

# Impact of Surface Active Ionic Liquids on the Cloud Points of Nonionic Surfactants and the Formation of Aqueous Micellar Two-Phase Systems

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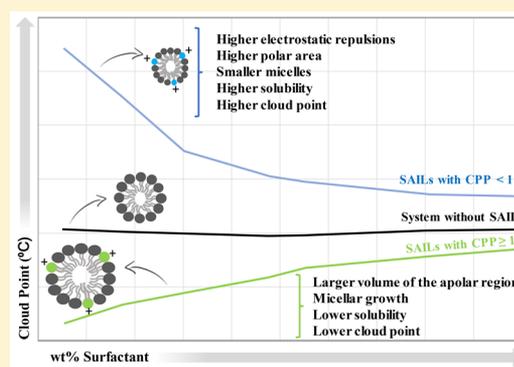
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## Supporting Information

**ABSTRACT:** Aqueous micellar two-phase systems (AMTPS) hold a large potential for cloud point extraction of biomolecules but are yet poorly studied and characterized, with few phase diagrams reported for these systems, hence limiting their use in extraction processes. This work reports a systematic investigation of the effect of different surface-active ionic liquids (SAILs)—covering a wide range of molecular properties—upon the clouding behavior of three nonionic Tergitol surfactants. Two different effects of the SAILs on the cloud points and mixed micelle size have been observed: ILs with a more hydrophilic character and lower critical packing parameter ( $CPP < 1/2$ ) lead to the formation of smaller micelles and concomitantly increase the cloud points; in contrast, ILs with a more hydrophobic character and higher CPP ( $CPP \geq 1$ ) induce significant micellar growth and a decrease in the cloud points. The latter effect is particularly interesting and unusual for it was accepted that cloud point reduction is only induced by inorganic salts. The effects of nonionic surfactant concentration, SAIL concentration, pH, and micelle  $\zeta$  potential are also studied and rationalized.



## 1. INTRODUCTION

Surfactants are used for a wide variety of applications from detergents and cleaning products, to textile, leather, paper, paint, coating, and plastics, as well as in formulation of personal care and food products.<sup>1</sup> They can also be used to form aqueous micellar two-phase systems (AMTPS) that hold a great potential in the separation of biocompounds by cloud point extraction. These are thermo-reversible systems, which present two macroscopic liquid phases with very distinct surfactant concentrations, one rich in surfactant and other colloidal components, known as coacervate,<sup>2</sup> in equilibrium with another relatively dilute, surfactant-poor liquid phase, above a temperature known as the cloud point.<sup>3</sup> These cloud points correspond to the boundary between the monophasic and biphasic regions, forming a binodal curve with a lower critical solution temperature (LCST).<sup>4</sup> To explore the use of AMTPS for bioseparations, but also for the design of formulations using these surfactants, it is crucial to have an adequate knowledge of their phase behavior, in particular of the binodal curve and the phases present.<sup>5,6</sup>

The AMTPS were first reported by Watanabe and Tanaka<sup>3</sup> for the concentration of zinc ions and later on, Bordier and co-workers<sup>7</sup> successfully applied these systems to proteins extraction. Since then, they have proved helpful in the

purification of many biomolecules such as a variety of proteins,<sup>5,6,8</sup> antibodies,<sup>9</sup> antibiotics,<sup>10</sup> antimicrobial agents,<sup>11,12</sup> phenolic compounds,<sup>13</sup> and dyes.<sup>5,14</sup> The particularity of these systems is that they only require a surfactant and water to be formed, making the process greener and more biocompatible than the conventional liquid–liquid extraction processes based on hazardous organic solvents. Furthermore, it is relevant to highlight that, even though there are numerous nonionic surfactants available in a market which is estimated to be worth around \$40 billion worldwide by 2021,<sup>1</sup> most have their cloud points poorly characterized. Nonionic surfactants are more eco-friendly as they can be prepared from renewable sources<sup>1</sup> and they weakly bind to biomolecules.<sup>15</sup> Some of the most important nonionic surfactants are the polyoxyethylene alkyl ethers, with their cloud points being dependent upon the balance between the alkyl chain length, which promotes hydrophobicity, and the number of the oxyethylene (EO) groups, which confer a hydrophilic character. Hence, for surfactants with the same alkyl chain length, the cloud point increases with the number of

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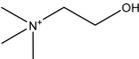
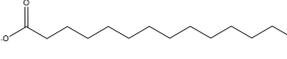
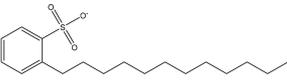
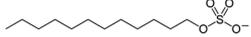
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Table 1. Structure of the Cations and Anions Composing the SAILs Used in This Study and Their Respective CMCs at 25 °C<sup>a</sup>

Family	Cation	Anion	Abbreviation	CMC (mM)	E <sub>110</sub> (kJ/mol)	β	
Imidazolium		Cl <sup>-</sup>	[C <sub>10</sub> mim]Cl	55 <sup>23</sup>	-29.65	0.83	
			[C <sub>12</sub> mim]Cl	15 <sup>23</sup>	-29.42	0.82	
			[C <sub>14</sub> mim]Cl	4 <sup>23</sup>	-29.22	0.82	
		2 Br <sup>-</sup>	[C <sub>14</sub> Im-6-ImC <sub>14</sub> ][Br] <sub>2</sub>	0.27 ± 0.01	-22.00	0.65	
Pyridinium		Cl <sup>-</sup>	[C <sub>16</sub> py]Cl	0.96 <sup>24</sup>	-26.75	0.76	
			[C <sub>16</sub> py]Br	0.65 <sup>25</sup>	-20.66	0.62	
Ammonium		Br <sup>-</sup>	[N <sub>1,1,1,1</sub> ]Br	---	-21.37	0.64	
			[N <sub>2,2,2,2</sub> ]Br	---	-9.27	0.37	
			[N <sub>3,3,3,3</sub> ]Br	---	-7.95	0.34	
			[N <sub>4,4,4,4</sub> ]Br	---	-7.81	0.34	
			[N <sub>1,1,1,6</sub> ]Br	---	-17.19	0.55	
			[N <sub>1,1,1,8</sub> ]Br	---	39.80 ± 0.20	-16.46	0.53
			[N <sub>1,1,1,10</sub> ]Br	---	25.20 ± 0.25	-16.08	0.52
			[N <sub>1,1,1,12</sub> ]Br	---	15.60 <sup>26</sup>	-15.80	0.52
			[N <sub>1,1,1,14</sub> ]Br	---	3.80 <sup>26</sup>	-15.53	0.51
			[N <sub>1,1,1,16</sub> ]Br	---	0.92 <sup>26</sup>	-15.28	0.50
			[N <sub>1,1,1,2,(C7H7)</sub> ]Br	---	1.18 ± 0.01	-14.89	0.50
			[N <sub>1,1,1,14</sub> ]Br	---	0.08 ± 0.00	-10.95	0.41
			[N <sub>1,1,1,16</sub> ]Br	---	0.06 ± 0.00	-10.89	0.41
		2 Br <sup>-</sup>	[N <sub>1,1,1,4</sub> -6-N <sub>1,1,1,4</sub> ][Br] <sub>2</sub>	0.85 ± 0.03	-13.26	0.46	
Phosphonium		Br <sup>-</sup>	[P <sub>8,8,8,8</sub> ]Br	nd	-1.59	0.20	
			[P <sub>6,6,6,14</sub> ]Br	3.13 ± 0.15	-1.60	0.20	
		Cl <sup>-</sup>	[P <sub>6,6,6,14</sub> ][Dec]	nd	-11.96	0.43	
			[P <sub>6,6,6,14</sub> ][TMP <sub>P</sub> ]	nd	-2.86	0.23	
		Cl <sup>-</sup>	[P <sub>6,6,6,14</sub> ]Cl	3.36 ± 0.07	-2.13	0.21	
			[P <sub>4,4,4,14</sub> ]Cl	4.69 ± 0.18	-9.27	0.37	

Table 1. continued

Family	Cation	Anion	Abbreviation	CMC (mM)	$E_{HB}$ (kJ/mol)	$\beta$
Cholinium			[Ch][Tetradec]	7.02 ± 0.03	-9.63	0.38
Alkylbenzene-sulfonates	Na <sup>+</sup>		SDBS	0.63 <sup>27</sup>	---	---
Alkyl sulfates	Na <sup>+</sup>		SDS	8.0 <sup>28</sup>	---	---

<sup>a</sup>nd: not determined due to low solubility in water. References 23–28 are cited in the body of the table graphic.

oxyethylene groups; conversely, for an identical number of oxyethylene groups, an increase in chain length promotes the cloud point lowering.<sup>16</sup> The coacervation results from a subtle balance of electrostatic interactions, hydrophobic associations, hydrogen bonds, van der Waals forces and other weak interactions, which in turn affect both solute–solute and solute–solvent interactions. In general, when solute–solute interactions are weakened (or solute–solvent enhanced), coacervation is disfavored or suppressed, while when solute–solute interactions are enhanced (or solute–solvent weakened), phase separation is induced.<sup>2</sup> For nonionic surfactants, Lindman et al.<sup>17,18</sup> suggested that the conformational changes of the polar poly(oxyethylene) chains on heating induce the phase separation. The conformation of C–C bond becomes less polar as the temperature increases, resulting in stronger chain–chain than chain–water interactions. Thus, the hydrated shell of the poly(oxyethylene) chains is broken at high temperature, leading to enhanced chain–chain interactions and phase separation.

The surfactants cloud points can be easily manipulated by adding inorganic salts,<sup>19,20</sup> ionic surfactants,<sup>18,21</sup> or water-soluble polymers and fatty alcohols<sup>20</sup> to the system. Recently, we showed that surface active ionic liquids (SAILs) could also modify the cloud point of nonionic surfactants both by increasing and decreasing it,<sup>5</sup> unlike that observed for common surfactants.<sup>18,21</sup> While in conventional AMTPS without additives the operation temperature is controlled by the surfactant structure alone, the use of additives could provide a further control of the separation temperature, and hopefully of the yield and selectivity of the extraction.<sup>5</sup> For labile biomolecules, such as proteins and enzymes for which the AMTPS is an appropriate purification process, the operational temperature range is quite narrow, often without the reach of the conventional nonionic surfactants. Moreover, the use of inorganic salts may also be deleterious to the proteins purification or stability. The study here reported is thus relevant not only to improve the understanding of the underlying mechanisms behind phase separation in AMTPS containing SAILs<sup>5</sup> but also to foster the application of these systems to the extraction and purification of biomolecules.<sup>5,6,8–10</sup>

This work is aimed at an in-depth exploration and characterization of the phase diagrams of three nonionic biocompatible surfactants from the Tergitol family,<sup>20</sup> and the effect of SAILs on their cloud points. Distinct families of SAILs, namely imidazolium, phosphonium, ammonium and pyridinium are evaluated and several SAIL features are analyzed, such as the anion type, the cation symmetry as well as the cation alkyl side chain length. These mixed systems are further characterized through dynamic light scattering (DLS) and surface  $\zeta$  potential

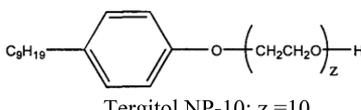
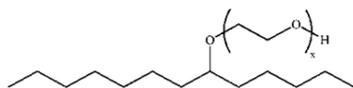
in order to ascertain the IL influence on the micelle size and charge.

## 2. EXPERIMENTAL SECTION

**2.1. Materials.** The phosphonium-based ILs, namely trihexyltetradecylphosphonium chloride, [P<sub>6,6,6,14</sub>]Cl (97.7%); trihexyltetradecylphosphonium bromide, [P<sub>6,6,6,14</sub>]Br (96.0%); trihexyltetradecylphosphonium decanoate, [P<sub>6,6,6,14</sub>][Dec] (99%); trihexyltetradecylphosphonium bis(2,4,4-trimethylpentyl)phosphinate, [P<sub>6,6,6,14</sub>][TMPP] (93.0–95.0%); tetraoctylphosphonium bromide, [P<sub>8,8,8,8</sub>]Br (95.0%); and tributyltetradecylphosphonium chloride, [P<sub>4,4,4,14</sub>]Cl (97.1%), were kindly supplied by Cytec. The imidazolium-based ILs 1-decyl-3-methylimidazolium chloride, [C<sub>10</sub>mim]Cl (>98%); 1-dodecyl-3-methylimidazolium chloride, [C<sub>12</sub>mim]Cl (>98%); and 1-methyl-3-tetradecylimidazolium chloride, [C<sub>14</sub>mim]Cl (>98%), were acquired from Iolitec (Ionic Liquid Technologies, Heilbronn, Germany). The other ILs studied, namely hexadecylpyridinium bromide, [C<sub>16</sub>py]Br (97.0%); hexadecylpyridinium chloride monohydrate, [C<sub>16</sub>py]Cl·H<sub>2</sub>O (99.0%); tetramethylammonium bromide, [N<sub>1,1,1,1</sub>]Br (≥98%); tetraethylammonium bromide, [N<sub>2,2,2,2</sub>]Br (≥96%); tetrapropylammonium bromide, [N<sub>3,3,3,3</sub>]Br (≥98%); tetrabutylammonium bromide, [N<sub>4,4,4,4</sub>]Br (≥98%); dodecyltrimethylammonium bromide, [N<sub>1,1,1,12</sub>]Br (≥98%); tetradecyltrimethylammonium bromide, [N<sub>1,1,1,14</sub>]Br (≥99%); cetyltrimethylammonium bromide, [N<sub>1,1,1,16</sub>]Br (≥98%); and benzyl-dodecyl-dimethylammonium bromide, [N<sub>1,1,12,(C7H7)</sub>]Br (>99%), were supplied by Sigma-Aldrich and (1-hexyl)trimethylammonium bromide, [N<sub>1,1,1,6</sub>]Br (≥98%), was purchased at Alfa Aesar. The *n*-octyltrimethylammonium bromide, [N<sub>1,1,1,8</sub>]Br (>98%); decyltrimethylammonium bromide, [N<sub>1,1,1,10</sub>]Br (>99%); and dimethyldipalmitylammonium bromide, [N<sub>1,1,16,16</sub>]Br (>97%), were acquired at TCI, Tokyo Chemical Industry Co., Ltd. Sodium dodecyl sulfate (SDS) and sodium dodecylbenzenesulfonate (SDBS) were attained from AppliChem Panreac and Sigma-Aldrich, respectively. Finally, *N*-(*N*-hexyl-*N,N*-dimethyl-*N*-tetradecylammonium)-*N,N*-dimethyl-*N*-tetradecylammonium dibromide, [N<sub>1,1,14-6-N<sub>1,1,14</sub></sub>]Br<sub>2</sub>; 3-(1-tetradecyl-3-hexylimidazolium)-1-tetradecylimidazolium dibromide, [C<sub>14</sub>Im-6-ImC<sub>14</sub>]Br<sub>2</sub>; *N,N*-dimethyl-*N,N*-di(tetradecyl)ammonium bromide, [N<sub>1,1,14,14</sub>]Br; and cholinium tetradecanoate, [Ch][Tetradec], were synthesized in-house by using well-established procedures,<sup>22</sup> their structures having been confirmed by nuclear magnetic resonance (NMR). All SAIL structures are presented in Table 1.

The nonionic surfactants Tergitol NP-10, Tergitol 15-S-7, and Tergitol 15-S-9, presented in Table 2, were purchased from

Table 2. Tergitol Surfactants Studied in This Work and Their Main Properties<sup>29</sup>

Surfactant	Structure	HLB	Average MW / g mol <sup>-1</sup>	CMC / mM (at 25°C)
Tergitol NP-10	 Tergitol NP-10: z = 10	13.2	642	0.086
Tergitol 15-S-7		12.1	515	0.074
Tergitol 15-S-9	Tergitol 15-S-7: x = 7 / Tergitol 15-S-9: x = 9	13.3	607	0.086

Sigma-Aldrich with a purity  $\geq 99\%$ . The McIlvaine buffer components, namely sodium phosphate dibasic heptahydrate,  $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$  (purity  $\geq 99\%$ ), and citric acid monohydrate,  $\text{C}_6\text{H}_8\text{O}_7 \cdot \text{H}_2\text{O}$  (purity  $\geq 99\%$ ), were acquired from Panreac AppliChem.

**2.2. Methods.** **2.2.1. Cloud Points.** The cloud points of the systems composed of nonionic surfactants and McIlvaine buffer (Table S1), in absence and presence of ILs as cosurfactants were measured using the cloud point method.<sup>30</sup> The cloud point of each surfactant/IL mixture was determined by visually identifying the temperature at which it became turbid during heating. The cloud point was taken as the temperature at which the test tube labeling was no longer visible; special precautions were used to ensure identical conditions for all measurements. Given the good reproducibility obtained, two or three determinations were sufficient for each system, and the average value was considered. Mixtures with 0.5 to 17.5 wt % of surfactant and 0 or 0.3 wt % of each IL tested were prepared in an aqueous solution of 0.18 M McIlvaine buffer (pH 7.0) up to a final volume of 10 mL, as previously established.<sup>5</sup> The systems were heated between 0 and 100 °C in a temperature controlled water bath with a precision of  $\pm 0.01$  °C (ME-18 V Visco-Thermostat, Julabo). This procedure was repeated to study the pH effect upon the cloud points using Tergitol 15-S-7 for pH values between 3.0 and 8.0 with the same McIlvaine buffer (Table S1). This pH effect was also evaluated by studying the cloud points of these systems in water in the same pH range but this time obtained by the use of acid (HCl) and alkaline (NaOH) solutions, thus minimizing the effect of the salt concentrations resulting from the use of the buffer. Finally, the Tergitol 15-S-7 was also used to evaluate the effect of the IL concentration and nature, with 0.3, 0.5, 0.7, and 1.0 wt % for solutions with 4 and/or 10 wt % of surfactant.

**2.2.2. Dynamic Light Scattering.** DLS measurements using a Malvern Zetasizer Nano-ZS from Malvern Instruments were carried out to evaluate the micelle size of the systems studied. Mixture points containing 1 wt % of surfactant and 0 or 0.3 wt % of IL, in McIlvaine buffer at pH 7.0, were selected to analyze the impact of the IL incorporation into the micelles. Mixtures containing 10 wt % of Tergitol 15-S-7 and SAIL concentrations of 0, 0.3, 0.5, 0.7, or 1.0 wt % were also investigated to evaluate the effect of distinct SAIL/surfactant ratios. These measurements were carried at 10 °C in order to guarantee that all systems were below their cloud points and the measurements only concerned the size of micelles that were homogeneously present in solution.<sup>31</sup> Samples were irradiated with red light (HeNe laser, wavelength of 665 nm) and the intensity fluctuations of the scattering light were detected at a backscattering angle of 173° to

generate an autocorrelation function. The cumulant analysis of this function provided by software DTS v 7.03 yielded the particle size (intensity-based Z-average) and their distribution width (PDI, polydispersity index). The hydrodynamic radii of the aggregates were further determined using the Stokes–Einstein equation assuming spherical aggregates, and a low volume fraction of the dispersed particles. Consequently, the determined values must be considered with caution and regarded as approximations, allowing essentially to establish qualitative trends in size effects. For each sample, at least six measurements were measured, and the average size and standard deviation were determined.

**2.2.3. Surface  $\zeta$  Potential Measurements.** Surface  $\zeta$  potential measurements were carried out to access the surface charge of the micelles of 10 wt % of Tergitol 15-S-7 and of mixed micelles composed of 10 wt % of Tergitol 15-S-7 and 0.3 wt % of an IL of each family, in distilled water. This was accomplished through a Malvern Zetasizer Nano-ZS from Malvern Instruments at 10 °C. The electrophoretic mobility,  $\mu$ , was measured using a combination of electrophoresis and laser Doppler velocimetry, and  $\zeta$  was calculated from  $\mu$  using the Henry equation; a dielectric constant of 78.5, a medium viscosity of 0.89 cP and a  $f(\kappa a)$  function value of 1.5 (Smoluchowsky approximation) were used. The solutions pH was adjusted using 0.2 M of HCl and 0.3 wt % of NaOH.

**2.2.4. Determination of the Critical Micelle Concentration by Electrical Conductivity Measurements.** The electrical conductivity of the solutions of each IL in ultrapure water was measured using a SevenMulti conductimeter (Mettler Toledo Instruments) at 25 °C, within an uncertainty of  $\pm 0.01$  mS.cm<sup>-1</sup>. The breaking point in the linear dependency of the specific conductivity with the concentration gives the CMC of each compound. However, it was impossible to determine the CMC of  $[\text{P}_{6,6,6,14}][\text{Dec}]$ ,  $[\text{P}_{6,6,6,14}][\text{TMPP}]$ , and  $[\text{P}_{8,8,8,8}]\text{Br}$  due to their low water solubility.

**2.2.5. COSMO-RS.** COSMO-RS<sup>32</sup> is a thermodynamic model that combines quantum chemistry, based on the dielectric continuum model known as COSMO (conductor-like screening model for real solvents), with statistical thermodynamic calculations. COSMO calculations are performed in an ideal conductor, meaning that molecules are assumed as surrounded by a virtual conductor environment, and the interactions are completely made on the conductor interface, taking into account the electrostatic screening and the backpolarization of the solute molecule. In what concerns the molecular interactions present in SAILs the most significant modes are the electrostatic misfit energy, and the hydrogen-bonding energy, EHB, defined according to the following equation:

$$E_{\text{HB}} = a_{\text{eff}} C_{\text{HB}} \min(0; \min(0; \sigma_{\text{donor}} + \sigma_{\text{HB}}) \times \max(0; \sigma_{\text{acceptor}} - \sigma_{\text{HB}})) \quad (1)$$

which is described as a function of the polarization charges of the two interacting segments ( $\sigma_{\text{acceptor}}$ ,  $\sigma_{\text{donor}}$ ) and where  $a_{\text{eff}}$  is the effective contact area between two surface segments,  $C_{\text{HB}}$  is the hydrogen-bond strength, and  $\sigma_{\text{HB}}$  is the threshold for hydrogen-bonding.

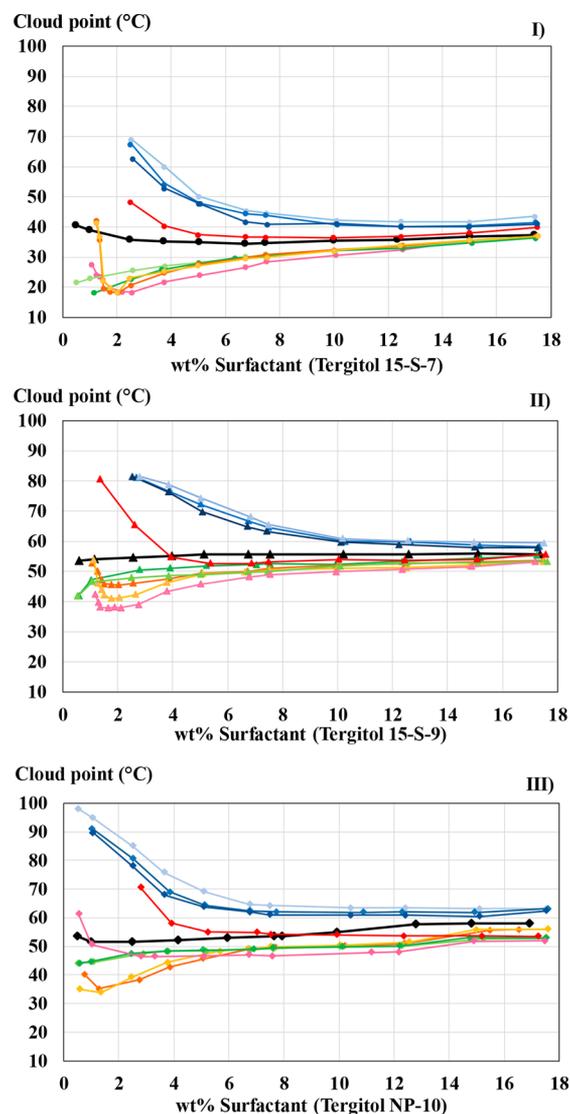
A number of conformations are available for the IL ions studied. In all the studied compounds the lowest energy conformer was employed in the COSMO-RS calculations. Moreover, independent files for the IL cation and anions were used. An equimolar cation–anion mixture was used to specifically determine the  $E_{\text{HB}}$  values of a pure SAIL. SAILs are here described by independent ions (known as [C + A] model, which treats the ILs as the sum as the individual ionic species).

The molecular geometries of all compounds were optimized at the B3LYP/6-31++G\* computational level in the ideal gas phase using the quantum chemical Gaussian 03 package.<sup>33</sup> The ideal screening charges on the molecular surface for each species were calculated by the continuum solvation COSMO model using the BVP86/TZPV/DGA1 level of theory.<sup>34</sup> Subsequently, COSMO files were used as an input in COSMOtherm code to calculate the partition coefficient ( $E_{\text{HB}}$ , kJ mol<sup>-1</sup>), using the parametrization (BP\_TZVP\_C30\_1201).

### 3. RESULTS AND DISCUSSION

**3.1. Cloud Point Curve Profile of the Neat and Mixed Systems: Effect of SAIL Molecular Structure.** As discussed above, it is essential for the design of cloud point extraction processes to know the cloud point phase diagrams of the surfactants. The measurements of the cloud point phase diagrams of neat surfactants and their mixtures with SAILs were carried out and the results are presented in Figures 1 and S1 (Supporting Information). Herein, two distinct families of SAILs were chosen, namely based in the imidazolium ([C<sub>10</sub>mim]Cl, [C<sub>12</sub>mim]Cl, and [C<sub>14</sub>mim]Cl) and phosphonium ([P<sub>6,6,6,14</sub>]X, X = Cl, Br, [TMPP], and [Dec]; [P<sub>4,4,4,14</sub>]Cl; and [P<sub>8,8,8,8</sub>]Br) structures. These ILs possess distinct chemical structures allowing the evaluation of different effects such as the influence of (i) cation (polar head) nature, (ii) the cation alkyl side chains (hydrophobic moiety), (iii) the symmetry of the cation, and the (iv) anion (counterion) nature.

The binodal curves were determined by the visual identification of the cloud point for all the mixture points with distinct concentrations of a nonionic surfactant, and SAIL as cosurfactant at a fixed concentration of 0.3 wt % and 0.18 M McIlvaine buffer pH 7.0. First, the cloud points of Tergitol NP-10, Tergitol 15-S-7 and 15-S-9, without any cosurfactant, were measured to characterize the phase behavior of each neat surfactant (Figures 1 and S1) and to evaluate the effect of the IL upon the cloud points (Figure 1). These results allow the evaluation of the influence of an aromatic ring in the surfactant structure by comparing Tergitol NP-10 with the others, and the effect of the increase in the number of EO groups in the surfactant alkyl chain by comparing Tergitol 15-S-7 and Tergitol 15-S-9. Tergitol 15-S-9 displays a larger number of EO groups (hence a more hydrophilic character), thus its cloud points are higher than those of Tergitol 15-S-7, in agreement with the results previously reported for the polyoxyethylene alkyl ether family<sup>16,31,35</sup> and for the Tergitol 15-S-series.<sup>20</sup> In fact, more EO groups (each EO unit takes roughly 2–3 hydration water



**Figure 1.** Binodal curves of Tergitol solutions with 0.3 wt % of ILs, at pH 7.0, corresponding (I) to (●) Tergitol 15-S-7, (II) to (▲) Tergitol 15-S-9, and (III) to (◆) Tergitol NP-10: (light green) [P<sub>6,6,6,14</sub>]Cl; (dark green) [P<sub>6,6,6,14</sub>]Br; (yellow) [P<sub>6,6,6,14</sub>][Dec]; (orange) [P<sub>6,6,6,14</sub>]-[TMPP]; (red) [P<sub>4,4,4,14</sub>]Cl; (pink) [P<sub>8,8,8,8</sub>]Br; (light blue) [C<sub>10</sub>mim]-Cl; (medium blue) [C<sub>12</sub>mim]Cl; and (dark blue) [C<sub>14</sub>mim]Cl. The black binodal curves correspond to the neat systems.

molecules)<sup>36</sup> imply a more extended hydration level of the polar region of the micelles and that, in turn, promotes the higher solubility of the surfactant.<sup>31</sup> The cloud points previously reported in literature for these surfactants<sup>20</sup> were determined in water whereas ours were determined in McIlvaine buffer at pH 7.0, which led to a decrease in the cloud points for Tergitol 15-S-9 from 60 °C<sup>20</sup> to 54.1 ± 0.2 °C. This reduction is due to the salting-out effect of the buffer.<sup>37</sup> The binodal curve of the Tergitol NP-10 is presented in Figure 1-III and in Figure S1 (Supporting Information), and it also displays cloud points above 50 °C as a result of the high number of ethoxylate groups in the surfactant structure. However, it should be noticed that the presence of an aromatic ring in this surfactant induces a reduction in the cloud points when compared to Tergitol 15-S-9, which displays a similar number of ethoxylate groups, the main difference being the presence of this ring. The cloud points also follow the surfactant HLB, which represents the balance between the

surfactant hydrophilic and lipophilic moieties. Higher HLB values (which is the case of NP-10 and 15-S-9, cf. Table 2) indicate a more hydrophilic character leading to higher cloud points.<sup>38</sup>

As previously mentioned, the SAILs on this study were kept at a fixed concentration of 0.3 wt %, which corresponds to ca. 10 mM for the imidazolium family and around 5 mM for the phosphonium family, while varying the surfactant concentration from 0.5 to 17.5 wt % (~8–10 mM to ~270–340 mM, depending on the surfactant). This means that, with the exception of [C<sub>10</sub>mim]Cl and [C<sub>12</sub>mim]Cl, all the remaining SAILs are above their CMC (Table 1). In any case, it is the nonionic surfactant that controls the mixed micelle formation since it is present in much higher concentrations, and its CMC is significantly lower than those of the SAILs.

In the binodal curves presented in Figure 1, it is possible to observe that the addition of different ILs affects the cloud points in different ways. Unlike widely accepted and reported in the specialized literature,<sup>18,21</sup> it is not just an increase in cloud points that is observed by the introduction of the ionic surfactant. Here, the cloud points are observed to either increase or decrease, depending on the SAIL nature as discussed below. In contrast to previous work on the effects of ionic surfactants,<sup>18,21</sup> the cloud points curves show that the SAIL effect is less pronounced at high concentrations of nonionic surfactant. For concentrations above 6 wt %, the effect of the nonionic surfactant is increasingly dominant and the effect of the IL becomes marginal. This can be rationalized by a decrease in the SAIL/surfactant ratio owing to the fact that the IL concentration is always constant whereas the surfactant concentration increases. For the imidazolium-based ILs ([C<sub>10</sub>mim]Cl, [C<sub>12</sub>mim]Cl, and [C<sub>14</sub>mim]Cl) and [P<sub>4,4,4,14</sub>]Cl, the ILs with a more hydrophilic character induce an increase in the cloud points, and the increase in the SAIL alkyl chain, increasing their hydrophobicity, decreases the effect upon the cloud points. In contrast, the more hydrophobic phosphonium-based ILs ([P<sub>6,6,6,14</sub>]X, X = Cl, Br, [TMPP], and [Dec]; and [P<sub>8,8,8,8</sub>]Br), induce a significant decrease in the cloud points, which was not previously observed with ionic surfactants. These effects are summarized in Table 3, based on the analysis of each system at a surfactant concentration of 1 wt %.

The SAILs' hydrophobicity can be related to its hydrogen-bond basicity,  $\beta$ , or to the COSMO  $E_{\text{HB}}$  descriptor reported in Table 1. These parameters express the SAIL hydrogen-bond ability and have been shown to provide a good description of the SAIL hydrophobicity. SAILs with a lower  $\beta$ , and lower absolute  $E_{\text{HB}}$ , are less able to establish hydrogen-bonds and thus present a more hydrophobic character. However, from the correlations of the cloud points with these descriptors (Figure S3 in Supporting Information), it is clear that hydrophobicity alone, i.e., enthalpic interactions, are not enough to provide a complete explanation of the effect of the SAILs upon the cloud points and that another, more entropic, parameter is required to fully explain the results here reported. Further insight on these results can be gained by considering the critical packing parameter (CPP) of the SAILs. The CPP is a dimensionless parameter that determines the overall packing shape of a surfactant and is defined as the ratio  $\nu_{\text{hc}}/(a_0 l_c)$ , where  $\nu_{\text{hc}}$ ,  $l_c$ , and  $a_0$  are the volume and critical length of the hydrophobic portion of the molecule and  $a_0$  is the optimal headgroup area.<sup>39–41</sup> The CPP does not contain fixed molecular sizes but rather average quantities that depend on the interactions at play. The type of preferred aggregate formed is determined by the adopted molecular shape and respective CPP: for a cone, with  $\text{CPP} \leq 0.33$ , spherical micelles; for a truncated

**Table 3. Effect of the SAIL's Anion, Cation, Symmetry, and Length of Alkyl Size Chain upon the Cloud Point (CP) for Mixed Systems of Tergitol-Based Surfactants, at 1 wt % of Tergitol**

	Tergitol 15-S-7	Tergitol 15-S-9	Tergitol NP-10
anion effect (for [P <sub>6,6,6,14</sub> ] <sup>+</sup> )	[Dec] <sup>-</sup> > [TMPP] <sup>-</sup> > Br <sup>-</sup> > Cl <sup>-</sup>	[Dec] <sup>-</sup> > [TMPP] <sup>-</sup> > Br <sup>-</sup> > Cl <sup>-</sup>	[Dec] <sup>-</sup> > [TMPP] <sup>-</sup> > Cl <sup>-</sup> > Br <sup>-</sup>
cation effect (for n = 14, Cl)	[C <sub>14</sub> mim] <sup>+</sup> > [P <sub>4,4,4,14</sub> ] <sup>+</sup> > [P <sub>6,6,6,14</sub> ] <sup>+</sup>	[C <sub>14</sub> mim] <sup>+</sup> > [P <sub>4,4,4,14</sub> ] <sup>+</sup> > [P <sub>6,6,6,14</sub> ] <sup>+</sup>	[P <sub>4,4,4,14</sub> ] <sup>+</sup> > [C <sub>14</sub> mim] <sup>+</sup> > [P <sub>6,6,6,14</sub> ] <sup>+</sup>
alkyl chain length effect (for [C <sub>n</sub> mim]Cl)	[C <sub>10</sub> mim] <sup>+</sup> > [C <sub>12</sub> mim] <sup>+</sup> > [C <sub>14</sub> mim] <sup>+</sup>	[C <sub>10</sub> mim] <sup>+</sup> > [C <sub>12</sub> mim] <sup>+</sup> > [C <sub>14</sub> mim] <sup>+</sup>	[C <sub>10</sub> mim] <sup>+</sup> > [C <sub>12</sub> mim] <sup>+</sup> > [C <sub>14</sub> mim] <sup>+</sup>
cation symmetry effect (for n = 3, 2, Br)	[P <sub>6,6,6,14</sub> ] <sup>+</sup> > [P <sub>8,8,8,8</sub> ] <sup>+</sup>	[P <sub>8,8,8,8</sub> ] <sup>+</sup> > [P <sub>6,6,6,14</sub> ] <sup>+</sup>	[P <sub>6,6,6,14</sub> ] <sup>+</sup> > [P <sub>8,8,8,8</sub> ] <sup>+</sup>

<sup>a</sup>Some surfactants show cloud points above 100 °C; for these cases, the trends are based on the extrapolation of the binodal curve.

cone, with  $CPP = 0.33-0.5$ , cylindrical micelles; for  $CPP \approx 0.5-1$ , bilayer disks and vesicles; for cylinders,  $CPP \approx 1$ , planar bilayers (lamellar phases); and for an inverted wedge-shaped molecule,  $CPP > 1$ , inverted structures (reverse cylinders and spheres). SAILs with large ionic headgroup areas and relatively low  $\nu_{hc}$  have  $CPP \leq 1/2$ —e.g., single-chained imidazolium and quaternary ammonium surfactants<sup>42</sup> and gemini surfactants<sup>43,44</sup>—corresponding to the hydrophilic SAILs in Table 1. They will decrease the effective CPP in the mixed micelle (leading to smaller micelles, as will be shown in section 3.2), promoting an increase in solubility and hence in cloud point of the mixture. Conversely, the double-chained quaternary ammonium and bulky phosphonium-based SAILs, with large  $\nu_{hc}$  and relatively small headgroup areas have  $CPP \approx 1$  or larger (hydrophobic SAILs, Table 1);<sup>41</sup> they will increase the effective CPP in the mixed micelles (leading to larger aggregates, cf. section 3.2), which ultimately results in a decrease in solubility and hence in cloud point.

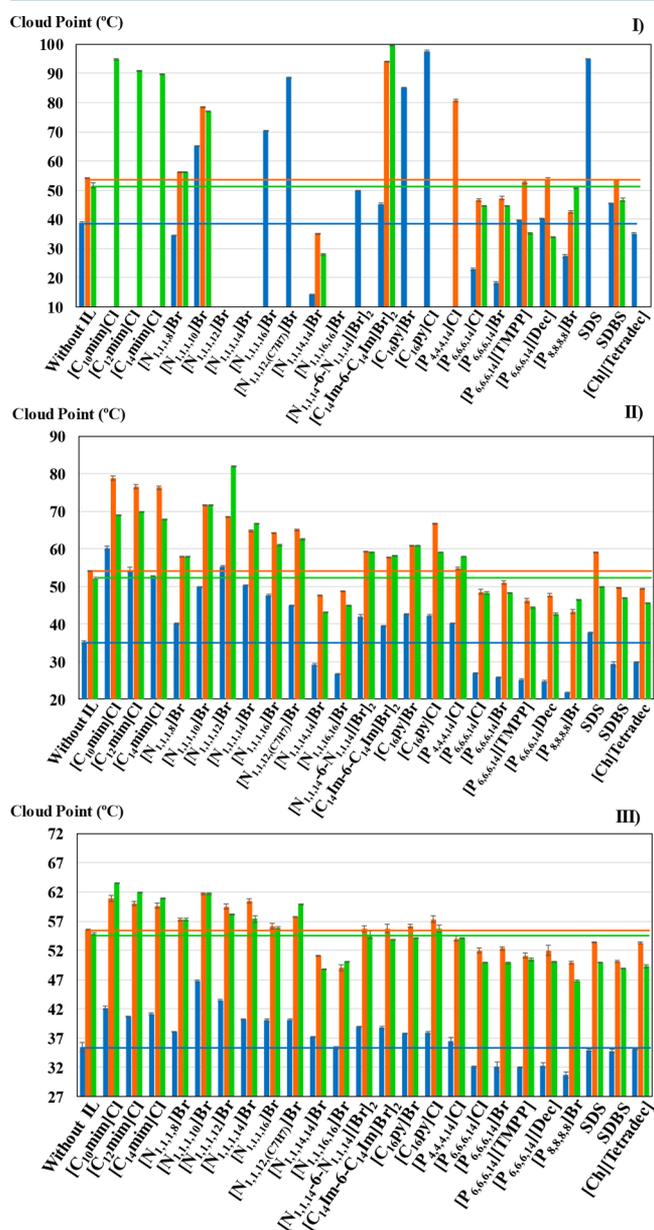
Regarding the anion effect, it can be seen that  $[\text{Dec}]^-$  (decanoate) and  $[\text{TMPP}]^-$  (bis(2,4,4-trimethylpentyl)-phosphinate) induce a stronger effect than  $\text{Cl}^-$  and  $\text{Br}^-$ , since the former are bulky counterions ions with a more hydrophobic character and the respective SAILs have  $CPP \geq 1$ . On the other hand, the imidazolium cation causes the greatest impact on the cloud points (inducing higher cloud points) when compared to the phosphonium cation. In particular, the effects are more significant upon reducing the cation alkyl chain length for both imidazolium-based IL and for  $[\text{P}_{4,4,4,14}]^+$  compared to  $[\text{P}_{6,6,6,14}]^+$ . Concerning the cation geometry ( $[\text{P}_{8,8,8,8}]^+$  vs  $[\text{P}_{6,6,6,14}]^+$ ), asymmetry favors a larger decrease in cloud points for Tergitol 15-S-7 and NP-10, while for Tergitol 15-S-7, it is the symmetric cation that leads to a larger effect.

In summary, it can be stated that the cation type and symmetry, anion type, and alkyl chain length present a significant effect on the cloud points at lower surfactant concentrations. It is the hydrophobicity and CPP of the SAIL that seem to play the dominant role on these effects.

Tergitol NP-10 presents an aromatic ring in its structure that may be responsible for the more pronounced influence of the aromatic SAILs in the system, owing to  $\pi-\pi$  interactions that can be established between the aromatic rings of the compounds. As a result, the micelles headgroups are more available to interact with the water molecules, increasing the hydration level around the micelles and thus, increasing the cloud points of the mixed systems ( $\Delta T \approx +50^\circ\text{C}$ ).<sup>18,31</sup> On the other hand, it is well-known that water can be a good solvent at low temperatures, as can be seen by the lower cloud point results obtained for the phosphonium-based mixed systems, and a poor solvent at high temperatures, since the interactions between the nonionic surfactant and the SAILs' headgroups with water will be stronger, hence promoting their higher solubility.<sup>18</sup> Therefore, the cloud point of these systems will be higher. These results are consistent with some of our previous results,<sup>5</sup> in which it was observed that for the nonionic surfactant Triton X-114 that also features an aromatic ring in its structure, the effect of the aromatic SAILs presence is also quite pronounced at low surfactant concentration.

**3.1.1. Effect of Surfactant Concentration.** To further extend the study of the effect of SAILs upon the cloud points, three systems, composed of 1, 4, and 10 wt % of surfactant, were chosen. These systems were selected to represent a concentration range in which it was previously observed a dominant effect of the SAIL upon the binodal curve, at 1 and 4 wt % (Figure

2, parts I and II), or a dominant effect of the surfactant, at 10 wt % (Figure 2.III). A number of SAILs and anionic surfactants,

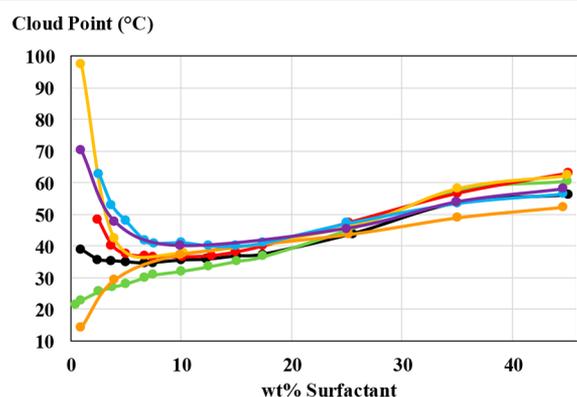


**Figure 2.** Cloud point of Tergitol surfactants without and with 0.3 wt % of SAIL for 1 (I), 4 (II) and 10 wt % (III) of each surfactant: (blue) Tergitol 15-S-7; (orange) Tergitol 15-S-9, and (green) Tergitol NP-10.

distinct from those studied above, namely  $[\text{N}_{1,1,1,8}]^+\text{Br}$ ,  $[\text{N}_{1,1,1,10}]^+\text{Br}$ ,  $[\text{N}_{1,1,1,12}]^+\text{Br}$ ,  $[\text{N}_{1,1,1,14}]^+\text{Br}$ ,  $[\text{N}_{1,1,1,16}]^+\text{Br}$ ,  $[\text{N}_{1,1,12}(\text{C}_{7\text{H}_7})]^+\text{Br}$ ,  $[\text{N}_{1,1,14,14}]^+\text{Br}$ ,  $[\text{N}_{1,1,16,16}]^+\text{Br}$ ,  $[\text{N}_{1,1,14-6-\text{N}_{1,1,14}}]^+\text{Br}_2$ ,  $[\text{C}_{14}\text{Im-6-ImC}_{14}]^+\text{Br}_2$ ,  $[\text{C}_{16}\text{py}]^+\text{Cl}$ ,  $[\text{C}_{16}\text{py}]^+\text{Br}$ , SDS, SDBS, and  $[\text{Ch}][\text{Tetradec}]$ , were used in this study. Most of them, due to their hydrophilic nature and  $CPP < 1/2$ , behave like the imidazolium-based SAILs. Nonetheless, when a second long alkyl chain is introduced into  $[\text{N}_{1,1,1,14}]^+\text{Br}$ , forming  $[\text{N}_{1,1,14,14}]^+\text{Br}$ , the cloud points are reduced due to the enhanced CPP and more hydrophobic character of the SAIL, highlighting the effect of the hydrophobicity in the decrease of the cloud points. This SAIL and  $[\text{N}_{1,1,16,16}]^+\text{Br}$  are similar double-chained surfactants, forming fluid bilayer structures in water (vesicles and lamellar liquid crystals) above their gel-to-liquid crystal (or chain melting)

transition temperature,  $T_m$ . For 1 wt % of surfactant, it was impossible, however, to solubilize  $[N_{1,1,16}]Br$  (this is likely due to the higher  $T_m$  associated with the longer alkyl chains, which hinders the mixing). On the other hand, when two  $[C_{14}mim]Cl$  are linked together forming  $[C_{14}Im-6-C_{14}Im]Br_2$ , there is still an increase in the cloud point albeit smaller than that for the  $[C_{14}mim]Cl$ .  $[C_{14}Im-6-C_{14}Im]Br_2$  is also a double-chained SAIL, but differs from the former ones in that it possesses two charged headgroups (forming a so-called gemini surfactant), which increases its hydrophilic character. Moreover, it self-aggregates into micelles, which further helps promoting the solubility of the nonionic surfactants.

Furthermore, when anionic surfactants or SAILs such as SDS, SDBS, and  $[Ch][Tetradec]$  are considered, it is possible to observe three distinct behaviors for 1 wt % of surfactant: SDS is extremely hydrophilic and hence induces extremely high cloud points for Tergitol 15-S-9 and Tergitol NP-10 (higher than 100 °C) whereas, in the other extreme,  $[Ch][Tetradec]$ , the most hydrophobic of these three compounds, is impossible to dissolve in aqueous solutions at 1 wt % of these two surfactants; in between lies SDBS, a surfactant with a phenyl connecting the sulfonate group with the alkyl chain and therefore more hydrophobic than SDS. When the nonionic surfactant concentration is increased, the SAIL/surfactant ratio decreases and as result, the surfactant dominates and the cloud point of the mixtures containing three anionic surfactants are close to those of 10 wt % of surfactant. This dominant effect is still visible, although much attenuated, for surfactant concentrations up to 45 wt %, as shown in Figure 3 for distinct SAIL families.

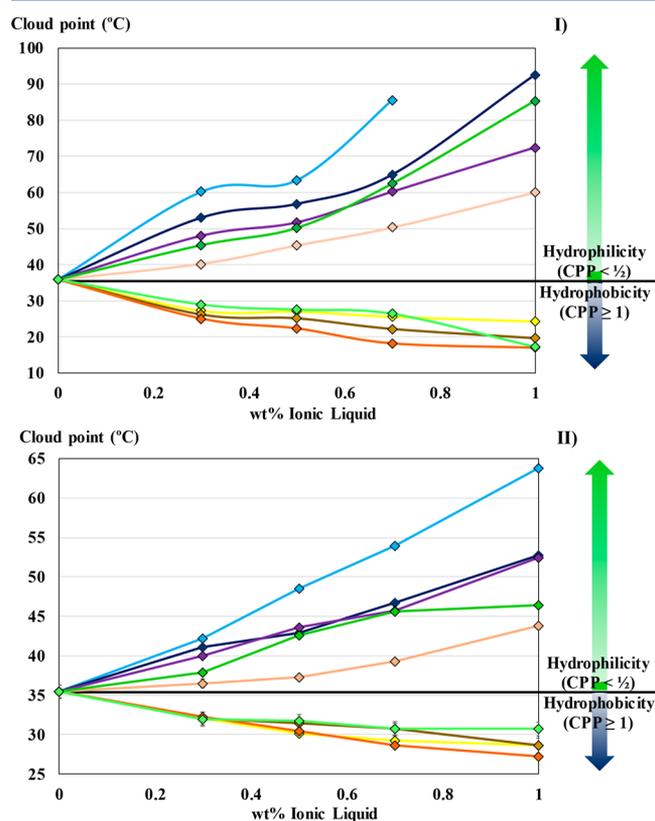


**Figure 3.** Phase diagrams for the Tergitol 15-S-7 at 0 and 0.3 wt % of SAILs belonging to distinct families, in McIlvaine buffer pH 7.0: (black) without SAIL; (light blue)  $[C_{14}mim]Cl$ ; (yellow)  $[C_{16}py]Cl$ ; (purple)  $[N_{1,1,1,16}]Br$ ; (orange)  $[N_{1,1,1,14}]Br$ ; (red)  $[P_{4,4,4,14}]Cl$ ; (light green)  $[P_{6,6,6,14}]Cl$ .

Nevertheless, the results for  $[Ch][Tetradec]$  show consistently a decrease in the cloud points when compared to the solutions of neat nonionic surfactant. A more detailed discussion on the effect of the SAILs from the ammonium family, and the effect of the alkyl chain length, will be presented below.

**3.1.2. Effect of SAIL Concentration.** So far, the results reported show that the SAIL addition to the nonionic surfactant induces significant changes into its cloud points with only 0.3 wt % of IL, *i.e.*, *ca.* 5 and 10 mM for the phosphonium and imidazolium families, respectively. It is, however, important to evaluate the impact of the SAILs concentration on the cloud points of the mixed systems. This study was carried out by varying the SAIL concentration from 0 to 1.0 wt %,

corresponding to a maximum SAIL concentration of *circa* 10–40 mM, depending on the SAIL used, while the Tergitol 15-S-7 concentration was maintained at 4 and 10 wt % ( $\sim$ 78 and  $\sim$ 194 mM, respectively). This allowed not only the study of the effect of the SAIL concentration upon the phase diagram but also the evaluation of the influence of different SAIL/surfactant ratios and verify if the surfactant would still be dominant at the higher concentrations. It should be noted that the lowest surfactant concentration, namely 1 wt %, was not considered since it is already known that in this region, the IL impact upon the cloud point is very pronounced. As a result, for the more hydrophilic and more hydrophobic SAILs, the cloud point would be more difficult to determine because it would be higher than 100 °C or lower than 0 °C, respectively. Figure 4 displays these results, in

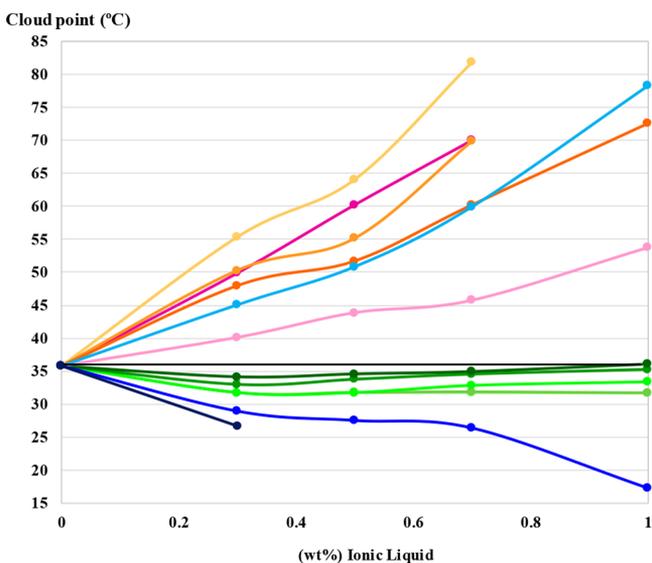


**Figure 4.** Effect of the SAIL concentration, from 0 to 1.0 wt %, on the cloud points of I) 4 and II) 10 wt % of Tergitol 15-S-7 for the systems with (light blue)  $C_{10}mimCl$ ; (dark blue)  $C_{14}mimCl$ ; (dark green)  $[C_{16}Py]Cl$ ; (orange)  $[P_{4,4,4,14}]Cl$ ; (yellow)  $[P_{6,6,6,14}]Cl$ ; (brown)  $[P_{6,6,6,14}]Br$ ; (red)  $[P_{6,6,6,14}][TMPP]$ ; (purple)  $[N_{1,1,1,16}]Br$ ; (light green)  $[N_{1,1,1,14}]Br$ .

which it is possible to observe that, when the SAIL concentration of the most hydrophobic SAILs (phosphonium-based) is increased, the cloud points decrease by almost 10 °C, for both surfactant concentrations, when compared to the original system without SAIL. Alternatively, when the concentration of the hydrophilic SAILs is increased, the cloud point also increases, reaching temperatures of nearly 50 and 30 °C higher than those of the original system (without SAIL) for 4 and 10 wt % of surfactant, respectively. For the mixed systems with 1.0 wt %  $[C_{10}mim]Cl$ , the cloud point was above 100 °C and thus it could not be determined. These results show that, even at the highest surfactant concentration, the SAIL addition to the system has a

big impact on the cloud points, although attenuated by the decreasing SAIL/surfactant ratio.

**3.1.3. Effect of the Alkyl Chain of Quaternarium Ammonium Salts and SAILS.** Inorganic salts can also be used to manipulate the cloud points of surfactants based on their *salting-in/out* ability.<sup>19,20</sup> Thus, we compared the cloud points of Tergitol 15-S-7 in the presence of several ammonium-based salts and SAILS, whose overall alkyl chain length was increased, to assess the similarities/differences between the ammonium salts and the quaternarium ammonium SAILS. To do so, aqueous solutions with 4 wt % of Tergitol 15-S-7 and 0 to 1.0 wt % of the salts were selected, since in this region the SAIL/surfactant ratios are higher, allowing a more pronounced effect upon the cloud points as discussed before. These results are displayed on Figure 5. Here, the five ammonium salts/ILs, [N<sub>1,1,1,1</sub>]<sup>+</sup>Br<sup>-</sup>, [N<sub>2,2,2,2</sub>]<sup>+</sup>Br<sup>-</sup>,



**Figure 5.** Effect of the IL character and concentration, from 0 to 1.0 wt %, on the cloud points of 4 wt % of Tergitol 15-S-7 of systems: (black) without IL; (light green) [N<sub>1,1,1,1</sub>]<sup>+</sup>Br<sup>-</sup>; (olive green) [N<sub>2,2,2,2</sub>]<sup>+</sup>Br<sup>-</sup>; (medium green) [N<sub>3,3,3,3</sub>]<sup>+</sup>Br<sup>-</sup>; (dark green) [N<sub>4,4,4,4</sub>]<sup>+</sup>Br<sup>-</sup>; (ochre) [N<sub>1,1,1,6</sub>]<sup>+</sup>Br<sup>-</sup>; (magenta) [N<sub>1,1,1,8</sub>]<sup>+</sup>Br<sup>-</sup>; (yellow) [N<sub>1,1,1,10</sub>]<sup>+</sup>Br<sup>-</sup>; (orange) [N<sub>1,1,1,12</sub>]<sup>+</sup>Br<sup>-</sup>; (pink) [N<sub>1,1,1,14</sub>]<sup>+</sup>Br<sup>-</sup>; (red) [N<sub>1,1,1,16</sub>]<sup>+</sup>Br<sup>-</sup>; (light blue) [N<sub>1,1,12,(C7H7)</sub>]<sup>+</sup>Br<sup>-</sup>; (medium blue) [N<sub>1,1,14,14</sub>]<sup>+</sup>Br<sup>-</sup>; (dark blue) [N<sub>1,1,16,16</sub>]<sup>+</sup>Br<sup>-</sup>.

[N<sub>3,3,3,3</sub>]<sup>+</sup>Br<sup>-</sup>, [N<sub>4,4,4,4</sub>]<sup>+</sup>Br<sup>-</sup> and [N<sub>1,1,1,6</sub>]<sup>+</sup>Br<sup>-</sup>, are compared with the SAILS [N<sub>1,1,1,8</sub>]<sup>+</sup>Br<sup>-</sup>, [N<sub>1,1,1,10</sub>]<sup>+</sup>Br<sup>-</sup>, [N<sub>1,1,1,12</sub>]<sup>+</sup>Br<sup>-</sup>, [N<sub>1,1,1,14</sub>]<sup>+</sup>Br<sup>-</sup>, [N<sub>1,1,1,16</sub>]<sup>+</sup>Br<sup>-</sup>, [N<sub>1,1,12,(C7H7)</sub>]<sup>+</sup>Br<sup>-</sup>, [N<sub>1,1,14,14</sub>]<sup>+</sup>Br<sup>-</sup>, and [N<sub>1,1,16,16</sub>]<sup>+</sup>Br<sup>-</sup>. As can be seen, all ammonium salts induce a slight decrease in the cloud points compared to the IL-free systems due to a minor *salting-out* effect. This effect becomes weaker with the increase of the IL alkyl chain length owing to the lower ability of the IL to form hydration complexes with water.

The SAILS present a different behavior among them, as the results previously discussed suggested. When the SAIL incorporates the micelle, it controls the environment around through its hydrophobicity and CPP, as discussed before. Therefore, [N<sub>1,1,1,12</sub>]<sup>+</sup>Br<sup>-</sup>, [N<sub>1,1,1,14</sub>]<sup>+</sup>Br<sup>-</sup>, [N<sub>1,1,1,16</sub>]<sup>+</sup>Br<sup>-</sup>, and [N<sub>1,1,12,(C7H7)</sub>]<sup>+</sup>Br<sup>-</sup> increase the mixture cloud points due to their more hydrophilic character and lower CPP which cause higher micellar solubility, i.e. which favor solute–solvent interactions at the expense of solute–solute interactions. On the other hand, [N<sub>1,1,14,14</sub>]<sup>+</sup>Br<sup>-</sup> and [N<sub>1,1,16,16</sub>]<sup>+</sup>Br<sup>-</sup> reduce the cloud points for the opposite reason: more hydrophobic character and much higher CPP led to decreased solubility. It was not possible to determine

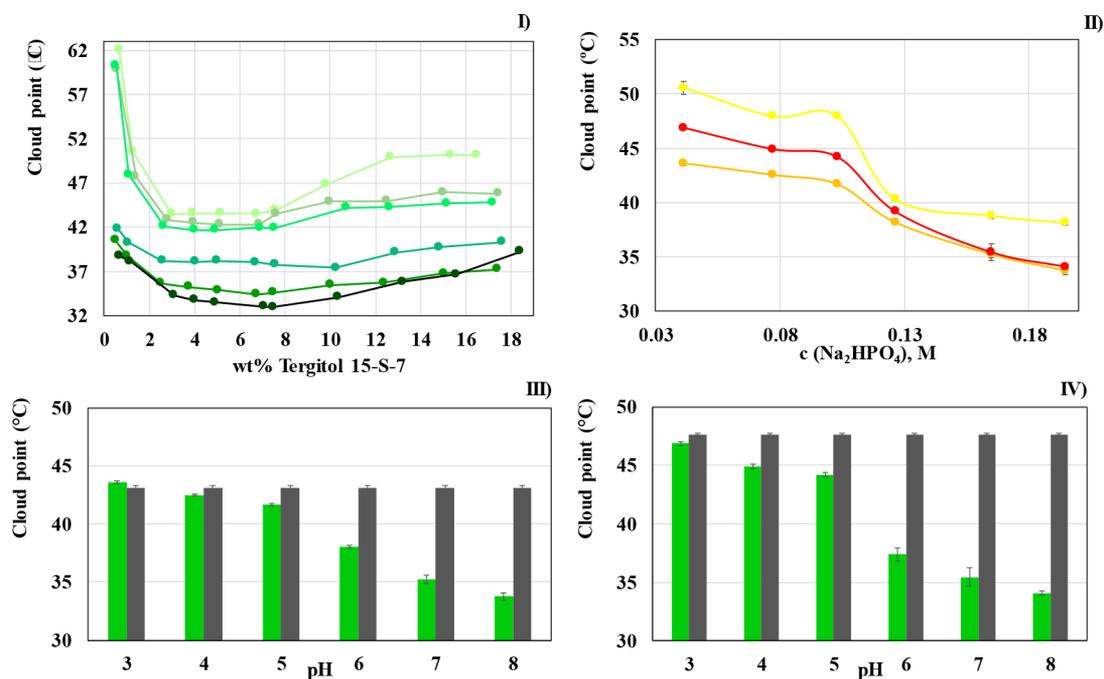
the cloud points at 1.0 wt % of SAIL for the more hydrophilic ones, since they are higher than 100 °C. Regarding [N<sub>1,1,1,8</sub>]<sup>+</sup>Br<sup>-</sup> and [N<sub>1,1,1,10</sub>]<sup>+</sup>Br<sup>-</sup>, both of them are close to, or below, their CMC so they, at these concentrations, show an intermediate behavior between a SAIL and an electrolyte. Thereby, further studies were carried out by keeping the surfactant at 4 wt % while the SAIL concentration was increased to 2 wt %, which is a concentration above the CMC for both compounds, namely 2.0 and 2.8 times the CMC of [N<sub>1,1,1,8</sub>]<sup>+</sup>Br<sup>-</sup> and [N<sub>1,1,1,10</sub>]<sup>+</sup>Br<sup>-</sup>, respectively. Herein, the cloud points for [N<sub>1,1,1,8</sub>]<sup>+</sup>Br<sup>-</sup> and [N<sub>1,1,1,10</sub>]<sup>+</sup>Br<sup>-</sup> are >100 °C and 97.5 ± 0.5 °C, respectively, which is in agreement with what would be expected. Moreover, when [N<sub>1,1,1,12</sub>]<sup>+</sup>Br<sup>-</sup>, [N<sub>1,1,12,(C7H7)</sub>]<sup>+</sup>Br<sup>-</sup> and [N<sub>1,1,14,14</sub>]<sup>+</sup>Br<sup>-</sup> are compared, it is easily understood why [N<sub>1,1,12,(C7H7)</sub>]<sup>+</sup>Br<sup>-</sup> presents an intermediate cloud point enhancement: its aromatic ring enables a more hydrophobic character when compared with [N<sub>1,1,1,12</sub>]<sup>+</sup>Br<sup>-</sup>, though not enough to resemble [N<sub>1,1,14,14</sub>]<sup>+</sup>Br<sup>-</sup>. This can be further confirmed by the respective CMC values (Table 1). Unfortunately, the big difference in the solubility between [N<sub>1,1,16,16</sub>]<sup>+</sup>Br<sup>-</sup> and [N<sub>1,1,14,14</sub>]<sup>+</sup>Br<sup>-</sup> made impossible to solubilize [N<sub>1,1,16,16</sub>]<sup>+</sup>Br<sup>-</sup> in concentrations higher than 0.3 wt % and provide a more complete comparison between the two compounds.

**3.1.4. Effect of pH.** Since this study is aimed at the development of AMTPS for use in cloud point extraction of proteins and other biomolecules, the McIlvaine buffer was used to control the pH. In order to evaluate the pH effect upon the cloud points, the Tergitol 15-S-7 systems were used and their cloud points measured in the pH range from 3.0 to 8.0, using two distinct approaches. In the first approach, the McIlvaine buffer was used, since it can provide a wide range of pH. The results from Figure 6.I) would suggest that the increase in the pH leads to a decrease in the system cloud points. To understand if this was an effect of the pH or of the concentration of the buffer that could be inducing the *salting-out* of the surfactant,<sup>37</sup> a second approach was considered, where the pH was adjusted by the addition of small amounts of acid (HCl) or alkaline (NaOH) solutions. The results for this approach are displayed in Figures 6, parts III) and IV), in which it is shown that the pH does not have any influence upon the system cloud points, as would be expected for a nonionic surfactant. Instead, the decrease in cloud points in Figure 6.I) is due to the strong *salting-out* effect of Na<sub>2</sub>HPO<sub>4</sub> present in the McIlvaine buffer, as shown in Figure 6.II).

The results here reported demonstrate the versatility of the cloud point phase diagrams of nonionic surfactants, and the possibility to tune the cloud points to meet a specific target by the proper choice of the surfactant, the SAIL, at very low concentrations (5–40 mM), and the buffer.

**3.2. Micelle Size and Charge: DLS and ζ Potential Study.** In order to further understand the mechanism by which the IL modifies the cloud point of these systems, i.e. to ascertain whether the IL added to the system is incorporated into the micelles and does not behave as a simple electrolyte, dynamic light scattering (DLS) and ζ potential measurements were carried out for the mixture point of 1 wt % of surfactant and 0 and 0.3 wt % of SAIL, in McIlvaine buffer at pH 7.0 for the DLS measurements and in water for ζ potential.

Since nonionic micelles will in principle display zero (or near-zero) surface charge, any clearly positive or negative ζ potential values will ascertain the incorporation of SAILS into the micelle. The results from Figures 7.I) to 7.IV) corroborate this hypothesis, showing that, for a wide pH range, the micelle charge is always positive in the presence of a cationic SAIL and



**Figure 6.** (I) Cloud points for Tergitol 15-S-7 without IL and with Mcllvaine buffer: (light green) pH 3.0; (olive green) pH 4.0; (aqua green) pH 5.0; (medium green) pH 6.0; (dark green) pH 7.0; (black) pH 8.0. (II) Cloud points for Tergitol 15-S-7 without IL and with Mcllvaine buffer at distinct pH by varying  $\text{Na}_2\text{HPO}_4$  concentration for 1 (yellow), 4 (orange) and 10 (red) wt % of surfactant. (III and IV) Cloud points at 4 and 10 wt % of Tergitol 15-S-7: (medium green) in Mcllvaine buffer at distinct pH values and (gray) in water at the same pH.

negative for SDS and an anionic SAIL as shown in Figures 7.V) and 7.VI). Thereby, the SAILS seem to be incorporated into the micelles and confer them a charge according to the SAIL ionic nature.

Finally, a  $\zeta$  potential measurement for  $[\text{N}_{2,2,2,2}]\text{Br}$  as the IL was carried out in order to confirm the hypothesis that this IL acts merely as an electrolyte. The fact that we were not able to measure any surface charge for the micelles formed in the presence of this compound supports this hypothesis.

Herein, we have also studied the micelle size changes induced by the various nonionic surfactants investigated in this work. The results were analyzed assuming spherical micelles whose diameters, in nm, are presented in Figure 8.

When the three nonionic surfactants are compared, it can be observed that Tergitol 15-S-9 forms the smallest micelles. This may be a result of its higher HLB value as it has already been reported that, for surfactants belonging to the same series, the surfactant with higher HLB values will display smaller micelles.<sup>38</sup>

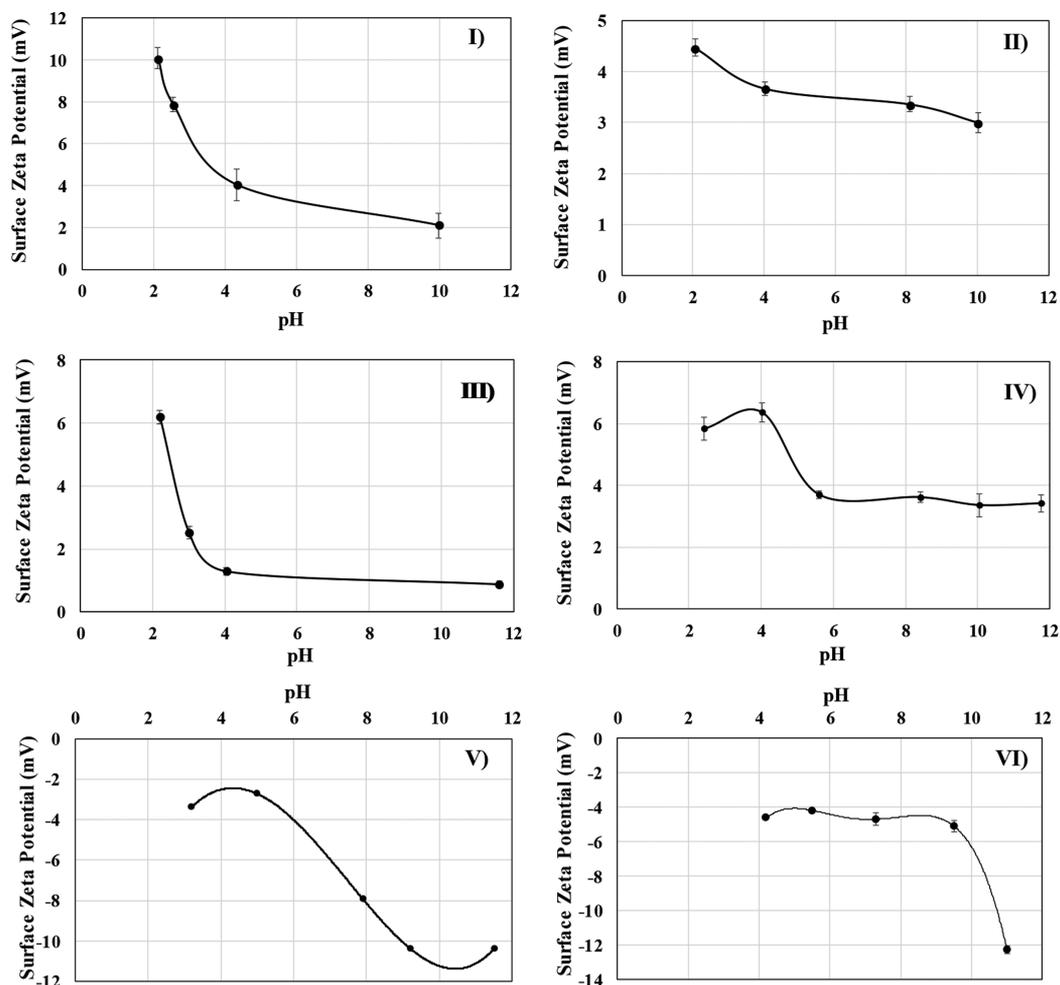
For the systems with SAILS, two distinct behaviors were observed: either a slight decrease in micelle size or micellar growth induced by the SAILS, as shown in Figure 8. These two behaviors correlate well with the effect upon the cloud points. The compounds that increase the cloud point decrease the micelle size, while those that decrease the cloud point of the nonionic surfactant induce a significant micellar growth. The decrease in size of the micelles in the presence of ionic surfactants has been previously reported<sup>45</sup> and it seems to be due to a decrease in the aggregation number of the micelles. The original nonionic micelles break up when the SAIL is added and new SAIL/nonionic micelles reform with smaller number of total molecules due to the onset of headgroup electrostatic repulsions brought about by the ionic nature of the SAIL. The opposite behavior, leading to a substantial increase of the micelles was not previously reported, as this is the first time that an ionic surfactant is observed to induce a decrease of the cloud point of a nonionic

surfactant. This increase, that may result in the loss of sphericity of the micelles, is very relevant for cloud point extractions by AMTPS since the larger micelles may become able to more easily accommodate biomacromolecules (e.g., proteins) inside.

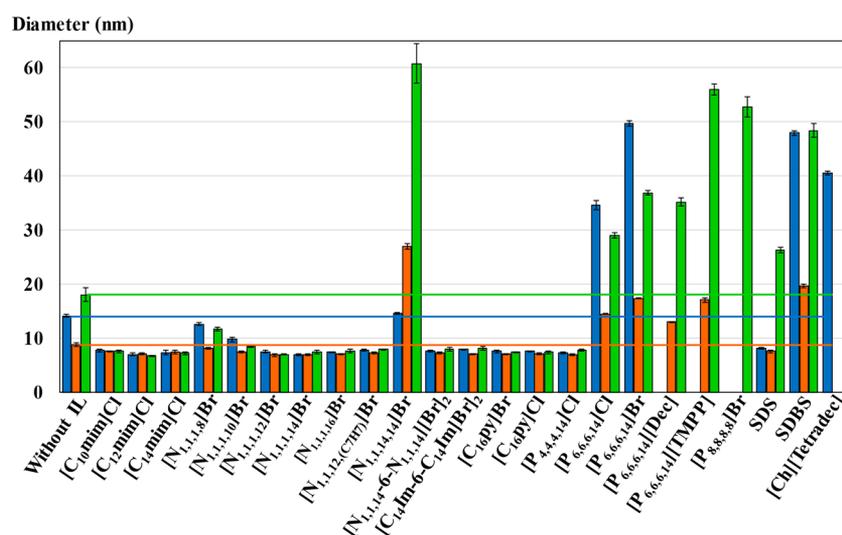
The behavior here observed is in line with the interpretation based on the SAILS CPP, described in section 3.1. The SAILS influence the micelle size and shape through the effective  $a_0$  or  $v_h$  when they mix with the nonionic surfactant. Quaternary ammonium and imidazolium surfactants with charged headgroup present a  $\text{CPP} < 1/2$ , causing an increase in the effective  $a_0$  in the mixed micelle, due to the combined effect of their conical shape and headgroup electrostatic repulsions. As a result, the CPP decreases hence promoting a decrease in micellar size (as observed) and this typically leads to an increase in solubility and consequently in cloud point.  $[\text{P}_{4,4,4,14}]\text{Cl}$  seems to behave similarly.

On the other hand, the incorporation of bulky hydrophobic SAILS, such as  $[\text{P}_{6,6,6,14}]\text{X}$  ( $\text{X} = \text{Cl}^-$ ,  $\text{Br}^-$ ,  $[\text{Dec}]^-$ ,  $[\text{TMPP}]^-$ ), or  $[\text{P}_{8,8,8,8}]\text{Br}$  ( $\text{CPP} \geq 1$ ) increases the effective  $v_{hc}$  in the mixed micelles and hence induce substantial micellar growth. This is also the case of the double-chained surfactants  $[\text{N}_{1,1,14,14}]\text{Br}$  and  $[\text{N}_{1,1,16,16}]\text{Br}$ , with  $\text{CPP} \approx 1$ , known to form bilayer aggregates (vesicles and lamellar phases). Micellar growth in nonionic surfactant systems leads to a poorer solubility in water and a decrease in cloud point.

Owing to the fact that  $[\text{N}_{1,1,1,8}]\text{Br}$  and  $[\text{N}_{1,1,1,10}]\text{Br}$  are below their CMC, their size appears to be intermediate between the IL-free system and a mixed micelle with the more hydrophilic SAILS. Therefore, and similarly to what was done for the cloud points, a mixture point using Tergitol 15-S-7 was prepared with both SAILS at 2 wt %. The DLS results show that these ILs are indeed able to reduce the size of the micelles like the other SAILS when their concentration is above the CMC, displaying diameters of around 6 and 9 nm for  $[\text{N}_{1,1,1,8}]\text{Br}$  and  $[\text{N}_{1,1,1,10}]\text{Br}$ , respectively.



**Figure 7.**  $\zeta$  potential for SAILs belonging to distinct families, namely (I)  $[P_{6,6,6,14}]Cl$ , (II)  $[C_{16}py]Cl$ , (III)  $[P_{4,4,4,14}]Cl$ , (IV)  $C_{12}mimCl$ , (V)  $[Ch][Tetradec]$ , and (VI) SDBS. Each system contains 10 wt % of Tergitol 15-S-7 and 0.3 wt % of a SAIL.

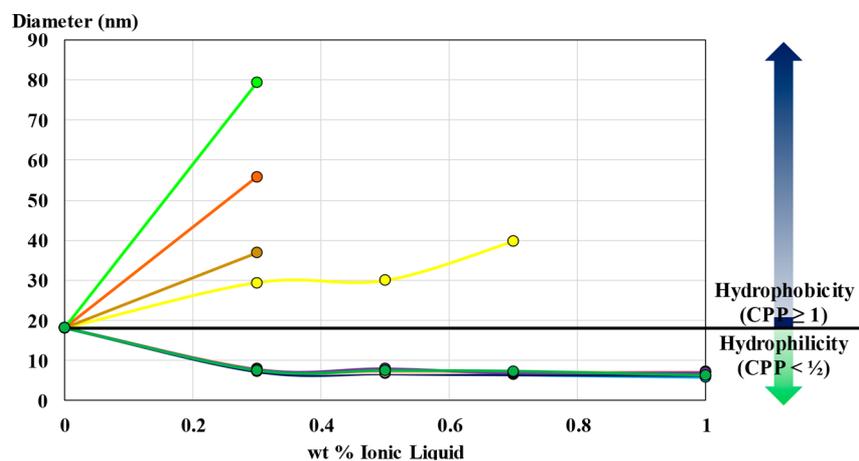


**Figure 8.** Micelles size for (blue) Tergitol 15-S-7, (orange) Tergitol 15-S-9, and (green) Tergitol NP-10. The systems without IL are composed of 1 wt % of surfactant and McIlvaine buffer pH 7.0 and the mixed systems are constituted by 1 wt % of surfactant, 0.3 wt % of IL and McIlvaine buffer pH 7.0.

For the mixed systems containing of  $[P_{6,6,6,14}][TMPP]$  and  $[P_{6,6,6,14}][Dec]$ , it was not possible to determine the diameter of a single micelle for Tergitol 15-S-7 since the system was already slightly turbid. The micelle diameter of the mixed systems with

$[P_{8,8,8,8}]Br$  was also not determined for the Tergitol 15-S-series for the same reason.

Regarding the impact of the IL concentration on the micelle size (Figure 9 and Figure S2), we can observe the same tendency



**Figure 9.** Effect of the IL concentration on the micelles size for the 1 wt % Tergitol NP-10 solution: (gray) system without IL; (light blue)  $C_{10}\text{mimCl}$ ; (dark blue)  $C_{14}\text{mimCl}$ ; (dark green)  $[C_{16}\text{py}]\text{Cl}$ ; (brown)  $[P_{4,4,4,14}]\text{Cl}$ ; (yellow)  $[P_{6,6,6,14}]\text{Cl}$ ; (light purple)  $[P_{6,6,6,14}]\text{Br}$ ; (orange)  $[P_{6,6,6,14}][\text{TMPP}]$ ; (purple)  $[N_{1,1,1,16}]\text{Br}$ ; (light green)  $[N_{1,1,1,14}]\text{Br}$ .

previously discussed for the cloud points. For 1 wt % of Tergitol NP-10 (the surfactant for which more SAILs could be studied), it was observed that the increase in the IL concentration lead to a further micellar growth for the most hydrophobic SAILs since they display a high CPP. Regarding the more hydrophilic SAILs, this concentration increase does not seem to affect much the micelle size that are already at their lowest value with just 0.3 wt % of SAIL. For Tergitol 15-S-7 (Figure S2) the increase in the IL concentration enhances even more the effect already observed for the two types of SAILs.

#### 4. CONCLUSIONS

The effect of SAILs upon the cloud points for systems of three nonionic surfactants, namely Tergitol 15-S-7 and 15-S-9 and Tergitol NP-10, were studied. The results show the cloud points to be significantly influenced by the IL incorporation into the micelles, even at concentrations as low as 0.3 wt % (5–10 mM). Interestingly, both increases and, for the first time, decreases of the cloud points were observed, depending on the nature of the SAIL added to the system. We highlight here that according to the literature, the typical effect of conventional ionic surfactants is the dramatic increases in cloud points, while lowerings have only been observed in the case when simple electrolyte was also added; herein no simple electrolyte is needed, as the hydrophobic SAILs cause *per se* this effect.

Overall the effects on the cloud points, the DLS and  $\zeta$  potential data allow us to postulate some general trends. SAILs belonging to the imidazolium, ammonium (with only one long alkyl chain) and pyridinium families, being charged and with  $\text{CPP} < 1$ , induce the formation of smaller mixed micelles, promote water–headgroup interactions and thus increase the system cloud points. On the other hand, the phosphonium-based SAILs and ammonium with two long alkyl chains, despite being charged, have a  $\text{CPP} \geq 1$  and hence confer a more hydrophobic micellar environment; this causes micellar growth, weakened headgroup–water interactions, and a decrease in the cloud point. These two distinct behaviors are even more pronounced with the increase of the SAIL concentration.

#### ■ ASSOCIATED CONTENT

##### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jpcc.7b02972.

Table with McIlvaine buffer composition, figure with the binodal curves of Tergitol surfactants in absence of SAILs, figure with the effect of the SAIL concentration on the micelles size of 10 wt % Tergitol 15-S-7 solutions, and figure with dependency of the cloud points of the 4% solution of Tergitol 15-S-7 with 0.3% SAIL on the hydrophobicity of the SAILs (PDF)

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##### Notes

The authors declare no competing financial interest.

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#### ■ ABBREVIATIONS

AMTPS, aqueous micellar two-phase systems; CMC, critical micellar concentration; CPP, critical packing parameter; DLS, dynamic light scattering; EO, oxyethylene; HLB, hydrophilic–lipophilic balance; LCST, lower critical solution temperature; NMR, nuclear magnetic resonance; SAILs, surface active ionic liquids;  $T_m$ , melting temperature

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