Ionic Liquids

DOI: 10.1002/anie.200604402

LCST-Type Phase Changes of a Mixture of Water and Ionic Liquids Derived from Amino Acids**

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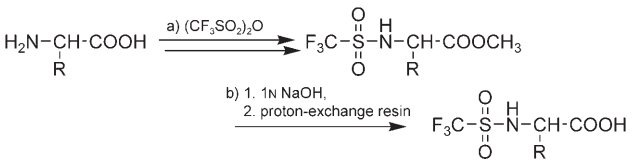
Ionic liquids (ILs)[1] are organic salts designed to melt below 100 °C, in particular at room temperature, which have characteristic properties such as negligible volatility[2] and nonflammability over a wide temperature range. There is increasing interest in ILs that have functional groups designed for specific applications.[3] Many reactions have already been studied in ILs; most proceed as in ordinary molecular liquids. Cooperative action of ILs with molecular liquids should also be significant. The partition coefficients of many molecules in IL/molecular solvent mixtures have been determined.[4] Reversible phase control of the mixture is important in proceeding from the start of the reaction to the separation of products. Some phase-separation behavior has already been reported, including pressure-controlled IL/supercritical CO_2 mixtures[5] and temperature-driven IL/alcohol[6] and IL-K_3PO_4/water systems.[7] Seddon et al. recently reported that an immiscible pair of ILs mixed upon heating to give a monophase.[8]

We have previously synthesized ILs from 20 different amino acids and studied the effect of functional groups of the side chain on their physicochemical properties.[9] Hydrophobic and chiral ILs that are insoluble in water have also been prepared by chemical modification of the amino acids.[10] By measuring the solubility of these amino acid derived ILs in water, we found that a mixture of newly prepared IL and water exhibited unique phase behavior. The mixture showed phase separation with a lower critical solution temperature (LCST). LCST-type phase separation has been found in some polymer solutions. Conversely, ILs such as [bmim][BF_4] (bmim = 1-butyl-3-methylimidazolium),[11] ionic compounds, and molecular liquids generally displayed phase separation with an *upper* critical solution temperature, because the solubility of these compounds in water increases with temperature. Few reports exist of LCST-type phase separation of IL/molecular liquid mixtures.[12] However, the LCST phase diagram reported was only observed at high and limited IL content (60–65 %). There was no direct demonstration of clear phase separation above the critical temperature. It is desirable to arrange similar LCST-type phase separation in water/IL mixtures, because the partition coefficient of environmentally effective materials in the water phase is of great interest; at present there are no reports of LCST-type phase separation in such a mixture. LCST-type phase separation with water also offers advantages in the study of thermosensitive biological compounds, such as enzymes, peptides, and hormones. In the present study, we synthesized ILs that exhibit LCST-type phase separation with water. We discuss the effect of water content and of component-ion structure on the phase-separation temperature of a mixture with water.

The amino group on the amino acid was modified using a synthetic procedure similar to one we have already reported.[9b,13] *N*-Trifluoromethanesulfonyl amino acid methyl ester was synthesized by reaction of trifluoromethanesulfonic anhydride with amino acid methyl ester (Scheme 1 a). Of



Scheme 1. Preparation of *N*-trifluoromethanesulfonyl amino acids. For R, see Figure 1.

the natural amino acids, L-valine, L-leucine, L-isoleucine, and L-phenylalanine were selected as starting materials, as they have no reactive functional group on the side chain. To hydrolyze the methyl ester groups, the amino acid derivative was treated with 1N NaOH solution at 0 °C for 5 h, and the sodium ions were removed with proton-exchange resin (Amberlite IR120(H)). The product was washed with hexane to give *N*-trifluoromethanesulfonyl amino acid (Scheme 1 b).

As a counter cation to couple the *N*-trifluoromethanesulfonyl amino acid, we used the tetra-*n*-butylphosphonium cation ([P_{4444}]), which provides hydrophobic amino acid ILs.[10] A tri-*n*-butyloctylphosphonium cation ([P_{4448}]) was also used as a more hydrophobic cation than [P_{4444}]. A solution of [P_{4444}][OH] was donated by Hokko Chem. Co. Ltd. In the case of [P_{4448}], an aqueous solution of [P_{4448}][OH] was prepared by passing an aqueous solution of [P_{4448}][Br] through an anion-exchange resin.[9a,10] These phosphonium hydroxide aqueous solutions were mixed with a slightly smaller amount

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[**] K.F. acknowledges the financial support of the Japan Society for the Promotion of Science (Research Fellowship for Young Scientists). This study was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan (17205020 and 17073005), and the 21st Century COE program of "Future Nano-Materials" in Tokyo University of Agriculture & Technology. LCST: lower critical solution temperature.

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of trifluoromethanesulfonyl amino acid, and the ILs were extracted from the mixed solutions with chloroform. After evaporation, the product (Figure 1) was dried in vacuo for at least 24 h at 80 °C. The structure of the resulting ILs was confirmed by ^{1}H NMR spectroscopy (JEOL JNM-LA500, JNM-ECX400), ESI time-of-flight (TOF) mass spectrometry (JEOL JMS-T100LC), and elemental analysis (Elementar vario EL III; see Experimental Section).

Figure 1. Structure of the prepared ILs. Tf: trifluoromethanesulfonyl.

The thermal properties of the resulting ILs were determined by differential scanning calorimetry (DSC; Seiko Instrument Inc. DSC120). Salts with [P_{4444}] were solid, with melting points in the range 50–65 °C (Table 1). [P_{4444}] is known

Table 1: Physicochemical properties of the prepared ILs.

	m.p. [°C]	$[\alpha]^{[a]}$ [deg cm^3 g^{-1} dm^{-1}]
[P_{4444}][Tf-Val]	51	4.5
[P_{4444}][Tf-Leu]	64	9.8
[P_{4444}][Tf-Ile]	51	3.6
[P_{4444}][Tf-Phe]	64	1.5
[P_{4448}][Tf-Leu]	−50[b]	7.0

[a] $c = 1.0$ g cm^{-3} (g/100 mL MeOH). [b] Glass transition temperature.

to provide salts with high melting points even after coupling with Tf_2N (ca. 86 °C),[14] so these melting points are quite low for phosphonium salts. It should be possible to lower them by using asymmetric cations. However, [P_{4448}][Tf-Leu] displayed no melting point but did have a glass transition temperature, which reflected a stable supercooling phase. We also measured the chirality of the resulting ILs by optical rotation measurement (JASCO DIP-1000). Table 1 summarizes the specific rotation values of the ILs prepared.

Figure 2 shows photographs of a graded series in a two-phase system (upper phase water; lower phase [P_{4444}][Tf-Leu]). These mixtures were cooled gradually with stirring, and then heated after formation of the monophase. The metal bar penetrating into the vessel was a temperature sensor, and the IL phase was colored by Nile Red,[15] which was insoluble in the aqueous phase. Upon cooling of the two-phase system,

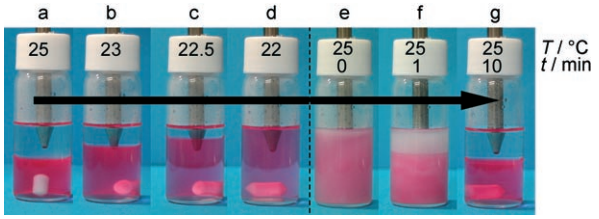

Figure 2. Temperature dependence of the phase behavior of a [P_{4444}]-[Tf-Leu]/water mixture.

the volume of the IL phase increased gradually (Figure 2a–c) until a completely miscible state appeared at 22 °C (Figure 2d). As is clear from a video, this behavior is a result of water dissolving in the IL phase as cooling proceeds (see Supporting Information). The monophase mixture was left for a few minutes at 22 °C, but particle phase separation was not confirmed. This homogeneous mixture demonstrates that the IL and water are completely miscible below 22 °C. An increase in the temperature of the liquid induced phase separation and generated a cloudy suspension (Figure 2e), then macroscopic phase separation (Figure 2f). The separate water and IL phases finally became clear (Figure 2g). The milky phase can be explained as the formation of emulsions from the homogeneous mixture, as the solubility of water in the IL decreases with the increase of temperature. The sequence of the phase behavior (Figure 2a→g) as the temperature varies is reversible. Nile Red always dissolved in the IL phase alone.

The phase-separation temperature can be determined as the cloud point; we analyzed the effect of the mixing ratio on phase separation. As all the ILs synthesized in this study exhibited LCST-type phase behavior with water, the LCST-type phenomenon does not depend on the specific structure of the side chain on the anions. Also, amino acid ILs containing a carboxylic acid protected as the methyl ester[10] did not exhibit LCST-type phase separation. These results indicate that free carboxyl groups on hydrophobic amino acid anions play an important role in LCST-type phase separation. The phase-separation temperature always varied with the water content, and the increasing water content in the mixture lowered the phase-separation temperature (Figure 3). This trend is consistent with the observation that the ILs dissolve more water with cooling. The phase-separation temperature in the phase diagram was monotonic in the water content, even at 90 wt % water with [P_{4444}][Tf-Phe]. In the high-water-content region these ILs were not fully dissolved, and remained solid at room temperature except for [P_{4448}][Tf-Leu]. In the case of [P_{4448}][Tf-Leu], the phase-separation temperature reached the freezing point of water (see Figure 3). Accordingly, further experiments cannot be carried out with more than 60 wt % water in open conditions.

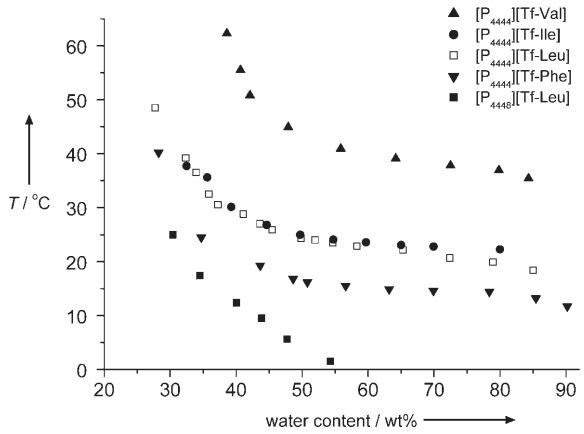

Figure 3. Phase-separation temperature versus water content.

Similarly, an increase in hydrophobicity of the side chain caused the phase-separation temperature to fall. As the solubility of water is less in the more hydrophobic ILs, a lower IL temperature is needed to dissolve the same amount of water. The hydrophobicity of the ILs could also be controlled by changing the structure of the component cation. With a more hydrophobic cation than [P_{4444}], the phase-separation temperature of [P_{4448}][Tf-Leu] was about 15 °C lower than in the [P_{4444}] system. These results imply that the phase-separation temperature of the mixture can be controlled by the side-chain structure on the starting amino acid, by the alkyl chain length of the cation, and by the water/IL ratio. To exploit the various separation processes, information is needed on the phase-separation temperature of the mixture according to the structure and water content. Introduction of a functional group, such as a catalyst, on the starting amino acid side chain would readily provide LCST-type functionalized ILs with water.

In summary, we have synthesized ILs that exhibit LCST-type phase separation with water. The phase-separation temperature of these mixtures depends reproducibly on the ion structure and water content. Although the mechanism of the LCST-type phase behavior of the ILs is not clear, these ILs could have a great impact on reaction and separation processes.

Experimental Section

Synthesis and characterization of *N*-trifluoromethanesulfonyl amino acid: Amino acid was added to methanol, which had been pretreated with thionyl chloride at 0 °C, and was stirred overnight. The mixture was then filtered to remove unreacted amino acid, and the filtrate was concentrated under reduced pressure (yield 80–90 %). The resulting white solid was suspended in dichloromethane, and bimolar triethylamine was added with stirring. A solution of trifluoromethanesulfonic anhydride in dichloromethane was added to the mixture under a dry nitrogen gas atmosphere at −78 °C. The mixture was then stirred overnight at room temperature. The resulting solution was washed with dilute hydrochloric acid and then with saturated aqueous sodium chloride. The concentrated dichloromethane solution was shaken with diethyl ether under reduced pressure. The extract was purified on silica gel (MeOH/$CHCl_3$ 1:5) to provide the corresponding *N*-trifluoromethanesulfonyl amino acid methyl ester (ca. 50–60 % yield). To hydrolyze the methyl ester groups, this compound was treated with 1N NaOH solution at 0 °C for 5 h, and sodium ions were then removed with proton-exchange resin (Amberlite IR120(H)). The product was washed with hexane to give *N*-trifluoromethanesulfonyl amino acid (50–60 % yield).

[Tf-Val]: *N*-Trifluoromethanesulfonylvaline: ^{1}H NMR (500 MHz, $CDCl_3$, relative to tetramethylsilane (TMS)): $\delta = 0.97$ (d, $J = 3.5$ Hz, 3H), 1.09 (d, $J = 3.5$ Hz, 3H), 2.30 (m, $J = 16$ Hz, 1H), 4.14 (t, $J = 2.5$ Hz, 1H), 5.68 ppm (d, $J = 5.5$ Hz, 1H); ESI-TOF-MS: *m*/*z* calcd for $C_6H_{10}NO_4SF_3$ $[M-1]^-$: 248.20; found: 248.19; elemental analysis calcd (%) for $C_6H_{10}NF_3O_4S$: C 28.92, H 4.04, N 5.62, F 22.87, O 25.68, S 12.87; found: C 29.07, H 3.90, N 5.48.

[Tf-Leu]: *N*-Trifluoromethanesulfonylleucine: ^{1}H NMR (500 MHz, $CDCl_3$, relative to TMS): $\delta = 1.00$ (q, $J = 4.3$ Hz, 6H), 1.7 (m, $J = 35$ Hz, 2H), 1.87 (m, $J = 20$ Hz, 1H), 4.28 (m, $J = 12$ Hz, 1H), 5.55 ppm (d, $J = 4.8$ Hz, 1H); ESI-TOF-MS: *m*/*z* calcd for $C_7H_{12}NO_4SF_3$ $[M-1]^-$: 262.23; found: 262.21; elemental analysis calcd (%) for $C_7H_{12}NF_3O_4S$: C 31.94, H 4.59, N 5.32, F 21.65, O 24.31, S 12.18; found: C 31.72, H 4.41, N 5.05.

[Tf-Ile]: *N*-Trifluoromethanesulfonylisoleucine: ^{1}H NMR (400 MHz, $CDCl_3$, relative to TMS): $\delta = 0.97$ (t, $J = 7.6$ Hz, 3H), 1.06 (d, $J = 3.2$ Hz, 3H), 1.23 (m, $J = 22.4$ Hz, 1H), 1.47 (m, $J = 16.4$ Hz, 1H), 2.02 (m, $J = 12.6$ Hz, 1H), 4.20 (q, $J = 7.2$ Hz, 1H), 5.73 ppm (d, $J = 4.8$ Hz, 1H); ESI-TOF-MS: *m*/*z* calcd for $C_7H_{12}NO_4SF_3$ $[M-1]^-$: 262.23; found: 262.22; elemental analysis calcd (%) for $C_7H_{12}NF_3O_4S$: C 31.94, H 4.59, N 5.32, F 21.65, O 24.31, S 12.18; found: C 32.14, H 4.88, N 5.18.

[Tf-Phe]: *N*-Trifluoromethanesulfonylphenylalanine: ^{1}H NMR (400 MHz, $CDCl_3$, relative to TMS): $\delta = 3.22$ (q, $J = 8.7$ Hz, 2H), 4.58 (m, $J = 7.1$ Hz, 1H), 5.52 (d, $J = 4.6$ Hz, 1H), 7.18 (q, $J = 4.6$ Hz, 2H), 7.34 ppm (m, $J = 10.5$ Hz, 3H); ESI-TOF-MS: *m*/*z* calcd for $C_{10}H_{10}NO_4SF_3$ $[M-1]^-$: 296.24; found: 296.23; elemental analysis calcd (%) for $C_{10}H_{10}NF_3O_4S$: C 40.41, H 3.39, N 4.71, F 19.17, O 21.53, S 10.79; found: C 40.40, H 3.48, N 4.54.

Synthesis and characterization of phosphonium-type ILs: A solution of [P_{4444}][OH] (Hokko Chem. Co.) was used without further purification. An aqueous solution of [P_{4448}][OH] was prepared by passing an aqueous solution of [P_{4448}][Br] through anion-exchange resin (Amberlite IRA400(OH) (SUPELCO)). These phosphonium hydroxide aqueous solutions were mixed with slightly less trifluoromethanesulfonyl amino acids, and the corresponding ILs were extracted from the mixed solutions with chloroform. After evaporation, the product was dried in vacuo for at least 24 h at 80 °C.

[P_{4444}][Tf-Val]: Tetra-*n*-butylphosphonium trifluoromethanesulfonyl valine salt: [P_{4444}][Tf-Val] (2.0 g) was obtained from Tf-Val (1.5 g, 6.0 mmol); 65 % yield. ^{1}H NMR (400 MHz, $CDCl_3$, relative to TMS): $\delta = 0.96$ (m, $J = 38$ Hz, 18H), 1.52 (m, $J = 11.2$ Hz, 16H), 2.25 (m, $J = 10.8$ Hz, 1H), 2.34 (m, $J = 14.4$ Hz, 8H), 3.78 ppm (s, 1H); ESI-TOF-MS: *m*/*z* calcd for $[C_{16}H_{36}P][C_6H_9NO_4SF_3]$: positive ion $[P_{4444}]^+$: 259.43; found: 259.26; negative ion [Tf-Val]$^-$: 248.20; found: 248.19; elemental analysis calcd (%) for $C_{22}H_{45}NF_3O_4PS$: C 52.05, H 8.94, N 2.76, F 11.23, O 12.61, P 6.10, S 10.79; found: C 52.14, H 8.94, N 2.50; T_{decomp} 274 °C.

[P_{4444}][Tf-Leu]: Tetra-*n*-butylphosphonium trifluoromethanesulfonyl leucine salt: [P_{4444}][Tf-Leu] (1.4 g) was obtained from Tf-Leu (1.0 g, 3.8 mmol); 71 % yield. ^{1}H NMR (500 MHz, $CDCl_3$, relative to TMS): $\delta = 1.02$ (m, $J = 53.5$ Hz, 18H), 1.52 (t, $J = 3$ Hz, 16H), 1.66 (m, $J = 36.5$ Hz, 2H), 1.92 (m, $J = 20$ Hz, 1H), 2.31 (s, 8H), 3.90 ppm (q, $J = 6$ Hz, 1H); ESI-TOF-MS: *m*/*z* calcd for $[C_{16}H_{36}P][C_7H_{11}NO_4SF_3]$: positive ion $[P_{4444}]^+$: 259.43; found: 259.26; negative ion [Tf-Leu]$^-$: 262.23; found: 262.22; elemental analysis calcd (%) for $C_{23}H_{47}NF_3O_4PS$: C 52.96, H 9.08, N 2.69, F 10.93, O 12.27, P 5.94, S 6.15; found: C 52.91, H 8.73, N 2.52; T_{decomp} 257 °C.

[P_{4444}][Tf-Ile]: Tetra-*n*-butylphosphonium trifluoromethanesulfonyl isoleucine salt: [P_{4444}][Tf-Ile] (1.6 g) was obtained from Tf-Ile (1.0 g, 3.8 mmol); 80 % yield. ^{1}H NMR (400 MHz, $CDCl_3$, relative to TMS): $\delta = 0.89$ (t, $J = 7.6$ Hz, 3H), 0.97 (m, $J = 16.4$ Hz, 15H), 1.24 (m, $J = 13.2$ Hz, 1H), 1.52 (m, $J = 2.4$ Hz, 17H), 1.92 (m, $J = 0.6$ Hz, 1H), 2.30 (t, $J = 12.8$ Hz, 8H), 3.83 ppm (t, $J = 0.8$ Hz, 1H); ESI-TOF-MS: *m*/*z* calcd for $[C_{16}H_{36}P][C_7H_{11}NO_4SF_3]$: positive ion $[P_{4444}]^+$: 259.43; found: 259.27; negative ion [Tf-Ile]$^-$: 262.23; found: 262.22; elemental analysis calcd (%) for $C_{23}H_{47}NF_3O_4PS$: C 52.96, H 9.08, N 2.69, F 10.93, O 12.27, P 5.94, S 6.15; found: C 52.88, H 9.31, N 2.53; T_{decomp} 267 °C.

[P_{4444}][Tf-Phe]: Tetra-*n*-butylphosphonium trifluoromethanesulfonyl phenylalanine salt: [P_{4444}][Tf-Phe] (1.3 g) was obtained from Tf-Phe (1.0 g, 3.4 mmol); 70 % yield. ^{1}H NMR (400 MHz, $CDCl_3$, relative to TMS): $\delta = 0.97$ (t, $J = 7.2$ Hz, 12H), 1.49 (m, $J = 3.6$ Hz, 16H), 2.25 (m, $J = 12.8$ Hz, 8H), 3.19 (m, $J = 21.8$ Hz, 2H), 4.17 (t, $J = 4.4$ Hz, 1H), 7.24 ppm (m, $J = 41$ Hz, 5H); ESI-TOF-MS: *m*/*z* calcd for $[C_{16}H_{36}P][C_{10}H_9NO_4SF_3]$: positive ion $[P_{4444}]^+$: 259.43; found: 259.27; negative ion [Tf-Phe]$^-$: 296.24; found: 296.23; elemental analysis calcd (%) for $C_{26}H_{45}NF_3O_4PS$: C 56.20, H 8.16, N 2.52, F 10.26, O 11.52, P 5.57, S 5.77; found: C 55.99, H 8.20, N 2.39; T_{decomp} 240 °C.

$[P_{4448}][Tf\text{-}Leu]$: Tri-*n*-butyloctylphosphonium trifluoromethanesulfonyl leucine salt: $[P_{4448}][Tf\text{-}Leu]$ (1.7 g) was obtained from Tf-Leu (1.0 g, 3.8 mmol); 77% yield. ^1H NMR (400 MHz, $CDCl_3$, relative to TMS): $\delta = 0.94$ (m, $J = 29.4$ Hz, 18H), 1.31 (m, $J = 13.2$ Hz, 8H), 1.52 (m, $J = 4$ Hz, 17H), 1.68 (m, $J = 13.2$ Hz, 1H), 1.91 (m, $J = 13.6$ Hz, 1H), 2.37 (m, $J = 20.4$ Hz, 8H), 3.85 ppm (t, $J = 5.6$ Hz, 1H); ESI-TOF-MS: *m*/*z* calcd for $[C_{20}H_{44}P][C_7H_{11}NO_4SF_3]$: positive ion $[P_{4448}]^+$: 315.54; found: 315.31; negative ion $[Tf\text{-}Leu]^-$: 262.23; found: 262.22; T_{decomp} 259 °C.

Received: October 27, 2006
Revised: December 5, 2006
Published online: February 2, 2007

Keywords: amino acids · chirality · ionic liquids · LCST · phase behavior

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