



Determination of Binary Stability Constant of the Complexes of Ni(II) and Mn(II) Ions with Cysteine

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ABSTRACT

Conventional chelators have been reported to be toxic, non-biodegradable, and rigid towards the recovery of bonded metal ions. The drawbacks with these chelators necessitate a search for their alternatives such as amino acids. Therefore, binary complexes of biologically important transition metal ions; Ni(II) and Mn(II) with cysteine have been studied potentiometrically at about 27 °C in aqueous medium using Irving-Rossotti titration technique. The results obtained were used to evaluate the proton-ligand and metal-ligand stability constants. The proton-ligand stability constants were; $\log K_1H$ 8.4 (pKa for thiol group) and $\log K_2H$ 10.7 (pKa value for NH₂-group). The binary metal-ligand stability constant values for 1:1 (M: L) complexes, $\log K$ as evaluated were found as Ni(II) > Mn(II); which is in agreement with the Irving–Williams order of the divalent metals of 3d series. Hence, these binary metal complexes could be applied as a medium of transporting chemotherapeutic drugs to target sites or detoxifying poisonous substances which possesses donor atoms with chelating capability. This finding also agreed with previous claimed that cysteine could be applied to transport metals to or away from target sites.

Keywords: Binary stability constant, Cysteine, Potentiometric titration, Transition metal ions

INTRODUCTION

Many chelating agents have been widely used to transport metals to or away from target sites due to their ability to form strong bonds with different metal ions. However, good number of these commonly used chelating agents have been reported to be toxic, non-biodegradable, and rigid towards the recovery of bonded metal ions (Asemave, 2016). The inherent drawbacks with these chelators necessitate a search for their alternatives (Ishola *et al.*, 2020); which are nontoxic and flexible for recovering bound metal ions. On the other hand, amino acids are regarded as essential integral foundation of living organisms. Amino acids unite to form proteins which are abundant in our body system. The reactions of proteins with metals present in our bodies are well known to exist. Thus, characterizing amino acids (such as metal-ligand stability constants) is essential for their potential applications (Belkher *et al.*, 2019) and gaining insight into the metal-protein activity in the body. Amino acids are metal ions coordinating agents via their amino (NH₂), carboxylic (COO⁻) groups etc (Asemave *et al.*, 2015 and Asemave *et al.*, 2012). Thus, they can be used as antidote to metal poisoning (Belkher *et al.*, 2019). Hence amino acids are great alternatives of the traditional chelants (Asemave, 2018).

The presence of metals in biological fluids has significant influence on the therapeutics (Al-

Rashdi *et al.*, 2018). Thus, the study of metal complexes of biologically active ligands is important because it will be helpful to understanding the interaction between the protein and metals in the biological systems. In addition, these studies will help us to identify the atoms or groups that are responsible for binding to metal ions, or are used in retention of toxic heavy metal ions (Belkher *et al.*, 2019). The degree of metal-ligand complex formation is therapeutically useful as the pharmacological relevance of a drug is related to its status (either in free or complexed form) (Kosasy *et al.*, 2011). Cobalt is found in vitamins (B₁₂ & B₉) that facilitate the natural production of red blood cells. More so, nickel can replace other metal ions in enzymes and proteins which then bind to cellular compounds containing O, S, and N atoms such as enzyme and nucleic acids. The deficiency of Ni can profusely impair intestinal absorption of iron and thus causes anemia. In addition, 90% of glucose and glycogen levels in the liver and serum are reduced upon nickel deficit (Belkher *et al.*, 2019).

Although there are many methods for studying the stability of proton-ligand and metal-ligand complexes, however, pH-metry is most frequently used because of its accuracy and reliability (Al-Rashdi *et al.*, 2018 and Nandurkar and Rathore, 2017). In the determination of formation constants of complexes some of these

precautions are considered. The concentration of the ligand should be higher than that of the metal so as to prevent hydrolysis of metal ions. Secondly, the ionic strength must be kept at ≤ 0.2 M to hinder the formation of ion pair between the anionic species and the cationic species or strong electrolytes (Kosasy *et al.*, 2011). Furthermore, it has been revealed that the stability constants increase when metal ion with high covalent index interacts with a ligand that possesses high polarizability (Ishola *et al.*, 2020). Therefore, we report the comparison of potentiometric binary stability constant of complexes of some biologically important transition metal ions with cysteine using Calvin-Bjerrum titration technique as applied by Irving & Rossotti (Adam *et al.*, 2011), to enable us validate previous claim about the metal-cysteine complexes of these metal ions.

MATERIALS AND METHODS

Materials/Apparatus/Equipments

All the potentiometric measurements were carried out by pH-meter. The meter was calibrated using standard buffer pH ≈ 4.00 , pH ≈ 7.00 , and pH ≈ 9.00 respectively. Cysteine, NaOH, HCl, NiCl₂ and MnCl₂ used were all of analytical grade. Distilled water was used for the preparation of the solutions.

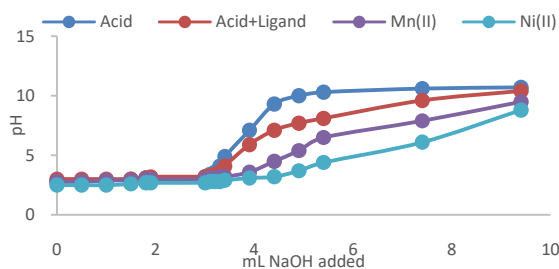


Figure 1: The titration curves of cysteine and its metal ions (II) complexes

Proton-Ligand Stability Constant

From Figure 1 the titration curves indicate that the ligand and metal curves are shifted to the right of the acid titration curve. The shift is due to the release of proton from the ligand as previously observed (Ishola *et al.*, 2020; Kosasy *et al.*, 2011; Belkher *et al.*, 2019 and Al-Rashdi *et al.*, 2018). This confirms the formation of proton-ligand and metal-ligand complexes (Adam *et al.*, 2011) through displacement of proton(s) from the ligand (Ishola *et al.*, 2020). The values of n_A (the degree of formation of the proton complex) were determined by employing Equation 1 as previously described by Gayakwad *et al.* (2017); where Y =number of replaceable hydrogen ion; V° =total volume 50mL; V_1 =volume of alkali required by the acid;

Potentiometric Studies Procedure

The Irving and Rossotti titration technique was used as similarly reported (Al-Rashdi *et al.*, 2018; Kosasy *et al.*, 2011 and Adam *et al.*, 2011). The following solutions were prepared and titrated against 0.04 M of standard CO₂-free NaOH solution at about 27°C.

- 3 mL 0.04 M HCl
- Solution (a) + 4 mL 0.03 M cysteine.
- Solution (b) + 2 mL 0.04 M metal (Ni(II) and Mn(II)) chloride solutions, respectively.

In all the titrations, the total volume was maintained constant at 50mL. The method of Calvin-Bjerrum as adopted by Irving and Rossotti has been employed to determine log K values (Belkher *et al.*, 2019 and Al-Rashdi *et al.*, 2018).

RESULTS AND DISCUSSION

The Irving-Rossotti potentiometric titration

The proton dissociation constants of the cysteine and its complexes of Mn(II) and Ni(II) have been determined in aqueous medium at 0.04M NaOH and 27 °C. Therefore, the potentiometric titration curves of cysteine and its metal complexes are presented in Figure 1. During the titrations, no precipitate was formed indicating there is no tendency for formation of hydroxo complexes (Ishola *et al.*, 2020).

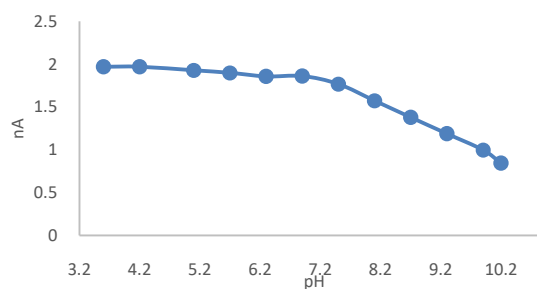


Figure 2: pH-nA curves for Cysteine

V_2 =volume of alkali used by acid and ligand; N° =concentration of alkali; E° =total strength of acid; and TcL° = total concentration of ligand. Therefore, from the method of point wise calculation of stability constant we have the following Equations 2 and 3 (Janrao *et al.*, 2014), respectively. Thus, integral method of stability constant determination can be applied on the Equations 2 and 3 above. That is, by putting the value of $n_A = 0.5$ in Equation 2, we obtain $\log K_2H = pH$. Similarly, by putting the value of 1.5 for n_A in the Equation 3, we obtain $\log K_1H = pH$. It means if we plot a graph between n_A and pH then the corresponding values of pH at n_A equal to 0.5 and 1.5 gives $\log K_2H$ and $\log K_1H$, respectively (Belkher *et al.*, 2019 and Al-Rashdi *et al.*, 2018).

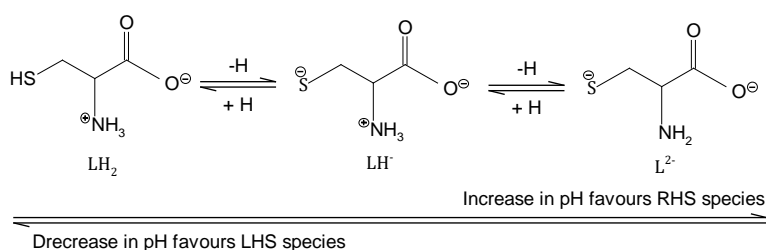
Hence, the proton ligand formation curve was obtained by plotting the degree of formation of the proton complex, n_A (as determined from Equation 1) against pH values (Figure 2). The values of $\log K_1H$ and $\log K_2H$ were then determined from the curves corresponding to n_A values of 0.5 and 1.5 as earlier explained. Note that $\log K_1H$ and $\log K_2H$ represent the first and second proton formation constants of ligand, respectively. This implied that the $\log K_1H$ of 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 in the cysteine (Scheme 1). The condition of the experiment did not permit the determination of the pKa value for the COOH group. However, it is reasonable to say that the thiol group also is involved in the complex

formation of these metal ions and the cysteine (Al-Rashdi *et al.*, 2018 and Alturigi *et al.*, 2020). Similarly, Al-Mohaimed and Alothman (2019) observed that S-methylcysteine exhibits pKa value of 8.65 and has found that the sulfur atom contributes in the complex formation process.

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

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

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



Scheme 1: Proton dissociation from -SH and -NH₂ of cysteine

Metal-Ligand Stability Constant

The binary stability constant was determined using Irving and Rossotti Potentiometric technique (Kosasy *et al.*, 2011). Again, by comparing the pH titration curves of the free ligand to that of the complex solution, a drop in pH was observed indicating the complex formation. Therefore, the average number of ligands attached per complex ion (\bar{n}) can be calculated from the following Equation 4 (Kosasy *et al.*, 2011). In the Equation 4, 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 as given in Equation 1. The free ligand exponent, pL was calculated using Equations 5 (Kosasy *et al.*, 2011; Belkher *et al.*, 2019 and Al-Rashdi *et al.*, 2018). According to point wise method for stability constants determination, $\log K_1$ and $\log K_2$ can be expressed as given in Equations 6 and 7, respectively (Janrao *et al.*, 2014). Thus, by using integral method, put the value of $\bar{n} = 0.5$ in Equation 6 to form $\log K_1 = pL$. Likewise, by putting the value of $\bar{n} = 1.5$ in the Equation 7, we obtain $\log K_2 = pL$. It means if we plot a graph between \bar{n} and pL then the corresponding values of pL at \bar{n} equal to 0.5 and 1.5 gives $\log K_1$ and $\log K_2$, respectively (Belkher *et al.*, 2019; Al-Rashdi *et al.*, 2018; and Kosasy *et al.*, 2011). Subsequently, plots of \bar{n} vs pL (Figures 3 and 4) were made as previously performed (Al-Rashdi *et al.*, 2018). After the plot, then the stability

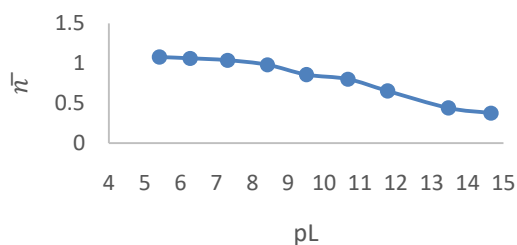
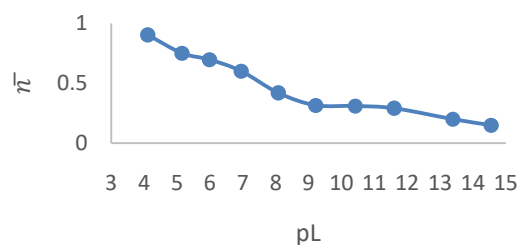
constants were obtained and presented in Table 1. The stability constant for $\bar{n} = 1.5$ were not favoured or found at the condition of these experiments. Usually, formation constant or the pL value at $n = 0.5$ indicates a 1:1, metal: ligand complex; whereas, the pL value at $n = 1.5$ shows a 1:2, metal: ligand and a less stable complex (Kosasy *et al.*, 2011). The values of the stability constants, (1: 1, M: L) were 7.5 and 12.8 for Mn(II) and Ni(II), respectively. The order of the stability constants is: Ni(II) > Mn(II); which is in agreement with the Irving-Williams order of the divalent metals of 3d series metal ions. In addition, lack of formation of 1: 2, M: L in this work may be due to the experimental conditions such as the nature of metal ion, concentration of ligand, and ionic strength etc as similarly supported in the past (Al-Rashdi *et al.*, 2018).

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

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

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

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

Figure 3: Plot of \bar{n} against (pL) Ni(II)-CysFigure 4: Plot of \bar{n} against (pL) Mn(II)-Cys**Table 1: Characteristics properties of the metal ions and their Binary stability constants of the Metal: Cys complexes**

ions	RI / pm	Z	IP(kJ/mol)	EN	Species	Log K_1 (M: L; 1:1)
Ni (II)	72	28	2490	1.75	Ni (II) -Cys	12.8
Mn (II)	80	25	2226	1.6	Mn (II) -Cys	07.5

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

In the report of Adam *et al.* (2011), the binary metal complexes of Cu(II) and Ni(II) with some amino acids showed formation 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 (Adam *et al.*, 2011). They also used the Irving and Rossotti titration technique (Adam *et al.*, 2011). Ishola *et al.* (2020) and 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 (Ishola *et al.*, 2020). These values of formation constants are similar to the ones we found here. Furthermore, potentiometric determination of stability constant of coordination complex of pyrazinamide with Fe(III) was carried out by Kosasy *et al.* (2011). The pL at 0.5 showed M: L; 1:1 complex of 2.75 stability constant for Fe(III)- pyrazinamide; and the pL value at $n=1.5$ (indicates a 1:2, M: L, less stable complex) gave stability of 1.6 (Kosasy *et al.*, 2011). More so, 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 (STZ) and glycine have been studied potentiometrically at $25\text{ }^\circ\text{C} \pm 0.1\text{ }^\circ\text{C}$ and $I = 0.1\text{ M NaClO}_4$ in 25% (v/v) pure ethanol-water medium (Al-Rashdi *et al.*, 2018). The obtained results show that both Al(III) and Zr(IV) ions form (1:1), (1:2), and (1:3) metal: ligand complexes (Al-Rashdi *et al.*, 2018). Also, some metal ions like; Zr(IV), Sr(II), Al(III), Fe(III), Th(IV), and Pb(II) form (1:1) and (1:2) M: L complexes. Contrary, Co(II), Cr(III), Ti(II) and La(III) only gave complex of 1:1 M: L as reported in our work (Esmailzadeh & Mashhadiagha, 2017). This may be due to the nature of metal ion, concentration of ligand and ionic strength (Al-Rashdi *et al.*, 2018). Again, the order of stability of the different binary complexes formed between the STZ and the metal ions as they investigated was in

the expected Irving-Williams order (Al-Rashdi *et al.*, 2018): Fe(III) > Co(II) > Ti(II) > Zr(IV) > Al(III) > La(III) > Cr(III) > Sr(II) > Pb(II) > Th(IV). In another development, complex formation equilibria of 2-hydroxy-1-naphthoic acid with Cu(II), Ni(II), Co(II) and Mn(II) and the ternary complexes involving Cu(II), 2-hydroxy-1-naphthoic acid, and some amino acids containing different functional groups were investigated. The stability of the complexes followed the trend Cu(II) > Ni(II) > Co(II) > Mn(II) which is in agreement with the Irving-Williams order of the divalent metals of 3d series metal ions (Ahmed *et al.*, 2021). Meanwhile, proton-ligand stability constant and metal-ligand stability constant of chlorosubstituted pyrazoles and isoxazoles by Calvin Bjerrum titration as applied by Irving-Rossotti was also reported (Nandurkar and Rathore, 2017). Their metal-ligand stability constants were within the range of 5.343 - 3.644 (Nandurkar and Rathore, 2017). Belkher *et al.* (2019) also used Irving-Rossotti titration technique for potentiometric studies of stability constant of the complexes of some essential transition metal ions with *L-Valine* and found the order of stability as Cu(II) > Ni(II) > Co(II), as similarly observed in this research work.

Therefore, assuming the interaction of the metal ion and the ligand is electrostatic; the stability constants for complexes of metal ions of the same charge should be inversely proportional to metal ion radius (RI) (Ahmed *et al.*, 2021) for ions of similar electronic configuration. However, this is untrue with metal ions of different groups of the periodic system. That is one of the reasons for the trend of stability of the complexes in this work; Ni(II) > Mn(II). More so, the M:L stability constant is directly proportional to the electronegativity, atomic number, and ionization potential of the metal as described in Table 1, but inversely proportional to the ionic radii (Ahmed *et al.*, 2021).

Beside this, the observed trend of the binary stability constants here again is in accordance with the fact that increasing electronegativity (EN) of the metal ions will decrease the electronegativity difference between the metal atom and the donor atom of the ligand. Thus, the metal–ligand bond would have more covalent character, resulting into greater stability of the metal complex.

CONCLUSION

The binary complexes of biologically important transition metal ions of Ni (II) and Mn (II) with cysteine have been studied potentiometrically at about 27°C in aqueous medium using Irving-Rossotti titration technique. The data obtained of the Irving-Rossotti titration technique were used to evaluate the proton-ligand and metal-ligand stability constants. The proton-ligand stability constants were; $\log K_1H$ 8.4 (pKa for thiol group) and $\log K_2H$ 10.7 (pKa value for NH₂-group). The binary metal-ligand stability constant values for 1:1 (M: L) complexes, $\log K$ as evaluated were found in the order of Ni(II) > Mn(II); which is in agreement with the Irving-Williams order of the divalent metals of 3d series metal ions. Hence, these binary metal complexes could be applied as a medium of transporting chemotherapeutic drugs to target sites or detoxifying poisonous substances which possesses donor atoms with chelating capability. This result also agreed with previous claimed that cysteine is suitable for use to move metals to or away from target sites.

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