Chemistry 478 — Molecular Modeling

Laboratory #7 — Global Optimization of Polyalanine Octapeptide

In this lab you will attempt to locate the global potential energy minimum for a capped octapeptide of polyalanine. Two different techniques will be explored: a molecular dynamics-based simulated annealing (SA) protocol, and Monte Carlo Minimization (MCM) on a modified "barrierless" potential surface.

Protocol

(1) Build the peptide sequence ACE-ALA-ALA-ALA-ALA-ALA-ALA-ALA-ALA-NME, which is an octomer of alanine capped with an acetyl group at the *N*-terminus and an *N*-methyl amide group at the *C*-terminus. You can build the peptide using FFE, by choosing the **`PROTEIN`** program from the modeling menu and entering the sequence. Or you can run the TINKER **`PROTEIN`** program manually in a terminal window. Choose the Amber 99SB force field (*i.e.*, the file **`amber99sb.prm`** in the /params directory of your TINKER installation). If you build the peptide manually, create a keyfile (**`.key`**) containing the key word option **`PARAMETERS /user/your-username/tinker/params/amber99sb.prm`**. By default, the peptide will be constructed in an extended conformation similar to a strand of β-sheet. Check the structure by looking at it in Force Field Explorer (FFE).

(2) Using the **`ANNEAL`** program from within a terminal window, we next perform a simulated annealing run on the peptide. This is an MD-based protocol that starts at a high temperature, and slowly lowers the temperature over the course of a simulation. The SA procedure first equilbrates at the high temperature, and starts a longer "cooling" phase. Before starting the run, add the **`ARCHIVE`** option to your key file. Use 100000 steps at 1000K for the equilibration, and then 1000000 steps to cool from 1000K to 0K. Accept the default of a 1.0 fs time step, but use an exponential (**`E`**) cooling schedule instead of the linear default. Save a trajectory snapshot every 1.0 ps instead of the 0.1 ps default value. The program will save the trajectory frames to a **`.arc`** file.

(3) Next, perform a Monte Carlo Minimization calculation using the TINKER **`MONTE`** program. Start from your original extended peptide conformation, and run for perhaps 5000 Monte Carlo steps, using torsional moves (**`T`**, instead of Cartesian), and at the default temperature of 500K. Before starting, comment out or remove the **`ARCHIVE`** keyword in your keyfile. This will force **`MONTE`** to save intermediate structures in numbered files (**.001**, **.002**, *etc*.) instead of to an **`.arc`** file.

Questions

(1) Use FFE to view the trajectory generated by your SA run. What kind of structure is generated by the end of the computation? How much lower in energy is the final SA structure compared to your original extended structure? You can use the **`ANALYZE`** program to get the energy of individual structures. Why do you think the SA structure is

lower in energy? We have run the SA calculation in the “gas phase”. How would use of a solvation model affect your results?

(2) The **MONTE** program saves a new structure every time it finds one lower in energy than the current lowest energy structure. So the highest numbered saved file will be the one with the lowest energy. View the lowest energy MCM structure in FFE. Is it higher or lower in energy than the final SA structure. Why? Take a look at the number and quality of the hydrogen bonds formed in the MCM structure and compare with the SA structure.

(3) Do you think the results you have found for the octapeptide will scale to larger structures? Why? What structure do you expect to be the “gas phase” global minimum as the paptide sequence becomes longer?

(4) Have a great Spring Break !