Amino Acid Ionic Liquids

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FIGURE 1. Design of amino acids for functional ionic liquids.

ABSTRACT

The preparation of ionic liquids derived from amino acids, and their properties, are outlined. Since amino acids have both a carboxylic acid residue and an amino group in a single molecule, they can be used as either anions or cations. These groups are also useful in their ability to introduce functional group(s). Twenty different natural amino acids were used as anions, to couple with the 1-ethyl-3-methylimidazolium cation. The salts obtained were all liquid at room temperature. The properties of the resulting ionic liquids (AAILs) depend on the side groups of the amino acids involved. These AAILs, composed of an amino acid with some functional groups such as a hydrogen bonding group, a charged group, or an aromatic ring, had an increased glass transition (or melting) temperature and/or higher viscosity as a result of additional interactions among the ions. Viscosity is reduced and the decomposition temperature of imidazolium-type salts is improved by using the tetrabutylphosphonium cation. The chirality of AAILs was maintained even upon heating to 150 °C after acetylation of the free amino group. The amino group was also modified to introduce a strong acid group so as to form hydrophobic and chiral ionic liquids. Unique phase behavior of the resulting hydrophobic ionic liquids and water mixture is found; the mixture is clearly phase separated at room temperature, but the solubility of water in this IL *increases* upon cooling, to give a homogeneous solution. This phase change is reversible, and separation occurs again by raising the temperature a few degrees. It is extraordinary for an IL/water mixture to display such behavior with a lower critical solution temperature. Some likely applications are proposed for these amino acid derived ionic liquids.

1. Introduction

Molten salts at ambient temperature containing only ions and no solvent are referred to as "ionic liquids".[1] Ionic liquids have very different properties from molecular liquids, making them promising substances for use in a variety of fields. Variation of the ion species is a great advantage in organic salts. However, in spite of the enormous number of combinations of cation and anion, based on the diversity of organic ions, there are limited types of *effective* ions for ionic liquids (ILs), having physicochemical properties suitable for applications. It is almost impossible to synthesize *perfect* ILs, which combine all desirable properties, such as nonvolatility,[2] thermal stability, low melting temperature, high decomposition temperature, low viscosity,[3] and zero toxicity.[4] It is therefore necessary to prepare "object-oriented" or "task-specific" ionic liquids.[5] This involves the design of ions to minimum specifications which depend on the purpose or field of application.

A relatively straightforward way to prepare functional IL systems is to mix functional molecules with ILs. This is a convenient and effective method of preparing ILs for certain applications.[6] However, these additives will bring their own properties. For example, ILs containing volatile organic compounds would have considerable vapor pressure, which can be a serious drawback in spite of their otherwise excellent properties. It is important to find a general method for the design of various functional or task-specific ILs, and to this end, we have been studying amino acid-based ILs. We first reported ILs composed of imidazolium cations and amino acid (AA) anions.[7] Since the AA contains both an amino group and a carboxylic acid residue in a single molecule, with various side groups and a chiral carbon atom, AAs are candidates to act as a platform for functional ILs (Figure 1).[8] One great merit of the AAs is their low cost. It is easy to obtain pure AAs in large quantities at low cost. There are further advantages of AAs, including biodegradability[9] and biological activity.[10] The availability of AAs as both anions and cations is another advantage. Below, a summary is presented of the preparation and properties of ionic liquids composed of amino acids (AAILs). Chemical modifications of the carboxylic acid residue or amino group, for functional design of the ILs, is included.

2. Amino Acid-Based Ionic Liquids: A Prototype

2.1. Imidazolium Cation-Based AAILs. There are fewer papers on the structural design of anions for forming useful ILs than for cations. We expect there to be a limited number of anion species for ILs with low melting temperature (T_m) or easier modification of a series of onium cations. A series of AAs are, however, expected to provide liquid salts with the potential for chemical modification. Since AAs are zwitterionic and are stabilized by electrostatic interaction between the carboxylate anion and the protonated amino group, there have been no challenges

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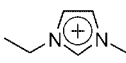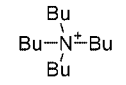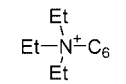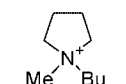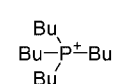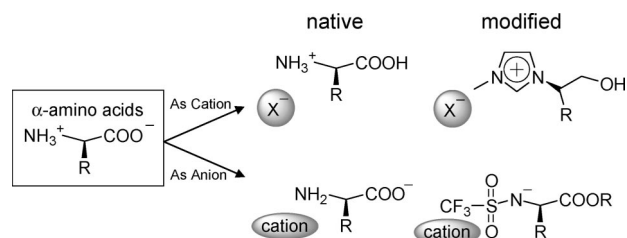
Scheme 1. Preparation of Amino Acid Ionic Liquids by the Neutralization Method

to prepare ILs from these AAs. There exist many amino acid salts in biological systems. These natural examples inspired us to prepare ILs with amino acids.

Preparation of AAILs was first undertaken with 1-ethyl-3-methylimidazolium cation, [emim], which is a cation commonly used in preparing many ILs. In the initial stage, we aimed to prepare [emim][AA] salts by anion exchange. Anion exchange reactions should be effective when the target salts are water insoluble whereas the byproducts (generally inorganic salts) are water soluble. Hydrophobic target salts could then be obtained by simple washing with water. In the case of water soluble products, purification cannot be carried out by simple washing. Also, while this is in principle a good method of preparing silver salts such as AgBr or AgCl, there is some concern over these silver salts dissolving into the ILs formed.[11] Since halogen anion content is a major issue in the preparation of ILs, these methods are not recommended for the preparation of halogen-free ILs.

We then prepared AAILs by a neutralization method. This method is also simple, involving the mixing of onium hydroxide and free acid. For this neutralization, [emim]OH was mixed with acid (HY) to prepare salts and water as a byproduct.

To prepare [emim]OH (**2**) aqueous solution, we used anion exchange resin (Scheme 1). An aqueous solution of **2** prepared in this way was added to a slight excess of an equimolar amino acid aqueous solution so as to prepare **3**. The product **3** was dried *in vacuo* for 24 h at 80 °C. These AAILs did not exhibit a melting point but did have a definite glass transition temperature (T_g). This means that the AAILs (**3**) are in the supercooled state or are glassy materials (Figure 2).

Although the negative charge is located on a carboxylate anion, AAILs had widely differing T_g values, from −65 to 6 °C, reflecting their side chain structures. Figure 3 shows the relation between the ionic conductivity at 25 °C of various ILs (including **3**) and T_g. The ionic conductivity is given by the product of the number of carrier ions and their mobility.[12] Since ion mobility is influenced by the viscosity of the ion conduction path, a matrix having lower T_g should provide for faster ion migration at a given temperature. Figure 3 clearly shows this relation: ILs with lower T_g have higher ionic conductivity at 25 °C.[13] For AAs with no functional side group, such as glycine, alanine, leucine, and valine, there was a clear relationship between ionic conductivity and T_g.

In contrast, deviation from the relationship (dotted line in Figure 3) was found for fewer AAILs having some functional groups. This implies that some intra- (and inter-) molecular interactions influence the ionic conductivity. In other words, introduction of a functional group such as a hydrogen bond donor or acceptor lowers the

ionic conductivity through intra/intermolecular interactions. These data strongly suggest that it is not easy to introduce functionalities into an IL without degrading the physicochemical properties.[14]

2.2. Phosphonium Cation-Based AAILs. The thermal stability of these [emim][AA]s was less satisfactory. They began to decompose at approximately 200 °C. We worked with the phosphonium cation and also the ammonium, pyrrolidinium, and pyridinium cations. These cations were

FIGURE 2. Amino acid ionic liquids prepared by coupling [emim] with AAs. Upper row (left to right): [emim][Leu] (R = CH₂CH(CH₃)₂, R is the side chain amino acid shown in Scheme 1), [emim][Lys] (R = (CH₂)₄NH₂), [emim][Met] (R = (CH₂)₂SCH₃), [emim][Phe] (R = CH₂C₆H₅), [emim][Pro] ((2-pyrrolidine)COO⁻), [emim][Ser] (R = CH₂OH), [emim][Thr] (R = CH(OH)CH₃), [emim][Trp] (R = CH₂(3-indolyl)), [emim][Tyr] (R = CH₂C₆H₄OH), and [emim][Val] (R = CH(CH₃)₂). Lower row (left to right): [emim][Ala] (R = CH₃), [emim][Arg] (R = (CH₂)₃NHC(=NH)NH₂), [emim][Asn] (R = CH₂CONH₂), [emim][Asp] (R = CH₂COOH), [emim][Cys] (R = CH₂SH), [emim][Gln] (R = (CH₂)₂CONH₂), [emim][Glu] (R = (CH₂)₂COOH), [emim][Gly] (R = H), [emim][His] (R = CH₂(4-imidazolyl)), and [emim][Ile] (R = CH(CH₃)CH₂CH₃).

FIGURE 3. Relation between the ionic conductivity of amino acid ionic liquids and their glass transition temperature T_g.

Table 1. Thermal Properties of Various Alanine Salts[a]

	Cation	$T_g/°C$	$T_m/°C$	$T_{decomp}/°C$
4		-57	ND	212
5	Bu−N±Bu (Bu, Bu)	ND	76	162
6	Et−N±C₆ (Et, Et)	-40	ND	150
7	(pyrrolidinium) Me Bu	-64	77	176
8	Bu−P±Bu (Bu, Bu)	-70	ND	286

[a] ND: not detected.

used to prepare ILs, with alanine (Ala) as a typical amino acid. Salts **5** and **7** prepared from symmetric ammonium and pyrrolidinium cations are solid, with a melting point above 70 °C. On the other hand, the asymmetric ammonium salt **6** has only a glass transition temperature, at −40 °C, and is a highly viscous liquid (Table 1). Though some quaternary ammonium salts become liquid at room temperature, their thermal decomposition temperatures of 150–170 °C were about 50 °C lower than that of the imidazolium cation-based AAIL, **4**. These results indicate that adequate thermal stability and lowered melting point were scarcely attained with ammonium cations. On the other hand, the tetrabutylphosphonium cation-based AAIL **8** exhibited higher thermal stability and lower glass transition temperature than those of the imidazolium-based AAIL, **4**.

Taking these preliminary results into account, all 20 distinct amino acids were neutralized by $[P_{4444}][OH]$. These $[P_{4444}][AA]$ salts were obtained as liquids at room temperature, except for $[P_{4444}][Glu]$ (T_m = 101.7 °C), $[P_{4444}][His]$ (T_m = 85.9 °C), and $[P_{4444}][Asn]$ (T_m = 83.0 °C).[15] A total of 16 salts out of the 20 had a lower T_g than that of the corresponding [emim] salt. Viscosity follows a similar pattern. For example, [emim][Gly] had the lowest viscosity (486 cP at 25 °C) of the [emim][AA] salts. In fact, five amino acids (Ala, Met, Leu, Gly, and Val) formed less viscous ILs by coupling with the $[P_{4444}]$ cation than [emim][Gly]. These $[P_{4444}]$ salts were even less viscous than the $[P_{66614}][Tf_2N]$ salt (450 cP at 25 °C). These data show that the amino acids combine with the phosphonium cation to give compounds with desirable properties. This was not predicted from any previous database.

2.3. Polarity of Amino Acid Ionic Liquids. Polarity is a further important property of ILs, because the solubility of the solute, the reaction efficiency as solvent, and the miscibility with other solvents are influenced by the IL properties.[16] To determine the polarity of the ILs, several

Table 2. Kamlet–Taft Parameters for a Series of Amino Acid Ionic Liquids

	[emim]			$[P_{4444}]$		
	π^*	α	β	π^*	α	β
[Ala]	1.10	0.479	1.036	1.029	0.914	1.308
[Asp]	1.137	0.523	0.882	1.052	0.103	1.077
[Gln]	1.135	0.57	1.031	solid	solid	solid
[Glu]	1.132	0.563	0.957	solid	solid	solid
[Gly]	1.201	*	1.199	1.039	0.183	1.302
[His]	1.239	0.462	0.917	solid	solid	solid
[Lys]	1.056	*	1.212	1.011	0.295	1.317
[Met]	1.071	0.408	1.14	0.997	0.925	1.34
[Ser]	1.10	0.514	1.032	1.106	0.042	1.099
[Val]	1.044	0.519	1.069	0.926	0.919	1.381

suitable probes, mainly solvatochromic dyes, have been reported.[17] The Kamlet–Taft parameters, determined with the three probes *N,N*-diethyl-4-nitroaniline, 4-nitroaniline, and Reichardt's dye, are useful parameters in considering the hydrogen bond acidity, hydrogen bond basicity, and dipolarity/polarizability, respectively.[18] From the maximum absorption wavelength of these dyes in ILs, the hydrogen bond acidity (α), hydrogen bond basicity (β), and dipolarity/polarizability (π^*) were calculated.

AAILs exhibited strong hydrogen bond basicity (β between 0.88 and 1.38). These β values are larger than those of ILs reported previously (Table 2). ILs exhibiting strong hydrogen bond basicity were expected to dissolve cellulose and other biopolymers effectively.[19] Since hydrogen bond basicity is due mainly to the anion of ILs, [bmim][Cl] is frequently used as the IL, since it has the greatest hydrogen bond basicity (β = 0.95). However, almost all ILs containing Cl⁻ have melting points above room temperature, because the strong hydrogen bond basicity induced an increase of hydrogen bonding with the cation, as well as a strong electrostatic interaction force involving the relatively small anion. These chloride salts required heating for use as solvents for target compounds. As well as exhibiting stronger hydrogen bond basicity than chloride salts, these AAILs are liquid at room temperature. They are expected to be polar solvents for scarcely soluble compounds (due mainly to intermolecular hydrogen bonding).

AAILs composed of AAs having hydrogen donating properties, such as the carboxylic acid residue and the hydroxyl group, displayed relatively low hydrogen bond basicity. This can be explained by the weakened interaction between the dye and the carboxylic acid residue, through the interaction of these hydrogen bonding groups with the anion. The cation species also influences the β value. The value of β for [emim][Ala] was 1.036, but that for $[P_{4444}][Ala]$ it is 1.308.

The cation species is known to affect the hydrogen bond acidity (α). The hydrogen bond acidity (α value) was around 0.5 for imidazolium salts, as a result of the extensive contribution of a proton at the 2 position of the imidazolium ring. On the other hand, the α value of phosphonium salts was influenced by the anion species because there was no specific interaction between this cation and the dye molecule. From analysis of the phosphonium salts, the hydrogen bond acidity of AAILs was
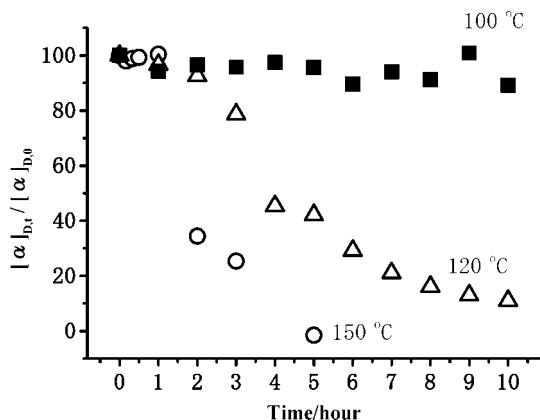
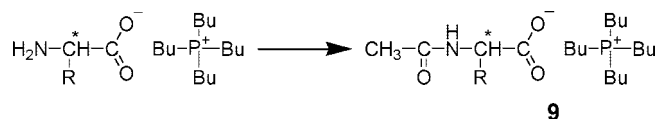**FIGURE 4.** Temperature and time dependence of the chiral stability of $[P_{4444}][Val]$.

FIGURE 5. Acetylated amino acid exhibits excellent chiral stability after salt formation.

Scheme 2. Preparation of Hydrophobic Amino Acid Anions by Introducing a Trifluoromethanesulfonyl Group

determined. The AAILs containing AAs having a hydrogen bonding group have greater hydrogen bond acidity than those without such groups.

The dipolarity/polarizability (π^* value) is attributed to the interaction between π electrons and the charge. There has been no detailed discussion of this point, because most ILs have almost identical π^* values. ILs are known to homogeneously disperse carbon nanotubes through π–π interactions. Some ILs having larger π^* values are expected to solubilize many π conjugated organic materials. The side chain structure of the AA did not affect the π^* value of the AAILs, but some influence of cation species was found: the imidazolium salts had larger π^* values than the phosphonium ones, suggesting a stronger π–π interaction between the imidazolium cation ring and the dye molecule. Compared to general ILs, AAILs were found to have stronger hydrogen bond basicity, equivalent hydrogen bond acidity, and equivalent dipolarity/polarizability. Since the AAILs are liquid at room temperature and are more polar than ordinary ILs, these AAILs are expected to be suitable as polar solvents. The solubilizing ability of these AAILs will be analyzed for a variety of materials, including polymers.

2.4. Chiral Stability of Amino Acid Ionic Liquids. AAILs are chiral.[20] To prevent the racemization of AAILs by heating during synthesis, AAILs were prepared without heating but were treated by freeze-drying, followed by the ordinary purification. The degree of optical rotation (the [α] value) of AAILs was influenced by the side chain structure. The ratio of the optical rotation value for the heated sample to that for a sample with no heat treatment ($t = 0$), ($[\alpha]_{D,t}/[\alpha]_{D,0}$) was used as a measure of chiral stability. As seen in Figure 4, the ratio ($[\alpha]_{D,t}/[\alpha]_{D,0}$) for $[P_{4444}][Val]$ showed a small decrease even after heating at 100 °C for 10 h. Against this, the ratio gradually decreased with heat treatment at 120 °C.[21] Furthermore, 50% samples were racemized within 2 h at 150 °C. To improve the thermal stability, we acetylated the amino groups as shown in Figure 5. The AA salt (**9**), composed of acetylated AA and $[P_{4444}]$, exhibited excellent thermal stability, and no racemization was found after maintaining it at 150 °C for 10 h.
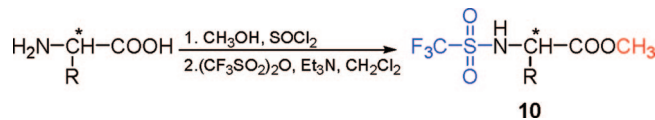
3. Functionalization of Amino Acid Ionic Liquids

3.1. Hydrophobic and Chiral Ionic Liquids. As mentioned above, all amino acids have two functional groups, such as a carboxylic acid residue and an amino group, available for a wide variety of chemical modifications. The AAILs mentioned above are all water soluble. Hydrophobicity is also important for functional ILs.[5](a) Incorporation of water insolubility in AAILs makes them suitable as reaction media, extraction media, and separation media, as well as having an airproof and waterproof liquid phase. Preparation of hydrophobic ILs is generally easy by using hydrophobic anions such as bis(trifluoromethanesulfonyl)imide [Tf_2N] anion or hexafluorophosphate anion. However, there are limited numbers of hydrophobic anions for ILs, and their functional design is quite difficult. We therefore sought to prepare hydrophobic AAILs by introducing a trifluoromethyl group.[22]

Trifluoromethanesulfonyl anhydride was added to the corresponding amino acid methyl ester to obtain **10**, as shown in Scheme 2. We chose 1-butyl-3-methylimidazolium ([bmim]) and *n*-tetrabutyl phosphonium ($[P_{4444}]$) as cations to form salts with **10**. The corresponding salts (**11–16**) were prepared by neutralization with [bmim]OH or $[P_{4444}]$OH, since $[P_{4444}]$ is already known to be an excellent partner for AAs, and it sometimes generates less viscous and thermally stable ILs with AAs (Figure 6). The salts (**11–14**) had a glass transition temperature but no melting point. Salt **16** has a melting point $T_m = 13.8$ °C. Except for **15** ($T_m = 61.2$ °C), all salts were liquid at room temperature. In view of the T_m value of $[P_{4444}][Tf_2N]$ of 86 °C,[23] the $[P_{4444}]$ cation is an excellent partner of chemically modified AAs. The T_g value increased gradually with elongation of the alkyl chain of AA.

The same tendency was also found for AAILs prepared with imidazolium cations. The viscosity was clearly affected by the T_g, so that their viscosity also depends on the alkyl chain length.

3.2. Phase Separation of an AAILs/Water Mixture. To study the phase behavior, the prepared hydrophobic AAILs were mixed with water. The hydrophobic AAILs were mixed with an equal volume of pure water and stirred. The [bmim] salts (**11–13**) were all miscible with water. However, all the $[P_{4444}]$ salts (**14–16**) were immiscible with water. The water content of **14** and **16** was found to be 5.1 and 2.9 wt %, respectively. By comparing **14** to **16,** it
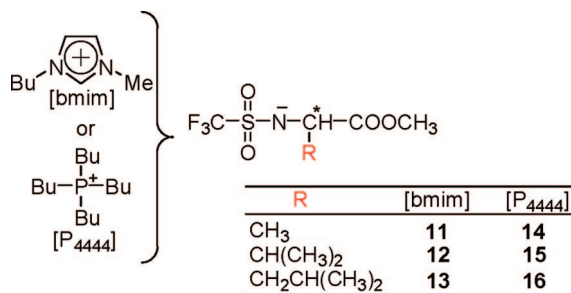
FIGURE 6. Hydrophobic ionic liquids (**11**–**16**) derived from amino acids.
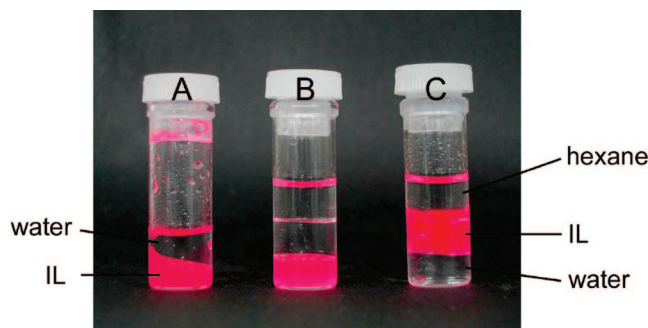

FIGURE 7. Three-phase liquid system composed of hexane/IL/water: (A) **16** mixed with water; (B and C) before and after stirring the mixture of hexane/**16**/water. The IL phase was colored with Nile Red.

is clear that the alkyl chain length corresponds to the hydrophobicity. The choice of AA may control the hydrophobicity and accordingly the water content after vigorous mixing with water. As references, the amount of water for [bmim][Tf$_2$N] is 1.98 wt % and that for [emim][Tf$_2$N] is 1.99 wt %.[24] These data clearly show that hydrophobic ILs, comparable to the typical [Tf$_2$N] salts, are readily prepared using modified AAs.

Interestingly, some organic solvents were also partly soluble in these AAILs. The density of the IL phase varied upon dissolving molecular liquids. Since the density of hydrophobic AAIL (**16**) is around 1.15 g cm^{-3}, the density change relates directly to the layer position after phase separation with molecular liquids. The IL phase was dyed with Nile Red[25] to distinguish it. Even after mixing with water, **16** was located as the lower phase (Figure 7A).

Three liquid layers were obtained by mixing water, hexane, and **16** (Figure 7B). Water and hexane were both partly soluble in **16**, but its density reached 0.98 g cm^{-3} after vigorous mixing. A change of layer sequence occurred with mixing (Figure 7C). This was due to the 35 wt % hexane content in **16**. Although there are many examples of solubilization of organic solvents in hydrophobic ILs, most hydrophobic ILs are heavy (around 1.4 g cm^{-3}) and the density never fell below 1.0 g cm^{-3}. This change in layer sequence is unique for relatively "light" but chiral ILs. Such changes might be applied in novel reactions or in separation processes or devices.

3.3. LCST Behavior of AAILs with Water. We prepared less hydrophobic AA anions by making the methyl ester of the carboxylic acid group unprotected, as in Scheme

Scheme 3. Hydrolysis of Methoxycarbonyl Groups on Amino Acid Derivatives
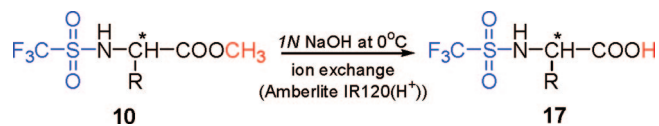
3. Of the natural amino acids, valine, leucine, iso-leucine, and phenylalanine were chosen as starting materials, since they have no reactive functional group on the side chain. The hydrophobic AA derivative **10** was hydrolyzed to **17** as shown in Scheme 3. Then, as with AAILs (Scheme 1), salts **18**–**22** were prepared by neutralization of **17** with the corresponding tetraalkylphosphonium hydroxide. The thermal properties and optical rotation values of the resulting salts (**18**–**22**) are shown in Figure 8.

These salts have melting points around 51–64 °C (Figure 8). The [P$_{4444}$] cation gives organic salts with relatively high melting points. The melting point of the salt was high even after coupling with [Tf$_2$N] anion (approximately 86 °C), so that T_m in Figure 8 is quite low for tetrabutylphosphonium salts.[23] The asymmetric cation is effective in lowering the T_m of the salt. However, **20** (with cation [P$_{4448}$]) had no melting point but did have a glass transition temperature and, therefore, a stable supercooled phase. We determined the chirality of the resulting ILs by optical rotation measurements, as shown in Figure 8. Chirality was also maintained at a temperature of 150 °C.

Figure 9 shows photographs of the temperature dependence of the phase separated system (upper phase, water; lower phase, IL (**19**)). In Figure 9, the metal rod going into the vessel was a thermosensor, and the IL phase was colored by Nile Red, which was insoluble in the aqueous phase. Upon cooling the two-phase system, the volume of the IL phase increased gradually (as seen in Figure 9a–d); then a completely miscible state was reached at 22 °C (Figure 9e). This should be due to the increased solubility of water in **19** with cooling. These salts were mixed homogeneously with water at lower temperatures, while separate phases resulted at higher temperatures.[26] Such a reversible phase transition is classified as "lower critical separation temperature (LCST)" behavior. LCST behavior has been found in polymer blends[27] but is rare for low molecular weight liquid mixtures. The triethylamine/water mixture shows LCST behavior.[28] There is no previous report on the LCST behavior of IL/water mixtures. The solubility of most materials increases with

entry	cation	R	$T_m/$°C	$[\alpha]_D^{25}$
18	[P$_{4444}$]	CH(CH$_3$)$_2$	51	4.5
19	[P$_{4444}$]	CH$_2$CH(CH$_3$)$_2$	64	9.8
20	[P$_{4448}$]	CH$_2$CH(CH$_3$)$_2$	-50*	7.0
21	[P$_{4444}$]	CH(CH$_3$)C$_2$H$_5$	51	3.6
22	[P$_{4444}$]	CH$_2$(C$_6$H$_5$)	64	1.5

*T_g (°C)

FIGURE 8. Structure and properties of amino acid-derived ILs used in the experiments.
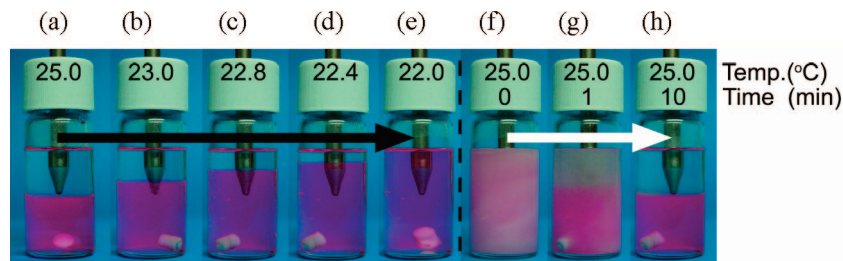
FIGURE 9. Phase separated state of a **19**/water mixture as a function of temperature.

heating. In the case of liquid/liquid mixtures, an inverse phase transition is seen. A homogeneous phase was obtained by heating, and cooling of the homogeneous liquid mixture produced a phase separation due to the decreased solubility. This was called "upper critical separation temperature (UCST)" behavior; there are many examples of it. Accordingly, the LCST behavior of the AAILs/water mixture observed here is very rare.

No phase separation occurred when the mixed solution was kept still at 22 °C or below. Upon gentle heating, phase separation occurred, and a cloudy suspension (Figure 9f) was seen when the solution temperature was heated to 25 °C. The suspension separated into phases after 1 min (Figure 9g) and reached a stable phase separated state (Figure 9h) within 10 min. This phase transition is thermally reversible. A major reversible phase change inducible by a small temperature change, as seen in Figure 9, should be useful in many processes.

The phase separation temperature (T_c) is specified as the clouding point. All AAILs synthesized in this study (**18–22**) exhibited LCST-type phase behavior with water. This clearly implies that the LCST-type phenomenon does not depend on the specific structure of the side chain on the AA anions. Furthermore, AAILs containing anions in which the carboxylic acid residue was protected with a methyl ester (**14–16**) did not exhibit LCST-type phase separation after mixing with water at any mixing ratio. These results imply that free carboxyl groups on the hydrophobic amino acid anions play a key role in LCST-type phase separation. The phase separation temperature of the mixture depends on the water content for all AAILs analyzed here (**18–22**). The T_c values of the series **18**, **19**, **21**, and **22** of IL/water mixtures (50/50 by wt %) were respectively 40, 25, 25, and 15 °C. The increasing water content in the mixture always lowered the T_c, as seen in Figure 10. This trend is consistent with the observation that water dissolves more in ILs with cooling. At very high water content, most of these ILs were not fully miscible because the solubility limit was exceeded.

An increasing number of papers has been published on chemical reactions in ILs. Hydrophobic ILs are useful as solvent in allowing for the separation and isolation of reaction products, which is often otherwise difficult. The negligible vapor pressure of ILs is one of their advantages, but it is also a serious problem. Extraction is sometimes used to separate products from ILs. From this point of view, hydrophobic ILs are a better reaction matrix than hydrophilic ILs that mix freely with water. The extraction efficiency may be related to the extent of contact of the
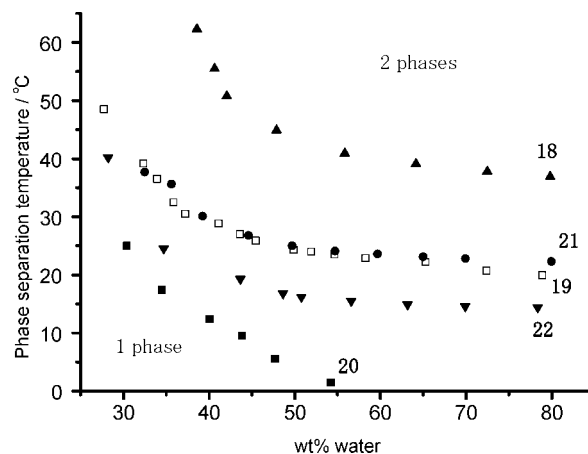
FIGURE 10. Phase separation temperature of IL/water mixtures.

IL phase and the extractant; it is usually improved by vigorous mixing. Extraction should be greatly improved by exploiting the reversible phase change of the IL/water mixture with a small temperature change. There have been several previous attempts to control the phase change of IL/solvent mixtures.[29] Many partner liquids are possible for ILs, including supercritical carbon dioxide, organic solvents, water, and salt-containing water. Phase changes in IL/IL mixtures have also been reported recently.[30] There is no report of IL/water mixtures showing LCST-type behavior. The present system appears to be unique.

This phase change can also be used for feeding starting materials, catalysts, enzymes, and cofactors. In particular, it should be helpful for enzymes or other catalysts that display high activity within very narrow ranges of physicochemical conditions, such as temperature or pH. Heating the medium usually damages the catalytic activity of enzymes. The UCST-type phase change, with less sensitivity to temperature, is not suitable for biological use. Most biological macromolecules denature irreversibly upon heating. The temperature sensitive LCST-type phase change should be best for such biological materials. The T_c value can be adjusted to room temperature or a nearby optimum temperature by exploiting the above-mentioned parameters. The reversible phase change between a homogeneous mixture and separated phases can be implemented simply by changing the temperature of the solution by a few degrees. Enzymes can be introduced into the IL phase after poly(ethylene oxide) (PEO) modification.[31] Further modification of alkyl chains onto these PEO-modified enzymes makes them water insoluble and
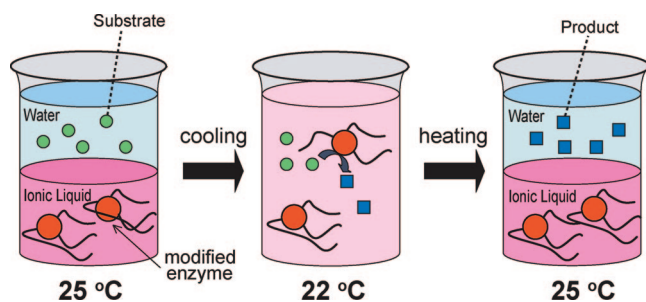
FIGURE 11. Biocatalysis system with a thermomorphic ionic liquid/water mixture.

IL soluble. With these modified enzymes and LCST-type phase separation, a unique reaction process can be proposed, as shown in Figure 11. Wide applications await this phase change of IL/water mixtures.

4. Concluding Remarks and Outlook

The design of component ions is important to the development of functional ionic liquids. Functional design of the ILs at the molecular level is not yet systematic, so that it is important to develop new ion species and investigate the ILs that include them. Other strategies for preparing new ILs include the mixing of two, three, or more different ILs. It is still necessary to analyze the basic properties of ILs prepared by the coupling of new ion species. Here, we have introduced several new ILs derived from amino acids. We emphasize the wide variety of amino acids and consequently of ILs that can be prepared. These AAILs may open a door to new applications of ILs.

The introduction of functional groups onto component ions clearly influences the properties of the corresponding ILs. In general, these chemical modifications lessened the advantageous properties such as low viscosity, low melting point, and high decomposition temperature. The resulting ILs should nevertheless be useful in specific applications.

The future of AAILs is highly promising. ILs derived from natural ions herald a new research field, of "natural ILs" or "bio-ILs". AAILs can be expected to find application in all of the biological, medical, and pharmaceutical sciences.

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