



Hydrophobic and low-density amino acid ionic liquids

Junko Kagimoto, Satomi Taguchi, Kenta Fukumoto, Hiroyuki Ohno*

Department of Biotechnology, Tokyo University of Agriculture and Technology, Koganei, Tokyo 184-8588, Japan

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ABSTRACT

A series of tetraalkylphosphonium amino acid salts was synthesized to determine the effect of ion structure, in particular the length of alkyl chains, on physico-chemical properties such as density, viscosity, glass transition temperature, and decomposition temperature. The resulting alkylphosphonium amino acid ionic liquids (AAILs) all had low density, from 0.886 to 0.945 g cm⁻³ at 25 °C. The density was tunable by varying the alkyl-chain length, regardless of the symmetry of the phosphonium cations. When the alkyl chains on the phosphonium cation were hexyl or longer, the AAILs were phase-separated upon mixing with water because of their hydrophobicity, and floated on top of the water phase. The water content in the ILs depended on the amino acid side chains and on the alkyl-chain length on the cations.

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1. Introduction

Ionic liquids (ILs) have a potentially unique combination of properties, such as negligible vapor pressure, high thermal stability, and high ionic conductivity, because of the wide capability for design of the ions. These unique properties have led researchers to design novel solvents for deployment in chemical, electrochemical, and biochemical reactions [1]. Many hydrophobic ILs have been reported, as replacements for hydrophobic organic molecular liquids. Most of these contain fluorinated anions such as hexafluorophosphate (PF₆⁻) [2] or bis (trifluoromethylsulfonyl)imide ([TF₂N⁻]) [3]. The electron withdrawing effect of halide atoms, particularly fluorine, on the anion acts to weaken the electrostatic interaction force through a reduction of anionic charge density, as well as making the salt hydrophobic. These hydrophobic ILs generally undergo phase separation with water. This phase separation has the capability to provide a liquid–liquid extraction system as well as yielding heterogeneous reaction media. Rogers et al. [4] and Zhao et al. [5] have used ILs in liquid–liquid extraction of metal ions, organic compounds, bio-molecules, and even gases.

Small amounts of water in the IL phase are known to be important for the dissolving of proteins. Such ILs are expected to act as a novel and effective reaction medium for biochemistry [6–8]. Fujita et al. reported that cytochrome c (Cyt. c) dissolved in hydrated choline dihydrogen phosphate; remarkably, they observed excellent thermal stability and redox activity of the dissolved Cyt. c for longer than 18 months. These observations demonstrate that ILs containing small amounts of water can be useful solvents for proteins or other biological molecules. Since most water molecules bind strongly with ions to generate the hydrated state, they exhibit very low vapor pressure, like ordinary ILs. The amount

of water must be carefully controlled when water-miscible ILs are used for this purpose. New water/hydrophobic IL systems, containing carefully chosen small quantities of water, should be useful in fields beyond biochemistry.

We have reported previously that amino acids are valuable anions for the preparation of ILs, by coupling them with suitable cations. Amino acid ionic liquids (AAILs) were first prepared using 1-ethyl-3-methylimidazolium cation ([emim]⁺), which is a common cation used in the preparation of ILs [9,10]. All [emim][AA]s with 20 different natural amino acids are liquid at room temperature. However, [emim][AA]s have poor thermal stability, decomposing at around 200 °C. To overcome this disadvantage we then considered phosphonium cations, which have good electrochemical stability [11] and thermal stability [12,13] but not a favorable melting point or viscosity. Phosphonium cation-based salts have not been closely analyzed, because of their higher melting point. Phosphonium cations nevertheless prove to be excellent partners for amino acids [14]. We confirmed that tetrabutyl-phosphonium amino acid salts ([P_{4,4,4,4}][AA]) have greater thermal stability (*T*_{dec}: 190–319 °C) and lower glass transition temperatures than those of [emim][AA] [14]. The study of [P_{4,4,4,4}][AA] also found that the side groups of amino acids have a strong influence on their physico-chemical and thermal properties. Some AAILs have recently been proposed as liquids for efficient CO₂ capture [15,16]. Also, those with proline act as an efficient reaction medium for *N*-benzyloxycarbonylation [17]. We have prepared hydrophobic AAILs by introducing a trifluoromethylsulfonyl group on the amino group [18]. The mixture of the hydrophobic AAILs with water exhibited interesting phase behavior, with a “lower critical separation temperature” [19] below which AAILs and water mixed homogeneously; heating to above this temperature led to phase separation. This behavior is reversible by small temperature change. These results clearly show that combinations of hydrophobic AAILs and water have unique and potentially useful phase behavior.

* Corresponding author. Tel./fax: +81 42 388 7024.

E-mail address: ohnoh@cc.tuat.ac.jp (H. Ohno).

ILs based on ammonium cations, such as imidazolium, pyrrolidinium and pyridinium cations, have been investigated extensively in a large number of papers [20–23]. Recently, phosphonium cations have been proposed as component cations of ILs with better thermal and electrochemical stability than using ammonium cations [11,12,24–27]. Of the phosphonium cations, trihexyl(tetradecyl)phosphonium cation has been studied most [13,28–31]. Although there have been some studies of the physico-chemical and thermal properties of ILs prepared with different phosphonium cations [11,26,27], few comparative reports exist of phosphonium-type ILs. Detailed systematic analysis has been necessary for further application of these phosphonium-type ILs.

In the present study, we prepared hydrophobic AAILs ($[P_{n,n,n,m}]$ [amino acid]), where n or m denotes the carbon number of alkyl chains on the phosphonium cation) by introducing long alkyl chains on the phosphonium cations.

2. Experimental

2.1. Materials

Tri- n -octylphosphine and all amino acids used (L-glycine, L-alanine, L-leucine, L-isoleucine, L-lysine, L-phenylalanine, L-proline, L-serine, L-aspartic acid, L-glutamic acid, and L-valine) were purchased from Wako Chem. Co. Tetraoctylphosphonium bromide and hexylbromide were purchased from Aldrich. Heptylbromide, decylbromide, dodecylbromide, and octadecylbromide were purchased from Tokyo Chemical Industry Co. Tetra- n -pentyl-phosphonium bromide, tetra- n -heptylphosphonium bromide, tetra- n -decyl-phosphonium bromide, tetra- n -dodecyl-phosphonium bromide and tetra- n -tetradecylphosphonium bromide were supplied from Hokko Chem. Co. 4-Fluoro-L-phenylalanine, and *s*-2-amino-3-[3-(trifluoromethyl phenyl)] propionic acid were donated by Asahi Glass Co.

2.2. Synthesis of amino acid ionic liquids

Amino acid ionic liquids (AAILs) containing asymmetric phosphonium cations were prepared in the following three steps: (1) quaternization of tri-alkylphosphine; (2) anion exchange from halide anions to hydroxide; and (3) neutralization with amino acids. AAILs containing symmetric cations were prepared from the corresponding tetraalkyl phosphonium salts by anion exchange followed by neutralization with amino acids. As an example, the synthesis procedure of $[P_{8,8,8,10}][Leu]$ was mentioned as follows:

- (1) Quaternization of tri-alkylphosphine: Tri- n -octylphosphine (8.00 g; 0.022 mol) was dissolved in toluene (20 mL) and a small excess of decylbromide (5.30 g; 0.024 mol) was added. The resulting solution was stirred at 100 °C for 48 h under N_2 atmosphere. Toluene was then removed at 50 °C by evaporation, and the residue was recrystallized in hexane (300 mL) in a freezer. Tri- n -octyldecylphosphonium bromide ($[P_{8,8,8,10}][Br]$) was obtained as a white powder after removing the solvent (yield 80 %).
- (2) Anion exchange: $[P_{8,8,8,10}][Br]$ (10.0 g) was dissolved in a water/methanol (1:9 w/w) mixed solvent (total 200 mL). The mixed solution was passed through an anion-exchange column filled with Amberlite[®] IRN-78, so as to collect a dilute solution of tri- n -octyldecylphosphonium hydroxide ($[P_{8,8,8,10}][OH]$).
- (3) Neutralization with amino acids: the $[P_{8,8,8,10}][OH]$ aqueous solution was added to an aqueous solution of slight excess of L-leucine (2.50 g; 0.019 mol). After gentle mixing for 30 min, the solvent was evaporated slowly at 50 °C. After most of the solvent had evaporated, acetonitrile (60 mL) and methanol (40 mL) were added, and the mixture was stirred vigorously for

30 min. As free amino acid is insoluble in the mixture of acetonitrile and methanol, the solution was filtered to remove unreacted L-leucine. After the filtrate had been evaporated, water (50 mL) was added to the solution, giving rise to two phase separation in which the lower phase was water with some unreacted L-leucine, and the upper phase was decyl-tri- n -octylphosphonium leucine $[P_{8,8,8,10}][Leu]$. After removal of the upper phase, 50 mL of water was added and the solution was thoroughly mixed. We repeated this procedure several times to wash out the water-soluble fraction from the product. The residual solution was dried *in vacuo* for 1 day at 70 °C.

2.3. Characterization

The structure of AAILs was confirmed by 1H NMR spectroscopy (500 MHz, JEOL). Tetramethylsilane (TMS) was used as an inner reference for the 1H NMR measurements.

2.4. Measurement of physico-chemical and thermal properties of AAILs

The glass transition temperature (T_g) and melting temperature (T_m) of the resulting AAILs were measured using a differential scanning calorimeter (DSC-6220, Seiko Instruments) in the range from −140 to +200 °C, with a heating rate of 10 °C min^{−1}. The decomposition temperature (T_{dec}) was measured by means of thermogravimetry/differential thermal analysis, using a TG/DTA 220 (Seiko Instruments) with a scan rate of 10 °C min^{−1} in N_2 atmosphere. The viscosity of our series of AAILs was measured by a cone/plate viscometer (LVDV-1+, Brookfield). Density was measured by a density/specific gravity meter (DA-100, Kyoto Electronic Manufacturing Co.).

2.5. Water content of AAILs

Upon adding a small excess of water to each amino acid ionic liquid, we often observed phase separation. The top phase (AAIL phase) was pipetted out and the water content was determined using a TG/DTA 220 (Seiko Instruments).

3. Results and discussion

Most of the $[P_{n,n,n,m}][AA]$ s synthesized in this study were liquid at room temperature; the exceptions were $[P_{8,8,8,8}][Glu]$ and $[P_{12,12,12,12}][Leu]$. When $[P_{n,n,n,m}][AA]$ had a long alkyl chain ($n \geq 6$), these were hydrophobic and accordingly underwent phase separation with water. The IL phase sat above the water phase after mixing (Fig. 1), because their density was less than that of water.

3.1. Density

The density of the synthesized AAILs ranges from 0.886 to 0.945 g cm^{−3} at 25 °C, consistently less than that of water. AAILs containing phosphonium cations had lower density than those containing imidazolium cations, due to long alkyl chains on the phosphonium cation. For example, Del Sesto et al. reported this trend in the density of $[P_{8,8,8,8}][Tf_2N]$ [12] and $[bmim][Tf_2N]$ (1.07 and 1.43 g cm^{−3}, respectively) [22]. Long alkyl chains are known to lower the density of the corresponding ionic liquids. We analyzed the effect of the number of carbon atoms in the cations on the density of $[P_{n,n,n,n}][Leu]$, as shown in Fig. 2. The density depends mainly on the number of carbon atoms, regardless of the symmetry of cations. A similar tendency has been reported for imidazolium salts, in which an increase in the alkyl chain in the imidazolium reduces the salt density [30,32,33].

When the cation was fixed to $[P_{8,8,8,8}]$, the salt density increased in the following order with respect to the amino acid anions; $[Leu] <$

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