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Original article

The Determination of The Stability Constants of Mixed Ligand Comlexes of Creatinine-L-Cysteine and Creatinine-L-Cysteine Hydrochloride With Co(Ii), Cd(Ii), Zn(Ii), Mn(Ii): Using Potentiometric Method

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In this study, a potentiometric titration technique has been used to determine stability constants for the various complexes of Zn(II), Co(II), Cd(II) and Mn(II) with creatinine and two amino acids. Stability constants of ternary systems have been evaluated by the method suggested by Irving-Rossotti at 25°C and 0.11M ionic strength (kept constant with $NaClO_4$) in aqueous solution. In addition, the conditional constants were calculated as a function of pH. The maximum values of the conditional formation constants were found to be in accordance with the mixed-ligand complex formation constants in a given pH region. In addition, the mole fractions of different species from mixed complexes were calculated by means of formation constants. The values of stability constants of mixed-ligand complexes at 25°C were calculated as follows: logK=3.20 for Zn(II)-L-cysteine-creatinine,$logK_1$=4.24 and $logK_2$=3.58 for Co(II)-L-cysteine-creatinine$_2$, logK=3.22 for Cd(II) - L-cysteine – creatinine, logK=3.65 for Mn(II) - L-cysteine – creatinine and logK=5.34 for Co(II)-BDHL-cysteine-creatinine, logK=5.30 for Cd(II)-BDHL-cysteine-creatinine, $logK_1$=5.35 and $logK_2$=3.93 for Zn(II) - BDHL-cysteine - creatinine$_2$, $logK_1$=5.40 and $logK_2$=3.49 for Mn(II) - BDHL-cysteine - creatinine$_2$.

Key words: Creatinine, L-cysteine, BDHL-cysteine, Zinc(II), Cobalt(II), Cadmium(II) and Manganez(II) complexes, Mixed complex, Stability constants.

L-Sistein - kreatinin'in ve L-sistein.HCl (BDHL-sistein) - kreatinin'in Co(II), Cd(II), Zn(II), Mn(II) ile Karışık Komplekslerinin Kararlılık Sabitlerinin Potansiyometrik Yöntemle Tayini

Bu çalışmada kreatinin ve iki aminoasit'in Co(II), Cd(II), Zn(II), Mn(II) ile oluşturduğu karışık komplekslerin kararlılık sabitleri potansiyometrik titrasyon yöntemi ile tayin edilmiştir. Üçlü komplekslerin stabilite sabitleri Irving Rossotti yöntemi ile 25°C de ve iyonik kuvvet $NaClO_4$ ile sabit tutularak (0.11M) sulu çözeltide incelenmiştir. Ayrıca oluşan komplekslerin koşullu oluşum sabitleri pH'a bağlı olarak hesaplanmış ve belirli bir pH bölgesinde koşullu oluşum sabitinin maksimum olduğu değerin deneysel olarak bulunan kararlılık sabiti ile uyum içinde olduğu gözlenmiştir. Hesaplanan koşullu oluşum sabitlerinden yararlanılarak karışık kompleksten türeyen çeşitli türlerin bağıl bollukları incelenmiştir. İyonik kuvvet $NaClO_4$ ile I=0.11 de sabit tutulmuştur. 25°C da L-sistein ve kreatinin'in metal komplekslerinin kararlılık sabitleri: Zn(II)-L-sistein-kreatinin için logK=3.20, Co(II)-L-sistein-kreatinin$_2$ için $logK_1$=4.24 ve $logK_2$=3.58, Cd(II)-L-sistein-kreatinin için logK=3.22, Mn(II)-L-sistein-kreatinin için logK=3.65 ve Co(II)-BDHL-sistein-kreatinin için logK=5.34, Cd(II)-BDHL-sistein-kreatinin için logK=5.30, Zn(II)-BDHL-sistein-kreatinin$_2$ için $logK_1$=5.35 ve $logK_2$=3.93, Mn(II)-BDHL-sistein- kreatinin$_2$ için $logK_1$=5.40 ve log K_2=3.49 olarak hesaplanmıştır.

Anahtar kelimeler: Kreatinin, L-sistein, BDHL-sistein, Çinko(II), Kobalt(II), Kadmiyum(II), Mangan(II) kompleksleri, Karışık kompleks, Kararlılık sabiti

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INTRODUCTION

The complexation properties of an aqueous sample toward metal ions are of great interest, since they determine the distribution of the metal ions between different species and thus their solubility, mobility and toxicity.The stability constants of metal complexes with drugs are useful in elucidating the mechanism action of drugs (1). Although chelate stability constants have been published for many metal ions with amino acids, many different methods and varying temperatures and ionic strengths have been employed. Because of the biological importance of these ligands, several of the reported metal-stability constants have been redetermined and those of several new metal chelates have now been measured at constant temperature and ionic strength (2).

The determination of the structure of metal cysteine complexes is extremely important as model compounds for understanding how cysteine-rich proteins, such as metallothioneins and phytochelatins, uptake and bind metals.

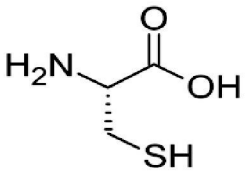

Figure 1. L-cysteine

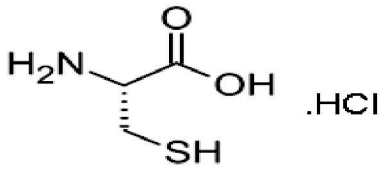

Figure 2. L-cysteine hydrochloride (BDHL-Cysteine)

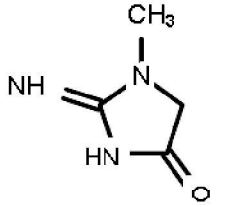

Figure 3. Creatinine

L-Cysteine is a protein amino acid that exists naturally as a protein in most living organisms. Although most cysteine is found in proteins, small amounts of cysteine are also located in body fluids and in plants in non-protein form. L-Cysteine is considered a nonessential amino acid, meaning that sufficient amounts are produced by the body itself. L-Cysteine a thiol compound (which therefore contains a sulfhydryl, SH, group), is a precursor of taurine in organisms and is normally obtained from the diet and by a transsulfuration pathway from methionine. L-Cysteine can also be transformed into glucose and used by the body as a source of energy. L-Cysteine strengthens the protective lining of the stomach and intestines, which may help prevent damage caused by aspirin and similar drugs. Additionally, L-Cysteine may play an important role in the communication between immune system cells. There is no known medical condition directly caused by cysteine deficiency,but low cysteine levels may reduce one's ability to prevent free radical damage and may result in impaired function of the immune system (3).

Electrosynthesis of the thiol, L-cysteine hydrochloride via the reduction of the disulphide, L-cysteine hydrochloride in an acid electrolyte: RS–SR+2H +2e → 2RSH (4) where R=CH2CH(NH2·HCl)COOH, is an important fundamental (4) and industrial (5) process. This synthesis is used in the Far East, in the USA and in Europe to produce around 1500 tonnes per annum of the high value amino acid product, and its derivatives, for a variety of applications in the foodstuffs, cosmetics and pharmaceutical industries (6). These applications require either L-Cysteine free base or, more often, the hydrochloride salt.

Creatinine, is a metabolic product of creatine and phosphocreatine origatinating from skeletal muscles and dietary meat through urea cycle. The assesment of creatinine levels in human blood or urine becomes clinically very important and it is now the most requested analyte in the clinical laboratory. Creatinine ($C_4H_7N_3O$) is produced from creatine, a molecule of major importance for energy production in muscles. Creatinine (creat) is transported through the bloodstream to the kidneys. The kidneys filter out most of the creatinine and dispose of it in the urine (7,8). Creatinine is an important analyte of clinical significance that is used for the determination of renal glomerular filtration rate and kidney dys-functioning and

muscle disorder (9). The complexation ability of creatinine is well recognised and studies on the metal ion interactions with creatinine may be helpful in deciphering creatinine metabolic pathways (10). Although literature survey reveals that creatinine and L-cysteine mixed complexes have not been reported so far. The aim of this study are to investigate stability of mixed ligand complexes of L-cysteine, creatinine and BDHL-cysteine, creatinine presence of the metal ions in aqueous media by potentiometric titration method at 25° C under nitrogen atmosphere and ionic strength of 0.11M sodium perchlorate (11). By analysing the conditions of formation of complex's reactions the pH space in which reactions occur, the periods of reaction's occurence, their adherence to the concentration and the mole amounts which is necessary for a complete reaction of these metals and ligands are found (12-14).

EXPERIMENTAL

Materials and Methods

Stocks solutions of metal ions, NaOH, $HClO_4$, $NaClO_4$ were prepared from analytical reagent grade chemicals obtained from Merck, who also provided the ligands creatinine and L-cysteine. Solutions were made up under N_2 atmosphere in decarbonated H_2O. A Metrohm 654 digital pH-meter, with a combined glass electrode assembly, was used. Double distilled water was used for the preparation of solutions. Fresh solutions were prepared at the time of use. The concentrations of cobalt (II), zinc (II), cadmium (II) and manganez (II) ions in the solutions were typically kept ca. $1.0\ 10^{-2}$ M and determined accurately by titration with standard ethylenediaminetetraaceticacid (EDTA). The ionic strength was maintained constant at 0.10 ± 0.01 mol/L with $NaClO_4$ in all titrations which were carried out at 25 °C. A Metrohm Multi-Burette E-485 was used as the burette. The pH-meter, which was accurate to 0.01 pH unit was standardized before each titration using buffer solutions of citrate-hydrochloric acid (pH=4 at 20 °C) and phosphate (pH=7 at 20 °C). Computer calculations were performed on the metric data.

The Determination of Protonation Constants

In order to determine the protonation constants, the solutions including $HClO_4$ and ligand + $HClO_4$ solutions were titrated potentiometrically using 0.1N NaOH (Figure 4-11). Average $\bar{n}_A$ values were calculated from the titration curves. For the calculation, the following equation was used.

$$n_A = y + \frac{(v_1 - v_2)(N + E^0)}{(V^0 + v_1)\,T_L^0}$$

Where:
V^o = volume at the beginning: 50 mL
N = normality of the base: 0.1 N
TL^o= total molar ligand concentration
for L-cysteine and creatinine: $2.00\ 10^{-3}$ M
E° = concentration of acid: $1.05\ 10^{-2}$ M
y = the number of protons given
for L-cysteine: 2
for BDHL-cysteine: 2
for creatinine: 0

The volumes of v_1 and v_2 were read from the titration curves which contain $HClO_4$ and ligand + $HClO_4$. $\bar{n}_A$ values which correspond to different pH values were calculated by using the volumes of v_1 and v_2 , were plotted in function of pH, i.e. $\bar{n}_A = f(pH)$.

The protonation constants and the acidity constants of Creatinine, L-Cysteine and BDHL-Cysteine which were used as ligands were determined (Table 1).

The Determination of Stability Constants

The stability constants of the binary complexes were determined potentiometrically using the Irving-Rossotti method (11).

Therefore the mixtures which contain the metal ions were titrated with standard 0.100 N NaOH solution potentiometrically and the titration curves were plotted (Figure 4-11). $\bar{n}_L$ values were calculated using the equation given below. pL values were calculated using $\bar{n}_L$ values to calculate the stability constants. The following equation was used to calculate $\bar{n}_L$ values:

$$n_L = \frac{(v_3 - v_2)\,[N + E^0 + T_L^0 (y - n_A)]}{(V^0 + v_2).\, n_A .T_M^0}$$

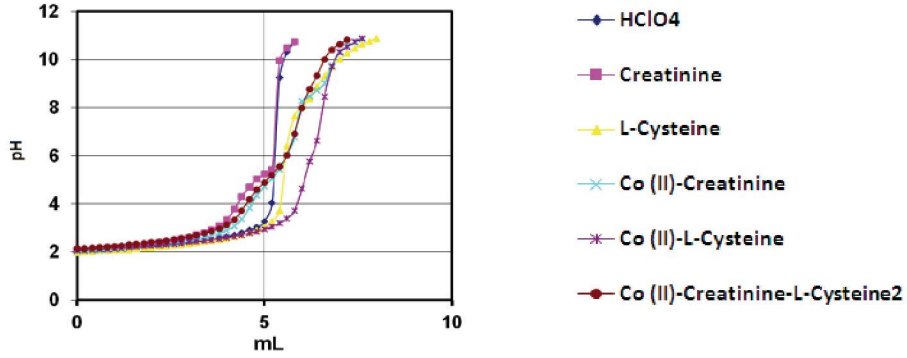

Figure 4. Potentiometric titration curves of ligands and mixed ligand complex.

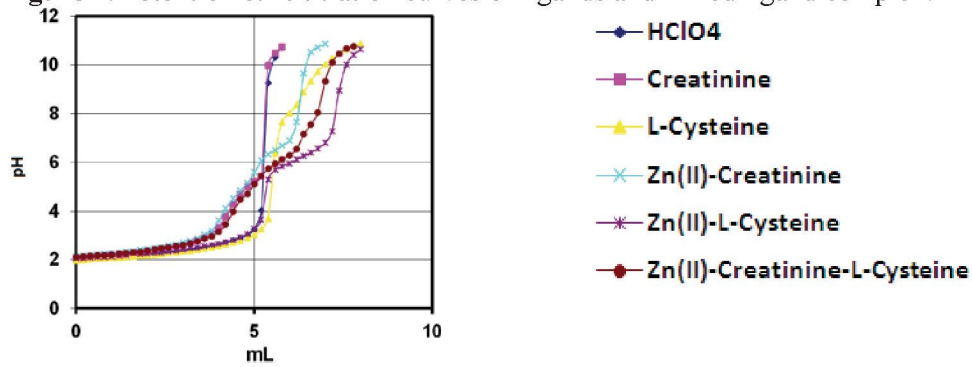

Figure 5. Potentiometric titration curves of ligands and mixed ligand complex.

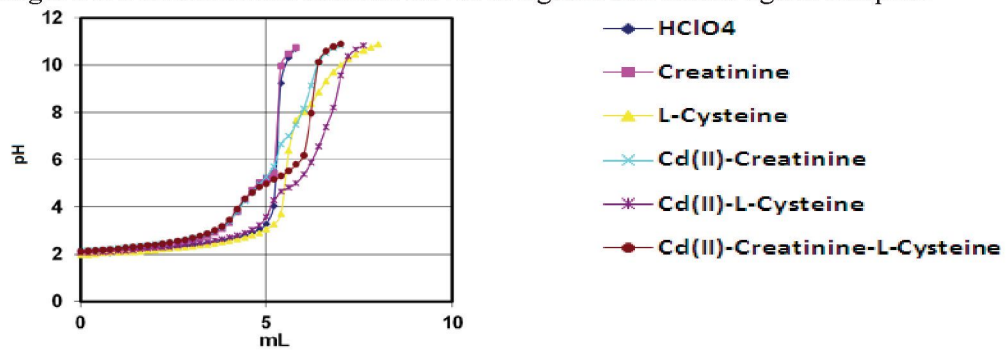

Figure 6. Potentiometric titration curves of ligands and mixed ligand complex.

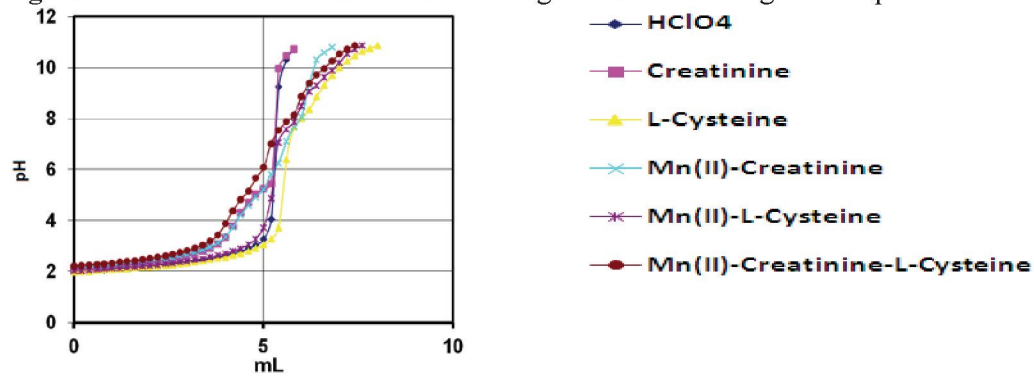

Figure 7. Potentiometric titration curves of ligands and mixed ligand complex

Where:
V° = volume at the beginning: 50 mL
N = normality of the base: 0.1 N
$T_L°$ = total molar ligand concentration: $2.00\ 10^{-3}$
E° = concentration of acid: $1.05\ 10^{-2}$ M
y = the number of protons given
for L-cysteine: 2
for BDHL-cysteine : 2
for creatinine : 0

T_M°= total molar metal concentration: 1.00 10^{-3}M The following equation was used to calculate pL values.

$$pL = \log \left(\frac{1+\beta_1[H^{\pm}] + \beta_2[H^{\pm}]^2}{T_L^0 - n_L . T_M^0} \right)$$

pL values were calculated using β values. The relation $\bar{n}_L = f(pL)$ was plotted using $\bar{n}_L$ and pL values which were calculated for each metal ion. The stability constants were determined from these graphs (Table 2).

The values found are in agreement with literature values (15,16). In order to establish stability constants of the mixed ligand complexes, the Irving-Rossotti method was

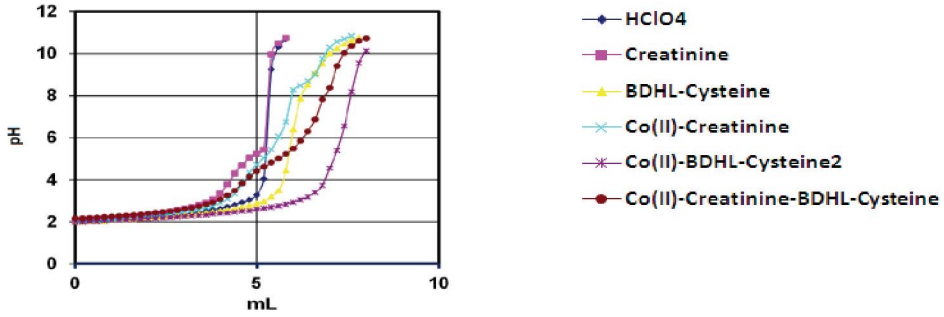

Figure 8. Potentiometric titration curves of ligands and mixed ligand complex

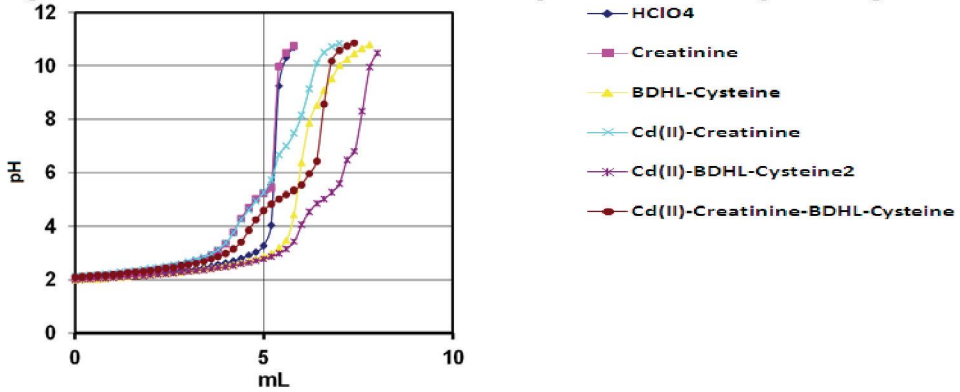

Figure 9. Potentiometric titration curves of ligands and mixed ligand complex

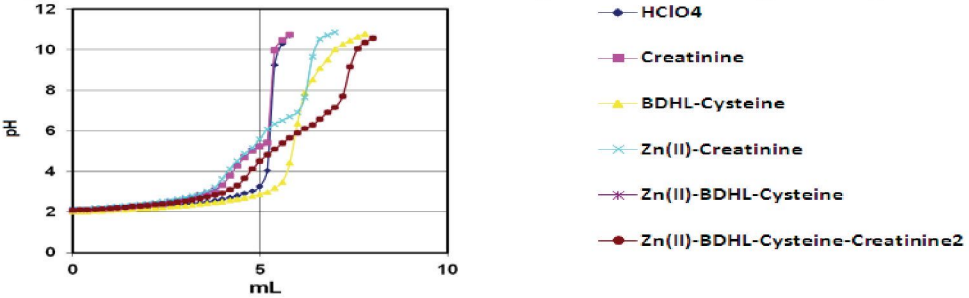

Figure 10. Potentiometric titration curves of ligands and mixed ligand complex

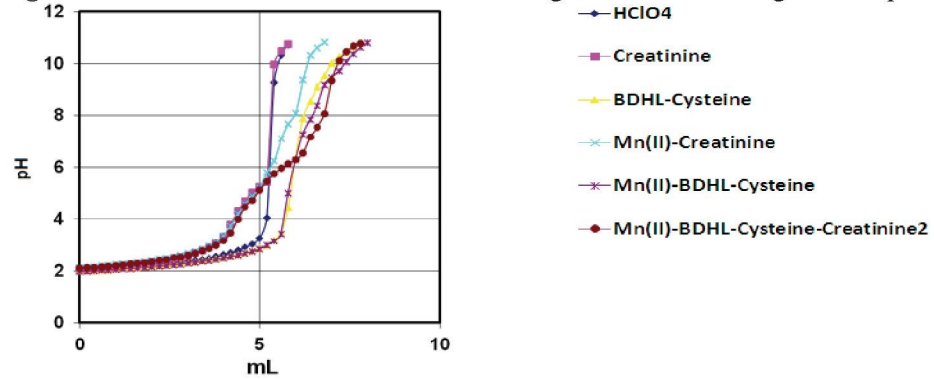

Figure 11. Potentiometric titration curves of ligands and mixed ligand complex.

also used (11).

The stability constants derived from the complexes of all ligands and the metals were evaluated and the ligand which has a lower stability constant was selected as the second ligand, i.e., Y, for confirming the formation of a "true" mixed-ligand complex where Y would be bound to the already formed ML as the initial 1:1 complex. The hypothesited reaction scheme is as follows:

$$M + L \leftrightarrows ML$$

$$ML + Y \leftrightarrows MLY$$

$$MLY + Y \leftrightarrows MLY_2$$

The mixtures of metal which consisted and ligands were titrated potentiometrically. The $\bar{n}_L$=f(pL) graphs (Figure 12-19) as plotted using $\bar{n}_L$ and pL values which were calculated from titration curves. The seperation among ($HClO_4$), ($Y+HClO_4$) and ($Y+HClO_4$ + L + M) plots in all potentiometric titration curves showed the formation of a mixed complex (Figures.4-11). The approach of Irving-Rossotti to binary systems was applied for the mixed system. It was based on the fact that the system (M+L) having the higher stability constant behaved as the "lone" metal in the binary system capable of accepting the second ligand. The results are summarized in Table 2.

In addition, the conditional formation constants were calculated and were plotted as a function of pH (Figure 20-27).

The mole fractions of different species of mixed complexes were found by means of the calculated formation constants and were plotted as a function of pH (Figure 28-35).

Table 1 . The protonation constants of ligands

Creatinine	$\log K=4.90$	-	-
L-cysteine	$\log K_1=10.20$	$\log K_2=7.80$	$\log K_3=2.05$
BDHL-cysteine	$\log K_1=9.70$	$\log K_2=2.05$	

Table 2. The stability constants of binary and ternary complexes

Ligand-Metal	**$\log K_1$**	**$\log K_2$**
Co(II)-L-cysteine	12.75	-
Zn(II)- L-cysteine	9.01	-
Cd(II)- L-cysteine	12.70	-
Mn(II)- L-cysteine	4.78	-
Co(II)-BDHL- cysteine $_2$	10.60	9.58
Cd(II)-BDHL- cysteine $_2$	8.12	7.60
Zn(II)-BDHL- cysteine	9.04	-
Mn(II)-BDHL- cysteine	3.95	-
Co(II)- creatinine	2.89	-
Cd (II)- creatinine	3.00	-
Zn(II)- creatinine	2.94	-
Mn(II)- creatinine	3.02	-
Zn(II)-L-cysteine-creatinine	3.20	-
Co(II)-L-cysteine-creatinine$_2$	4.24	3.58
Cd(II)-L-cysteine-creatinine	3.22	-
Mn(II)-L-cysteine-creatinine	3.65	-
Co(II)-BDHL-cysteine-creatinine	5.34	-
Cd(II)-BDHL-cysteine-creatinine	5.30	-
Zn(II)-BDHL-cysteine-creatinine$_2$	5.35	3.93
Mn(II)-BDHL-cysteine-creatinine$_2$	5.40	3.49

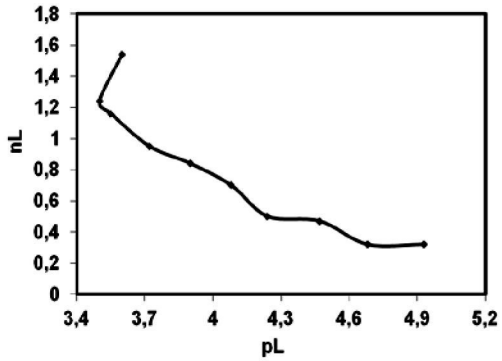

Figure 12. nL=f (pL) curves for Co(II) - L-cysteine - creatinine$_2$

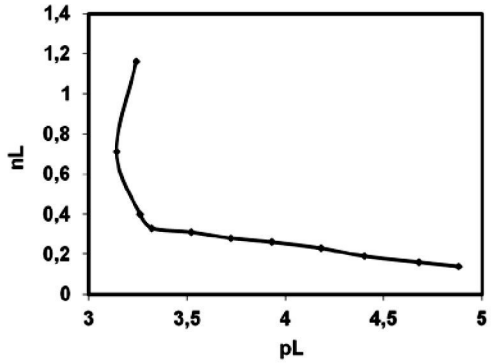

Figure 13. nL=f (pL) curves for Zn(II) - L-cysteine - creatinine

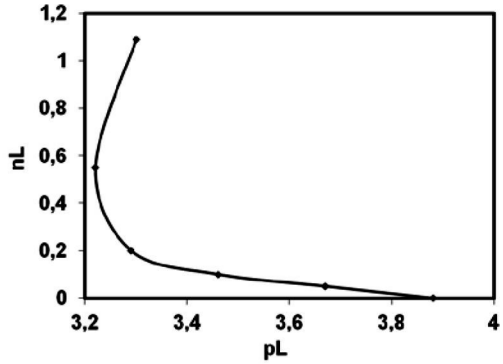

Figure 14. n_L=f (p_L) curves for Cd(II)-L-cysteine-creatinine

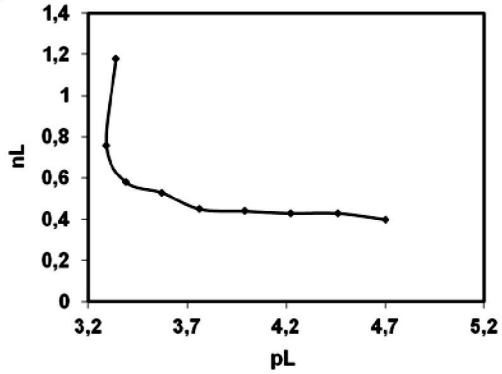

Figure 15. n_L=f (p_L) curves for Mn(II) - L-cysteine – creatinine

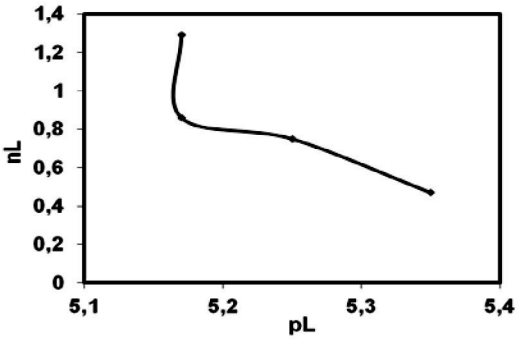

Figure 16. n_L=f (p_L) curves for Co(II) - BDHL-cysteine – creatinine

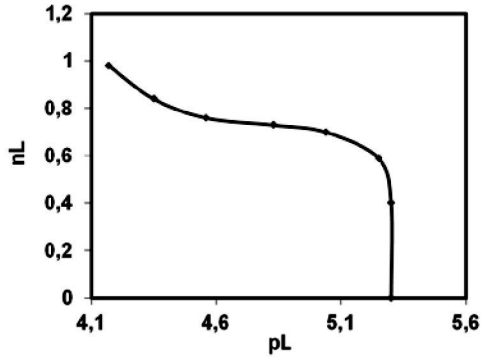

Figure 17. n_L=f (p_L) curves for Cd(II) - BDHL – cysteine – creatinine

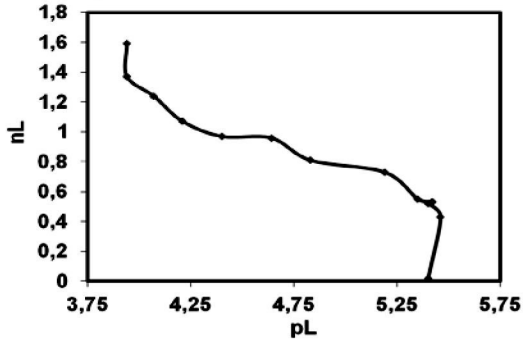

Figure 18. n_L=f (p_L) curves for Zn (II) - BDHL-cysteine - creatinine$_2$

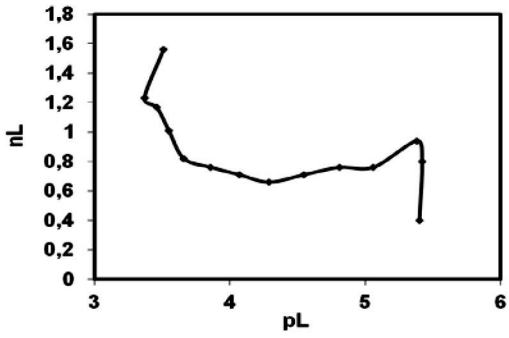

Figure 19. n_L=f (p_L) curves for Mn (II) - BDHL-cysteine - creatinine$_2$

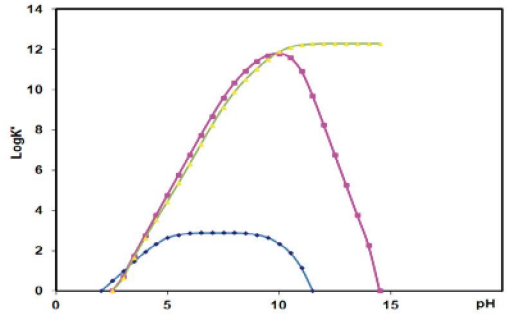

Figure 20. Conditional formation curve

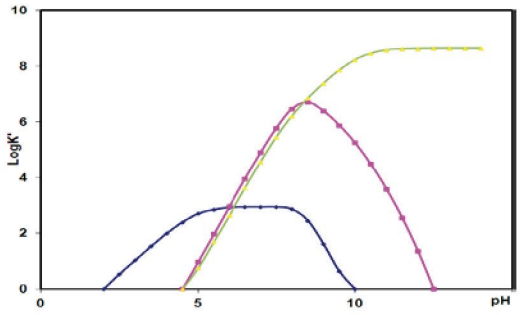

Figure 21. Conditional formation curve

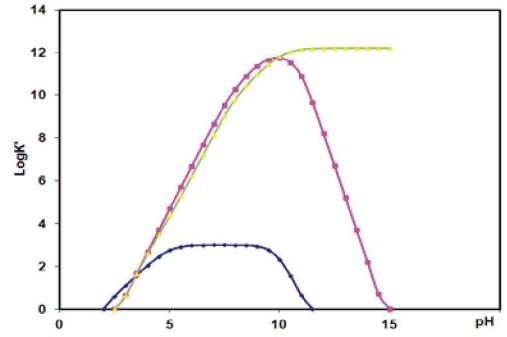

Figure 22. Conditional formation curve

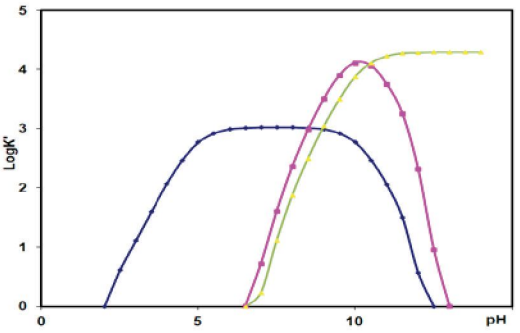

Figure 23. Conditional formation curve

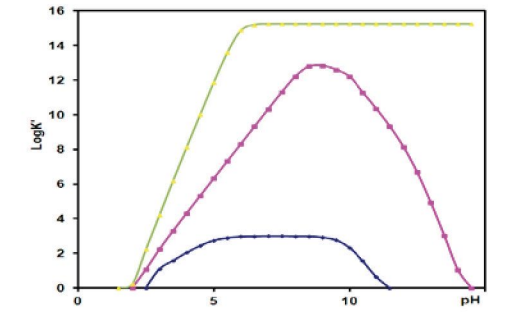

Figure 24. Conditional formation curve

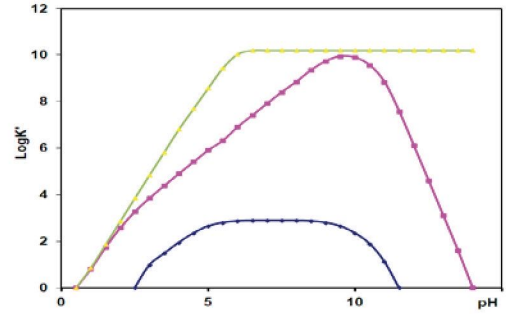

Figure 25. Conditional formation curve

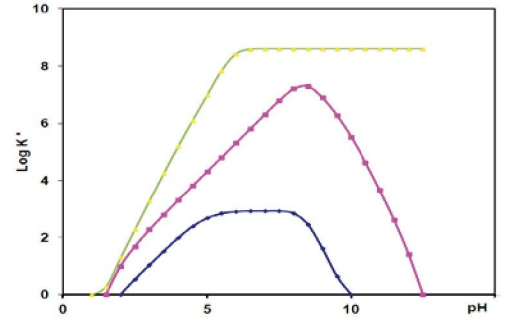

Figure 26. Conditional formation curve

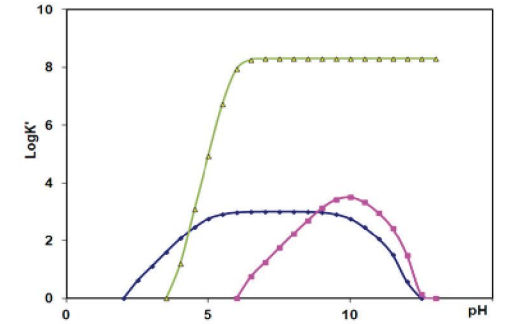

Figure 27. Conditional formation curve

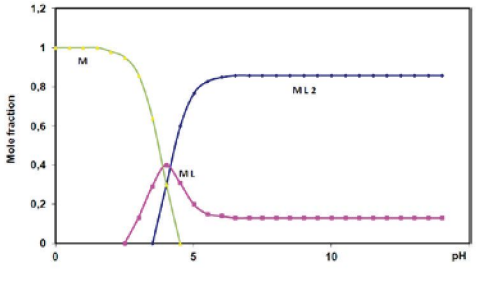

Figure 28 . Mole fraction diagram of the Co (II) - L-cysteine - creatinine$_2$ complexes as a function of pH

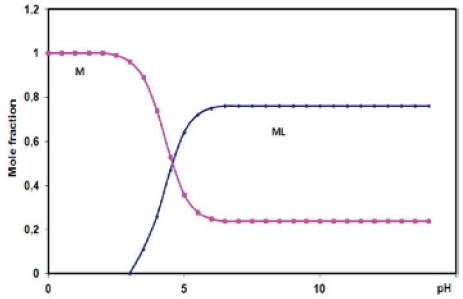

Figure 29 . Mole fraction diagram of the Zn (II) - L-cysteine - creatinine complexes as a function of pH.

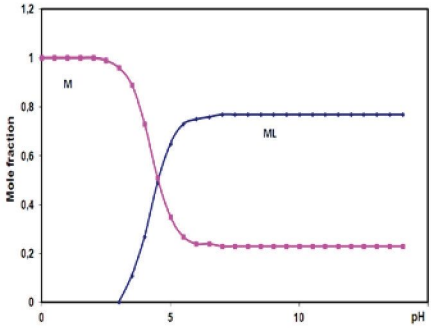

Figure 30 . Mole fraction diagram of the Cd (II) - L-cysteine - creatinine complexes as a function of pH

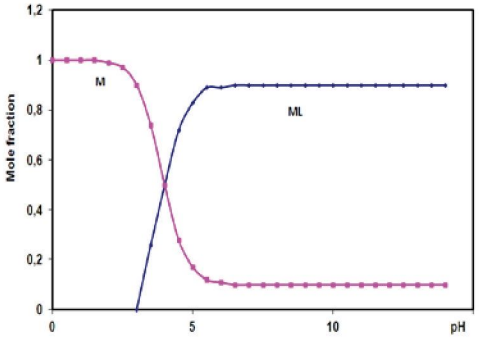

Figure 31 . Mole fraction diagram of the Mn(II) –L –cysteine - creatinine complexes as a function of pH

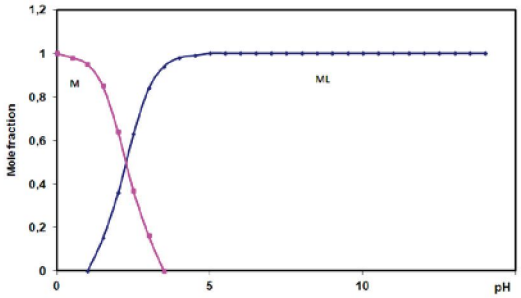

Figure 32 . Mole fraction diagram of the Cd (II) - BDHL-cysteine - creatinine complexes as a function of pH

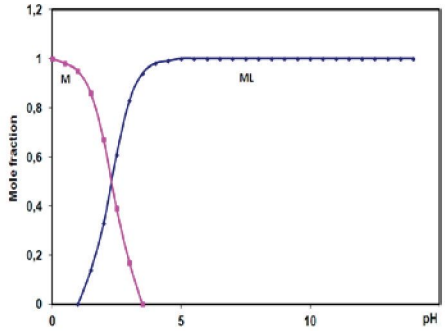

Figure 33 . Mole fraction diagram of the Co(II)-BDHL-cysteine-creatinine complexes as a function of pH

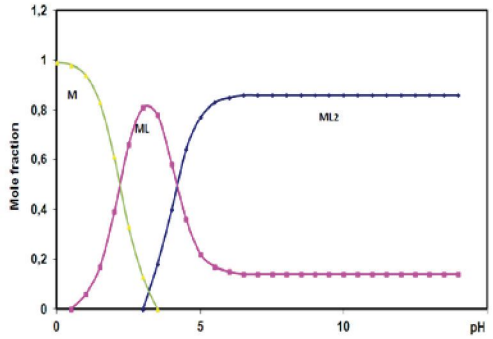

Figure 34. Mole fraction diagram of the Mn(II) - BDHL-cysteine – creatinine$_2$complexes as a function of pH

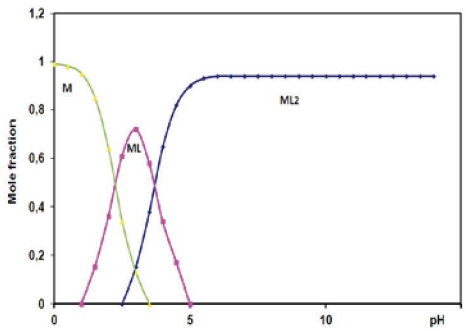

Figure 35. Mole fraction diagram of the Zn (II) - BDHL-cysteine - creatinine$_2$ complexes as a function of pH

RESULTS AND DISCUSSION

To form complex of some metals is defined as detoxification or a protective mechanism.

L-cysteine and BDHL-cysteine improves the ability to detoxify the body and helps eliminate heavy metals and chemical substances. creatinine is produced from creatine, a molecule of major importance for energy production in muscles. In the light of this information we found the stability of metal complexes of L-cysteine, BDHL-cysteine and creatinine. We aimed to formed complexes with aminoacids, existing body metabolism, and metals for further studies.

In this study the conditional formation constants were calculated and these constants were found to be in agreement with the formation constants of mixed systems. This result affords us to find the stability constants of mixed complexes. In this calculation, the pK values of ligands and the formation constants of complexes which they formed with metals are used as data. The conditional formation constants, namely the stability constants of mixed complex can also be calculated. The difference between the formation constants of mixed and binary systems is a parameter which characterizes the formation behaviour of mixed ligand complexes (17-21).

$$\Delta \log K = \log K_{MLY} - \log K_{MY}$$

The difference is a equilibrium constant of the following equation.

$$ML + MY \quad MLY + M \quad (1)$$

If ΔlogK is negative, then equilibrium (1) favours the left hand side.

The conditional formation constant equals the "β values" of the mixed complex. The formation contants of mixed complex found in this work are in agreement with the calculated conditional formation constants of $\beta_2 = K_1 . K_2$ for mixed complex.

Co(II) - L-cysteine - creatinine$_2$, Zn(II) - L-cysteine - creatinine, Cd(II) - L-cysteine - creatinine, Mn(II)-L-cysteine - creatinine and Co(II) - BDHL-cysteine - creatinine, Cd(II) - BDHL-cysteine – creatinine, Zn (II) - BDHL-cysteine - creatinine$_2$, Mn (II) - BDHL-cysteine - creatinine$_2$ systems are also in agreement with our observations systems are also in agreement with our observations.

Mole fraction diagrams show that the percentage (98 %) of mixed ligand complexes formed at pH 4. It also that indicate binary ligand percentage concentration decrease as the percentage concentration of ternary complex species increases with increase in pH.

CONCLUSION

In summary, in our study we have determined the stability constants of binary and ternary complexes of creatinine and two aminoacids (L-Cysteine and BDHL-Cysteine). The conditional formation constants were calculated and these constants were found to be in agreement with the formation constants of mixed systems. Also mole fraction diagrams show the formation of ternary complexes.

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