Supporting Information Available

Effects of Biomolecular Flexibility on Alchemical Calculations of Absolute Binding Free Energies

Supplemental Material

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Supporting Figures

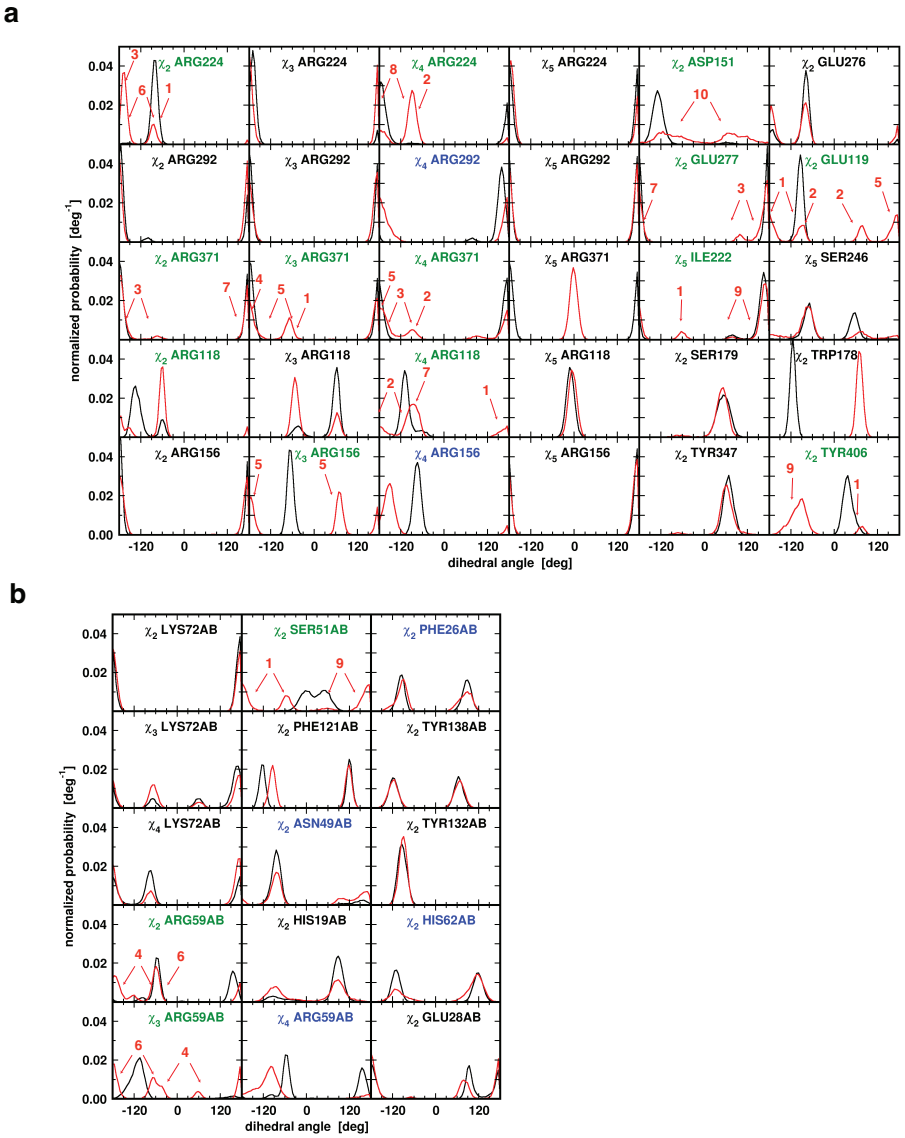

Figure S1: Analysis of torsional angle sampling for (a) N1 and (b) RmlC (both monomers A and B) active site residues during the TI calculations. Normalized probability distributions for the dihedrals monitored throughout all $J = 10$ *long* simulations at $\lambda = 0$ (black) and $\lambda = 1$ (red) are shown. Green residue labels highlight increased flexibility, for residues with additional observed peaks when going from $\lambda = 0$ to $\lambda = 1$. A new configuration is considered visited if the new peak represents at least 3% of the ensemble. For each $\lambda = 1$ peak, the number of trajectories contributing is given. Blue residue labels indicate residues for which a significant (>20°) peak shift occured at $\lambda = 1$.

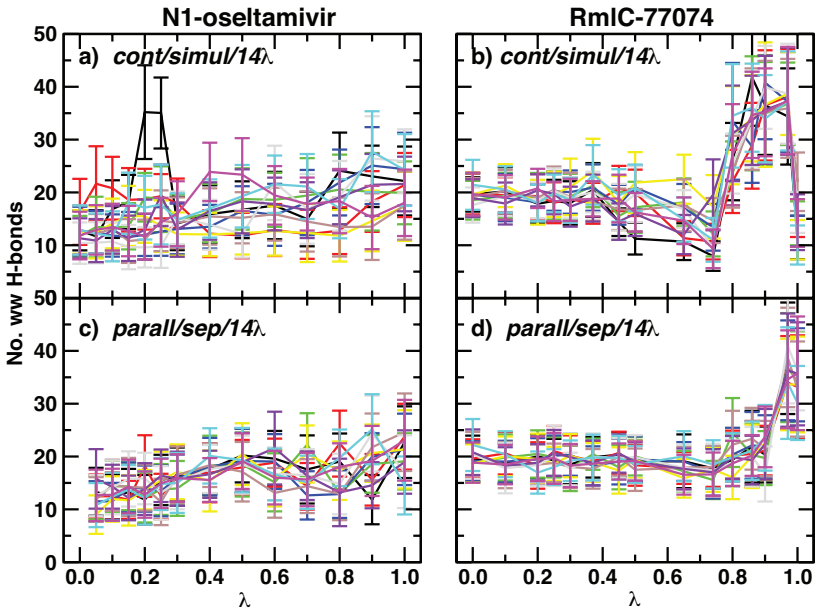

Figure S2: N1 and RmlC active site hydration behavior for varied IT-TI protocols. The average and standard deviation for water-water hydrogen bonds within a 5 Å radius around the ligand for N1 (a, c) and RmlC (b, d) is shown for the protocols labeled as in Table 1.

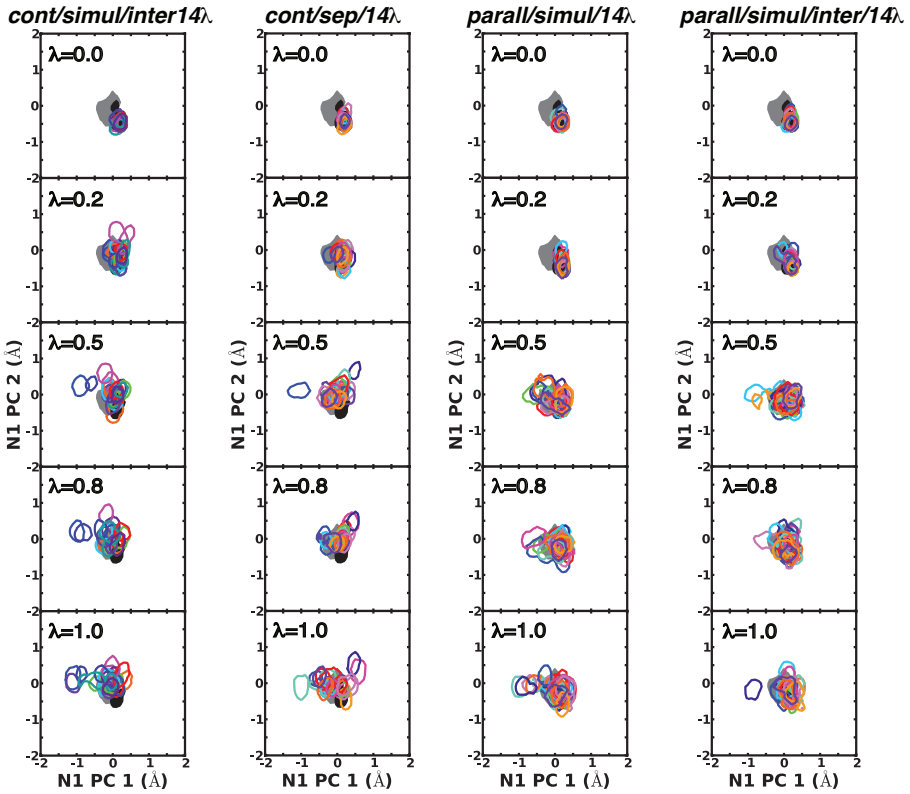

Figure S3: Receptor flexibility as captured by 2 dominant principal components (PC) of active site residue fluctuations from varied *medium* IT-TI protocols for N1. Protocols are labeled as in Table 1 and the free energy results are summarized in Table 2. See Figure 3 for color coding.