

When Does TMAO Fold a Polymer Chain and Urea Unfold It?

Supporting Information

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Effect of the polymer bead parameter ϵ_b on the polymer conformational equilibrium

To investigate how variations of the polymer bead parameter ϵ_b affect its behavior in the various solutions we repeated our simulations using 3 other values of ϵ_b (0.4, 0.6 and 0.8 kJ/mol). Note that the lower the value of this energy parameter the more hydrophobic is the chain. Results are presented in Figure S1.

In pure water the unfolded state gets stabilized relative to the collapsed state as ϵ_b decreases (that is $\Delta G_{F \rightarrow U}$ gets less positive) as ϵ_b decreases. When changing the ϵ_b parameter, there is a competition between two opposite effects: first, as ϵ_b decreases this will decrease the interaction between beads and water molecules, thereby increasing the hydrophobic character of the chain and driving the polymer towards toward collapsed configurations. However at the same time, the intramolecular interactions will decrease, which would favor more extended states. Our results

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suggest that this later contribution dominates. In 1 M TMAO solution we observe that the protective effect is very sensitive to variations in ϵ_b : indeed the protecting role evidenced above at $\epsilon_b = 1$ kJ/mol is moderate to almost nonexistent when the chain is really hydrophobic (low values of $\epsilon_b = 0.4$ and 0.6 kJ/mol), in agreement with a previous study:¹ the osmolyte effect becomes more prominent only for $\epsilon_b = 0.8$ and 1.0 kJ/mol. In strong contrast with TMAO and in agreement with a previous study,² urea still readily denatures hydrophobic polymers at small $\epsilon_b = 0.4$ kJ/mol yet its denaturing effect becomes more prominent as ϵ_b increases.

Effect of a different forcefield for TMAO on the free energy profile

The force-field we have employed throughout our entire study for TMAO (known as “Kast model”)³ has also been recently modified by Garcia and coworkers⁴ and a new forcefield, termed the ‘osmotic model’ has also been proposed by them. We repeated our umbrella sampling simulations for free energy profile at 1 M using this modified version of this force-field. As shown in the Figure S2, its effect on the polymer chain is similar to that obtained from the original “Kast model” of TMAO .

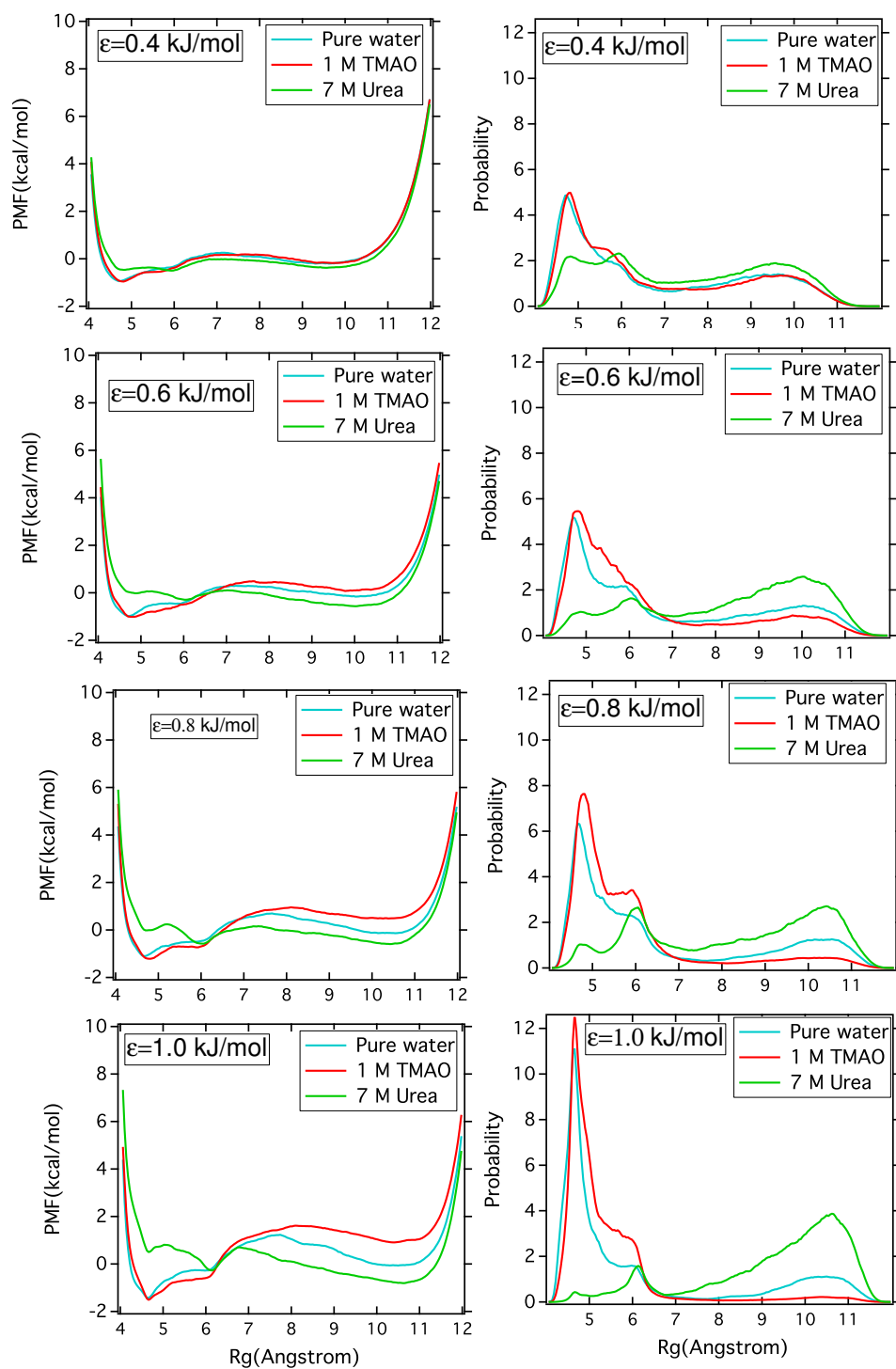


Figure S1: PMFs along the radius of gyration (left) and the corresponding probability distributions (right) for four different polymer dispersion interactions ($\epsilon = 0.4$ kJ/mol, 0.6 kJ/mol, 0.8 kJ/mol and 1.0 kJ/mol) in three aqueous solutions (water, blue; TMAO, red and urea, green). The PMFs $W(R_g)$ are normalized so that $\int_0^\infty \exp(-W(r)/k_B T) dr = 1$

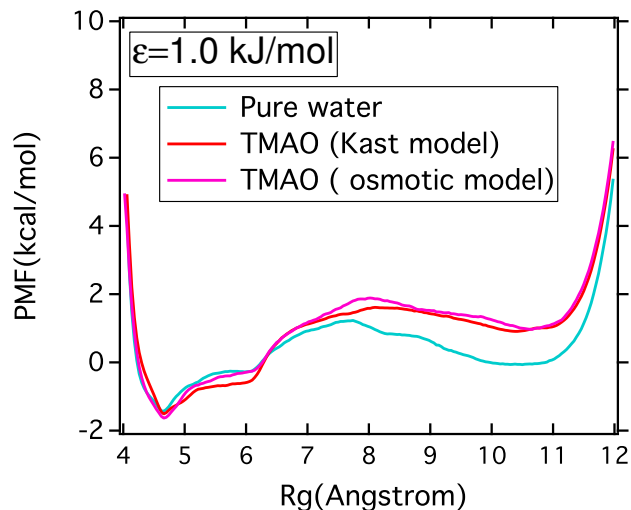


Figure S2: Effect of different TMAO forcefields on free energy profile of polymeric chain in 1 M TMAO. ‘Osmotic model’ is the modified version of TMAO forcefield as proposed by Garcia and co-workers and ‘Kast model’ is the original TMAO forcefield (used in the rest of the current study). We also show the free energy profile of the polymeric chain in pure water.

Effect of a different water model on the free energy profile

All the results reported in the main article were obtained using the SPC/E water model.⁵ However, for the purpose of testing the robustness of our results with respect to the different water models, we have repeated our computation of free energy profiles using a different water model, namely TIP4P water,⁶ mainly because it was used in our previous work on urea.² Figure S3 compares the effect of the two different water models on the free energy profiles of the polymeric chain ($\epsilon_b = 1.0$ kJ/mol) in different osmolyte solutions. The common trend prevalent in all free energy profiles corresponding to TIP4P water model is that the free energy barrier $\Delta G_{F \rightarrow U}^\ddagger$ for the transformation from the compact to the extended state in pure water and in 1 M TMAO are respectively higher for TIP4P water than for SPC/E water. For 7 M urea, the extent of free energy of stabilization of extended conformations is negligibly more favorable in SPC/E water than in TIP4P water. But, interestingly, the relative free energy difference $\Delta \Delta G_{F \rightarrow U}$ of the chain in going from pure water to 1 M TMAO solution or 7 M urea solution is almost the same for both SPC/E and TIP4P water models.

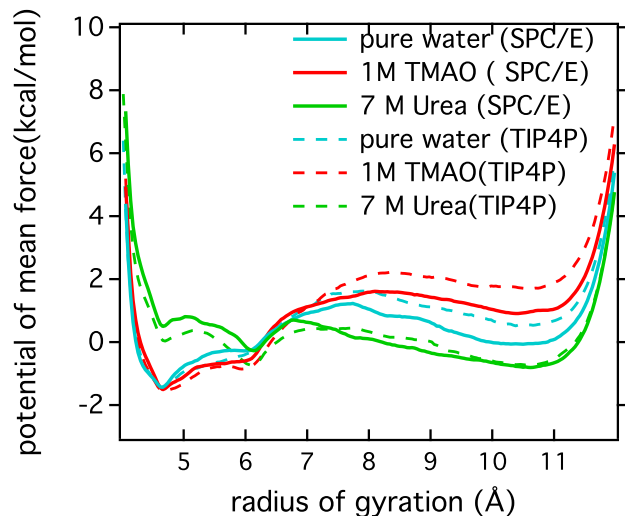


Figure S3: Comparison of different free energy profiles of polymer chain ($\epsilon_b = 1.0$ kJ/mol) obtained using SPC/E water model (solid lines) with that obtained from TIP4P water model (dashed lines).

Thermodynamic integration

As detailed in the Methods section, we performed free-energy perturbation calculations to estimate the cost of inserting water or cosolvent molecules at different positions in the polymer hydration shell, or in the bulk. The interactions of the molecule being inserted were slowly turned on in two stages: in the first stage only the van der Waals interactions were turned on, and in the second stage the electrostatic interactions were turned on. Thermodynamic integration thus yields two contributions to the transfer free energy. In Figure S4, we present results of thermodynamic integration for the two stages and compare insertion of a single TMAO at a given position in the bulk, in the hydration shell of the polymer in a collapsed configuration, and in the hydration shell of the polymer in an extended configuration. The thermodynamic data confirms that van der Waals contribution to the free energy of inserting a single TMAO is more favorable near a collapsed conformation than near an extended conformation, and it more than compensates the favorable electrostatic contribution near an extended conformation than that near the collapsed conformation. In Figure S5, we present the same data for inserting a single urea molecule in the urea solution, where the reverse trend is observed: the more favorable electrostatic contribution to the free energy of inserting a

single urea near the extended conformation overcomes the favorable van der Waals contribution to free energy of inserting a single urea near the collapsed conformation.

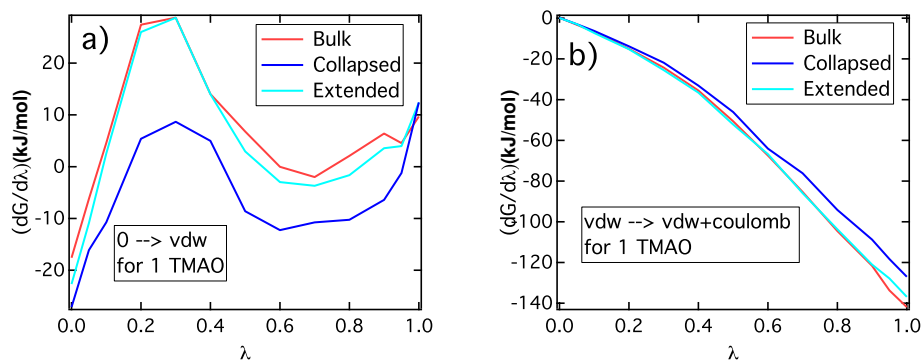


Figure S4: Comparison of thermodynamic integration profile of turning on a) the van der Waals interactions and then b) the electrostatic interaction of a single TMAO molecule near the polymer for different polymer conformations in 1 M TMAO solution.

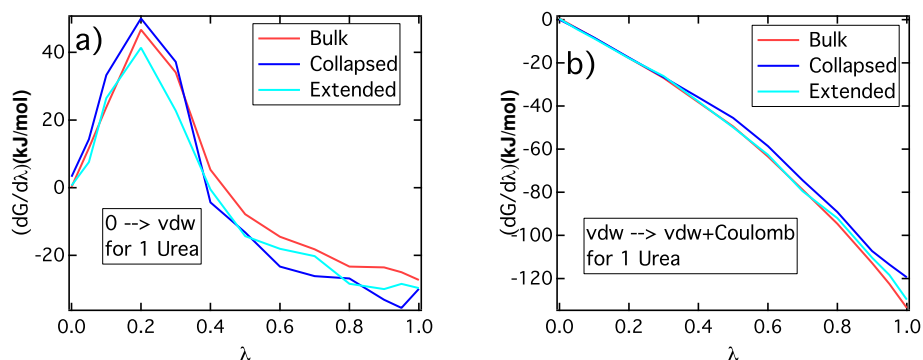


Figure S5: Comparison of thermodynamic integration profile of turning on a) the van der Waals interactions and b) the electrostatic interactions of a single urea molecule near the polymer for different polymer conformations in 7 M urea solutions.

Energy distribution in the polymer first hydration shell

Table S1 provides details on the respective net average energies and the individual van der Waals and electrostatic contributions to these energies for a single cosolute molecules (TMAO and urea). The observed trends in the average energy analysis are consistent with that found from the FEP study — TMAO interacts preferentially with the polymer collapsed state because of the favorable LJ contribution. In contrast, a slight stabilization of urea in the extended polymer hydration shell with respect to the collapsed state is found to be driven by the electrostatic contribution.

Table S1: Different average energy contributions (in units of kcal/mol) of single cosolute molecules in the first solvation shell of the polymer in 1 M TMAO and 7 M urea. ΔE^{bulk} represents the difference with respect to the bulk solution. Standard deviations are given within parentheses.

System	E_{vdw}	$E_{coulomb}$	E_{total}	ΔE^{bulk}
TMAO				
bulk	-3.824(2.22)	-29.510(4.71)	-33.334(3.82)	0
collapsed	-5.853(2.62)	-27.985(4.90)	-33.838(3.93)	-0.504
extended	-5.404(2.41)	-28.231(4.83)	-33.635(3.89)	-0.301
urea				
bulk	-5.079(2.55)	-28.234(5.16)	-33.313(4.21)	0
collapsed	-8.451(2.54)	-26.329(4.90)	-34.780(3.98)	-1.467
extended	-8.002(2.61)	-26.993(4.89)	-34.995(3.99)	-1.682

Decomposition of the solvent contributions to polymer collapse

In the pure solvent as well as in a mixture of water and a cosolute (TMAO or urea), the contribution of the species k to the free-energy difference between the collapsed and the extended state can be expressed as

$$\Delta G_k^{C-E} = N_k^E \mu_k^E - N_k^C \mu_k^C \quad (1)$$

where N_k^C (respectively N_k^E) is the number of solvent molecules of type k in the first hydration shell of the polymer in a collapsed (respect. extended) configuration, and μ_k^C (respect. μ_k^E) their associated chemical potentials. We can define the relative changes for both quantities as $N_k^E = N_k^C + \delta N_k$ and $\mu_k^E = \mu_k^C + \delta \mu_k$. Substituting N_k^E and μ_k^E in Eq. 1 leads after simplification to

$$\Delta G_k^{C-E} = N_k^C \delta \mu_k + \mu_k^C \delta N_k + \delta N_k \delta \mu_k \quad (2)$$

The first term on the right hand side of Eq. 2 represents the contribution of the change in chemical potential, for a fixed number of molecules in the hydration shell; the second term represents the contribution of the change in the hydration number for a fixed chemical potential. The last one is a second-order term, whose contribution is expected to be minor.

Table S2: Different free-energy contributions (in units of kcal/mol) of Eq. 2

Case	$N_k^C \delta \mu_k$	$\mu_k^C \delta N_k$	$\delta N_k \delta \mu_k$	ΔG_k^{C-E}
TMAO	+5.2	-0.2	+0.10	+5.1
urea	-3.5	-4.5	-1.6	-9.6
water (bulk)	+0.8	-6.2	+0.4	-5.0
water (TMAO)	-2.4	-3.1	-1.4	-6.9
water (urea)	-1.1	-1.4	-0.4	-2.9

The different free-energy contributions for each solvent type is given in Table S2. In all cases, the chemical potential of a water or cosolute (TMAO and urea) molecule in the hydration shell is lower than in bulk, so that $\mu_k^C \delta N_k$ is negative. This represents the main contribution to the free-energy difference induced by water (in all solutions) and urea, showing that the large change in the

hydration number is responsible for the increased solvent-induced stability of the unfolded state over the collapsed one. The situation is markedly different for TMAO. The large change in μ_s when going from collapsed to extended is bringing a large $\delta N_s \delta \mu_s$ contribution, which is positive and not totally compensated by the $\mu_s^C \delta N_s$ term (the $\delta N_s \delta \mu_s$ term brings an additional positive contribution). Therefore the total free-energy difference is positive, in strong contrast with what is observed for urea and water.

The above decomposition also suggests that an osmolyte's behavior cannot be predicted from the sign of $\delta \mu_s$ alone. Indeed the main δN_s contribution (which is equal to $\mu_s^C \delta N_s$) can overcome that of $\delta \mu_s$ if the following criteria are met: (i) the stabilization in the polymer hydration shell with respect to the bulk is large, but the variation between the collapsed and the extended state is small ($\mu_s \ll 0$ and $\delta \mu_s \approx 0$); (ii) the osmolyte can accumulate in the hydration shell, i.e. δN_s is largely positive. In other words, this situation can arise if the relative variations of the hydration number when going from collapsed to extended conformations are larger than that of the associated chemical potentials, even if the cosolute molecules are more stable around the collapsed conformations.

References

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