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Potentiometric Study of Complexation of Gentamicin with Mn (II) Metal Ions

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ABSTRACT: Most of the transition metals form complexes. There are different kinds of ligands used for complexation. Metals can play an important role in modifying the pharmacological properties of known drugs after coordinating with it .The stability constants for the metal complexes are widely used in various fields such as biological processes, analytical processes, separations techniques, pharmaceuticals etc. The present work consists of the determination of the stability constant of Gentamicin antibiotics with bivalent metal ion Mn (II) in 50% (v/v)ethanol- water medium at three different temperatures (30, 35 and 40°C) and ionic strength 0.1 M ($NaNO_3$). It is observed that a Mn (II) and Gentamicin antibiotic forms 1:1and 1:2 complexes. The thermodynamic parameters Gibbs free energy change (ΔG), enthalpy change (ΔH) and entropy change (ΔS) were also calculated from stability constants value at three temperatures .All the thermodynamic parameters were found to be negative.

Keywords: Transition metals; Ligand; Metal complexes; Thermodynamic parameters; Stability constant; Ionic strength and Potentiometric.

INTRODUCTION: Gentamicin is an aminoglycosides antibiotic composed of a mixture of related gentamicin components and fractions and is used to treat many types of bacterial infections, particularly those caused by Gram-negative organisms.[1] Gentamicin is also ototoxic and nephrotoxic, with this toxicity remaining a major problem in clinical use[1]. Active against a wide range of bacterial infections, mostly Gram-negative bacteria including Pseudomonas, Escherichia coli, Proteus, etc. and the Gram-positive Staphylococcus. Gentamicin is also used in molecular biology research as an antibacterial agent in tissue and cell culture, to prevent contamination of sterile cultures. Chemically it is 2-[4,6-diamino-3-[3-amino-6-[1-(methylamino)ethyl]oxan-2-yl]oxy-2-hydroxycyclohexyl]oxy-5-methyl-4-(methylamino)oxane-3,5-diol.

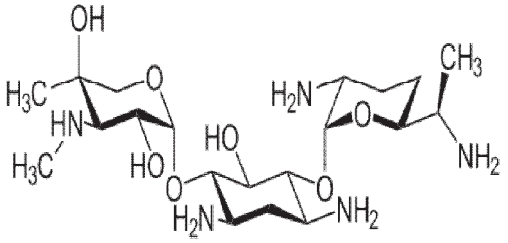

Figure 1: Chemical structure of Gentamicin.

Chemistry of antibiotics attracts many researchers because of its application in medical field. Some antibiotics functions as ligand. Co-ordination complexes are formed by the metal ion and molecules or ions (ligand).A wide variety of inorganic and organic ions and molecules, which may be conjugate bases of weak or strong acids, act as ligand[2 & 3]. Metal complexes play a vital role in nature; they have been extensively used in clinical applications. The stability of metal antibiotics complexes plays an important role in the biological, biochemical and chemical activities. The metal ligand selectively and strength of metal-ligand bonds depends on stability constants. pH-metric titration method is the best available experimental technique for the study of complexation .

A stability constant (formation constant, binding constant) is equilibrium constant for the formation of a complex in solution. It is a measure of the strength of the interaction between the reagents that come together to form the complex. The stability constant(s) provide the information required to calculate the thermodynamic properties of the complex (es) in solution. There are many areas of application in chemistry[4], biology and medicine. The present work describes the interaction between Mn (II) metal ions with Gentamicin as ligand in 50% (v/v) ethanol- water medium has been determined by pH meter. The stability constants and thermodynamic parameters (ΔH, ΔG and ΔS) were determined in 50% (v/v) ethanol- water medium at three different temperatures (30, 35 and

40°C) and ionic strength 0.1 M ($NaNO_3$) by the Calvin, Bjerrum titration methods adopted by Irving and Rossotti. It is observed that a Mn (II) and Gentamicin antibiotic forms 1:1and 1:2 complexes. Bjerrum half integral method and least square method are used for determination of metal ligand stability constants.

MATERIALS AND METHODS: Materials and solution: In the present work Gentamicin has been used as ligand. All the chemicals used were of AR grade .The metal ion solution prepared from its corresponding nitrate are standardized volumetrically by titration with standard disodium salt of EDTA in presence of suitable indicator[5 & 6]. All the solution used in this titration was prepared in double distilled water. All the measurements were done at 303K, 308K and 313K in 50% (v/v) ethanol-water medium at constant ionic strength 0.1 M ($NaNO_3$). The pH measurements were done on Systronic pH meter model 132E and using a combination electrode. The pH meter was calibrated with suitable buffers (pH=4 & 7) before use time to time.

Potentiometric method: The compositions of a set of test solution for each metal ion were as follows:

(i) 1.5 ml HNO_3 (0.01 M) + 2.0 ml $NaNO_3$ (1.0 M) + 3 ml KNO_3 (0.01 M) + 3.5 ml H_2O + 10.0 ml ethanol.

(ii) 1.5 ml HNO_3 (0.01 M) + 2.0 ml $NaNO_3$ (1.0 M) + 3 ml KNO_3 (0.01 M) + 5 ml Gentamicin (0.01 M) + 1.0 ml H_2O + 7.5 ml ethanol.

(iii) 1.5 ml HNO_3 (0.01 M) + 2.0 ml $NaNO_3$ (1.0 M) +0.5 ml metal nitrate (0.01 M) + 5 ml Gentamicin (0.01 M) +3.5 ml H_2O + 7.5 ml ethanol.

The ligands were titrated against standard NaOH solution using Calvin-Bjerrum and Calvin-Wilson pH titration methods.

The proton-ligand and metal- ligand stability constant was determined by Calvin-Bjerrum[7 & 8] pH titration as modified by Irving and Rossitti[9]. The formation curves have been plotted from the $\overline{n}$ and pL values and are shown in figures (2A, 2B and 2C).

Determination of the Thermodynamic parameters: The thermodynamic parameters such as Gibbs free energy change (ΔG), enthalpy change (ΔH) and entropy change (ΔS) for formation of complexes were determined. The Gibbs free energy change (ΔG) is calculated by using:

$$-\Delta G = 2.303\ RT \log K$$

Where; R = Universal gas constant, log K = Stability constant and T= temperature in K

The enthalpy change is calculated by the slope of the plot of log K vs 1/T:

$$\text{Slope} = -\Delta H / 2.303\ R$$

The entropy change for complex formation was calculated by:

$$\Delta S = (\Delta H - \Delta G) / T$$

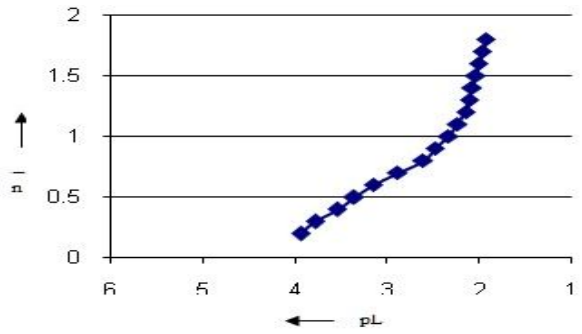

Figure 2(A): Formation curve of Gentamicin-Mn (II) complexes in 50% (v/v) ethanol-water medium at temperature 303K.

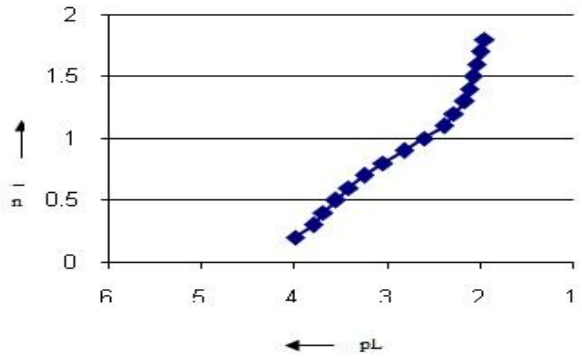

Figure 2(B): Formation curve of Gentamicin-Mn (II) complexes in 50% (v/v) ethanol-water medium at temperature 308K.

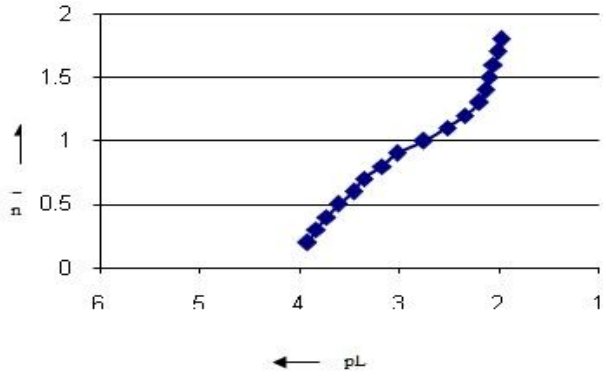

Figure 2(C): Formation curve of Gentamicin-Mn (II) complexes in 50% (v/v) ethanol-water medium at temperature 313K.

RESULTS AND DISCUSSION: The stability constant values of complexation of Mn (II) ions with Gentamicin using Potentiometric pH method have been represented in Table 1. It shows that the values of stability constant decreases with an increase in temperature showing there by that lower temperature favors the formation of stable complexes[10] .The degree of ionization also increases for a used ligand with temperature. Using stability constant values at three temperatures thermodynamic parameters ΔG, ΔH and ΔS have also been calculated and presented. Thermodynamic parameters have been shown in Table 2.

The Gibbs free energy (ΔG) was found to have negative values which show that the formation of complex process is spontaneous. The negative values of change in entropy (ΔS) indicate higher order in the complexation process. The change in enthalpy (ΔH) values indicate the complexation reaction to be exothermic, in fair agreement with increasing stability suggesting lower temperatures favours the chelation process. The overall change in the values of ΔH and ΔS at 308K indicate that the complex formations of Gentamicin in 50% (v/v) ethanol-water medium are both enthalpy and entropy stabilized.

Table 1: Stability Constant of Gentamicin Mn (II) Complex at temperature 303, 308 and 313K.

Temperature	Bjerrum half integral method			Weighted least square method		
	$\log k_1$	$\log k_2$	$\log \beta_2$	$\log k_1$	$\log k_2$	$\log \beta_2$
303K	4.210	2.586	6.796	4.134	2.701	6.835
308K	4.010	2.482	6.492	3.900	2.679	6.579
313K	4.000	2.430	6.430	3.780	2.590	6.370

Table 2: Thermodynamics parameters for Gentamicin Mn (II) complex in 50% (v/v) ethanol –water at 0.1 mol dm^{-3} $NaNO_3$.

Temperature	Gibbs Energy Change (KJ mol^{-1})			Enthalpy Change (303-313K kJ mol^{-1})			Entropy Change at 308 K (kJ$mol^{-1}k^{-1}$)		
	$-\Delta G_1$	$-\Delta G_2$	$-\Delta G_{\beta 2}$	$-\Delta H_1$	$-\Delta H_2$	$-\Delta H_{\beta 2}$	$-\Delta S_1$	$-\Delta S_2$	$\Delta S_{\beta 2}$
303K	23.9837	15.6700	39.6537	62.0496	18.9155	80.9651	126.7861	10.1188	136.9049
308K	22.9995	15.5989	38.5984						
313K	22.6537	15.5220	38.1757						

ΔG_1, ΔH_1 and ΔS_1 values have been derived from log k_1; ΔG_2, ΔH_2 and ΔS_2 values have been derived from log k_2; $\Delta G_{\beta 2}$, $\Delta H_{\beta 2}$ and $\Delta S_{\beta 2}$ values have been derived from log β_2.

CONCLUSION: In present study, the Mn (II) ion form 1:1 and 1:2 complexes with Gentamicin. The values of the thermodynamic parameters ΔG, ΔH and ΔS were calculated and were found to be negative. The stability constants values of metal-antibiotic complexes decreases with an increase in temperature .Stability constant values provide informations to biochemist for designing of new drugs.

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