

Design and synthesis of hydrophobic and chiral anions from amino acids as precursor for functional ionic liquids†

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Hydrophobic ionic liquids composed of tetrabutylphosphonium cation and chiral anions derived from amino acids modified with trifluoromethane sulfonyl groups have been synthesized using a simple method.

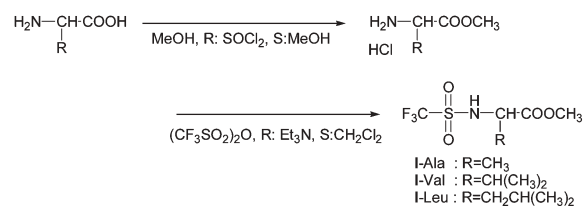
Ionic liquids (ILs)¹ are designer liquids with the possibility of our choosing their physico-chemical properties and solvent properties such as polarity,² melting point,³ ionic conductivity,⁴ and viscosity. Choice of component organic ions may generate ILs suitable for specific tasks.⁵ Our recent investigations strongly suggest the value of amino acids as components of ILs; we have already reported some ILs having natural amino acids as anion, hereafter referred to as amino acid ILs (AAILs).⁶ Physico-chemical properties of AAILs, including thermal properties, viscosity, polarity, and solubility of organic compounds, are strongly affected by the properties of the amino acids. Use of natural amino acids as component ions also make AAILs environmentally friendly, with biodegradability⁷ and reduced toxicity.⁸ AAILs furthermore provide a chiral environment without any complicated procedure, by simply neutralizing the chiral amino acids with the corresponding onium hydroxide, such as [emim][OH]. Further design for function of ILs is expected to be possible by chemical modification of the amino group, carboxyl group, or various functional groups on the side chain of the amino acid.⁹

There are various functionalised ILs, but hydrophobic ILs containing a chiral anion have not yet been reported. Hydrophobicity should provide various advantages for chiral ILs.¹⁰ The designability of the amino acid as a component of ILs has the potential to produce hydrophobic and chiral ionic liquids. In the present study we synthesized hydrophobic ILs by modification of the amino acid, and we studied their physico-chemical properties. Hydrophobic ILs are generally obtained when the cation and/or anion has a long alkyl chain, or the anion is fluorinated, as in hexafluorophosphate (PF₆⁻), bis(trifluoromethane) sulfonylimide (TF₂N⁻), and so on. Introduction of long alkyl chains to amino acids should provide hydrophobic ILs, but the additional interaction between alkyl chains through secondary binding forces (such as the van der Waals force) increased the melting point of the resulting ILs, and the interaction sometimes generates liquid-crystalline salts.¹¹ An increase in viscosity was also found due to the high formula weight of the component ions. Similarly, hydrophilic groups such as the carboxyl group and

amino group on an α -carbon led to interaction between component ions. ILs are more useful in applications when they have lower viscosity and stability over a wide temperature range. In the present work, we prepared chiral and hydrophilic amino acid derivatives by introducing both the trifluoromethane sulfonyl group and methyl ester group.

Amino acid was added to methanol which had been pre-treated with thionyl chloride at 0 °C, and then stirred overnight. Among natural amino acids, L-alanine, L-valine, or L-leucine were used as starting materials, because they have no functional group in the side chain. The effect of alkyl chain length on the properties of ILs should also be considered, so as to eliminate the effect of additional interactions such as hydrogen bonding. The mixture was then concentrated under reduced pressure. The resulting white solid was suspended in dichloromethane and a bimolar amount of triethylamine was added with stirring. Trifluoromethanesulfonic anhydride dissolved in dichloromethane was added to the mixture under a dry nitrogen atmosphere at -78 °C, and the mixture then stood overnight at room temperature. The resulting solution was washed with dilute hydrochloric acid and saturated aqueous sodium chloride. Then concentrated dichloromethane solution was added *in vacuo*, giving rise to an oil which was purified by column chromatography on silica gel (MeOH/CHCl₃ = 1 : 5) to provide the corresponding *N*-trifluoromethane sulfonyl amino acid methyl ester (Scheme 1). A similar synthetic procedure of the introduction of a trifluoromethanesulfonyl group to the amino group on some peptides has been reported by Radom *et al.*¹² These amino acid derivatives were obtained as hydrophobic white crystals (see note†1 and ESI†).

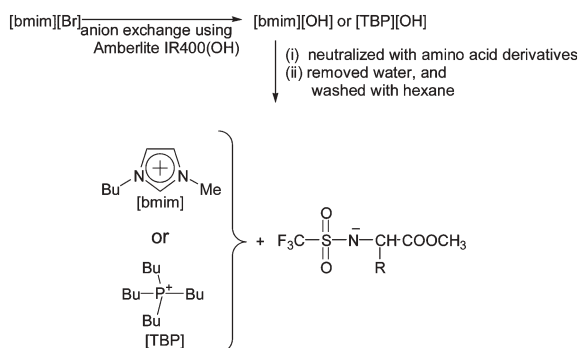
As the cation combined with amino acid derivatives, we chose both 1-butyl-3-methylimidazolium ([bmim]) and *n*-tetrabutylphosphonium ([TBP]) as shown in Scheme 2. A [bmim] is a typical cation used to provide many ILs. On the other hand, [TBP] sometimes generates less viscous and thermally stable AAILs than conventional imidazolium-based AAILs.^{6a} Furthermore, concentrated, pure, and stable [TBP][OH] aqueous solution is commercially available. The [TBP][OH] was a gift from Hokko Chem. Co. and was used without further purification. In the case of [bmim],



Scheme 1 Preparation of hydrophobic amino acid derivatives.

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Scheme 2 Preparation of hydrophobic chiral ILs.

[bmim][OH] aqueous solution was prepared from [bmim][Br] using anion exchange resin¹³ (Amberlite IRA400(OH) (SUPELCO)). However, this [bmim][OH] is not particularly stable, and it should be used immediately after preparation. These onium hydroxide aqueous solutions were neutralized with excess amino acid derivatives having the trifluoromethanesulfonyl group, and the mixed solutions were then dried to remove water. Since unreacted fluorinated amino acid derivative is soluble in hexane, the reaction mixture was washed several times with hexane. The product was dried *in vacuo* for at least 2 days at 70 °C, in preparation for DSC (Seiko Instrument Inc. DSC120) measurement, thermogravimetric analysis (heating rate: 10 °C min⁻¹ under N₂ atmosphere, Seiko Instrument Inc. TG/DTA 220), viscosity measurement, and optical rotation measurement. The structure of the ILs prepared was confirmed by electrospray ionization–TOF–mass spectrometry (JEOL JMS-T100LC) and ¹H NMR (JEOL JNM-LA500) (see notes§§2 and ESI†). The amount of water was confirmed at less than 0.2 wt% by Karl Fischer coulometric titration (Kyoto Electronics. MKC-510N).

Table 1 summarizes thermal properties of the ILs synthesized. Except for [TBP][I-Val], all ILs prepared are room temperature ILs. The melting point (*T_m*) and glass transition temperature (*T_g*) of these synthesized ILs were higher than those of typical hydrophobic ILs such as [bmim][Tf₂N] (*T_m* -4 °C).³ However, in the case of ILs with [TBP] cation, the imide anion derived from amino acid led to a lower melting point than [TBP][Tf₂N] (*T_m* 86 °C).¹⁴ Amino acid derived imide anions gave superior ILs to [Tf₂N] when partnered with phosphonium cations. Since the asymmetric structure of component ions results in poor packing of ions, disordering of the component amino acid derived imide anion would reduce the *T_m* of ILs. The synthesized ILs also showed a gradual increase in *T_g* according to the length of the side chain of the starting amino acid. A similar effect of the alkyl chain

Table 1 Physico-chemical properties of synthesized amino acid derived ILs

	<i>T_m</i> /°C	<i>T_g</i> /°C	<i>T_{decomp}</i> /°C	η/cP^a	$[\alpha]_D^{25b}$
[bmim][I-Ala]	ND	-62.8	260	520	-24.6
[bmim][I-Val]	ND	-42.4	253	3080	-24.5
[bmim][I-Leu]	ND	-37.5	237	4180	-22.1
[TBP][I-Ala]	ND	-54.0	253	700	-8.4
[TBP][I-Val]	61.2	-69.2	277	—	-18.9
[TBP][I-Leu]	13.8	ND	264	2130	-16.3

^a At 25 °C. ^b *c* = 1.0 (g per 100 ml MeOH). ND: not detected.

length on *T_g* has been observed in imidazolium based AAILs.^{6a} The decomposition temperature (*T_{decomp}*) of these ILs was around 250 °C as seen in Table 1. This should be attributable to the presence of ester bond.

Viscosity was measured using a cone-plate viscometer (Brookfield DV-1+). The viscosity of the ILs prepared was affected mainly by their *T_g*, and increased according to the alkyl side chain length, since viscosity at room temperature is governed mainly by *T_g*. In general, chiral ILs have higher viscosity, and are mixed in use with less viscous ILs. A mixture of chiral IL with achiral ionic liquid would contribute the lower density of the chiral component. In fact, the ILs prepared were less viscous than some other chiral ILs.¹⁵ The asymmetric imide anion structure and relatively small formula weight of the anion would generate ILs of less viscosity than conventional chiral ILs. In general, imide anions such as [Tf₂N], [dca],¹⁶ and [TSAC]¹⁷ generate less viscous ILs than carboxylate anion type ILs, and amino acid derived imide anions should give rise to less viscous ILs than natural amino acid based ILs. Introduction of imide structure on the amino acid increased the viscosity of ILs, however.

We confirmed the chirality of anions and corresponding ILs by optical rotation measurement (JASCO DIP-1000). Trifluoromethanesulfonyl amino acid methyl ester was obtained as white crystals showing chirality (see ESI†). The specific rotation values of the ILs prepared are also summarized in Table 1. We first confirmed that neutralization of onium hydroxide with amino acid, followed by drying at 70 °C for 24 hours, caused no significant racemization of the corresponding ILs. All rotation values of these ILs are negative, so that these ILs are levorotatory. We have confirmed that these ILs maintain their chirality even after heating at 100 °C for a few hours (data not shown here). The present procedures involved no asymmetric syntheses and/or optical resolution, so that these conveniently prepared chiral ILs have great potential as chiral solvents in various applications. We obtained chiral ILs simply by neutralization, without special purification procedures such as chiral separation with column.

To determine the hydrophobicity of the prepared ILs, they were shaken with an equal volume of water by vortex mixing for 2 min. Some ILs showed phase separation (Fig. 1). The [bmim] salts were wholly miscible with water, but [TBP] systems showed two phase separation. Hydrophobic alkyl chains covering the phosphorus

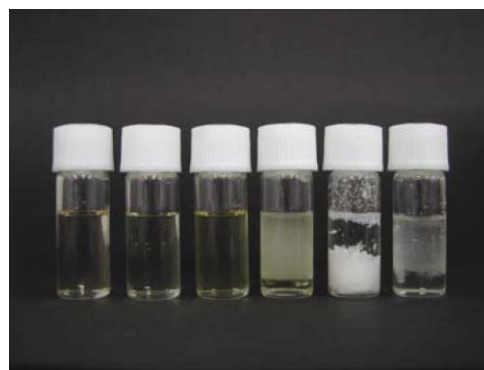


Fig. 1 Mixtures of ILs with water after vortex mixing for 2 minutes. (left to right): [bmim][I-Ala], [bmim][I-Val], [bmim][I-Leu], [TBP][I-Ala], [TBP][I-Val], [TBP][I-Leu]. The top of [TBP] systems is aqueous-rich phase and the bottom is IL-rich phase.

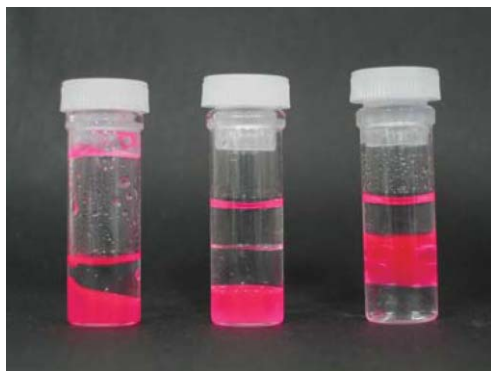


Fig. 2 Three-phase system of hexane–IL–water. Left: [TBP][I-Leu] with water, centre: before mixing of hexane–water–[TBP][I-Leu], right: after mixing of hexane–[TBP][I-Leu]–water. The IL phase was coloured with Nile Red.

atom may contribute to hydrophobicity. We then analyzed the water content of the phase-separated IL phase using the Karl Fischer titration. The water content of the IL-rich phase of the [TBP][I-Ala] system was 5.1 wt%; [TBP][I-Ala] dissolved slightly in water. For [TBP][I-Leu] the water content was 2.9 wt%, which induced distinct separation with an aqueous phase. By comparing [TBP][I-Ala] with [TBP][I-Leu], we infer that phase separation behaviour of the prepared ILs is influenced by the alkyl chain length of the side chain of the amino acids. This clearly shows that hydrophobicity of the ILs is easily controllable by changing the side chain of the amino acids used.

A three-phase system was constructed by mixing the above two-phase system (water–[TBP][I-Leu]) with hexane. [TBP][I-Leu] generally had higher density (1.150 g cm^{-3} at 25°C) than water; the bottom phase was rich in ionic liquid (Fig. 2, left). The IL phase was coloured by Nile Red for easier recognition. With further addition of hexane to this mixture (Fig. 2, center), the phase sequence is hexane, water, and [TBP][I-Leu]. However, vortex mixing of these phases generated an IL phase less dense than water (Fig. 2, right). The density of [TBP][I-Leu] falls to 0.979 g cm^{-3} by dissolving about 35 wt% hexane. Although some hydrophobic ILs were also mixed with hexane, these ILs, such as [bmim][Tf₂N] (1.429 g cm^{-3}), are denser than water. Use of amino acids as starting materials readily generates hydrophobic ILs. Furthermore, the amino acids can themselves have various functional groups so as to generate novel ILs, and chemical modification of these functional groups (such as introduction of a blocking group) has been studied. These advantages make amino acids highly suitable starting materials in the design of novel functional ILs.

In conclusion, we have designed a new family of hydrophobic and chiral anions from amino acids that form unique ILs. Combined with [TBP] cation, amino acid derivatives yielded hydrophobic ILs. Although properties such as melting point, viscosity, and hydrophobicity were not improved over typical hydrophobic ILs [bmim][Tf₂N], these syntheses are the first simple preparations of hydrophobic ILs having chiral anion. The use of different amino acids as starting materials allows choice of the physico-chemical properties of the prepared IL.

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Notes and references

‡ *Characterization of [TBP][I-Ala]*. [TBP][I-Ala]: Tetrabutylphosphonium trifluoromethanesulfonylalanine methyl ester salt. ¹H NMR (500 MHz, CDCl₃, δ/ppm relative to TMS): 0.97(t, *J* = 7 Hz, 12H), 1.32(d, *J* = 3.5 Hz, 3H), 1.52(m, *J* = 11.4 Hz, 16H), 2.28 (m, *J* = 14.5 Hz, 8H), 3.74(s, 3H), 4.12(q, *J* = 10.5 Hz, 1H). ESI–TOF–MS: Calcd. for [C₁₆H₃₆P][C₅H₇NO₄SF₃]: [TBP]⁺: *m/z* = 259.43; Found: 259.33, [I-Ala][−]: *m/z* = 234.17; Found: 233.82.

§ *Characterization of [I-Ala]*. [I-Ala]: *N*-Trifluoromethanesulfonylalanine methyl ester. ¹H NMR (500 MHz, CDCl₃, δ/ppm relative to TMS): 1.54 (d, *J* = 3.8 Hz, 3H), 3.83 (s, 3H), 4.32 (q, *J* = 10.8 Hz, 1H), 5.68 (s, 1H). ESI–TOF–MS: Calcd. for C₅H₈NO₄SF₃ [M − 1 + 2Na]⁺: *m/z* = 280.15; Found: 280.06, [M − 1][−]: *m/z* = 234.17; Found: 233.82. [*α*] = −26.3 (*c* = 1.0 g per 100 ml MeOH), *T*_m = 68.0 °C, *T*_{decomp.} = 119.6 °C.

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