Chemistry 478 — Molecular Modeling

Laboratory #9 — Relative Hydration Free Energy of Monovalent Ions

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

Protocol

(1) Copy 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 molecular dynamics simulation.

(3) Run a short MD simulation on each ion-water system using the **DYNAMIC** program. Suggested simulation parameters might be a 10 ps total length with 2.0 fs steps (this would be 5000 total steps). You should save trajectory snapshots every 0.1 ps and use the NVT ensemble with a thermostated temperature of 298K.

(4) The **BAR** program will take two trajectory archives for two different "states", and will attempt to compute the free energy difference between the states using the original free energy perturbation formula (FEP), as well as Bennett acceptance ration method (BAR). Use this program and your trajectories from (3) to estimate the hydration free energy difference between chloride and bromide ion, $\Delta\Delta G$ (Cl^- -> Br^-).

(5) Now try to use **BAR** to estimate the free energy of solvation difference for the sodium and potassium ions. This will probably "fail". Why?

(6) In order to determine $\Delta\Delta G$ (Na^+ -> K^+), you will need to create some "intermediate" ions whose parameter fall between those for sodium ion and potassium ion. Copy the **sodium.xyz** and **sodium.key** files to some name of your choice (*e.g.*, intermediate1.xyz and .key). Edit the new **.key** file to change the two vdw parameters to values between those for sodium and potassium. 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.

(7) Repeat steps (2) and (3) to produce a short MD simulation for your fictitious intermediate ion.

(8) Run **BAR** to find the free energy to convert sodium ion into your intermediate ion, and then to convert the intermediate ion into potassium ion. Does this procedure converge for both steps? If not, you will need to create further intermediate states along the path in "parameter space" from sodium to potassium ion. Continue until you have a reasonable estimate of $\Delta\Delta G$ (Na^+ -> K^+).

Questions

(1) What is the **BAR** program computing? Briefly explain the difference between the FEP and BAR algorithms, and the reasons for BAR being preferred over FEP. *[Note: Bennett's original BAR paper, and a recent review of free energy methods are in the Reading & References section on the course web site.]*

(2) Look up the "experimental" hydration free energies for each of the ions. These values can be found on the internet, or in most general chemistry textbooks. How close are your free energy differences to experiment?

(3) Do the free energy perturbation values (FEP) you computed exhibit "hysteresis"? What is the origin of this effect?

(4) What is the computed overall "error bars" for your hydration free energy differences as computed with the Bennett acceptance ratio method? If you have time, run longer MD simulations (maybe 100 ps) and compute the $\Delta\Delta G$ values. Does the error decrease in line with what you would expect for such additional 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 small free energy difference?

(6) In this lab, you have computed *relative* free energy differences. How would you compute *absolute* hydration free energies? What additional steps and procedures would be needed to estimate the absolute energies?