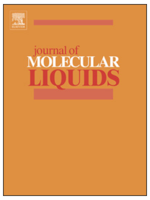
Journal of Molecular Liquids xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Journal of Molecular Liquids

journal homepage: www.elsevier.com/locate/molliq



Hydrogen bonding in ethanol–water and trifluoroethanol–water mixtures studied by NMR and molecular dynamics simulation

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ARTICLE INFO

Article history:
Received 23 May 2015
Received in revised form 12 June 2015
Accepted 16 June 2015
Available online xxxx

Keywords:
^{1}H NMR chemical shift
Electron donicity
Electron acceptability
Hydrogen bonding ability
Trifluoromethyl group
Electron drawing

ABSTRACT

^{1}H NMR measurements were conducted on aqueous mixtures of ethanol (EtOH) and 2,2,2-trifluoroethanol (TFE) at 25.0 and −10.0 °C with varying alcohol mole fraction x_{alc}. At 25.0 °C the TFE hydroxyl proton and water protons in TFE–water mixtures could not be individually observed on the NMR time scale due to the fast exchange between both protons. By cooling at −10.0 °C, the peaks of the alcohol hydroxyl and water protons became distinguishable in both aqueous EtOH and TFE mixtures over the entire x_{alc} range. The alcohol hydroxyl and water protons in both alcohol mixtures at −10.0 °C were gradually deshielded with decreasing x_{alc}, suggesting the increase in the number of the hydrogen bonds in the mixtures. In particular, the NMR results showed that the hydrogen bonds between the alcohol hydroxyl group and water strengthen in both mixtures below $x_{\mathrm{alc}} \approx 0.2$. Moreover, the water structure by hydrogen bonding among water is enhanced in the mixtures below the same mole fraction. To clarify the contribution of the alcohol hydroxyl hydrogen and oxygen atoms in the hydrogen bonding for both mixtures, molecular dynamics (MD) simulations were made on aqueous EtOH and TFE systems at −10.0 °C. The hydrogen bonding abilities of the EtOH hydroxyl hydrogen and oxygen atoms are comparable with each other. The ability of the TFE hydroxyl hydrogen is higher than EtOH, while that of the TFE oxygen is much lower than EtOH. The present results suggested that the higher hydrophobicity of TFE compared to EtOH is mainly attributed to the two lone pairs of the oxygen with the lower electron donicity.

1. Introduction

In various chemical reactions, such as synthesis and extraction, alcohol–water binary mixtures are often utilized as solvents. This is because the physicochemical properties of the solvents, such as dielectric constant, can be easily altered by changing the mixing ratio of alcohol to water [1]. However, most of the researchers determine the mixing ratio of alcohol–water binary solvents by trial and error.

It has been known that the secondary structure of proteins, such as α-helix and β-sheet, may be promoted in their aqueous solutions on adding alcohol [2–4]. In particular, fluorinated alcohols of 2,2,2-trifluoroethanol (hereinafter abbreviated as TFE or T) and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) may more remarkably promote the secondary structure of proteins in their aqueous solutions [5–9]. Many researchers have tried to elucidate the relation between the promotion for the structure of proteins and the physicochemical properties of alcohol–water binary mixtures. The previous studies on bee venom melittin and bovine β-lactoglobulin in various alcohol–water mixtures showed that the order of effectiveness of various alcohols on the structure of both proteins is common though the apparent conformational transitions are significantly different to each other [9–13]. The effect of fluorinated alcohols of TFE and HFIP on the secondary structure of proteins is more marked compared to that of aliphatic alcohols like ethanol (abbreviated as EtOH or E). In addition, the previous studies have revealed that solvent clusters formed in the alcohol–water mixtures is the most prominent key to the promotion of the secondary structure of the proteins [13]. In fact, our previous studies by small-angle neutron scattering (SANS) technique showed that alcohol clusters and water clusters coexist in alcohol–water mixtures, particularly, in the aqueous mixtures of TFE [14] and HFIP [15]. Probably, fluorinated alcohol clusters and water clusters give the hydrophobic and hydrophilic solvation fields to protein molecules involving hydrophobic and hydrophilic moieties.

The marked cluster formation of fluorinated alcohols in aqueous solutions may arise from their higher hydrophobicity of the trifluoromethyl group and the lower hydrogen bonding ability of the hydroxyl oxygen atom than those of aliphatic alcohols. In fact, the electron density of the TFE hydroxyl oxygen atom is lower compared to that of EtOH because of the electron-negativity of the fluorine atoms. The Gutmann's donor number D_N of TFE as a scale of the electron donicity is still ambiguous due probably to the very low donicity, whereas that for ethanol is 20 [16]. In contrast, the Mayer–Gutmann's acceptor

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http://dx.doi.org/10.1016/j.molliq.2015.06.050

Please cite this article as: M. Matsugami, et al., Hydrogen bonding in ethanol–water and trifluoroethanol–water mixtures studied by NMR and molecular dynamics simulation, J. Mol. Liq. (2015), http://dx.doi.org/10.1016/j.molliq.2015.06.050

number A_N (53.3) for TFE [17] as a scale of the electron acceptability is much larger than that (37.1) for ethanol because of the higher positivity of the TFE hydroxyl hydrogen [16]. For water, the donor and acceptor numbers are $D_N = 18.0$ and $A_N = 54.8$, respectively [16,17].

Thus, a comparison of the hydrogen bonding ability between EtOH and TFE is of interest to understand the solvent properties of EtOH–water and TFE–water mixtures on the molecular scale. We have made large-angle X-ray scattering (LAXS) experiments on EtOH–water and TFE–water mixtures at 25.0 °C to clarify the structure of both mixtures at the molecular level [14,18,19]. The number of the O···O hydrogen bonds estimated from the X-ray radial distribution function for pure TFE is slightly smaller than that for pure EtOH. In addition, the increase in the hydrogen bonds for TFE–water mixtures less easily progresses with decreasing TFE mole fraction from 1 to 0.2 (with increasing water content) compared to that for EtOH–water mixtures. In both EtOH and TFE mixtures, the increase in the hydrogen bonds is almost saturated against the decrease in the alcohol mole fraction from 0.2. These features of the TFE mixtures are mainly attributed to the weaker hydrogen bonds between TFE and water molecules due to the lower electron donicity of the TFE hydroxyl oxygen atom. Moreover, the steric hindrance of the trifluoromethyl group may affect the weaker hydrogen bonds of TFE. However, we could not distinguish the contributions of the hydrogen bonding of the hydroxyl hydrogen and oxygen atoms of alcohol molecules because LAXS gives the total number of the O···O hydrogen bonds of alcohol–alcohol, alcohol–water, and water–water as a result of the close distances of the O···O hydrogen bonds among them. Additionally, LAXS cannot give the information on the hydrogen atoms in the mixtures due to the negligible low X-ray scattering power of hydrogen atom. Thus, the contributions of the electron donicity and acceptability of the alcohol hydroxyl group to the mixing state of EtOH–water and TFE–water could not be exactly evaluated in the previous study.

In the present study, to clarify the effects of the hydroxyl oxygen and hydrogen atoms of EtOH and TFE on the mixing of alcohol and water, ^{1}H NMR measurements and molecular dynamics (MD) simulations have been made on both alcohol–water mixtures over the entire range of alcohol mole fraction x_{alc}. Especially, ^{1}H NMR measurements have been conducted on both mixtures at −10.0 °C as well as 25.0 °C to separately observe the ^{1}H NMR peaks of the alcohol hydroxyl and water proton atoms. The MD simulations were performed on both alcohol–water binary systems at −10.0 °C. The MD simulations enabled us to individually evaluate the numbers of the hydrogen bonds per alcohol and per water. Based on the ^{1}H NMR chemical shifts of alcohol and water molecules and the numbers of the hydrogen bonds estimated from the MD simulations, the hydrogen bonding abilities of EtOH and TFE in the alcohol–water mixtures are discussed on the molecular scale.

2. Experimental

2.1. Sample solutions

EtOH–water binary mixtures were prepared by weighing EtOH (Wako Pure Chemical, grade for HPLC) and doubly distilled water to reach EtOH mole fractions of $x_{EtOH} = 0.002$, 0.01, 0.05, 0.1, 0.15, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, and 0.9. TFE (Tokyo Chemical Industry, extra grade) and doubly distilled water were also mixed to prepare TFE–water mixtures at TFE mole fractions $x_{TFE} = 0.002$, 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, and 0.9.

2.2. ^{1}H NMR spectroscopy

^{1}H NMR spectra of the EtOH–water and TFE–water mixtures at 25.0 and −10.0 °C were recorded on a 300 MHz FT-NMR spectrometer (JEOL, JNM AL300) with varying x_{alc}. The sample solution was placed in a sample tube (Shigemi, PS-001-7) with 5 mm inner diameter. An external double reference tube (Shigemi), which has a capillary shape with a blown-up sphere at its base, was inserted into the sample tube containing the mixtures. Hexamethyldisiloxane (HMDS) (Wako Pure Chemical, high purity grade) was used as a reference substance for the proton atoms. The deviation from the desired temperatures was controlled within ±0.1 °C by a mixture of dry cold stream from liquid nitrogen and hot air by heater.

The observed chemical shifts were corrected for the volume magnetic susceptibility of the sample solutions by the double external reference method [20–22]. In addition, the magnetic susceptibility of the sample solutions at −10.0 °C was normalized to that at 25.0 °C through

$$\delta^{T_r}(T) = \delta(T) - (4\pi/3)\{\chi_{ref}(T) - \chi_{ref}(T_r)\} \times 10^6 + \delta_{cap}(T) - \delta_{cap}(T_r), \qquad (1)$$

to directly compare between ^{1}H chemical shifts measured at both temperatures [20]. T_r and T are a fixed reference temperature and a sample temperature, respectively; in the present experiments, $T_r = 25.0$ °C and $T = -10.0$ °C. The $\delta(T)$ and $\delta^{Tr}(T)$ represent the chemical shift observed at T and the shift normalized at T_r, respectively. $\chi_{ref}(T)$ and $\delta_{cap}(T)$ are the volume magnetic susceptibility and the chemical shift of the reference substance in the capillary part of the double reference tube at T, respectively. For HMDS at $T_r = 25.0$ °C, the term of $-(4\pi / 3)\{\chi_{ref}(T) - \chi_{ref}(T_r)\}$ corresponds to $3.306 \times 10^{-3} \times (25.0 - T)$.

2.3. MD simulations

MD calculations were conducted on EtOH–water and TFE–water binary systems over the entire x_{alc} range at an interval of 0.1. The MD program package of GROMACS 4.0.7 was used in the present simulations [23]. The total numbers of atoms for each system were set to be 6000 in a cubic cell under a periodic boundary condition, and the *NPT* ensemble was utilized during the calculations. The bond stretching terms concerned with all of the hydrogen atoms were constrained using the LINCS algorithm [24]. The leap-frog method was applied to the integration with a time step of 0.5 fs [25]. The cutoff radius for Lennard–Jones interactions was 10 Å, and the Coulomb interactions were truncated using the particle mesh Ewald method [26]. The temperature and pressure were controlled at −10.0 °C and 0.1 MPa by Nosé–Hoover [27] and Parrinello–Rahman methods [28], respectively. The time constants for the thermostat and barostat were 0.1 and 1.0 ps, respectively.

The van der Waals parameters and atomic point charges for EtOH and TFE molecules were employed from the OPLS-AA force field [29]. The rigid body TIP5P model was used for water molecules [30]. The force field parameters of alcohols were summarized in Table S1 of the electronic Supplementary data, together with the notation of the atoms (Figs. S1 and S2). For all of the systems, the equilibration at −10.0 °C and 0.1 MPa took 12 ns, and then the calculations were continued for 20 ns. The site–site intermolecular radial distribution functions for the H···O interactions between the alcohol hydroxyl groups, the alcohol hydroxyl group and water, and water molecules were derived from the trajectory for the last 20 ns. The radial distribution functions were shown in Figs. S3–S6 in the electronic Supplementary data. The coordination numbers of the H···O interactions were estimated from the area of the first peak observed in the site–site intermolecular radial distribution function integrated to the first minimum of 2.5 Å.

3. Results and discussion

3.1. ^{1}H NMR spectra

In Fig. 1, ^{1}H NMR spectra of the EtOH–water binary mixtures at 25.0 °C and various EtOH mole fractions x_{EtOH} are depicted by the red lines. Two small peaks at 0 ppm and less than 0 ppm in each spectrum arise from the reference substance of HMDS in the capillary and sphere parts of the double reference tube, respectively. In the spectrum of pure EtOH ($x_{EtOH} = 1$), peaks at 1.1, 3.5, and 5.2 ppm are assigned to the EtOH methyl, methylene, and hydroxyl protons, respectively. When water is

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