

## ACS Technology Fellowship Final Report

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### Summary

The purpose of this project was to design molecular simulations for use by students in General Chemistry classes. By simulating chemical phenomena and drawing their own conclusions about chemical principles, students can 'own' concepts more readily than they could in a traditional 'lecture' type setting.

### Software and Hardware

Our initial plan was to use freeware such as Tinker and Force field Explorer. We decided to implement the initial experiments in general chemistry molecular modeling in Spartan (commercial) and Arguslab 4.0 (freeware). Thus, in Fall 2005 and Spring 2006 we used these programs to get a feel for the ability to the students to learn the software and bridge the textbook/modeling gap. As a result of the excellent feedback we have had on these methods, we plan to implement more permanent 'modules,' as described in the original proposal, in Tinker and FFE in the next academic year. These modules may be available to the public as soon as December 2006.

Our local chemistry computer lab is equipped with 6 computers and is available 24 hours a day to students. We installed Arguslab and Spartan on these computers (Arguslab granted us a free site license, and we purchases the Spartan licenses from Wavefunction Inc.). We could then have class in the room, with students doubling-up to do in clas examples, and we could assign homework to be completed on these computers.

### Summer Planning

In designing the outline for a General Chemistry class featuring molecular simulations, it was decided that a mid-semester introduction of modeling techniques would work out best, as the students would have a firm basis of knowledge to build off of. I have planned a mid-semester "modeling workshop" for my students which will take up two class periods and the time in between. During this time students will learn the software, learn how to run and trouble shoot simple simulations, and make sure they have sufficient resources to use the software. After this workshop the curriculum goes into molecular structure, intermolecular forces, phase changes, and kinetic molecular theory. All of these topics are amenable to molecular simulations.

## Molecular Modeling exercises

1. The initial introduction to modeling occurred on the first day of class. As a motivational tool, we used Arguslab (free, [www.planaria-software.com/](http://www.planaria-software.com/)) to view the crystal structure of HIV-1 Protease, an enzyme which plays a large part in AIDS, complexed with an inhibitor (free, pdb structure 1W5X, 1W5Y, 1W5Z, for example, at <http://www.rcsb.org/pdb> ). When inhibitors are bound to the enzyme active site, the production of new viruses is slowed and the spread of HIV is slowed in turn. We used this example to show how we can take this enzyme, zoom in on the active site, and see what molecular interactions are leading to the inhibition. We also discussed how knowledge of what the active site looked like in 3D can help with the rational design of drugs that can help to inhibit the enzyme.
2. Periodic trends and the chemical bond: After discussing Lewis structure and hybridization, we used Spartan and Arguslab to show some structure optimizations on small molecules. Specifically, we drew methane, ethanol, and acetic acid in very poor initial structures. The class was able to identify why the structures were 'bad.' We then allowed the program to 'optimize' the structures to see how the quantum mechanical methods underlying the programs reach the same structures that we do using dot structures and hybridization. We also showed examples of how, if you draw the beginning structure badly enough, the program cannot find the correct structure. This reinforces the idea that while these programs are helpful, they are not a substitute for chemical intuition.

In discussing bond polarity, we allowed Arguslab to draw the electron density for the three above mentioned molecules. The students at this point have had their basic quantum mechanics and can understand what the electron density, or the 'total electron cloud' is. In methane we see uniform electron clouds between the carbon and the protons. In ethanol we see a slightly more polar electron cloud between the oxygen and the proton. In the acetic acid we see the very polar bond between the oxygen and the proton. This serves to highlight bond polarity and introduces the concept of acidity.

The students were then given a homework assignment to open some files I saved for them: one was acetylsalicylic acid and the other was acetaminophen. The students were to optimize the structures, make sure the bond angles made sense according to their chemical intuition, have the program draw the electron density, and the answer the question: why is acetaminophen better for people who are prone to heartburn? This exercise was well received by the class.

3. Intermolecular forces: The drug LSD competes with neurotransmitters for active sites in the brain proteins. We had the students draw the structures for LSD and a neurotransmitter in the best initial structure they could, and then let the program (Spartan) optimize the structures. Since these are larger molecules, the optimization are not as straight-forward as with the smaller molecules, and the

role of the user is more important in drawing the initial structure. Once the structures were optimized, the program was used to calculate the dipole moment of the molecules. This is important for the binding of the molecules to the active sites. Finally, we drew a water molecules in with the LSD and neurotransmitter molecules in such an orientation that hydrogen bonding could occur between the two. This was meant to simulate the strength with which the LSD or neurotransmitter molecules could bind to the active sites. We then calculated the interaction energy between the two and found that LSD in fact binds more strongly than the neurotransmitter does.

4. Phase changes: We designed and experiment using molecular mechanics using Tinker and FFE wherein we would fill a box with CO<sub>2</sub> atoms and adjust the volume and temperature in the box to see the behavior of the ensemble. This can be used to illustrate the PV diagrams on phase changes and can relate molecular motions to these phase changes. Unfortunately, the aftermath of Hurricane Katrina caused us to lose two class days and we were unable to fit this exercise into the semester.

## **Assessment**

We used pre- and post-class attitudinal surveys to ascertain the degree to which students enjoyed/learned from the activities. Our data was overwhelmingly positive, with one comment that while the student did not enjoy most of the class, they did like the modeling portion.

## **Future Work**

Encouraged by the success of these exercises, we plan on creating 'modules' containing the input files and brief instructions for these using Arguslab (for the electronic structure related activities) and Tinker with FFE (for the molecular mechanics related activities). These will be more easy to use by the students and will not require so much of a learning curve. The design of the modules will take place in summer of 2006 and the implementation will take place in the 2006/2007 academic year. We plan to make these modules available to the public after their initial evaluation and debugging.

More modules will be designed as well, and input on chemical phenomena that are amenable to this type of exercise are welcome.