Supporting Information for: "Empirical Optimization of Interactions between Proteins and Chemical Denaturants in Molecular Simulations"

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1. Supporting methods.

Activity coefficient

We reported the same derivative of the activity coefficient as shown in Weerasinghe and Smith [1], which is defined as

$$a_{uu} = (\frac{\partial \ln a_u}{\partial \ln c_u})_{p,T} = \frac{1}{1 + c_u(G_{uu} - G_{uw})} \tag{S1}$$

where G_{uu} and G_{uw} are the KB integrals between denaturant and denaturant, and between denaturant and water, and a_u is the activity coefficient of the denaturant. Therefore a_{uu} can be calculated from KB integrals from radial distribution functions in the simulations.

In experiment, activity coefficient can be related to the osmotic coefficient data using partial molar Gibbs excess energy:

$$\bar{G}_{ex} = -\phi RT M_w \nu m_u = RT \ln a_w \tag{S2}$$

where M_w is the molar mass of water, m_u molality of denaturant, ν van't Hoff factor related to number of ions per molecule of solute, and the a_w activity coefficient of water. The activity coefficient of water is related to the activity coefficient of denaturant a_u that we are interested in through Gibbs-Duhem equation:

$$x_w d \ln a_w + \nu x_u d \ln a_u = 0 \tag{S3}$$

assuming different types of ions (i.e. Gdm^+ and Cl^-) have the same activity coefficient. Since most osmotic coefficient data were measured in molality scale, we calculated the molality activity coefficient γ first defined as:

$$\gamma = a_u / m_u. \tag{S4}$$

Together with Eqs. S2 and S3, we can calculate molality activity coefficient γ from molality osmotic coefficient ϕ by

$$d \ln \gamma = d\phi + \phi \frac{dm_u}{m_u} - \frac{dm_u}{m_u} \tag{S5}$$

via numerical integration, in which m_u is the molality of denaturant. We showed a_{uu} as a function of molar concentration in Figure S7. Of the three independent osmotic coefficient data sets for urea [2, 3, 4] we found, the resulting activity coefficients were almost identical.

Partial molar volume

In simulations, partial molar volumes were calculated from KB integral through

$$\bar{V}_w = \frac{1 + c_u(G_{uu} - G_{uw})}{\eta} \tag{S6}$$

$$\bar{V}_u = \frac{1 + c_w(G_{ww} - G_{uw})}{\eta} \tag{S7}$$

$$\eta = c_w + c_u + c_w c_u (G_{ww} + G_{uu} - 2G_{uw}) \tag{S8}$$

which are the same as used in KBFF paper[1]. In experiment, partial molar volumes were calculated from the densities and concentrations of the denaturants, following Eq. 2 and 3 shown in Gucker's work [5].

2. Supporting tables.

Table S1. FRET efficiency of Csp-M34 in different urea concentrations from two independent experimental measurements.

[Urea] (M)	Expt 1	Expt 2
0.33	0.797	0.805
0.37	0.794	0.802
0.55	0.786	0.794
0.70	0.778	0.786
0.93	0.770	0.779
1.00	0.766	0.774
1.22	0.759	0.768
1.38	0.753	0.761
1.63	0.744	0.754
1.89	0.734	0.744
2.39	0.718	0.726
2.86	0.705	0.715
3.26	0.696	0.706
3.75	0.683	0.693
4.38	0.669	0.679
4.89	0.656	0.666
5.90	0.635	0.646
6.84	0.617	0.629
7.70	0.601	0.611
8.98	0.576	0.587

TABLE S2. FRET efficiency of Csp-M34 in different GdmCl concentrations from two independent experimental measurements.

[GdmCl] (M)	Expt 1	Expt 2
0.017	0.804	0.812
0.051	0.805	0.813
0.16	0.803	0.811
0.23	0.794	0.801
0.57	0.766	0.775
0.98	0.743	0.752
1.01	0.741	0.750
1.46	0.713	0.722
1.96	0.693	0.702
2.41	0.673	0.683
2.87	0.657	0.667
3.36	0.636	0.647
3.83	0.624	0.635
4.76	0.595	0.606
5.64	0.569	0.581
6.69	0.543	0.554
7.20	0.528	0.540
7.21	0.524	0.536

3. Supporting figures.

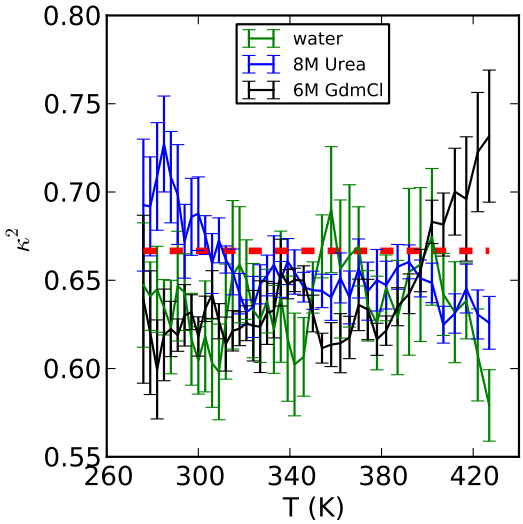

Figure S1. Static orientation factor κ^2 for the dyes in Csp-M34 in different solvent conditions. Red dashed line shows the expected value when the dyes have no orientation preference.

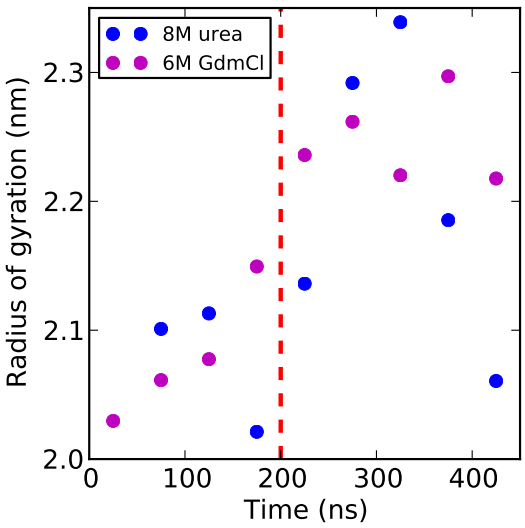

FIGURE S2. Time window average of radius of gyration for the Csp-M34 in 8M urea and 6M GdmCl with Amber ff03ws·KBFFs. The window size is 50 ns, and the data is plotted at the center of the window. The red dashed line shows the starting time of productive simulations.

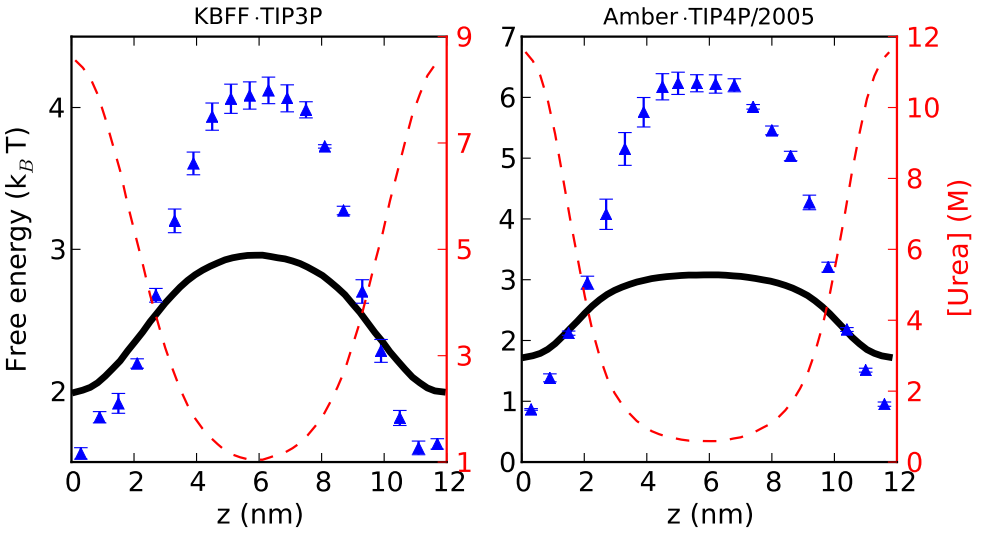

FIGURE S3. Transfer free energy of Gly_4 from water to urea solutions, for additional combinations of denaturant and water models. Left: KBFF·TIP3P; Right: Amber·TIP4P/2005. Red curves represent the urea concentration profile; black curves represent the free energy of the protein solute $F(z)$ expected from experimental transfer free energies given this concentration profile; and blue symbols represent the observed free energy $F(z)$ for the solute from the force field model. In both cases, the transfer free energy from water to urea is too favourable.

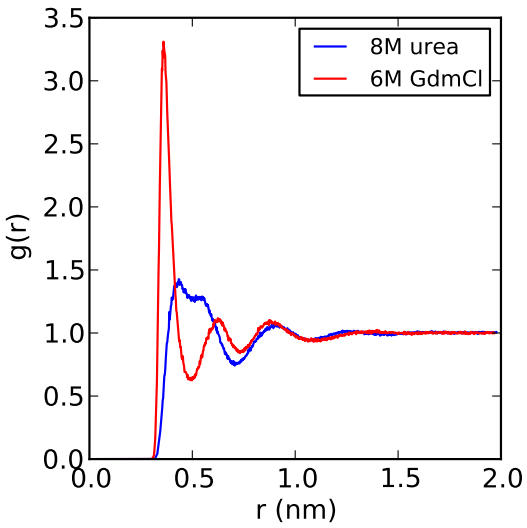

FIGURE S4. Radial distribution function between the tryptophan side-chain of $C(AGQ)_nW$ and urea molecules in 8M urea (blue) and guanidinium ions in 6M GdmCl (red). Center of mass is used for the distance calculation between different groups. The force field is Amber ff03ws·KBFFs.

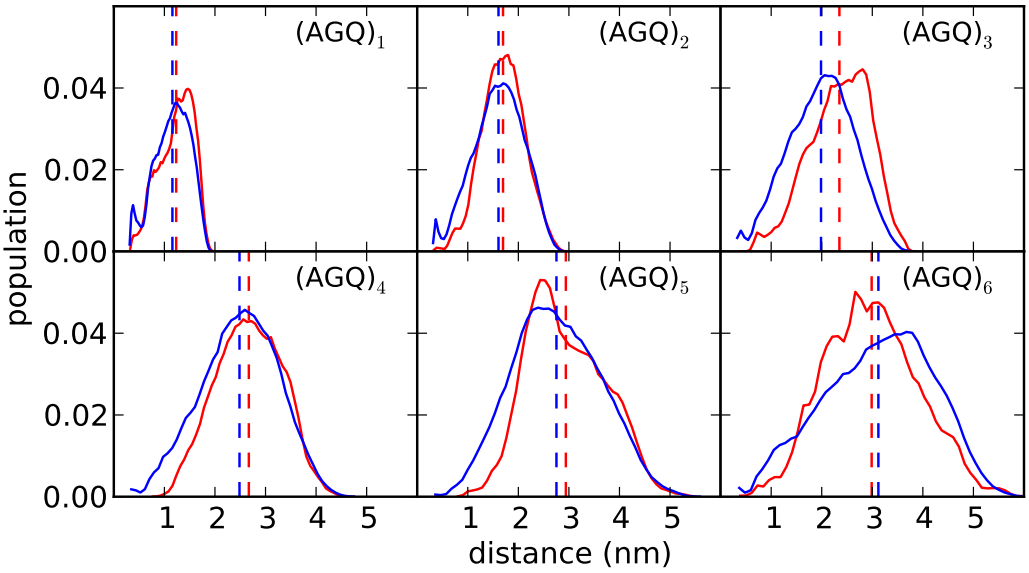

FIGURE S5. The distribution of minimum distances between the sulfur in the cysteine side-chain and the heavy atoms of the tryptophan indole ring system in C(AGQ)$_n$W in 8M urea (blue) and 6M GdmCl (red). The force field is Amber ff03ws·KBFFs. Dash lines show the average value of the minimum distance mentioned above.

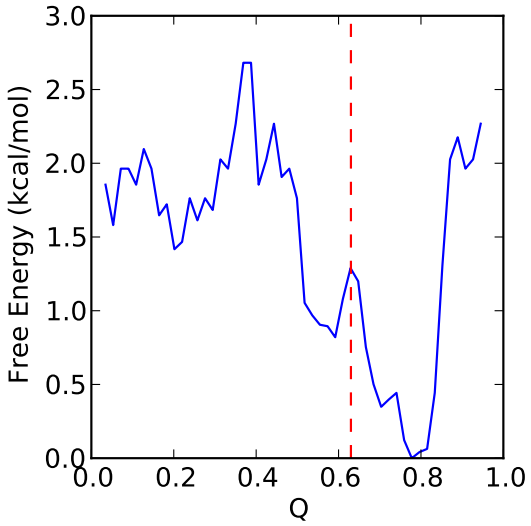

FIGURE S6. Free energy of the Trp cage mini protein along fraction of native contacts Q. $Q = 0.63$ is shown by the vertical red line and is used as the criterion to define the folded and unfolded states.

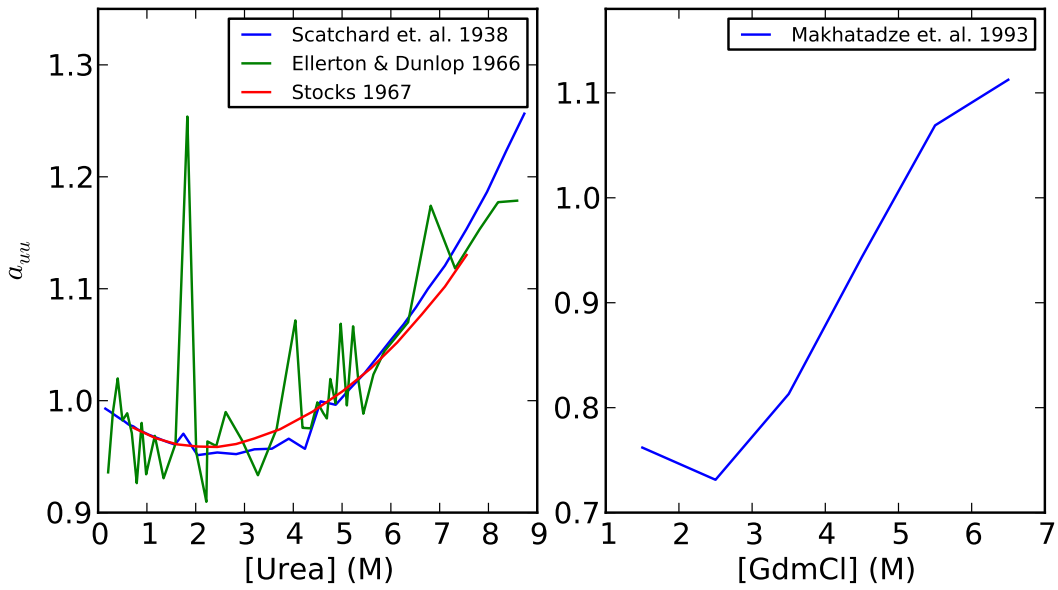

FIGURE S7. Derivative of the activity coefficient a_{uu} for urea (left) and GdmCl (right). The urea experimental data are from references [2, 3, 4] and the GdmCl experimental data are from reference [6].

References

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