

# Double-Stimuli-Responsive (Temperature and pH) Aqueous Biphasic Systems Comprising Ionic Liquids

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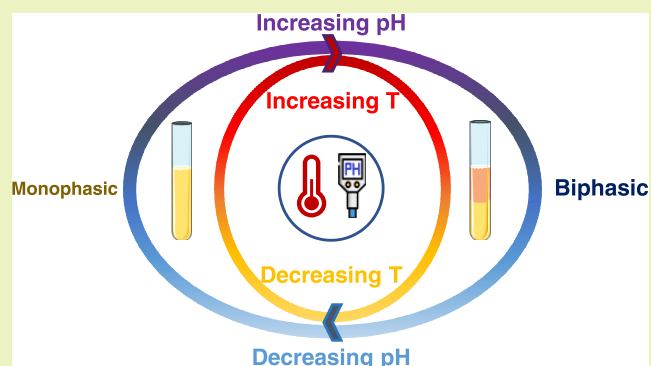
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**ABSTRACT:** Aqueous biphasic systems (ABS) can integrate multiple unit operations and operate under continuous mode, contributing to the development of sustainable separation processes. Encouraged by the designer solvent features of ionic liquids (ILs), we herein propose their use as components of double-stimuli-responsive (temperature- and pH-driven) ABS. Resorting to choline-alkanoate-based ILs as the pH-responsive components and poly(propylene glycol) (PPG 400) as the thermo-responsive component, the ABS ternary phase diagrams are determined at various temperature (25–45 °C) and pH (3–7) conditions. While the liquid–liquid phase diagram response to temperature obeys a lower critical solution temperature-like behavior, the response to pH correlates with the  $pK_a$  of the IL anion parent acid. The simultaneous responsiveness to temperature and pH is then shown, whose results inspire the development of customizable separation techniques as proved with the simultaneous (one-step) separation of two dyes. By a proper customization of the IL chemical structure and stimuli applied, ABS may be designed to improve the performance and sustainability of separation processes.

**KEYWORDS:** aqueous biphasic system, stimulus, temperature, pH, ionic liquid



## INTRODUCTION

The development of sustainable processes in the chemical and biotechnology industries is crucial to achieve the goals of the UN 2030 Agenda for Sustainable Development.<sup>1</sup> Reductions in the total number of unit operations and resources, novel production operating modes based on continuous processing, cyclic approaches, and alternative solvents, as well as the processes miniaturization, are promising tools to improve sustainability.<sup>2,3</sup> As industries start to be conscious of these practices, energy savings, process performance, and cost efficiency can be maximized.<sup>2</sup> In addition to standard large-scale operations, such as distillation<sup>4</sup> and gas drying,<sup>5</sup> biphasic liquid–liquid systems can be used within the concept of process intensification by integrating reactions and separation steps and easily adapting to continuous processing.<sup>6</sup> Besides the improved technological simplicity and flexibility, liquid–liquid systems enable an easy reuse/recovery of reactants and an efficient extraction of products.<sup>6</sup> Examples of applications involving the enantioseparation of chiral aromatic acids in liquid–liquid countercurrent processes<sup>7</sup> and the etherification reaction of benzyl chloride in liquid–liquid–liquid systems<sup>8</sup> have been reported. However, the recurrent use of organic solvents in these processes generates environmental concern and limits their biotechnological usefulness. Thus, finding

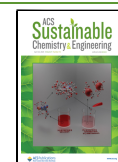
alternatives that adhere to the green chemistry and sustainability guidelines while suiting biotechnological applications is an issue that remains unsettled.<sup>9</sup>

Among the proposed routes to fulfill these needs is the use of aqueous biphasic systems (ABS).<sup>10</sup> These are composed of at least two, often nonvolatile, 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.<sup>11</sup> ABS are endowed with a water-rich environment and an operating condition-dependent behavior, being deemed as mild extraction/separation processes. It has been shown that ABS can be used in several integrated biotech-based processes, such as in extractive bioconversions,<sup>12,13</sup> enzymatic reactions,<sup>14</sup> and biopharmaceutical manufacturing.<sup>15</sup> Furthermore, following the addition of ionic liquids (ILs) as ABS components,<sup>16</sup> significant improvements have been accomplished in the

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efficiency, yield, and selectivity of numerous extraction and separation processes.<sup>17</sup> Indeed, if well designed, IL-based ABS outperform their conventional polymer-based counterparts in terms of customization degree and coverable hydrophobic–hydrophilic range.<sup>10,18</sup> The merit of IL-based ABS as high-performance extraction and separation platforms is nowadays well-established, even when considering labile molecules of relevant biotechnological applicability (e.g., recombinant proteins, nucleic acids).<sup>19–21</sup>

Despite their relevance, the integration and intensification of IL-based ABS have only recently started to gather momentum. In this domain, stimuli-responsive IL-based ABS have been proposed as viable approaches to integrate multiple process unit operations, in which isolated stimuli have been proposed.<sup>22,23</sup> In stimuli-responsive IL-based ABS, not only the operating conditions induce transitions from mono- to biphasic regimes (and vice versa) but also the IL and the second phase-forming component can be tailored to better fit these requirements.<sup>22,23</sup> Stimuli-responsive IL-based ABS resorting to photo/light,<sup>24</sup> CO<sub>2</sub>,<sup>25</sup> temperature,<sup>26</sup> and pH<sup>23</sup> have been investigated. For instance, temperature-responsive IL-based ABS have been reported as efficient extraction techniques, as shown with carotenoids<sup>27</sup> and proteins<sup>22</sup> and as integrated biocatalytic strategies.<sup>28</sup> In turn, an integrated production–separation platform based on pH-responsive IL-based ABS has shown to overcome the harsh conditions and long times usually involved in the production 5-hydroxymethylfurfural—a key building block for the chemical industry.<sup>23</sup> In this previous work,<sup>23</sup> response to pH was achieved by the speciation of the salt and not by the speciation of the IL as attempted in the current work—see discussion below.

While the use of a single stimulus has been the investigated strategy to produce stimuli-responsive ABS, the use of several stimuli simultaneously may create new opportunities. Double-stimuli-responsive systems provide a higher degree of customization of the target application and thus can be more easily adapted to industrial applications. Combining a thermo-sensitive polymer and a pH-sensitive polymer as the phase-forming agents is the most pursued route to develop double-stimuli-responsive ABS.<sup>29–32</sup> To the best of our knowledge, the development of IL-based ABS with double responsiveness to temperature and pH was not previously reported.

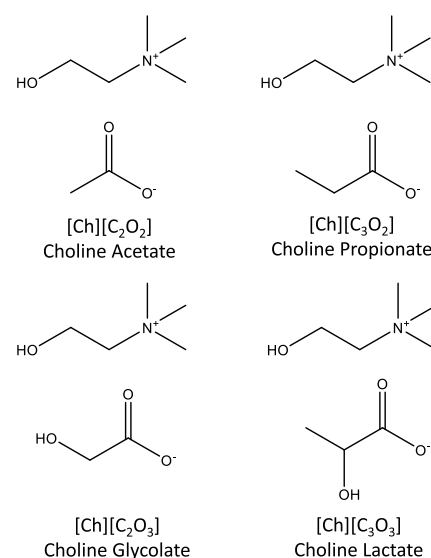
The basis for the development of temperature-dependent ABS relies on the possibility of these (at least) ternary mixtures to the present one of the two following behaviors:<sup>33</sup> (i) lower critical solution temperature (LCST), where the ABS formation ability is increased by increasing the temperature or (ii) upper critical solution temperature (UCST), where the ABS formation ability is decreased by increasing the temperature. In conventional ABS, it is well-established that polymer + polymer ABS may present a UCST-like behavior,<sup>34,35</sup> while polymer + salt ABS, whose formation is ruled by a salting-out effect, usually show an LCST-like behavior.<sup>36,37</sup> In IL + polymer ABS, either UCST-like or LCST-like behaviors are typically induced depending on the IL–polymer pair.<sup>38,39</sup> Regarding pH-responsive ABS, the use of salts and ILs, whose constituent ions must follow speciation as a function of the pH, is mandatory.<sup>23,40</sup>

Herein, we take full advantage of the multiplicity of interactions and stimuli-induced phase transitions occurring in IL-based ABS, particularly by using ILs and polymers able to simultaneously respond to pH and temperature. Double-stimuli-responsive (temperature and pH) ABS comprising ILs

are here proposed for the first time, while showcasing their potential as customizable separation platforms. To accomplish the goal of developing double-stimuli-responsive ABS, ILs able to respond to the pH and a polymer able to respond to temperature have been chosen as phase-forming components. The ternary phase diagrams of the ABS were initially determined at different temperatures and pH values, allowing to represent the effect of the stimuli in the ABS liquid–liquid phase behavior. These systems were then applied to (one-step) separate two dyes to showcase the applicability of the proposed systems as effective and versatile separation platforms.

## MATERIALS AND METHODS

**Materials.** The ILs under study were the following: choline acetate, [Ch][C<sub>2</sub>O<sub>2</sub>]; choline propionate, [Ch][C<sub>3</sub>O<sub>2</sub>]; choline glycolate, [Ch][C<sub>2</sub>O<sub>3</sub>], and choline lactate, [Ch][C<sub>3</sub>O<sub>3</sub>]. The chemical structures of the ILs are presented in Figure 1, together

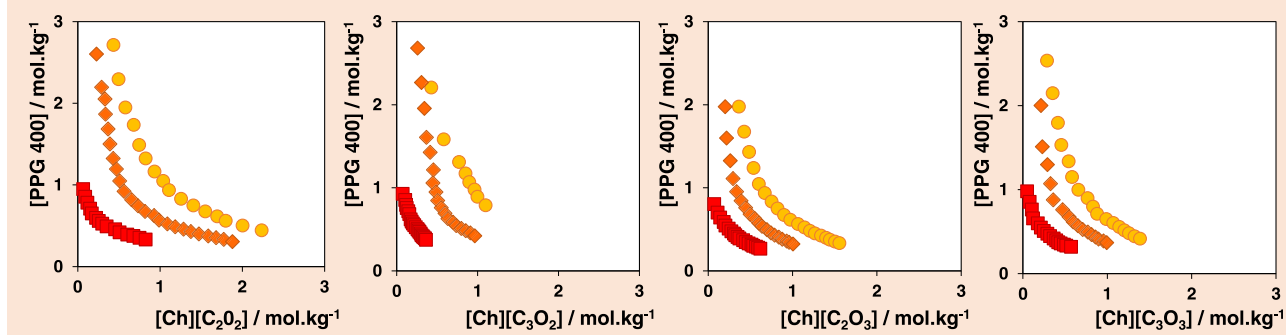


**Figure 1.** Chemical structures, names, and abbreviations of the ILs investigated.

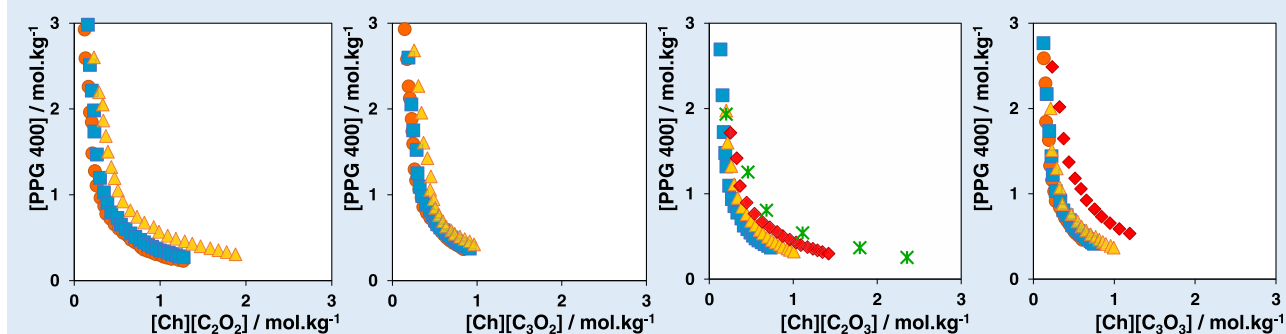
with their names and abbreviations. Except for the commercially acquired [Ch][C<sub>2</sub>O<sub>2</sub>] (purity 98% from Iolitec), all remaining ILs were synthesized in house following well-established procedures based on neutralization reactions.<sup>41,42</sup> For the synthesis, choline bicarbonate (purity 80%), purchased from Sigma, propionic acid (99% purity) from Acros Organics, and glycolic acid (99% purity) and lactic acid (88–92% purity), both from Sigma-Aldrich, were used. For the washing steps, ethyl acetate (analytical purity) purchased from Fischer Chemical was used. For water content determinations, the analyte Hydranal - Coulomat AG was obtained from Riedel-de Haën. The purity was confirmed by proton and carbon nuclear magnetic resonance (<sup>1</sup>H and <sup>13</sup>C NMR) using deuterium oxide (D<sub>2</sub>O) (99.9 atom % D) containing 0.05 wt % of 3-(trimethylsilyl)propionic-2,2,3,3-*d*<sub>4</sub> acid, sodium salt (TSP) from Sigma-Aldrich. All information on the IL synthesis procedure, as well as purity confirmation by NMR, is available in the Supporting Information (Table S1). Poly(propylene glycol) with an average molecular weight of 400 g mol<sup>-1</sup> (PPG 400) was obtained from Sigma-Aldrich. The Brilliant Blue FCF (E133) (>98% purity) was obtained from Vahine, and Sudan III (>99% purity) was acquired at Merck.

**Determination of the Liquid–Liquid Phase Diagrams.** The phase diagrams of the ternary systems composed of each IL, PPG 400, and water were determined for three temperatures (25, 35, and 45 °C) and pH values within the range of 3–7 (according to the pK<sub>a</sub> of the respective acid or the pH of the initial IL aqueous solution) in all

## (a) Temperature responsiveness



## (b) pH responsiveness



**Figure 2.** Response to temperature or pH of ABS composed of PPG 400 + IL + H<sub>2</sub>O. Binodal curves presented are for variable temperatures of 25 °C (solid yellow circle), 35 °C (solid orange diamond), and 45 °C (solid red square) under pH 5 (a) or variable pH values of 3 (green asterisk), 4 (solid red diamond), 5 (solid yellow triangle), 6 (solid blue square), and 7 (solid orange circle) under 35 °C (b).

possible combinations. The temperature was maintained at the desired value using a window bath with a precision of  $\pm 0.01$  °C (ME-18 V Visco-Thermostat, Julabo). The pH of aqueous solutions of ILs was adjusted by adding the same acid as used in the IL synthesis, using a Metrohm 827 pH lab pH meter with an uncertainty of  $\pm 0.1$ .

For the binodal curve determination, the cloud point titration method was employed.<sup>22,23</sup> To a PPG 400 aqueous solution at 60 wt %, an aqueous solution of ILs (at concentrations ranging from 60 to 70 wt % depending on the IL) was added drop by drop and under constant agitation until a cloudy mixture was identified. This point indicates that a biphasic regime is reached. Afterward, the addition of pure water drop by drop and under constant agitation was performed until the solution turned limpid. At this stage, a monophasic region is reached. Following the addition of the IL solution or water, the ternary mixture compositions were determined through weight quantification (within  $\pm 10^{-4}$  g). The experimental binodal curves were adjusted by the original equation proposed by Merchuk et al.<sup>43</sup> and its modified versions presented in the Supporting Information (eqs S1–S5).

#### Determination of the Stimulus-Responsive Region Extent.

The extent of the stimulus-responsive region corresponds to the Euclidian distance between two mixture compositions of the binodal curves determined at the upper and lower extremes of the condition (temperature or pH) under appraisal (see eq S6 in the Supporting Information). The two mixture compositions used for the determination of the extent of each stimulus-responsive region correspond to [IL] = [PPG] and were calculated by the intersection of a line that passes through the graph origin with the respective binodal curve, considering the weight percent data. Figure S1 in the

Supporting Information provides a schematic representation on how these determinations have been made.

**Separation of Dyes Using Stimuli-Responsive ABS.** For the evaluation of dyes separation in stimuli-responsive ABS, Sudan III was previously dissolved in PPG 400, while E133 was added directly to the system. For partition studies involving temperature, the mixture point used was composed of 7 wt % [Ch][C<sub>2</sub>O<sub>2</sub>] + 20 wt % PPG 400 (at pH 9). Temperature responsiveness was proved by varying the temperature from 25 (monophasic) to 50 °C (biphasic). For partition studies regarding the pH, the mixture composition adopted was 8 wt % [Ch][C<sub>2</sub>O<sub>2</sub>] + 32 wt % PPG 400 (at 25 °C). pH responsiveness was confirmed by a pH variation from pH 9 (biphasic) to 5 (monophasic) through the addition of acetic acid. Biphasic mixtures were left to reach the equilibrium overnight, after which the phases were separated, weighed, and collected for quantification purposes.

The dye content in each phase was assessed by UV–visible spectroscopy with the absorbance of the phases measured at a wavelength of 633 nm for E133 and 348 nm for Sudan III using a SYNERGYIHT microplate reader. Blank systems without dyes were also prepared to address the interference of the ABS phase-forming compounds.

Both dyes (one-step) separate to opposite ABS phases. Accordingly, the extraction efficiency of E133 ( $EE_{E133}$ , %) was determined according to eq 1

$$EE_{E133}, \% = \frac{Abs_{E133}^{IL} \times w_{IL}}{Abs_{E133}^{IL} \times w_{IL} + Abs_{E133}^{PPG} \times w_{PPG}} \times 100 \quad (1)$$

where  $Abs_{E133}^{IL}$  and  $Abs_{E133}^{PPG}$  are the absorbance of E133 at 633 nm in the IL-rich and in the PPG-rich phase, respectively.  $w_{IL}$  and  $w_{PPG}$  are the weight of the IL-rich and the PPG-rich phase, respectively.

Table 1.  $pK_a$  of the Acids Used for the IL Synthesis and Their Relationship with the pH Dependency of IL-Based ABS<sup>ab</sup>

Acid/IL anion	pKa	ABS formation				
		pH 3	pH 4	pH 5	pH 6	pH 7
Propanoic Acid/[C <sub>3</sub> O <sub>2</sub> ] <sup>-</sup>	4.75					
Acetic Acid/[C <sub>2</sub> O <sub>2</sub> ] <sup>-</sup>	4.54					
Lactic Acid/[C <sub>3</sub> O <sub>3</sub> ] <sup>-</sup>	3.78					
Glycolic Acid/[C <sub>2</sub> O <sub>3</sub> ] <sup>-</sup>	3.53					N.D. <sup>a</sup>

<sup>a</sup>N.D.: not determined due to the impossibility of reaching this pH at ternary compositions able to form ABS. <sup>b</sup>Red cells: no ABS formation; green cells: ABS formation.  $pK_a$  values were retrieved from Chemaxon.<sup>51</sup>

The extraction efficiency of Sudan III ( $EE_{\text{Sudan III}}$ , %) was determined according to eq 2

$$EE_{\text{Sudan III}} \% = \frac{\text{Abs}_{\text{Sudan III}}^{\text{PPG}} \times w_{\text{PPG}}}{\text{Abs}_{\text{Sudan III}}^{\text{PPG}} \times w_{\text{PPG}} + \text{Abs}_{\text{Sudan III}}^{\text{IL}} \times w_{\text{IL}}} \times 100 \quad (2)$$

where  $\text{Abs}_{\text{Sudan III}}^{\text{PPG}}$  and  $\text{Abs}_{\text{Sudan III}}^{\text{IL}}$  are the absorbance of Sudan III at 348 nm in the PPG-rich and the IL-rich phase.  $w_{\text{PPG}}$  is the weight of the PPG-rich phase, while  $w_{\text{IL}}$  is the weight of the IL-rich phase.

## RESULTS AND DISCUSSION

Four choline-based ILs sharing the same cation, choline, while varying the organic acid-derived anion have been here studied for the development of double-stimuli-responsive ABS, namely [Ch][C<sub>2</sub>O<sub>2</sub>], [Ch][C<sub>3</sub>O<sub>2</sub>], [Ch][C<sub>2</sub>O<sub>3</sub>], and [Ch][C<sub>3</sub>O<sub>3</sub>]<sup>-</sup>—cf. Figure 1 with the respective chemical structures. These were chosen due to the possibility of modifying the anion speciation in solution by altering the pH, at amenable conditions, thus enabling an easy response to this stimulus. These ILs were paired with the polymer PPG 400, which is a thermo-responsive polymer in aqueous solution, to create ABS. In addition to their valuable features as stimuli-responsive chemicals, decision-making in selecting PPG 400 and choline-based ILs was also supported by their acknowledged potential as phase-forming components in the ABS field. Currently, it is well-established that PPG 400 is able to form ABS with choline-based ILs, e.g., those comprising anions derived from Good's buffers,<sup>44</sup> amino acids,<sup>45</sup> and other organic acids.<sup>46</sup> By addressing the simultaneous effect of temperature and pH on the ABS formation, this study further contributes to enlarge the range of responsive systems available for process design. Moreover, ABS composed of PPG 400 and choline-based ILs have been shown to be a biocompatible extraction/separation platform,<sup>47</sup> further highlighting the potential of these systems.

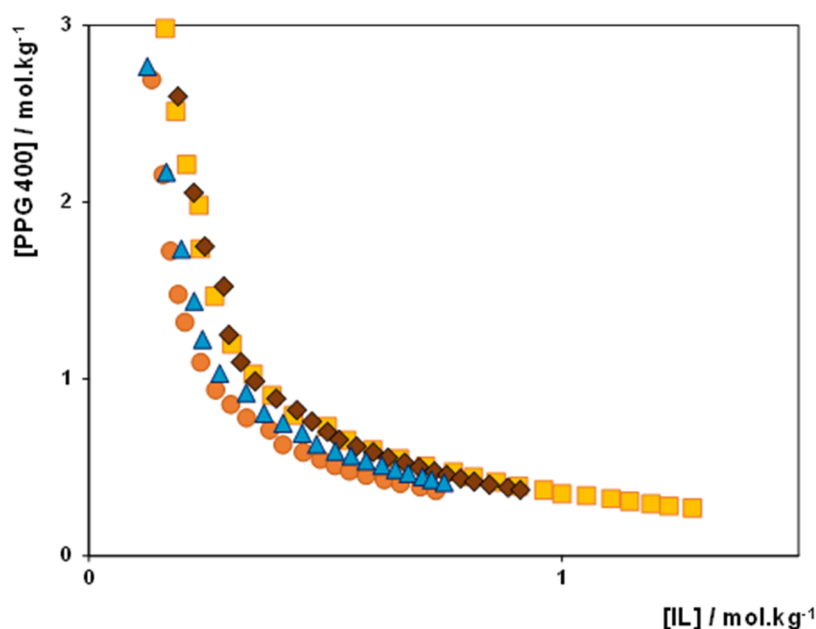
To appraise the response to temperature and pH, the ternary phase diagrams of ABS were determined within a temperature range from 25 to 45 °C and a pH range from 3 to 7. The temperature or pH dependency of the ABS can thus be appraised by the respective binodal curves, comparing the largest biphasic/monophasic area while fixing the other condition, that is pH or temperature, respectively. Figure 2 shows the responsiveness of ABS to both stimuli for representative conditions. Experimental binodal data (Tables S2–S15) and their fitting and correlation parameters (Tables S16–S29), as well as all of the remaining possible representations (Figures S2–S9), are provided in the Supporting Information.

Figure 2a shows the effect of temperature on the ABS formation ability, by fixing the pH at a value of 5 as a representative condition. It should be highlighted that the same trend was found for all ILs under investigation regardless

of the pH applied (cf. Figures S2–S5 in the Supporting Information). In general, there is an increase in the facility of two-phase formation by an increase in temperature. Based on this tendency, it is possible to conclude that all ternary mixtures bearing choline-based ILs + PPG 400 + H<sub>2</sub>O present an LCST-like behavior, following the LCST of PPG 400–water binary mixtures.<sup>48,49</sup>

Figure 2b depicts the pH response at a fixed temperature of 35 °C. Based on the binodal curves presented, decreasing the pH generally translates into a downgrade in the ability to form two phases. The same trend is found for all of the temperatures studied; however, it is more evident at lower temperature, i.e., 25 °C, with a partial overlapping being observed for the phase diagrams at different pH values obtained at 45 °C (cf. Figures S6–S9 in the Supporting Information). The pH response is directly related to the  $pK_a$  of the IL anion corresponding acid, as shown in Table 1, and the percentage of neutral versus negatively charged species as a function of the pH. Representations of the speciation curves of the acids are given in the Supporting Information (Figures S10–S13). Below the  $pK_a$ , the largest fraction of the ILs is in their neutral state—the corresponding acid—while above the  $pK_a$ , negatively charged ions are more prevalent, i.e., a higher percentage of ILs is in solution. Overall, the reduction of pH toward values closer to the  $pK_a$ , thus leading to neutral species of the corresponding acid, reduces the ABS formation ability. Moreover, below the  $pK_a$  of the respective acid, in concentration regions for which anionic species become minimal, the appearance of ABS is not observed. Accordingly, ILs bearing anions derived from acids of lower  $pK_a$ , i.e., lactic and glycolic acids versus propanoic and acetic acids (cf. Table 1), have the capacity to form ABS at lower pH. When IL anions are present in solution, their interactions with water are more likely to occur than PPG 400–water and PPG 400–IL interactions. Since the ABS formation mechanism is driven by the IL anions and their ability to form hydration complexes,<sup>46</sup> the decrease of the pH toward values closer to the  $pK_a$  of the corresponding acid reduces the concentration of anions present and the ABS formation ability, explaining the trend observed for all ILs under study.

Overall, the response to both stimuli of the proposed IL + polymer ABS is guided by an interplay of interactions between the three constituents,<sup>50</sup> herein consisting of PPG 400–water, IL–water, and PPG 400–IL interactions. Particularly, hydrogen bonding interactions and hydrophobic effects are significantly affected by temperature or pH. An increase in temperature favors the occurrence of hydrophobic effects, while decreasing hydrogen bond interactions leads to the observation of the previously mentioned LCST-like behavior. On the other hand, the response to pH is mainly driven by ion–dipole interactions between the IL anions and water.

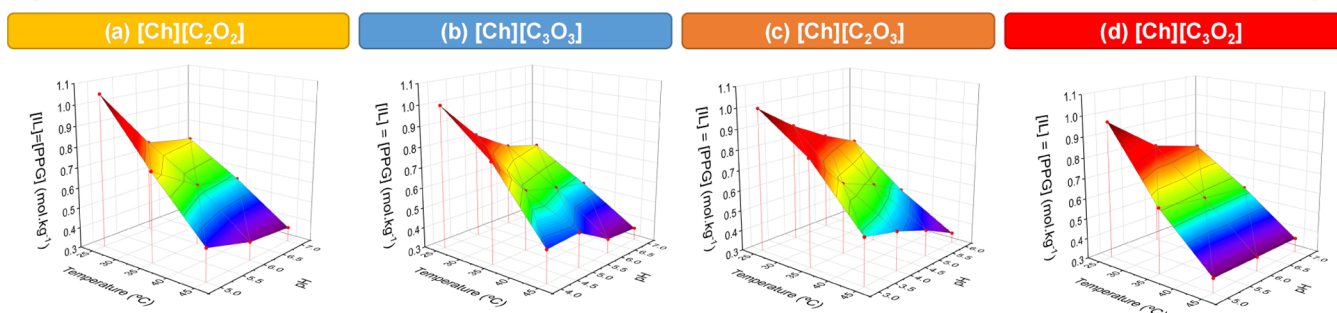


**Figure 3.** Binodal curves of the systems composed of PPG 400 + IL + H<sub>2</sub>O at 35 °C and pH 6: [Ch][C<sub>2</sub>O<sub>2</sub>] (solid yellow square), [Ch][C<sub>3</sub>O<sub>2</sub>] (solid brown diamond), [Ch][C<sub>2</sub>O<sub>3</sub>] (solid orange circle), and [Ch][C<sub>3</sub>O<sub>3</sub>] (solid blue triangle).

**Table 2.** pH- and Temperature-Responsive Regions Accounting for the Distance between the Binodal Curves for the IL + PPG 400 + H<sub>2</sub>O Systems

fixed condition	pH-responsive region (wt %)			temperature-responsive region (wt %)				
	25 °C	35 °C	45 °C	3	4	5	6	7
[Ch][C <sub>2</sub> O <sub>2</sub> ]	7.5	5.5	4.2			12.3	8.9	9.0
[Ch][C <sub>3</sub> O <sub>2</sub> ]	4.6	0.7	0.9			13.9	10.2	8.3
[Ch][C <sub>2</sub> O <sub>3</sub> ]	7.6	9.2	4.2	12.7	11.3	10.0	9.3	
[Ch][C <sub>3</sub> O <sub>3</sub> ]	8.5	9.1	3.3		13.1	10.4	9.5	7.9

### Double responsiveness



**Figure 4.** Double responsiveness to temperature and pH of ABS composed of PPG 400 + IL + H<sub>2</sub>O. The red points on the graphics correspond to the points that define the binodal curves of the system, being [IL] = [polymer].

To get full mileage out of the ILs' "designer solvent" features, it is important to shed light on the impact of the IL anion in ABS formation and response to both stimuli. In Figure 3, it is shown the comparison on their ability to form ABS for a representative set of conditions: 35 °C and pH 6. The remaining possible representations are provided in Figures S14–S18, Supporting Information. Although some slight variations are found depending on the set of pH/temperature conditions, the ability to form ABS can be ranked as follows: [Ch][C<sub>2</sub>O<sub>2</sub>] ≤ [Ch][C<sub>3</sub>O<sub>2</sub>] < [Ch][C<sub>3</sub>O<sub>3</sub>] ≤ [Ch][C<sub>2</sub>O<sub>3</sub>]. Since all ILs present the same cation, the differences in ABS formation are derived from the anion. Particularly, the number

of carbons in the alkyl chain, which dictate the hydrophilic–hydrophobic character of the IL, and the number of hydroxyl groups that governs the capacity of the IL for hydration play a relevant role in ABS formation. Here, it is possible to study (i) the influence of hydroxyl groups on the formation of two phases by comparing the behavior of [Ch][C<sub>3</sub>O<sub>2</sub>] versus [Ch][C<sub>3</sub>O<sub>3</sub>] and [Ch][C<sub>2</sub>O<sub>2</sub>] versus [Ch][C<sub>2</sub>O<sub>3</sub>] and (ii) the influence of the anion alkyl chain length by comparing the behavior of [Ch][C<sub>2</sub>O<sub>2</sub>] versus [Ch][C<sub>3</sub>O<sub>2</sub>] and [Ch][C<sub>2</sub>O<sub>3</sub>] versus [Ch][C<sub>3</sub>O<sub>3</sub>]. While the addition of a hydroxyl group in the anion enhances the range of concentrations in which a two-phase system is observed, the alkyl chain elongation has a less

significant impact on the IL + PPG ABS under investigation. Since this effect seems to be more pronounced for  $[\text{Ch}][\text{C}_2\text{O}_3]$  than  $[\text{Ch}][\text{C}_3\text{O}_3]$  for most sets of temperature and pH conditions tested (see also Figures S14–S18 in the Supporting Information), an influence of a hydrophilic–hydrophobic balance in the behavior of the systems herein reported can be anticipated.

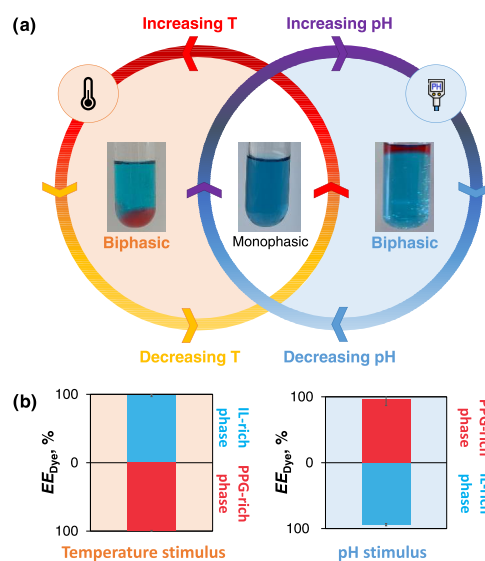
Table 2 provides the temperature- and pH-responsive region extent for the different IL-based ABS studied, which was determined using the distance between the binodal curves at the respective extreme conditions. Among the ILs studied,  $[\text{Ch}][\text{C}_3\text{O}_2]$  followed by  $[\text{Ch}][\text{C}_2\text{O}_2]$  are the ones generally presenting smaller pH-responsive regions. The use of  $[\text{Ch}][\text{C}_2\text{O}_3]$  and  $[\text{Ch}][\text{C}_3\text{O}_3]$ , instead, enlarges the pH-responsive regions. As previously mentioned, this is due to the lower  $\text{p}K_a$  of the parent acids and wider range of workable pH conditions (cf. Table 1). For temperature, comparable responsive regions are found for all of the ILs under investigation despite the pH condition. Indeed, the response to temperature is dominated by the PPG 400, which is common for all systems.

Figure 4 depicts the double-responsiveness behavior of the studied systems and, together with Table 2, allows enlightening on how the conjugation of both stimuli works and which stimulus is the most influential for ABS formation. In general, increasing the temperature turns the pH effect significantly less pronounced. On the other hand, there is a constant and pronounced effect of temperature on the binodal curves, which intensifies at  $\text{pH} \leq 5$ . It is thus clear that temperature has a higher impact in the formation of ABS than the pH, with the response to the pH being weaker with the increase in temperature.

The potential of the developed double-stimuli-responsive IL-based ABS was evaluated with a proof-of-concept application—the simultaneous separation of two dyes: Sudan III and Brilliant Blue FCF (E133). The use of dyes as model molecules provides a clear visual perception on the phenomenon of temperature and pH responsiveness, that is, the transition from mono- to biphasic systems upon temperature/pH variations. To evaluate the partition of both dyes, studies were performed using  $[\text{Ch}][\text{C}_2\text{O}_2]$  as the representative IL under the following conditions: (i) for the temperature-responsiveness assessment, the mixture composition adopted was 7 wt %  $[\text{Ch}][\text{C}_2\text{O}_2]$  + 20 wt % PPG 400 at pH 9 with a temperature variation from 25 to 50 °C; (ii) for the pH-responsiveness assessment, the mixture composition adopted was 8 wt %  $[\text{Ch}][\text{C}_2\text{O}_2]$  + 32 wt % PPG 400 at 25 °C together with a variation of the pH from 9 to 5. All numerical values of the partition parameters—extraction efficiencies ( $\text{EE}_{\text{Sudan III}}$  and  $\text{EE}_{\text{E133}}$ , %)—are detailed in the Supporting Information (cf. Table S30).

Figure 5 shows the concept of double-stimuli-responsive ABS through the application of temperature and pH. As visually perceived and further confirmed by the determination of the partition parameters, the two dyes selectively partition to opposite phases in one step, by the application of both stimuli. Sudan III partitions to the (more hydrophobic) polymer-rich phase, while E133 partitions to the (less hydrophobic) IL-rich phase. The hydrophobicity/hydrophilicity of these dyes explains the observed partition tendencies: Sudan III is considered an oil-soluble compound, given its octanol/water partition coefficient ( $\log K_{\text{ow}}$ ) of 7.63,<sup>52</sup> while E133 is a hydrophilic dye with a  $\log K_{\text{ow}}$  of  $-4.94$ .<sup>53</sup>

There is a transition from a monophasic to a biphasic mixture rising the temperature from 25 to 50 °C, further



**Figure 5.** Application of double-stimuli-responsive IL-based ABS in the separation of dyes: (a) description of the double-stimuli-responsive IL-based ABS concept and (b) extraction efficiencies of both dyes ( $\text{EE}_{\text{Dye}}$ , %) obtained using ABS composed of  $[\text{Ch}][\text{C}_2\text{O}_2]$  and PPG 400 upon application of temperature and pH stimuli. The blue bars represent the  $\text{EE}_{\text{E133}}$  to the IL-rich phase, while the red bars represent the  $\text{EE}_{\text{Sudan III}}$  to the PPG 400-rich phase.

allowing the complete (one-step) separation of both dyes, with 100 and 98% of Sudan III and E133 partitioning to opposite phases, respectively. Under the conditions tested, the polymer-rich and IL-rich phases correspond to the bottom and top phases, respectively. In the case of pH responsiveness, the enhanced ability to separate Sudan III from E133 ( $\text{EE}_{\text{Sudan III}} = 96\%$  and  $\text{EE}_{\text{E133}} = 94\%$  for the polymer-rich and IL-rich phase, respectively) is maintained at pH 9. These results also reveal that, under the conditions adopted, an inversion of the phases takes place because of variations in the phases' densities and in line with previous observations with  $[\text{Ch}][\text{C}_2\text{O}_2]$  + polymer ABS.<sup>54</sup> Such a feature allows further increasing the tunable degree of IL-based ABS sensitive to stimuli.

## CONCLUSIONS

In this work, IL-based ABS showing a double response to external stimuli, namely, temperature and pH, are proposed. Following the acquisition of the binodal data of ABS comprising choline-alkanoate-based ILs and PPG 400 under distinct temperature/pH conditions, it was shown that temperature response shows an LCST-like behavior, whereas the pH response is dependent on the anion parent organic acid  $\text{p}K_a$  and the fraction of neutral versus negatively charged species present in the aqueous medium. Furthermore, it was demonstrated that double-stimuli-responsive ABS can separate the dyes Sudan III and E133 in one step, by applying any of the stimulus, enlightening on their performance as sustainable separation techniques.

Overall, double-stimuli-responsive IL-based ABS can be developed and customized to the needs of different applications. The ability to simultaneously respond to two stimuli, in this case temperature and pH, makes ABS more easily adjusted to the optimal conditions, selectivity requirements, and equipment available. On the one hand, double-stimuli-responsive ABS have an extra degree of freedom in the development of separation processes when compared to more

conventional temperature-responsive ABS since more than one stimulus can be used to finely tune the partition of molecules. On the other hand, these systems hold high potential for process integration and intensification, such as in extraction–purification and reaction–separation processes. Since different process operations may require different optimal conditions of temperature and/or pH, a more fit-for-purpose and efficient process integration can be achieved. By applying an external stimulus or a combination of two stimuli, transitions between monophasic and biphasic regimes can be promoted, contributing to more sustainable processes. In this regard, more than one operation step can be simultaneously performed in “one-pot” and under continuous mode, further saving resources and increasing process efficiency. It is expected that the double-stimuli responsiveness of the systems here presented would enhance the flexibility of applications while opening new perspectives for chemical, pharmaceutical, and biotechnological companies.

## ■ ASSOCIATED CONTENT

### SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acssuschemeng.3c00059>.

IL synthesis protocol, NMR spectra of ILs, binodal data in weight percent, correlation parameters of the experimental binodal data, binodal curve representations, speciation curves of acids, and extraction efficiencies of dyes (PDF)

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A.F.C.S.R.: investigation, formal analysis, and writing—original draft; J.M.B.: investigation; E.V.C.: investigation; J.A.P.C.: supervision and writing—review & editing; F.A.e.S.: visualization, supervision, writing—review & editing, funding acquisition, and project administration; M.G.F.: conceptualiza-

tion, supervision, writing—review & editing, funding acquisition, and project administration.

### Notes

The authors declare no competing financial interest.

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## ■ ABBREVIATIONS

ABS, aqueous biphasic systems; ILs, ionic liquids; LCST, lower critical solution temperature; UCST, upper critical solution temperature; PPG, poly(propylene glycol); E133, Brilliant Blue FCF; EE, extraction efficiency

## ■ REFERENCES

- (1) United Nations General Assembly. *Transforming Our World: The 2030 Agenda for Sustainable Development*; United Nations Department of Economic and Social Affairs Sustainable Development, 2015.
- (2) Charpentier, J.-C. In the Frame of Globalization and Sustainability, Process Intensification, a Path to the Future of Chemical and Process Engineering (Molecules into Money). *Chem. Eng. J.* **2007**, *134*, 84–92.
- (3) Chen, C.; Wong, H. E.; Goudar, C. T. Upstream Process Intensification and Continuous Manufacturing. *Curr. Opin. Chem. Eng.* **2018**, *22*, 191–198.
- (4) Fang, J.; Cheng, X.; Li, Z.; Li, H.; Li, C. A Review of Internally Heat Integrated Distillation Column. *Chin. J. Chem. Eng.* **2019**, *27*, 1272–1281.
- (5) Esmaeili, A. Supersonic Separation of Natural Gas Liquids by Twister Technology. *Chem. Eng. Trans.* **2016**, *52*, 7–12.
- (6) Kraume, M.; Enders, S.; Drews, A.; Schomäcker, R.; Engell, S.; Sundmacher, K. *Integrated Chemical Processes in Liquid Multiphase Systems: From Chemical Reaction to Process Design and Operation*; Walter de Gruyter GmbH & Co KG, 2022.
- (7) Holbach, A.; Godde, J.; Mahendrarajah, R.; Kockmann, N. Enantioseparation of Chiral Aromatic Acids in Process Intensified Liquid–Liquid Extraction Columns. *AIChE J.* **2015**, *61*, 266–276.
- (8) Katole, D. O.; Yadav, G. D. Process Intensification and Waste Minimization Using Liquid-Liquid-Liquid Tri-Phase Transfer Catalysis for the Synthesis of 2-((Benzyloxy) Methyl) Furan. *Mol. Catal.* **2019**, *466*, 112–121.
- (9) Anastas, P. T.; Warner, J. C. *Tools of Green Chemistry. Green Chemistry: Theory and Practice*; Oxford University Press, 2000.
- (10) Iqbal, M.; Tao, Y.; Xie, S.; Zhu, Y.; Chen, D.; Wang, X.; Huang, L.; Peng, D.; Sattar, A.; Shabbir, M. A. B.; et al. Aqueous Two-Phase System (ATPS): An Overview and Advances in Its Applications. *Biol. Proced. Online* **2016**, *18*, No. 18.
- (11) Albertsson, P.-Å. Partition of Proteins in Liquid Polymer–Polymer Two-Phase Systems. *Nature* **1958**, *182*, 709–711.
- (12) Ooi, C. W.; Hii, S. L.; Kamal, S. M. M.; Ariff, A.; Ling, T. C. Extractive Fermentation Using Aqueous Two-Phase Systems for

Integrated Production and Purification of Extracellular Lipase Derived from Burkholderia Pseudomallei. *Process Biochem.* **2011**, *46*, 68–73.

(13) Chen, J.; Ding, Z.; Pan, H.; Cao, X. Development of PH-Responsive Polymer and Citrate Aqueous Two-Phase System for Extractive Bioconversion of Cefprozil. *Talanta* **2017**, *174*, 256–264.

(14) Sánchez-Rangel, J. C.; Jacobo-Velázquez, D. A.; Cisneros-Zevallos, L.; Benavides, J. Primary Recovery of Bioactive Compounds from Stressed Carrot Tissue Using Aqueous Two-phase Systems Strategies. *J. Chem. Technol. Biotechnol.* **2016**, *91*, 144–154.

(15) Silva, M. F. F.; Fernandes-Platzgummer, A.; Aires-Barros, M. R.; Azevedo, A. M. Integrated Purification of Monoclonal Antibodies Directly from Cell Culture Medium with Aqueous Two-Phase Systems. *Sep. Purif. Technol.* **2014**, *132*, 330–335.

(16) Gutowski, K. E.; Broker, G. A.; Willauer, H. D.; Huddleston, J. G.; Swatoski, R. P.; Holbrey, J. D.; Rogers, R. D. Controlling the Aqueous Miscibility of Ionic Liquids: Aqueous Biphasic Systems of Water-Miscible Ionic Liquids and Water-Structuring Salts for Recycle, Metathesis, and Separations. *J. Am. Chem. Soc.* **2003**, *125*, 6632–6633.

(17) Basaiahgari, A.; Gardas, R. L. Ionic Liquid-Based Aqueous Biphasic Systems as Sustainable Extraction and Separation Techniques. *Curr. Opin. Green Sustainable Chem.* **2021**, *27*, No. 100423.

(18) Pereira, J. F. B.; Rebelo, L. P. N.; Rogers, R. D.; Coutinho, J. A. P.; Freire, M. G. Combining Ionic Liquids and Polyethylene Glycols to Boost the Hydrophobic–Hydrophilic Range of Aqueous Biphasic Systems. *Phys. Chem. Chem. Phys.* **2013**, *15*, 19580–19583.

(19) Desai, R. K.; Streefland, M.; Wijffels, R. H.; Eppink, M. H. M. Extraction and Stability of Selected Proteins in Ionic Liquid Based Aqueous Two Phase Systems. *Green Chem.* **2014**, *16*, 2670–2679.

(20) Athira, K. K.; Gardas, R. L. Insights into the Partitioning of DNA in Aqueous Biphasic System Containing Ammonium-Based Ionic Liquid and Phosphate Buffer. *Fluid Phase Equilib.* **2022**, *558*, No. 113463.

(21) Capela, E. V.; Santiago, A. E.; Rufino, A. F. C. S.; Tavares, A. P. M.; Pereira, M. M.; Mohamadou, A.; Aires-Barros, M. R.; Coutinho, J. A. P.; Azevedo, A. M.; Freire, M. G. Sustainable Strategies Based on Glycine–Betaine Analogous Ionic Liquids for the Recovery of Monoclonal Antibodies from Cell Culture Supernatants. *Green Chem.* **2019**, *21*, 5671–5682.

(22) Passos, H.; Luís, A.; Coutinho, J. A. P.; Freire, M. G. Thermoreversible (Ionic-Liquid-Based) Aqueous Biphasic Systems. *Sci. Rep.* **2016**, *6*, No. 20276.

(23) Ferreira, A. M.; Cláudio, A. F. M.; Válega, M.; Domingues, F. M. J.; Silvestre, A. J. D.; Rogers, R. D.; Coutinho, J. A. P.; Freire, M. G. Switchable (PH-Driven) Aqueous Biphasic Systems Formed by Ionic Liquids as Integrated Production–Separation Platforms. *Green Chem.* **2017**, *19*, 2768–2773.

(24) Li, Z.; Feng, Y.; Liu, X.; Wang, H.; Pei, Y.; Gunaratne, H. Q. N.; Wang, J. Light-Triggered Switchable Ionic Liquid Aqueous Two-Phase Systems. *ACS Sustainable Chem. Eng.* **2020**, *8*, 15327–15335.

(25) Xiong, D.; Wang, H.; Li, Z.; Wang, J. Recovery of Ionic Liquids with Aqueous Two-Phase Systems Induced by Carbon Dioxide. *ChemSusChem* **2012**, *5*, 2255–2261.

(26) Zafarani-Moattar, M. T.; Shekaari, H.; Jafari, P. Thermodynamic Study of Aqueous Two-Phase Systems Containing Biocompatible Cholinium Aminoate Ionic-Liquids and Polyethylene Glycol Dimethyl Ether 250 and Their Performances for Bovine Serum Albumin Separation. *J. Chem. Thermodyn.* **2019**, *130*, 17–32.

(27) Gao, J.; Fang, C.; Lin, Y.; Nie, F.; Ji, H.; Liu, S. Enhanced Extraction of Astaxanthin Using Aqueous Biphasic Systems Composed of Ionic Liquids and Potassium Phosphate. *Food Chem.* **2020**, *309*, No. 125672.

(28) Muñoz-Mouro, A.; Ferreira, A. M.; Coutinho, J. A. P.; Freire, M. G.; Tavares, A. P. M.; Gullón, P.; González-García, S.; Eibes, G. Integrated Biocatalytic Platform Based on Aqueous Biphasic Systems for the Sustainable Oligomerization of Rutin. *ACS Sustainable Chem. Eng.* **2021**, *9*, 9941–9950.

(29) Wang, Z.; Chen, X.; Wan, J.; Cao, X. Study of Microbial Transglutaminase Partitioning in Thermo-PH-Responsive Aqueous

Two-Phase Systems. *Appl. Biochem. Biotechnol.* **2020**, *192*, 1176–1190.

(30) Ma, S.; Li, F.; Tan, Z. Enantioselective Liquid-Liquid Extraction of Tryptophan Enantiomers by a Recyclable Aqueous Biphasic System Based on Stimuli-Responsive Polymers. *J. Chromatogr. A* **2021**, *1656*, No. 462532.

(31) Wei, Y.; Chen, X.; Yang, T.; Wan, J.; Cao, X. Partition of Tea Saponin with a Novel Recyclable Thermo-PH Aqueous Two-Phase Systems. *Appl. Biochem. Biotechnol.* **2021**, *193*, 3062–3078.

(32) Wang, Y.; Yang, T.; Zeng, H.; Wan, J.; Cao, X. Study of Lincomycin Partition in a Recyclable Thermo-PH Responsive Aqueous Two-Phase System. *Process Biochem.* **2021**, *109*, 27–36.

(33) Chakraborty, A.; Sen, K. Impact of PH and Temperature on Phase Diagrams of Different Aqueous Biphasic Systems. *J. Chromatogr. A* **2016**, *1433*, 41–55.

(34) Machado, F. L. C.; Coimbra, J. S. d. R.; Zuniga, A. D. G.; da Costa, A. R.; Martins, J. P. Equilibrium Data of Aqueous Two-Phase Systems Composed of Poly (Ethylene Glycol) and Maltodextrin. *J. Chem. Eng. Data* **2012**, *57*, 1984–1990.

(35) Forciniti, D.; Hall, C. K.; Kula, M.-R. Influence of Polymer Molecular Weight and Temperature on Phase Composition in Aqueous Two-Phase Systems. *Fluid Phase Equilib.* **1991**, *61*, 243–262.

(36) Dilip, M.; Griffin, S. T.; Spear, S. K.; Rodriguez, H.; Rijksen, C.; Rogers, R. D. Comparison of Temperature Effects on the Salting Out of Poly (Ethylene Glycol) versus Poly (Ethylene Oxide)–Poly (Propylene Oxide) Random Copolymer. *Ind. Eng. Chem. Res.* **2010**, *49*, 2371–2379.

(37) Fontana, D.; Ricci, G. Poly (Ethylene Glycol)-Based Aqueous Biphasic Systems: Effect of Temperature on Phase Equilibria and on Partitioning of 1, 10-Phenanthroline–Copper (II) Sulphate Complex. *J. Chromatogr. B: Biomed. Sci. Appl.* **2000**, *743*, 231–234.

(38) Freire, M. G.; Pereira, J. F. B.; Francisco, M.; Rodríguez, H.; Rebelo, L. P. N.; Rogers, R. D.; Coutinho, J. A. P. Insight into the Interactions That Control the Phase Behaviour of New Aqueous Biphasic Systems Composed of Polyethylene Glycol Polymers and Ionic Liquids. *Chem.—Eur. J.* **2012**, *18*, 1831–1839.

(39) e Silva, F. A.; Pereira, J. F. B.; Kurnia, K. A.; Ventura, S. P. M.; Silva, A. M. S.; Rogers, R. D.; Coutinho, J. A. P.; Freire, M. G. Temperature Dependency of Aqueous Biphasic Systems: An Alternative Approach for Exploring the Differences between Coulombic-Dominated Salts and Ionic Liquids. *Chem. Commun.* **2017**, *53*, 7298–7301.

(40) Berton, P.; Tian, H.; Rogers, R. D. Phase Behavior of Aqueous Biphasic Systems with Choline Alkanoate Ionic Liquids and Phosphate Solutions: The Influence of PH. *Molecules* **2021**, *26*, No. 1702.

(41) Pernak, J.; Syguda, A.; Mirska, I.; Pernak, A.; Nawrot, J.; Prądyńska, A.; Griffin, S. T.; Rogers, R. D. Choline-derivative-based Ionic Liquids. *Chem.—Eur. J.* **2007**, *13*, 6817–6827.

(42) Muhammad, N.; Hossain, M. I.; Man, Z.; El-Harbawi, M.; Bustam, M. A.; Noaman, Y. A.; Mohamed Alitheen, N. B.; Ng, M. K.; Hefter, G.; Yin, C.-Y. Synthesis and Physical Properties of Choline Carboxylate Ionic Liquids. *J. Chem. Eng. Data* **2012**, *57*, 2191–2196.

(43) Merchuk, J. C.; Andrews, B. A.; Asenjo, J. A. Aqueous Two-Phase Systems for Protein Separation: Studies on Phase Inversion. *J. Chromatogr. B: Biomed. Sci. Appl.* **1998**, *711*, 285–293.

(44) Lee, S. Y.; Khoiroh, I.; Coutinho, J. A. P.; Show, P. L.; Ventura, S. P. M. Lipase Production and Purification by Self-Buffering Ionic Liquid-Based Aqueous Biphasic Systems. *Process Biochem.* **2017**, *63*, 221–228.

(45) Zafarani-Moattar, M. T.; Shekaari, H.; Jafari, P. Design of Novel Biocompatible and Green Aqueous Two-Phase Systems Containing Cholinium L-Alaninate Ionic Liquid and Polyethylene Glycol Dimethyl Ether 250 or Polypropylene Glycol 400 for Separation of Bovine Serum Albumin (BSA). *J. Mol. Liq.* **2018**, *254*, 322–332.

(46) Quental, M. V.; Caban, M.; Pereira, M. M.; Stepnowski, P.; Coutinho, J. A. P.; Freire, M. G. Enhanced Extraction of Proteins Using Cholinium-Based Ionic Liquids as Phase-Forming Components of Aqueous Biphasic Systems. *Biotechnol. J.* **2015**, *10*, 1457–1466.



(47) Tian, H.; Berton, P.; Rogers, R. D. Choline-Based Aqueous Biphasic Systems: Overview of Applications. *Fluid Phase Equilib.* **2019**, *502*, No. 112258.

(48) Li, Z.; Liu, X.; Pei, Y.; Wang, J.; He, M. Design of Environmentally Friendly Ionic Liquid Aqueous Two-Phase Systems for the Efficient and High Activity Extraction of Proteins. *Green Chem.* **2012**, *14*, 2941–2950.

(49) Pavlíček, J.; Rotrekl, J.; Bogdanić, G.; Wichterle, I.; Izák, P. Vapor-Liquid and Liquid-Liquid Equilibria in the Water+ Poly (Propylene Glycol) System. *J. Mol. Liq.* **2021**, *337*, No. 116336.

(50) Neves, C. M. S. S.; Shahriari, S.; Lemus, J.; Pereira, J. F. B.; Freire, M. G.; Coutinho, J. A. P. Aqueous Biphasic Systems Composed of Ionic Liquids and Polypropylene Glycol: Insights into Their Liquid–Liquid Demixing Mechanisms. *Phys. Chem. Chem. Phys.* **2016**, *18*, 20571–20582.

(51) *Marvin*, version 22.18; Chemaxon, 2022. <https://www.chemaxon.com> (accessed Oct, 2022).

(52) Hao, L.-S.; Liu, M.-N.; Xu, H.-M.; Yang, N.; Nan, Y.-Q.; Deng, Y.-T. Partitioning of Dyes, Free Anthraquinones, and Tanshinones in Aqueous Two-Phase Systems of Cationic/Anionic Surfactants. *J. Dispersion Sci. Technol.* **2015**, *36*, 1047–1058.

(53) National Center for Biotechnology Information. PubChem Compound Summary for CID 78165, 2-(N-Morpholino)-ethanesulfonic Acid, 2021. [https://pubchem.ncbi.nlm.nih.gov/compound/2-N-Morpholino\\_ethanesulfonic-acid](https://pubchem.ncbi.nlm.nih.gov/compound/2-N-Morpholino_ethanesulfonic-acid) (retrieved Oct 09, 2021).

(54) Pereira, J. F. B.; Kurnia, K. A.; Cojocar, O. A.; Gurau, G.; Rebelo, L. P. N.; Rogers, R. D.; Freire, M. G.; Coutinho, J. A. P. Molecular Interactions in Aqueous Biphasic Systems Composed of Polyethylene Glycol and Crystalline vs. Liquid Cholinium-Based Salts. *Phys. Chem. Chem. Phys.* **2014**, *16*, 5723–5731.

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