

Potentiometric Studies on The Complexes of Cu(II), Cd(II), Co(II), Ni(II), Pb(II) and Zn(II) With Gabapentin

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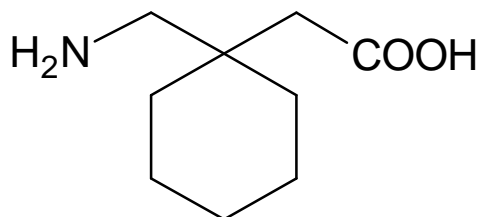
Abstract

Potentiometric studies have been carried out on complexes of gabapentin (chemically 2-[1-(aminomethyl)cyclohexyl]ethanoic acid) with Cu(II), Cd(II), Co(II), Ni(II), Pb(II) and Zn(II) in 50% v/v dioxane-water medium at three different temperatures (35, 45 and 55°C) and ionic strength 0.1 mol L⁻¹ (KNO₃). Calvin-Bjerrum pH titration technique as used by Irving and Rossotti has been applied to determine stability constants of the complexes. Free energy, enthalpy and entropy changes have also been evaluated.

Keywords: Metal ions, Gabapentin, Potentiometric method, Stability constant, Free energy, Enthalpy, Entropy.

1. Introduction

Gabapentin is a prescription drug that was initially approved to help manage epilepsy. Nowadays, gabapentin has been widely used as a medication to relieve neuropathic pain(1,2,3), diabetic neuropathy (4). Gabapentin is well tolerated in most patients, has a relatively mild side-effect profile (5). The drug is related to gamma-aminobutyric acid (GABA), a neurochemical that possesses inhibitory properties. In brain cells, these inhibitory actions prevent excitatory electrical impulses from spreading to neighboring cells. As a result, gabapentin probably prevents the spread of abnormal excitatory activity in the brain at least in part, by mimicking the actions of GABA (6). Gabapentin is best known under the brand name Neurontin manufactured by Pfizer.



Gabapentin (2-[1-(aminomethyl)cyclohexyl]ethanoic acid)

As some of the metal ions such as Lead and Copper are responsible for the epilepsy and neuropathic pain. So these metal ions can be metabolized with the gabapentin by forming complexes with them.

The present paper deals with the determination of protonation constants of the ligand and the stability constants of the complexes and thermodynamic parameters of Cu(II), Cd(II), Co(II), Ni(II), Pb(II) and Zn(II) complexes with gabapentin using potentiometric pH method in 50% v/v dioxane-water medium at three temperatures (35 ± 0.1 , 45 ± 0.1 and $55 \pm 0.1^\circ \text{C}$) and at an ionic strength of 0.1 mol L^{-1} (KNO_3). The method of Calvin-Bjerrum [7, 8] as adopted by Irving and Rossotti [9] has been employed to determine log K values.

2. Experimental

All chemicals used were of analytical grade. The Gabapentin tablets (Intas Pharmaceutical, Ahmedabad, India) were purchased from the market and used as sample. Dioxane was purified by the recommended procedure [10]. Ligand solution was prepared in doubly distilled deionized water. Metal salt solutions were prepared by dissolving the corresponding metal salt in doubly distilled deionized water and standardized by standard volumetric methods. pH measurements were done on ATC pH meter model 132E using a glass calomel electrode assembly in 50% v/v dioxane-water medium at three temperatures (35 ± 0.1 , 45 ± 0.1 and $55 \pm 0.1^\circ \text{C}$) and at an ionic strength of 0.1 mol L^{-1} (KNO_3). The pH meter was calibrated with suitable buffers before use.

The three solutions (total volume 50 mL in each case) were prepared as follows: (A) 2.5 mL of 0.01 mol L^{-1} HCl, (B) 2.5 mL of 0.01 mol L^{-1} HCl + 5.0 mL of 0.025 mol L^{-1} ligand, (C) 2.5 mL of 0.01 mol L^{-1} HCl + 5.0 mL of 0.025 mol L^{-1} ligand + 2.5 mL of 0.01 mol L^{-1} metal ion solution. An appropriate quantity of potassium nitrate solution (1.0 mol L^{-1}) was added to maintain the desired ionic strength (0.1 mol L^{-1}). Solutions A, B and C were titrated against potassium hydroxide (0.05 mol L^{-1}) prepared in 50% v/v dioxane-water. The three curves were

obtained from the plots of pH versus volume of alkali required and are referred to as (i) acid (ii) ligand (iii) complex titration curves.

3. Result and Discussion

The values of n_A , (the degree of formation of the proton complex) was calculated [7] by employing the following Equation 1:

$$n_A = Y + \frac{(V' - V'')(N + E^0)}{(V^0 + V')T_L^0} \quad (1)$$

Where Y = number of replaceable hydrogen ion, V^0 = total volume 50ml, V' = volume of alkali required by the acid, V'' = volume of alkali used by acid and ligand, N = concentration of alkali, E^0 = total strength of acid, T_L^0 = total concentration of ligand.

The proton ligand formation curve was obtained by plotting the degree of formation (n_A) of the proton complex against pH values. The values of $\log K_2H$ were obtained from the curves corresponding to n_A values of 1.5. The protonation constants at three different temperatures were calculated by various computational methods [7,11] and are summarized in Table 1.

The values of n (average number of ligand molecules attached per metal ion) were calculated using equation 2

$$n = \frac{(V''' - V'')(N + E^0)}{(V^0 + V'')n_A T_M^0} \quad (2)$$

Where V''' = volume of alkali used for acid + ligand + metal ion, T_M^0 = total concentration of the metal ion, rest of term symbols are as given in equation 1. And the free ligand exponent, pL was calculated using equation 3 as given below:

$$pL = \log_{10} \left[\frac{\sum_{n=0}^{n=j} \beta_n^H (1/\text{antilog } \beta)^n \cdot \frac{V^0 + V''}{V^0}}{T_L^0 - nT_M^0} \right]$$

Where β_n^H = proton ligand stability constant, other term symbols are same as in Equation 1 and 2.

The values of n obtained for metal-ligand system indicates the formation of 1:1 and 1:2 complexes. Bjerrum half-integral method [9], interpolation at various n values, graphical method extended to dioxane-water mixture by Van Uiter and Haas [12] was used to calculate the $\log K_1$ and $\log K_2$ values. In addition, $\log K_1$ and $\log K_2$ values were also obtained by pointwise calculation method using the following equations:

$$\log K_1 = pL - \log (1-n)/n$$

$$\log K_2 = pL - \log (2-n)/(n-1)$$

The values of $\log K_1$ and $\log K_2$ have also been determined at three different concentration of metal ion while keeping the ligand concentration constant. The $\log K_1$ and $\log K_2$ values were found identical within the experimental error at all concentration of metal ion, hereby indicating the formation of 1:1 and 1:2 complexes. The mean values of concentration stability constants ($\log K_1$ and $\log K_2$) are summarized in Table 1. The overall order of stability ($\log \beta_2$) is $\text{Cu(II)} > \text{Pb(II)} > \text{Cd(II)} > \text{Co(II)} > \text{Ni(II)} > \text{Zn(II)}$. The greater stability of Co(II) than Ni(II) may be attributed to the additional stabilisation due to John-Teller distortion present in case of Co(II) similar to Cu(II) and to favourable entropy effect, while the partial oxidation of Co(II) is not absolutely ruled out.

Table 1. protonation constants on 2-[1-(aminomethyl)cyclohexyl]ethanoic acid and stability constants of its complexes at three temperatures

| Metal ion | Temperature (°C) | Constant | $-\Delta G$ (kJ/mol) | ΔH (kJ/mol) | ΔS (J mol ⁻¹ deg ⁻¹) |
|----------------|------------------|-------------------------|----------------------|---------------------|---|
| H ¹ | 35 | LogK ¹ H | | | |
| | 45 | LogK ¹ H | | | |
| | 55 | LogK ¹ H | | | |
| Cu(II) | 35 | Log β_2 10.41642 | 7.87179 | 5.58023 | 43.67540 |
| | 45 | Log β_2 7.639935 | 6.59119 | -27.15408 | -64.66317 |
| | 55 | Log β_2 10.08285 | 8.08746 | -28.32009 | -61.68485 |
| Cd(II) | 35 | Log β_2 6.11846 | 5.65735 | -8.25407 | -8.43093 |
| | 45 | Log β_2 4.684271 | 3.91469 | 40.46201 | 139.54936 |
| | 55 | Log β_2 8.121768 | 6.71785 | 41.13691 | 145.8982 |
| Co(II) | 35 | Log β_2 3.894939 | 19.94763 | 38.10352 | 188.47778 |
| | 45 | Log β_2 6.160351 | 20.59838 | -32.25072 | -36.64256 |
| | 55 | Log β_2 7.8467561 | 30.33589 | -21.26578 | 27.65278 |
| Ni(II) | 35 | Log β_2 3.713285 | 25.43229 | -37.11025 | -37.91542 |
| | 45 | Log β_2 3.3690348 | 17.25563 | 12.88658 | 94.78685 |
| | 55 | Log β_2 6.0023272 | 25.61623 | -30.46298 | -14.77666 |

(Table 1 continued)

| Metal ion | Temperature (°C) | Constant | -ΔG (kJ/mol) | ΔH (kJ/mol) | ΔS (J mol ⁻¹ deg ⁻¹) |
|-----------|------------------|------------------------------|--------------|-------------|---|
| Zn(II) | 35 | Log β ₂ 4.053809 | 20.76127 | 1.67924 | 72.85882 |
| | 45 | Log β ₂ 3.9090018 | 20.01965 | -10.39177 | 30.27636 |
| | 55 | Log β ₂ 4.2515138 | 21.78463 | -25.71977 | -11.99739 |
| Pb(II) | 35 | Log β ₂ 9.1299141 | 7.32502 | -2.91889 | 14.30563 |
| | 45 | Log β ₂ 7.9985882 | 6.89427 | 10.95605 | 56.13308 |
| | 55 | Log β ₂ 9.1130612 | 7.49603 | 2.41682 | 22.86112 |

The values of overall changes in energy (ΔG°) enthalpy (ΔH°) and entropy (ΔS°) accompanying complexation have been determined using temperature coefficient and Gibb's Helmholtz equation (Table 1). The values of ΔG° were obtained from the equation $\Delta G^\circ = -RT \ln \beta$. The values of ΔS° were calculated by using the following equation:

$$\Delta S^\circ = \frac{\Delta H^\circ - \Delta G^\circ}{T}$$

The free energies of formation (ΔG°) of complexes have more negative values with increase of temperature, showing that complex formation is a spontaneous process.

4. Conclusion

The results of the potentiometric studies on complexes of 2-[1-(aminomethyl)cyclohexyl]ethanoic acid of Cu(II), Cd(II), Co(II), Ni(II), Pb(II) and Zn(II) in 50% v/v dioxane-water medium using Calvin-Bjerrum pH titration technique indicates that the order of stability is Cu(II) > Pb(II) > Cd(II) > Co(II) > Ni(II) > Zn(II). This order is in accordance with Irving-Williams order of stability [13]. The negative free energy change indicates the spontaneity of the complex formation process.

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