



Regular Article

Aggregation behavior of non-cytotoxic ester functionalized morpholinium based ionic liquids in aqueous media

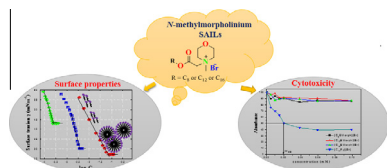


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GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:

Received 15 November 2014

Accepted 19 January 2015

Available online 30 January 2015

Keywords:

Morpholinium SAILs

Aggregation

Surface activity

Thermal stability

Cytotoxicity

ABSTRACT

Ester functionalized surface active ionic liquids (SAILs), $[C_n\text{EMorph}][\text{Br}]$, where $n = 8, 12$ and 16 , comprising of long hydrophobic chain appended with ester functionality connected to *N*-methylmorpholine group have been synthesized and investigated for their aggregation behavior and cytotoxicity. A variety of state of art techniques viz. tensiometry, conductometry, isothermal titration calorimetry (ITC), spectrofluorometry, dynamic light scattering (DLS) and atomic force microscopy (AFM) have been employed to get insight into the various aspects of aggregation behavior. The investigated SAILs have been found to possess lower critical aggregation concentration (*cac*) and greater adsorption efficacy at air–solution interface as compared to earlier reported non-functionalized SAILs or conventional ionic surfactants. Further, the thermal stability of these morpholinium cationics has been evaluated by thermal gravimetric analysis (TGA). These SAILs have been found to be non-cytotoxic in the concentration range generally required for different biological applications as judged by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay on the C6 glioma cell line. The dependence of characteristic properties of aggregation on alkyl chain length has been established.

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1. Introduction

Ionic liquids (ILs) are an important class of compounds comprising of ionic species and are liquid at or below 100 °C. Owing to their well-established unique physicochemical properties, ILs are a subject of immense interest in the avenue of material, biological and chemical sciences [1–7]. ILs have been tested for their applicability in various fields such as in organic transformations [8],

liquid–liquid extractions [9], gas adsorption and separation [10], as lubricant additives [11,12], as electrolyte in solar cells [13], and as solvent as well as template for dispersion and synthesis of nanoparticles, respectively [14] depending on the nature of constituent ions.

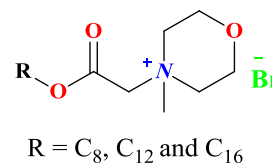
One important class of ILs is amphiphilic ILs, where ILs having hydrophobic alkyl chain longer than four carbon atoms have been considered as surface active ionic liquids (SAILs). The investigations on aggregation behavior of SAILs have gained momentum in the recent times. Numerous SAILs based on a variety of cationic head groups such as pyridinium [15], imidazolium [16], morpholinium

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[17], amino acids [18] and pyrrolidinium [19], have been synthesized, characterized and investigated for their aggregation behavior. These SAILs have been found to self-assemble where characteristic properties of aggregates depend on the nature of the solvent and nature of the constituent ions of SAILs. In recent times, SAILs composed of 1-alkyl-3-methylimidazolium cation ($[C_n\text{mim}]^+$) have been widely investigated in the field of colloid and interface science [16,20–26]. In this regard, Zheng et al., have studied the aggregation behavior of long chain imidazolium based ILs, $[C_n\text{mim}][\text{Br}]$, in aqueous medium [25]. Wang et al., have investigated the effect of counterions on the aggregation behavior of $[C_8\text{mim}][\text{X}]$ ($\text{X} = [\text{Cl}]^-$ or $[\text{Br}]^-$, $[\text{NO}_3]^-$, $[\text{CH}_3\text{COO}]^-$, $[\text{CF}_3\text{COO}]^-$, $[\text{CF}_3\text{SO}_3]^-$, and $[\text{ClO}_4]^-$) in aqueous medium [26]. Blesic et al., have studied the influence of polar head group on critical aggregation concentration (*cac*) of SAILs, 1-dodecyl-3-methylpyridinium bromide, $[C_{12}\text{mpy}][\text{Br}]$, 1-methyl-1-dodecyl piperidinium bromide, $[C_{12}\text{mpip}][\text{Br}]$, and 1-methyl-1-dodecylpyrrolidinium bromide, $[C_{12}\text{mpyr}][\text{Br}]$ in aqueous solutions [27]. Our own group has reported the aggregation behavior of a variety of SAILs including those based on amino acid based cations [15–17] where it has been established that the nature of ionic head group, cation and length of alkyl chain governs the aggregation behavior of SAILs. Further, a careful examination of literature regarding aggregation of SAILs reveals that the introduction of an amide [17], ether or hydroxyl [28], and ester group [29], in the molecular structure of SAILs led to marked changes in their surface as well as bulk behavior. In this regard, the hydrophobic alkyl chain of SAILs is a key moiety which can be functionalized with a variety of functional groups to achieve better aggregation behavior of SAILs. In this scenario, amide functionalized morpholinium based SAILs and ester functionalized imidazolium and pyridinium based SAILs possessing better surface active properties as compared to conventional ionic surfactants or non-functionalized SAILs have been reported [17,29]. The presence of easily cleavable functional group such as an ester group, if present in SAIL structure, has been found to increase the proclivity of SAILs towards biodegradation [30]. Beside their physicochemical study, some of the SAILs have also been recently explored in biological applications owing to their antimicrobial nature [29] and as a gene or drug delivery carrier [31,32]. They have been found to enhance the permeability of DNA/drug through biological membrane. Therefore it is of interest from biological point of view to explore and access the bio-physicochemical properties of newly synthesized SAILs. Further, survey of the literature regarding synthesis and investigation on aggregation behavior of SAILs manifest that investigations on morpholinium based SAILs are much lacking [17,33].

Pursuant to continued research on functionalized SAILs [17,28], we herein, report the synthesis, aggregation behavior and cytotoxicity of a series of three ester functionalized morpholinium based SAILs, $[C_n\text{EMorph}][\text{Br}]$ where $n = 8, 12$ and 16 , in aqueous medium. A variety of parameters characteristic to aggregation such as critical aggregation concentration (*cac*), surface tension at the *cac* (γ_{cac}), adsorption efficiency (pC_{20}), effectiveness of surface tension reduction (Π_{cac}), Gibbs free energy of the aggregation (ΔC_{agg}^0), Gibbs free energy of adsorption (ΔC_{ads}^0), and aggregation number (N_{agg}) etc., have been deduced utilizing tensiometry, conductivity, steady-state fluorescence and isothermal titration calorimetry (ITC) measurements. Dynamic light scattering (DLS) and atomic force microscopy (AFM) have been employed to get information about size and shape of the aggregates. The novel aspect of the present work lies in the fact that there exists no report on synthesis, self-assembly and cytotoxicity behavior of ester functionalized morpholinium based SAILs. The present work is expected to encourage other research groups to carry out such studies to get better surface active properties of SAILs along with lower cytotoxicity leading to advancement in colloidal and interfacial sciences.



Scheme 1. Molecular Structure of the Investigated ester functionalized SAILs.

2. Material and methods

2.1. Materials

Octanol (>99.0%), lauryl alcohol (>99.0%), cetyl alcohol (>99.0%), cetylpyridinium chloride (>99.0%), 1-methylmorpholine (>99.0%), bromoacetic acid (>99.0%), pyrene (>99.0%) and *p*-toluenesulfonic acid monohydrate (>98.5%) were purchased from Sigma Aldrich, India. Chloroform (AR grade), methanol (AR grade), acetone (AR grade) and diethyl ether (AR grade) were purchased from SD fine-chem Ltd, Mumbai, India. Millipore water having resistivity 18.2 M Ω was used in all experiments. The synthesis methodology of investigated SAILs, $[C_n\text{EMorph}][\text{Br}]$, and characterization data has been provided in [Scheme S1](#) and [Annexure S1 \(Supporting Information\)](#), respectively. [Scheme 1](#) shows the molecular structure of the investigated SAILs.

2.2. Methods

Surface tension measurements were performed using a Data-Physics DCAT II automated tensiometer employing the Wilhelmy plate method. The temperature of the measurements was controlled by a Julabo thermostat within the accuracy of ± 0.1 K. Before each measurement, Wilhelmy plate was cleaned and dried with caution to avoid any contamination. The data was obtained in triplicate and found to be accurate within ± 0.1 mN m⁻¹. The specific conductance was measured using a digital conductivity meter (Systronics 308) employing a cell of unit cell constant. Prior to the measurements, the conductivity cell was calibrated using aqueous solutions of KCl at different concentrations. Temperature of the measurement cell was controlled with a Julabo water thermostat within ± 0.1 K. Measurements were performed in triplicate with an uncertainty of less than 0.5%. The calorimetric measurements were made using a MicroCal ITC200 microcalorimeter, equipped with an instrument controlled Hamilton syringe having a volume capacity of 40 μL . The titration was performed automatically by adding 2 μL aliquots of prepared concentrated stock solution of SAILs into the sample cell containing 200 μL of water with continuous stirring of 600 rpm. The enthalpy change at each addition was measured and plotted against the concentration of SAILs by using origin software provided with the instrument. Fluorescence measurements were performed in the range 350–500 nm using a Perkin–Elmer Luminescence spectrometer LS-55 and pyrene as an external fluorescent probe at an excitation wavelength of 334 nm using an excitation and emission slit width of 2.5 nm, each. The concentration of pyrene was kept as 0.002 mM to avoid the formation of excimer. Temperature of the measurement cell was controlled using a built-in peltier device with the accuracy of ± 0.1 K. Pyrene fluorescence quenching experiment was performed to get the aggregation number (N_{agg}) of aggregates using cetylpyridinium chloride as quencher. DLS measurements were performed using a light scattering apparatus (Zeta-sizer, nano-series, nano-ZS) Malvern Instruments, equipped with a built-in temperature controller having an accuracy of ± 0.1 K. The sample was contained in a quartz cuvette of path length 1 cm. All the measurements were made in back scattering mode at a scattering angle of 173°. Data was analyzed using the standard algorithms and is

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