Chemistry 430 — Simulation in Chemistry & Biochemistry

Laboratory #5 — Relative Hydration Free Energy of Monovalent Ions

In this lab you will calculate the difference in hydration free energy between chloride ion and bromide ion, as well as other relative free energies involving sodium, potassium, chloride and bromide ions. Two alternate methods, the Zwanzig Free Energy Perturbation (FEP) formula and the Bennett Acceptance Ratio (BAR) method, are used to analyze the MD sampling and determine free energy results.

Protocol

(1) Copy all the files for the lab from the course web site. There should be a **`.xyz`** and **`.key`** file for each of the ions we will consider: Na^+, K^+, Cl^- and Br^-. The **`.xyz`** files contain a single copy of the ion in a cubic box with 214 water molecules. The **`.key`** files define the box size, distance cutoff values for vdw and Ewald summation, and also contain the parameter definitions for the individual ions. In addition, there is a small parameter file (**`tip3p.prm`**) containing the TIP3P water model values.

(2) Using the Tinker **`minimize`** program, perform an energy minimization on each ion-water box to a final RMS gradient convergence value of 1.0 kcal/mol/Ång. It is always a good idea to at least "lightly minimize" a system prior to attempting a molecular dynamics simulation.

(3) Run a short MD simulation on each of the four ion-water systems using the **`dynamic`** program. Suggested simulation parameters might be a trajectory of 100 ps total length with 2.0 fs steps (this would be 50000 total steps). You should save trajectory snapshots every 0.1 ps and use the NVT ensemble with a thermostated target temperature of 298K (typical "room temperature", at least in a warm room!).

(4) The Tinker **`bar`** program will take two trajectory archive files for two different "states", and will attempt to compute the free energy and enthalpy/entropy difference between those states using the original free energy perturbation formula (FEP), as well as the Bennett acceptance ratio method (BAR). Calculation of thermodynamics using **`bar`** involves two stages: (1) producing a summary **`.bar`** file with the energies for both trajectory archives under the control of the force field parameters for both states, and (2) performing the FEP and BAR calculations on the data in the **`.bar`** file.

(5) First, we will use the **`bar`** program and your trajectories from step (3) to estimate the hydration free energy difference between chloride and bromide ion, $\Delta\Delta G$ (Cl^- -> Br^-). Run the program in a terminal window and select option (1) to create a **`.bar`** file using as input the **`.arc`** files from your chloride and bromide MD trajectories and the temperature of 298K. This will make a **`.bar`** file whose base name will be the same as the first archive file you entered. Then rerun the **`bar`** program and select option (2). Give the program the name of the **`.bar`** file you just created, and have it omit the first 10 ps of your 100 ps MD

run by starting at trajectory frame 101 and ending at 1000 (this assumes you ran for 100 ps, saving every 0.1 ps, for each system).

(6) The **`bar`** program will produce various estimates of the free energy, enthalpy and entropy difference between the solvation of chloride and bromide in water. Probably the most trustworthy value is the free energy difference computed via the BAR method.

(7) Now repeat the procedure from the previous steps and use **`bar`** to estimate the free energy difference for the solvation of sodium and potassium ions. This attempted calculation will probably fail. What happened? Why?

(8) In order to determine $\Delta\Delta G$ (Na^+ -> K^+), you will need to create some version of a "hybrid" or "intermediate" ion whose parameters are interpolated between those for sodium ion and potassium ion. Copy the **`sodium.xyz`** and **`sodium.key`** files to some name of your choice (*e.g.*, **`hybrid.xyz`** and **`.key`**). Edit the new **`.key`** file to change the two vdw parameters for sodium ion to values intermediate between those for the sodium and potassium ions. Note the first vdw parameter is the Lennard-Jones ion radius in Angstroms, and the second is the "well depth" in kcal/mol for the ion.

(9) Repeat steps (2) and (3) to produce a 100 ps MD simulation for your fictitious, alchemical "hybrid" ion with the intermediate vdw parameters.

(10) Use the **`bar`** program to find the free energy for converting a sodium ion into your intermediate ion, and then to convert the intermediate ion into a potassium ion. Does this procedure converge for both steps? If not, you will need to create additional intermediate states along the pathway in "vdw parameter space" between sodium to potassium ion. Continue until you are able to calculate a reasonable estimate for the $\Delta\Delta G$ of hydration for the (Na^+ -> K^+) interconversion.

Questions

(1) Look up the "experimental" hydration free energies for each of the ions. These values can be found in most general chemistry textbooks, or via simple web searches. An older, widely cited, compendium of values from Tissandier, *et al*. is provided on the lab web site (**`jpca-102-7787-98.pdf`**, see Table 6), and more recent values are plentiful on the literature and on the internet. How close are your computed free energy differences to the experiment estimates?

(2) How does the BAR algorithm for estimating free energies work, and what is the **`bar`** program is computing? Briefly explain the difference between the FEP and BAR algorithms, and the reason for BAR being generally preferred over FEP. *[Note: Bennett's original BAR paper, and some reviews of free energy methods are in the Reading & References section on the course web site.]*

(3) Do any of the free energy perturbation values (FEP) you computed during this lab exhibit "hysteresis", *i.e.*, cases where the "forward" and "backward" FEP estimates are substantially different? What is the origin of this effect?

(4) What are the computed overall "error bars" for your hydration free energy differences as determined by the Bennett acceptance ratio method? If you have time, run longer MD simulations (maybe 1000 ps = 1 ns) and recalculate the $\Delta\Delta G$ values. Does the error decrease in line with what you would expect with the additional statistical sampling?

(5) The experimental hydration free energies for potassium ion and chloride ion are quite similar. Thus, $\Delta\Delta G$ (K^+ -> Cl^-) should be reasonably close to zero. Try using **`bar`** to estimate this free energy difference directly from your potassium and chloride simulations. Why does this fail, in spite of the fact that the "correct answer" is a very small free energy difference?

(6) In this lab, you have determined *relative* free energy differences. How might you compute the *absolute* hydration free energies for these ions? What additional steps and procedures would be needed to estimate the absolute energies? What is even meant by an *absolute* free energy?