Research Paper

Evaluation of Stability Constants of Gabapentine with Copper (II), Cobalt (II) And Nickel (II)

Chemistry

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ABSTRACT *Potentiometric studies have been carried out on complexes of gabapentine (chemically 2-[1-(aminomethyl) cyclohexyl] ethanoic acid) with Cu(II), Co(II) and Ni(II). Calvin-Bjerrum pH-titration technique as used by Irving and Rossotti has been applied to determine stability constants in mixed solvents at 25 ± 1oC. The present study reports the protonation constants of this ligand and stability constants of its metal complexes in aqueous, ethanol-water (25% and 50%, v/v) and dioxane-water (25% and 50%, v/v) mixtures. Metal-ligand stability constants fall in the order of Cu (II)>Co (II)>Ni (II) which in agreement with those reported by Irving stability order.*

INTRODUCTION

Gabapentine is a prescription drug that was initially approved to help to manage epilepsy[1]. Now a days gabapentine has been widely used as a medication to relieve neuropathic pain[1-3] and diabetic neuropathy[4]. Gabapentine is well tolerated in most patients, has relatively mild side effect profiles[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, gabapentine probably prevent the spread or abnormal excitatory activity in the brain at least in part, by mimicking the actions of GABA[6]. Gabapentine is best known under the brand name Neurontin manufactured by Pfizer.
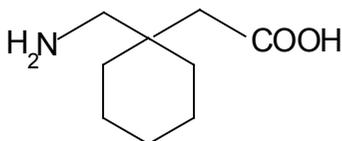
Gabapentine (2-[1-aminomethy1] cyclohexyl)] ethanoic acid)
Some of the metal ions such as lead and copper are responsible for the epilepsy and neuropathic pain. So these metal ions can be metabolized with the gabapentine by forming complexes with them.

The present work deals with the determination of proton-ligand constant of ligand and metal-ligand stability constants of Cu(II), Co(II) and Ni(II) complexes with gabapentine using potentiometric method in aqueous medium, 25% alcohol -water medium (v/v), 50% alcohol-water medium (v/v), 25% dioxane-water medium (v/v) and 50% dioxane-water medium (v/v) at different ionic strengths (0.1 M and 0.2 M) of NaClO$_4$ at 25 ± 1°C. The Calvin-Bjerrum[7, 8] as adopted by Iriving and Rossotti[9] has been employed to determine stability constant values.

EXPERIMENTAL

All chemicals used were of analytical grade. The Gabapentine tablets (Intas Pharmaceutical, Ahamedabad, India) were prcured and used as a ligand. Ethanol and dioxane were purified by the standard procedures[10]. Ligand solution was prepared in double distilled deionized water. Metal salt solutions were prepared by dissolving the corresponding metal salt in double distilled deionized water and standardized by standard volumetric methods[10]. pH measurements were done on Elico pH-meter model L1-122 with electrode (combined glass and calomel) was used to determine the hydrogen ion concentration during potentiometric titrations in aqueous medium, 25% alcohol-water medium (v/v), 50% alcohol-water medium (v/v), 25% dioxane-water medium (v/v) and 50% dioxane -water medium (v/v) at

different ionic strengths (0.1 M and 0.2 M) of NaClO$_4$ at 25 ± 1°C.

Calvin-Bjerrum Technique

The experimental procedure involves the acid titration, ligand titration and metal titration. The details of titrations are shown in the **Table-1** to **Table-5.** The total volume in all the cases was 50 ml.

Table-1
T = 25 ± 1 °C Aqueous medium μ = 0.1M / 0.2M NaClO$_4$

Solution (Initial concentration)	Acid titration	Ligand titration	Metal titration
HClO$_4$ (0.01M)	5.0 ml	5.0 ml	5.0 ml
NaClO$_4$ (1M / 2M)	5.0 ml	5.0 ml	5.0 ml
Water	40 ml	35 ml	30.0 ml
Ligand	-----	5.0 ml	5.0 ml
Metal	-----	----	5.0 ml

Table-2
T = 25 ± 1 °C 25% Ethanol-water μ = 0.1M / 0.2M NaClO$_4$

Solution (Initial concentration)	Acid titration	Ligand titration	Metal titration
HClO$_4$ (0.01M)	5.0 ml	5.0 ml	5.0 ml
NaClO$_4$ (1M / 2M)	5.0 ml	5.0 ml	5.0 ml
Ethanol	12.5 ml	12.5 ml	12.5 ml
Water	27.5 ml	22.5 ml	17.5 ml
Ligand (0.01M)	-----	5.0 ml	5.0 ml
Metal (0.01M)	-----	----	5.0 ml

Table-3
T = 25 ± 1 °C 50% Ethanol-water μ = 0.1M / 0.2M NaClO$_4$

Solution (Initial concentration)	Acid titration	Ligand titration	Metal titration
HClO$_4$ (0.01M)	5.0 ml	5.0 ml	5.0 ml
NaClO$_4$ (1M / 2M)	5.0 ml	5.0 ml	5.0 ml
Ethanol	25.0 ml	25.0 ml	25.0 ml
Water	15.0 ml	10.0 ml	5.0ml
Ligand (0.01M)	-----	5.0 ml	5.0 ml
Metal (0.01M)	-----	------	5.0 ml

Table-4
T = 25 ± 1 ºC 25% Dioxane-water μ = 0.1M / 0.2M NaClO$_4$

Solution (Initial concentration)	Acid titration	Ligand titration	Metal titration
HClO$_4$ (0.01M)	5.0 ml	5.0 ml	5.0 ml
NaClO$_4$ (1M / 2M)	5.0 ml	5.0 ml	5.0 ml
Dioxane	12.5 ml	12.5 ml	12.5 ml
Water	27.5 ml	22.5 ml	17.5 ml
Ligand (0.01M)	-----	5.0 ml	5.0 ml
Metal (0.01M)	-----	------	5.0 ml

Table-5
T = 25 ± 1 ºC 50% Dioxane-water μ = 0.1 M/ 0.2M NaClO$_4$

Solution (Initial concentration)	Acid titration	Ligand titration	Metal titration
HClO$_4$ (0.01M)	5.0 ml	5.0 ml	5.0 ml
NaClO$_4$ (1M / 2M)	5.0 ml	5.0 ml	5.0 ml
Dioxane	25.0 ml	25.0 ml	25.0 ml
Water	15.0 ml	10.0 ml	5.0ml
Ligand (0.01M)	-----	5.0 ml	5.0 ml
Metal (0.01M)	-----	-------	5.0 ml

RESULTS AND DISCUSSIONS
The values of n$_A$ (proton-ligand formation number) were calculated[7] by employing the following equation (1)   :

$$\overline{n}_A = Y - \frac{(V_2 - V_1)(N + E^0)}{(V_0 + V_1) \, T^0_L} \quad \ldots \ldots \ldots \ldots (1)$$

where Y is the number of replaceable protons, E^0 and T^0_L are initial concentrations of mineral acid and the reagent respectively, V$_1$ and V$_2$ are the volumes of alkali of normality N required for the acid and reagent titrations respectively at a given pH and V$_0$ is the initial volume of the titrating solution.

The proton ligand formation curves were obtained by plotting the values of n$_A$ vs pH. pK$_a$ value correspond to the pH at which n$_A$ is equal to 0.5.

The metal-ligand stability constants were obtained through evaluation of n, the metal-ligand formation number, using equation (2):

$$\overline{n} = \frac{(V_3 - V_2)\left[(N + E^0) + T^0_L (Y - \overline{n}_A)\right]}{(V_0 + V_2) \, T^0_M \, \overline{n}_A} \quad \ldots \ldots \ldots \ldots (2)$$

where V$_3$ and V$_2$ are the volumes of alkali required for the metal complex and the reagent titrations respectively, at a given pH, and T^0_M is the initial concentration of meta(II) ions. The remaining quantities have the same significance as given in equation (1) for n$_A$ evaluation. pL values are evaluated by the equation (3).

$$pL = \frac{\log[\text{antilog}(pK_a - pH)]}{T^0_L - \overline{n} \, T^0_M} \times \frac{V_0 + 2V_2}{V_0} \quad \ldots (3)$$

Thus with the help of n and pL values, the formation constants were obtained through n vs pL values. The values of n obtained for metal-ligand system indicates the formation 1:1 and 1:2 complexes.

Proton-ligand stability constant value of gabapentine
The proton-ligand stability constant values of the ligand in aqueous medium, 25% alcohol-water (v/v), 50% alcohol-water (v/v), 25% dioxane-water (v/v) and 50% dioxane-water (v/v) at constant ionic strengths (0.1 M and 0.2 M) and at 25 ± 1 ºC are represented in **Table-6** and the representative set of the potentiometric titration curves of the free ligand and complexed gabapentine ligand as a typical example in aqueous medium at

0.1M and 0.2M ionic strengths are shown in (**Fig. 1** & **Fig. 2**).

The proton-ligand stability constant values are essentially required in the determination of metal-ligand stability constants. The average number of protons associated per ligand molecule (n$_A$ values) have been calculated from the acid and ligand titration curve using equation (1). The maximum value of n$_A$ for these ligands is around 1.00, indicating that, the dissociable proton is only one. The pH values at n$_A$= 0.5 corresponds to dissociation constant of the ligand.

Ligand exhibits only one pKa value in the range of 9.054 to 10.854 in 0.1 M ionic strength and 8.895 to 10.409 in 0.2 M ionic strengths respectively in different solvent media, this can be attributed to the ionization of –NH$_2$ group of the gabapentine.

It is seen from the **Table-6** that the pKa values gradually decreases as the ionic strength increases at constant temperature and also effect of different solvent media (dielectric constants) on pKa values[11].

Aqueous media

Fig. 1   Ionic strength = 0.1 M

Fig. 2   Ionic strength = 0.2 M
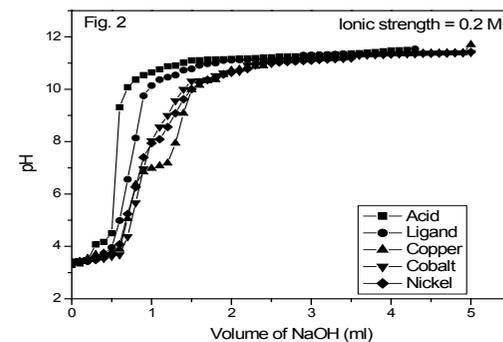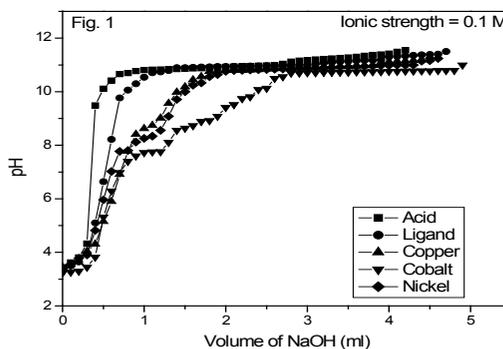
Metal-ligand stability constant values of gabapentine
The metal-ligand stability constants of Cu(II), Co(II), and Ni(II) ions with the ligand has been determined in aqueous medium, 25% alcohol-water (v/v), 50% alcohol-water (v/v), 25% dioxane-water (v/v) and 50% dioxane-water (v/v) at constant ionic strengths (0.1 M and 0.2 M) and at 25 ± 1 ºC). The values of n and pL are calculated using the equations (2) and (3). The values of n obtained for metal-ligand system indicates the formation of 1:1 and 1:2 complexes. The greater stability of Co (II) than Ni (II) may be attributed to the additional stabilization due to John-Teller distortion present in case of Co (II) similar to Cu (II).

From **Table-7**, it is evident that the stepwise formation constants log K and log β values decreases as ionic strength increases. This observation is in agreement with Debye-Hukel equation[12, 13].

Table- 6

Solvent	Ionic strength = 0.1 M	Ionic strength = 0.2 M
	pKa	pKa
Water	9.054	8.895
25% Alcohol-water	10.304	9.199
50% Alcohol-water	10.854	9.846
25% Dioxane-water	10.485	9.210
50% Dioxane-water	10.821	10.409

Table-7
Stability constants

Solvent	Ionic strength = 0.1 M						Ionic strength = 0.2 M					
	Copper (II)		Cobalt (II)		Nickel (II)		Copper (II)		Cobalt (II)		Nickel (II)	
	log k	log β	log k	log β	log k	log β	log k	log β	log k	log β	log k	log β
Water	5.644	3.900	5.554	5.025	4.519	4.230	5.499	5.032	5.476	3.536	4.442	3.835
25% Alcohol-water	7.705	3.764	7.407	4.093	7.199	3.809	6.383	3.779	6.248	3.724	5.942	3.872
50% Alcohol-water	8.048	4.044	7.767	3.996	7.597	4.044	6.854	3.933	6.513	3.787	6.287	3.707
25% Dioxane-water	8.615	6.005	7.170	5.650	6.348	4.68	5.943	4.486	5.803	4.486	5.715	3.714
50% Dioxane-water	7.084	3.884	6.922	3.929	6.256	3.730	6.609	3.855	5.806	3.862	5.566	3.937

CONCLUSION
The results of the potentiometric studies on complexes of 2-[1-(aminomethyl) cyclohexyl] ethanoic acid) with Cu(II), Co(II) and Ni(II) using Calvin-Bjerrum pH-titration technique as used by Irving and Rossotti indicates that the order of stability is Cu(II) > Co(II) > Ni(II).This order is in accordance with Irving-Williams order of stability[14] and formation constants log K and log β values decreases as ionic strength increases. This observation is in agreement with Debye-Hukel equation[12, 13].

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