

# Controlling the Formation of Ionic-Liquid-based Aqueous Biphasic Systems by Changing the Hydrogen-Bonding Ability of Polyethylene Glycol End Groups

Jorge F. B. Pereira,<sup>\*[a, b]</sup> Kiki A. Kurnia,<sup>[c]</sup> Mara G. Freire,<sup>[c]</sup> João A. P. Coutinho,<sup>[c]</sup> and Robin D. Rogers<sup>\*[a, d]</sup>

The formation of aqueous biphasic systems (ABS) when mixing aqueous solutions of polyethylene glycol (PEG) and an ionic liquid (IL) can be controlled by modifying the hydrogen-bond-donating/-accepting ability of the polymer end groups. It is shown that the miscibility/immiscibility in these systems stems from both the solvation of the ether groups in the oxygen chain and the ability of the PEG terminal groups to preferably hydrogen bond with water or the anion of the salt. The remov-

al of even one hydrogen bond in PEG can noticeably affect the phase behavior, especially in the region of the phase diagram in which all the ethylene oxide (EO) units of the polymeric chain are completely solvated. In this region, removing or weakening the hydrogen-bond-donating ability of PEG results in greater immiscibility, and thus, in a higher ability to form ABS, as a result of the much weaker interactions between the IL anion and the PEG end groups.

## 1. Introduction

The search for more sustainable separation and purification processes has led to the use of aqueous biphasic systems (ABS), as an alternative to typical liquid–liquid extraction methods, which frequently employ volatile and hazardous solvents.<sup>[1]</sup> ABS are water-rich systems combining two different compounds (polymer/polymer, polymer/salt, salt/salt, etc.) that above certain concentrations lead to an immiscible liquid–liquid region.<sup>[1]</sup> Although ABS that combine different polymer/polymer or polymer/salt pairs have been studied and characterized since the middle of the last century, renewed interest arose when a new type of system was observed by the combination of two salts in an aqueous solution.<sup>[2]</sup>

Salt/salt ABS using ionic liquids (ILs; salts with melting points lower than 100 °C) have overcome some of the polarity limitations of the traditional polymer/polymer or polymer/salt ABS, thus allowing higher extraction yields and purification fac-

tors.<sup>[2,3]</sup> ILs have been key in the development of new separation processes using ABS, as they exhibit interesting solvation and design properties, thus allowing that an extraction process to be tailored by using appropriate cation–anion combinations.<sup>[3]</sup> Although ABS composed of ILs and organic/inorganic salts have been described as platforms to enhance the extraction of diverse biomolecules from aqueous media,<sup>[4]</sup> in several cases, selectivity between similar biomolecules couldn't be achieved.<sup>[4c,5]</sup>

To overcome some of the limitations of ABS composed of ILs and conventional salts, we recently demonstrated the possibility of their formation by using polyethylene glycol (PEG)–IL combinations.<sup>[6]</sup> The first evidence revealed that PEG–IL-based ABS are far more interesting and complex than initially realized,<sup>[6a]</sup> thus motivating additional experimental and simulation studies.<sup>[6b,7]</sup> These works revealed that despite the hydration capability of the isolated ions in aqueous media, which is dominant in salt–salt ABS, the interactions between ILs and PEG are significant in the formation of ABS,<sup>[7]</sup> and additional important interactions must be considered, such as cation–PEG, anion–PEG, cation–anion, water–anion, and cation–water interactions.<sup>[6b]</sup> More recently, cholinium carboxylate ILs have also been successfully applied in the formation of ABSs with PEG, and it further highlighted the importance of PEG–IL interactions in the phase-splitting mechanism.<sup>[8]</sup> Furthermore, the efficiency of PEG–IL ABS in separating different molecules, such as antibiotics, antioxidants, alkaloids, and dyes, validated not only the applicability of these systems for efficient purification processes, but also for selective techniques that allow the separation of similar molecules from aqueous media.<sup>[6c,8,9]</sup>

Taken together, the previous reports<sup>[6]</sup> suggested that if one could control the hydrogen-bond-donor or -acceptor ability of PEG, by replacing the terminal OH group with OMe or NH<sub>2</sub>

[a] Prof. Dr. J. F. B. Pereira, Prof. Dr. R. D. Rogers  
Department of Chemistry, The University of Alabama  
Tuscaloosa, AL 35487 (USA)

[b] Prof. Dr. J. F. B. Pereira  
Department of Bioprocess and Biotechnology  
School of Pharmacy  
UNESP—São Paulo State University  
14801-902—Araraquara, SP (Brazil)  
E-mail: jfbpereira@fcar.unesp.br

[c] Dr. K. A. Kurnia, Dr. M. G. Freire, Prof. Dr. J. A. P. Coutinho  
Chemistry Department, CICECO, University of Aveiro  
3810-193 Aveiro (Portugal)

[d] Prof. Dr. R. D. Rogers  
Chemistry Department, McGill University  
Montreal, QC H3A 0B8 (Canada)  
E-mail: robin.rogers@mcgill.ca

Supporting Information for this article is available on the WWW under <http://dx.doi.org/10.1002/cphc.201500146>.

groups, this would allow the capability of the PEG to interact with the IL and water to be tuned, and consequently, control of the size of the biphasic region. To explore this hypothesis, herein, we investigate the phase behavior of aqueous combinations of two ILs with anions of different basicity, namely the weakly basic cholinium chloride ([Ch]Cl) and the strongly basic cholinium acetate ([Ch][OAc]), with PEGs of different molecular weight and with OH (hydrogen-bond donor and acceptor), NH<sub>2</sub> (stronger hydrogen-bond acceptor, weaker donor), and OMe (hydrogen-bond acceptor, virtually no donation) end groups, as shown in Figure 1.

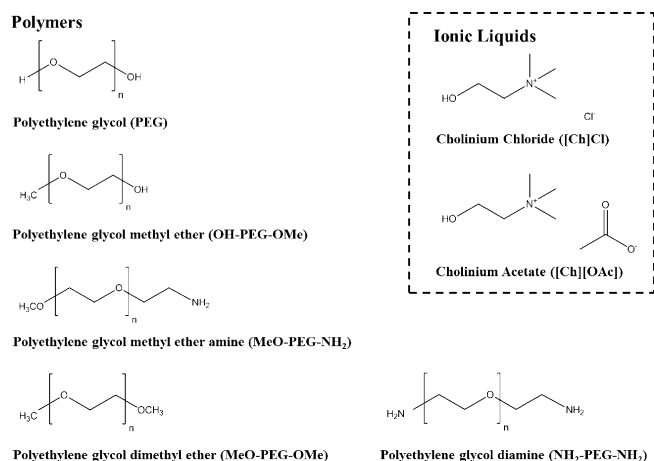


Figure 1. Chemical structure of the studied polymers and ionic liquids.

## 2. Results and Discussion

### 2.1. Removing One Hydrogen-Bond Donor from PEG

The alcohol end groups of the PEG molecules are the only source of strong hydrogen-bond-donating ability. We, therefore, began our investigation by removing a hydrogen-bond donor from one end of the PEG molecule by replacing an OH group with a OMe group. Such PEGs, having one OH end group and the other end group alkylated with a methyl group, with average molecular weights (MWs) of 350 (OH-PEG-350-OMe), 550 (OH-PEG-550-OMe), and 750 g mol<sup>-1</sup> (OH-PEG-750-OMe) were combined with [Ch]Cl and [Ch][OAc] and their phase diagrams were compared with aqueous mixtures of PEG-600 and PEG-400. Aqueous solutions of [Ch]Cl (70 wt%), [Ch][OAc] (90 wt%), and of each PEG (from 90 wt% to pure) were prepared and used to determine the binodal curves at 25 °C (± 1 °C) and atmospheric pressure, according to literature procedures.<sup>[10]</sup> The experimental binodal curves in units of molality (mole of solute per kg of solvent) are shown in Figure 2 and detailed experimental weight fraction data are provided in Tables S1 and S2 in the Supporting Information.

For the methylated PEGs, the MW trend usually observed in PEG-salt ABSs is as follows: polymers of higher MW require less salt to induce phase separation.<sup>[6,11]</sup> However, there is a small increase in the ability to form ABS (i.e., a larger biphasic region) when one OH end group is replaced by OMe. For example, OH-PEG-OMe induces phase demixing at equivalent

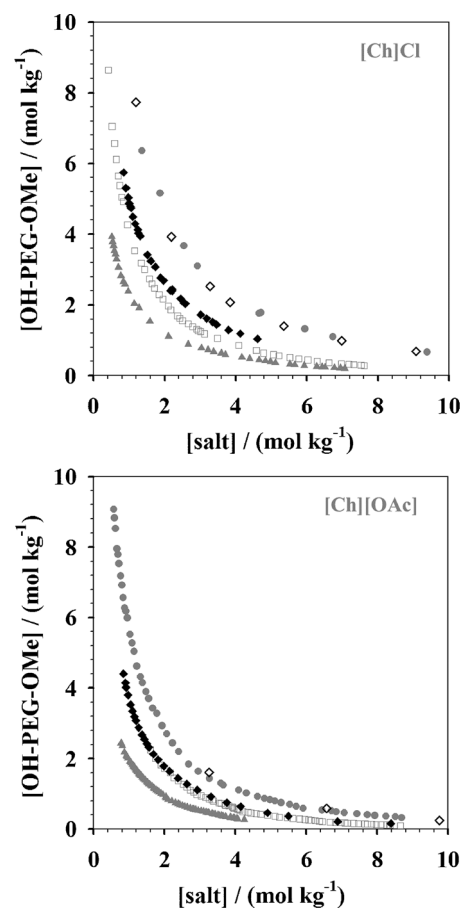
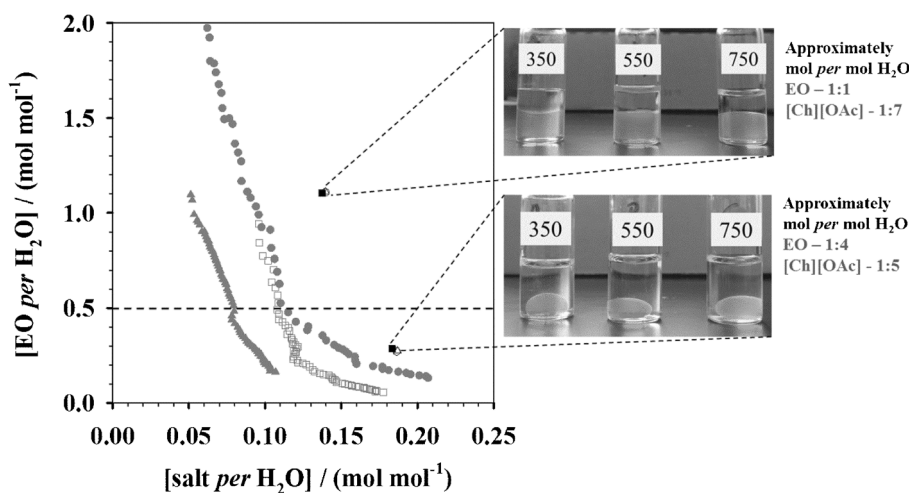


Figure 2. Experimental solubility data at 25 °C and atmospheric pressure for ABS composed of [Ch]Cl (top) or [Ch][OAc] (bottom) ionic liquids with OH-PEG-OMe of molecular weights: 350 g mol<sup>-1</sup> (●), 550 g mol<sup>-1</sup> (○), and 750 g mol<sup>-1</sup> (▲) [compared with PEG-400 (◇) and PEG-600 (◆)].

or lower polymer concentrations even with a lower MW: OH-PEG-350-OMe ≈ PEG-400 and OH-PEG-550-OMe > PEG-600. These trends are observed for both salts, although the differences in these polymer pairs are smaller for the ABS containing the more basic anion ([Ch][OAc]-based ABS).

To further probe the effects of hydrogen bonding, we chose to examine the phase diagrams of the IL that contains the stronger hydrogen-bond-acceptor anion, [Ch][OAc], in more detail. The phase diagrams were replotted (Figure 3) as the number of ethylene oxide (EO) units of each polymer per water molecule (mol of EO per mol of H<sub>2</sub>O) versus the ratio of salt to water (mol of salt per mol of H<sub>2</sub>O) to emphasize any effects related to hydrogen bonding. In addition, for the three OH-PEG-OMe/[Ch][OAc] ABS, two mixtures in the biphasic region were prepared at different molar ratios of H<sub>2</sub>O:EO:[Ch][OAc].

The macroscopic appearance of ABS with two different compositions shown in Figure 3 suggests that changing the phase composition (higher or lower polymer content), or the respective OH-PEG-OMe MW, results in different partitioning of water between the co-existing phases. Analysis of the individual phases by <sup>1</sup>H NMR spectroscopy identified the top phase as the [Ch][OAc]-rich phase and the bottom phase as the OH-



**Figure 3.** Experimental solubility data for ABS composed of OH-PEG-OMe + [Ch][OAc] + H<sub>2</sub>O at 25 °C and atmospheric pressure for different OH-PEG-OMe molecular weights: 350 g mol<sup>-1</sup> (●), 550 g mol<sup>-1</sup> (□), 750 g mol<sup>-1</sup> (▲) and two different mixture points for each ternary system [350 g mol<sup>-1</sup> (○), 550 g mol<sup>-1</sup> (■), 750 g mol<sup>-1</sup> (△)]. Methyl eosin dye was added to facilitate visual analysis.

PEG-OMe-rich phase. For high polymer concentrations, a change in the meniscus between the two phases is observed with increasing MW; this results from the increasing hydrophobicity difference between the phases. This effect is further enhanced when the systems contain low concentrations of OH-PEG-OMe (approximately 1.25:1:5 EO/[Ch][OAc]/H<sub>2</sub>O), for which the polymer-rich phase assumes a spheroid configuration suggesting that, in this phase, the water is fully surrounded by the polymer, which results in the bottom phase having a high hydrophobicity, and consequently, large surface-tension differences between the phases.

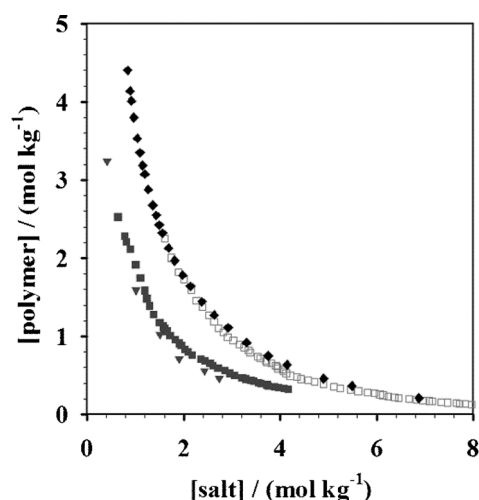
The behavior observed for the three OH-PEG-OMe polymers suggests that [Ch][OAc]-H<sub>2</sub>O interactions dominate those of OH-PEG-OMe-H<sub>2</sub>O and/or OH-PEG-OMe-[Ch][OAc], which is in agreement with the high basicity of the acetate anion. Such preferential ionic solvation would induce the dehydration of the OH-PEG-OMe, and consequently, results in a reduction of the volume of the OH-PEG-OMe-rich phase. However, at higher OH-PEG-OMe concentrations (approximately 7:1:7 EO/[Ch][OAc]/H<sub>2</sub>O), preferential hydration of the polymer-rich phase is clearly observed with an increase in the volume of the OH-PEG-OMe-rich phase and a volumetric decrease of the IL-rich phase.

Additionally, in Figure 3, it is shown that, at higher polymer concentrations, the OH-PEG-550-OMe-based ABS exhibits a different binodal shape than the ABS of the other two PEGs. The OH-PEG-550-OMe binodal curve approaches that of OH-PEG-350-OMe at a high polymer content, therefore suggesting that the effect of the MW is minimal in this region of the phase diagram. These deviations in the binodal curves were, however, accentuated upon decreasing the MW of the polymer. The removal of one hydrogen-bond donor from the PEG polymers with higher MWs does not noticeably affect the phase behavior, as the solvation of the aliphatic chain plays the dominant role, whereas for low-MW polymers the end groups seem to also play an important role.

## 2.2. Changing the Hydrogen-Bonding Donor/Acceptor Balance of PEG

The analysis of the OH-PEG-OMe-based ABS suggested that removal of a single hydrogen-bond-donating end group from PEG plays a significant role in the formation of an ABS. To further test this hypothesis, ABS were prepared with a combination of disubstituted PEGs and [Ch][OAc]. Four different types of PEG polymers were chosen with approximately the same MW, including those with two hydrogen-bond-donor end groups (PEG-600), one hydrogen-bond donor (OH-PEG-550-OMe), and no hydrogen-bond

donors (MeO-PEG-500-OMe). In addition, to study the hydrogen-bond donor/acceptor balance, we investigated NH<sub>2</sub>-PEG-600-NH<sub>2</sub>, in which the OH groups on both ends of the PEG were replaced with NH<sub>2</sub>, which is a stronger acceptor and weaker hydrogen-bond donor than OH. The same cloud point titration methodology was used to determine the phase diagrams, at 25 °C and atmospheric pressure (Figure 4). Detailed



**Figure 4.** Experimental solubility data at 25 °C and atmospheric pressure for ABS composed of [Ch][OAc] with MeO-PEG-500-OMe (■), OH-PEG-550-OMe (□), PEG-600 (◆), and NH<sub>2</sub>-PEG-600-NH<sub>2</sub> (▼).

weight fraction compositions are provided in the Supporting Information (Tables S3 and S4).

The binodal curves depicted in Figure 4, indicate that the ability to promote two phases follows the trend: NH<sub>2</sub>-PEG-600-NH<sub>2</sub> > MeO-PEG-500-OMe ≫ OH-PEG-550-OMe ≈ PEG-600. Although the replacement of one OH by one OMe doesn't significantly change the ability of the polymer to

induce ABS formation, the replacement of both OH end groups of PEG by two OMe or two NH<sub>2</sub> results in major increases in the biphasic region, meaning that lower concentrations of these polymers are needed to induce phase separation.

The results for MeO-PEG-500-OMe are perhaps easier to rationalize. Removing both strong hydrogen-bond donors (i.e. OH) eliminates any hydrogen bonding from the PEG termini to the polymer itself, to other polymers, to water, and to the acetate anion. The PEG molecules only form hydrogen bonds to the acetate anion or to any other PEG polymer through the terminal OH groups, whereas water and the cholinium cation could still donate hydrogen bonds to the PEG ether oxygen atoms. This could easily result in phase separation at lower polymer concentrations by making the PEG less compatible with water or the IL.

The results for NH<sub>2</sub>-PEG-600-NH<sub>2</sub> are somewhat more unexpected, as although this polymer has a more hydrophilic character than PEG-600, it presents a biphasic region equivalent to MeO-PEG-500-OMe. To understand this phenomenon, one needs to better understand the nature of the hydrogen-bond-donating and -accepting ability of NH<sub>2</sub> compared to OH. To achieve this understanding, we turned our attention to the use of density functional theory (DFT) through computational techniques, namely the electrostatic potential-derived (CHelpG) and conductor-like screening models for real solvents (COSMO-RS). The CHelpG method calculates the charge point of individual atoms of the studied PEG and its derivatives; in contrast, COSMO-RS allows us to investigate the ability of individual atoms to act as either hydrogen-bond donors (Hb don3) or hydrogen-bond acceptors (Hb acc3). The detailed description of the CHelpG calculation, Hb don3, and Hb acc3, can be found in the literature.<sup>[12]</sup> Together, these methods permit us to investigate the charge distribution of the studied PEG and its derivatives and, ultimately, their ability to interact with water or [Ch][OAc]. With CHelpG,<sup>[12a]</sup> charges of atoms composing various functionalized PEG-400 molecules were calculated by using Gaussian 03, Revision D.02 at the TZVP level of theory.<sup>[13]</sup> The HB don3 and HB acc3<sup>[14]</sup> were also calculated at the same level of theory by using the COSMOthermX program with the parameter file BP TZVP C20 0111 (COSMOlogic GmbH & Co KG, Leverkusen, Germany). In addition, we also calculated the CHelpG charges and Hb bond3 and Hb don3 of water. Detailed CHelpG and COSMO-RS calculations are given in the Supporting Information, together with the atom coordinates, CHelpG charges, HB don3, and HB acc3 for all atoms (Tables S10–S16).

Water molecules consist of three atoms, two hydrogens and an oxygen, and have the capacity to act as both a hydrogen-bond donor and acceptor. Detailed analysis of Table S10 in the Supporting Information reveals that the ability of water to act as a hydrogen-bond donor arises from its hydrogen atoms, whereas the oxygen atoms contribute to its hydrogen-bond-acceptor ability. Compared with a PEG molecule, which might be “considered” as a water molecule with the hydrogen atom substituted by bulky polyethylene glycol, the polymer has an improved capacity as a hydrogen-bond acceptor, which can be

attributed to the presence of multiple ether oxygen atoms. However, a change in the terminal group of the PEG from OH, to NH<sub>2</sub> or to OMe, leads to a change in its capacity as a hydrogen-bond donor. In this respect, the more hydrophilic character of NH<sub>2</sub>-PEG-400-NH<sub>2</sub> is believed to result from the enhanced hydrogen-bond-accepting ability of the N atom (of the NH<sub>2</sub> groups) compared to that of the O atom (of the OH groups) in conventional PEGs, as shown in Table 1 and Fig-

**Table 1.** HB don3 and HB acc3 of functionalized PEG-400 molecules retrieved from COSMO-RS using the BP TZVP C30 1301 parameterization.

Compounds	HB don3	HB acc3
PEG-400	4.03	27.63
OH-PEG-400-NH <sub>2</sub>	2.07	30.07
NH <sub>2</sub> -PEG-400-NH <sub>2</sub>	0.09	30.47
OH-PEG-400-OMe	2.00	26.28
MeO-PEG-400-OMe	0.00	24.71
MeO-PEG-400-NH <sub>2</sub>	0.06	28.58

ure S1 in Supporting Information, in which higher partial negative charges on the N atoms than the O atom are observed. Higher hydrogen-bonding energies to the amine (O–H⋯N 29 kJ mol<sup>-1</sup>) are present compared with those of the hydroxy groups (O–H⋯O 21 kJ mol<sup>-1</sup>).<sup>[15]</sup> As a result of these differences, there will be stronger interactions between water and the NH<sub>2</sub> groups making dehydration of the polymer more difficult.

The dominant interactions of the PEG terminal groups were also previously shown to result from a competition for their solvation between water and the IL anion.<sup>[7b,16]</sup> The hydroxy group can act as a good hydrogen-bond donor or acceptor, and thus, favorably interacts with the acetate or chloride anions, whereas the amine group, due to its stronger hydrogen-bond-acceptor and weaker hydrogen-bond-donor character, does not interact as strongly with the acetate anion (also a hydrogen-bond acceptor). The much weaker interaction between the IL acetate anion and the amine group makes this more-hydrophilic PEG derivative less soluble in cholinium acetate, as observed experimentally and confirmed by the infinite dilution activity coefficients reported in Table 2, thus leading to easier formation of ABS (larger biphasic region).

**Table 2.** Activity coefficients at infinite dilution of functionalized PEG-400 molecules in H<sub>2</sub>O and [Ch][OAc] at 25 °C estimated by COSMO-RS using the BP TZVP C30 1301 parameterization.

Compounds	lnγ <sup>∞</sup>	
	H <sub>2</sub> O	[Ch][OAc]
PEG-400	-5.31	-2.09
OH-PEG-400-NH <sub>2</sub>	-7.56	-0.63
NH <sub>2</sub> -PEG-400-NH <sub>2</sub>	-9.38	0.07
OH-PEG-400-OMe	-4.23	-0.62
MeO-PEG-400-OMe	-2.80	0.93
MeO-PEG-400-NH <sub>2</sub>	-7.20	0.42



### 2.3. The Key to the Formation of PEG–IL ABS

The results described above reveal the importance of hydrogen bonding, particularly hydrogen-bond donation from PEG to the anion, in the formation of PEG-based ABS, and demonstrate how even small changes in the chemical structure of the polymer can affect phase separation. In particular, although the data confirms the importance of the hydration of the ethylene oxide units, it emphasizes the relevance of the hydrogen-bond-donor ability of the PEG end groups, as the balance of competitive hydrogen-bonding interactions can readily alter phase formation.

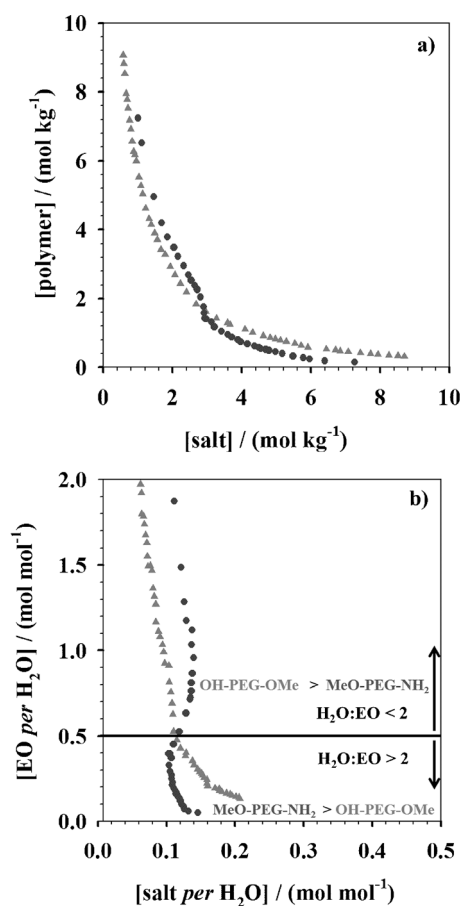
Figure 4 indicates that changing both end groups will increase the biphasic region, but that the mechanism for this depends on the type of functionalization. In an attempt to further explore the relative importance of hydrogen bonding and functionalization of PEGs in the formation of ABS, two additional phase diagrams combining [Ch][OAc] with OH–PEG–350–OMe and MeO–PEG–350–NH<sub>2</sub> were determined and are compared in Figure 5. These polymers (Figure 1) are distinguished by having only one hydrogen-bonding end group that is either a stronger donor (OH) or a stronger acceptor (NH<sub>2</sub>). To compare the respective binodal curves with the previ-

ous ones, and to obtain more information on the molecular level interactions, the binodal curves were plotted both in units of molality (mol of solute per kg of solvent; Figure 5a) and in mol of PEG ethylene oxide (EO) units per mol of H<sub>2</sub>O (Figure 5b) versus mol of salt per mol of H<sub>2</sub>O. The detailed weight fraction data are presented in Table S9 of the Supporting Information.

The data in Figure 5a reveal that an inversion in the ability of the two polymers to form ABS occurs at approximately 3 mol kg<sup>-1</sup> of [Ch][OAc]. Furthermore, the data plotted in Figure 5b show a change in the relative ability to induce the biphasic region at 0.5 mol EO unit per mol of H<sub>2</sub>O (equivalent to 2 mol of H<sub>2</sub>O per EO), thus suggesting that a reversal in the ability to form ABSs occurs when the EO units are saturated with hydrogen bonds.<sup>[17]</sup> A change in the behavior between the region above/below 0.5 mol of EO per mol of H<sub>2</sub>O is also observed in Figure 3 for ABSs composed of [Ch][OAc] and OH–PEG–OMe with a higher MW, namely OH–PEG–750–OMe and OH–PEG–550–OMe. Above an average of 2 mol of water per EO unit, MeO–PEG–350–NH<sub>2</sub> becomes fully solvated and exhibits a higher capability to phase separate than OH–PEG–350–OMe (below this value the trend is the reverse).

The relative ability of these polymers to form ABS with [Ch][OAc] seems to change with the relative amount of phase-forming components in solution (from high polymer concentrations to high salt concentrations). The phase diagrams in Figure 5a reveal that making one end group more hydrophilic (i.e. substituting OH with NH<sub>2</sub>) enhances, as expected, the polymer solubility in the aqueous phase, therefore decreasing its ability to create an immiscible region when the concentration of polymer is high and the concentration of [Ch][OAc] is below 10 mol%. In this region, the formation of ABS seems to be controlled by water solvation of the polymer, as the concentration of [Ch][OAc] is small. Conversely, when the concentration of water is higher than 2 mol of H<sub>2</sub>O per EO and the [Ch][OAc] concentration is higher than 10 mol%, the phase diagrams show an inversion in phase behavior and MeO–PEG–NH<sub>2</sub> becomes less soluble than OH–PEG–OMe, thus enlarging the two-phase region. This suggests a change in the phase separation mechanism, such that it is no longer dominated by the water solvation of the polymer, but by mutual interactions between the polymer and [Ch][OAc].

As discussed in the Section 2.2, interactions between the acetate anion and the NH<sub>2</sub> terminal groups of the PEG are not as favorable as those with OH, as shown by their infinite dilution activity coefficients; this is because both the acetate anion and the NH<sub>2</sub> group are preferentially hydrogen-bond acceptors. The change observed here is, thus, related to a situation where one moves from a system with high polymer and low salt concentrations, in which the phase separation is dominated by water solvation of the polymer, towards a system with high [Ch][OAc] and low polymer concentration, in which phase separation is dominated by [Ch][OAc]–polymer interactions. In this region, the replacement of OH by NH<sub>2</sub> will invert the dominant interactions, with the polymer with NH<sub>2</sub> end groups having more favorable interactions with water (NH<sub>2</sub>–H<sub>2</sub>O > OH–



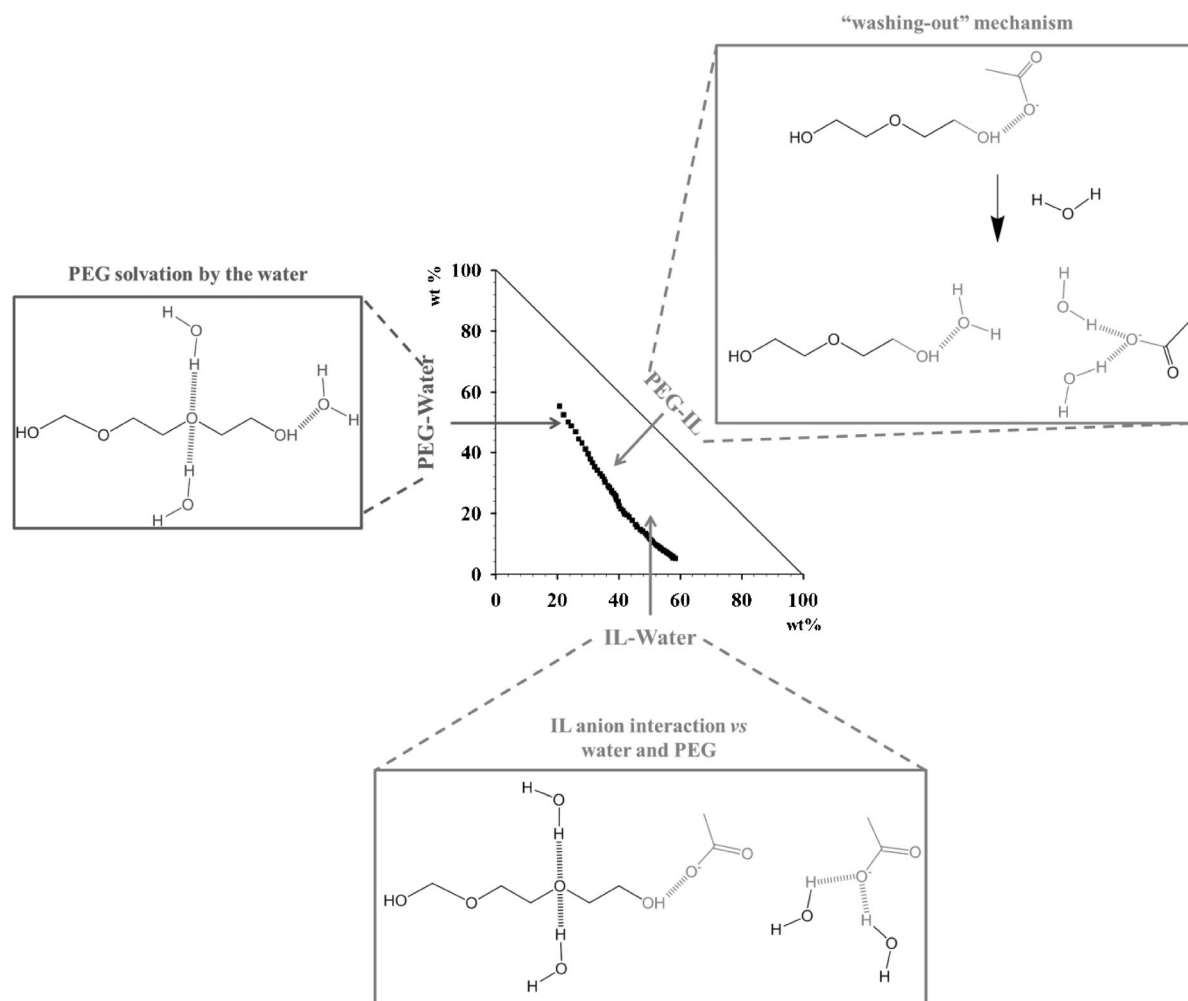
**Figure 5.** Experimental solubility data at 25 °C and atmospheric pressure for ABS composed of [Ch][OAc] with OH–PEG–350–OMe (▲) and MeO–PEG–350–NH<sub>2</sub> (●).

H<sub>2</sub>O), but less favorable interactions with acetate (NH<sub>2</sub>-OAc < OH-OAc), thus leading to an inversion in the phase behavior.

Previously, we demonstrated<sup>[7]</sup> for PEG-IL ABS, that in the region with a low water content (close to the binary mixture PEG-IL) the hydroxy groups of PEG and the anion interact strongly, and upon addition of water these interactions are disrupted, thus inducing liquid-liquid demixing. However, herein differences in the ability to form ABS were observed in the regions close to the two other binary systems: PEG-water (with low salt content) and IL-water (with low PEG content). The results reported here suggest that for each binary mixture a different mechanism is acting: PEG solvation by water will dominate the demixing close to the PEG-water binary mixture, whereas the interaction balance between the IL anion/water and PEG will control demixing close to the IL-water binary mixture. A schematic phase diagram representing each favorable mechanism versus the ternary phase region is depicted in Figure 6. Ongoing work should provide more details about these mechanisms.

### 3. Conclusions

In summary, this innovative study was aimed at understanding polymer solvation in aqueous salt solutions. The formation of the related ABS was ascertained by changing of the hydrogen-bonding-donor or -acceptor capabilities of the polymer terminal groups (functionalized with OH, OMe, or NH<sub>2</sub>). All the phase diagrams reported here demonstrate the complexity of PEG-IL ABS, in which the immiscible region is a result of a delicate balance of interactions between the various compounds present in the system. It is shown that the miscibility/immiscibility of these systems stems not only from the solvation of the ether groups in the polymer chain, as previously admitted, but also from the capability of the PEG terminal groups to preferably form hydrogen bonds with water or with the salt anion. The removal of even one hydrogen bond from the PEG molecule can noticeably affect the phase behavior; especially in those regions of the phase diagram where the EO units of the polymeric chain are completely solvated. In this region of the phase diagrams, removing or weakening the hydrogen-bond-donating ability of PEG results in greater immiscibility, as



**Figure 6.** Schematic phase diagram representing the favorable mechanisms that control the ABS formation. The binodal curve used as example is from the ternary system composed of OH-PEG-350-OMe + [Ch][OAc] + water at 25 °C.

a result of the much weaker interactions between the IL anion (in this case acetate) and the PEG end group (e.g., NH<sub>2</sub>). Thus, by controlling the donor/acceptor character of the PEG terminal groups, it is possible to control the biphasic region over a rather wide range.

The tailoring of PEG-IL ABS has been previously accomplished<sup>[6b,7,8]</sup> by the judicious choice of IL ions, but here it is shown that the same level of control can be achieved by controlling the nature of the terminal groups of the PEG. Moreover, the most interesting phenomenon observed, is the possibility to switch the ability of the polymer to form ABS by modifying the polymer to interact better with water and worse with the IL or vice versa. Although the study reported here has helped us to better understand the formation of PEG-IL ABS for various types and compositions of PEG and ILs, and to define the potential to tailor these liquid-liquid extraction systems, further studies are still required, such as the evaluation of speciation effects and the investigation of the formation of preferential polymer-water hydration shells. The next challenge will be to use this knowledge for the selective extraction of complex biomolecules that are only stable under specific conditions (e.g., proteins and biopharmaceuticals), while envisaging their pharmaceutical and biotechnological applications.

## Acknowledgements

We thank the Novartis-Massachusetts Institute of Technology (MIT) Center for Continuous Manufacturing (CCM) for financial support. Jorge F. B. P. acknowledges financial support (process reference 2014/16424-7) from FAPESP (São Paulo Research Foundation Brazil). ara .G. F. acknowledges the European Research Council (ERC) for the Starting Grant ERC-2013-StG-337753. The authors thank Parker D. McCrary for help in the synthesis of PEG-amine-based polymers.

**Keywords:** aqueous biphasic systems · hydrogen bonding · ionic liquids · polyethylene glycol · polymers

- [1] a) P. Å. Albertsson, *Partition of cell particles and macromolecules*, 3rd Ed., Wiley, New York, 1986; b) B. Y. Zaslavsky, *Aqueous Two-Phase Partitioning*, Marcel Dekker Incorporated, New York, 1995.
- [2] K. E. Gutowski, G. A. Broker, H. D. Willauer, J. G. Huddleston, R. P. Swatloski, J. D. Holbrey, R. D. Rogers, *J. Am. Chem. Soc.* **2003**, *125*, 6632–6633.
- [3] M. G. Freire, A. F. M. Cláudio, J. M. M. Araújo, J. A. P. Coutinho, I. M. Marrucho, J. N. Canongia Lopes, L. P. N. Rebelo, *Chem. Soc. Rev.* **2012**, *41*, 4966–4995.

- [4] a) S. Shahriari, L. C. Tome, J. M. M. Araújo, L. P. N. Rebelo, J. A. P. Coutinho, I. M. Marrucho, M. G. Freire, *RSC Adv.* **2013**, *3*, 1835–1843; b) M. G. Freire, C. L. S. Louros, L. P. N. Rebelo, J. A. P. Coutinho, *Green Chem.* **2011**, *13*, 1536–1545; c) M. G. Freire, C. M. S. S. Neves, I. M. Marrucho, J. N. Canongia Lopes, L. P. N. Rebelo, J. A. P. Coutinho, *Green Chem.* **2010**, *12*, 1715–1718; d) H. Passos, A. C. A. Sousa, M. R. Pastorinho, A. J. A. Nogueira, L. P. N. Rebelo, J. A. P. Coutinho, M. G. Freire, *Anal. Methods* **2012**, *4*, 2664–2667; e) S. P. M. Ventura, V. Santos-Ebinuma, J. F. B. Pereira, M. S. Teixeira, A. Pessoa, J. A. P. Coutinho, *J. Ind. Microbiol. Biotechnol.* **2013**, *40*, 507–516; f) S. P. M. Ventura, R. L. F. de Barros, J. M. de Pinho Barbosa, C. M. F. Soares, Á. S. Lima, J. A. P. Coutinho, *Green Chem.* **2012**, *14*, 734–740.
- [5] A. M. Ferreira, J. A. P. Coutinho, A. M. Fernandes, M. G. Freire, *Sep. Purif. Technol.* **2014**, *128*, 58–66.
- [6] a) M. G. Freire, J. F. B. Pereira, M. Francisco, H. Rodriguez, L. P. N. Rebelo, R. D. Rogers, J. A. P. Coutinho, *Chem. Eur. J.* **2012**, *18*, 1831–1839; b) J. F. B. Pereira, K. A. Kurnia, O. A. Cojocar, G. Gurau, L. P. N. Rebelo, R. D. Rogers, M. G. Freire, J. A. P. Coutinho, *Phys. Chem. Chem. Phys.* **2014**, *16*, 5723–5731; c) J. F. B. Pereira, L. P. N. Rebelo, R. D. Rogers, J. A. P. Coutinho, M. G. Freire, *Phys. Chem. Chem. Phys.* **2013**, *15*, 19580–19583.
- [7] a) L. I. N. Tomé, J. F. B. Pereira, R. D. Rogers, M. G. Freire, J. R. B. Gomes, J. A. P. Coutinho, *Phys. Chem. Chem. Phys.* **2014**, *16*, 2271–2274; b) L. I. N. Tomé, J. F. B. Pereira, R. D. Rogers, M. G. Freire, J. R. B. Gomes, J. A. P. Coutinho, *J. Phys. Chem. B* **2014**, *118*, 4615–4629.
- [8] T. Mourão, L. C. Tomé, C. Florindo, L. P. N. Rebelo, I. M. Marrucho, *ACS Sustainable Chem. Eng.* **2014**, *2*, 2426–2434.
- [9] a) J. F. B. Pereira, F. Vicente, V. C. Santos-Ebinuma, J. M. Araújo, A. Pessoa, M. G. Freire, J. A. P. Coutinho, *Process Biochem.* **2013**, *48*, 716–722; b) J. F. B. Pereira, S. P. M. Ventura, F. A. Silva, S. Shahriari, M. G. Freire, J. A. P. Coutinho, *Sep. Purif. Technol.* **2013**, *113*, 83–89.
- [10] J. F. B. Pereira, A. S. Lima, M. G. Freire, J. A. P. Coutinho, *Green Chem.* **2010**, *12*, 1661–1669.
- [11] a) B. Y. Zaslavsky, *Aqueous two-phase partitioning, physical chemistry and bioanalytical applications*, Academic Press, New York, 1995; b) M. T. Zafarani-Moattar, R. Sadeghi, *Fluid Phase Equilib.* **2001**, *181*, 95–112; c) M. E. Taboada, J. A. Asenjo, B. A. Andrews, *Fluid Phase Equilib.* **2001**, *180*, 273–280.
- [12] a) C. M. Breneman, K. B. Wiberg, *J. Comp. Chem.* **1990**, *11*, 361–373; b) A. Klamt, *COSMO-RS from quantum chemistry to fluid phase thermodynamics and drug design*, 2005, Amsterdam, The Netherlands: Elsevier.
- [13] University of Karlsruhe and Forschungszentrum Karlsruhe GmbH, TURBOMOLE V6.1 **2009**, 1989–2007, 25 GmbH, since 2007; available from <http://www.turbomole.com>.
- [14] Eckert, F., A. Klamt. COSMOtherm, Version C3.0, Release 13.01, COSMOlogic GmbH & Co. KG, Leverkusen, Germany, 2013.
- [15] a) O. Markovitch, N. Agmon, *J. Phys. Chem. A* **2007**, *111*, 2253–2256; b) J. W. Larson, T. B. McMahon, *Inorg. Chem.* **1984**, *23*, 2029–2033; c) J. Emsley, *Chem. Soc. Rev.* **1980**, *9*, 91–124.
- [16] H. Rodriguez, M. Francisco, M. Rahman, N. Sun, R. D. Rogers, *Phys. Chem. Chem. Phys.* **2009**, *11*, 10916–10922.
- [17] M. Pochylski, F. Aliotta, Z. Blaszczyk, J. Gapinsky, *J. Phys. Chem. B* **2006**, *110*, 20533–20539.

Received: February 22, 2015

Published online on ■■■, 2015

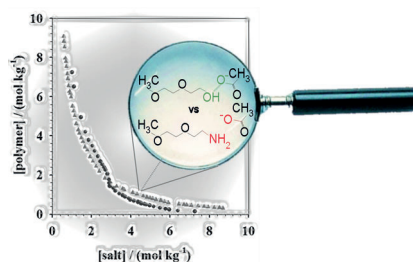
## ARTICLES

J. F. B. Pereira,\* K. A. Kurnia, M. G. Freire,  
J. A. P. Coutinho, R. D. Rogers\*

■ ■ - ■ ■



**Controlling the Formation of Ionic-Liquid-based Aqueous Biphasic Systems by Changing the Hydrogen-Bonding Ability of Polyethylene Glycol End Groups**



**Great ABS!** The hydrogen-bond-donating strength of polyethylene glycol end groups strongly affects the immiscibility of ionic liquids in aqueous biphasic systems, as a result of changing the strength of the interactions with the anion.



