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Stability of binary and ternary copper (II) complexes of 2((4-methyl-5-nitro-6-(pyrrolidine-1-yl)pyrimidine-2-yl)amino) propionic acid in aqueous solution

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Abstract. The acidity and stability constants of M (MNPPAP) (MNPPAP: 2((4-methyl-5-nitro-6-(pyrrolidine-1-yl)pyrimidine-2-yl)amino)propionic acid) M: Cu^{2+}, Cu $(Bpy)^{2+}$ (Bpy: 2,2′-Bipyridine), or $Cu(Phen)^{2+}$ (Phen: 1,10-Phenanthroline) complexes were determined by potentiometric pH titration. It is shown that the stability of the binary Cu (MNPPAP) complex is determined by the basicity of the carboxylate group on one side and amine group on the other side. It is demonstrated that the equilibrium, $Cu(Har)^{2+}$ (Har: Heteroaromatic ligand such as Bpy or Phen) + Cu(MNPPAP) $\rightleftharpoons$ Cu(Har)(MNPPAP) + Cu^{2+}, is displacement due to the well known experience that mixed ligand complexes formed by a divalent 3d ion, a heteroaromatic N base, and an O donor ligand possessing increased stability. The other part of this displacement amounts, on average, to no increased stability of the mixed ligand Cu (Bpy)(MNPPAP) and Cu(Phen)(MNPPAP) complexes. The stability constants were determined by potentiometric pH titration in aqueous solution. The order of the stability constants was reported. A comparative investigation between ternary complexes of MNPPAP, Trp (Trp: L-Tryptophan) and Gly (Gly: Glycine) is made. The comparison of stability constants of these ternary complexes show that Cu (Har) (MNPPAP) and Cu (Har) (Gly) exist in open form, but Cu (Har)(Trp) is found near 100% in closed form. The differences between the above mentioned stability constants are based on stacked form of Cu (Har) (Trp), and provide increased stability compared with Cu (Har)(MNPPAP).

1. Introduction

Peptides interact with metal ions primarily through side chain functional groups, although there are many examples of peptide amide nitrogens functioning as donor atoms with certain metal ions. Many physiologically important peptides function as metal complexes [1,2]. The chemical structure of MNPPAP is shown in Figure 1. MNPPAP contains identical chemical structure like amino acids, so that we expect similar chemical properties [3].

Among the side chains of amino acids, the indole moiety is the most potent electron donor [4]. Indeed, charge-transfer-type interactions between tryptophan or other indole derivatives and nucleosides or nucleotides occur in aqueous solution [5-9]. Based on the above mentioned essential role of amino acids, it is interesting to study the interaction of other metal ions with MNPPAP. Because of the essential roles of

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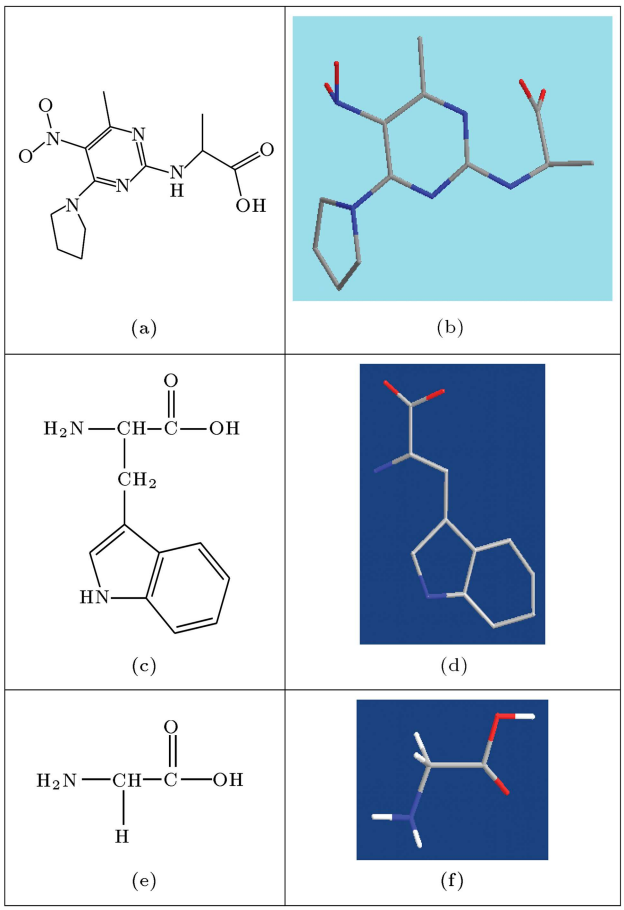

Figure 1. Chemical formula of MNPPAP (a,b), L-Tryptophan (c,d) and Glycine (e,f).

amino acids in biological systems, it is important to investigate their interactions with different ternary metal ion complexes and the regarding complex binding.

The importance of noncovalent interactions for the shape of macromolecules, and the selectivity in natural system are generally accepted, and especially hydrophobic and stacking interactions have been considered in mixed ligand complexes [8-10].

It is interesting to investigate the complex building of ternary systems with MNPPAP. We would like to determine the thermodynamic constants of ternary complexes such as Cu(Har)(MNPPAP).

2. Experimental

2.1. Materials

Copper(II) nitrate trihydrated, sodium nitrate, potassium hydrogen phthalate and standard solutions of sodium hydroxide (titrasol), 2,2′-bipyridyl, 1,10-phenanthroline, nitric acid, EDTA and the buffer solutions of pH 4.0, 7.0 and 9.0 were purchased from Merck company, Darmstadt. MNPPAP was prepared by Bagherzadeh [10] whose purification was carried out carefully and was about 98%. All the starting materials were pro analysis and used without further purification. Water was purified by Mili-Q water purification system, deionized and distillated.

2.2. pH titrations

Reagents: Carbonate-free sodium hydroxide 0.03 M was preparated and standardized against sodium hydrogen phthalate and a standard solution of nitric acid 0.5 mM. Copper (II) nitrate solution (0.03 M) was prepared in water and calibrated with standard solution of EDTA 0.1 M (triplex).

2.3. Apparatus

All pH titrations were performed using a Metrohm 794 basic automatic titrator (Titrino), coupled with a Hero thermostating bath at 25°C (±0.1°C) and a Metrohm combined glass electrode (Ag/AgCl). The pH meter was calibrated with Merck standard buffer solutions (4.0, 7.0 and 9.0).

2.4. Procedure

For the determination of acid dissociation constants of the ligand MNPPAP, an aqueous solution (0.3 mM) of the protonated ligand was titrated with 0.03 M NaOH at 25°C under nitrogen atmosphere and ionic strength of 0.1 M, $NaNO_3$. For the determination of binary (one ligand and Cu^{2+}) and ternary systems (Cu^{2+}, one of the other L ligand (Har) and MNPPAP), the ratios used were 1:1:1, Cu (II): MNPPAP: Har, 0.3 mM. This solution was titrated with 0.03 M NaOH under the same conditions mentioned above. Each titration was repeated seven times in order to check the reproducibility of the data (Figure 2).

2.5. Calculation

The acid dissociation constants, $K^{H}_{H_2(\mathrm{MNPPAP})}$ and $K^{H}_{H(\mathrm{MNPPAP})}$ for H_2(MNPPAP) were calculated by an algebraic method [11,12]. The equilibria involved in the

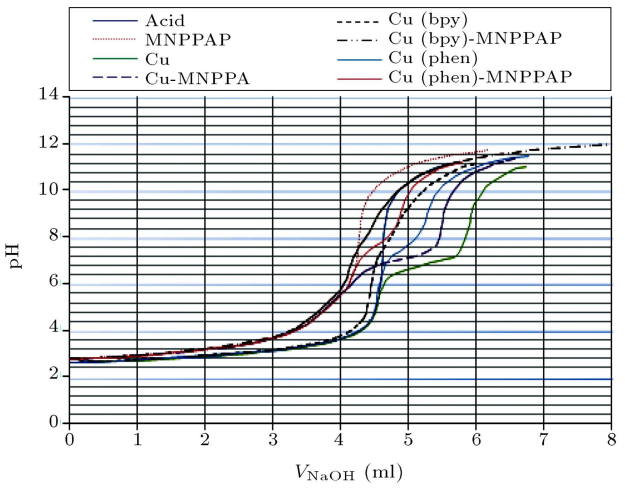

Figure 2. pH titration of acid, MNPPAP, Cu, Cu(MNPPAP), Cu(Bpy), Cu(Bpy)(MNPPAP), Cu(Phen), Cu(Phen)(MNPPAP).

formation of 1:1 complex of MNPPAP and a divalent metal ion will be discussed below.

The stability constants $K^{M}_{M(\mathrm{MNPPAP})}$ for the metal ions M^{2+} complexes were calculated with a computer connected to a printer for each pair of titrations by taking into account the species H^{+}, H_2(MNPPAP), H(MNPPAP)$^{-}$, MNPPAP^{2-}, M^{2+}, and M(MNPPAP). Throughout, the data were collected (every 0.1 pH unite) from about 10% complex formation to a neutralization degree of about 90% or the beginning of the hydrolysis of $M^{2+}_{(aq)}$, the latter was evident from the titration without MNPPAP. The values calculated individually for $K^{M}_{M(\mathrm{MNPPAP})}$ showed no dependence on pH or on the excess amount of M^{2+}.

2.5.1. Acidity constants

MNPPAP can accept one proton on carboxalate group for which the deprotonation equilibriums reads:

$$\mathrm{H_2(MNPPAP)} \leftrightharpoons \mathrm{H^{+} + H(MNPPAP)^{-}}, \tag{1a}$$

$$K^{H}_{H_2(\mathrm{MNPPAP})} = [\mathrm{H(MNPPAP)^{-}}][\mathrm{H^{+}}] / [\mathrm{H_2(MNPPAP)}]. \tag{1b}$$

MNPPAP can release one other proton from amine group according to the deprotonation equilibrium:

$$\mathrm{H(MNPPAP)^{-}} \leftrightharpoons \mathrm{H^{+} + MNPPAP^{2-}}, \tag{2a}$$

$$K^{H}_{H(\mathrm{MNPPAP})} = [\mathrm{MNPPAP^{2-}}][\mathrm{H^{+}}] / [\mathrm{H(MNPPAP)^{-}}]. \tag{2b}$$

Also the two protons in H_2(MNPPAP) are certainly bound at the terminal acetate group and amine group, i.e. it is released from -CO_2H or -NH- according to equilibriums (1) and (2). These values are as accepted, close to the pK_a values of -CO_2H which is 2.92 [8].

2.5.2. Stability of binary and ternary complexes

If we abbreviate for simplicity Cu^{2+}, Cu(Bpy)$^{2+}$, and Cu(Phen)$^{2+}$ with M^{2+}, one may write the following two equilibriums:

$$\mathrm{M^{2+} + H(MNPPAP)^{-}} \leftrightharpoons \mathrm{M(H;MNPPAP)^{+}}, \tag{3a}$$

$$K^{M}_{M(H;\mathrm{MNPPAP})} = [\mathrm{M(H;MNPPAP)^{+}}] / [\mathrm{M^{2+}}][\mathrm{H(MNPPAP)^{-}}], \tag{3b}$$

$$\mathrm{M^{2+} + (MNPPAP)^{2-}} \leftrightharpoons \mathrm{M(MNPPAP)}, \tag{4a}$$

$$K^{M}_{M(\mathrm{MNPPAP})} = [\mathrm{M(MNPPAP)}] / [\mathrm{M^{2+}}][\mathrm{MNPPAP^{2-}}]. \tag{4b}$$

The experimental data of the potentiometric pH titrations may be analyzed by considering the above mentioned equilibriums (1) through (4), if the evaluation is not carried into the pH range where hyrdroxide complex formation occurs.

The stability of ternary complexes may be evaluated by the equilibrium:

$$\mathrm{mA + nB + qM + rH} \leftrightharpoons \mathrm{A_mB_nM_qH_r}, \tag{5a}$$

where M is the metal ion, H is the proton, A and B are the ligands. The global stability constants for the ternary complexes may be represented as following:

$$\log \beta_{\mathrm{pqrs}} = [\mathrm{A_mB_nM_qH_r}] / [\mathrm{A}]^{\mathrm{m}}[\mathrm{B}]^{\mathrm{n}}[\mathrm{M}]^{\mathrm{q}}[\mathrm{H}]^{\mathrm{r}}. \tag{5b}$$

It is possible to define the stability constants for ternary complexes in relation to their binary ones [9], represented by:

$$\mathrm{M + L_1} \leftrightharpoons \mathrm{ML_1}, \tag{6a}$$

$$K^{M}_{M(L_1)} = [\mathrm{ML_1}] / [\mathrm{M}][\mathrm{L_1}], \tag{6b}$$

$$\mathrm{ML_1 + L_2} \leftrightharpoons \mathrm{ML_1L_2}, \tag{7a}$$

$$K^{M}_{M(L_1L_2)} = [\mathrm{ML_1L_2}] / [\mathrm{ML_1}][\mathrm{L_2}]. \tag{7b}$$

Differences between the stability constants of the ternary and binary complexes show the tendency of the formation of ternary species [10]. This could be expected by Eq. (8):

$$\Delta \log K = \log K^{ML_1}_{M(L_1L_2)} - \log K^{M}_{M(L_2)}, = \log K^{ML_2}_{M(L_1L_2)} - \log K^{M}_{M(L_1)}. \tag{8}$$

The difference between the constant obtained from experimental data and those calculated statistically using Eq. (8) indicates the possibility of ligand-ligand interaction.

3. Results and discussion

3.1. Potentiometric analyses

The model of species for these ternary systems that was used in superquad program includes all the species of Table 1 as well as the hydrolysis of Cu^{2+} [11,12]. The stability constants of the binary complexes were refined separately using the titration data of this system in a 1:1 and 1:2 ligand: Cu^{2+} ratio in the same conditions of temperature and ionic strength. They were fixed and, consequently, only ternary species were refined in ternary model of the species. The results are summarized in Table 1 and Figure 2.

As we can use from Figure 2, the first and second curves belong to acid and ligand (MNPPAP). The

Table 1. Logarithm of the stability constants of binary and ternary complexes of M^{2+} at 25°C, 0.1 M, $NaNO_3^*$.

$pK^H_{H_2(\mathrm{Trp})} = 2.22 \pm 0.08$	$pK^H_{H(\mathrm{Trp})} = 9.14 \pm 0.03$
$pK^H_{H_2(\mathrm{Gly})} = 2.49 \pm 0.08$	$pK^H_{H(\mathrm{Gly})} = 9.36 \pm 0.03$
$pK^H_{H_2(\mathrm{MNPPAP})} = 2.92 \pm 0.04$	$pK^H_{H(\mathrm{MNPPAP})} = 5.15 \pm 0.02$

No.	Species	$\log K^a$	$\Delta \log K^b$	Ref.
1	Cu(Trp)	8.05 ± 0.05	–	[13]
2	Cu(Bpy)(Trp)	9.02 ± 0.06	0.97 ± 0.08	–
3	Cu(Phen)(Trp)	9.36 ± 0.08	1.31 ± 0.09	–
4	Cu(Gly)	7.06 ± 0.08	–	[14]
5	Cu(Bpy)(Gly)	5.95 ± 0.08	-1.11 ± 0.11	[14]
6	Cu(Phen)(Gly)	6.12 ± 0.07	-0.94 ± 0.11	[14]
7	Cu(MNPPAP)	3.40 ± 0.03	–	[15]
8	Cu(Bpy)(MNPPAP)	3.57 ± 0.08	0.17 ± 0.09	–
9	Cu(Phen)(MNPPAP)	3.33 ± 0.08	-0.07 ± 0.09	–

*: The given errors are three times the standard error of the mean value or the sum of the propabable systematic errors;

a: according to Eq. (4);

b: according to Eq. (8).

comparison of these both curves shows the delayed deprotonation of ligand. The buffer depression of the ligand-curve is higher than acid curve. This means that the basicity of ligand in this region is much higher than acid. The regarding calculation of this difference provides us with the acidity constants of the ligand. The third curve represents the titration of copper (II) ion and as we can see, the formation of hydroxo complex is distinguishable when pH $>$ 5.5. This means for us, that the received data upper than 5.5 cannot use for the calculation of the stability constants. The fourth curve shows the titration of copper (II) in present of ligand. This means that the interaction between copper (II) ion and ligand can take place when pH $<$ 5.5. Also similar to the last case, the fifth and seventh curves show the titration of $Cu(bpy)^{2+}$ and $Cu(phen)^{2+}$ without ligands. Identical to the third curve, the formation of hyroxo complex takes place when pH $>$ 5.5. The sixth and eighth curves show the titration of $Cu(bpy)^{2+}$ and $Cu(phen)^{2+}$ in the presence of ligand (MNPPAP). The interaction between two systems $Cu(bpy)^{2+}$ and $Cu(phen)^{2+}$ with ligand for the formation of ternary complexes is considered when pH $<$ 5.5. The received data in this region is summarized and calculated for determination of complex stability constants (Section 2.5). The last mentioned constants represent the thermodynamic data of inter- and intramolecular interaction in these ternary complexes.

The order of the resulted stability constants are $Cu^{2+} < Cu(Bpy)^{2+} < Cu(Phen)^{2+}$ for Trp and $Cu^{2+} \approx Cu(Bpy)^{2+} \approx Cu(Phen)^{2+}$ for MNPPAP. Figure 3 shows schematic structures of the species with interactions according to equilibrium relationships (4) and (7) for Cu(Phen)(Trp). The difference between stability

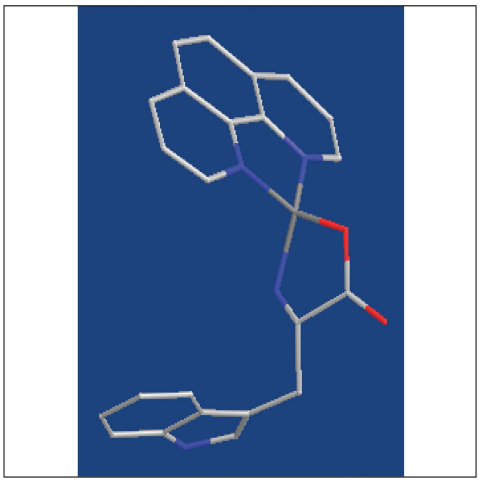

Figure 3. Schematic structures of the species with interactions according to equilibrium relationships (4) and (7) for Cu(Phen)(Trp). The structure in the right part of the figure was drawn with the program CS Chem 3D, version 3.5, from Cambridge Software Corporation.

constants according to Eq. (8) show that mixed ligand complexes [16-19] formed by a divalent 3d ion, a heteroaromatic N base and an O donor ligand possess increased stability. It has to be further emphasized that the basicity of the carboxylate group in aqueous solution is very low and consequently this also applies to the coordinating properties of this group.

Comparison of the stability constants for the Cu(Bpy)(MNPPAP) and Cu(Phen)(MNPPAP) complexes in Table 1 with the corresponding values for Cu(MNPPAP) indicates no increased stability of the mixed-ligand species. It is well known for a number of Cu(Har)(L) complexes that there is no in-

tramolecular stack between the aromatic ring systems of 2,2′-Bipyridine and 1,10-phenanthroline and the heteroaromatic ring of MNPPAP (opened form ↔ closed form) [10]. The difference between the above mentioned constants, if exists, demostrates the experimentally ligand-ligand stack interaction in the Cu(Har)(MNPPAP) complexes.

As seen from the experimentally results from Table 1, there is no increased stability constants in case of Cu(Har)(Gly), meaning that there is no indication of intramolecular stack interactions. For this reason, we can use the stability constants of Cu(Har)(Gly) as opened form in our next calculations.

By employing Eq. (8), the following definition may be adopted:

$$\begin{aligned}\Delta\Delta \log \mathrm{K} =& \Delta \log \mathrm{K_{cl}} - \Delta \log \mathrm{K_{op}} \\ =& \Delta \log \mathrm{K_{Cu(Phen)(MNPPAP)}} \\ & - \Delta \log \mathrm{K_{Cu(Phen)(Gly)}},\end{aligned} \tag{9}$$

where cl represents the closed form of Cu(Phen)(MNPPAP), and op stands for the open form of Cu(Phen)(MNPPAP).

It is evident that the coordination spheres of Cu^{2+} ions on both sides of this equilibrium are identical, consequently the value for $\Delta\Delta$ logK is a true reflection of the extent of the intramolecular hydrophobic or stacking interaction in Cu(Har)(MNPPAP) complexes. The corresponding results are listed in the fourth column of Table 2.

Now we can define the intramolecular and thus dimensionless equilibrium constant K_I which for the open and closed forms is given by

$$\mathrm{K}_I = [\mathrm{Cu(Phen)(L)}]_{\mathrm{cl}}/[\mathrm{Cu(Phen)(L)}]_{\mathrm{op}}. \tag{10}$$

The observed increased complex stability is linked to K_I by:

$$\mathrm{K}_I = 10^{\Delta\Delta \log K} - 1. \tag{11}$$

Knowledge of K_I allows calculation of percentage of the macrochelated form according to [10]:

$$\%\mathrm{Cu(Har)(L)} = 100 * \mathrm{K}_I/(1 + \mathrm{K}_I). \tag{12}$$

The results of the calculations of the above mentioned equations are summarized in Table 2.

Comparison of the percentage of the macrochelated form, according to Eq. (12), in Table 2 shows the high stacking tendency of Trp based on heteroaromatic structure of indole moiety [5].

The distinctive structural characteristic of tryptophan is that it contains an indole functional group. It is an essential amino acid as demonstrated by its growth effects on rats [2,3]. Now it is interesting to investigate the complex building of ternary systems with Trp. The comparison of stability constants of these ternary complexes show that Cu(Har)(Gly) exists in open form but Cu(Har)(Trp) is found near 100% in closed form (the last column in Table 2). The differences between the stability constants are based on evidence of no stacked form of Cu(Har)(MNPPAP). Based on the structural properties of MNPPAP, there is evidently no possibility for intramolecular interactions referred to as the stack in Cu(Har)(MNPPAP). The reported results in Table 2 provide evidence for this conclusion.

This is interesting, because the ternary complexes of Trp indicate activity in biological systems. This might be used, for example in the case of cell separation. The inhibition of DNA cleavage and blocking of cell divisions can be influenced by strong stack building of Har and Trp with nucleotide bases.

4. Conclusion

MNPPAP contains identical chemical structure like amino acids, so that we expect similar chemical prop-

Table 2. Extent of intramolecular stack formation in ternary Cu(Har)(L) complexes as calculated from stability constants (Eq. (7)). Intramolecular and dimensionless equilibrium constant K_I (Eq. (11)) and percentage of stacked $\mathrm{Cu(Har)(L)_{cl}}$ species (Eq. (12)) in aqueous solution at 25°C, 0.1 M, $NaNO_3^*$.

No.	Species[a]	$\Delta \log \mathrm{K}$[b]	$\Delta\Delta \log \mathrm{K}$[c]	K_I[d]	$\%\mathrm{Cu(Har)(L)_{cl}}$[e]
1	Cu(Bpy)(Trp)	0.97 ± 0.08	2.08 ± 0.14	119.23 ± 38.76	99.17 ± 0.27
2	Cu(Phen)(Trp)	1.31 ± 0.09	2.25 ± 0.14	176.83 ± 57.34	99.44 ± 0.18
3	Cu(Bpy)(Gly)	-1.11 ± 0.11	–	–	–
4	Cu(Phen)(Gly)	-0.94 ± 0.11	–	–	–
5	Cu(Bpy)(MNPPAP)	0.17 ± 0.09	–	–	–
6	Cu(Phen)(MNPPAP)	-0.07 ± 0.09	–	–	–

*: The given errors are three times the standard error of the mean value or the sum of the propabable systematic errors.

[a]: From Table 1; [b]: According to Eq. (8); [c]: According to Eq. (9);

[d]: According to Eq. (11); [e]: According to Eq. (12).

erties. In contrast to amino acids, MNPPAP contains a secondary amine group. Secondary amine groups are normally inhibited groups for easy coordination. On the other hand, it is possible that a metal ion simultaneously coordinates to carboxyl group and the N(3) pyrimidine ring, thus forming a macrochelate.

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