Study on Interactions Between Imidazolium Based Surface Active Ionic Liquid and Drug at Different Temperature and Concentrations

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Abstract. The present study aims to investigate the molecular interactions of surface active ionic liquid (IL), 1-pentadecyl-3 methyl imidazolium bromide [C$_{15}$mim]Br with drug chloramphenicol in aqueous solution. For this the conductivity measurements have been employed to indicate [C$_{15}$mim]Br –chloramphenicol interactions. The evaluation of Micellar and interfacial parameters such as critical micelle concentration and various thermodynamic parameters such as standard free energy of micellization, standard entropy of micellization and standard enthalpy of micellization has been carried out.

1. Introduction
A main direction of global research is to know and find those sorts of compounds which are environment friendly or less hazardous to environment and having the unique properties. Ionic liquids are one of these compounds that are environment friendly in nature and are reported as multipurpose materials by various researchers [1-5]. Ionic liquids have fascinated the different scientific disciplines to capture their applications due to the numerous properties. Ionic liquids are defined as ionic compounds that contain both the asymmetric cation and anion which exist in the liquid state and having the temperature below 100 °C [6-7]. Ionic liquids have provided a new face of chemistry due to its unlimited potential [8]. The properties of ionic liquids such as slight vapour pressure, large thermal stability, low toxicity and outstanding solvation ability allows their use in different fields like extractions, separation processes, in organic synthesis and reactions in electrochemistry and in polymer chemistry [9-13]. Ionic liquids also act as amphiphilic molecules due to the presence of long alkyl chain and hydrophilic head groups. Ionic liquid with hydrophobic long alkyl tail and hydrophilic head groups known as the surface active ionic liquids due to their behaviour like surfactants. Pharmaceutically active compounds like drugs are habitually poorly soluble in aqueous, which display very low bioavailability at their point of action [14-15]. So it is more important and challenging to establish the new way for the pharmaceutical drug to enhance their solubility for their better bioavailability for the action [16]. Chloramphenicol is an antibiotic that is used for the treatment of bacterial infections. This includes treatment of conjunctivitis. Micelles plays a significant role over the various useful drugs carrier, it is due to the very small nano size structures of micelles. Micelles entraps the drug molecules in their hydrophobic core to increase the biological activities and better drug delivery Various disciplined utilizing the drugs with different additives [17-20]. In our present work we are examining the micellization behavior of SAIL[C$_{15}$mim][Br] in the presence of drug chloramphenicol at different temperatures (298.15K, 308.15K and 318.15K) as well as in presence of (0.10, 0.25 and 0.50) wt. %, of drug chloramphenicol that are further employed to find various thermodynamic parameters of micellization.
2. Experimental

2.1. Materials
All starting chemicals employed in the study were used as obtained from the supplier. The additional information related to the mass fraction purity of the chemical and the method of purification used is given in Table 1. Double distilled deionized water has been used to prepare the stock solutions of drug chloramphenicol and SAIL 1-pentadecyl-3-methylimidazolium bromide.

| Chemicals                        | Source                  | Purification Method | Mass Fraction Purity# |
|----------------------------------|-------------------------|---------------------|-----------------------|
| 1 pentadecyl 3-methyl imidazolium bromide | SIGMA ALDRICH           | None                | >0.99                 |
| Chloramphenicol                  | HIMEDIA Laboratories Pvt. Ltd | None                | >0.98                 |

# As declared by supplier

2.2. Conductivity measurements
The specific conductance ($\kappa$) of the solutions both in pure or mixture form has been determined by using Systronics 306 digital conductivity meter equipped with a conductivity cell having unit cell constant and at temperatures ranging from 298.15K to 318.15K with a difference of 10K. The conductivity cell has been calibrated by using aqueous KCl solution in suitable concentration range before measurements. Sartorius CPA 225 D weighing Balance has been utilized for sample preparation. Doubly distilled deionized water obtained from Millipore, Milli-Q Academic water purification system has been utilized to prepare the samples. The temperature was controlled to within ±0.1K by a high accuracy refrigerated circulating thermostated water bath with a temperature range of 0–100 °C provided by Macro Scientific Works Pvt. Ltd., Delhi. The stock solutions of ionic liquid were introduced by means of micropipette in a drug solution and conductivity of the solution was measured.

3. Results and discussions
The interactions between a Surface active ionic liquid, 1-pentadecyl-3-methyl imidazolium bromide, [C_{15}mim][Br] and drug chloramphenicol have been investigated for various compositions using conductometric measurements at 298.15, 308.15 and 318.15 K.

3.1. Critical micelle concentration (CMC) of [C_{15}mim][Br] in presence of chloramphenicol
The conductivity, $\kappa$, of surface active ionic liquid $[C_{15}mim][Br]$ has been evaluated in presence of different wt% of drug chloramphenicol in aqueous solution at different temperatures i.e. (298.15, 308.15, 318.15) K as given in table 2 and table 3.

**Table 2** $\kappa$ ($\mu$S cm$^{-1}$) of $[C_{15}mim][Br]$ in presence of 0.1 wt.% and 0.25 wt % of Chloramphenicol

| Concentration (mM) | 0.1 wt % of drug chloramphenicol | 0.25 wt % of drug chloramphenicol |
|--------------------|----------------------------------|----------------------------------|
|                    | 298.15K | 308.15K | 318.15K | 298.15K | 308.15K | 318.15K |
| 0.294              | 29.11   | 35.44   | 49.62   | 25.75   | 34.00   | 45.77   |
| 0.437              | 40.13   | 47.77   | 67.62   | 35.25   | 44.83   | 63.90   |
| 0.577              | 51.27   | 60.59   | 83.19   | 47.85   | 57.69   | 76.41   |
| 0.714              | 62.38   | 74.30   | 97.47   | 56.48   | 68.22   | 94.58   |
| 0.849              | 71.37   | 87.21   | 111.80  | 65.55   | 80.59   | 108.80  |
| 0.981              | 78.69   | 96.96   | 126.00  | 72.40   | 90.82   | 121.40  |
| 1.111              | 82.85   | 104.40  | 138.10  | 76.78   | 96.29   | 131.40  |
| 1.239              | 87.40   | 111.60  | 147.90  | 82.13   | 101.95  | 138.60  |
| 1.364              | 90.00   | 116.00  | 156.30  | 85.43   | 107.80  | 147.00  |
| 1.486              | 95.20   | 120.80  | 163.20  | 90.29   | 112.10  | 152.80  |
| 1.607              | 101.90  | 126.40  | 169.50  | 96.96   | 118.10  | 157.00  |
| 1.726              | 104.80  | 131.00  | 175.30  | 99.60   | 123.60  | 164.20  |
| 1.842              | 108.30  | 134.90  | 181.00  | 103.10  | 125.00  | 172.00  |
| 1.957              | 111.70  | 138.90  | 185.10  | 106.50  | 129.90  | 177.10  |
| 2.069              | 114.80  | 143.60  | 193.60  | 109.90  | 134.60  | 182.50  |
| 2.179              | 118.30  | 148.90  | 199.60  | 112.70  | 137.00  | 188.20  |
| 2.288              | 123.20  | 154.20  | 205.60  | 115.20  | 141.80  | 193.80  |
| 2.395              | 128.60  | 158.20  | 210.90  | 117.00  | 145.00  | 199.50  |
| 2.500              | 130.70  | 162.50  | 215.70  | 120.20  | 150.90  | 204.50  |
| 2.603              | 133.40  | 166.20  | 218.80  | 124.40  | 154.80  | 209.60  |
| 2.705              | 136.50  | 171.90  | 223.10  | 128.00  | 157.80  | 213.30  |
| 2.805              | 140.90  | 176.40  | 229.10  | 131.90  | 161.90  | 218.10  |
| 2.903              | 143.00  | 180.70  | 231.80  | 133.10  | 165.50  | 222.40  |

uncertainties are $s(T) = \pm 0.1$ K, $s(\kappa) = \pm 0.0001$ mS/cm

The plots of conductivity versus concentration of surface active ionic liquid $[C_{15}mim][Br]$ at different weight percent(0.10, 0.25 and 0.50) of drug chloramphenicol have been embodied in figure 2. The linear variation in the conductivity values with increased concentration of ionic liquid $[C_{15}mim][Br]$ shows both pre-micellar and post-micellar regions. At a specific concentration of ionic liquid, there is an abrupt change in the conductivity value that produces a sharp break point in the plots. This break point in the graph provides the value of critical micelle concentration(CMC). This point refers to formation of micelle. There is large rise in conductivity values before micelle formation because of large number of ions but this increase in value of conductivity becomes little slower as the formed micelles have lower mobility than the single ions.

There is a decrease in CMC values with increasing concentration of drug chloramphenicol. The decrease in cmc value is due to formation of hydrogen bonding of drug chloramphenicol with water molecules that decreases the tendency of drug molecules into the core of aggregate with the protons present in the imidazolium ring resulting in the adsorption of drug molecules on the surface of the aggregates. The micellization behaviour depends on the repulsive electrostatic forces between the charged head groups that postpones the process of aggregation and the favouring of aggregation process occurs due to attractive hydrophobic interactions between the long alkyl chain of SAILs. The adsorption of the drug molecules results in the reduction of electrostatic forces and hence the cmc decreases.
Figure 2. Specific conductance ($\kappa$) versus concentrations of $[C_{15}\text{mim}]\text{[Br]}$ in (a) 0.10 wt. % and (b) 0.25 wt. % of aqueous Chloramphenicol solutions at temperatures (298.15, 308.15, 318.15) K.
### Table 3. $\kappa$ (µS cm$^{-1}$) of [C$_{15}$mim][Br] in presence of 0.50 wt.% of Chloramphenicol at (298.15, 308.15, 318.15) K.

| Concentration (mM) | 0.50wt % of drug chloramphenicol | $\kappa$ (µS cm$^{-1}$) |
|-------------------|---------------------------------|--------------------------|
|                   | 298.15 K                        | 308.15K                  | 318.15K                  |
| 0.294             | 21.64                           | 32.10                    | 41.25                    |
| 0.437             | 30.03                           | 43.23                    | 55.00                    |
| 0.577             | 42.01                           | 53.00                    | 64.57                    |
| 0.714             | 50.38                           | 64.22                    | 83.23                    |
| 0.849             | 59.96                           | 78.00                    | 99.81                    |
| 0.981             | 63.39                           | 84.32                    | 103.90                   |
| 1.111             | 67.66                           | 90.49                    | 115.90                   |
| 1.239             | 72.46                           | 93.40                    | 126.70                   |
| 1.364             | 78.04                           | 96.00                    | 134.90                   |
| 1.486             | 82.80                           | 102.10                   | 143.30                   |
| 1.607             | 87.29                           | 107.90                   | 149.30                   |
| 1.726             | 91.00                           | 111.20                   | 155.20                   |
| 1.842             | 94.00                           | 115.20                   | 160.00                   |
| 1.957             | 96.60                           | 118.80                   | 166.70                   |
| 2.069             | 100.43                          | 122.20                   | 169.60                   |
| 2.179             | 103.90                          | 125.60                   | 173.10                   |
| 2.288             | 106.60                          | 127.20                   | 177.60                   |
| 2.395             | 109.00                          | 130.10                   | 181.50                   |
| 2.500             | 111.00                          | 135.80                   | 187.80                   |
| 2.603             | 113.60                          | 138.40                   | 190.70                   |
| 2.705             | 116.96                          | 144.90                   | 194.20                   |
| 2.805             | 118.50                          | 147.90                   | 198.70                   |
| 2.903             | 120.30                          | 150.20                   | 202.40                   |

Standard uncertainties $s$ are $s(T) = \pm 0.1$ K, $s(\kappa) = \pm 0.0001$ mS/cm.

### Table 4 CMC, degree of counter ion dissociation ($\alpha$) of [C$_{15}$mim][Br] in different wt.% of drug chloramphenicol at temp (298.15, 308.15, 318.15) K.

| Chloramphenicol (wt.%) | CMC (mM) | $\alpha$ |
|------------------------|----------|----------|
|                        | $T = 298.15$ K | $T = 308.15$ K | $T = 318.15$ K |
| 0.10                   | 0.9270   | 1.0326   | 1.1248   |
| 0.25                   | 0.8966   | 0.9215   | 1.1024   |
| 0.50                   | 0.8206   | 0.9113   | 1.0429   |

Standard uncertainties $s$ are $s(T) = \pm 0.1$ K, $s(CMC) = \pm 0.0001$ mM.
The value of counter-ion dissociation \( (\alpha) \) can be identified by the ratio of slopes in post-micellar region \((S_2)\) to pre-micellar region \((S_1)\) as indicated by equation (1).

\[
\alpha = \frac{S_2}{S_1} \quad (1)
\]

The value of counter-ion dissociation \( (\alpha) \) decreases with the increase in concentration of drug molecules that displays that smaller number of ions are present in stern layer. The critical micelle concentration (CMC) and degree of counter-ion dissociation \( (\alpha) \) of system at different concentrations and temperatures of ionic liquid \([\text{C}_{15}\text{mim}][\text{Br}]\) has been reported in table 4.

3.2 Effect of increasing temperature on the critical micelle concentration (CMC) of \([\text{C}_{15}\text{mim}][\text{Br}]\)

The micellization behaviour of SAIL \([\text{C}_{15}\text{mim}][\text{Br}]\) is strongly affected by temperature and hence the CMC values. The value of critical micelle concentration (CMC) of surface active ionic liquid \([\text{C}_{15}\text{mim}][\text{Br}]\) increases with the increase in temperature of system. The increase in temperature destroys the arrangement of water molecules neighbouring the hydrophobic head groups which disfavours the micellization phenomenon and hence giving rise to increase in value of CMC.

![Figure 3](image1.png)  
**Figure 3.** Plot of degree of counter ion dissociation \( (\alpha) \) of \([\text{C}_{15}\text{mim}][\text{Br}]\) in (0.1, 0.25, 0.50) wt.% of chloramphenicol at temperatures (298.15, 308.15, 318.15) K.

![Figure 4](image2.png)  
**Figure 4.** Plot of critical micelle concentration (CMC) of \([\text{C}_{15}\text{mim}][\text{Br}]\) in (0.1, 0.25, 0.50) wt.% of chloramphenicol at temperatures (298.15, 308.15, 318.15) K.

The influence of increasing temperature and concentration of ionic liquid \([\text{C}_{15}\text{mim}][\text{Br}]\) and chloramphenicol on the critical micelle concentration (CMC) and degree of counter ion dissociation \( (\alpha) \) can be well understood by observing the figure 3 and figure 4.

3.3 Determination of thermodynamic parameters of micellization

The various thermodynamic parameters of micellization such as Gibbs free energy of micellization \(\Delta G^0_m\), standard enthalpy \(\Delta H^0_m\) and entropy of micellization \(\Delta S^0_m\) has been determined by utilizing the values of counter ion dissociation \( (\alpha) \) and critical micelle concentration(CMC). The value of these parameters obtained in \([\text{C}_{15}\text{mim}][\text{Br}]\) has been shown in table 5 at different temperatures and concentration of chloramphenicol(0.10, 0.25 and 0.50 wt%)

3.3.1. The standard Gibbs’ free energy of micellization \(\Delta G^0_m\)

The standard Gibbs’ free energy of micellization \(\Delta G^0_m\) of ionic liquids in aqueous medium of drug has been measured by applying the succeeding equation [1]

\[
\Delta G^0_m = (2-\alpha) RT (\ln X_{CMC}) \quad (2)
\]
Where \( \alpha \) is the degree of counter ion dissociation, \( T \) is temperature and \( R \) is gas constant. The values of \( \alpha \) has been tabulated in table 4. The value of \( \alpha \) counter ion dissociation, falls with the rise in concentration of the drug chloramphenicol that specifies increase in the counter ion binding. Lower \( \alpha \) value indicates stronger binding of anions on the micellar surface that resulted in reduction of electrostatic repulsion between head groups, henceforth supporting the declining fashion of CMC values. The negative values of \( \Delta G^0_m \) for all concentrations of [C\(_{15}\) mim][Br] and also for temperatures directs the spontaneity of the process of micellization. These negative values tend to become more negative by the addition of [C\(_{15}\) mim] [Br] as well as with the increase in temperature. This infers that the addition of [C\(_{15}\) mim] [Br] and the rise in temperature makes the micellization process more feasible.

### Table 5. The standard Gibbs’ free energy of micellization (\( \Delta G^0_m \)), the enthalpy of micellization (\( \Delta H^0_m \)), and the entropy of micellization (\( \Delta S^0_m \)) of [C\(_{15}\) mim][Br] in different wt.% of chloramphenicol at temperatures (298.15, 308.15, 318.15) K.

| Chloramphenicol(wt%) | \( \Delta G^0_m \) (kJ·mol\(^{-1}\)) | \( \Delta H^0_m \) (kJ·mol\(^{-1}\)) | \( \Delta S^0_m \) (J·mol\(^{-1}\)·K\(^{-1}\)) |
|---------------------|-------------------------------|-------------------------------|---------------------------------|
| 0.1                 | -42.503                       | -11.139                       | 105.20                          |
| 0.25                | -43.138                       | -12.040                       | 104.30                          |
| 0.50                | -43.528                       | -13.907                       | 99.35                           |
|                     | \( T = 298.15 \) K            |                               |                                 |
| 0.1                 | -43.150                       | -11.803                       | 101.73                          |
| 0.25                | -43.777                       | -12.660                       | 100.98                          |
| 0.50                | -44.275                       | -14.760                       | 95.78                           |
|                     | \( T = 308.15 \) K            |                               |                                 |
| 0.1                 | -44.004                       | -12.526                       | 98.94                           |
| 0.25                | -44.199                       | -13.415                       | 96.76                           |
| 0.50                | -44.652                       | -15.557                       | 91.45                           |
|                     | \( T = 318.15 \) K            |                               |                                 |

Standard uncertainties \( s \) are \( s (\Delta G^0_m) = \pm 0.03 \) kJ·mol\(^{-1}\), \( s (\Delta H^0_m) = \pm 0.02 \) kJ·mol\(^{-1}\), \( s (\Delta S^0_m) = \pm 0.02 \) J·mol\(^{-1}\)·K\(^{-1}\).

#### 3.3.2. The enthalpy of micellization (\( \Delta H^0_m \))

The enthalpy of micellization, \( \Delta H^0_m \) has been determined by the following equation (3) [1]

\[
\Delta H^0_m = -RT^2 \left( 2-\alpha \right) \frac{d(\ln X_{CMC})}{dT}
\]

A survey of \( \Delta H^0_m \) Data from table 5 confirms the exothermic nature of the micellization process. The value of \( \Delta H^0_m \) become more negative by the addition of ionic liquid and increasing concentration of chloramphenicol and with the increase in temperature as observed from the data given in table 5.

#### 3.3.3. The entropy of micellization (\( \Delta S^0_m \))

The following equation (4) has been utilized for the calculation of entropy of micellization[1]

\[
\Delta S^0_m = \left( \Delta H^0_m - \Delta G^0_m \right) / T
\]

The values of \( \Delta S^0_m \) are given in table V. The values of \( \Delta S^0_m \) and \( \Delta H^0_m \) decreases with increasing weight % of chloramphenicol as well as with increase in temperature. This indicates the process of micellization is entropy driven at lower concentrations but at higher concentrations it is enthalpy driven. as indicated by positive values of \( \Delta S^0_m \) and negative values of \( \Delta H^0_m \).

#### 4. Conclusion

In the present study, the aggregation behaviour of ionic liquid [C\(_{15}\) mim][Br] in presence of drug chloramphenicol at several temperatures and concentrations in aqueous solutions by employing conductivity measurements. Degree of counter ion dissociation, critical micelle concentration and various thermodynamic parameters have been evaluated. The decrease in cmc value with increasing concentration of the drug is due to the existence of cation-π interactions amid SAIL and drug molecules. The negative values of \( \Delta G^0_m \) and \( \Delta H^0_m \) for all temperatures and concentrations of
[C_{15}mim][Br] reveals the spontaneity and exothermic nature of the micellization process. The higher values of \( \Delta S_m^0 \) as compared to \( \Delta H_m^0 \) indicates that the micellization process is predominantly entropically favourable at lower concentration but at higher concentrations it is enthalpy driven in nature. The drug delivery of various drugs becomes easier due to the adsorption of drug molecules on micellar surface that finds remarkable probable utility.

5. References

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