Chemistry 430 — Simulation in Chemistry & Biochemistry

Laboratory #2 — Conformational Analysis of Alanine Dipeptide

In this lab you will find the local minima of "Alanine Dipeptide" (*i.e.*, Ace-Ala-NMe) using three different protein force field "molecular mechanics" models, both in the gas phase and using the Generalized Born implicit solvent model.

Protocol

(1) If you have not already done so, set up Tinker and FFE on your computer. You can download both packages from the Software Resources section of the course website. FFE comes as the **`ffe-macosx-8.7.2.dmg`** installation kit. Move this file to your Desktop and just "double click" on the file to install. FFE will be under /Tinker-FFE in your home directory. For Tinker, move the gzipped tar file (**`tinker-8.10.5-macos.tar.gz`**) to your home directory. Then in a terminal window run the command **`gunzip tinker-8.10.5-macos.tar.gz`**, followed by **`tar xvf tinker-8.10.5-macos.tar`** on the downloaded file. After all of this, Tinker will be under /tinker in the same home directory. If not already there, drag the FFE executable (~/Tinker-FFE/ffe/Force Field Explorer.app) to your dock. Add the line **`set path = ($path $HOME/tinker/bin)`** to the **`.tcshrc`** file in your home directory, or add an analogous line to your **`.bashrc`** file if you are using bash as your shell.

(2) Use these programs to run calculations with the OPLS-AA, Amber ff99SB and CHARMM22-CMAP force fields. Create a directory to contain the files you will generate in this lab. In this directory, use a text editor to construct three key files, **`opls.key`**, **`amber.key`** and **`charmm.key`**. Each file should contain a single line pointing to the appropriate parameter file (*i.e.*, oplsaa.prm, amber99sb.prm and charmm22cmap.prm). The parameter files are in the /params area of your Tinker installation. For example, the line **`PARAMETERS /user/"yourname"/tinker/params/oplsaa.prm`** will specify the OPLS-AA parameter file and should go into the file **`opls.key`**. In each of the three files, add one more line containing the Tinker keyword **`ENFORCE-CHIRALITY`**.

(3) In a terminal window, run the Tinker **`protein`** program to construct alanine dipeptide for each of the three force fields. The sequence has three "amino acid residues", which should be input as in the order: "**`ACE`**", "**`ALA`**", "**`NME`**".

(4) Open the structures in turn using FFE. Go to the "Keyword Editor" panel and check that the correct force field is being used, and the above keywords are active. From the "Modeling Commands" panel, run the **`scan`** program for each structure, using automatic selection of torsional angles (option 0), an energy threshhold of 10 kcal/mol (instead of the default value of 100.0), and an RMS gradient of 0.0001. The minima will be written to a TINKER archive coordinates file (**`opls.arc`**, *etc.*). Open the **`.arc`** files in FFE and look through the sequence of minima found by the **scan** program by playing the **`.arc`** file as a "trajectory movie". Alternatively, you can run the scan program in a terminal window, instead of via the FFE GUI interface. To do this, just enter **`scan`** in the terminal and answer the questions interactively using the above values.

(5) The calculations in step (4) were run on a single, isolated molecule in the gas phase. For each of the three force fields, repeat the **scan** calculation with the Generalized Born (GB) solvation model activated. The GB model places the dipeptide molecule into a bath of "implicit" water, thereby mimicking the presence of solvent without explicitly including solvent molecule in the computation. To turn on use of the GB solvation model, you should add the keyword phrase **`SOLVATE GBSA`** to each of the **`.key`** files. Alternatively, this keyword can be activated via the FFE Keyword Editor.

(6) Construct separate "Ramachandran plots" for each force field, both with and without GB solvation, to show the position and energy of each of the minima. You can find the values of the phi and psi angles interactively using FFE, or you can run the Tinker **`analyze`** program on the **`.arc`** file from each scan calculation. If using **`analyze`**, include the **`D`** option to get detailed output. Then the phi and psi angle values can be found in the list of torsional angles for each structure.

Questions

(1) How many minima did you find for each of the six scan calculations (three force fields, gas phase and solvated)? Why do the numbers of minima found differ? What is the lowest energy "gas phase" structure for the dipeptide? Why is its energy so low? What about the 2nd through 4th lowest gas phase structures? Rationalize the relative energies of these four lowest energy conformations. These four structures are not as strongly preferred once GB solvation is included in the force field energy. Why?

(2) The procedure used by the **`scan`** program is sometimes referredone as "Low Mode Search" or LMOD. The original article on this method is *Journal of the American Chemical Society*, ***118***, 5011-5019 (1996). Read this paper, which is located in the directory for this lab, and briefly describe how the method works. While this *JACS* paper is quite old, versions of this basic method are still widely used for conformational search projects. An analysis of more recent methods similar to LMOD is found in *Bioorganic Medicinal Chemistry*, ***21***, 7898-7920 (2013). Both of these research papers are provided on the course web site.

(3) Repeat any one of the scan conformational searches using alanine tripeptide (Ace-Ala-Ala-NMe). Now how many minima do you find? Do you expect the number of minima to grow linearly or exponentially with the length of the peptide? Explain. How large of a peptide structure do you think could be completely searched using this method?

In a similar fashion, if you have time, try to use scan to find all the minima for the *n*-alkanes: methane, ethane, propane, butane, pentane, hexane, *etc*. Extended *n*-alkane **`.xyz`** and **`.key`** files for use with the OPLS-AA force field are on the lab website as **`alkanes.tar.gz`**.

(4) If you have the time and/or interest (not required!), figure out how to use Tinker to restrain the phi and psi angles of alanine dipeptide (more keywords!, I can help with this...). Then use the Tinker **`minimize`** program to find the minimum energy of the dipeptide on a regular grid of phi/psi values. You can use this data to construct a full Ramachandran map as a 2-D contour plot of the energy as a function of the "phi" and "psi" peptide backbone torsional angles.