



## Self-assembly and antimicrobial activity of long-chain amide-functionalized ionic liquids in aqueous solution



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### ABSTRACT

Surface active amide-functionalized ionic liquids (ILs) consisting of a long alkyl chain (C<sub>6</sub>–C<sub>14</sub>) connected to a polar head group (methylimidazolium or pyridinium cation) via an amide functional group were synthesized and their thermal stability, micellar properties and antimicrobial activity in aqueous solution investigated. The incorporation of an amide group increased the thermal stability of the functionalized ionic liquids compared to simple alkyl chain substituted ionic liquids. The surface activity and aggregation behaviour in aqueous solution of amide-functionalized ionic liquids were examined by tensiometry, conductivity and spectrofluorimetry. Amide-functionalized ILs displayed surface activity and their critical micelle concentration (cmc) in aqueous media decreased with the elongation of the alkyl side chain as occurs for typical surfactants. Compared to non-functionalized ILs bearing the same alkyl chain, ionic liquids with an amide moiety possess higher surface activity (*p*C<sub>20</sub>) and lower cmc values. The introduction of an amide group in the hydrophobic chain close to the polar head enhances adsorption at the air/water interface and micellization which could be attributed to the H-bonding in the headgroup region. The antimicrobial activity was evaluated against a panel of representative Gram-negative and Gram-positive bacteria and fungi. Amide-functionalized ILs with more than eight carbon atoms in the side chain showed broad antimicrobial activity. Antibacterial activities were found to increase with the alkyl chain length being the C<sub>12</sub> homologous the most effective antimicrobial agents. The introduction of an amide group enhanced significantly the antifungal activity as compared to non-functionalized ILs.

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### 1. Introduction

Ionic liquids are currently receiving increasing interest as a new class of non-molecular, ionic solvents in organic synthesis, catalysis, separation processes and preparation of nanostructured materials [1–6]. Most widely studied ILs are comprised of bulky, asymmetric N-containing organic cations in combination with any wide variety of anions, ranging from simple inorganic anions to more complex organic species [1]. Due to their negligible vapour pressure and non-flammability they are regarded as environmentally friendly alternatives to volatile organic solvents. In addition, their properties such as hydrophilicity/hydrophobicity and miscibility with organic solvents or water can be tuned by changing the N-alkyl substituents and/or the anion [7,8]. Moreover, the incorporation of functional groups as a part of the cation and/or anion

can impart a particular capability to the ionic liquid for specific purposes [9]. For example, long-chain ether-functionalized ionic liquids have been reported as novel media for specific homogenous enzymatic reactions [10] and a hydrophobic amide-functionalized ionic liquid has been used for selective extraction of tryptophan with higher extraction efficiency [11].

Imidazolium and pyridinium ionic liquids with alkyl side chains longer than four are generally regarded as amphiphilic compounds and behave as typical cationic surfactants in aqueous solution [12–16]. The self-organization of ionic liquids in aqueous solution may have significant effects on a variety of processes such as the extraction of compounds from IL-containing systems, the synthesis and purification of bulk ILs, the formation of dispersed or phase separated systems, etc. [17]. On the other hand, it can be expected that the incorporation of a specific functional group in the alkyl side chain attached to the cation affects the surface properties of amphiphilic ILs. Recent studies have reported that COOH-functionalized imidazolium ILs [18], long-chain β-hydroxy-γ-alkyloxy-N-methylimidazolium ILs [19] and

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amphiphilic imidazolium and pyridinium ILs with an ester group in the alkyl tail [20] show superior surface activity compared with simple alkyl chain substituted derivatives [16].

Long-chain imidazolium- and pyridinium-based ionic liquids can exhibit, besides to interfacial activity, significant biological activity against bacteria and fungi [16,17,21]. Cornellas et al. [16] found that antimicrobial activity of amphiphilic imidazolium and pyridinium ILs is closely related to their surfactant properties. Likewise, toxicology data indicate a strong correlation between the length of the alkyl chain attached to the IL cation and the resulting toxicity [22,23]. On the other hand, some authors have analyzed the effect of incorporating a specific functional group in the IL structure on its biological activity. Morrissey et al. [24] reported a notable diminution of the antimicrobial activity for imidazolium ILs containing ether or polyether side chains compared with the alkyl substituted derivatives whereas Garcia et al. [20] observed a significant increase in antifungal activity for ILs by introducing an ester moiety.

The ability of some organic functionalities to modify the specific properties of the ionic liquids by their incorporation in the cation and/or anion structure prompted us to synthesize a series of long-chain amide-functionalized ionic liquids in order to investigate the effect of a strong hydrogen bonding functionality, the amide group, on the physico-chemical and biological properties of amphiphilic ILs. In the present work, two series of ionic liquids based on imidazolium and pyridinium cations containing an amide functional group in the hydrophobic side chain attached to the polar head, 1-alkylcarbonylmethyl-3-methylimidazolium bromides and 1-alkylcarbonylmethylpyridinium bromides, have been synthesized and the effect of incorporating a strong hydrogen bonding functionality on their thermal stability, aggregation behaviour and antimicrobial activity investigated. The research is expected to contribute to further development of new functionalized ILs with higher surface and biological activities and improved thermal stability for specific purposes such as separation processes, biocatalysis and preparation of nanostructured materials.

## 2. Experimental

### 2.1. Synthesis of long-chain amide-functionalized ionic liquids

1-Alkylcarbonylmethyl-3-methylimidazolium bromides [ $C_n$ AMeImBr] and 1-alkylcarbonylmethylpyridinium bromides [ $C_n$ APyrBr] were synthesized in two steps using standard methodology [24–26]. First step involved the reaction of the commercially available amines with bromoacetyl bromide to form the desired alkylating agents. Subsequent alkylation of either methylimidazole or pyridine led to the imidazolium- or pyridinium-based ionic liquids, respectively. Experimental details of the synthesis and analytical data and spectra of the ILs synthesized are reported in the Supplementary data (Appendix A). The molecular structures of the amide functionalized ILs synthesized are given in Fig. 1.

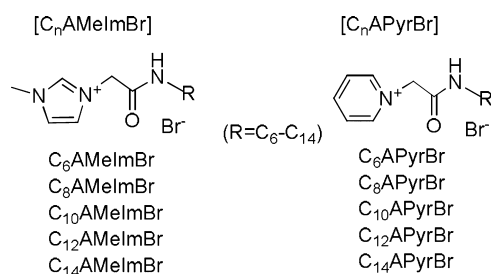


Fig. 1. Structure of the amide-functionalized ionic liquids.

### 2.2. Thermal stability measurements

Thermal stability of the amide-functionalized ILs was measured with a Mettler Toledo TGA/STGA 851 thermal gravimetric analyzer using a nitrogen atmosphere. All samples were run in aluminium pans by using a nitrogen flow rate of 20 mL/min. Thermograms were recorded using a heating rate of 10 °C/min from 25 to 550 °C.

### 2.3. Conductivity measurements

Conductivity was measured at 25 °C using an Orion Conductivity Cell 913005MD with epoxy/graphite electrode in conjunction with a Thermo Orion 5 Star multiparameter instrument with a cell constant of 0.475 cm<sup>-1</sup>.

### 2.4. Surface tension measurements

Surface tension was measured at 25 °C by the Wilhelmy plate technique using a Krüss K-12 tensiometer. Glass containers and plate were cleaned with chromic acid solution and rinsed thoroughly with distilled water. The plate was flame dried before each measurement. Surface tension was considered to be at equilibrium when the standard deviation of five consecutive measurements did not exceed 0.10 mN/m.

### 2.5. Fluorescence measurements

Steady-state fluorescence measurements were performed with a Shimadzu RF 540 spectrofluorometer equipped with a thermostated cell holder at 25 °C. Both excitation and emission band slits were fixed at 2 nm. All data were acquired using quartz cells with a 1 cm path length. Pyrene was used as fluorescence probe and its concentration was kept at 1 × 10<sup>-6</sup> M.

#### 2.5.1. Steady state fluorescence measurements for $C_n$ AMeImBr

The emission spectra of micelle-solubilized pyrene were employed for the determination of the cmc values of the amide-functionalized imidazolium-based ILs. Pyrene exhibits a fine structure in the 370–400 nm region of the steady-state fluorescence emission spectra. The nature and the intensity are extremely dependent on the polarity of the environment. The ratio of the first to the third vibronic peaks,  $I_1/I_3$  ( $I_1$  at 374 nm and  $I_3$  at 384 nm), shows the greatest solvent dependency and hence can be used to probe the micropolarity of the aggregates and obtain the cmc of the long-chain imidazolium-based ILs in aqueous solution [27,28].

#### 2.5.2. Steady state fluorescence measurements for $C_n$ APyrBr

Fluorescence probe, pyrene, was used in order to ascertain the onset of the aggregation of pyridinium-based ionic liquids in water [15,20]. The excitation wavelength used for pyrene-containing samples was 332 nm. The fluorescence was collected at 374 nm, the wavelength of the first vibronic emission band, and the ratio  $I_0/I$  (fluorescence intensity of pyrene in absence,  $I_0$ , and presence,  $I$ , of ionic liquid) was determined.

### 2.6. Antimicrobial activity

Antimicrobial tests were carried out using bacteria and fungi which are stored in our laboratory. Microorganisms were *Kocuria rhizophila* ATCC9341, *Staphylococcus epidermis* ATCC12228, *Staphylococcus aureus* ATCC5638, *Escherichia coli* ATCC27325, *Klebsiella pneumonia* ATCC13882, *Pseudomonas aeruginosa* ATCC9027, *Candida albicans* ATCC10231 and *Bacillus subtilis* ATCC6633. The antimicrobial activities were determined in vitro on the basis of the minimum inhibitory concentration (MIC) values [29] defined as the lowest concentration of antimicrobial agent that inhibits the

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