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Binding interactions of anesthetic drug with surface active ionic liquid

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ABSTRACT

The application of aggregation behavior of a surface active ionic liquids (SAILs), 1-dodecyl-3-methylimidazolium chloride [C_{12}mim][Cl] and 1-tetradecyl-3-methylimidazolium chloride [C_{14}mim][Cl] in drug delivery of lidocaine hydrochloride has been investigated from surface tension and fluorescence measurements at 298.15 K and from conductance at 288.15, 298.15 and 308.15 K. Critical aggregation concentration (*CAC*), degree of ionization (α), and various thermodynamic parameters like Gibbs free energy of aggregation ($\Delta G^{\circ}_{agg.}$) standard enthalpy of aggregation ($\Delta H^{\circ}_{agg.}$) and standard entropy of aggregation ($\Delta S^{\circ}_{agg.}$) are calculated using conductivity measurements. The surface activity of the ILs in various mixed solvents are examined from surface tension measurements by calculating various surface parameters like maximum surface excess concentration (Γ_{max}), minimum surface area per ionic liquid molecule (A_{min}), adsorption efficiency (pC_{20}), effectiveness of surface tension reduction (Π_{cac}) surface tension at *CAC* (γ_{cac}), *p* (packing parameter), and *CAC* at different compositions. Fluorescence measurements have been employed to get detailed insight of the local microenvironment of the aggregates, and critical aggregation concentration (*CAC*). Decrease in the *CAC* values was observed with the increase in the amount of drug which is attributed to the balancing between electrostatic and hydrophobic interactions. This shows that the spontaneity of aggregation process of IL increases with the increase in the concentration of drug.

1. Introduction

Ionic liquids (ILs) have a number of fascinating properties, such as negligible vapor pressure, nonflammability, high thermal stability, remarkable solvation abilities [1,2], exhibit low toxicity, antimicrobial activity [3,4] and a wide range of applications covers their use in extraction and separation, biocatalysts, organic synthesis, electrochemistry, polymer science, and lubricants [5–7]. The presence of long alkyl chain in ILs make them somewhat more special as they start behaving like surfactants and are referred to as surface-active ionic liquids (SAILs) [8–10]. Hence, by considering the base of structure-activity relationships (SARs), it can be assumed that like cationic surfactants SAILs also possess surface-active properties and tend to form micelles in aqueous solutions [11]. Thereby, these ILs can be used in place of conventional cationic surfactants due to their unique applications in many fields of daily life [12]. These ILs are also found to have enormous biological applications by virtue of their antimicrobial activity [13–15]. The aforementioned applications of these SAILs have generated our interest in exploring the behavior of SAILs towards lidocaine hydrochloride drug. The most widely studied SAILs are imidazolium cation based ILs [9,16–18]. Additionally, the main thing about the imidazole ring is its presence in many biomolecules like the amino acid histidine, which has an imidazole side chain and plays a vital part in many biological activities. The hydrophobicity of ILs can be changed by varying the alkyl chain length, the type of headgroup, and the nature and size of the counterion. This allows a fine-tuning of both the structure and delicate dynamics of their micellar aggregates [4]. SAILs have a good and important scope in pharmaceutical sciences due to their ability to enhance the permeability of drugs across the biological membranes. As the micelles have small size and the stability of drug molecules in micelles is high, they can be used as drug carriers, which is more advantageous as compared to other drug carriers [19]. Moreover, to increase bioavailability, to minimize the loss and degradation and to prevent harmful side effects of drug micelles can be used as drug carriers, which is due to the reason that the micelles minimize the drug's contact with inactivating species like enzymes and others present in biological fluids as compared to free drug molecules [20,21]. Although there are many reports in the literature on interactions of drugs with conventional surfactants, but limited study has been done on the interactions of SAILs with drugs [22–24]. Rangel-Yagui et al. [25] have figured out the solubility of drug molecules with surfactants and concluded that micelles act as better drug carriers. Mahajan et al. [26] have investigated the binding ability of drug with surface-active ionic liquids. They found that SAILs act as better drug carrier as compared to conventional cationic surfactants. Sanan et al. [27] have studied the effect of composition and dilution on the micellar transition in cationic IL-Ibuprofen aqueous mixtures.

Since SAILs are known to exhibit low toxicity and have better surface active properties than conventional surfactants, they can be used to

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study their interactions with drugs. Keeping these properties of SAILs in view, an attempt has been made to study the applications of $[C_{12}mim][Cl]$ and $[C_{14}mim][Cl]$ as drug carrier. The drug chosen for the study is lidocaine hydrochloride, which is a local anesthetic drug. It is used intravenously for the treatment of ventricular arrhythmias, which occurred during the course of open-heart surgery. Lidocaine Hydrochloride is also used effectively for the treatment of liver diseases and renal failure. This drug was found to be safe and highly effective [28,29]. To make it more effective an attempt has been made to study this drug with SAILs by studying the aggregation behavior using surface tension, conductance, and fluorescence techniques. The aforementioned applications of SAILs have motivated us to explore the interactions between them. This allows the evolution of number of SAILs in curing numerous diseases and in the development of pharmaceuticals. Literature survey revealed that until now no exhaustive work has been done to study the interaction between SAILs and lidocaine hydrochloride. In this present study, the surface tension and conductivity measurements have been done to study the influence of lidocaine hydrochloride on the degree of ionization (α), critical micelle concentration (cmc) and other solution properties. A number of thermodynamic parameters like Gibbs free energy of aggregation ($\Delta G^{\circ}_{agg.}$), standard enthalpy of aggregation ($\Delta H^{\circ}_{agg.}$), standard entropy of aggregation ($\Delta S^{\circ}_{agg.}$) and various interfacial parameters like maximum surface excess concentration ($\Gamma_{max.}$), minimum surface area per ionic liquid molecule (A_{min}), adsorption efficiency (pC_{20}) effectiveness of surface tension reduction (Π_{cac}), surface tension at *CAC* (γ_{cac}), and *p* (packing parameter) of $[C_{12}mim][Cl]$ and $[C_{14}mim][Cl]$ were obtained from conductivity and surface tension measurements. The probable location of drugs adsorption in the micelles of SAILs was identified by studying their micellization behavior. For enhanced understanding of the surrounding microenvironment of ILs aggregates, the fluorescence spectroscopy has been used by using pyrene as a polarity probe. The obtained *CAC* values are well agreed with each other and with literature value obtained by Sharma et al. [30]. The molecular structure and molecular formulae of the compounds used in the study are presented in Scheme 1. A pictorial presentation of the binding of the drug molecules with the aggregates is shown in Scheme 2.

2. Experimental

2.1. Reagents

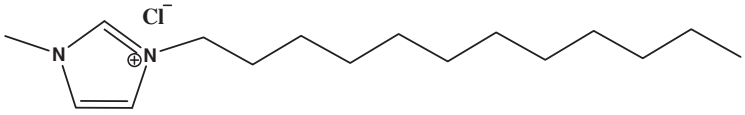
The ILs included in the study were $[C_{12}mim][Cl]$ and $[C_{14}mim][Cl]$ which were synthesized in our lab. The different compositions of drug i.e. 0% (w/w), 0.5% (w/w), 1% (w/w), 2.5% (w/w), and 5% (w/w) were prepared. The drug studied was acquired from Sigma Aldrich with purity (≥99%). Pyrene (≥99%) was also a Sigma Aldrich product. The complete details of chemicals studied in the present work are tabulated in Table 1. The solutions were prepared from triply distilled deionized and degassed water having specific conductivity $\leq 3 \times 10^{-6}$ S cm^{-1}.

2.2. Synthesis of SAILs $[C_{12}mim]Cl$ and $[C_{14}mim]Cl$

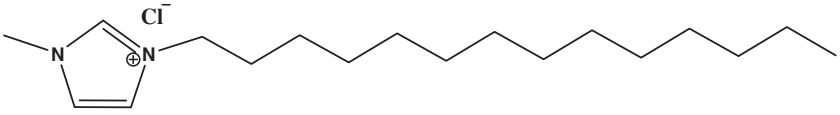
The surface active ionic liquid 1-dodecyl-3-methylimidazolium chloride $[C_{12}mim][Cl]$ and 1-tetradecyl-3-methylimidazolium chloride $[C_{14}mim][Cl]$ were synthesized according to the procedure mentioned elsewhere [31] by reacting n-chlorododecane and n-chlorotetradecane respectively with n-methylimidazole in acetonitrile media and then refluxing the solution at 90 °C for 72 h under the atmosphere of N_2. In order to remove the unreacted reactants, final product was washed many times with ethyl acetate after cooling at room temperature. Excess ethyl acetate was decanted and the left ethyl acetate was eliminated by evaporating it under vacuum in order to get the required product followed by drying it in vacuum oven for 72 h to receive the final product. Karl-Fischer titration analysis was used to find the water content in the ILs, which were <300 ppm and 290 ppm respectively and kept in a dry place before using. The SAILs were then characterized by ^{1}H NMR technique for getting chemical shifts of different protons in $CDCl_3$ operating at a frequency of 300 MHz whose δ values in ppm are given below and agreed well with those reported in [32]:

$[C_{12}mim][Cl]$: 0.88 (3H, t), 1.25–1.32 (18H, m), 1.88–1.93 (2H, m), 4.32 (2H, t), 7.35 (1H, d), 7.61 (1H, d), 4.13 (3H, s), 10.47 (1H, s).

$[C_{14}mim][Cl]$: 0.83 (3H, t), 1.23–1.32 (22H, m), 1.87–1.90 (2H, m), 4.24 (2H, t), 7.52 (1H, d), 7.55 (1H, d), 3.93 (3H, s), 10.20 (1H, s).

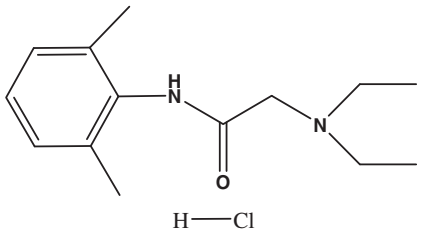


1-Dodecyl-3-methylimidazolium chloride



1-Tetradecyl-3-methylimidazolium chloride

and



Lidocaine hydrochloride

Scheme 1. Molecular structure and molecular formulae of SAILs and the drug.