and 10, 3 and 4, and 1 and 2. Can you find them?

We typically only want to make one conformer change at a time, to see the effect that that change has on the energy of the molecule. As a demonstration, the podcast tutorial does a conformational analysis – also known as a potential energy scan (PES), or a coordinate scan – on one of the rotatable bonds. We’ll rotate the bond between atoms 2 and 3.

In describing molecular geometries (another term for molecular structure), we have to identify these aspects of the molecule:

1. the number and types of atoms – this molecule has carbon, oxygen, and hydrogen, with the structure $C_9H_8O_4$
2. the types of bonds – in this molecule we have single and double bonds
3. the bond lengths, the distances between two atoms. We measure bond lengths in units of angstroms (Å), which is $10^{-10}$ meters.

4. the bond angle, measured between three atoms, in units of degrees

5. the dihedral angles, measured between four atoms, also in units of degrees. When you are doing potential energy scans, you almost always do those on top of dihedral angles.

![Figure 2: Aspirin coordinate scan data](image)

To do the potential energy scan, we need to freeze or fix all of the bond lengths, bond angles, and dihedral angles with the EXCEPTION of the one that I want to rotate. You will see in the podcast tutorial that in looking at what is known as a z-matrix that you will fix all of the bond lengths, angles, and dihedrals. We will scan the one dihedral angle that we want to see rotated.

Given that we want to rotate the bond between atoms 2 and 3, we need to choose two atoms on either side. Looking at the picture, the dihedral angle that I want to scan is the dihedral angle between 1-2-3-4. In doing a scan, you want to rotate that bond around 360 degrees, and you’ll do it in 36 degree increments (meaning I’ll do 100 steps).

Once we run the scan, we get a set of data, showing the value of the dihedral angle and the energy associated with that angle, and a plot (graph) of that data. What you should see in the graph is that the molecule has its lowest energy value (most stable conformers) between about 30-220 degrees. You should also see that the molecule is very unstable (high energy value) around the 220 degree dihedral angle.

The explicit mechanics of how to do this scan are available on the podcast tutorial.
2 Computational Approach

You should practice this lab with the aspirin molecule, trying to duplicate the results that you see above and in the podcast tutorial.

For this lab, you want to do a conformational analysis (potential energy scan, coordinate scan – we use these terms interchangeably, so get used to it!).

Zantac is shown in Figure 4. Find the sulfur atom (yellow, with an S in it). We want to rotate the bond to the right of the sulfur atom (the bond between sulfur and the carbon to the right of the sulfur atom in this picture). You can find this molecule on the computational chemistry server (http://chemistry.ncssm.edu), under the "Fragment" section under the "Build" menu. Zantac is a drug, so you will find it under that category.

You are expected to be able to determine which four atoms are the appropriate atoms to scan, using the Z-matrix tool under the "Tool" menu in the molecular editor. Again, if you are new to this, you are encouraged to watch the podcast tutorial.

Your computational engine for this calculation should be MOPAC, with the PM3 level of theory. Zantac has no charge, and a multiplicity of 1. By default, the calculation type will be coordinate scan.

For this lab, submit a 250 to 300 word abstract and a copy of your PES graph, all in one Word document, saved as LastnameLab#1.doc (or .docx), so, by way of example, GotwalsLab#1.doc. Upload your file to WebAssign by the date and time listed on WebAssign.
For this abstract, you should include some information about the molecule in general, including its empirical formula, the number of rotatable bonds that you can identify, and any other structural characteristics that you consider to be important and/or relevant.

For your lab abstract: this a a one paragraph, roughly 250-300 word description of what you did in this lab. A typical lab abstract has these components:

1. One sentence that describes the purpose of the lab. The sentence should clearly state the research question that the activity is trying to answer.

2. One or two sentences that describe the computational approach to this problem. You should describe in general terms how you did this lab. You should absolutely describe which computational engine you used, which calculation type you used, and the theory used.

3. One or two sentences that describes your computational results. This can include numerical data, but does not include all data, does not have tables, and does not include bulleted or lists of items. There are no graphics permitted in an abstract.

4. Write a concluding sentence. Your concluding sentence should answer the research question. The question is: can you determine what the research question is?