



**Table S1. Acceptance ratios of the replicate simulations at different NCMC step amounts for the MUP-1 system.** Each simulation was run for 10,000 BLUES iterations. The number of NCMC steps were varied from 1,250 to 30,000 steps and the number of MD steps was 1,000 steps in all cases

<i>n</i> NCMC steps	Replicate 1	Replicate 2	Replicate 3	Replicate 4	Replicate 5	Replicate 6	Replicate 7	Replicate 8	Replicate 9	Replicate 10	Replicate 11	Replicate 12
1,250	0.001	0.002	0.001	0.001	0.002	0.001	0.001	0.001	0.001	0.002		
2,500	0.004	0.004	0.002	0.002	0.005	0.003	0.003	0.004	0.004	0.003	0.003	
5,000	0.011	0.012	0.009	0.010	0.011	0.010	0.012	0.010	0.011	0.012		
7,500	0.016	0.028	0.020	0.018	0.012	0.024	0.028	0.032	0.032	0.024	0.028	0.012
10,000	0.036	0.028	0.008	0.036	0.020	0.020	0.016	0.036	0.024	0.028	0.028	
15,000	0.012	0.040	0.020	0.048	0.044	0.016	0.028	0.032	0.036	0.040		
20,000	0.028	0.040	0.030	0.024	0.044	0.044	0.020	0.016	0.036	0.044	0.032	0.024
30,000	0.036	0.036	0.032	0.020	0.032	0.036	0.016	0.016	0.028	0.024	0.036	0.024

**Table S2. Acceptance ratios of all attempted moves for each replicate simulation of the HSP90 protein-ligand system.** Shown is the acceptance ratio for four replicate simulations. It took an average of 1693 BLUES iterations to hydrate the cavity.

<i>n</i> NCMC steps	Replicate 1	Replicate 2	Replicate 3	Replicate 4
2,500	0.004	0.002	0.002	0.002

**Table S3. Shown here are the average acceptance rate of all BLUES moves, the average number of force evaluations across 4 replicates for the buried cavity in the HSP90 system to become hydrated, and the average wallclock time in hours for BLUES to hydrate HSP90.** It took an average of 1693 BLUES iterations to hydrate the HSP90 cavity, and each BLUES iteration consisted of a single NCMC move (consisting of 2,500 NCMC steps) and 1,000 MD steps.}

<i>n</i> NCMC steps	Average acceptance rate of all BLUES moves	Average number of force evaluations to hydrate the HSP90 cavity	Average wallclock time to hydrate the HSP90 cavity
2,500	0.2%	$5.9 \times 10^6$	31 hours