Journal of Molecular Liquids 230 (2017) 261–270

Contents lists available at ScienceDirect

Journal of Molecular Liquids

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

Solvation power of HFIP for the hydrophilic and the hydrophobic moieties of L-leucine studied by MD, IR, and NMR techniques

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ARTICLE INFO

Article history:
Received 28 September 2016
Received in revised form 5 December 2016
Accepted 6 January 2017
Available online 10 January 2017

Keywords:
Solvation structure
Spatial distribution functions
C—O stretching vibrations
C—H stretching vibrations
Electron density
Blueshift hydrogen bond

ABSTRACT

The solvation properties of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) in its aqueous binary solvents have been evaluated using L-leucine (Leu) as a probe molecule by both theoretical and experimental approaches. Thus, molecular dynamics (MD) simulations, infrared (IR) and ^{1}H and ^{13}C NMR spectroscopic experiments have been conducted on Leu-HFIP-water solutions with varying the HFIP mole fraction from $x_{HFIP} = 0$ to 1. Spatial distribution functions (SDFs) obtained from the MD simulations showed that the Leu carboxylate group is gradually solvated by HFIP molecules with increasing x_{HFIP}, instead of water molecules. Thus, the replacement of water by HFIP for the carboxylate group progresses as the x_{HFIP} rises. This was proved by the C—O stretching vibrations and the ^{13}C chemical shift of the carboxylate group. On the contrary, the Leu aminium group is preferentially solvated by water below $x_{HFIP} = 0.7$. However, HFIP molecules begin to solvate the aminium group above this mole fraction. The trifluoromethyl groups of HFIP significantly enclose the alkyl group of Leu even at the low x_{HFIP}. By surrounding the Leu alkyl group with the HFIP trifluoromethyl groups, the C—H stretching vibrations of Leu blueshift with increasing x_{HFIP}. Simultaneously, the hydrogen and carbon atoms of the Leu alkyl group are electronically shielded as the x_{HFIP} rises. The MD pair correlation function $g(r)_{HCLeu\text{-}FHFIP}$ showed the H—F interactions between the Leu alkyl hydrogen and the HFIP fluorine atoms with the distance of 2.75 Å. Consequently, the present results proved that the HFIP trifluoromethyl groups may interact with the Leu alkyl group through the blueshift hydrogen bonds of C—H···F—C.

1. Introduction

The effect of alcohols on the secondary structure of peptides and proteins has been well known in the biochemistry field. The α-helix and β-sheet of peptides and proteins may often be promoted in their aqueous solutions when alcohol is added into them. Especially, the effect of fluorinated alcohols on the secondary structure of peptides and proteins is more significant than aliphatic alcohols.

There have been the systematic investigations on the promotion of the α-helical structure of the bee venom peptide of melittin and the bovine protein of β-lactoglobulin in their aqueous binary solvents with various alcohols, such as ethanol, propanol, 2,2,2-trifluoroethanol (TFE), and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) [1–5]. The ellipticity at 222 nm in the circular dichromic spectra of the peptide and protein is more significantly enhanced by adding alcohol into their aqueous solutions in the order of HFIP > TFE > 2-propanol > ethanol > methanol. Plausible causes for the alcohol-induced secondary structure of the peptides, such as dielectric constant and pH of the alcohol-water binary solvents, have been examined in the investigations [1–5]. The most plausible reason has been found in the investigations; that is, the solvent clusters of alcohol molecules formed in the binary solvents most strongly correlated to the promotion of the secondary structure of the peptide and protein. Small-angle X-ray scattering (SAXS) intensities suggested that the alcohol clusters are more stably formed in the aqueous solutions in the above order [5]. The significant formation of HFIP and TFE clusters in their aqueous solutions has also been proved by our small-angle neutron scattering (SANS) experiments [6,7]. Probably, the hydrophobic environment of fluorinated alcohol clusters encloses the hydrophobic moieties of peptide and protein to stabilize their secondary structure. However, the interactions between alcohol molecules and the hydrophobic moiety of peptides in the alcohol clusters have not been clarified on the microscopic scale even by the systematic investigations.

We have found that the hydrophobic alkyl moieties of simple amphiphilic solutes, such as diols [8] and amides [9–11], are more strongly solvated by TFE and HFIP molecules compared to aliphatic alcohols like ethanol and 2-propanol. In some cases, the solvation of the hydrophobic moiety of amphiphilic solutes by HFIP induces phase separation of HFIP-water binary solvents [9–11]. In other words, HFIP clusters are gradually evolved around the hydrophobic moiety of such solutes with increasing HFIP content due to the solvation for the moiety. Water clusters are

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http://dx.doi.org/10.1016/j.molliq.2017.01.018
0167-7322/

finally excluded from HFIP clusters enhanced around the solutes, resulting in phase separation of the HFIP-water binary solvents. The interactions between alcohol molecules and peptides have been observed using NMR nuclear Overhauser effect (NOE) technique [12–17]. In particular, the stable interactions of the hydrophobic moieties of peptides, such as the alkyl and phenyl groups, with the trifluoromethyl groups of TFE and HFIP molecules have been observed using heteronuclear $^{1}H\{^{19}F\}$ NOE. These previous results suggest that the special interaction surely acts between the trifluoromethyl groups of the fluorinated alcohols and the hydrophobic moieties of peptides. However, the NOE intensities are merely in inverse proportion to the distance between the magnetically excited atom and the observed atom, but do not give us the information on the microscopic interaction between them. Thus, it is still unknown what interaction acts between them.

In our previous investigation, we have also found that the solubility of an amino acid like Leu for alcohol-water binary solvents is higher in the order of HFIP > TFE > methanol > ethanol >2-propanol [18]. For example, Leu can be dissolved in HFIP-water binary solvents at 50 mmol dm^{-3} over the entire range of HFIP mole fraction x_{HFIP}. However, Leu at the same concentration cannot be dissolved in the 2-propanol-water solvents above the 2-propanol mole fraction of $x_{2\text{-}PrOH} \approx 0.2$. The solvation structure of Leu in aqueous binary solvents of various alcohols in the alcohol mole fraction range of $x_A \le 0.3$ has been clarified by IR and NMR spectroscopic measurements and MD simulations. According to the acid dissociation constants [19], Leu exists as a zwitterion in a neutral solution as shown in Fig. 1. Our results showed that the oxygen atoms of the Leu carboxylate group are most easily hydrogen-bonded with the HFIP hydroxyl hydrogen atoms among the alcohols examined. Thus, water molecules that are initially hydrogen-bonded with the carboxylate group in the water solvent are easily replaced by HFIP molecules with increasing x_{HFIP}. Additionally, the hydrophobic alkyl group of Leu may interact with the trifluoromethyl groups of the fluorinated alcohol of TFE and HFIP. The IR and NMR results revealed that HFIP molecules more remarkably induce the blueshift of the C—H stretching vibrations and the shielding of the hydrogen and carbon atoms of the Leu alkyl group compared to TFE molecules. In contrast, the C—H vibrations slightly redshift and the alkyl hydrogen and carbon atoms are deshielded in aliphatic alcohol-water binary solvents with increasing alcohol content. Thus, we have concluded that the blueshift hydrogen bonds of C—H···F—C may be formed between the Leu alkyl group and the trifluoromethyl groups of the fluorinated alcohols, especially, HFIP. In many reports, the term of "*blueshift hydrogen bond*" has been often used for the weaker interactions, such as the C—H···F—C interaction, with the blueshifting of the C—H vibration in contrast to the conventional stronger hydrogen bonds, such as O—H···O, with the redshifting of the O—H vibration. The formation of the blueshift hydrogen bonds, such as the C—H···O interaction, has so far been proposed by many researchers [20–31]. However, most of the reports have been made using theoretical techniques such as a density functional theory (DFT). There have been a few reports on the experimental evidences for the blueshift hydrogen bonding [18,32–34]. Thus, to establish the formation of the blueshift hydrogen bonds, further experimental researches should be made in various solution systems. Especially, the blueshift hydrogen bond of the C—H···F—C interactions has been less investigated even by theoretical calculations compared to the C—H···O interactions [29–31].

In the present investigation, to clarify the reasons why only HFIP-water binary solvents can dissolve Leu into them over the entire mole fraction range on the microscopic scale, MD simulations and IR and NMR spectroscopic measurements were conducted on Leu-HFIP-water solutions above $x_{HFIP} = 0.3$. Furthermore, we aimed at elucidating the formation of the blueshift hydrogen bonds between Leu and HFIP molecules in the ternary solutions. Based on the results obtained from the present and previous [18] investigations, we discuss the unique solvation properties of HFIP in its aqueous binary solvents over the entire x_{HFIP} at the molecular level.

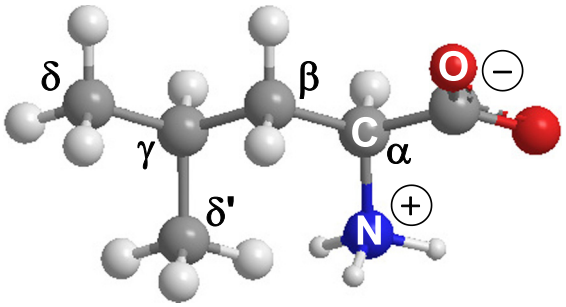

Fig. 1. Structure of L-leucine (Leu) with the notation of atoms.

2. Experimental section

2.1. Sample solutions

Deuterium oxide (D_2O) (Cambridge Isotope Laboratories, D contents of 99.9%) was used for preparing sample solutions of IR measurements, whereas doubly distilled water (H_2O) was employed for sample solutions of NMR experiments. HFIP (Tokyo Chemical Industry, high purity grade) was used without further purification. HFIP and D_2O or H_2O were mixed at desired x_{HFIP} to prepare HFIP-water binary solvents. Leu (Aldrich, 99.0%) was dried at 130 °C in a vacuum oven before use. Dried Leu was dissolved into the HFIP-water binary solvents at the Leu concentrations of 50 and 70 mmol dm^{-3} for IR and NMR experiments, respectively. D_2O solutions were handled under nitrogen atmosphere in a glove box.

2.2. MD simulations

Solvation structure of Leu in HFIP-water systems at $x_{HFIP} = 0.5$, 0.7, and 1 was simulated by MD calculation with an *NTP* ensemble at 298 K and 1 atm. All of the simulated systems consisted of three Leu molecules and 1497 molecules of HFIP and water in a cubic cell under a periodic boundary condition. The compositions of the systems are summarized in Table 1, together with those at $x_{HFIP} = 0$, 0.05, 0.1, and 0.2 simulated in the previous investigation [18]. In the simulations, bending and torsion terms for the intramolecular interactions and the Lennard–Jones and Coulomb terms for the intermolecular interactions were taken into account by the potential function,

$$E = \sum_{\text{angle}} K_\theta(\theta-\theta_0)^2 + \sum_{\text{torsion}} \frac{V_n}{2}\{1+\cos(n\phi-\phi_0)\} + \sum_{i<j}\left[4\varepsilon_{ij}\left\{\left(\frac{\sigma_{ij}}{R_{ij}}\right)^{12}-\left(\frac{\sigma_{ij}}{R_{ij}}\right)^{6}\right\}+\frac{1}{4\pi\varepsilon_0}\frac{q_iq_j}{R_{ij}}\right], \quad (1)$$

where the subscript "0" indicates the equilibrium values for bond angles and torsion angles, σ_{ij} and ε_{ij} are 6–12 Lennard-Jones parameters for

Table 1
Compositions of Leu–water and Leu–HFIP–water systems examined by MD simulations and d_{MD} and d_{exp} are the densities (g cm^{-3}) derived from the simulations and determined experimentally, respectively.

x_{HFIP}	Numbers of molecules in a MD cell			d_{MD}	d_{exp}
	Leu	HFIP	Water		
0[a]	6	0	2994	0.9762	0.9997
0.05[a]	6	150	2844	1.1431	1.1548
0.1[a]	6	300	2694	1.2412	1.2567
0.2[a]	6	600	2394	1.3681	1.3819
0.5	3	748	748	1.5207	1.5285
0.7	3	1048	449	1.5482	1.5688
1	3	1497	0	1.6072	1.6072

[a] Ref. [18].