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Binary Stability Constants Studies of Cu and Mn-Complexes with Cysteine and Cephalexin

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ABSTRACT

Binary complexes of Cu(II) and Mn(II) with cysteine and cephalexin have been studied potentiometrically at about 27 ± 2 °C in aqueous medium using Irving-Rossotti titration technique for proton-ligand (P-L) and metal-ligand (M-L) stability constants evaluation. The proton-ligand stability constants for cysteine and cephalexin were: log K_1H 8.4 (pKa for thiol group), log K_2H 10.7 (pKa for NH_2-group), log K_1H 5.2 (pKa for carboxyl group), and log K_2H 6.82 (pKa for amine group), respectively. The binary metal-ligand stability constant (logK) values for 1:1 were found in the order of Cu(II) > Mn(II) for both ligands in conformity to the Irving–Williams order of the divalent transition metals of the period 4. Though the redox-active nature of Cu(II)-Cysteine atmosphere likely compromised the Cu(II)-Cysteine stability constant. By and large, M-L stability constants of Mn and Cu with cysteine and cephalexin have been re-established. This finding agreed with previous studies claimed that cysteine is fit for use in transporting target metals. In general, the studies have strengthened the idea that drugs and amino acids are able to interact with metals in our body system to a specific extent in terms binding constant.

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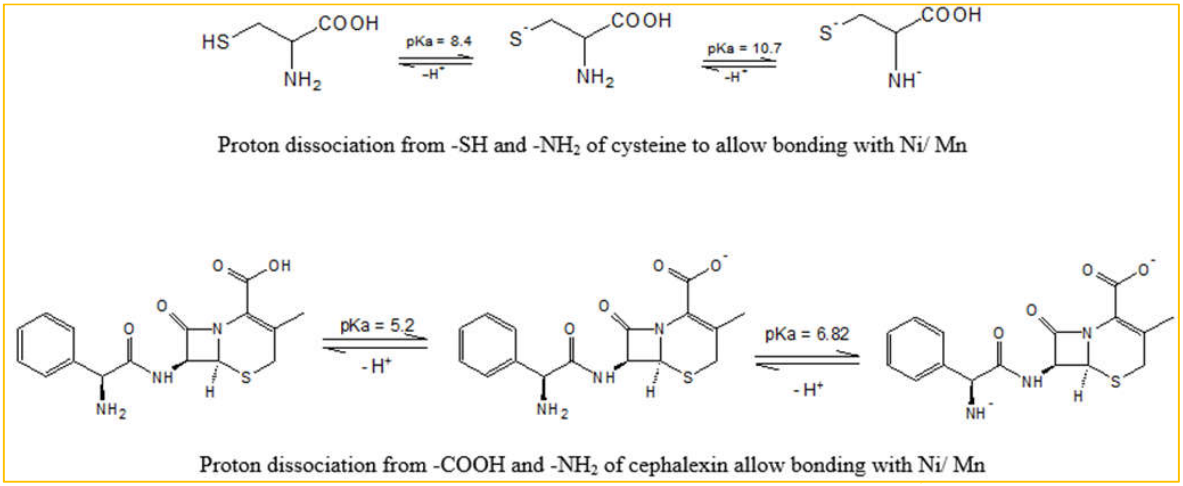
GRAPHICALABSTRACT



Introduction

Amino acids are essential integral part of foundation of living organisms. Amino acids unite to form proteins which are abundant in our body system. The proteins interaction with metals present in our bodies is then inevitable. Thus, the study metal-ligand constants of amino acids and drugs are essential for their potential applications [1] and gaining insight into the metal-protein and metal-drug activities in the body. Amino acids bind to metals ions via their amino (NH_2), carboxylic (COO^-) groups, etc. [2,3]. Thus, they are used as antidote to metal poisoning [1] and as chelants in general [4]. Many chelating agents have been used to move metals to or away from target sites because of their ability to form strong bonds with different metal ions. However, good number of these traditional chelating agents have been reported to be toxic, non-biodegradable, and rigid towards the recovery of ligated metal ions [5]. The inherent drawbacks with these chelators necessitate a search for their alternatives [6] which are nontoxic and flexible for recovering bound metal ions. The therapeutics we used are influenced by the presence of metals in our biological fluids [7]. Thus, the study of metal complexes of biologically active ligands can define the degree of the formation constant between the metal and the amino acids, or the drug. In addition, these studies can identify the specific atoms or groups that are responsible for binding to metal ions, or are used in removal of toxic heavy metal ions [1]. In addition, the extend of metal-ligand complex formation is therapeutically useful because the function of a drug is related to its mode- i.e. either in free or complexed form [8]. Furthermore, important physiological reactions are facilitated by Cu-containing enzymes. In general, Cu(II) is known to form complexes with proteins, peptides, and enzymes in the living organisms [1]. Manganese (Mn) facilitates the formation of connective tissue, bones, blood clotting factors, and sex hormones. Mn again helps in fat and carbohydrate metabolism, calcium absorption, blood sugar regulation, and for normal brain and nerve function. Many methods exist for the study of proton-ligand and metal-ligand stability constants. However, as a result of accuracy and reliability, pH-metry technique is frequently used [7,9].

Some of the following precautions are taken during the determination of M-L formation constants: The metal concentration should be lesser than that of ligand so as to prevent hydrolysis of metal ions; secondly, the ionic strength should be observed at ≤ 0.2 M to prevent the tendency of anionic species and the cationic species or strong electrolytes ion pair formation [8]. Furthermore, it has been revealed that the reaction of metal ion with high covalent

index with ligand of high polarizability increases the M-L stability constants [6]. This study reports binary stability constants studies of Cu- and Mn - complexes with cysteine and cephalexin using Calvin-Bjerrum titration (10) technique as applied by Irving & Rossotti (10), to enable us validate previous claim about the metal-cysteine complexes of these metal ions. Of course, the work will strengthen the idea that drugs and amino acids/ proteins interact with metals in our body system to a specific extent in terms of binding constant. Cysteine and cephalexin chosen here have similar functional groups (thiol, C=O, COOH, and amine).

Experimental

Materials/ apparatus/ equipment

Cephalexin and cysteine were obtained without further purification. A fresh sample was taken and a solution was prepared for each titration to overcome hydrolysis. The metal salts and other reagents were all of analytical grade. Stock solutions of the metal salts, HCl, and NaOH were prepared in double-distilled water. The potentiometric measurements were carried out by pH-meter. The meter was calibrated using standard buffers of pH 4.00 and pH 9.00.

Potentiometric studies procedure

The potentiometric studies were carried by using Irving and Rossoti titration technique [7-8,10]. These solutions were prepared and titrated against 0.04 M NaOH free of CO_2 at 27 ± 2 °C.

(a) 3 mL 0.04 M HCl

(b) Solution (a) + 4 mL 0.03 M cysteine/ cephalexin

(c) Solution (b) + 2 mL 0.04 M metal (Cu(II) and Mn (II)) chloride solutions, respectively.

The total volume in each run of the above titration was kept at 50 mL. Thus, log K values were subsequently determined using the Calvin-Bjerrum method as adopted by Irving and Rossotti [1,7].

Results and Discussion

The irving-rossotti potentiometric titration

The proton–ligand formation constants of the cephalexin and cysteine and the binding constants of their complexes with Cu(II) and Mn(II) have been determined in aqueous medium at 27 ± 2 °C. Therefore, the potentiometric titration curves of cysteine and cephalexin and their Cu(II) and Mn(II) complexes are presented in Fig. 1 and 3, respectively. In addition, no hydroxo complexes were found since there was no precipitate found during the titration [6].

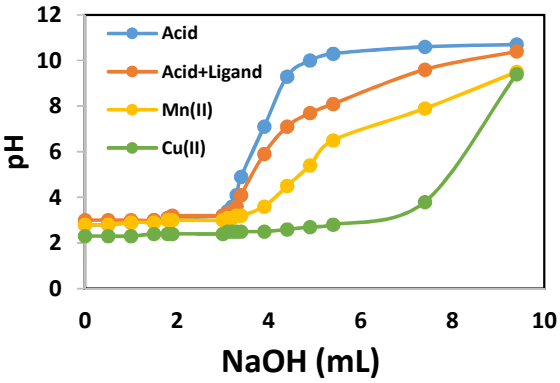


Fig. 1. The titration curves of cysteine and its Mn(II) and Cu(II) ions complexes

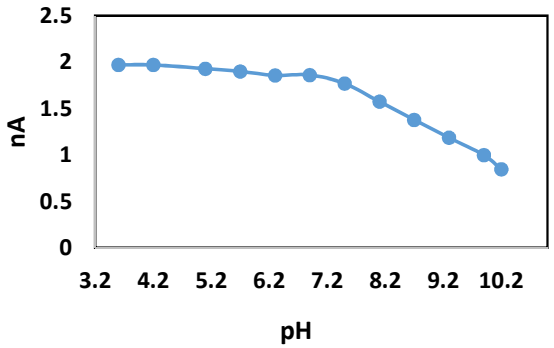


Fig. 2. pH-nA curves for cysteine

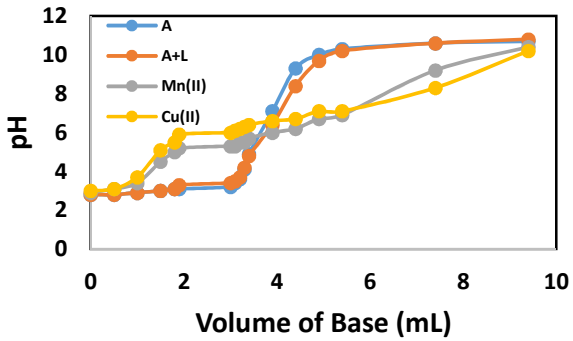


Fig. 3. The titration curves of cephalexin and its Mn(II) and Cu(II) ions complexes

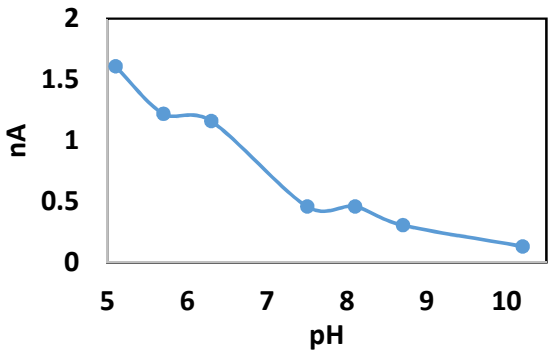


Fig. 4. pH-nA curves for cephalexin

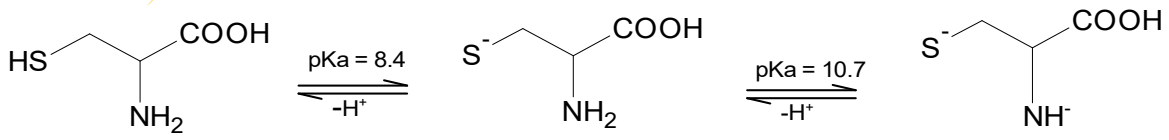
Proton-ligand stability constant

From Figures 1 and 3 (at least at pH above 7 in the case of cephalexin), the titration curves indicate that the ligand and metal curves are below the acid titration curve in each case. This change in the curve trend is due to the release of proton from the ligands (cysteine and cephalexin) [1,6-8]. Hence, the cysteine and cephalexin bonded to the metals via displacement of proton(s) [6,10]. In addition, in Fig. 1, the cysteine released protons right from the pH of 2.8 and above. Whereas, for cephalexin (whose pKa are 5.2 and 6.82) released proton at pH of about 7 and above. General understanding is that a molecule is often protonated at pH less than its pKa value. The degree of formation of the proton complex (n_A) was evaluated according to Equation 1 [11]. Y = number of replaceable hydrogen ion; V° = total volume 50 mL; V_1 = volume of alkali required by the acid; V_2 = volume of alkali used by acid and ligand; N^o = concentration of alkali; E° = total strength of acid; and TcL° = total concentration of ligand. Therefore, to find the proton-ligand stability constant (pKa), integral method was applied on the Equations 2 and 3 [12]. From this approach if we put the value of n_A = 0.5 in Equation 2, then log K_2H = pH. Also, when 1.5 is taken for n_A in the Equation 3, we obtain log K_1H = pH. Consequently, if a plot is made for n_A versus pH, the resulting values of pH for n_A = 0.5 and 1.5 becomes log K_2H and log K_1H, respectively [1,7]. Therefore, from the plots of n_A versus pH (see Fig. 2 for cysteine and Fig. 4 for cephalexin), the values of log K_1H (first proton-ligand formation constant) and log K_2H (the second proton-ligand formation constant) were evaluated accordingly. It was observed for the cysteine - see Scheme 1 - that the log K_1H 8.4 (lower pKa value) corresponds to the proton from thiol group and log K_2H 10.7 (higher pKa value) is associated to the proton of the NH_2-group. On the otherhand, log K_1H 5.2 (lower pKa value) corresponds to the proton from -COOH group and log K_2H 6.82 (higher pKa value) is associated to the proton of the NH_2-group in the cephalexin as described in Scheme 2. The pKa value for the COOH group in the cysteine was not observed due to the condition of the experiment. Thus, the thiol group got (of the cysteine) involved in the complex formation [7,13]; in addition to the COOH and the amine groups (in the cysteine and the cephalexin). According to Al-Mohaimeed and Alothman, S-methylcysteine exhibits pKa value of 8.65. They were of the opinion that the thiol group contributes in the complex formation process [14].

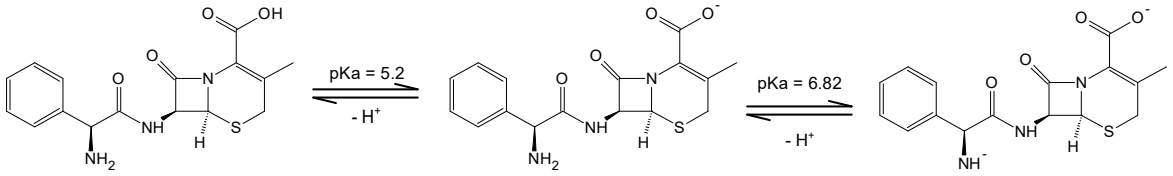
$$n_A = Y - \frac{(V_2 - V_1)(N^o + E^o)}{(V^o + V_1)T_{CL}{}^o} \quad (1)$$

$$\log K_2 = pH + \log \frac{n_A}{1 - n_A} \quad (2)$$

$$\log K_1 = pH + \log \frac{n_A - 1}{2 - n_A} \quad (3)$$



Scheme1. Proton dissociation from -SH and -NH_2 of cysteine



Scheme2. Proton dissociation from -COOH and -NH_2 of cephalexin

Metal-ligand stability constant

The Irving and Rossotti Potentiometric technique was used for the determination of the binary M-L stability constant [8]. As earlier observed that there was drop in pH of the titration curve of the free ligand to that of the ligand + M indicating the complex formation. Hence, the average number of ligands attached per complex ion **(**$\bar{n}$) were evaluated by Equation 4 [8], where V_n = volume of alkali used for acid + ligand + metal ion titration; TcM^o = total concentration of the metal ion, the rest of the terms are familiar from Equation 1. The free ligand exponent, pL were then obtained by applying the Equations 5 [1,7-8]. The log K_1 and log K_2 can be expressed as given in Equations 6 and 7, respectively; from the point wise method for binary M-L stability constant determination [12]. By the consideration of the integral method and taking $\bar{n}$ = 0.5 in Equation 6; logK_1 = pL. In a similar way, logK_2 = pL (using the Equation 7) when $\bar{n}$ = 1.5. In a nutshell, in the plot of $\bar{n}$ vs pL, the corresponding values of pL for $\bar{n}$ = 0.5, or 1.5 gives log K_1 and log K_2, respectively [1,7-8]. Subsequently, in this work, plots of pL vs $\bar{n}$ were made and the binary M-L stability constants were deduced, as presented in Table 1. However, the stability constants for $\bar{n}$ = 1.5 (M: L; 1: 2) were not found at the conditions of these experiments. The 1:2; M: L complex are often less stable in relation to 1: 1 counterpart [8]. The values of the stability constants, (1: 1, M: L) were 7.50 and 33.2 for Mn(II) and Cu(II), respectively for cysteine. In the case of cephalexin, the M: L stability constants were 3.2 and 3.4 for Mn(II) and Cu(II), respectively. The order of the stability constants is: Cu(II) > Mn(II) in both cysteine and cephalexin which conforms to the Irving–Williams order of the M^{2+} metal ions of 3d series [7][15]. In addition, the absence of 1: 2 (M: L) complexes in this work may be due to the experimental conditions such as the concentration of ligand, and ionic strength, etc. [7]. In general, Cu(II) -Cys complexes are found to be very unstable [16] because Cu(II) has high tendency to oxidize cysteine [16]. Therefore, the redox-active phenomenon of Cu-Cys environ can yield range of unusual coordination species [17]. In essence, the binary M-L stability constant of the Cu(II) – Cys as seen in this work is likely compromised.

$$\bar{n} = \frac{(V_n - V_2)(N^o + E^o)}{(V_o + V_2)n_A TcM^o} \quad (4)$$

$$pL = \log\left[\frac{1 + \beta_1[H^+] + \beta_2[H^+].^2}{(TcL^o - \bar{n}TcM^o)} \times \frac{V_o + V_3}{V_o}\right] \quad (5)$$

$$\log K_1 = \log\frac{\bar{n}}{1-\bar{n}} + pL \quad (6)$$

$$\log K_2 = pL + \log\frac{(\bar{n}-1)K_1[L]}{(2-\bar{n})K_1[L]} \quad (7)$$

Table1. Properties of the metal ions and their binary M-L stability constants

Ions	RI pm	Z	IP kJ/mol	EN	Species	Log K_1 (M: L; 1:1)
Cu(II)	73	29	2704	1.75	Cu (II)-Cys	33.2
Cu(II)	73	29	2704	1.75	Cu (II)- Cplx	03.4
Mn(II)	80	25	2226	1.6	Mn (II) -Cys	07.5
Mn(II)	80	25	2226	1.6	Mn (II) -Cplx	03.2

Note: Cys = cysteine, cplx = cephalexin, RI = ionic radius, Z = atomic number, IP = ionization potential, and EN = Allred-Rochow electronegativity

Moreover, Adam et al. [10] reported the binary stability constants of Cu(II)-leucine and Ni(II)-leucine as 8.15 and 5.87, respectively, and 8.12 and 5.78 for Cu(II)- isoleucine and Ni(II)-isoleucine, respectively [10]. On the otherhand, Ishola et al. [6] found that the binary formation constants of Cu(II) - L-tyrosine, Co(II) - L-tyrosine, and Pb(II) - L-tyrosine were 6.40, 4.20, and 6.98, respectively [6]. Similarly, M-L stability constants evaluation of Cu(II) and Mn(II) complexes of chlorosubstituted pyrazoles and isoxazoles by Calvin Bjerrum titration as applied by Irving-Rossotti were gotten within the range

of 5.343-3.644 [9]. These values are comparable to the ones we found here. Again, the potentiometric determination of stability constant of Fe(III) - pyrazinamide was carried out by Kosasy et al. [8]. They observed M-L stability constants of 2.75 and 1.6 for 1: 1 and 1:2 complexes, respectively. Binary and ternary complexes of Fe(III), Pb(II), Co(II), Al(III), La(III), Sr(II), Cr(III), Ti(II), and Zr(II)) with sulphathiazole and glycine were potentiometrically studied [7]. While Al(III) and Zr(IV) ions formed M: L complexes of 1:1, 1:2, and 1:3 (7); Zr(IV), Sr(II), Al(III), Fe(III), Th(IV), and Pb(II) produced 1:1 and 1:2, M: L complexes. On the contrary, the report of Esmaielzadeh and Mashhadiagha has it that Co(II), Cr(III), Ti(II) and La(III) only formed 1:1, M: L complexes with Schiff base ligand [18]; as similarly seen in this current report.

The stability constants in general should be inversely proportional to metal ion radius (RI) for M-L complexes of same metal ion charge with similar electronic configuration [15]. However, for metal ions of different groups this is untrue. Thus, the Cu(II) complexes have higher stability constants because Cu(II) has smaller ionic radius than Mn(II). Furthermore, M-L stability constants are noted to be directly proportional to the EN, Z, and IP of the metal, as described in Table 1. Moreover, increasing the EN of the metal ions will decrease the EN difference between the metal atom and the donor atom of the ligand. Thus, the M-L bond would have more covalent character, resulting into greater stability of the metal complex [15].

Conclusion

Therefore, the binary complexes of Cu(II) and Mn(II) with cysteine and cephalexin have been studied potentiometrically at about 27 ± 2 °C in aqueous medium using Irving-Rossotti titration technique for P-L and M-L stability constants evaluation. The P-L stability constants for cysteine and cephalexin were: log K_1H 8.4, log K_2H 10.7; and log K_1H 5.2, log K_2H 6.82, respectively. The binary M-L stability constant (logK) values for 1:1 were found in the order of Cu(II) > Mn(II) for both ligands in conformity to the Irving-Williams order of the M^{2+} transition metals of the period 4. Though the redox-active nature of Cu(II)-Cysteine atmosphere likely compromised the Cu(II)-Cysteine stability constant. By and large, M-L stability constants of Mn and Cu with cysteine and cephalexin have been re-established. This finding agreed with previous claimed that cysteine is fit for use in transporting target metals. In general, the studies have strengthened the idea that drugs and amino acids are able to interact with metals in our body system to a specific extent in terms binding constant.

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Declarations

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Consent to participate: Not applicable.
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