Chemistry 478 — Molecular Modeling

Laboratory #5 — 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 web site for this lab. FFE comes as the **`ffe-macosx-6.3.2.dmg`** installation kit that you can just "double click" on to install. For TINKER, move the gzipped tar file (**`tinker-macosx-6.3.2.tar.gz`**) to your home directory. Then run **`gunzip`** followed by **`tar xvf`** on the downloaded file. After all of this, FFE will be under /MolecularTools in the home directory, and TINKER will be under /tinker in your home directory. You should drag the FFE executable (~/MolecularTools/ffe/Force Field Explorer.app) to your dock. Also, add **`set path = ($path $HOME/tinker/bin)`** to the **`.tcshrc`** file in your home directory, if this line is not already present.

(2) We will 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 contain a single line pointing to the appropriate TINKER parameter file (*i.e.*, oplsaa.prm, amber99sb.prm and charmm22cmap.prm). For example, the line **`PARAMETERS /user/"yourname"/tinker/params/oplsaa.prm`** will specify the OPLS-AA parameter file. The parameter files are in the /params area of your TINKER installation. In each of the three files, add two additional lines. One line should contain the TINKER keyword **`ENFORCE-CHIRALITY.`** The other additional line should be the keyword **`ARCHIVE`**.

(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 "residues", input as 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 keyword are active. From the "Modeling Commands" panel, run the **`scan`** program for each structure, using an energy cutoff of 10 kcal/mol, and defaults for all other parameters. The minima will be written to a TINKER archive coordinates file (**`opls.arc`**, *etc*.).

(5) For each of the three force fields, repeat the scan calculation with the Generalized Born solvation model activated. You can add the keyword phrase **`SOLVATE GBSA`** to each of the **`.key`** files, or the keyword can be activated via the FFE Keyword Editor.

(6) Construct separate Ramachandran plots for each force field, 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?

(2) The procedure used by the scan program is sometimes referred to in the literature as "Jumping between Wells" or "Basin Hopping". Look this up on in the literature and on the web, and describe how it works. To get you started, you might want to take a look at an interesting review from David Wales group at Cambridge University in *Journal of Physical Chemistry B*, ***110***, 20765-20776 (2006).

(3) Repeat any one of the scan conformational searches using alanine tripeptide (Ace-Ala-Ala-NMe). Now how many minima do you find? How large of a peptide structure do you think could be completely searched using this method?

(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 2-D Ramachandran map contour plot of the energy as a function of phi and psi.