International Journal of Advances in Engineering and Management (IJAEM)
Volume 2, Issue 3, pp: 413-418 www.ijaem.net ISSN: 2395-5252

Determination of Stability Constants of Cefotaxime-Co (III) Complex at Different Temperatures by Continuous Variation Method

I.E. Otuokere [1], O.V. Ikpeazu [2] and K.K. Igwe [3]

1. Department of Chemistry, Michael Okpara University of Agriculture, Umudike, Nigeria
2. Department of Biochemistry, Abia State University, Uturu
3. Department of Vet Biochemistry and Animal Production, Michael Okpara University of Agriculture, Umudike, Nigeria
Corresponding Author: I.E. Otuokere

Date of Submission: 25-07-2020 Date of Acceptance: 05-08-2020

ABSTRACT: Cefotaxime is a broad-spectrum antibiotic with activity against numerous Gram-positive and Gram-negative bacteria. It has donor atoms which enables it to act as a complexing agent. The formation of Co(III) complex with cefotaxime has been studied colorimetrically at an absorption maximum of 630 nm at different temperatures using continuous variation method. The data showed that Co(III) and cefotaxime combine in the molar ratio of 1:1 at pH 7.4 with ionic strength maintained using 0.1M KNO_3. The stability constants of the complex were calculated to be 5.62 x 10^3, 2.80 x 10^3 and 1.62 x 10^3 at 25, 35 and 40 ^oC respectively. ΔG value for complex were 2.14 x 10^4, 2.03 x 10^4 and 1.92 x 10^4 at 25, 35 and 40 ^oC respectively. From the values of the stability constants and Gibbs free energies, it was deduced that cefotaxime is a good complexing agent and can be an efficient antidote in the therapy of cobalt overload or poisoning.

KEYWORDS: Cefotaxime, cobalt, complex, continuous variation, Gibbs free energies, stability constant.

I. INTRODUCTION

Cefotaxime is a broad-spectrum antibacterial agent with inhibitory activity against various Gram-positive and Gram-negative bacteria. Given its broad spectrum of activity, cefotaxime has been used for treatment of various infections such as lower respiratory tract infections, genitourinary system infections, gynecologic infections, sepsis, intra-abdominal infections and CNS infections [1]. As a β-lactam third-generation cephalosporins, cefotaxime is potent against numerous Gram-positive and Gram-negative bacteria, including infections with resistance to classic β-lactams such as penicillin. These bacteria often give rise to infections of the lower respiratory tract, skin, central nervous system, bone, and intra-abdominal cavity. While regional susceptibilities must always be considered, cefotaxime typically is effective against these organisms [1]. Cefotaxime, like other β-lactam antibiotics, does not only inhibit the growth of bacteria and cyanobacteria, but also block the division of cyanelles, the photosynthetic organelles of the glaucophytes, and resist the division of chloroplasts of bryophytes. In contrast, it has no inhibitory potential on the plastids of highly developed vascular plants **[2].** Cefotaxime can be injected intramuscular or by intravenous infusion. Cefotaxime is metabolized by liver cells and largely excreted in urine, dosage adjustments may be necessary in people with renal or hepatic impairment [3, 4]. The structure of cefotaxime is shown in Figure 1.

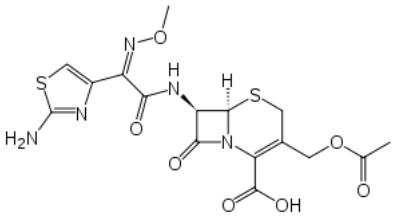

Figure 1: Structure of cefotaxime

Cobalt is a essential component of vitamin B12 (hydroxocobalamin) and a vital coenzyme of cell mitosis. Moreover, cobalt is vital for amino acids and some proteins formation in order to produce myelin sheath in nerve cells [5,6]. Cobalt is also involved in the creation of neurotransmitters, which are essential for correct functioning of the organism [5]. Cobalt salts stimulate the production of erythropoietin, which is the most vital function in the activation of different

International Journal of Advances in Engineering and Management (IJAEM)
Volume 2, Issue 3, pp: 413-418 www.ijaem.net ISSN: 2395-5252

phases of erythropoiesis, which, in turn, is connected with the production of erythrocytes in bone marrow [7,8]. Deficiency of cobalt is associated with disturbances in vitamin B12 synthesis, which causes anaemia and hypofunction of thyroid and activate the risk of developmental abnormalities in infants [5]. However, excess of cobalt increases the activity of thyroid and bone marrow, which in turn leads to overproduction of erythrocytes, fibrosis in lungs and asthma [9].

Cefotaxime is able to sequestrate metal ions due to the presence of C=O, NH_2, COOH, COOR, NH and NO electron donating groups. The synthesis and antibacterial activity of cefotaxime complexes of Mn(II), Fe(II), Co(II), Ni(II), Cu(II) and Cd(II) have been reported [10]. Spectra analysis suggested a tetrahedral geometry (Figure 2) for the metal complexes of cefotaxime [10].

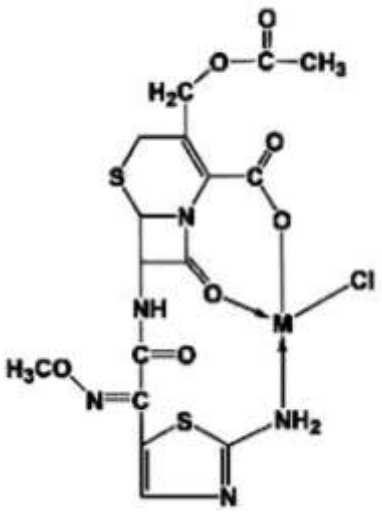

Figure 2: Tentative structure of cefotaxime metal complexes, M = Mn(II), Co(II), Ni(II), Cu(II) and Cd(II)

The amino, β-lactamic and carboxylic groups of cefotaxime formed thermodynamically stable saturated rings by interacting with transition metals [10]. Many authours have reported spectrophotometric study of stability constant of metal complexes [11-13]. However, to the best of our knowledge, stability constants of cefotaxime – Co(III) complex at different temperatures have not been reported in literature. These stability constants are useful to study the effects of cefotaxime on trace elements and mineral metabolism. It is possible that changes in trace element and mineral concentration induced by cefotaxime can be an efficient antidote in the therapy of cobalt overload or poisoning. We hereby present colorimetric determination of stability constants and thermodynamic parameters of cefotaxime- Co(III) complex at 25 and 40 ^{o}C respectively.

II. EXPERIMENTATION

Instrumentation

Absorbance measurements were performed on auto colorimeter ME-51. Orion Versa Star Pro pH Benchtop meter (VSRAR10 series) was used for pH measurements.

Reagents

All the chemicals used were of analytical grade purity. Cefotaxime was purchased from Nitin Life sciences Limited, Indian $Co(NO_3)_2.6H_2O$ was purchased from Merck Germany. Double-distilled water was used throughout the experiment.

Preparation of 2 x 10^{-2} M $Co(NO_3)_2.6H_2O$

$Co(NO_3)_2.6H_2O$ (5.821 g, 20 m mol, M. Wt. = 291.03 g/mol) was dissolved in freshly distilled water in a 250 cm^3 beaker and was made up to the mark in a 1000 cm^3 volumetric flask.

Preparation of 2 x 10^{-2} M cefotaxime

Cefotaxime (9.1094 g, 20 m mol, M. Wt. = 455.47 g/mol) was dissolved in freshly distilled water in a 250 cm^3 beaker and was made up to the mark in a 1000 cm^3 volumetric flask.

Procedure for continuous variation method

$Co(NO_3)_2.6H_2O$ (2 x 10^{-2} M) (0, 1,2, 3, 4, 5, 6 cm^3) was pippeted out and transferred into seven 50 cm^3 volumetric flasks. Cefotaxime (1 x 10^{-2} M) (6, 5, 4, 3, 2, 1, 0 cm^3) was added, respectively to the Co(III) solution so that the mole fraction remained constant. The pH adjusted to 7.4 and ionic strength maintained constant by using 0.1 M KNO_3. Their absorbance were measured at 630 nm (maximum absorbance of the complex) and at a temperature of 25, 35 and 40 ^{o}C, respectively.

Calculation of stability constant

Equation 1 [14] was applied in the calculation of stability constant.

$$K_{cef-Co} = \frac{1-\alpha}{m^m \cdot n^n (\alpha)^{m+n} (C)^{m+n-1}} - - - - \text{Equation 1}$$

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 2, 3 and 4 [14].

International Journal of Advances in Engineering and Management (IJAEM)
Volume 2, Issue 3, pp: 413-418 www.ijaem.net ISSN: 2395-5252

$$A_\alpha = A_o - A_{max} - - - - - - - - Equation\ 2$$

$$A_{max} = \varepsilon bC - - - - - - - - - - Equation\ 3$$

$$\alpha = \frac{A_\alpha}{\varepsilon bC} - - - - - - - - - - Equation\ 4$$

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.

ΔG was calculated using equations 5.

$$\Delta G^\theta = -RTInK_{cef-Co} - - - - - - - - Equation\ 5$$

The stoichiometry mole fraction (SMF) of the complex using continuous variation method was calculated using equation 6.

$$SMF = \frac{m}{1-m} - - - - - - - - - Equation\ 6.$$

III. RESULTS AND DISCUSSION

Absorption spectra of cefotaxime-Co(III) complex is shown in Figure 3. Experimental data of cefotaxime-Co(III) complex at 630 nm by continuous variation method is reported in Table 1. Figure 4,5 and 6 shows Job's curves for stability constants of equimolar solutions at 25, 35 and 40 ^oC. Calculated stability constant values and Gibbs free energies are shown in Table 2.

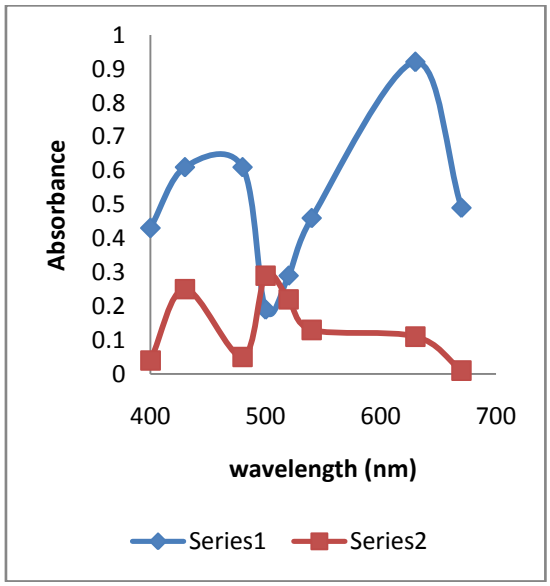

Figure 3: Absorption spectra of cefotaxime-Co(III) complex (2 x 10^{-2} M) (series 1) and $Co(NO_3)_2.6H_2O$ (2 x 10^{-2} M) (series 2)

The electronic spectra of cefotaxime-Co(III) complex and $Co(NO_3)_2.6H_2O$ are shown in Figure 3. The absorption spectra were recorded at wavelength range of 400 – 670 nm. The reaction of cefotaxime with $Co(NO_3)_2.6H_2O$ was investigated at different temperatures i.e. 25, 35 and 40 ^oC. It was observed that cefotaxime with $Co(NO_3)_2.6H_2O$ formed a milky colour, water soluble complex. The absorption maximum of the complex was 630 nm. Cefotaxime and $Co(NO_3)_2.6H_2O$ does not absorb significantly at this wavelength hence 630 nm was used for the analytical measurements. In aqueous solution, cobalt exist as $[Co(H_2O)_6]^{3+}$, and λ max was observed at 500 nm. Cobaltaquo complex is a labile complex because water behaved as a weak ligand. Cefotaxime displaced water from $[Co(H_2O)_6]^{3+}$ to form a stable cefotaxime-Co(III) complex.

Table 1: Experimental data of cefotaxime-Co(III) complex at 630 nm by continuous variation method

S/N	$Co(NO_3)_2.6H_2O$ (2 x 10^{-2} M)	Cefotaxime (2 x 10^{-2} M)	Mole fraction of Co(III)	Absorbance at 630 nm		
				25 ℃	35 ℃	40 ℃
1	0.00	6.00	0.00	0.02	0.02	0.01
2	1.00	5.00	0.17	0.07	0.10	0.12
3	2.00	4.00	0.33	0.22	0.21	0.21
4	3.00	3.00	**0.50**	**0.33**	**0.32**	**0.31**
5	4.00	2.00	0.66	0.26	0.26	0.26
6	5.00	1.00	0.83	0.14	0.14	0.14
7	6.00	0.00	1.00	0.01	0.01	0.01

International Journal of Advances in Engineering and Management (IJAEM)
Volume 2, Issue 3, pp: 413-418 www.ijaem.net ISSN: 2395-5252

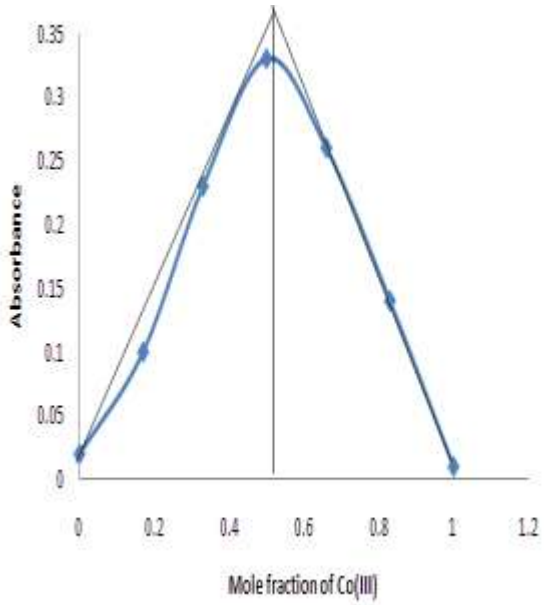

Figure 4 Job's curves for stability constants of equimolar solutions at 25 ^{o}C

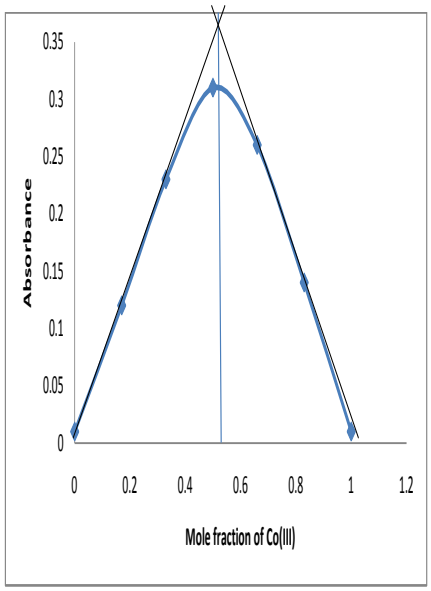

Figure 6: Job's curves for stability constants of equimolar solutions at 40 ^{o}C

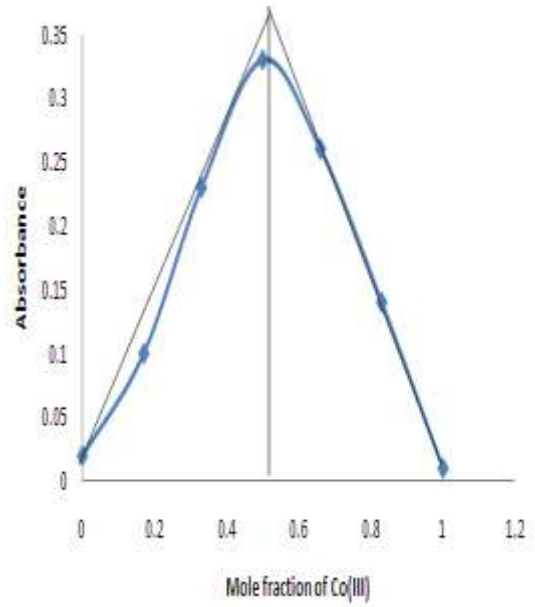

Figure 5: Job's curves for stability constants of equimolar solutions at 35 ^{o}C

The extrapolated value at the point of cross-section on continuous variation plot (Figures 4, 5 and 6) corresponded to the total absorbance of the complex, indicating that the complex formation process has been completed. The mole fraction of Co(III) at the point of intersection are 0.53, 0.53 and 0.52 at 25, 35 and 40 ^{0}C respectively. Application of equation 8, yields SMF of 1.13 1.13 and 1.08 at 25, 35 and 40 ^{0}C respectively This corresponded to metal:ligand ratio of 1:1. This was in agreement with the proposed structure reported by Anacona and Silva [10].

Table 3: Calculated stability constant values and Gibbs free energies

S.No	Method	Metal: ligand ratio	Stability constant			ΔG (J)		
			25 ^{o}C	35 ^{o}C	40 ^{o}C	25 ^{o}C	35 ^{o}C	40 ^{o}C
1	Continuous variation	1:1	5.62 x 10^{3}	2.80 x 10^{3}	1.62 x 10^{3}	2.14 x 10^{4}	2.03 x 10^{4}	1.92 x 10^{4}

Continuous variation method suggested 1:1 metal:ligand ratio. The positive values of the stability constants implied that the complex was stable. Tirmizi and Co-workers reported positive

values of stability constant for cimetidine – Ni complex at different temperatures using continuous variation and mole ratio methods [12]. Waranyoupalin and Co-workers also reported positive stability constant values using continuous variation and mole ratio methods [13]. The results of stability constant suggested that cefotaxime could be effective against Co(III) toxicity. It could be efficient as Co(III) complexing agent in the therapy of cobalt overload. The negative values of the free energies showed that the complexes were formed spontaneously. The values of the stability constants decrease with increase in temperature . Job's method supported the metal to ligand ratio of 1:1 as evidenced from the results of elemental analysis of Co(III)-cefotaxime complex reported by Anacona and Silva [10]. This showed that the complex was stable both at room temperature and higher temperatures.

IV. CONCLUSION

A simple and rigorous method to the determination of the stability constant of the cefotaxine-Co(III) complex by means of colorimeter depending on the theoretical interpretation of the stoichiometry has been evaluated. Cefotaxime formed a reasonably stable complex with Co(III). The stability constant results suggested that cefotaxime used in the study is a good chelator agent and can be an efficient antidote in the therapy of Co(III) overload or poisoning.

REFERENCES

[1]. U.S. Food and Drug Administration. (2016). U.S. Department of Health and Human Services. Claforan Sterile (cefotaxime for injection, USP) and Injection (cefotaxime injection, USP).

[2]. Kasten, B. and Reski, R. 1997. β-Lactam antibiotics inhibit chloroplast division in a moss (Physcomitrella patens) but not in tomato (Lycopersicon esculentum),. Journal of Plant Physiology. 150 (1–2): 137–40. doi:10.1016/S0176-1617(97)80193-9.

[3]. Bertels, R.A., Semmekrot, B.A., Gerrits, G.P. and Mouton, J.W. 2008. Serum concentrations of cefotaxime and its metabolite desacetyl-cefotaxime in infants and children during continuous infusion". Infection. 36 (5): 415–20. doi:10.1007/s15010-008-7274-1.

[4]. Coombes, J.D. 1982. Metabolism of cefotaxime in animals and humans". Reviews of Infectious Diseases. 4 (Suppl 2): S325 – 329. doi:10.1093/clinids/4.Supplement_2.S325.

[5]. Battaglia, V., Compagnone, A. and Bandino, A. 2009. Cobalt induces oxidative stress in isolated liver mitochondria responsible for permeability transition and intrinsicapoptosis in hepatocyte primary cultures. Int J Biochem Cell Biol., 41: 586-594.

[6]. Ortega, R., Bresson, C. and Fraysse, A. 2009. Cobalt distribution in keratinocyte cells indicates nuclear and perinuclear accumulation and interaction with magnesium and zinc homeostasis. Toxicol Letters, 188: 26-32.

[7]. Simonsen, L.O., Brown, A.M. and Harbak, H. 2011. Cobalt uptake and binding in human red blood cells. Blood Cell Mol Dis., 46: 266-276.

[8]. Simonsen, L.O., Harbak, H. and Bennekou, P. 2012. Cobalt metabolism and toxicology – a brief update. Sci Total Environ., 432: 210-215.

[9]. Lombaert, N., Lison, D., Van Hummelen, P. and Kirsch-Volders, M. 2008. In vitro expression of hard metal dust (WC-Co) – responsive genes in human peripheral blood mononucleated cells. Toxicol Appl Pharmacol,, 227: 299-312.

[10]. Anacona, J.R. and Silva, G.D. 2005. Synthesis and antibacterial activity of cefotaxime metal complexes, Journal of Chilean Chemical Society, 50(2): 447 – 450.

[11]. Reková, M., Vanura, P. and Jedináková-Krízová, V. 2009. Determination of Protonation Constants and Stability Constants of Lanthanides with Derivative of H_4DOTA Complexes by the UV-VIS Spectrophotometry and Potentiometry, The Open Inorganic Chemistry Journal, 3: 26 – 32

[12]. Tirmizi, F.H., Wattoo, F.H., Wattoo, M.H.S., Sarwar, S., Memon, A.N. and Ghangro, A.B. 2012. Spectrophotometric study of stability constants of cimetidine–Ni(II) complex at different temperatures, Arabian Journal of Chemistry, 5: 309–314

[13]. Waranyoupalin, R., Wongnawa, S., Wongnawa, M., Pakawatchai, C., Panichayupakaranant, P. and Sherdshoopongse, P. 2009. Studies of complex formation between curcumin and Hg(II) by spectrophotometric method: A new approach to overcome peak overlap, Cent. Eur. J. Chem. 7(3): 388-394

[14]. Abbas, R.F. 2017. Spectrophotometric determination of stability constant by classical and Modified Varagas equations

for procaine penicillin G using diazotization reaction depending on stoichiometric curves, International Journal of ChemTech Research, 10(2): 485 – 496.

International Journal of Advances in Engineering and Management
ISSN: 2395-5252

IJAEM

Volume: 02 Issue: 01 DOI: 10.35629/5252

www.ijaem.net
Email id: ijaem.paper@gmail.com