I. Method

Hydration free energies were computed using explicit-water molecular dynamics simulations and thermodynamic integration (TI) method. Polar and non-polar solvation free energies were computed separately. TI for non-polar hydration free energy was carried out using 15 windows with the coupling parameter, λ = [0.00, 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.50, 0.60, 0.70, 0.80, 0.90, 1.00]. TI for polar hydration free energy was carried out using 11 windows, with the coupling parameter, λ = [0.00, 0.10, 0.20, 0.30, 0.40, 0.50, 0.60, 0.70, 0.80, 0.90, 1.00]. Free-energy differences between successive lambda windows were computed using Bennett Acceptance Ratio (BAR) method.

Molecular dynamics simulations and free-energy analysis were performed using GROMACS simulation package (v. 4.5.5). Each of the structures was first solvated with TIP3P water in a 30Å cubic box. The system was energy minimized using the steepest-descent algorithm, and further equilibrated for 500ps under *NPT* conditions. Temperature was maintained at 300K using the velocity rescaling method, with the time constant set to 0.1 ps. An isotropic pressure of 1 bar was maintained using Berendsen's weak coupling method, with the time constant set to 1.0 ps. Production runs were carried under NPT conditions for a simulation time of 5 ns for each window of TI, and the first 500 ps was considered as equilibration for each window and discarded from free-energy analysis. A 2 fs integration time step with the leap-frog integration algorithm was used in all simulations. Periodic boundary conditions were applied in all three coordinate dimensions. The Particle-Mesh-Ewald (PME) method was used for electrostatic interactions, with a direct space cutoff of 10Å, and cubic interpolation (PME order = 4) for the calculation of long-range interactions in the reciprocal space, with a Fourier transform grid of 1.2Å maximum. Lennard-Jones (LJ) interactions were cut off at 10A. The bond-lengths of water molecules were constrained to their equilibrium lengths with the SHAKE algorithm, allowing for a 2 fs time step.

II. Structures and force-field parameters

Initial structures of all the compounds were obtained from SAMPL4 website. All the force-field parameter were generated from these initial structures. Bonded (bond, angle, and torsion) and van der Waals parameters were assigned according to the GAFF force-field using the TLEAP program in AmberTools package (V. 13). Partial charges were assigned according to the AM1-BCC method, computed using the Antechamber program in AmberTools package (V. 13). Parameter (.prmtop) and coordinate (.inpcrd) files generated by Antechamber were converted to GROMACS format using amb2gmx.pl script (http://ffamber.cnsm.csulb.edu/ffamber-tools.html).