



Cite this: *Phys. Chem. Chem. Phys.*,  
2018, 20, 10978

Received 23rd December 2017,  
Accepted 19th March 2018

DOI: 10.1039/c7cp08592c

rsc.li/pccp

## Design and properties of functional zwitterions derived from ionic liquids

Hiroyuki Ohno,  \*<sup>a</sup> Masahiro Yoshizawa-Fujita <sup>b</sup> and Yuki Kohno <sup>c</sup>

A zwitterion, an ion pair where cation and anion are covalently tethered, is known to be a type of salt. These ions have not been recognised as interesting, but they are physicochemically unique and fascinating ions. In the present review, some functional zwitterions derived from ionic liquids are mentioned to emphasise the usefulness of the tethering of the component cations and anions of ionic liquids. Basic properties, advantages and disadvantages after the functional design of zwitterions, and some applications are summarised.

### 1. Introduction

Textbooks of physical chemistry tell us that salts such as sodium chloride (NaCl) are solid at room temperature. Their melting points ( $T_m$ ) are quite high but this is the function of ion–ion interaction forces. The  $T_m$  of NaCl is about 800 °C and with increasing the radii of the component ions, the  $T_m$  decreases. For example,  $T_m$  of cesium chloride (CsCl) is 645 °C, which further

decreases when organic ions are used instead of alkali metal cations. The  $T_m$  values of tetrapropylammonium chloride and 1-ethyl-3-methylimidazolium chloride are 241 °C and 87 °C, respectively. This tendency can be comprehended as the dawn of low-temperature melting salts known as “ionic liquids”. There are increasing numbers of reports on these unique materials and many applications have been proposed in quite diverse areas. With the progress of ionic liquids (ILs), there have been several demands to improve on the drawbacks of ILs. The science of functional zwitterions (ZIs) originated from this viewpoint and is growing wildly. The present review mentions the initial stages of functional ZIs arising from IL studies, and their development targeted toward some applications. Our aim is to summarise our fundamental studies based on ZIs derived from ILs. Unlike well-known and general zwitterionic

<sup>a</sup> Department of Biotechnology, Tokyo University of Agriculture and Technology, Naka-cho, Koganei 184-8588, Tokyo, Japan. E-mail: ohnoh@cc.tuat.ac.jp

<sup>b</sup> Department of Materials and Life Sciences, Sophia University, 7-1 Kioi-cho, Chiyoda-ku, Tokyo 102-8554, Japan

<sup>c</sup> National Institute of Advanced Industrial Science and Technology (AIST), 4-2-1, Nigatake, Miyagino-ku, Sendai 983-8551, Japan



**Hiroyuki Ohno**

activities are concentrated on the science of ionic liquids, especially the design of functional ionic liquids. He has published more than 660 papers, reviews, and book chapters.

*Hiroyuki Ohno received his PhD degree in 1981 from Waseda University, Tokyo, Japan. After working at Waseda University and Case Western Reserve University (USA), he moved to Tokyo University of Agriculture and Technology (TUAT) as an associate professor in 1988. He was promoted to professor in 1997. Then, he served as a director of the university library, vice dean, and dean for his university. He is now the president of TUAT. FRSC since 2008. His recent research*



**Masahiro Yoshizawa-Fujita**

activities are concerned with the design of ionic liquids, especially for battery research and biomass processing.

*Masahiro Yoshizawa-Fujita was born in Hitachi, Japan in 1973. He received his PhD degree (2002) from Tokyo University of Agriculture and Technology (Japan). During his PhD studies, he received a Research Fellowship for Young Scientists at the Japan Society for the Promotion of Science (JSPS). He spent two years as a postdoctoral research fellow at Monash University (Australia). He moved to Sophia University as an Assistant Professor in 2006. He*



compounds such as amino acids, the IL-derived ZIs are quite a new class of materials that have unique properties reflecting those of ILs. This paper contains studies of ZIs prepared from ion pairs of ILs, and the interesting properties of the ZIs are described in terms of ion conductive materials, liquid–liquid biphasic systems, and model interfaces of cell membranes.

## 2. Ionic liquids and zwitterions

ILs, salts with very low melting points empirically below 100 °C, are quite interesting liquid-state materials composed only of ions. Since there are many reviews and books on the ILs,<sup>1–5</sup> we do not want to go into the details of the physicochemical properties of ILs. Here, we briefly compare the ILs and functional ZIs. The word “zwitterion” means an ion pair where the cation and anion are covalently tethered. It is easy to compare ordinary ion pairs (especially ILs) and ZIs as shown in Fig. 1. In ordinary ILs, cations and anions are independently mobile under the influence of not only electrostatic forces but also hydrogen bonding and dispersion forces from other ions. There are many chances to exchange partners of ions in such ILs. However, ZIs keep their ion pairs in spite of many interactions from other ions, since the ion pair has been tethered covalently. This is a big difference between ZIs and ILs, especially mixed ILs. ZIs are not new and have been known from a long time ago; for example, amino acids are typical ZIs at moderate pH in an aqueous medium. As shown in Fig. 1, functional ZIs derived from ILs are expected to show properties of ILs. The initial motivation to develop ZIs was from the need to develop ILs as solvents for electrochemical devices. For example, only lithium ions should be transported in the electrolyte solution for lithium-ion batteries. In such a case, for the efficient transportation of target ions, other component ions should not be transported.

Obviously, all ions are mobile and migrate along with a potential gradient in electrochemical cells. To suppress the migration of component ions under the potential gradient, there are two



Fig. 1 An ordinary ion pair and ZI.

Table 1 Comparison of ZIs with free ion pair of ILs

Properties	ILs	ZIs
Melting point	Low	High
Decomposition temperature	High to moderate	High to moderate
Vapour pressure	Quite low	Quite low
Ionic conductivity	High	Quite low
Density	Low to high	Low to high

prospective candidates for satisfying the requirements, namely, ZIs and polymers. Since the net charge of ZIs is neutral, they do not migrate, even under a potential gradient.

Charged polymers, especially both cations and anions are covalently bound to the chains, are quite large and their diffusion is extremely small since there are no free counterions. There are a few reviews on polymerised ILs,<sup>5–8</sup> and one can find many interesting scientific areas surrounding the polymerised ILs.

In comparing the basic properties of functional ZIs with ordinary ILs, as shown in Table 1, there are some similar properties as well as completely different ones. The most distinct difference is seen in the bulk ionic conductivity. It is obvious that ZIs show small DC conductivity, but they show reasonably high AC conductivity. A detailed discussion will be given later, but it should be noted here that the use of ZIs is effective for suppressing long-range ion migration when ILs are used as electrolyte solutions for DC-driven devices.

## 3. Zwitterions as electrolyte materials

### 3.1. The design of non-mobile ions under the potential gradient

Since ILs have high ion densities and high mobility of their component ions, they also have a high ionic conductivity. Furthermore, ILs can dissolve a variety of salts and have been actively investigated as new electrolyte materials.<sup>5,9</sup> Although ILs have a number of physical properties superior to organic solvents, they are not suitable solvents for transporting the ions produced by the dissociation of added salts like lithium salts and sodium salts. Since the IL itself, which is used as a solvent, is composed of ions, their component ions also migrate along with the potential gradient. Generally, the number of component ions of IL used as a solvent is much larger than that of added ions; *i.e.*, when it is desired to transport only specific ions, for example, lithium cations and protons as the electrolyte material of rechargeable batteries and fuel cells, respectively, a low target-ion transference number is a serious problem. To achieve a high target-ion transference number, ZIs have been proposed as new electrolyte materials to critically suppress the



Yuki Kohno

and Technology (AIST) as a researcher in 2016. His current research focus is on the design of ionic liquid-based reaction–separation systems.

*Yuki Kohno received his PhD degree from Tokyo University of Agriculture and Technology (TUAT), Japan in 2012. After working as a post-doctoral research fellow in TUAT, he joined University of Colorado Boulder (CU), USA in 2013. During this period, he received a fellowship from the Japan Society for the Promotion of Science (JSPS Postdoctoral Fellowships for Research Abroad). He moved to the National Institute of Advanced Industrial Science*







PEGDME/LiTF<sub>2</sub>N without ZIs (below 4.5 V vs. Li/Li<sup>+</sup>), even at low ZI content. The cycle stability of PEGDME/LiTF<sub>2</sub>N with **7** was better than the electrolyte without the ZI within the cut-off voltage range of 3.0–4.6 V for the charge–discharge tests of Li/LiCoO<sub>2</sub> cells.<sup>32</sup> AC impedance spectra indicated that the increase in interface resistance between the cathode and electrolyte was suppressed in the presence of **7**.

ILs containing ZIs have also been studied as the electrolytes for lithium-metal and lithium-ion batteries. Byrne *et al.* reported that ionic conductivity was improved by the addition of ZIs and inorganic nanofillers.<sup>17</sup> The addition of ZIs to ILs led to the improvement of the diffusion coefficient of lithium ions, the formation of a thinner solid electrolyte interface (SEI), and the improvement of coulombic efficiencies for the lithium plating–stripping reaction.<sup>18,33</sup> The effect of the addition of pyrrolidinium ZI, **8**, in an IL electrolyte on the charge–discharge tests of Li/LiCoO<sub>2</sub> and graphite/Li cells has been investigated.<sup>34</sup> The Li/LiCoO<sub>2</sub> cells containing **8** exhibited stable coulombic efficiency and much higher discharge capacities in the cut-off voltage range of 3.0–4.6 V, compared to the cells without ZI. The increase in the interface resistance between cathode and electrolyte was suppressed the same as PEGDME electrolytes. Moreover, the intercalation–deintercalation reaction was stable in the graphite/Li cells containing **8**. These results indicated that ZIs would be useful electrolytes for improving the performance of lithium-metal and lithium-ion batteries, especially at high cut-off voltages.

**3.2.3. Zwitterion/acid complexes.** The complex of **9** and an equimolar amount of trifluoromethanesulfonic acid (HTf) was obtained as a viscous liquid at room temperature.<sup>35</sup> When the complex was heated even under reduced pressure, no weight loss was observed up to the boiling point of HTf (162 °C under ordinary pressure). These complexes have been confirmed to be non-volatile acid solutions. On the other hand, ZI/acid complexes have been used as both solvent and catalyst in various organic reactions.<sup>36–39</sup> These features allow their application not only as solvents for organic synthesis but also as non-volatile proton conductors.

ZI **10** was mixed with given amounts of 1,1,1-trifluoro-*N*-(trifluoromethylsulfonyl)methanesulfonamide (HTf<sub>2</sub>N), and the proton conductivity was evaluated.<sup>40,41</sup> ZI **10** and HTf<sub>2</sub>N were solids at room temperature, but the complexes formed were viscous liquids at room temperature. When the concentration of HTf<sub>2</sub>N was in the range of 30 and 80 mol%, their complexes showed only *T<sub>g</sub>*, which decreased with increasing the acid concentration, and the lowest value of –55 °C was observed at 50 mol%. The complexes showed a constant value of about –55 °C in the range above 50 mol%. The conductivity of complexes of **10**/HTf<sub>2</sub>N increased with increasing the acid concentrations. When the acid concentration was 50 mol%, the complex exhibited the highest value of about 10<sup>–4</sup> S cm<sup>–1</sup> at 25 °C. At above 50 mol%, the conductivity did not change and showed a constant value of about 10<sup>–4</sup> S cm<sup>–1</sup> at 25 °C. There is an obvious correlation between *T<sub>g</sub>* and the conductivity, the same as for the complexes of ZIs and lithium salts.

PFG-NMR measurements were carried out to evaluate the self-diffusion coefficients of the component ions.<sup>41</sup> The acid

concentration dependence on self-diffusion coefficients was different from that between *T<sub>g</sub>* and conductivity. For HTf<sub>2</sub>N fractions above 50 mol%, the self-diffusion coefficient of all component ions increased. When the acid concentration was 50 mol%, protons, derived from HTf<sub>2</sub>N were found to be the fastest diffusion species. These results indicate that ZIs cannot induce the dissociation of excess HTf<sub>2</sub>N, and the HTf<sub>2</sub>N behaves as a molecular acid in the complexes. Superior proton transport properties were observed when ZI **10** was equimolarly mixed with HTf<sub>2</sub>N.

### 3.3. Liquid zwitterions

**3.3.1. Correlation between chemical structure and melting point.** Typical ZIs are solids at room temperature; it is difficult to lower their melting points. As described above, solid ZIs became liquid at room temperature after mixing specific inorganic salts and acids. Their liquid complexes have attracted attention as new electrolyte materials. However, many of the complexes gradually crystallise to the solid state after a few weeks. Rocha *et al.* reported that the mixtures of cholinium carboxylate-type ZIs (**11**, **12**) and LiTF<sub>2</sub>N maintained a liquid state even after six months of storage at room temperature.<sup>42</sup> Since the water contents of these complexes were over 0.2 wt% (2000 ppm), these values greatly affected the various physical properties including phase transitions. In order to maintain a stable liquid state for a long period of time, it is important to develop “liquid ZIs” which are liquids without any additives (including residual water) at room temperature.

The *T<sub>m</sub>* values of ZIs are summarised in Table 2.<sup>11,33,43–45</sup> The *T<sub>m</sub>* values of the ZIs synthesised to date have been mostly above 100 °C. The chemical structure of the ions constituting ZIs was substantially the same as that of ILs, but the *T<sub>m</sub>* was considerably different. Since both cations and anions are covalently tethered, the degrees of freedom of the ions are greatly restricted. Crystallisation rapidly occurs due to the strong electrostatic attraction between the ZIs themselves. This would be responsible for higher *T<sub>m</sub>*. There are three notable points for the molecular design in order to lower the *T<sub>m</sub>* of ZIs, namely, the cation structure, anion structure, and spacer structure connecting the cation and anion.

To analyse the cation effect, imidazolium cation, ammonium cation, and pyridinium cation have been used as the cationic unit of ZIs. When comparing the *T<sub>m</sub>* of these ZIs having sulfonate anions, imidazolium cations exhibited relatively low *T<sub>m</sub>* among those ZIs having three different types of cationic structure.

Table 2 *T<sub>m</sub>* values of neat ZIs

Sample no.	<i>T<sub>m</sub></i> /°C	Sample no.	<i>T<sub>m</sub></i> /°C
1	175	8	129
2	178	9	158
3	104	10	179
5	148	13	293.5 <sup>a</sup>
6	87	14	183
7	107		

<sup>a</sup> Decomposition temperature.





of fitting the VFT equation. In any complex, the temperature dependence of the ionic conductivity showed an upper convex curve and obeyed the VFT equation. The ion conduction in ZI/LiTF<sub>2</sub>N complexes should therefore be dominated by the viscosity of the complexes.

The ionic conductivity of the 15/LiTF<sub>2</sub>N complex was  $9.2 \times 10^{-5}$  S cm<sup>-1</sup> at 80 °C, which was almost the same as that of the 10/LiTF<sub>2</sub>N complex. The ionic conductivity of 16/LiTF<sub>2</sub>N complex was  $3.8 \times 10^{-4}$  S cm<sup>-1</sup> at 80 °C, which was 4 times higher than that of the 15/LiTF<sub>2</sub>N complex. The 16/LiTF<sub>2</sub>N complex had the lowest  $T_g$  among the complexes prepared in this study. This could be the reason for such a high ionic conductivity. The introduction of the ether bond on the side chain was effective to not only decrease the  $T_m$  of the ZIs but also improve the ionic conductivity.

Generally, the composites having a greater amount of lithium salts showed higher ionic conductivity up to a certain amount. The lithium-salt concentration dependence of the conductivity and  $T_g$  was investigated for ZI 16.<sup>50</sup> Two kinds of lithium salts, LiTF<sub>2</sub>N and lithium bis(fluorosulfonyl)imide (LiFSI), were used. Lithium-salt concentration was in the range between 20 and 90 mol%. When the lithium salt concentration was in the range of 20 to 50 mol%, the  $T_g$  of 16/lithium-salt complexes were in the range of -40 to -30 °C. When the lithium-salt concentration was greater than 50 mol%, the  $T_g$  of the complexes monotonously increased. However, when the lithium-salt concentration was 80 mol%, the  $T_g$  of 16/LiTF<sub>2</sub>N and 16/LiFSI was -10 and -32 °C, respectively. It is worth mentioning that the  $T_g$  decreased in such high lithium-salt conditions.

In the lithium-salt concentration range between 20 and 50 mol%, the complexes exhibited a constant conductivity of about  $10^{-5}$  S cm<sup>-1</sup> at 40 °C. In the salt-concentration range of 60 to 70 mol%, the ionic conductivity decreased due to increasing  $T_g$ . When the LiTF<sub>2</sub>N concentrations were 60 and 70 mol%, the ionic conductivity of each complex was about  $10^{-7}$  and  $10^{-8}$  S cm<sup>-1</sup> at 40 °C, respectively. At the LiTF<sub>2</sub>N concentration of 80 mol%, the ionic conductivity increased drastically. The complex of 16 with 80 mol% LiFSI exhibited the highest ionic conductivity of  $1.2 \times 10^{-5}$  S cm<sup>-1</sup> at 40 °C. In the lithium-salt concentration range between 20 and 80 mol%,  $T_g$  and conductivity showed a correlation according to the conventional perception. The ionic conductivity was improved by adding a small amount of ZI in LiTF<sub>2</sub>N and LiFSI.

Liquid ZIs were effective in improving the ionic conductivity. In order to apply them as electrolyte materials,  $t_{Li^+}$  was also an important parameter as mentioned above. The  $t_{Li^+}$  of 15, 10, and 16 with an equimolar amount of LiTF<sub>2</sub>N were 0.15, 0.10, and 0.15, respectively, at 40 °C,<sup>50</sup> which were much lower than that of the systems described above. ZIs 15 and 16 having the ether bond exhibited the highest  $t_{Li^+}$  among the three ZIs. The introduction of the ether bond was thought to lead to a decrease in  $t_{Li^+}$ , but the opposite results were obtained. The ion-dipole interaction between the lithium ion and ether oxygen promotes the dissociation of lithium salts, and lithium-ion conduction along with the ether oxygens may occur.<sup>14</sup> The  $t_{Li^+}$  of 16 with LiFSI 50 and 80 mol% were 0.20 and 0.46, respectively.<sup>50</sup>

The 16/LiFSI complexes had greater  $t_{Li^+}$  than the 16/LiTF<sub>2</sub>N complexes due to lower coordination strength between the FSI anion and the lithium ion compared with that of TF<sub>2</sub>N anion.<sup>51</sup> The combination of ZIs and LiFSI represents an interesting matrix for electrochemical applications.

### 3.4. Polymerised zwitterions

Polymerised zwitterions, that possess both cationic and anionic groups on one repeating unit, are being considered as novel ion conductive alternatives to polyether-based solid polymer electrolytes, due to the highly dipolar character of their zwitterionic groups.<sup>43</sup> Research on the solid polymer electrolytes have so far mainly involved the use of polyether matrices because these polyether chains can dissolve salts and transport the dissociated ions along with the intramolecular and intermolecular motion of these polyether chains.<sup>52</sup> Polymer matrices with both high polarity and low  $T_g$  are rare because polar materials generally have high  $T_g$ . However, the ionic conductivity of certain polyether systems was approximately  $10^{-4}$  S cm<sup>-1</sup> at room temperature, and it was difficult to improve their conductivity. Although polymerised ZIs contain no carrier ions, they can provide desirable carrier ions upon the addition of salts to their matrices. In addition, some of these with low  $T_g$  have been reported.<sup>53</sup> It is therefore possible to realise selective ion transport in the polymerised ZIs. If the resulting matrix can form a solid film over a wide temperature range, many useful ionic devices can be realised.

For polyelectrolytes, the charges may be located either on the pendant side chains of different monomer units or the same monomer unit. According to the suggestion of Lowe *et al.*,<sup>54</sup> we also expanded the definition of polymerised ZIs (polyZIs) to all polymers that possess both cationic and anionic groups. Polyampholytes refer to the polymers that possess the charged groups on different monomer units, while polybetaine refers to the polymers that possess the cationic and anionic groups on the same monomer unit.

**3.4.1. Polyampholytes.** Polyampholytes are readily obtained by the polymerisation of IL monomers synthesised by the neutralisation of polymerisable acids and bases.<sup>55</sup> Fig. 8 shows the structure of typical polyampholytes. For 21 and 22, both monomers were colourless transparent liquids at room temperature and had only low  $T_g$  below -70 °C. 21 showed no endothermic events in DSC measurements, whereas 22 had the  $T_g$  at -31 °C, indicating that 22 maintained a high flexibility of the charged units even after polymerisation. The ionic conductivities of both polyampholytes were below  $10^{-9}$  S cm<sup>-1</sup>, most likely due to there being no ions that can migrate over long distances in their matrix.

Lithium salts were added to both polyampholytes so as to generate carrier ions that can migrate over a long-distance. Three distinct lithium salts, LiTF<sub>2</sub>N, LiBF<sub>4</sub>, and LiCF<sub>3</sub>SO<sub>3</sub>, were used as additives, and the polyampholytes were mixed with equimolar amounts of lithium salts to the charged units on the polymer chains. It is well-known that these anions form ILs after mixing with imidazolium cations.<sup>9</sup> The ionic conductivity of 21 mixed with LiBF<sub>4</sub> and LiCF<sub>3</sub>SO<sub>3</sub> were approximately  $10^{-9}$  S cm<sup>-1</sup>,





and imidazolium cations were almost the same before and after polymerisation. The ionic conductivity of **25** and **26**, in which the imidazolium cation was fixed on the main chain, was very low even after adding  $\text{LiTf}_2\text{N}$  to the matrix. Compounds **27** and **28** with the counter anion on the main chain had ionic conductivities three or four orders higher than **25** and **26**. The distance between the polymer main-chain and the imidazolium cation is also essential for maintaining high ionic conductivity in polybetaines.

The dipole moments of zwitterionic side groups in polybetaines composed of aliphatic ammonium cations have been reported by Galin *et al.*<sup>43</sup> Their dipole moments depend on the distance between the cationic and anionic groups. This suggests that these polybetaines have varied solvation power towards ionic guest species. Although the spacer distances between the cations and the anions were nearly identical, the ionic conductivities of **26** and **27** were very different. This supports that the distance between the polymerisable groups and the imidazolium cation is important in maintaining high ionic conductivity as mentioned above.

Recently, a polybetaine with an organoborate was synthesised *via* the dehydrocoupling polymerisation of lithium 9-borabicyclo[3,3,1]nonane hydride and 1,3-dihydroxyethyl-imidazolium bromide.<sup>66</sup> The chemical structure of the polybetaine with organoborate **29** is unique because both cationic and anionic charges are located on the polymer main-chain (so-called linear-type polybetaines). The ionic conductivity of **29**/ $\text{LiTf}_2\text{N}$  mixture was  $3.4 \times 10^{-6} \text{ S cm}^{-1}$  at  $50^\circ\text{C}$  in spite of a relatively high  $T_g$  of  $-6^\circ\text{C}$ . Although the imidazolium cation was fixed on the main-chain for **29**, the ionic conductivity was almost equal to that of **27** and **28** with low  $T_g$ . This may be due to the difference in the ion conduction mechanism between linear-type polybetaines and pendant-type polybetaines.

Galín *et al.* blended the tail-end-type polybetaines with alkali metal salts such as iodides, tetrafluoroborates, thiocyanates, perchlorates, trifluoromethanesulfonates, or tetraphenylborates, and performed the structural and electrochemical analyses for the mixtures.<sup>67</sup> The tail-end type refers to polybetaines since zwitterionic groups are bound to the polymer backbone *via* the end of the hydrophobic tail. Compound **30**, with sulfonate as the ZI moiety, was fully characterised as amorphous by X-ray powder diffraction patterns, due to a flexible spacer between the zwitterionic moiety and the polymer backbone. The polybetaine blends with alkali metal salts showed hexagonal and lamellar structures. The development of superstructures occurred upon solubilisation of salts, indicating that the microphase separation was promoted by the presence of dissociated ions. The stoichiometric blends of **30** with various alkali metal salts had  $T_g$  between  $97$  and  $186^\circ\text{C}$ . The ionic conductivity of the stoichiometric blends was in the range from  $0.4$  to  $4.3 \times 10^{-3} \text{ S cm}^{-1}$  at  $T_g + 30^\circ\text{C}$ . Although the stoichiometric blend with  $\text{NaCF}_3\text{SO}_3$  or  $\text{NaSCN}$  showed higher values, the relationship between superstructure and the ionic conductivity is still unclear for amphiphilic zwitterions.

Compound **31**, containing the dicyanoethenolate anion was individually blended with three different alkali metal salts,

$\text{LiClO}_4$ ,  $\text{NaSCN}$ , or  $\text{NaCF}_3\text{SO}_3$ .<sup>53</sup> Both  $\text{LiClO}_4$  and  $\text{NaSCN}$  were miscible up to the stoichiometric mixture, while the solubility of  $\text{NaCF}_3\text{SO}_3$  was less than the stoichiometric value. This was significantly different from **30** having the sulfonate anion tail, which gave a stoichiometric mixture even with  $\text{NaCF}_3\text{SO}_3$ . The dicyanoethenolate anion seemed to have less power to solvate alkali metal ions. The ionic conductivity of **31** was about  $10^{-3} \text{ S cm}^{-1}$  at  $T_g + 30^\circ\text{C}$ , which was almost the same as that of **30** containing various other salts.

Recently, sulfobetaine-containing copolymers were synthesised in order to control their morphology. Strehmel *et al.* reported the free-radical copolymerisation of **32** with *n*-butylmethacrylate (BMA) in ILs.<sup>68–70</sup> The miscibility of the monomer segments in their copolymers was influenced by the chemical structure of the ILs. The maximum content of the less polar monomer segments, BMA, in the copolymers increased when ILs that contain a long alkyl chain as a less polar group were used for copolymerisation. The copolymerisation of BMA is quite effective for decreasing the  $T_g$  of polysulfobetaines.<sup>71</sup> On the other hand, the tail-end-type polybetaines were used as nanostructural templates in water.<sup>72</sup> The mixtures consisting of **33**, methylmethacrylate, a sulfonic monomer, and water formed a basic bicontinuous microemulsion and were polymerised to obtain transparent membranes. These strategies can be quite appealing for obtaining highly ion conductive polybetaines.<sup>73</sup>

## 4. Zwitterions for aqueous biphasic systems

In addition to the remarkable progress in the design of ZIs as electrolyte materials, we recently focused on the physicochemical properties of ZIs after mixing with water. Since many ZIs have high melting points, many ZIs undergo solid/liquid-type phase separation even after adding water. In contrast, suitably designed ZIs show liquid/liquid-type phase separation to form aqueous biphasic systems (ABS). In this section, recent developments for the ZI-based ABS are summarised.

### 4.1. Thermoresponsive phase behaviour of zwitterion/water mixtures

The IL-based ABS, in which ILs are phase-separated from water to form two liquid–liquid phases, have been widely investigated to apply them as alternatives to volatile organic solvent-based ABS. ILs, consisting of fluorinated anions such as  $\text{TF}_2\text{N}$  anions and hexafluorophosphate anions, are immiscible with water, and easily give the ABS.<sup>74</sup> Water-miscible ILs also have a chance to phase-separate from water by further addition of phase-splitting promoters such as inorganic salts.<sup>75</sup> The separated phases of these IL-based ABS are generally stable regardless of outer stimuli such as temperature. On the other hand, our studies demonstrated that suitably designed ILs with moderate hydrophobicity underwent highly temperature-sensitive lower critical solution temperature (LCST)-type phase behaviour after mixing with water.<sup>76–78</sup> These IL/water mixtures exhibited homogeneous states in a certain temperature range but were





content of hydrophobic ILs. General hydrophobic ILs are characterised by their very low saturated water content when mixed with water. Meanwhile, they could be more useful if various compounds were dissolved and stabilised in them. The solubility of water-soluble compounds including proteins in ILs is significantly influenced by the water content. Some hydrophilic ILs containing a small amount of water, classified as hydrated ILs, are capable of dissolving many kinds of proteins.<sup>84–86</sup>

Given the previous results on the hydrated ILs, improving the hydrated state of hydrophobic ILs would be effective for stable dissolution of proteins. Although it is possible to control the water content of hydrophobic ILs by designing component ions, it is difficult to precisely and successively tune the desired amount of saturated water amount in the ILs by this method. Simply adding hydrophilic ILs should also work for controlling the water content. However, possible ion exchange among the mixed ions could remove the unique properties of these ILs. The ZIs features (*i.e.*, inhibition of ion exchange reaction) could also function in this case.

Several imidazolium-based ZIs with sulfonate anions were mixed with a typical hydrophobic IL such as 1-butyl-3-methylimidazolium Tf<sub>2</sub>N ([C<sub>4</sub>mim][Tf<sub>2</sub>N]), and a given amount of water was then added to the mixture. While the saturated water content of neat [C<sub>4</sub>mim][Tf<sub>2</sub>N] was as low as 0.4 wt%, the amount was improved successively up to 17.8 wt% by adding hydrated 3-(1-butyl-3-imidazolio)propanesulfonate-type ZI: **7** (Fig. 3).<sup>87</sup> The solubility and stability of cytochrome *c* (Cyt. *c*), a representative water-soluble heme protein, in the hydrophobic IL/**7**/water (1:1:8 by mol) were then analysed. As shown in Fig. 10, we found that Cyt. *c* was soluble in the hydrated mixture, while Cyt. *c* was totally insoluble in the neat [C<sub>4</sub>mim][Tf<sub>2</sub>N]. The addition of the **7**/water mixture, therefore, facilitated the dissolution of Cyt. *c* in the hydrophobic IL.

The aforementioned imidazolium-type ZI systems, however, improved the water content of hydrophobic IL only in the homogeneous state. After adding an excess amount of water to obtain ABS, the increased amount of saturated water content in the IL phase was quite small. This could be because **7** was mainly dissolved in an aqueous layer due to its highly hydrophilic character. In this regard, we conceived that sufficiently hydrated ZIs being selectively partitioned in hydrophobic IL phases should allow improvement of the water content even in the separated IL phase. We then designed ZIs with finely balanced hydrophobicity that satisfied the requirements.

Fig. 11 (left) shows the structure of the as designed phosphonium-type ZI, **38**. In this study, buffered aqueous potassium phosphate solution (PKB, 100 mmol L<sup>-1</sup>, pH 7.0) was used for potential bio-engineering applications. [C<sub>4</sub>mim][Tf<sub>2</sub>N]/PKB

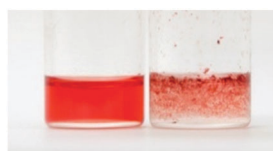


Fig. 10 Photograph of Cyt. *c* (3 mg mL<sup>-1</sup>) mixed with [C<sub>4</sub>mim][Tf<sub>2</sub>N] (right), and [C<sub>4</sub>mim][Tf<sub>2</sub>N]/**7**/water mixture (left).



Fig. 11 Structure of phosphonium-type ZI, **38** (left); saturated water content of the separated IL phase as a function of mixing fractions of ZI in the IL/ZI mixture (right).

mixture with a volume ratio of 1/10 was prepared, and then **38** was added to the mixture. As shown in Fig. 11 (right), the addition of **38** effectively improved the saturated water content of the IL phase from 0.4 wt% to 62.8 wt%.<sup>88</sup> It clearly suggests that the suitably hydrophobic **38**, comprised of the phosphonium cation with long alkyl chains and sulfonate anions, was partitioned in the IL phase, promoting the increase in the maximum water content in the IL phase.

To visually detect the effect of the water content, we checked the solubility of proteins in these mixtures. We chose Cyt. *c* as a typical protein that can easily be detected by the naked eye as red, due to the heme chromophore. The distribution behaviour of Cyt. *c* between the [C<sub>4</sub>mim][Tf<sub>2</sub>N]/**38** mixed phase and PKB phase was then analysed to clarify the effectiveness of the addition of **38**.<sup>88</sup> Obviously, as seen in the photograph in Fig. 12, Cyt. *c* moved from the PKB upper phase to the IL bottom phase upon increasing the added amount of **38**. The distribution ratio (*D*) was then calculated from the absorbance of Cyt. *c* in each phase. When an equimolar amount of **38** was mixed with [C<sub>4</sub>mim][Tf<sub>2</sub>N], the *D* value reached 94%. Since Cyt. *c* was not soluble in both pure and buffer-saturated [C<sub>4</sub>mim][Tf<sub>2</sub>N], it was confirmed that **38** facilitated the dissolution of Cyt. *c* in the [C<sub>4</sub>mim][Tf<sub>2</sub>N]. Spectroscopic analyses confirmed that both the higher-order structure of Cyt. *c* in the vicinity of the heme and its redox activity were maintained in the hydrated IL phase. Furthermore, the Cyt. *c* dissolved in the IL phase can be re-extracted into the aqueous phase by adding PKB with higher concentrations. It follows that Cyt. *c* can be dissolved selectively, stably and reversibly in the [C<sub>4</sub>mim][Tf<sub>2</sub>N] phase by adding **38**.<sup>88</sup> The use of suitably designed ZIs as additives to hydrophobic ILs would be a powerful strategy to control the solubility of bio(macro)molecules in both homogeneous and phase-separated states.

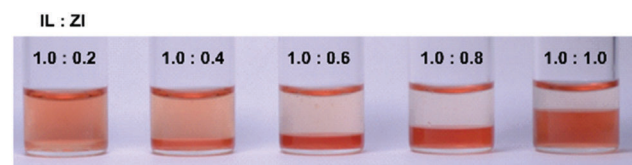


Fig. 12 Extraction of Cyt. *c* from the buffered aqueous upper phase to the [C<sub>4</sub>mim][Tf<sub>2</sub>N] phase by increasing the added amount of ZI **38**.



## 5. Zwitterions as a model interface for cell membranes

It is well-known that phospholipid-based cell membranes play an important role in discriminating intracellular fluid from the extracellular fluid. As initially shown in the famous fluid mosaic model of the cell membrane,<sup>89</sup> the major component of the cell membrane is phospholipids. When looking at the structure of phospholipids carefully, we can find that they are ZI derivatives (Fig. 13). The hydrophilic part of the phospholipid is phosphorylcholine, a pair made up of the cholinium cation and phosphonate anion. This pair has already been analysed to be an excellent medium for a series of proteins when a small amount of water was added.<sup>84–86</sup> This means that the mixture of phosphorylcholine and a small amount of water should be regarded as a liquid model of the hydrophilic part of the cell membrane. This kind of homogeneous ZI/water mixture should be used as a model fluid for membrane components, especially for membrane proteins. It is rather difficult to analyse the activity of proteins on the cell membrane; however, the hydrated phosphorylcholine is a homogeneous liquid, and it is rather easy to analyse the properties and reactivity of membrane proteins in it. This is quite a hot topic and results will be reported in the near future.

It should be mentioned that the surface of the cell membrane can be comprehended to be the assembly of hydrated phosphorylcholine-type ZIs. Since there are concentrated proteins and other molecules, intracellular fluid in the cells should contain no free water. This situation is totally the same as hydrated phosphorylcholine-type ZI. This could be the reason why the pair of the cholinium cation and phosphonate anion showed excellent compatibility with many proteins.<sup>89</sup> In both cases, there is no free water and all water molecules are strongly bound to ions. This unusual situation could contribute to the stable preservation of proteins and other biological molecules. As suggested above, this hydrated ZI is useful for analysing the dynamic and static behaviour of membrane proteins not in the membrane but in a homogeneous solution. This enables us to detect some physicochemical properties of such membrane proteins with conventional apparatus. The dissolution of membrane proteins and other membrane-components in such hydrated ZI is now in progress.



Fig. 13 Schematic representation<sup>90</sup> of the cell membrane, and the structure of a typical phospholipid that can be regarded as a zwitterion-derivative.

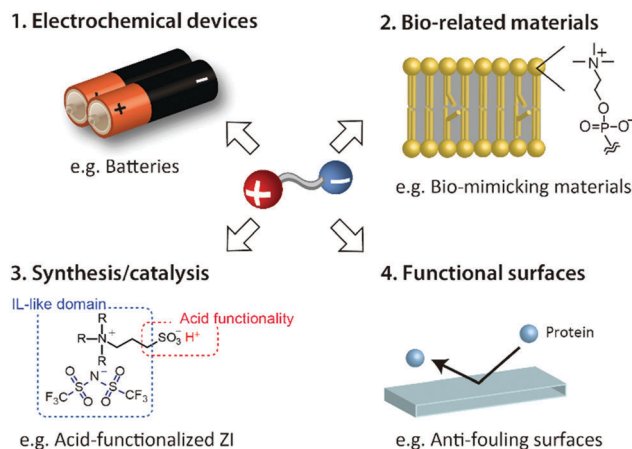


Fig. 14 Expected applications of IL-derived ZIs.

## 6. Future aspects

As mentioned above, ZIs derived from ILs are quite a new class of materials that have unique properties. The introduction of the properties of ILs into ZIs improved their unfavourable inherent properties such as very high  $T_m$ . Basic studies on these ZIs should increase with the attention and expectations of the functional ILs. Some expected applications of IL-derived ZIs are summarised in Fig. 14. These include electrochemical devices, bio-related materials, synthesis/catalysis, and functional surfaces. Although some of these applications have already been investigated by us and other groups, we have not mentioned the details of the studies in this review paper.

## 7. Conclusions

Zwitterions, derived from ionic liquids have unique properties such as relatively low glass transition temperature, small ion conductivity and unique phase behaviour after mixing with water. Furthermore, the mixture of certain zwitterions and a small amount of water can be regarded as an excellent fluid model of cell membranes. These unique properties are comprehended as arising from the nature of ILs and the tethering of both component ions. The development of such zwitterions will be accelerated with the development of ILs.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

Most of this mini-review is from the results of our recent study (H. O.). All these studies have been supported by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (KAKENHI) (17H01225, 24750112, 16K17954). Authors also acknowledge considerable efforts of staffs and students working for ILs and ZIs in our laboratory.





- 53 M. Galin, A. Mathis and J.-C. Galin, *Polym. Adv. Technol.*, 2001, **12**, 574–582.
- 54 A. B. Lowe and C. L. McCormick, *Chem. Rev.*, 2002, **102**, 4177–4189.
- 55 M. Yoshizawa, W. Ogihara and H. Ohno, *Polym. Adv. Technol.*, 2002, **13**, 589–594.
- 56 S. Besner, A. Vallée, G. Bouchard and J. Prud'homme, *Macromolecules*, 1992, **25**, 6480–6488.
- 57 W. Ogihara, N. Suzuki, N. Nakamura and H. Ohno, *Polym. J.*, 2006, **38**, 117–121.
- 58 A. Bozkurt, W. H. Meyer, J. Gutmann and G. Wegner, *Solid State Ionics*, 2003, **164**, 169–176.
- 59 K. D. Kreuer, A. Fuchs, M. Ise, M. Spaeth and J. Maier, *Electrochim. Acta*, 1998, **43**, 1281–1288.
- 60 M. F. H. Schuster, W. H. Meyer, M. Schuster and K. D. Kreuer, *Chem. Mater.*, 2004, **16**, 329–337.
- 61 A. Noda, M. A. B. H. Susan, K. Kudo, S. Mitsushima, K. Hayamizu and M. Watanabe, *J. Phys. Chem. B*, 2003, **107**, 4024–4033.
- 62 P. K. Singh, V. K. Singh and M. Singh, *e-Polym.*, 2007, **7**, 335–368.
- 63 A. Laschewsky, *Polymers*, 2014, **6**, 1544–1601.
- 64 M. Yoshizawa and H. Ohno, *Chem. Lett.*, 1999, 889–890.
- 65 M. Yoshizawa and H. Ohno, *Electrochim. Acta*, 2001, **46**, 1723–1728.
- 66 A. Narita, W. Shibayama, N. Matsumi and H. Ohno, *Polym. Bull.*, 2006, **57**, 109–114.
- 67 M. Galin, E. Marchal, A. Mathis and J.-C. Galin, *Polym. Adv. Technol.*, 1997, **8**, 75–86.
- 68 V. Strehmel, A. Laschewsky and H. Wetzels, *e-Polym.*, 2006, **6**, 131–140.
- 69 V. Strehmel, *Macromol. Symp.*, 2007, **254**, 25–33.
- 70 V. Strehmel, H. Wetzels, A. Laschewsky, E. Moldenhauer and T. Klein, *Polym. Adv. Technol.*, 2008, **19**, 1383–1390.
- 71 R. H. Brown, A. J. Duncan, J.-H. Choi, J. K. Park, T. Wu, D. J. Leo, K. I. Winey, R. B. Moore and T. E. Long, *Macromolecules*, 2010, **43**, 790–796.
- 72 L. M. Gan, P. Y. Chow, Z. Liu, M. Han and C. H. Quek, *Chem. Commun.*, 2005, 4459–4461.
- 73 S. Ueda, J. Kagimoto, T. Ichikawa, T. Kato and H. Ohno, *Adv. Mater.*, 2011, **23**, 3071–3074.
- 74 P. Bonhôte, A.-P. Dias, N. Papageorgiou, K. Kalyanasundaram and M. Grätzel, *Inorg. Chem.*, 1996, **35**, 1168–1178.
- 75 M. G. Freire, A. F. M. Claudio, J. M. M. Araujo, J. A. P. Coutinho, I. M. Marrucho, J. N. C. Lopes and L. P. N. Rebelo, *Chem. Soc. Rev.*, 2012, **41**, 4966–4995.
- 76 K. Fukumoto and H. Ohno, *Angew. Chem., Int. Ed.*, 2007, **46**, 1852–1855.
- 77 Y. Kohno, H. Arai, S. Saita and H. Ohno, *Aust. J. Chem.*, 2011, **64**, 1560–1567.
- 78 Y. Kohno and H. Ohno, *Chem. Commun.*, 2012, **48**, 7119–7130.
- 79 Y. Kohno and H. Ohno, *Phys. Chem. Chem. Phys.*, 2012, **14**, 5063–5070.
- 80 H. Ohno, K. Fujita and Y. Kohno, *Phys. Chem. Chem. Phys.*, 2015, **17**, 14454–14460.
- 81 Y. Fukaya and H. Ohno, *Phys. Chem. Chem. Phys.*, 2013, **15**, 14941–14944.
- 82 Y. Mieno, Y. Kohno, S. Saita and H. Ohno, *Chem. – Eur. J.*, 2016, **22**, 12262–12265.
- 83 S. Saita, Y. Mieno, Y. Kohno and H. Ohno, *Chem. Commun.*, 2014, **50**, 15450–15452.
- 84 K. Fujita, D. R. MacFarlane and M. Forsyth, *Chem. Commun.*, 2005, 4804–4806.
- 85 K. Fujita and H. Ohno, *Biopolymers*, 2010, **93**, 1093–1099.
- 86 K. Fujita, D. R. MacFarlane, M. Forsyth, M. Yoshizawa-Fujita, K. Murata, N. Nakamura and H. Ohno, *Biomacromolecules*, 2007, **8**, 2080–2086.
- 87 Y. Ito, Y. Kohno, N. Nakamura and H. Ohno, *Chem. Commun.*, 2012, **48**, 11220–11222.
- 88 Y. Ito, Y. Kohno, N. Nakamura and H. Ohno, *Int. J. Mol. Sci.*, 2013, **14**, 18350–18361.
- 89 S. J. Singer and G. L. Nicolson, *Science*, 1972, **175**, 720–773.
- 90 Figure partly modified from the original one: <http://genkir.yokup.com/mainhp/category66/entry553.html>.

