Organic Chemistry I Laboratory

Molecular Modeling and Melting Points: Identifying Trends in Physical Properties

**Background Reading**


- Melting Points: Pg 73-88.

**Background Scenario:**

Molecular modeling has added greatly to our understanding of organic chemistry. The rapid development of computational chemistry software with easy-to-use graphical interfaces has allowed chemists to firmly establish these methods in research at both the industrial and academic level. Unfortunately, the use of computations to predict or explain chemical phenomena is still fraught with pitfalls. The point of this lab/computer exercise is to acquaint you with the molecular modeling software (PC-Spartan Pro), refine your technique of taking melting points, give you more experience finding physical properties for specific substances in the literature, and to stress the fact that chemical intuition must be used to interpret the computational and experimental data.

**Scientific Methodology**

You will be determining whether or not different calculable physical properties of compounds correlate with the experimentally found melting points of a series of compounds. The molecular modeling software PC-Spartan Pro will be used to find an optimized molecular geometry, starting from a geometry based on the crystal structure data found in the primary chemical literature. Once the geometry is optimized, the total surface area and net dipole will be calculated for each of the compounds. Potential hydrogen bonding sites will also be determined for each molecule. Since we know that the melting point of a particular solid is somehow related to the forces which hold molecules together in the crystal lattice, it is reasonable to predict that Van der Waals, dipole-dipole and/or H-bonding could correlate with the melting point data. The total surface area will relate to the potential Van der Waals attraction, net dipole data will relate to potential dipole-dipole attractions, and the number of H-bonding sites can be related to potential H-bonding attractions between molecules. Propose a hypothesis which can be answered from analysis of the above data.

**Understanding the Techniques**

Computational chemistry and molecular modeling are fast growing areas within chemistry. The recent advances in computer hardware and the development of user friendly graphical interfaces has allowed computational chemistry to reach the undergraduate level. While you will not be held responsible for understanding all of the math being performed during the modeling exercises used in organic chemistry, (those who continue into physical chemistry will learn of Schrödinger's equation, Hamiltonians and eigenvalues) it is necessary for you to have a basic understanding of the applications and limitations of molecular modeling.

The total energy of a molecule depends upon its geometry. Even small changes in structure can lead to rather large changes in total energy of a molecule. Frequently, molecular modeling is used to determine the lowest energy conformation of a particular molecule or the energy of a specific, reactive conformation. Knowledge of these energy values allows prediction of the number of molecules able to attain a specific reactive geometry (conformation) under specific reaction conditions. The algorithms used to compute likely molecular geometries, rely on calculating an energy for a specific geometry, slightly changing the geometry, calculating the new energy and comparing to see if the geometry change has resulted in a decrease of total energy. This iterative process can be done relatively quickly with today's computers. An energy minimum results when any small change the computer makes to the molecule's geometry results in an increase in total energy. Complex molecules have an infinite number of conformations and many energy minums. Each molecule will have one "global minimum" which corresponds to the lowest energy conformation of the molecule. Unfortunately, the way the computers determine energy minima, there is no way for the computer to automatically find this global energy minimum. Instead, experimenters must minimize the molecule's energy starting from several different possible conformations then choose the lowest energy conformation. In today's experiment, the starting conformation will correspond to the crystallographic data known for each of the compounds (Figure 1.).

---

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>Ref.</th>
<th>Dihedral Angle (absolute value)</th>
</tr>
</thead>
</table>
| Benzil              | ![Benzil structure](image) | 2    | $\theta_{1-2-3-4} = 102^\circ$  
                  |                    |      | $\theta_{1-2-7-8} = 164^\circ$  
                  |                    |      | $\theta_{4-2-5-6} = 15.6^\circ$ |
| Benzoic Acid        | ![Benzoic Acid structure](image) | 3    | $\theta_{1-2-3-4} = 0^\circ$    |
| ortho-Toluic Acid   | ![ortho-Toluic Acid structure](image) | 4    | $\theta_{1-2-3-4} = 0^\circ$    
                  |                    |      | $\theta_{5-6-7-8} = 180^\circ$   |
| Salicylic Acid      | ![Salicylic Acid structure](image) | 5    | $\theta_{1-2-3-4} = 0^\circ$    
                  |                    |      | $\theta_{5-6-7-8} = 0^\circ$    |
| 4-Hydroxybenzoic Acid | ![4-Hydroxybenzoic Acid structure](image) | 6    | $\theta_{1-2-3-4} = 0^\circ$    
                  |                    |      | $\theta_{5-6-7-8} = 0^\circ$    |
| Benzoin             | ![Benzoin structure](image) | 7    | $\theta_{1-2-3-5} = 56.0^\circ$ 
                  |                    |      | $\theta_{2-3-5-6} = 35.5^\circ$ 
                  |                    |      | $\theta_{6-5-8-10} = 41.7^\circ$ 
                  |                    |      | $\theta_{4-3-7-9} = 0^\circ$    |

**Figure 1.** Dihedral angles taken from the crystallographic data

There are three different types of calculations which will determine the total energy for a given molecular conformation, molecular mechanics, semi-empirical, and ab-initio. Molecular mechanics calculations are the simplest of the above types of calculations. Molecular mechanics treats molecules as balls and springs. The different atoms of the molecule represent the balls and will have different weights depending on the mass of the atom. Bonds in the molecules are treated as springs which connect the balls (atoms). This allows the bonds to be stretched or compressed and the total number of intramolecular forces to be calculated. Empirical values which describe how the springs behave are chosen to reproduce the available experimental data. Molecular mechanics calculations are the quickest to perform on a molecule but because they need explicit parameterization, these methods do not typically work well with reactive, short-lived reactive intermediates such as transition states. Molecular mechanics calculations are typically used on large molecular systems such as proteins and complex carbohydrate structures. Semi-empirical calculations are based in quantum chemistry and give information regarding the molecular orbitals of a molecule. These calculations require some

paramaterization but not to the extent of molecular mechanics. The specific semi-empirical algorithm we will use is called AM1. This is probably the most popular algorithm for organic applications. It provides a good account of equilibrium structures, and usually reproduces transition-state geometries obtained from higher level (ab-initio) calculations. While AM1 generates very good molecular geometries, it does not provide an acceptable account of reaction thermochemistry. Therefore, when we need to calculate the energetics of a particular organic reaction, we will compute a molecular geometry using AM1 and then plug that geometry into a different algorithm to determine the energetics. The highest level calculations are the ab-initio methods. These methods are very time consuming and can presently only be applied to small and medium sized molecules.

Understanding the Experiment

The aim of this exercise is to correlate the experimentally determined melting points with the number of H-bonding sites, the calculated surface areas and net dipoles of the individual compounds. The melting point of a compound should be related to at least one of these factors since they all relate to how individual molecules can interact with each other. Analyzing the potential H-bonding sites in a molecule is a qualitative exercise which will suggest the potential number of H-bonds which could mole molecules together. It is important to realize that identifying H-bonding sites does not mean that the individual molecules will be oriented in the proper position to actually form the maximim number of H-bonds. Also, the strength of H-bonds is dependent upon the specific positioning of the donor and receptor areas. The surface area of the molecule is determined from calculating the shapes and sizes of the molecular orbitals. The surface area of the molecule will be related to the total amount of Van der Waals attractions which can exist between molecules. From the equilibrium electron positioning, the molecular dipole can be determined. Both the surface area and dipole are quantitative measurements calculated from the semi-empirical AM1 algorithm. You will experimentally determine the melting point of each of the compounds in Figure 1 (previous page). Next you will analyze the theoretical data to determine which property most closely correlates with the experimental data. Finally, you will propose an explanation which relates the theoretical data with the experimental results.

Procedure

Determine the melting point range for each of the compounds in Figure 1. Look up the literature melting points to compare with your experimental values. The remainder of the experiment will be performed using the PC-Spartan Pro molecular modeling software package. Use the help guide to aid you in building and locking the dihedral angles within the molecules. Molecules are built by selecting the group or correctly hybtidized atom from the builder portion of the screen and then clicking in the view area. If there is already a partially built molecule in the view area, then you add onto that molecule by adding the new piece to an open valence (yellow bond) on the partially built molecule. Once the molecule is built, it is important to remember that setting up the calculation and starting the calculation are two separate steps.

Setting the dihedral angle.

Spartan will have a geometry pull-down menu. A dihedral angle can be frozen by selecting constrain dihedral under the geometry pull-down menu. Once this option has been selected, you need to identify the dihedral angle by either selecting the four atoms or three bonds which form the dihedral angle. Type in the value for the dihedral angle and check the constrain box. If using the Spartan-Pro software, you need to check the lock box (it has a picture of a padlock) before you can change the angle. Click Done which you have finished.

Setting up the calculation

Under the Setup pull down menu, select calculation. In the new pop-up window, set theTitle (name of compound), Task (geometry optimization), Level (AM1), and check the constraints box (this will tell the computer to use the dihedral angles you have set). Click OK. At this point the calculation is setup but not running. To start the calculation, select submit from under the setup pull-down menu. This actually starts the calculation. The computer should prompt you that the calculation has started. The computer will also prompt you after the calculation has completed. Once the calculation has completed, select Output from under the Display menu to view the results. Print the output for a hardcopy of the optimized energy. Select Properties from under the Display pull-down menu and then select Dipole to view the calculated dipole of your molecule. Write this value on the printout of the energy calculations.

Results

Build a table which contains all of the following information:

<table>
<thead>
<tr>
<th>Compound</th>
<th>Molecular weight</th>
<th>Experimental mp</th>
<th>Literature mp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat of formation</td>
<td>Dipole</td>
<td>Surface area</td>
<td>H-bond acceptor sites</td>
</tr>
</tbody>
</table>
Organize your results to highlight the property which seems to correlate best with the melting point. Your discussion should explain the data with respect to melting point. You may find that not all of the data has any easily determinable correlation with the melting point data. Make certain the following questions are addressed.

1. Based on your experimental results, what is the order of melting points for the compounds (from lowest to highest). Do the experimental results agree with the literature results?
2. How well do the dipole calculations predict the relative order of melting?
3. Is there any correlation between the surface areas of the compounds and their relative order of melting?
4. Is there any correlation between the molecular weights of the compounds and their relative order of melting?
5. Do the number of H-bond donor and acceptor sites provide any insight into the relative order of melting?
6. How well did the computations predict the properties of the molecules in this experiment?
7. In what situations did they (the computations) correctly predict the experimental trends? In what situations did they incorrectly predict the trends?