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Exploring molecular and thermodynamic properties of zwitterions vs ionic liquids: A comprehensive computational analysis to develop advanced separation processes

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Abstract: Zwitterions ionic liquids (ZIs) are compounds in which both counterions are covalently tethered, conferring them with unique characteristics; however, most of their properties are still unknown, remaining a bottleneck to exploit practical applications. Herein, molecular and fluid properties of ZIs and their mixtures are explored by means of quantum chemical analysis based on density functional theory (DFT) and COSMO-RS method, and compared against homologous ILs, to provide a comprehensive overview on the effect of the distinct structures on their physicochemical and thermodynamic behavior. Overall, ZIs were revealed as compounds with higher polarity and stronger hydrogen bonding capacity, implying higher density, viscosity and melting point, and even lower volatility than structurally similar ILs. Phase equilibrium of binary and ternary systems support stronger attractive interactions between ZIs and polar compounds, whereas higher liquid-liquid immiscibility with non-polar compounds may be expected. Ultimately, the performance of ZIs in the wider context of separation processes is illustrated, while providing molecular insights to allow their selection and design for relevant applications.

Introduction

Ionic liquids (ILs) are a broad category of organic salts consisting entirely of ions, which present melting points below 100° C - although are typically liquid at room temperature - and display unique properties including negligible volatility, non-flammability, high ionic conductivity and thermal stability.[1] Additionally, their physicochemical properties can be fine-tuned by appropriate selection of the counterions structure, allowing the design of task-specific ILs for target applications. As a result of such exceptional properties, ILs are considered designer solvents for a variety of chemical and industrial processes,[2] including environmentally benign alternatives to conventional organic compounds in separation technologies. For instance, ILs have proved promising in gas absorption applications,[3] such as carbon capture [4] and acidic gas removal.[5] Ionic liquids have been proposed as sustainable solvents for extraction,[6] including as azeotrope breakers,[7] as separating agents in refinery related processes,[8] and for dissolution and recovery of bio-derived materials.[9] Other areas where ILs have gained increasing attention include organic synthesis and catalyst [10] as well as electrochemical applications and energy storage.[11] Recently, IL mixtures have been proposed as an efficient strategy to control the physicochemical properties and thermodynamic behavior of ILs containing systems; however, ion exchange upon mixing may affect their solution properties hindering their practical applications. [12]

Since Ohno and co-workers pioneered the synthesis of new zwitterionic-type molten salts (ZIs), in which cation and anion are tethered together in intramolecular form, hence avoiding the formation of undesired ion pairs, new avenues were opened for material design and applications.[13] In particular, they synthesized a series of imidazolium cations containing covalently-bounded anionic sites (i.e. sulfonate or sulfonamide groups) displaying remarkable ion conductive properties while preventing ion migration under the influence of electrical potential gradient. Moreover, these compounds acted as excellent ion conductive materials upon mixing with other salts, particularly lithium bis(trifluoromethanesulfonyl)imide (LiTFSI), for which were proposed as a medium for selective target ion transport.[14] This motivated further research on ZI/Li salt mixtures to better understand the role of the structural factors on relevant properties including ionic conductivity and Li transference numbers for electrochemical applications.[15] Furthermore, addition of ZIs to mixtures composed of ILs and Li salts was demonstrated to improve mass transport limitations, increasing the rate of lithium-metal deposition/dissolution while enhancing the reversibility of the process, which is promising in developing more efficient and safer rechargeable lithium-metal batteries.[16] Later studies were devoted to further explain the zwitterionic effects on IL/Li salts mixtures and their electrochemical properties for battery applications.[17]

Apart from their well reported use in electrochemistry, zwitterionic compounds have been also proposed as suitable additives for systematically controlling the water content of hydrophobic ILs,[18] setting the ground for novel enzymatic reactions and product separation processes of target water-soluble compounds including proteins. In particular, it has been reported that the saturated water content of the hydrophobic IL [bmim][NTf_2] can be modified by addition of suitable zwitterions (i.e. 3-(1-butyl-3-imidazolio)propanesulfonate, C4Im3S), accomplishing the dissolution and stabilization of model heme proteins such as Cytochrome *c* (cyt *c*); moreover, IL recycling and protein recovery was performed by addition of excess water. Having demonstrated the potential of ZI-water systems as efficient media for isolation of target compounds, the synthesis of new types of ZIs and their affinity with water was further studied. For instance, new hydrophobic phosphonium phosphonate-type ZIs displaying lower critical solution temperature (LCST) phase behavior were developed, in which the hydrogen bonding ability could be finely tuned by temperature-induced changes in the presence of water.[19] Afterwards, novel thermoresponsive systems consisting on a series of ammonium-based ZIs were proposed, where dynamic phase transitions showing both lower critical solution temperature (LCST) and upper critical solution temperature (UCST) behavior were accomplished by ZIs mixtures having suitable hydrophilicity–hydrophobicity balance over a narrow temperature range.[20] Such ZI-water mixtures showing unique characteristics may have great potential in interface science and could act as platform for dissolution and extraction of

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biomolecules and other valuable solutes. Recently, the ability of water soluble ammonium-based ZIs to form aqueous biphasic systems (ABS) in presence of salts have been reported,[21] showing a thermoreversible behavior at near room temperature that can be tuned from UCST to LCST by modifying the length of the ZI alkyl chains, which proved useful in the separation of amino acids mixtures. Lately, amino acid derived imidazolium-based and ammonium-based ZIs have been reported for the green synthesis of ILs via hydrothermal decarboxylation, with potential application as sustainable solvents in the Heck reaction and cellulose dissolution.[22]
Up to date, most research studies on zwitterionic materials focus on their physicochemical characterization, mainly thermal properties and conductivity,[13c, 23] melting point [24] and behavior in aqueous solution.[25] However, a comprehensive overview of relevant molecular and thermodynamic properties of zwitterions, as well as an illustrative comparison with their ionic liquid counterparts, still needs to be provided for a better understanding of the effect of their distinct structures on their physicochemical and thermodynamic performance. Likewise, as described above, the applications of zwitterionic compounds have been mainly limited to electrochemistry and design of thermoresponsive systems, with just a few proof of concept studies demonstrating their feasibility as separating agents of target bio-derived materials; however, the potential applications of zwitterionic-type molten salts in the wider context of relevant separation processes, including gas absorption, extraction of aromatic hydrocarbons and separation of azeotropic mixtures, need to be further explored. In this regard, the application of predictive tools that enable fast and reliable screening of solvents for specific applications is of great interest, for which quantum chemical calculations based on continuum solvation model have been widely used to model solvent effects and describe the intermolecular interactions of systems.[26] In particular, the quantum chemical approach COSMO-RS (Conductor like Screening MOdel for Real Solvents) developed by Klamt and co-workers,[27] which computes the screening charge density (σ) on the molecular surface as the basis to calculate the chemical potential (μ) of each specie in solution and derived thermodynamic properties, has been remarkably recognized as an efficient method to describe the equilibrium thermodynamics of fluids while providing molecular insights. Over the last years, the suitability of COSMO-RS to predict the performance of ionic liquid-type novel solvents has been broadly reported.[28] For instance, COSMO-RS has proven to be useful for predicting pure compound properties of ILs including densities [29] and polarities.[30] In addition, COSMO-RS has been successfully applied to understand the thermodynamic behavior of binary systems containing ILs for CO_2 capture,[31] NH_3 absorption[32] and separation of volatile organic compounds (VOCs);[33] to predict the phase equilibria of systems composed of alcohol-ILs [34] and water-ILs; [35] to describe the miscibility trends of IL mixtures; [36] to explain the thermodynamic properties of mixtures containing ILs and organic solvents; [37] and for the interpretation of the solvation behavior of biomolecules in ILs, such as cellulose, [38] alkaloids [39] or polyphenols.[40] Likewise, COSMO-RS has been used to compute the LLE and VLE of ternary systems involving ILs to separate petrochemical fractions with high commercial value, including olefins/paraffins [41] or aromatics/aliphatics,[42] as well as for modelling the solubility of CO_2 in toluene + IL mixtures to induce liquid phase split after extraction.[43] Recently, the ternary VLE data of systems containing alcohol + water + piperazine-based zwitterionic Good's buffer were predicted using COSMO-RS for the selection and design of suitable mass separating agents for azeotropic mixtures.[44]
Under this scenario, herein we propose the application of quantum chemical and COSMO-RS methods to unveil the mechanisms responsible of the distinct behavior of structurally homologous ILs and ZI compounds, while predicting important physicochemical and thermodynamic properties for target practical applications. Overall, this paper provides a further understanding of the molecular and thermodynamic behavior of zwitterions in comparison with their conventional ionic liquid counterparts, while proposing a comprehensive roadmap for developing advanced separation strategies based on novel ionic liquids and zwitterionic-type molten salts and materials.

Computational details:

-*Quantum chemical calculations:* ZIs and ILs geometries were optimized using Turbomole v.7.1 [45] software. A molecular model of ion-pair was selected to describe de IL compounds [31b]. Optimizations were carried out using COSMO solvation model [46] and DFT calculations with B88-P86 (bp) [47] functional and TZVP basis set with RI approximation.[48] Vibrational frequencies were calculated to ensure the existence of a minimum of electronic energy. As a result of this calculation, a COSMO file is created with energies, geometries and polarized charge of the σ-surface. Gas-phase (energy) files needed to estimate gas properties with COSMO-RS were created at the same computational approach but using gas-phase environment instead of COSMO solvation model.
Dipole moments and NMR data were calculated using Gaussian v09 E.01 [49] software. In this case, single point DFT calculations using previously optimized geometries were carried out at B3LYP/6-311++G** computational level. NMR calculations were performed using GIAO method and TMS B3LYP/6-311+G** GIAO reference is used to analyze and compare NMR experimental data.
-*COSMO-RS calculations:* COSMO and Energy files created by TURBOMOLE were used by COSMOtherm C30_1601 software [50] to perform COSMO-RS calculations using BP_TZVP_C30_1601 parametrization. COSMO-RS theory [27, 46, 51] was used to predict the thermodynamic properties of the systems involving ZIs and ILs at 25 ºC: vaporization enthalpy of neat compounds and activity coefficients, excess properties and liquid-liquid equilibria of the studied solutions. In addition, COSMO-RS method provides the contributions of the different intermolecular interactions [hydrogen bond (HB), polar-misfit (MF) and van der Waals (vdW)] to the excess enthalpy of the studied mixtures, allowing the analysis of the ZI/IL system behavior from a molecular point of view. Density and viscosity calculations were performed using the QSPR approaches implemented by default in COSMOtherm, which uses COSMO-based descriptors.[50]

Results and discussion

Pure compound analysis

-*Molecular structures:* Table 1 collects the optimized molecular structures of a representative sample of zwitterionic compounds synthesized by different authors.[13c, 18-20, 23-24] These ZIs - presenting remarkable structural differences and a variety of functional groups- were selected with the aim of covering a wide range of molecular and solvent properties.

Table 1. Zwitterions and ionic liquids structure

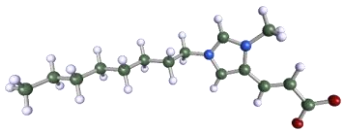
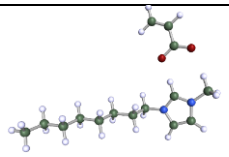
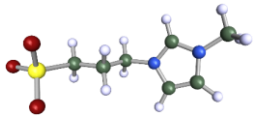
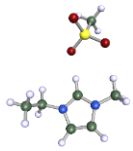
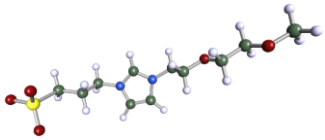
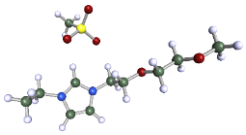
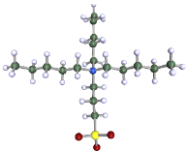
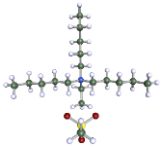
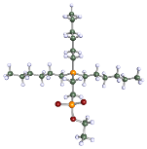
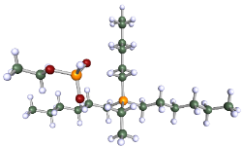
ZI structure	IL structure
 3c[24]	 [omim][propenoate]
 C1im3S[18]	 [emim][$MeSO_3$]
 C1(C2O)2im3S[23]	 [C1(C2O)2im][$MeSO_3$]
 N555C3S[20]	 [N_{5552}][$MeSO_3$]
 P6C2P[19]	 [P_{6662}][$EtPO_3$]

Table S1 collects other 16 zwitterionic compounds included in this study, previously reported in bibliography. For comparison purposes, the available ZIs are grouped according to structural similarity. Table 1 also presents the optimized geometries of the proposed homologous ILs, designed using anions and cations commonly employed in commercial ILs. The main difference between the most stable structure of the ZI and its homologous IL is the presence of local interactions between the hydrogen bond acceptor groups of the anion and the hydrogen atoms of the cation, whereas such kind of interactions are sterically impeded in the case of ZIs.

-*COSMO-RS analysis:* Quantum-chemical founded COSMO-RS method has been widely used to analyze the solvent/solute nature of chemical compounds [29, 52] and to predict the thermodynamic properties of mixtures containing ILs.[31b, 31c, 32, 34, 36-37, 41-42, 53] COSMO-RS theory allows calculating the thermodynamic properties of fluids only using the 3D polarized charge distribution (σ-Surface) of individual molecules, which is collected in 2D histogram named σ-Profile. Therefore, the σ-Profile histogram provides valuable information on the polarity of a compound and the potential interactions with surrounding molecules in the fluid media. Figure 1 compares the σ-Profiles and σ-Surface of 3c ZI and its homologue IL [omim][propenoate].

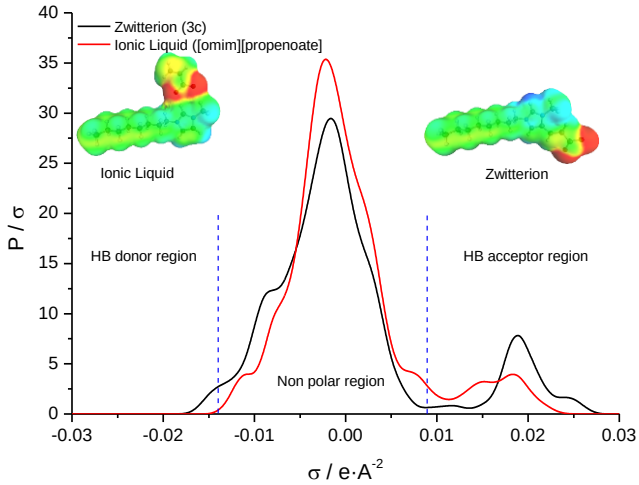


Figure 1. Comparison between σ-profile of zwitterion 3c and its homologous ionic liquid [omim][propenoate].

The σ-Profile represents the polarized charge density $p^X(\sigma)$ of the molecular surface in the field of polarity σ and it can be divided into three different regions according to the following criteria: the hydrogen bond (HB) donor region ($\sigma < -0.0082$ e/Å^2), the HB acceptor region ($\sigma > +0.0082$ e/Å^2) and the nonpolar region ($-0.0082 < \sigma < +0.0082$ e/Å^2). As can be seen, the charge densities of these compounds are mainly located in the non-polar region of their σ-Profiles, ascribable to their alkyl groups and N-heterocyclic ring (green color in σ-Surface). However, both structures present functional groups (carboxylate) with negative charge (red color in σ-Surface) shifted to the positive pole of the field σ. Remarkably, these peaks in 3c ZI are located at higher positive values of polarity, indicating the stronger HB acceptor character of the carboxylate group in comparison with the homologous IL. In addition, both structures present hydrogen atoms in the imidazolium ring (blue color in σ-Surface) with polarized charge located in the HB donor region, but again ZI is described as a more acidic compound than the corresponding IL. In sum, COSMO-RS describes 3c ZI as a more polar structure with stronger HB donor and HB acceptor groups than the homologue IL [omim][propenoate]. This is easily explainable analyzing the molecular structures in Table 1 and the corresponding σ-Surface in Figure 1 and 2: the strong local interaction between the counterions in [omim][propenoate] implies charge compensation, diminishing the HB donor and HB acceptor capacity of the cation and the anion, respectively. These differences are less pronounced when the ZIs present weaker polar basic groups (propenoate>$EtPO_3$>$MeSO_3$)[54] or weaker polar acidic groups (for instance, hydrogen atoms of alkyl chain in ammonium or phosphonium structures of, respectively, N555C3S and P6C2P ZIs), as can be seen in Figure 2. In these cases, the σ-Profiles of ZIs and their homologue ILs are more similar, even when the charge densities of ZIs still cover a wider range of polarity, what implies slightly higher polarity in ZI compounds than in the ILs. Similar conclusions are reached when analyzing σ-

Profile and σ-Surface of other ZIs reported in Figure 2. In general, the selected zwitterions are described as compounds with a broad non-polar region formed by aliphatic or aromatic groups, presenting weak acidic cations (ammonium, phosphonium, and imidazolium) and very electronegative and basic anions (carboxylate, sulfonate, phosphate, etc.). Complementary information is provided by the σ-potentials calculated by COSMO-RS method, which describe their interaction energy with compounds displaying a charge density [$p^X(\sigma)$] with polarity σ.

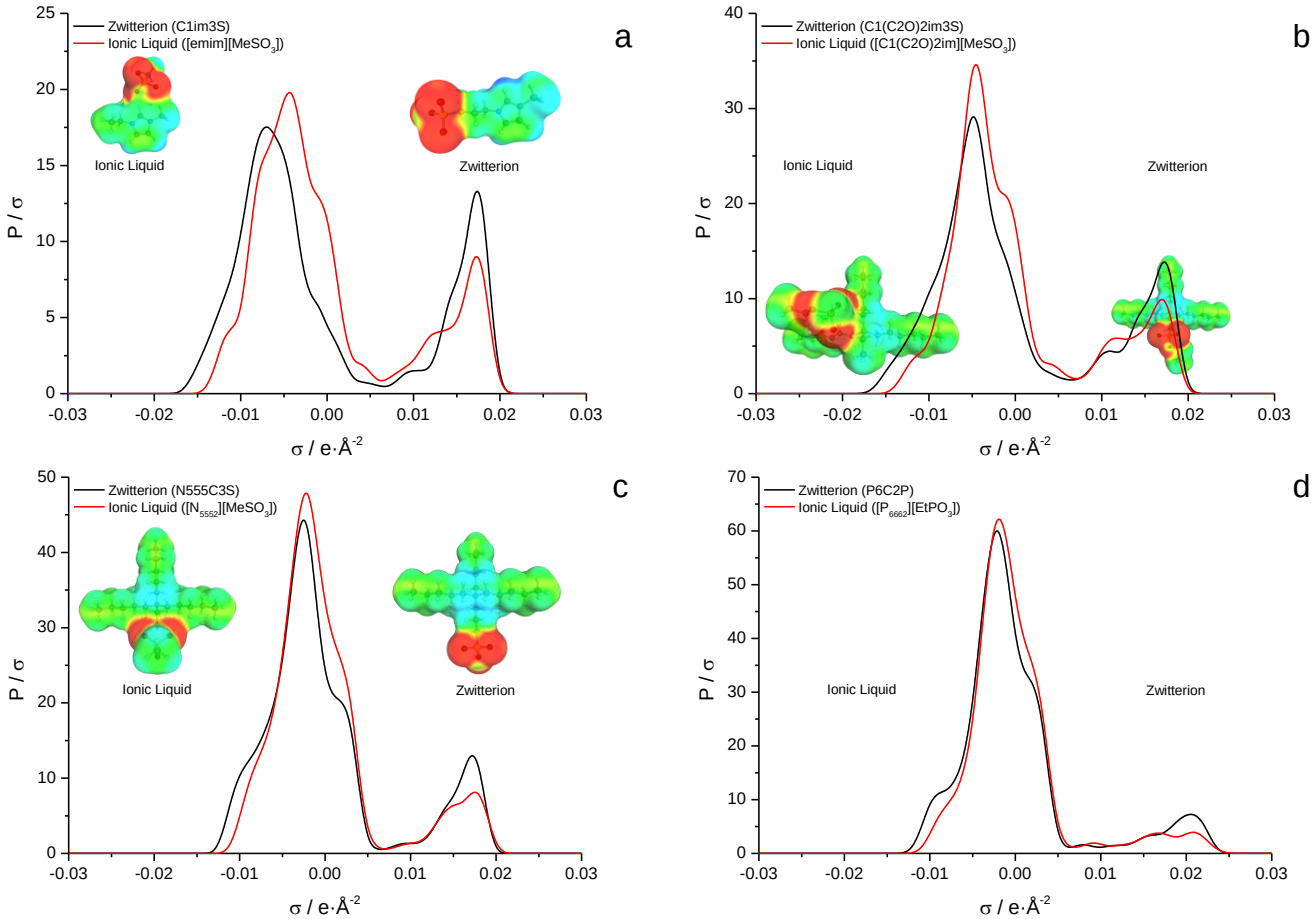


Figure 2. Comparison between σ-profile of zwitterions and their ionic liquids analogues.

Figure 3 compares the σ-Potentials of 3c zwitterion and its analogous IL [omim][propenoate].

The main difference is the higher capacity of ZI to establish attractive interactions with molecules presenting polar HB donor groups; i.e. 3c ZI is again described as a compound with stronger HB acceptor character than [omim][propenoate]. On the other hand, 3c presents slightly less endothermic behavior with polar HB acceptor molecules, ascribable to the more acidic hydrogen atoms of the imidazolium ring, which are free of cation-anion local interactions.

In sum, attending to COSMO-RS analysis, stronger intermolecular interactions with polar compounds (whether acid

or basic) are expected from ZI than from the corresponding IL. Regarding the potential interactions with non-polar solvents, there are no significant differences between 3c ZI and [omim][propenoate] IL. Other ZIs in Table 1, including weaker HB donor and acceptor groups, present more similar σ-Potentials to their homologous ILs, only evidencing less repulsive interactions with molecules presenting polar basic groups.

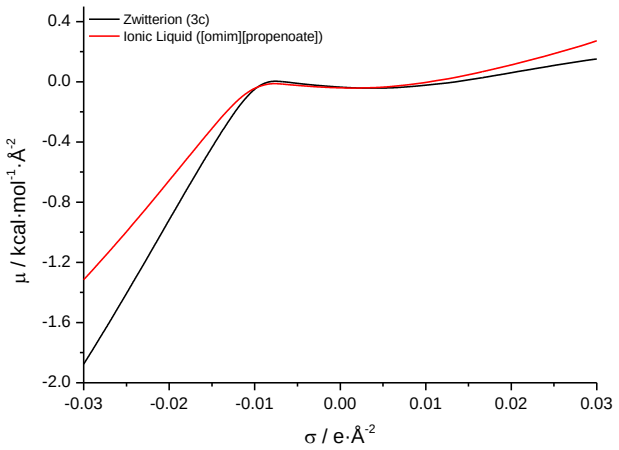


Figure 3. σ-Potential of zwitterion 3c compared with [omim][propenoate].

The analysis of such electronic information supports the above conclusions: In ZI, the charged groups are covalently separated; then, the similarity with the homologue IL decreases (Table 2) when the cation-anion interactions are stronger, because of both the higher HB donor and HB acceptor capacity of the cation and anion, respectively (Table 3). A subsequent conclusion is that these ZIs present higher HB acceptor and HB donor capacity compared to the homologue ILs, due to the absence of HB cation-anion interactions. Higher HB σ-moment values imply greater attractive interactions with molecules having opposite groups. As seen in Figures 1 and 2, [$EtPO_3$] anion peak is more basic than the other anions (>σ values), and for this reason it is the anion with stronger HB acceptor interactions.

On the other hand, from Table 3, it is seen that large cations such as phosphonium and ammonium have weak interactions with the anion; therefore, there is less competition between anion and solute as illustrated by the fact that the differences in HB acceptor

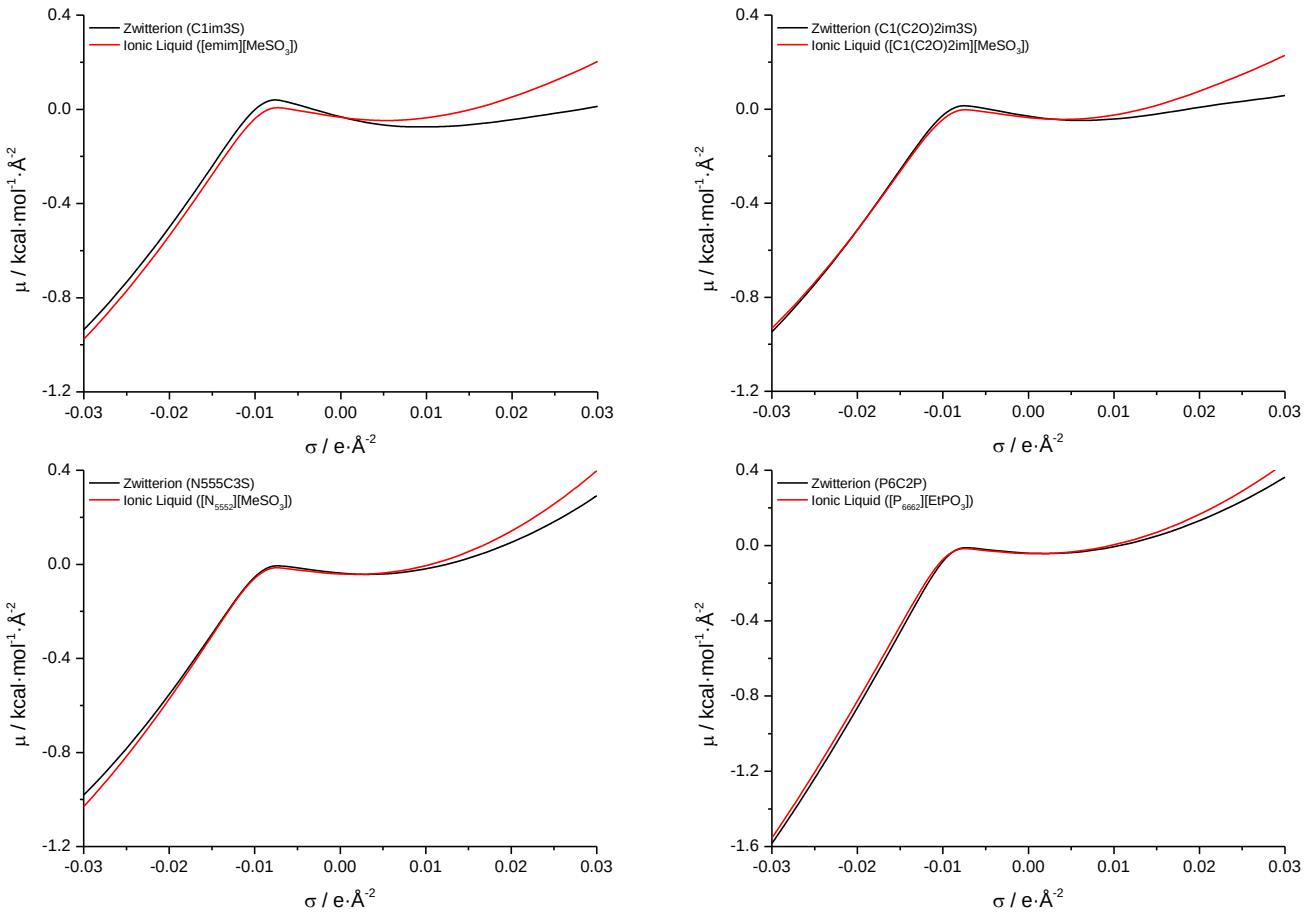


Figure 4. Comparison between σ -potential of zwitterions and their ionic liquids analogues.

Similar differences in behavior are found in other zwitterions reported in bibliography (see Figure 4 and S2 in Supplementary Material), observing that zwitterionic structures preserve the interaction capacity of strong polar functional groups, whereas competitive effects related to cation-anion interactions decrease the polarity of the ILs, in good agreement with the relatively low dielectric constants of ILs reported in bibliography.[55]

COSMO-RS method also provides the statistical similarity of the σ-profiles and σ-potentials (Table 2 and Table S4 in Supplementary Material) and the hydrogen-bond σ-moments (Table 3 and Table S5 in Supplementary Material) of ZIs and ILs. moments are lower than with compounds where strong cation-anion interactions may exist.

Finally, the hydrogens of the ZIs have greater capacity to form hydrogen bonds because they are outside the interactions of the anion, thus being more acidic (i.e. H-2 of the imidazolium ring or hydrogens near the P or N atom of phosphonium or ammonium cationic sites).

Table 2. COSMOtherm similarity of σ-profile and σ-potential of zwitterion and homologue IL

Zwitterion	Ionic Liquid	σ-profile [p(σ)]	σ-potential [kcal·mol^{-1}·Å^{-2}]
3c	[omim][propenoate]	0.52	0.14
C1im3S	[emim][$MeSO_3$]	0.59	0.22
C1(C2O)2im3S	[C1(C2O)2im][$MeSO_3$]	0.63	0.49
N555C3S	[N5552][$MeSO_3$]	0.78	0.58
P6C2P	[P6662][$EtPO_3$]	0.71	0.53

Table 3. COSMOtherm hydrogen bond (HB) σ-moments of zwitterions and homologue IL

Zwitterion	HB bond acceptor	HB bond donor	Ionic Liquid	HB bond acceptor	HB bond donor
3c	31.8	2.0	[omim] [propenoate]	14.6	0.3
C1im3S	26.9	2.2	[emim][$MeSO_3$]	18.5	0.4
C1(C2O)2im3S	28.9	2.6	[C1(C2O)2im] [$MeSO_3$]	20.3	0.5
N555C3S	25.6	0.1	[N_{5552}] [$MeSO_3$]	19.5	0.00
P6C2P	32.5	0.04	[P_{6662}] [$EtPO_3$]	20.9	0.00

NMR analysis: Nuclear magnetic resonance (NMR) technique has been widely used for obtaining a molecular-based understanding of the structural features of the IL and the interactions between cation and anion.[53e, 56] Table 4 collects the experimental [18-20, 23-24] and calculated ^{1}H NMR data of the most acidic hydrogen atoms of the studied ZI and homologue ILs.

Table 4. Experimental and Theoretical ^{1}H NMR signals

Zwitterion	Signal	Exp.	Theo.	Ionic Liquid	Theo.
3a	H-2	7.9	7.2	[bmim]	14.9
	H-4	7.2	7.0	[propenoate]	7.0
3c	H-2	8.0	7.3	[omim]	14.9
	H-4	7.2	7.0	[propenoate]	7.1
C1im3S	H-2	8.8	7.9	[emim] [$MeSO_3$]	13.1
	H-4	7.5	7.2		7.8
	H-5	7.5	7.6		7.8
C11im3S	H-4	7.3	7.2	[emmim]	6.9
	H-5	7.5	7.3	[$MeSO_3$]	7.2
C1(C2O)2im3S	H-2	9.1	7.8	[C1(C2O)2im]	12.5
	H-5	7.8	7.7	[$MeSO_3$]	7.2
N555C3S	N/A	3.7	3.3	[N_{5552}] [$MeSO_3$]	5.7
					5.7
	N/A	3.2	2.9		2.8
					3.0
P6C2P	N/A	3.9	3.4	[P_{6662}] [$EtPO_3$]	7.5
		4.0	4.3		
	N/A	2.5	2.5		5.8
			2.6		5.9
	N/A	2.3	1.6		3.9
		2.4	1.9		3.9

As can be seen, quantum chemical calculations, performed by the GIAO method at the B3LYP/6-311++G** computational level, show general good agreement with the experimental trend. For the case of imidazolium-based compounds, homologue ILs present higher ^{1}H NMR chemical shift value of heterocyclic H atoms than the corresponding ZIs. These results indicate stronger hydrogen bond interactions between the cation and the anion in the neat imidazolium-based IL fluid, which are sterically hindered in ZIs. In addition, the differences in ^{1}H NMR ZI/IL signals diminish from 3c to P6C2P, in agreement with the conclusion of higher similarities between both compounds when the cation and/or anion do not present strong HB donor or acceptor groups. Similar conclusions are achieved when analyzing the atomic distances and Mulliken charges (Tables S2 and S3 in Supporting Information) of HB donor and acceptor groups of ZIs and ILs: as example, the longer C-H distance and higher positive and negative charges of, respectively, H and O atoms in ILs agree with the presence of stronger HB cation-anion interactions than in ZIs.

Dipole moment: Table 5 (and Table S6 in Supplementary Material) compares the calculated dipole moments of ZIs with homologue ILs. Remarkably, the dipole moments of zwitterionic compounds are very high, practically twice than their analogous ionic liquids. This is because the charges in ZIs are more separated in space, without possibility of interacting with each other.[57] Therefore, a major expected difference will be the higher polarity of the ZIs respect to ILs with similar structure.

Table 5. Calculated dipole moment of zwitterions and homologue ionic liquids

Zwitterion	Dipole moment [Debye]	Ionic Liquid	Dipole moment [Debye]
3c	24.6	[omim][propenoate]	13.0
C1im3S	29.4	[emim][$MeSO_3$]	15.2
C1(C2O)2mim3S	30.0	[C1(C2O)2mim][$MeSO_3$]	15.1
N555C3S	26.5	[N_{5552}][$MeSO_3$]	16.0
P6C2P	20.6	[P_{6662}][$EtPO_3$]	14.6

Density and molecular volume: COSMO-RS has been successfully used to predict the density of ILs with very different nature. [29] Table 6 (and Table S7 in Supplementary Materials) collects the calculated density and molecular volume of studied zwitterionic and IL compounds at 298 K.

Table 6. Calculated density and molecular volume of zwitterions and ionic liquids at 298 K by COSMO-RS.

Zwitterion	ρ (g/ml)	Mol. Vol. (Å^3)	MW	Ionic Liquid	ρ (g/ml)	Mol. Vol. (Å^3)	MW
3c	1.05	417	264	[omim] [propenoate]	0.99	446	266
C1im3S	1.32	257	204	[emim][$MeSO_3$]	1.24	277	206
C1(C2O)2im3S	1.21	401	292	[C1(C2O)2mim] [$MeSO_3$]	1.18	414	294
N555C3S	1.01	576	350	[N_{5552}][$MeSO_3$]	0.97	603	352
P6C2P	0.98	719	423	[P_{6662}][$EtPO_3$]	0.96	736	425

As can be seen in Figure 5, ZIs present similar but slightly higher density (<10%) than the homologue ILs. Based on COSMO-RS analysis, the fluid density of these compounds is mainly determined by their molecular volume, which is lower in ZIs than in homologue ILs because the counterions are linked by intramolecular bonds. In addition, higher dipole moments and stronger HB donor and acceptor groups in ZIs imply higher attractive intermolecular interactions, with the consequent volume contraction and higher density of the fluid.

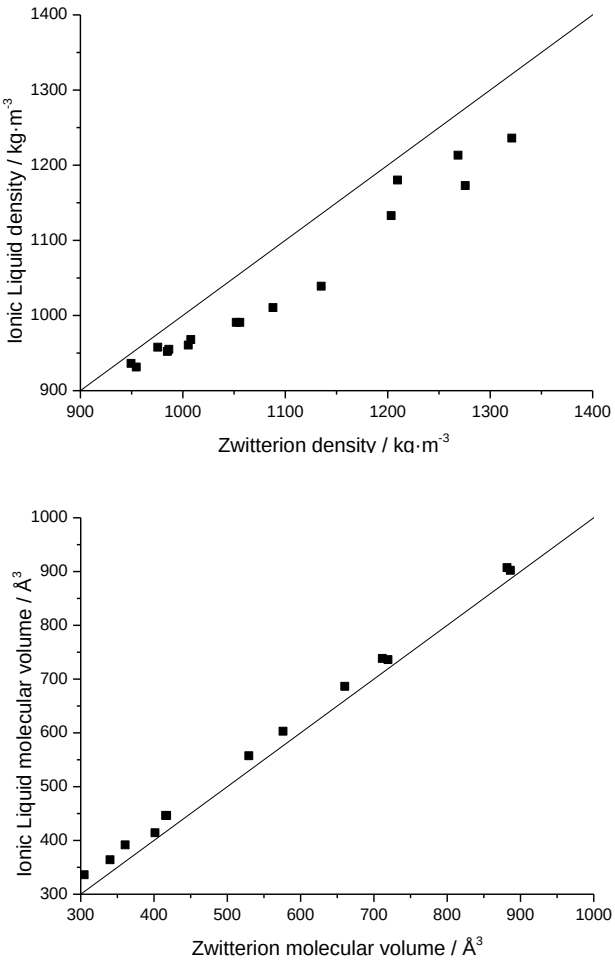


Figure 5. Comparison of zwitterions and ionic liquids densities (A) and molecular volumes (B).

Viscosity: COSMOtherm allows estimating the room temperature viscosity of compounds by using a Quantitative Structure Property Relationship (QSPR) method based on COSMO-RS molecular descriptors. Unfortunately, the quantitative predictability of this model is low compared to other thermodynamic properties predicted by COSMO-RS theory. However, based on the favorable qualitative prediction trends obtained in previous studies on ILs, COSMO-RS estimations are used herein to explore the qualitative differences of viscosity in ZIs and ILs (Figure 6, Table 7 and Table S8 in Supplementary Material). It should be noted, anyhow, that some of the zwitterionic compounds in Table 8 are solid at 298 K.

Table 7. Zwitterion and ionic liquid viscosity estimated by COSMO-RS at 298 K.

Zwitterion	Viscosity [cP]	Ionic Liquid	Viscosity [cP]
3c	84316	[omim][propenoate]	613
C1im3S	6076	[emim][$MeSO_3$]	259
C1(C2O)2im3S	108948	[C1(C2O)2im][$MeSO_3$]	1925
N555C3S	9093	[N_{5552}][$MeSO_3$]	810
P6C2P	37685	[P_{6662}][$EtPO_3$]	1665

COSMO-RS results indicate very high viscosities of the studied zwitterionic compounds, in agreement with previous evidences of organic ZIs.[13c, 17, 23, 58]

In fact, estimated viscosities of ZIs are one to twice order of magnitude higher than those of the homologue ILs. Taking into account the relatively high viscosity of ILs compared to conventional organic solvents, current results present ZIs based on IL counterions as new kind of fluids presenting very high viscosity among the known solvents (Figure 6). The viscosity of a liquid at a fixed temperature can be expected to depend on molecular properties such as molecular volume, molar weight, polarizability and dipole moment. [59] Analyzing the reported values of these properties (Tables 4 and 5), it is concluded that the viscosity of both ZIs and ILs generally increases in a similar trend as dipole moments; these results evidence a main intrinsic characteristic of zwitterionic compounds based on IL counterions: their higher polarity and viscosity as solvents.

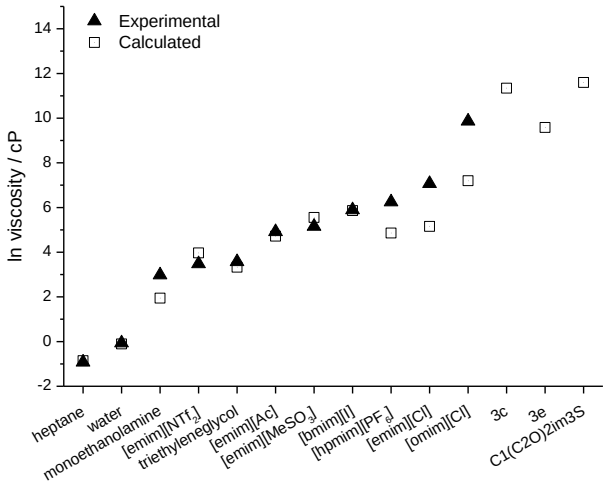


Figure 6. Experimental and calculated by COSMOtherm viscosities for a representative set of organic compounds, ionic liquids and zwitterions

Melting points: One of the critical points in selecting ILs for practical applications is the melting temperature, since it determines the operating liquid window. Table 8 collects the experimental melting points of all the compounds studied in this work. Unfortunately, reliable COSMO-RS predictions of melting points for these compounds were not obtained. Anyhow, attending to the available experimental values, it can be concluded that zwitterionic compounds clearly present higher melting points than the structurally similar ILs, what is assignable to their higher polarity and stronger HB donor/acceptor groups. A previous study regarding the crystallinity of zwitterions demonstrates a high degree of coupling between molecules,[60] which is consistent with the strong intermolecular interactions causing the high density, viscosity and melting temperature of ZIs.

Table 8. Comparison of experimental melting temperatures of zwitterions and homologue ILs

Zwitterion	Melting temperature [K]	Ionic Liquid	Melting temperature [K]
3c	314	[omim][propenoate]	unknown
C1im3S	489	[emim][$MeSO_3$]	308

C1(C2O)2im3S	liquid at room temperature	[C1(C2O)2im] [$MeSO_3$]	unknown
N555C3S	430	[N_{5552}][$MeSO_3$]	unknown
P6C2P	441	[P_{6662}][$EtPO_3$]	unknown

Enthalpy of vaporization: Vaporization enthalpy calculations were carried out for the studied ZIs and homologue ILs by applying COSMO-RS theory (Table 9 and Table S9 in Supplementary Material); this methodology has already been validated for ILs, providing satisfactory results.[52c, 61] Higher enthalpies of vaporization in ZIs than in structurally similar ILs are generally observed, in coherence with the higher polarities of the former compounds: greater cohesive forces between the different molecules are expected in ZIs and, consequently, more energy is required to vaporize the compound. In sum, these new kind of ZIs are described as compounds with high polarity, high viscosity and very low volatility, even lower than those of ILs with similar structural features.

Table 9. Comparison of calculated enthalpy of vaporization of zwitterions vs homologue ILs

Zwitterion	H.vap. [kJ·mol^{-1}]	Ionic Liquid	H.vap. [kJ·mol^{-1}]
3c	268	[omim][propenoate]	151
C1im3S	190	[emim][$MeSO_3$]	148
C1(C2O)2im3S	210	[C1(C2O)2im] [$MeSO_3$]	173
N555C3S	203	[N_{5552}][$MeSO_3$]	172
P6C2P	181	[P_{6662}][$EtPO_3$]	172

Binary mixture analysis

In order to evaluate the general thermodynamic behavior of the studied ZIs as solvents, COSMO-RS was used to obtain the activity coefficients at infinite dilution of conventional chemical compounds in ZIs and the homologue IL solvents. This approach has been previously used to classify the interactions between ILs and common compounds attending to their chemical nature.[53g]

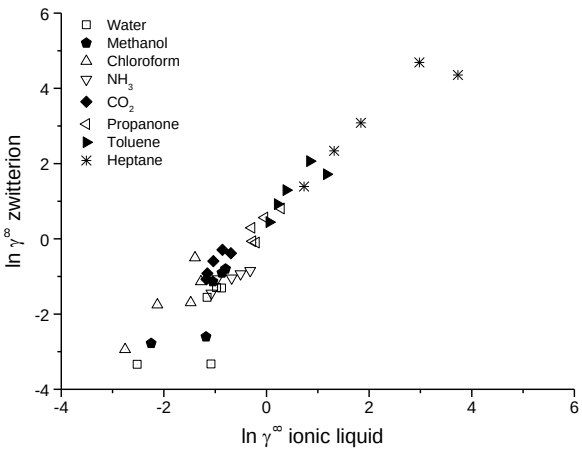


Figure 7. Comparison of activity coefficients at infinite dilution of a diverse set of solutes in zwitterions and its analogous ionic liquid.

As can be seen in Figure 7, the mixtures involving the studied ZIs present a wide variety of thermodynamic behaviors: from nearly ideal mixtures (ZI/IL+ NH_3, CO_2 or propanone: γ_i^∞ ~1) to systems with strong positive deviations (ZI/IL+ aromatic or aliphatic compounds: γ_i^∞ >1) or strong negative deviations (ZI/IL+ water, alcohol or chloroform: γ_i^∞ <1) from ideality given by Raoult's law. Similar results were found with the corresponding mixtures involving the homologue ILs (Figure 7), but in this case the competitive cation-anion interactions seem to decrease the range of γ_i^∞ values; this is, ZI mixtures with common chemical compounds present stronger deviations from ideality than those formed by ILs. The activity coefficient is directly related to the excess Gibbs free energy and, consequently, to the enthalpic and entropic terms of equation 3.

$$\frac{g^E}{RT} = \sum_i x_i \ln \gamma_i = \frac{h^E}{RT} - \frac{s^E}{R} \qquad \text{(eq.3)}$$

Figure 8A presents the excess Gibbs free energy and enthalpy of the equimolar mixtures of ZI+common chemical compound, calculated by COSMO-RS at 298 K. The excess properties of the mixtures involving the analogue ILs present a very similar trend (Figure 8B). It is concluded that the mixing behavior of these systems is mainly governed by the enthalpy; i.e., determined by the intermolecular interactions between the mixture components.

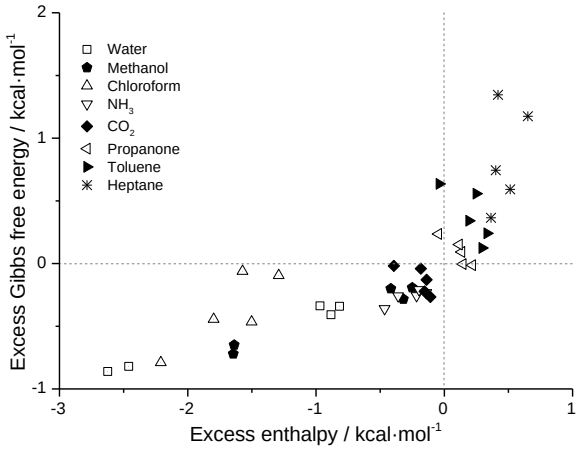
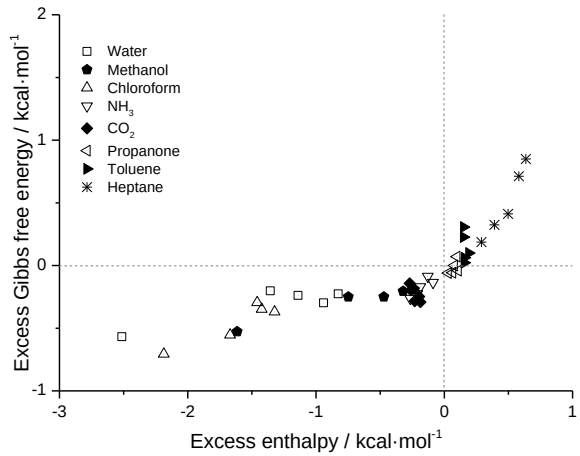
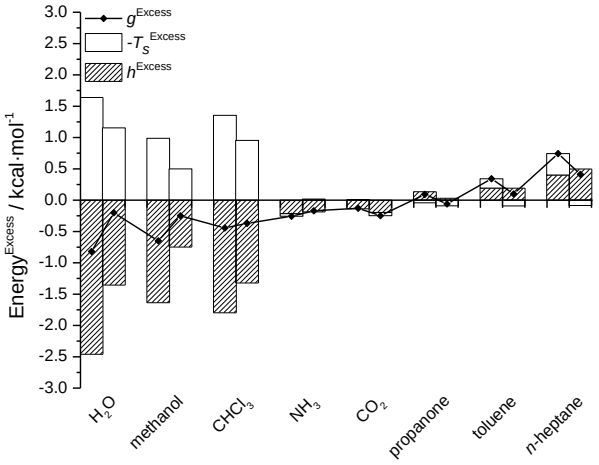


Figure 8. Excess Gibbs free energy and excess enthalpy calculated for a representative set of solutes and zwitterions (A) or ionic liquid (B) mixtures.



The mixing phenomena evolves from endothermic to exothermic depending on both structures of ZI/IL and common compound. The entropy of the system generally decreases with the mixture, reaching to g^E less negative or more positive. Figure 9A illustrates more clearly the structural effects on the mixing excess properties for the cases of zwitterion 3c and IL [omim][propenoate]. As can be seen, polar compounds with HB donor character (as water, methanol and chloroform) present strong exothermic mixtures with 3c, determining the negative g^E values, even when entropic contribution decreases the spontaneity of the mixture. COSMO-RS provides the contributions of the different intermolecular interactions to the h^E, (Figure 9B), which is a valuable information contributing to understand the mixing phenomena at molecular level.[31b, 36, 53d, 53e, 53g]



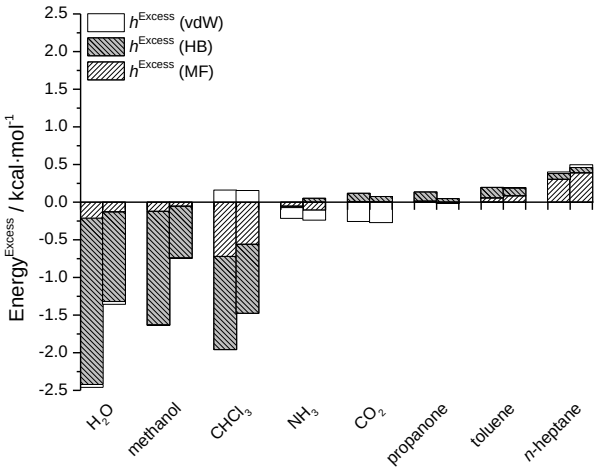
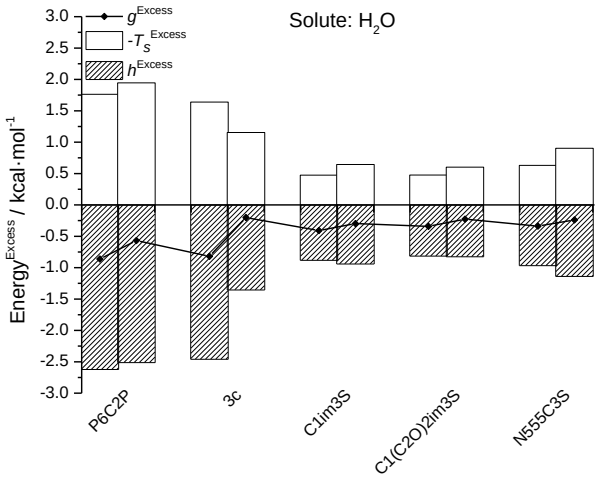


Figure 9A. Calculated excess properties (enthalpy, entropy and Gibbs free energy) of equimolar mixtures of common chemical compounds and zwitterion 3c (left bar) or IL [omim][propenoate] (right bar) by COSMO-RS at 298K. **Figure 9B.** Description of the excess enthalpy of equimolar mixtures of common chemical compounds and zwitterion 3c (left bar) or IL [omim][propenoate] (right bar) in terms of the intermolecular interaction contributions [h^E (MF), h^E (HB), and h^E (vdW)] computed by COSMO-RS at 298K.

Current results indicate that thermodynamically favorable mixtures are related to attractive HB interactions between the acidic groups of the common chemical component (as water, methanol or chloroform) and the HB acceptor groups of the ZI 3c, described in previous section. In contrast, non-polar solutes (as n-heptane) have unfavorable mixtures with ZI 3c as depicted by positive g^E, in this case, the mixing behavior is dominated by the endothermicity of the mixture, ascribable to repulsive electrostatic interactions between components and the loss of HB interactions within the mixture, and the decreasing of the entropy. On the other hand, mixtures of ZI 3c with polar compounds containing moderately weak HB acceptor groups (as propanone or NH_3) present h^E and s^E values close to zero, describing a nearly ideal mixture behavior.

Figure 9 also presents the calculated excess properties of the mixtures involving the analogue ILs. In general, the qualitative mixing behavior is similar than in ZIs, only obtaining lower g^E absolute values in ILs, in coherence of the above description of ZIs as more polar compounds with stronger HB acceptor or donor groups.



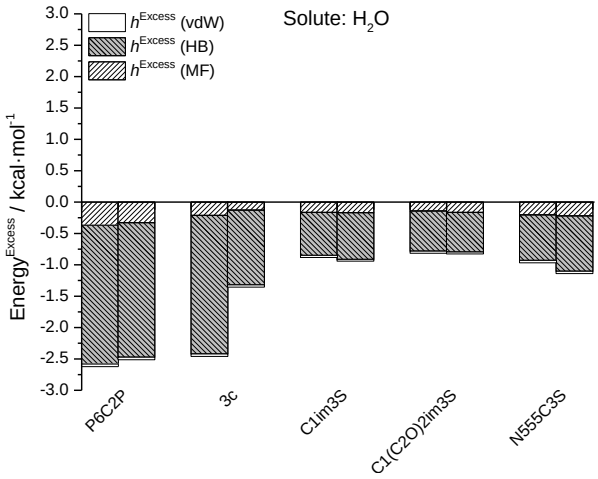


Figure 10A. Calculated excess properties (enthalpy, entropy and Gibbs free energy) of equimolar mixtures of water and zwitterions (left bar) or ILs (right bar) by COSMO-RS at 298K. **Figure 10B.** Description of the excess enthalpy of equimolar mixtures of water and zwitterions (left bar) or ILs (right bar) in terms of the intermolecular interaction contributions [h^E (MF), h^E (HB), and h^E (vdW)] computed by COSMO-RS at 298K.

In order to analyze the effect of the ZI structure on the mixing behavior, the excess properties of equimolar mixtures of different ZIs (and the homologue ILs) were calculated with water (polar acid-amphoteric compound, Figure 10), ammonia (polar basic

compound, Figure 11) and n-heptane (non-polar compound, Figure 12)

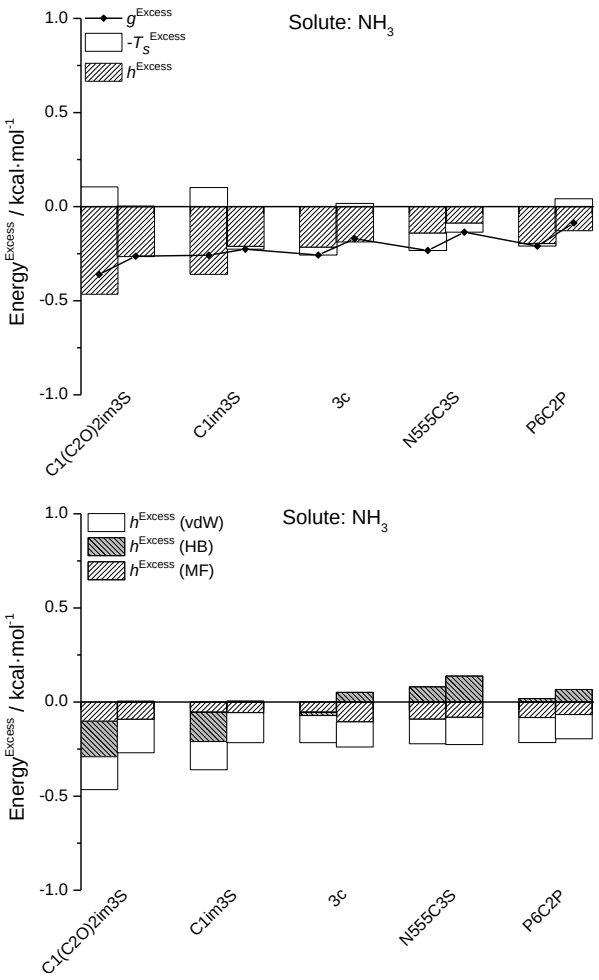


Figure 11A. Calculated excess properties (enthalpy, entropy and Gibbs free energy) of equimolar mixtures of ammonia and zwitterions (left bar) or ILs (right bar) by COSMO-RS at 298K. **Figure 11B.** Description of the excess enthalpy of equimolar mixtures of ammonia and zwitterions (left bar) or ILs (right bar) in terms of the intermolecular interaction contributions [h^E (MF), h^E (HB), and h^E (vdW)] computed by COSMO-RS at 298K.

For the case of mixtures with water, a strong dependence of excess properties on the zwitterionic structure is observed. Clearly, the presence of strong HB acceptor groups in the ZI (as phosphonate in P6C2P or carboxylate in 3c) promotes attractive interactions with water, which determine the mixing properties of these systems. Other ZIs with weaker basic polar groups (as sulfonate in C1im3S or N555C3S) present less exothermic mixtures, due to the weaker HB interactions between ZI and water. The mixtures of water with the homologue ILs show similar trends, but weaker interactions are generally found. Only the compound 3c presents remarkably stronger HB attractive interactions with water than the corresponding IL ([omim][propenoate]), due to the presence of competitive HB cation-anion interactions in the IL, which are not present in the zwitterionic structure.

In the case of mixtures of ZIs with polar basic compounds (as ammonia, Figure 11), the values of excess properties are remarkably lower, mainly due to the similar kind of interactions happening in mixture and pure compounds (as we noted above, the studied ZIs are also polar basic compounds). Thus, we can see in Figure 11B that small values of excess enthalpy in these mixtures are related to slight changes in different intermolecular interactions (van de Waals, HB, polar-misfit) from pure to mixture fluids. The mixtures of ammonia with the corresponding IL present very similar behavior.

As we noted, the mixtures of ZIs with non-polar compounds (as n-heptane, Figure 12) are not thermodynamically favored; in other words, the appearance of two immiscible liquid phases may be expected. The positive g^E values are mainly determined by the endothermic behavior of the mixture and, interestingly, increase with the dipole moment of ZI compound (Table 5). Attending Figure 12B, the unfavorable mixing behavior of n-heptane+ZI is related to repulsive electrostatic interactions (MF) between the non-polar compound and the strongly polar ZI and, in a minor extent, to the loss of hydrogen bonds in the mixture.

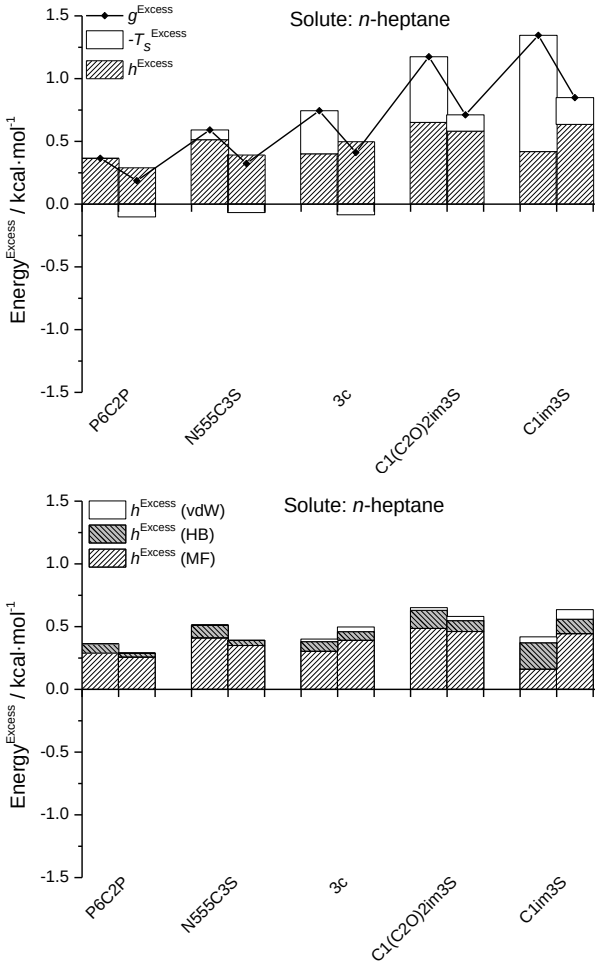


Figure 12A. Calculated excess properties (enthalpy, entropy and Gibbs free energy) of equimolar mixtures of n-heptane and zwitterions (left bar) or ILs (right bar) by COSMO-RS at 298K. **Figure 12B.** Description of the excess enthalpy of equimolar mixtures of n-heptane and zwitterions (left bar) or ILs (right bar) in terms of the intermolecular interaction contributions [h^E (MF), h^E (HB), and h^E (vdW)] computed by COSMO-RS at 298K.

Based on current COSMO-RS analysis, zwitterionic solvents present high capacity to separate acidic polar compounds with ability to form hydrogen bonds. Therefore, they can be very interesting in applications to separate acid gases (as H_2S) or volatile organic compounds (as methanol) by absorption process. In addition, the high polarity of ZIs will promote high immiscibility with non-polar solvents as aliphatic hydrocarbons. Based on these characteristic, ZIs may be solvents with enhanced properties (respect to structurally similar ILs) to be used in liquid-liquid extraction to separate polar solutes from rich-aliphatic mixtures.

Ternary mixture analysis

IL have been extensively investigated as extracting agents to separate different compounds from aliphatic mixtures by liquid-liquid extraction.[62] Examples of solutes of industrial interest successfully separated by ILs are aromatic compounds (as toluene),[62a] S-heterocyclic compounds (as thiophene),[62b] N-heterocyclic compounds (as pyridine)[62c] and alcohols (as ethanol).[62d, 62e] In this study, COSMO-RS method was used to evaluate the performance of ZIs as extracting agents by comparison to the results obtained using structurally similar ILs.

For this purpose, COSMO-RS was applied to describe the liquid-liquid equilibria of ternary mixtures composed by n-heptane, ZI/IL and different solutes, including toluene (Figure 13), thiophene (Figure 15), pyridine (Figure 16) and ethanol (Figure 19) at 298K. Previous studies with these compounds support the ability of COSMO-RS to describe their LL equilibria with ILs.[42, 53h, 63] In addition, thermodynamic parameters commonly used to select an adequate extracting solvent were calculated by COSMO-RS: i) partial miscibility of ZI/IL in aliphatic phase,ii) partition coefficient (β) of the solute between extract and raffinate phases and iii) high selectivity (S) for the solute respect to the aliphatic compounds. Table 10 collects the solubility of the above studied ZI/IL compounds in n-heptane. In addition, Tables 10-13 report the partition coefficient (β^{∞}) and selectivity (S^{∞}) of solutes at infinite dilution for ZI/IL based systems calculated by COSMO-RS at 298K. Tables 10-13 also include the results obtained with sulfolane (Tetrahydrothiophene 1,1-dioxide) as benchmark solvent used in the industry to separate the aromatic compounds, S- or N-heterocyclic compounds and alcohols from aliphatic mixtures.[64]

ILs or mixtures of ILs have been proposed as solvents with enhanced properties to separate aromatic compounds from fuels (as alternative to volatile organic compounds as sulfolane).[65] One main advantage of ILs is their extremely low volatility, which avoids solvent loss and facilitates the regeneration stage in the process. As we noted, ZIs present even lower vapor pressure than ILs. Other important characteristic of ILs to be used in aromatic-aliphatic separation by liquid-liquid extraction is the high immiscibility of ILs in aliphatic compounds. As shown in Table 10, the solubility of ZI 3c (see other cases in Table S10 in Supplementary Material) in n-heptane is even lower than that found for the corresponding homologue IL [omim][propenoate]. Remarkably, the solubility of n-heptane in zwitterion-rich phase is also lower than in IL-rich phase. This is an important factor, since the recovery of aliphatic compounds from the extract stream is a difficult issue that determines the expense of the process and the quality of the aromatic products.[66]

Figure 13A. Tie-lines for the LLE for the ternary mixtures: A) heptane (1) + toluene (2) + zwitterion 3c (3); and **Figure 13B.** heptane (1) + toluene (2) + IL [omim][propenoate] calculated by COSMO-RS at 298 K.

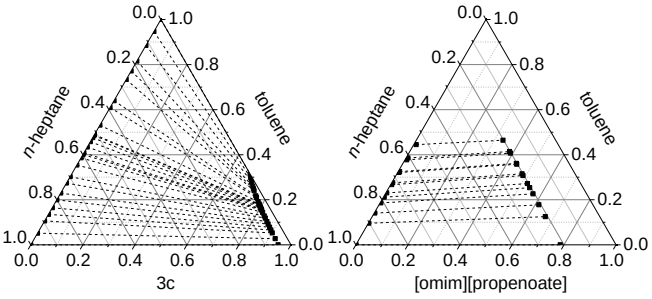
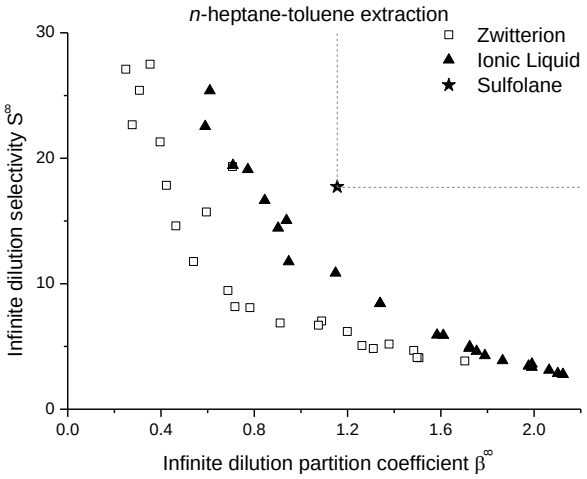


Figure 14. Selectivity (S) and partition coefficient (β) at infinite dilution calculated by COSMOtherm for heptane-toluene ZI/IL systems and compared



with sulfolane as reference solvent.

Table 10. Calculated values of ZI/IL solubility (mol fraction) in n-heptane and the solute distribution ratio (β^{∞}) and selectivity (S^{∞}) at infinite dilution, T = 298.15K and atmospheric pressure for heptane-toluene-ZI/IL systems compared with sulfolane as solvent.

Compound	Zwitterion			Ionic Liquid		
	Solub. [mol frac]	β^{∞}	S^{∞}	Solub. [mol frac]	β^{∞}	S^{∞}
3c	0.05	0.5	11.8	0.21	1.3	8.4
C1im3S	0.01	0.4	27.5	0.02	0.6	25.4
C1(C2O)2im3S	0.01	0.3	27.1	0.05	0.8	16.6
N555C3S	0.11	0.8	8.1	0.35	1.9	5.9
P6C2P	0.29	1.3	5.1	1-phase	-	-
sulfolane	0.04	1.2	17.7	-	-	-

Figure 13, 14 and Table 10 (and Table S10 in Supplementary Material) present an overview of the thermodynamic performance in toluene-n-heptane separation of the ZIs studied in this work, including the liquid-liquid equilibrium ternary systems and the values of β^{∞} and S^{∞}, compared to those of the homologue ILs and the benchmark solvent sulfolane.

Taking into account that the solvent performance increases with the extraction capacity and selectivity (higher β^{∞} and S^{∞} values), sulfolane is a preferred extracting agent to IL solvents and these to ZIs. Of course, several ILs and mixtures of ILs –using different anions and cations than in this work- have been reported with enhanced properties with respect to sulfolane to separate aliphatic-aromatic mixtures [42, 62a, 65a, 67].

Nevertheless, current results indicate that ZIs are not particularly good candidates for this extraction, unless the selectivity was a determinant factor. These results are easily understood attending to the unfavorable intermolecular interactions observed between ZIs and non-polar compounds as toluene.

The analysis of LLE data for the ternary systems composed by S-heterocyclic (thiophene) and N-heterocyclic (pyridine) compounds + n-heptane + ZI/ILs provide similar conclusions (See Figures 15-18, Table 11-12 and Table S11-S12 in Supplementary Material). Zwitterionic solvents allow obtaining lower partial miscibility of both raffinate (aliphatic-rich) and extractant (zwitterion-rich) phases, but at the expense of lower extraction capacity. In the case of pyridine, the main role played by the entropic contribution in these systems[53h] seems to introduce an additional difference between ZIs and ILs, again unfavorable for ZI selection in this particular application. None of the studied ZIs and ILs can be considered clear alternatives to sulfolane solvent.

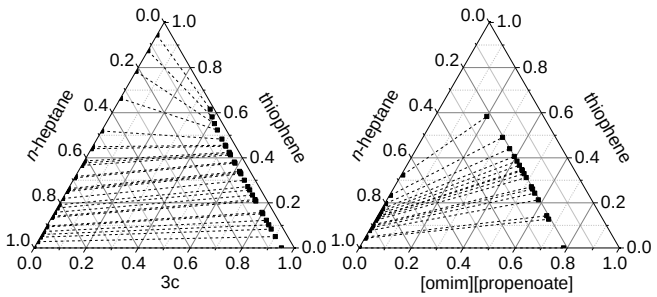


Figure 15A. Tie-lines for the LLE for the ternary mixtures: A) heptane (1) + thiophene (2) + zwitterion 3c (3); and **Figure 15B.** heptane (1) + thiophene (2) + IL [omim][propenoate] calculated by COSMO-RS at 298 K.

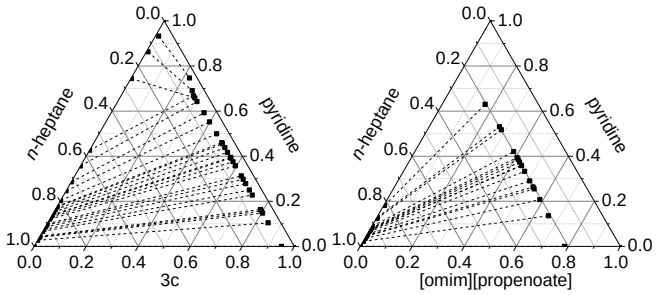


Figure 16A. Tie-lines for the LLE for the ternary mixtures: A) heptane (1) + pyridine (2) + zwitterion 3c (3); and **Figure 16B.** heptane (1) + pyridine (2) + IL [omim][propenoate] calculated by COSMO-RS at 298 K.

Table 11. Calculated values of the solute distribution ratio (β) and selectivity (S) at infinite dilution, T = 298.15 K and atmospheric pressure for heptane-thiophene - ZI/IL systems compared with sulfolane as solvent.

Compound	Zwitterion		Ionic Liquid	
	β^{∞}	S^{∞}	β^{∞}	S^{∞}
3c	1.9	41.0	3.4	21.3
C1im3S	2.1	159.1	3.0	123.3
C1(C2O)2im3S	1.3	137.5	3.2	63.3
N555C3S	2.5	25.6	4.0	15.0
P6C2P	3.7	14.7	4.1	8.6
sulfolane	3.9	59.1	-	-

Table 12. Calculated values of the solute distribution ratio (β) and selectivity (S) at infinite dilution, T = 298.15 K and atmospheric pressure for heptane-pyridine - ZI/IL systems compared with sulfolane as solvent.

Compound	Zwitterion		Ionic Liquid	
	β^{∞}	S^{∞}	β^{∞}	S^{∞}
3c	4.2	90.6	7.4	46.3
C1im3S	4.1	320.4	5.8	243.0
C1(C2O)2im3S	3.3	361.3	6.7	131.1
N555C3S	4.9	51.1	6.7	25.0
P6C2P	5.7	23.1	6.1	12.7
sulfolane	7.9	120.7	-	-

Figure 17. Selectivity (S) and partition coefficient (β) at infinite dilution calculated by COSMOtherm for heptane-thiophene ZI/IL systems and compared with sulfolane as reference solvent.

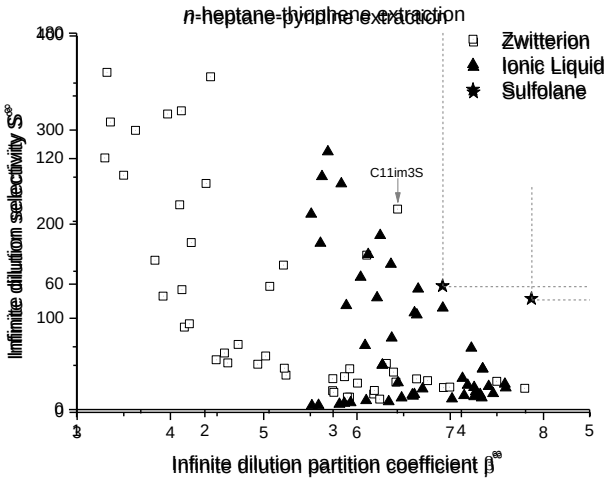


Figure 18. Selectivity (S) and partition coefficient (β) at infinite dilution calculated by COSMOtherm for heptane-pyridine ZI/IL systems and compared with sulfolane as reference solvent.

The case of alcohol extraction from aromatic mixtures using zwitterionic compounds is remarkably different. Figure 19-20 and Table 13 (see other cases in Table S13 in Supplementary Material) show that zwitterionic solvents present HB acceptor groups that increase the selectivity of ethanol separation up to one order of magnitude respect to the homologue ILs, but remarkably, also increase the extraction capacity by a maximum factor of three respect to the corresponding ILs.

The comparison to the performance of the industrial solvent sulfolane presents ZIs as even more promising candidates to separate polar HB donor compounds (as ethanol) from aliphatic mixtures (n-heptane); for instance, the ZI 3c -which is liquid at nearly room temperature- presents both partition coefficient (β^{∞}) and selectivity (S^{∞}) one order of magnitude higher than those obtained with sulfolane.

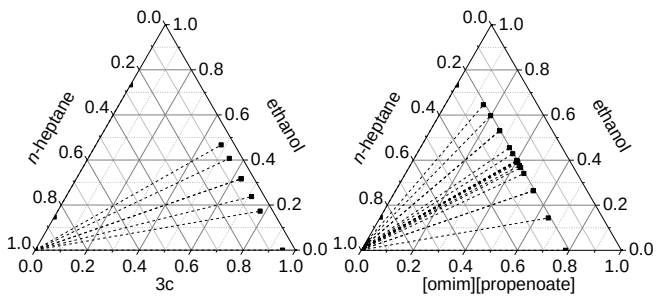


Figure 19A. Tie-lines for the LLE for the ternary mixtures: A) heptane (1) + ethanol (2) + zwitterion 3c (3); and **Figure 19B.** heptane (1) + ethanol (2) + IL [omim][propenoate] calculated by COSMO-RS at 298 K.

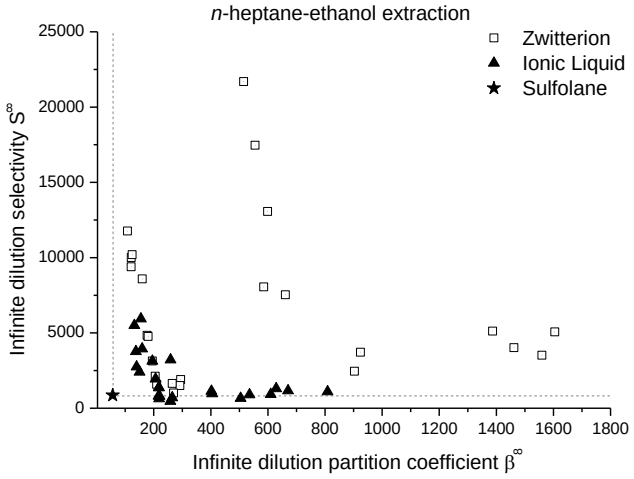


Figure 20. Selectivity (S) and partition coefficient (β) at infinite dilution calculated by COSMOtherm for heptane-ethanol ZI/IL systems and compared with sulfolane as reference solvent.

Table 13. Calculated values of the solute distribution ratio (β) and selectivity (S) at infinite dilution, T = 298.15 K and atmospheric pressure for heptane-ethanol - ZI/IL systems compared with sulfolane as solvent.

Compound	Zwitterion		Ionic Liquid	
	β^{∞}	S^{∞}	β^{∞}	S^{∞}
3c	599	13069	218	1372
C1im3S	121	9393	132	5506
C1(C2O)2im3S	108	11767	140	2754
N555C3S	205	2126	217	810
P6C2P	924	3716	629	1306
sulfolane	56	862	-	-

Conclusions

A quantum chemical analysis based on density functional theory (DFT) and COSMO-RS approach has been performed to evaluate the solvent and mixing properties of zwitterions (ZIs), using analogous ionic liquids (ILs) for comparison purposes. Computational results described this new kind of ZI materials as compounds with high polarity, high viscosity and very low volatility, even lower than those of ILs with similar structural features. As a result of the intramolecular covalent tethering of the cationic and anionic sites, ZIs display stronger hydrogen bond (HB) donor or acceptor character than their ILs counterparts; accordingly, ZIs provide higher separation capacity for polar organic compounds and lower miscibility with non-polar compounds, since their thermodynamic mixing behavior is largely driven by enthalpic changes. Consequently, favorable applications of ZIs in relevant separation processes involving gas-liquid or liquid-liquid immiscible phases have been further explored. For instance, it was revealed that extraction of alcohols from aromatic mixtures using ZIs with HB acceptor groups increased the ethanol selectivity by one order of magnitude and the extraction capacity threefold in comparison with homologous ILs. Interestingly, both partition coefficient and selectivity of ethanol in ZIs are one order of magnitude higher than in the industrial solvent sulfolane, widely used to separate alcohols from aliphatic mixtures. Overall, this study provides a comprehensive molecular and thermodynamic understanding of novel zwitterionic-type molten salts while revealing their performance in relevant absorption and extraction operations, envisaging their promising application in advanced separation processes.

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Keywords: DFT • Ionic Liquids • Zwitterion • COSMO-RS • Properties

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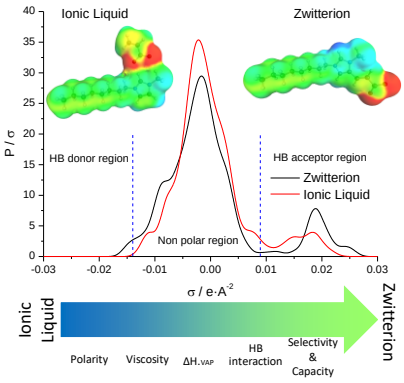
Entry for the Table of Contents (Please choose one layout)

Layout 1:

FULL PAPER

Molecular and fluid properties of zwitterions and their mixtures are explored by quantum chemical analysis based on density functional theory (DFT) and COSMO-RS method, and compared against homologous ionic liquids, to provide a comprehensive overview on the effect of the distinct structures on their physicochemical and thermodynamic behavior in order to apply them as separation agents.



*D. Moreno, VR. Ferro, M. Gonzalez-Miquel, J. Palomar**

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Exploring structural and thermodynamic properties of zwitterions vs ionic liquids: A comprehensive molecular analysis of the consequences of molecular arrangement in separation processes

Layout 2:

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