Supplementary Information

Convergence Criteria for Single-step Free-energy Calculations: The Relation between the Π Bias Measure and the Sample Variance

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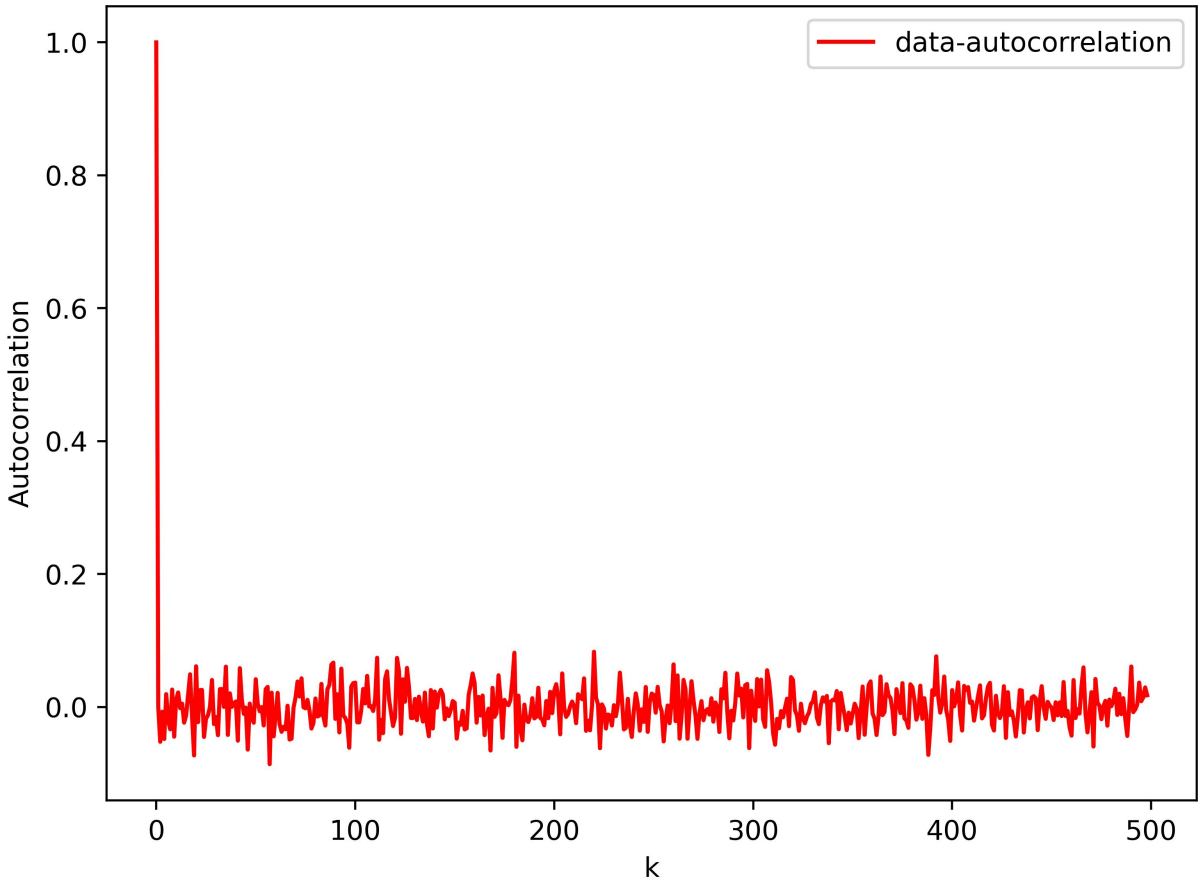

Figure S1: Autocorrelation of random numbers.

Table S1: The minimum sampling size required to reach $\Pi \geq 0.5$ for different values of $\sigma_{\Delta U}$, assuming a Gaussian distribution.

$\sigma_{\Delta U}$	N_{min}
0.50	10
0.75	22
1.00	60
1.25	192
1.50	719
1.75	3166
2.00	16398
2.25	100118
2.50	721964
2.75	6158734
3.00	62227738

Table S2: Average values of Π, w_{max}, and $\Delta\Delta G_{\mathrm{CA}}$ for simulations of Gaussian distributions with a varying $\sigma_{\Delta U}$ and 200 samples. 100 simulations were performed to obtain uncertainties of all values, presented as standard deviations over these simulations (thus, the standard errors are 10 times smaller).

$\sigma_{\Delta U}$	Π_{Av}	w_{max}	$\Delta\Delta G_{\mathrm{CA}}$
0.50	1.78±0.00	0.04±0.00	0.00±0.00
0.75	1.36±0.00	0.08±0.00	0.00±0.00
1.00	0.96±0.00	0.14±0.00	0.01±0.00
1.25	0.57±0.00	0.22±0.00	0.05±0.01

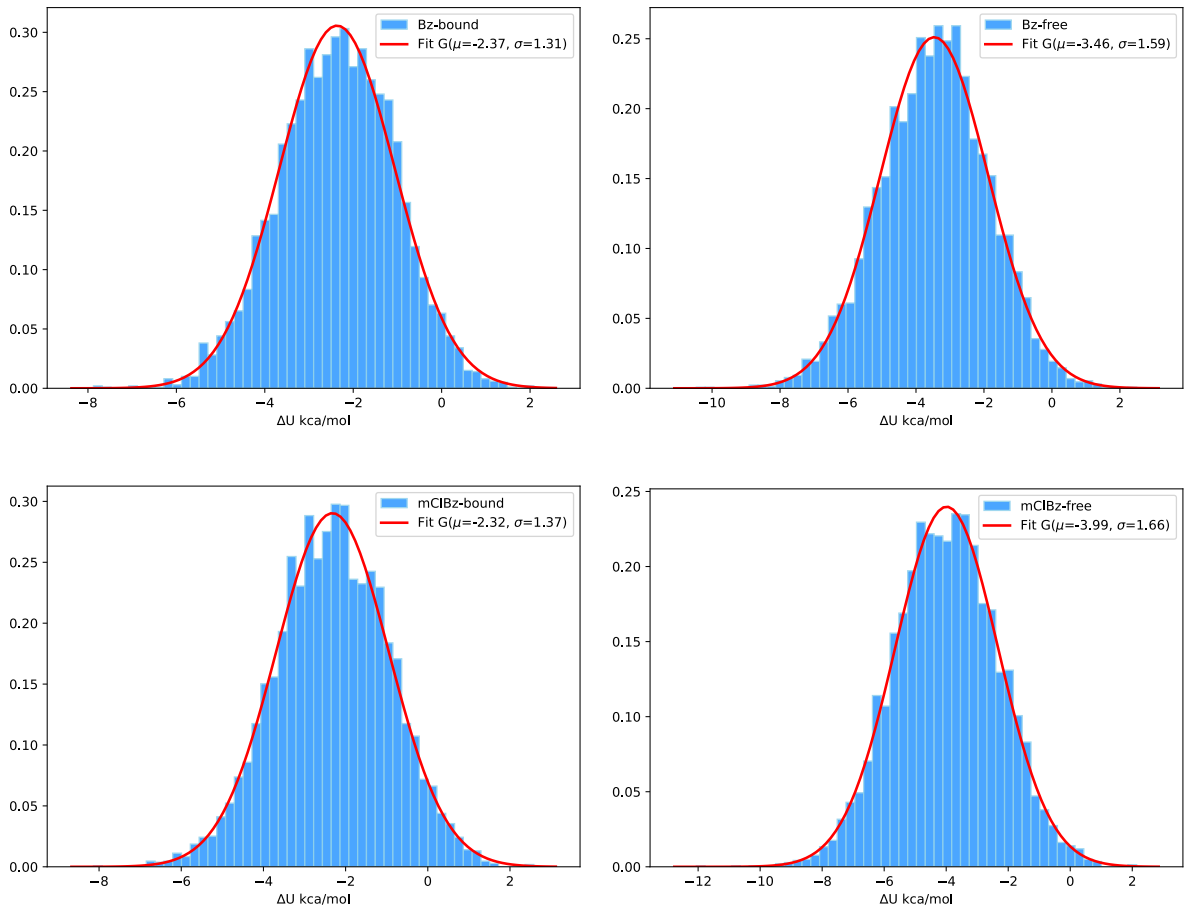

Figure S2: Distributions of ΔU for Bz and mClBz when bound or not bound to the octa-acid deep-cavity host, together with Gaussian fits.