

Molecular Dynamics Simulations of Dimethyl Sulfoxide and Dimethyl Sulfoxide–Water Mixture

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Constant-pressure constant-temperature MD simulations at ambient conditions have been carried out to evaluate three different potential models for DMSO, both as pure liquid and in the (1:3) DMSO–H₂O mixture, based on structural, thermodynamical, and dynamical properties. All the three models for DMSO: OPLS, P2, and NPS, the last one proposed by us, gave a good description of liquid DMSO. In combination with the SPC/E and TIP3P water models, these three potential functions were applied to predict excess mixing functions, reorientational correlation times and diffusion coefficients of the (1:3) DMSO–water binary system. Results obtained with the P2 and NPS models in combination with the SPC/E model for water agreed better with experiment than the OPLS model with either TIP3P or SPC/E water. The new NPS potential model was further used for an analysis of the spatial solvation structure around DMSO in the 1:3 mixture of DMSO–water, based on pairwise spatial distribution functions of atomic number densities. To reveal key structural features and molecular topologies beyond the first solvation shell, a new type of multiparticle spatial distribution function was introduced. Statistical analysis of the hydrogen-bond network, in the system with a large excess of acceptors, revealed DMSO·2H₂O but not the previously suggested DMSO·3H₂O complexes. Also the widely accepted picture of the DMSO·2H₂O complexes needs a revision since many of these water molecules were further bound to nearby DMSO molecules. Moreover, another typical configuration, consisting of two DMSO and three water molecules, of which one was bridged to the two DMSO molecules, was found. In general, the heavy and slowly moving DMSO molecules are stronger competitors for available donated hydrogen bonds than water molecules.

1. Introduction

Many liquid mixtures, known as mixed solvents, show unusual and often spectacularly deviating properties from what can be observed for the pure components they are made of.¹ For example, many substances dissolve easily in solvent mixtures, while they are hardly soluble in the pure components and *vice versa*. Mixtures containing alcohols, acetonitrile, and dimethyl sulfoxide (DMSO) are characteristic examples. Including both aqueous and nonaqueous mixtures of them.¹

Naturally, the properties of these mixed solvents depend on the mutual concentration of the components. Previous studies on binary mixtures show that there exist several concentration intervals with distinct different structural and thermodynamical properties upon changing the proportions of the components (see reference 2, and references therein). The mixture of DMSO and water is, due to its associative character, one of the most striking examples.³ This system shows a strongly nonideal behavior, reflected in a number of physical properties, such as the freezing temperature, excess mixing volume, and other thermodynamic functions, translational and rotational diffusion constants and viscosity, to mention a few. When plotted against the composition, many of these properties go through of a maximum or a minimum value at $X_{\text{DMSO}} = 0.25\text{--}0.35$.

On the basis of NMR^{4,5} observations, it has been proposed that aqueous solutions of DMSO contain complexes with either

two or three water molecules attached to one single DMSO molecule, held together by strong hydrogen bonds. These complexes apparently remain stable during several rotational correlation time periods of the individual molecules.⁵ Close to its incredibly low freezing point of $-62\text{ }^{\circ}\text{C}$, which is more than 80° below the normal freezing point of pure DMSO, the 1:3 mixture of DMSO and water behaves essentially like a one-component system,⁶ indicating an existence of a stable solvation complex and behaving like a distinct component in the mixture at these conditions. The very low freezing point has made it to a popular cryosolvent. Mixtures of DMSO and water have also been used in biological applications ranging from antibacterial activity to membrane permeability.³ Most of these effects are, however, still not well understood.

Computer simulations, such as the Monte Carlo (MC) and molecular dynamics (MD) are now standard tools in studies of biological systems and in drug design. Most of these studies are carried out in water solution and require water models giving a realistic natural environment for biomolecules. The great importance of water as a solvent is reflected in the rich choice of available water models which have been tested in hundreds of simulation studies. Particularly, the potential models should reproduce the dielectric properties as well as provide intermolecular hydrogen bonds. The solvent should also reproduce the proper diffusion coefficient at the used temperature. It should be mentioned that many water models give diffusion coefficients in simulations, carried out at room temperatures, corresponding to very much higher, biologically irrelevant temperatures.

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Often it is of interest to carry out computer simulations of organic and even biomolecular systems in other solvents than water. However, potential models for other liquids are not always as thoroughly evaluated as water models for which there is a large number of interaction potentials reported in the literature. This is particularly true for solvent mixtures. In the case of DMSO there are, however, several potential models developed and some of these have been used even in the simulations of aqueous mixtures. The influence of DMSO on molecular liquid structure of water has been discussed on the basis of radial distribution functions (RDFs) by Vaisman and Berkowitz,⁷ by Luzar and Chandler⁸ and by Borin and Skaf.⁹ Typical molecular configurations, including DMSO·2H₂O clusters have been revealed in the simulations and the average number of hydrogen bonds between DMSO and water has been estimated.⁸ DMSO was found to “enhance” the structure of water in very dilute solutions, while a further increase in DMSO concentration in the solution led to a “breakdown” of the water structure.⁷

However, lack of reliable experimental data concerning the molecular liquid structure in the binary solutions makes the evaluation of the potential functions difficult. Weighted sums of the Fourier transformed RDFs for both heavy atoms and hydrogens for DMSO and the binary system at 298 K were obtained by Luzar et al.^{10,11} by means of neutron diffraction, considering incoherent scattering to be negligible. These data shed light on molecular structure of liquid DMSO. However, the structure of the binary system is far too complex to be derived from three weighted RDFs. Moreover, the uncertainties in the area of the first peak are high (up to 30%). Thermodynamic properties and kinetic characteristics, such as translational diffusion coefficients and rotational correlation times in pure components and binary system have been studied fairly extensively. The ability of a molecular model to accurately reproduce the thermodynamic mixing functions and mobility of such associated mixture indicates that the molecular structure is also described fairly reasonably in many earlier studies. Diffusion constants also reflect stability of hydrogen bond structure in associated liquids, and subsequently influence the structure and dynamics of macromolecules in such solutions substantially.

Simulation studies are reported where large organic solutes are dissolved in DMSO or in aqueous mixture of DMSO.^{12,13} Recent MD simulation of disaccharide α -D-Manp-(1 \rightarrow 3)- β -D-Glcp-OMe in a 1:3 DMSO–water mixture showed that the conformational behavior of the solute crucially depends on the model used for the solvent.¹³ This shows the importance of carefully evaluating the solvent interaction potential functions against available experimental data.

In the present work we report constant pressure (NPT) MD studies of both pure DMSO and 1:3 DMSO–water mixture. Three different parameter sets for DMSO are tested against experimental data on density, heat of evaporation, mobility and molecular structure of the pure component at $T = 303$ K and $p = 1$ atm. Thereafter, these three models in combination with two different potential models for water are applied to simulate the 1:3 DMSO–water mixture at the same conditions. Excess mixing functions and mobility in the binary solution are considered in connection with hydrogen bond structure and dynamics for each of the model systems.

Finally, a detailed analysis of the liquid structure of the 1:3 DMSO–water mixture has been carried out using the DMSO potential model suggested in this work. Standard spatial distribution functions are used to investigate the first solvation

TABLE 1: Parameters of Intermolecular Potentials for Dimethyl Sulfoxide^a

	P2	OPLS	NPS
ϵ_{O}/k (K)	35.99	140.86	71.06
σ_{O}/k (Å)	2.80	2.93	2.92
ϵ_{S}/k (K)	119.96	198.71	168.18
σ_{S}/k (Å)	3.40	3.56	3.66
ϵ_{CH_3}/k (K)	147.94	80.49	11.51
σ_{CH_3}/k (Å)	3.80	3.81	3.76

^a Molecular geometry for all three models: $r_{\text{OS}} = 1.53$ Å, $r_{\text{SC}} = 1.80$ Å, $\angle\text{OSC} = 106.75^\circ$, $\angle\text{CSC} = 97.4^\circ$. Partial charges assigned to each site (in units of e): $q_{\text{O}} = -0.459$, $q_{\text{S}} = 0.139$, $q_{\text{C}} = 0.160$.

shell around the solute. In attempt to visualize key structural and topological features beyond the first shell, a new approach, based on multiparticle spatial distribution functions is introduced. As a complement to the three-dimensional analysis, rigorous and systematic statistical analysis of the hydrogen bonds is carried out, revealing a more complex hydrogen bond network structure than the now widely accepted picture of DMSO complexes with 2 or 3 water molecules attached to it.

2. Computational Aspects

2.1. Molecular Models. In this work we use several simple rigid potential models for the both components, DMSO and water, with the intermolecular pair-potential represented in a usual manner, as a sum of pairwise Coulombic and Lennard-Jones contributions:

$$U(r_{ij}) = 4\epsilon_{ij}((\sigma_{ij}/r_{ij})^{12} - (\sigma_{ij}/r_{ij})^6) + q_i q_j / 4\pi\epsilon_0 r_{ij} \quad (1)$$

where r_{ij} is the distance between sites i and j and ϵ_{ij} and σ_{ij} are energetic and geometric parameters of the Lennard-Jones potential for this pair of sites. q_i and q_j are the partial charges assigned to each site. Lennard-Jones parameters for unlike interactions ($i \neq j$) were calculated from those for like interactions through the simple combination rules:

$$\epsilon_{ij} = (\epsilon_{ii}\epsilon_{jj})^{1/2}, \quad \sigma_{ij} = (\sigma_{ii} + \sigma_{jj})/2 \quad (2)$$

The Lennard-Jones part of the potential was cut off at 15 Å without shifting it. The Ewald summation method was applied to account the long-range electrostatic interactions.

In the present study, the SPC/E model of Berendsen et al.¹⁴ has been used for water. This model is known to give a good agreement with experimental radial distribution functions and diffusion coefficient for pure water at ambient temperatures. As the second water model we used the TIP3P model of Jorgensen et al.¹⁵ Another common choice for simulations of macromolecules in aqueous solutions.

A number of simple models have been developed to model DMSO as a liquid. As in the case of existing water models, different DMSO models are able to describe reasonably well different properties of the pure liquid.^{16,17} We have chosen the OPLS potential¹⁸ and the P2 potential by Luzar and Chandler.⁸ Both of them have been used in simulations of peptides and carbohydrates^{12,13} in DMSO solution. In both models, the united-atom presentation of the methyl groups is applied. Both models have the same molecular geometry, taken from crystallographic data,¹⁹ and atomic charges are calculated at the RHF/6-31G* level of approximation by Rao and Singh.²⁰ Parameters of the models are given in Table 1. According to Skaf,¹⁷ both these models reproduce the internal energy and diffusion coefficient with a reasonable accuracy. The agreement with the neutron

diffraction data on molecular structure⁸ of the pure liquid is less satisfactory.^{16,17}

2.1.1. New Parameter Set for DMSO. We also introduce a new set of Lennard-Jones parameters for DMSO, in which we have used the set of parameters, given by Rao and Singh²⁰ (denoted RS hereafter) as a starting point. Their model shows a good agreement with the neutron diffraction data on the molecular structure of liquid DMSO. However, compared to the experimental values, the RS model gives the internal energy as much as 30% too low and the self-diffusion coefficient of DMSO about 3 times too high.

In attempt to find a set of parameters to provide reasonably good results for the liquid structure, density, energy, and translational diffusion we could reach a good compromise. Our parameters are added in Table 1. The three parameter sets, shown in the table, differ considerably from each other. The OPLS model assigns a large van der Waals energy term to the oxygen atom (ϵ_O). For the P2 potential this value is about 3 times smaller, while larger energy constants are assigned to the methyl groups. In our set of parameters, the ϵ_O value is closer to those in SPC and TIP water models and ϵ_{CH_3} is close to that for ethane molecule by Vrabc and Fischer.²¹ Effective atomic diameters σ also change up to 5 % from one model to another, which is a considerable difference for this geometrical parameter.

2.2. Simulation Details. MD simulations were carried out within the NPT ensemble at $T = 303$ K and $p = 1$ atm with several model systems. First, simulations of pure DMSO were performed using the P2 and OPLS models and the new parameter set (NPS). Also, one reference simulation of pure SPC/E water was carried out for verification and comparison. In the simulations of the pure components, the cubic periodic box was filled with 256 molecules. The binary systems were made bigger to avoid possible size effects, consisting of 128 molecules of DMSO and 384 molecules of water. The simulation software used was the M.Dyna Mix package²² and the equations of motion were solved using the Verlet leapfrog scheme with the time step of 1fs. Covalent bonds were constrained by applying the SHAKE algorithm.²³ Temperature and pressure were maintained with N ose–Hoover thermostat.^{24,25} Each system was simulated over 250 ps and the statistics were collected during the last 150 ps.

Translational diffusion coefficients were calculated from the mean square displacement using the Einstein relationship. Distinct regions of linear dependence of the mean square displacement (MSD) on time were observed for all systems. Rotational mobility of the molecules was characterized by rotational-reorientational correlation times τ_1 and τ_2 for the dipole vectors, estimated from the corresponding autocorrelation functions, which were assumed to decay exponentially at $\tau \geq 1$ ps. The heat of vaporization $\Delta H_{l \rightarrow v}$ was estimated from the calculated internal energy, assuming the coexisting vapor to be an ideal gas. The hydrogen bonds were determined by the geometrical criteria: we considered two oxygen atoms to form a hydrogen bond via a hydrogen atom if the distance between two oxygens is shorter than 3.4   and the O–H...O angle is within $180^\circ \pm 60^\circ$.

3. Results and Comparison of DMSO Models

Most of previous simulations of DMSO have been carried out at constant volume conditions at an “experimental” density. Simulations reported in this work have been carried out at constant pressure. In doing so, the density of the fluid may deviate from the experimental value. However, this prevents a

TABLE 2: Calculated and Experimental Density, Heat of Vaporization, Self-diffusion Coefficients, Rotational–Reorientational Correlation Times of Liquid Dimethyl Sulfoxide at $T = 303$ K and Water at $T = 298$ K ($p = 1$ atm)

	P2	OPLS	NPS	exptl	SPC/E	exptl
ρ (g/cm ³)	1.092	1.0772	1.091	1.091	1.01	1.0
$\Delta H_{l \rightarrow g}$ (kJ/mol)	51.32	51.57	51.97	52.75 ^a	−40.1	−41.2 ^a
D (10 ^{−9} m ² /s)	1.15	0.95	0.89	0.95	2.51	2.36 ^b
τ_1 (ps)	6.16	6.67	6.91			
τ_2 (ps)	3.2	3.0	3.2	5.2 ^c	2.8	2.8 ^c

^a Calculated from the heat of evaporation and specific heat,²⁶ assuming the coexisting vapor to be ideal. ^b Reference 27. ^c Reference 5.

possible violation of the fluid structure and mobility due to the packing effects, caused by differences between the actual simulated and experimental pressure.

3.1. Results for Pure DMSO. **3.1.1. Thermodynamical and Dynamical Properties.** Table 2 shows a number of thermodynamical and dynamical properties of pure DMSO calculated using the three potential models. Both the P2 and NPS potentials represent the experimental liquid density at 303 K and 1 atm very well. Since the Lennard-Jones spheres of the OPLS model are slightly larger, this potential model correspondingly underestimates the liquid density by roughly 2%, a considerable deviation for a liquid density.

The heat of evaporation $\Delta H_{l \rightarrow v}$ can be predicted rather accurately by all three models. It is worth mentioning that the RS model,²⁰ which gives the best agreement with the experimental RDF among suggested potential models, underestimates the heat of evaporation by ca. 30%.

In the case of self-diffusion coefficients, we have used the NMR data of Packer and Tomlinson²⁷ as the experimental reference for translational diffusion coefficients D both for pure DMSO and DMSO–water binary system. Their results complement those of Cebe et al.²⁸ The OPLS model gives nearly an exact agreement with the experimental self-diffusion coefficient (Table 2), while the P2 model overestimates the self-diffusion of DMSO by roughly 12 %. The NPS model underestimates it slightly. We notice that our values of D_v for the P2 and OPLS models agree well with those of ref 17. The minor disagreements may be due to differences in temperature and density. However, they differ substantially from $D_v = 1.7 \times 10^{-9}$ m²/s for P2 potential, reported in ref 16.

All three models underestimate the rotational mobility of DMSO molecules, compared to the O-17 NMR relaxation results of Kovacs and Kowalewski⁵ (Table 2). According to ref 16, $\tau_2 = 3.2$ ps for P2 model at 298 K and 1 atm, agreeing reasonably with our results. Rotational correlation time for DMSO obtained in the work of ref 29 using Rayleigh scattering is even longer but the Rayleigh τ_2 , unlike that from NMR, is not a single particle property. Longer correlation times were also obtained in the NMR study of Packer and Tomlinson²⁷ (see 5, 30 for discussion).

3.1.2. Liquid Structure. The radial distribution functions (RDF) for the NPS model and the weighted sums of the RDFs for the heavy atoms from the simulation and experiment¹¹ are shown in Figure 1. The structure of pure DMSO has been extensively investigated previously.^{8,11} Nevertheless, it is worth noticing that the radial distribution functions were found to be surprisingly insensitive to the used Lennard-Jones parameters. The obtained difference between different models was even less pronounced, than in the canonical simulation of Skaf.¹⁷ This indicates that molecular structure of DMSO is may largely be

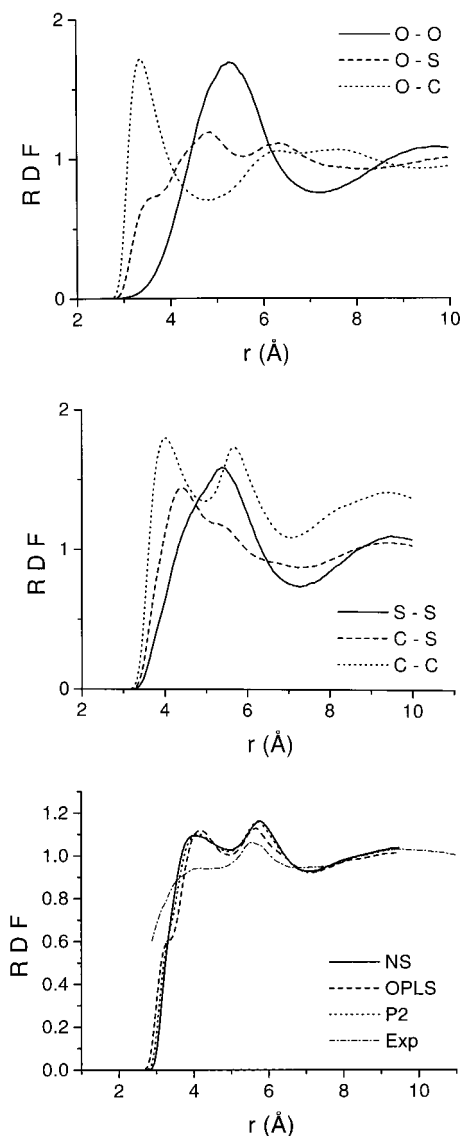


Figure 1. (a,b) radial distribution functions in liquid DMSO at $T = 303$ K and $p = 1$ atm calculated with the new parameter set. (c) calculated and experimental¹¹ weighted sum of radial distribution functions for heavy atoms. Experimental temperature is 298K.

determined by packing effects. To achieve a better agreement with the experiment, one may need either to consider an all-atom model or to assume that due to polarization effects the partial charges in the liquid are different from those of an isolated molecule.

3.2. Results for the 1:3 Mixture of DMSO and Water.

Generally, a good description of the behavior of the pure components is not sufficient to an accurate prediction of the properties of a nonideal associated binary system, such as the mixture of DMSO and water, when simple combination rules are used for the cross interactions.

3.2.1. Thermodynamical Features and Dynamical Behavior.

The DMSO–water binary system exhibits a strongly nonideal behavior, reflected in a high positive heat of mixing and negative excess mixing volume. These features are qualitatively reproduced by all models, applied in the present work (Table 3). However, the quantitative differences between the models are rather significant. It is clear from Table 3 that the results of using P2 and NPS models for DMSO, when combined with the SPC/E potential for water, are much closer to the experi-

mental thermodynamical data than OPLS model, either with SPC/E or TIP3P water potential.

The mobility of the both molecular components becomes overestimated with the OPLS potential. The high self-diffusion coefficients and the short reorientational-rotational correlation times in the OPLS–TIP3P system may be due to the TIP3P water model, which overestimates the mobility in the pure component. However, similar tendencies can be observed even for the OPLS–SPC/E system, although the diffusion is well described in the one-component liquids. Also, the fact that the OPLS models have been parametrized without Ewald summation whereas the present simulations have been carried out with Ewald sum may play some role. Much better agreement was achieved with NMR data^{5,31} for the self-diffusion coefficients using the P2 and NPS parameter sets for DMSO in combination with the SPC/E model for water (Table 3). This result is consistent with the higher density in these systems. Nevertheless, the calculated reorientational correlation times are still considerably shorter, than those obtained experimentally. Partially this can be explained by the fact that NMR spectra are measured for deuterated water in ref 5, and that a higher DMSO concentration was used in.³¹ It should be noted that in the previous work by Gordalla and Zeidler,³² substantially shorter correlation times (around 8 ps) were measured. This was later commented and assumed to be an effect of the fixed O–H bond length.³¹ It should also be mentioned that a direct comparison with the NMR relaxation measurements is not completely appropriate since the reorientational correlation times in this work are calculated for the dipole vector rather than for the vector along the O–H bond. The observations from the experiments,^{5,31} however, make it clear that the presence of DMSO slows down the rotational mobility of the water molecules in the binary mixture.

3.2.2. Solution Structure. Radial distribution functions between the water oxygens (Figure 2) in pure SPC/E water and in binary systems show that the water molecules in the mixture are more strongly correlated with each other than those in pure water. No noticeable difference in the height of the first peak of $g(r_{OO})$ can be observed between the three different DMSO models. However, the average number of water–water hydrogen bonds, calculated based on the geometry criteria, is somewhat higher in the OPLS–SPC/E and OPLS–TIP3P systems (Table 3). This indicates that in the other models, the hydrogen bonds are somehow distorted, i.e., a somewhat larger amount of hydrogen bonds have their O–H...O angles less than 120° . Correlations between water and DMSO oxygens for the different models differ quite substantially from each other. The P2–SPC/E model shows the highest peak of the radial distribution function between water and DMSO oxygens (Figure 3) and highest number of the DMSO–water hydrogen bonds (Table 3). The weakest peak and the lowest number of hydrogen bonds were obtained, when the OPLS model for DMSO molecule was employed. On the other hand, when two DMSO sites are considered, the RDFs show more pronounced peaks and higher coordination numbers (Figure 4) in OPLS–SPC/E and OPLS–TIP3P systems.

3.2.3. Residence Times for Solute–Solvent Hydrogen Bonds.

The stability of the complexes formed by DMSO and water molecules was examined based on the residence times of the water oxygen atoms next to the DMSO oxygen. An occurrence of a “residence” was recorded when the distance between the DMSO and water oxygens was less than 3.4 Å. Occasions of residence lasting a shorter time than 0.2 ps were not taken into account and an occasion was considered to be broken, when

TABLE 3: Some Calculated and Experimental Physical Properties and Average Numbers of Hydrogen Bonds $n^{(h)}$ in (1:3) Dimethylsulfoxide: Water Mixture at $T = 303$ K and $p = 1$ atm (I = P2-SPC/E, II = NPS-SPC/E, III = OPLS-SPC/E, and IV = OPLS-TIP3P)

	I	II	III	IV	exptl
ρ , g/cm ³	1.0628	1.0636	1.0319	1.0312	1.0772 ^a
$\Delta\bar{V}_{\text{mix}}$, cm ³ /mol	-0.493	-0.501	-0.220	-0.185	-0.833 ^a
$\Delta\bar{H}_{\text{mix}}$, KJ/mol	-2.65	-2.61	-0.72	-0.74	-2.96 ^a
$D_{\text{DMSO}} \times 10^9$, m ² /s	0.59	0.51	0.88	1.23	0.61 ^b
$D_{\text{H}_2\text{O}} \times 10^9$, m ² /s	0.78	0.71	1.49	2.55	1.01 ^b
$\tau_{\text{DMSO}}^{(1)}$ (ps)	16.7	14.4	13.9	8.27	
$\tau_{\text{H}_2\text{O}}^{(1)}$ (ps)	10.3	11.7	8.9	5.1	
$\tau_{\text{DMSO}}^{(2)}$ (ps)	5.4	4.5	4.1	2.8	12.5 ^c
$\tau_{\text{H}_2\text{O}}^{(2)}$ (ps)	3.7	4.1	3.6	2.8	10.1, ^c 16.8 ^d
$n_{\text{H}_2\text{O}-\text{H}_2\text{O}}^{(h)}$, per H ₂ O mol.	2.73	2.88	2.91	2.96	
$n_{\text{DMSO}-\text{H}_2\text{O}}^{(h)}$, per DMSO mol.	1.79	1.51	1.38	1.33	
$n_{\text{total}}^{(h)}$, per H ₂ O mol.	3.32	3.38	3.36	3.41	

^a Reference 33. ^bReference 27. ^c Reference 5. ^d Reference 31 at 298 K for 32 mol % DMSO in water.

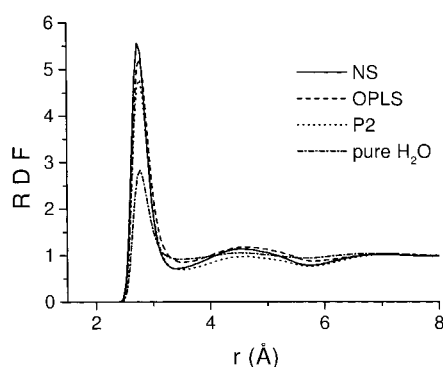


Figure 2. $\text{O}_{\text{H}_2\text{O}}-\text{O}_{\text{H}_2\text{O}}$ radial distribution functions in 1:3 DMSO-water binary solution (1–3) and pure SPC/E water (4) at $T = 303$ K and $p = 1$ atm.

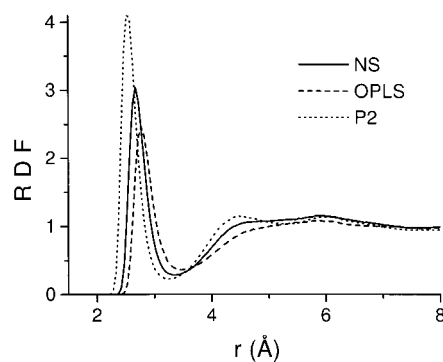


Figure 3. $\text{O}_{\text{DMSO}}-\text{O}_{\text{H}_2\text{O}}$ radial distribution functions in 1:3 DMSO-water binary solution. Notes are the same as in Figure 2.

the distance between two residing oxygens exceeded 3.5 Å, or when it exceeded 3.4 Å during a time interval of 0.2 ps.³⁴

During the simulations, residence times up to 18, 12, 8, and 6 ps could be obtained for P2-SPC/E, NPS-SPC/E, OPLS-SPC/E, and OPLS-TIP3P systems, correspondingly. The $\text{O}_{\text{DMSO}}-\text{O}_{\text{H}_2\text{O}}$ residence times in the OPLS-SPC/E and particularly in the OPLS-TIP3P systems were shorter than those in the P2-SPC/E and NPS-SPC/E systems. This is consistent with the higher self-diffusion coefficients and shorter reorientational correlation times in systems with the OPLS model for DMSO. If we assume that one DMSO molecule is connected to two water molecules at any moment (this is not exactly true—see below), and the probabilities of each hydrogen bond to break are independent, we obtain the values of 7.1, 6.2, and 4.1 ps as the average lifetime of $\text{DMSO}\cdot 2\text{H}_2\text{O}$ complexes in the P2-

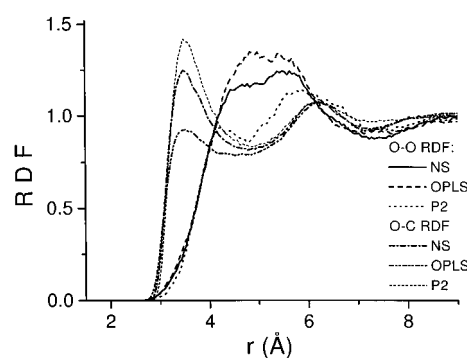


Figure 4. $\text{O}_{\text{DMSO}}-\text{O}_{\text{DMSO}}$ and $\text{O}_{\text{DMSO}}-\text{C}$ radial distribution functions in 1:3 DMSO-water binary solution. Notes are the same as in Figure 2.

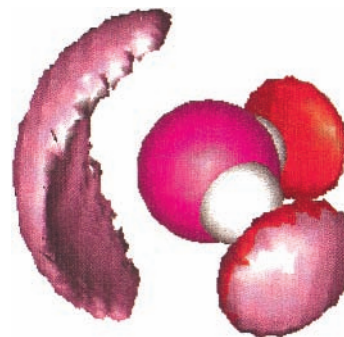


Figure 5. Spatial distribution functions for water and DMSO oxygens around water molecule in 1:3 DMSO-water solution at $T = 303$ K and $p = 1$ atm, calculated using P2-SPC/E model. Isosurfaces in magenta show regions in the local coordinate system attached to the water molecule, where local concentration of water oxygens is 4 times as higher as the average. Clouds in red show the same for DMSO oxygens.

SPC/E, NPS-SPC/E, OPLS-SPC/E systems, respectively. Observe, that these values exceed the corresponding lifetimes of hydrogen bonds in liquid water which are of order of 2–3 ps. They also exceed the rotational-reorientational correlation times of individual DMSO molecules in the solution, thus confirming the previous experimental observations of ref 5.

3.2.4. General Observations. In general, the OPLS parameter set, in combination with both the SPC/E and TIP3P water models, predicts a more hydrophobic solvation of the DMSO molecule in solution, compared to that obtained for the NPS and particularly the P2 model. Most likely the reason is the

larger diameter (σ) and the larger van der Waals interaction constant (ϵ) assigned to the DMSO oxygen in the OPLS parameter set since all models have both same geometry and partial charges. In the P2 parameter set, the ϵ_0 parameter is so small that the configurational energy of the van der Waals interaction between the DMSO oxygen and the other DMSO sites is almost negligible compared to the energy of hydrogen bonding to water molecules, making the intermolecular interactions between the CH_3 groups more pronounced. Again, the NPS model shows results more similar to the P2 model. These results are, in most of cases, in a fair agreement with experimental data. We have carried out a more detailed analysis of structure of 1:3 DMSO–water mixture using the NPS model (see next Section).

4. Spatial Solvation Structure around DMSO

While water molecules can be both double donors and double acceptors of hydrogen bonds, leading ideally to a tetrahedral water coordination, DMSO can only accept hydrogen bonds (Figure 5). As a result of this, any water–DMSO liquid mixture contains an excess of hydrogen bond acceptors (and lacks hydrogens to be donated). Water and DMSO both compete as acceptors of hydrogen bonds, donated by water molecules found next to them. Apparently this leads to some rather interesting solvation effects and hydrogen bond structure in the water–DMSO mixtures.

According to previous computer simulations of aqueous solutions of DMSO and water–DMSO mixtures, DMSO·2H₂O complexes are frequently found^{7,8} as typical molecular configurations. While the DMSO·2H₂O complexes can clearly be observed in the MD trajectories of water–DMSO mixture simulations using all combinations of potential models, the question remains if the anomalous behavior of this mixture at 0.3–0.35 molar ratio of DMSO would be because of complexes where three water molecules are attached to it, as was suggested previously.⁴ For example, there is a possibility for a third water molecule from the second hydration shell to form hydrogen bonds to the first two water molecules already donating their protons to the oxygen in the $>\text{S}=\text{O}$ group. If available, the composition of our (1:3) DMSO–water mixture should favor these kind of DMSO·3H₂O complexes.

4.1. Pairwise Spatial Correlations. Figure 6 shows a spatial distribution of water oxygen around DMSO molecule. The ring around the DMSO oxygen corresponds to typical positions of water oxygens while forming hydrogen bonds with DMSO. Integration of this maxima yields a coordination number of 1.66, indicating that most of the time, two water molecules are bound to the DMSO oxygen. If the two water molecules are in the first solvation shell, they are located on the opposite sides of the ring. Interestingly, there are no preferential orientations of these two waters relative to DMSO methyl groups.

Quite importantly, no preferential position for a third water molecule was found even at a rather low iso-density threshold of SDF (data not shown), except a broad and diffuse region from the methyl side of DMSO. The observed maximum in the water SDF on the methyl side of DMSO can be interpreted as a pure hydrophobic effect resulting a somewhat enhanced mutual structure among the surrounding water molecules. It should be stressed that if all-atomic models were used, instead of united atom models, there could also be a weak attraction to the midpoint of the three hydrogens as a net effect from the three C–H bond polarity. This is frequently observed in quantum chemical calculations of water–hydrocarbon dimers.

Figure 7 shows spatial distributions of DMSO oxygens and methyl groups around a DMSO molecule. It is clear that DMSO

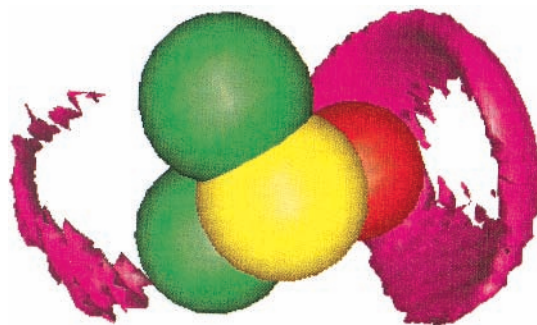


Figure 6. Spatial distribution function of water oxygen around DMSO. Isosurface of SDF at level 3.8 is drawn.



Figure 7. Spatial distribution function of DMSO oxygen (red) and carbon (green) around DMSO in 1:3 DMSO–water mixture. Isosurfaces of SDF at level 3 are drawn.

molecules prefer head-to-tail contacts: oxygen toward methyl groups and *vice versa*. The methyl groups form a ring shaped maxima around the oxygen, similar to that formed by the water oxygens in Figure 6, but at a somewhat larger distance from the oxygen. Methyl groups can therefore occasionally substitute water molecules in the first coordination shell of the DMSO oxygen. There exist also configurations with two waters and one methyl group in the first coordination shell of DMSO oxygen (see below).

4.2. Multiparticle Spatial Distributions. Figures 6 and 7 both use the standard definition of spatial distribution functions,³⁵ when the local coordinate system is attached to one single molecule in the center. These types of SDFs can, for example, be reduced to normal radial distribution functions by averaging over the angular components. However, using this type of SDFs, it is not always possible to extract information about mutual positions and orientations of three or more molecules forming relatively stable and long-living configurations. Therefore, we introduce here a “multiparticle” spatial distribution function (MP–SDF) in which the local coordinate system is defined by the positions of the atoms belonging to different molecules (three or more), at the condition that these molecules are in some “typical” long-enough living configuration, e.g., when the distances between the atoms correspond to the first maxima of the corresponding radial distribution functions.³⁴ In fact, such distribution functions are simply projections of three- or four-body correlation functions in the three-dimensional space.

In Figure 8, we display a MP–SDF of both water oxygens and hydrogens obtained by fixing the local coordinate system

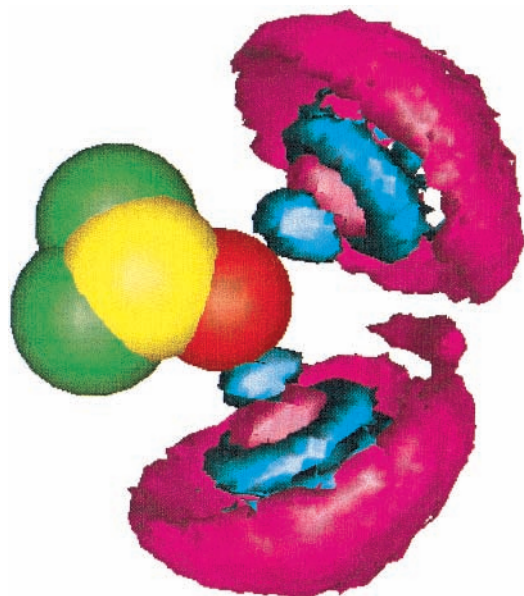


Figure 8. Spatial distribution function of water oxygen (magenta) and hydrogen (light blue) in local coordinate system defined by DMSO oxygen and oxygens of two water molecules at the condition that the distance between DMSO oxygen and water oxygen is 2.65 ± 0.3 Å and between the water oxygens is 4 ± 0.4 Å. The isosurfaces of SDF are drawn at level 3.2.

on the DMSO oxygen and the oxygens of two water molecules, bound to the DMSO molecule, shown previously in Figure 6. One can now clearly see where the water molecules of the second hydration shell are typically located. It is also interesting that these distributions have an almost perfect axial symmetry relative to the hydrogen bond between DMSO and water. This means that the positions of the water molecules in the second hydration shell do not correlate with the orientation of the DMSO molecule, but are rather determined by the orientation of the water molecule in the first hydration shell they are connected to. This MP–SDF also clearly shows that, based on the simulation results, there is no special “third” bound water molecule in the second hydration shell as was proposed previously.⁴

Figure 9a,b show MP–SDFs of DMSO oxygens and methyl groups in the same coordinate system as defined in Figure 8. One can see from the figures that another DMSO molecule can actually enter the first hydration shell of DMSO, already containing two water molecules. These two DMSO molecules prefer to orient themselves nearly perpendicular to each other. Moreover, they appear to share one water molecule which in this case has two hydrogen bonds directed to each of the DMSOs.

The analysis of the both types of spatial distribution functions, based on simulation results, reveals no stable $\text{DMSO}\cdot\text{3H}_2\text{O}$ complexes in the 1:3 DMSO–water mixtures. Moreover, even the resulting picture of the $\text{DMSO}\cdot\text{2H}_2\text{O}$ complexes needs to be corrected. Even if DMSO molecules typically have two water molecules hydrogen-bonded to it, as observed in previous computer simulations, many of these water molecules are further bound to other DMSO molecules. Therefore, instead of well-separated $\text{DMSO}\cdot\text{2H}_2\text{O}$ complexes, a more complex network of long-living hydrogen bonds appears to be present in the solution.

5. Hydrogen Bond Statistical Analysis

To complement the above analysis and to gain a somewhat deeper insight into the liquid structure of the 1:3 DMSO–water

TABLE 4: Statistical Analysis of Hydrogen Bonds in (1:3) DMSO–Water Mixture, Showing Fractions of Molecules Having a Given Number of Donated and Accepted Hydrogen Bonds (Only Accepted for DMSO)^a

		Accepted Bonds for DMSO					
		0	1	2	3		
		0.021	0.445	0.495	0.038		
		H ₂ O					
donated bonds to		accepted bonds					
H ₂ O	DMSO	0	1	2	3	sum	
0	0	0.0 (0.0)	0.001 (0.0)	0.001 (0.001)	0.0 (0.0)	0.002	
1	0	0.001 (0.0)	0.037 (0.032)	0.019 (0.024)	0.001 (0.001)	0.058	
0	1	0.001 (0.001)	0.022 (0.020)	0.013 (0.015)	0.001 (0.001)	0.037	
2	0	0.006 (0.007)	0.252 (0.256)	0.196 (0.193)	0.012 (0.011)	0.467	
1	1	0.005 (0.005)	0.190 (0.194)	0.152 (0.146)	0.008 (0.008)	0.354	
0	2	0.001 (0.001)	0.046 (0.044)	0.032 (0.033)	0.002 (0.002)	0.081	
sum		0.015	0.549	0.413	0.023	1	

^a For water molecules, the last column shows the total distribution of donated H-bonds, irrespectively to the number of accepted bonds, and the last row shows the total distribution of accepted bonds. The numbers in parentheses are the products of total probabilities of the given number of accepted and donated bonds (see text for more details).

mixture, we have carried out a fairly detailed analysis of existing hydrogen bonds formed by each molecule in the mixture. The hydrogen bonds are determined by the geometrical criterium as already defined in section 2. For each molecule we have calculated the probability to have a certain number of hydrogen bonds. The summary of the statistics is given in Table 4.

For DMSO molecules we find, that about half of them have two hydrogen bonded water molecules, while a somewhat smaller part have only one water molecule hydrogen bonded to it. A small fraction of DMSO molecules (roughly 3 %) have three simultaneous hydrogen bonded water molecules attached to them. The occasions of having three water molecules in the first hydration shell are, however, so rare that they do not appear in the spatial distribution functions. Also, they are not of the proposed form of the $\text{DMSO}\cdot\text{3H}_2\text{O}$ complexes as they all occupy the first shell.

The average number of hydrogen bonds per DMSO molecule, 1.51, is only slightly less than the coordination number of 1.66, calculated from the integration of the first maximum of $O_w - O_{\text{DMSO}}$ RDF up to 3.4 Å. This means that nearly 90% of water molecules found in the DMSO first hydration shell also form a hydrogen bond to it.

To collect statistics of hydrogen bonds to water molecules is more complicated. Besides that water molecules can both donate and accept hydrogen bonds, they can also donate hydrogen bonds both to other water molecules and to DMSO. Thus, a “hydrogen-bonded state” of a water molecule may be determined by the following three integers: the number of accepted bonds, the number bonds donated to water and the number of bonds donated to DMSO. Table 4 displays the distribution of water molecules over such states. The last column in Table 4 shows the total distribution over donated hydrogen bonds irrespectively on the number of accepted bonds. The last row shows the total distribution over the number of accepted bonds. The figures in parentheses are the products of total probabilities of the given number of accepted and donated bonds. An interesting observation is that these products closely coincide with the actual

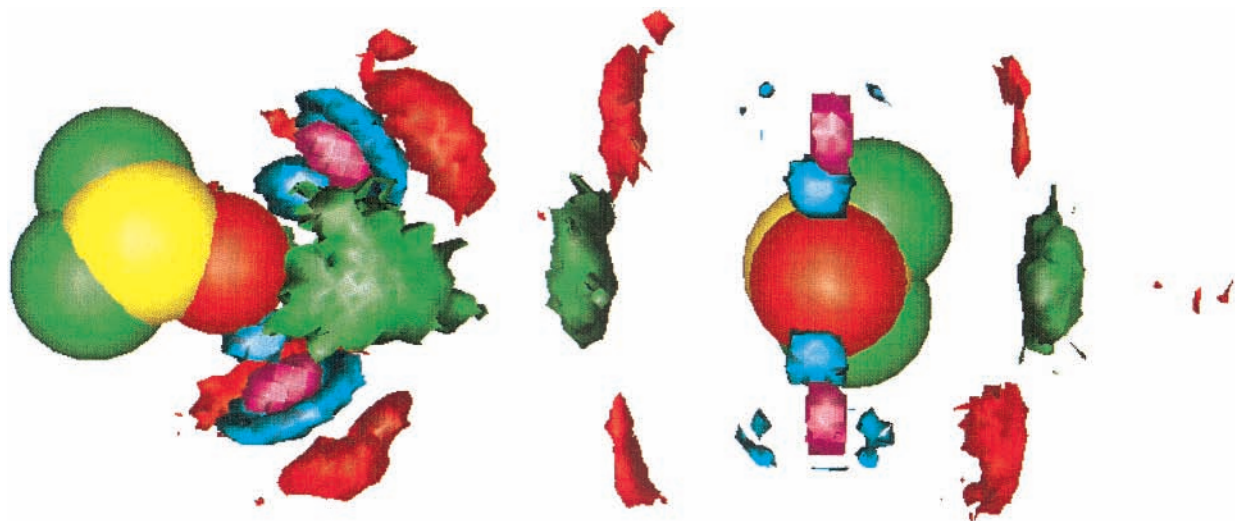


Figure 9. Spatial distribution function of DMSO oxygen (red) and carbon (green) as well of water hydrogen (light blue) in local the coordinate system defined by the DMSO oxygen and the oxygens of two water molecules at the same condition as Figure 8. Views from different sides are shown in (a) and (b). Isosurfaces of SDF are drawn at levels: 2.8 for DMSO oxygen, 3.5 for DMSO carbon, 8 for hydrogens, (a) and 16 for hydrogens (b). Average positions of two water oxygens are shown in magenta.

probability for a water molecule to have given number and type of accepted and donated bond found in the simulation. This means that the correlations between the number of donated and accepted hydrogen bonds for water molecules are absent or almost negligible. This has been observed previously for pure water,³⁶ while in this work it is demonstrated even for the water–DMSO mixture.

Considering the total number of accepted hydrogen bonds for DMSO molecules and water; for water we have a higher fraction of molecules with one accepted bond but smaller fraction of molecules with 2 accepted bonds. As a result, water molecules have less accepted hydrogen bonds per molecule than DMSO.

The analysis of donated hydrogen bonds shows that more than 90% of water molecules have two donated bonds. This fraction is substantially higher than found in pure water (about 75%), which is due to excess of acceptor sites coming from DMSO molecules. Another interesting observation concerns to which molecular components the waters donate their hydrogen bonds. If we assume equal probabilities of all acceptor sites; then having in mind that the number of water molecules is 3 times the number of DMSO, the probabilities must be $0.75^2 = 0.562$ to have two bound water molecules, $2(0.25)(0.75) = 0.375$ to have one water and one DMSO and $0.25^2 = 0.0627$ to have two DMSO molecules. The corresponding fractions from Table 4 are 0.52, 0.39 and 0.09, respectively. Thus, the states with two bound water molecules are underrepresented, while the states with one water and one DMSO are slightly overrepresented and the states with two DMSO bonded to a water molecule are about 40% overrepresented compared to a hypothetical case with an equal probabilities of all acceptor sites.

The fraction of water molecules having two hydrogen bonded DMSO is high enough to become visible in spatial distribution functions (Figure 9). One can evaluate that about half of the DMSO molecules are bound to another DMSO through a bridge of one water molecule. On the other hand, this fraction is not high enough to form longer [–water–DMSO–water–DMSO–] chains. Thus, another typical complex (in addition to the common DMSO·2H₂O complexes) is formed by two DMSO and three water molecules. An example of 2DMSO·3H₂O complex is shown in Figure 10. This particular example is rather spectacular because the displayed five molecules form a ring

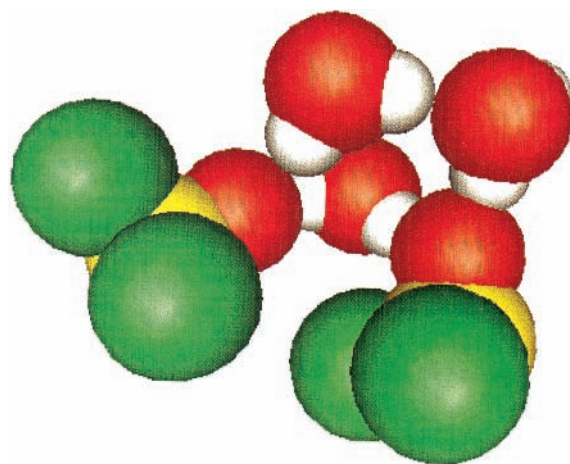


Figure 10. A snapshot of a typical complex formed by two DMSO and three water molecules.

of hydrogen bonds. There exist also 2DMSO·3H₂O complexes which do not form a ring of hydrogen bonds (if the water molecule which is in front in Figure 10 is turned away to another direction). Our simulation shows that such configurations can be found in any momentary snapshot from the trajectory. Note also that positioning of molecules in Figure 10 correlates nicely with the spatial distribution function displayed in Figure 9.

The observed 2DMSO·3H₂O complexes resemble the DMSO–H₂O–DMSO aggregations, observed recently by Borin and Skaf^{9,37,38} in their MD simulations using the P2 DMSO model. The latter complex was found predominantly in DMSO-rich water–DMSO mixtures. Our study shows that this kind of aggregation can exist even in mixtures with a less DMSO content but each DMSO molecule gain an additional water molecule resulting in 2DMSO·3H₂O structures.

6. Conclusion

This work is based on a series of investigations in a successive order with the ultimate goal to reveal the spatial solvation structure and topological features in the 1:3 molar mixture of dimethyl sulfoxide and water. A mixed solvent showing a highly nonideal behavior and extremely low freezing point.

In the first part of this work, we have carried out NPT simulations of DMSO at ambient conditions to verify two

common potential models and a third model, parametrized by ourselves. These models are P2⁸ and OPLS,¹⁸ and what we call a new parameter set (NPS), devised to fit the experimental liquid density and internal energy at 303 K and 1 atm. The geometry and partial charges assigned to the atoms of DMSO molecule are the same for all three models, but the Lennard-Jones parameters used in the different models vary substantially. Good prediction of the properties of neat liquid DMSO, such as the density, heat of evaporation, self-diffusion coefficient, and rotational correlation time has been achieved for all three model systems. The molecular structure of neat liquid DMSO turned out to be quite insensitive to the used Lennard-Jones parameters and showed a reasonably good agreement with the experimental data.

Being aware that good-quality interaction potentials for pure liquids do not necessarily guarantee good results when used to simulate mixtures of them, we carried out, as the second part of this work, a further study to find out the behavior of the three DMSO models when put to work along with two common water models to simulate mixtures thereof. As the water we used the SPC/E and TIP3P models. This showed for the OPLS–TIP3P combination, that although the properties of the pure components were well reproduced, this pair of models failed to predict the strongly nonideal behavior of the binary system. In fact, using both TIP3P and SPC/E as water models. These simulations simply showed a more hydrophobic solvation of DMSO in water than was expected from experimental mixing volume and enthalpy, as well as self-diffusion coefficients and rotational correlation times. We account such a behavior of the model system to the high van der Waals energy parameters assigned to DMSO oxygen in the OPLS potential. Both the P2 and NPS potentials show a more hydrophilic solvation of DMSO molecule yielding in a much better agreement with the experimental data.

Finally, a detailed study of the three-dimensional structural properties of the 1:3 DMSO–water mixture was performed using the NPS potential model together with the SPC/E water as solvent. This analysis was carried out by combining radial and spatial distribution functions with a statistical analysis of hydrogen bond states. A new type of many-body spatial distribution function was introduced to analyze secondary features beyond the first solvation shell.

This study confirmed the presence of DMSO·2H₂O but not DMSO·3H₂O complexes. Moreover, another typical configuration, consisting of two DMSO and three water molecules, one of which bridges the two DMSOs, was found. The statistical hydrogen bond analysis revealed that DMSO molecules are stronger competitors for available donated hydrogen bonds than water molecules.

The clustering of DMSO in the DMSO·2H₂O and 2DMSO·3H₂O complexes in 1:3 DMSO–water mixture forces a substantial fraction of water molecules to be bound to themselves. Most likely they will form microclusters in some empty spaces left by DMSO–water complexes in the same way as was found previously in the mixtures of water and acetonitrile.^{2,39} Besides being partly a normalization effect, this may explain the rather high first maxima of water–water RDF (Figure 3). These high maxima reflect stronger positional correlations of waters in DMSO–water mixture. On the contrary, orientational correlations between these waters are reduced which is manifested by the lower fraction of water–water hydrogen bonds.

One can also conclude, that DMSO molecules turn out to be stronger competitors to accept available donated hydrogen bonds than water molecules, correlating quite nicely with the fact that the lifetime of water–DMSO hydrogen bonds is longer than that for water–water hydrogen bonds (see section 3). The most typical complexes DMSO molecules form with water are the ones with DMSO together with two hydrogen bonded waters and the 2DMSO·3H₂O complexes, found in this work. Of course, the slow moving DMSOs, being roughly 4 times heavier than water molecules, provide an ideal and stable platform for water molecules donate their hydrogens.

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