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. The initial geometries were optimized at HF/6-31G* level of quantum-mechanical (QM) theory, using Gaussian G09 software (revision A.1). All the force-field parameters were generated from these optimized geometries. Bonded (bond, angle, and torsion) and van der Waals parameters were assigned according to the GAFF force-field using the TLEAP program in AmberTools (V. 13) package. Partial charges were computed using the Restrained Electrostatic Potential (RESP) method, from electrostatic potentials computed at HF/6-31G* level of QM theory. RESP charges were obtained from the electrostatic potentials using the Antechamber program (AmberTools13). 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).