

# A Simple Approach to Achieve Self-Buffering Protic Ionic Liquid-Water Mixtures

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**Abstract:** Ionic liquid (IL)-water mixtures have drawn increasing attention in a range of applications ranging from chemical synthesis and separation to bioscience and energy applications. The acid-basic nature of ILs is often an important property to be considered when selecting and designing ILs. Herein, we evaluated this IL property by correlating the stoichiometry of a protic IL and pH of IL-water mixtures. We then developed a simple method to achieve self-buffering protic IL-water mixtures by titrating buffering agents. The rule of buffering protic IL-water mixtures was proposed to be linearly related to pIL ion concentration and correlated with ionicity. Through this approach, self-buffering capability can be achieved in protic IL-water mixtures without significantly changing the ion concentration.

## Introduction

Ionic liquids (ILs) are salts with melting points below 100 °C. One of the most attractive properties of ILs is the tunability of the component ions. As designable solvents, ILs have been extensively studied in numerous research fields over the past two decades and extensive efforts have been devoted to developing novel IL systems<sup>[1]</sup>. Understanding of key IL properties is essential for the design process. Some key IL properties include polarity, hydrophobicity, viscosity, purity, Kamlet-Taft parameters and acid-basic properties<sup>[1a, 1e, 2]</sup>.

Since water is the most universal fluid in nature and essential for most creatures<sup>[3]</sup>, using water as co-solvent for ILs has been an approach employed by many applications<sup>[4]</sup>. In particular, studies on IL-water mixtures using hydrophilic ILs, whose properties have been partially modulated by the water (e.g., polarity, viscosity, ionic strength and hydrogen-bonding interactions)<sup>[5]</sup>, are of great interest for bioseparation, biopreservation and biocatalysis<sup>[6]</sup>. In this regard, the benefits of IL-water mixtu

res are simplified purification of proteins, improved solubility of hydrophobic substrates, advanced stabilization of enzymes and the suppression of side reactions of enzymatic reactions<sup>[7]</sup>. Hydrophilic ILs mixed with water have been studied and identified into 3 states as outlined before<sup>[4a]</sup>: (1) Hydrated IL with no free water contained (normally around 80wt% or 25 mol% ILs) and it was reported to stabilize proteins<sup>[8]</sup>, however, it was too viscous to perform enzymatic

reactions<sup>[9]</sup>; (2) IL-water mixture containing 20-80 wt% water (approximately 2 mol% – 20 mol% ILs) with incompletely dissociated ions<sup>[4a, 10]</sup>, which can be used for biocatalysis<sup>[11]</sup>. (3) Salt solution with dissociate ions in more than 80 wt% water (below 2 mol%), and it was mostly studied but it loses most IL properties and resembles the ordinary salts. And thus it is likely to be involved in ion specific effect rather than IL effect<sup>[6a, 12]</sup>. Likely, the boundary of the three states varies with different types of ILs.

Numerous studies have demonstrated the combination of cation and anion of ILs greatly influenced the pH of IL-water mixtures, which is significant for bio-applications<sup>[6a, 13]</sup>. A class of ILs, protic ILs (pILs) formed by Brønsted acid and Brønsted base with transferred proton, is a good case for the study since some of the pKa values of the precursor acid or base are known<sup>[14]</sup>. Dai and coworkers have used acids with different pKa to tune the basicity of pILs<sup>[15]</sup>, which could consequently impact the pH of pIL-water mixtures. Previous studies also indicated that  $\Delta pK_a$  (the difference in the pKa values of precursor base and acid) is important to the ionicity of pILs<sup>[16]</sup>. The ionicity refers to the degree of ionic dissociation<sup>[17]</sup>, which also would affect the pH of aqueous ILs. To overcome the intrinsic pH, a few studies developed IL-water mixtures with controlled pH by mixing or adding a small amount of acid or base with slightly changing ion concentration and some systems have been used for biocatalysis<sup>[11b, 18]</sup>. However, this system is similar to a non-stoichiometric IL-water mixtures with volatile components and unknown buffering region. In this case, IL buffers were developed, such as self-buffering ionic liquids (mainly Good's buffer ILs)<sup>[19]</sup> and IL-buffer biphasic systems<sup>[20]</sup>. However, the former non-aqueous IL buffer only lies at a limited pH region and the selection of ions is confined, e.g., hydrated choline dihydrogen phosphate buffer was developed with controllable proton activity<sup>[21]</sup>, but the ion concentration dramatically increased by adding an acid/base species owing to the buffering nature of dihydrogen phosphate and hence the nature of the anion has been totally changed. As for the IL-buffer biphasic systems, namely hydrophobic ILs/water systems, the lower critical solution temperature (LCST)-type phase transition of IL-water mixtures has showed to facilitate the extraction of proteins. However, the selection of ILs and condition of phase changes are limited, and a major drawback is that most ILs affect the pH of the aqueous buffer solution.

Up to now, most studies on aqueous IL buffers focused on the IL salt solutions (state 3) and hydrated ILs (state 1). IL salt solutions lack IL specific properties and are simply salt

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solutions, while hydrated ILs typically have limited and/or unrecognizable pH regions although some studies have investigated the dissociation constants in ILs<sup>[22]</sup>. However, only a few reliable results are available on bio-applications using self-buffering IL-water mixtures (state 2 containing approximately 2–20 mol% ILs), such as chloroperoxidase-catalyzed oxidation<sup>[11c]</sup> and protease-catalyzed ligation<sup>[11d]</sup>. And little research has been conducted on developing stable, biocompatible and controllable self-buffering IL-water mixtures. Here most of the IL properties are retained and thereby this IL–water region is the most promising for bio-applications.

In the present work, a series of hydrophilic pILs formed by simple amines and acids with different pKa was selected (Table 1). We first evaluated the influence of stoichiometry of pILs on proton transfer of pILs (the proton exchange from the Brønsted acid to base) and pH of pIL-water mixtures (ca. 8 mol%). This will help those who use pIL-water mixtures and consider precursor acid or base as impurity. Then a strategy using buffering agent to overcome the intrinsic pH limitations of most pIL-water mixtures ranging around 2–20 mol% is proposed.

**Table 1.** Cations and anions of pILs used in this study.

Cations		pKa	Anions		pKa*
Triethylammonium (Tea)		10.7	Nitrate (N)	$\text{NO}_3^-$	-1.4
Ethylammonium (Ea)		10.7	Mesylate (Ms)	$\text{CH}_3\text{SO}_3^-$	-1.9
Propylammonium (Prpa)		10.7	Acetate (Ac)	$\text{CH}_3\text{COO}^-$	4.8
n-Butylammonium (Bta)		10.6	Formate (For)	$\text{HCOO}^-$	3.8
Heptylammonium (Hpta)		10.7			

\* denotes the pKa values of the conjugated acids of the anions.

## Results and Discussion

### Effect of Stoichiometry on pH

Owing to the proton transfer of pILs, the hydrogen bond between cation and anion differs from aprotic ILs. However, the proton transfer also varies with pILs. Firstly, whether the stoichiometries of acid and base affect the proton transfer (or proton activity, which is represented by N-H chemical shift from NMR since the shift of this exchangeable proton has information about how strongly the proton is associated with the base) of pILs and pH of pIL-water mixtures were evaluated. This N-H chemical shift is a good indicator of proton transfer which has been studied over years<sup>[23]</sup>. TeaMs was selected as it has previously been used in bio-applications<sup>[11b, 24]</sup>.

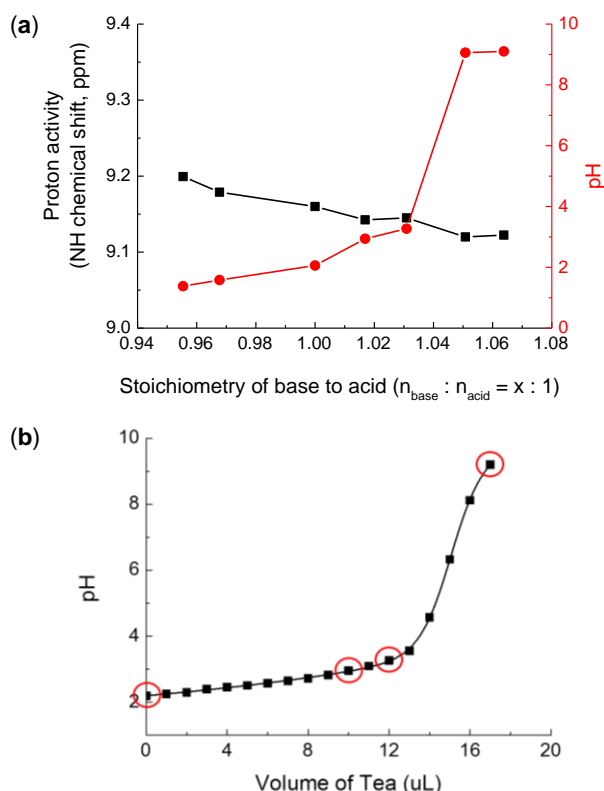
Figure 1a shows the proton activity of TeaMs and pH of TeaMs-water mixtures (49.9 wt% or 8.3 mol% which equals

to molar ratio of water and pIL 11:1) as a function of stoichiometry of base to acid ( $n_{\text{base}} : n_{\text{acid}} = x : 1$ ). It is seen that the proton activity of non-stoichiometric TeaMs shifted downfield in a narrow range from 9.20 ppm to 9.12 ppm along with stoichiometry  $x$  from 0.95 to 1.06. The change in the N-H shift to slightly higher fields in acid rich environment and to slightly lower field in base rich environments suggests that the absolute proton transfer is being influenced. This is expected that N-H peak is sensitive to the acidic/basic environment. The absolute shift observed is small less than 1 ppm. When larger amounts of excess base or acid is used larger shift are observed in this peak<sup>[25]</sup>. Some similar observations on N-H shift have also been reported for pIL mixtures<sup>[26]</sup>. Thus in this study, it can be deduced that the influence of stoichiometry of the pIL on the proton transfer of TeaMs seems to be negligible. Interestingly, the pH of TeaMs-water mixtures at 8.3 mol% gradually increased initially (stoichiometry  $x = 0.95 - 1.03$ ), but in the range of stoichiometry  $x = 1.03 - 1.06$ , pH changed from 3.27 to 9.1. Generally, this two different trends of proton activity of non-stoichiometric TeaMs and the pH of pIL-water mixtures indicate that these two values are not directly related, considering that the addition of water totally changed the proton transfer of ILs<sup>[5d]</sup>. Regarding the acidity of TeaMs-water mixtures, the anion dominates the intrinsic pH since the strength of methane sulfonic acid ( $\text{pKa} = -1.9$ ) is much stronger than that of trimethylamine ( $\text{pKa} = 10.75$ ). Also, the excess hydronium ions resulted from the equilibrium of all ions including hydronium, hydroxide, dissociated cation and anion in the mixtures, and it has been discussed previously<sup>[11b]</sup>. Nonetheless, when  $x$  reached to 1.03, the pH increase indicates that the excess hydronium was buffered by the base triethylamine and the pH became influenced by the base.

To further understand the process of pH increase by the excess base, Figure 1b shows a representative pH-metric titration profile of TeaMs-water mixtures (8.3 mol% pIL) with addition of neat triethylamine. It can be seen that pH of TeaMs-water solution was initially in the range of 2–3 with the addition of trimethylamine up to  $x = 1.03$ . Further additions resulted in a dramatic pH increase, while additions beyond  $x = 1.06$  led to phase separation. This is probably owing to the hydrophobicity of triethylamine and it is in agreement with previous study on triethylammonium acetate which shows that this tertiary amine might be not easily protonated<sup>[27]</sup>. Due to this limitation, no plateau was observed for additions up to  $x = 1.05$ , and it could be assumed that precursor amine might be only an additive for TeaMs-water mixtures. Moreover, it is seen that a small amount of excess base or acid (e.g., 3 mol% excess base) greatly impacted the pH of aqueous pILs. Although this buffered TeaMs-water mixture could be used as a catalytic media for enzymes at certain pH, it is unlikely that this system could bear the pH change which occurs during the bio-applications<sup>[11b]</sup>. This ultimately limits the performance of the proteins or enzymes. Furthermore, this

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approach of using the corresponding base of the pIL creates a volatile component of the solution<sup>[28]</sup>.



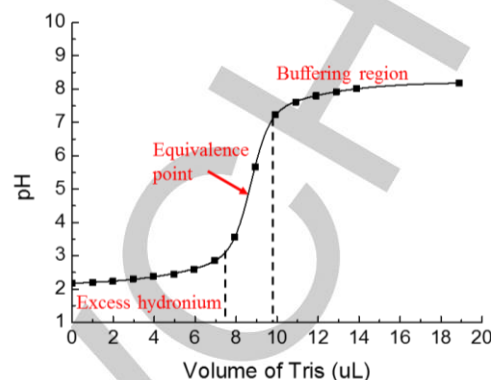
**Figure 1.** (a) Proton activity of TeaMs and pH of non-stoichiometric TeaMs-water mixtures (at 8.3 mol%) as a function of stoichiometry of base to acid ( $n_{\text{base}} : n_{\text{acid}} = x : 1$ ). (b) pH-metric titration profile of TeaMs-water mixtures (at 8.3 mol%) with addition of triethylamine. The red circles represent the stoichiometry  $x = 1.00, 1.02, 1.03$  and  $1.05$ , respectively.

### Titration of TeaMs with Buffering Agents

Considering the rapid pH shift of the non-stoichiometric TeaMs-water solution, another strategy to buffer pIL-water mixtures was investigated by using buffering agents.

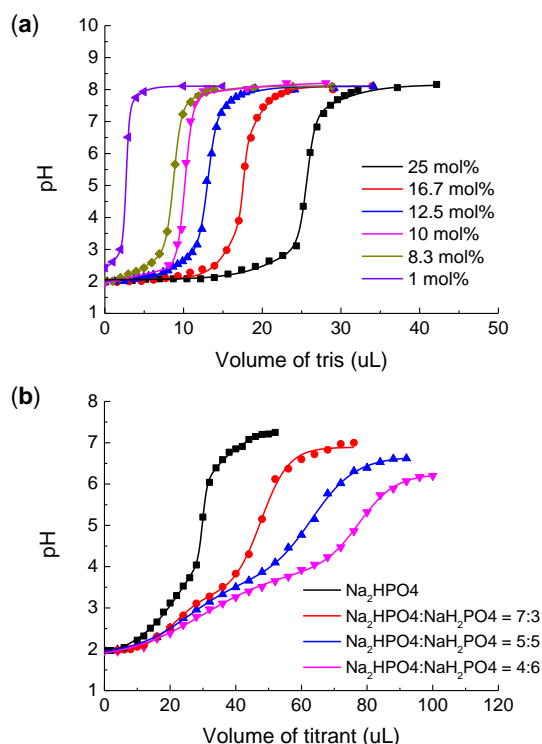
Figure 2 shows a representative pH-metric titration profile of TeaMs-water mixtures (at 8.3 mol%) with addition of the well-known “Tris buffer” ( $(\text{HOCH}_2)_3\text{CNH}_2$ , 2 mol/L).  $\text{pK}_a$  of Tris is 8.1 and Tris buffer ranges from pH 7 to 9. Generally, the added Tris increased the pH until a new equilibrium was established and the curve displayed three domains. TeaMs-water possessed a short plateau and the first plateau corresponds to the excess hydronium ions resulted from the relative strong acidity of the conjugated acid of the anion. Increasing the amount of Tris, the equivalence point is observed showing a clear pH jump. Further increasing Tris concentration resulted in a new buffering plateau corresponding to the Tris buffer. It could be inferred that addition of excess Tris might reach a second equivalence point, however, the ion concentration (referring to the molar concentration of the pIL) will be totally changed and not the focus of the study here. Indeed, this buffering approach only

decreased the ion concentration of TeaMs in water by less than 10% of its original value (from 8.33 mol% to 8.21 mol% at pH 8). This enables pIL properties to be maintained in line with state 2 IL-water mixtures mentioned above.



**Figure 2.** pH-metric titration profile of TeaMs-water mixtures (8.3 mol%) with addition of Tris (2 mol/L).

In order to investigate if this method can be used for other ion concentration of the pIL and pH, Figure 3a shows pH-metric titration profile of TeaMs-water mixtures by Tris at different ion concentration ranging from 1-25 mol%. The buffering regions were all maintained at around pH 8, while the amount of buffering agents increased as a function of pIL ion concentration and dilution effects upon Tris addition were negligible. By using the concentrated phosphate buffer (2 mol/L), the self-buffering TeaMs-water mixtures at different pH can also be obtained (Figure 3b). Because of the three  $\text{pK}_a$  values of phosphoric acid, it is seen that the first equivalence point was reached by a small pH jump to about 3 ( $\text{pK}_{a1}$  of phosphoric acid = 2.12). Addition of excess titrant, the disodium hydrogen phosphate, or the  $\text{pK}_{a2} = 7.21$ , gave rise to a second pH jump, leading to a buffer plateau at different pH, i.e. around pH 7.3, 6.9, 6.6 and 6.2, respectively. The pH is consistent with the trend of pH of the original aqueous phosphate mixtures, i.e., pH 8, 7.2, 6.8 and 6.4, respectively. Moreover, it can be seen that more basic solutions, e.g.,  $\text{Na}_2\text{HPO}_4$ , increased the pH more quickly compared with the others. In other words, more buffering agents were required if the pH of pIL-water mixtures was closer to the pH of the buffering agent.

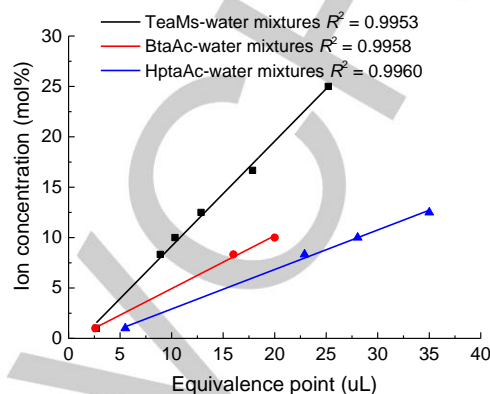


**Figure 3.** pH-metric titration profile of TeaMs-water mixtures (8.3 mol%): (a) by Tris as a function of molar concentration of TeaMs and (b) by aqueous phosphate mixtures (2 mol/L, the ratio denotes mass ratio of sodium dihydrogen phosphate and disodium hydrogen phosphate) for achieving different pH buffered regions.

## Rules of Buffering

Next, we investigated the rules of self-buffering pIL-water mixtures and if all pIL-water mixtures can be buffered by applying the same set of rules. Since the buffering agents used depend on the intrinsic pH influenced by the anion and dissociated ions of pILs, we suggest that the ionicity impacts the equivalence point of the titration. Herein, we included another two pILs with reported ionicity, butylammonium acetate (BtaAc) and heptylammonium acetate (HptaAc)<sup>[16b]</sup>. TeaMs has a better ionicity with the  $\Delta pK_a$  much higher than the other two. The ionicity of BtaAc is a little higher than that of HptaAc according to Walden plot, which consists of the log (equivalent conductivity) plotted against the fluidity<sup>[17b]</sup>. Figure 4 shows the correlation between equivalence point of the pH-titration curves by Tris (Figure S1 contains titration curves for both pILs) and molar concentration. A good fit between these two values was obtained in all three pIL-water mixtures. In regards to the equivalence point, it could represent the degree of dissociated ions of pILs since these ions were titrated quantitatively by Tris. Therefore, by comparing the three different pILs, the relation between ionicity and ion dissociation as a function of ion concentration could be inferred. This plot emphasizes the fact that (1) as for one pIL, the water dissociates the pIL linearly as a function of water content, and (2) at same ion concentration,

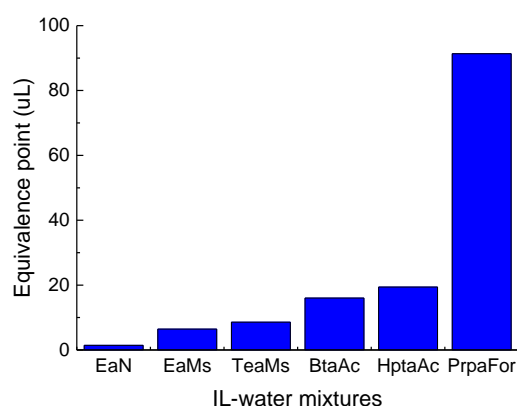
pILs with poorer ionicity dissociate more in water (being hydrated). Also, according to this curve, we assume that, if the ion concentration extended to 100%, we could know the relative degree of the unprotonated ions and a self-buffering neat ILs might be achieved. Thus pH titration could be an excellent way to get insights into ionicity of pILs.



**Figure 4.** Correlation between pIL ion concentration and equivalent point; equivalent points were obtained from of pH-metric titration profiles of pIL-water mixtures by Tris (2 mol/L) at different pIL molar concentrations (1.0 mol% to 16.7 mol%)(Figure S1).

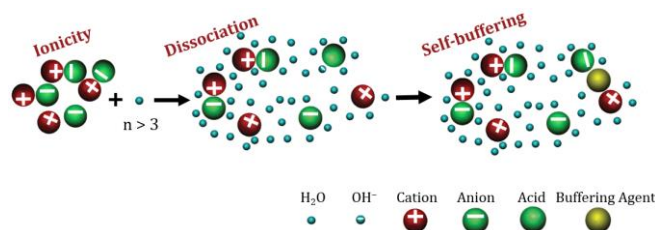
We then performed additional titrations on different pILs at 8.3 mol% as shown in Figure 5. Ethylammonium nitrate (EaN) has been reported as a good pIL with strong proton transfer while ethylammonium mesylate (EaMs) with a high  $\Delta pK_a$  also shows a good ionicity<sup>[16a]</sup>. Another pIL n-propylammonium formate (PrpaFor) with poor ionicity reported before<sup>[29]</sup> was also included. Generally, carboxylate base pILs have poor ionicity owing to the high  $pK_a$  of carboxylic acids (weak acids). Figure 5 shows the equivalence points corresponded to the trend of ionicity for the pILs studied. EaN required a very small amount of buffering agent, on the contrary, maximum Tris (91 uL) achieved the self-buffering PrpaFor-water mixture at pH 8 (Figure S2). In principle, the low ionicity, the less ion species and more aggregates and neutral species (precursor acid/base), thus resulting to the more buffering agents used to change the pH. From another hand, considering the high  $pK_a$  of carboxylic acid, it could be assumed that the weak acids will be formed as a molecular state in the solution, while the simple amine normally has similar  $pK_a$  (around 10) with a high dissociation. As a result, there is an equilibrium of the carboxylate ion and carboxylic acid. For example of PrpaFor, with adding Tris in the pIL-water mixtures, the reaction towards  $2CH_3CH_2CH_2NH_3^+ + 2CH_3COO^- + H_2O \rightarrow 2CH_3CH_2CH_2NH_3^+ + CH_3COO^- + CH_3COOH + OH^-$ . However, the equilibrium of ions in water depends on the relative strength of precursor acid and base, for instance, the equilibrium of EaN might lead to more  $H_3O^+$  as previous work mentioned<sup>[30]</sup>.





**Figure 5.** The equivalence point of pH titration profiles as a function of pIL-water mixtures (8.3 mol%). Equivalence points were acquired from pH-metric titration profiles (Figure S2).

On the basis of the arguments outlined above, the change of pH during buffering pIL-water mixtures can be described as shown in Figure 6. (1, Ionicity): pILs favor the formation of cations and anions owing to the proton transfer. The high ionicity of pILs (more ion species) leads to the complete proton transfer and strong hydrogen bonding network<sup>[17a, 31]</sup>. Depending on the ionicity, there might exist ion pairs, dissociated ions, ion pair aggregates, and even neutral species. And it is likely that those certain amount of species impact the acid-base property of neat pILs, as reported before<sup>[14b]</sup>. (2, dissociation) Along with the addition of water, changing from state 1 to state 2, pILs tend to be linearly dissociated into separated cation and anion, ion pair, or aggregates<sup>[10c, 32]</sup>. The ratio of these components depends on the ionicity of pILs and the equilibrium of all components leads to a pH value of pILs-water mixtures. Notably, the pH is dominated by the difference of the strength of the conjugated base and acid. Since the pKa of the base (the simple amine) is normally similar, it could be assumed the pKa of anions dominates the pH of the pIL-water mixtures, e.g., a weak acid forms a basic solution and vice versa. (3, self-buffering) In order to attain self-buffering pIL-water mixtures and maintain the pIL ion concentration, the addition of buffering agent could shift the equilibrium of the components even for pILs with relatively high ionicity. Specifically, the small amount of buffering agent competed with the associated ions and neutral species. It is hypothesized that the ionicity predominates the buffering agents used for pIL-water mixtures, in another word, pILs with poorer ionicity requires more buffering agents. As it stands, this is a good strategy of achieving self-buffering pIL-water mixtures without altering ion concentration.



**Figure 6.** Schematic illustration of the dissociation of ions and self-buffering in pIL-water mixtures.  $n > 3$  refers to the molar ratio of water and pIL above 3 where the ion concentration of pILs is normally less than 25 mol%.

As a note, our proposed method may be limited in other types of pILs. It is much applicable if the pH of self-buffering agent is much higher than the pH of pIL-water mixtures. For example, we did not achieve the typical pH titration curve using a small amount of Tris at high concentrations of BtaAc and HptaAc. In these cases, we could select other buffering agents, such as a range of Good's buffers (like HEPES, TAPS, or CAPS)<sup>[33]</sup>.

## Conclusions

In this work, we evaluated the proton activity and pH of TeaMs-water mixtures (ca. 8 mol% or 50 wt%) as a function of stoichiometry of base to acid, indicating that the stoichiometry markedly changed the pH while proton activity is not directly related to pH. Then a strategy was developed to achieve self-buffering pIL-water mixtures. By comparing pH titration profiles of different pIL-water mixtures, we suggest that the buffering process is linearly related to pIL ion concentration and correlates with ionicity. Through the careful control of the relative stoichiometry and the use of self-buffering agent, this convenient and cost-effective method could help the optimization and utilization of pIL-water mixtures (state 2) in processes which are sensitive to pH, such as bioseparation, biopreservation and biocatalysis. This methodology might be extended to hydrated pILs or neat pILs based on the relation of ion concentration and ionicity.

## Supporting Information Summary

Experimental section and pH-metric titration profile of pIL-water mixtures (TeaMs, BtaAc, HptaAc, EaN, EaMs and PrpaFor) can be found in the Supporting Information.

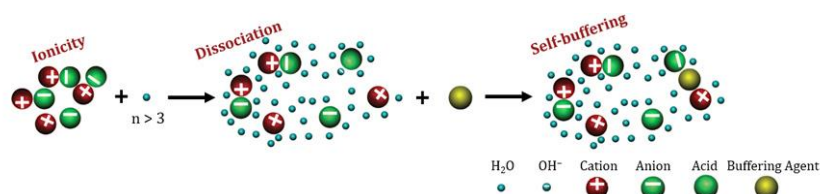
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**Keywords:** dissociation • ionicity • protic ionic liquid • self-buffering

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A simple method to achieve self-buffering protic IL-water mixtures at certain pH has been developed. The approach proceeded by titrating the buffering agents without altering the ion concentration. It is suggested that the buffering process is related to the pIL ionicity, dissociation and ion concentration.