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pH-Metric Studies of Acid-Base Equilibria on the mixed Cu(II) Complexes with Pyrazine-2,3-Dicarboxylic Acid and Amino Acids

Reda A. Ammar[1,2], *Ayman Nafady*[1,3], *Mona F. Amin*[2], *Muneerah M. Al-Mogren*[1] *and Eman M. Shoukry*[2]

[1] Department of Chemistry, Faculty of Science, King Saud University, Riyadh, Saudi Arabia
[2] Department of Chemistry, Faculty of Science, Al Azhar University, Cairo, Egypt
[3] Department of Chemistry, Faculty of Science, Sohag University, Sohag, Egypt

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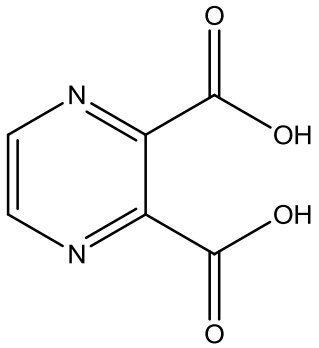
In this study, acid-base equilibria involved in the complex formation of Copper (II) ion with pyrazine-2,3-dicarboxylic acid (PDC) and amino acids (L) ligands have been determined potentiometrically in 20% (*v/v*) ethanol-water mixture, at 25 °C and an ionic strength (*I)* of 0.10 mol/L ($NaClO_4$). The relative stabilities of the ternary complexes are compared with those of the corresponding binary complexes in terms of *Δ log K* values. Importantly, the possible formation of mixed-ligand complexes by simultaneous mechanisms has been confirmed by comparison with constructed theoretical curves. Additionally, species distributions in solution for all complexes were precisely evaluated. pH-studies of these systems clearly indicate that the concentration of the ternary complexes increases with increasing pH. This behaviour attests that complex formation is more favoured in physiological pH range (6-7), whereas protonated ternary complexes become highly favourable at lower pH's.

Keywords: Stability constant, Acid-Base Equilibria, Pyrazine-2,3-dicarboxylic acid, Mixed ligand, Cu(II) complexes.

1. INTRODUCTION

Pyrazine-2,3-dicarboxylic acid (PDC), Fig.1, is an efficient N–O donors and exhibits diverse range of coordination modes[1-3]. Owing to the presence of two adjacent carboxylate groups (O donor atoms) PDC can act as a chelating and bridging ligand for different metal ions and has been the focus of extensive studies over last few decades [4-11]. In this regard metal complexes containing pyrazine-2,3-dicarboxylic acid ligand have been extensively investigated because of their wide applications and growing interest in supramolecular chemistry and material science. Examples include sodium [12], cesium [13], potassium [14], lithium [15] and rubidium [16] complexes. Binary and ternary pyrazine-

2,3-dicarboxylic acid complexes of divalent metal ions M(II) also have been reported in both solution and solid state [17-19]. Such complexes are very interesting from both the chemical and biological point of view. In the present study, equilibrium and the stability constants of mixed complexes composed of pyrazine-2,3-dicarboxylic acid and amino acids having different functional groups with Cu(II) were determined using potentiometric titration in 20% (*v/v*) ethanol-water mixture, at 25 °C and an ionic strength (*I)* of 0.1mol/L ($NaClO_4$).



Pyrazine-2,3-dicarboxylic acid

Figure 1. Chemical structure of pyrazine-2,3-dicarboxylic acid.

2. EXPERIMENTAL

2.1 Materials and Reagents

All chemicals were of guaranteed grade and used without further purification. Pyrazine-2,3-dicarboxylic acid (PDC) was obtained from Merck Company. The amino acids and related compounds (L), glycine, alanine, valine, proline *β*- phenylalanine, methionine, threonine, *S*-methylcysteine, methylamine .HCl, histidine .HCl, histamine .2HCl, penicillamine, lysine, ornithine .HCl, aspartic acid and cysteine were purchased from Sigma Chem. Co. Stock solutions of $NaClO_4$ and $HClO_4$ (analytical reagent grade, Merck) were prepared in deionized water. HClO4 was used for the preparation of the stock solutions of copper (II) to prevent hydrolysis and standardized by using standard EDTA solution [20]. The ionic strength of each solution was adjusted to 0.10 mol/L $NaClO_4$. Carbonate free NaOH (titrant) was prepared and standardized against a potassium hydrogen phthalate solution.

2.2 Apparatus

Potentiometric measurements were performed with a Metrohm 686 titroprocessor equipped with a 665 Dosimat (Switzerland-Herisau). The titroprocessor and electrode were calibrated with standard buffer solutions, prepared according to NBS specification [21]. Thus, when the titrations were performed in a 20% (*v/v*) ethanol-water mixture, the measured pH values were corrected by subtracting a value of 0.04 pH from the pH-meter readings [22, 23].

2.3 Potentiometric investigations

All solutions were virtually titrated against standard solution 0.1 mol/L of carbonate free NaOH in an atmosphere of pure N_2 gas at 25 ºC The pH-metric titrations were carried out in a 20% (*v/v*) ethanol-water mixture under ionic strength of 0.1 mol/L, adjusted with $NaClO_4$. Solutions (40 ml each) having a concentration of 1.25×10^{-3} mol/L of the primary ligand (PDC) and/or the secondary ligand (L) were utilized to determine the ligands proton constants. For the determination of the binary systems, solutions containing either the amino acids (L), or PDC and Cu(II) ion were titrated at 1:1 and 1:2 metal to ligand ratios, in addition to 2:1 for Cu(II)- PDC. The concentration of Cu(II) solutions in all binary systems was 1.25×10^{-3} to 2.50×10^{-3} mol/L. The stability constants of mixed ligand complexes were determined by titrating 40 ml Cu(II) solution, PDC, and amino acids, all having a concentration of 1.25×10^{-3} mol/L, giving rise to molar ratios of 1:1:1 at a fixed ionic strength I = 0.10 mol/L ($NaClO_4$) at 25 ◦C (thermostated). For all titrations, $HClO_4$ solution was added to ensure full protonation of ligands.

2.4 Calculations

Stability constants were calculated by the computer program HYPERQUAD [24] Trial values of the log *β's* of the ternary complexes were refined while the constants pertaining the ligand protonation and its binary Cu(II) complexation were held constant. The obtained results are shown in *Table 1*. Distribution diagrams for the various systems were calculated and plotted by HYSS program [25]. Evidently, the computed results are more precise and reliable.

3. RESULTS AND DISCUSSION

The proton dissociation constants of the studied amino acids have been re-determined by means of the data obtained from potentiometric titrations in 20% (v/v) ethanol-water, at 25 °C and ionic strength (*I)* of 0.10 mol/L $NaClO_4$ in order to obtain values under the same experimental procedures employed for binary and ternary systems. Importantly, our estimated values are in a good agreement with data reported in literature [26].

3.1 Protonation Equilibria of PDC

Only two deprotonation steps, of the four possible ones, can be determined for PDC in the fully protonated form (H_4L^{2+}) in the titrable pH range with *pKa* values of 2.72 and 3.98. The two processes are assigned to the pyrazine $–NH^+$ and the –COOH groups, respectively. The calculated acid dissociation constants, *pKa,* are in a good agreement with reported values [27]. Owing to its very high acidity, the deprotonation of the first $–NH^+$ group is not detectable. A comparison with 2-pyridinecarboxylic acid, for which the reported *pKa* values of are 1 and 5.19 [28] indicates that the presence of a second nitrogen atom in the aromatic ring significantly reduces the basicity of the $–NH^+$ group. On the other hand, the carboxylic group slightly increases the basicity of the second $–NH^+$ group with respect to pyrazine for which a p*K*a of 0.65 is reported [29].

The increase in basicity is due to the formation of a cyclic structure, which stabilizes the $–NH^+$ form through an internal hydrogen bonding between the protonated pyrazine nitrogen atom and the –COOH group. Because of the strong internal hydrogen bond between COOH and $COO^–$, one of the two carboxylic groups is protonated only at pH > 1. This effect had already been observed for 2,3-pyridinedicarboxylic [30]. Species distribution diagram for various protonated forms of the ligand is shown in Fig. 2.

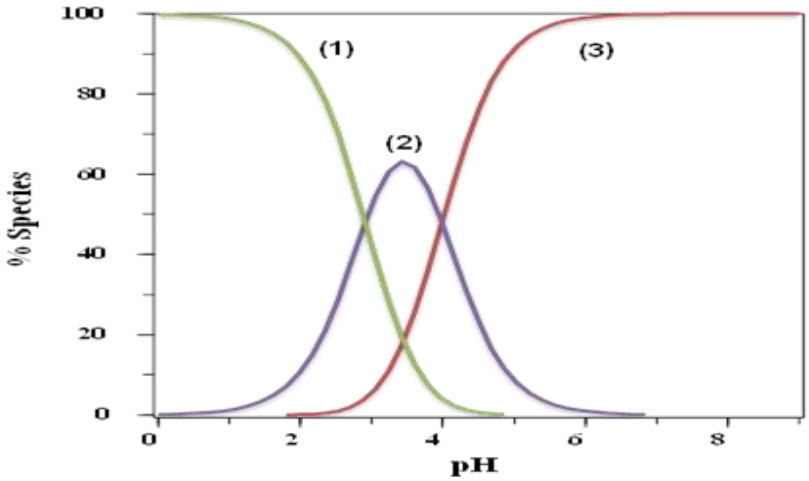


Figure 2. Species distributions as a function of pH of pyrazine-2,3-dicarboxylic acid(PDC). Species: (1) $PDCH_2$; (2) PDCH; (3) PDC.

3.2. Cu(II)-Amino Acids and Cu(II)- PDC Binary Systems

The values of the formation constants of all binary species are listed in *Table 1*. The formation constants were determined by fitting potentiometric data on the basis of possible composition models. In the binary system of (Cu(II)- PDC) the selected model with the best statistical fit was found to consist of Cu(PDC), $Cu(PDC)_2$ and $Cu_2(PDC)_2H_{-2}$ species, in which five membered chelate rings are formed by the (Npyr, COO donor set).

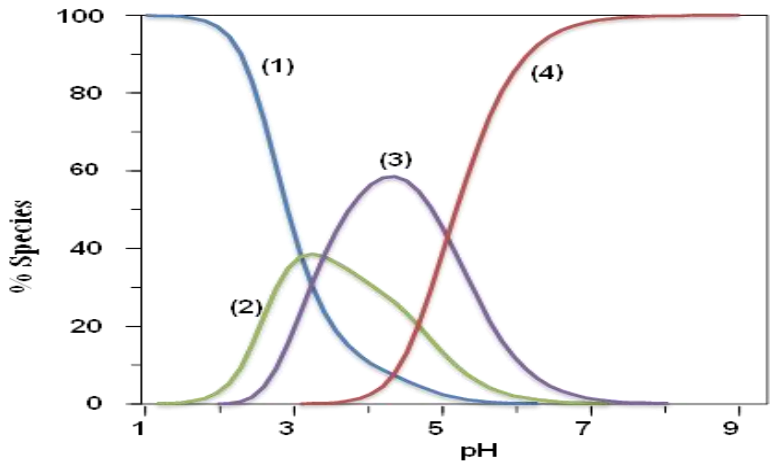


Figure 3. Species distributions as a function of pH of Cu(II)- PDC. Species: (1) Cu(II); (2) Cu(II)PDC; (3) $Cu(II)PDC_2$; (4) $Cu(II)_2PDC_2H_{-2}$.

While in case of (Cu(II)- L), the selected model was found to consist of Cu(L), $Cu(L)_2$ species. Species distribution diagram of Cu(II)- PDC system is shown in Fig. 3. The concentration of the $Cu_2(PDC)_2H_{-2}$ dimer increases in solution with increasing the pH and attains a maximum concentration of 98.68% at pH 7.5 with decreasing stability of Cu(PDC) and $Cu(PDC)_2$ species. In all Cu-L species distribution diagrams, Cu(L) species are formed early (pH around 3) due to the great affinity between Cu(II) and the amino group, which has its proton displaced in order to complexate.

Table 1. Stability constants of the ternary species in the Cu(II)-PDC-amino acid systems and proton-association constants and their binary stability constants at 25°C and 0.1 mol/L ionic strength.

System	*l*	*p*	*q*	r^a	log β^b	Δ log K
pyrazine-2,3-dicarboxylic	0	1	0	1	3.98(0.01)	
acid	0	1	0	2	6.70(0.02)	
	1	1	0	0	4.92(0.02)	
	1	2	0	0	9.64(0.01)	
	2	2	0	-2	1.79(0.04)	
Glycine	0	0	1	1	9.32(0.02)	
	0	0	1	2	11.60(0.01)	
	1	0	1	0	8.11(0.02)	
	1	0	2	0	15.07(0.03)	
	1	1	1	0	12.66(0.04)	-0.37
Alanine	0	0	1	1	9.33(0.01)	
	0	0	1	2	11.70(0.02)	
	1	0	1	0	8.00(0.03)	
	1	0	2	0	14.64(0.01)	
	1	1	1	0	12.54(0.02)	-0.38
Valine	0	0	1	1	9.39(0.02)	
	0	0	1	2	11.65(0.01)	
	1	0	1	0	8.16(0.02)	
	1	0	2	0	14.99(0.02)	
	1	1	1	0	12.23(0.01)	-0.85
β-phenylalanine	0	0	1	1	9.00(0.01)	
	0	0	1	2	11.04(0.03)	
	1	0	1	0	7.86(0.01)	
	1	0	2	0	14.85(0.01)	
	1	1	1	0	12.16(0.01)	-0.62
Proline	0	0	1	1	10.29(0.00)	
	0	0	1	2	12.09(0.03)	
	1	0	1	0	8.74(0.02)	
	1	0	2	0	14.45(0.05)	
	1	1	1	0	12.97(0.02)	-0.69
Methylamine	0	0	1	1	10.42(0.01)	
	1	0	1	0	6.67(0.02)	
	1	0	2	0	11.66 (0.05)	
	1	1	1	0	8.11(0.02)	
	1	1	2	0	11.21(0.05)	-0.38

Table 1. (Continued)

System	*l*	*p*	*q*	r^a	log β^b	Δ log K
Threonine	0	0	1	1	9.01(0.01)	
	0	0	1	2	11.12(0.02)	
	1	0	1	0	8.22(0.01)	
	1	0	2	0	14.90(0.02)	
	1	1	1	0	12.02(0.02)	-1.21
	1	1	1	-1	4.20(0.01)	
Aspartic acid	0	1	0	1	9.71(0.01)	
	0	1	0	2	13.06(0.02)	
	1	0	1	0	8.65(0.03)	
	1	0	2	0	15.34(0.02)	
	1	1	1	0	12.87(0.01)	-0.70
S-methylcysteine	0	0	1	1	8.31(0.01)	
	0	0	1	2	11.40(0.02)	
	1	0	1	0	8.85(0.02)	
	1	1	1	0	12.34(0.02)	-1.43
Methionine	0	0	1	1	9.06(0.01)	
	0	0	1	2	11.32(0.04)	
	1	0	1	0	8.86(0.01)	
	1	0	2	0	14.60(0.01)	
	1	1	1	0	12.77(0.02)	-1.01
Ornithine	0	0	1	1	10.32(0.02)	
	0	0	1	2	19.10(0.02)	
	1	0	1	3	21.39(0.02)	
	1	0	1	0	11.90(0.05)	
	1	0	2	0	16.30(0.06)	
	1	1	1	0	16.23(0.02)	-0.59
	1	1	1	1	24.10(0.02)	
Histamine	0	0	1	1	9.71(0.01)	
	0	0	1	2	15.62(0.05)	
	1	0	1	0	10.52(0.02)	
	1	0	2	0	17.56(0.01)	
	1	1	1	0	14.97(0.01)	-0.47
	1	1	1	1	21.51(0.01)	
Histidine	0	0	1	1	9.56(0.01)	
	0	0	1	2	15.21(0.03)	
	1	0	1	0	10.89(0.01)	
	1	0	2	0	18.23(0.04)	
	1	1	1	0	15.56(0.03)	-0.25
	1	1	1	1	20.44(0.01)	

Table 1. (Continued)

System	*l*	*p*	*q*	r^a	log β^b	Δ log K
Lysine	0	0	1	1	10.23(0.01)	
	0	0	1	2	18.41(0.01)	
	1	0	1	0	10.81(0.05)	
	1	0	2	0	18.89(0.07)	
	1	1	1	0	14.61(0.03)	-1.12
Pencillamine	0	0	1	1	10.15(0.01)	1.06
	0	0	1	2	16.78(0.02)	
	1	0	1	0	11.45(0.03)	
	1	0	2	0	19.52(0.05)	
	1	1	1	0	17.43(0.04)	
	1	1	1	1	21.88(0.01)	
Cysteine	0	0	1	1	9.52(0.01)	
	0	0	1	2	17.73(0.03)	
	1	0	1	0	8.98(0.03)	
	1	0	2	0	17.03(0.04)	
	1	1	1	0	17.33(0.01)	3.43
	1	1	1	1	20.74(0.07)	

[a] *l*, *p* and *q* are the stoichiometric coefficient corresponding to Cu(II), PDC (or amino acids) and H^+, respectively. [b] standard deviations are given in parentheses.

3.3 Equilibria Associated with Formation of Ternary Complex

The stability constants β_{lpqr} of a generalized complex species was defined as follows (charges are omitted for simplicity)

$$_l(Cu) + p(PDC) + q(L) + r\,(H) \rightleftharpoons (Cu)_l\,(PDC)_p\,(L)_q\,(H)_r \quad (1)$$

$$\beta_{_{lpqr}} = \frac{[Cu_l\,(PDC)_p\,(L)_q\,(H)_r]}{\left[Cu^l\,(PDC)^p\,(L)^q\,(H)^r\right]} \quad (2)$$

The complexes species are simply referred to as the combination of *lpqr* and the formation constant is expressed as β_{lpqr}.

The titration data of the ternary complexes with amino acids (L) and PDC fit satisfactorily with formation of the species: Cu(PDC), $Cu(PDC)_2$, $Cu_2(PDC)_2H_{-2}$, Cu(L), $Cu(L)_2$, Cu(PDC)(L) and Cu(PDC)(LH). The formation of mixed-ligand complex by simultaneous mechanisms may be confirmed by comparing the theoretical curve, conducted based on the calculated formation constants and the experimental titration data points as shown in Fig. 4 for the glycine system, taken as a representative example. The good fit obtained is indicative of the validity of the complex formation model. Amino acids form 1110 complexes but methylamine forms 1110 and 1120 complexes (*Table*

1). The methylamine complex (1110) is less stable than those of amino acids. This indicates that amino acids function as bidentate ligands coordinating through the amino and carboxylate groups.

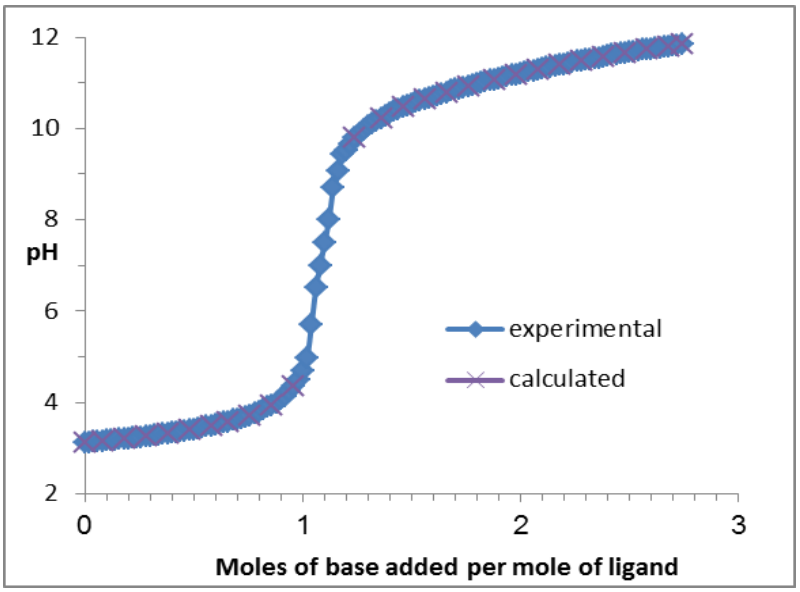


Figure 4. Potentiometric titration curves of Cu(II) –A- glycine system.

Threonine forms, in addition to the Cu(PDC)(L) complex, the Cu(PDC)(LH_{-1}) species. The latter complex is formed through induced ionization of the *β*-alcohol group as mentioned in the literature [31]. Aspartic acid has two carboxylic and one amino group as potential chelating centers. It may coordinate either *via* the two carboxylate groups or by the amino and one carboxylate group. Interestingly, the stability constant of the aspartic acid complex is within the range of those for simple amino acids. This finding may imply that aspartic acid coordinates *via* the amino and one carboxylate group only rather than the two carboxylate groups. By way of similarity, ornithine has two amino and one carboxylic group. Its stability constant is higher than those of amino acids, thereby indicating that binding of ornithine case most likely to occur *via* the two amino groups. However, our results clearly show that ornithine forms in addition to the 110 complex, the 111 species.

Unlike ornithine, the stability constant of the complex, Cu-PDC-lysine, is in fair agreement with those of *α*-amino acids. This may be taken to indicate that lysine most likely chelates through the *α*-amino and carboxylate groups, as chelates formed through binding with the two amino groups will form strained eight-membered rings. The stability constant value of the histidine complex is higher than that of α-amino acids and close to that of histamine (*Table 1*). This indicates that histidine is coordinating in a histamine-like way.

Computer analysis of the pH-titration data revealed the formation of the ternary complexes with thiol-containing ligands as penicillamine and cysteine, Cu(PDC)L and the corresponding protonated species Cu(PDC)LH. The acid dissociation constants of the protonated ternary complex ($log\ \beta_{1111} - log\ \beta_{1110}$) obtained with penicillamine and cysteine are 4.45 and 3.41 respectively. The fact that the values obtained in this study are less than those reported previously [32] implies that the $[-NH_3]^+$ and –SH groups are most likely to take part in complex formation.

3.4 Effect of pH on equilibrium concentrations of copper (II) complexes

Estimation of equilibrium concentrations of copper (II) complexes as a function of pH provides a useful picture of metal ion binding in biological systems. In all of the species distributions, the concentration of the ternary complexes increases with increasing pH, thereby making complex formation more favoured in physiological pH range. Protonated ternary complex species have been found to be highly favoured at lower pH values.

The parameter Δ *log K* values are generally used to indicate the relative stability of the ternary complexes as compared to the binary ones as in equations:

$$Cu(PDC) + Cu(L) \rightleftharpoons Cu(PDC)(L) + Cu$$

$$\Delta \log K = \log K^{Cu(PDC)}_{Cu(PDC)L} - (\log K^{Cu}_{Cu(PDC)} + \log K^{Cu}_{Cu(L)})$$

Δ log *K* for distorted octahedral complexes has been calculated to be negative and equal to -0.9. The *Δ* log *K* values, Table (1), are invariably negative. This means that the amino acid forms more stable complex with free Cu(II) ion than with the Cu–PDC complex. This is expected statistically since more coordination positions are available for binding the secondary ligand by Cu(II) ion than Cu–DCP complex. Positive values are considered as evidence of enhanced stability as a result of intermolecular ligand–ligand interactions, hydrogen bonding, the *π*-back donation effect, and/or hydrophobic effects.

4. CONCLUSION

In summary, the present investigation describes the formation equilibria of copper (II), pyrazine-2,3-dicarboxylic acid (PDC), and amino acids. The stability constants of complexes were determined potentiometrically in 20 % (*v/v*) ethanol-water media at 25 ºC having ionic strength of 0.10 mol/L $NaClO_4$. The relative stabilities of the ternary complexes are compared with those of the corresponding binary complexes and explained in view of their *Δ* log *K* values. Finally, species distributions in solution for all complexes were also evaluated. It is concluded that the concentration of the ternary complexes increases with increasing pH, signaling the possibility that complex formation is more favoured in physiological pH range, whereas protonated ternary complexes are found to be highly favoured at lower pH's.

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