Fine Control of LCST-type Phase Transition of Ionic Liquid/Water Mixtures

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Chapter 1

Ionic liquid/water mixtures showing unique phase behavior
1.1 Ionic liquids

1.1.1 Definition of ionic liquids

Ionic liquids (ILs) are salts, that are composed of entirely ions, with very low melting temperature.\(^1\),\(^2\),\(^3\) Generally, salts are given this classification when they have a melting point below 100 °C. However, this value is arbitrary and has no special physico-chemical meaning. These compounds commonly have a wide liquid range, negligible vapor pressure, flame retardant, and high ion density. These unique characteristics have propelled ILs into the scientific spotlight, as they often make them superior to conventional molecular liquids. The first water and air stable ILs, the 1-ethyl-3-methylimidazolium cation with either the methanesulfonate or tetrafluoroborate anion, were discovered by Cooper and Sullivan, and by Wilkes et al. in the 1990s.\(^4\),\(^5\) This discovery circumvented previous stability problems with ordinary temperature molten salts,\(^6\) beginning new trends in battery electrolyte and reaction solvent research that have continued until today.\(^1\),\(^3\),\(^7\)

The correlation between the structure of the ion pair and the properties of the resulting ILs has continued to be a key theme in developing potential applications for these novel materials. Typical examples of component ion structures are shown in Figure 1-1. Quaternary onium cations like 1-methyl-3-alkylimidazolium have been widely used because the weak electrostatic interaction of their highly delocalized aromatic ring leads to lower melting temperatures.\(^8\) Later research revealed that quaternary phosphonium-based ILs have an even wider electrochemical window and better thermal stability than nitrogen-containing ILs.\(^9\),\(^10\),\(^11\) Meanwhile, a comparatively larger number of anions have been operated as constituent of ILs, including fluorinated anions like tetrafluoroborate (BF\(_4\)), hexafluorophosphate (PF\(_6\)), and bis(trifluoromethanesulfonyl)imide (TF\(_2\)N). ILs designed with these species have the advantage of being low in viscosity and hygroscopicity. More ecological halogen-free systems have also been developed using alkylsulfonate,\(^12\) alkylcarbonylate,\(^13\) and amino acid anions.\(^14\)

![Figure 1-1](image-url) Typical ion structures of ionic liquids.
Furthermore, additional functional groups can be further incorporated into ILs to yield particular properties and new applications. These functionalized ILs is called the “Task Specific Ionic Liquids (TSILs)”.15

1.1.2 Physico-chemical properties of ionic liquids

Since physico-chemical properties of ILs strongly varied depending on the component ion structures, many ILs have been studied for a long time with sophisticated equipment. In respect of that topic, honorable researchers have been summarized in several reviews and books.1,3,16 Considering applications of ILs, melting temperature ($T_m$) is one of key parameter, and is described thermodynamically by the following equation.

$$T_m = \frac{\Delta_m H^o}{\Delta_m S^o}$$

where $\Delta_m H^o$ is the melting enthalpy and $\Delta_m S^o$ is the melting entropy. This equation indicates that low $T_m$ of ILs were observed when $\Delta_m H^o$ is small or $\Delta_m S^o$ is large. These thermodynamic changes result from configurational diversity and structural flexibility of component ions. When organic ion with long alkyl chain was introduced to ILs, they get many rotational degrees of freedom. If that ion had asymmetric alkyl chain, these effects are larger due to the increase of structural flexibility, which should make $T_m$ lower. However, long alkyl chains do not always lower the $T_m$; for example, the $T_m$ of 1-tridecyl-3-methylimidazolium tetrafluoroborate ([C$_{13}$mim]BF$_4$) is higher than that of 1-dodecyl-3-methylimidazolium tetrafluoroborate ([C$_{12}$mim]BF$_4$).17 This is due to Van der Waals interaction among hydrocarbon chains come to have a major impact on the $T_m$ when ILs have more than threshold alkyl number on the component ions. Of course, alkyl chain length is not the only factor that affects $T_m$. Additional properties could be incorporated to ILs by linking reactive functional groups to component ions covalently. They have a tendency to show higher $T_m$ values than that of non-functionalized ILs because additional functional groups sometimes produce inconvenient interaction between cation and anion, which lead increase of $\Delta_m H^o$. These facts make things more difficult to design ILs with desirable physico-chemical properties.

The endless potential combinations of cations and anions makes it difficult to predict the relation between the structure of each component ion and the properties of the resulting ILs as a whole. Therefore it is crucially important to perform extensive characterization of ILs. Holbrey’s group and Hamaguchi’s group first achieved the structural polymorphism of ILs, 1-butyl-3-methylimidazolium chloride ([C$_4$mim]Cl), by using spectroscopically analysis18,19. Holbrey and co-worker demonstrated single crystal X-ray diffraction and identified the presence of two or more polymorphism in [C$_4$mim]Cl, which differ only in the configuration of the butyl chain on the imidazolium cation.18 At the same time, Hamaguchi and co-worker analyzed liquid [C$_n$mim]X (X = Cl, Br, I, or BF$_4$) using Raman spectroscopy and found two rotational
isomers, one in a \textit{trans} configuration and the other in a \textit{gauche} configuration around the ethylene group close to the imidazolium ring in liquid state of $[\text{C}_4\text{mim}]\text{X}$.\textsuperscript{19} These structural variety offer low $T_m$ as well as other unique physico-chemical properties. In addition to depressed $T_m$, this structural variety often allows for supercooled states over a wide temperature range. To add to the previous analyses, Endo and Nishikawa elucidated the thermodynamic phase behavior of $[\text{C}_4\text{mim}]\text{PF}_6$ by combining Raman spectroscopy with calorimetric techniques. Three types of structural isomers were discovered for crystalline $[\text{C}_4\text{mim}]\text{PF}_6$, with all three existing in the liquid and supercooled liquid state.\textsuperscript{20} These complicated ion state is attributed to the very slow dynamics that ILs exhibit compared to molecular solvents. Note that this kind of multiple analysis is necessary to determine the “TRUE” physico-chemical properties of any IL.

The measurement of IL properties is particularly sensitive to the conditions employed, as well as to the presence of impurities such as excess halogen, decomposition matter, and molecular solvents. Furthermore, thermal history always influences IL thermodynamic phase transitions.\textsuperscript{20} In addition to thermal properties, viscosity, density, and other fluid properties can also be affected by impurities.\textsuperscript{21} Therefore, it is important to carefully identify final products after IL synthesis using NMR, IR, mass spectrometry, and/or elementary analysis.

\subsection*{1.1.3 Significance of ionic liquid/water mixtures}

During the early stage in the studies of ILs, many researchers have been focused on the physico-chemical properties of “NEAT” ILs, and pioneered unique applications and technologies in such field as energy, biotechnology, and nanotechnology by using them.\textsuperscript{7,16,22,23} As mention above, contamination such as water molecules have been rejectable impurity when properties of neat ILs were designed. However, there should be an upper limit to developing ILs having desired properties and functions by only designing their cation and anion. In recent years, mixture of ILs and molecular solvents have been recognized as good system in order to tune physico-chemical properties. Among the molecular solvents, water is the most promising covalent partner due to its unique solvent properties, which it derives from its large dipole moment and three-dimensional hydrogen bonding network.\textsuperscript{24} Addition of water molecules should alter IL properties, which makes it possible to design solvents for specific applications beyond the neat ILs.

The physico-chemical properties of IL/water mixtures change dramatically depended on their molar ratio. The properties of aqueous mixtures with high IL concentrations are especially interesting, given that they cannot be explained by considering the mixture to be a conventional aqueous inorganic salt system. Below, we summarize basic properties and recent developments of IL/water mixtures as novel functional fluids.
1.2 Ionic liquid/water mixture

1.2.1 Phase behavior of ionic liquid/water mixtures

While ILs cannot contribute to air pollution due to their negligible vapor pressure, they show unique phase behavior with water. In considering the practical application, the phase behavior of ILs when mixed with water is a particularly important aspect, and is highly dependent on the component ions. Note that the ionic nature of ILs makes most of them miscible with water; these are defined as hydrophilic ILs in this thesis. Some hydrophilic IL mixtures containing small amounts of water, classified as hydrated ILs, are capable of dissolving proteins without causing significant damage to their higher-order structures.25,26 Furthermore, proteins dissolved this way are stable for a longer time than those in buffer solution. These unique character exceeded the performance of buffer solution was only observed in the aqueous mixture at high IL concentration. Conversely, some ILs containing fluorinated anions, such as hexafluorophosphate (PF$_6^-$) and bis(trifluoromethanesulfonyl)imide ([Tf$_2$N]), yield stable liquid-liquid separated phases when mixed with water; these are defined as hydrophobic ILs in this thesis. These biphasic systems have been used as extraction and reaction media for various compounds.27,28

It is widely accepted the phase behavior of IL/water mixtures is governed by the total hydrophobicity/hydrophilicity of the constituent cation and anion of ILs. However, there is still uncertainty as to how to judge the hydrophobicity of a given ion, though several methodologies have been developed that measure this feature.29,30 In order to predict phase behavior of IL/water mixtures, it was very important to estimate the hydrophobicity of component ions. The octanol-water partition coefficient ($K_{ow}$), while used to assess environmental risk, has proven valuable in determining the hydrophobicity of compounds.31,32 This value is calculated by dividing the concentration of IL in the octanol phase by that in the water phase of a biphasic solution. For [C$_n$mim]Cl, $K_{ow}$ values increase with the length of the alkyl chain on the imidazolium ring. Meanwhile, changing the anion gives $K_{ow}$ values in the following order: [Tf$_2$N]$^-$ > PF$_6^-$ > Cl$^-$ > NO$_3^-$ > Br$^-$ > BF$_4^-$.

Welton and co-worker estimated the strength of hydrogen bonding between water molecules and IL anions using IR bands corresponding to the antisymmetric ($v_3$) and symmetric ($v_1$) stretching modes of water;33,34 bonding strength decreased in the following order: PF$_6^-$ > SbF$_6^-$ > BF$_4^-$ > ClO$_4^-$ > [Tf$_2$N]$^-$ > CF$_3$SO$_3^-$ > NO$_3^-$ > CF$_3$CO$_2^-$, This order correlates well with hydrogen bonding basicity ($\beta$) derived from solvatochromic dye.35 Wakai and co-worker also elucidated the strength of the interaction between water and anion, this time by analyzing temperature dependent NMR spin-lattice relaxation times.34 The rotational correlation time ($\tau_{2R}$) ratio of water to benzene was used as a parameter of water-anion interaction; its value for [C$_4$mim]Cl was found to be even larger than that for [C$_4$mim]PF$_6$, which indicates stronger attraction on the part of the Cl$^-$.
anion than for the $\text{PF}_6^-$ anion. Lynden-Bell and co-worker subjected molecular dynamics calculations on the rotational dynamics for the $[\text{C}_1\text{mim}]\text{Cl}$ and $[\text{C}_1\text{mim}]\text{PF}_6$ after mixing with water. Although the results for cations differ slightly from those for NMR relaxation analysis, the anion effect on the dynamics observed is supported by the slower dynamics in the aqueous $[\text{C}_1\text{mim}]\text{Cl}$ than the $[\text{C}_1\text{mim}]\text{PF}_6$. Furthermore, Koga and co-worker developed a hydrophobicity/hydrophilicity map based on a 1-propanol (1P) probing methodology, in which they studied the effect of increasing salt concentration on excess partial molar enthalpy of 1P ($H_{1P}^E$) in a 1P/IL/water mixture with high water composition. By analyzing the developed $H_{1P}^E$ chart, they experimentally indexed relative hydrophobicity on a two-dimensional map (Figure 1-2) that showed typical component ions for ILs are more strongly hydrophobic and more strongly hydrophilic character than inorganic ions. Though hydrophobicity/hydrophilicity of ions could be individually determined with this methodology, authors stated that it is premature to generalize the concept of 1P probing method due to lack of number of evaluated ion species.

![Figure 1-2](image-url)
Finally, water content in the IL-rich phase has been used as a means by which to compare ion hydrophobicity.\textsuperscript{39,40} Coutinho and co-worker studied the mutual solubility of water with [Tf\textsubscript{2}N]-based hydrophobic ILs employing a series of nitrogen-containing cations such as imidazolium ([C\textsubscript{n}mim]), pyridinium ([C\textsubscript{n}mpy]), pyrrolidinium ([C\textsubscript{n}mpyr]), and piperidinium ([C\textsubscript{n}mpip]) families. They determined hydrophobicity for each family ranked as follows: [C\textsubscript{n}mim] < [C\textsubscript{n}mpy] ≤ [C\textsubscript{n}mpyr] < [C\textsubscript{n}mpip] by comparing the maximum water content of IL-rich phase. Meanwhile, Ohno and co-worker developed a hydrophilicity index (HI), defining it as the number of water molecules per ion pair in the separated IL-rich phase at 60 °C. Hydrophobic phosphonium cations were used as the IL counterion to provide the best indicator for anion hydrophobicity, with the ranking as follows: Cl\textsuperscript{−} < Br\textsuperscript{−} < [BzSO\textsubscript{3}]\textsuperscript{−} < [TsO]\textsuperscript{−} < [DMBS]\textsuperscript{−} < CF\textsubscript{3}COO\textsuperscript{−} < [TMBS]\textsuperscript{−} < NO\textsubscript{3}\textsuperscript{−} < CF\textsubscript{3}SO\textsubscript{3}\textsuperscript{−} < [BF\textsubscript{4}]\textsuperscript{−} < [Tf\textsubscript{2}N]\textsuperscript{−}.

Unfortunately, determining the hydrophobicity of the constituent ions only goes so far; for example, [C\textsubscript{8}mim]BF\textsubscript{4} is miscible with water but [C\textsubscript{8}mim][Tf\textsubscript{2}N] is not, despite the fact that the BF\textsubscript{4}\textsuperscript{−} anion is more hydrophobic than the [Tf\textsubscript{2}N]\textsuperscript{−} anion according to some of the methods described above. Further studies on ion hydrophobicity are clearly required.

1.2.2 Physico-chemical properties of ionic liquid/water mixtures

The presence of water in ILs remarkably affects the interionic interactions and alters their properties to a significant extend. Therefore, it is very important to understand the mixing state in IL/water mixture at a bulk, micro, and molecular level both experimentally and theoretically. Most ILs are known as hygroscopic to varying degrees, and that be harmful or useful depending on the situation.\textsuperscript{21,41,42} Hydrophilic ILs such as [C\textsubscript{8}mim]Cl or [C\textsubscript{8}mim]NO\textsubscript{3} absorbed much more water from the atmosphere than hydrophobic [C\textsubscript{8}mim][Tf\textsubscript{2}N].\textsuperscript{21} Such water absorption could occur slowly over hours or days, yielding saturation levels determined by the ambient humidity and temperature. With increasing temperature and humidity, the degree of hygroscopicity in all ILs increased. Estimating this parameter, or the maximum water content, is important in the design of any new IL/water mixture.

Hydrophilic ILs were freely miscible with water, which means there was no maximum water content. The corresponding value for hydrophobic ILs, meanwhile, is strongly dependent on the constituent ions. Seddon and co-worker measured maximum water content of several imidazolium based ILs with Karl-Fisher titration method.\textsuperscript{21} ILs with [PF\textsubscript{6}]\textsuperscript{−} were highly hydrophobic and contained less mount of water than [BF\textsubscript{4}]\textsuperscript{−} based ILs (Figure 1-3). Cation effects were also mentioned, with increasing alkyl chain lengths dropping the solubility of water in ILs and vice versa significantly. However, note that the solubility of water in ILs is several orders of magnitude higher than the solubility of ILs in water.\textsuperscript{43}
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Figure 1-3 Maximum water content at ambient temperature (ca. 22 °C) for [C\text{\textit{n}}\text{mim}]PF\text{\textsubscript{6}} (n = 4 to n = 8) (white) and for [C\text{\textit{n}}\text{mim}]BF\text{\textsubscript{4}} (n = 6 to n = 10) (gray).

Changes in water content can change the strong intermolecular hydrogen bonding interactions between water and the constituent ions, leading to significant changes in, among others, viscosity,\textsuperscript{21,44,45} density,\textsuperscript{21} surface tension,\textsuperscript{46,47} and polarity.\textsuperscript{48,49} The high dielectric constant of water is effective at weakening the electrostatic interactions between cation and anion, dropping the viscosity much more than a molecular solvent with a low dielectric constant, such as chloroform.\textsuperscript{50} Pulsed-field gradient in-echo NMR analysis has revealed that water-separated ion pairs exist in IL/water mixtures, as opposed to the contact ion pairs in neat ILs.\textsuperscript{51} This is consistent with other results which indicate that water molecules do not self-associate in this medium, but rather form 1:2 type hydrogen bonded anion···HOH···anion complexes.\textsuperscript{33}

Addition of small amount water do not always lead drastic change in physiochemical properties. Seddon and co-worker investigated the effect of water content on the density of [C\text{\textit{4}mim}]BF\text{\textsubscript{4}}. The density did not vary a great deal at low water content, whereas it decreased rapidly towards that of pure water at high water content.\textsuperscript{21} Water content dependence on the surface tension showed the similar tendency with that on density. There was little or no influence on the surface tension value in ILs after mixing small amount of water.\textsuperscript{46} At other times, complicated interactions between the constituents gave unexpected and unpredictable changes. For example, the polarity of some systems, as measured through features like the Kamlet-Taft parameters, gave higher or lower values than either of the pure materials, a phenomenon known as the synergetic effect. The resulting versatility of these mixtures gives them enormous potential.
1.2.3 Potential applications of ionic liquid/water mixtures

Various applications can result from exploiting this feature of IL/water mixtures. These have shown great promise in biochemistry in particular. In general, buffer solutions are composed of aqueous mixtures with small amounts of salts, and are generally the best media available for proteins. As salt concentration increases, proteins denature due to salting out, which results from the electrostatic shielding of the protein surface by the strength of the ion charges. This means that neat ILs are effectively unable to dissolve proteins without conformational change.\(^52,53\) On the other hand hydrated ILs have been efficient at doing so while still maintaining the protein ternary structure. For example, Fujita and co-worker showed that choline dihydrogenphosphate ([Ch][DHP])-type hydrated IL was able to preserve protein function over an extended period of time.\(^25,26\) Likewise, Angell and co-worker reported reversible thermal folding behavior in hydrated ILs.\(^54,55\) Meanwhile, Weingärtner and co-worker ordered the effects of IL species in water mixtures on protein stability, denaturation or aggregation, formation of folding/unfolding intermediates, and enzymatic activity.\(^56,57,58\) Cations and anions were ranked as Hofmeister series, a classification of ions in order of their ability to induce protein changes.\(^59\) The observed Hofmeister for IL cation and anion series point toward hydrophobic interactions as an important factor to control ion-specific effects on the proteins. Understanding for these interesting phenomenon take a facilitating role to gather considerable attention to the collaboration of biomolecules with IL/water mixtures. In spite of tough challenge for protein science, many researcher have conducted a usability of IL/water mixtures for crystallization,\(^60,61\) aggregation,\(^62,63\) and refolding behavior.\(^64,65\)

The other use of IL/water mixtures is separation, condensation, and reaction media as liquid-liquid biphasic systems. In this case, hydrophobic ILs containing \([\text{ Tf}_2\text{N}]^-\) or PF\(_6^-\) anion have been commonly used. Rogers and co-worker initially studied partition coefficients of several aromatic compounds in \([\text{C}_4\text{mim}]\text{PF}_6/\text{water}\) and strongly correlated them with their K\(_{OW}\) values.\(^27\) They also reported pH-dependent partition behavior of mineral acids in the same hydrophobic IL/water biphasic system.\(^66\) These system have been spread to wilder targets such as organic compounds,\(^67\) metal ions,\(^68,69\) and proteins.\(^28,70\)

To extract hydrophilic compound like metal ions or proteins into the hydrophobic IL-rich phase, addition of extractant is often required. Newer work has even lead to the development of aqueous biphasic systems (ABSs) in which aqueous hydrophilic IL/inorganic salt mixtures formed biphasic systems due to the salting out effect of kosmotropic inorganic salts.\(^71\) Carbohydrates, amino acids, and polymers have also been used to prepare these solutions, leading to a wide variety of solvation properties.\(^72\) Since both phases contain large amounts of water, they have been applied to biomaterials work in pharmaceutical,\(^73,74\) alkaloid,\(^75,76\) amino acid,\(^77,78\) and enzyme research.\(^79,80\) Kragl and co-worker found that IL of Ammonoeng 110\(^{TM}\)
containing oligoethyleneglycol unit is highly effective for preparing ABS and shows great biocompatible. This medium was used to effect an alcohol dehydrogenase enzymatic reaction; both conversion and yield were enhanced over traditional systems due to the stabilization of the enzyme and the increased solubility of the hydrophobic substrates.\textsuperscript{79}

The interface of these mixtures also exhibit several distinct properties, though research of this is still in its infancy. Ouchi and co-worker achieved microscopic structure at interfaces between [C\textsubscript{4}mim]PF\textsubscript{6} and molecular liquids by IR-visible sum frequency generation (SFG).\textsuperscript{81} According to the SFG spectroscopy, butyl chain on the [C\textsubscript{4}mim]\textsuperscript{+} cation is oriented toward the molecular liquid rich phase at the interface of CCl\textsubscript{4}/[C\textsubscript{4}mim]PF\textsubscript{6} or butanol/[C\textsubscript{4}mim]PF\textsubscript{6}. While butyl chain on the [C\textsubscript{4}mim]\textsuperscript{+} cation found to be randomly oriented at the IL/water interface, which is consistent with molecular dynamic study.\textsuperscript{82} These unique interface formed between ILs and water promise a competent works. Pioneering work on the efficient use of IL/water interface was carried out by Kimizuka et al.\textsuperscript{83} They successfully synthesized single crystalline gold nanosheets by photoreduction of Au(OH)\textsubscript{4}\textsuperscript{-} ions at the interface of IL and water (Figure 1-4). ILs provided the reactive interface with water and also act as interface stabilizing agents, which behave similarly to oil-in-water emulsion system. Since the solubility of various compounds can be tuned by changing the IL ion pair, this technique has been extended not just to metal nanosheets but to capsules,\textsuperscript{84} microcrystals,\textsuperscript{85} enzymatic reactions,\textsuperscript{86,87} and polymerization\textsuperscript{88} as well.

These beneficial applications of IL/water mixtures are attributed to the fact that ILs can serve as bi-or multi-functional materials by varying their component ions.

**Figure 1-4.** Schematic illustration of the formation of ultrathin gold nanosheets. Photoreduction of Au(III) ions occur at the[C\textsubscript{4}min]PF\textsubscript{6}/water interface and the formed nanosheets are extracted inside the ILs microdroplet.
1.3 Temperature driven phase transition of ionic liquid/water mixtures

1.3.1 Typical examples of temperature driven phase transition

IL-based aqueous systems are characterized not only by their static phase behavior, but by stimuli-driven dynamic phase transitions as well. One of the most attested of these is temperature driven dynamic phase transition, which can be further subdivided into two types, upper critical solution temperature (UCST)-type and lower critical solution temperature (LCST)-type. The UCST-type phase transition is common situation, in which phase separation occurs as temperature is lowered. A typical phase diagram for this phenomenon tracking temperature versus mole fraction gives a concave curve, where the lowest temperature forms a homogeneous solution (Figure 1-5 Type A). As dictated by thermodynamic considerations, these binary mixtures spontaneously move to minimize their free energy by minimizing energy and maximizing entropy. In general, homogeneous mixtures have more entropy than biphasic mixtures, which means that miscibility is favored in this regard from an entropic point of view. When the solution temperature is low, however, contribution of entropic effect decreases. At sufficiently low temperature, miscibility is governed solely by the minimization of energy. In the study of molecular level, attractive interaction between unlike molecules is significantly weaker than it is between the same or similar molecules, which promote the formation of clusters with the same (or similar) kind of molecules in a mixture. Eventually phase separation is accomplished almost irrespective of the degree for the entropy of mixing. This is a reason why low temperature immiscibility occurs.

In contrast, the LCST-type phase transition is another situation, in which phase separation occurs as temperature is higher. A typical phase diagram for this phenomenon tracking temperature versus mole fraction gives a concave curve, though one that is distinct from the one generated for the UCST-type (Figure 1-5 Type B). LCST-type phase transition is seen in the mixture involving specifically strong interaction between the component species, like hydrogen bonding. Note that while hydrogen bonding lowers the energy of the system, it lowers the entropy as well. When the strength of hydrogen bonding between unlike molecules is higher, the energy of the miscible phase is lower than that of the immiscible one. At sufficiently low temperature, entropy loss cannot compete with this energy decrease because energy benefit through the hydrogen bonding is much larger than it. However if the constituents of the mixture are of very distinct size, (compositional and orientational) entropic effect also take on a major significance for determining phase behavior. Nevertheless, as temperature increases, the overall decrease in entropy due to the disruption in hydrogen bonding could eventually prevail, resulting in forming liquid-liquid phase separation. This is a reason why high temperature immiscibility occurs.
Figure 1-5 Typical phase diagrams of temperature dependence liquid-liquid two phase system. While areas represent homogeneous phase and brown areas do two phase regions. UCST and LCST denote upper critical solution temperature and lower critical solution temperature, respectability.

More generally, these thermodynamic considerations can result in six distinct phase diagrams, displayed in Figure 1-5. Note that both UCST-type and LCST-type phase transitions result when the thermodynamic balance between energy and entropy collapse, albeit at different temperatures. Therefore simple phase diagrams of Type A and B can be interpreted as particular cases of Types C and D if the experiment is limited to low or high temperature, if evaporation or crystallization of either one occur, or if the temperature of solution reaches 0 K before phase transition. Alternatively, Types C and D can be interpreted as phase equilibria for metastable superheated and supercooled states. Type E in turn can be considered a subset of Type D in which UCST and LCST curves blend, resulting in an hourglass-shaped phase diagram. In a similar manner, Type F can be considered a subset of Type C, as a case in which neither UCST or LCST are observed within the liquid range. From these thermodynamic fact, temperature versus mol fraction phase diagram can be understood.

Several examples of temperature driven phase transitions, mostly for IL/water mixtures, are summarized in Table 1 (all ILs are denoted as abbreviated name). UCST-type phase transition is common situation, in which the miscibility of two liquids increases with increasing
temperature. In fact, a lot of binary mixtures exhibit this type of phase behavior including ILs after mixing with water or other molecular solvents (Table 1-1 entry 1-8 as typical examples). On the other hand, LCST-type phase transitions are only commonly observed in mixtures with very distinct differences in molecular size, such as binary systems of polymers and water. There are only a few examples of an LCST-type phase transition in the IL/molecular solvent mixtures until recently. However, an LCST-type phase transition itself had been already reported in a couple of organic salt/water mixtures. For example, Weingärtner and co-workers found that an aqueous solution of [N₄₄₄₄]SCN exhibited both UCST- and LCST-type transitions (entry 9). This appears to be the first example of an aqueous salt mixture showing an LCST-type transition, yet, strictly speaking, it does not qualify as an IL/water mixture, since the \( T_m \) of [N₄₄₄₄]SCN is 127 °C. At the same time, some \( n \)-alkylammonium salts found to show LCST-type phase transition after mixing with water. In 2002 Rebelo and co-workers reported a [C₄mim]PF₆/water/ethanol ternary system exhibiting an LCST, despite the fact that both the binary mixtures [C₄mim]PF₆/water and [C₄mim]PF₆/ethanol show only UCST-type phase transition. As regards IL/water mixture, the author’s group was the first to report an LCST-type phase transition for an IL/water mixture that used an IL designed from the \( N \)-trifluoromethanesulfonyl amino acid anion ([Tf-AA]⁻) and the tetra-\( n \)-butyl phosphonium cation (entry 13 and Figure 1-6). Further research has explored the factors required for eliciting LCST-type transitions after mixing with water, in order to demonstrate the design strategy for temperature driven phase transitions of the IL/water mixture, and details will be provided in the next section.

An LCST-type phase transition of IL/organic solvent is also potential interest to solution chemistry. Seddon and coworkers reported mixed IL systems showing both UCST- and LCST-type phase transition after adding chloroform (entry 27). Some other IL mixtures show LCST-type phase transitions with benzene (entry 28), toluene (entry 29), and ether derivative (entry 30). [C₄mim]PF₆/trifluoromethane, meanwhile, showed an LCST-type phase change under high pressure (entry 31). Yuan and co-workers reported a [C₁mim]I/1,4-dipropoxypillar[5]arene (DPP5)/chloroform ternary system that exhibited LCST-type transitions due to the host-guest interaction between [C₁mim]I and DPP5 (entry 32).
### Table 1-1: Temperature driven phase behavior of ILs with solvents

<table>
<thead>
<tr>
<th>Entry</th>
<th>IL</th>
<th>Solvent</th>
<th>Phase behavior</th>
<th>$T_c / ^\circ C$</th>
<th>Molar ratio (solvent : IL)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[C$_4$ mim]BF$_4$</td>
<td>Water</td>
<td>UCST</td>
<td>4.4</td>
<td>13 : 1</td>
<td>103, 104</td>
</tr>
<tr>
<td>2</td>
<td>[C$_8$ mim]BF$_4$</td>
<td>Water</td>
<td>UCST</td>
<td>&lt;df&gt;</td>
<td>&lt;df&gt;</td>
<td>105</td>
</tr>
<tr>
<td>3</td>
<td>[Bet][Tf$_2$N]</td>
<td>Water</td>
<td>UCST</td>
<td>56</td>
<td>20 : 1</td>
<td>106</td>
</tr>
<tr>
<td>4</td>
<td>[N$_{10-cx}$][Tf$_2$N]</td>
<td>Water</td>
<td>UCST</td>
<td>72</td>
<td>19 : 1</td>
<td>107</td>
</tr>
<tr>
<td>5</td>
<td>[P$_{4444}$][Fum]</td>
<td>Water</td>
<td>UCST</td>
<td>62</td>
<td>50 : 1</td>
<td>108</td>
</tr>
<tr>
<td>6</td>
<td>[C$_6$H$_4$OCf$_3$mim][X]</td>
<td>Aliphatic, aromatic, hydrocarbons</td>
<td>Depending upon structure of hydrocarbons</td>
<td>&lt;df&gt;</td>
<td>&lt;df&gt;</td>
<td>109</td>
</tr>
<tr>
<td>7</td>
<td>[P$_{tox}$][X]</td>
<td>Aliphatic hydrocarbons</td>
<td>UCST</td>
<td>33</td>
<td>37 : 1</td>
<td>110, 111</td>
</tr>
<tr>
<td>8</td>
<td>[C$_4$ mim][X]</td>
<td>Alcohols</td>
<td>UCST</td>
<td>&lt;df&gt;</td>
<td>&lt;df&gt;</td>
<td>112, 113</td>
</tr>
<tr>
<td>9</td>
<td>[N$_{4444}$][SCN]$^a$</td>
<td>Water</td>
<td>UCST and LCST</td>
<td>150</td>
<td>18 : 1</td>
<td>91</td>
</tr>
<tr>
<td>10</td>
<td>[N$_{444}$$^b$][Br]$^c$</td>
<td>Water</td>
<td>LCST</td>
<td>-23</td>
<td>Increasing upon increasing n values</td>
<td>92</td>
</tr>
<tr>
<td>11</td>
<td>[N$_{44}$$^c$][I]$^d$</td>
<td>Water</td>
<td>UCST and LCST</td>
<td>73, 59</td>
<td>25 : 1</td>
<td>93</td>
</tr>
<tr>
<td>12</td>
<td>[C$_4$ mim]PF$_6$</td>
<td>Water/ethanol</td>
<td>LCST</td>
<td>15</td>
<td>5.5 : 4.5 : 1 (ethanol : water : IL)</td>
<td>94</td>
</tr>
<tr>
<td>13</td>
<td>[P$_{444}$$^e$][Tf-AA]</td>
<td>Water</td>
<td>LCST</td>
<td>[Tf-Val]: ca. 45</td>
<td>50 : 50$^f$ (by weight)</td>
<td>95</td>
</tr>
<tr>
<td>14</td>
<td>[P$_{444}$$^e$][Mal]</td>
<td>Water</td>
<td>LCST</td>
<td>22</td>
<td>20 : 1</td>
<td>108</td>
</tr>
<tr>
<td>15</td>
<td>[C$_4$ mim][FeCl$_3$]</td>
<td>Water</td>
<td>LCST</td>
<td>&lt;df&gt;</td>
<td>&lt;df&gt;</td>
<td>114</td>
</tr>
<tr>
<td>16</td>
<td>[P$_{444}$$^e$][CF-COO]</td>
<td>Water</td>
<td>LCST</td>
<td>29</td>
<td>37 : 1</td>
<td>96</td>
</tr>
<tr>
<td>17</td>
<td>[P$_{444}$$^e$][2,4,6-alkyl-benzencesulfonate]</td>
<td>Water</td>
<td>LCST</td>
<td>[Tos]: 53</td>
<td>[Tos]: 44 : 1</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>[N$_{444}$$^e$][TMBS]</td>
<td>Water</td>
<td>LCST</td>
<td>53</td>
<td>47 : 1</td>
<td>96</td>
</tr>
<tr>
<td>19</td>
<td>[P$_{444}$$^e$][Br]</td>
<td>Water</td>
<td>LCST</td>
<td>24</td>
<td>14 : 1</td>
<td>96</td>
</tr>
<tr>
<td>20</td>
<td>[P$_{444}$$^e$]CH$_3$SO$<em>3$ + [P$</em>{444}$$^e$][CF-COO]</td>
<td>Water</td>
<td>LCST</td>
<td>Increasing upon increasing fraction of [P$_{444}$$^e$]CH$_3$SO$_3$</td>
<td>&lt;df&gt;</td>
<td>96</td>
</tr>
<tr>
<td>21</td>
<td>[P$_{444}$$^e$][BzIm]</td>
<td>n = 4, 8 Water</td>
<td>LCST</td>
<td>n = 4: 4, 8</td>
<td>n = 8: 72 : 1$^e$</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>[P$_{444}$$^e$][Sal]</td>
<td>Water</td>
<td>LCST</td>
<td>30</td>
<td>50 : 50$^f$ (by weight)</td>
<td>116</td>
</tr>
<tr>
<td>Table 1 continued</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>[P&lt;sub&gt;n&lt;/sub&gt;666n][EtO]HPO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Water</td>
<td>LCST</td>
<td>n = 6; 33, n = 8; 15</td>
<td>50 : 1&lt;sup&gt;e&lt;/sup&gt;</td>
<td>117</td>
</tr>
<tr>
<td>24</td>
<td>[P8C2P]&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Water</td>
<td>LCST</td>
<td>11</td>
<td>35 : 1&lt;sup&gt;e&lt;/sup&gt;</td>
<td>118</td>
</tr>
<tr>
<td>25</td>
<td>[P&lt;sub&gt;n&lt;/sub&gt;4444][SS]</td>
<td>Water</td>
<td>LCST</td>
<td>33</td>
<td>49 : 1</td>
<td>119</td>
</tr>
<tr>
<td>26</td>
<td>[P&lt;sub&gt;n&lt;/sub&gt;666n][MC3S]</td>
<td>Water</td>
<td>LCST</td>
<td>35</td>
<td>50 : 50&lt;sup&gt;e&lt;/sup&gt; (by weight)</td>
<td>120</td>
</tr>
<tr>
<td>27</td>
<td>[C&lt;sub&gt;n&lt;/sub&gt;mim][Tf&lt;sub&gt;n&lt;/sub&gt;N] + [C&lt;sub&gt;n&lt;/sub&gt;mim][Tf&lt;sub&gt;n&lt;/sub&gt;N]</td>
<td>Chloroform</td>
<td>UCST and LCST</td>
<td>UCST; 32 – 97, LCST; −13 – 32, 97 –</td>
<td>117</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>[C&lt;sub&gt;n&lt;/sub&gt;mim][Tf&lt;sub&gt;n&lt;/sub&gt;N]</td>
<td>Benzene</td>
<td>UCST and LCST</td>
<td>UCST; 45</td>
<td>55 : 1</td>
<td>117</td>
</tr>
<tr>
<td>29</td>
<td>[N&lt;sub&gt;n&lt;/sub&gt;4444]Br</td>
<td>Toluene</td>
<td>LCST</td>
<td>25 + 100</td>
<td>36 : 1 (0.1 MPa)</td>
<td>99</td>
</tr>
<tr>
<td>30</td>
<td>[N&lt;sub&gt;n12204&lt;/sub&gt;][Tf&lt;sub&gt;n&lt;/sub&gt;N]</td>
<td>Various ethers</td>
<td>LCST</td>
<td></td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>31</td>
<td>[C&lt;sub&gt;n&lt;/sub&gt;mim]PF&lt;sub&gt;6&lt;/sub&gt;</td>
<td>Trifluoromethane</td>
<td>LCST</td>
<td></td>
<td></td>
<td>101</td>
</tr>
<tr>
<td>32</td>
<td>[C&lt;sub&gt;n&lt;/sub&gt;mim][I] + 1,4-dipropoxypillar[5]arene (DPP5)</td>
<td>Chloroform</td>
<td>LCST</td>
<td>50</td>
<td>IL : DPP5 = 5 : 1 (IL conc.: 0.27 M in chloroform&lt;sup&gt;e&lt;/sup&gt;)</td>
<td>102</td>
</tr>
</tbody>
</table>

* Although these organic salts do not suit the definition of ILs, it is of significance to mention here because of their structural analogy to ILs; <sup>a</sup> Phase transition temperature; <sup>b</sup> At critical composition; <sup>c</sup> Not available; <sup>d</sup> Critical composition was not observed, or not described.
1.3.2 Required factor for ionic liquids to show LCST-type phase transition

Author’s group firstly appointed amino acids and/or amino acid derivatives as a component anion of ILs.\textsuperscript{14,95,121} When some amino acid derivatives introduced a trifluoromethanesulfonyl group on the amino reside were coupled with tetra-\textit{n}-butylphosphonium cation, prepared ILs showed interesting phase behavior after mixing with water.\textsuperscript{95} This was a first report of IL/water mixture to show LCST-type phase transition, which underwent phase separation upon heating and became homogeneous phase again upon cooling (Figure 1-6). Soon afterwards, author’s group prepared tetra-\textit{n}-butylphosphonium based IL with maleate anion to show LCST-type phase transition with water.\textsuperscript{108} Since this phase transition was reversibly controlled by the small temperature change, LCST-type phase transition of IL/water mixtures would be expected as various applications, including biopolymer separation and purification technology.\textsuperscript{122,123} Even though some IL/water were found to show LCST-type phase transition, there was no comprehensive study for analyzing required factor for ILs to show that from a structural design point of view.

Accordingly the author’s group moved on to analyze required factor for this type of phase transition. Phase transition temperature ($T_c$) of tetrabutylphosphonium $N$-trifluoromethanesulfonlyphenylalanine ([P$_{4444}$][Tf-Phe]) was 16°C after mixing with an equal weight of water. When the alkyl chain on the side chain was shortened from [P$_{4444}$][Tf-Phe] to [P$_{4444}$][Tf-Val], $T_c$ value decreased (Table 1-1 entry 13).\textsuperscript{95} which clearly indicates that hydrophobicity of the component ions influences LCST-type phase behavior with water. In term of cation structure, \textit{n}-alkylphosphonium cations were considered sufficient candidate to study how hydrophobicity of component ions impact on LCST-behavior with water. Based on these previous facts, several phosphonium based ILs composed of anions having different hydrophobicity were synthesized. These prepared ILs were mixed with an equal weight of water (50wt%), cooled to 0°C, and then gradually heated to 70°C; an increase in turbidity was used as an indication of an LCST-type transition. Meanwhile, IL/water mixtures that showed no phase transition allowed for the ILs to be classified as hydrophilic or hydrophobic appropriately.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure1-6.png}
\caption{Visual appearance of LCST-type phase behavior.}
\end{figure}
Table 1-2 shows a series of ions ordered according to this phase behavior; it clearly suggests that the hydrophobicity of both the cation and anion governs phase behavior. Interestingly, LCST-type transitions seem to occur in ILs that are on the border between being hydrophilic and hydrophobic. In other words, ILs having less than a threshold hydrophobicity have an opportunity to undergo LCST-type phase transition with water. LCST-type phase behavior is also observed in ILs formed from a less hydrophobic cation and a more hydrophobic anion, or from a more hydrophobic cation and a less hydrophobic anion (Table 1-1 entry 15, 21, 22).\textsuperscript{114,115,116} Again, because it is so difficult to estimate total hydrophobicity, it is hard to determine when a particular IL will show LCST-type behavior in water without empirical testing. For example, a series of [P\textsubscript{5555}]\textsuperscript{+}-based ILs showed no such behavior (Table 1-2). Estimation of total hydrophobicity of both cation and anion is one of major challenges for adequately designing ILs to show LCST-type phase transition with water.

In an attempt to quantify the necessary range of hydrophobicity, the amount of dissolved water in the separated IL-rich phase was evaluated at 60 °C, and calculated into the number of water molecules per an ion pair (hydrophilicity index; HI).\textsuperscript{40} HI also depends strongly on the hydrophobicity of the component ions. Less hydrophobic ions lead to higher HI values; for example, [P\textsubscript{5555}][Tf\textsubscript{2}N] was classified as hydrophobic, given its HI of approximately 0.16 (Table 1-3). While the calculated HI values ranged fairly widely, none exceeded 6. However, a

Table 1-2 Phase behavior of ILs after mixing with an equal weight of water at temperature from 0°C to 70°C.

<table>
<thead>
<tr>
<th>Hydrophobicity of cations</th>
<th>[N\textsubscript{4444}]\textsuperscript{+}</th>
<th>[P\textsubscript{4444}]\textsuperscript{+}</th>
<th>[P\textsubscript{4448}]\textsuperscript{+}</th>
<th>[P\textsubscript{5555}]\textsuperscript{+}</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH\textsubscript{3}SO\textsubscript{3}\textsuperscript{−}</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Cl\textsuperscript{−}</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>×</td>
</tr>
<tr>
<td>Br\textsuperscript{−}</td>
<td>○</td>
<td>○</td>
<td>LCST</td>
<td>×</td>
</tr>
<tr>
<td>NO\textsubscript{3}\textsuperscript{−}</td>
<td>○</td>
<td>○</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>*[BzSO\textsubscript{3}]\textsuperscript{−}</td>
<td>○</td>
<td>○</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>*[TsO]\textsuperscript{−}</td>
<td>○</td>
<td>LCST</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>*[DMBS]\textsuperscript{−}</td>
<td>○</td>
<td>LCST</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>CF\textsubscript{3}COO\textsuperscript{−}</td>
<td>○</td>
<td>LCST</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>*[TMBS]\textsuperscript{−}</td>
<td>LCST</td>
<td>LCST</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>CF\textsubscript{3}SO\textsubscript{3}\textsuperscript{−}</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>BF\textsubscript{4}\textsuperscript{−}</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>*[Tf\textsubscript{2}N]\textsuperscript{−}</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
</tbody>
</table>

○: miscible with water, ×: scarcely miscible with water.
Chapter 1

Table 1-3 Hydrophilicity index (HI) of several ILs shown in Table 1-2.

<table>
<thead>
<tr>
<th>Hydrophobicity of cations</th>
<th>CH$_3$SO$_3^-$</th>
<th>[P$_{4444}$]$^+$</th>
<th>[P$_{4448}$]$^+$</th>
<th>[P$_{5555}$]$^+$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl$^-$</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>5.3±0.6</td>
</tr>
<tr>
<td>Br$^-$</td>
<td>○</td>
<td>○</td>
<td>6.7±0.3</td>
<td>4.3±0.4</td>
</tr>
<tr>
<td>NO$_3^-$</td>
<td>○</td>
<td>○</td>
<td>2.9±0.1</td>
<td>2.1±0.2</td>
</tr>
<tr>
<td>*[BzSO$_3$]$^-$</td>
<td>○</td>
<td>○</td>
<td>5.0±0.2</td>
<td>4.0±0.4</td>
</tr>
<tr>
<td>*[TsO]$^-$</td>
<td>○</td>
<td>18.8±0.7</td>
<td>4.7±0.2</td>
<td>3.9±0.1</td>
</tr>
<tr>
<td>*[DMBS]$^-$</td>
<td>○</td>
<td>8.9±0.4</td>
<td>4.4±0.5</td>
<td>3.6±0.1</td>
</tr>
<tr>
<td>CF$_3$COO$^-$</td>
<td>○</td>
<td>9.0±0.6</td>
<td>4.6±0.1</td>
<td>3.6±0.1</td>
</tr>
<tr>
<td>*[TMBS]$^-$</td>
<td>15.9±0.2</td>
<td>8.1±0.3</td>
<td>4.1±0.1</td>
<td>3.2±0.1</td>
</tr>
<tr>
<td>CF$_3$SO$_3^-$</td>
<td>—</td>
<td>—</td>
<td>0.71±0.02</td>
<td>0.45±0.05</td>
</tr>
<tr>
<td>BF$_4^-$</td>
<td>—</td>
<td>—</td>
<td>0.61±0.03</td>
<td>—</td>
</tr>
<tr>
<td>*[TF$_2$N]$^-$</td>
<td>—</td>
<td>—</td>
<td>0.21±0.03</td>
<td>0.16±0.01</td>
</tr>
</tbody>
</table>

○: miscible with water, —: solid at 60°.

A large amount of water remains in the IL phase after LCST separation; in consideration of this and the correlation between the observed phase behavior and HI values, it was determined that only ILs with HIs above 7 could undergo LCST-type transitions.

Based on these values, the author’s group successfully synthesized several ILs containing polymerizable groups on the constituent ions that showed LCST-type behavior. Free radical polymerization of the monomers resulted in the preparation of a novel polyelectrolyte to show LCST-type phase change in water.\textsuperscript{124}
1.3.3 Analysis of LCST-type phase behavior of ionic liquid/water mixture

Ever since some ILs found to show LCST-type phase transition after mixing with water, many types of ILs have been designed and synthesized based on the adequate range of hydrophobicity of component ions. However, there had been little research investigating LCST-type dynamic phase transitions of IL/water mixtures.

Gao and co-worker investigated the temperature driven aggregate behavior of tetrabutylphosphonium trifluoroacetate ([P$_{4444}$]CF$_3$COO)/water mixtures upon heating. According to dynamic light scattering (DLS), UV-vis spectrometry analysis, and freeze-fracture transmission electron microscopy (FF-TEM), [P$_{4444}$]CF$_3$COO showed long-living aggregate in water without using any surfactants, which behaves like the swelling behavior consistent with a microemulsion. The aggregate size was enlarged during the heating process, and remarkable increase in aggregate size was observed at the temperature near the $T_c$. When the temperature of solution was additionally elevated above the $T_c$ value, liquid-liquid biphasic system composed of IL-rich phase and water-rich phase was formed. This indicates that [P$_{4444}$]CF$_3$COO/water mixtures undergo a mesoscopic phase change in which water molecules squeeze out of the IL-rich phase, leading to the formation of microemulsion-like aggregates toward the macroscopic phase separation (Figure 1-7).

![Figure 1-7](image)

**Figure 1-7** Schematic model of the aggregate behavior of [P$_{4444}$]CF$_3$COO in water at different temperatures

Wu and co-worker performed two-dimensional infrared correlation spectroscopy (2D IR) to analyze the dynamic phase transition of tetrabutylphosphonium styrenesulfonate ([P$_{4444}$][SS]) and its polymer (poly[P$_{4444}$][SS]) after mixing with water. 2D IR is very useful method in determining sequential order of different chemical groups through the analysis of both synchronous and asynchronous spectra. A few typical vibration modes were observed in monomer [P$_{4444}$][SS]/water mixtures (e.g., C-H group of [P$_{4444}$]$^+$ cation and SO$_3^-$ group of [SS]$^-$ anion). Synchronous correlation of these vibrations suggested heating to near the $T_c$ would first result in the C-H groups responding to aggregation, after which the hydrogen bonds
between water and the SO$_3^-$ groups would begin to break. Of the poly[P$_{4444}$][SS]/water mixtures, however, it’s SO$_3^-$ groups of polymerised anions that were primarily wrapped into the inside of aggregated globules, subsequently [P$_{4444}$]$^+$ cations would distribute at the surround of globules in the PIL aqueous solution. Additional measurements using differential scanning calorimetry (DSC), NMR, and FT-IR revealed that synergetic variations of the [P$_{4444}$]$^+$ cations and [SS]$^-$ anions in the [P$_{4444}$][SS]/water mixture resulted in randomly aggregated globules during heating. However, in the polymer mixture, the repeated [SS]$^-$ anion units were primarily wrapped inside the aggregated globules, after which the [P$_{4444}$]$^+$ cations distributed around the globules after phase transition (Figure 1-8).

**Figure 1-8** Schematic illustration of the dynamic phase transition mechanism of [P$_{4444}$][SS] and poly[P$_{4444}$][SS] aqueous solutions during the heating and cooling processes.
### 1.3.4 Phase transition temperature of IL/water mixture to show LCST

Some IL/water mixture found to show LCST-type phase transition and their properties have been characterized. Phase transition temperature is one of the most important property to study the temperature driven phase transition. Since the miscibility in LCST mixtures decreases upon heating, the phase transition temperature should partly depend on the mole fraction in addition to the ion structure. Figure 1-9 shows phase diagram for the \([P_{4444}]^{\cdot}[2,4,6\text{-alkyl-benzenesulfonat}]\)/water mixture (Table 1-1 entry 17). As expected, the data, which curves in a typical concave fashion, is dependent on both of these points, with the lowest critical temperature near a ratio of 0.97. Meanwhile, introducing only a methyl group to the benzenesulfonate anion drops the transition temperature by 10-15 °C. In other words, it is very difficult to finely control phase transition temperature by only changing ion structure. Further approaches are needed to fine tune this phase transition behavior further if it is to be efficiently and practically utilized.

![Phase diagram for a series of tetrabutylphosphonium ([P4444]) based ILs after mixing with certain amount of water.](image)

**Figure 1-9** Phase diagram for a series of tetrabutylphosphonium ([P4444]) based ILs after mixing with certain amount of water.
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1.4 Aims of this study

The aim of this thesis is to construct a more precise method by which to control this feature of phase transition temperature. While ion design is clearly the first step in this process, it provides only stepwise changes. Mixing ILs is a practical method by which to control properties gradually and arbitrarily and to expand on the potential of this system.

The unique properties of IL/water mixtures are likely to make them useful media for many biological and chemical processes in the near future, but it is first necessary to optimize these mixtures for practical use. The phase behavior of IL/water mixtures strongly depends on the hydrophobicity of the component ions, with most mixtures undergoing static phase behavior regardless of temperature. The author’s group first reported unique mixtures in which separated phases were formed upon heating. We have designed many ILs that exhibit LCST-type phase transition with water, and have found this feature dependent on a particular hydrophobicity threshold. Applying this feature on a broader scale will require finer temperature control, among other improved properties. This in turn can be accomplished by mixing two or more ILs with different physicochemical properties. By finely controlling phase separation temperature, IL/water mixtures may eventually be usable in the design of functional interfaces in many scientific and technological fields.

1.5 Reference


M. G. Freire, C. M. S. Neves, I. M. Marrucho, J. N. Canongia Lopes, L. P. N. Rebelo and J. A. P.

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Chapter 2

Control of LCST-type phase behavior with water by mixing different amino acid ionic liquids
2.1 Introduction

ILs composed in part of [Tf$_2$N]$^-$ or [PF$_6$]$^-$ anions are hydrophobic and provide stable liquid-liquid biphasic systems in water.\cite{1} These systems have been developed to the point where they can be used in reactions, purifications, and extractions, among other processes. Unfortunately, hydrophobic ILs can only dissolve or partition compounds with relatively low polarity; high polar materials can only be used in the IL-rich phase of such biphasic systems by using additives. This problem highlights a growing need for polar ILs that can still partition with water. For instance, extraction of cellulose from biomass and hydrolysis of the extracted cellulose into oligosaccharide or glucose in ILs are some of important biological processes.\cite{2} For that reason, design of thus IL/water mixtures is significant challenge for development in the practical processes.

As described in Chapter 1, phase behavior strongly depends on the total hydrophobicity of both the cations and anions. The author’s group previously reported that ILs with a hydrophobicity below a certain threshold show LCST-type phase transitions after mixing with water (Figure 2-1), in which a homogeneously mixed solution was split off to form separated phases upon heating.\cite{3} Phase transition temperature ($T_c$) also depended on the hydrophobicity of component ions, which higher value of $T_c$ was observed in more hydrophilic ILs to show LCST-type phase transition with water. In addition, higher water content of the separated IL rich phase was found in the mixtures showing LCST compared with hydrophobic IL/water mixtures. These data indicated that the hydration state of ILs is also important factor that determines the hydrophobicity of IL/water mixtures.

![Figure 2-1](image)

**Figure 2-1** Correlation between hydrophobicity of component ions and phase behavior of resulting ILs after mixing with water.
Generally, polar ILs are hydrophilic and water miscible. Mixing hydrophilic ILs with hydrophobic ILs is simple way to control hydrophobicity toward the LCST-type phase change. However this way results in the lowering the polarity of ILs. Another possibility is dehydration of ions after mixing different hydrophilic ILs, which means interaction between different ions is formed to construct two phase aqueous system. In chapter 2, we attempt to achieve the dehydration of ions by mixing two different polar and hydrophilic ILs having hydrogen bonding donor or accepter, which should lead total hydrophobicity of ILs to gain without lowering polarity (Figure 2-1).
2.2 Experiments

*Preparation of ILs*

Trihexyl-\(n\)-octylphosphonium L-lysinate ([P\(_{6668}\)]\{Lys\}), trihexyl-\(n\)-octylphosphonium L-aspartate ([P\(_{6668}\)]\{Asp\}), trihexyl-\(n\)-octylphosphonium L-serinate ([P\(_{6668}\)]\{Ser\}), trihexyl-\(n\)-octylphosphonium L-alaninate ([P\(_{6668}\)]\{Ala\}), and trihexyl-\(n\)-octylphosphonium L-glutamate ([P\(_{6668}\)]\{Glu\}) were synthesised by neutralised trihexyl-\(n\)-octylphosphonium hydroxide ([P\(_{6668}\)]OH) and corresponding amino acids. [P\(_{6668}\)]OH was prepared by passing trihexyl-\(n\)-octylphosphonium bromide ([P\(_{6668}\)]Br) through a column filled with anion exchange resin (Amberlite IRN 78) in methanol-water mixture. [P\(_{6668}\)]Br was obtained by refluxing trihexyolphosphate (TCI: T1005) with octylbromide (TCI: 1-Bromoocotane) in hexane under dry nitrogen at 80 °C for 48 h. All amino acid ionic liquids (AAILs) were dried *in vacuo* for at least 24 h at 40 °C before experiments. The structures of these AAILs were confirmed by \(^1\)H NMR.

**[P\(_{6668}\)]\{Lys\} Trihexyl-\(n\)-octylphosphonium L-lysinate**

\(\delta_H\) (400 MHz; CDCl\(_3\); \(\delta/\text{ppm relative to TMS}\)): 0.82-0.96 (12H, m, CH\(_2\)CH\(_3\)), 1.20-1.37 (20H, m, CH\(_3\)CH\(_2\)CH\(_3\) and (CH\(_2\))\(_3\)CH\(_2\)CH\(_2\)(CH\(_2\))CH\(_3\)), 1.37-1.60 (20H, m, P-CH\(_2\)CH\(_2\)CH\(_2\), NH\(_2\)-CH\(_2\)CH\(_2\)CH\(_2\)), 1.60-1.71 (1H, m C-CH\(_3\)H-CH\(_2\)), 1.75-1.88 (1H, m C-CH\(_3\)H-CH\(_2\)), 2.36-2.52 (8H, m, P-CH\(_3\)), 2.62-2.70 (2H, m, NH\(_2\)-CH\(_2\)), 3.12-3.17 (1H, m, C-H).

**[P\(_{6668}\)]\{Asp\} Trihexyl-\(n\)-octylphosphonium L-aspartate**

\(\delta_H\) (400 MHz; CDCl\(_3\); \(\delta/\text{ppm relative to TMS}\)): 0.80-0.99 (12H, m, CH\(_2\)CH\(_3\)), 1.20-1.40 (20H, m, CH\(_3\)CH\(_2\)CH\(_3\) and (CH\(_2\))\(_3\)CH\(_2\)CH\(_2\)(CH\(_2\))CH\(_3\)), 1.41-1.61 (16H, m, P-CH\(_2\)CH\(_2\)CH\(_2\)), 2.22-2.39 (8H, m, P-CH\(_3\)), 2.52-2.61 (1H, m COOH-CH\(_2\)), 2.68-2.78 (1H, m COOH-CH\(_2\)), 3.58-3.66 (1H, m, C-H).

**[P\(_{6668}\)]\{Ser\} Trihexyl-\(n\)-octylphosphonium L-serinate**

\(\delta_H\) (400 MHz; CDCl\(_3\); \(\delta/\text{ppm relative to TMS}\)): 0.84-0.96 (12H, m, CH\(_2\)CH\(_3\)), 1.22-1.39 (20H, m, CH\(_3\)CH\(_2\)CH\(_3\) and (CH\(_2\))\(_3\)CH\(_2\)CH\(_2\)(CH\(_2\))CH\(_3\)), 1.42-1.61 (16H, m, P-CH\(_2\)CH\(_2\)CH\(_2\)), 2.30-2.43 (8H, m, P-CH\(_3\)), 2.22-2.29 (1H, m OH-CH\(_2\)), 3.52-3.45 (1H, m OH-CH\(_2\)), 3.65-3.73 (1H, m, C-H).

**[P\(_{6668}\)]\{Ala\} Trihexyl-\(n\)-octylphosphonium L-alanate**

\(\delta_H\) (400 MHz; CDCl\(_3\); \(\delta/\text{ppm relative to TMS}\)): 0.82-0.95 (12H, m, CH\(_2\)CH\(_3\)), 1.22-1.38 (23H, m, CH\(_3\)CH\(_2\)CH\(_3\), (CH\(_2\))\(_3\)CH\(_2\)CH\(_2\)(CH\(_2\))CH\(_3\) and C-CH\(_3\)), 1.42-1.61 (16H, m, P-CH\(_2\)CH\(_2\)CH\(_2\)),
Chapter 2

2.36–2.49 (8H, m, P-CH₂), 3.24–3.32 (1H, m, C-H).

\([P_{6668}]\text{[Glu] Trihexyl-n-octylphosphonium L-glutamate}\)

\(\delta_H (400 \text{ MHz}; \text{CDCl}_3; \delta/\text{ppm relative to TMS}): 0.81-0.95 (12H, m, CH₃), 1.19-1.39 (20H, m, CH₂CH₂CH₃ and (CH₂)₃CH₂CH₂(CH₂)₂CH₃), 1.42-1.63 (16H, m, P-CH₂CH₂CH₂), 1.97-2.21 (2H, m COOH-CH₂CH₃), 2.25–2.39 (8H, m, P-CH₂), 2.39-2.59 (2H, m, COOH-CH₂CH₂), 3.48-3.56 (1H, m, C-H).

\(^{13}\text{C NMR measurements of } [P_{6668}]_i[Lys]_n[Glu]_1/n\text{/water mixtures}\)

\(^{13}\text{C NMR spectroscopy was performed on } [P_{6668}]_i[Lys]_n[Glu]_1/n\text{/water using a double NMR tube technique at 25 °C. } [P_{6668}]_i[Lys]_n\text{ and } [P_{6668}]_i[Glu]\text{ were individually mixed with pure water to reach a concentration of 0.92 mol·kg}^{-1}, \text{ after which they were mixed to the desired molar ratio. Since mixtures of pure water and } [P_{6668}]_i[Lys]_0.15[Glu]_0.85, [P_{6668}]_i[Lys]_0.25[Glu]_0.75, [P_{6668}]_i[Lys]_0.33[Glu]_0.67, \text{ or } [P_{6668}]_i[Lys]_0.5[Glu]_0.5\text{ were phase separation at 25°C, only separated AAIL rich phase (upper phase) was put into the inner tube, and the outer tube was filled with deuterated chloroform containing tetramethylsilane (TMS) as an internal standard. } ^{13}\text{C NMR spectra were obtained by using JEIL JNM-ECA500.}\)

\(\text{Estimation of Kamlet-Taft parameters}\)

The Kamlet-Taft parameters of a series of AAILs and aqueous mixture were measured as follows protocol. Two different solvatochromic probe dyes, \(N,N\text{-diethyl-4-nitroaniline}\) and 4-nitroaniline, were mixed with aqueous AAILs and gently stirred into the solution for this purpose. A dry methanol solution was added to the neat AAILs and was then removed by vacuum drying at 40 °C. To prevent dye aggregation, the dye concentration in each sample was set as low as possible while still being to provide an absorbance greater than 0.1.

These dye solutions were set in quartz cells with an optical path length of 0.1 mm. The temperature of the quartz cell was kept at 25 °C. The maximum absorption wavelengths (\(\lambda_{\text{max}}\)) were then determined, after which the Kamlet-Taft parameters of \(\beta\) and dipolarity (\(\pi^*\)) were calculated from the following equations:

\[
\beta = (1.035\delta_{(N,N-diethyl-4-nitroaniline)} + 2.64 - \delta_{(4-nitroaniline)})/2.80
\]

\[
\pi^* = 0.314(27.52 - \delta_{(N,N-diethyl-4-nitroaniline)})
\]
2.3 Unique phase behavior of mixtures of amino acid ionic liquids after adding with water

Amino acid ionic liquids (AAILs) were selected because they satisfied the requirements described above and because of the structural diversity that they offer. Amino acid anions are polar and hydrophilic, so that [P6668][Lys] and [P6668][Asp] are both hydrophilic and underwent homogeneous phase with water. When aqueous solution of [P6668][Lys] and [P6668][Asp] were mixed until they became equimolar, the resulting mixture got muddy. After coming to stable equilibrium, the [P6668][Lys]₀.₅[Asp]₀.₅/water mixture formed a clear liquid-liquid biphasic system, and the AAILs rich phase floated on the top of the water rich phase. (Figure 2-2). Furthermore, this mixture formed a homogeneous solution when cooled, confirming the formation of a successful LCST-type system. The [P6668][Lys] has a dissociated carboxylate residue on its α-carbon and an additional amino group on the side chain, while the [Asp]⁻ ion contains an additional carboxylate group on the side chain instead. Author’s group previously reported that the mixture of [C₂mim][Lys] and [C₂mim][Asp] shows higher dipolarity than that of each AAIL due to hydrogen bonding interaction between the amino group of [Lys]⁻ and the carboxyl group of [Asp]⁻ on their side chains.

Phase behavior of [P6668]₁[Lys]₀.₅[Asp]₀.₅/water mixture was attributed to similar interaction between the side chains of [Asp]⁻ and [Lys]⁻ toward dehydration of the AAILs in the resulting solution.

Figure 2-2 Phase behaviour with water for [P6668][Lys], [P6668][Asp], and their equimolar mixture at 25 °C. Concentration of ILs in all aqueous solution is 0.92 mol·kg⁻¹.
2.4 Analysis of interaction between different amino acid anions

2.4.1 Impact of combination of amino acid anion on the phase behavior with water

In order to explain the phenomenon in Figure 2.2, effect of combination of amino acid anion species on the phase behavior of AAILs/water mixtures was studied. To do this, [P_{6668}][Ser] and [P_{6668}][Ala] were synthesized, because each of them have hydroxyl and methyl groups on their terminal amino acid side chains, respectively, so that they help to investigate the relationship between anion combinations and phase behavior (Table 1). Two types of AAILs were selected from [P_{6668}][Lys], [P_{6668}][Asp], [P_{6668}][Ser] and [P_{6668}][Ala], and each AAIL aqueous solution (0.92mol·kg\(^{-1}\)) was mixed equimolarly. [P_{6668}][Ser] has hydrogen bonding ability but it is not strong enough to strengthen the hydrophobicity for showing phase separation after mixing with [P_{6668}][Asp] in an aqueous solution. Likewise, the terminal methyl group in [P_{6668}][Ala] could not hydrogen bond at all; unsurprisingly, all the mixtures formed with this AAIL were homogenous under all conditions. Present results clearly indicated that an interaction between amino and carboxyl residues played a key role for the formation of the AAIL to undergo phase separation after mixing with water through lowering hydration via competitive hydrogen bonding.

To confirm that the hydrogen bonding between side chains of amino acids was an important factor in the preparation of a biphasic system in the hydrophilic AAILs/water mixtures, [P_{6668}][Glu] was studied to be effective as well as [P_{6668}][Asp]. While [P_{6668}][Glu] was water soluble, [P_{6668}][Lys]_{0.5}[Glu]_{0.5} formed separated phases after mixing with water (Table 2.1). This result clearly demonstrates the importance of the combined amino and carboxyl groups in achieving phase separation.

### Table 2.1 Phase behavior of various AAILs mixtures after adding water. Concentration of all mixtures was 0.92mol·kg\(^{-1}\). AAIL aqueous solutions were mixed equimolarly.

<table>
<thead>
<tr>
<th>Mixture of AAILs</th>
<th>Terminal side chin of AAs</th>
<th>Phase behavior with water</th>
</tr>
</thead>
<tbody>
<tr>
<td>[P_{6668}][Lys]<em>{0.5}[Asp]</em>{0.5}</td>
<td>-NH(_2), -COOH</td>
<td>Phase separation</td>
</tr>
<tr>
<td>[P_{6668}][Lys]<em>{0.5}[Ser]</em>{0.5}</td>
<td>-NH(_2), -OH</td>
<td>Homogeneous solution</td>
</tr>
<tr>
<td>[P_{6668}][Lys]<em>{0.5}[Ala]</em>{0.5}</td>
<td>-NH(_2), -CH(_3)</td>
<td>Homogeneous solution</td>
</tr>
<tr>
<td>[P_{6668}][Asp]<em>{0.5}[Ser]</em>{0.5}</td>
<td>-COOH, -OH</td>
<td>Homogeneous solution</td>
</tr>
<tr>
<td>[P_{6668}][Asp]<em>{0.5}[Ala]</em>{0.5}</td>
<td>-COOH, -CH(_3)</td>
<td>Homogeneous solution</td>
</tr>
<tr>
<td>[P_{6668}][Ser]<em>{0.5}[Ala]</em>{0.5}</td>
<td>-OH, -CH(_3)</td>
<td>Homogeneous solution</td>
</tr>
<tr>
<td>[P_{6668}][Lys]<em>{0.5}[Glu]</em>{0.5}</td>
<td>-NH(_2), -COOH</td>
<td>Phase separation</td>
</tr>
</tbody>
</table>
2.4.2 NMR analysis of the interaction between different amino acid anions

$^{13}$C NMR was used to analyze the interaction between the amino and carboxyl residues in the $[\text{P}_{6668}]_{n}[\text{Lys}]_{n}[\text{Glu}]_{n}$/water mixture. In $[\text{P}_{6668}]_{n}[\text{Lys}]_{n}[\text{Glu}]_{n}$/water mixtures, “$n$” denoted the mol fraction of $[\text{P}_{6668}][\text{Lys}]$. In general, carboxyl groups give peaks at very low magnetic fields. In the case of $[\text{P}_{6668}][\text{Glu}]$, they are found as two signals at approximately 175 and 181 ppm (Figure 2-3 A; $n = 0$). As $[\text{P}_{6668}][\text{Lys}]$ content increased, signals shifted to a lower magnetic field, indicating dissociation of the carboxyl residue due to hydrogen bonding. Meanwhile, the signal of the carbon adjoining the side chain of $[\text{P}_{6668}][\text{Lys}]$ indicates the condition of the amino residue; the signal for just $[\text{P}_{6668}][\text{Lys}]$ in water was seen at approximately 41.0 ppm (Figure 2-3 B; $n = 1.00$), though it shifted to 39.5 ppm as the $[\text{P}_{6668}][\text{Glu}]$ content increased. Considering these data of Figure 2-3 with Table 2-1, it is strongly suggested that interaction between amino and carboxyl residues is driving force to show phase separation after mixing with water due to dehydration of anions.

![Figure 2-3](image-url)  

**Figure 2-3** $^{13}$C NMR spectra of $[\text{P}_{6668}]_{n}[\text{Lys}]_{n}[\text{Glu}]_{n}$/water mixtures at various molar ratio at 25 °C. (A) Chemical shifts for carboxyl groups on $[\text{P}_{6668}][\text{Lys}]$ and $[\text{P}_{6668}][\text{Glu}]$ in the range of 174-183 ppm. (B) Chemical shifts for adjoining carbon of side chain of amino group on $[\text{P}_{6668}][\text{Lys}]$ in the range of 39.0-42.0 ppm. The spectra ($n = 0.10$-$0.50$) in (B) are shown as a magnified view.
2.5 Phase diagram of amino acid ionic liquid/water mixtures with different composition

Figure 2-4 describes the concentration dependence of [P_6668][Lys] on the phase behavior of the [P_6668][Lys][Asp]_{1-n}/water and [P_6668][Lys][Glu]_{1-n}/water mixtures. These mixtures were placed in an ice water bath until they reached 0 °C, and then heated gradually to 70 °C. $T_c$ for LCST was determined as the cloud point during heating by naked eyes. As shown in Figure 2-4 A, the [P_6668][Lys][Asp]_{1-n}/water mixtures were homogeneous for small mole fractions of [P_6668][Lys], reaching LCST-type phase transition for $n = 0.15–0.67$. The phase transition temperature was also dependent on the mole fraction of [P_6668][Lys]; the [P_6668][Lys]_{0.33}[Asp]_{0.67}/water mixture had the lowest phase transition temperature, at 6 °C.

A similar phase diagram was generated for the [P_6668][Lys][Glu]_{1-n}/water mixtures (Figure 2-4 B). Homogenous solutions were still obtained for small amounts of [P_6668][Lys]. LCST-type phase transition was observed in [P_6668][Lys]_{0.15}[Glu]_{0.85}/water mixture at 19°C. Subsequently [P_6668][Lys][Glu]_{1-n}/water show phase separation regardless of temperature over a “n” range of 0.25-0.50. An LCST-type phase transition was found again in the [P_6668][Lys]_{0.69}[Glu]_{0.31}/water mixture. Conclusively homogeneous solution was shown in the [P_6668][Lys][Glu]_{1-n}/water mixture when the mole fraction of [P_6668][Lys] was in between 0.75 and 1.0.

To investigate mixtures of AAIL to show phase separation regardless temperature in more detail, water contents of separated AAIL-rich phase were measured. To do so, the [P_6668][Lys][Asp]_{1-n}/water mixtures ($n = 0.15–0.50$) were placed in a water bath at 30 °C until they came to a stable liquid-liquid equilibrium, at which point the water content of the AAIL-rich phase was determined by the Karl-Fischer titration method. Water content of
AAIL-rich phase in [P6668][Lys]_n[Glu]_1/ω-water mixtures (n = 0.25-0.50) was lower than that of mixture showing LCST-type phase behavior (Table 2-2). This tendency was consistent with our previous study. The lowest water content was observed in the [P6668][Lys]_{0.33}[Glu]_{0.67}/ω-water mixtures. This is the same mole fraction that gave the lowest phase transition temperature for the [Asp] trials, indicating that mol fraction of [P6668][Lys] to give the most hydrophobic one was 0.33 but not 0.50. These results suggest that hydrogen bonding is not the only factor and other factors may partly affect the phase behavior of the [P6668][Lys][Asp]_1/ω-water and [P6668][Lys][Asp]_1/ω-water mixtures.

Table 2-2 Phase behavior of [P6668][Lys]_[Glu]_[ω]/water mixtures at various proportion. Concentration of AAILs in aqueous solution is 0.92 mol·kg⁻¹.

<table>
<thead>
<tr>
<th>mol fraction of [P6668][Lys] (n)</th>
<th>0</th>
<th>0.10</th>
<th>0.15</th>
<th>0.25</th>
<th>0.33</th>
<th>0.50</th>
<th>0.67</th>
<th>0.75</th>
<th>1.0</th>
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<tbody>
<tr>
<td>phase behavior</td>
<td></td>
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<tr>
<td></td>
<td>H¹</td>
<td>H¹</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LCST³ (Tc = 19 °C)</td>
<td>S²</td>
<td>S²</td>
<td>S²</td>
<td>S²</td>
<td>S²</td>
<td>S²</td>
<td>S²</td>
<td>S²</td>
</tr>
<tr>
<td></td>
<td>LCST³ (Tc = 39 °C)</td>
<td>H¹</td>
<td>H¹</td>
<td>H¹</td>
<td>H¹</td>
<td>H¹</td>
<td>H¹</td>
<td>H¹</td>
<td>H¹</td>
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<tr>
<td>WC (wt%)</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>36.8</td>
<td>30.4</td>
<td>27.2</td>
<td>35.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*¹ Homogeneous solution at temperature in the range from 0 °C to 70 °C.
*² Phase separation at temperature in the range from 0 °C to 70 °C.
*³ Mixture showed lower critical solution temperature (LCST)-type phase transition, and *⁴ Tc represents phase separation temperature.
*⁴ Water content of separated AAIL rich phase at 30°C.
2.6 Polarity of amino acid ionic liquid rich phase after phase separation

We have demonstrated that LCST-type phase transition of IL/water mixture could be prepared by mixing hydrophilic and polar AAILs. Kamlet-Taft parameters are widely used to study the polarity of many molecular solvent as well as ILs.\(^6\) \(\beta\) and \(\pi^*\) were therefore determined using the solvatochromic probe dyes \(N,N\)-diethyl-4-nitroaniline and 4-nitroaniline. Both \([\text{P}_{6668}][\text{Lys}]\) and \([\text{P}_{6668}][\text{Asp}]\) showed strong hydrogen bonding in the anhydrous state, with \(\beta\) values of 1.28 and 1.21, respectively. Since Kamlet-Taft parameters are generally determined at 25 °C, \([\text{P}_{6668}][\text{Glu}]\) could not be compared due to its high \(T_m\).

Table 2-2 summarizes the water content and Kamlet-Taft parameters for the separated AAIL phases. The \(\beta\) value of the separated AAIL phase in the \([\text{P}_{6668}][\text{Lys}]_{0.33}[\text{Asp}]_{0.67}/\text{water}\) biphasic system was 0.67, which is much larger than that of conventional fluorinated hydrophobic ILs. Compared with \([\text{P}_{6668}][\text{Lys}]_{0.33}[\text{Asp}]_{0.67}/\text{water}\) mixture, higher \(\beta\) value was observed in separated AAIL rich phase of \([\text{P}_{6668}][\text{Lys}]_{0.33}[\text{Glu}]_{0.67}/\text{water}\) mixture. This is consistent with the previous data that the \(\beta\) value of polar IL decreased with increasing water content. A lower water content of the separated AAIL phase had a role in to keeping the \(\beta\) value high. The \([\text{P}_{6668}][\text{Lys}]_{0.33}[\text{Asp}]_{0.67}/\text{water}\) mixture underwent LCST-type phase transition, and lower water content of separated IL rich phase should be found at higher temperature.\(^3\) The water content of the separated AAIL rich phase in the \([\text{P}_{6668}][\text{Lys}]_{0.33}[\text{Asp}]_{0.67}/\text{water}\) mixture at 60 °C was lower than that at 25 °C, resulting in greater \(\beta\) value of AAIL rich phase at 60°C. These results strongly suggested that the polarity of AAIL/water biphasic systems can be tuned by selecting suitable mixing partners as well as temperature.

Table 2-3 Water content and Kamlet-Taft parameters of the AAIL-rich phase in AAILs-water biphasic systems.

<table>
<thead>
<tr>
<th>Separated AAIL rich phase</th>
<th>Temp.(°C)</th>
<th>Water content (wt%)</th>
<th>Kamlet-Taft parameters</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>[P(<em>{6668})][Lys](</em>{0.33})[Asp](_{0.67}/\text{water})</td>
<td>25</td>
<td>34.0±0.9</td>
<td>(\beta) 0.67 (\pi^*) 1.10</td>
<td></td>
</tr>
<tr>
<td>[P(<em>{6668})][Lys](</em>{0.33})[Glu](_{0.67}/\text{water})</td>
<td>25</td>
<td>32.5±0.9</td>
<td>(\beta) 0.69 (\pi^*) 1.07</td>
<td></td>
</tr>
<tr>
<td>[P(<em>{6668})][Lys](</em>{0.33})[Asp](_{0.67}/\text{water})</td>
<td>60</td>
<td>28.0±0.8</td>
<td>(\beta) 0.71 (\pi^*) 1.07</td>
<td></td>
</tr>
</tbody>
</table>
Chapter 2

2.7 Conclusion

We approached LCST-type phase transition of IL/water mixture by mixing two types of hydrophilic AAILs. Combination of AAILs with additional amino and carboxyl residues was only case to gain hydrophobicity of AAILs. This is due to the dehydration of anions via hydrogen bonding interaction between functional groups on their side chains. Overall, LCST-type phase transitions were possible using this methodology, but required careful selection of the mixing partners and ratios. Furthermore, the separated AAIL phases in these systems showed higher β values than conventional hydrophobic ILs. Present methodology is quite effective to prepare polar-polar biphasic system as well as temperature driven phase transition of IL/water mixture having adequate hydrophobicity.

2.8 Reference

Chapter 3

Zwitterion-type ionic liquid mixtures to show temperature driven phase transition with water
3.1 Introduction

IL-based aqueous biphasic systems hold great potential due to their attractive features, especially with respect to how tunable their properties can be. Through the careful design of their ion structures, we have affected unique and reversible thermoresponsive phase behavior of IL/water mixtures. These IL/water mixtures hold great potential as media for the high efficiency condensation, purification, and extraction of synthetic targets.

We previously reported that ILs with a hydrophobicity below a given threshold level undergo LCST-type phase transition after mixing with water. Additionally, the phase transition temperature \( T_c \) of these mixtures is dependent on the hydrophobicity of the component ions. However, there should be an upper limit to finely control the \( T_c \) value by only designing their component ions. In order to better control this value, we employed a mixed IL system, as discussed in Chapter 2. Though this mixing technique provides excellent property control, it also generates undesired ion pairs that sometimes adversely affect solution properties. Ion exchange in extraction and separation processes is another concern given the many useful substances, such as pharmaceuticals, perfumes, and biopolymers that could ionize in aqueous solution.

One of simple way to suppress ion exchange is through the use of IL zwitterions (ZIs) in which the cation and anion are covalently tethered. It is expected that the ion pairs are retained even in homogenous mixtures of ZIs with other compounds. While ZIs can have very similar chemical structures to ILs, there is no experimental data suggesting that the phase behavior of ZI/water mixtures could be modified in the same ways. In this chapter, we investigate what would be required for ZIs to show similar phase behavior by analyzing its relationship with hydrophobicity.
3.2 Experimental

Preparation of zwitterions

Four types of zwitterions, \(N,N,N\)-tripentyl-3-sulfonyl-1-propaneammonium (\(N_{555}C3S\)), \(N,N,N\)-trihexyl-3-sulfonyl-1-propaneammonium (\(N_{666}C3S\)), \(N,N,N\)-trioctyl-3-sulfonyl-1-propaneammonium (\(N_{888}C3S\)), and \(N,N\)-dihexyl-\(n\)-monopentyl-3-sulfonyl-1-propaneammonium (\(N_{665}C3S\)) were synthesized according to the following procedure.

Aqueous sodium hydroxide (NaOH, 2 mol) was introduced dropwise into a mixture of tetrahydrofuran (THF) and the desired alcohol (\(R_1\)-OH, 1 mol) at 0 °C. Then, benzensulfonyl chloride was added and the solution was stirred at room temperature for 4 h. After THF was removed by evaporation, the resulting thick product was extracted with dichloromethane (CCl\(_2\)H\(_2\)) and washed sequentially with pure water, a saturated aqueous solution of sodium bicarbonate, and finally with pure water again. The resulting CCl\(_2\)H\(_2\) phase was dried in vacuo to give the product \(i\) as a viscous liquid.

A THF solution of product \(i\) (1 mol), aqueous NaOH (2 mol), and dialkylamine (1.1 mol) was heated to 50 °C and kept there for 4 h. The reaction mixture was then filtered through filter paper and evaporated to remove THF. The resulting product was extracted with CCl\(_2\)H\(_2\) and washed with pure water. After removal of CCl\(_2\)H\(_2\) by evaporation, dimethylformamide (DMF) and an excess amount of acetic anhydride was added. The resulting mixture was purified by flash column chromatography on silica gel (eluent: CCl\(_2\)H\(_2\), CCl\(_2\)H\(_2\)/MeOH = 9 : 1); only the fractions with the desired molecular weight, as confirmed by mass spectrometry, were collected to yield product \(ii\).

Product \(ii\) and 1,3-propanesultone were dissolved in acetone under nitrogen. The obtained solution was stirred for 2 d at 60 °C. After acetone was removed by evaporation, the residual liquid was repeatedly washed with excess amounts of anhydrous diethyl ether. The
resulting solid was dissolved in dichloromethane and passed through a column filled with aluminum oxide. The final solution was purified by recrystallization from ethylacetate/methanol to give the final product as a white powder. The ZIs were then dried in vacuo at 60 °C for 24 h. The chemical structures of N_555C3S, N_666C3S, N_888C3S, and N_665C3S were confirmed by ^1H NMR.

N_555C3S N,N,N-Tripentyl-3-sulfonyl-1-propaneammonium
δH (400 MHz; CDCl3; δ/ppm relative to TMS): 0.93 (9H, t, J =7.02), 1.37 (12H), 1.70 (6H), 2.16 (2H), 2.92 (2H, t, J =5.83), 3.19 (6H), 3.72 (2H). Elemental analysis (%): Found: C, 61.66; H, 11.79; N, 3.92; C/N, 15.75. C_{18}H_{39}O_{3}NS calcd: C, 61.84; H, 11.25; N, 4.01; C/N, 15.43.

N_666C3S N,N,N-Trihexyl-3-sulfonyl-1-propaneammonium
δH (400 MHz; CDCl3; δ/ppm relative to TMS): 0.89 (9H, t, J =6.57), 1.33 (18H), 1.69 (6H), 2.15 (2H), 2.93 (2H, t, J =5.90), 3.16 (6H), 3.75 (2H). Elemental analysis (%): Found: C, 64.17; H, 12.17; N, 3.47; C/N, 18.49. C_{21}H_{45}O_{3}NS calcd: C, 64.40; H, 11.58; N, 3.58; C/N, 18.01.

N_888C3S N,N,N-Tryoctyl-3-sulfonyl-1-propaneammonium
δH (400 MHz; CDCl3; δ/ppm relative to TMS): 0.88 (9H, t, J =6.73), 1.30 (30H), 1.69 (6H), 2.16 (2H), 2.91 (2H, t, J =6.71), 3.18 (6H), 3.71 (2H). Elemental analysis (%): Found: C, 67.96; H, 12.41; N, 2.89; C/N, 23.54. C_{27}H_{57}O_{3}NS calcd: C, 68.16; H, 12.08; N, 2.94; C/N, 23.15.

N_665C3S N,N-dihexyl- n-monopentyl-3-sulfonyl-1-propaneammonium
δH (400 MHz; CDCl3; δ/ppm relative to TMS): 0.91 (9H), 1.34 (16H), 1.70 (6H), 2.16 (2H), 2.93 (2H, t, J =5.90), 3.17 (6H), 3.76 (2H)
3.3 Required factor for zwitterion to show LCST with water

3.3.1 Water miscibility and thermal properties of ammonium based zwitterions

A series of novel ammonium-type ZIs with different alkyl chains were prepared (Table 3-1). The \( T_m \) of these ZIs was determined by DSC measurements (SII DSC 6220), while decomposition temperatures (\( T_d \)) were determined by TG/DTA measurements (SII TG/DTA 7200). First, the prepared ZIs were tested for water miscibility by adding 10-60 water molecules per ZI. Temperature effects on phase behavior were tested by cooling the resulting solution to 0 \( ^\circ \text{C} \) and then heating it gradually to 70 \( ^\circ \text{C} \). \( N_{555}\text{C3S} \), the compound with the shortest alkyl chain length, was hydrophilic and readily formed a homogeneous solution with water. Meanwhile, both \( N_{666}\text{C3S} \) and \( N_{888}\text{C3S} \) were hydrophobic and insoluble in water.

We previously found that ILs having less than threshold hydrophobicity underwent LCST-type phase transition after adding certain amount of water molecules. Based on this observation and the previous results, \( N_{665}\text{C3S} \) was synthesized in an attempt to develop a ZI close to that borderline. As expected, \( N_{665}\text{C3S} \) showed LCST-type behavior with water. These data imply that the phase behavior of ZI/water mixture is governed by the similar tendency of the phase behavior of IL/water mixtures.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Structure</th>
<th>( T_m )*1 (( ^\circ \text{C} ))</th>
<th>( T_d )*2 (( ^\circ \text{C} ))</th>
<th>Water miscibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>( N_{555}\text{C3S} )</td>
<td>( \text{H}_{11}\text{C}_5\text{N}^+\text{SO}<em>3\text{H}</em>{11}\text{C}_5 )</td>
<td>157</td>
<td>253</td>
<td>miscible</td>
</tr>
<tr>
<td>( N_{665}\text{C3S} )</td>
<td>( \text{H}_{11}\text{C}_5\text{N}^+\text{SO}<em>3\text{H}</em>{11}\text{C}_6 )</td>
<td>180</td>
<td>245</td>
<td>LCST*-type phase change</td>
</tr>
<tr>
<td>( N_{666}\text{C3S} )</td>
<td>( \text{H}_{13}\text{C}_6\text{N}^+\text{SO}<em>3\text{H}</em>{13}\text{C}_6 )</td>
<td>202</td>
<td>250</td>
<td>immiscible (solid-liquid)</td>
</tr>
<tr>
<td>( N_{888}\text{C3S} )</td>
<td>( \text{H}_{17}\text{C}_8\text{N}^+\text{SO}<em>3\text{H}</em>{17}\text{C}_8 )</td>
<td>180</td>
<td>234</td>
<td>immiscible (solid-liquid)</td>
</tr>
</tbody>
</table>

*1Melting temperature  *2Decomposition temperature  *3Lower critical solution temperature
3.3.2 Phase behavior of ZI/water mixture to show LCST-type phase transition

Figure 3-2 shows phase diagram of N₆₆₅C₃S/water mixture as a function of number of added water molecules per a ZI. This mixture gave a concave curve that was typical of LCST-type phase transitions.² The \( T_c \) value for the mixtures depended on the number of water molecules per a ZI. When 40 water molecule per a ZI was added to N₆₆₅C₃S, resulting mixture had lowest \( T_c \) value at 10°C.

As described in Chapter 1, the amount of dissolved water molecules in the separated IL rich phase is one of criterion by which to study IL hydrophobicity. The Author’s group proposed a “Hydrophilicity index (HI)”, which is the number water molecules per an IL in separated IL rich phase at 60°. We have calculated HI value for both hydrophobic and LCST-type phase transition of IL/water mixtures, and studies correlation between HI and phase behavior of these mixtures. Of IL to undergo an LCST-type phase transition, HI value must exceed 7. Furthermore HI value had a strong correlation with \( T_c \) value. \( T_c \) value for IL/water mixtures to show LCST was higher with increasing HI value (Figure 3-3; black symbol)

When 50 wt% of water was added to N₆₆₅C₃S, the resulting mixture showed an LCST-type phase transition at 11 °C. The water content of the ZI phase, 35 wt%, yielded an HI value of 11, surprising in that it both was much higher than expected based on the \( T_c \) correlation between HI and \( T_c \) values in IL/water system (Figure 3-3). It is worthy noted that HI value of 11 is sufficiently large enough to show LCST-type phase transition. These results suggested that LCST-type phase transition of ZI/water mixtures could be design through the required factor for IL to show LCST-type phase transition after mixing with water.
3.3.3 Effect of mixing zwitterions with different hydrophobicity on the phase behavior with water

As with the IL/water mixtures, it is difficult to control the $T_c$ values of the ZI/water mixtures just through chemical modification of their structures. Again, since hydrophobicity is a major factor in determining ZI/water mixture phase behavior, mixing ZIs with different hydrophobicity, as was done with ILs, should be quite effective in providing further control.

Here we have studied the effect of mixing ratio of ZIs to successively change the total hydrophobicity of the ZI mixtures. Since only $N_{555}C3S$ was water miscible, we studied the phase behavior of the $N_{555}C3S/N_{888}C3S$ and $N_{555}C3S/N_{666}C3S$ mixtures. When $N_{555}C3S$ and $N_{888}C3S$ was mixed equimolarily, the mixture containing 10-35 water molecules per ZI underwent solid-liquid phase separation. Homogeneous solution or liquid-liquid biphasic system was not seen in the $N_{555}C3S/N_{888}C3S$ and $N_{555}C3S$ and $N_{666}C3S$ mixtures. When $N_{555}C3S$ and $N_{666}C3S$ were mixed equimolarily (Table 3-2, Entry 2), the mixture containing 15 water molecules per ZI was homogeneous solution, even while the one with more than 20 water molecules per ZI underwent biphasic system. From now on, the ZI/water mixtures were abbreviated as $i_{/water} [n]$, where $i$ and $n$ denote the entry number and number of added water molecules per a ZI, respectively. None of the $i_{/water}$ mixtures showed any temperature

<table>
<thead>
<tr>
<th>Entry (i)</th>
<th>$N_{555}C3S : N_{666}C3S$ (mol/mol)</th>
<th>Number of water molecules per ZI (n)</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
<th>35</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.44 : 0.56</td>
<td>homogeneous solution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>biphasic system</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.50 : 0.50</td>
<td>homogeneous solution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>homogeneous solution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.56 : 0.44</td>
<td>homogeneous solution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>homogeneous solution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.60 : 0.40</td>
<td>homogeneous solution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>homogeneous solution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.64 : 0.36</td>
<td>homogeneous solution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>homogeneous solution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.67 : 0.33</td>
<td>homogeneous solution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>homogeneous solution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*1 Upper critical solution temperature, *2 Lower critical solution temperature
dependency between 0 and 70 °C. A slight increase in hydrophobicity of the ZI/water mixture in this case should lead to phase separation for less water. With this in mind, 1/water_{15} mixtures predictably formed biphasic systems due to increasing molar ratio of more hydrophobic N_{666}C3S relative to 2/water_{15} mixtures. Likewise, decreasing the total hydrophobicity of the ZI mixture by increasing the mole fraction of the relatively hydrophilic N_{555}C3S necessitated a larger amount of water to provide a similar result.

Throughout these experiments, some ZI mixtures underwent dynamic phase transitions between the conditions needed for homogeneous mixtures and biphasic systems. Very interestingly, these systems showed not only LCST-type phase transitions but UCST-type transitions as well, as shown in Table 3-2. For example, 3/water_{20} showed LCST- and UCST-type phase transitions for T_c values of 28 and 6 °C, respectively. These unique phase transitions were seen in only a small range, because phase behavior of 3/water_{15} and 3/water_{25} did not undergo such dynamic phase changes upon heating or cooling. Likewise, when a larger molar ratio of N_{555}C3S was used, larger number of water molecules were needed, which is consistent with the observations above.

Next, the effect of water concentration on T_c was investigated for 4/water_n and 6/water_n in order to examine these two temperature driven phase transitions more closely. Phase transition temperatures of 4/water_{26} were 27°C (LCST) and 11°C (UCST) respectively. Subsequently an LCST was found to increase with decreasing number of water molecules per ZI (Figure 3-4, closed circles), and a UCST was found to decrease with decreasing it (Figure 3-4, closed squares). 6/water_n mixtures followed a similar trend (Figure 3-4, open symbol), though with higher T_c values. Using a greater ratio of the more hydrophilic N_{555}C3S should yield higher T_c values. These results clearly demonstrate that the phase transition temperatures of the prepared mixtures can be finely controllable by the mixing ratio of ZI and water.

![Figure 3-4](image.png)

**Figure 3-4** Phase transition temperature of 4/water_n mixtures (closed mark) and 6/water_n mixtures (open mark). Circle point denote LCST and square point do UCST.
3.4 Water content of zwitterions/water mixture to show both LCST- and UCST-type phase transitions

As discussed in chapter 1, the LCST mechanism not the same as UCST one. This means that properties of biphasic system after LCST-type phase transition or UCST-type phase transition should also be different. Water content plays an important role in this regard. As seen in Table 3-2, 6/water$_{35}$ mixture has two $T_c$s at 17 and 41°C. We previously reported that the water content of the separated IL rich phase changes dramatically near $T_c$. Therefore the liquid-liquid equilibrium of this mixture was studied at 7°C and 51°C, those are 10 °C lower or higher than the $T_c$s.

As shown in Figure 3-5 left, 6/water$_{35}$ mixture formed liquid-liquid biphasic system after UCST-type phase transition and the volume of the water-rich phase in this mixture was notably greater than that of the ZI rich phase. On the other hand, the two phases were roughly equal in volume after an LCST-type phase transition (Figure 3-5, right). These results indicate that distribution of water molecules should be different after different types of phase transitions. Water content of each phase was examined with Karl Fischer titration technique, and the values obtained were shown in Figure 3-5. Water content of water-rich phase was similar value after both phase transitions. However ZI rich phase after LCST-type phase transition contains more water molecule than ZI rich phase after UCST-type phase transition. This is consistent with the proposed mechanism for the UCST-type transition; water immiscible N$_{666}$C$_3$S was mainly partitioned into the ZI-rich phase and contained only a small amount of N$_{555}$C$_3$S due to its insolubility in water.

Note that the relative water content of the ZI system is different from the IL system since the ion pairs are fixed. These unique characteristics of ZI/water mixtures would provide an interesting and useful interface with water. Recently interface of ILs and water have got much

![7 °C](image)

67.2wt% <....

39.6wt% <....

![30 °C](image)

heating

UCST

![51 °C](image)

heating

cooling

LCST

70.6wt%

56.8wt%

Figure 3-5 Visual appearance and water content of 6/water$_{35}$ mixture before and after phase transitions.
attention as being useful for enzymatic reactions, template of biopolymer, and synthesis of inorganic nanostructure. Since dynamically variable interface could be prepared by N555C3S/N666C3S/water mixtures to show temperature driven phase transition, these mixtures would contribute significantly to interfacial science.

3.5 Conclusion

Through the study to analyze the required factors for ZI/water mixtures to show temperature driven dynamic phase transition, we have found ammonium based ZIs having adequate hydrophobicity showed LCST with water. Hydrophilic N555C3S was miscible with water and relatively hydrophobic N666C3S was immiscible with water. As ZI having hydrophobicity between N555C3S and N666C3S, N665C3S was synthesized and found to show LCST-type phase transition with water. In addition to design of chemical structure of ZIs, mixing different ZI was performed to control total hydrophobicity. When N555C3S and N666C3S were mixed in a suitable molar ratio and with the appropriate amount of water, they not only showed LCST-type phase transitions but UCST-type transitions as well. Both phase transition temperatures were controllable by the ratio of ZIs to water. Furthermore, water content in biphasic system composed of N555C3S/N666C3S/water mixture varied dramatically by small change of temperature.

3.6 Reference

Chapter 4

Evaluation of hydrophobicity of additives thorough LCST-type phase transition of ionic liquid/water mixture
4.1 Introduction

Separation and purification in biological and chemical processes usually require numerous steps with high energy and chemical consumption. One of the major challenges in this regard is the development of fast, efficient, and recyclable downstream processes for the extraction of target compounds from mixtures. We have developed temperature driven phase transitions in IL/water mixtures, in which one and two phase systems can be reversibly generated by small temperature changes. Since there is no need for particles to travel through an interface in such a system, it is likely that this technology will be developed for more advanced separation technologies.

The phase behavior of IL/water mixtures is dependent on the total hydrophobicity of the component ions. This makes the challenge of evaluating cation and anion hydrophobicity particularly important. Therefore, several methods have been developed to study this parameter. For instance, octanol-water partition coefficient (K_{ow}) is traditional assessment procedure not only for detection of hydrophobicity but also for environmental risk.\textsuperscript{1} For the evaluation of hydrophobicity, IL distributed in octanol rich phase with higher efficiency were classified more hydrophobic. The other way to detect ion hydrophobicity was reported as spectroscopic analysis\textsuperscript{2,3}, computational studies,\textsuperscript{4,5} and thermodynamic measurement\textsuperscript{6,7}. However it have been much trouble to detect the component ion for IL having desired phase behavior with water. This is because obtained hydrophobicity do not sometimes reflect real phase behavior of IL/water mixtures. Further studies on the hydrophobicity of component ions are required for the comprehensive prediction of IL/water phase behavior.

In chapters 2 and 3, we have developed LCST-type phase transition of IL/water and ZI/water mixtures in order to finely control phase transition temperature (T_c) by mixing different hydrophobicity of salts. The T_c value was arbitrarily selected after mixing suitable molar ratio of salts. Results indicated that that an LCST-type IL/water mixture could be suitable candidate for evaluating the hydrophobicity of target ions by determining the value of T_c after adding salts consisting of the target ion species. This methodology would permit the comparison of differences in the hydrophobicity of the target ions. In this chapter, we develop this system in greater detail.
4.2 Experimental

*Preparation of ionic liquids*

In this chapter, a series of $[P_{4444}]^+$-based and $\text{CF}_3\text{COO}^-$-based salts were selected. $[P_{4444}]^+$-based salts combined with $[\text{Tf}_2\text{N}]^-$, $\text{CF}_3\text{SO}_3^-$, and $\text{BF}_4^-$ were prepared by anion exchange with $[P_{4444}]\text{Br}$ and the corresponding alkali metal salts. Other $[P_{4444}]^+$-based salts were synthesized by neutralizing tetrabutylphosphonium hydroxide ($[P_{4444}]\text{OH}$; donated by Hokko) with the corresponding acids. Meanwhile, $[\text{C4pyr}]\text{CF}_3\text{COO}$, $[\text{N}_{4444}]\text{CF}_3\text{COO}$, and $[P_{5555}]\text{CF}_3\text{COO}$ were synthesized by neutralizing trifluoroacetic acid with the corresponding hydroxide solutions; these, in turn, were synthesized by passing $[\text{C4pyr}]\text{Br}$, $[\text{N}_{4444}]\text{Br}$, and $[P_{5555}]\text{Br}$ through a column filled with anion exchange resin (Amberlite IRN 78). $[\text{C4mim}]\text{CF}_3\text{COO}$ was prepared by refluxing 1-butylimidazole with methyl trifluoroacetate in toluene under dry nitrogen at 50 °C for 24 h. All salts were dried in vacuo for at least 24 h at 60 °C before any experiments were performed. The structure and purity of the salts were confirmed by $^1\text{H}$ NMR and elemental analysis.

$[P_{4444}]\text{CH}_3\text{SO}_3$ Tetrabutylphosphonium methanesulfonate

$\delta_{\text{H}}$ (400 MHz; DMSO; δ/ppm relative to TMS): 0.92 (12H, t, $J = 13.8$, $\text{CH}_2\text{CH}_3$), 1.38–1.47 (16H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.15–2.22 (8H, m, $\text{P-CH}_2$), 2.29 (3H, s, $\text{S-CH}_3$).

Elemental analysis (%): Found: C, 55.06; H, 11.48; N, 0. $\text{C}_{17}\text{H}_{39}\text{O}_3\text{PS} \cdot \text{H}_2\text{O}$ calcd: C, 54.81; H, 11.09; N, 0.

$[P_{4444}]\text{Cl}$ Tetrabutylphosphonium chloride

$\delta_{\text{H}}$ (400 MHz; DMSO; δ/ppm relative to TMS): 0.92 (12H, t, $J = 14.2$, $\text{CH}_2\text{CH}_3$), 1.40–1.49 (16H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.30 (8H, m, $\text{P-CH}_2$).

Elemental analysis (%): Found: C, 61.12; H, 13.03; N, 0. $\text{C}_{16}\text{H}_{36}\text{ClP} \cdot \text{H}_2\text{O}$ calcd: C, 61.42; H, 12.24; N, 0.

$[P_{4444}]\text{Br}$ Tetrabutylphosphonium bromide

$\delta_{\text{H}}$ (400 MHz; DMSO; δ/ppm relative to TMS): 0.98 (12H, t, $J = 19.7$, $\text{CH}_2\text{CH}_3$), 1.48–1.62 (16H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.39–2.54 (8H, m, $\text{P-CH}_2$).

Elemental analysis (%): Found: C, 53.75; H, 10.37; N, 0. $\text{C}_{16}\text{H}_{38}\text{BrP} \cdot \text{H}_2\text{O}$ calcd: C, 53.76; H, 10.72; N, 0.

$[P_{4444}]\text{TsO}$ Tetrabutylphosphonium $p$-toluenesulfonate

$\delta_{\text{H}}$ (400 MHz; DMSO; δ/ppm relative to TMS): 0.93 (12H, t, $J = 11.0$, $\text{CH}_2\text{CH}_3$), 1.37–1.45 (16H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.14–2.28 (8H, m, $\text{P-CH}_2$), 2.50 (3H, s, $\text{Ph-CH}_3$), 7.11 (2H, d, $J = 5.96$, $\text{Ph-CH}_3$).

51
Ph-H), 7.47 (2H, d, J = 5.48, Ph-H).
Elemental analysis (%): Found: C, 63.40; H, 10.24; N, 0. C_{23}H_{43}O_3PS • 0.25H_2O calcd: C, 63.49; H, 10.08; N 0.

\([\text{P}_{4444}]\text{NO}_3\) Tetrabutylphosphonium nitrate
\(\delta_H\) (400 MHz; DMSO; \(\delta/\text{ppm relative to TMS}\)): 0.92 (12H, t, \(J = 12.4, \text{CH}_2\text{CH}_3\)), 1.40–1.46 (16H, m, \(\text{CH}_2\text{CH}_2\text{CH}_3\)), 2.21 (8H, m, P-CH_3).
Elemental analysis (%): Found: C, 59.31; H, 11.47; N, 4.27; C/N, 13.88. C_{16}H_{36}NO_3P calcd: C, 59.79; H, 11.29; N, 4.36; C/N, 13.71.

\([\text{P}_{4444}]\text{CF}_3\text{COO}\) Tetrabutylphosphonium trifluoroacetate
\(\delta_H\) (400 MHz; DMSO; \(\delta/\text{ppm relative to TMS}\)): 0.92 (12H, t, \(J = 14.2, \text{CH}_2\text{CH}_3\)), 1.38–1.48 (16H, m, \(\text{CH}_2\text{CH}_2\text{CH}_3\)), 2.16–2.23 (8H, m, P-CH_3).
Elemental analysis (%): Found: C, 56.75; H, 10.19; N, 0. C_{18}H_{36}F_3O_2P • 0.5H_2O calcd: C, 56.68; H, 9.78; N, 0.

\([\text{P}_{4444}]\text{BF}_4\) Tetrabutylphosphonium tetrafluoroborate
\(\delta_H\) (400 MHz; CDCl_3; \(\delta/\text{ppm relative to TMS}\)): 0.97 (12H, t, \(J = 13.7, \text{CH}_2\text{CH}_3\)), 1.51–1.53 (16H, m, \(\text{CH}_2\text{CH}_2\text{CH}_3\)), 2.14–2.21 (8H, m, P-CH_3).
Elemental analysis (%): Found: C, 55.47; H, 10.50; N, 0. C_{16}H_{36}BF_4P calcd: C, 55.50; H, 10.48; N, 0.

\([\text{P}_{4444}]\text{CF}_3\text{SO}_3\) Tetrabutylphosphonium trifluoromethanesulfonate
\(\delta_H\) (400 MHz; DMSO; \(\delta/\text{ppm relative to TMS}\)): 0.92 (12H, t, \(J = 14.2, \text{CH}_2\text{CH}_3\)), 1.38–1.48 (16H, m, \(\text{CH}_2\text{CH}_2\text{CH}_3\)), 2.14–2.22 (8H, m, P-CH_3).
Elemental analysis (%): Found: C, 50.02; H, 9.01; N, 0. C_{17}H_{36}F_3O_3PS calcd: C, 49.98; H, 8.88; N, 0.

\([\text{P}_{4444}]\text{[Tf}_2\text{N]}\) Tetrabutylphosphonium bis(trifluoromethanesulfonyl) imide
\(\delta_H\) (400 MHz; DMSO; \(\delta/\text{ppm relative to TMS}\)): 0.92 (12H, t, \(J = 13.8, \text{CH}_2\text{CH}_3\)), 1.38–1.47 (16H, m, \(\text{CH}_2\text{CH}_2\text{CH}_3\)), 2.14–2.21 (8H, m, P-CH_3).
Elemental analysis (%): Found: C, 40.07; H, 6.79; N, 2.43; C/N, 16.50. C_{18}H_{36}F_6NO_4PS_2 calcd: C, 40.07; H, 6.72; N, 2.60; C/N, 15.43.

\([\text{C}4\text{mim}]\text{CF}_3\text{COO}\) 1-butyl-3-methylimidazolium trifluoroacetate
\(\delta_H\) (400 MHz; CDCl_3; \(\delta/\text{ppm relative to TMS}\)): 0.95 (3H, t, \(J = 24.3, \text{CH}_2\text{CH}_3\)), 1.27–1.41 (2H, m, \(\text{CH}_2\text{CH}_3\)), 1.80–1.92 (2H, m, NCH_2CH_3), 4.01 (3H, s, NCH_3), 4.20–4.30 (2H, m, NCH_2).
7.41-7.45 (1H, m, NCHCHN), 7.51-7.48 (1H, m, NCHCHN), 10.14-10.02 (1H, m, NCHN).
Elemental analysis (%): Found: C, 47.24; H, 6.39; N, 11.10; C/N, 4.26. C_{10}H_{15}F_{3}N_{2}O_{2} calcd: C, 47.28; H, 6.03; N, 11.03; C/N, 4.29.

[C4pyr]CF_{3}COO 1-butylpyridinium trifluoroacetate
\(\delta_H (400 \text{ MHz; CDCl}_3; \delta/\text{ppm relative to TMS})\): 0.94 (3H, t, \(J = 21.5, \text{CH}_2\text{CH}_3\)), 1.29–1.47 (2H, m, \text{CH}_2\text{CH}_3), 1.94–2.08 (2H, m, NCH_2CH_2), 4.78-4.91 (2H, m, NCH_2), 8.02-8.17 (2H, m, NCHCH), 8.45-8.56 (1H, m, NCHCHCH), 9.41-9.52 (2H, m, NCH).
Elemental analysis (%): Found: C, 52.95; H, 6.31; N, 5.64; C/N, 9.39. C_{11}H_{14}F_{3}NO_2 calcd: C 53.01, H 5.66, N 5.62; C/N, 9.43.

[N4444]CF_{3}COO Tetrabutylammonium trifluoroacetate
\(\delta_H (400 \text{ MHz; CDCl}_3; \delta/\text{ppm relative to TMS})\): 1.00 (12H, t, \(J = 14.8, \text{CH}_2\text{CH}_3\)), 1.40–1.56 (24H, m, \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3), 2.30–2.33 (8H, m, \text{P-CH}_2).
Elemental analysis (%): Found: C, 60.76; H, 10.84; N, 3.90; C/N, 15.58. C_{18}H_{36}F_{3}NO_2 calcd: C, 60.82; H, 10.21; N, 3.94; C/N, 15.43.

[P5555]CF_{3}COO Tetrapentylphosphonium trifluoroacetate
\(\delta_H (400 \text{ MHz; DMSO; } \delta/\text{ppm relative to TMS})\): 0.91 (12H, t, \(J = 14.0, \text{CH}_2\text{CH}_3\)), 1.33–1.56 (24H, m, \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3), 2.30–2.33 (8H, m, \text{P-CH}_2).
Elemental analysis (%): Found: C, 61.01; H, 10.05; N, 0. C_{22}H_{44}F_{3}P\cdot 0.25\text{H}_2\text{O} calcd: C, 61.02; H, 10.36; N 0.
Chapter 4

4.3 Effect of added salts on the phase transition temperature.

4.3.1 Impact of added ion species on the phase transition temperature

The author expected that the hydrophobicity of ions could be evaluated by changes in the $T_c$ value for LCST-type phase transitions resulting from the addition of salts consisting of the target ion species. $[P_{4444}]$CF$_3$COO was selected as a standard baseline by which to track changes in $T_c$ because it undergoes an LCST-type phase transition at a moderate temperature of 32 °C when mixed with an equal weight of water. Multiple ion species were then selected for testing, though each contained either the $[P_{4444}]^+$ cation or the CF$_3$COO$^-$ anion in order to keep the system as simple as possible (Figure 4-1). The $T_c$ value was determined visually based on the point at which the solution under testing became turbid under heating. Below the hydrophobicity of ions was compared from the relation between $T_c$ values and the concentration of the added salts.

**Figure 4-1** Chemical structure of component ions for evaluating hydrophobicity

Figure 4-2 shows the $T_c$ values of $[P_{4444}]$CF$_3$COO/water mixtures obtained after adding $[P_{4444}]^+$-based salts with different anion species. When water miscible ILs, $[P_{4444}]$CH$_3$SO$_3$, $[P_{4444}]$Cl, $[P_{4444}]$Br, $[P_{4444}]$NO$_3$, and $[P_{4444}]$[TsO] were added to the standard mixture, the $T_c$ values became higher than that of standard solution; these salts gave $T_c$ values of 50, 47, 39, 34, and 33 °C, respectively, at a concentration of 0.20 M. $[P_{4444}]$BF$_4$ and $[P_{4444}]$CF$_3$SO$_3$ concentrations of 0.20 M gave $T_c$ values of 18 and 17 °C, respectively. Although $[P_{4444}]$[Tf$_2$N] was insoluble at concentrations above 0.10 M, the observed decrease in $T_c$ relative to concentration was greater than for any other salt. This gives a hydrophobicity ranking of the anions used in this study as follows: CH$_3$SO$_3^-$ < Cl$^-$ < Br$^-$ < [TsO]$^-$ < NO$_3^-$ < CF$_3$COO$^-$ < BF$_4^-$ < CF$_3$SO$_3^-$ < [Tf$_2$N]$^-$.  

**Figure 4-3** gives the $T_c$ values derived for the $[P_{4444}]$CF$_3$COO/water mixture after mixing with CF$_3$COO$^-$-based salts having different cation species. The selected water miscible ILs, [C4min]CF$_3$COO, [C4pyr]CF$_3$COO, and $[N_{4444}]$CF$_3$COO, all have the same alkyl chain length on the cation and are therefore suitable for comparing other differences between structure and hydrophobicity. When three water-miscible ILs were mixed into the standard solution, higher
values of $T_c$ were found than that for the [P$_{4444}$]CF$_3$COO/water mixture. As the concentration of [C4mim]CF$_3$COO, [C4pyr]CF$_3$COO, and [N$_{4444}$]CF$_3$COO reached just 0.20 M, the $T_c$ values were 41, 40, and 35 °C, respectively. Despite their similar structure, this suggests that the 1-butylpyridinium cation is more hydrophobic than the 1-butyl-3-methylimidazolium cation. The water insoluble [P$_{5555}$]CF$_3$COO dropped the $T_c$ as expected. This provides a final cation hydrophobicity ranking as follows: [C4mim]$^+$ < [C4pyr]$^+$ < [N$_{4444}$]$^+$ < [P$_{4444}$]$^+$ < [P$_{5555}$]$^+$. Since the change in $T_c$ from that for the [P$_{4444}$]CF$_3$COO/water mixture (50 wt%) was greater when the concentration of added salts increased, it should be possible to evaluate small differences in the hydrophobicity of anions.

**Figure 4-2** Impact of added anion species on the phase separation temperature ($T_c$) of [P$_{4444}$]CF$_3$COO/water mixtures. The black point (●) denotes the value of $T_c$ for the mixture with no other salt.

**Figure 4-3** Impact of added cation species on the phase separation temperature ($T_c$) of [P$_{4444}$]CF$_3$COO/water mixtures. The black point (●) denotes the value of $T_c$ for the mixture with no other salt.
4.3.2 Impact of added zwitterion species on the phase transition temperature

Hydrophobicity of zwitterion-type ionic liquids (ZIs) is another notable investigation. As described in chapter 3, the ZI/water mixtures were able to undergo temperature driven phase transitions that were also determined by constituent ion hydrophobicity. The present system was therefore developed by combining the [P4444]CF3COO/water standard mixture with the three ammonium-based ZIs used in chapter 3.

Figure 4-4 shows the $T_c$ values derived using this system; the overall effects are similar to those observed in Figures 4-2 and 4-3. The hydrophilic ZI, N555C3S, clearly increases the $T_c$ while the hydrophobic ZI, N666C3S, decreases it. Though N666C3S is insoluble in water, our investigation suggested that it is less hydrophobic than the fluorinated anion-based ILs. Of N665C3S showing LCST-type phase transition with water, there is only a minor change in $T_c$ value even at the concentration of 0.4M. Concentrations of 0.2 M gave $T_c$ values of 39, 33, and 29 °C for N555C3S, N665C3S, and N666C3S, respectively. These results suggest that the present LCST-type IL/water mixture is a simple system suitable for determining the order of hydrophobicity of ions by comparing the change in $T_c$ values of the standard IL/water mixture after adding the target ions.

Figure 4-4 Impact of added zwitterion species on the phase separation temperature ($T_c$) of [P4444]CF3COO/water mixtures. The black point (●) denotes the value of $T_c$ for the mixture with no other salt.
4.4 Relation between phase transition temperature and water content of ionic liquid rich phase

The maximum water content in the separated IL rich phase is one of key parameters of hydrophobic ILs in comparing the hydrophobicity of ion, and author’s group also have identified ion hydrophobicity from the maximum water content of the separated IL-rich phase. Author’s group measured the maximum water content of separated IL rich phase of a series of hydrophobic ILs. Overall, water content increased for more hydrophilic ions, but did not change regardless of temperature. In the case of IL/water mixtures showing an LCST-type phase transition, the maximum water content of the separated IL phase is strongly affected by temperature, and increased significantly at temperature near $T_c$. We therefore measured the maximum water content of the separated IL phase at 10 °C higher than $T_c$ for [P4444]CF3COO/water standard mixtures with single added ions at up to concentrations of 0.2 M.

Figure 4-5 clearly shows that higher water content is accompanied by an increased $T_c$. It is considerable that the salting out effect also influenced maximum water content by generally dropping it, especially when hydrophilic ILs were added. However, this value increased with decreasing hydrophobicity, meaning that salting out plays a minimal role when compared to the effect of added salts. These results strongly reinforced the hypothesis that the change in the $T_c$ value is due to the hydrophobicity of target ions.

![Figure 4-5 Relation between phase transition temperature ($T_c$) of the mixture and the maximum water content of the separated IL rich phase at the temperature 10°C higher than $T_c$.](image)
Increasing concentration generally increased $T_c$, in addition to complicating measurements; hydrophobic salts, for instance, caused $T_c$ to drop below the freezing point of the water phase. In the present study, we prepared 0.20 M salt solutions; further testing to determine the best concentration will be necessary in order to evaluate other salts due to the reasons mentioned above.

In addition, some hydrophobic salts, such as $[\text{P}_{4444}]\text{[Tf}_2\text{N]}$ and $\text{N}_{666}\text{C}_3\text{S}$, are poorly soluble in pure water, making it difficult to detect any change in $T_c$. The solubility of hydrophobic salts can be increased by allowing the more hydrophobic system or by increasing the IL content of the system to show an LCST-type phase transition.

### 4.5 Conclusion

This chapter outlines the development of a simple system for evaluating ion hydrophobicity by exploiting temperature driven LCST-type phase transitions in IL/water mixtures, allowing us to compare even small differences. The LCST-type phase transition is analyzed visually in this method to determine $T_c$, making it easy to study the properties of both binary as well as more complex systems.

### 4.6 Reference

Chapter 5

General Conclusion
This thesis expressed fine control of temperature driven phase transition of ionic liquid (IL)/water mixtures by mixing different physico-chemical properties of ILs. Author’s group previously found ILs having less than threshold hydrophobicity showed LCST with water. Based on this guide, ILs with different hydrophobicity were mixed up to adjust hydrophobicity for precise $T_c$ control. Required factor for zwitterion-type ionic liquid (ZI) to show LCST-type phase transition was also investigated by mixing ammonium based ZIs with different alkyl chain. Finally, author proposed a simple system for evaluating the hydrophobicity of additives by exploiting an LCST-type phase transition of IL/water mixture.

Chapter 1 gave a general introduction of IL/water mixtures, with a particular focus on temperature driven phase transitions. The objective of this thesis was also outlined.

In Chapter 2, IL/water mixtures used to show LCST-type phase transitions were prepared by mixing hydrophilic and polar AAILs. The author prepared a series of trihexyl-$n$-octylphosphonium-based hydrophilic AAILs with various functional groups on their terminal side chains. Pairs of these species were mixed with each other in an equal molar ratio, but only those with an amino and carboxyl residue on their side chains, respectively, were able to form biphasic aqueous systems. This is due to the dehydration and resulting interaction between these residues. Water content and hydrogen bonding basicity of the AAIL phase could also be controlled by selecting the appropriate mixing partners and temperature.

In Chapter 3, the author focused on developing ZIs as aqueous biphasic systems given the inherent advantages of keeping the ion pairs covalently attached. The primary focus of the study was to determine the required factor to form ZI/water mixtures, which would exhibit temperature driven dynamic phase transitions. In doing so, the author developed ammonium-based ZIs with adequate hydrophobicity that exhibited LCST with water. The relatively short chained ZI $N_{555}C3S$ was hydrophilic and miscible with water, even while $N_{666}C3S$ was neither. When $N_{555}C3S$ and $N_{666}C3S$ were mixed in a suitable molar ratio, they exhibited not only LCST-type phase transitions with water but UCST-type as well. Both $T_c$s were dependent on the ZI/water ratio. Furthermore, water content of the ZI phase in the $N_{555}C3S/N_{666}C3S$ /water mixture varied dramatically for small changes in temperature.

In Chapter 4, the author proposed a simple system for evaluating ZI or ion hydrophobicity by exploiting the LCST-type phase transition of IL/water mixtures. A $[P_{4444}]CF_3COO$/water mixture was selected as a standard solution. Hydrophilic salts caused the $T_c$ value to rise, while hydrophobic salts caused it to fall. Ions were ranked relative to each
other by hydrophobicity based on the relationship between the phase transition temperature and the concentration of the added salt. Since $T_c$ could be readily determined visually, this technique makes it easy to study ZI and ion hydrophobicity.

Chapter 5 provides general conclusions and analyzes the future potential of this work. In this thesis, fine control of temperature driven phase transitions in IL/water and ZI/water mixtures was accomplished by exploiting hydrophobicity differences between different ions. The tunable characteristics of the resulting systems provide an interesting and potentially useful interface with water. The author is convinced that the techniques developed in this thesis will contribute to functional separation and purification media while also providing a favorable interface for new reactions.
List of publications

Original papers

[1] Yuki Kohno, Shohei Saita, Yongjun Men, Jiayin Yuane and Hiroyuki Ohno
“Thermoresponsive polyelectrolytes derived from ionic liquids”
Polymer chemistry, in press. [Chapters 2 and 3]

[2] Shohei Saita, Yuki Mieno, Yuki Kohno, Hiroyuki Ohno
“Ammonium based zwitterions showing both LCST- and UCST-type phase transitions after mixing with water in a very narrow temperature range”
Chemical Communications, 2014, 50, 15450-15452 [Chapter 3]

[3] Shohei Saita, Yuki Kohno, Nobuhumi Nakamura, and Hiroyuki Ohno
“Ionic liquids showing phase separation with water prepared by mixing hydrophilic and polar amino acid ionic liquids”
Chemical Communications, 2013, 49, 8988-8990. [Chapter 2]

[4] Shohei Saita, Yuki Kohno, Hiroyuki Ohno
“Detection of small differences in the hydrophilicity of ions using the LCST-type phase transition of an ionic liquid–water mixture”
Chemical Communications, 2013, 49, 93-95. [Chapter 4]

Reference

[1] Yuki Kohno, Shohei Saita, Kenichi Murata, Nobuhumi Nakamura, Hiroyuki Ohno
“Extraction of proteins with temperature sensitive and reversible phase change of ionic liquid/water mixture”
Polymer Chemistry, 2011, 2, 862-867.

“Material design of ionic liquids to show temperature-sensitive LCST-type phase transition after mixing with water”

“Density fluctuations in aqueous solution of ionic liquid with lower critical solution temperature: mixture of tetrabutylphosphonium trifluoroacetate and water”

Book

[1] 松本拓郎、黒田浩介、税田祥平、鶴巻晃子、阿部充、田口怜美、藤田恭子、西村直美、中村欽文、大野弘幸 「イオン液体の略称」 イオン液体サーキュラー 第一号 2013年 (Japanese)
Acknowledgements

A series of study in this thesis was carried out at Tokyo University of Agriculture and Technology from April 2009 – March 2015 under the direction of Professor Hiroyuki Ohno. This thesis deliver the control of temperature driven LCST-type phase transition of ionic liquid/water mixture.

First of all, I would like to express the deepest gratitude to Professor Hiroyuki Ohno for his tough tutelage, pointed advice, and continuous support. He always say that “scientist have got to be persistent to get new science” and “we must challenge if anyone do not challenge”. He gave the author many chances to express our works at international symposiums, to collaborate other laboratories including foreign countries. I will never forget the experience in Ohno-Nakamura laboratory, and go to the nest step with Ohno-Nakamura laboratory sprit.

I wish to appreciate Professor Nobuhumi Nakamura for his encouragement, pointed suggestion and advise. He always support my research from perspective of physical chemistry.

I am very grateful to Dr. Yuki Kohno. I learned from Dr. Yuki how to carry out science, how to make a presentation, and how to become good guy.

I am very grateful to Associate Professor Kyoko Fujita, Associate Professor Takahiro Ichikawa, Associate Professor Mitsuru Abe, and Dr Naomi Nishimura for their support and encouragement.

I appreciate the significant contribution made by Ms. Yuki Deguchi, Mr. Yuki Mieno, Mr. Ryuhei Oka. Without their support, I cannot find my way to Ph.D. I also deeply thank my coworker graduated before getting my Ph. D. Mr Yoritsuga Ito, Takashi Ando for their discussion.

I wish to express my appreciation to Professor Udo Kragl in Rostock University. I have been to his laboratory for three month to collaborate our and your aqueous two phase system. I believe aqueous two phase system can separate many compounds but we can cross national interface very easily.

Finally, I express my deep gratitude for my parents, Mr Takehisa Saita and Ms. Etsuko Saita for their financial support and unstinting assistance.

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November 2014