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Micellar Studies of Local Anticonvulsant Gabapentin in Aqueous Electrolyte Solution

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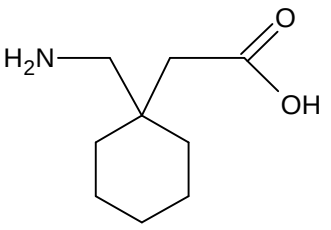
Abstract

Specific conductivity of aqueous electrolyte solution of anticonvulsant gabapentin (2-[1-(aminomethyl)cyclohexyl]ethanoicacid) has been determined in the temperature range of 303-338 K. The critical micelle concentrations (cmc), ionization degree (α) and the counterion binding of the micelle (β), were estimated from the dependence of specific conductivity on concentration. Thermodynamic parameters, such as standard Gibbs free energy (ΔG^o), enthalpy (ΔH^o) and entropy (ΔS^o) of micellization, were estimated by the mass action model.

Keywords: Gabapentin; Conductivity; Micellization; Enthalpy; Entropy; Standard Gibbs free energy.

1. Introduction

Gabapentin has been widely used as a medication to relieve pain, especially neuropathic pain [1,2] and is well tolerated in most patients. It has a relatively mild side-effect profile [3], and passes through the body unmetabolized. Gabapentin is similar in structure to the neurotransmitter GABA but is not believed to act on the same brain receptors. Its exact mechanism of action is unknown, but its therapeutic action on neuropathic pain is thought to involve voltage-gated calcium ion channels [4]. The structure for gabapentin is shown below:



Gabapentin

Thermodynamic studies of hexadecyltrimethylammonium bromide and hexadecylpyridinium bromide are also reported in the literature [5,6]. Andrimainty et. al. studied

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the micellization of anaesthetic heptacainium chloride in aqueous electrolyte solution [7,8]. This article reports the studies on conductivity measurements of gabapentin in aqueous electrolyte solution (0.2 mol L^{-1} NaCl) at various temperatures. In the present study, the temperature dependence of the cmc, ionization degree (α) and the counterion binding of the micelles (β), in the temperature range of 303-338 K were taken in to consideration. This behavior was analyzed using a Power-law equation on the basis of reduced variables. The cmc, ionization degree (α) and the counterion binding of the micelles (β) were estimated from the data. The temperature dependence of log cmc was fitted to the function of second-degree polynomial. From the fitting parameters, thermodynamic functions, such as standard Gibbs free energy (ΔG^o), enthalpy (ΔH^o), and entropy of micellization, were estimated by assuming that the system conforms to the 'mass action model'. An enthalpy-entropy compensation phenomenon for the studied system has been found [9].

2. Material and Methods

Gabapentin tablets (Intas Pharmaceutical, Ahmedabad, India) were purchased from the market and used as sample. Sodium chloride (NaCl) used for preparing stock solution was supplied by SISCO Research Laboratories, Mumbai, India. From the stock solution (0.01 mol L^{-1}) of gabapentin prepared in (0.2 mol L^{-1}) NaCl various concentrations of dilute solution were prepared in temperature range 303-338K controlled by thermostat. The cmc were determined by electrical conductometry. A model ME 976 C Digital conductivity meter was used for the conductivity measurements of the Gabapentin solutions. Cell constant of the conductivity cell used for the measurements was 1 Seimen cm^{-1}.

3. Results and Discussion

Conductance results were used to estimate the values of cmc, α and β at several temperatures. In Fig 1, the conductivity vs. concentration of gabapentin is presented in 0.2 mol L^{-1} NaCl in the range from 303 to 338 K. It was observed that after addition of gabapentin at different concentrations to 0.2 M NaCl solution, the conductance of the solution increases from its original value.

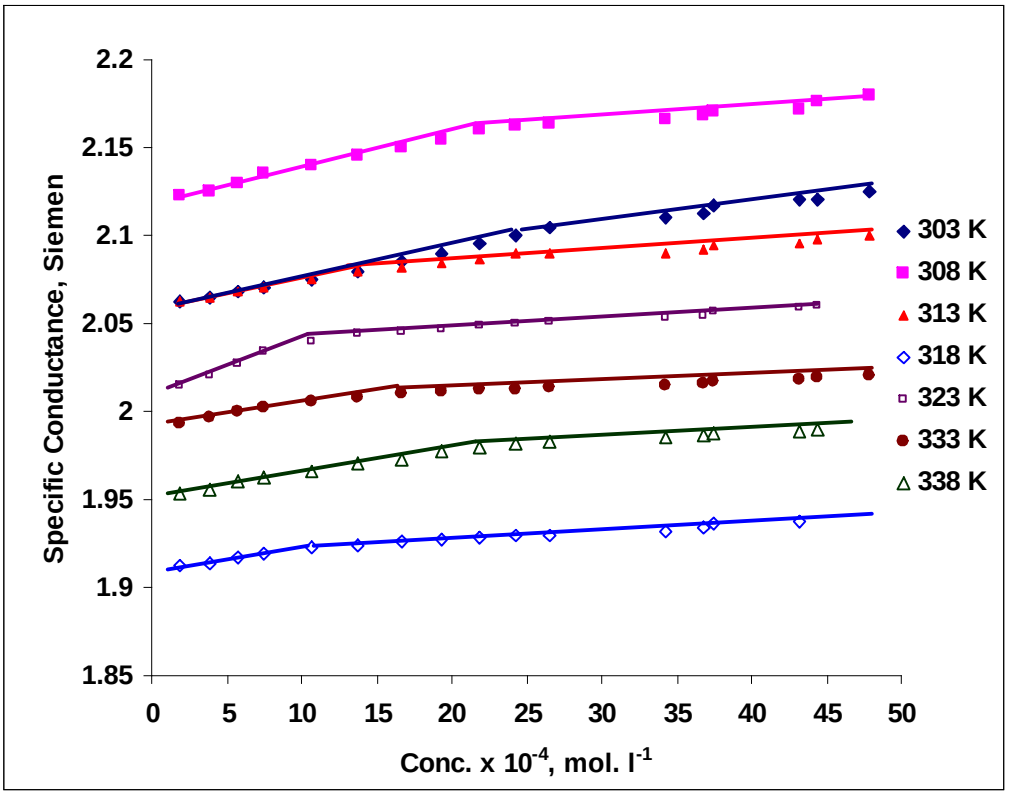

Fig 1. Electrical conductivity vs. concentration of the Gabapentin at different temperatures.

In this figure, breaks in the specific conductivity vs. concentration plots can be observed. These breaks are generally attributed to the beginning of formation of micelles, i.e. to cmc. In order to estimate the values of cmc, we fit the linear fragments, above and below the breaks and we treat the concentration at which intersection of these lines occurs as the cmc (Table1). Ionization degree of the micelles (α), has been calculated as the ratio of the slopes of the two intersecting lines (Table 1) and then β is calculated using the formula $\beta = 1-\alpha$ [10-12]. The range of β was found within $0 \leq \beta \leq 1$ for the temperature range. The bound counterions are in equilibrium with the free counterions. However, with the rise in temperature, the values first increase and then decrease suggesting the shift of equilibrium towards counterion binding finally. The temperature dependence of cmc is shown in Fig 2. The minimum of the curve is close to 321.6 K according to the fit. Gabapentin is a surface-active compound as is shown by surface tension values of gabapentin at five different concentrations at 303 K Table 2.

Table 1. Cmc values and ionization values for gabapentin at various temperatures.

Temperature, K	cmc, mol L^{-1}	Ionization degree (a)	Specific conductance of 0.2M NaCl solution, Siemen
303	24.24	0.64	1.30
308	21.87	0.42	1.38
313	13.79	0.61	1.49
318	10.71	0.32	1.55
323	10.71	0.21	1.69
333	16.66	0.27	1.85
338	21.87	0.32	1.95

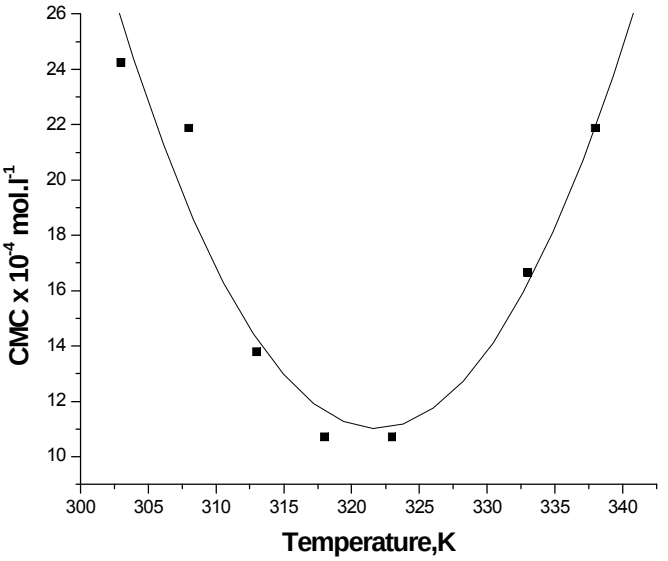

Fig 2. The values cmc as a function of temperature for the Gabapentin

Table 2. Surface tension of gabapentin at different concentrations at 303 K.

Concentration of gabapentin, mM	Surface tension, dyne cm^{-1}
1	60.66
2	62.21
5	63.78
10	65.37
20	67.73

The temperature dependence of the cmc can be described by a power law between the reduced cmc and reduced temperature, c_r and T_r, respectively. The reduced variables are defined as $c_r = c_{cmc} / c^*_{cmc}$ and $T_r = T / T^*$, where c^*_{cmc} and T^* are the cmc and temperature values

at the minimum of the U-shaped curve (Figure 2). Values T_r and c_r can be related to each other through the following equation [13,14].

$$|c_r\text{-}1| = A + B_1|T_r\text{-}1| + B_2|T_\rho - 1|^2 \quad (1)$$

Where A, B_1 and B_2 are the constants, which appear to be characteristic to the surfactant system.

When a set of cmc-temperature data is given, and excellent fit of polynomial functions to the cmc data is made, accurate c^*_{cmc} and T^* values can be obtained. The second-order polynomial function was fitted to the compound data in Fig 2. The values of c^*_{cmc} = 0.0011017 mol L^{-1} and T^* = 321.6K. Figure 3 shows the results of the fittings of equation (1) to the cmc data of Fig 2.

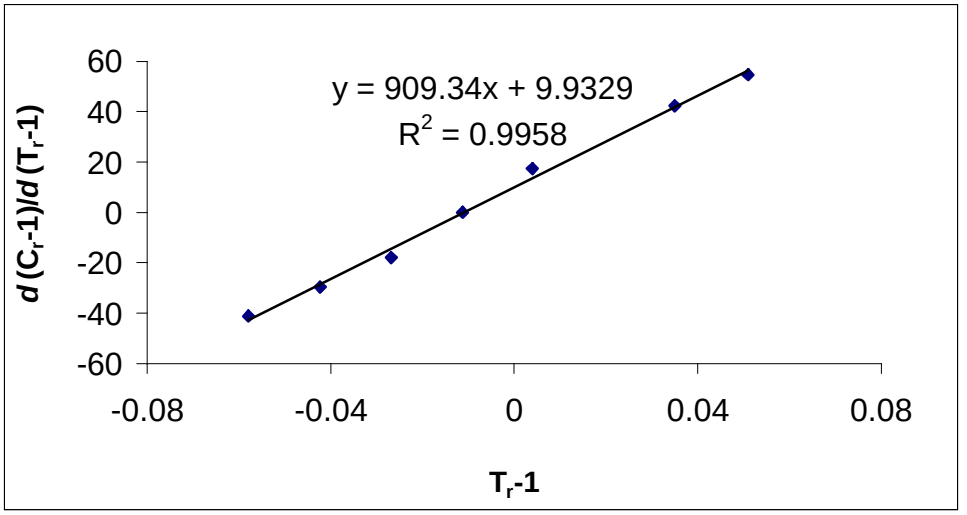

Fig 3. Fit of Eq. (1) to Gabapentin data of Fig 2

The fit was excellent with the correlation coefficient close to 1. This fit was then used to determine the values of constants. Equation 1 can be written in the derivative form as:

$$d\,(C_r\text{-}1)/d\,(T_r\text{-}1) = B + 2C\,(T_r\text{-}1) \quad (2)$$

From the fitting parameters, Gibbs free energies (ΔG^o), enthalpies (ΔH^o), and entropies (ΔS^o) of micellization as a function of temperature were estimated. The mass action model was applied to micelle formation to calculate the thermodynamic micellization parameters. The free energy of micellization ΔG^o, can be given by the equation:

$$\Delta G^o = -\,(2 - \beta)\,RT \ln cmc \quad (3)$$

Hence, ΔG^o was calculated using the cmc and β previously determined. The enthalpy of micellization, ΔH^o was calculated from the equation

$$\Delta H^o = (2 - \beta)\, RT^2\, [\ln cmc/\, T] \quad (4)$$

The entropy contribution of micellization DS^o, was determined from the equation

$$\Delta S^o = (\Delta H^o - \Delta G^o)/T \quad (5)$$

The results of ΔG^o, ΔH^o and ΔS^o calculated by these equations, are summarized in Table 3. Based on the present results it can be generalized that the micellization process is exothermic at low temperature and becomes endothermic at higher. Free energy (ΔG^o) is negative in the whole temperature range studied. On the other hand, the entropy of micellization is negative at lower temperature and becomes positive at higher temperature. The value ΔG^o is the sum of the enthalpic (ΔH^o) and entropic ($-T\Delta S^o$) contributions. As the temperature increased, the entropic contributions to the free energy decreased, whereas, the enthalpic contribution increases. Several chemical processes exhibit a linear relation between ΔH^o and ΔS^o. This phenomenon is known as enthalpy- entropy compensation [9,15,16]. The enthalpy-entropy compensation shown for the micellization of the Gabapentin in Figure 4 indicates that change in enthalpy is almost compensated by corresponding change in entropy resulting in smaller net free energy change.

Table 3. Thermodynamic parameters for micellization of Gabapentin

Temperature (K)	ΔG^o (kJ mol^{-1})	ΔH^o (kJ mol^{-1})	ΔS^o (kJ $mol^{-1}K^{-1}$)	$-T\Delta S^o$ (kJ mol^{-1})
303	-13.173	-53.076	-0.1317	39.903
308	-11.220	-56.475	-0.1469	45.255
313	-11.995	-34.240	-0.0711	22.245
323	-7.706	-21.183	-0.0417	13.477
333	-9.889	42.468	0.1572	-52.357
338	-11.445	52.428	0.1889	-63.873

In general the compensation effect can be described by the relationship given below:

$$\Delta H^o = \Delta H^* + T_c\, \Delta S^o \quad (6)$$

Where T_c is the so-called compensation temperature and ΔH^* is the intercept. T_c = 325.25 K for the present system.

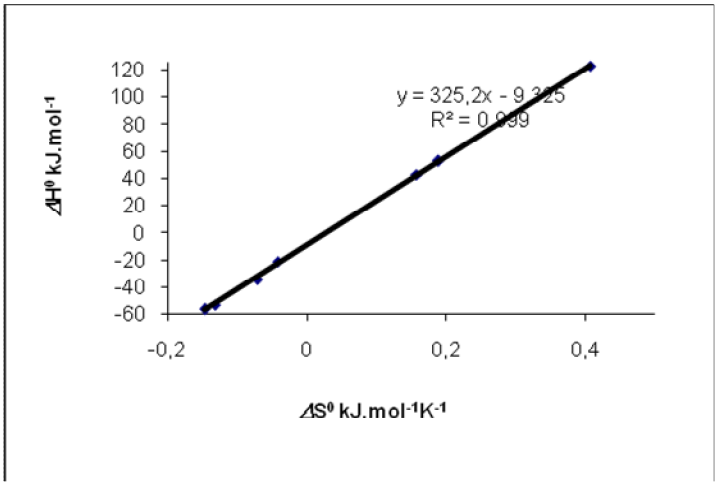

Fig 4. Enthalpy-entropy compensation plot for Gabapentin

4. Conclusion

Gabapentin is found to be a surface active molecule. Using dependence of conductivity values on concentration, critical micelle concentrations (cmc), ionization degree (a) and the counterion binding of the micelle (β) for gabapentin, at different temperatures were calculated. Applying the mass action model various thermodynamic parameters, such as standard Gibbs free energy (ΔG^o), enthalpy (ΔH^o) and entropy (ΔS^o) of micellization were calculated.

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