Supplementary Material for

Hydrophobic association and solvation of neopentane in Urea, TMAO and Urea-TMAO solution

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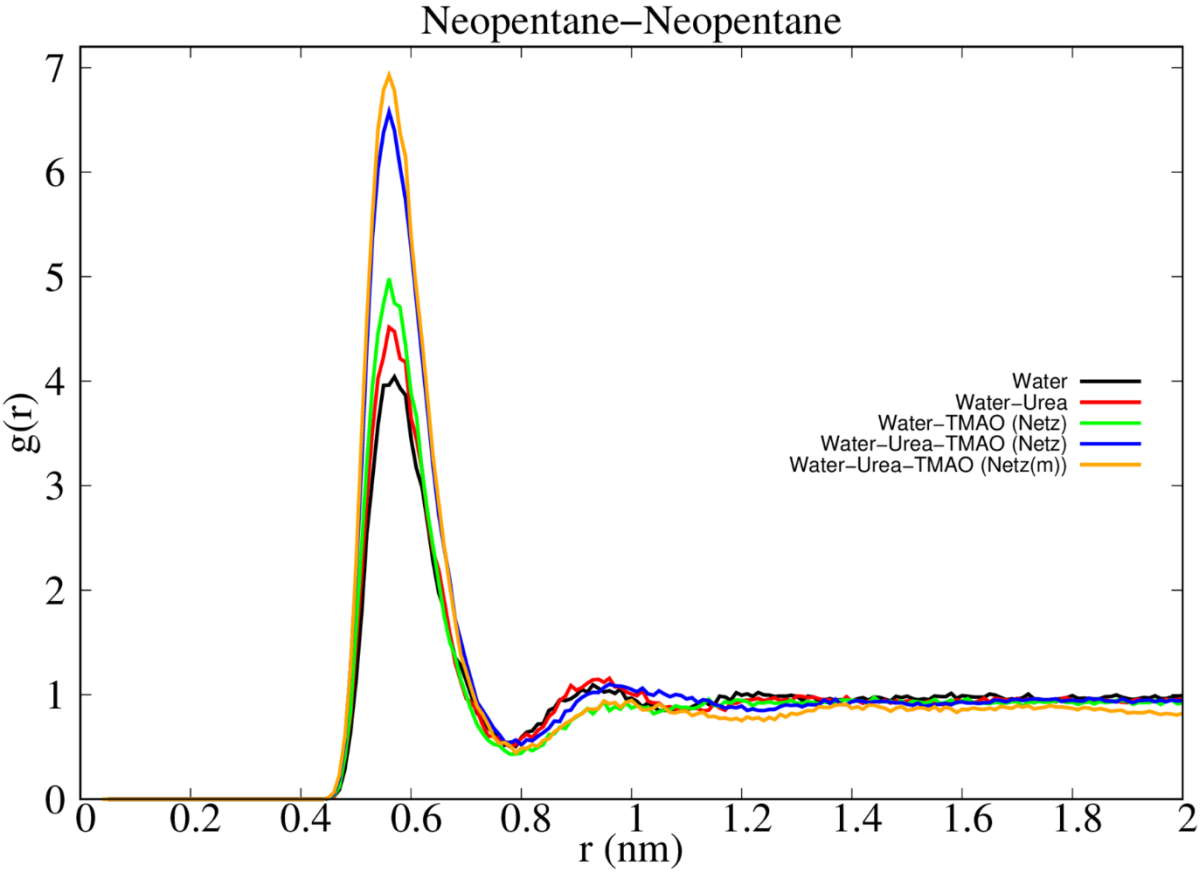

Fig. S1. Radial distribution functions between neopentane-neopentane in water-TMAO (Netz), Water-urea, Water-urea-TMAO (Netz) and water-urea-TMAO (Netz(m)) mixtures.

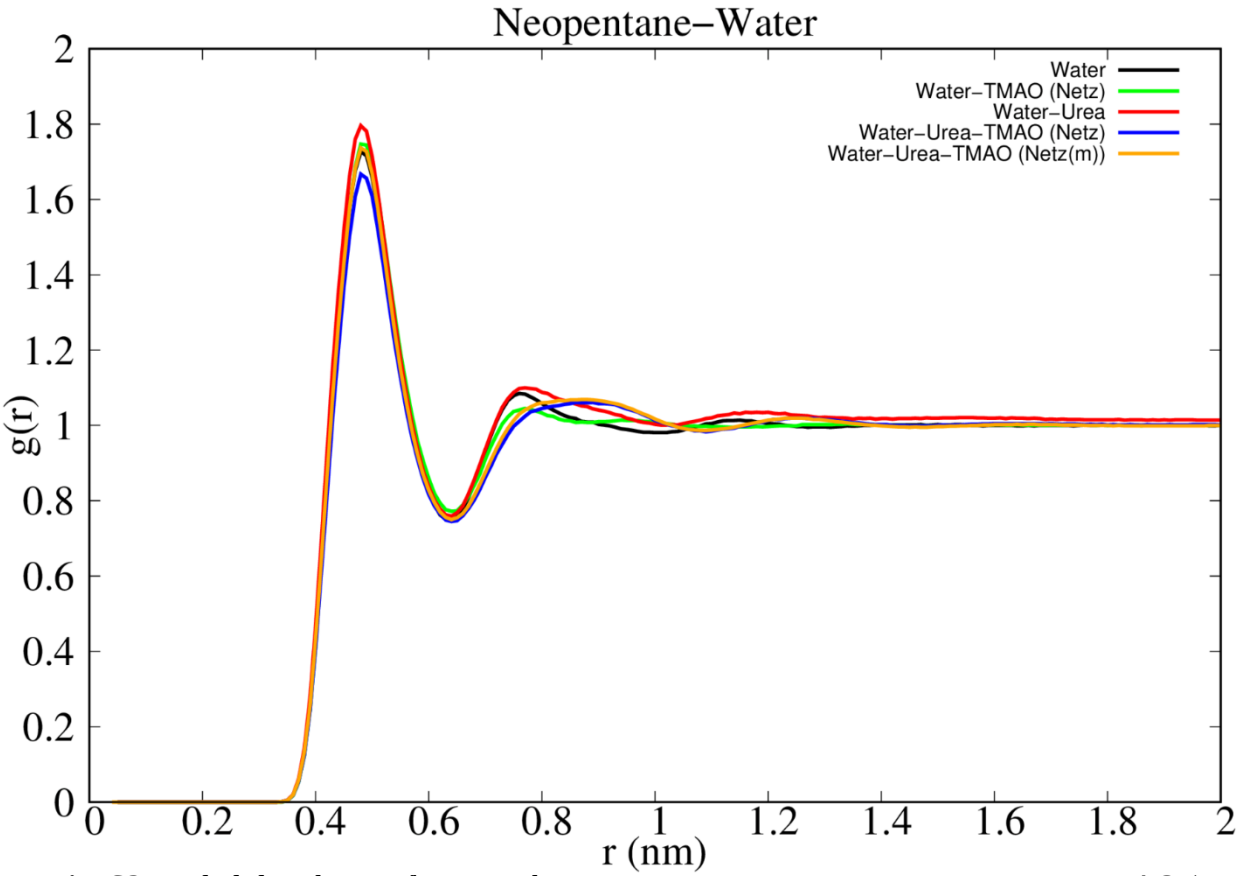

Fig. S2. Radial distribution functions between neopentane-water in water, water-TMAO (Netz), Water-urea, Water-urea-TMAO (Netz) and water-urea-TMAO (Netz(m)) mixtures.

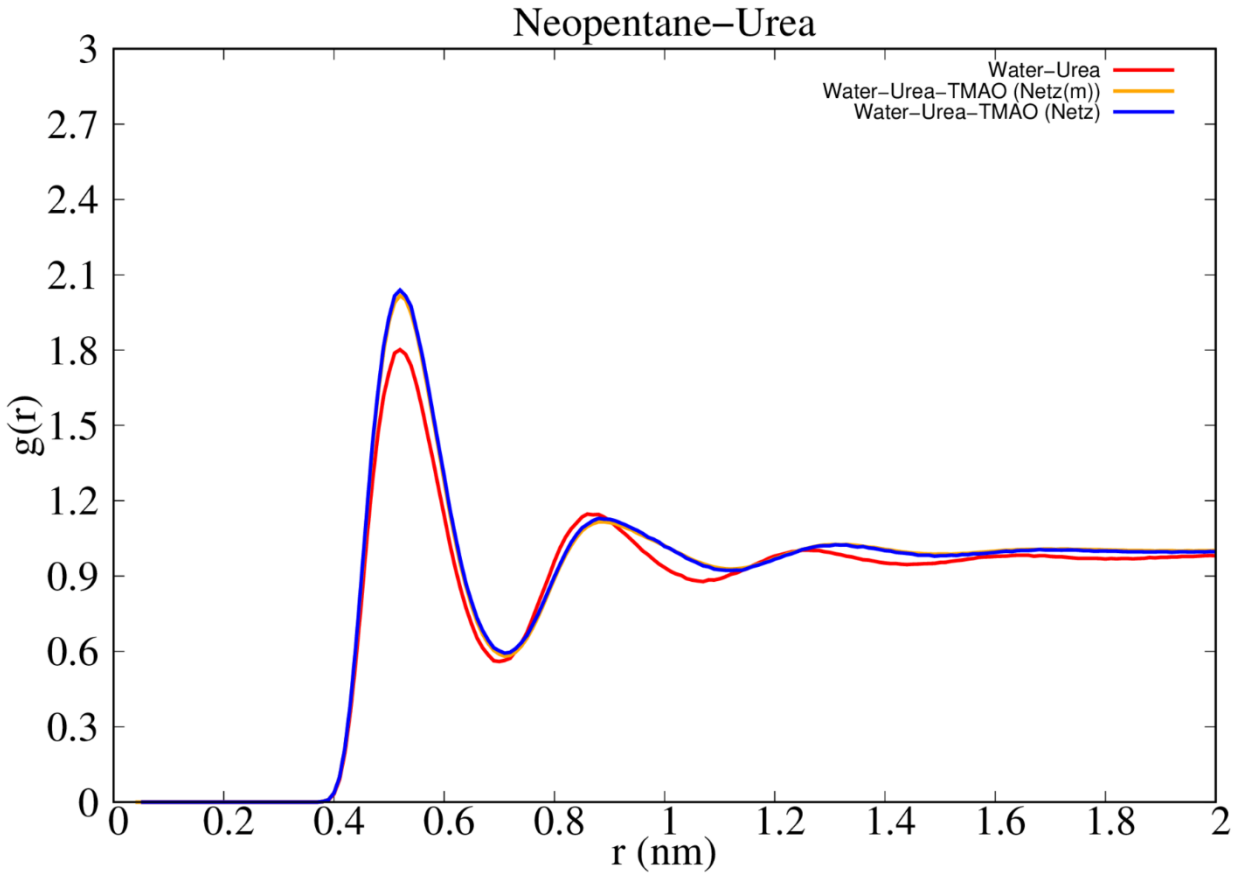

Fig. S3. Radial distribution function between neopentane-Urea in Water-Urea, water-Urea-TMAO (Netz(m)) and water-urea-TMAO (Netz) mixtures.

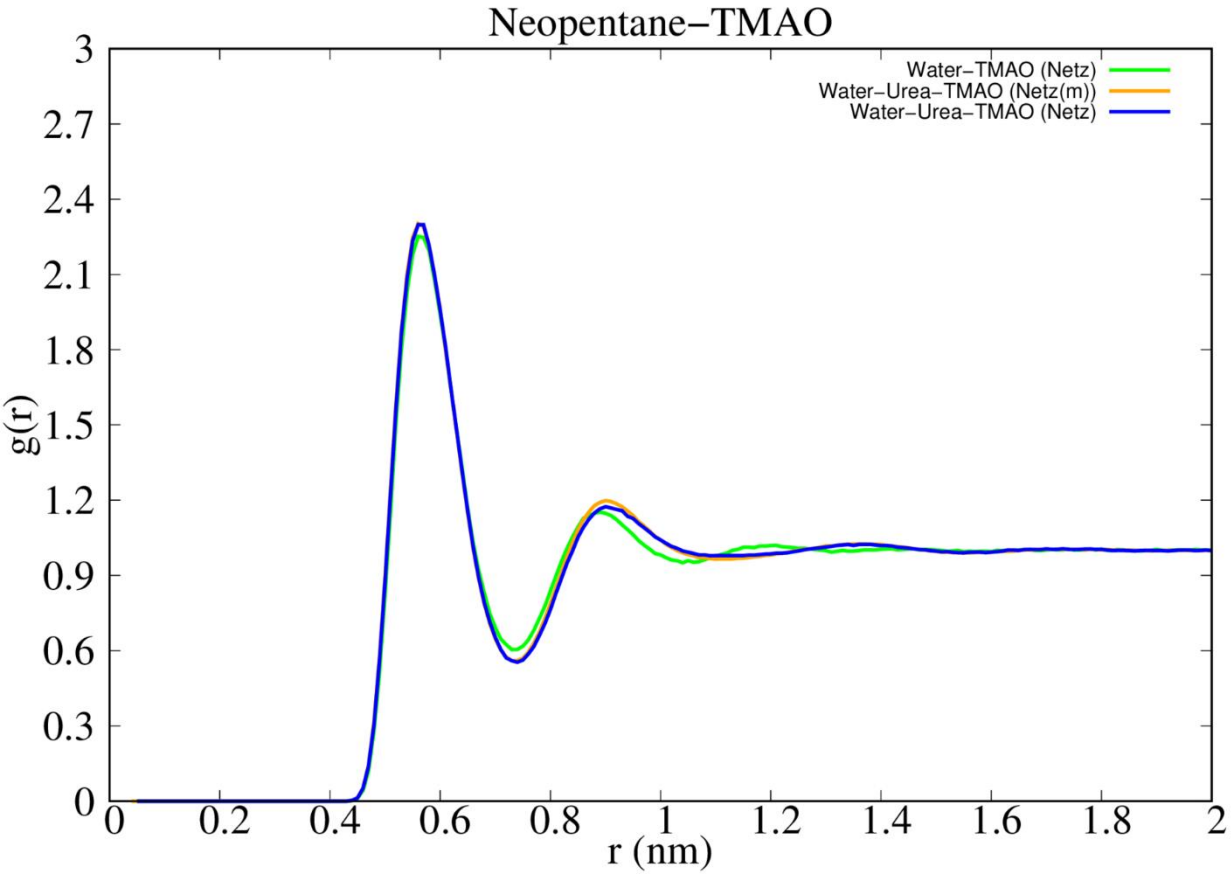

Fig. S4. Radial distribution function between neopentane-TMAO in water-TMAO (Netz), water-Urea-TMAO (Netz(m)) and water-urea-TMAO (Netz) mixtures.

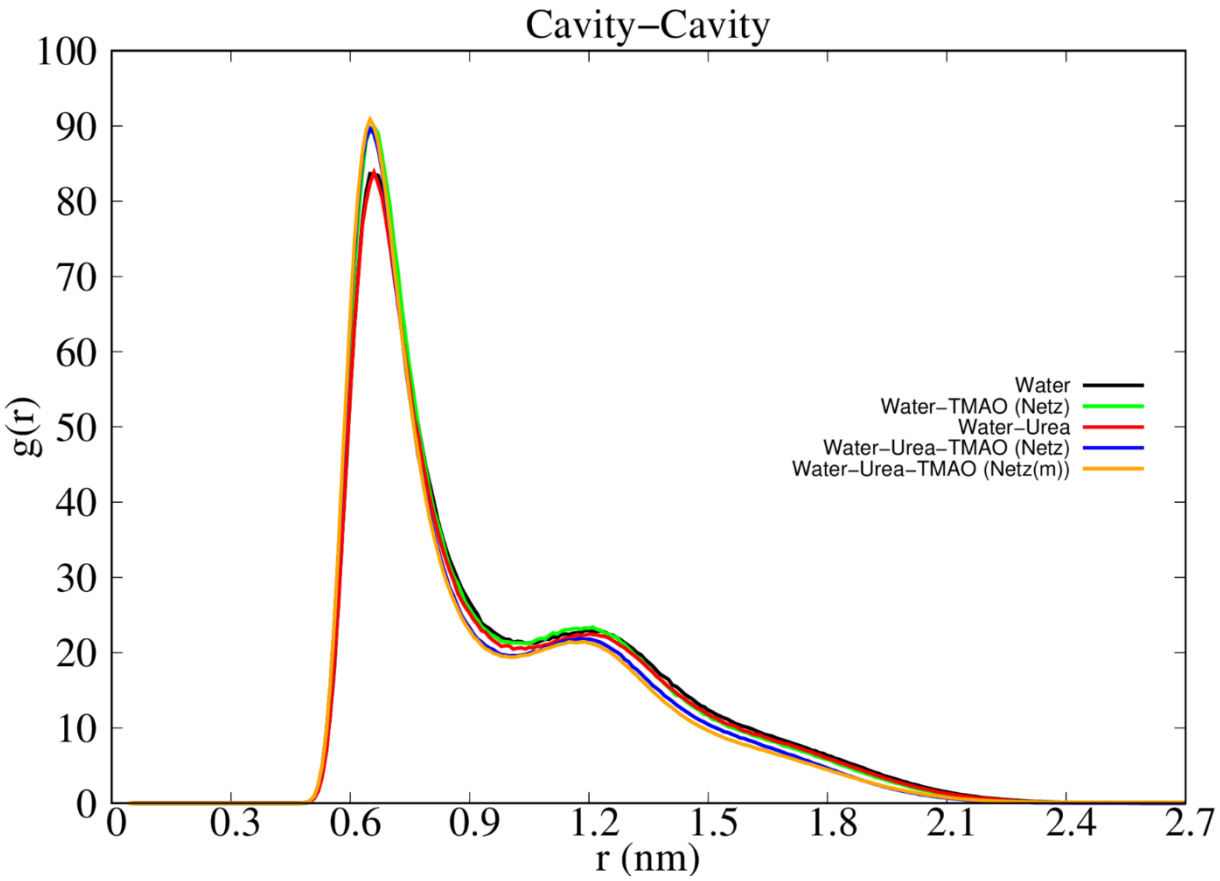

Fig. S5. Radial distribution functions between cavity-cavity in water, water-TMAO (Netz), Water-Urea and water-Urea-TMAO (Netz) and water-Urea-TMAO (Netz(m)) mixtures.

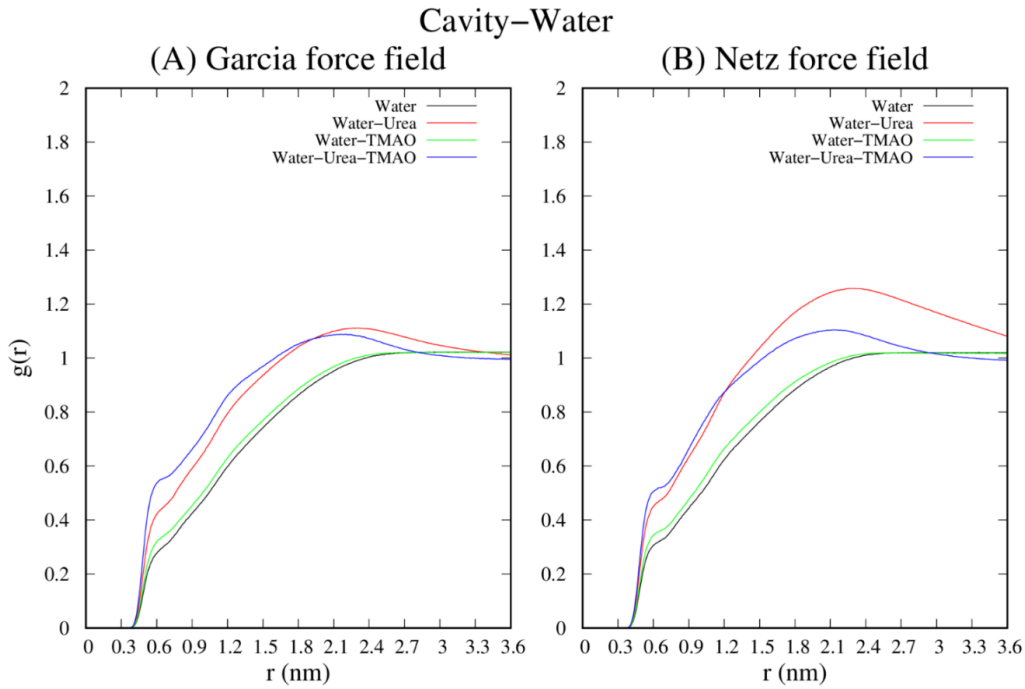

Fig. S6. Radial distribution functions between cavity-water in water (w), water-urea (w-ua), water-TMAO (w-ta) and water-urea-TMAO (w-ua-ta) mixtures for Garcia (A) and Netz (B) force fields.

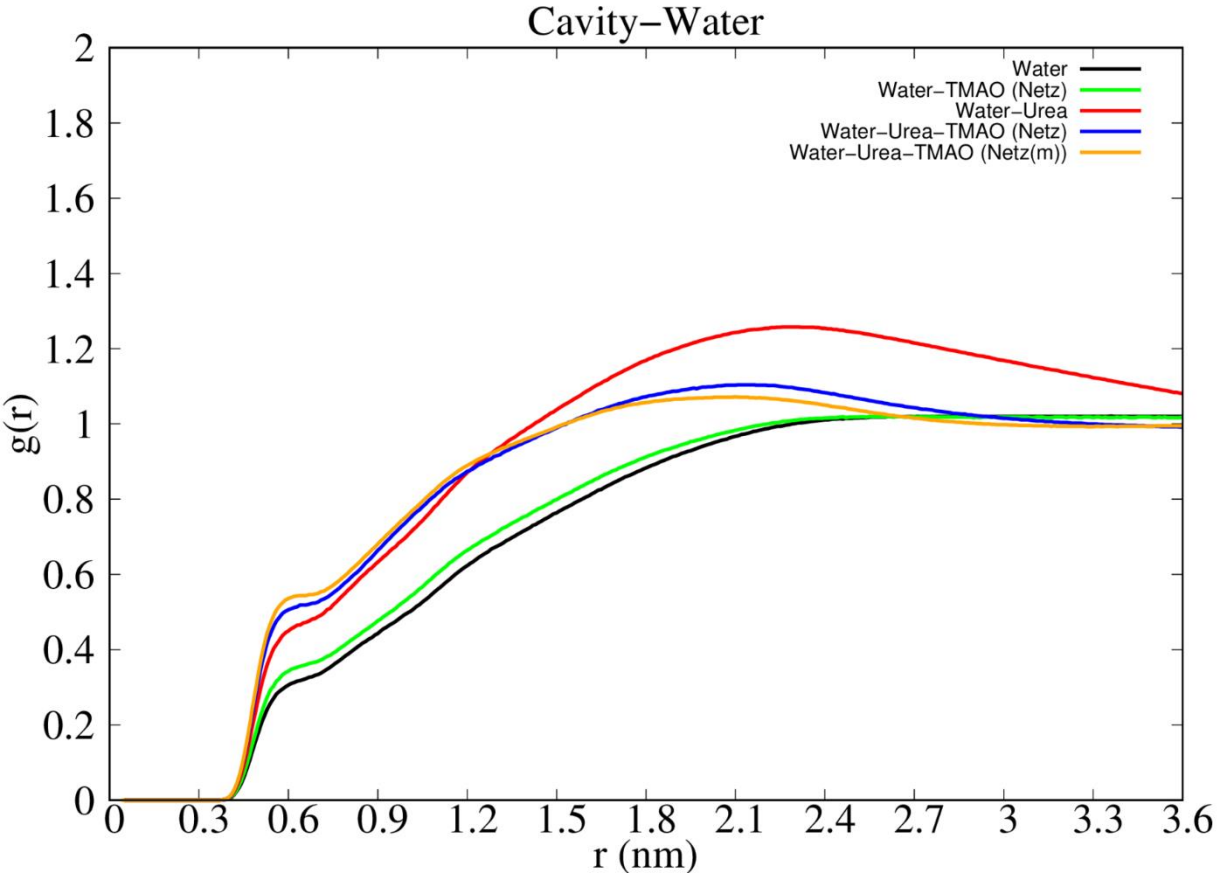

Fig. S7. Radial distribution functions between cavity-water in water, water-TMAO (Netz), water-urea, water-urea-TMAO (Netz) and water-urea-TMAO (Netz(m)) mixtures.

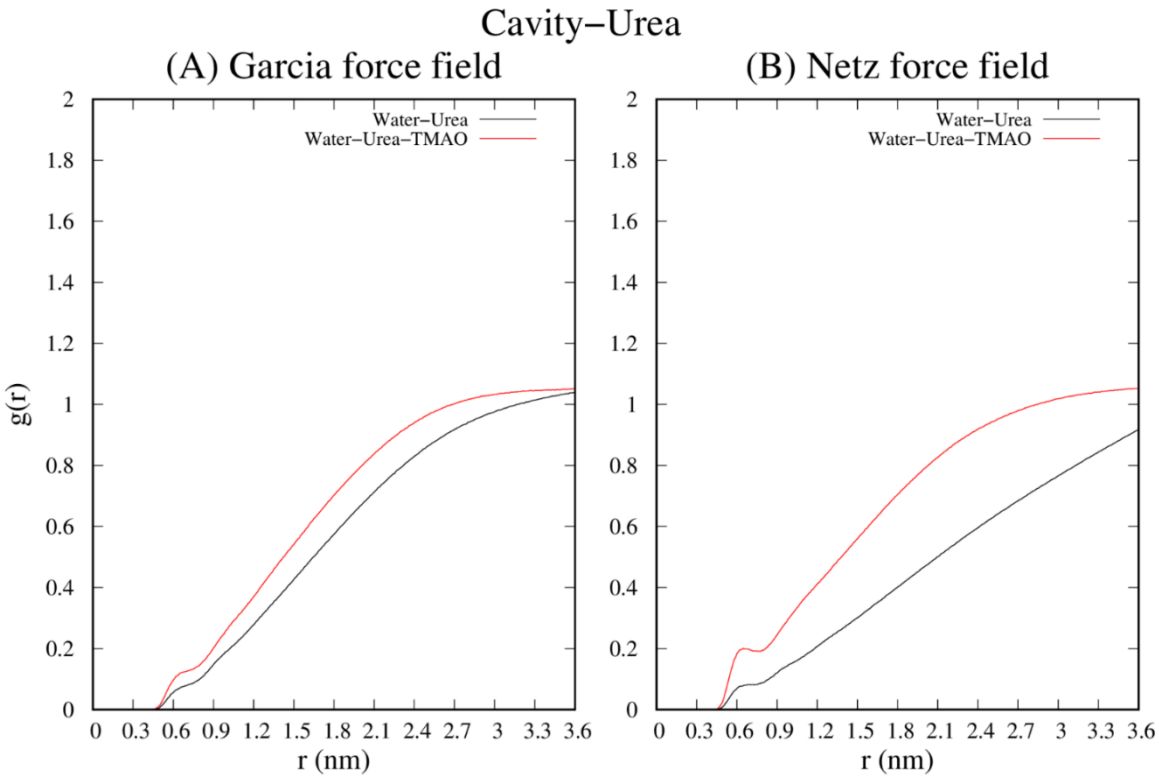

Fig. S8. Radial distribution function between cavity-urea in water-urea (w-ua) and water-urea-TMAO (w-ua-ta) mixtures for Garcia (A) and Netz (B) force fields.

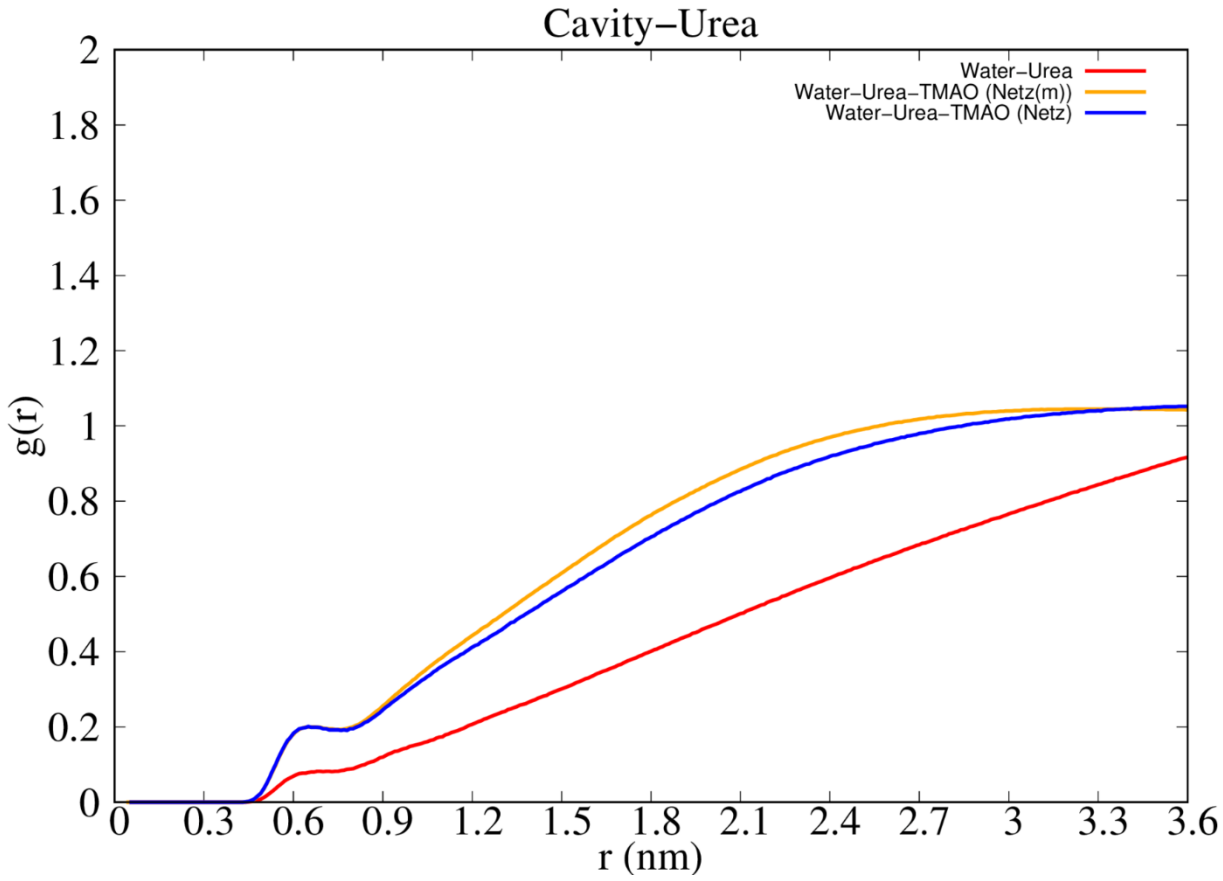

Fig. S9. Radial distribution functions between cavity-Urea in in water-TMAO (Netz) and water-urea-TMAO (Netz(m)) and water-urea-TMAO (Netz) mixtures.

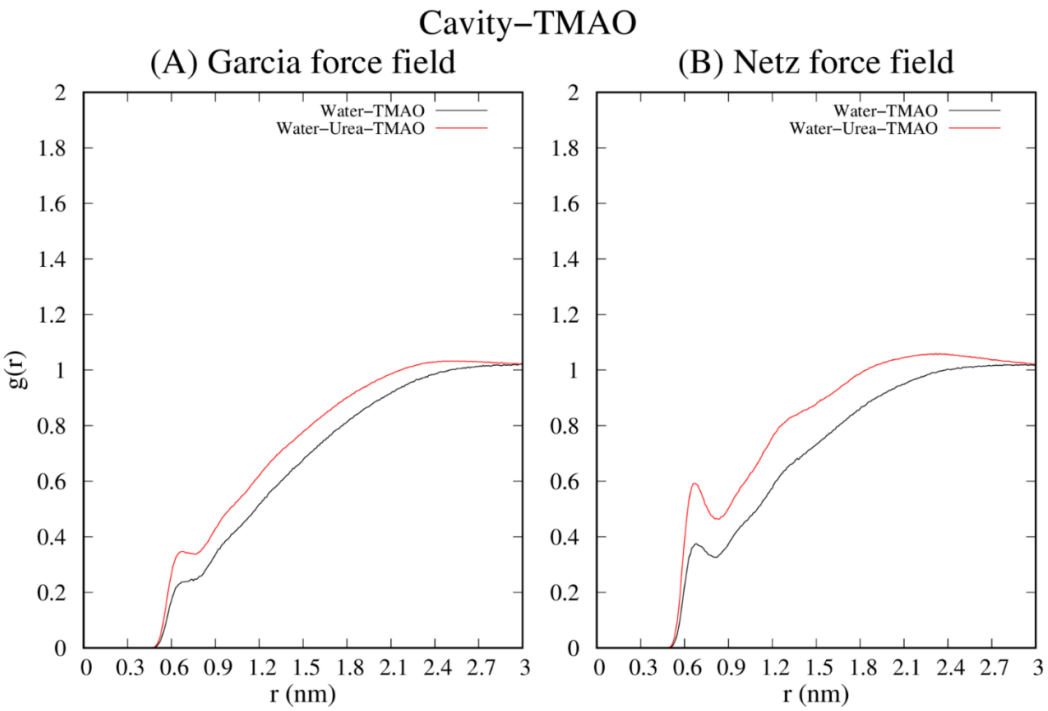

Fig. S10. Radial distribution function between cavity- and TMAO molecules in water-TMAO (w-ta) and water-urea-TMAO (w-ua-ta) mixtures for Garcia (A) and Netz (B) force fields.

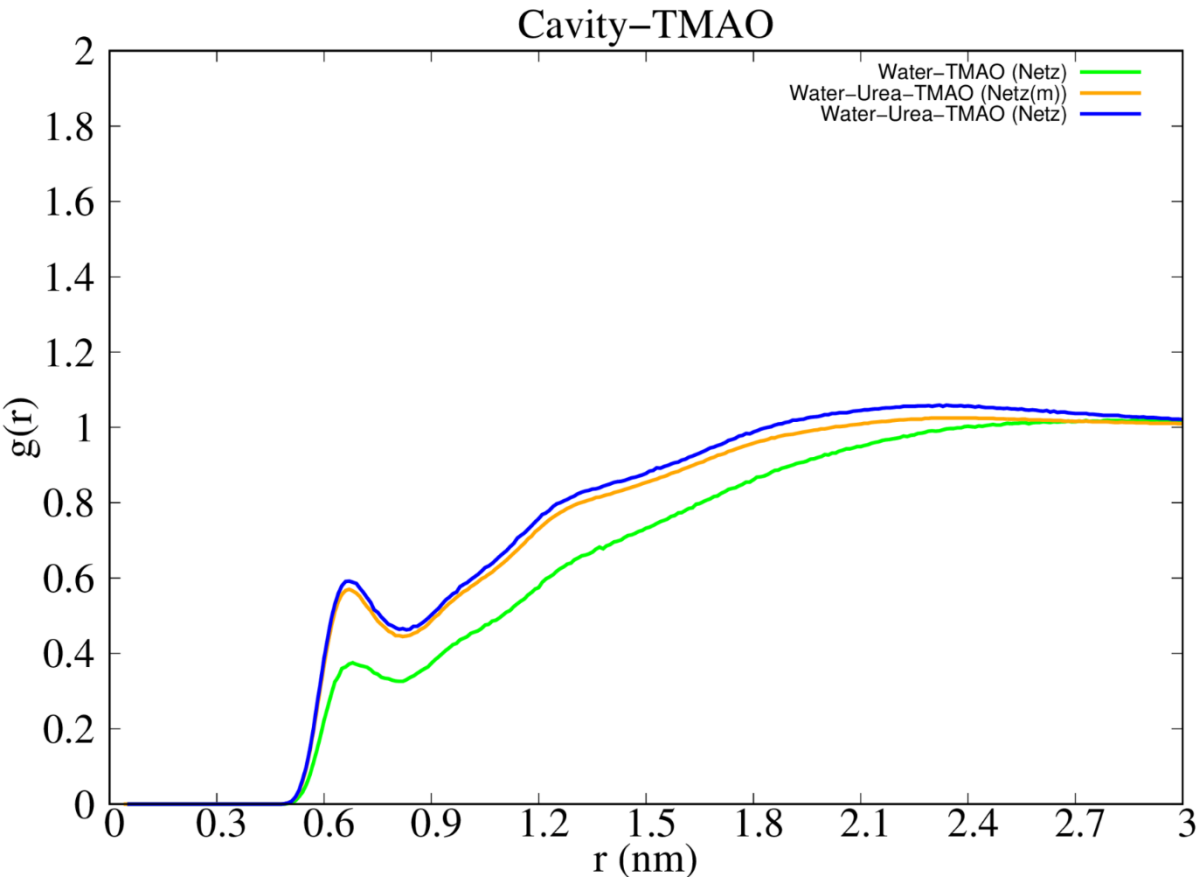

Fig. S11. Radial distribution functions between cavity-TMAO in water-TMAO (Netz) and water-urea-TMAO (Netz(m)) and water-urea-TMAO (Netz) mixtures.

Table S1. Preferential binding coefficients of neopentane with urea and TMAO cosolvents.

Mixtures	Preferential binding coefficients (γ)					
	GARCIA		NETZ		NETZ(m)	
	Urea	TMAO	Urea	TMAO	Urea	TMAO
water-urea	-2.01±0.07		-2.91±0.38			
water-TMAO		0.18±0.017		-0.05±0.04		
water-urea-TMAO	-1.56±0.24	-0.12±0.03	-0.46±0.32	-0.11±0.05	-0.88±0.22	-0.08±0.04

Table S2. Preferential binding coefficients of cavity with urea and TMAO cosolvents.

Mixtures	Preferential binding coefficients (γ)					
	GARCIA		NETZ		NETZ(m)	
	Urea	TMAO	Urea	TMAO	Urea	TMAO
water-urea	-16.57±0.08		-19.97±0.118			
water-TMAO		-2.17±0.03		-1.56±0.04		
water-urea-TMAO	-17.28±0.18	-4.51±0.04	-14.90±0.43	-2.30±0.08	-14.99±0.72	-3.00±0.12

Table S3. Solute-solvent interaction energy using Garcia, Netz and Netz(m) force field in water, water-urea, water-TMAO and water-urea-TMAO mixtures. The values are in kJ/mol and errors are less than 1 kJ/mol.

Solvent	Interaction Energy (E_{total})/(kJ/mol)		
	Garcia Model	Netz Model	Netz(m) Model
Water	-34	-36	
Urea-water	-39	-41	
TMAO-water	-43	-45	
Urea-TMAO-water	-50	-50	-51

Table S4. The excess chemical potential obtained by inserting a methane cavity in water, water-Urea, water-TMAO and water-urea-TMAO mixtures for Netz force field.

S. No.	ΔG_{cavity}/(kJ/mol)
Water	37.5±0.5
Water-Urea	41.7±0.4
Water-TMAO	41.4±0.7
Water-Urea-TMAO	46.4±1.6

1. Running coordination numbers (RCNs)

The running coordination numbers are defined as

$$n_{\alpha\beta} = 4\pi\rho_{\beta}\int_{r_1}^{r_2} r^2 g_{\alpha\beta}(r)dr \qquad \text{(S1)}$$

where $n_{\alpha\beta}$ represents the number of atoms of type β surrounding α in a shell extending from r_1 to r_2 and ρ_β is the number density of β type species in the system. In the case of RCNs calculation in first coordination shell, r_1 is zero and r_2 is the first minimum of radial distribution functions (RDFs). For calculations of the RCNs in the second coordination shell, r_1 is the first minimum of the RDFs and r_2 is the second minimum of the RDFs.

Table S5. The running coordination numbers (values in the rows) around Neopentane in the 1st solvation shell and 2nd solvation shell. Here, N_{neo}= the number of neopentane molecules.

	Garcia model		Netz model	
Mixtures	N_{neo} (in 1st solvation shell)	N_{neo}(in 2nd solvation Shell)	N_{neo} (in 1st solvation shell)	N_{neo} (in 2nd solvation shell)
Iw	0.187	0.198	0.144	0.191
IIw-ua	0.206	0.221	0.16	0.204
IIIw-tmao	0.169	0.191	0.155	0.169
IVw-ua-tmao	0.217	0.225	0.212	0.200

Table S6. The running coordination numbers (values in the rows) around Neopentane in the 1st solvation shell. Here, N_{H2O} = the number of water molecules, N_{Urea} = the number of urea molecules, N_{TMAO} = the number of TMAO molecules.

Mixtures	Neopentane					
	Garcia			Netz		
	N_{H2O}	**N_{Urea}**	**N_{TMAO}**	**N_{H2O}**	**N_{urea}**	**N_{TMAO}**
I_w	36.9	0	0	35.8	0	0
$II_{w\text{-}ua}$	23.8	6.3	0	23.7	6.7	0
$III_{w\text{-}tmao}$	27.9	0	4.0	28.2	0	4.0
$IV_{w\text{-}ua\text{-}tmao}$	13.1	7.2	4.0	14.9	7.4	3.8

Table S7. The running coordination numbers (values in the rows) around repulsive neopentane Cavity. Here, N_{H2O} = the number of water molecules, N_{urea} = the number of urea molecules, N_{TMAO} = the number of TMAO molecules.

Mixtures	Cavity					
	Garcia			Netz		
	N_{H2O}	**N_{Urea}**	**N_{TMAO}**	**N_{H2O}**	**N_{Urea}**	**N_{TMAO}**
Cw	8.2	0	0	7.3	0	0
Cw-ua	7.6	0.5	0	7.1	0.6	0
Cw-tmao	6.8	0	1.4	6.5	0	1.0
Cw-ua-tmao	5.0	1.3	2.1	5.5	0.9	1.3