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Sustainable design for environment-friendly mono and dicationic cholinium-based ionic liquids

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ABSTRACT

Cholinium-based ionic liquids are receiving crescent interest in diverse areas of application given their biological compatibility and potential for industrial application. In this work, mono and dicationic cholinium ionic liquids as well as cholinium derivatives were synthesized and their toxicity assessed using the luminescent bacteria *Vibrio fischeri*. A range of cholinium derivatives was synthesized, using different amines and the correspondent brominated derivatives, through the alkylation of the amine with the halide in MeCN. The results indicate that their toxicity is highly dependent on the structural modifications of the cholinium cation, mainly related to the alkyl side or linkage chain length, number of hydroxyethyl groups and insertion of carbon–carbon multiple bonds. The data indicated that it is possible to perform environmentally advantageous structural alterations, namely the addition of double bonds, which would not negatively affect *V. fischeri*. Moreover, the dicationic compounds revealed a significantly lower toxicity than the monocationic counterparts. The picture emerging from the results supports the idea that cholinium derivatives are promising ionic liquids with a low environmental impact, emphasizing the importance of a careful and directed design of ionic liquid structures.

1. Introduction

"Green Chemistry" is commonly defined as the "design of chemical products and processes which reduce or eliminate the use and generation of hazardous substances" (Anastas and Warner, 1998). Notable efforts have been made focusing on the design of safer and more environmentally benign solvents, having in mind their increasing importance in the development of clean manufacturing processes. Because conventional organic solvents are often toxic, flammable and volatile, there is a crescent need for the search of new solvents and reaction media. In the last 10 years, ionic liquids (ILs) were the focus of several studies contemplating diverse areas of expertise, namely organic transformations (Haumann and Riisager, 2008), electrochemistry (Hapiot and Lagrost, 2008), nanotechnology (Ichikawa et al., 2007), biotechnology (van Rantwijk and Sheldon, 2007), process engineering (Greaves and Drummond, 2008), organic synthesis (Olivier-Bourbigou et al., 2010), and separation technologies (Han and Armstrong, 2007). Particular applications in the extraction and recovery of different (bio)molecules from fermentation broths (Ventura et al., 2013a, 2012a) or pharmaceutical wastes (e Silva et al., 2014) have been investigated. Most of the ILs used so far are characterized by a bulky organic cation (imidazolium, pyridinium, pyrrolidinium, piperidinium, ammonium, phosphonium and more recently cholinium also known as choline), substituted with alkyl chains of different lengths, types and functionalizations, and conjugated with distinct anions. Although a "more benign" nature of ILs relatively to traditional solvents is normally claimed by the authors in the field, supported on their negligible vapor pressure (reduced potential as atmospheric pollutants), ILs are wrongly labeled as "greener solvents". In fact, ILs are thermally and chemically stable, are non-flammable and have a tunable solubility in several organic compounds. However, they have a notably variable solubility in water (Freire et al., 2008, 2009, 2010) which is the most probable route favoring ILs inflow to aquatic ecosystems. Their physicochemical

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properties depend upon inter and intramolecular interactions and are, subsequently, strictly related with the countless cation/anion combinations. Nevertheless, such high flexibility can be problematic when the aim is to establish which ILs may cause serious human and environmental damage. Despite several efforts trying to make predictions regarding untested ILs through mathematical models based on quantitative structure–activity relationships, QSAR, the limitations as to the prediction of IL ecotoxicity are considerable (Matzke et al., 2010). Although model predictions should gain favor in the future as a relevant tool within the sustainable development of new ILs, these limitations make it still necessary to carry out systematic experimental studies considering the full characterization of ILs, in particular for the new ionic species synthesized. An ultimate use for comprehensive databases enclosing the (eco)toxicological profile of ILs is the support of compliance with regulatory demands when large-scale applications are intended, *e.g.* sense the REACH directive (EC, 2007) in the European Union and the United Nations Agenda 21 (Agenda 21, 2004) worldwide. According to the REACH rules, extensive IL toxicity studies with different test systems are required (Kulacki et al., 2011; Matzke et al., 2010; Petkovic et al., 2011; Pham et al., 2010; Ventura et al., 2012b, 2010, 2013b, 2013c). This knowledge is needed to provide a relevant set of information on the properties of these new chemicals, allowing their prospective risk assessment that supports the final decision on marketing authorization. In this context, the body of literature dealing with ILs, and specifically contributing to the related toxicity database, has been increasing. However, it should be noticed that most of the studies lie on the toxicity analysis of conventional ILs, namely those containing the imidazolium cation, conjugated with several anions (Frade and Afonso, 2010; Kulacki and Lamberti, 2008; Matzke et al., 2010; Petkovic et al., 2011; Pham et al., 2010; Ventura et al., 2012b; 2010, 2013b; 2013c). A considerable amount of data already related the toxicity with the introduction of oxygenated groups, mainly in the imidazolium family, the results indicating that such modification decreases the toxicity (Frade et al., 2007; Pretti et al., 2009; Samori et al., 2007; Stolte et al., 2007a; 2007b).

In fact, the number of new IL families is continuously increasing and, with it, the need for their full toxicological evaluation. Two of the most recent IL cation structures are the quaternary ammonium and its derivative, the cholinium, commonly known as choline. Albeit the increasing interest in the cholinium cation as a promising candidate to design "greener" ILs, provided that choline is a naturally occurring nutrient (Zeisel and Da Costa, 2009), the toxicity of this family is still poorly studied and the interpretation of its toxicological behavior is consequently very deficient and overgeneralized. Therefore, researchers are paying increasing attention on the toxicities of ILs, particularly on those containing the cholinium cation or cholinium derivative structures (Frade et al., 2013; Hou et al., 2013; Nockemann et al., 2007; Pernak and Chwala, 2003; Pernak et al., 2007; Ventura et al., 2014; Wang et al., 2007). Pernak et al. (2007) for example, synthesized a wide range of cholinium derivatives sharing distinct anions. With the *N* in alkoxy group varying between 6 and 12 carbons, the derivatives were found to be increasingly active against the microorganisms investigated.

Dicationic ILs are new structures characterized by the presence of two cations conjugated with two anions and connected by a principal alkyl chain where each cation has also substituted alkyl chains (Messali et al., 2013). The interest in dicationic ILs is increasing due to their higher thermal stability when compared with their monocationic counterparts. The suitability of dicationic compounds as reaction media was now studied when high temperatures are required (Han and Armstrong, 2005), to be used for capillary gas chromatography columns coating as stationary phases (Liu et al., 2012). The use of dicationic ILs enables a higher flexibility in the manipulation/tunability of their physicochemical properties; yet the knowledge available on their (eco)toxicological profile is limited (Steudte et al., 2014). Steudte et al.(2014), have performed a systematic toxicological evaluation where imidazolium-based dicationic ILs (central chain varying from 1 to 6 carbons) and their toxic effects towards several model systems, namely the acetylcholinesterase (AChE) enzyme, the promyelocytic leukemia rat cell line (IPC-81 cells), the green algae *Scenedesmus vacuolatus* and the cladoceran *Daphnia magna*, were included (Steudte et al., 2014).

In a former study (Ventura et al., 2014) the ecotoxicological effects of structural changes in the anion moiety of cholinium-based ILs, measured on the basis of the luminescence inhibition induced in *Vibrio fischeri,* were focused. As a follow-up, variations in the cation core are covered in the present work, which aims specifically at describing the synthesis of mono and dicationic cholinium derivatives, having in mind the characterization of each one of these structures in terms of their toxicity towards the same test system *V. fischeri*. In fact, the works are connected, since they both contribute for the development of knowledge of the ILs' structures/toxicity relationship, with the ultimate final goal of creating heuristic rules for the ILs design, which is often mentioned, but rarely studied. The synthesis of 17 monocationic and 8 dicationic cholinium (or cholinium-derivative) ILs conjugated with the bromide anion (Br^-) is reported and their toxicity against the luminescent marine bacteria *V. fischeri* is evaluated and reported. The monocationic structures were selected to evaluate the influence of alkyl chains lengths and their functionalization with a double or triple bond, the number of hydroxyethyl groups at the cation and the substitution of an alkyl chain by a hydrogen atom. The dicationic cholinium derivatives allow evaluating the effects of the length of the linkage alkyl chain (used to connect the two cations) and the number of hydroxyethyl groups substituted in the alkyl chains.

2. Material and methods

2.1. General procedure for the synthesis of choline derivatives

A range of choline derivatives was synthesized, using different amines, *e.g.* 2-(dimethylamino)ethanol, *N*-methyldiethanolamine, diethanolamine and triethanolamine, and the correspondent brominated derivatives. Most of the quaternary ammonium salts (Series **A** and **B**; Table 1) were prepared by alkylation of a tertiary amine with the correspondent brominated derivative. Likewise, the bisquaternary ammonium salts (Series **C**; Table 2) were synthesized by alkylation of a tertiary amine with an alkyl dihalide (Scheme 1). The synthesized ILs are stable at room temperature, and thus they can be stored at this temperature once carefully closed (to avoid the accumulation of water, since some of them are hygroscopic).

The synthesis was run in general as follows (details for each salt are provided as Supplementary information; S4–S14).

Series **A** (Table 1)—In an Aldrich ace pressure tube (Z181064) at room temperature, a solution of the correspondent brominated derivative (45 mmol) dissolved in MeCN (5 mL) was added to a solution of 2-(dimethylamino)ethanol (4.1 g, 45 mmol) in MeCN (5 mL). The reaction mixture was heated overnight at 60 °C, unless stated. For compounds **A1** and **A3**, the salt precipitated during the reaction, while for compound **A7**, the salt precipitated when the Aldrich ace pressure tube was cooled until room temperature. Diethyl ether was added and the salt was filtered and dried under vacuum. For compounds **A2**, **A4**, **A5**, **A6** and **A8**, in which the reaction mixture was liquid-, the solvent was evaporated and diethyl ether was added to precipitate the final product. The salt (IL) was then filtered and dried under vacuum.

Series **B** (Table 1)—In an Aldrich ace pressure tube (Z181064) at room temperature, the brominated derivative (45 mmol), the tertiary amine or diethanolamine (for **B1**) (45 mmol) and MeCN (5 mL) were added. If indicated, a catalytic amount of sodium iodide was added to the reaction mixture. The reaction mixture was heated at 60 °C overnight, unless stated. For compounds **B1**, **B2**, **B3**, **B5**, **B6**, **B7** and **B8**, the solvent was removed by evaporation under vacuum to obtain the correspondent ammonium salt. For compound **B4** after the reaction reach the room temperature, diethyl ether was added to precipitate the salt. This final product was then filtered and dried under vacuum.

Series **C** (Table 1)—In an Aldrich ace pressure tube (Z181064) at room temperature the brominated derivative (42 mmol), the tertiary amine (84 mmol) and MeCN (5 mL) were added. If indicated, a catalytic amount of sodium iodide was added to the reaction