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A critical assessment of the mechanisms governing the formation of aqueous biphasic systems composed of protic ionic liquids and polyethylene glycol†

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An extensive study on the formation of aqueous biphasic systems (ABS) using aqueous solutions of protic ionic liquids (PILs) and polyethylene glycol (PEG) was performed in order to understand the mechanisms underlying the phase separation. Aqueous solutions of PEG polymers with different molecular weights (600, 1000, 2000, and 3400 g mol⁻¹) and several *N*-alkyl-, dialkyl-, and trialkyl-ammonium salts of acetate, propanoate, butanoate, hexanoate and octanoate were prepared and their ability to form ABS at several temperatures assessed. The ternary liquid–liquid phase diagrams were determined at several temperatures, as well as binary PIL (or salt)–PEG–1000 and salt–water solubility data to better clarify the mechanisms responsible for the phase separation. All data gathered indicate that the formation of PEG–PIL-based ABS is mainly governed by the PIL–PEG mutual interactions, where PILs with a higher solubility in the polymer exhibit a lower aptitude to form ABS displaying thus a smaller biphasic region, for which a direct correlation was identified. The effects of the molecular weight and temperature of the polymer were also addressed. The increase of the PEG hydrophobicity or molecular weight favours the phase separation, whereas the effect of temperature was found to be more complex and dependent on the nature of the PIL, with an increase or decrease of the biphasic regime with an increase in temperature.

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Introduction

In order to avoid the use of organic solvents in the extraction of target compounds from aqueous solutions, efforts have been made in the development of aqueous biphasic systems (ABS). Due to their benign environment for biomolecules, ABS are gaining importance in biotechnological- and pharmaceutical-related industries, and are being scaled-up for industrial applications.^{1–4} Usually ABS are formed using polyethylene glycol (PEG) because it easily forms a biphasic system with

aqueous solutions of inorganic salts (*e.g.*, K₂HPO₄, K₃PO₄, K₂CO₃, KOH, Na₂HPO₄, or Na₂SO₄)^{5–7} and with other polymers (*e.g.*, dextran, derivatives of starch,⁶ cellulose, polyvinyl alcohol,⁸ hydroxypropyl starch (HPS),⁹ or ethylhydroxy ethyl cellulose (EHEC)¹⁰). Although conventional PEG-based ABS have been widely studied in the last few decades, their application has been limited by the low polarity range between their coexisting phases,¹¹ resulting thus in systems with low selectivity.

In 2003, one of us demonstrated the creation of ABS by the addition of an inorganic salt (K₃PO₄) to aqueous solutions of a hydrophilic ionic liquid (IL, [C₄C₁im]Cl).¹² ILs are commonly defined as molten salts with melting temperatures lower than 100 °C, constituted by large organic cations and organic or inorganic anions with disperse charges that decrease the cation–anion interactions.^{13,14} Since aprotic ILs provide additional physical and chemical features over common solvents, they have been proposed as potential candidates to be used in the creation of ABS.^{13,15} Remarkably, IL-based ABS have been shown to overcome some of the main limitations of typical polymer–salt or polymer–polymer systems since it is possible to tailor the properties and affinities of the IL-rich phase by adequately choosing the IL chemical structure.¹⁶ In general, IL-based ABS have shown a

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† Electronic supplementary information (ESI) available: Experimental weight fraction data for the binodal curves; the detailed synthesis procedures of PILs and the description of characterization measurements; pH values of each PIL-based ABS in the monophasic region; and the nominal values of each minimum concentration point (C). See DOI: 10.1039/c6cp06289j

better extractive performance compared to traditional polymer-based ABS.¹⁵

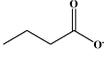
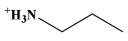
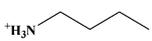
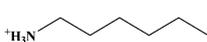
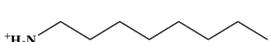
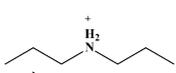
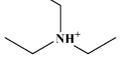
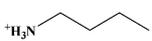
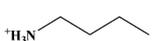
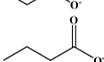
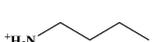
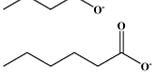
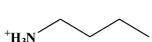
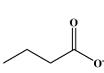
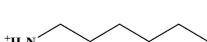
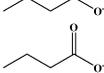
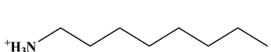
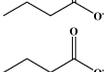
Among all the IL-based ABS studied hitherto, the more recent polymer-IL-based ABS boost their applicability since they increase the hydrophilic and hydrophobic range of the coexisting phases, allowing thus more selective separations to be achieved.^{15–17} Although PEG-IL-ABS provide better control of the selective partitioning,^{18,19} they are also far more complex, particularly when considering the mechanisms which dominate their phase demixing.^{20–24} It has been demonstrated that besides the solvation of ions in water, in PEG-IL-ABS other types of interactions, mainly those between the polymer and the IL, have a strong influence in the molecular processes behind phase separation.^{20,21}

Protic ILs (PILs) provide additional physical and chemical features over aprotic ones.²⁵ This particular subset of ILs are easily produced through the combination of a Brønsted acid and a Brønsted base. Besides the common features of ILs, PILs exhibit as a key characteristic the proton transfer from the acid to the base, allowing the presence of proton-donor and -acceptor sites,

which are fundamental to create hydrogen-bonded networks.^{25,26} In addition, some PILs are distillable, with their boiling temperatures lower than their decomposition temperature.^{25,27} PILs are also more economic alternatives compared to the more expensive aprotic-based ILs. Accordingly, PILs have also been proposed as potential candidates to be used in the preparation of ABS with polymers;²⁸ yet, the molecular-level mechanisms responsible for liquid-liquid demixing are still poorly investigated and understood.

Due to the particular features of PILs and the respective ABS, this work aims at understanding the chemistry behind the formation of PEG-PIL ABS, and in particular at evaluating how their cation/anion alkyl chain length and the balance of proton acceptance and proton donation takes place and influences the phase separation. For this purpose, novel ternary phase diagrams of systems based on mixtures of three phase forming agents with strong hydrogen bonding ability (PILs, low molecular weight PEG polymers, and water) were experimentally determined at 298, 313, 323, 333 and 343 K. A series of structurally distinct PILs was selected to study the effects of both the alkyl chain length on the cation and the anion and cation isomerism through ABS

Table 1 Chemical structure and purity of the studied PILs, water content (%), melting point (m.p.) and their solubility in PEG-1000 at 323 K (mol mol⁻¹). The associated uncertainty associated with the water content is below 0.05 wt%, and the associated uncertainty of the PIL solubility is approximately 7% of the absolute value, according to the results of three replicates

Name (%purity)	Cation	Anion	Water content (%)	m.p. (K)	PIL solubility in PEG-1000 (mol mol ⁻¹)
Ammonium acetate [NH ₄][OAc] (99.0)	NH ₄ ⁺		1.10	387	0.59
Ammonium butanoate [NH ₄][But] (99.1)	NH ₄ ⁺		0.99	(Liquid at RT)	T.S.
Propylammonium acetate [C ₃ NH ₃][OAc] (98.9)			0.35	(Liquid at RT)	2.66
Butylammonium acetate [C ₄ NH ₃][OAc] (98.7)			1.25	(Liquid at RT)	2.91
Hexylammonium acetate [C ₆ NH ₃][OAc] (98.3)			0.83	326	2.14
Octylammonium acetate [C ₈ NH ₃][OAc] (99.0)			0.65	321	0.88
Dipropylammonium acetate [C ₃ C ₃ NH ₂][OAc] (98.1)			0.37	326	T.S.
Triethylammonium acetate [C ₂ C ₂ C ₂ NH][OAc] (99.4)			0.29	(Liquid at RT)	T.S.
Butylammonium propanoate [C ₄ NH ₃][Pro] (98.1)			0.66	(Liquid at RT)	2.16
Butylammonium butanoate [C ₄ NH ₃][But] (98.9)			0.52	(Liquid at RT)	1.65
Butylammonium hexanoate [C ₄ NH ₃][Hex] (98.0)			0.11	(Liquid at RT)	1.01
Propylammonium butanoate [C ₃ NH ₃][But] (98.7)			0.23	(Liquid at RT)	2.24
Hexylammonium butanoate [C ₆ NH ₃][But] (99.0)			0.16	(Liquid at RT)	0.78
Octylammonium butanoate [C ₈ NH ₃][But] (99.0)			0.79	305	0.59

formation with aqueous solutions of different molecular weight PEGs (600, 1000, 2000, 3400 g mol⁻¹). The PILs investigated comprise a range of salts of variable hydrophobicity and were synthesized by us²⁹ by the combination of different amines and carboxylic acids, and include propylammonium acetate, [C₃NH₃][OAc]; butylammonium acetate, [C₄NH₃][OAc]; hexylammonium acetate, [C₆NH₃][OAc]; octylammonium acetate, [C₈NH₃][OAc]; triethylammonium acetate, [C₂C₂C₂NH][OAc]; dipropylammonium acetate, [C₃C₃NH₂][OAc]; propylammonium butylacetate, [C₃NH₃][But]; hexylammonium butanoate, [C₆NH₃][But]; butylammonium butanoate, [C₄NH₃][But]; butylammonium propanoate, [C₄NH₃][Pro]; and butylammonium hexanoate, [C₄NH₃][Hex]. For comparison purposes, similar salts, namely ammonium acetate ([NH₄][OAc]) and ammonium butanoate ([NH₄][But]), were also evaluated as possible phase forming agents of PEG-PIL-based ABS.

Results and discussion

Properties and solubilities of PILs

Several ammonium-based PILs, namely [C₃NH₃][OAc], [C₄NH₃][OAc], [C₆NH₃][OAc], [C₈NH₃][OAc], [C₂C₂C₂NH][OAc], [C₃C₃NH₂][OAc], [C₄NH₃][But], [C₄NH₃][Pro], [C₄NH₃][Hex], [C₃NH₃][But], [C₆NH₃][But] and [C₈NH₃][But] (Table 1), were synthesized by us according to the procedure described previously by McCrary *et al.*,²⁹ and were used to evaluate the influence of the length of the cation and anion alkyl chains, as well as the cationic isomerism, on ABS formation when combined with four PEGs (PEG-600, PEG-1000, PEG-2000, and PEG-3400). The ammonium salts of some carboxylate anions were also investigated, namely [NH₄][OAc] and [NH₄][But]. The respective chemical structures, melting points (m.p.), water contents, and solubilities in PEG-1000 are presented in Table 1. It is important to note that the series of salts and PILs studied include one organic salt with a high melting temperature, [NH₄][OAc] (387 K), three PILs with melting temperatures ranging between 321 and 326 K, and the remaining PILs which are liquid at room temperature. As PILs were synthesized through the combination of a Brønsted acid and a Brønsted base, attention must be paid to the pH of each system, since at different pH values the species in equilibrium could change, as so will the respective solvation in aqueous media. For that, the pH of each system was determined (detailed data in the ESI[†]), being demonstrated that the pH of several samples composed of PILs or PEG-2000 and water revealed no noteworthy changes (pH range between 7.3 and 8.3), even when the PILs' nature or composition was changed.

To allow a better understanding of the phenomena behind the formation of each ABS, the solubility of each salt or PIL in PEG-1000 and in water was determined at 323 K. Firstly, the solubilities of all salts in water were ascertained at 323 K, and no liquid-liquid immiscibility was observed for most PILs, with the only exception observed with the highest melting temperature salt, [NH₄][OAc], which exhibits a solubility in water of 0.746 ± 0.002 mol mol⁻¹. PEG-600 was also added to PILs, and *vice versa*, and no liquid-liquid immiscibility was observed. These results confirm that all binary mixtures (water-PIL and PEG-600-PIL),

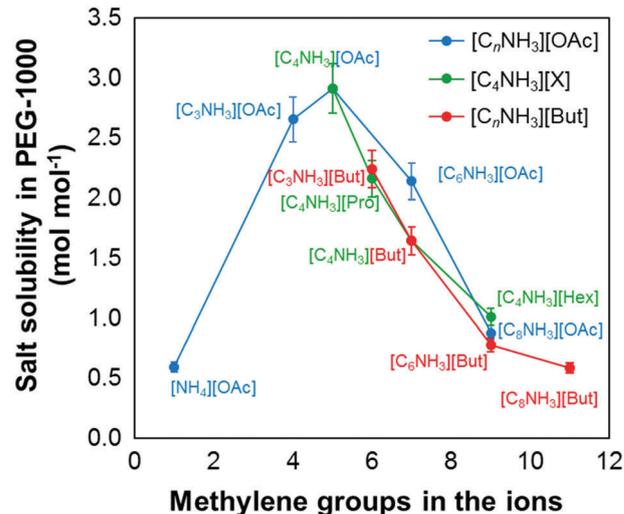


Fig. 1 Solubility of PILs or salts in PEG-1000 at 323 K and atmospheric pressure according to the total number of methylene groups in the ions of each ammonium salt. The associated error bars correspond to the uncertainty of results of three replicates.

with the exception of [NH₄][OAc], are completely miscible, and no ABS are formed. However, the solubility of the studied ammonium-based compounds in PEG-1000 is more limited. Fig. 1 depicts a schematic comparison of solubility data of all the PILs or salts in PEG-1000 at 323 K and atmospheric pressure. The solubilities of the PILs with the phase forming agents (water and polymer), reported in Table 1, are very useful for understanding the phase demixing phenomena discussed below.

According to the data exhibited in Table 1 and Fig. 1 (blue line), it is possible to observe that [NH₄][OAc] exhibits the lowest solubility in PEG-1000. Yet, when one hydrogen is replaced by a small alkyl chain ([C₃NH₃][OAc]), a significant increase of the PIL solubility in PEG-1000 is observed, reaching a maximum with [C₄NH₃][OAc]. This is in good agreement with the results obtained for aprotic ionic liquids based on the imidazolium cation,^{30–32} for which an increase in the alkyl side chain of the cation ([C₂C₁im]Cl to [C₆C₁im]Cl) enhances their solubility in PEG. However, the solubility of the [C_nNH₃][OAc]-based PILs with larger alkyl side chain length, such as *n* = 6 and 8, in PEG-1000 significantly decreases (a reduction of more than three-fold). As shown in Fig. 1, a decrease of the solubility of PILs in PEG-1000 for the series of [But]- and [C₄NH₃]-based PILs was also observed. When we compare all the solubility data in the polymer as a function of the total number of methylene groups of each PIL (or salt), it is evident that for the salts or “small” PILs (with less than 5 methylene groups in total), a positive solubility effect was observed with the increase of the number of carbons. On the other hand, when the ammonium-based PILs have more than 5 methylene groups, independently if these are in the cation or anion, the increase of the size of the alkyl chains leads to a significant reduction in the PIL-PEG solubilities.

In spite of the relationship between the PIL-PEG solubilities and the total number of methylene groups in the PIL structure,

it is important to note that, as presented in Table 1, there are three PILs, which are completely soluble in PEG-1000, independently of the number of carbons. $[\text{NH}_4][\text{But}]$ revealed a complete solubility in PEG-1000 at 323 K. The hexylammonium acetate isomers, $[\text{C}_2\text{C}_2\text{C}_2\text{NH}][\text{OAc}]$ and $[\text{C}_3\text{C}_3\text{NH}_2][\text{OAc}]$, with the same number of carbons in the cation core, have a completely different solubility behaviour from $[\text{C}_6\text{NH}_3][\text{OAc}]$ due to the larger structure of the cation, where the complete solubility of the two cationic isomers in the polymer was observed.

The differences in PIL (or salt)/PEG-1000 solubilities indicate that the total number of carbons in the ammonium compounds, and their corresponding cation and anion structures, have a strong influence on their miscibility behaviour. This preliminary evidence suggests that the formation of PIL-PEG-based ABS may be directly influenced not only by the physical state of the compounds (liquid or solid), but mainly by the strength of the cation-anion interactions and the PIL's hydrophobicity. In a previous work, we demonstrated that the solubility of cholinium-based salts in PEG-600 could be directly related to their physical state, where salts that are liquid at room temperature (RT) exhibit the highest solubilities.²¹ In this work, it was shown that the increase of the alkyl side chain in the anion of $[\text{Ch}][\text{C}_n\text{CO}_2]$ ($n = 1, 3$ and 4) ILs increases their solubility in PEG-600.²¹ Herein, even PILs that are liquid at room temperature are not completely miscible in PEG as observed before.²¹ Since we are using a larger PEG polymer with a lower H-bond donor aptitude and larger ability to establish dispersive-type interactions and ILs with a higher hydrogen-bond acidity and lower ability to establish dispersive-type interactions, the miscibility regime is quite different, and consequently, the solubilities of PILs seem to be a main result from PIL-PEG interactions.

Ternary phase diagrams – aqueous biphasic systems

After the study on the mutual solubilities of PILs and polymers, the formation of ABS was evaluated for a series of PEGs and PILs at different temperatures, as summarized in Table 2.

The PILs were chosen in order to evaluate the effect of the cation and anion alkyl chain length and isomerism of the cation in liquid-liquid demixing. In addition to the influence of PILs, the impact of the polymer size on the formation of ABS with $[\text{C}_8\text{NH}_3][\text{OAc}]$ was also evaluated. Finally, to check how the temperature affects the liquid-liquid equilibrium, the ternary phase diagrams of the systems composed of PEG-2000, and $[\text{NH}_4][\text{OAc}]$, $[\text{C}_3\text{NH}_3][\text{OAc}]$, $[\text{C}_4\text{NH}_3][\text{OAc}]$, $[\text{C}_6\text{NH}_3][\text{OAc}]$, $[\text{C}_4\text{NH}_3][\text{Pro}]$, $[\text{C}_3\text{NH}_3][\text{But}]$ and $[\text{C}_4\text{NH}_3][\text{OAc}]$ were determined at 323, 333 and 343 K. In general, no system investigated at 298 K was able to form an ABS. In the next sections, all the solubility curves of each ternary phase diagram are displayed as the total weight fraction of PEG (wt%) vs. the total molality of salt [mol of salt per kg of water], in which the molality was chosen in order to avoid distortions in comparisons that could be a direct consequence of the different molecular weights of the salts involved (the detailed weight fraction experimental data are provided in the ESI†).

Effect of the PIL cation in the formation of PEG-2000-based ABS

In order to evaluate the effect of the increase of the salt cation alkyl side chain length on ABS formation, ternary phase diagrams composed of acetate and butanoate-based PILs (or salts), PEG-2000, and water were determined at 323 K (Fig. 2).

From Fig. 2a, it is observed that the ability of [OAc]-based salts to promote a two-phase region is as follows: $[\text{C}_8\text{NH}_3][\text{OAc}] > [\text{NH}_4][\text{OAc}] > [\text{C}_6\text{NH}_3][\text{OAc}] > [\text{C}_3\text{NH}_3][\text{OAc}] > [\text{C}_4\text{NH}_3][\text{OAc}]$. Two opposite trends were observed: one for $[\text{C}_n\text{NH}_3][\text{OAc}]$ salts with larger cation alkyl chain length ($n = 6$ and 8) and another for salts with shorter cation alkyl chain length ($[\text{C}_3\text{NH}_3][\text{OAc}]$ and $[\text{C}_4\text{NH}_3][\text{OAc}]$). The first trend indicates that PILs formed by cations with larger alkyl side chains display a better performance for the formation of ABS, while for the IL cations with short alkyl chains the increase of the number of carbons reduces their ABS phase-forming ability. $[\text{C}_4\text{NH}_3][\text{OAc}]$ is the PIL that exhibits the narrowest biphasic region when combined with PEG-2000.

Table 2 Combinations of PEGs and PILs addressed to create ABS at 298, 303, 313, 323 and 343 K. The symbols ✓ and ✗ represent, respectively, the ability and non-ability to form ABS

PIL	PEGs (g mol ⁻¹) Temperature (K)	600		1000		2000					3400	
		298	323	298	323	298	313	323	333	343	298	323
[OAc]-based salts	$[\text{NH}_4][\text{OAc}]$	—	—	—	—	✗	—	✓	✓	✓	—	—
	$[\text{C}_3\text{NH}_3][\text{OAc}]$	—	—	—	—	✗	—	✓	✓	✓	—	—
	$[\text{C}_4\text{NH}_3][\text{OAc}]$	✗	✗	✗	—	✗	—	✓	✓	✓	✗	—
	$[\text{C}_6\text{NH}_3][\text{OAc}]$	—	—	—	—	✗	✓	✓	✓	✓	—	—
	$[\text{C}_8\text{NH}_3][\text{OAc}]$	✗	✗	✗	✓	✗	—	✓	—	—	✗	✓
	$[\text{C}_2\text{C}_2\text{C}_2\text{NH}][\text{OAc}]$ $[\text{C}_3\text{C}_3\text{NH}_3][\text{OAc}]$	—	—	—	—	—	—	✗	—	—	—	—
[Pro]-based salts	$[\text{C}_4\text{NH}_3][\text{Pro}]$	—	—	—	—	—	—	✓	✓	✓	—	—
[But]-based salts	$[\text{NH}_4][\text{But}]$	—	—	—	—	—	—	✗	—	—	—	—
	$[\text{C}_3\text{NH}_3][\text{But}]$	—	—	—	—	—	—	✓	✓	✓	—	—
	$[\text{C}_4\text{NH}_3][\text{But}]$	—	—	—	—	—	—	✓	✓	✓	—	—
	$[\text{C}_6\text{NH}_3][\text{But}]$	—	—	—	—	—	—	✓	—	—	—	—
	$[\text{C}_8\text{NH}_3][\text{But}]$	—	—	—	—	—	—	✓	—	—	—	—
[Hex]-based salts	$[\text{C}_4\text{NH}_3][\text{Hex}]$	—	—	—	—	—	—	✓	—	—	—	—

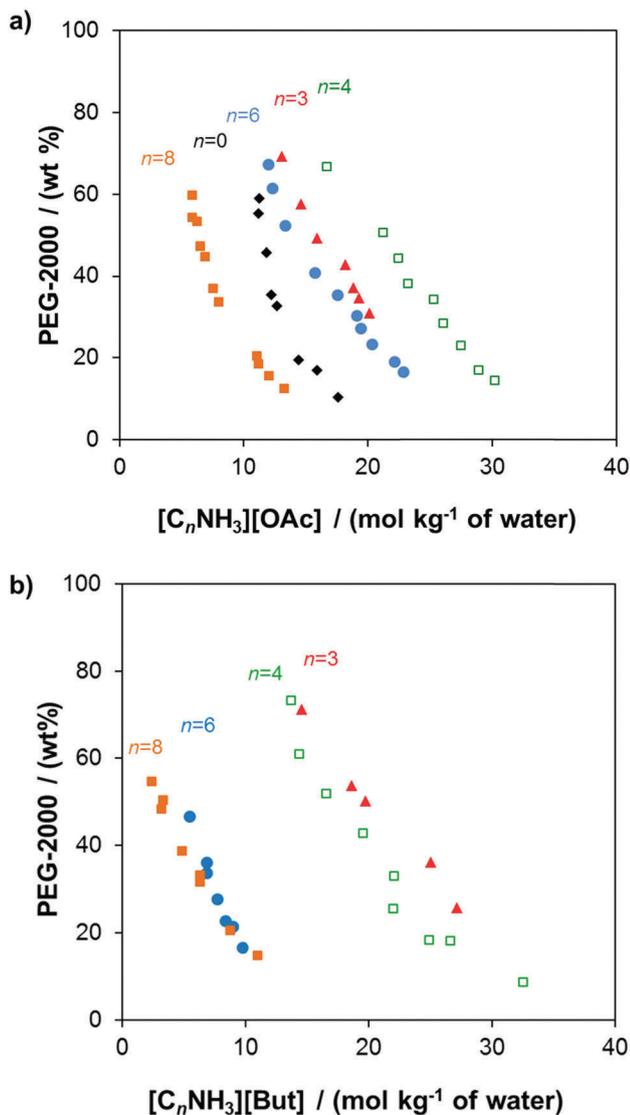


Fig. 2 Experimental solubility data for ABS composed of (a) $[C_nNH_3][OAc]$ + PEG-2000 and (b) $[C_nNH_3][But]$ + PEG-2000, at 323 K, where n is: 3 (\blacktriangle); 4 (\square); 6 (\bullet); 8 (\blacksquare). The ABS formed by PEG-2000 + $[NH_4][OAc]$ is represented by $n = 0$ (\blacklozenge). The associated uncertainty of the binodal curves is below 0.8%, according to the results of three replicates and considering the purity of the phase-forming components.

The pattern of ABS formation by the PILs mimics the solubility data trend, in which the lowest aptitude to form ABS was observed for the highly soluble PIL, $[C_4NH_3][OAc]$, and the highest liquid–liquid demixing capabilities obtained with the salts with lower solubility in PEG. Herein, the low solubility *vs.* high ABS formation profile shows that the higher the mutual interactions between the phase forming promoters, the lower the interactions with water, and consequently the lower their ability to form ABS.

Similarly, the effect of the increase of the cation alkyl chain of the IL was evaluated for $[C_nNH_3][But]$ -based ABS. The respective phase diagrams of the ABS composed of $[C_nNH_3][But]$ ($n = 3, 4, 6, 8$), PEG-2000 and water at 323 K are shown in Fig. 2b. An increase of the alkyl chain length in the cation in $[C_nNH_3][But]$ ILs leads to

an increase of the biphasic region in the order: $[C_8NH_3][But] \geq [C_6NH_3][But] \gg [C_4NH_3][But] > [C_3NH_3][But]$. Herein, the ABS composed of $[But]$ -based PILs show a single tendency, which is in good agreement with the decrease of the solubility of salts in PEG (red line in Fig. 1): $[C_8NH_3][But] < [C_6NH_3][But] \ll [C_4NH_3][But] < [C_3NH_3][But]$. Therefore, both solubility and ABS data suggest that the ABS formation is driven by the mutual solubilities between the PEG and the PIL, and therefore, by the specific interactions established between both phase-forming components. It is important to note that the largest PILs, $[C_8NH_3][But]$ and $[C_6NH_3][But]$, present almost the same solubility in PEG-1000, and consequently exhibit similar aptitudes to create polymer-based ABS. In this particular case, and due to the fact that ILs with long alkyl side chains tend to form phase-separated self-assembled structures, such as micelles in aqueous solutions above a critical concentration (micellization effect),³³ they tend to decrease their own capability to hydrogen bond with the PEG polymer. Hence, as the two phase forming agents do not exhibit special affinity between themselves, they are more easily separated and create ABS better.

Comparing the results depicted in Fig. 2a and b, a distinct trend is observed, in particular for the $[C_3NH_3]$ -based PILs, which exhibit the lowest ability to create a demixing region when combined with the $[But]^-$ anion while, on the other hand, the respective $[OAc]$ -based PIL has a higher ability to create ABS than $[C_4NH_3][OAc]$. Furthermore, the huge influence of the IL anion in the formation of ABS (or non-formation) is demonstrated with other ammonium-based salts, *e.g.*, in which a short alkyl side chain anion as acetate allows the formation of a biphasic regime, while $[NH_4][But]$ does not allow the formation of ABS with PEG-2000 at 323 K. $[NH_4][But]$ is liquid at room temperature, is totally soluble in PEG and water and does not induce biphasic-formation with PEG. The complete solubility of $[NH_4][But]$ in the polymer reveals favourable PIL–PEG interactions which inhibits the phase separation in the presence of water. The results obtained with both ammonium salts are in agreement with that reported for cholinium-based salts (or ILs),²¹ where the differences in interactions between crystalline and liquid salts at a given temperature (salting-out phenomenon *vs.* mutual interactions of the phase-forming agents) govern the formation of ABS composed of polymers and ILs. All these differences demonstrate that there is a strong influence of both the cation and the anion in the formation of ABS and, in some cases, the higher or lower ability to induce the biphasic region can be attributed to the different properties of a common anion (a detailed analysis of the influence of the PILs' anion is presented in the next section).

Besides the study of the influence of the alkyl chain length in the PIL cation, the effect of cationic isomerism in the systems composed of $[OAc]$ -based PILs and PEG-2000 at 323 K was also investigated. To this end, the ability of $[C_2C_2C_2NH][OAc]$ and $[C_3C_3NH_2][OAc]$ to form ABS was evaluated against that of $[C_6NH_3][OAc]$; however, it was found that none of these PILs have the aptitude to separate from PEG-2000 when mixed in a water-rich environment. Although these two PILs present the same number of carbons, $[C_3C_3NH_2][OAc]$ and $[C_2C_2C_2NH][OAc]$ present a more hydrophilic and less polar character than $[C_6NH_3][OAc]$

(which can be confirmed by the data in Table 1; $[C_2C_2C_2NH][OAc]$ and $[C_3C_3NH_2][OAc]$ are completely miscible in PEG-1000 and water). These results again suggest that the interactions between PEGs and PILs are the driving force behind the ABS formation, since the higher their mutual solubilities, the higher are their affinities/interactions and more difficult it is to create an ABS.

Effect of the PIL anion in the formation of PEG-2000-based ABS

In order to obtain a further understanding of the influence of the alkyl chain length of the anion, four ternary phase diagrams composed of $[C_4NH_3]$ -based PILs, PEG-2000 and water were determined at 323 K. The results obtained are depicted in Fig. 3.

Fig. 3 shows that keeping $[C_4NH_3]^+$ as the common cation, the influence of the alkyl chain in the anion follows the trend: $[Hex]^- \gg [But]^- > [Pro]^- > [OAc]^-$. This trend shows that an increase in the alkyl chain length of the anion leads to a larger biphasic region. As previously discussed, it is here again demonstrated that the ability to form PIL-PEG ABS is closely related to a decrease of the PIL solubility in PEG-1000 (Table 1 and the green line in Fig. 1). Previously, we have demonstrated that a complex balance of interactions drives PEG-IL ABS formation.^{11,21,22} As shown in MD simulation studies, the formation of PEG-IL-based ABS is favoured when polymers and ILs with non-favourable interactions are combined.²²

The experimental binodal curves of each PEG-PIL ABS were correlated using the empirical relationship described in eqn (1):³⁴

$$Y = A \exp(BX^{0.5} - CX^3) \quad (1)$$

where A , B and C are the correlation constants and X and Y are the weight concentrations (wt%) of PIL and PEG-2000, respectively.

From the fitted weight fraction data, the correlated binodal curve was then determined in the following units: mol of

ethylene oxide (EO) units of each polymer per kg of water *versus* mol of each PIL per kg of water. The fitted binodal curves were replotted in these units to allow the determination of a common point for all the systems (the point with the lowest phase forming agent's concentrations required to form ABS). The point on the binodal curve closest to the origin ($X, Y = 0, 0$) was then adopted as a measure of the liquid-liquid demixing ability of each system. The sum of moles of EO per kg of water and moles of salt per kg of water was then determined and designated as the minimum concentration point (MC) of each ABS. In Fig. 4 a correlation between MC and the number of methylene groups in the PIL ions is depicted for all the systems able to form two immiscible phases at 323 K (the nominal values of each MC are reported in the ESI†).

Fig. 4 shows a striking resemblance to Fig. 1, where a close relationship between the total number of methylene groups in the PIL ions and the corresponding minimum concentration point to form ABS is demonstrated. The ammonium salts with low capability to induce a biphasic region (higher values of MC) with PEG-2000 have 5 to 7 methylene groups in their corresponding ions, independently of these groups being attached to the cation or the anion. On the other hand, ABS composed of PEG-2000 and shorter or longer ammonium salts, with less than 5 or more than 7 methylene groups, respectively, exhibited the lowest values of MC (lower concentrations of phase forming agents), and consequently the highest aptitude to exhibit liquid-liquid demixing. The tendency shown in Fig. 5 is thus quite similar to the trend of the solubility of PILs in PEG-1000 depicted in Fig. 1, in which the ammonium salts highly soluble in the polymer display the lowest ability to form ABS.

From Fig. 4, it is clear that the PIL-PEG interactions occur not due to an exclusive effect of the type of cation or anion,

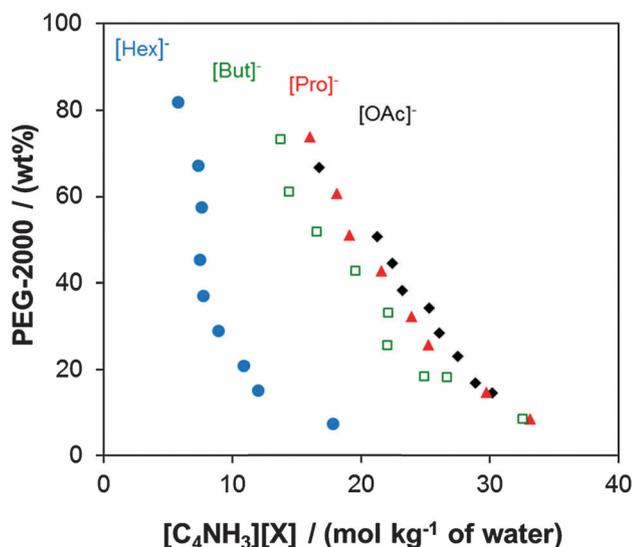


Fig. 3 Experimental solubility data for ABS composed of $[C_4NH_3][X]$ + PEG-2000 at 323 K where X is: $[OAc]^-$ (◆); $[Pro]^-$ (▲); $[But]^-$ (□); $[Hex]^-$ (●). The associated uncertainty of the binodal curves is below 0.8%, according to the results of three replicates and considering the purity of the phase-forming components.

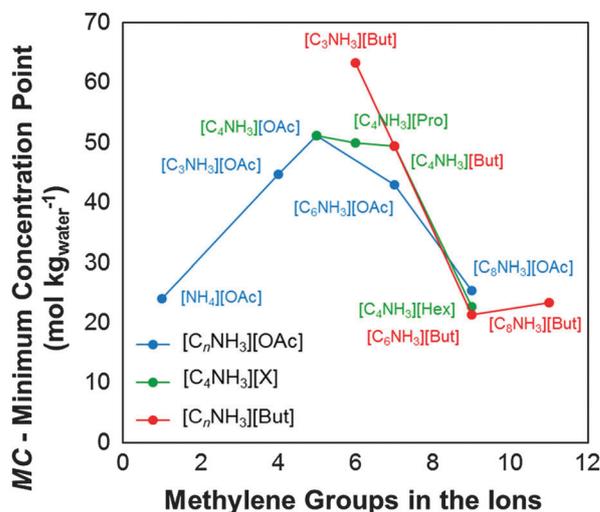


Fig. 4 Minimum concentration (MC) of PEG-2000 and salt required to form ABS at 323 K and atmospheric pressure as a function of the total number of methylene groups in the ions of each ammonium salt. The associated uncertainty of MC is below 0.8%, according to the results of three replicates and considering the purity of the phase-forming components.

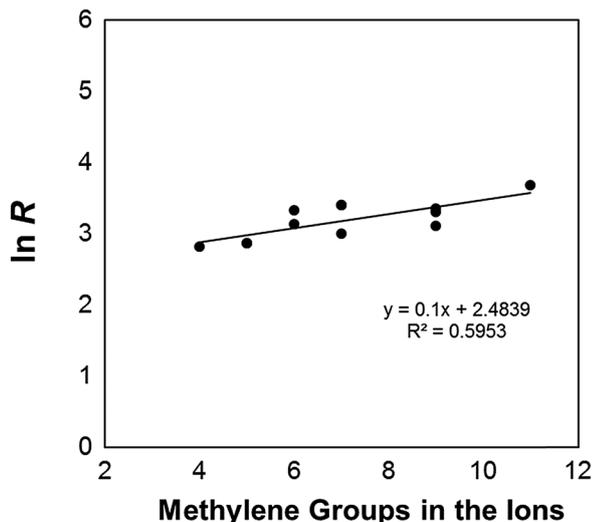


Fig. 5 Logarithmic function of R as a function of the total number of methylene groups in the ions of each ammonium salt. The associated uncertainty of $\ln R$ is below 1.0%, according to the results of three replicates and considering the purity of the phase-forming components.

but mainly a result of the total number of methylene groups present in the ions. Thus, in order to further prove a close relationship between the aptitude of PILs to form ABS (here designated as MC), the PILs' solubility (S) and the number of ions in methylene groups, the following parameter $R = MC/S$ was used. The logarithmic function of R versus the number of methylene groups of PILs is plotted in Fig. 5. This function can also be valuable to evaluate *a priori* whether a given PIL is able to form ABS based on more simple PIL-PEG binary solubility data.

The correlation depicted in Fig. 5 demonstrates that the ability to form ABS depends on the PIL-PEG solubilities and on the total size of the alkyl side chains of the ions (either anion or cation). Thus, it is clear that the PEG-IL interactions, expressed as their mutual solubilities, have an important role in the control of ABS formation.

Effect of the molecular weight of PEG in the formation of PIL-based ABS

The effect of the polymer molecular weight was also evaluated with the PIL with the highest aptitude to promote the formation of a two-phase region, $[C_8NH_3][OAc]$, by the determination of the respective ternary phase diagrams at 323 K – Fig. 6.

Fig. 6 shows that the ability of the polymer to induce liquid-liquid demixing follows the order: PEG-3400 > PEG-2000 > PEG-1000. It should be remarked that PEG-600 was unable to induce ABS formation when mixed with $[C_8NH_3][OAc]$. The results obtained indicate that polymers with a higher molecular weight are more able to promote phase separation, which is in agreement with the tendencies observed for conventional polymer-salt³⁵ and PEG-IL-based ABS.^{11,21} The tendencies observed are related to two factors: (i) the increase of the polymer hydrophobicity and consequent reduction of its water solubility/affinity; and (ii) reduction of the PEG-IL miscibility by the reduction of the number of terminal -OH groups per PEG molecule.

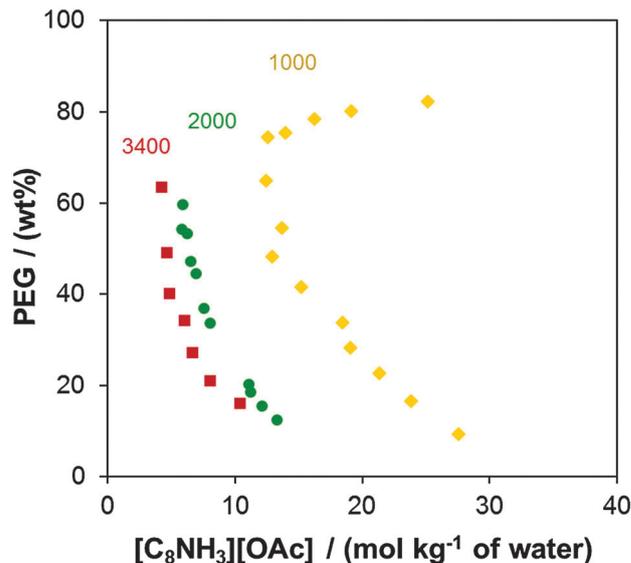


Fig. 6 Experimental solubility data for ABS composed of $[C_8NH_3][OAc]$ + water + PEG ($M_W = 1000 \text{ g mol}^{-1}$ (♦); $M_W = 2000 \text{ g mol}^{-1}$ (●), $M_W = 3400 \text{ g mol}^{-1}$ (■)) at 323 K. The associated uncertainty of the binodal curves is below 0.8%, according to the results of three replicates and considering the purity of the phase-forming components.

Effect of temperature in the formation of PEG-PIL-based ABS

In this section, we investigated how the increase of temperature changes the liquid-liquid equilibria of PIL-PEG-based ABS. For that purpose, seven PEG-2000/PIL pairs were tested at 3 temperatures, namely 323, 333, and 343 K. The results obtained are presented in Fig. 7a–g, where the presence of three behaviours with temperature is shown: (i) an increase of the immiscibility region with an increase in temperature for $[NH_4][OAc]$, $[C_3NH_3][OAc]$ and $[C_4NH_3][OAc]$ -based ABS; (ii) a decrease of the biphasic region with a decrease in temperature for the $[C_6NH_3][OAc]$ and $[C_4NH_3][But]$ -based systems; and (iii) a similar aptitude to induce the liquid-liquid demixing for the three temperatures studied with the $[C_4NH_3][Pro]$ and $[C_3NH_3][But]/PEG-2000$ systems. The first trend (i) is in close agreement with previous works regarding the effect of temperature in PEG/salt,^{36,37} PPG/[Ch]^{38,39} PEG/[Ch]⁺ ABS²¹ and PPG/IL ABS.⁴⁰ In these, an increase in the temperature decreases the mutual salt/IL-PEG/PPG hydrogen-bonding interactions and facilitates the creation of ABS.⁴¹ Moreover, it is well known that in conventional ABS composed of PEGs and salts, the temperature affects the liquid-liquid demixing process by disturbing the polymer-water hydrogen-bonding interactions, since this binary mixture has also a typical lower critical solution temperature (LCST) behaviour.⁴² It is important to note that for $[NH_4][OAc]$ the increase of temperature induces a large increase in the two-phase region, while for the PILs with longer alkyl chain lengths, $[C_3NH_3][OAc]$ and $[C_4NH_3][OAc]$, the same change in temperature has a less pronounced effect.

Fig. 7d and g, corresponding to ABS composed of $[C_6NH_3][OAc]$ and $[C_4NH_3][But]$, respectively, show the opposite effect (ii), where an increase in the temperature, from 313 K to 333 K, reduces the biphasic region or the ability to form ABS. These data demonstrate

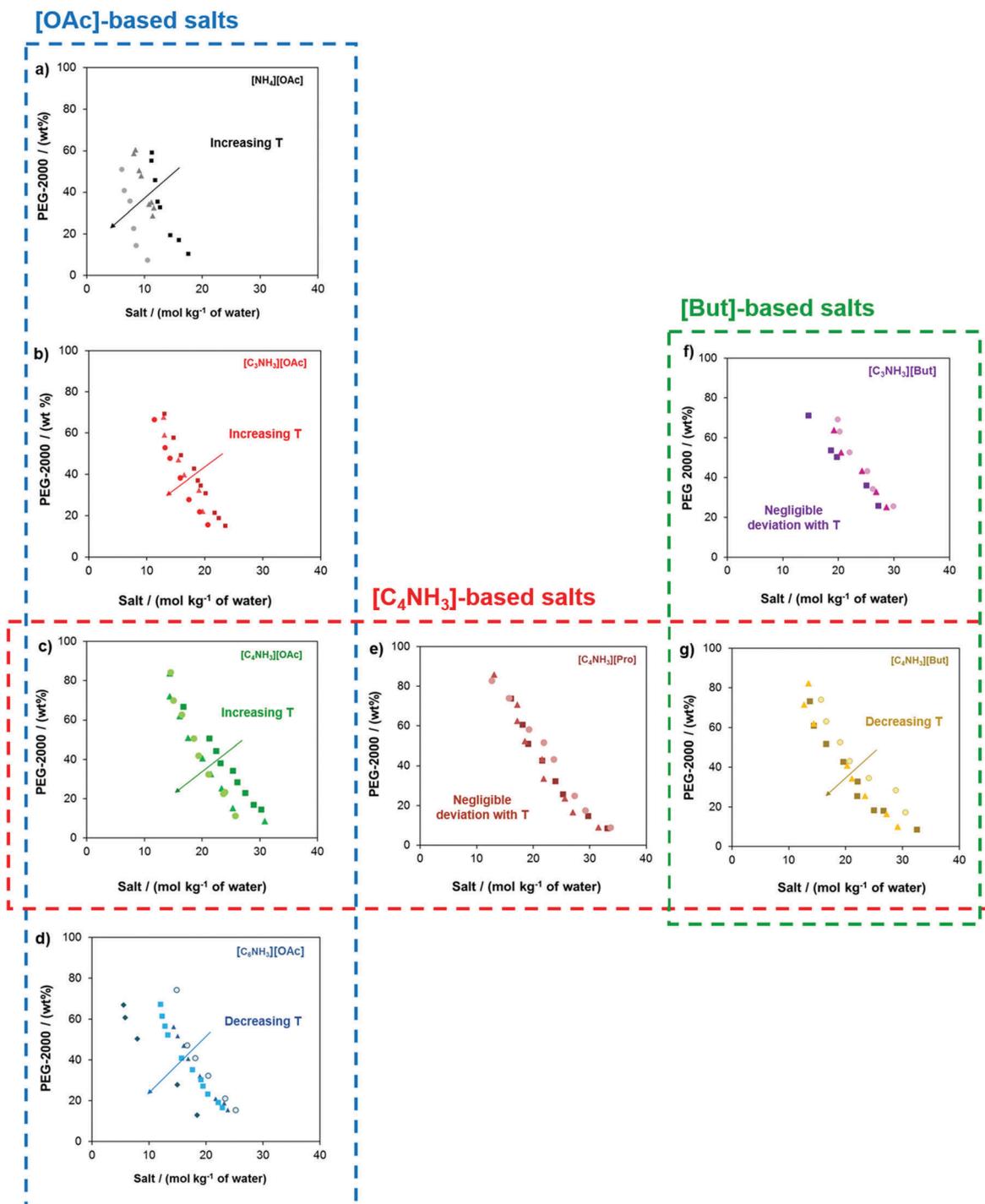


Fig. 7 Experimental solubility data for ABS composed of $[C_nNH_3][OAc]$ + water + PEG ($M_W = 1000 \text{ g mol}^{-1}$ (◆); $M_W = 2000 \text{ g mol}^{-1}$ (●), $M_W = 3400 \text{ g mol}^{-1}$ (■)) at different temperatures. The associated uncertainty of the binodal curves is below 0.8%, according to the results of three replicates and considering the purity of the phase-forming components.

that an inversion on the solubility pattern with temperature is not only a result of the size of the cation alkyl chain, but also a result of the size of the corresponding anion. This behaviour with temperature was previously observed in several ABS, namely those composed of ILs and inorganic salts;¹⁵ ILs and carbohydrates;⁴³ imidazolium-based ILs and PEGs;^{11,23} ammonium

halides with longer alkyl chains and PEGs;⁴⁴ and polymer-polymer mixtures.⁴⁵ This behaviour might be a result of charge distributions of the ions (in particular on the cation) and their ability to establish dispersive interactions, in addition to Coulombic and hydrogen-bonding interactions that occur in salt-based ABS. The second behaviour is an IL-polymer-like

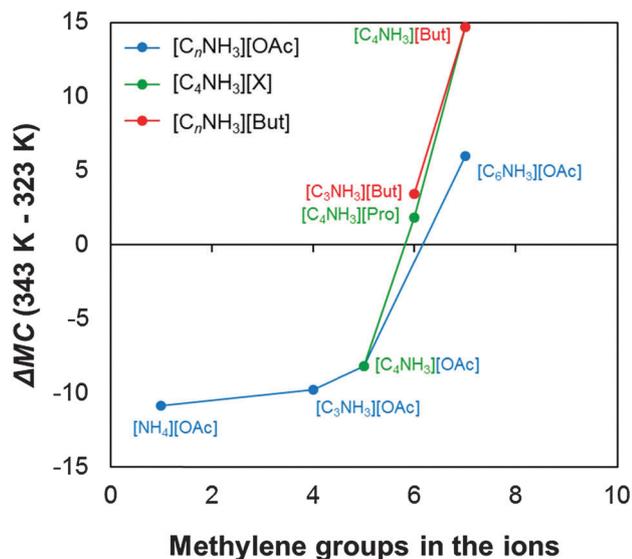


Fig. 8 Variation of the difference in the minimum concentration point (ΔMC) with temperature as a function of the total number of methylene groups in the ions of each ammonium salt. The associated uncertainty of ΔMC is below 1.6%, according to the results of three replicates and considering the purity of the phase-forming components.

behaviour and polymer-polymer like behaviour, in which the contribution of steric hindrance and dispersive effects start to be predominant in the solubility curves dependence with temperature.

This inversion of behaviour with temperature is quite interesting and proves the existence of different dominating effects which depend on the size and charge distribution of the PIL ions. These pieces of evidence are reinforced with the third effect observed (iii), in which the ability of [C₄NH₃][Pro] and [C₃NH₃][But] to induce a biphasic regime with PEG-2000 is essentially temperature independent. It seems that these PILs are at the border between the ammonium salts that enlarge and those that reduce the biphasic region with the increase of temperature.

In order to identify the “size” of the cation or anion alkyl chain length which causes the reversal of ABS formation ability with temperature, the deviation of ABS formation aptitude against temperature was determined. The approach described earlier using the minimum concentration point (MC), in which its temperature dependency was correlated as a function of the total number of methylene groups of each ammonium compound, was here adapted as ΔMC , which is the difference in the MC values between the highest temperature (343 K) and the lowest one (323 K). The representation of ΔMC against the total number of methylene groups in the ions is depicted in Fig. 8.

The correlation shown in Fig. 8 clearly shows that all systems formed by salts with less than 6 methylene groups as phase forming agents exhibit a salt-polymer-like behaviour (enlargement of the biphasic region with temperature), while when using PILs with 6 or more methylene groups the opposite effect is observed. The change in the trend observed when using 6 methylene groups in the ions is in good agreement with the inversion of the aptitude to form ABS presented in Fig. 5.

Conclusions

In this work, twelve ammonium-based PILs were synthesized in order to study their use in the formation of ABS with PEG and to better understand the molecular-level mechanisms behind the formation of these ternary systems. The PILs synthesized allowed the evaluation of the influence of the anion and cation alkyl chain length and the isomerism of the cation on the formation of ABS, while the PEGs selected allowed studying the effect of the polymer molecular weight (PEG-600, PEG-1000, PEG-2000 and PEG-3400). For comparison purposes, the ammonium salts with no-alkyl chains ([NH₄][OAc] and [NH₄][But]) in the cation were also investigated. To allow a better understanding of the phenomena behind the formation of each ternary phase diagram, the solubility of each PIL or salt in PEG-1000 and water was also determined. The overall gathered data allowed us to conclude that PILs with lower solubility in PEG have the highest capabilities to undergo phase splitting and to form ABS, while the highly soluble PILs are unable to form ABS. In fact, a close correlation was found between the minimum amount of phase-forming components required to form ABS and the solubility of PILs in the polymer, which further depends on the number of methylene groups at the PIL. These results support the notion that the mutual interactions occurring between the PEG and each PIL are the main driving force in the formation of the respective ABS. This study also revealed that an increase or decrease of the biphasic region can be achieved with an increase in temperature, which depends on the PIL used and the respective number of methylene groups.

Since most of the phase-forming agents used are quite stable, cheap and of low toxicity, these ABS can be seen as effective alternatives in several separation/purification processes aiming at the recovery of added-value compounds from biological or synthetic media.

Experimental

Materials

The PILs used in this work for the formation of ABS were synthesized in our laboratory according to the procedure previously described by McCrary *et al.*²⁹ For the synthesis of PILs with amine-based cations with different carboxylate anions the following compounds were used: *N*-propylamine (98%); *N*-butylamine (99.5%); *N*-hexylamine (99.5%); *N*-octylamine (99%); butyric acid ($\geq 99\%$); propanoic acid ($\geq 99\%$); and hexanoic acid ($\geq 99\%$). For the synthesis of [NH₄][But], ammonia (25% in water) from ChemLab and butyric acid ($> 99\%$) were used. All compounds were purchased from Sigma-Aldrich (St. Louis, MO, USA) as colorless liquids and used as received. Triethylamine (99%) and dipropylamine (99%) were purchased from Sigma-Aldrich (St. Louis, MO, USA), and were further distilled under vacuum prior to use to obtain colorless liquids. Glacial acetic acid (99.7%) was purchased from Macron (Center Valley, PA, USA) as a clear liquid and used as received. For comparison purposes [NH₄][OAc] (98%) was also used, which was supplied by Sigma Aldrich (St. Louis, MO, USA).

PEGs with average molecular weights of 600, 1000 and 3400 g mol⁻¹ (abbreviated as PEG-600, PEG-1000 and PEG-3400) were acquired from Sigma-Aldrich (St. Louis, MO, USA), while the one with an average molecular weight of 2000 g mol⁻¹ (PEG-2000) was purchased from Alfa Aesar. Double distilled water was used in all experiments.

Synthesis of PILs

Each carboxylic acid (300 mmol) was placed in a 100 mL vial, which was cooled to 273 K, under continuous stirring, using an ice water bath. Then, the corresponding alkylamine (300 mmol) was added drop-wise at 273 K. Afterwards, the mixture was stirred overnight while the temperature was allowed to slowly rise to ambient conditions. To reduce the volatile impurities to negligible values, all synthesized PILs were then dried under constant agitation in vacuum and at moderate temperature (323 K), for 48 h. Each PIL synthesis is described in detail in the ESI.† After the synthesis, all the PILs were characterized using differential scanning calorimetry (DSC) and proton and carbon nuclear magnetic resonance (¹H and ¹³C NMR). The residual water content was measured by Karl Fischer titration. The detailed specific procedures for all the characterization measurements are reported in the ESI.†

PIL or salt solubilities in PEG-1000 and water

The solubility measurements of ammonium-based salts or PILs in PEG-1000 and water were carried out at 323 K and atmospheric pressure. Small amounts of each ammonium-based salt were added to small glass vials with pre-weighed PEG-1000 (or water). Then, each binary mixture was vigorously agitated and the vials were visually analysed. If a second phase was not detected, more salt or PIL (approximately 20 mg) was added and the procedure was repeated. The saturation values were taken as the first solid or second liquid phase appearance. At this stage, the vials were finally weighted and the solubilities were determined gravimetrically within ±10⁻⁷ kg.

Ternary phase diagrams – aqueous biphasic systems

The phase diagrams were determined through the turbidometric titration method² at 298, 313, 323, 333, and 343 K (±1 K) under atmospheric pressure. Different ternary mixtures (ca. 1 g) of known composition at the biphasic region were prepared in closed glass tubes. Pure water was then added dropwise under continuous stirring until a limpid and monophasic solution was obtained. The addition of water was performed using a syringe through the septum of closed glass tubes. The total amount of water added was determined gravimetrically and the final mass fraction of each component calculated. All compositions were gravimetrically determined using an analytical balance Sartorius-AC 210P (within ±10⁻⁷ kg). The uncertainty associated with the weight fraction data of each phase diagram is below 0.8 wt%.

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