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# Effects of dimethyl sulfoxide on the hydrogen bonding structure and dynamics of aqueous N-methylacetamide solution

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**Abstract.** Effects of dimethyl-sulfoxide (DMSO) on the hydrogen bonding structure and dynamics in aqueous N-methylacetamide (NMA) solution are investigated by classical molecular dynamics simulations. The modifications of structure and interaction between water and NMA in presence of DMSO molecules are calculated by various site-site radial distribution functions and average interaction energies between these species in the solution. It is observed that the aqueous peptide hydrogen bond interaction is relatively stronger with increasing concentration of DMSO, whereas methyl-methyl interaction between NMA and DMSO decreases significantly. The DMSO molecule prefers to interact with amide-hydrogen of NMA even at lower DMSO concentration. The lifetimes and structural-relaxation times of NMA-water, water-water and DMSO-water hydrogen bonds are found to increase with increasing DMSO concentration in the solution. The slower translational and rotational dynamics of NMA is observed in concentrated DMSO solution due to formation of stronger inter-species hydrogen bonds in the solution.

**Keywords.** Aqueous NMA-DMSO solution; hydrogen-bond lifetime; structural relaxation times; self-diffusion coefficients; orientational relaxation times.

## 1. Introduction

Dimethyl sulfoxide (DMSO) is an important organic solvent, with immense significance in chemical and biological systems.[1] In addition to being an effective cryoprotectant,[2] it displays a myriad of pharmacological actions,[3,4] and also facilitates transport through biomembranes.[5–7] It is well-known that water-DMSO mixtures, exhibit non-ideal behaviour at 30-40 mole% of DMSO, and form DMSO-water molecular aggregates of varying stoichiometry, like 2:1[8] (in DMSO-rich aqueous solutions) as well as 1:2,[9,10] 2:3,[11] and 1:3[12] at low DMSO concentrations. While pressure-induced anomalous behaviour of these dynamical properties is observed at low concentrations of DMSO,[13] Pattanayak and Chowdhuri[14] have shown that these pressure related anomalies vanish at higher concentrations of DMSO due to disruption of water hydrogen bond network and formation of stable water-DMSO complexes. Bagchi and co-workers have found enhanced pair hydrophobicity[15] along with continuum percolation transition in water-DMSO mixtures[16] at $x_{DMSO} \sim 0.15$, which is responsible for anomalies at this concentration range. Recently, Idriisi *et al.,*[17] have carried out molecular dynamics simulations of water-DMSO mixtures

aided by Voronoi polyhedral analysis, which offer separate mechanisms for dilution of neat DMSO and water by the other component, owing to different affinities of mixing. The unique properties of aqueous solution of DMSO have prompted extensive experimental[18–24] as well as computer simulation studies.[8–12,14–17,25–31]

Addition of DMSO as a cosolvent in the aqueous environment of proteins can help us understand modulations of folding/unfolding equilibria, conformational flexibilities and protein-solvent interactions.[32–38] Experimental and molecular dynamics simulations studies have revealed aqueous DMSO-induced structural and conformational perturbations in proteins such as lysozyme[32,33] and bovine serum albumin,[35] preferential unfolding of alpha-helices over beta-sheets[37,38] as well as effects in protein behaviour like aggregation and stability.[39] Influence of DMSO, on aqueous solutions of the peptide N-acetyl-leucine-methylamide has been evaluated and it has been found that DMSO prefers to deplete the hydration layer around the peptide bond.[40] A natural starting point for such kind of investigations would be simple amides like N-methylformamide and N-methylacetamide which are models for peptide group linkages,[41,42] Studies of mixtures containing N-methylformamide or N-methylacetamide with neat DMSO have been documented in literature.[42–48] Borges and Cordeiro[45] have compared the behaviour of

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N-methylformamide in DMSO and water and have found the NMF-DMSO solvation shells to be better structured than in the aqueous one. The study suggested that DMSO may dislodge water molecules bonded to amide structures, promoting dehydration. It is also observed that NMF-DMSO interactions are stronger than both NMF-NMF[43,44] and NMF-water hydrogen bonds.[45] Infrared studies of Shaw and Li[46] show that DMSO effectively disrupts the inter-amide bonds of N-methylacetamide by acting as hydrogen bond acceptor to the NH group of NMA. Molecular associations between NMA-DMSO in its binary mixture in benzene solution have been predicted using dielectric relaxation measurements.[47] Molecular dynamics simulations by DeCamp and co-workers[48] reveal strong hydrogen bonding interaction between oxygen atom of DMSO and amide-hydrogen of NMA, which gives rise to amide I mode frequency shift in the NMA-DMSO system. In the light of the above studies, it would be interesting to build up a concrete idea of hydrogen bonding structure and dynamics of aqueous N-methylacetamide solution in presence of DMSO.

In this work, we have studied the effect of addition of DMSO to an aqueous environment of N-methylacetamide. We have carried out a series of molecular dynamics simulations of $\sim$1.13 $m$(mol/kg) aqueous N-methylacetamide (NMA) solutions with varying DMSO concentration, ranging from 0.0 $m$ to 14.232 $m$. The primary goal is to investigate the effects of DMSO on the hydrogen bonding structure and dynamics of aqueous NMA solution. We have calculated the number and energies of NMA–water, water–water, DMSO–water and NMA−DMSO hydrogen bonds along with their hydrogen-bond lifetime, and structural relaxation times at varying concentrations of DMSO. We have also provided the details of the translational and rotational dynamics of these molecules in these solutions.

The rest of the paper is organized as follows. In section 2, we describe the models and simulation details. In section 3.1, we present the structure and hydrogen bond properties of aqueous-NMA-DMSO solution. The lifetime and structural relaxation time of these hydrogen bonds are presented in section 3.2. The self-diffusion coefficients and orientational relaxation times of these associated molecules are discussed in section 3.3, and the conclusions are summarized in section 4.

## 2. Models and Simulation Details

In the present work, NMA, DMSO and water molecules are characterized by the multisite interaction models. In these models, the interaction between atomic sites of two molecules is expressed as

$$u\left(r_{ij}\right) = 4\varepsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^6\right] + \frac{q_i q_j}{r_{ij}} \quad (1)$$

where, $q_i$ is the charge of the $i$-th atom or ion. The Lennard-Jones parameters $\sigma_{ij}$ and $\varepsilon_{ij}$ are obtained by using the combination rules $\sigma_{ij} = (\sigma_i \sigma_j)/2$ and $\varepsilon_{ij} = \sqrt{\varepsilon_i \varepsilon_j}$, where $\sigma_i$ and $\varepsilon_i$ are the Lennard-Jones diameter and well-depth parameter for $i$-th atom. We have used OPLS potential parameters for NMA.[49] The DMSO molecules are modeled by the 4-site P2 model of Luzar and Chandler[9] which comprises of two methyl, one sulfur and one oxygen sites, with all sites acting both as Lennard-Jones and charge interaction sites. The methyl group in NMA and DMSO is considered to be a single interaction site and thus the hydrogen atoms of the methyl group are not considered explicitly here. For water, we have employed the extended simple point charge (SPC/E) potential.[50] The rigid geometry and the values of the potential parameters $q_i$, $\sigma_i$, and $\varepsilon_i$ for NMA, DMSO and water are taken from the literature.[9,49,50] The corresponding potential parameters for NMA, DMSO and water molecules are summarized in table 1.

The molecular dynamics simulations were carried out in a cubic box with a total of 490 particles of water and DMSO along with 10 *trans*-N-methylacetamide molecules. The simulations were performed at 308 K with six different concentrations of aqueous DMSO solution, ranging from pure water to 14.232 $m$(mol/kg) concentrated DMSO solution. We have employed the minimum image convention for calculation of the short-range Lennard-Jones interactions. The long-range electrostatic interactions were treated using the Ewald method[51] and for the integration over time, we adopted the leap-frog algorithm with time step of $10^{-15}$ s (1 fs).

**Table 1.** Values of Lennard-Jones and electrostatic interaction potential parameters for NMA, water and DMSO, *e* represents the magnitude of electronic charge.

| Name | Atom/Ion | $\sigma$ (Å) | $\varepsilon$ (kJ/mol) | Charge ($e$) |
|------|----------|--------------|------------------------|--------------|
| NMA | C | 3.75 | 0.4396 | 0.50 |
| | $CH_3(C)$ | 3.91 | 0.6699 | 0.0 |
| | O | 2.96 | 0.8793 | −0.50 |
| | N | 3.25 | 0.7118 | −0.57 |
| | $CH_3(N)$ | 3.80 | 0.7118 | 0.20 |
| | H | 0.0 | 0.0 | 0.37 |
| Water | O | 3.166 | 0.6502 | −0.8476 |
| | H | 0.0 | 0.0 | 0.4238 |
| DMSO | | 2.80 | 0.29922 | −0.459 |
| | S | 3.40 | 0.99741 | −0.139 |
| | $CH_3$ | 3.80 | 1.230 | 0.160 |

In the starting configuration, the NMA and solvent molecules were located on a face-centered-cubic lattice with random orientations of solvent molecules. In order to find the appropriate box size for a desired pressure at $T = 308$ K, we first carried out MD runs of 600–800 ps at a constant pressure of 0.1 MPa by employing the weak coupling scheme of Berendsen *et al*.[52] During this initial phase of the simulations, the volume of the simulation box was allowed to fluctuate, and the average volume was determined at the end of the simulation. The box length varied from 25.57 Å in 1.156 *m* DMSO concentration to 28.82 Å in 14.232 *m*DMSO solution. Subsequently, we carried out simulations in microcanonical ensemble with the fixed box size obtained previously for a given system at a given temperature ($T$) and pressure ($P$). While carrying out the simulations in a microcanonical ensemble, each system was equilibrated for 1.6-2.0 ns and the simulations were run for another 4–5 ns for the calculation of the structural and dynamical quantities. The average values of pressure of a system during the production phase of each simulation were found to be close to desired pressure $P = 0.1\pm0.4$ MPa.

## 3. Results and Discussion

### 3.1 *Solvation structure and hydrogen bond properties*

The influence of DMSO on the local structural properties of aqueous NMA solution is characterized by various NMA-water and NMA-DMSO pair correlation functions. In figure 1(a, b), we represent the radial distribution functions (RDFs) between carbonyl-oxygen of NMA and oxygen of water, and the carbonyl-oxygen of NMA and hydrogen of water. The first peak at 2.74 Å in figure 1a, representing the correlation between oxygen sites of NMA and water, arises due to the hydrogen bonding where NMA molecule acts as an acceptor for the hydrogen of a water molecule. The probability of this interaction is higher with increasing DMSO
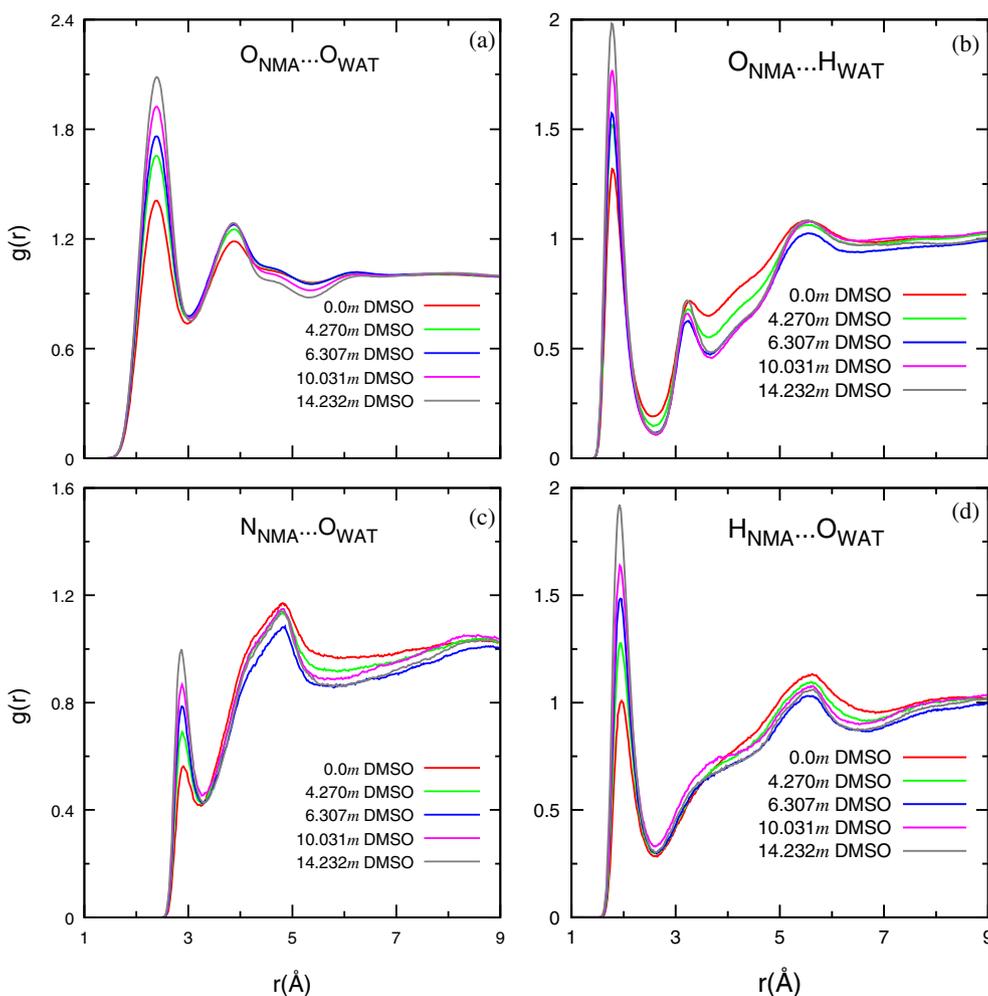


**Figure 1.** The radial distribution functions of aqueous NMA solution with varying concentrations of DMSO: **(a)** oxygen (NMA) – oxygen (water), **(b)** oxygen (NMA) – hydrogen (water), **(c)** nitrogen (NMA) – oxygen (water) and **(d)** hydrogen (NMA) – oxygen (water).

concentrations in the solution. The second peak at 4.94 Å indicates that all the water molecules present in the vicinity of NMA may or may not participate in hydrogen bonding as discussed in a previous study.[53]

The prominent first peak at 1.78 Å (figure 1b) is the characteristic of hydrogen bonding between hydrogen of water and the oxygen of NMA which is strengthened in presence of DMSO. It is observed that the addition of DMSO to aqueous NMA solution increases the peak height and shifts the position of first and second minima towards higher distances, whereas the position of the first and second maxima remains unchanged. This implies that there is no change in the hydrogen bond distance between carbonyl-oxygen of NMA and hydrogen of water. The radial distribution functions between nitrogen of NMA and oxygen of water, and the amide-hydrogen of NMA and oxygen of water are shown in figure 1(c, d). The characteristic peak of hydrogen bonding at 1.94 Å indicates that the amide-hydrogen of

NMA is donated to the oxygen of water. The hydrogen bonding length in this case is longer than the hydrogen bonds formed between oxygen of NMA and hydrogen of water, which implies that $O_{NMA}-H_{WAT}$ hydrogen bond, is stronger than $O_{WAT}-H_{NMA}$. This observation has also been supported by Koddermann and Ludwig,[54] that the hydrogen bond in which water donates a proton to the NMA carbonyl-group is 50% stronger than the one in which water accepts a proton from NMA. The hydrophobic solvation of methyl-groups of NMA can also be characterized by the $CH_3$-$O_{WAT}$ radial distribution function, as depicted in previous studies[55] and here we have calculated the number of water molecules present near to the methyl-surface by using the $r_{min}$ of $CH_3$-$O_{WAT}$ radial distribution function, *i.e.*, $r_{min} = 5.50$ Å. It is observed that the number of water molecules near to the methyl surface of NMA decreases from 16 (in case of aqueous NMA) to 8 in highly concentrated (14.232 *m*) DMSO solution.
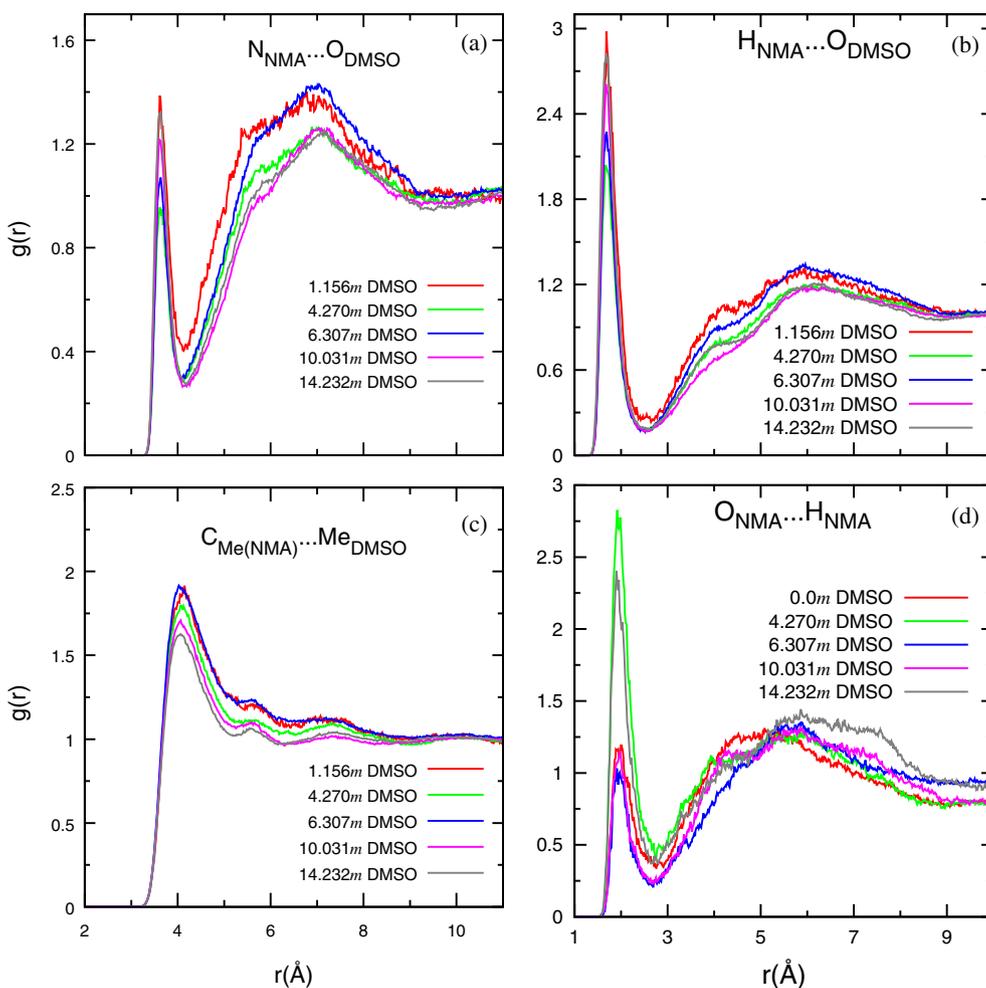


**Figure 2.** The radial distribution functions in aqueous NMA solution with varying concentrations of DMSO: **(a)** nitrogen (NMA) – oxygen (DMSO), **(b)** hydrogen (NMA) – oxygen (DMSO), **(c)** $CH_3$ group of NMA (attached to C) – $CH_3$ group of DMSO, and **(d)** oxygen (NMA) – hydrogen (NMA).

In figure 2(a, b), we have presented the radial distribution functions between nitrogen of NMA and oxygen of DMSO, and the amide-hydrogen of NMA and oxygen of DMSO. It is observed that DMSO acts as an acceptor for the amide hydrogen of NMA forming a hydrogen bond indicated by a peak at 1.68 Å as shown in their radial distribution function, (figure 2b). There is a significant reduction in the methyl-methyl interaction between the methyl-groups of NMA and DMSO molecules with increasing DMSO concentration as shown in the figure 2c. Hence, the DMSO molecule prefers to orient towards the amide containing site of NMA, which may strengthen the hydrogen bond between amide-hydrogen of NMA and oxygen of DMSO. The RDFs between the amide-hydrogen and oxygen of NMA are shown in figure 2d. It is observed that with increasing DMSO, the correlation between $O_{NMA}-H_{NMA}$ increases initially, decreases for the intermediate concentrations (6.307 $m$ – 10.031 $m$ DMSO) and shows stronger interactions again for the highest concentrations of DMSO considered here.

Since the $H_{NMA}-O_{DMSO}$ peak occurs at shorter distances than either $H_{NMA}-O_{WAT}$ or $H_{NMA}-O_{NMA}$, it shows that NMA forms the stronger hydrogen bonds with DMSO compared to water or itself. The first peak of g(r) between $N_{NMA}$-$O_{DMSO}$ occurs at 2.64 Å which is precisely the sum of 1.68 Å ($H_{NMA}$-$O_{DMSO}$ hydrogen bond) and 0.96 Å (N-H bond distance) which suggests collinearity of $O_{DMSO}$-$H_{NMA}$-$N_{NMA}$ atoms. This has also been observed in case of pure NMF-DMSO interactions and has been found comparable to the pattern exhibited by many hydrogen bonded liquids.[44]

Radial distribution functions for water-water, water-DMSO and DMSO-DMSO are well documented in literature[8,9,16,26] and we have shown some of these functions in Supporting Information (SI).

The average interaction energies between NMA-NMA ($E_{PP}$), NMA-water ($E_{PW}$), NMA-DMSO ($E_{PD}$), water-water ($E_{WW}$), water-DMSO ($E_{WD}$) and DMSO-DMSO ($E_{DD}$) have been calculated and the results are tabulated in table 2. It is found that the average interaction between NMA-water decreases from $-2.12$ kJ/mol

in aqueous NMA solution to -1.43 kJ/mol in 14.232 $m$ concentrated DMSO solution. The favorable interaction between NMA and DMSO is also observed with increasing DMSO concentration in the solution. The average water-water and water-DMSO interaction energies show a significant change in the solution, which indicates the alteration of hydrogen bond structure in the solution due to formation of stable interspecies hydrogen bonds between water and DMSO.

To calculate the hydrogen bond properties and dynamics of NMA-water, water-water, water-DMSO and NMA-DMSO hydrogen bonds, we use a set of *geometric criteria*,[14,56–59] where it is assumed that a hydrogen bond between two species exists, if the following distance and angular criteria are satisfied, *i.e.*, $R^{(OX)} < R_c^{(OX)}$, $R^{(OH)} < R_c^{(OH)}$, and $\theta < \theta_c$. In case of NMA-water, water-water, and water-DMSO hydrogen bonds, the distance and angular criteria are taken from previous studies.[14,56] The distance cutoff values can also be obtained from the positions of first minimum of the corresponding radial distribution functions shown in figure 1 (as well as in figures S1 and S2 given in S1). For hydrogen bond of amide hydrogen of NMA - oxygen of DMSO, $R^{(OX)}$ and $R^{(OH)}$ denote the distances of oxygen (DMSO)-nitrogen (NMA) and oxygen (DMSO)-hydrogen (NMA), and angle $\theta(= \theta^{(N_{NMA}O_DH_{NMA})})$ is the nitrogen(NMA)-oxygen(DMSO)-hydrogen (NMA) angle. The cut-off values for $O_{DMSO}-N_{NMA}$ and $O_{DMSO}-H_{NMA}$ distances are determined from the positions of the first minimum of the corresponding RDFs shown in figure 2(a,b). Regarding the angular cut-off $\theta_c$, we have used the cut-off angle $\theta_c = 45°$ for the existence of NMA-DMSO hydrogen bonds as the same $\theta_c$ is used for NMA-water, water-water and water-DMSO hydrogen bonds. In general, the *geometric criteria* of cut-off angle $\theta_c = 30°$ is used but to provide flexibility, the cut-off angle $\theta_c = 45°$ can also be used to accommodate the thermal motion.[59] We have calculated the probability of finding the different numbers of hydrogen bonds in these DMSO concentrated solutions. It is observed that the tetrahedral network structure of water is mainly affected by the DMSO molecule and the loss of four-hydrogen-bonded structure boosts up the distribution of lower number hydrogen bonds. In aqueous NMA solution, approximately 54% of the water molecules are four-hydrogen bonded and 10% are five-hydrogen bonded whereas the number reduces to 31% and 2.5%, respectively, in highly concentrated (14.232 $m$ DMSO) solution. On the other hand, the number of two and three-hydrogen-bonded water molecules increases from 7 and 32% to 20 and 43%, respectively, as we move from aqueous NMA to concentrated aqueous NMA-DMSO solution. It is also observed that the probability

**Table 2.** Average interaction energies (in kJ/mol) between the different species in the aqueous NMA- DMSO solution.

| $C_{DMSO}$ | $E_{PP}$ | $E_{PW}$ | $E_{PD}$ | $E_{WW}$ | $E_{WD}$ | $E_{DD}$ |
|---|---|---|---|---|---|---|
| 0.000 $m$ | $-0.103$ | $-2.12$ | – | $-43.69$ | – | – |
| 1.156 $m$ | $-0.093$ | $-2.00$ | $-0.201$ | $-41.95$ | $-3.36$ | 0.54 |
| 4.270 $m$ | $-0.093$ | $-1.80$ | $-0.436$ | $-37.65$ | $-8.00$ | 0.36 |
| 6.307 $m$ | $-0.069$ | $-1.64$ | $-0.652$ | $-35.15$ | $-10.56$ | $-1.00$ |
| 10.031 $m$ | $-0.060$ | $-1.52$ | $-0.810$ | $-31.00$ | $-14.56$ | $-2.29$ |
| 14.232 $m$ | $-0.068$ | $-1.43$ | $-0.940$ | $-27.04$ | $-17.90$ | $-3.80$ |

**Table 3.** Average number of NMA-water, water-water, DMSO-water and NMA-DMSO hydrogen bonds in aqueous NMA-DMSO solution, with varying concentration of DMSO. The quantities in brackets show the energies of the corresponding hydrogen bonds in kJ/mol.

| $C_{DMSO}$ | $>C=O\ldots H_W$ (per NMA) | $-N-H\ldots O_W$ (per NMA) | $O_W\ldots H_W$ (per Water) | $O_{DMSO}\ldots H_W$ (per DMSO) | $-N-H\ldots O_{DMSO}$ (per NMA) |
|---|---|---|---|---|---|
| 0.00 m | 1.85 (−19.446) | 0.87 (−18.45) | 3.68 (−18.56) | – | – |
| 1.156m | 1.75 (−19.821) | 0.85 (−18.61) | 3.60 (−18.69) | 2.11 (−28.15) | 0.03 (−34.86) |
| 4.270m | 1.55 (−20.174) | 0.82 (−18.81) | 3.41 (−19.03) | 2.00 (−28.48) | 0.07 (−35.31) |
| 6.307m | 1.37 (−20.540) | 0.83 (−19.36) | 3.30 (−19.21) | 1.95 (−28.68) | 0.10 (−35.46) |
| 10.031m | 1.30 (−20.821) | 0.78 (−19.18) | 3.10 (−19.62) | 1.87 (−28.85) | 0.15 (−35.58) |
| 14.232m | 1.24 (−20.890) | 0.74 (−19.81) | 2.89 (−20.02) | 1.75 (−29.05) | 0.20 (−35.76) |

of formation of 1:2 DMSO-water hydrogen-bonded complex is approximately 71-74% in all DMSO solutions. The average number and energies of hydrogen-bonds between different species in the solution are shown in table 3.

It is observed that the average number of NMA-water ($O_{NMA}$–$H_{WAT}$ and $H_{NMA}$–$O_{WAT}$) hydrogen bond decreases whereas the NMA-DMSO ($H_{NMA}$–$O_{DMSO}$) hydrogen bond increases per NMA with increasing DMSO concentration in the solution. Here, the NMA-DMSO hydrogen bond fraction (e.g., 0.20) indicates the probability of maximum number of DMSO molecules (*i.e.*, 20%) to form a single hydrogen bond with amide hydrogen of NMA. In figure 3, we have shown some snapshots of the hydrogen bonds between NMA, water and DMSO molecules. Apart from these, we have also observed several DMSO-water complexes of varying stoichiometry (1:2, 1:3 and 2:3), which are not shown here.

### 3.2 *Hydrogen bond dynamics -lifetime and structural relaxation time*

To calculate the hydrogen bond dynamics of NMA-water, water-water and water-DMSO, we define two hydrogen bond population variables $h(t)$ and $H(t)$, where $h(t)$ is unity when a particular NMA-water, water-water and water-DMSO pair is hydrogen bonded at time $t$ according to the adopted hydrogen-bond definition discussed above and $h(t)$ is zero otherwise. On the other hand, $H(t) = 1$ if the NMA-water, water-water
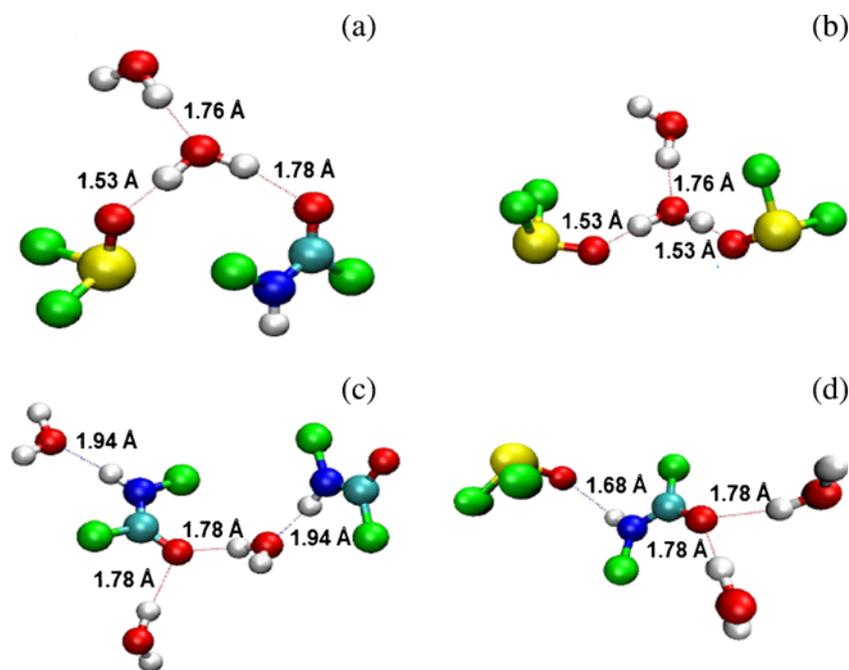


**Figure 3.** Snapshots of hydrogen bonding: **(a)** Water molecules bridging NMA and DMSO molecules; **(b)** Water and DMSO molecules; **(c)** NMA and water molecules; **(d)** NMA hydrogen bonded to water and DMSO molecules.

and water-DMSO pair remain continuously hydrogen bonded from $t = 0$ to time $t$, and it is zero otherwise.

To study the breaking dynamics of hydrogen bonds, we calculate the continuous hydrogen-bond time correlation function $S_{HB}(t)$, which is defined as[59–68]

$$S_{HB}(t) = < h(0)H(t) > / < h(0)^2 >, \quad (2)$$

where $< \cdots >$ denotes an average over all NMA-water, water-water, water-DMSO pairs. Clearly, $S_{HB}(t)$ describes the probability that an initially hydrogen bonded NMA-water, water-water and water-DMSO pair remain bonded at all times up to t. The associated integrated relaxation time $\tau_{HB}$ can be interpreted as the average lifetime of a hydrogen bond. In case of these hydrogen-bonds, the decay of time correlation function is calculated up to 30 ps depending on the proper convergence of this function.

Unlike the continuous correlation function $S_{HB}(t)$, the intermittent hydrogen-bond correlation function $C_{HB}(t)$ does not depend on the continuous presence of a hydrogen bond. It is defined as,[14,59–68]

$$C_{HB}(t) = < h(0)h(t) > / < h > . \quad (3)$$

The correlation function $C_{HB}(t)$ describes the probability that a hydrogen bond is intact at time t, given that it was intact at time zero, independent of possible breaking in the interim time. Thus, the dynamics of $C_{HB}(t)$ describes the structural relaxation of hydrogen bonds, and the associated relaxation times $\tau_R$ can be interpreted as the time scale of reorganization of NMA-water, water-water, water-DMSO bonds. The decay of time correlation function is calculated up to 100 ps depending on the smooth convergence of $C_{HB}(t)$. The initial decay of hydrogen-bond ($O_{NMA} \ldots H_{WAT}$) time correlation functions are shown in figure 4 and the concentration dependence results of NMA-water, water-water and DMSO-water hydrogen bond lifetime and structural relaxation times are shown in table 4.

It is found that the lifetime and structural relaxation time of all types of hydrogen bonds increases with DMSO concentration in the solution. The slower hydrogen bond dynamics in these solutions can be explained on the basis of the stability of these hydrogen bonds (table 3), and also the relative interaction between the species in the solution. It is interesting to note that the lifetime of hydrogen bond acceptance by carbonyl oxygen is increasing approximately four times in highly concentrated solution whereas the lifetime of amide-hydrogen donation to water is increased by only two times. So, comparative faster dynamics in case of $H_{NMA} \ldots O_{WAT}$ hydrogen bond strongly supports the fact that there is a choice for NMA molecule to donate its
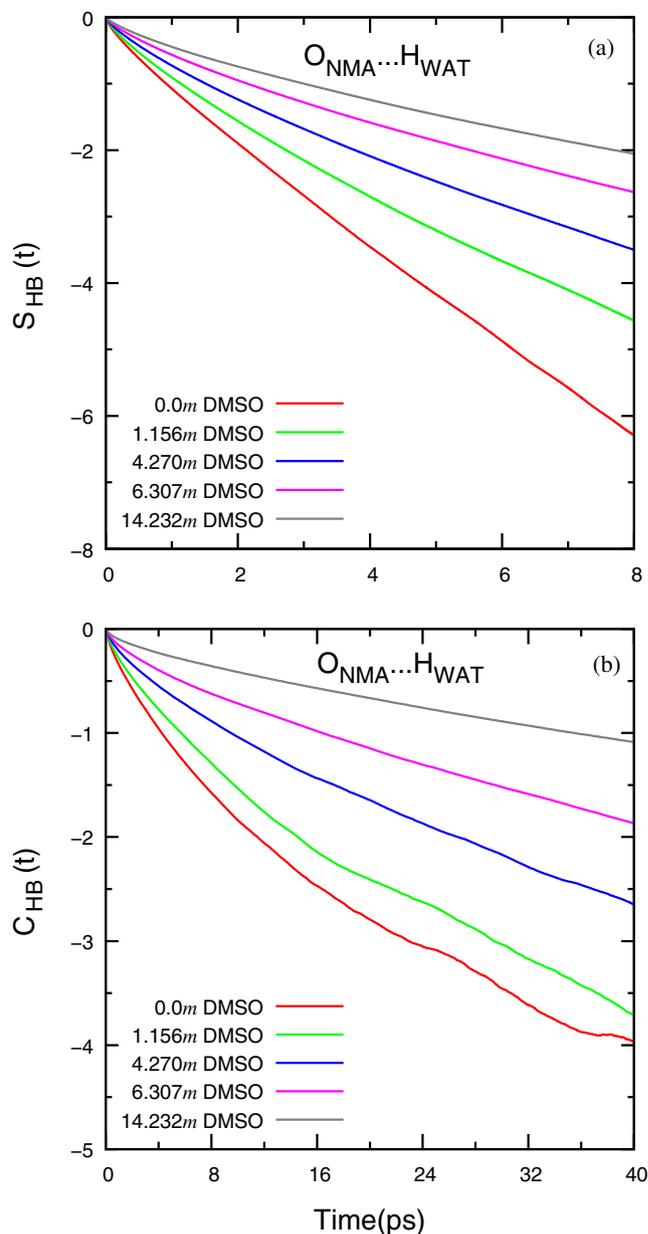


**Figure 4.** The decay of hydrogen bond correlation functions **(a)** $S_{HB}(t)$, and **(b)** $C_{HB}(t)$, in aqueous NMA solution with varying concentrations of DMSO.

amide hydrogen to the oxygen of water or DMSO. As DMSO concentration increases in the solution, the probability of formation of strong NMA-DMSO hydrogen bond is also increased as shown in figure 2b and table 3.

We have calculated the lifetime ($\tau_{HB}$) of NMA-DMSO hydrogen bond only in case of 10.031 and 14.232 $m$ concentrated solutions (due to higher probability of formation of hydrogen bond) and the respective values are $\tau_{HB} = 4.5 \pm 0.17$ and $4.7 \pm 0.19$

**Table 4.** The lifetime ($\tau_{HB}$) and structural-relaxation time ($\tau_R$) of NMA-water, water-water and DMSO-water hydrogen-bonds (in ps) in the solution, with varying concentration of DMSO.

| $C_{DMSO}$ | $\tau_{HB}^{O_{NMA}-H_W}$ | $\tau_{HB}^{H_{NMA}-O_W}$ | $\tau_{HB}^{O_W-H_W}$ | $\tau_{HB}^{O_{DMSO}-H_W}$ | $\tau_{R}^{O_{NMA}-H_W}$ | $\tau_{R}^{H_{NMA}-O_W}$ | $\tau_{R}^{O_W-H_W}$ | $\tau_{R}^{O_{DMSO}-H_W}$ |
|---|---|---|---|---|---|---|---|---|
| 0.00 $m$ | 1.0 | 0.95 | 1.22 | – | 6.30 | 4.46 | 7.70 | – |
| 1.156 $m$ | 1.30 | 1.06 | 1.33 | 2.87 | 7.90 | 5.56 | 9.27 | 15.7 |
| 4.270$m$ | 1.96 | 1.33 | 1.66 | 3.86 | 14.3 | 9.04 | 13.1 | 25.2 |
| 6.307$m$ | 2.22 | 1.49 | 2.01 | 4.40 | 17.8 | 10.3 | 18.2 | 32.7 |
| 10.031 $m$ | 2.87 | 1.83 | 2.47 | 5.67 | 28.3 | 16.9 | 26.1 | 42.6 |
| 14.232 $m$ | 3.56 | 1.98 | 3.21 | 6.29 | 36.0 | 23.6 | 40.1 | 51.4 |

ps. Standard deviation of the calculated hydrogen-bond lifetime shown in table 4, varies within 2% error limit.

### 3.3 *Self-diffusion coefficients and orientational relaxation times*

The translational self-diffusion coefficient $D_i$ of species $i$ is related to the time integral of the velocity-velocity autocorrelation function (VAF) by

$$D_i = \frac{k_B T}{m_i} \int_0^\infty C_v(t)dt, \qquad (4)$$

where $k_B$ is the Boltzmann's constant and $m_i$ is the mass of species $i$ and $C_v(t)$ is the velocity-velocity time correlation function, $C_v(t)$, defined by,

$$C_v(t) = \frac{< v_i(t).v_i(0) >}{< v_i(0).v_i(0) >}, \qquad (5)$$

where $v_i(t)$ is the velocity of the species $i$ at time t[69] and the average is calculated over all the species in the system and over the initial time. The translational self-diffusion coefficient can also be calculated from the long-time limit of the mean-square displacement (MSD)

$$D_i = \lim_{t\to\infty} \frac{< |\mathbf{r}(t) - \mathbf{r}(0)|^2 >}{6t}, \qquad (6)$$

where $\mathbf{r}(t)$ is the position of a species $i$ at time $t$, by a least-square fit of the long-time region of MSD as obtained from simulations. The diffusion coefficients calculated using these two different routes have been found to be quite close to each other and we have taken the average of the values obtained from these two routes for a given type of species. Our calculated self-diffusion coefficient values of NMA, water and DMSO in the solution are shown in figure 5a. In an earlier study[70] self-diffusion coefficients of water and DMSO, using SPC/E and P2 models for water and DMSO respectively, were determined and found to be comparable with the experimental results.[9,13,24,71–73]

The orientational motion of solvent molecules is analyzed by calculating the orientational time correlation function, $C_l^\alpha(t)$, defined by

$$C_l^\alpha(t) = \frac{< P_l[\mathbf{e}^\alpha(t).\mathbf{e}^\alpha(0)] >}{< P_l[\mathbf{e}^\alpha(0).\mathbf{e}^\alpha(0)] >}, \qquad (7)$$

where $P_l$ is the Legendre polynomial of rank $l$ and $\mathbf{e}^\alpha$ is the unit vector which points along the $\alpha$-axis in the molecular frame. In this work, we have calculated the time dependence of $C_l^\alpha(t)$ for $l = 2$, and for the three different $\mathbf{e}^\alpha$, molecular dipole vector $\mu$, N-H vector of NMA and the O-H vector of water.

The orientational correlation time $\tau_l^\alpha$, defined as the time integral of the orientational correlation function

$$\tau_l^\alpha = \int_0^\infty dt C_l^\alpha(t), \qquad (8)$$

were obtained by explicit integration of the data of $C_l^\alpha(t)$ from simulations up to 25 ps for NMA and DMSO, whereas for water we have taken t = 10-25 ps till the values are properly converged. Experimental discussion of the rotational diffusion of NMA at varying water content has been reported in the work done by Rezus and Bakker.[74,75] The orientational relaxation of the N-H and O-H vector can also be measured by $^1$H-$^{15}$N and $^{17}$O-$^1$H dipolar relaxation NMR experiments. However, we are not aware of any such experimental measurement of the aqueous NMA system with varying DMSO concentration. The orientational relaxation times of dipole vector of NMA, water and DMSO along with the orientational relaxation time of N-H vector of NMA and O-H vectors of water are presented in figure 5(b d).

In figure 5c we have shown the anisotropy decay of O-H vector of water molecules with varying DMSO concentration. The experimentally observed anisotropy decay is related to the second-order Legendre polynomial time correlation function as $2/5 C_2^\alpha(t)$, where $\alpha$ designates the orientation of the water O-H bond.[76] The slowest decay in the case of highly concentrated DMSO
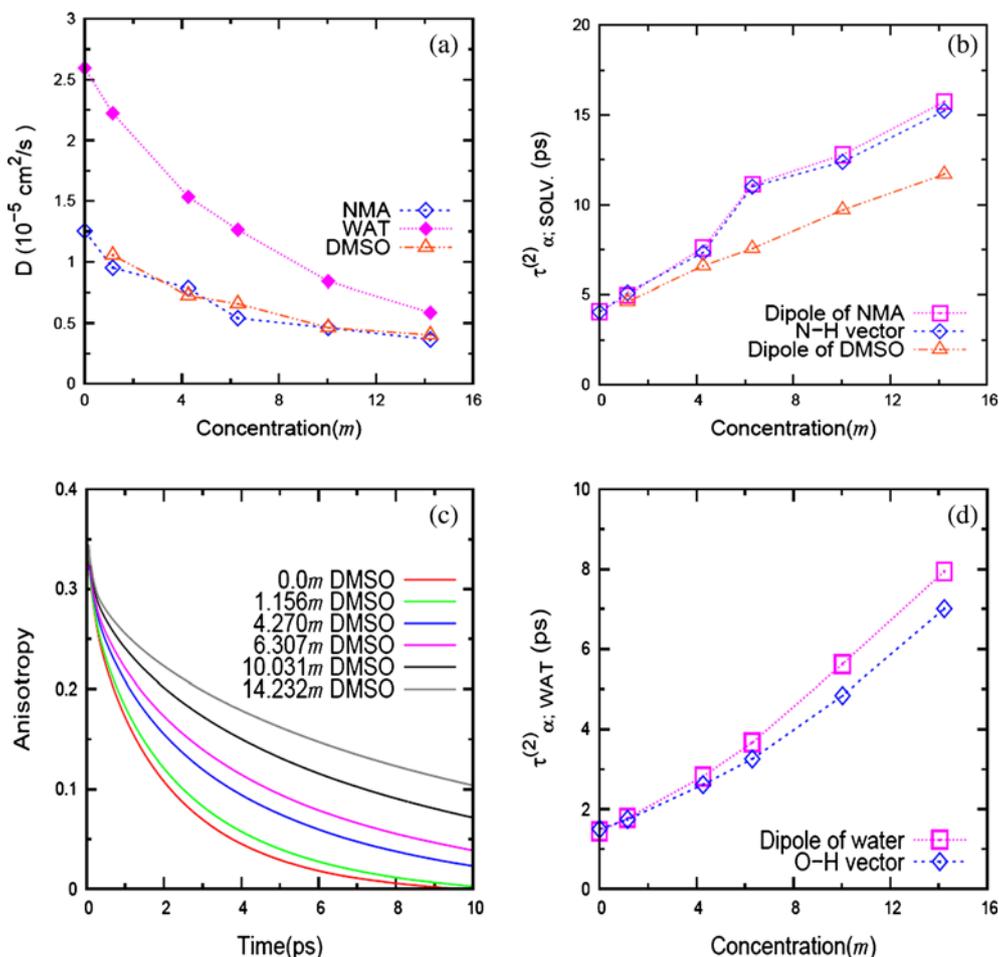
**Figure 5.** The **(a)** self-diffusion coefficients of NMA, water and DMSO, **(b)** the second rank dipole and N-H vector of NMA and the dipole vector orientational relaxation times of DMSO in aqueous NMA solution, **(c)** the anisotropy decay of water, **(d)** the second rank dipole and O-H vector orientational relaxation times of water, with varying concentrations of DMSO.

solution indicates that the water molecules rotate very slowly in the solution, which can be attributed to the presence of stable hydrogen bonded complexes in the solution. Such anisotropy decay plots representing water orientational relaxation in water-DMSO mixtures of various compositions have also been obtained experimentally by Fayer *et al.*,[23] using optical heterodyne detected optical Kerr effect (OHD-OKE) measurements. The slowing down of both translational and orientational motion of solutes and solvent molecules in concentrated solutions can be attributed to the presence of strong inter-species hydrogen bonds in these solutions as discussed above. The standard deviation of the dynamical data presented here is about 2-4% of the average values.

## 4. Conclusions

In this paper, we have presented the molecular dynamics simulation results of concentration dependent behaviour of aqueous NMA solution in presence of DMSO. We have considered six different concentrations of aqueous NMA-DMSO solution, ranging from 0.0 *m* to 14.232 *m* (mol/kg) DMSO. The primary goal is to investigate the effects of DMSO on the structure and dynamics of hydrogen bonds in aqueous NMA solution. We have also calculated the self-diffusion coefficients and orientational relaxation times of all associated particles present in the solution. The significant slowdown of translational and rotational dynamics of particles is observed with the addition of DMSO in the solution. We have calculated the statistics and energies of solute-solvent (NMA-water and NMA-DMSO) as well as solvent-solvent (water-water, DMSO-water) hydrogen bonds along with the solvation structure of NMA in aqueous DMSO solution. It is observed that compared to water, the DMSO molecules prefer to stay in the vicinity of amide-hydrogen of NMA. The strong hydrogen bonding interaction between the oxygen of DMSO and amide-hydrogen of NMA is observed as indicated by their corresponding radial distribution function. The

methyl-methyl interaction between NMA and DMSO reduces with increasing DMSO concentration in the solution, whereas DMSO prefers to interact through its methyl-groups. DMSO also replaced the water molecules from the methyl surface of NMA as the number changes from 16 in aqueous NMA solution to 8 in highly concentrated solution considered here ($14.232\ m$).

Since it is believed that the formation of strong interspecies hydrogen bond complexes is mainly responsible for the dynamical slowdown in these solutions, we have calculated the statistics and energies of NMA-water, water-water, water-DMSO and NMA-DMSO hydrogen bonds along with their lifetime and structural relaxation time. It is observed that lifetime and structural relaxation times of these hydrogen-bonds decay at slower rate with increasing DMSO concentration in the solution as the stabilities of these hydrogen bonds increase. In the case of highest concentrated DMSO solution, the lifetime of $O_{NMA}-H_{WAT}$ hydrogen bond is approximately four times when compared with aqueous NMA solution. On the other hand, the lifetime of $H_{NMA}-O_{WAT}$ hydrogen bond is only two times in $14.232\ m$ DMSO solution as compared with aqueous NMA ($0.0\ m$) solution. This provided the evidence for the disruption of $H_{NMA}-O_{WAT}$ hydrogen bond by DMSO molecules. The lifetime of $H_{NMA}-O_{DMSO}$ hydrogen bond shows significant stability as compared to $H_{NMA}-O_{WAT}$ hydrogen bond.

The present work is mainly focused on the effects of DMSO on the hydrogen bonding structure and dynamics of aqueous NMA solution. It is hoped that these findings may encourage experimental studies in this field. It would also be worthwhile to study the behavior of aqueous NMA or a small peptide in presence of some other cosolvents, like ethanol or trifluoroethanol, where hydrogen bond plays an important role. We will address this issue in near future.

## Supplementary Information (SI)

Interactions between water-water, water-DMSO and DMSO-DMSO atomic sites have been described by their pair correlation functions which are shown in figures S1, S2 and S3, respectively. Supplementary Information is available at www.ias.ac.in/chemsci.

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## References

1. Martin D, Weise A and Niclas H J 1967 *Angew. Chem. Int. Ed. Engl.* **6** 318
2. Lovelock J E and Bishop M W H 1959 *Nature* **183** 1394
3. Rammler D H and Zaffaroni A 1967 *Ann. N. Y. Acad. Sci.* **141** 13
4. Jacob S W and Herschler R 1986 *Cryobiology* **23** 14
5. Smondyrev A M and Berkowitz M L 1999 *Biophys. J.* **76** 2472
6. Sum A K and de Pablo J J 2003 *Biophys. J.* **85** 3636
7. Jacob S W and de la Torre J C 2015 In *Dimethyl Sulfoxide (DMSO) in Trauma and Disease* (New York: CRC Press)
8. Borin I A and Skaf M S 1999 *J. Chem. Phys.* **110** 6412
9. Luzar A and Chandler D 1993 *J. Chem. Phys.* **98** 8160
10. Vaisman I I and Berkowitz M L 1992 *J. Am. Chem. Soc.* **114** 7889
11. Vishnyakov A, Lyubartsev A P and Laaksonen A 2001 *J. Phys. Chem. A* **105** 1702
12. Kirchner B and Reiher M 2002 *J. Am. Chem. Soc.* **124** 6206
13. Baker E S and Jonas J 1985 *J. Phys. Chem.* **89** 1730
14. Chowdhuri S and Pattanayak S K 2013 *Mol. Phys.* **111** 135
15. Banerjee S, Roy S and Bagchi B 2010 *J. Phys. Chem. B* **114** 12875
16. Roy S, Banerjee S, Biyani N, Jana B and Bagchi B 2011 *J. Phys. Chem. B* **115** 685
17. Idrissi A, Marekha B, Kiselev M and Jedlovszky P 2015 *Phys. Chem. Chem. Phys.* **17** 3470
18. Tokuhiro T, Menafra L and Szmant H H 1974 *J. Chem. Phys.* **61** 2275
19. Soper A K and Luzar A 1992 *J. Chem. Phys.* **97** 1320
20. Engel N, Atak K, Lange K M, Gotz M, Soldatov M, Golnak R, Suljoti E, Rubensson J-E and Aziz E F 2012 *J. Phys. Chem. Lett.* **3** 3697
21. Yang L-J, Yang X-Q, Huang K-M, Jia G-Z and Shang H 2009 *Int. J. Mol. Sci.* **10** 1261
22. Banik D, Kundu N, Kuchlyan J, Roy A, Banerjee C, Ghosh S and Sarkar N 2015 *J. Chem. Phys.* **142** 054505
23. Wong D B, Sokolowsky K P, El-Barghouthi M I, Fenn E E, Giammanco C H, Sturlaugson A L and Fayer M D 2012 *J. Phys. Chem. B* **116** 5479
24. Cabral J T, Luzar A, Teixeira J and Bellissent-Funel M C 2000 *J. Chem. Phys.* **113** 8736
25. Luzar A, Soper A K and Chandler D 1993 *J. Chem. Phys.* **99** 6836
26. Soper A K and Luzar A 1996 *J. Phys. Chem.* **100** 1357
27. Harpham M R, Levinger N E and Ladanyi B M 2008 *J. Phys. Chem. B* **112** 283
28. Zhang N, Li W, Chen C and Zuo J 2013 *Comput. Theor. Chem.* **1017** 126
29. Mancera R L, Chalaris M, Refson K and Samios J 2004 *Phys. Chem. Chem. Phys.* **6** 94
30. Mancera R L, Chalaris M and Samios J 2004 *J. Mol. Liq.* **110** 147
31. Bagchi B 1998 *J. Mol. Liq.* **77** 177

32. Ghosh S, Chattoraj S, Chowdhury R and Bhattacharyya K 2014 *RSC Adv.* **4** 14378
33. Roy S, Jana B and Bagchi B 2012 *J. Chem. Phys.* **136** 115103
34. Batista A N L, Batista J M, Bolzani V S, Furlan M and Blanch E W 2013 *Phys. Chem. Chem. Phys.* **15** 20147
35. Pabbathi A, Patra S and Samanta A 2013 *Chem. Phys. Chem.* **14** 2441
36. Roy S and Bagchi B 2013 *J. Phys. Chem. B* **117** 4488
37. Roy S and Bagchi B 2014 *J. Phys. Chem. B* **118** 5691
38. Batista A N L, Batista J M, Ashton L, Bolzani V S, Furlan M and Blanch E W 2014 *Chirality* **26** 497
39. Tjernberg A, Markova N, Griffiths W J and Hallén D 2006 *J. Biomol. Screen.* **11** 131
40. Johnson M E, Malardier-Jugroot C and Head-Gordon T 2010 *Phys. Chem. Chem. Phys.* **12** 393
41. Guo H and Karplus M 1992 *J. Phys. Chem.* **96** 7273
42. Cordeiro J M M and Bosso A R S A 2010 *J. Mol. Liq.* **154** 36
43. Cordeiro J M and Soper A K 2013 *J. Chem. Phys.* **138** 044502
44. Cordeiro J M M and Soper A K 2011 *Chem. Phys.* **381** 21
45. Borges A and Cordeiro J M M 2013 *Chem. Phys. Lett.* **565** 40
46. Shaw Y H and Li N C 1970 *Can. J. Chem.* **48** 2090
47. Kumar R and Rangra V S 2011 *AIP Conf. Proc.* **1349** 517
48. DeCamp M F, DeFlores L, McCracken J M, Tokmakoff A, Kwac K and Cho M 2005 *J. Phys. Chem. B* **109** 11016
49. Jorgensen W L and Swenson C J 1985 *J. Am. Chem. Soc.* **107** 569
50. Berendsen H J C, Grigera J R and Straatsma T P 1987 *J. Phys. Chem.* **91** 6269
51. Allen P and Tildesley D J 1987 In *Computer Simulation of Liquids* (New York: Oxford University Press)
52. Berendsen H J C, Postma J P M, van Gunsteren W F, DiNola A and Haak J R 1984 *J. Chem. Phys.* **81** 3684
53. Allison S K, Bates S P, Crain J and Martyna G J 2006 *J. Phys. Chem. B* **110** 21319
54. Koddermann T and Ludwig R 2004 *Phys. Chem. Chem. Phys.* **6** 1867
55. Pattanayak S K and Chowdhuri S 2014 *J. Mol. Liq.* **194** 141
56. Pattanayak S K and Chowdhuri S 2011 *J. Phys. Chem. B* **115** 13241
57. Chandra A and Chowdhuri S 2002 *J. Phys. Chem. B* **106** 6779
58. Chowdhuri S and Chandra A 2003 *Chem. Phys. Lett.* **373** 79
59. Chowdhuri S and Chandra A 2006 *J. Phys. Chem. B* **110** 9674
60. Chowdhuri S and Pattanayak S K 2013 *J. Mol. Liq.* **180** 172
61. Luzar A and Chandler D 1996 *Nature (London)* **379** 53
62. Luzar A and Chandler D 1996 *Phys. Rev. Lett.* **76** 928
63. Chandra A 2000 *Phys. Rev. Lett.* **85** 768
64. Xu H and Berne B J 2001 *J. Phys. Chem. B* **105** 11929
65. Kumar R, Schmidt J R and Skinner J L 2007 *J. Chem. Phys.* **126** 204107
66. Mallik B S, Semparithi A and Chandra A 2008 *J. Phys. Chem. A* **112** 5104
67. Guardia E, Martí J, García-Tarrés L and Laria D 2005 *J. Mol. Liq.* **117** 63
68. Rapaport D 1983 *Mol. Phys.* **50** 1151
69. Hansen J P and McDonald I R 1986 In *Theory of Simple Liquids* (London: Academic Press)
70. Chowdhuri S and Chandra A 2003 *J. Chem. Phys.* **119** 4360
71. Packer K and Tomlinson D 1971 *Trans. Faraday Soc.* **67** 1302
72. Gordalla B and Zeidler M 1986 *Mol. Phys.* **59** 817
73. Gordalla B and Zeidler M 1991 *Mol. Phys.* **74** 975
74. Rezus Y and Bakker H 2008 *Chem. Phys.* **350** 87
75. Rezus Y L A and Bakker H J 2009 *J. Phys. Chem. B* **113** 4038
76. Laage D, Stirnemann G and Hynes J T 2009 *J. Phys. Chem. B* **113** 2428