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ACETAMINOPHEN-Mn(II) COMPLEX: DETERMINATION OF STOICHIOMETRY, STABILITY CONSTANTS AND GIBBS FREE ENERGIES AT DIFFERENT TEMPERATURES

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ABSTRACT

The stoichiometry, stability constants and Gibbs free energies of acetaminophen-Mn(II) were determined colorimetrically at 25 and 40 ^{o}C using continuous variation and mole ratio methods. The formation of Mn(II) complex with acetaminophen was studied colorimetrically at an absorption maximum of 430 nm at different temperatures. The data showed that Mn(II) and acetaminophen 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 1.25 x 10^2 and 1.25 x 10^2 using continuous variation method and 1.21 x 10^2 and 1.21 x 10^2 using mole ratio methods at 25 and 40 ^{o}C respectively. Calculated ΔG^{Θ} for the complex were - 1.19 x 10^4 and1.25 x 10^4 J using continuous variation method and - 1.19 x 10^4 J and - 1.25 x 10^4 J using mole ratio method at 25 and 40 ^{o}C respectively. It was concluded that acetaminophen is a good chelating agent and can be an efficient antidote in the therapy of Mn(II) overload or poisoning.

Keywords: Acetaminophen, complex, Gibbs free energy, manganese, stability constant

INTRODUCTION

Acetaminophen belongs to the class of drugs known as "aniline analgesics". It is the only drug in this class that is still in use today [1]. The benzene ring core of acetaminophen is substituted by one hydroxyl group and the nitrogen atom of an amide group in the para (1,4) position (Figure 1.1) [2]. It is not a nonsteroidal anti-inflammatory drug because it does not exhibit adequate anti-

inflammatory activity. It is a weak cyclooxygenase inhibitor [3,4]. This is despite the evidence that acetaminophen and nonsteroidal anti-inflammatory drugs have some closely related pharmacological activity [5]. Acetaminophen is used for the treatment of feverish condition in people of all ages [6]. The World Health Organization recommends that acetaminophen be administered to children with feverish condition only if their temperature is above 38.5 °C (101.3 °F) [7]. The efficacy of acetaminophen in children with feverish condition has been questioned [8] and a meta-analysis suggested that it is less effective than ibuprofen [9]. Acetaminophen does not have significant anti-inflammatory effects [10 – 12]. Acetaminophen is administered for the relief of mild to moderate pain [6]. The intravenous administration of the drug for the relief of short-term pain in accident and emergency units has been supported by limited evidence [13]. In adults, it appears to be effective for migraines, tension headaches, perineal pain after childbirth, and kidney stone pain [14].

Manganese is a trace element that is essential in human diet. It exists as a coenzyme in many biological processes such a macronutrient metabolism, bone formation, and free radical defense systems. It is a vital component of many proteins and enzymes [15]. The human biological system contains about 12 mg of manganese, mostly in the bones. It is also concentrated in the liver and kidneys [16]. In the brains of humans, manganese exists as manganese metalloproteins, most notably, it chelate with glutamine synthetase in astrocytes [16]. Excessive exposure, digestion or inhalation of manganese may leads to a disease known as manganism, a neurodegenerative condition that causes dopaminergic neuronal death and symptoms identical to Parkinson's disease [16].

. Synthesis, characterization and evaluation of anti-inflammatory activity of acetaminophen metal complexes have been reported [17]. On the basis of their study, it is proven that acetaminophen acted as a bidentate ligand coordinating to transition metals through phenol and carbonyl oxygen atom (Figure 1.2). For several decades, chelating agents have been used as antidote to combat metal poisoning [18]. Biological friendly complexing agents have been used effectively to chelate metals in patients with metal overload [18]. Many authors have reported the study of stability constant of drug- metal complexes [19 – 22]. Formation constant vary widely, large values indicate that the metal has high affinity for the ligand, provided the system is at equilibrium. As a whole, stability constant is a measure of the strength of the interaction between

the reagents that come together to form the complex. Stability constant can be key parameters for the investigation of equilibria in solution. They are very important in many fields such as environmental studies, medicinal, analytical and industrial chemistry.

However, to the best of authors knowledge, stoichiometry, stability constants and Gibbs free energies of acetaminophen – Mn(II) complex at different temperatures have yet not appeared in the literature. These stability constants are useful to study the effects of acetaminophen on trace metals and mineral metabolism. It is possible that changes in trace metal and mineral concentration induced by acetaminophen can be an efficient antidote in the therapy of Mn overload or poisoning. In this context, the aim of this study was to assess stoichiometry, stability constants and free energy change of acetaminophen-Mn(II) complex at 25 and 40 ^{o}C respectively.

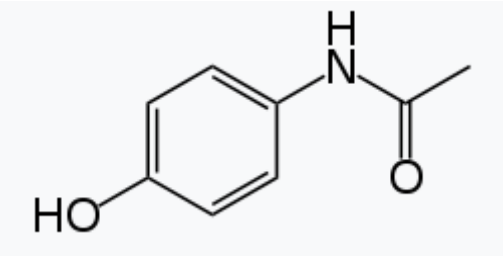

Figure 1.1 Chemical structure of acetaminophen

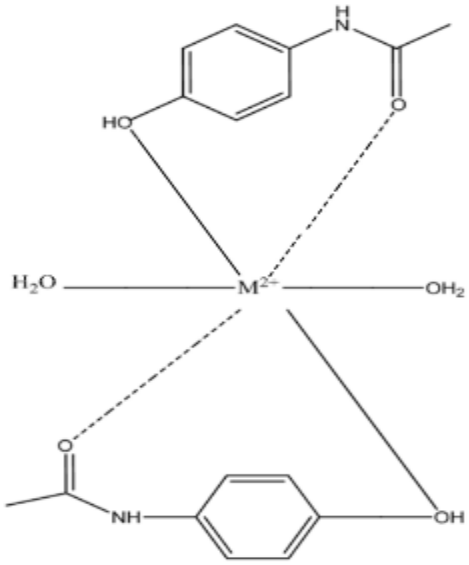

Figure 1.2: Proposed structure of acetaminophen metal complexes [17].

MATERIALS AND METHODS

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

All reagents used were of analytical grade purity. Acetaminophen was purchased from Liaoyuan City Baikag, Pharmaceutical Company Limited, China. $MnCl_2.4H_2O$ was purchased from Merck Germany. Double-distilled water was used throughout the experiment.

Preparation of 1 x 10^{-2} M $MnCl_2.4H_2O$

$MnCl_2.4H_2O$ (1.979 g, 10 m mol, M. Wt. = 197.90 g/mol) was dissolved in freshly distilled water in a beaker and was made up to the mark in a 1000 cm^3 volumetric flask.

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

Acetaminophen (1.511 g, 10 m mol, M. Wt. = 151.163 g/mol) was dissolved in freshly distilled water in a beaker and was made up to the mark in a 1000 cm^3 volumetric flask.

Procedure for continuous variation method

$MnCl_2.4H_2O$ (1 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. Acetaminophen (1 x 10^{-2} M) (6, 5, 4, 3, 2, 1, 0 cm^3) was added, respectively to the Mn(II) 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 430 nm (maximum absorbance of the complex) and at a temperature of 25 and 40 ^oC, respectively.

Procedure for mole ratio method

$MnCl_2.4H_2O$ (1 x 10^{-2} M) (2 cm^3) was pippeted out and transferred into each of the seven 50 cm^3 volumetric flasks. Acetaminophen (1 x 10^{-2} M) (1, 2, 3, 4, 5, 6, 7 cm^3) was added to each of the Mn(II) solution respectively. Their absorbance was measured at 430 nm ((maximum absorbance of the complex) and at a temperature 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 [22].

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

Where m is the mole fraction of metal ion.

Equation 2 [22] was applied to the calculation of stability constant.

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

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 [22].

$$A_\alpha = A_o - A_{max} - - - - - - - - - Equation\ 3$$

$$A_\alpha = \varepsilon bC - - - - - - - - - - Equation\ 4$$

$$\alpha = \frac{A_\alpha}{\varepsilon bC} - - - - - - - - - Equation\ 5$$

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 equation 6.

$$\Delta G^\theta = -RTInK - - - - - - - - - Equation\ 6$$

RESULTS AND DISCUSSION

The electronic spectra of acetaminophen-Mn(II) complex is shown in Figure 2

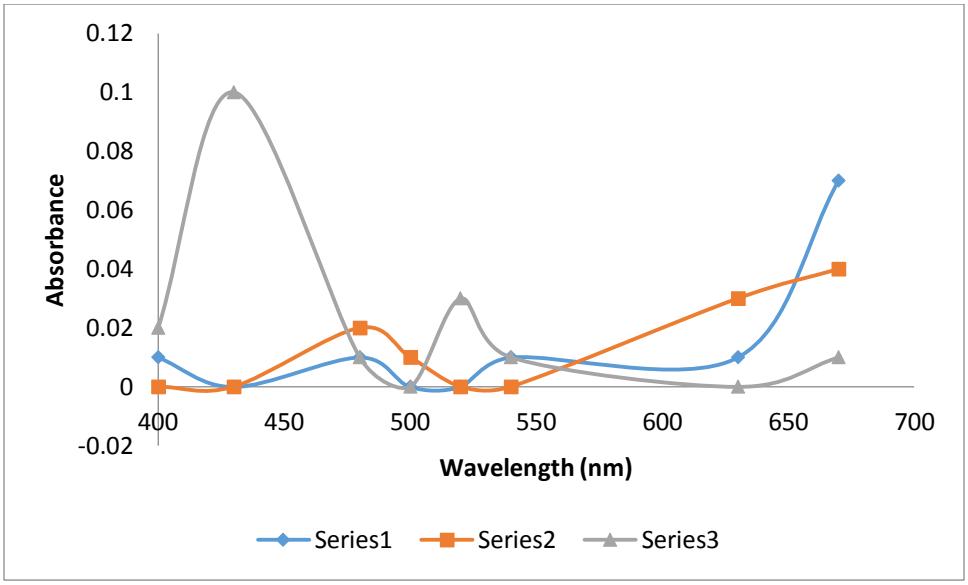

Figure 2: Absorption spectra of $MnCl_2.4H_2O$ (1 x 10^{-2} M) (series 1), acetaminophen (1 x 10^{-2} M) (series 2) and acetaminophen-Mn(II) complex (series 3)

The absorption spectra (Figure 2) shows the absorbance of $MnCl_2.4H_2O$ (series 1), acetaminophen (series 2) and acetaminophen-Mn(II) complex (series 3) at wavelength of 400 – 670 nm. The wavelength of maximum absorbance of the complex was 430 nm. At the wavelength, $MnCl_2.4H_2O$ and acetaminophen have weak absorbances. Therefore, this wavelength was used for the measurement of absorbance in the determination of the stoichiometry, stability constants and free energies. $MnCl_2.4H_2O$ absorbs maximally at wavelength of 670 nm, acetaminophen also absorbs maximally at this wavelength. It was observed that acetaminophen-Mn(II) complex gave a water soluble complex. In aqueous solution, Mn-aquo complex is a labile complex because water behaved as a weak ligand. Acetaminophen displaced water from Mn-aquo to form a stable acetaminophen - Mn(II) complex. Similar labile aquo complexes were also reported by Tirmizi and co-workers in their study of famotidine-Cu complex and cimetidine-Ni complex [19 – 21]. Tella and co–workers reported labile aquo complex in their study of Dapsone-Cu(II) stability constants [23].

Table 1: Experimental data of acetaminophen-Mn(II) complex at 430 nm by continuous variation method

S/N	$MnCl_2.4H_2O$ (1×10^{-2} M)	Acetaminophen (1×10^{-2} M)	Mole fraction of Mn(II)	Absorbance at 430 nm	
				25 ℃	40 ℃
1	0.00	6.00	0.00	0.00	0.00
2	1.00	5.00	0.17	0.01	0.01
3	2.00	4.00	0.33	0.02	0.02
4	3.00	3.00	0.50	0.01	0.01
5	4.00	2.00	0.66	0.00	0.00
6	5.00	1.00	0.83	0.00	0.00
7	6.00	0.00	1.00	0.00	0.00

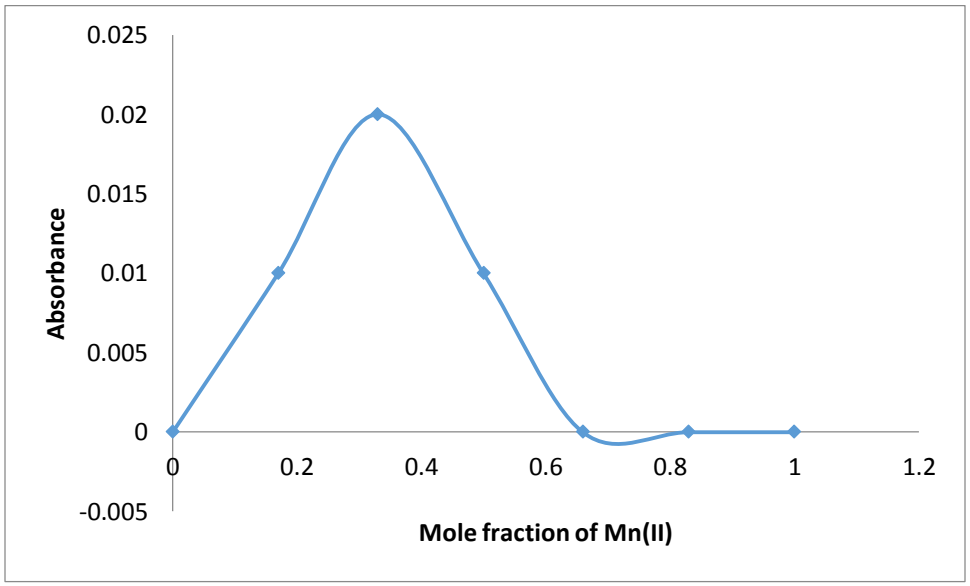

Figure 3: Job's curves for stability constants of equimolar solutions at 25 ºC

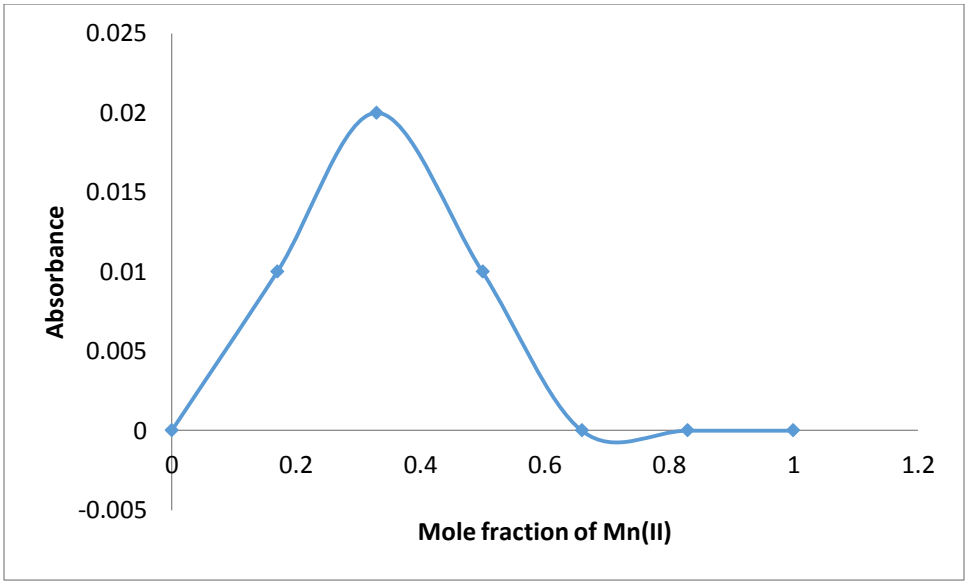

Figure 4: Job's curves for stability constants of equimolar solutions at 40 ^{o}C

For the continuous variation method, equation 1 was applied in calculation of stoichiometry.

$SMF = \frac{0.34}{0.66} = 0.52 \approx 1$ (at 25 ^{0}C) and $SMF = \frac{0.34}{0.66} = 0.52 \approx 1$ (at 40 ^{o0}C).

This corresponded to metal:ligand ratio of 1:1. The mole fraction of Mn(II) at the point of intersection are 0.34 and 0.34 at 25 and 40 ^{0}C respectively. The extrapolated value at the point of cross-section on continuous variation plot (Figures 3 and 4) 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 [19 – 22].

Table 2: Experimental data of acetaminophen-Mn(II) complex at 430 nm by mole ratio method

S/N	$MnCl_2.4H_2O$ (1×10^{-2} M)	Acetaminophen (1×10^{-2} M)	Vol of acetaminophen/ vol of Mn(II)	Absorbance at 430 nm	
				25 ℃	40 ℃
1	2.00	1.00	0.5	0.017	0.017
2	2.00	2.00	**1.0**	**0.020**	**0.020**
3	2.00	3.00	1.5	0.020	0.020
4	2.00	4.00	2.0	0.020	0.020
5	2.00	5.00	2.5	0.020	0.020
6	2.00	6.00	3.0	0.020	0.020
7	2.00	7.00	3.5	0.020	0.020

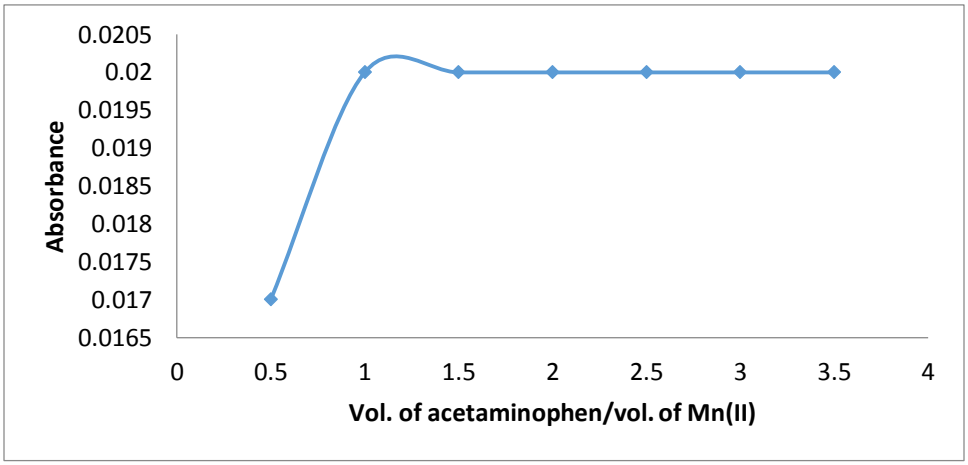

Figure 4: Mole ratio method curves for stability constant at 25 ^{o}C

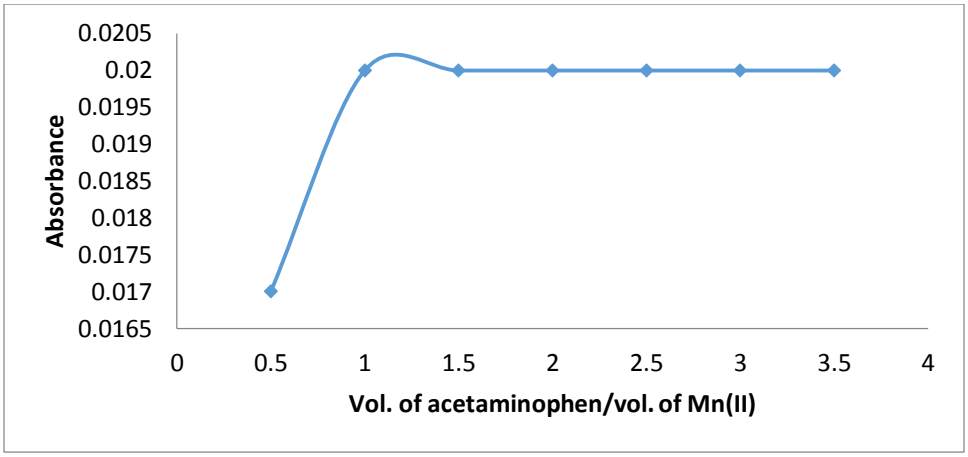

Figure 5: Mole ratio method curves for stability constant at 40 °C

The stoichiometry ratio of the complex was evaluated from the point where this curve changes its slope. The vol. of acetaminophen/vol. of Mn(II) at the point of intersection are 1.00 and 1.00 at 25 and 40 °C, *r*espectively. This corresponded to metal:ligand ratio of 1:1. The extrapolated value at the point of cross-section on mole ratio plot (Figures 4 and 5) corresponded to the total absorbance of the complex, indicating that the complex formation process has been completed. Several authors have also used mole ratio method in the determination of stoichiometry of metal complexes [19 – 22]. Hence, mole ratio technique is an established method for the determination of metal: ligand ratio in complexes.

Table 3: Calculated stability constant values and Gibbs free energies of acetaminophen-Mn(II) complex

S/N	Method	Metal: ligand ratio	Stability constant		ΔG^{Θ} (J)	
			25 °C	40 °C	25 °C	40 °C
1	Continuous variation	1:1	1.25×10^2	1.25×10^2	-1.19×10^4	-1.25×10^4
2	Mole ratio	1:1	1.21×10^2	1.21×10^2	-1.19×10^4	-1.25×10^4

Stability constant vary widely, large values indicate that the metal has high affinity for the ligand, provided the system is at equilibrium. As a whole, stability constant is an evaluation of the strength of the interaction between the reagents that come together to form the complex. The stability

constant and Gibbs free energies were calculated by applying equations 2, 3, 4, 5 and 6. The stability constant values showed that the complex was stable both at 25 ^{o}C and 40 ^{o}C. The values of the stability constants obtained from continuous variation compared well with that of mole ratio method. It can be seen from the Table 3 that the values obtained by both methods are in fair agreement. Increasing the temperature of chelation form 25 to 40 ^{o}C had no effect on the stability constant**.** The values of the stability constants were positive; this suggested that the complex was stable. Similar positive values of stability constant of complexes were reported by Tirmizi and co-workers using continuous variation and mole ratio methods [19 – 23]. Waranyoupalin and co-workers also reported positive stability constant values using continuous variation and mole ratio methods [24]. Continuous variation and mole ratio methods are established techniques in the determination of stability constant and Gibbs free energies. The results of stability constant suggested that acetaminophen could be effective in chelation therapy against Mn(II) toxicity. The negative values of the free energies suggested that the complexes were formed spontaneously.

CONCLUSION

Acetaminophen is a known analgesics that is used for the treatment of aches and pains. It formed a reasonably stable complex with Mn(II). The continuous variation method of analysis values compared well with the results obtained using mole ratio method of analysis. The Job's continuous variation and mole ratio methods data showed that Mn(II) and acataminophen combine in the molar ratio of 1:1. The stability constant results suggested that acataminophen used in the study is a good chelating agent and can be an efficient antidote in the therapy of Mn(II) overload or poisoning.

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