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Structures and Intermolecular Interactions in Dimethyl Sulfoxide-Water System Studied by All-atom Molecular Simulations

Rong Zhang*, Wen-juan Wu

Lab of Physical Chemistry, College of Pharmacy, Guangdong Pharmaceutical University, Guangzhou 510006, China

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An all-atom dimethyl sulfoxide (DMSO) and water model have been used for molecular dynamics simulation. The NMR and IR spectra are also performed to study the structures and interactions in the DMSO-water system. And there are traditional strong hydrogen bonds and weak C–H···O contacts existing in the mixtures according to the analysis of the radial distribution functions. The insight structures in the DMSO-water mixtures can be classified into different regions by the analysis of the hydrogen-bonding network. Interestingly, the molar fraction of DMSO (0.35) is found to be a special concentration by the network. It is the transitional region which is from the water rich region to the DMSO rich region. The stable aggregates of $(\text{DMSO})_m \cdot \text{S}=\text{O} \cdots \text{HW}-\text{OW} \cdot (\text{H}_2\text{O})_n$ might play a key role in this region. Moreover, the simulation is compared with the chemical shifts in NMR and wavenumbers in IR with concentration dependence. And the statistical results of the average number hydrogen bonds in the MD simulations are in agreement with the experiment data in NMR and IR spectra.

Key words: All-atom simulation, Chemical shift, Wavenumber, Dimethyl sulfoxide-water system, Hydrogen bond

I. INTRODUCTION

Dimethyl sulfoxide (DMSO) aqueous solutions are of special interest in view of their unique biological and physicochemical properties. They show a strong non-ideal behavior caused by the highly polar S=O group. It is found that at the molar fraction of DMSO $x_{\text{DMSO}} \approx 0.33$, the freezing point of water is depressed down to about -140°C in contrast to 18.6 and 0°C for the pure component of DMSO and water [1–5]. Polar site of DMSO molecule can interact with water forming strong hydrogen bonds, and its nonpolar sites can cause effects of hydration by forming weak C–H···O contacts [6–8].

A variety of experimental and theoretical methods have been performed to study the structures and hydrogen bonding of DMSO-water system. Molecular dynamics (MD) simulation has been proven to be particularly valuable for studying structures and interactions in mixtures system [9–14]. Spectral measurements such as NMR and IR spectra are highly powerful techniques which can be used to investigate structures and interactions in the mixtures [15–20]. Lei and co-workers carried out an all-atom MD simulation and compare with

excess enthalpy of DMSO-water mixing. The results showed good concentration dependences [1]. NMR and IR spectra were used to study the effect of the polar S=O group on hydration of the CH groups by Mizun and co-workers. They found that the strong hydrophilic S=O group in DMSO was a key site for inducing the anomalous polarization of water molecules in the water rich region and plays a dominant role in the formation of the hydration cluster of DMSO [16].

Although many researches have been carried out in the special system, the insight structures and interactions are still unclear. In the present work, we adopted an all-atom MD simulation combining with experimental results of NMR and IR methods to investigate the structures and interactions in the DMSO-water system. The radial distribution functions (RDFs), statistics of hydrogen bonding networks, chemical shifts and the wavenumbers were used to reveal the interactions and structures in the DMSO aqueous solutions. In the previous works, we have investigated the interactions and structures in the special associated systems such as amide-water mixtures, urea-water and 2,2,2-trifluoroethanol (TFE)-water systems [21–24]. Some interesting phenomena were observed in the mixtures. For instance, the two methyl groups in amide molecule were found to show different capabilities in forming weak C–H···O contacts in the mixtures from the RDFs. Furthermore, the temperature-dependent NMR results of the different methyl groups also show excel-

* Author to whom correspondence should be addressed. E-mail: zhangr@china.com.cn

lent agreement with the MD simulations [21, 22]. The all-atom MD simulations and spectra experiments are successful in revealing the structures and interactions in the solutions.

II. COMPUTATIONAL METHOD

A. Molecular models

Simple potential models were used for DMSO and water. The nonbonded interactions are represented by a sum of the Coulomb and Lennard-Jones terms with Eq.(1)

$$E_{ab} = \sum_i^{\text{ona}} \sum_j^{\text{onb}} \left[\frac{q_i q_j e^2}{r_{ij}} + 4\epsilon_{ij} \left(\frac{\sigma_{ij}^{12}}{r_{ij}^{12}} - \frac{\sigma_{ij}^6}{r_{ij}^6} \right) \right] f_{ij} \quad (1)$$

where E_{ab} is the interaction energy between molecules a and b. Standard combining rules are used via Eqs. (2) and (3).

$$\sigma_{ij} = \sqrt{\sigma_{ii}\sigma_{jj}} \quad (2)$$

$$\epsilon_{ij} = \sqrt{\epsilon_{ii}\epsilon_{jj}} \quad (3)$$

The same expression is used for intramolecular non-bonded interactions between all pairs of atoms ($i < j$) separated by three or more bonds. In Eq.(1), $f_{ij}=1.0$ except for intramolecular 1,4 interactions for which $f_{ij}=0.5$.

For the DMSO molecules and the water molecules, the simulations details should be consistent. The similar force field terms should be used and their force field parameters should be calibrated similarly. SPC (simple-point-charge) model [25] for water molecule and OPLS-AA (optimized potentials for liquid simulations-all atom) [26, 27] model for DMSO molecules are used. The potential parameters and symbol of the atom in the molecules are given in Table I.

B. Simulation details

MD calculations were carried out by a modified TINKER 4.2 molecular modeling package [28]. The simulations were performed out in the NPT ensemble at $T=298$ K and $P=101.3$ kPa with a total of $N=512$ molecules with the molar fraction of DMSO molecules at 0.05, 0.1, 0.15, 0.25, 0.35, 0.5, 0.65, 0.8, and 0.95. Periodical boundary conditions were used together with a sphere cutoff. The SETTLE algorithm was used to constrain the water geometry, and the SHAKE algorithm was applied to constrain the bond length of the DMSO molecules. The energies of the initial configurations were minimized using the MINIMIZE program in TINKER 4.2 package. The time step was 1 fs and the configurations were saved every 0.1 ps for analysis. The mixtures were sufficiently equilibrated to ensure that there were no systematic drifts in the potential energies with time. The equilibrations were followed by monitoring the RDFs as well as the fraction of molecules

TABLE I Potential parameters and symbol of the atoms for SPC water and DMSO.

	Atom	$\delta/\text{\AA}$	$\epsilon/(\text{J/mol})$	q/e
Water	OW ^a	3.1656	155.4	-0.8200
	HW ^b	0.0000	0.0	410.0
DMSO	S(S=O)	3.5600	395.0	0.1300
	O(S=O)	2.9300	280.0	-0.4200
	CT ^c	3.5000	60.0	-0.0350
	HC ^d	2.4200	150.0	0.0600

^a Oxygen atoms of water.

^b Hydrogen atoms of water.

^c Carbon atoms of DMSO.

^d Hydrogen atoms of DMSO.

of each species that contain a given number of hydrogen bonds. The statistics were collected during the last 100 ps.

C. Definitions

An analysis of hydrogen bonds was used to gain a deeper insight into the aqueous structures. The hydrogen bonds can be determined by the geometric criteria, and a geometric criterion used by Luzar and Chandler has been performed [29], such as a typical criterion of neat water: $r(\text{OW}\cdots\text{HW}) \leq 2.45$ \AA, $r(\text{OW}\cdots\text{OW}) \leq 3.60$ \AA, and the angle $\phi(\text{HW}-\text{OW}\cdots\text{OW}) \leq 30^\circ$. Although there are a great variety of researches, defining the weak C-H \cdots O hydrogen bond is still somewhat arbitrary. Different investigators have attempted to give some slightly different criteria for identifying such weak contact. The geometrical criteria for C-H \cdots O contact of small molecules: $r(\text{O}\cdots\text{H}) < 2.8$ \AA, 3.0 \AA $< r(\text{O}\cdots\text{O}) < 4.0$ \AA, and the angle $\phi(\text{C}-\text{H}\cdots\text{O}) > 110^\circ$ [30].

III. RESULTS AND DISCUSSION

A. $g(r)$ in DMSO-water system

In view of the inconclusive results about the liquid structure of DMSO, the all-atom simulation further gives an insight into the local structures in the DMSO-water system. The structures of the liquid can be characterized well by the RDF, $g(r)(x-y)$, which gives the probability of finding an atom of type y at distance r from an atom of type x . The typical $g(r)$ of the DMSO aqueous solutions is given in Fig.1. Based on the structures of the DMSO molecule, there are not only the traditional strong hydrogen bonds such as OW-HW \cdots OW, S=O \cdots HW but also weak C-H \cdots O contacts existing in the aqueous solutions. The distinct peaks near 1.8 \AA are observed in $g(r)[\text{O}-\text{HW}]$, and the intensities are also strong. The peaks of the second and third hydration shell are observed near 3.2 and 5.5 \AA which imply that the structures of DMSO aqueous solutions are more ordered. The short distances and

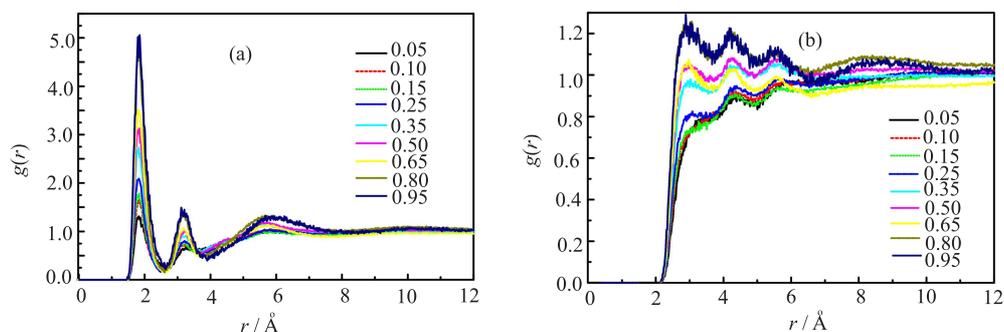


FIG. 1 RDF in the DMSO-water mixtures. (a) $g(r)[O-HW]$ and (b) $g(r)[OW-HC]$. For clarity, the reader can refer to the web version of this article.

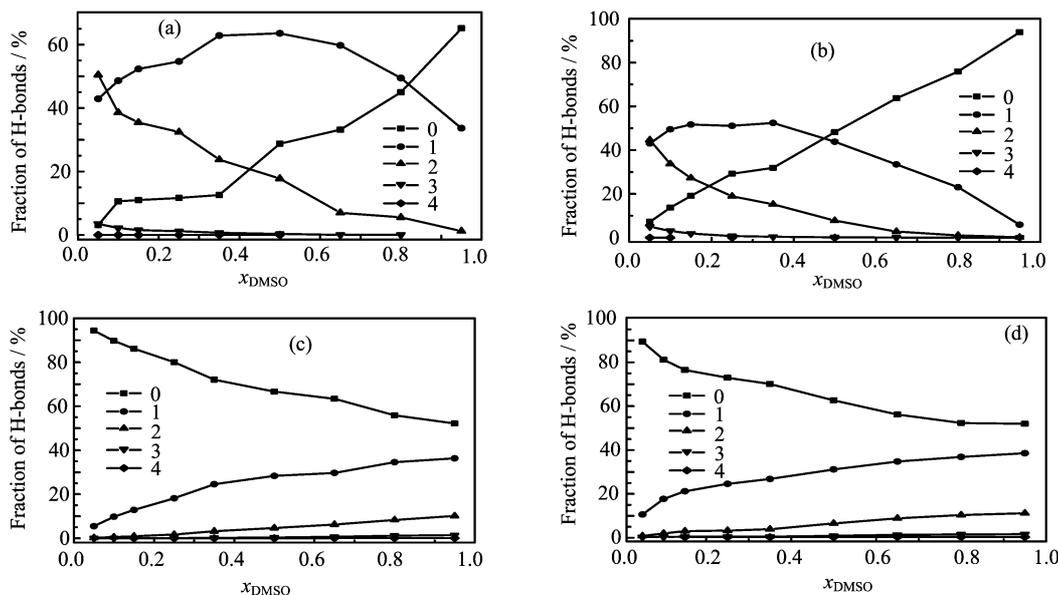


FIG. 2 Hydrogen-bonding network in the DMSO-water system. (a) $HW-OW\cdots HW$, (b) $S=O\cdots HW$, (c) $HW-OW\cdots HC$, and (d) $S=O\cdots HC$.

strong intensities exhibit that the hydrogen bonds of $S=O\cdots HW$ are very strong. Weak correlations between the oxygen atoms of water and the methyl group of DMSO are simultaneously observed in $g(r)[OW-HC]$. The first peaks near 2.8 Å of $g(r)[OW-HC]$ are obvious which shows that there are $C-H\cdots O$ contacts existing in the DMSO-water mixtures. The broad peaks of the RDFs also indicate that the intermolecular interactions are likely to include other weak interactions such as dipolar interactions and dispersions. So the weak $C-H\cdots O$ contacts can not be neglected in the mixtures even though the intensities of the weak $C-H\cdots O$ contacts are weaker than those of the strong hydrogen bonds.

B. Hydrogen-bonding network

To obtain the deeply insight into the structures and interactions of the DMSO-water system, hydrogen-bonding network is used in the MD simulations. One basic aspect of the hydrogen bonding network is the

probability distribution, describing the number and type of hydrogen bonds. The oxygen atoms of water and DMSO molecule compete as acceptors of hydrogen bonds. Moreover, the hydrogen atoms of water and methyl groups in DMSO compete as donors. It is the competition of these interactions which leads to hydrogen bonding networks in the DMSO-water mixtures. The hydrogen bonds are determined by a geometrical criterion of pure water as defined in above section. The results of the statistics are given in Fig.2. The number of free oxygen atom in water (OW) becomes large with the increasing of x_{DMSO} which is shown in Fig.2(a). The fractions of cluster for the OW atom accepting one hydrogen atoms of water (HW) increases until $x_{DMSO}=0.35$. The aggregates of OW accepting one or two HW are in high level in the water rich region. So the water molecules prefer to form hydrogen bonds with themselves in the water rich region. The stable clusters of water self-aggregates predominate. Another hydrogen bond of $S=O\cdots HW$ is shown in Fig.2(b). The free

TABLE II The fraction (%) of the accepted H-bonds for different hydrogen bonds at $x_{\text{DMSO}}=0.35$.

H-bonds	OW...HW	O...HW	OW...HC	O...HC
0	12.63	31.92	72.03	69.76
1	62.88	52.42	24.55	26.46
2	23.76	15.23	3.22	3.58
3	0.71	0.42	0.19	0.19

oxygen atoms of DMSO(O) increase with x_{DMSO} . The clusters of O atom accepting one protons are high in the water rich region, and then decrease at $x_{\text{DMSO}}=0.35$, which is similar to that in the OW-HW...OW hydrogen bonds. These imply that it is a special concentration at $x_{\text{DMSO}}=0.35$. Lei *et al.* also found that the largest deviations from the ideal mixing are shown near at $x_{\text{DMSO}}=0.35$ in the DMSO-water system [1]. The point of $x_{\text{DMSO}}=0.35$ is in the transitional region which is from the water rich region to the DMSO rich region. In this area, the DMSO and water clusters coexist in the mixtures. The hydrogen bonds of $\text{S}=\text{O}\cdots\text{HW}-\text{OW}$ are easily formed in this region which might play a role of bridge between the clusters of DMSO self-associate and the water self-associate molecules. This configuration of $(\text{DMSO})_m\cdot\text{S}=\text{O}\cdots\text{HW}-\text{OW}\cdot(\text{H}_2\text{O})_n$ might be the most stable mixing state of DMSO-water mixtures at the $x_{\text{DMSO}}\approx 0.35$. In Fig.2 (c) and (d), the aggregates of O and OW atom accepting one methyl proton both increase with x_{DMSO} which imply that the weak $\text{C}-\text{H}\cdots\text{O}$ contacts are not dominant in the water rich region. In summary, the oxygen atoms of water prefer its own hydrogen atom as acceptors. And the atom of HW can form the hydrogen bonds with atom of OW or O. With the number of DMSO molecules increasing, the structure of the water cluster is broken down, and the clusters of $(\text{DMSO})_m\cdot\text{S}=\text{O}\cdots\text{HW}-\text{OW}\cdot(\text{H}_2\text{O})_n$ become dominant. The fractions of the accepted hydrogen bonds (H-bonds) for these different hydrogen bonds at $x_{\text{DMSO}}=0.35$ are shown in Table II. The HW-OW...HW hydrogen bonds relate to the water self-aggregates. The $\text{S}=\text{O}\cdots\text{HW}$ reveals the cross-associate between the DMSO and water molecules. $\text{S}=\text{O}\cdots\text{HC}$ exhibits the DMSO self-aggregates. The fraction of the oxygen atom accepting one proton of $\text{S}=\text{O}\cdots\text{HW}$ is 52.42 which is in a high level, implying that the hydrogen bonds of $\text{S}=\text{O}\cdots\text{HW}-\text{OW}$ are easily formed. The results are in agreement with the analysis of the hydrogen bonding network.

C. NMR spectra

NMR spectra are often adopted to investigate intermolecular interactions in solution. Chemical shifts will move to low field and the values will become smaller after the hydrogen bond formation [21–22]. Thus, the variety of the chemical shifts can reflect the capability of forming hydrogen bonds. It is well known that the effects on the chemical shift of hydrogen bond are

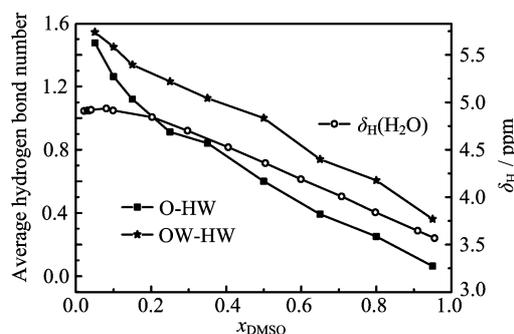


FIG. 3 Comparison between the average number of hydrogen bonds and the chemical shifts for hydrogen atom in the water at 296 K [16].

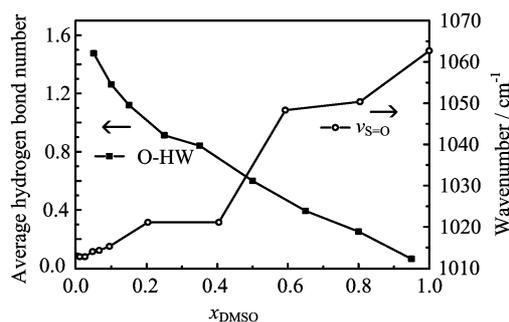


FIG. 4 Comparison between the average number of $\text{S}=\text{O}\cdots\text{HW}$ hydrogen bonds and the wavenumbers of $\text{S}=\text{O}$ stretching mode at 296 K [16].

much larger than the other intermolecular interaction effects such as van der Waals interaction. Mizuno and co-workers [16] have adopted the NMR spectra to get the chemical shifts of the hydrogen atom in DMSO-water system. The comparison between the average number hydrogen bonds in MD simulation and chemical shifts of hydrogen atoms with the concentration are given in Fig.3. The water molecules are apt to be more structured in the water rich region and the local tetrahedral coordination of water leads to a “break-down” with x_{DMSO} . δ_{HW} , the chemical shift of water hydrogen atom, is a measure of the electron density for the water protons. It can reflect the polarization of water molecules dissolving solutes. The HW atom can form strong hydrogen bonds of $\text{S}=\text{O}\cdots\text{HW}$ and $\text{HW}-\text{OW}\cdots\text{HW}$ which will lead to the variety of the chemical shifts with the concentration. In Fig.3, the average numbers of hydrogen bonds for $\text{S}=\text{O}\cdots\text{HW}$ and $\text{HW}-\text{OW}\cdots\text{HW}$ both decrease with the increasing of x_{DMSO} . On the other side, the values of δ_{HW} are also becoming smaller with the increasing of x_{DMSO} . The varieties of the chemical shifts and the MD simulations represent the consistent concentration dependences.

D. IR spectra

IR spectra are also highly powerful techniques used to study the structures and interactions in solutions.

The shifts of the wavenumber can reflect the hydrogen bonds in the liquid. A shift to lower wavenumber relative to reference state is called a red shift. Contrarily, a shift to higher wavenumber is called a blue shift [31]. The monomer is often used as the reference state. Strong hydrogen bonds will lead to red shifts, and the wavenumber will decrease. Comparison between the average number hydrogen bonds in MD simulation and wavenumbers of S=O stretching mode are given in Fig.4. In the water rich region, the numbers of S=O \cdots HW hydrogen bonds are in high level which will lead to the red shifts. The wavenumbers should be in the low level. And the number of S=O \cdots HW decrease with the concentration dependence which should result in the increase of the wavenumbers accordingly. The IR experiments actually exhibit the same result: the wavenumber of the S=O stretching mode is in the low level in the water rich region, then decrease with x_{DMSO} . The MD simulations show the agreement with the IR results.

IV. CONCLUSION

An all-atom MD simulation combined with experiment results of NMR and IR are adopted to investigate the structures and interactions in the DMSO-water system. The RDFs indicate that the strong hydrogen bonds and weak C-H \cdots O contacts coexist in the DMSO-water mixtures. The mixtures can be classified into different regions by the analysis of the hydrogen-bonding network. In the water rich region, the stable self-aggregates of water molecules are dominant. With the x_{DMSO} increasing, the structure of the water cluster is broken down. And $x_{\text{DMSO}}=0.35$ is found to be a special concentration. There are stable aggregates of the across associate $(\text{DMSO})_m \cdot \text{S}=\text{O} \cdots \text{HW} - \text{OW} \cdot (\text{H}_2\text{O})_n$ in this region. The statistical average number of hydrogen bonds is compared with chemical shifts in NMR and wavenumbers in IR. The results simulations and experiment data show good agreement. These two methods are proved to be successful in revealing the structures and interactions in the DMSO-water mixtures.

V. ACKNOWLEDGMENTS

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