Hydrogen bonding in protic and aprotic amide mixtures: Low-frequency Raman spectroscopy, small-angle neutron scattering, and molecular dynamics simulations

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ABSTRACT

The hydrogen-bonding interactions in protic and aprotic amide solvent mixtures, i.e., formamide (FA) and N,N-dimethylformamide (DMF), were investigated via low-frequency Raman spectroscopy, small-angle neutron scattering (SANS) experiments, and molecular dynamics (MD) simulations. In a neat amide system, the low-frequency Raman spectra $R(\nu)$s were well reproduced by the corresponding $S(\nu)$ spectra derived from the MD simulations. The observed peaks in $R(\nu)$s at around <200 cm^{-1} were assigned to the intermolecular interactions, particularly in terms of the hydrogen-bonding network formation and its dimensionality in the liquid state. The SANS experiments for the FA–DMF mixtures demonstrated that the FA molecules forming an extended three–dimensional hydrogen-bonding structure in the neat system interacted with DMF molecules through the hydrogen bonds in the mixtures over the whole range of solvent compositions, resulting in a homogeneous mixing state. Additionally, the $R(\nu)$ spectra for the mixtures were represented by the corresponding $S(\nu)$ spectra. From the $R(\nu)$ and $S(\nu)$ spectra of the FA–DMF mixtures, we found that (1) the Raman band at around 110 cm^{-1} mainly originates from the libration mode of amide molecules in the chain-like hydrogen-bonded structure and (2) the higher frequency band (approximately 200 cm^{-1}) was attributed to the libration of the FA molecule restricted by the three-dimensional hydrogen-bonded network, which remained even in the DMF-rich compositions.

1. Introduction

Formamide (FA) is a typical amide solvent with two proton donor sites at the $-$NH$_2$ group and one proton acceptor site at the C=O group, that forms a strong liquid structure through intermolecular $-$NH$\cdots$O=C$-$ hydrogen bonding [1–7]. The FA molecule has been often regarded as a simple model unit in peptide chains; thus, the hydrogen-bonding behaviors of amide molecules are an important issue in biochemistry for understanding the physicochemical properties of proteins [8–12].

The FA molecule can form a cyclic dimer and a chain-like structure because NH hydrogen locates at both *cis* and *trans* to the C=O group. Indeed, the hydrogen-bonding network in the crystalline state is constructed from these two types of structures [13]. To date, the intermolecular interactions of FA in the liquid state have been studied, e.g., the liquid structure based on X-ray diffraction reported by Ohtaki et al. implied that liquid FA comprises a chain-like structure and a distorted cyclic dimer structure to form two-dimensional networks

containing the two types of structures [1–3]. On the other hand, according to theoretical studies by means of molecular dynamics (MD) simulations, the liquid FA structure is regarded as a three-dimensional NH$\cdots$O hydrogen-bonding network and the cyclic dimers that are the dominant component of the crystalline phase play only a minor role in the network structure [5–7]. *N*-Methylformamide (NMF) with NH hydrogen *trans* to the C=O group forms only a chain-like structure in the liquid state, which has been established from several technics such as vibrational spectroscopy, dielectric relaxation, X-ray scattering, and molecular orbital/molecular dynamics simulations [4,14–22], as well as the studies in FA system as mentioned above. Thus, the dimensionality in the hydrogen-bonding network is higher for FA than for NMF. Indeed, the boiling and melting points and the viscosity are higher for FA than for NMF [23].

We reported the hydrogen-bonding structure in liquid NMF and its binary mixtures with aprotic amide *N,N*-dimethylformamide (DMF), which is a less structured solvent due to the dipole–dipole interactions [7,16]. We found that (1) the DMF molecules rupture the chain-like structure of NMF in the mixtures and (2) the DMF and NMF molecules are homogeneously mixed through hydrogen bonds over the entire range of solvent compositions in the mixture. On the other hand, it

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has been established that water with a three-dimensional hydrogen-bonding network is heterogeneously mixed with conventional organic solvents, such as alcohols, acetonitrile, and dioxane [24–26]. This is due to the presence of self-aggregated water clusters in the mixtures. This study investigates the effect of the hydrogen-bonding network dimensionality on the mixing state and the intermolecular interactions in binary solvent mixtures. The liquid structure and dynamics in the amide mixtures of protic FA (extended hydrogen-bonding network) and aprotic DMF (without hydrogen bonding) were studied using low-frequency Raman spectroscopy and MD simulations. The experimental results were discussed comparing with those of the mixtures of protic NMF (one-dimensional chain-like hydrogen bonding) and DMF. In addition, small-angle neutron scattering (SANS) experiments were performed for the FA–DMF mixtures to clarify the mixing state, homogeneous or heterogeneous, at the mesoscopic level.

2. Experimental

2.1. Materials

FA and NMF were dried over 3 Å molecular sieves for several weeks, distilled at 328 K under reduced pressure, and stored in a dark bottle with a P_2O_5 drying tube. DMF was dried over 4 Å molecular sieves for several weeks and distilled at 303 K under reduced pressure. The water content was checked by Karl Fischer titration to be <200 ppm. All materials and solutions were treated in a glove box under an argon atmosphere.

2.2. Low-frequency Raman spectroscopy

Raman spectra in the region of 10–400 cm^{-1} were measured using a dispersion Raman spectrometer (NR-1100; JASCO, Japan) with an argon ion laser operating at 514.5 nm. The optical resolution was 2.0 cm^{-1}, and the laser power was 500 mW. Neat DMF (or FA) in a vessel was mixed with neat FA (or DMF) using an auto-burette, and spectral data were accumulated at each titration point. The $R(\nu)$ spectra were obtained from measured $I(\nu)$ according to the following equation:

$$R(\nu) \approx I(\nu)(\nu_0 - \nu)^{-4}\nu[1 - \exp(-hc\nu/kT)] \tag{1}$$

where ν_0 and ν (cm^{-1}) represent the frequencies of the irradiated laser light and the Raman shift, respectively, and other parameters are physical constants or quantities of the usual meanings.

2.3. SANS

Sample solutions were prepared by mixing deuterated DMF(d_7) with undeuterated FA to obtain a high contrast of scattering for DMF. The SANS measurements for the mixtures of DMF mole fraction x_{DMF} = 0.1–0.9 were performed at 298 K using the SANS-U spectrometer installed on the JRR-3 reactor (JAEA, Tokai, Japan) [27]. A sample-to-detector distance of 2 m was employed to cover the momentum transfer q (= $4\pi\lambda^{-1}\sin\theta$, where λ and 2θ denote the wavelength of neutron beams (7 Å) and the scattering angle, respectively) from 0.02 Å to 0.15 Å. The transmission was measured with a ^{3}He detector located at the beam stopper position. SANS profiles corrected for background, using an empty cell, were normalized with respect to the scattering of polyethylene as a secondary standard material. The SANS profiles thus obtained were further corrected for incoherent scattering to obtain the scattering intensities $I(q)$. The incoherent scattering intensities were estimated according to the procedure reported in the literature [28].

2.4. MD simulations

MD simulations for neat solvents (FA, NMF, and DMF) and their binary mixtures (FA–DMF and NMF–DMF) were performed for an NTP ensemble (298 K and 1 atm) with 256 molecules using the Materials Explorer 5.0 program (Fujitsu, Japan). The simulation time was 500 ps for all the systems. The system was equilibrated for the first 300 ps with an interval of 0.2 fs, and the data collected at every 0.1 ps during 300–500 ps were analyzed to calculate the velocity autocorrelation and the atom–atom pair correlation functions. In this research, we performed the simulation using the five-point OPLS model to simply describe the intermolecular interaction dynamics in the complicated binary mixtures [29]. In the OPLS model, the hydrogen of the aldehyde group is not considered and the C–H group is treated as the united atom. Non-bonded intermolecular interactions are represented by a sum of the Lennard-Jones and Coulombic terms. The velocity autocorrelation function $C_\alpha(t)$ was calculated for the α-sites of the amides (α = O, C, N, and H), and $C_{center}(t)$ was also calculated for the center of mass for the solvent molecule. The average $C_\alpha(t)$ is given by the following equation:

$$\begin{aligned} C_\alpha(t) &= <v(t) \cdot v(0)> \\ &= \frac{1}{N_\alpha} \sum_1^{N_\alpha} v_\alpha(t + t_i) \cdot v_\alpha(t_i) \end{aligned} \tag{2}$$

where $v_\alpha(t)$ and N_α denote the velocity of particle α at time t and the number of particles, respectively. The corresponding power spectra were calculated using the following equation:

$$S_\alpha(\nu) = \frac{1}{\pi} \int_0^\infty C_\alpha(t) \cos\nu t \, dt. \tag{3}$$

The summation over all $S_\alpha(\nu)$s, i.e., $\Sigma S_\alpha(\nu)$, gives a total power spectrum, $S_{total}(\nu)$. The $S_{total}(\nu)$ was compared with the experimental $R(\nu)$ in terms of the frequency position. Here, note that the $S_{total}(\nu)$ is not suitable to directly compare to the experimental $R(\nu)$ in intensity. However, the $S_{total}(\nu)$ was useful for comparing with the $R(\nu)$ in frequency (i.e., time scale of the corresponding motions).

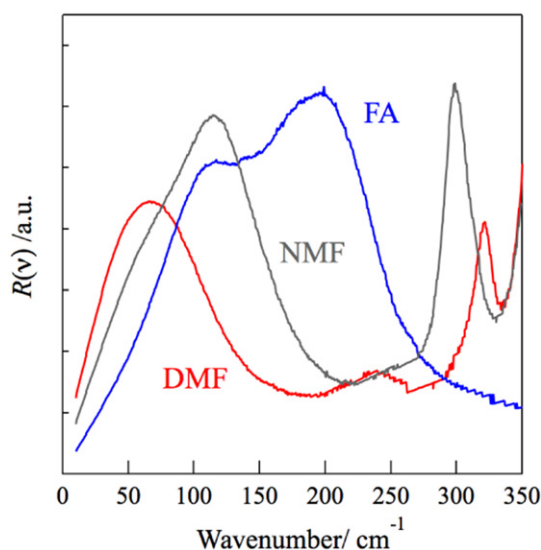**Fig. 1.** Low-frequency Raman spectra $R(\nu)$s observed for neat formamide (FA), N-methylformamide (NMF), and N,N-dimethylformamide (DMF).