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Widening the Stimuli-Responsiveness of Aqueous Biphasic Systems by Changing the Ionic Liquid Cation Basicity

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Abstract: Herein we demonstrate the formation of new stimuli-responsive aqueous biphasic systems (ABS), able to respond simultaneously to temperature and pH, or just to one stimulus, therefore allowing the design of more sustainable separation processes. This dual behavior is achieved with ABS formed by mono or dicationic protic ionic liquids as phase-forming components, being defined by the ionic liquid cation chemical structure or its basicity. While ABS comprising monocationic ionic liquids only respond to the effect of temperature, systems comprising dicationic ionic liquids are simultaneously affected by both temperature and pH variations. Dicationic ionic liquids are here identified as the key to unlock a double response to stimuli, which is due to the presence of two pK_a values afforded by the cation. The reported findings contribute to increase the customizability of double stimuli-responsive ABS based on ionic liquids, whose development was up to date limited to ionic liquids bearing pH-responsive anions, opening the door towards the development of more sustainable separation processes.

Aqueous biphasic systems (ABS) are liquid-liquid ternary systems formed by dissolving at least two, often non-volatile, compounds, conventionally a polymer and a salt or two polymers, that undergo liquid-liquid demixing in aqueous medium under particular operating conditions of pH, temperature, pressure, and concentration.^[1] Due to their high content in water, ABS have been proposed as sustainable liquid-liquid extraction systems.^[2] Besides the conventional polymer-salt- and polymer-polymer-based ABS studied since long, an increased interest appeared with the use of ionic liquids (ILs; asymmetric salts usually composed of an organic cation and an organic/inorganic anion, able to establish a richness number of interactions between their ions and other solutes/solvents when compared to Coulombic-dominated salts^[3]) as ABS phase-forming components, often leading to highly efficient/selective separation processes.^[4] More recently, ABS have witnessed a resurgence of interest to follow the progress of Chemical Engineering and Biotechnology fields, in which the development of stimuli-responsive

liquid-liquid systems to assist process integration, particularly in biocatalytic processes, has been underscored.^[5]

Stimuli-responsive ABS make use of the sensitivity of at least one of the phase-forming agents (e.g., polymers, salts, ILs) to the action of external stimuli, such as temperature.^[6] This allows switching between mono- and biphasic systems and, consequently, to integrate different process steps (e.g., reaction, product separation and ABS components/catalysts recovery and/or reuse).^[6a, 6c]

Despite the attention drawn towards the application of an isolated stimulus,^[7] double stimuli-responsive ABS are anticipated to be even more easily customizable to meet the operating needs and optimal conditions of chemical and biotechnological processes.^[8] We have previously shown the formation of IL-based ABS with simultaneous response to temperature and pH.^[8] In these systems, cholinium-alkanoate-based ILs acted as pH-responsive components, achieved by the speciation and different values of pK_a of the respective organic-acid-derived anions. In addition to the IL and water, polypropylene glycol with an average molecular weight of 400 g·mol⁻¹ (PPG 400) was used as the third, thermo-responsive component. Increasing the pH facilitated ABS formation as negatively charged species of the IL anion prevail, with the ability to create ABS as function of the pH, closely following the pK_a of the respective organic acid.^[8] Still, only ABS able to simultaneously respond to two stimuli have been identified.^[8]

Given the interest of these systems and the scarcity of their studies in the literature, there is still a gap on understanding stimuli-dependent behaviors and the possibilities of conjugation of phase-forming components to tailor the extent and/or dependencies of stimuli response. To bridge this gap, the toolbox of available IL-based double-stimuli (temperature and pH) responsive ABS is here expanded, and novel insights on the molecular-level mechanisms responsible for their formation are provided. Contrarily to our previous work that focused on the role of the IL anion, and only in which double stimuli-responsive have

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been developed,^[8] here we moved to the speciation of the IL cation, further leading to more customizable double-stimuli-responsive ABS. Mono- and dicationic protic ILs were investigated as ABS phase-forming components, being able to respond only to one stimulus or to simultaneously respond to two stimuli (pH and temperature). This behavior is defined by the IL chemical structure or its basicity, being here shown for the first time.

Protic ILs are easily synthesized by transferring a proton from a Brønsted acid to a Brønsted base.^[9] This mobile proton may thus offer the possibility of shifting from a single-phase to two-phase systems by playing with the pH of the medium. Furthermore, compared to their monocationic congeners, dicationic ILs are composed of two cations connected through a linkage alkyl chain and two anions,^[10] with two groups at the cation presenting speciation behavior. Due to the different values of pK_a of the cation respective bases, the possible cation speciation in solution

as a function of pH allows to project their response to two pH values.

We synthesized and used the following ILs: ethanolammonium chloride, $[N_{000(2OH)}]Cl$; diethanolammonium chloride, $[N_{00(2OH)(2OH)}]Cl$; diethylethanolammonium chloride, $[N_{022(2OH)}]Cl$; triethanolammonium chloride, $[N_{0(2OH)(2OH)(2OH)}]Cl$; N,N,N',N'-tetramethyl-ethane-1,2-diammonium dichloride, $[N_{011-C_2-N_{011}}]Cl_2$; N,N,N',N'-tetramethyl-propane-1,3-diammonium dichloride, $[N_{011-C_3-N_{011}}]Cl_2$; and N,N,N',N'-tetramethyl-butane-1,4-diammonium dichloride, $[N_{011-C_4-N_{011}}]Cl_2$. Chloride was chosen as the common counterion to guarantee that the speciation and ABS pH dependency is only dependent on the IL cation. Figure 1 provides the chemical structures and acronyms of the ILs studied, while details on their synthesis and purity (Table S1) are given in the Supporting Information.

| a) Monocationic ILs | | | |
|---------------------|----------------------------|----------------|----------------|
| Chemical Structure | Acronym | R ₁ | R ₂ |
| | $[N_{000(2OH)}]Cl$ | H | H |
| | $[N_{00(2OH)(2OH)}]Cl$ | H | $(CH_2)_2OH$ |
| | $[N_{022(2OH)}]Cl$ | CH_2CH_3 | CH_2CH_3 |
| | $[N_{0(2OH)(2OH)(2OH)}]Cl$ | $(CH_2)_2OH$ | $(CH_2)_2OH$ |

| b) Dicationic ILs | | |
|--------------------|-----------------------------|---|
| Chemical Structure | Acronym | n |
| | $[N_{011-C_2-N_{011}}]Cl_2$ | 2 |
| | $[N_{011-C_3-N_{011}}]Cl_2$ | 3 |
| | $[N_{011-C_4-N_{011}}]Cl_2$ | 4 |

Figure 1. Chemical structure and acronyms of monocationic a) and dicationic b) ILs synthesized and used in the development of stimuli-responsive ABS.

ABS were prepared with mono/dicationic ILs, water and polypropylene glycol with an average molecular weight of $400 \text{ g}\cdot\text{mol}^{-1}$ (PPG 400). These systems were designed to have a response to temperature afforded by the polymer, and a response to pH achieved with the IL cation speciation. The binodal curves of ABS were determined by the cloud point titration method under several combinations of temperature (from 25 to 45°C) and pH (from 4 to 9). The desired pH was achieved by adding HCl or the IL respective base, thus avoiding the addition of new species to

the medium that could affect the behaviors observed. All experimental binodal data and correlation parameters (Tables S2 to S41) are given in the Supporting Information, along with representations of the remaining binodal curves (Figures S1 to S14). The ABS response to temperature and/or pH can be ascertained using the extent of the biphasic/monophasic area of the binodal curves. In Figure 2, the response of ABS to both stimuli is demonstrated for representative conditions and two ILs, namely $[N_{000(2OH)}]Cl$ and $[N_{011-C_3-N_{011}}]Cl_2$.

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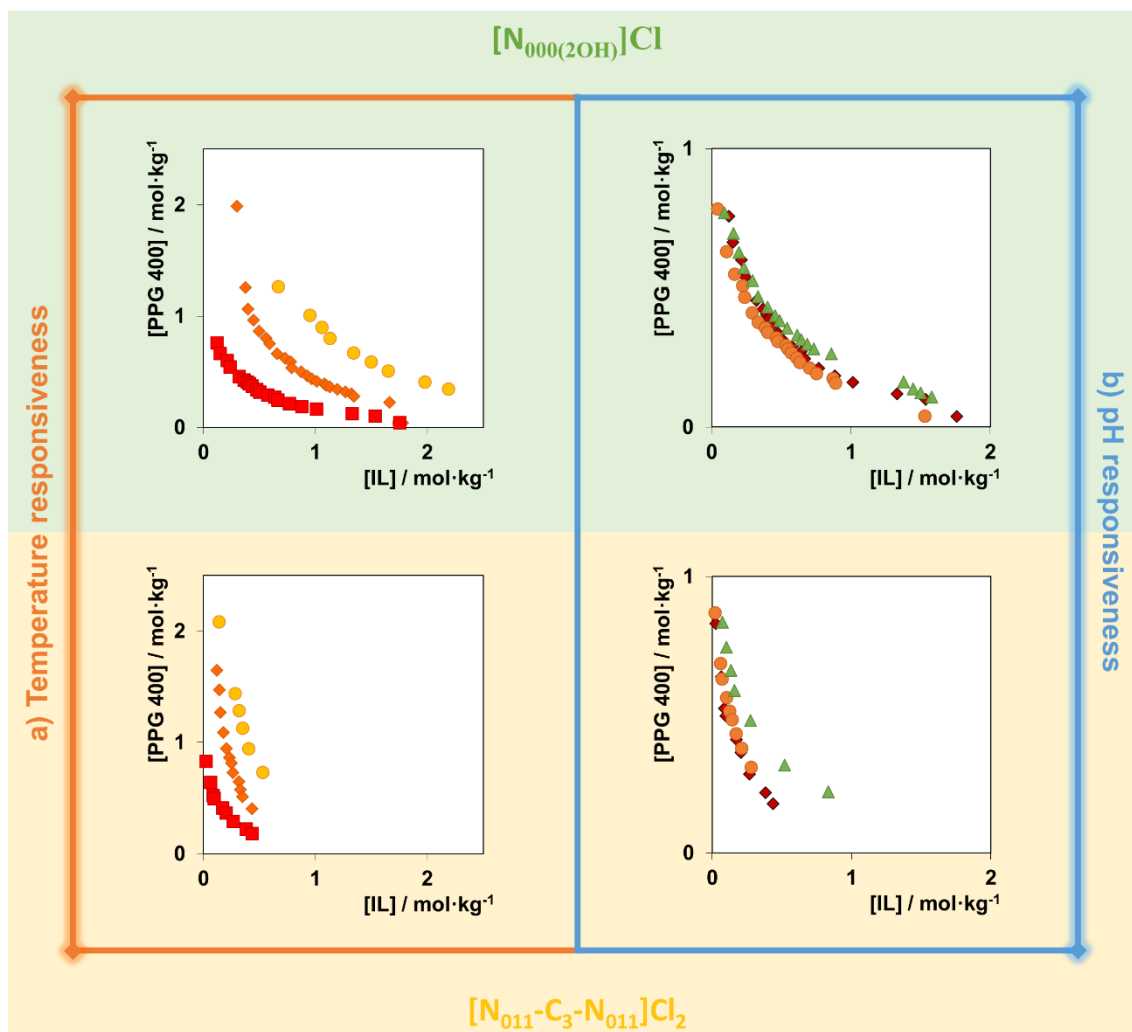


Figure 2. Temperature a) and pH b) responsiveness of systems composed of PPG 400 + IL + H₂O. Binodal curves presented are for the temperatures of 25°C (●), 35°C (◆) and 45°C (■) under pH 4; or variable pH values of 4 (◆), 7 (●) and 9 (▲) at 45 °C.

Figure 2a shows that an increment in the temperature favors the ABS formation regardless of the IL cation structure and pH (cf. Figures S1 to S7 in the Supporting Information for the remaining ILs). A Lower Critical Solution Temperature (LCST)-like behavior is followed by these systems regardless of the IL cationic structure, complying with the behavior of PPG 400-water^[11] and polymer-IL binary mixtures.^[12] It has been previously shown that the formation of IL-polymer ABS is dependent on the IL-polymer mutual solubilities, which result from the interactions (e.g., H-bonding, dispersive forces) established between the polymer and the IL, and how these are compensated by the interactions between the polymer or the IL and water.^[13] Due to the decrease in the H-bonding interactions at higher temperatures, PPG 400 interaction with water decreases, improving liquid-liquid demixing. Figure 2b shows that the two groups of ILs (mono and dicationic) display a different response to pH variation. As shown with [N_{000(2OH)}]Cl, and further confirmed for the remaining monocationic ILs (cf. Figures S8 to S11 in the Supporting Information), the binodal curves at various pH values overlap. With dicationic ILs,

on the other hand, the ability to form ABS shows a strong dependency with the pH. Being driven by the mutual solubilities of the IL and the polymer, IL-polymer ABS formation strongly correlates with the hydrophilic-hydrophobic character of the IL.^[13-14] Here, the pH response observed is related to the *pK_a* of the IL cation corresponding base - Table 1 - and, thus, to the percentage of positively charged and neutral species as a function of pH (cf. Figures S15 to S21 in the Supporting Information). The high *pK_a* values of the monocationic ILs (7.79-9.55) do not allow a significant pH-responsive behavior, being this type of systems mainly dependent on temperature.

The presence of *pK_a* values in dicationic ILs is the key to trigger a response to pH (cf. Table 1). At pH below the second (higher) *pK_a*, monocationic species prevail in solution, while further decreasing the pH to values below the first (lower) *pK_a*, there is a dominance of dicationic species. Accordingly, for systems comprising [N_{011-C₂-N₀₁₁Cl₂] and [N_{011-C₃-N₀₁₁Cl₂], a sharp pH-dependency is observed when moving from pH 9 to 7 (cf. Figures S12 to S14 in the Supporting Information). Under these conditions,}}

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the fraction of positively charged species increases, with divalent species appearing in solution. Further decreasing the pH from 7 to 4, binodal curves overlap in most conditions tested due to the similar concentration of neutral *versus* positively charged species irrespective of their valence. For the ABS comprising $[N_{011}\text{-C}_4\text{-N}_{011}]\text{Cl}_2$, the proximity of the two pK_a values translates into the overlapping of the binodal curves, with no response to pH variations.

Overall, with dicationic protic ILs, there is an increase in ABS phase separation by a decrease in the pH, following the IL cation ability to prevail in their ionic form. This behavior contrasts with our previous work,^[8] in which the pH-driven behavior was accomplished with the speciation of the IL anion, using anions derived from organic acids and with low pK_a values (*i.e.*, 3.53-

4.75). With these, the ABS formation ability was promoted by an increase in the pH, contrarily to the current work where the ABS formation is favored by a decrease in the pH. Since the speciation occurs at the IL anion,^[8] the improved ability to form ABS at higher pH results from the increased concentration of negatively charged species in solution.

Based on the aforementioned information, with further assistance of Table 1, it is possible to enlighten that, independently of the IL, the temperature has a more significant impact on the ABS formation than pH. At higher pH and lower temperatures, there is no formation of ABS for some monocationic ILs, *e.g.* $[N_{00(2OH)(2OH)}]\text{Cl}$, $[N_{022(2OH)}]\text{Cl}$ and $[N_{0(2OH)(2OH)(2OH)}]\text{Cl}$ at pH 9 and 25°C.

Table 1. pK_a of the bases used for the IL synthesis and their relationship with the pH dependency of IL-based ABS: ■ No ABS formation; ■ ABS formation.

| IL | $[N_{000(2OH)}]\text{Cl}$ | $[N_{00(2OH)(2OH)}]\text{Cl}$ | $[N_{022(2OH)}]\text{Cl}$ | $[N_{0(2OH)(2OH)(2OH)}]\text{Cl}$ | $[N_{011}\text{-C}_2\text{-N}_{011}]\text{Cl}_2$ | $[N_{011}\text{-C}_3\text{-N}_{011}]\text{Cl}_2$ | $[N_{011}\text{-C}_4\text{-N}_{011}]\text{Cl}_2$ |
|-----------------------|---------------------------|-------------------------------|---------------------------|-----------------------------------|--|--|--|
| pK_a ^[a] | 9.55 | 8.86 | 9.55 | 7.79 | 5.74; 9.01 | 6.91; 9.60 | 9.48; 10.09 |
| pH | 4 7 9 | 4 7 9 | 4 7 9 | 4 7 9 | 4 7 9 | 4 7 9 | 4 7 9 |
| T/(°C) | | | | | | | |

[a] pK_a values were retrieved from the Chemaxon (<https://www.chemaxon.com>) and correspond to the base used in the IL synthesis (by order): ethanolamine, diethanolamine, N,N-diethylethanolamine, triethanolamine, N,N,N',N'-tetramethyl ethylenediamine, N,N,N',N'-tetramethyl-1,3-propanediamine, and N,N,N',N'-tetramethyl-1,4-butanediamine. It should be noted that the pK_a value were obtained considering a temperature of 25 °C. Although they can slightly vary with the temperature, these values were always assumed for trending/comparison purposes.

Table 1 reveals that the relative hydrophobicity of the IL cation (presence of ethyl side chains and/or number of hydroxyethyl groups) plays a role in the ABS formation ability. Despite the same pK_a of the respective bases, $[N_{022(2OH)}]\text{Cl}$ has a higher mutual solubility with PPG 400 and lower capacity to interact with water than $[N_{000(2OH)}]\text{Cl}$ due to the presence of two ethyl groups instead of hydrogens (more protected amine group). ABS formation is thus hindered, particularly at lower temperatures. The same is true for $[N_{00(2OH)(2OH)}]\text{Cl}$ and $[N_{0(2OH)(2OH)(2OH)}]\text{Cl}$, whose bases have lower pK_a and more protected amine groups. Even at pH 4 and 7, where cationic species abound, $[N_{022(2OH)}]\text{Cl}$ and $[N_{0(2OH)(2OH)(2OH)}]\text{Cl}$ do not form ABS with PPG 400 under less favorable conditions of temperature. On the opposite, dicationic ILs promote liquid-liquid demixing in the entire range of tested conditions and regardless of the IL parent base pK_a . This is the result of the lower first pK_a value and lower mutual solubility with PPG 400 of divalent ions compared to their monovalent counterparts due to higher polarity. Moreover, double response to temperature and pH is only exhibited by systems composed of properly designed dicationic ILs. The pH-responsive region is larger for $[N_{011}\text{-C}_2\text{-N}_{011}]\text{Cl}_2$, followed by $[N_{011}\text{-C}_3\text{-N}_{011}]\text{Cl}_2$, in particular at the highest temperature tested. $[N_{011}\text{-C}_4\text{-N}_{011}]\text{Cl}_2$, however, lacks a significant pH-responsive region regardless of

temperature, likely due to its larger linkage alkyl chain that has higher ability to interact with PPG 400 by dispersive forces. Using protic ILs in the formation of stimuli-responsive ABS with PPG 400 results in a similar intensity of response to the temperature as the ILs with speciation in the anion previously reported by us.^[8] Generally, ILs with speciation in the anion provide broader pH-responsive regions in the respective ABS. However, and in addition to the opposite trend observed with the pH, ILs with speciation at the cation, such in the current work, show distinct extents of pH-responsive regions (negligible pH-driven behavior for monocationic ILs *versus* tailored pH-driven behavior for dicationic ILs). The fraction of anionic *versus* dicationic species in solution is similar (>98%) for the respective best pH conditions of ABS formation. At the most unfavorable pH conditions, however, the percentage of neutral species is generally higher (25.90-77.06% *versus* 1.99-49.20%) in the presence of ILs with speciation at the anion than at the cation (Figures S15 to S21 in the Supporting Information, as well as our previous work).^[8] In this case, the reduced ability for liquid-liquid demixing of neutral species is thus likely to enlarge the distance between the binodal curves at extreme values of pH. $[N_{011}\text{-C}_2\text{-N}_{011}]\text{Cl}_2$, on the other hand, provides an abnormal larger pH response at higher temperatures, since similar percentages of both neutral and monocationic species (49.20% and 50.77%,

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respectively) coexist at pH 9 (*cf.* Figure S19, in the Supporting Information). In addition to the expected effect of neutral *versus* charged species at a given pH in ABS formation, the impact of specific interactions between all the ABS constituents cannot be discarded due to structural differences of the ILs under analysis. As previously shown with other PPG-IL ABS,^[13] IL-PPG interactions are dominated by the IL anion, thus justifying the stronger response to pH of ABS ruled by the IL anion speciation. However, H-bonding and dispersive forces between the IL cation and the polymer can also exert an influence, which, if strong and favorable enough, limit ABS formation.^[13] Despite their generally weaker response to pH, ILs suffering speciation in the cation form ABS at different pH ranges ($4 \leq \text{pH} \leq 9$ vs. $3 \leq \text{pH} \leq 7$),^[8] adding an extra degree of flexibility in the development of double-responsive IL-based ABS. Furthermore, these pH-driven differences vanish at higher temperatures due to the overwhelming effect of temperature, representing an extra condition to tailor their ABS formation ability.

This work successfully demonstrates that it is possible to move from a single-stimulus (temperature) response to a double-stimuli (temperature and pH) response in ABS by just playing with the IL cation chemical structure or basicity. In comparison with the existing toolbox of double-responsive ABS, the range of operating conditions and stimuli dependencies is here extended by incorporating mono/dicationic protic ILs as ABS phase-forming components, further enhancing the customizability of separation processes and process integration.

Supporting Information

Experimental procedures and materials, NMR spectra of ILs and data, binodal data in weight percent, binodal curves representations, and speciation curves of bases. The authors have cited additional references within the Supporting Information.^[15]

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Keywords: monocationic/dicationic ionic liquid • aqueous biphasic systems • stimuli-responsive aqueous biphasic systems • sustainable separation process

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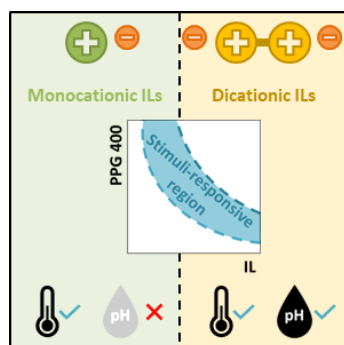
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In this work, we demonstrate the formation of novel stimuli-responsive aqueous biphasic systems (ABS), able to respond simultaneously to temperature and pH, or just to one stimulus. This was achieved with ABS formed by mono or dicationic protic ionic liquids as phase-forming components, being defined by the ionic liquid cation chemical structure or its basicity, presenting high impact in the design of more sustainable separation processes.

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