Micellization and antimicrobial properties of surface active ionic liquids containing cleavable carbonate linkages

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Abstract

Imidazolium-based ionic liquids (ILs) containing cleavable carbonate linkages, 1-alkyloxycarbonyloxyethyl-3-methylimidazolium chlorides with alkyl chains of 10, 12 and 14 carbon atoms, were synthesized and their self-assembly behavior and antimicrobial activity investigated. Differential scanning calorimetry and polarized optical microscopy studies reveal that carbonate-functionalized ILs form stable thermotropic smectic liquid crystalline phases in a wide range of temperatures. Surface activity and aggregation behavior of these new ILs were investigated by tensiometry, conductometry, potentiometry and spectrofluorimetry. The size of aggregates was examined by dynamic light scattering (DLS). Carbonate-functionalized ILs display higher adsorption efficiency and lower critical micelle concentration (cmc) than simple alkyl chain substituted ILs. The insertion of a carbonate ester moiety in the alkyl side chain favors adsorption at the air-water interface and micellization in the bulk solution when compared to non-functionalized ILs. DLS measurements show that small micelle-like aggregates are spontaneously formed above the cmc. Furthermore, carbonate-functionalized ILs were examined for their antimicrobial activity against a panel of clinically relevant microorganisms. Biological activity was found to increase with hydrophobicity. The presence of a carbonate ester moiety significantly enhances the antimicrobial efficiency as compared to non-functionalized ILs, being particularly remarkable the susceptibility of *Staphylococcus* sp. towards the action of these compounds. It has been demonstrated that the functionalization of the alkyl side chain of the imidazolium salts can modify not only the aggregation behavior but also lead to differences in both efficiency and spectrum of antimicrobial activity of amphiphilic ILs.

Introduction

Ionic liquids (ILs) are being intensively studied as a new type of solvents with non-molecular, ionic character in organic chemistry, biocatalysis, preparation of nanostructured materials, biomass treatment and enhanced oil recovery[1–7] among others. Most commonly investigated ionic liquids consist of asymmetric N-containing organic cations combined with inorganic or organic anions.[1] ILs are liquids below of 100 °C, possess very low vapor pressure and high thermal, chemical and electrochemical stability and tuneable properties regarding polarity and solvent miscibility. Because of their low vapor pressure and non-flammability they are perceived as eco-friendly alternatives to common volatile organic compounds. However, several issues should be considered to use this term for ILs as many of them are relatively toxic and non-biodegradable.[8]

One of the most outstanding aspects in ILs research is the large potential for tuning their properties through appropriate cation-anion combinations to accomplish specific technological demands.[9] Many ionic liquids have emerged as novel surface active compounds because of the amphiphilic character of their cation or anion and their aggregation behavior has been extensively investigated.[10,11] Varying the alkyl chain length and/or polarizability of the anion or cation is possible to modify the nature of the self-aggregated structures which can perform as specific micellar catalysts or as templates with optimized behavior for the synthesis of nanostructured materials. Numerous surface active ionic liquids (SAILs) based on imidazolium, pyridinium, piperidinium, pyrrolidinium and amino acids have been synthetized and investigated for their self-assembly behavior.[12–16] The effect of the counterion on micellization of 1-alkyl-3-methyl imidazolium salts has been extensively studied.[17–19] A review of literature regarding SAILs aggregation indicates that the insertion of a functional ester or amide group in the side chain leads to significant changes in their surface activity and micellization.[12,20–22] Furthermore, the introduction of a chemical or enzymatically hydrolysable functional group such an ester group favors the SAILS biodegradation.[8]

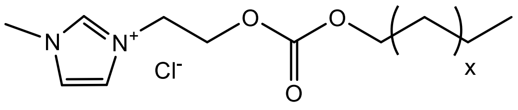
Because of their antimicrobial and antifungal activity amphiphilic ionic liquids have been examined for biological applications.[10,20,21,23] In addition, some ILs have been found able to enhance drug solubility and/or act as a carrier for drug delivery systems.[24,25] Consequently, ILs are being explored for a broad range of bio-applications including biosensors, protein stabilization and as media for biocatalytic reactions.[26–28] However, most of commonly used ionic liquids are not readily biodegradable compounds owing to the lack of a site of primary degradation in the molecule. Development of the next generation of ionic liquids should face the design of technically efficient ionic liquids that do not represent a threat to the environment.

Aimed at the improvement of physicochemical and biological properties of amphiphilic ionic liquids, herein we disclose the synthesis, aggregation behavior and antimicrobial properties of a series of novel imidazolium-based ionic liquids containing a cleavable carbonate linkage, 1-alkyloxycarbonyloxyethyl-3-methylimidazolium chlorides with alkyl chains of 10, 12 and 14 carbon atoms. The effect of the insertion of a hydrolysable carbonate ester moiety in the alkyl side chain on the surface activity and aggregation behavior of imidazolium-based ILs is investigated. Furthermore, the antimicrobial properties of these carbonate-functionalized ILs are examined against a panel of clinically relevant microorganisms.

Materials and methods

Synthesis of carbonate-functionalized ionic liquids $C_nCMeImCl$

Imidazolium-based ionic liquids with carbonate linkages, 1-alkyloxycarbonyloxyethyl-3-methylimidazolium chlorides containing C_{10}-C_{14} alkyl chains were prepared through synthetic protocols based on previously reported methods.[29–31] Procedures for the synthesis of the carbonate-functionalized imidazolium ILs and characterization data are given in Supporting Information (SI). Molecular structure of the herein synthetized ILs is shown in Figure 1.



x= 7, 9 and 11 for $C_{10}CMeImCl$, $C_{12}CMeImCl$ and $C_{14}CMeImCl$, respectively

Figure 1. Molecular structure of carbonate-functionalized ionic liquids

Thermal measurements

The thermal stability of carbonate-functionalized ILs was investigated using a thermogravimetric analyser (Mettler Toledo TGA/STGA 851) in N_2 atmosphere. Samples were analysed in aluminium pans applying a 20 mL/min nitrogen flow rate. Thermograms were registered increasing the temperature from 25 to 550 °C at a heating rate of 10 °C/min. Measurements of phase transition temperatures and enthalpies were conducted with a differential scanning calorimeter (Mettler Toledo DSC 821) coupled to a liquid nitrogen cryostat cooler (CF-50-PB). Samples under nitrogen atmosphere were cooling from room temperature to -100 ºC, followed by two heating-cooling cycles at 10 ºC/min.

Polarizing optical microscopy (POM)

Optical mesophase textures were characterized using a Leitz polarizing microscope equipped with a Mettler FP80 hot-stage and a Mettler FP80 central processor.

Conductivity measurements

Conductivity measurements were carried out at 25.0 ºC ± 0.1 °C using a Thermo Orion 5 Star multiparameter instrument equipped with an Orion Conductivity Cell 913005MD with epoxy/graphite electrode and cell constant of 0.475 cm^{-1}. All measurements were performed in triplicate and show an uncertainty of less than 0.7 %.

Surface tension measurements

Surface tension measurements were performed with a Krüss K12 tensiometer by means of the Wilhelmy plate method, at 25.0 ºC ± 0.1 °C. Prior to measurements, plate and glass vessels were cleaned with chromic mixture and rinsed with deionized water. The standard deviation to consider reached the equilibrium surface tension value was 0.1 mN/m for five consecutive determinations.

Fluorescence measurements

Steady-state fluorescence measurements were carried out at 25.0 ± 0.1 °C using a Shidmadzu RF 540 spectrofluorometer. Data were acquired using a 1 cm path length quartz cuvette. Pyrene was used as fluorescence probe. The emission spectra were recorded from 340 to 450 nm using an excitation wavelength of 332 nm. Excitation and emission band slits were kept at 2 nm. The aggregation number of the micelles (N_{agg}) was determined performing a pyrene fluorescence quenching experiment using cetylpyridinium chloride as quencher.

Dynamic light scattering measurements

Dynamic light scattering (DLS) measurements were conducted at 25.0 °C ± 0.1 °C using a light scattering apparatus (Zetasizer, nanoseries, nano-ZS) Malvern Instruments with a He-Ne laser (633 nm, 4 mW) equipped with a built-in temperature controller. Thirty repeated measurements were done for each sample. CONTIN algorithm was applied to obtain the size distribution of ionic liquid aggregates from DLS data.

Potentiometric measurements

The potential changes were measured at 25.0 ± 0.1 °C using a chloride ion-selective electrode 9617BNWP coupled to a Thermo Orion 5 Star Multiparameter Instrument using a thermostatic water bath to control the temperature. Measurements were conducted in triplicate with an uncertainty of less than 0.6%.

Antimicrobial Activity

Antimicrobial activity assessment was performed trough the determination of the minimum inhibitory concentration (MIC) values[32] by the broth microdilution method against seven strains of bacteria and one fungi (page S5, SI). Two-fold dilutions of the ionic liquids tested dissolved in Muller Hinton broth (prepared according to the manufacturer instructions with a final pH 7.3 ± 0.1 at 25 °C) were prepared to get a final concentration range in the microtiter plates from 1 to 256 μg/mL. 10 μL of a nutrient broth culture of each bacterial strain was added to achieve final inoculums of ca. 5×10^5 colony forming units per mL. Muller Hinton broth with and without bacterial inoculum served as growth and sterility controls, respectively. Setup of the microtiter plates for antimicrobial susceptibility testing is giving in Figure S1 (SI). MIC value was determined as the lowest concentration of ionic liquid that prevents visible growth of the microorganism in dilution wells after 24 h of incubation at 37 °C. All the tests were performed in triplicate in three independent experiments and the median values were used for MICs calculation.

Results and discussion

Thermal analysis

Thermal stability of carbonate-functionalized ILs was determined by thermogravimetric analysis (TGA). A characteristic thermal weight loss curve for the ILs investigated is showed in Supporting Information (Figure S2). Table 1 shows the decomposition temperature of the carbonate ionic liquids synthetized compared to other functionalized and non-functionalized imidazolium-based ionic liquids.

Table 1. Thermal decomposition temperatures (T_{onset}) of carbonate-functionalized ILs ($C_nCMeImCl$), non-functionalized ILs (CnMeImBr), ester-functionalized ILs ($C_nEMeImBr$) and amide-functionalized imidazolium-based ionic liquids ($C_nAMeImBr$)

	Ionic liquid	T_{onset} (ºC)
Carbonate-functionalized imidazolium ILs	C_{10}-$C_{14}CMeImCl$	260-280
Non-functionalized imidazolium ILs	C_{10}-$C_{14}MeImBr$	278-288[10]
Ester-functionalized imidazolium ILs	C_{10}-$C_{14}EMeImBr$	210-228[20]
Amide-functionalized imidazolium ILs	C_{10}-$C_{14}AMeImBr$	310-321[21]

All the carbonate-functionalized ionic liquids are thermally stable up to 260 ºC. The insertion of a carbonate linkage in the side chain does not affect to any significant extent the thermal stability of these organic salts as compared with non-functionalized imidazolium-based ionic liquids (Table 1), therefore, their range of operating temperatures can be considered similar. With regard to the incorporation of other functional groups (Table 1), carbonate-functionalized ILs are thermally more stable than ester-functionalized ILs but decompose at lower temperatures than amide-functionalized ILs. The latter ones are the only functionalized ILs with higher thermal stability than non-functionalized ionic liquids, which was attributed to the intermolecular hydrogen bonding imparted by the amide functionality.[21]

Differential scanning calorimetry (DSC) was applied to investigate first-order phase transitions of the ionic liquids synthetized. DSC revealed two phase transitions in the heating cycle corresponding to crystalline solid to liquid crystalline (S → LC) and liquid crystalline to isotropic liquid transitions (LC → L). Between those transitions lies the comparatively extended mesophasic region. Table 2 shows the transition temperatures and enthalpies from the onset temperatures of the first and second heating cycles of DSC thermograms. Assignments were corroborated by the POM analysis reported in next section.

Table 2. Transition temperatures and enthalpies from DSC thermograms for the $C_nCMeImCl$; first heating cycle correspond to the hydrated salts

		1st heating cycle		2nd heating cycle	
		T (ºC)	ΔH (kJ/mol)	T (ºC)	ΔH (kJ/mol)
$C_{10}CMeImCl$	S-LC	32.6	41.3	-3.5	16.6
	LC-L	(*)	(*)	126	2.7
$C_{12}CMeImCl$	S-LC	41.9	46.3	15.2	31.4
	LC-L	(*)	(*)	132	0.9~~1~~
$C_{14}CMeImCl$	S-LC	44.1	51.1	29.3	38.7
	LC-L	(*)	(*)	142	1.9

S, solid; LC, liquid crystalline; L, isotropic liquid; (*)LC to L transition too weak and broad to be accurately identified

Carbonate-functionalized ILs displayed thermal hysteresis when crystallized from liquid crystalline phases, with the solidification temperature lowered up to 15-35 ºC as a function of the alkyl chain length. The hysteresis behavior is similar to that reported by Bradley *et al.*[33] for long-chain 1-alkyl-3-methylimidazolium chlorides and bromides. On the first heating cycle, the hydrated chloride salts melt ca. 33-44 ºC with a large endothermic transition to a mesophase (Table 2). Samples were heated in open pans up to 180 ºC and maintained at this temperature for 5 minutes to attain complete *in situ* dehydration. On the subsequent cooling cycle and the second heating cycle the transition temperatures from solid to liquid crystal were reproducible and inferior to that of the initial heating cycle, as showed in Table 2. The mesophase cleared at higher temperature with a small endothermic transition (Table 2). The enthalpy of the endothermic crystal to mesophase transition increases with the alkyl chain length and is in the range of 41-51 KJ/mol in good agreement with the values reported for non-functionalized imidazolium halide salts.[33,34] The enthalpy of the mesophase-isotropic transition is small (1-3 KJ/mol) and consistent with the values found by others authors for amphiphilic imidazolium salts.[33]

Polarized optical microscopy (POM) characterization

The liquid crystal phases of $C_nCMeImCl$ were confirmed by POM (Figure 2). These phases are identified as thermotropic smectic A (SmA) phases on the basis of the texture displayed. SmA phases were already described for various long-chain imidazolium-based ILs.[34,35]

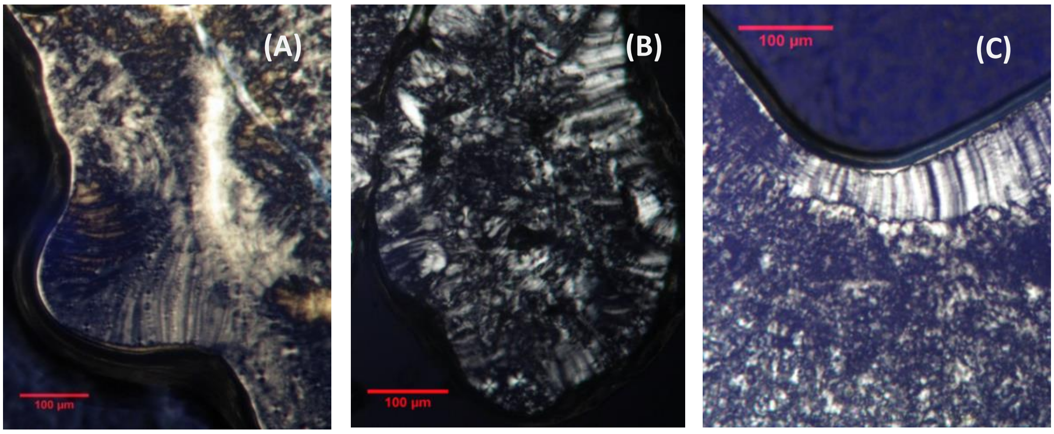


Figure 2. Polarized optical microscope photographs for: (A) $C_{10}CMeImCl$, (B) $C_{12}CMeImCl$ and (C) $C_{14}CMeImCl$ at 90 ºC, 60 ºC and 90 ºC, respectively.

Surface activity and aggregation behavior

Aggregation behavior of carbonate-functionalized ILs in aqueous solution was investigated by conductometry, tensiometry, potentiometry and fluorimetry techniques. These complementary techniques were used to study the successive steps of amphiphilic ionic liquid self-assembly. The data obtained are compiled in Table 3 and discussed below.

Table 3. Aggregation parameters of 1-alkyloxycarbonyloxyethyl-3-methylimidazolium chlorides, $C_nCMeImCl$, in aqueous solution at 25 ºC obtained by conductivity, surface tension, potentiometric and steady-state fluorescence measurements

	cmc^a (mM)	cmc^b (mM)	cmc^c (mM)	cmc^d (mM)	β	ΔG^o_{mic} (kJ/mol)	π_{cmc} (mN/m)	pC_{20}	cmc/C_{20}	A_{min} (nm^2)	ΔG^o_{ads} (kJ/mol)	I_1/I_3	N_{agg}
$C_{10}CMeImCl$	13.1	11.1	12.1	11.0	0.54	-31.8	34.2	2.4	2.7	0.47	-43.0	1.27	35
$C_{12}CMeImCl$	3.4	2.1	2.7	2.9	0.53	-36.7	34.0	3.3	3.9	0.81	-53.3	1.32	36
$C_{14}CMeImCl$	0.92	0.37	0.89	0.59	0.45	-39.7	34.0	4.4	9.0	1.33	-66.9	1.34	38

critical micelle concentration (cmc) values from [a]conductivity, [b]surface tension, [c]potentiometric and [d]fluorescence measurements, degree of counterion binding (β), Gibbs free energy of micellization (ΔG^o_{mic}), adsorption effectiveness (π_{cmc}), adsorption efficiency (pC_{20}), area per molecule (Amin), standard free energy of adsorption at the air-solution interface (ΔG^o_{ads}), polarity index (I_1/I_3) of pyrene in micelles and aggregation number (N_{agg}), of the carbonate-functionalized imidazolium-based ILs. Variation coefficient of cmc values obtained by conductometry, tensiometry, potentiometry and fluorimetry were ≤7%, ≤11%, ≤8% and ≤5%, respectively.

Conductivity measurements. The variation of the specific conductivity (κ) of carbonate-functionalized ILs in aqueous solution versus concentration at constant temperature (25 °C) was investigated. Representative conductometric profile for a C_nCMeImCl homologous is displayed in Figure 3.

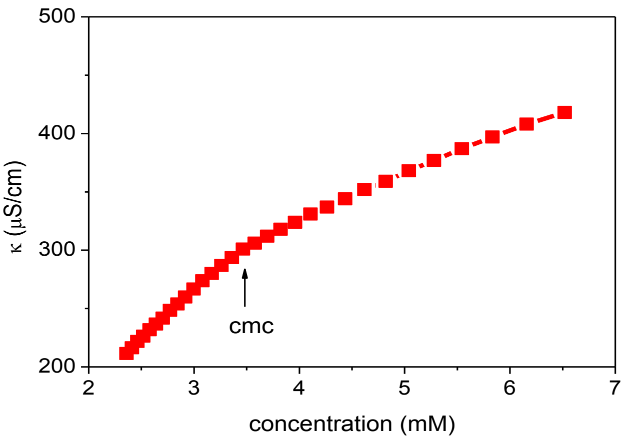


Figure 3. Specific conductivity as a function of ionic liquid concentration for C_{12}CMeImCl in water at 25 °C

The conductivity values can be adjusted to two straight lines of different slopes in pre- and post-micellization regions. The abrupt change in the slope results from the binding of some counterions to the micelle and to the lower mobility of the micelles compared to surfactant monomers. The cmc value corresponds to the intersection point. The ratio of the slopes above and below the cmc allows to calculate the counterion binding parameter, β.[36] This parameter estimates the counterions included in the Stern layer that counterbalance the electrostatic force opposing the aggregation process. The cmc values and β parameters determined by electrical conductivity measurements are given in Table 3.

A progressive decrease of the cmc value is observed for carbonate-functionalized ILs with lengthening the alkyl chain as described for non-functionalized amphiphilic ionic liquids,[10,37,38] other functionalized ILs [20,21,39] and for conventional ionic surfactants[40–42] due to the increased hydrophobicity.

According to the empirical Stauff-Klevens equation[43] a linear relationship can be established between log cmc and the number of carbon atoms in the alkyl chain (SI, Figure S3):

$$\log cmc = A - B \times n$$

where A and B are constants for a given homologous series at a constant temperature and depend on the nature of the hydrophilic head group and the effect on each additional methylene group on the cmc, respectively.[42] Constants A and B were found to be 4.0 and 0.29, respectively, for the investigated ILs. Therefore, carbonate-functionalized ILs exhibit a slope value within the range (0.28-0.30) found for common ionic surfactants,[42] simple alkyl chain substituted imidazolium ILs,[10,11,44] and other functionalized amphiphilic imidazolium ILs.[20,21] The Gibbs free energy of transfer a methylene group of the alkyl chain from bulk solution to a micellar aggregate calculated from the slope of the linear correlation[42] was -1.67 KJ/mol, a similar value to those reported for n-alkyl chain imidazolium ILs (-1.71 KJ/mol),[10] for ester containing imidazolium ILs (-1.71 KJ/mol)[20] and for amide-functionalized imidazolium ILs (-1.68 KJ/mol).[21]

Carbonate-functionalized ILs show cmc values four times lower (Table 3) than their non-functionalized 1-alkyl-3-methylimidazolium chloride analogous.[45,46] The insertion of a carbonate ester moiety in the alkyl chain near to the polar group gives rise to a notable decrease in the cmc likely due to the increased hydrogen bonding in the head group region.[20,36,41]

Compared to ester- and amide- functionalized imidazolium-based ionic liquids previously synthetized by our group, ILs with carbonate linkages exhibit similar cmc values than ester-functionalized homologous[20] whereas trend to form micelle aggregates at somewhat lower concentrations (around 1.5-fold lower) than amide-functionalized imidazolium ILs.[21]

The values of the counterion binding parameter (β) of carbonate-functionalized ionic liquids (0.45-0.54) (Table 3) are very similar to those published for single alkyl chain and amide-functionalized imidazolium chloride salts[12,45] and lower than those reported for single alkyl chain and ester- and amide-functionalized imidazolium bromide salts (0.62-0.74).[10,20,21] Differences in the binding parameter values can be attributed to the influence of the anion size. Thus, the smaller value of β arises from the lower ability of the chloride anion of binding to micelles and decreasing the electrostatic repulsion among the cationic headgroups of ILs, which results in the cmc increase.

The standard Gibbs energy of micellization (ΔG^{o}_{mic}) of carbonate ILs was obtained from the equation:[47]

$$\Delta G^{0}_{mic} = (2 - \beta)\mathrm{RT}\ln \mathrm{x}_{cmc}$$

where β is the binding parameter and x_{cmc} is the cmc expressed as a mole fraction. The values of ΔG^{o}_{cmc} calculated for carbonate-functionalized ILs are shown in Table 3. The standard Gibbs free energy of formation of micelles becomes more negative with lengthening the alkyl chain which provides evidence of hydrophobic interactions governing micellization.

Surface tension measuraments. The surface activity of carbonate ILs has been examined by surface tension measurements. Equilibrium surface tension (γ) versus logarithm of ionic liquid concentration in water at 25 °C is plotted in Figure 4.

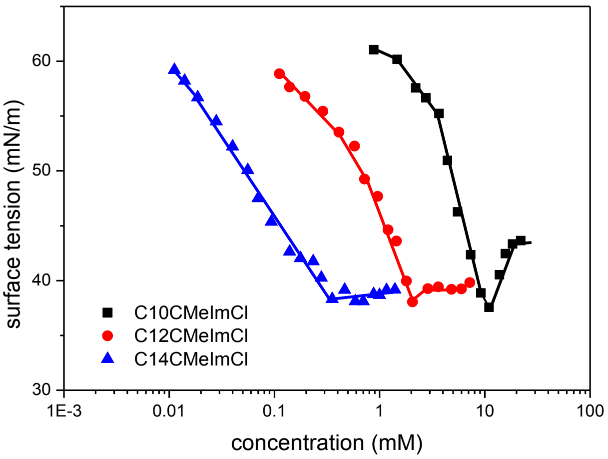


Figure 4. Plots of equilibrium surface tension versus concentration of carbonate-functionalized ILs in water at 25 °C

Surface tension progressively diminishes with increasing IL concentration up to attain a plateau where a nearly constant surface tension value is observed. For C_{10}CMeImCl a sharp minimum of surface tension is observed immediately before reaching a plateau. The appearance of a minimum on the surface tension curve was also described for 1-alkyl-3-methylimidazolium salts and amide-functionalized imidazolium ILs with C_8 and C_{10} alkyl chains.[10,37,45] Such minimum has been attributed to the presence of surface micelles before bulk aggregation and re-settlement of a surface monolayer above the cmc. In this work, the cmc value has been assigned to the concentration where the minimum was observed. The cmc values for ILs with carbonate linkages obtained from tensiometry (Table 3) decrease with lengthening the alkyl chain and are consistent with those obtained by conductometry.

From the surface pressure isotherms the surfactant effectiveness to reduce the solvent surface tension (Π_{cmc}) and the adsorption efficiency (pC_{20}) were also estimated.[42] Π_{cmc} is defined as:

$$\Pi_{cmc} = \gamma_o - \gamma_{cmc}$$

where γ_o and γ_{cmc} is the surface tension of the solvent and the solution at cmc, respectively. The pC_{20} parameter is calculated as:

$$pC_{20} = -\log C_{20}$$

where C_{20} is the surfactant concentration needed to reduce the surface tension of pure solvent by 20 mN/m. The Π_{cmc} and pC_{20} values of the carbonate-functionalized ILs are reported in Table 3. Π_{cmc} indicates the maximum reduction of surface tension produced by dissolution of surface active ionic liquid molecules.

Carbonate-functionalized ILs investigated present similar values of effectiveness (Π_{cmc}) to those reported for 1-alky-3-methylimidazolium chloride salts.[13,48]Adsorption efficiency (pC_{20}) of the ILs examined (Table 3) increases linearly as the alkyl chain length increases, i.e., carbonate-functionalized ionic liquids become more efficiently adsorbed at the air-liquid interface and reduce more efficiently the surface tension with increasing its hydrophobicity. Carbonate-functionalized ILs reduce more efficiently the surface tension than single alky chain imidazolium salts,[15] show a similar ability in reducing surface tension to that of ester-functionalized ILs [20] and greater than that of amide-containing imidazolium ILs.[21]

The Gibbs adsorption isotherm equation was used to estimate the maximum adsorption per molecule at the interface (Γ_{max}) and, inversely, the average area per molecule residing at the surface, $A_{min.}$[42] A_{min} increases with lengthening the alkyl chain which indicates a looser arrangement of the molecules of carbonate-functionalized IL at the air- liquid interface. The standard free energy of adsorption (ΔG^o_{ads}) was calculated from the next equation:[42]

$$\Delta G^o_{ads} = \Delta G^o_{min} - \frac{\Pi_{cmc}}{\Gamma_{max}}$$

The values of ΔG^o_{ads} obtained (Table 3) become more negative with the elongation of the alky chain. The higher magnitude of ΔG^o_{ads} compared to ΔG^o_{mic} reveals that adsorption at the air-water interface is more favoured than micellization in the bulk.

As previously discussed, the insertion of a carbonate ester functional group in the alkyl side chain of the imidazolium-based ionic liquid alters both its micellization in the bulk as well as its adsorption at the interface. To assess the relative effect of the carbonate ester moiety on these mentioned processes the cmc/C_{20} ratio[42] was calculated (Table 3). The introduction of a carbonate group leads to a substantial augmentation of the cmc/C_{20} ratio as compared to simple alkyl chain substituted homologues[15] which means that for carbonate-functionalized ILs adsorption is more favored than micellization likely because of the presence of a bulky hydrophilic group.

Potentiometric measurements. Potentiometric measurements using a Cl^- selective electrode were also performed to determine the cmc of the amphiphilic ionic liquids investigated. Figure 5 illustrates the relationship between the electrode potential (ΔE) and the surfactant concentration for C_{14}CMeImCl.

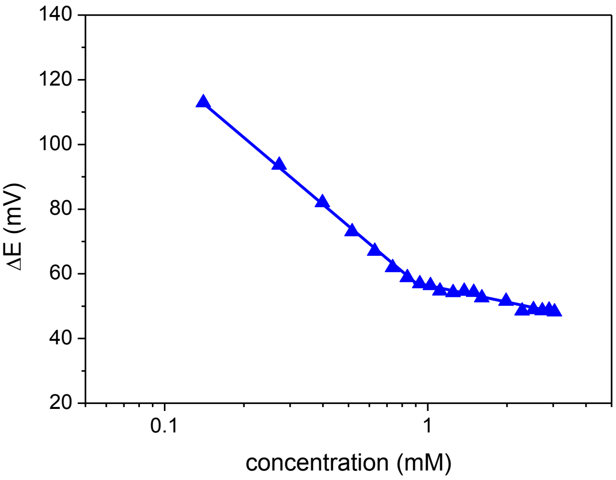


Figure 5. Electrode potential variation (ΔE) as a function of C_{14}CMeImCl concentration at 25 °C

The cmc values (Table 3) determined as the break point in the ΔE-log C plot are consistent with those obtained by conductivity and surface tension measurements. The results obtained by potentiometry confirm the higher tendency of carbonate-functionalized ILs to form aggregates with increasing the alkyl chain length.

Fluorescence measurements. The self-assembly of carbonate-functionalized ILs in aqueous solution has been also investigated by steady state fluorescence measurements employing pyrene as solvatochromic probe. The intensity ratio of the first (I_1) to the third (I_3) vibronic peaks of pyrene is a polarity index of the microenvironment of the fluorescent probe and has been determined as a function of the ionic liquid concentration (Figure 6A). The abrupt decrease in I_1/I_3 intensity indicates the formation of aggregates. The data were well fitted to sigmoidal Boltzmann type curves and the cmc values were taken as the middle point of transitions.

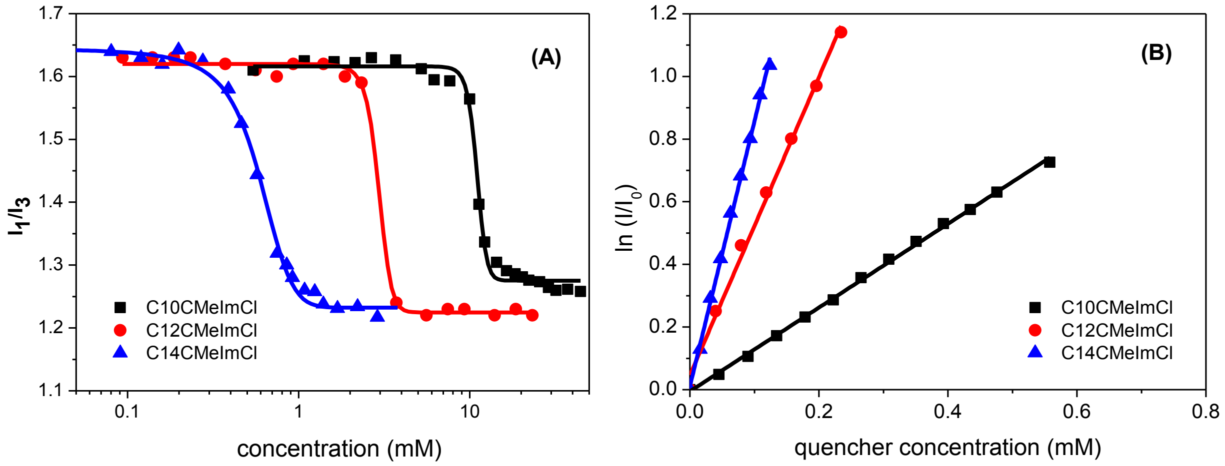


Figure 6. (A) Variation of I_1/I_3 ratio with IL concentration and (B) variation of ln (I_0/I) with quencher concentration in aqueous solution at 25 ºC

The cmc values are shown in Table 3. It can be observed that the cmc values derived from fluorescence measurements are consistent with those determined by conductivity, surface tension and potentiometric measurements.

The intensity ratio of vibronic peaks 1 and 3 (I_1/I_3) above the cmc can be contemplated as a polarity indicator of the micellar interior and can be applied to get information about compactness of aggregates. I_1/I_3 slightly decreases with the increase of the alkyl chain length indicating an increasing compactness of the aggregate on going from C_{10} to C_{12}-C_{14} carbonate-functionalized ILs. It can be attributed to augmented hydrophobic interactions with elongation of alkyl chain.

The static fluorescence quenching method has been also applied to determine the micellar aggregation number of carbonate-functionalized ILs. Pyrene and cetylpyridinium chloride were used as fluorescence probe and quencher, respectively. Probe and quencher concentrations were adjusted to maintain Poisson distribution.[49] The equation used to obtain the aggregation number (N_{agg}) was:[50]

$$ln\frac{I_0}{I} = \frac{N_{agg}C_Q}{C_{IL} - cmc}$$

where I and I_0 are the fluorescence intensities with and without quencher, respectively, at 374 nm wavelength; C_{IL} and C_Q are the concentrations of the investigated ionic liquids and quencher, respectively. Figure 6B shows the plot of ln (Io/I) as a function of the quencher concentration for the carbonate-functionalized ionic liquids.

From the slope of the linear plot between ln (I_0/I) and C_Q, the aggregation number, N_{agg}, was calculated using a fixed ionic liquid concentration above the corresponding cmc values (C_{IL}= 68, 12 and 5.3 mM for C_{10}, C_{12} and C_{14}CMeImCl, respectively). The N_{agg} values obtained for the imidazolium ILs with carbonate linkages are given in Table 3. It can be observed that the aggregation numbers for the three homologues are similar and somewhat lower than those reported for non-functionalized 1-alkyl-3-methylimidazolium chlorides[36] and for the conventional cationic surfactants alkyltrimehtylammonium bromides.[51]

Size of the micellar aggregates

Size of aggregates of carbonate-functionalized ILs in aqueous solution was determined by dynamic light scattering (DLS) measurements. DLS measurements to obtain the hydrodynamic diameter (D_h) of the micelles were carried out at concentrations 3-fold superior to the cmc value. Characteristic intensity- and number weighted size distribution profiles obtained for the ILs studied are shown in Figure 7.

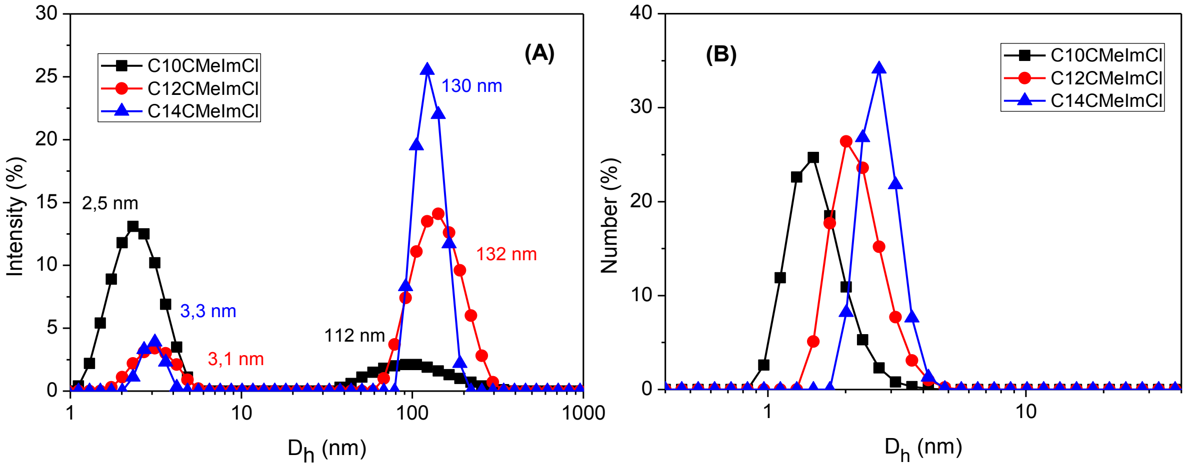


Figure 7. Size distribution profiles of micellar solutions of carbonate-functionalized ILs in terms of % intensity (A) and % number (B) obtained from DLS measurements

From intensity distribution profiles (Figure 7A), two size distributions are obtained for carbonate-functionalized ILs, one with a hydrodynamic diameter, D_h, at maximum scattering intensity in the range of 2.5-3.3 nm and the other one with D_h in the range 110-130 nm. The smaller and bigger D_h values are assigned to the existence of micelles and micellar aggregates, respectively. Number-weighted size distributions (Figure 7B) show that the number of small micelles is predominant against micellar agglomerates. Consequently, the D_h value corresponding to small micelles has been taken into account for further discussion. The average particle size for the surface active ionic liquids studied at a concentration three times superior to the cmc was: 2.5, 3.1 and 3.3 nm for C_{10}, C_{12} and C_{14}CMeImCl, respectively. Micelles seem to grow slightly in size with elongation of the alkyl chain for the carbonate-functionalized ILs. D_h value obtained for C_{12}CMeImCl micelles is consistent with the reported value of 2.7 nm determined by DLS for the corresponding amide-functionalized counterpart.[12] D_h values of micelles formed by carbonate-functionalized imidazolium-based ILs were found to be somewhat lower than two-fold the hydrocarbon extended chain length of the cation (around 1.4, 1.7 and 1.9 nm for the decyl, dodecyl and tetradecyl hydrocarbon chains, respectively, according to Tanford[52]) which indicates the formation of tightly packed spherical micelles. This fact suggests the spontaneous formation of small micelle-like aggregates when self- assembly of carbonate-functionalized ILs occurs.

Antimicrobial activity

The antimicrobial activity of the carbonate-functionalized imidazolium-based ILs synthetized was assessed against a range of clinically relevant microorganisms including seven strains of bacteria, four Gram-positive cocci and bacilli and three Gram-negative rods, and one strain of fungi. Microbiological toxicity was assessed by determining the minimum inhibitory concentration (MIC) values which are summarized in Table 4.

Table 4. MIC values for 1-alkyloxycarbonyloxyethyl-3-methylimidazolium chlorides, $C_nCMeImCl$

Microorganisms	MIC (μM)		
	$C_{10}CMeImCl$	$C_{12}CMeImCl$	$C_{14}CMeImCl$
Gram-positive cocci			
Kocuria rhizophila	93	21	20
Staphyloccocus epidermidis	46	21	10
Staphyloccocus aureus	46	11	5
Gram-positive bacilli			
Bacillus subtilis	93	21	20
Gram-negative rods			
Escherichia coli	186	85	79
Klebsiella pneumoniae	742	171	R
Pseudomonas aeruginosa	742	341	R
Fungi			
Candida albicans	186	42	40

MIC: the lowest concentration of compound that prevents visible growth of the microorganism tested, R: resistant microorganism at the highest concentration tested (256 mg/L)

Imidazolium-based ILs with carbonate linkages exhibit a broad spectrum of antimicrobial activity (Table 4). These compounds show high antimicrobial activity (MICs from 2 to 64 mg/L) against Gram-positive and fungi and moderate activity against Gram-negative bacteria (MICs from 32 to > 256 mg/L). It results particularly remarkable the susceptibility of *Staphylococcus* sp. (*S. aureus* and *S. epidermidis*) to the action of these novel surface active ILs.

Gram-positive and fungi were found to be clearly more sensitive to these compounds than Gram-negative bacteria. Differences in susceptibility towards the action of the surface active ionic liquids can be justified on the basis of the structural differences between Gram-negative and Gram-positive bacteria.[53] Surface active imidazolium-based ionic liquids are structurally related to quaternary ammonium compounds which are known to be active membrane agents, i.e., with a target site predominantly at the cytoplasmic membrane. Amphiphilic cationic compounds produce an impairment of the structural organization of the cytoplasmic membrane in bacteria through electrostatic interaction and insertion into the lipid domains of the cell membrane and other adverse effects to the bacterial cell.[54] Gram negative outer membrane may protect the bacteria from the entry of ionic surface active compounds that would normally disrupt the inner membrane or the peptidoglycan cell wall whereas the bacterial cell wall of Gram positive bacteria may adsorb these compounds and carry them to the inner cell membrane.

Mean MIC values for the carbonate-functionalized homologues against Gram-positive, Gram-negative and fungi are plotted in Figure S4. The antimicrobial activity of the carbonate-functionalized ILs trends to increase with elongation of the alkyl chain as previously reported for other amphiphilic ionic liquids.[10,20,21,23,55] Maximum antimicrobial efficiency is found for C_{14}CMeImCl against Gram-positive and fungi and for C_{12}CMeImCl against Gram-negative bacteria (Figure S4). The maximum biological effect at a specific chain length is associated with the combination of various physicochemical parameters such as hydrophobicity, adsorption and accumulation at the cell wall, cmc, transport in the test medium and aqueous solubility.[56] The antimicrobial activity of carbonate ILs will depend on their adsorption on cell wall membrane and subsequent penetration inside the living cell to alter the permeability of the membrane. Some of the physicochemical parameters previously mentioned show opposite trends resulting in maximum activity at a determined chain length. For the carbonate-functionalized ILs, the elongation of the alkyl chain of carbonate ILs is accompanied by a decrease in the cmc (Table 3), therefore, the monomer surfactant concentration at the cell membrane becomes lower for longer homologues. On the other hand, free energy of adsorption (ΔG^{o}_{ads}) of carbonate-functionalized ILs largely increases with the hydrophobic chain length (Table 3) suggesting a rise in the migration rate of the surfactant to the cell wall interface with lengthening the alkyl chain. For the ILs examined, the combined action of these variables determines that the C_{12}-C_{14} homologues present the largest tendency to be adsorbed at the bacterial/water interface and hence show the highest antimicrobial efficiency.

The antimicrobial efficiency of carbonate-functionalized ILs is clearly superior to non-functionalized ILs because, at the same alkyl chain length, MICs values for carbonate ILs are from 4 to 25- fold lower against Gram-positive bacteria and the antifungal activity increases from 4 to 37-fold regarding to non-functionalized ILs.[10] Hence, the insertion of a carbonate ester group in the alkyl side chain enhances significantly the antimicrobial and antifungal activity of the imidazolium salts. This could be attributed to the higher adsorption efficiency (pC_{20}) of carbonate-functionalized ILs as compared to non-functionalized ILs[15] that would promote the interaction with cell bacterial membrane. As compared with other functionalized imidazolium-based ILs, the antimicrobial efficiency of carbonate ILs results to be somewhat higher, i.e., MICs values from 2 to 8-fold lower, than those corresponding to ester- and amide-functionalized counterparts.[20,21]

Conclusions

Imidazolium-based surface active ionic liquids containing carbonate linkages exhibit a thermal stability similar to that of non-functionalized ILs and form thermotropic ionic liquid crystals which adopt smectic mesophases. These compounds display surface activity and their cmc values decrease with lengthening the alkyl chain as takes place for cationic surfactants in aqueous solution. As compared to non-functionalized ILs, the insertion of a carbonate ester moiety in the alkyl chain favours adsorption at the air-water interface and self-aggregation in the bulk solution. Carbonate-functionalized ILs show higher tendency to aggregate and form micelles at a concentration range 3-5 fold lower than non-functionalized ILs. Compared to other functionalized ILs, the cmc values are similar to those corresponding to ester-functionalized counterparts and slightly lower than those of amide-functionalized homologues. DLS measurements indicate that carbonate ILs form small micelle-like aggregates above the cmc. Micelles seem to be slightly more compact on going from C_{10} to C_{12}-C_{14} whereas aggregation numbers are similar for the three homologues. Regarding biological activity, carbonate-functionalized ILs present a wide spectrum of antimicrobial activity against clinically relevant microorganisms. Biological activity of ILs rises with the hydrophobic character of the molecule, the optimum biological effect is found for C_{12} homologues against Gram-negative bacteria and for C_{14} homologues against Gram-positive and fungi. As compared to non-functionalized ILs, the introduction of a carbonate ester group in the alkyl chain enhances significantly the antimicrobial activity against fungi and Gram-positive being particularly remarkable the efficacy and selectivity of these compounds against *Staphylococcus* sp. It has been proved that functionalization of the alkyl side chain of the imidazolium salts can modify not only the aggregation behavior but also lead to changes in both efficiency and spectrum of antimicrobial activity of amphiphilic ILs. These findings can contribute to the development of safer ILs with better physicochemical and biological properties for preparation of nanostructured materials, biocatalysis and biotechnological applications.

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Supporting Information (SI) contents: Synthesis and characterization data of carbonate-functionalized ILs (pages S2-S4); Microorganism strains for testing antimicrobial susceptibility (page S5); Setup of the microtiter plates for antimicrobial susceptibility testing (Figure S1); TGA curve (Figure S2); Effect of alkyl chain length on the cmc (Figure S3); Mean MIC values of carbonate-functionalized homologues on Gram-positive, Gram-negative and fungi (Figure S4).

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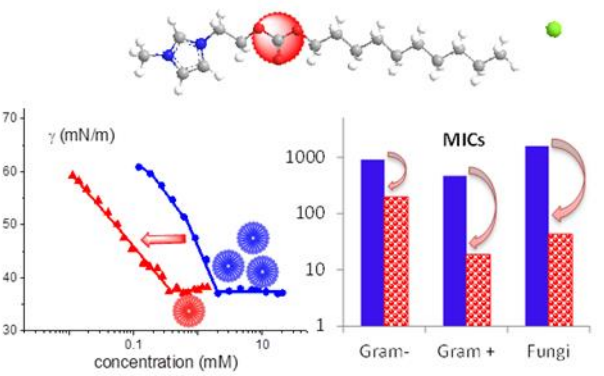
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50
40
30
0.1
10
concentration (mM)
MICs
1000
100
10
1
Gram-
Gram +
Fungi