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Partition Coefficients of Alkaloids in Biphasic Ionic-Liquid-Aqueous Systems and their Dependence on the Hofmeister Series

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The aim of this work is to test the potential of hydrophobic phosphonium-based ionic liquids for the extraction of caffeine and nicotine from aqueous phases through the determination of the alkaloids' partition coefficients. It was found that the caffeine partitioning for the ionic-liquid-rich phase increases with the ionic liquid hydrogen-bonding accepting capability (or water content), while for nicotine a nearly opposite behavior was observed. In addition, both the influence of the ionic concentration of the aqueous solution (ranging from 0.0 mol · kg^{-1} to 3.0 mol · kg^{-1}), and the salt nature (with K- and Na-based salts), in the partitioning of caffeine for the ionic-liquid-rich phase were investigated. The influence of the inorganic salt nature in the alkaloid partitioning for the ionic-liquid-rich phase closely follows the Hofmeister series.

INTRODUCTION

In the past few years, ionic liquids (ILs) have become a hot topic of research in the chemical, biotechnological, and chemical engineering fields. Ionic liquids are salts with melting temperatures well below to those displayed by inorganic salts, and are at the liquid state at temperatures near or at room temperature—the replacement of at least one high charge density ion by an organic and more complex one typically reduces the melting temperature of the salt. Due to the intrinsic ionic character of ionic liquids, they present negligible vapor pressures at ambient conditions (1,2), and are therefore excellent candidates for the replacement of ordinary volatile organic solvents used in various extraction techniques. Moreover, ionic

liquids—by the proper choice of the ions that compose them—allow the tailoring of their physical/chemical properties, and hence of their solvation ability for distinct compounds. Most of these liquid salts are nano-structured fluids, that is, they are composed of a polar network (comprising the high charge-density regions of the ions) and apolar regions (commonly constituted by alkane-type moieties). These distinct domains allow the accommodation of different solutes in the bulk of the ionic fluid (3–5). This feature of ionic liquids distinguishes them from the majority of molecular solvents, and coupled to their improved physical properties, has prompted research towards their use as novel extractive phases.

Ionic liquids have the flexibility to be designed either as hydrophobic or as hydrophilic fluids. Hydrophobic ionic liquids usually form ionic-liquid-water two phase systems due to their immiscibility with aqueous media. They are generally constituted by fluorinated ions or by ions with long alkyl side chains (6–8). On the other hand, hydrophilic ionic liquids are miscible with water and cannot be directly used in liquid-liquid extractions from aqueous environments. In this context, hydrophilic ionic liquids have been investigated as constituents of ternary mixtures composed of an ionic liquid, an inorganic salt, and water, aiming at forming aqueous biphasic systems (9–11). Besides the large interest devoted to ionic-liquid-based aqueous biphasic systems as improved extractive routes (12–19), the use of hydrophobic ionic liquids as extractive phases was seldom explored (20–27), since the partition coefficients of common solutes are consistently lower for biphasic systems composed of hydrophobic ionic liquids (12,27). Two recent reviews regarding this topic are available on literature (28,29). Nevertheless, from a fundamental point of view, hydrophobic ionic liquids are particularly valuable to gather further insights on the partitioning of the solutes and to understand the phenomenon responsible for the

migration of the solutes for a specific phase. In aqueous biphasic systems, the presence of an inorganic salt (usually a strong salting-out species) can mask the results, and the interpretation of the partitioning phenomenon is more complex.

In this work we investigated the extraction of alkaloid solutes from aqueous solutions using phosphonium-based ionic liquids as extractive solvents. Among the various hydrophobic ionic liquids available, long chain phosphonium-based compounds present a low solubility in water and enhanced capability for the selective separation of ethanol-water mixtures (26–31), and further advantages over their imidazolium- and pyridinium-counterparts. Phosphonium-based ionic liquids are thermally more stable and the kinetics of the salt formation is faster (32). In addition, phosphonium-based salts do not have acidic protons, and are thus more stable towards nucleophilic and alkaline conditions (32). These ionic liquids are also less expensive, and have been used at an industrial scale (33,34). Two-phase systems composed of phosphonium-based ionic liquids and water have shown to be successful in the extraction of short chain organic acids (L-lactic, L-malic, and succinic acids) (22,23,35). Furthermore, aqueous two-phase systems composed of hydrophilic phosphonium-based ionic liquids, K_3PO_4, and water were also investigated in the extraction of amino acids, colorants, and alkaloids (14). To the best of our knowledge, no further reports were found in the literature regarding the extraction of added-value products from aqueous phases making use of phosphonium-based ionic liquids.

In the present study, two alkaloids, caffeine and nicotine, whose molecular structures are depicted in Fig. 1, were used to assess the potential of phosphonium-based ionic liquids as extractive phases for biomolecules. Both caffeine and nicotine are well known botanical insecticides (36–38). Nicotine, 1-methyl-2(3-pyridyl)pyrrolidine, is a major alkaloid found in tobacco plants. However, the high nicotine mammalian toxicity ($LD_{50} = 50\,mg \cdot kg^{-1}$) has been a major drawback when considering the high risks involved during its extraction, handling, and application in the field (36). Still, nicotine mammalian toxicity could be reduced when formulated as emulsions, since emulsifiers and stabilizers that adsorb at the oil-water interface could act as shielding
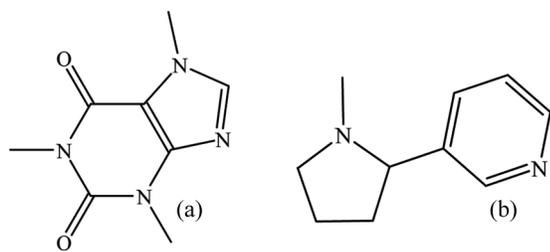
barriers (36). High-performance liquid chromatography (HPLC) (39–40), capillary electrophoresis (41), and gas chromatography (GC) methods (42,43) have been reported for the analysis of nicotine and its metabolites in tobacco leaves. Nevertheless, most methods employed are expensive, make use of environmentally harmful volatile organic solvents for the extraction step, and require complex and time-consuming extraction procedures. Caffeine, an alkaloid of the methylxanthine family, 1,3,7-trimethylxanthine, is naturally produced by a number of plant species, including coffee, tea, maté, and guaraná. Caffeine acts as a chemical defense in these plants since it presents repellent or toxicant properties. More complex formulations, such as those composed of caffeine and fatty acids increases the caffeine insecticide activity (38) due to the formation of complexes that result from the hydrogen-bonding between the carboxylic acid and the caffeine imidazole ring (44). The current and commercially available methods for extracting caffeine (for instance, for decaffeinating black tea) are solvent-based extraction techniques that use ethyl acetate, methylene chloride, or supercritical carbon dioxide (45,46). For uses other than human consumption, the extraction of caffeine from aqueous solution is carried out with chloroform and methylene chloride solvents (47). Caffeine is usually quantified with spectroscopic or mass spectrometry methods, such as the Fourier Transform Infrared (FTIR) spectroscopy (48), HPLC with UV detection (49), liquid chromatography-tandem mass spectrometry (50), and planar chromatography coupled with electrospray ionization mass spectrometry (51).
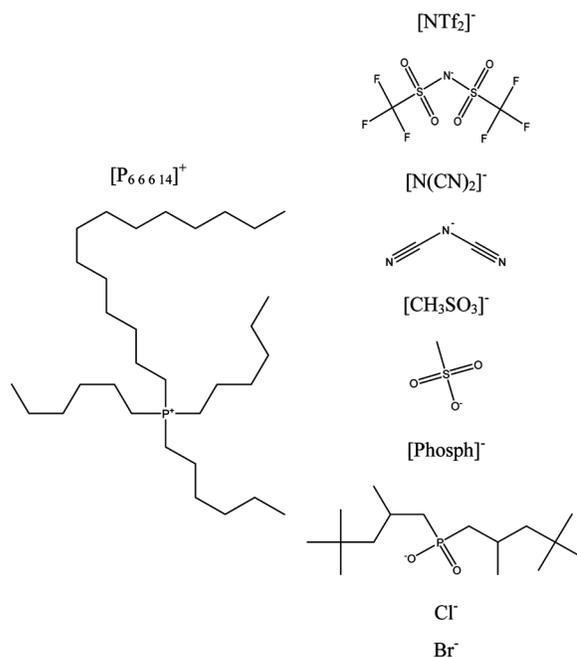

FIG. 2.   Ionic structures of the [$P_{6\ 6\ 6\ 14}$]-based ionic liquids used as extractive phases.

FIG. 1.   Molecular structures of caffeine **(a)** and nicotine **(b)**.

The partition coefficients of caffeine and nicotine, between phosphonium-based ionic liquids and aqueous systems, were determined at 298.15 K. The influence of the ionic liquid anion in the partition coefficients was investigated making use of the common tetradecyltrihexylphosphonium cation combined with the following anions: bis(trifluoromethylsulfonyl)imide, dicyanimide, methanesulfonate, bis(2,4,4-trimethylpentyl)phosphinate, bromide, and chloride – ionic structures depicted in Fig. 2. To gather additional insights into the influence of inorganic salts towards the partition coefficients (Hofmeister series dependence (52–54)), as well as on the ionic concentration (ranging from $0.0 \, \text{mol} \cdot \text{kg}^{-1}$ to $3.0 \, \text{mol} \cdot \text{kg}^{-1}$ of salt), a large range of potassium- and sodium-based salts was employed.

EXPERIMENTAL
Materials

The partitioning solutes, nicotine (with nominal purity $\geq 99 \, \text{wt}\%$) and caffeine, (with nominal purity $\geq 98.5 \, \text{wt}\%$) were obtained from Sigma-Aldrich and Marsing & Co. Ltd., respectively. Both alkaloids were used without further purification. Their chemical structures are shown in Fig. 1.

The partition coefficients of caffeine and nicotine between the ionic-liquid-rich and aqueous-rich phase were determined with the following ionic liquids: tetradecyltrihexylphosphonium bis(trifluoromethylsulfonyl)imide, $[P_{6\ 6\ 6\ 14}][Ntf_2]$ (mass fraction purity $>98\%$); tetradecyltrihexylphosphonium bromide, $[P_{6\ 6\ 6\ 14}]Br$ (mass fraction purity ≈ 96–98%); tetradecyltrihexylphosphonium chloride, $[P_{6\ 6\ 6\ 14}]Cl$ (mass fraction purity ≈ 93–95%); tetradecyltrihexylphosphonium methanesulfonate $[P_{6\ 6\ 6\ 14}][CH_3SO_3]$ (mass fraction purity ≈ 98–99%); tetradecyltrihexylphosphonium dicyanimide, $[P_{6\ 6\ 6\ 14}][N(CN)_2]$ (mass fraction purity $\approx 97\%$), and tetradecyltrihexylphosphonium bis(2,4,4-trimethylpentyl)phosphinate $[P_{6\ 6\ 6\ 14}][Phosph]$ (mass fraction purity $\approx 93\%$). The halides (whenever impurities) mass fraction content is $< 10^{-3}$ for all samples. All ionic liquids were kindly provided by Cytec Industries Inc. All ionic liquid samples were initially purified by repeatedly washing them with ultra pure water (under constant stirring) as previously described (55). After removing the aqueous-rich phase, the samples were additionally dried and purified under high vacuum ($10^{-3} \, \text{Pa}$) and moderate temperature (343 K) for at least 48 h. At this stage, the water mass fraction content for all the studied ionic liquids, determined with a Metrohm 831 Karl–Fischer coulometer, was $< 12 \times 10^{-4}$. The purity of each phosphonium-based ionic liquid was evaluated, after both purification steps, by ^{31}P, ^{1}H, ^{13}C, and ^{19}F NMR spectra. The final purity of all ionic liquids was confirmed to be $>99 \, \text{wt}\%$ (55). The ionic structures of the tetradecyltrihexylphosphonium-based ionic liquids are displayed in Fig. 2.

The water used for equilibration was double distilled, passed by a reverse osmosis system, and further treated with a MilliQ plus 185 water purification apparatus.

The salts used to prepare the aqueous-rich phases where potassium- or sodium-based, viz. KCl ($\geq 99.5 \, \text{wt}\%$ from Pronalab), KPF_6 ($\geq 98.0 \, \text{wt}\%$ from Fluka), $K_2Cr_2O_7$ ($\geq 99.5 \, \text{wt}\%$ from Panreac), K_3PO_4($\geq 98.0 \, \text{wt}\%$ from Sigma-Aldrich), KNO_3 ($> 98 \, \text{wt}\%$ from Panreac), KH_2PO_4 ($\geq 99 \, \text{wt}\%$ from Panreac), KCH_3CO_2 ($\geq 99 \, \text{wt}\%$ from Riedel-de Haën), NaCl ($\geq 99.9 \, \text{wt}\%$ from Normapur), $NaCH_3SO_3$ ($\geq 98 \, \text{wt}\%$ from Sigma-Aldrich), Na_2SO_4 ($> 99.8 \, \text{wt}\%$ from LabSolve), Na_2CO_3 ($\geq 97.7 \, \text{wt}\%$ from Carlo Erba), $NaHSO_4$ ($\geq 97 \, \text{wt}\%$ from Panreac), and $NaBF_4$ ($\geq 98 \, \text{wt}\%$ from Fluka).

Experimental Procedure

Aqueous solutions of caffeine and nicotine at 5.0×10^{-2} and $6 \times 10^{-2} \, \text{mol} \cdot \text{dm}^{-3}$, respectively, were prepared and used in the equilibrium with each ionic-liquid-rich phase at a volume ratio of 1:1 ($2.00 \, \text{cm}^3$ of each phase). Aqueous solutions of each salt were gravimetrically prepared (within $\pm 10^{-4} \, \text{g}$) in the concentration range from (0.0 to 3.0) $\text{mol} \cdot \text{kg}^{-1}$ (or to the upper limit of the salt solubility in water at 298 K). The biphasic solution was left under moderate agitation for 4 h at 298.15 (± 0.01 K) to facilitate the partitioning of the alkaloids between the two phases. The temperature was maintained by means of an air oven (with a PID temperature controller driven by a calibrated Pt100 (class 1/10) temperature sensor inserted in an aluminum block) (6–8). After stirring, the samples were centrifuged during 20 min at 4500 rpm to completely separate both phases, and placed again in the thermostatized oven for 30 min (without agitation) to avoid partitioning deviations that could merely be a result of small temperature differences. After this period, the two phases were separated and the alkaloids quantification was carried out by UV spectroscopy, using a SHIMADZU UV-1700 Pharma-Spec Spectrometer, at the wavelengths of 261 and 274 nm (maximum absorption peaks of nicotine and caffeine, respectively) and making use of previously established calibration curves. Possible interferences of the inorganic salt and of the ionic liquid with the analytical method were taken into account and found to be of no significance at the used dilution regime. At least 4 samples of the aqueous phases of each aqueous-IL mixture were quantified, and the respective standard deviations were determined.

The partition coefficients of caffeine and nicotine were determined as the ratio of the concentration of each alkaloid in the IL and in the aqueous-rich phase – as described below,

$$K_{\text{caf}} = \frac{[\text{caf}]_{\text{IL}}}{[\text{caf}]_{\text{aq}}} \qquad (1)$$

$$K_{nic} = \frac{[nic]_{IL}}{[nic]_{aq}} \qquad (2)$$

where K_{caf} and K_{nic} are the partition coefficients of caffeine and nicotine, respectively, $[caf]_{IL}$ and $[nic]_{IL}$ are the concentration of each alkaloid in the IL-rich phase, and $[caf]_{aq}$ and $[nic]_{aq}$ are the concentration of each alkaloid in the aqueous phase.

The phosphonium-based biphasic systems present a top layer that corresponds to the ionic-liquid phase while the bottom is the aqueous phase. The only exception was the [Ntf$_2$]-based system, where an inversion of the phases was observed—a consequence of the high density of the fluorinated anion (55).

RESULTS AND DISCUSSION

The experimental partition coefficients of caffeine and nicotine, at 298.15 K and at atmospheric pressure, between [P$_{6\ 6\ 6\ 14}$]-based ionic liquids and water are presented in Fig. 3. The numerical experimental data and associated standard deviations are given as supporting information.

The success of an extractive system depends on the ability to manipulate the properties of each phase, with the objective of obtaining adequate partition coefficients and a high selectivity for specific solutes. The caffeine partitioning for the ionic-liquid-rich phase increases in the following anion order ([P$_{6\ 6\ 6\ 14}$]-based ionic liquids): [Ntf$_2$]$^-$ < [N(CN)$_2$]$^-$ < [CH$_3$SO$_3$]$^-$ < [Phosph]$^-$ ≈ Br$^-$ < Cl$^-$. On the other hand, the partitioning of nicotine follows a nearly opposite pattern, increasing in the order of [P$_{6\ 6\ 6\ 14}$]-based fluids: Cl$^-$ < Br$^-$ < [CH$_3$SO$_3$]$^-$ < [Ntf$_2$]$^-$ ≈ [Phosph]$^-$ < [N(CN)$_2$]$^-$. As a result, it is shown that the choice of ionic liquids composed of different anions proved to have a

great influence towards the partition coefficients of the alkaloids, as also previously observed with the extraction of organic acids (35).

Caffeine partitions preferentially to ionic liquids with an enhanced hydrophilic character, while nicotine partitions to those that are more hydrophobic. This feature mirrors that of the affinity of both alkaloids for organic-rich or aqueous-rich phases. Octanol-water partition coefficients (K_{ow}) for caffeine and nicotine are, respectively, 0.85 and 14.79 (56), corroborating thus the preferential affinity of caffeine for aqueous phases and of nicotine for organic phases. Although both alkaloids are water soluble (in a limited range), the methyl-pyrrolidine ring of nicotine contributes to a less-polar character and its affinity for organic phases, while the caffeine purine ring, with two attached oxygen atoms, enhances the alkaloid polarity and, therefore, to its lower affinity for organic fluids. The results obtained in this work are in good agreement with a previous work reported by us (15) where the partition coefficients of both alkaloids were investigated in ionic-liquid-based aqueous biphasic systems. Nicotine also presented an enhanced affinity for fluorinated ionic liquids or those composed of more hydrophobic anions (15). Nevertheless, it should be remarked that in such work (15), only hydrophilic imidazolium-based ionic liquids were used combined with a strong salting-out species (K$_3$PO$_4$).

Taking into account the molecular structures of the alkaloids depicted in Fig. 1, and of the [P$_{6\ 6\ 6\ 14}$]-based fluids displayed in Fig. 2, the partitioning of caffeine and nicotine between the aqueous phase and the ionic-liquid-rich phase seems to be ruled by different factors including:

i) hydrogen-bonding interactions between the non-bonding electron pairs present in the oxygen and nitrogen atoms of the alkaloids and the ionic liquid anions;
ii) dispersive type interactions between alkyl groups of the alkaloids and the long alkyl side chains of the phosphonium-based cation.

From the results shown in Fig. 3, it seems that the hydrogen-bonding interactions play a dominant role. The quaternary-phosphonium-based ionic liquids investigated show four alkyl chains and no aromatic character, which is in turn responsible for their lower affinity for aqueous phases (30). Their water miscibility derives essentially from the polar water hydrogen bonding to the anions (30,55). Therefore, the water solubility in the studied ionic liquids was also represented in Fig. 3. Figure 3 shows that there is a close relationship between the partition coefficients values and the water solubility in the neat ionic liquids. For a similar cation, the partition coefficient of caffeine, a hydrophilic solute, increases with the increase of the water content in the ionic liquid, and hence with the hydrogen-bond accepting capability of the ionic liquid anion. On the other hand, a nearly opposite behavior is
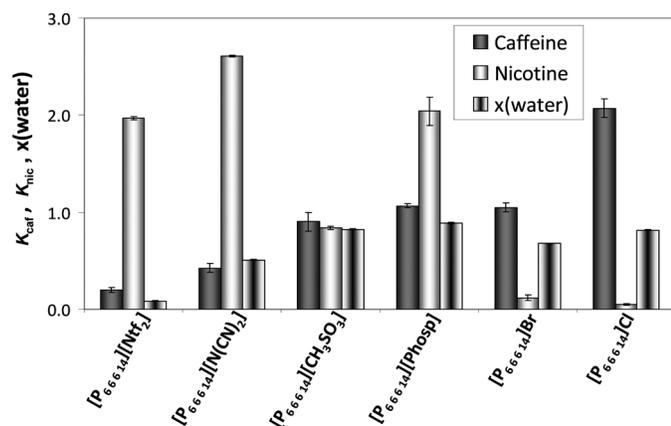

FIG. 3. Partition coefficients of caffeine (K_{caf}) and nicotine (K_{nic}) between the [P$_{6\ 6\ 6\ 14}$]-based ionic liquids and water at 298.15 K, and mole fraction solubility of water (x(water)) in the pure ionic liquids (30,55) at 298.15 K.

observed with the partitioning of nicotine—a more hydrophobic solute with lower hydrogen-bonding ability. The main exceptions to this pattern were verified with the extraction of nicotine using the ionic liquids $[P_{6\,6\,6\,14}]$ $[N(CN)_2]$ and $[P_{6\,6\,6\,14}][Phosph]$. In these cases other phenomena in the partitioning behavior, probably related to the flexibility or mobility of the anions, should be also involved and result in a more complex scenario.

It is well accepted that the ionic strength of the aqueous solutions influences the partitioning of solutes. The effect of salts on the aqueous solubility of charged molecules, such as proteins, has been well described for many years (52). The qualitative order of the ions' salting-in/salting-out inducing ability on macromolecules is known as the Hofmeister series (52). The solutes' migration can be tailored for one phase (or another) by the addition of salting-in or salting-out salts. Aiming at achieving a deeper understanding of the underlying molecular phenomena controlling the solutes partitioning, particularly regarding the interactions between water and ionic liquids, between ionic liquids and salts, and between ionic liquids and the alkaloids, several sodium- and potassium-based salts were employed as major constituents of the aqueous phases. Anions are typically more polarizable than cations since they present a more diffuse valence electronic configuration (53). Thus, the anions' hydration is usually stronger than that of cations and, as a result, their salting-in/salting-out effects are more pronounced. For this reason, two cations (Na^+ and K^+) were combined with a large set of anions. The obtained partition coefficients of caffeine between $[P_{6\,6\,6\,14}]Br$ and distinct aqueous salt solutions, at 298.15 K, are depicted in Figs. 4 and 5. The partition coefficient values and respective standard deviations are reported in Supporting Information.
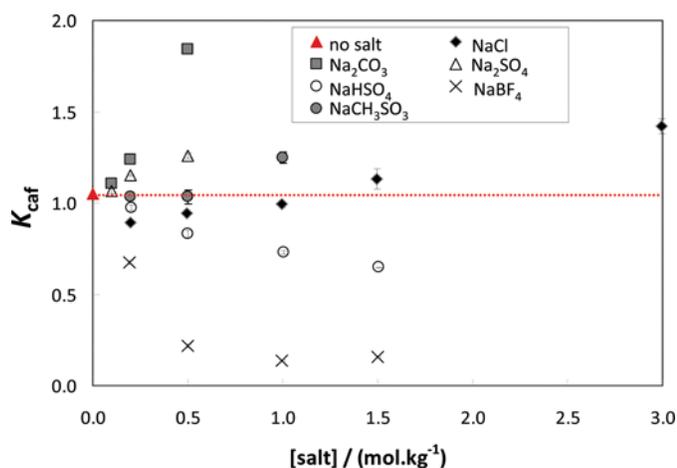

FIG. 5.   Partition coefficients of caffeine (K_{caf}) between the $[P_{6\,6\,6\,14}]Br$ and various K-based salt aqueous phases as a function of the salt concentration at 298.15 K. (Color figure available online)
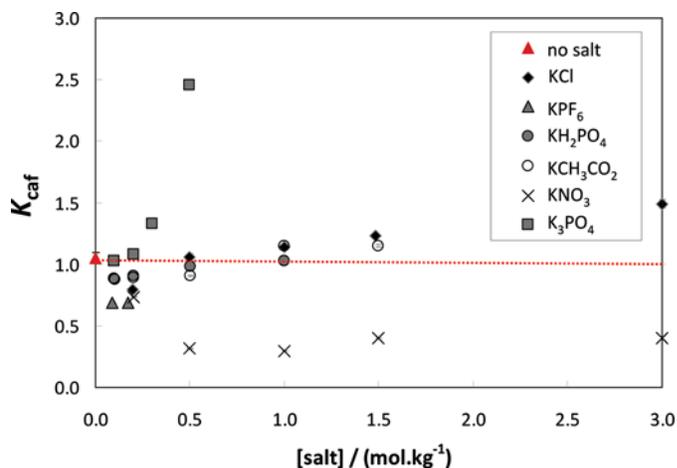
Recently, we have proposed that the salting-in phenomenon results from the direct ion binding of the low charge density ions to hydrophobic moieties while the salting-out effect is a direct consequence of an entropic effect resulting from the preferential formation of water-ion hydration complexes (which further causes the dehydration of the solute and the increase of the surface tension of the cavity) (53,54). Therefore, in this work, salting-out inducing salts will tend to form hydration complexes and to decrease the hydrogen bond ability between water and caffeine, and thus, the partitioning coefficients for the ionic-liquid-rich phase will increase. On the contrary, salting-in inducing salts will interact with the hydrophobic moieties of caffeine (and/or of the ionic liquid) leading to a decrease in the partition coefficients of the alkaloid for the ionic-liquid-rich phase.

In Figs. 4 and 5 both salting-in and salting-out phenomena of caffeine from aqueous solutions are observed. For the sodium-based salts, the partition coefficients of caffeine for the ionic-liquid-rich phase increase for the Na_2CO_3 and Na_2SO_4 salts (two strong salting-out agents), and also for NaCl and $NaCH_3SO_3$ at concentrations higher than $1.5\,mol \cdot kg^{-1}$. On the other hand, $NaHSO_4$ and $NaBF_4$ induce the caffeine salting-in for the aqueous phase, thus leading to a reduction of the partition coefficients. NaCl presents, however, a more complex behaviour inducing the salting-in of caffeine at the aqueous phase at low concentrations (below $1.5\,mol \cdot kg^{-1}$). An analogous effect was previously observed by us (53,54) for the solubility of ionic liquids in aqueous solutions of NaCl. Moreover, up to $0.5\,mol \cdot kg^{-1}$, the $NaCH_3SO_3$ salt has a marginal effect on the partition coefficients of caffeine.

For the potassium-based salts, K_3PO_4 was the strongest salting-out species investigated, while KCl and KCH_3CO_2

FIG. 4.   Partition coefficients of caffeine (K_{caf}) between the $[P_{6\,6\,6\,14}]Br$ and various Na-based salt aqueous phases as a function of the salt concentration at 298.15 K. (Color figure available online)

also lead to an increase of the caffeine partition coefficient at concentrations higher than $1.0 \, mol \cdot kg^{-1}$. KNO_3 and KPF_6 induce a monotonically decrease of the partition coefficient of caffeine, and are thus salting-in inducing salts. As observed with the sodium-based salts, the salting-in phenomenon (at low salt concentrations) followed by salting-out (at higher salt concentrations) were observed with the salts KCl, KCH_3CO_2 and KH_2PO_4.

The general trend on the salts' aptitude in increasing the caffeine partition coefficients is as follows (from salting-out to salting-in regimes): $K_3PO_4 > KCH_3CO_2 \approx KCl \approx KH_2PO_4 > KPF_6 > KNO_3$ and $Na_2CO_3 > Na_2SO_4 > NaCH_3SO_3 > NaCl > NaHSO_4 > NaBF_4$. In summary, both for Na- and K-based aqueous solutions, the partition coefficients of caffeine, in the presence of aqueous salt solutions, closely follow the Hofmeister series (53,54).

CONCLUSIONS

Ionic liquids are novel solvents with a rather specific blend of physical and solution properties that make of them interesting for a wide array of applications in separation science. Ionic liquids are good solvents for the most distinct species and can be tailored as polar or less polar phases by a proper selection of the ions that compose them. Hydrophobic ionic liquids can form biphasic systems with aqueous media and are thus suitable for use in liquid-liquid extractions.

In this work, the potential of hydrophobic ionic liquids for the extraction of alkaloids from aqueous systems was investigated. The partition coefficients of caffeine and nicotine between the ionic-liquid-rich and the aqueous-rich phases were determined with tetradecyltrihexylphosphonium-based ionic liquids combined with the anions bis(trifluoromethylsulfonyl)imide, methanesulfonate, dicyanimide, bis(2,4,4-trimethylpentyl)phosphinate, bromide, and chloride.

The partitioning of caffeine (a more polar compound) for the ionic-liquid-rich phases increases with the ionic liquid hydrogen-bonding accepting ability of the anion, that is, with the increase on the water content, while for nicotine (a less polar compound) a nearly opposite behavior was observed.

Aiming at tailoring the partition coefficients and to gain a broader picture on the effect of inorganic salts through the partitioning behavior, additional studies on the partition coefficients of the alkaloids with distinct aqueous salt solutions were performed. Both the salt nature and the aqueous solution ionic strength were investigated. The partition coefficients of caffeine undergo both salting-in and salting-out phenomena and the observed pattern closely follows the Hofmeister series.

ACKNOWLEDGEMENTS

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