Hydration and self-aggregation of a neutral cosolute from dielectric relaxation spectroscopy and MD simulations. The case of 1,3-dimethylurea

Electronic Supporting Information

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Dielectric relaxation spectroscopy

Table S1. Densities, $d / \text{g cm}^{-3}$, molarities, c / M, and viscosities, $\eta / \text{Pa s}$, of solutions of solute molality, $m / \text{mol kg}^{-1}$, of 1,3-DMU solutions in water at 25 °C

m	d	С	η
0.1171	0.998125	0.1157	0.9081
0.2578	0.999283	0.2519	0.9392
0.4999	1.001267	0.4794	1.0192
0.9902	1.005312	0.9156	1.1140
1.9801	1.013050	1.7079	1.3758
3.0481	1.020534	2.4521	1.6582
3.9219	1.026174	2.9910	1.9170
6.1348	1.037657	4.1322	2.5342
8.0196	1.045250	4.9118	3.2191

Table S2. Solute molarity, c / M, amplitudes, S_j , and relaxation times, τ_j / ps , of the resolved modes j = 1...4, static, ε , infinite frequency permittivity, ε_{∞} , and reduced error function, χ^2 , obtained with a 4D fit of the dielectric spectra of 1,3-DMU in water at 25 °C (parameter values followed by "F" not adjusted).

с	S ₁	<i>S</i> ₂	S ₃	S 4	τ1	τ2	τ3	τ4	€s	ε∞	χ ² ·10 ³
0.1157	0.31	8.13	63.52	3.20	37.4F	12.0	8.39	0.46	78.43	3.27	27.5
0.2519	1.39	14.32	56.55	3.81	38.2F	12.1	8.31	0.53	78.96	2.89	77.4
0.4794	3.60	20.74	48.34	1.29	39.5F	12.4	8.29	1.01	79.47	5.50	62.3
0.9156	7.29	32.44	33.38	1.36	41.3	13.0	8.29	1.28	79.82	5.35	82.4
1.7079	16.27	36.18	21.05	2.43	48.8	14.3	9.17	2.10	81.51	5.59	81.2
2.4521	24.96	36.46	14.38	1.82	59.9	15.7	9.69	2.07	83.24	5.63	109.5
2.9910	30.10	34.62	12.58	1.02	67.0	18.0	8.87	1.99	84.30	5.98	97.7
4.1322	41.93	26.63	10.99	2.24	90.6	22.7	10.3	1.62	86.47	4.67	17.0
4.9118	48.86	21.79	10.54	1.54	115	28.1	12.2	3.12	88.16	5.43	21.0



Fig. S1. Relaxation times of bulk and slow water, as well as of 1,3-DMU as a function of solution viscosity for solutions of 1,3-DMU in water at 25 °C.



Fig. S2. First-order rotational correlation times of 1,3-DMU, $\tau_{rot,1}$, as a function of solution viscosity. Symbols represent experimental data; the line represents the Stokes-Debye-Einstein fit.

Molecular dynamics simulations

Force field details

atom	q / e	<i>c</i> ⁽⁶⁾ / kJ nm ⁶ mol ⁻¹	<i>c</i> ⁽¹²⁾ / kJ nm ¹² mol ⁻¹	σ / nm	ε / kJ mol ⁻¹							
	1,3-DMU											
С	0.7686	4.7890·10 ⁻³	1.3750·10 ⁻⁵	0.3770	0.4170							
0	- 0.6308	1.9880·10 ⁻³	1.7644·10 ⁻⁶	0.3100	0.5600							
Ν	- 0.5532	1.8096·10 ⁻³	1.6374·10 ⁻⁶	0.3110	0.5000							
H _N	0.3410	5.4763·10 ⁻⁶	8.5198·10 ⁻¹¹	0.1580	0.0880							
C _H	- 0.1264	1.6793·10 ⁻³	1.8032·10 ⁻⁶	0.3200	0.3910							
H _c	0.0899	2.9297·10 ⁻⁵	7.1526·10 ⁻⁹	0.2500	0.0300							
	H ₂ O											
O _W	- 0.8476	2.6173·10 ⁻³	2.6341.10-6	0.3166	0.6505							
Hw	0.4238	0.0000	0.0000	0.0000	0.0000							

Table S3. Non-bonded parameters for the customized KBFF model of 1,3-DMU and the SPC/E water model

Table S4. Bond parameters for the customized KBFF model of 1,3-DMU^a

	bonds							
bond	<i>r</i> ₀ / nm	k	x₀ / kJ mol⁻¹ nm⁻²					
C – O	0.1234		502282.80					
C – N	0.1365		417460.40					
H _N - N	0.1004		374000.00					
C _H – N	0.1449		376428.78					
C _H – H _C	0.1090		292272.60					
	angles							
angle	ϑ_0 / degree	k	r _ϑ / kJ mol ^{−1} rad ^{−2}					
N – C – O	122.1		501.7314					
$C - N - H_N$	120.1		292.5000					
C – N – C _H	121.4		504.1218					
$C_H - N - H_N$	118.5	377.8412						
H _C – C _H – N	110.6	418.4000						
$H_c - C_H - H_c$	108.4		292.8800					
N – C – N	115.8		502.5000					
	improper dihedr	als						
improper	ω_0 / degree	k	ω / kJ mol ⁻¹ rad ⁻²					
C – N – N – O	0.0		167.42309					
$N - H_N - C_H - C$	0.0		167.42309					
$C_H - H_C - H_C - N$	- 37.6		334.84617					
	dihedrals							
dihedral	δ / degree	k_{φ} / kJ mol ⁻¹	n					
$H_N - N - C - O$	- 180.0	33.5	2					
$O - C - N - C_H$	- 180.0	33.5	2					
H _C – C _H – N – C	180.0	1.0	6					

^{*a*} Potential functions are the following:

bonds, $V_b\left(r_{ij}\right) = \frac{1}{4}k_{ij}^b\left(r_{ij} - b_{ij}\right)^2$; angles, $V_a\left(\theta_{ijk}\right) = \frac{1}{2}k_{ijk}^\theta\left(\theta_{ijk} - \theta_{ijk}^0\right)^2$; improper dihedrals, $V_{id}\left(\xi_{ijkl}\right) = \frac{1}{2}k_{ijkl}^{\xi}\left(\xi_{ijkl} - \xi_{ijkl}^0\right)^2$; dihedrals, $V_d\left(\phi_{ijkl}\right) = k_{ijkl}^{\phi}\left(1 + \cos(n\phi - \delta)\right)$.

1,3-DMU hydration and aggregation

Table S5. Positions of the first, $r_{min,1}$, and second, $r_{min,2}$, minima in the 1,3-DMU – O_W and 1,3-DMU – C pRDFs and corresponding
hydration, $CN_{MD}(H_2O)$, and coordination, $CN_{MD}(DMU)$, numbers in the 1,3-DMU-water mixtures

<i>c </i> M	r ^{1,3-DMU–O} w / Å ^{min,1}	<i>CN</i> MD(H₂O)	r ^{1,3-DMU–C} / Å _{min,1}	CN ¹ _{MD} (DMU)	r ^{1,3-DMU−C} / Å _{min,2}	CN ² _{MD} (DMU)
0.4755	3.8	21.7	4.4	0.3	5.8	0.6
0.9327	3.8	20.2	4.3	0.7	5.7	1.3
1.7373	3.8	18.1	4.2	1.2	5.7	2.3
3.0463	3.8	15.7	4.1	1.8	5.7	3.8
4.0780	3.7	13.6	4.1	2.1	5.7	4.8
4.9172	3.7	11.8	4.0	2.5	5.6	5.9



Fig. S3. Radial distribution functions relating two interacting centers C and O_w in 3.0 M 1,3-DMU(aq).

2D distributions of the 1,3-DMU nearest surrounding. In order to determine the local structure around 1,3-DMU and in particular the orientation of the hydrating water molecules the following analysis was performed: First, five key vectors were defined. The first and second vectors, $\bar{n_i}$ (i = 1, 2), are a normal (perpendicular) to the planes of the 1,3-DMU and H₂O molecules (here and later on i = 1 for the reference and i = 2 for the observed molecules); the third vector, \bar{c} , connects the C atom of the reference 1,3-DMU with the water oxygen, O_W, or the carbonyl C atom of another 1,3-DMU molecule. The fourth and fifth are vectors, d_i (i = 1, 2), parallel to the dipole moment vectors of 1,3-DMU and H₂O. Second, three angles were specified, where α is the angle between $\bar{n_1}$ and \bar{c} , and γ the angle between d_1 and d_2 , see Fig. S4. Based on these definitions, the combined distribution functions (CDFs) relating the C – O_W respectively C – C distances, *i.e.* r_{C-O_W} and r_{C-C} , to the above angles were determined individually for each of the three nearest neighbors. In order to avoid ambiguities due to hydration shell overlap, the corresponding 1,3-DMU – H₂O CDFs were calculated for the 0.48 M solution. The corresponding 1,3-DMU – 1,3-DMU CDFs were determined for the 3.0 M solution. The resulting CDFs are shown in Fig. S5.



Fig. S4. Representative vectors and angles used for describing the relative orientation of surrounding (index "2") H_2O (left) and 1,3-DMU molecules (right) with respect to the reference 1,3-DMU molecule (index "1").



Fig. S5. (Left)Combined distribution functions relating the C – O_W distances, r_{C-O_w} , and the three representative angles α (first row), β (second row) and γ (third row) for the first, second and third nearest H₂O molecule hydrating 1,3-DMU at c = 0.48 M (*cf.* Fig. 8 of the main text). **(Right)** Corresponding CDFs relating the C – C distances, r_{C-C} , of the reference solute to the three nearest 1,3-DMU molecules to the angles α , β and γ for c = 3.0 M (*cf.* Fig. 9).

Obviously, the angle α describes the mutual orientation of the planes of the reference molecule and surrounding species with respect to each other. In case of parallel alignment, α must be close to 0 or 180° while in T-shaped orientations $\alpha \approx 90°$ or 270°. As seen in Fig. S5, the first H₂O neighbor in the 0.48 M solution (*cf.* Fig. 8 of the main text) orients its molecular plane perpendicular to that of 1,3-DMU as α is distributed between 60° and 120°. Neighbors 2 and 3 do not show a clear orientation of their planes with respect to the solute. Integration of the RDF $g_{C-O_w}(r)$ (Fig. S3) up to its first minimum (4.4 Å) considering constraints for α yields for the 0.48 M solution that on average 1.1 H₂O molecules show parallel alignment (Table S6), whereas most of the H₂O molecules in the first hydration shell (3.4 out of 7.1 in total) orient their planes perpendicular to that of the reference 1,3-DMU. Beyond 4.4 Å no specific orientation of H₂O planes is observed (see Fig. S6).

Table S6.Coordination numbers obtained from integrating the RDF $g_{C-O_w}(r)$ up to its first, $r_{min,1}$, respectively second, $r_{min,2}$,minimum. For the first also partial values for particular ranges of the angles α , β and γ are given.

c / M	$r_{\min,1} =$	$r_{\min,2} =$			$r_{\min,1} = 4.4$	Å			
	= 4.4 Å	= 6.6 Å	α < 30°, α > 150°	60° < α < 120°	eta < 30°, eta > 150°	60° < β < 120°	γ < 30°	γ < 45°	γ < 60°
0.4755	7.1	34.1	1.1	3.4	1.5	2.9	0.8	1.6	2.5
0.9327	6.7	30.9	1.0	3.2	1.3	2.8	0.8	1.6	2.5
1.7373	6.1	26.3	0.9	3.0	1.1	2.7	0.7	1.5	2.3
3.0463	5.3	23.9	0.8	2.6	0.9	2.5	0.7	1.3	2.1
4.0780	4.9	21.7	0.7	2.4	0.8	2.3	0.6	1.3	1.9
4.9172	4.5	21.7	0.6	2.3	0.7	2.3	0.6	1.2	1.8



Fig. S6. Combined distribution functions relating the C – O_W (top row) respectively C – C (bottom row) distances to the three angles α (first column), β (second column) and γ (third column) of Fig. S4. The distributions were calculated at c = 0.48 M for 1,3-DMU – H₂O interactions and at 3.0 M for 1,3-DMU – 1,3-DMU interactions.

The $r_{C-OW} - \beta$ CDFs give additional information on the position of the neighbors surrounding the reference 1,3-DMU molecule. If these are located in the reference plain β must be close to 90° whereas values of 0° and 180° indicate a placing of the observed particle exactly above or below the reference. If β is within the ranges $0^{\circ} \leq \beta \leq 30^{\circ}$ or $150^{\circ} \leq \beta \leq 180^{\circ}$ and the planes of reference and observed molecule are parallel to each other ($\alpha \approx 0^\circ$ or 180°) their mutual orientation is parallel-displaced. This is the case for the H₂O molecule closest to the solute as β is mainly < 30° or > 150°. The second neighbor exhibits a broad distribution of β with a slight predominance of the out-of-plane location, whereas the third H₂O shows a weak preference for an in-plane position. For the remaining four H₂O molecules at r_{C-O_w} < 4.4 Å the probability of finding these within the 60° < β < 120° region decreases. In general, 2.9 out of the 7.1 H₂O molecules within r_{C-O_w} = 4.4 Å are located more or less in the plane of the 1,3-DMU molecule (Table S6). Finally, the angle y describes the mutual orientation of the dipole vectors, with approximately parallel alignment indicated by y < y30°. It is evident from Fig. S5 that the first three neighboring H₂O molecules orient their dipole moments parallel to that of the reference 1,3-DMU. Moreover, this tendency increases from the first to third water molecule. For further neighbors parallel orientation of the dipoles becomes less and less pronounced (data not shown). According to the analysis of simulation snapshots the first neighbor is almost exclusively H-bonded to the carbonyl oxygen of the solute. The second is either H-bonded to carbonyl oxygen or the hydrogen atoms of the amino groups with a preference for the former. The third next H₂O definitely prefers to Hbond to both amino hydrogens, which explains why this water molecule is best aligned with the solute dipole. Thus, analysis of the dipole moment vectors shows essentially parallel alignment of the dipole moments of 1,3-DMU and of the three nearest H₂O molecules in its first hydration shell (Fig. S6), albeit with an angular distribution in the range $0^{\circ} \le \gamma \le 30^{\circ}$. Since from the ~26 water dipoles of the first hydration layer (Fig. 4) wobbling around the solute only the "frozen" component parallel to the solute dipole and H-bonded to 1,3-DMU as a consequence – will disappear from the DRS signal, this explains why $Z_{ib} \approx 1.6$ was found experimentally. At the same token, this explains the large effective dipole moment of $\mu_{eff,1}$ = (11.3 ± 0.6) D of 1,3-DMU at $c \rightarrow 0$.

Table S7. Coordination numbers obtained from integrating the RDF $g_{C-C}(r)$ up to its first, $r_{min,1}$, respectively second, $r_{min,2}$, minimum. For the first also partial values for particular ranges of the angles α , β and γ are given.

c/M	<i>r</i> _{min,1} =	r _{min, 2} =			<i>r</i> _{min,1} =5.0 Å			
•,	= 5.0 Å	= 7.5 Å	$\alpha < 30^\circ, \alpha > 150^\circ$	60° < α < 120°	β < 30°, β > 150°	60° < β < 120°	γ < 60°	y > 120° 0.05 0.08 0.14 0.20 0.23 0.24
0.4755	0.17	0.65	0.06	0.04	0.06	0.03	0.05	0.05
0.9327	0.31	1.26	0.10	0.09	0.10	0.07	0.10	0.08
1.7373	0.56	2.41	0.18	0.17	0.18	0.15	0.20	0.14
3.0463	0.86	4.01	0.26	0.29	0.26	0.26	0.32	0.20
4.0780	1.03	5.00	0.30	0.35	0.29	0.32	0.39	0.23
4.9172	1.14	5.77	0.32	0.40	0.32	0.37	0.45	0.24

With regard to solute-solute interactions at c = 3.0 M the closest 1,3-DMU molecule also orients its plane parallel to the plane of the reference 1,3-DMU as the regions with the highest intensity of the $r_{C-C} - \alpha$ CDF are found at $r_{C-C} < 5.0$ Å and $\alpha < 30^\circ$, $\alpha > 150^\circ$. For the second neighbor, a broader distribution is observed with a slight predominance of parallel plane orientation as long as r_{C-C}

< 5.0 Å but with a marked distribution of α in the range 60-120° at 5.0 < r_{c-c} / Å <7.5. This suggests a T-shaped solute orientation in this region. The third neighbor is preferably located in the range of the second maximum of $g_{c-c}(r)$ and shows also T-shaped orientation. Note, that only 0.9 1,3-DMU molecules were found by integrating the $g_{c-c}(r)$ RDF up to the first minimum and a further 3.2 molecules are within the 5.0 < r_{c-c} / Å < 7.5 (Table S7).

Similar to the nearest H₂O molecule, also the first 1,3-DMU neighbor prefers the location above and below ($\beta < 30^{\circ}$ and $\beta > 150^{\circ}$) the plane of the reference solute molecule (Fig. S5). For the second neighbor this distribution preserves with half as large intensity while the third neighbor does not show any preferred orientation with respect to the reference plane. Together with the finding that the first two neighbors orient their planes parallel to the reference solute, one can conclude that these three 1,3-DMU molecules have an enhanced probability to form the parallel-displaced stacks. It should be mentioned that for 29% (0.26 out of 0.89) of the solute molecules placed within first minimum of $g(r)_{C-C}$ (5.0 Å) the angle β assumes values between 60 and 120°. In accordance with simulation snapshots this corresponds to structures where1,3-DMU molecules are H-bonded via H and O atoms and thus form head-to-tail aggregates.

Figure S5 shows that for the first two 1,3-DMU molecules next to the reference the maximum intensity of the $r_{C-C} - \gamma$ CDF corresponds to 20° < γ < 50°. The third neighbor possesses a very broad distribution without preferred dipole-dipole correlations. For the 3.0 M solution 36% (0.32 out of 0.89) of the 1,3-DMU molecules within $r_{C-C} < 5.0$ Å orient their dipoles roughly parallel to the reference (γ < 60°). It should be noted that this number slightly increases with increasing solute concentration, rising to 0.45 out of 1.14 molecules at 4.9 M. On the other hand, the same trend with concentration is also observed for the 1,3-DMU molecules with anti-parallel orientation located within the first (5.0 Å) and second (7.4 Å) minimum of the C – C RDF. The number of solute molecules with orientations 120° < γ < 180° rises from 0.20 to 0.24 when going from 3.0 M to 4.9 M. Thus, these solute molecules with anti-parallel orientation partly compensate the effect on $\mu_{eff,1}$ induced by those with parallel orientation. This explains why the experimentally determined effective dipole moment of 1,3-DMU does not change with concentration.

1,3-DMU reorientation



Fig. S7. First, l = 1, second, l = 2, and third-order, l = 3, Legendre polynomials of the ACFs for the reorientation of the *x*, *y*, and *z* vectors (see inset of Fig. 10 for definition) of 1,3-DMU at c = 3.0 M.

In order to obtain the reorientational correlation times, $\tau'_{u,1}$, corresponding to the *x*, *y*, and *z* vectors of 1,3-DMU, we analyzed ln $C_{x,1}$, ln $C_{y,1}$ and ln $C_{z,1}$ as a function of time. To allow direct comparison of the $\tau'_{u,1}$ values to the rotational correlation time, $\tau_{rot,1}$, found with DRS (see manuscript for details), only linear parts of the simulated ln $C_{u,1}(t)$ functions at long times were considered. Table S8 summarizes the corresponding slopes, $S(\ln C_{u,1})$, calculated reorientational correlation times, $\tau'_{u,1}$, as well as the times (in parentheses of columns 2, 4 & 6) up to which ln $C_{u,1}(t)$ was linear.

Table S8. Slopes, $S(\ln C_{u,1})$, and associated correlation times, $\tau'_{u,1}$ (in ps), of the linear parts of natural logarithms of the reorientational ACFs, $C_{u,1}$, of the vectors $\mathbf{u} = \mathbf{x}$, \mathbf{y} , and \mathbf{z} describing 1,3-DMU rotation. The quantities given in parenthesis in columns 2, 4 & 6 show the time (in ps) up to which $\ln C_{u,2}(t)$ was linear.

	coluii	1113 2, 4 & 0 3	now the time (in p3) up to w	$u_{u,1}(t)$ was	sincu.	
<i>c/</i> M	S(In C _{x,1})	$\tau'_{\mathbf{x},1}$	<i>S</i> (In <i>C_{y,1})</i>	$\tau'_{\mathbf{y},1}$	$S(\ln C_{z,1})$	$\tau'_{z,1}$
0.4755	-0.0495 ± 7·10 ⁻⁴ (75)	20.2 ± 0.3	-0.0348 ± 1·10 ⁻⁴ (100)	28.77 ± 0.09	-0.058 ± 1·10 ⁻³ (70)	17.4 ± 0.3
0.9327	-0.0389 ± 5·10 ⁻⁴ (100)	25.7 ± 0.3	-0.03176 ± 9·10 ⁻⁵ (120)	31.48 ± 0.09	-0.0467 ± 6·10 ⁻⁴ (100)	21.4 ± 0.3
1.7373	-0.0265 ± 4·10 ⁻⁴ (150)	37.8 ± 0.5	-0.02672 ± 9·10 ⁻⁵ (150)	37.4 ± 0.1	-0.0348 ± 5·10 ⁻⁴ (120)	28.7 ± 0.4
3.0463	-0.0163 ± 2·10 ⁻⁴ (200)	61.4 ± 0.9	-0.0203 ± 1·10 ⁻⁴ (200)	49.3 ± 0.3	-0.0236 ± 2·10 ⁻⁴ (200)	42.5 ± 0.4
4.0780	-0.0120 ± 1·10 ⁻⁴ (300)	83.3 ± 0.8	-0.01762 ± 7·10 ⁻⁵ (220)	56.7 ± 0.2	-0.0196 ± 2·10 ⁻⁴ (220)	51.7 ± 0.4
4.9172	-0.00891 ± 9·10 ⁻⁵ (400)	112 ± 1	-0.01546 ± 7·10 ⁻⁵ (250)	64.7 ± 0.2	-0.0164 ± 1·10 ⁻⁴ (250)	61.0 ± 0.5

Residence times and H-bond dynamics



Fig. S8. RDFs for the site-site interactions in 3.0 M 1,3-DMU(aq).



Fig. S9. Combined distribution functions between $H_2O - H_2O$ (A), 1,3-DMU – H_2O (B, C) and 1,3-DMU – 1,3-DMU (D) pairs in the 3.0 M 1,3-DMU aqueous solution. Radial distribution corresponds to the donor – acceptor distance ($O_W - O_W$ for A, O – O_W for B, N – O_W for C and N – O for D); angular distributions shows hydrogen bond – donor – acceptor angle $\boldsymbol{\theta}$ ($H_W - O_W - O_W$ for A, H_W – $O_W - O$ for B, $H_N - N - O_W$ for C and $H_N - N - O$ for D). The framed areas correspond to the regions of H-bonding.



Fig. S10. Intermittent contact ACFs for the $O_W - O_W$, $O - O_W$, $H_N - O_W$, $C_H - O_W$ and C - C pairs (**A**) and intermittent H-bond ACFs for the $O_W - O_W$, $O - O_W$, $H_N - O_W$, and $O - H_N$ pairs (**B**) in the 3.0 M 1,3-DMU solution.



Fig. S11. Relative probabilities of finding 0 to 3 H-bonds between the carbonyl oxygen and surrounding water molecules (A), the amino group and water (B), both amino groups and water (C), and the carbonyl oxygen and 1,3-DMU (D) as a function of 1,3-DMU concentration. The error bars were obtained by averaging the results of histograms on the first five 1,3-DMU molecules in each system.