BBSI Lab Assignment for 6/11/2003

For today’s assignment, you will be doing a combination of several different computational techniques. Listed below are 5 different exercises, try and do several of these exercises; we listed more than you need to do, but not everybody is interested in the same areas of computational chemistry, so this will give you a choice to find out and explore different areas. In the exercise below, there is quantum chemistry, molecular dynamics, docking, Brownian dynamics, and Monte Carlo examples. The last two will take advantage of programming skills that some of you have.

I.) Quantum Chemistry Calculations

For the quantum mechanical calculations we will calculate the actual energy of a hydrogen bond between 2 water molecules and between a methanol and water molecule. To do this, we will use the following equation:

$$\Delta E = E(AB) - E(A) - E(B),$$

where this shows the interaction energy ($\Delta E$) to be equal to the energy of the complex (the two molecules together) minus the energies of the individual components (molecules in this case). We will do the interaction energies with the Hartree-Fock (HF) level of theory between the two sets of molecules ($H_2O-H_2O$ and $MeOH-H_2O$) with three basis sets, the STO-3G, 3-21G, and 6-31G* basis sets. This means that there will be a total of 12 optimizations (4 for each basis set; a water, a methanol, a water and methanol together, and two waters together) that you will need to do, this will not take that long! Then all you have to do is some math. All of the energy outputs will be in hartrees, the units of energy is usually used in citations is kcal/mol (1 kcal/mol = 627.5095 hartrees).

To do the calculations in Gaussian03, we will build the z-matrices in GaussView (you can also do this manually, which needs to be done for large/complex systems that are much more trivial than this). Open GaussView 3.07 (I will refer to it as GV below) and you will see ethane on the screen. Click on the tab in the middle of the screen that says Carbon Tetrahedral. This will open up the Select Element window. You can choose any element you want by clicking on the periodic table and selecting the correct geometry at the bottom of the screen. If you want to replace an atom, click on it before you open the element selector window and choose the new element and geometry to replace it with (ex. Click on a hydrogen of a water molecule and open the Select Element window, choose Carbon with a tetrahedral arrangement, this will give you methanol).

To do the quantum calculations, have the molecule in question to be the foremost view window open. Select Calculate→Gaussian at the top of the main GV window. In the Gaussian Calculation Setup window, click on Opt + Freq. under Job tab; this will do an optimization plus a frequency analysis. You can choose your level of theory and basis set under the Method tab. You can select the basis set by clicking on the default basis set (3-21G) and changing it; you can add polarized and diffuse function with the two next columns next to the basis set. The default level of theory
should be HF, which is what we will be using in these optimizations. More on where to find the energies in the output files will be shown to you by the instructor in lab.

II.) Molecular Dynamics Simulations

In the Molecular Dynamics section, we will look at how a molecule explores the energy landscape in both the gas phase and in solution. We will notice what areas of the energy surface will be changed the most and how this affects the path of the dipeptide in the course of the simulation.

For the Molecular dynamics (MD) study of conformations, we will do simulations in solution and in the gas phase. For the MD simulations, we will look at the blocked alanine dipeptide as we did on Mon. To start, make the contour map again which will only take a minute. This will show us which conformation(s) the dipeptide will mostly like be situated in (with respect to the $\phi/\psi$ angles). To do the molecular dynamics simulation, go to Compute $\rightarrow$ Conformations $\rightarrow$ Dynamics (be sure to click the box at the bottom to open the Database Viewer). Do the simulations for the gas phase (with no solvation) and in solution (notes from Mon. should be online) for 100 picoseconds apiece (the time steps given are in femtoseconds). Do the solution simulations twice, one with explicit (build a water box around dipeptide) and the other with implicit water (use the solvation term in the potential control).

In the main screen go to Close on the right side of the main screen and discard the data (hope you still have the $\phi/\psi$ plot open). In the Database viewer, go to File $\rightarrow$ Dynamics Animator (the structure should reappear in the main screen). In the main screen, click on Dihedrals to measure the dihedrals (both the $\phi$ and $\psi$ angles). As you move through the simulations by advancing the frames one or more than one at a time (you will see how in the Dynamics Animator), follow the $\phi/\psi$ angles in the in Dihedral contour plot that was made in the beginning of this exercise. Notice how the molecule makes its “path” around the energy landscape. Why do you think that it follows this path? Does the path and the contour map change from going from the gas phase to solution phase (yes, you need to make another contour plot for the solution phase blocked alanine dipeptide)? What factors do you think influences the change(s) in the energy landscape and the path of the dipeptide through the simulation?

III.) Docking Simulations

In the Docking exercise, we will show you how to dock a drug/inhibitor (or anything else) into the active site or the proposed active site of a molecule. From the earlier labs, we will show the factors that play a part in the stability of the docked structure and how you might be able to enhance the structure to find more favorable interactions. An example of this might be modifying a drug so it binds better in an active site.

For the docking example, we will use carbonic anhydrase II with a sulfonamide inhibitor (your choice of sulfonamides when downloading)
1.) Prepare the protein by adding hydrogens, removing water molecules, and removing ions (except the zinc in the active site). This can be easily done in the sequence editor.

2.) Prepare the substrate by adding hydrogens and fixing the bond types by having the substrate selected and going to Edit→Fix.

3.) Select a force field in the Potential Control. In this case, use the MMFF94 force field.

4.) Select the Substrate and go to Compute→Simulations→Dock. Make the docking box large enough to allow the substrate to fully rotate and translate out of the pocket (active site). Also, center the docking box over the active site.

5.) Analyze the results by looking at the energy values, pocket surface, H bonds, ect.

6.) Modify the substrate, repeat the docking process and try to determine whether the new substrate binds better or worse. Use your chemical intuition to make choices about how to modify the substrate (ex. Don’t use a hydrophobic amino acid in a hydrophilic area of the pocket)

IV.) Monte Carlo and Brownian Dynamics Programming

The following two exercises are for those interested in writing a program to perform some simulations. These programs may be written in FORTRAN, C/C++ or in Mathcad. It is up to the individual with which language they are most comfortable in programming.

1. The following function represent a one-dimensional energy landscape that contains two minima.

\[ E(x) = Ax^4 + Bx^3 - 2x^2 \sqrt{AC} \]

The given parameters, A = 4, B = 0, C = 700, lead to both wells with equal minima and symmetrically on each side of 0. The following graph is an illustration of the energy surface:
Write a Monte Carlo program that will sample this energy landscape. Initially write the program such that you sample one of the two wells with a 40% acceptance of configurations, then modify your program sample both wells. In this case you may need to implement the replica exchange algorithm. Quantities you should consider printing include the average energy, average position, and perhaps a histogram of the position. If you cannot figure out the replica exchange algorithm you may want to try modifying the function to lower the barrier so that you sample both wells. Also try changing the function so that one well is higher than the other.

Refer to the provided papers for assistance on the replica exchange method.

2. In this problem you are to write a simple Brownian dynamics program to calculate the bimolecular diffusion – controlled rate constant for two spheres. Initially write your program so that you calculate the rate constant between two non-interacting spheres. Then include an interparticle interaction as that described in the Northrup, Allison, and McCammon 1984 JCP paper. Compare your results with those for the test cases given in the paper.