

All-Atom Molecular Dynamic Simulations and Relative NMR Spectra Study of Weak C–H···O Contacts in Amide–Water Systems

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Received: November 30, 2004; In Final Form: February 10, 2005

Amide–water mixtures are studied by all-atom molecular dynamics (MD) simulations and the relative temperature-dependent NMR experiment. The weak C–H···O contacts are found in the amide–water systems theoretically and experimentally. The statistical results of the average numbers of hydrogen bonds indicate that the methyl groups in amide molecules represent different capabilities in forming the weak C–H···O contacts. The statistics also imply that the C–H···O contacts are more obvious in the amide-rich region than those in the water-rich region. The temperature-dependent NMR spectra are also adopted to investigate the weak C–H···O contacts in the amide–water systems. The relative chemical shifts of the methyl groups are in good agreement with the MD simulations.

1. Introduction

Recently, a variety of experimental and theoretical methods have been extensively applied to study the interactions of peptides.^{1–8} Interactions among these peptide groups play an essential role in the structures and properties of the biological systems, such as proteins and nucleic acids as well as in the behavior of many solvent systems. And the recognition of the widespread incidence of the weak C–H···O contacts and the realization of its importance in biological structures has led to an increasing interest in describing its physical properties in recent years.^{9–12} Weak contacts such as C–H···O exist widely in important biological systems such as nucleic acids, proteins, and carbohydrates, which may be the key to protein folding.¹²

Simple amide systems have been investigated extensively as models of peptide bonds because of their presence as a repeating unit in biological macromolecules and some polymers.^{13–30} Spectral measurements such as NMR are highly powerful techniques which can be used to investigate the structures and the interactions in the mixtures.^{16–23} For instance, variable temperature-dependent NMR and IR were performed to study the amide–amide hydrogen bond by Gellman and co-workers.¹⁶ Ludwig et al.²² found that there existed strong cooperative effects in the NMA molecular clusters by the temperature dependence of NMR and IR. Molecular dynamics (MD) simulations and density functional theory (DFT) calculations have been widely used in the investigation of the interactions in mixtures.^{24–30} Buck et al.²⁴ adopted the MD simulation and energy minimization to investigate hydrogen-bonding interactions in the NMA–water mixtures, whose energy surfaces were determined by the interactions of entire peptide groups or water molecules rather than by single donor and acceptor groups. Torii²⁶ and co-workers performed ab initio molecular orbital (MO) on NMA–water systems to investigate the effects of hydration on the structure and vibrational force field of the peptide groups. It is found that the wavenumbers of NMA are

strongly affected by both the dielectric effect and formation of hydrogen bonds. In addition, DFT calculations were used to investigate the proton chemical shifts in model peptides by Sitkoff.²⁵ The close contacts were found to deshield protons involved in close nonbonded contacts that typically occur in hydrogen bonds. More recently, Vargas^{29,30} and co-workers found that the C–H···O=C interactions played a crucial role in stabilizing the self-association dimers of NMA and DMF molecules by high-level ab initio calculations.

In previous papers, we have investigated the interactions and structures in the NMA–water system.^{31–32} Some interesting phenomena were observed in the mixture, such as the weak C–H···O contacts. In the present work, we adopted MD simulations combined with NMR experiment to investigate the intermolecular interactions, especially the weak C–H···O contacts in the amide–water system. The amide molecules include NMA (*N*-methylacetamide), DMF (*N,N*-dimethylformamide), and DMA (*N,N*-dimethylacetamide) molecules. The statistics of hydrogen-bonding networks and relative chemical shifts were used to reveal an insight into interactions in the amide–water mixture.

2. Computational Methods

2.1. Molecular Models. Simple rigid potential models were used for both amide and water. The nonbonded interactions are represented by a sum of the Coulomb and Lennard-Jones terms with eq 1:

$$E_{ab} = \sum_i \sum_j^{on a \text{ on } b} [q_i q_j e^2 / r_{ij} + 4\epsilon_{ij}(\sigma_{ij}^{12} / r_{ij}^{12} - \sigma_{ij}^6 / r_{ij}^6)] f_{ij} \quad (1)$$

where E_{ab} is the interaction energy between molecules a and b. Standard combining rules are used via eq 2:

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

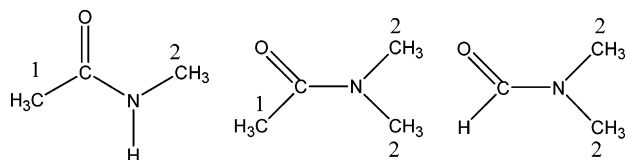
The same expression is used for intramolecular nonbonded interactions between all pairs of atoms ($i < j$) separated by three or more bonds. In eq 1, $f_{ij} = 1.0$ except for intramolecular 1,4

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TABLE 1: Potential Parameters for SPC Water and NMA, DMF, and DMA Molecules

atom	σ (Å)	ϵ (kJ/mol)	q (e)
SPC			
OW	3.1656	0.1554	−0.8200
HW	0.0000	0.0000	0.4100
NMA			
C (C=O)	3.7500	0.1050	0.5000
O	2.9600	0.2100	−0.5000
N	3.2500	0.1700	−0.5000
C ₁ (C—CH ₃)	3.5000	0.0660	−0.1800
C ₂ (N—CH ₃)	3.5000	0.0660	0.0200
H (N—H)	0.0000	0.0000	0.3000
H ₁ (C—CH ₃)	2.4200	0.0150	0.0600
H ₂ (N—CH ₃)	2.5000	0.0300	0.0600
DMF			
C (C=O)	3.7500	0.1050	0.5000
O	2.9600	0.2100	−0.5000
H ₁ (C=O)	2.4200	0.0150	0.0000
N	3.2500	0.1700	−0.1400
C ₂ (N—CH ₃)	3.3000	0.087	−0.1100
H ₂ (N—CH ₃)	2.5000	0.030	0.0600
DMA			
C (C=O)	3.7500	0.1050	0.5000
O	2.9600	0.2100	−0.5000
N	3.2500	0.1700	−0.1400
C ₁ (C—CH ₃)	3.5000	0.0660	−0.1800
C ₂ (N—CH ₃)	3.5000	0.0660	0.0200
H ₁ (C—CH ₃)	2.4200	0.0150	0.0600
H ₂ (N—CH ₃)	2.5000	0.0300	0.0600

SCHEME 1: Structures of NMA, DMA, and DMF Molecules^a

^a Numbers printed in blue denote different types of the two methyl groups in amide molecules.

interactions for which $f_{ij} = 0.5$. The SPC model³³ for the water molecule and the OPLS-AA^{12,34} (optimized potentials for liquid simulations—all atom) model for amide molecules are performed. Table 1 lists the potential parameters of the pure components. The structures of NMA, DMF, and DMA molecules are displayed in Scheme 1, respectively.

2.2. Simulation Details. MD calculations were carried out using a modified TINKER 4.1 molecular modeling package.³⁵ The simulations were performed in the *NPT* ensemble at $T = 298$ K and $P = 1$ atm with a total of 512 molecules except the NMA–water system at $T = 308$ K. 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 amide molecules. The energies of the initial configurations were minimized using the MINIMIZE program in the TINKER 4.1 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 of each species that had a given number of hydrogen bonds. The statistics were collected during the last 100 ps.

2.3. Definitions. An analysis of hydrogen-bonding networks was used to gain deeper insight into the aqueous structures. Here a geometric criterion that is the same as that used by Luzar and

TABLE 2: Calculated and Experimental Thermodynamic Properties of Pure Liquids

liquid	ΔH_{vap} (kcal/mol)		ρ (g cm ^{−3})	
	calcd	exptl	calcd	exptl
NMA ^a	13.27	13.30 ^b	0.947	0.946 ^c
DMA	11.95	11.75 ^b	0.932	0.936 ^b
DMF	10.90	11.10 ^d	0.934	0.944 ^d
SPC	10.69	10.51 ^d	0.983	0.997 ^d

^a NMA data are in the temperature of 308 K. ^b Experimental data are taken from ref 34. ^c Experimental data are taken from ref 37. ^d Experimental data are taken from ref 12.

Chandler has been performed,³⁶ such as a typical criteria of neat water: $R(\text{OW}\cdots\text{HW}) \leq 2.45$ Å, $R(\text{OW}\cdots\text{OW}) \leq 3.60$ Å, and the angle $\Phi(\text{HW}-\text{OW}\cdots\text{OW}) \leq 30^\circ$. Geometrical criteria¹² were used for the C—H...O contact: $R(\text{O}\cdots\text{H}) < 2.8$, $3.0 < R(\text{O}\cdots\text{O}) < 4.0$ and the angle $\Phi(\text{C}-\text{H}\cdots\text{O}) > 110^\circ$.

3. Experimental Section

NMR spectra were measured using a Bruker DMX 500 spectrometer operating at 500 MHz at different temperatures with an accuracy of ± 0.1 K. A 2-mm capillary tube, in which the deuterated dimethyl sulfoxide (DMSO-*d*₆) was sealed, was placed at the center of a 5-mm sample tube filled with the chemical shift reference of sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) and the sample solution. The ¹H NMR spectra of DMA–water and DMF–water at 298, 313, 328, and 343 K and those of the NMA–water mixtures at 308, 323, 338, and 353 K were measured, respectively.

4. Results and Discussion

4.1. Pure Substance. **4.1.1. All-Atom Molecular Dynamic Simulations.** The density and heat of vaporization of the liquid are important measures of the size of the molecules and the strength of the interaction. Calculated properties of neat NMA, DMA, DMF, and water are listed in Table 2, which are compared with experimental values. The calculated densities and heat of vaporizations agree with the experimental values well.

The structure 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 a distance r from an atom of type x . The atom types have been defined in Table 1. Those $g(r)$'s that concern intermolecular interactions of the amide molecules are displayed in Figure 1. There are distinct peaks near 2.8 Å in the $g(r)$'s of the three amide molecules, which implies the existence of some weak C—H...O contacts. For the NMA molecules, there are strong interactions in the carbonyl oxygen atom bonded with an amide hydrogen atom.³² The $g(r)[\text{O}-\text{H}_1]$ presents more distinct peaks near 2.8 Å than that of $g(r)[\text{O}-\text{H}_2]$. In the DMA molecule, there are two distinct peaks near 2.8 Å of the two methyl groups. And $g(r)[\text{O}-\text{H}_1]$ shows higher peaks than those of $g(r)[\text{O}-\text{H}_2]$, which is similar to that of the NMA molecule. The $g(r)[\text{O}-\text{H}_1]$ presents higher peaks than those of $g(r)[\text{O}-\text{H}_2]$ in both the NMA and DMA liquids, which indicates that the H₁ atom exhibits better capabilities in forming the weak C—H...O contacts than the H₂ atom. For DMF, there is only one methyl group in the molecule. The distinct peaks near 2.8 Å show that the H₂ atom of DMF exhibits better capabilities in forming the weak C—H...O contacts than the H₂ atom of NMA. The first peaks of the RDFs in weak interaction are broader than those of the strong hydrogen bonding, which implies that the intermolecular interactions are likely to include the weak

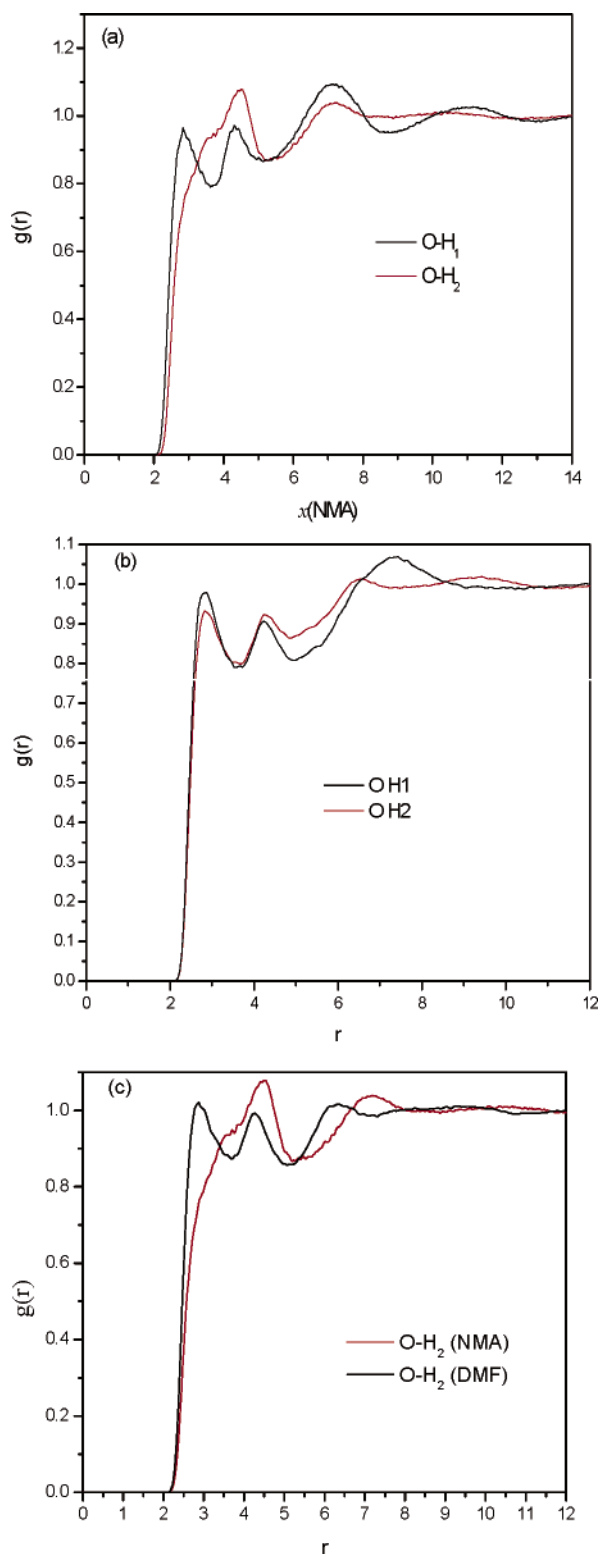


Figure 1. $g(r)$'s of neat amide. (a) NMA, (b) DMA, (c) DMF compared with NMA. Distances are in angstroms. The atom types refer to those in Table 1.

hydrogen bonds as well as other weak interactions such as dipolar interactions and dispersions.¹²

4.2. Amide–Water Mixture. **4.2.1. Hydrogen-Bonding Networks.** A detailed analysis of hydrogen-bonding networks in the mixtures was carried out to gain deeper information on the aqueous structures. One basic aspect of the hydrogen-bonding networks is the probability distribution, describing the number and type of hydrogen bonds that a molecule is engaged

in with the other one. The carbonyl and the water oxygen atoms compete as acceptors of hydrogen bonds. Moreover, the water and the amide hydrogen atoms compete as donors of hydrogen bonds. It is the competition of the four hydrogen-bonding interactions that lead to hydrogen-bonding networks in the amide–water mixtures.

4.2.2. Weak C–H \cdots O Contacts. The $g(r)$'s of the pure material indicate that weak C–H \cdots O contacts exist in the amide system, which represents different capabilities in forming weak C–H \cdots O contacts of different groups. The average number of hydrogen bonds per acceptor (oxygen atom of water or amide molecule) was calculated to gain deeper information on the aqueous structures.^{12,36} The statistical results of the average numbers of the C–H \cdots O hydrogen bonds also show the different abilities in forming the C–H \cdots O contacts of the hydrogen atoms in NMA, DMA, and DMF aqueous solutions which are shown in Figures 2–4. The definition of the hydrogen bonds is given in section 2.3. The average numbers of the C–H \cdots O hydrogen bonds are larger than those of the H₂ atoms in the NMA and DMA molecule in Figure 2. Figure 3 indicates the better capabilities of H₁ atoms in forming the weak C–H \cdots O contacts than those of the H₂ atoms. Similarly, H₂ atoms of NMA molecule present worse capabilities in forming the weak C–H \cdots O contacts than those of the H₂ atoms of DMF molecules that are shown in Figure 4. The average numbers of the C–H \cdots O and the C–H \cdots O in NMA and DMA molecules are both small in the water-rich region. With the increase of the amide molecules, the average numbers of the C–H \cdots O and the C–H \cdots O are different. The H₁ atoms show better capabilities in forming the weak C–H \cdots O contacts than the H₂ atoms in the amide-rich region, which also indicates the C–H \cdots O contacts are more obvious in the amide-rich region than in the water-rich region.

4.2.3. Comparison to NMR Experiment. NMR spectroscopy is often used to investigate intermolecular interactions in solution. However, there is still a little spectral data over the entire composition range for aqueous mixtures.³⁸ It is also an inherently insensitive technique. It is not easy to obtain accurate chemical shifts with concentration and temperature dependence. The relative chemical shifts, therefore, were used in the investigation of NMR spectroscopy.³²

The chemical shifts of H₂ atom (δ_{H_2} 's) are used as a reference standard in the NMA molecules. The smaller chemical shifts of the H₂ atom in $\delta_{\text{N-CH}_3}$'s are used as the reference standard in DMF and DMA molecules. Because the H₁ and H₂ atoms are in the same molecule, the relative chemical shifts compared with the chemical shifts of the HC₁ atom (δ_{HC_1}) in the same molecule are independent of the reference.³² The relative chemical shifts of the hydrogen atoms in the NMA, DMF, and DMA aqueous solutions are given in Figure 5.

Hydrogen-bonding interactions are sensitive to temperature. Chemical shift moves to high field with an increase of temperature. A strong hydrogen bond results in a greater shift than a weak hydrogen bond. The varieties of the relative chemical shifts with temperature also reflect the capabilities of forming hydrogen bonds.

For an NMA molecule, the relative chemical shifts of the H₁ atom ($\Delta\delta_{\text{H}_1}$'s) decrease with the increase of temperature, indicating that the H₁ atom is a better donor than the H₂ atom. The H₁ atom is more favored in forming C–H \cdots O weak contacts than the H₂ atom.³² The two N–CH₃ groups of the DMF molecule are in nonequivalent magnetic environments.¹² The two discrete N–CH₃ resonances can often be observed in NMR spectra. The relative chemical shifts of the two N–CH₃

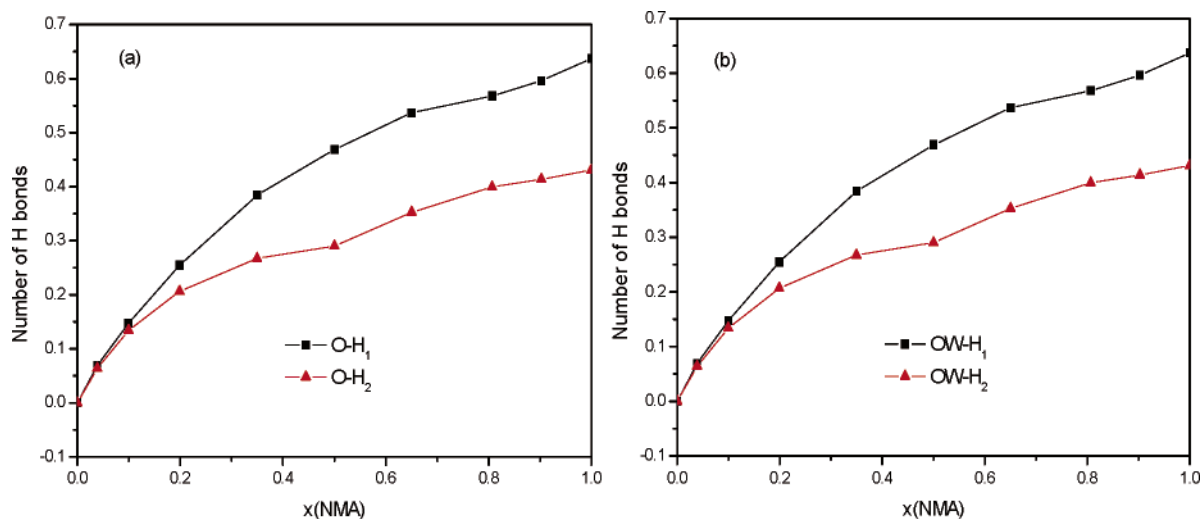


Figure 2. The average numbers of the C—H...O hydrogen bonds in NMA–water mixtures. (a) Average numbers of H_1 and H_2 atoms accepting hydrogen bonds to O. (b) Average numbers of H_1 and H_2 atoms accepting hydrogen bonds to OW. The atom types refer to those in Table 1.

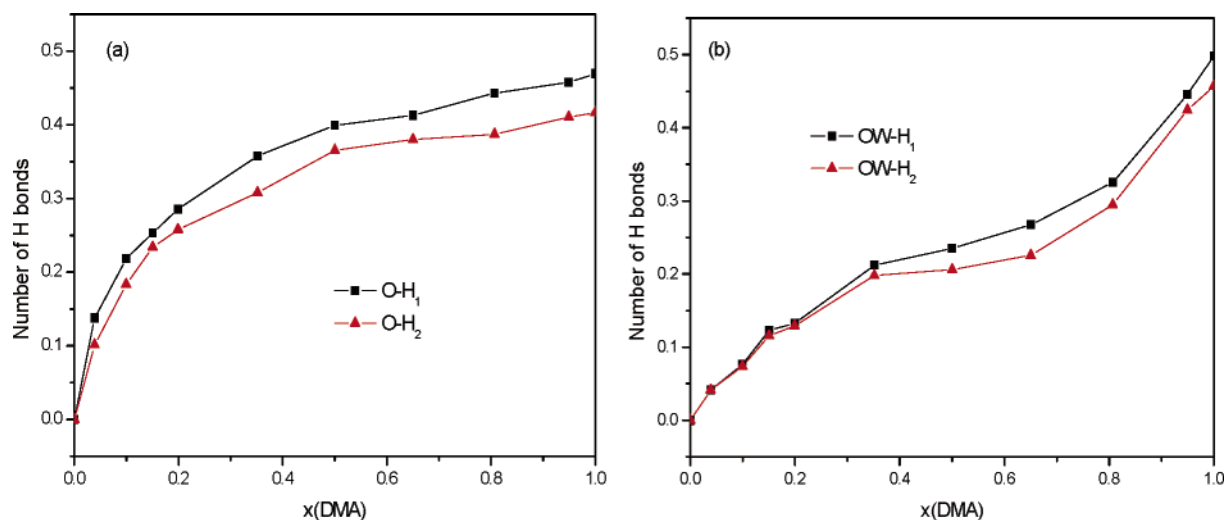


Figure 3. The average numbers of the C—H...O hydrogen bonds in DMA–water mixtures. (a) Average numbers of H_1 and H_2 atoms accepting hydrogen bonds to O. (b) Average numbers of H_1 and H_2 atoms accepting hydrogen bonds to OW. The atom types refer to those in Table 1.

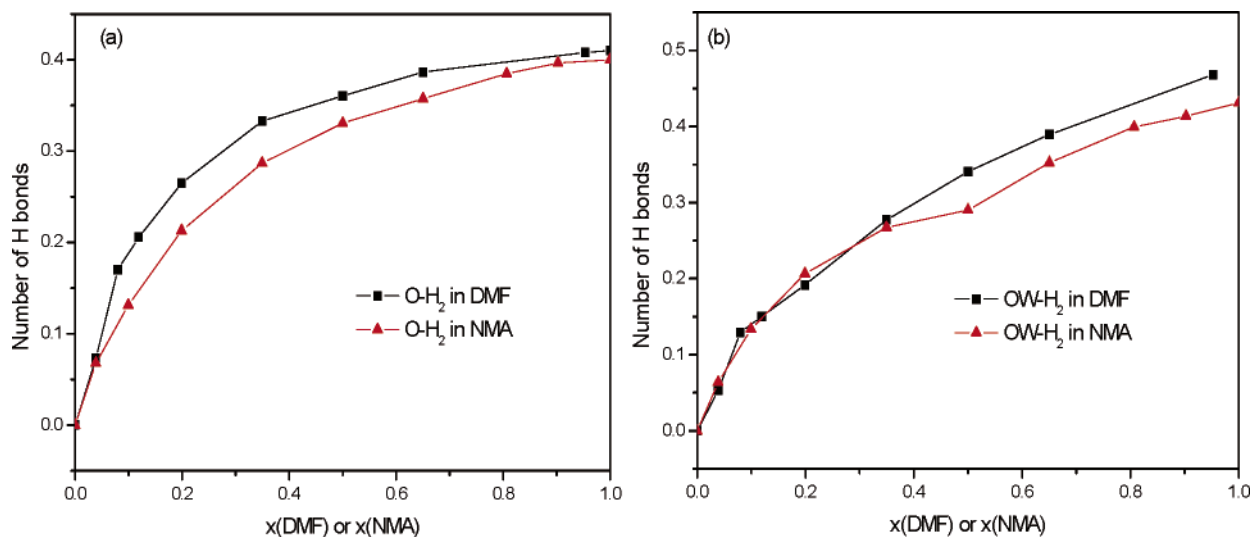


Figure 4. The average numbers of the C—H₂...O hydrogen bonds in DMF–water and NMA–water mixtures. (a) Average numbers of H_2 atoms accepting hydrogen bonds to O. (b) Average numbers of H_2 atoms accepting hydrogen bonds to OW. The atom types refer to those in Table 1.

groups, $\Delta\delta_{\text{N}-\text{CH}_3}$, reflect the magnetic anisotropy of the amido. For the DMA molecule, the H_1 atom which connects with the carbonyl and the H_2 atom which connects with the nitrogen atom

also show different temperature dependences in NMR experiments. The $\Delta\delta_{\text{H}_1}$'s decrease more rapidly with the temperature than the $\Delta\delta_{\text{H}_2}$'s, which implies that the H_1 atom is more favored

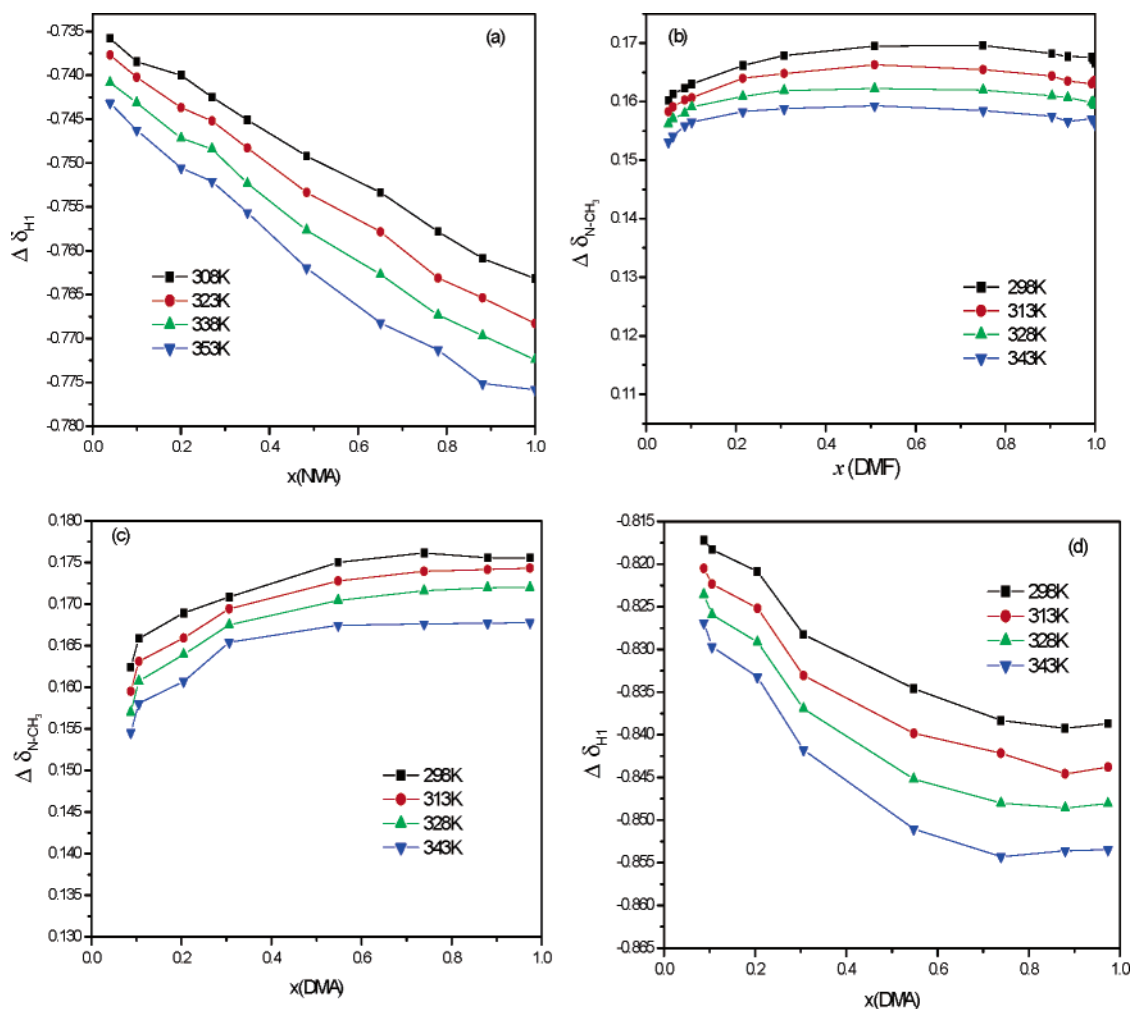


Figure 5. Relative temperature-dependent chemical shifts of H atoms. (a) Relative chemical shifts of the H_1 atom ($\Delta\delta_{H1}$) in an NMA molecule. (b) $\Delta\delta_{N-CH_3}$ in a DMF molecule. (c) $\Delta\delta_{N-CH_3}$ in a DMA molecule. (d) $\Delta\delta_{H1}$ in a DMA molecule. The atom types refer to those in Table 1.

in forming C–H \cdots O weak contacts than the H_2 atom of the DMA molecule. This situation is similar to that of the NMA. The relative chemical shifts of the two N–CH $_3$ groups in Figure 5d also reflect the magnetic anisotropy of the amide. The varieties of the relative chemical shifts in the NMA–water and the DMA–water mixtures with temperatures in the water-rich region are smaller than those in the amide-rich region in Figure 5a,c,d, indicating that the H_1 atom seems to be more favored in forming C–H \cdots O weak contacts in the amide-rich region. It also implies that the C–H \cdots O contacts are more obvious in the amide-rich region. The NMR experiments and the MD simulations show agreements.

5. Conclusion

Simple amide systems have been investigated extensively as models of peptide bonds. The all-atom models of the NMA, DMF, and DMA aqueous solutions have been adopted for molecular dynamics simulations. It is the competition of the acceptors or donors in forming hydrogen-bonds interaction that lead to hydrogen-bonding networks in the amide–water mixtures. The $g(r)$'s of the pure material indicate that the weak C–H \cdots O contacts exist in the amide system. The statistical results of the average numbers of the C–H \cdots O hydrogen bonds further reveal the different abilities in forming the C–H \cdots O contacts in the NMA, DMA, and DMF aqueous solutions. The H_1 atoms represent better capabilities in forming the weak C–H \cdots O contacts than those of the H_2 atoms, especially in the amide-

rich region. The temperature-dependent NMR experiments indicate that the methyl groups of the amide molecule show different capabilities in forming the weak C–H \cdots O hydrogen bonds in the mixture, which show agreement with the MD simulations. The all-atom MD simulations and the relative chemical shifts are successful in investigating the weak C–H \cdots O contacts in amide–water mixtures. The simulations and the NMR spectra are in agreement. The weak C–H \cdots O interactions play an important role in forming the stable secondary structures in proteins. We expect that these methods are applicable to investigate more important phenomena in biochemistry.

Acknowledgment. This work was supported by the National Natural Science Foundation of China (No. 29976035) and Zhejiang Provincial Natural Science of China (No. RC01051).

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