Absolute Hydration Free Energies of Ions Under Periodic Boundary Conditions

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The additive empirical force field of a monatomic ion is composed of the charge and the Lennard-Jones (LJ) parameters, *i.e.*, the well-depth parameter, ε, and the distance parameter, R_{min}, at which the potential reaches the minimum.[1] A set of LJ parameters for monocations have been developed by utilizing molecular dynamics simulations under a solvent boundary potential (SBP). A full account of the force field development is in progress and this communication addresses consideration of the air-water phase potential in calculating the absolute free energy of hydration by calculating free energies of hydration, ΔG_{hyd}, in the presence of periodic boundary conditions (PBC).

In brief, ΔG_{hyd} is calculated through the following steps. First, one mole of ideal gas of volume 0.024788 m^3 is confined into the volume of 0.001 m^3 at 298.15 K and 1 bar. The entropic contribution is $\Delta G_1 = -RT \ln(0.001/0.024788) = 7.958$ kJ mol^{-1}, where R is the gas constant and T is the absolute temperature. Second, the van der Waals particle with the LJ parameters R_{min} and $\varepsilon = 0.0$ is inserted at the center of a sphere of radius 1.6 nm that includes 572 TIP3P[2] water molecules equilibrated at 298.15 K and 1 bar under SBP.[3] The hydration free energy, ΔG_2, of the uncharged fictitious atom is calculated by thermodynamic perturbation with the soft core potential[4] where ε is increased to the value of the particle in steps of 41.84 J mol^{-1}. Third, the van der Waals particle of given R_{min} and ε is charged to +1e in 11 steps including 0.05, 0.15, 0.25, 0.35, 0.45, 0.55, 0.65, 0.75, 0.85, 0.95, and 1.0. The charging steps yield the free energy change ΔG_3 by using the weighted histogram analysis method.[5]

Langevin molecular dynamics at constant temperature and pressure is performed for 20 ps per each window with the time step of 1 fs. The last 17.5 ps of each window are used to compute the free energy change. The Langevin friction coefficient is set to 25 ps^{-1} for TIP3P oxygen atoms. The nonbonding cutoff options are electrostatic switching and van der Waals switching functions with cut-on, cut-off, cut-nonbond distances of 1.8, 2.0 and 2.2 nm, respectively. O-H and H-H distances of water are fixed by applying the SHAKE constraint.[6] All calculations were performed with the CHARMM program version c35b1.[7]

The hydration free energies of monovalent cations are obtained as a function of LJ parameters: R_{min}, spanning from 40 pm to 480 pm with the interval of 40 pm and ε spanning from 0.08368 kJ mol^{-1} to 1.00416 kJ mol^{-1} with the interval of 0.08368 kJ mol^{-1}. Interpolation of the LJ parameters tested allows identification of parameters that yield the experi-

mental ΔG_{hyd}. The interpolation procedure does not yield a unique parameter pair but a functional relation between R_{min} and ε, reflecting the parameter correlation problem.[8] To overcome this, based on the ion hydration model of Marcus,[9] ε values are estimated to be most compatible with the CHARMM parameters of sodium and potassium ions, and R_{min} values determined with the Marcus-based ε values. Marcus compiled experimental absolute DG_{hyd}, of selected monovalent cations are listed in Table 1 together with the LJ parameters.

For the monovalent cations listed in Table 1, the ionic solution is constructed with a periodic boundary condition (PBC). The ion is created at the center of the cubic box with the edge of 2.5 nm, which contains 522 TIP3P water molecules equilibrated at 298.15 K and 1 bar. The default nonbond cutoff scheme of the CHARMM force field is utilized: constant dielectric with the electrostatic shifting and the van der Waals switching cutoff functions with cut-on, cut-off and cut-nonbond distances of 1.0, 1.2, and 1.4 nm, respectively. The particle mesh Ewald method treats the long range electrostatic interactions.[10] The same thermodynamic perturbation protocol is employed for coupling the dispersion and charging cycles as in the free energy calculations under SBP.

In Table 1, ΔG_2 is the hydration free energy of the van der Waals atom. It is unfavorable to hydrate large uncharged atoms. The free energy change upon charging to +1e, ΔG_3,

Table 1. Experimental hydration free energies and calculated free energy components of monovalent cations[a]

Ion	ΔG_{hyd}[b]	ε	$R_{min}/2$	ΔG_2[c]	ΔG_3[d]	ΔG_{calc}[e]
Li$^+$	-475	0.1670	107.67	-0.34	-434.65	-475.27
Na$^+$	-365	0.2007	160.76	0.69	-328.51	-368.11
K$^+$	-295	0.3600	198.81	5.57	-265.26	-299.97
Rb$^+$	-275	0.4022	213.15	7.05	-245.94	-279.18
Cs$^+$	-250	0.4910	233.24	11.42	-225.09	-253.95
Cu$^+$	-525	0.1852	86.20	-0.46	-487.89	-528.64
Ag$^+$	-430	0.2870	121.43	-0.20	-392.83	-433.31
Au$^+$	-575	0.3563	63.14	-0.66	-541.41	-582.35
Ti$^+$	-300	0.4067	193.07	5.80	-269.61	-304.10

[a]ΔG's and ε are in kJ mol^{-1} and $R_{min}/2$ is in pm. [b]ΔG_{hyd} is the absolute free energy of hydration compiled by Marcus.[9] [c]ΔG_2 is the hydration free energy of the van der Waals atom. [d]ΔG_3 is the free energy for the charging step from 0.0 e to +1.0 e. [e]$\Delta G_{calc} = \Delta G_1 + \Delta G_2 + \Delta G_3 + F\phi$ is the total free energy of hydration including the entropic contribution, $\Delta G_1 = 7.958$ kJ mol^{-1} and the contribution due to the phase potential −0.500 V of TIP3P water.

dominates the total free energy of hydration. The thermodynamic cycles including the entropic component, $\Delta G_1 + \Delta G_2 + \Delta G_3$, systematically yield less negative free energies of hydration than the experimental values. The difference average is 44.37 kJ mol^{-1} with the standard deviation of 1.85 kJ mol^{-1}.

Accurate calculation of free energies of hydration requires that all the relevant physical phenomena be taken into account. In the experimental regimen an ion is transferred into the bulk water by crossing the air-water interface, which contributes the electrostatic free energy due to the phase potential ϕ. For an ion of valence z, the free energy change is $+zF\phi$, where F is the Faraday constant 96.485 kJ mol^{-1} V^{-1}. The phase potential estimated from the simulation of water-vapor system is -0.500 V for the TIP3P water model.[10] While the SBP does effectively include the phase potential, the thermodynamic perturbation paths under PBC require to include the process of crossing the air-water boundary.

The calculated free energy of hydration $\Delta G_{calc} = \Delta G_1 + \Delta G_2 + \Delta G_3 + F\phi$ is listed in Table 1. While all calculated free energies reproduce the experimental data with less than 2% error, the calculation tends to yield lower free energy of hydration. The deviation is -3.9 kJ mol^{-1} on the average. The phase potential of -0.460 V would give a perfect match with the value expected from simulations under SBP. The discrepancy can be attributed to several aspects of the simulations: the SBP does not fully compensate the air-water boundary potential, the phase potential may be slightly less negative than -0.500 V for the TIP3P water, and/or the particle mesh Ewald treatment of the long range electrostatic interactions is not sufficient for the ionic solution.

In order to obtain the absolute hydration free energy of an ion from molecular dynamics simulations of PBC systems, it is essential to add the free energy change for crossing the air-water boundary against the phase potential. Considering the multitude of simulation protocols and traits, the force field derived from free energy simulations under SBP is viable for molecular systems solvated with TIP3P water under PBC.

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