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Colorimetric Determination of Stability Constant of Trimethoprim-Cu(II) Complex at Different Temperatures by Continuous Variation Method

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ABSTRACT

Trimethoprim is an antibiotic that is mainly used for the treatment of bladder infections. Continuous variation method was applied in the calculation of stability constant of trimethoprim-Cu(II) complex depending on the theoretical explanation of the stoichiometry. The formation of Cu(II) complex with trimethoprim was studied colorimetrically at an absorption maximum of 480 nm at 25, 30, 35 and 40 ^{o}C. The data showed that Cu(II) and trimethoprim combine in the molar ratio of 1:1 at pH 7.4 with ionic strength maintained using 0.1M KNO_3. Calculated stability constants values were 6.00 x 10^4, 3.80 x 10^4, 2.61 x 10^4 and 1.89 x 10^4 at 25, 30, 35 and 40 ^{o}C respectively. Calculated ΔG^{θ} for the complex were -2.73 x 10^4, -2.66 x 10^4, -2.60 x 10^4 and -2.56 x 10^4 at 25, 30, 35 and 40 ^{o}C respectively. The stoichiometry, stability constant and Gibbs free energy results suggested that trimethoprim used in the study is a potent chelating agent and can be an efficient antidote in the therapy of Cu(II) overload or poisoning.

KEYWORDS: *Trimethoprim, copper, complex, stability constant*

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INTRODUCTION

Trimethoprim is an antibiotic that is mainly used for the treatment of bladder infections [1]. It is also used in the treatment of middle ear infections and travelers' diarrhea [1]. With sulfamethoxazole or dapsone it may be administered for the treatment of *Pneumocystis* pneumonia in people with HIV/AIDS [1]. It is taken orally [1]. Trimethoprim works by inhibiting folate metabolism through dihydrofolate reductase in some bacteria which results in their death.[1]

Copper is an important trace metal that is vital to the health of humans. In humans, copper is vital for the proper functioning of organs and metabolic processes. The complex homeostatic mechanisms of the human body ensure a constant supply of available copper, while removing excess copper whenever necessary. However, like all essential elements and nutrients, too much or too little nutritional ingestion of copper can result in a corresponding condition of copper excess or deficiency in the body, each of which has its own unique set of adverse health effects [2].

The Synthesis and characterization of trimethoprim metal complexes have been reported [3]. Trimethoprim metal complexes were characterized by different spectroscopic methods: Ultraviolet-visible, Fourier transform infrared, conductivity measurements, thermal analysis (TG) and magnetic susceptibility measurement [3]. The results of the experiment showed that the coordination of trimethoprim drug with the transition metal ions occurred through nitrogen of pyrimidinyl ring. Square planar geometry was suggested for Mn(II), Ni(II), Cu(II) complexes while Cr(III) and Co(II) complexes have an octahedral geometry. The complexes have electrolyte properties [3].

For several decades, chelating agents have been used as antidote to combat metal poisoning [4, 5]. Biological friendly sequestrating agents have been used effectively to chelate metals in patients with metal overload [4-6]. 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 [4-6] Many authors have reported the study of stability constant of drug- metal complexes [6-9]. However, to the best of our knowledge, the stability constant of trimethoprim–Cu(II) complex at different temperatures have not been reported elsewhere in literature. Therefore, the

present study is aimed at determining the stability constant of trimethoprim–Cu(II) complex using continuous variation. Information on stability constants of this complex can be useful in analysisng the effects of trimethoprim on copper ion and other electroactive divalent trace metals. It is possible that changes in trace metal and mineral concentration induced by trimethoprim can be an efficient antidote in the therapy of Cu overload or poisoning. The chemical structure of trimethoprim is shown in Fig. 1 while the chemical structure of the proposed complexes is shown in Fig. 2.

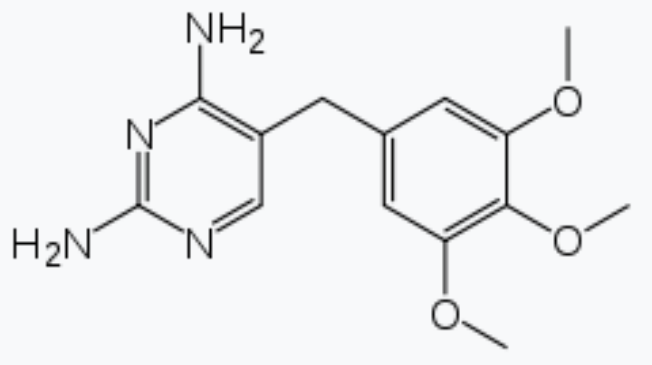

Figure 1: The chemical structure of trimethoprim

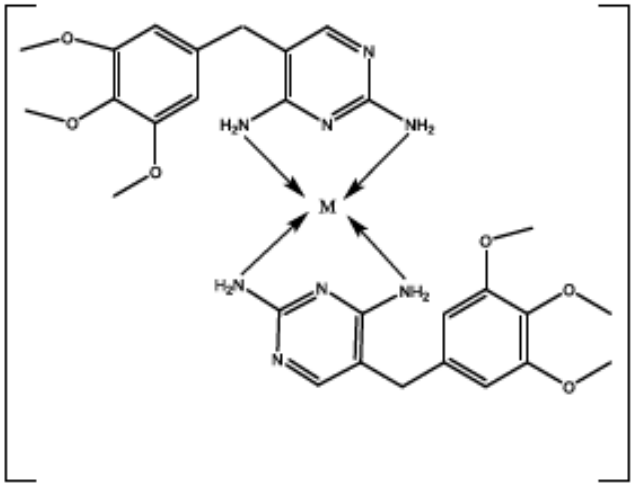

Figure 2: Square planar geometry of trimethoprim-Cu(II) complex.

Materials and Methods

Reagents

Reagents used for the study were of analytical grade. Trimethoprim was purchased from Andhra Organics Limited, Indian. $CuSO_4$ was purchased from Merck & Co., Inc USA. Double-distilled water was used throughout the experiment.

Preparation of 1 x 10^{-2} M $CuSO_4$

$CuSO_4$(1.566 g, 10 Mmol, molar weight= 156.60 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 trimethoprim

Trimethoprim (2.903 g, 10 Mmol, molar weight = 290.32 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 $CuSO_4$ were pipetted into seven different 50 cm^3volumetric flasks respectively. Exactly 6, 5, 4, 3, 2, 1, 0 cm^3 of 1 x 10^{-2} M of trimethoprim was added to the respective flasks containing Cu(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 480 nm (maximum wavelength of absorbance of the complex) and at temperatures of 25 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 [10].

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

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 [10].

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

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

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

where A_{max} is absorbance value of the maximum at experimental curve that represents the maximum quantity of the complex that is formed. Ao is absorbance value corresponding to the intersect point of the theoretical straight lines. Aα 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 trimethoprim-Cu (II) complex is shown in Fig. 3

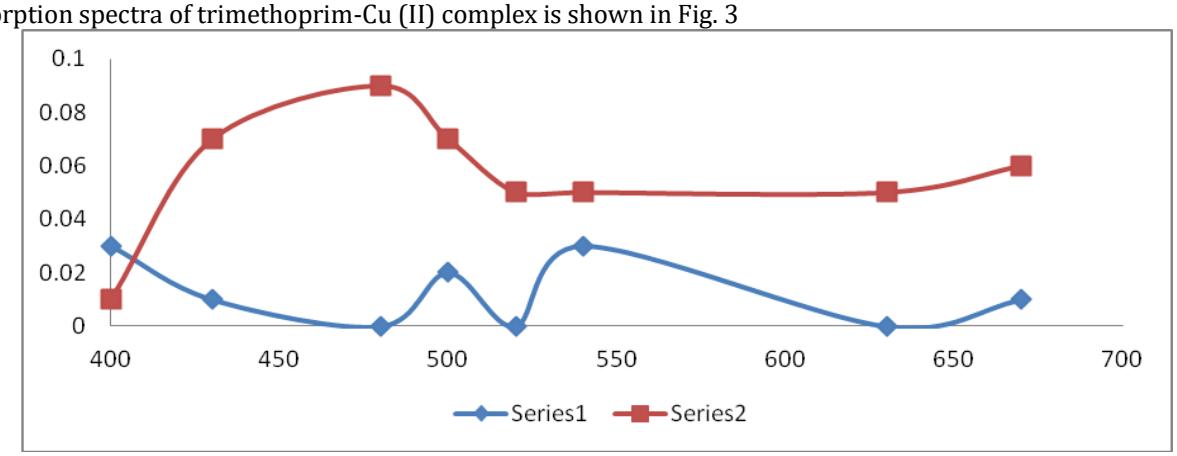

Fig. 3: Absorption spectra of $CuSO_4$ (1 x 10^{-2} M) (series 1) and trimethoprim-Cu(II) complex (series 2)

The absorption spectra (Fig. 3) shows the absorbance of $CuSO_4$ (series 1) and trimethoprim-Cu(II) complex (series 2) at wavelength of 400 – 700 nm. It was observed that the wavelength of maximum absorbance of the complex was 480 nm. At this wavelength, $CuSO_4$ displayed minimal absorbance. Since the complex maximum absorbance was 480 nm, it was used for the analytical measurement in the determination of the stoichiometry, stability constants and free energies. The maximum absorbance of $CuSO_4$ was observed at wavelength of 540 nm. It was observed that trimethoprim-Cu(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 Cu-aquo complex. During complexation, trimethoprim displaced water from Cu-aquo to form a stable trimethoprim-Cu(II) complex. Similar labile aquo complexes were also reported by several authors in their study of stability constant of complexes [5 -11].

Table 1: Experimental data of trimethoprim-Cu(II) complex at 480 nm by continuous variation method

S/N	$CuSO_4$ (1x 10^{-2} M)	Sulfamethoxazole (1 x 10^{-2} M)	Mole fraction of Cu(II)	Absorbance at 430(nm)			
				25 ℃	30 ℃	35 ℃	40 ℃
1	0.000	6.000	0.000	0.01	0.03	0.02	0.03
2	1.000	5.000	0.170	0.03	0.05	0.04	0.04
3	2.000	4.000	0.330	0.05	0.06	0.05	0.05
4	3.000	3.000	**0.500**	**0.10**	**0.10**	**0.10**	**0.10**
5	4.000	2.000	0.660	0.07	0.07	0.07	0.07
6	5.000	1.000	0.830	0.04	0.04	0.04	0.04
7	6.000	0.000	1.000	0.02	0.03	0.02	0.03

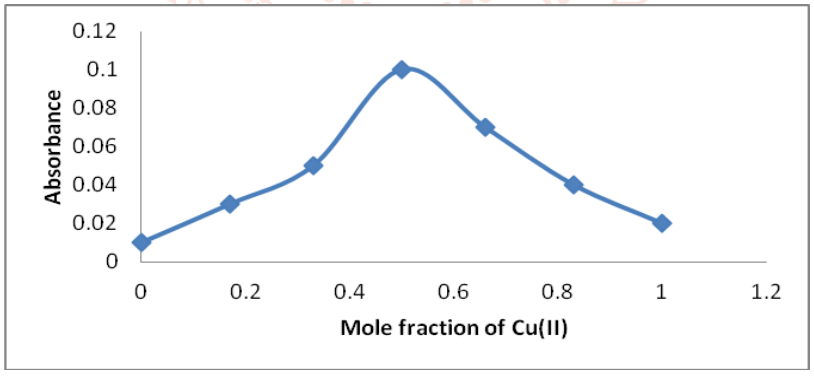

Figure 4: Job's curve of equimolar solutions at 25 °C

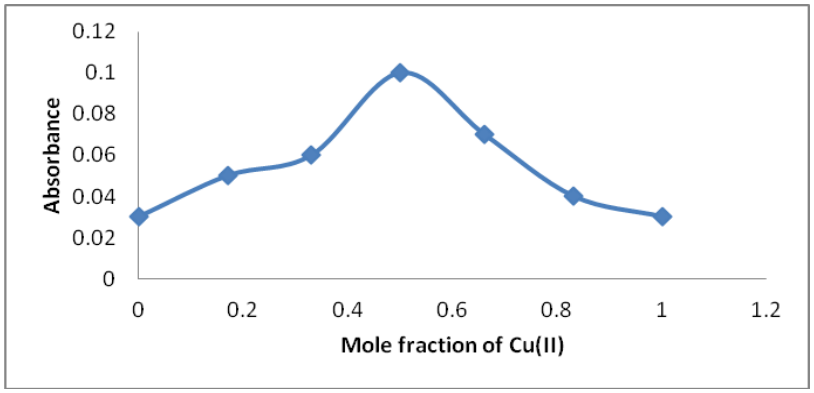

Figure 5: Job's curve of equimolar solutions at 30 °C

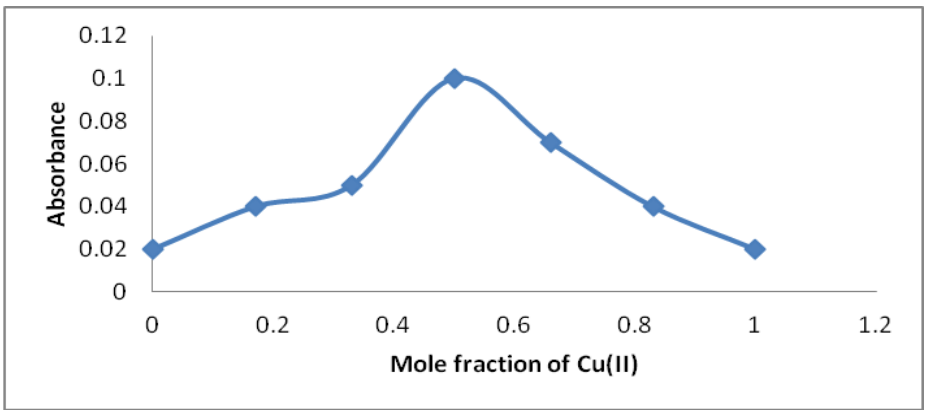

Figure 6: Job's curve of equimolar solutions at 35 °C

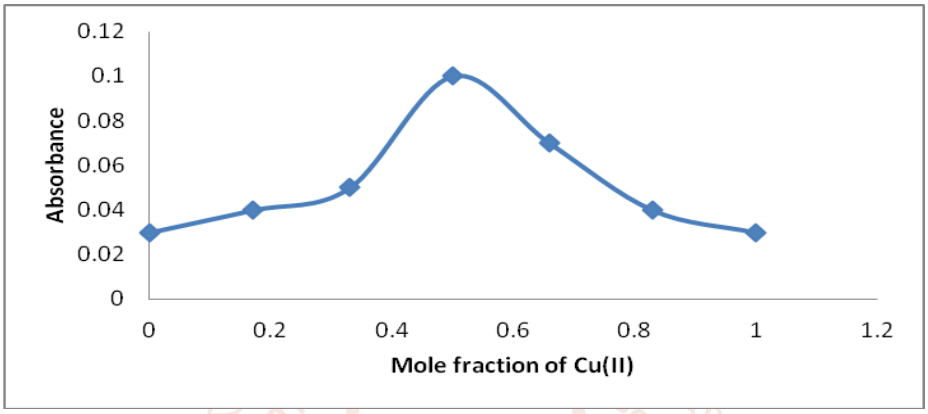

Figure 7: Job's curve of equimolar solutions at 40 °C

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 of the complex

SMF = $\frac{0.50}{0.50}$ = 1.00 (25 °C), SMF = $\frac{0.50}{0.50}$ = 1.00 (30 °C), SMF = $\frac{0.50}{0.50}$ = 1.00 (35 °C), SMF = $\frac{0.50}{0.50}$ = 1.00 (40 °C),

The soichiometry calculation corresponded to metal:ligand ratio of 1:1. 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 [5-11].

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

S/N	Temperature (°C)	M:L ratio	Stability constant	ΔG^{θ} (J)
1	25	1:1	6.00×10^4	-2.74×10^4
2	30	1:1	3.08×10^4	-2.66×10^4
3	35	1:1	2.61×10^4	-2.60×10^4
4	40	1:1	1.89×10^4	-2.56×10^4

Calculation of the stability constant and Gibbs free energies were based on equations 2, 3, 4, 5 and 6 respectively. The large values of the stability constant indicate that the metal has high affinity for the ligand, provided the system is at equilibrium. Stability constant is an evaluation of the strength of the interaction between the reagents that come together to form the complex The values of the stability constant showed that the complex was stable at 25, 30, 35 and 40 °C. Increasing the temperature of coordination from 25 to 40 °C decrease the stability constant values. This suggested that the complex formation reaction is exothermic reaction. 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 [5-11]. Continuous variation is an established techniques in the determination of stability constant and Gibbs free energies. The results of stability constant suggested that trimethoprim could be effective in chelation therapy against Cu(II) toxicity. The negative values of the free energies suggested that the complexes were formed spontaneously.

Conclusion

The Job's continuous variation methods data showed that Cu(II) and trimethoprim combine in the molar ratio of 1:1. The stability constant results suggested that the complex was stable. Trimethoprim used in the study is a potent chelating agent and can be an efficient antidote in the therapy of Cu(II) overload or poisoning.

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