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Binding interactions of anesthetic drug with surface active ionic liquid

Amalendu Pal *, Alka Yadav

Department of Chemistry, Kurukshetra University, Kurukshetra 136119, India

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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

* Corresponding author.
E-mail address: palchem21@gmail.com (A. Pal).

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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

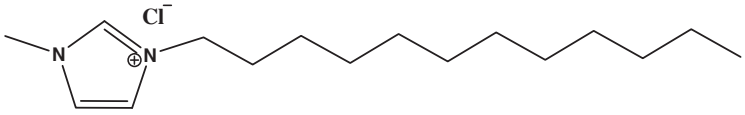
The ILs included in the study were $[C_{12}mim][Cl]$ and $[C_{14}mim][Cl]$ which were synthesized in our lab. The different compositions of drug i.e. 0% (w/w), 0.5% (w/w), 1% (w/w), 2.5% (w/w), and 5% (w/w) were prepared. The drug studied was acquired from Sigma Aldrich with purity (≥99%). Pyrene (≥99%) 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 $[C_{14}mim]Cl$

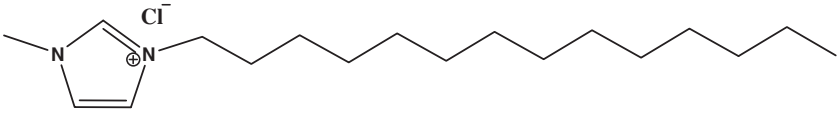
The surface active ionic liquid 1-dodecyl-3-methylimidazolium chloride $[C_{12}mim][Cl]$ and 1-tetradecyl-3-methylimidazolium chloride $[C_{14}mim][Cl]$ were synthesized according to the procedure mentioned elsewhere [31] by reacting n-chlorododecane and n-chlorotetradecane respectively with n-methylimidazole 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).

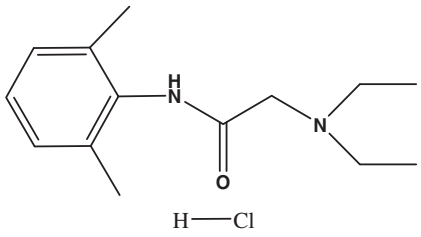


1-Dodecyl-3-methylimidazolium chloride



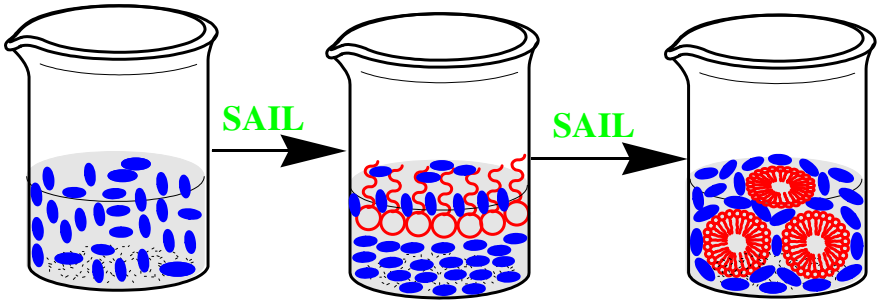
1-Tetradecyl-3-methylimidazolium chloride

and



Lidocaine hydrochloride

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



Scheme 2. Schematic diagram showing interactions between the molecules of lidocaine hydrochloride and the ionic liquid molecules.

2.3. Instruments and methods

The samples were prepared using an A & D Co. limited electronic balance (Japan, model GR-202) with a precision of 0.01 mg by weighing the required amount of chemicals. The SAILs were characterized by ^{1}H NMR spectra taken on a Brüker FT-NMR spectrometer using $CDCl_3$ as an external solvent.

2.3.1. Surface tension measurements

Du Nuoy tensiometer (ring detachment method) was used for obtaining surface tension measurements, which was purchased from SD Hardsons Ltd. having a precision of ± 0.01 mN m^{-1}. The ring used in the study was platinum-iridium ring with a mean circumference of 6.00 cm and was calibrated before performing each experiment. The experiments were performed at 298.15 K and water thermostat was used to maintain the temperature in a double walled water-jacketed flow dilution cell having an uncertainty of 0.01 K. The values were measured in triplicate, and the mean value was taken into consideration. The ring was cleaned properly with triply distilled de-ionized degassed water followed by subjecting the ring to a high temperature flame to remove the residues of IL surfactant after each measurement.

2.3.2. Conductance measurements

The conductance measurements of all the studied systems were obtained using a digital conductivity meter at a temperature range of 288.15–308.15 K having an uncertainty of 0.01 K in a double walled water-jacketed flow dilution cell. The conductivity meter used was CM-183 microprocessor based EC-TDS analyser with ATC probe and conductivity cell with platinized platinum electrodes were purchased from Elico Ltd., India. The cell constant of the cell was found to be 1.0014 cm^{-1}. The uncertainty of the measurements was <4%.

2.3.3. Fluorescence measurements

For getting fluorescence emission spectra, the samples were prepared by dissolving aqueous solutions of SAILs with drug in pyrene at room temperature. Model RF-5301PC with blazed holographic grating excitation and emission monochromators fitted with a 150 W Xenon lamp was used to obtain fluorescence emission spectra. The quartz cuvette and the fluorometer used were purchased from Shimadzu. The stock solution of pyrene and the solutions for fluorescence measurements were prepared properly as mentioned in our earlier study [33]. For obtaining emission spectra the excitation wavelength was kept at 334 nm in the range of 350–600 nm using an excitation and emission slit width of 3 nm. The interactions between the drug and the surface active ionic liquids were investigated using fluorescence technique into two ways. Firstly, the aggregation behavior of both the ionic liquids has been studied by using an external hydrophobic probe, pyrene and secondly, by studying the effect of addition of ionic liquids on the maxima fluorescence intensity of the drug.

(a) *CAC measurements.* The characterization of the aggregates has been done by employing fluorescence method using pyrene as an external probe. The concentration of the pyrene was kept 1×10^{-6} M and its spectra were recorded from 350 to 600 nm keeping the excitation wavelength at 334 nm. The excitation and emission slit width were kept 5 and 3 nm respectively. After each addition the solutions were kept for 5 min in order to attain the thermal equilibrium. At least three measurements were taken and the mean value was considered. The *CAC* of both ILs was obtained by taking the ratio of the first to the third vibronic peaks i.e. I_1/I_3 which is very sensitive to the polarity of the surrounding microenvironment, versus the concentration of ionic liquids as shown in Fig. 4. The curves were fitted sigmoidally and the mid-point of which gives the *CAC* of the system.

(b) *Steady State Fluorescence measurements.* In order to understand the nature of the interactions between the drug and the ionic liquids fluorescence-quenching method has been studied by titrating the drug with ionic liquids. The fluorescence emission spectra of the lidocaine hydrochloride were recorded in the range of 250–400 nm at an excitation wavelength of 290 nm keeping the excitation and emission slit width of 5 and 3 nm respectively. The concentrations of the drug and the ionic liquids were kept 0.01 mM. The titrations were performed by adding the ionic liquids successively into the quartz cuvette containing 2 ml of drug solution and recorded the fluorescence intensities.

Table 1
Specification of chemicals.

Chemical name	Provenance	Mass fraction purity (%)
1-Methylimidazole	Acros Organics	99.0
1-Chlorododecane	Sigma-Aldrich, USA	≥99.0
1-Chlorotetradecane	Sigma-Aldrich, USA	≥99.0
Lidocaine Hydrochloride	Sigma-Aldrich, USA	≥99.0
Chloroform-d	SD Fine Chemicals, India	99.8
Pyrene	Sigma-Aldrich, USA	≥99.9
Methanol	Rankem, India	≥99.0

3. Results and discussion

The interactions between SAILs, 1-dodecyl-3-methylimidazolium chloride [C_{12}mim][Cl] and 1-tetradecyl-3-methylimidazolium chloride [C_{14}mim][Cl] with lidocaine hydrochloride have been studied in different compositions using tensiometry, conductometry, and fluorometry at 298.15 K.

3.1. Surface tension measurements

The surface tension method is an appropriate method that not only helps in investigating the aggregation behavior of SAILs but also gives important information about the adsorption process that is taking place on the interface. Surface tension method has been used to investigate the aggregation, interfacial behavior and interactions of the SAILs

[C_{12}mim][Cl] and [C_{14}mim][Cl] with lidocaine hydrochloride at 298.15 K. The *CAC* values gained from various techniques are tabulated in Table 2, which are well agreed with each other. By putting forth the well known Gibbs equation, a series of various surface parameters like *CAC*, pC_{20}, Π_{cac} (surface pressure at the interface), γ_{cac}, (surface tension at *CAC*), and $A_{min.}$(minimum area occupied by a single molecule), Γ_{max} (maximum surface excess concentration), and *p* (packing parameter) have been obtained which are provided in Table 3. Fig. 1 (a) and (b) show the variation in the surface tension of [C_{12}mim][Cl] and [C_{14}mim][Cl] with different concentration of lidocaine hydrochloride at 298.15 K. Initially, the surface tension decreases constantly with the increase in the concentration of SAILs but it becomes constant after a certain point, which is due to the reason that in the bulk phase, the aggregates start forming and at the surface layer, the concentration becomes almost constant. The breakpoint appeared in the plots represent the *CAC* values and the value of surface tension at *CAC* gives γ_{cac}. Π_{cac} denotes the reduction in the surface tension to a minimum when the IL added to the solvents. Therefore, Π_{cac} measures the effectiveness of IL in reducing the surface tension of the solvent. Π_{cac} can be obtained by using Relation (1):

$$\Pi_{cac} = \gamma_o - \gamma_{cac} \quad (1)$$

where γ_o is the surface tension of the pure solvent.

Gibbs adsorption isotherms explain the reduction in the surface tension when the ILs get adsorbed at the surface. Γ_{max} is the maximum surface excess concentration and the adsorbed amount of the IL which can be calculated by using the following relation [34]:

$$\Gamma_{max} = -\frac{1}{nRT}\left[\frac{d\gamma}{d\ln C}\right] \quad (2)$$

where T is the absolute temperature, R is the gas constant, C is the concentration of IL in bulk solution, and n is the number of ionic species in the solution upon dissociation in water. A decrease in the values of Γ_{max} was observed on increasing drug concentration indicating the lowering of packing of IL molecules at the interface.

Further A_{min} was evaluated by using the following equation, which represents the minimum surface area occupied by an IL molecule at the surface of the solution [34,35]:

$$A_{min} = 10^{20}/N_A\,\Gamma_{max} \quad (3)$$

where N_A is the Avogadro number. Also, A_{min} gives the information about the packing density of the IL at the interface. A decrease in the packing of IL molecules at the interface was observed on increasing the concentration of drug as a result of which A_{min} increases at the surface. The adsorption efficiency denoted by pC_{20} was achieved by using the following relation [34–36]:

$$pC_{20} = -\log C_{20} \quad (4)$$

Table 2
Experimentally determined *CAC* of IL in the presence of lidocaine hydrochloride in different weight percentages from various techniques at 298.15 K.

Solvent	Critical aggregation concentration (mmol kg^{-1})		
	Surface tension	Conductance	Fluorescence
[C_{12}mim][Cl]			
0%	15.22[a]	16.6[a]	8.97[a]
0.5%	7.85	12.4	7.00
1%	5.38	6.5	4.83
2.5%	3.94	4.6	3.21
5%	2.15	2.2	2.06
[C_{14}mim][Cl]			
0%	3.63[a]	3.47[a]	3.20[a]
0.5%	1.25	1.41	1.19
1%	0.97	0.63	0.62
2.5%	0.46	0.45	0.40
5%	0.33	0.36	0.28

[a] The *CAC* values obtained are cited in literature [30].

Table 3
Various surface active parameters of aggregation of [C_{12}mim]Cl and [C_{14}mim]Cl at 298.15 K.

Solvent	Surface parameters					
	γ_{cac}	Π_{cac}	$\Gamma_{max}\times10^6$	A_{min}	p	pC_{20}
[C_{12}mim][Cl]						
0%	34.58	37.42	2.16	0.77	0.55	2.30
0.5%	38.70	26.55	1.92	0.87	0.49	2.56
1%	35.55	22.15	1.64	1.01	0.42	2.44
2.5%	36.00	19.85	1.11	1.50	0.28	Nd
5%	34.00	18.75	0.93	1.79	0.24	Nd
[C_{14}mim][Cl]						
0%	34.15	36.65	2.25	0.74	0.57	2.89
0.5%	36.85	28.40	2.02	0.82	0.51	3.24
1%	36.55	21.15	1.53	1.09	0.39	3.20
2.5%	36.38	19.47	1.36	1.22	0.35	Nd
5%	35.94	16.81	1.06	1.57	0.27	Nd

γ_{cac} , Π_{cac}, $\Gamma_{max.}$, and $A_{min.}$ are expressed in mN m^{-1}, mN m^{-1}, mol cm^{-2}, and $Å^2$ $molecule^{-1}$ respectively.
Nd - not detected.

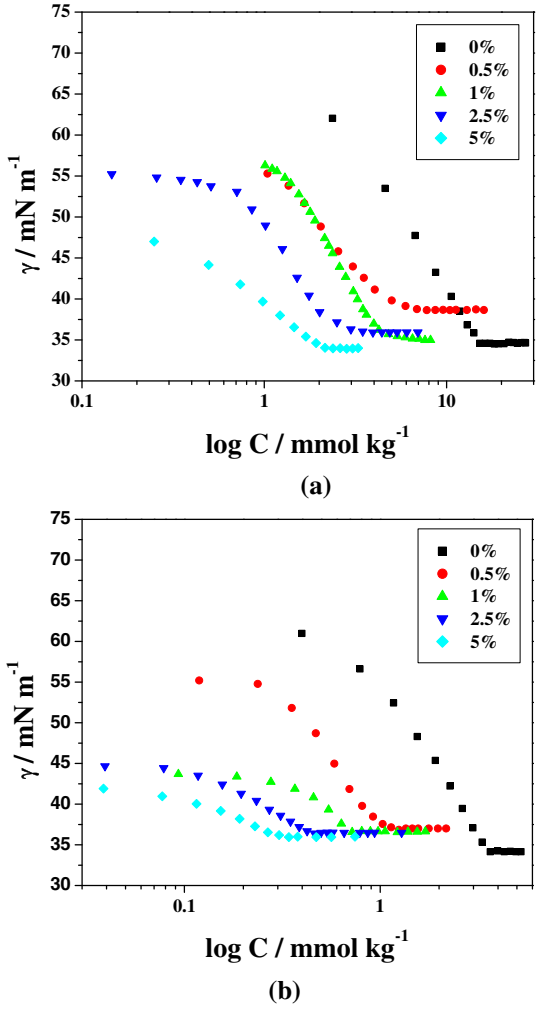


Fig. 1. Variation of surface tension as a function of SAILs concentration (a) [C_{12}mim][Cl] and (b) [C_{14}mim][Cl] in aqueous and aqueous-drug mixtures at 298.15 K for varying composition of mixed solvents: (■) 0% (w/w); (●) 0.5% (w/w); (▲) 1% (w/w); (▼) 2.5% (w/w) and (♦) 5% (w/w).

where C_{20} has its usual meaning. The greater value of pC_{20} depicts the larger adsorption efficiency and better will be the surface activity of the SAIL. The values of pC_{20} can only be achieved for pure water, 0.5% and 1% of the drug for both ionic liquids as the surface tension could not be reduced to C_{20} for the remaining mixtures. A perusal of the data of pC_{20} reveals the better surface activity of $[C_{14}mim][Cl]$ as compared to $[C_{12}mim][Cl]$.

The packing parameter (p) has been evaluated by using the following relation which helps in determining the shapes of the aggregates [35]:

$$P = V_o/l_c A_{min.} \tag{5}$$

where V_o represents the volume occupied by the long alkyl chain groups and l_c gives the length of the long alkyl chain present in the mid of the aggregate were determined using Tanford's formulae [37]:

$$V_o = [27.4 + 26.9\,(n_c - 1)]2\ \left(Å^3\right) \tag{6}$$

$$l_c = [1.54 + 1.26\,(n_c - 1)]\ (Å) \tag{7}$$

Generally, in both the above formulae the number of carbon atoms taken is one less than the total number of carbon atoms in the hydrocarbon chain (n_c) which is due to the reason that the first carbon atom attached to the long alkyl chain is more solvated and is considered a portion of it. Keeping concentration about 10 times of the *CAC*, the obtained values of p for pure ILs is higher than 0.33, which indicates the formation of vesicles. From Table 3, it can be observed that with the increase in the concentration of drug, the shape of the aggregates changes from vesicles to cylindrical to spherical [38]. This is due to the reason that the drug molecules are residing primarily in the outer surface of aggregates which consequently increases the A_{min}. Therefore, the value of p decreases and the structure of the aggregates transforms accordingly.

By making use of surface active parameters, free energy of a surface at equilibrium ($G_{min}{}^{s}$) and standard Gibbs free energy change required for adsorption ($\Delta G^{\circ}_{ad.}$) were also evaluated in order to investigate the effect of addition of drug on the aggregation behavior of SAILs using following relations [36,39]:

$$\Delta G^{\circ}_{ad.} = \Delta G^{\circ}_{agg.} - \frac{\Pi_{cmc}}{\Gamma_{max}} \tag{8}$$

$$G^{s}_{min} = A_{min} \cdot \Pi_{cac} \cdot N_A \tag{9}$$

where $\Delta G^{\circ}_{agg.}$ is standard Gibbs free energy of aggregation achieved from conductivity measurements using Eq. (10). A perusal of the data from Table 4 reveals that the values of $\Delta G^{\circ}_{ad.}$ are more negative than their corresponding $\Delta G^{\circ}_{agg.}$ indicating the primary process which is taking place is the adsorption process as compared to aggregation. From the table it is very clear that $\Delta G^{\circ}_{ad.}$ has negative values, which shows that some work has to be done in transferring the SAIL monomers at the interface to the aggregation stage [40]. $G^{s}_{min.}$ represents the free energy of a surface at equilibrium, a thermodynamic quantity which is introduced by Sugihara et al. [41]. Its lower values indicate the formation of highly thermodynamically stable surface as a result of which it has attained greater surface activity. From Table 4, it can be seen that the values of $G^{s}_{min.}$ are increasing with the increase in the concentration of drug molecules, so it can be concluded that on increasing the concentration of drug the bulk phase is becoming more stable than the surface phase [41].

Table 4
Degree of counterion dissociation, α and thermodynamic parameters: standard free energy of aggregation ($\Delta G^{\circ}_{agg.}$), standard enthalpy of aggregation ($\Delta H^{\circ}_{agg.}$), standard entropy of aggregation ($\Delta S^{\circ}_{agg.}$), standard Gibbs free energy of adsorption ($\Delta G^{\circ}_{ad.}$) and free energy of the surface at equilibrium ($G^{s}_{min.}$) of SAILs $[C_{12}mim][Cl]$ and $[C_{14}mim][Cl]$ at 298.15 K.

Solvent	Thermodynamic parameters					
	α	$\Delta G^{0}_{agg.}$	$\Delta H^{0}_{agg.}$	$T\Delta S^{0}_{agg.}$	ΔG^{0}_{ad}	$G^{s}_{min.}$
$[C_{12}mim][Cl]$						
0%	0.35	−33.14	−8.53	24.60	−50.46	16.01
0.5%	0.34	−34.54	−7.15	27.39	−48.37	20.16
1%	0.33	−37.41	−5.91	31.51	−50.92	21.68
2.5%	0.32	−39.16	−5.00	34.16	−57.04	32.43
5%	0.30	−42.64	−4.32	38.32	−62.80	36.56
$[C_{14}mim][Cl]$						
0%	0.36	−39.26	−14.84	24.42	−55.55	15.18
0.5%	0.35	−43.26	−8.17	35.09	−57.32	18.24
1%	0.34	−46.95	−7.87	39.08	−60.77	23.89
2.5%	0.33	−48.55	−7.14	41.41	−62.87	26.75
5%	0.32	−49.83	−4.37	45.46	−65.69	33.91

Standard uncertainties are $\Delta G^{\circ}_{agg.} = \pm 0.02$ (kJ mol^{-1}), $\Delta H^{\circ}_{agg.} = \pm 0.01$ (kJ mol^{-1}), $\Delta S^{\circ}_{agg.} = \pm 0.02$ (JK^{-1} mol^{-1}), $\Delta G^{\circ}_{ad.} = \pm 0.02$ (kJ mol^{-1}), $G^{s}_{min.} = \pm 0.02$ (kJ mol^{-1}), T $= \pm 1 \times 10^{-2}$ K.

3.2. Conductance measurements

3.2.1. Determination of CAC

The *CAC* values of SAILs obtained from conductance at 298.15 K in aqueous and aqueous solutions of lidocaine hydrochloride at different weight percentages are provided in Table 2. The variation profiles of conductance of $[C_{12}mim][Cl]$ in aqueous and aqueous solution of lidocaine hydrochloride at different weight percentages at 298.15 K are given in Fig. 2 (a), (b) and (c) and for $[C_{14}mim][Cl]$ the conductance profiles are provided in Fig. 3 (a), (b) and (c). Fig. 4 (a) and (b) represent, the variation in *CAC* of SAILs with temperature as a function of different weight percentages of lidocaine hydrochloride. The *CAC* value of both the SAILs in aqueous media obtained from conductivity measurements agreed well with those reported by Sharma et al. [30]. From the conductivity profiles, it can be seen that the electrical conductivity increases with the increase in the concentration of ionic liquids. This variation in the curve implies the onset of aggregation point and the breakpoint indicates the *CAC* value. From Table 2 it can be observed that the *CAC* of $[C_{14}mim][Cl]$ is lower than $[C_{12}mim][Cl]$ which is due to the presence of long alkyl chain in $[C_{14}mim][Cl]$ as compared to $[C_{12}mim][Cl]$ and therefore has better surface activity than $[C_{12}mim][Cl]$.

A close look at Table 2 reveals that for a particular SAIL, the *CAC* decreases with the increase in the concentration of lidocaine hydrochloride. This may be due to the fact that lidocaine hydrochloride molecules being slightly polar in nature forms hydrogen bonding with water which counter balances the lateral pressure that tend to push the drug molecules into the core of the aggregates and also with the protons present in the imidazolium ring of the SAILs as a result of which the drug molecules get adsorbed on the surface of the aggregates [42]. This kind of adsorption of the drug molecules on the surface of the aggregates decreases the electrostatic repulsions among the head groups of the aggregates thereby decreasing the work required for the aggregation. The aggregation process depends on the two opposite interactions. First, the electrostatic forces of repulsions between the charged head groups, which delay the aggregation process and second, the attractive hydrophobic interactions between the long alkyl chain of SAILs, which favors the aggregation process. Here the electrostatic repulsions are being reduced by the adsorption of the drug molecules on the surface of the aggregates and hence the cac decreases.

3.2.2. Effect of temperature on CAC

The variation of the *CAC* with temperature are shown in Fig. 4 (a) and (b). The curves obtained to be a U-shaped curve. This behavior of the curve can be explained by considering two opposite factors. Firstly with increasing temperature, the degree of hydration of head group

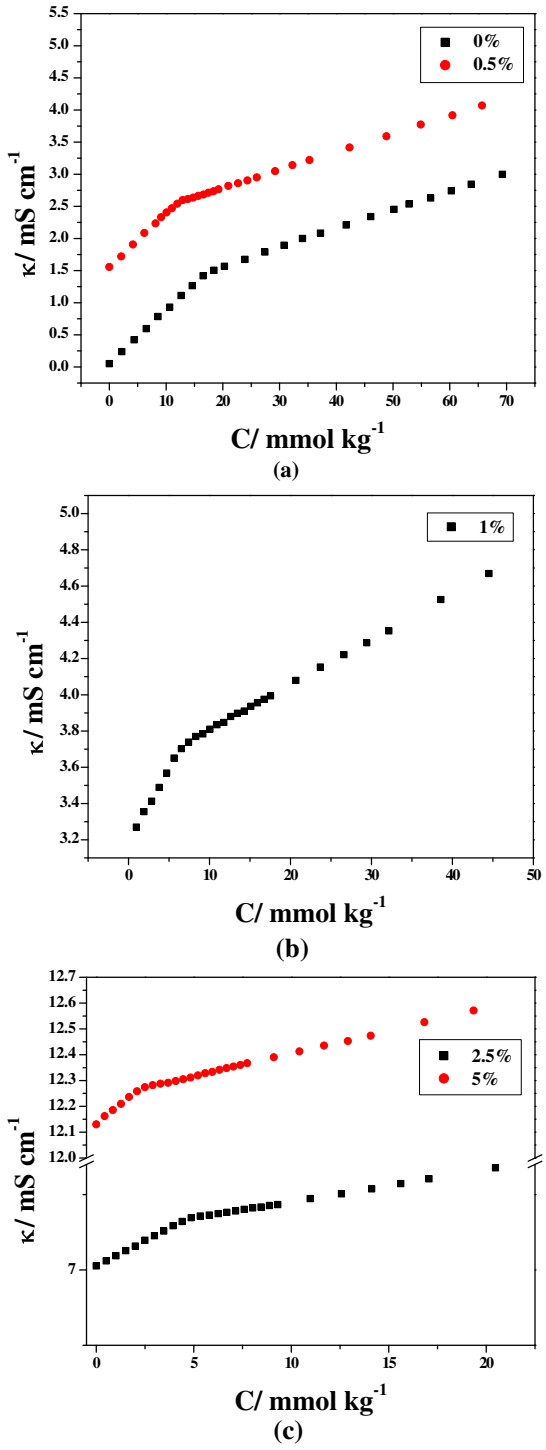


Fig. 2. Specific conductance showing variation in cac of aqueous and aqueous-drug mixtures of [C_{12}mim][Cl] at 298.15 K for varying composition of mixed solvents: (a) (■) 0% (w/w); (●) 0.5% (w/w); (b) (■) 1% (w/w); (c) (■) 2.5% (w/w) and (●) 5% (w/w).

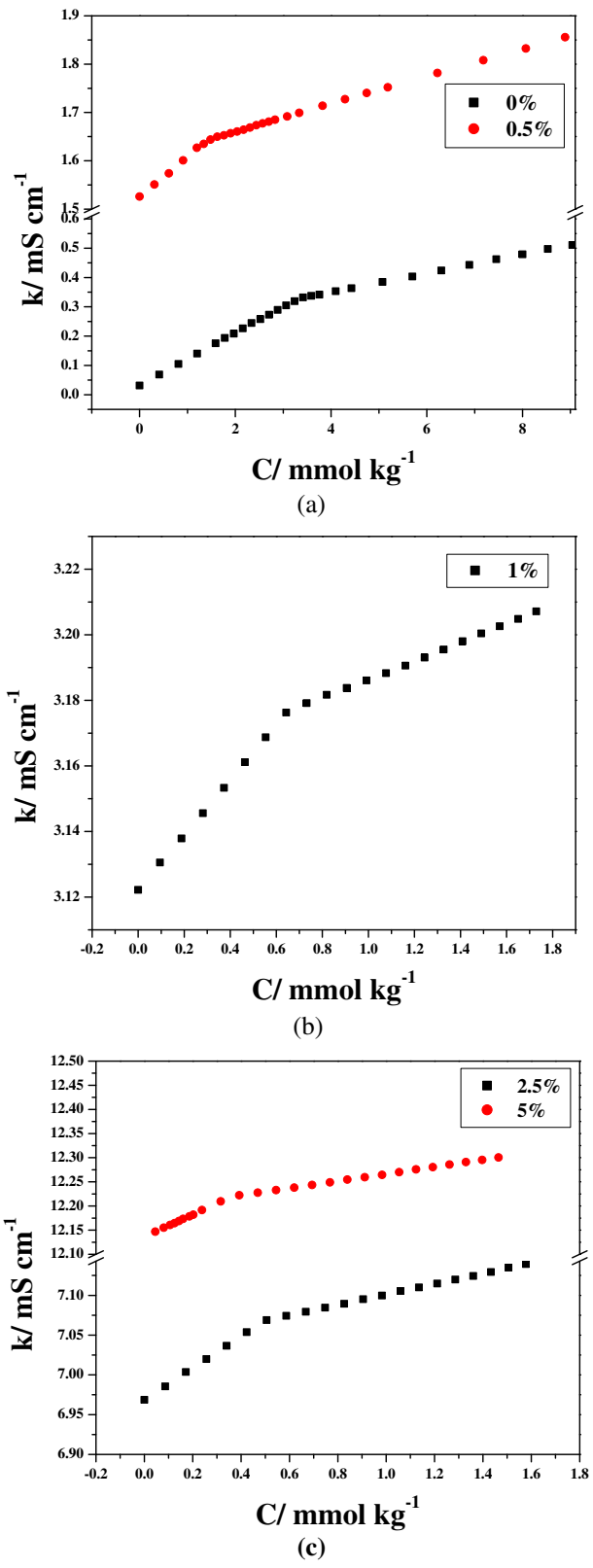


Fig. 3. Specific conductance showing variation in cac of aqueous and aqueous-drug mixtures of [C_{14}mim][Cl] at 298.15 K for varying composition of mixed solvents: (a) (■) 0% (w/w); (●) 0.5% (w/w); (b) (■) 1% (w/w); (c) (■) 2.5% (w/w) and (●) 5% (w/w).

decreases as a result of which the hydrophobicity of solute increases that supports aggregation. Secondly, with the increase in temperature there will be disruption in the structure of water molecules surrounding the hydrophobic part, which unfavors the aggregation process, and consequently *CAC* increases. Thus, the first effect dominates at low temperature while the second effect dominates after reaching *CAC* point [43].

3.2.3. Thermodynamics parameters of aggregation

The various thermodynamic parameters were evaluated from conductivity measurements. By using the concept of mass action model,

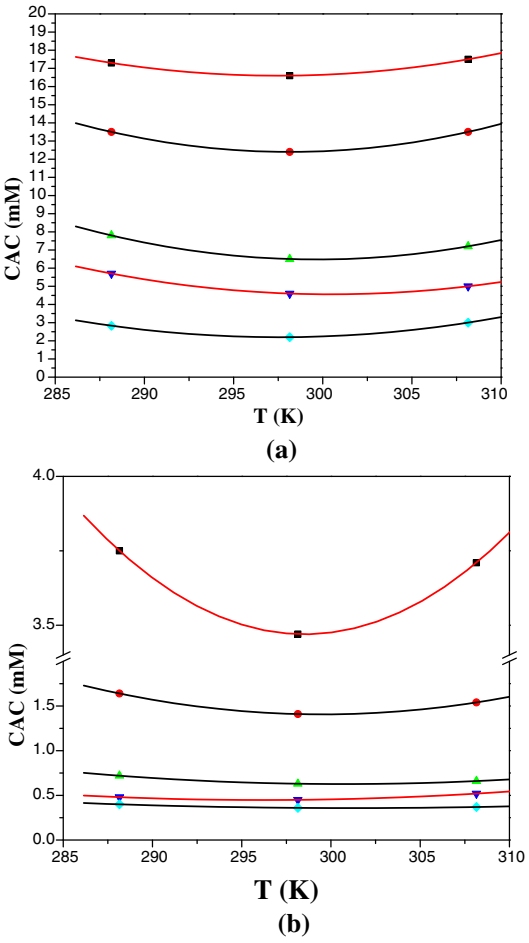


Fig. 4. Specific conductance showing variation in cac of aqueous and aqueous-drug mixtures of (a) [C_{12}mim][Cl] and (b) [C_{14}mim][Cl] at 288.15 K; 298.15 K and 308.15 K for varying composition of mixed solvent: (■) 0% (w/w); (●) 0.5% (w/w); (▲) 1% (w/w); (▼) 2.5% (w/w) and (♦) 5% (w/w).

$\Delta G^{\circ}_{agg}$of SAILs in aqueous solutions of drug were calculated by applying the following equation [44].

$$\Delta G^{\circ}_{agg.} = (2-\alpha)RT \ln x_{cac} \tag{10}$$

where T is temperature, α is the degree of counterion ionization, and R is gas constant. The values of α are tabulated in Table 4. The value of α, counterion dissociation, decreases with the increase in the amount of the drug which indicates an increase in the counterion binding in the stern layer of the aggregates. Lower the α value, stronger will be the binding of anions on the aggregate surface resulting in the decrease in the electronic repulsions among the head groups on the aggregate surface, which favors the aggregation process, and thereby supporting the decreasing trend of *CAC* values [17]. The obtained values of ΔG°_{agg} are negative supporting the aggregation process and becomes more negative with the increasing concentration of drug which justifies the obtained trend for *CAC* values. This suggests that these SAILs have good drug binding ability as compared to conventional surfactants.

The variation of the standard enthalpy ($\Delta G^{\circ}_{agg.}$) can be obtained using Gibbs-Helmholtz equation [36]:

$$\Delta H^{\circ}_{agg.} = -RT^2\left[(2-\alpha)\frac{d\ln x_{cac}}{dT} + \ln x_{cac}\frac{d(1-\alpha)}{dT}\right] \tag{11}$$

And by using the values of $\Delta H^{\circ}_{agg.}$ and, $\Delta G^{\circ}_{agg.}$ the standard entropy of aggregation ($\Delta S^{\circ}_{agg.}$) can be achieved from the equation [36]:

$$\Delta S^{\circ}_{agg.} = \left(\frac{\Delta H^{\circ}_{agg.} - \Delta G^{\circ}_{agg.}}{T}\right) \tag{12}$$

The above-mentioned thermodynamic parameters calculated from these equations are presented in Table 4. A perusal of $\Delta H^{\circ}_{agg.}$ data from Table 4 demonstrates the exothermic nature of the aggregation process. According to Nusselder and Engberts, the main force that drives this whole process towards the direction of formation of aggregates having negative $\Delta H^{\circ}_{agg.}$ is the hydrophobic interactions [45]. Though the aggregation process is exothermic but with the increase in the concentration of drug the process becomes less exothermic which shows that there is less thermal agitation in the solution as a result of which the molecules form aggregates more easily and hence *CAC* decreases. The large and positive values of entropy indicate that the aggregation process is entropy driven which states that the tendency of the hydrophobic group to shift from the solvent to the inside of the aggregate provides the driving force for the formation of aggregates and favors the aggregation process. From Table 4, it is very clear that $\Delta G^{\circ}_{agg.}$ is mostly contributed by $\Delta S^{\circ}_{agg.}$.

3.3. Fluorescence measurements

Fluorescence method has been performed for confirming the interactions between the SAIL molecules and the drug molecule. It not only helps in determining the *CAC* of the SAILs but also the aggregation number and the effect of concentration of SAILs on the quenching behavior of the drug.

3.3.1. Determination of CAC

Fluorescence method has been done in order to verify the results obtained from surface tension and conductance at 298.15 K. Fig. 5 (a) and (b) show the variation of I_1/I_3 with SAILs concentration in different compositions of the drug. I_1/I_3 ratio is very sensitive to the polarity of the medium and as the polarity of the medium decreases this ratio also decreases. The polarity scale of pyrene is described by the ratio I_1/I_3 of the fluorescence intensities bands at I_1(Ca. 376 nm) and I_3(Ca. 387 nm). As pyrene is sensitive to the polarity of the medium, the ratio I_1/I_3 of pyrene increases on moving from non-polar to the polar medium [33]. This unique feature of pyrene makes it a suitable probe for determining the *CAC* of SAILs in aqueous solutions of drug as the polarity of solution generally differs from the microenvironment of the core of aggregates. From the fluorescence profiles, it is very clear that the ratio I_1/I_3 remains static up to a certain concentration and then decreases very speedily and after then becomes stable on increasing SAIL's concentration. This discontinuity in the curve implies the onset of aggregation. Pyrene shows this unique type of behavior due to its hydrophobic nature because pyrene molecules get incorporated into the hydrophobic inner core of the aggregates and pyrene sense non-polar environment in the inner core as a result of which the value of I_1/I_3 ratio in the curve decreases [33]. The *CAC* values obtained from fluorescence validates our result obtained from surface tension and conductance and are provided in Table 2.

3.3.2. Effect of SAILs on the fluorescence intensity of the drug

Further evaluation of the interactions between lidocaine hydrochloride and the ionic liquids was done in terms of binding constant and free energy change. The polarity of the medium highly affects the fluorescence emission spectra of the fluorophore because the fluorophore stays in the excited state for more time which further exposed to the relaxed environment containing solvent molecules which are oriented around the dipole moment of the excited state. Therefore, for getting fluorescence emission spectra, the amount of ionic liquids was varied

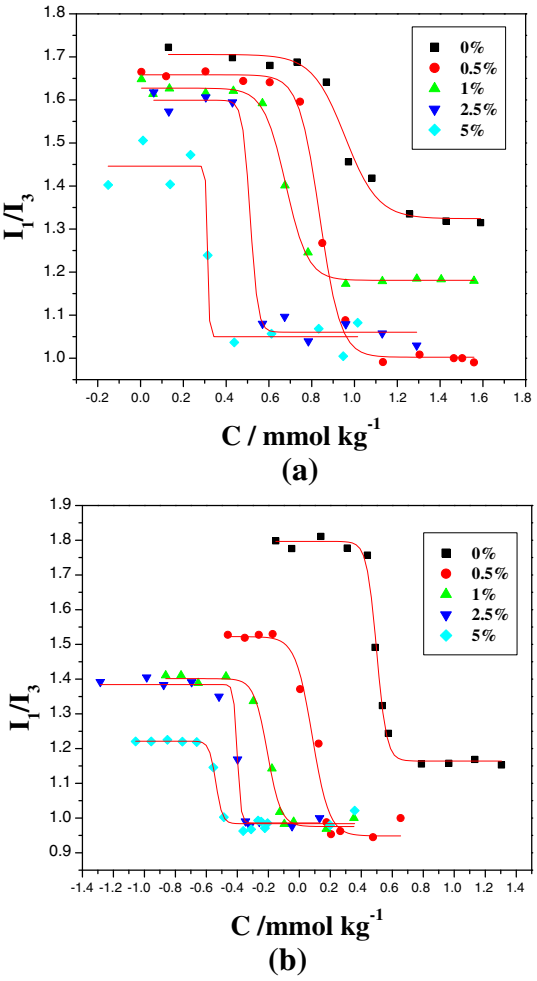


Fig. 5. Pyrene (1 μM) I_1/I_3 versus log of concentration of (a) [C_{12}mim][Cl] and (b) [C_{14}mim][Cl] in presence of aqueous and aqueous-drug mixtures at 298.15 K for varying composition of mixed solvents: (■) 0% (w/w); (●) 0.5% (w/w); (▲) 1% (w/w); (▼) 2.5% (w/w) and (♦) 5% (w/w).

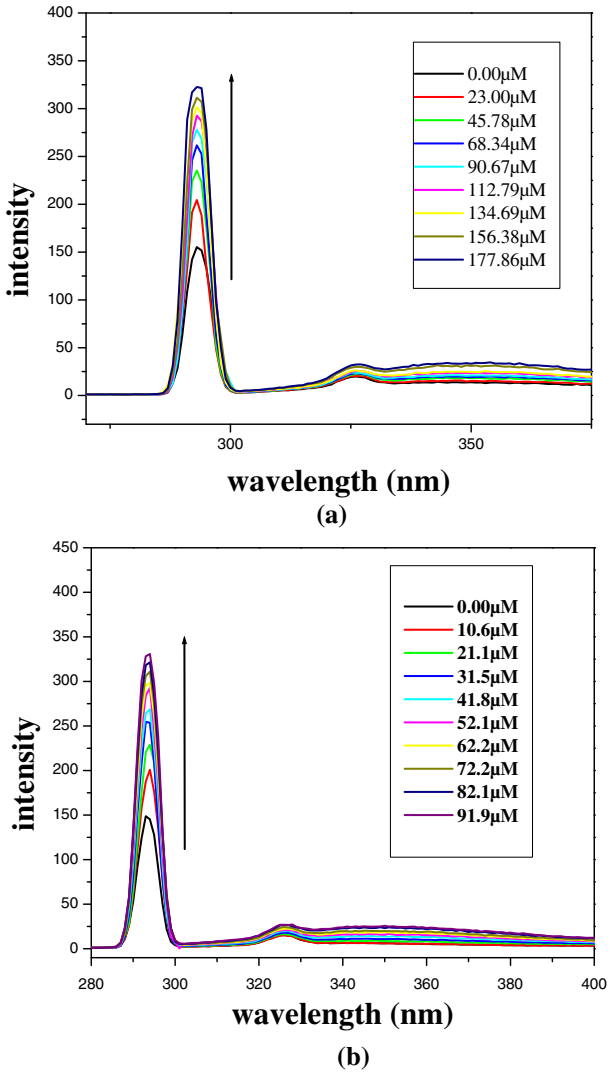


Fig. 6. Fluorescence spectra of lidocaine hydrochloride with the increasing concentration of (a) [C_{12}mim][Cl] and (b) [C_{14}mim][Cl] at 298.15 K.

keeping the concentration of the drug constant [27]. This variation in fluorescence intensity of the drug by [C_{12}mim][Cl] is shown in Fig. 6 (a) and variation from [C_{14}mim][Cl] is shown in Fig. 6 (b). From these profiles, it can be seen that the fluorescence intensity increases with the increase in the concentration of both the ionic liquids. The drug molecule is excited from ground state to the first singlet state due to the transference of electron density from N atom to the benzene ring having π character. On adding SAILs to the solution, there will be cation-π interactions and hydrogen bonding between ionic liquid and drug molecules which results in the perturbation of the environment around the drug molecules and consequently there will be an increase in the fluorescence intensity. This increase in the fluorescence intensity of drug may be due to the increase in the band gap between the excited and the ground state [22].

The binding constant and the stoichiometric ratio of all the drug-SAIL([C_{12}mim][Cl] and [C_{14}mim][Cl]) complex i.e. DS were evaluated by using Benesi-Hildebrand (B-H) equation [22]:

$$\left(\frac{1}{I-I_0}\right) = \frac{1}{k(I_1-I_0)[DS]^n} + \left(\frac{1}{(I_1-I_0)}\right) \tag{13}$$

The values of the binding constant for complexes of [C_{12}mim][Cl] and [C_{14}mim][Cl] ionic liquids obtained were 1400 and 2430 M^{-2} respectively. The double reciprocal B-H plots of $(I\text{-}I_0)^{-1}$ versus $1/[DS]^n$ for both the complexes are shown in Fig. 7 which show a linear relationship and give the stoichiometric ratio 1:1 for the drug-SAIL complex (considering n as 1). The same results were obtained for [C_{14}mim][Cl] ionic liquid. Further, by using the value of *K* the free energy

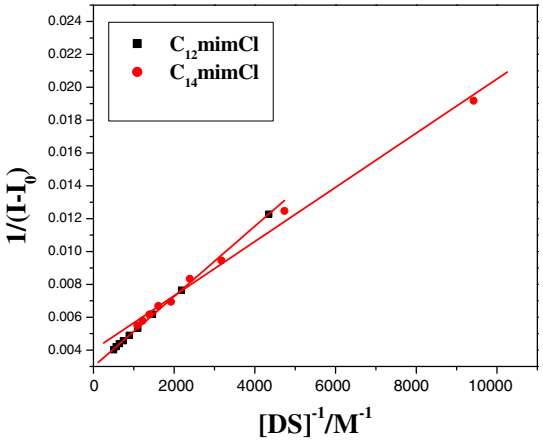


Fig. 7. Benesi-Hildebrand plot by using the changes in the Fluorescence spectra of lidocaine hydrochloride with the increasing concentration of [C_{12}mim][Cl] and [C_{14}mim][Cl] at 298.15 K.

change (ΔG) for the complex formation of the drug and the ionic liquid can be calculated using the below mentioned equation [22].

$$\Delta G = -RT \ln K \quad (14)$$

The values of ΔG for complexes of $[C_{12}mim][Cl]$ and $[C_{14}mim][Cl]$ ionic liquids obtained were −17.964 and −19.325 kJ mol^{-1} respectively. The negative values of ΔG indicate the feasibility of the formation of drug-SAIL complex at room temperature. The values of K and ΔG reveal that the formation of the complex $[C_{14}mim][Cl]$-drug has greater feasibility than $[C_{12}mim][Cl]$-drug complex.

4. Conclusion

The present study deals with the effect of the addition of a local anesthetic drug lidocaine hydrochloride on the aggregation and interfacial behavior of $[C_{12}mim][Cl]$ and $[C_{14}mim][Cl]$ by employing surface tension, conductivity, and fluorescence measurements. The results obtained from these techniques are in good agreement with each other. The *CAC* decreases with the increase in the concentration of the drug, which is due to the presence of cation-π interactions between the SAIL molecules and the drug molecules. The negative value of $\Delta G^{\circ}_{agg.}$ indicates the spontaneity of the aggregation process. The surface tension technique was very helpful in obtaining the interfacial parameters, which comes out to be very favorable in explaining the behavior at the interface. The steady state fluorescence measurements have been used to obtain binding constant, free energy change for the formation of drug-SAIL complexes and the stoichiometric ratios. This investigation shows the pivotal role of lidocaine hydrochloride in modulating the aggregation properties of surfactant like ILs. A comparative study has been done in order to investigate the better surface activity among both the ionic liquids. The main picture of the work is that the drug molecules get adsorbed on the surface of the aggregates and thereby helping in the drug delivery, which would serve for tremendous potential applications of SAILs.

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