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Research Article

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Determination of Stability Constant of Sulfamethoxazole-Zn(II) complex at Different Temperatures by Continuous Variation Method

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Abstract Sulfamethoxazole is a sulfanomide antibiotic that is used for the treatment of gram positive and gram negative bacteria. Continuous variation method was applied in the calculation of stability constant of sulfamethoxazole-Zn(II) complex depending on the theoretical explanation of the stoichiometry. The formation of Zn(II) complex with sulfamethoxazole was studied colorimetrically at an absorption maximum of 630 nm at 25, 30, 35 and 40 °C. The data showed that Zn(II) and sulfamethoxazole combine in the molar ratio of 1:4 at pH 7.4 with ionic strength maintained using 0.1M KNO_3. Calculated stability constants values were 3.52×10^{10}, 8.14×10^{9}, 2.78×10^{9} and 4.36×10^{8} at 25, 30, 35 and 40 °C respectively. Calculated ΔG^{Θ} for the complex were -6.02×10^{4}, -5.75×10^{4}, -5.57×10^{4} and -5.18×10^{4} at 25, 30, 35 and 40 °C respectively. The stoichiometry, stability constant and Gibbs free energy results suggested that sulfamethoxazole used in the study is a good chelating agent and can be an efficient antidote in the therapy of Zn(II) overload or poisoning.

Keywords Sulfamethoxazole, zinc, complex, stability constant

Introduction

Sulfamethoxazole is a sulfanomide antibiotic that is used for the treatment of gram positive and gram negative bacteria [1]. It is on the world health organization list of essential medicine. If was first introduced in America in 1961 [2]. It works by preventing the synthesis of folic acid (vitamin B9) in bacteria that require their own folic acid synthesis for survival [3]. It is used in combination with trimethoprim for the treatment of urinary tract infection [4]. Its side effects are nausea, vomiting, loss of appetite and skin rashes.

Zinc is required for catalytic activity of over 200 enzymes [5]. It plays an essential role in boosting immunity [5]. Zinc functions can be categorized as catalytic, regulatory and structural [6]. It has been estimated that over two million people in the developing countries are deficient of Zu [7]. Although zinc is required for good health, excess zinc is harmful.

The ligational, spectroscopic and evaluating antimicrobial investigations of sulfamethoxazole drug complexes formulas with Mn(II), Cu(II), Ni(II), Zn(II), Y(III), La(III), Nd(III) and Gd(III) metal ions have been reported [8]. These sulfamethoxazole complexes were synthesized and characterized by elemental analysis, molar conductance, magnetic susceptibility, UV-vis, IR and 1H-NMR spectroscopy. The IR spectral data suggested that the coordination sites of sulfamethoxazole are the sulfonyloxygen and SO_2-NH sulfonamide nitrogen as a bidentate ligand. From the microanalytical data, the stoichiometry of the complexes was 1:2 (metal: ligand).

For several decades, chelating agents have been used as antidote to combat metal poisoning [9]. Biological friendly sequestrating agents have been used effectively to chelate metals in patients with metal overload [9]. However, chelating capacity is a function of stability constant indicating that the effectiveness of a drug to chelate with a metal ion depends on the stability constant and other parameters [10] Many authors have reported the study of stability constant of drug- metal complexes [11-15]. However, to the best of our knowledge, the stability constant of sulfamethoxazole–Zn(II) complex at different temperatures have not been reported elsewhere in literature. Therefore, the present study is aimed at determining the stability constant of sulfamethoxazole-Zn(II) complex using continuous variation. Information on stability constants of this complex can be useful in analysisng the effects of sulfamethoxazole on copper ion and other electroactive divalent trace metals. It is possible that changes in trace metal and mineral concentration induced by sulfamethoxazole can be an efficient antidote in the therapy of Zn overload or poisoning. The chemical structure of sulfamethoxazole is shown in Fig. 1 while the chemical structure of the proposed complexes is shown in Fig. 2.

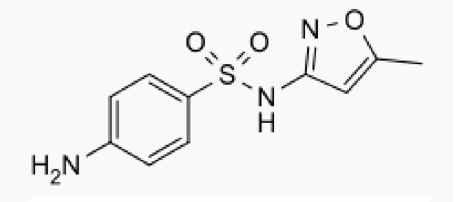

Figure 1: Chemical structure of sulfamethoxazole

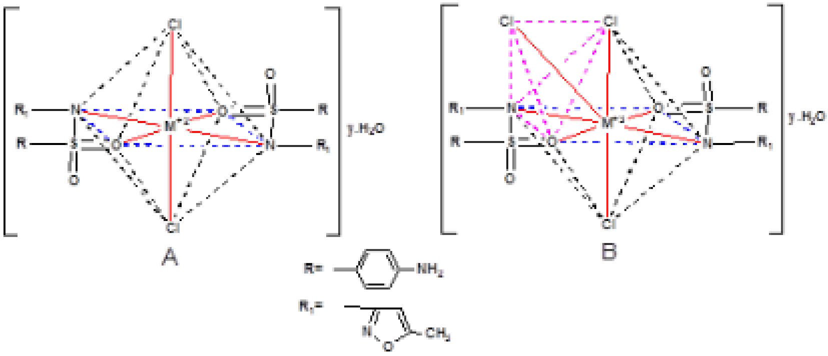

Figure 2: Geometry of sulfamethoxazole complexes

Materials and Methods

Reagents

Reagents used for the study were of analytical grade. Sulfamethoxazole was purchased from Andhra Organics Limited, Indian. $ZnCl_2$ was purchased from Merck & Co., Inc USA. Double-distilled water was used throughout the experiment.

Preparation of 1 x 10^{-2} M $ZnCl_2$

$ZnCl_2$ (1.362 g, 10 Mmol, molar weight= 136.29 g/mol) was dissolved in freshly distilled water contained in a 250 cm^3 beaker and was made up to the mark in a 1000 cm^3 volumetric flask.

Preparation of 1 x 10^{-2} M sulfamethoxazole

sulfamethoxazole (2.532 g, 10 Mmol molar weight = 253.279 g/mol) was dissolved in freshly distilled water in a 250 cm^3beaker and was made up to the mark in a 1000 cm^3 volumetric flask.

Procedure for continuous variation method

Exactly 0, 1,2, 3, 4, 5, 6 $cm^3$of 1 x 10^{-2} M $ZnCl_2$ were pipetted into seven different 50 cm^3 volumetric flasks respectively. Exactly 6, 5, 4, 3, 2, 1, 0 cm^3 of 1 x 10^{-2} M of sulfamethoxazole was added to the respective flasks containing Zn(II) solution. The pH was adjusted to 7.4 while the ionic strength was maintained constant using 0.1 M KNO_3. The absorbance of each solution was measured at 630 nm (maximum wavelength of absorbance of the complex) and at temperatures of 25, 30, 35 and 40 ^oC respectively.

Calculation of stoichiometry, stability constant and free energy

The stoichiometry mole fraction (SMF) of the complex using continuous variation method was calculated using equation 1 [14].

$$SMF = \frac{m}{1-m} \qquad (1)$$

where m is the mole fraction of the metal ion. The stability constant was calculated using the classical method expressed in equation 2,

$$K_{st} = \frac{1-\alpha}{m^m . n^n (\alpha)^{m+n} (C)^{m+n-1}} \quad (2)$$

where C is the concentration of the complex at stoichiometry point, α is the degree of dissociation, m and n are the corresponding stoichiometric coefficients of metal and ligand respectively. The degree of dissociation (α) was calculated using equations 3, 4 and 5 [14].

$$A_\alpha = A_o - A_{max} \quad (3)$$

$$A_{max} = \varepsilon bC \quad (4)$$

$$\alpha = \frac{A_\alpha}{\varepsilon bC} \quad (5)$$

where A_{max} is absorbance value of the maximum at experimental curve that represents the maximum quantity of the complex that is formed. A_o is absorbance value corresponding to the intersect point of the theoretical straight lines. A_α is the absorbance value of the part of dissociated concentration of complex. ε is molar absorptivity, b is cell thickness, C is a concentration of complex at stoichiometry point.

The Gibbs free energy was calculated using the Helmholtz Gibb equation (equation 6),

$$\Delta G^\theta = -RTInK \quad (6)$$

Results and Discussion

The absorption spectra of $ZnCl_2$ and sulfamethoxazole-Zn(II) complex are shown in Fig. 3.

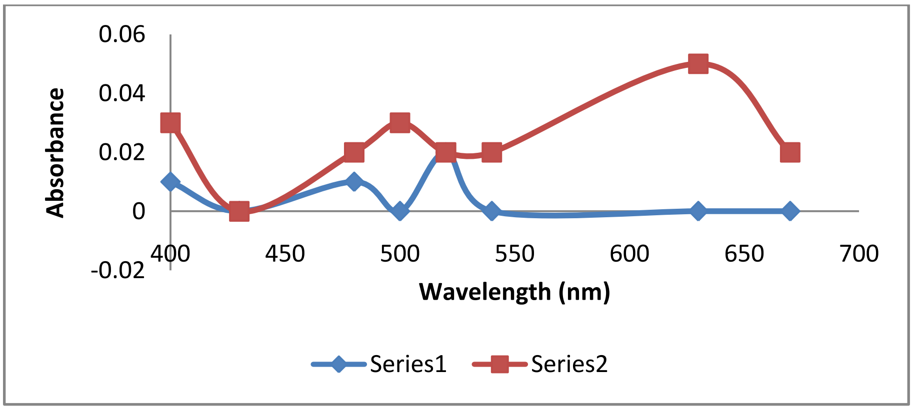

Figure 3: Absorption spectra of $ZnCl_2$ (1×10^{-2} M) (series 1) and sulfamethoxazole-Zn(II) complex (series 2)

The absorption spectra (Fig. 3) shows the absorbance of $ZnCl_2$ (series 1) and sulfamethoxazole-Zn(II) complex (series 2) at wavelength of 400 – 700 nm. It was observed that the wavelength of maximum absorbance of the complex was 630 nm. At this wavelength, $ZnCl_2$ displayed minimal absorbance. Since the complex maximum absorbance was 630 nm, it was used for the analytical measurement in the determination of the stoichiometry, stability constants and free energies. The maximum absorbance of $ZnCl_2$ was observed at wavelength of 540 nm. It was observed that sulfamethoxazole-Zn(II) complex gave a water soluble complex in aqueous solution, This may be attributed to the ability of water to act as a weak monodentate ligand in forming labile Zn-aquo complex. During complexation, sulfamethoxazole displaced water from Z-aquo to form a stable sulfamethoxazole-Zn(II) complex. Similar labile aquo complexes were also proposed by several authors in their determination of stability constant [11-13, 15].

Table 1: Experimental data of sulfamethoxazole-Zn(II) complex at 630 nm by continuous variation method

S/N	$ZnCl_2$ (1×10^{-2}M)	Sulfamethoxazole (1×10^{-2} M)	Mole fraction of Cu(II)	Absorbance at 630(nm)			
				25 ºC	30 ºC	35 ºC	40 ºC
1	0.000	6.000	0.000	0.00	0.00	0.00	0.00
2	1.000	5.000	0.170	0.00	0.00	0.00	0.00
3	2.000	4.000	0.330	0.00	0.00	0.00	0.00
4	3.000	3.000	0.500	0.01	0.00	0.00	0.00
5	4.000	2.000	0.660	0.02	0.01	0.00	0.02
6	5.000	1.000	0.830	0.03	0.03	0.03	0.03
7	6.000	0.000	1.000	0.00	0.00	0.00	0.00

The Job's curves at 25, 30, 35 and 40 °C are shown in Figures 4, 5, 6 and 7 respectively. Equation 1 was applied in calculation of stoichiometry.

$SMF = \frac{0.81}{0.19} = 4.26 \approx 4$ (at 25 ^{0}C), $SMF = \frac{0.81}{0.19} = 4.26 \approx 4$ (at 30 °C), $SMF = \frac{0.81}{0.19} = 4.26 \approx 4$ (at 35 °C), $SMF = \frac{0.80}{0.20} = 4$ (at 40 °C).

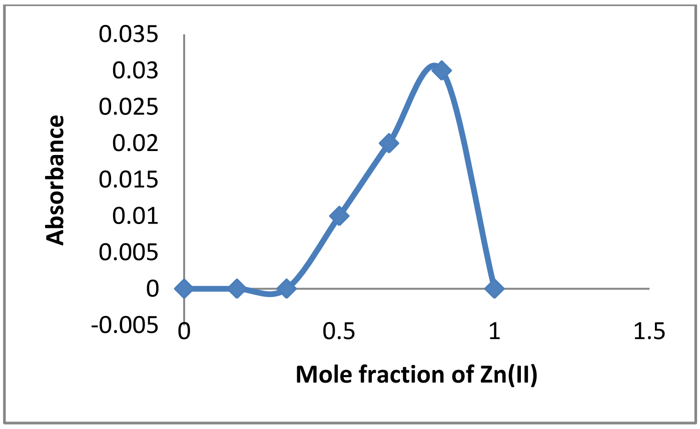

Figure 4: Job's curve of equimolar solutions at 25 °C

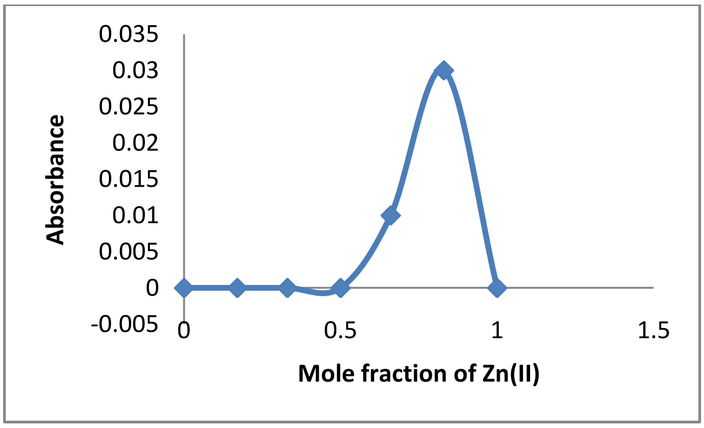

Figure 5: Job's curve of equimolar solutions at 30 °C

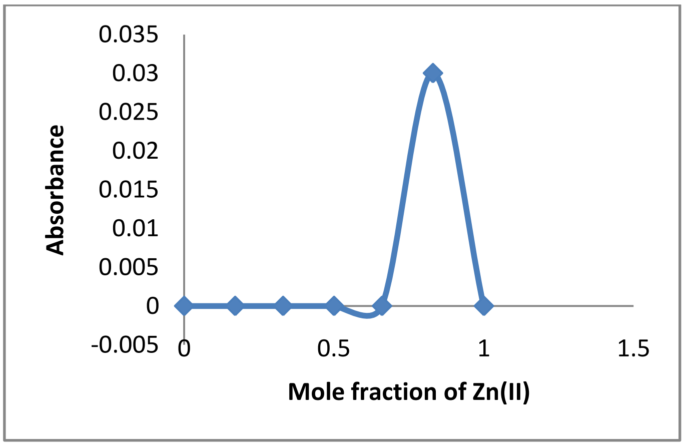

Figure 6: Job's curve of equimolar solutions at 35 °C

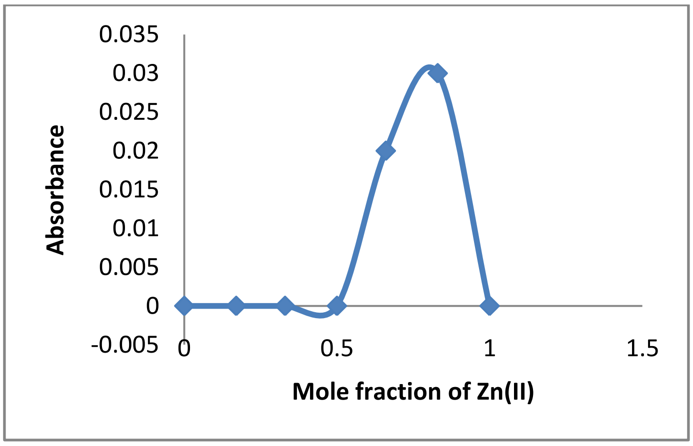

Figure 7: Job's curve of equimolar solutions at 40 °C

This corresponded to metal:ligand ratio of 1:4. The extrapolated value at the point of cross-section on continuous variation plot (Figs. 4, 5, 6 and 7) corresponded to the total absorbance of the complex, indicating that the complex formation process has been completed. Several authors have also applied continuous variation method in the determination of metal:ligand ratio in complexes [13 - 15].

Table 2: Calculated stability constant and Gibbs free energies of sulfamethoxazole-Zn(II) complex using continuous variation method

S/N	Temperature (^{o}C)	M:L ratio	Stability constant	ΔG^{Θ} (J)
1	25	1:4	3.52×10^{10}	-6.02×10^{4}
2	30	1:4	8.14×10^{9}	-5.75×10^{4}
3	35	1:4	2.78×10^{9}	-5.57×10^{4}
4	40	1:4	4.36×10^{8}	-5.18×10^{4}

Stability constant is an evaluation of the strength of the interaction between the reagents that come together to form the complex. Large values indicate that the metal has high affinity for the ligand, provided the system is at equilibrium. Calculation of the stability constant and Gibbs free energies were based on equations 2, 3, 4, 5 and 6 respectively. The values of the stability constant showed that the complex was stable at 25, 30, 35 and 40 ^{o}C. Increasing the temperature of coordination from 25 to 40 ^{o}C displayed observable significant effect on the stability constant. As the temperature was increased from 25 – 40 ^{o}C, the stability constant decreases. The values of the stability constants were positive, indicating that the complex is stable. Positive stability constant values using continuous variation have also been reported by several authors [9 – 15]. Continuous variation is an established techniques in the determination of stability constant and Gibbs free energies. The results of stability constant suggested that sulfamethoxazole could be effective in chelation therapy against Zn(II) toxicity. The negative values of the free energies suggested that the complexes were formed spontaneously.

Conclusion

Sulfamethoxazole is a sulfanomide that is used for the treatment of gram positive and gram negative bacteria It formed a reasonably stable complex with Zn(II). The Job's continuous variation methods data showed that Zn(II) and sulfamethozaxole combine in the molar ratio of 1:4. The stability constant results suggested that sulfamethozaxole used in the study is a good chelating agent and can be an efficient antidote in the therapy of Zn(II) overload or poisoning.

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