SUPPLEMENTARY MATERIAL
Interactions of a DNA G-quadruplex with TMAO and Urea: A Molecular Dynamics Study on Co-Solute Compensation Mechanisms

Ewa Anna Oprzeska-Zingrebe and Jens Smiatek*

November 18, 2020

1 Details of the simulated systems

Concentrations of co-solutes	**Nr of TMAO molecules**	**Nr of urea molecules**	**Nr of water molecules**	**Length of the simulation box [nm]**
pure water	0	0	46360	11.21747
pure water (vdW)	0	0	46360	11.22607
1M TMAO	853	0	41565	11.04971
1M TMAO (vdW)	853	0	41565	11.04472
2M urea	0	1707	40430	11.08887
2M urea (vdW)	0	1707	40430	11.08320
1M TMAO + 2M urea	853	1707	35764	10.93209
1M TMAO + 2M urea (vdW)	853	1707	35764	10.91885

Table 1: Details of the simulated systems. Label 'vdW' refers to the systems for which the correction of Lennard-Jones parameters according to Ref. [1] was applied.

2 Lennard-Jones parameters and partial charges of atoms

	atom	σ (nm)	ϵ (kJ/mol)	charge (e)
water (TIP3P)	O	0.3151	0.6364	-0.834
	H	0.0000	0.0000	+0.417
urea (KBFF)	C	0.3770	0.4170	+0.921
	O	0.3100	0.5600	-0.675
	N	0.3110	0.5000	-0.693
	H	0.1580	0.0880	+0.285
TMAO (Garcia)	C	0.3041	0.2826	-0.260
	O	0.3266	0.6379	-0.815
	N	0.2926	0.8360	+0.605
	H	0.1775	0.0773	+0.110

Table 2: Lennard-Jones parameters and charges in the models of urea, TMAO and water.

*Institute for Computational Physics, University of Stuttgart, Allmandring 3, D-70569 Stuttgart, Germany. Email: smiatek@icp.uni-stuttgart.de

3 Electrostatic and Lennard-Jones interaction energies between DNA, TMAO, urea and water in the systems simulated with ParmBSC1 (top) and ParmBSC1 with vdW correction (bottom) force fields

System	Coulomb-SR DNA-TMAO [kcal/mol]	LJ-SR DNA-TMAO [kcal/mol]	Coulomb-SR DNA-urea [kcal/mol]	LJ-SR DNA-urea [kcal/mol]	Coulomb-SR DNA-water [kcal/mol]	LJ-SR DNA-water [kcal/mol]
pure water	-	-	-	-	-1756.31	-78.20
1M TMAO	-20.32	-19.61	-	-	-1696.96	-58.15
2M urea	-	-	-101.66	-97.96	-1580.46	-29.49
1M TMAO + 2M urea	-18.09	-16.34	-116.20	-112.43	-1535.17	-28.37

Table 3: Electrostatic and Lennard-Jones interaction energies between DNA and other components of the solution.

System	Coulomb-SR DNA-TMAO [kcal/mol]	LJ-SR DNA-TMAO [kcal/mol]	Coulomb-SR DNA-urea [kcal/mol]	LJ-SR DNA-urea [kcal/mol]	Coulomb-SR DNA-water [kcal/mol]	LJ-SR DNA-water [kcal/mol]
pure water (vdW)	-	-	-	-	-1760.44	-65.95
1M TMAO (vdW)	-19.77	-21.50	-	-	-1750.91	-62.78
2M urea (vdW)	-	-	-97.72	-94.41	-1594.26	-32.98
1M TMAO + 2M urea (vdW)	-18.06	-17.23	-117.03	-117.44	-1621.63	-32.45

Table 4: Electrostatic and Lennard-Jones interaction energies between DNA and other components of the solution in the systems simulated with ParmBSC1 (vdW) force field.

4 Electrostatic and Lennard-Jones interaction energies between TMAO, urea and water in the systems simulated with ParmBSC1 (top) and ParmBSC1 with vdW correction (bottom) force fields

System	Coulomb-SR TMAO-urea [kcal/mol]	Coulomb-SR TMAO-water [kcal/mol]	Coulomb-SR urea-water [kcal/mol]	Coulomb-SR water-water [kcal/mol]
pure water	-	-	-	-5.12e+05
1M TMAO	-	-29776.82	-	-4.47e+05
2M urea	-	-	-32740.02	-4.30e+05
1M TMAO + 2M urea	-715.65	-28662.36	-31555.79	-3.67e+05
System	**LJ-SR TMAO-urea [kcal/mol]**	**LJ-SR TMAO-water [kcal/mol]**	**LJ-SR urea-water [kcal/mol]**	**LJ-SR water-water [kcal/mol]**
pure water	-	-	-	71540.74
1M TMAO	-	-905.53	-	64493.19
2M urea	-	-	-4271.56	62384.95
1M TMAO + 2M urea	-819.75	-509.86	-3781.60	55243.49

Table 5: Electrostatic and Lennard-Jones interaction energies between the components of the solution in simulated systems.

System	Coulomb-SR TMAO-urea [kcal/mol]	Coulomb-SR TMAO-water [kcal/mol]	Coulomb-SR urea-water [kcal/mol]	Coulomb-SR water-water [kcal/mol]
pure water (vdW)	-	-	-	-5.12e+05
1M TMAO (vdW)	-	-29402.63	-	-4.47e+05
2M urea (vdW)	-	-	-32722.34	-4.30e+05
1M TMAO + 2M urea (vdW)	-715.87	-28654.24	-31521.86	-3.67e+05
System	**LJ-SR TMAO-urea [kcal/mol]**	**LJ-SR TMAO-water [kcal/mol]**	**LJ-SR urea-water [kcal/mol]**	**LJ-SR water-water [kcal/mol]**
pure water (vdW)	-	-	-	71536.44
1M TMAO (vdW)	-	-920.10	-	64529.51
2M urea (vdW)	-	-	-4276.56	62391.64
1M TMAO + 2M urea (vdW)	-821.04	-511.62	-3786.33	55218.16

Table 6: Electrostatic and Lennard-Jones interaction energies between the components of the solution in systems simulated in ParmBSC1 (vdW) force field.

The cross-interaction energies between TMAO, urea and water are much higher than the interaction energies of either of them with DNA, and count up to four orders of magnitude. Moreover, electrostatic energies for TMAO-urea interactions are roughly two orders of magnitude lower than the energies between either TMAO or urea and water. This corresponds to our earlier observations from hydrogen bond analysis, indicating that both co-solutes do not interact with themselves. A more elaborate analysis of TMAO, urea and water cross-interactions can be found in Ref. [2].

5 Number of hydrogen bonds between TMAO, urea and water

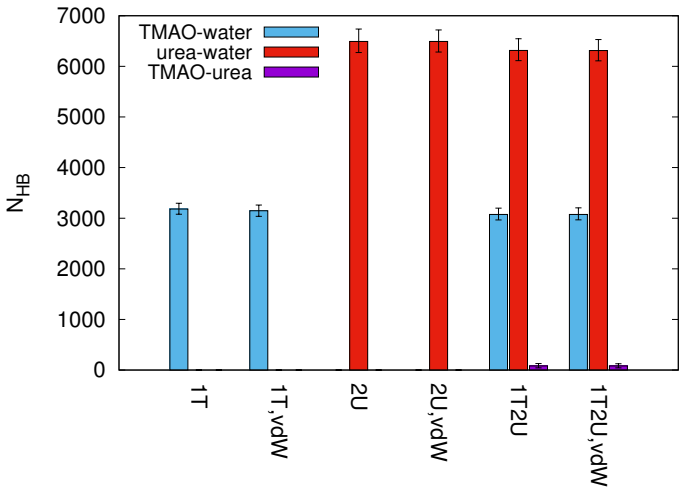

Figure 1: Number of hydrogen bonds between co-solutes and water and co-solutes themselves for the simulations in unmodified and vdW-modified force field. Definitions of short-hand notations are given in Table 1 in the main text.

System	N_{HB} TMAO-water	N_{HB} urea-water	N_{HB} TMAO-urea
1T	3181.655	0	0
1T,vdW	3147.033	0	0
2U	0	6492.919	0
2U,vdW	0	6492.117	0
1T2U	3075.079	6315.182	81.150
1T2U,vdW	3074.557	6312.543	81.158

Table 7: Average number of hydrogen bonds between particular co-solutes and water for the systems simulated in unmodified and vdW-modified (index "vdW") ParmBSC1 force field. Definitions of short-hand notations are given in Table 1 in the main text.

It can be observed that there are nearly no hydrogen bonds formed between TMAO and urea, which is in agreement with other studies [3, 2, 4, 5]. Urea forms double as much H-bonds with water as TMAO, which is associated with its molecular structure. TMAO has only one H-bond acceptor group, whereas urea has both acceptor and donor groups. What is remarkable is that there are nearly no differences between the number of H-bonds formed between each of the co-solutes and water, regardless whether they are present in pure water solution separately or in 1:2 molar mixtures.
Although small discrepancies between the values of H-bond numbers calculated for ParmBSC1 and ParmBSC1_vdW force fields exist, the general conclusion is valid for both force fields.

References

[1] C. Yang, M. Kulkarni, M. Lim, and Y. Pak, "*In silico* direct folding of thrombin-binding aptamer G-quadruplex at all-atom level," *Nucl. Acids Res.*, vol. 45, no. 22, pp. 12648–12656, 2017.

[2] E. A. Oprzeska-Zingrebe and J. Smiatek, "Aqueous mixtures of urea and trimethylamine-N-oxide: Evidence for kosmotropic or chaotropic behavior?," *J. Phys. Chem. B*, vol. 123, pp. 4415–4424, 2019.

[3] W. J. Xie, S. Cha, T. Ohto, M. Bonn, J. Hunger, and Y. N. et al., "Large hydrogen-bond mismatch between TMAO and urea promotes their hydrophobic association," *Chem*, vol. 4, pp. 2615–2627, 2018.

[4] J. Hunger, N. Ottosson, K. Mazur, M. Bonn, and H. J. Bakker, "Water-mediated interactions between trimethylamine-N-oxide and urea.," *Phys. Chem. Chem. Phys.*, vol. 17, no. 1, pp. 298–306, 2015.

[5] C. J. Sahle, M. A. Schroer, I. Juurinend, and J. Niskanen, "Influence of TMAO and urea on the structure of water studied by inelastic X-ray scattering," *Phys. Chem. Chem. Phys.*, vol. 18, no. 24, pp. 16518–16526, 2016.