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Ternary Complexes in Solution: Complex Formation Between Copper(II), Zinc(II), Cadmium(II) and Ligands of Biological Importance

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The stability constants of ternary complexes of the *MAL* type have been determined for Cu(II), Zn(II) and Cd(II). The ligands chosen for this study belong to the biologically important ones viz. Bipyridyl (*A*) and Nitrilotriacetic acid (*L*). Log K_{MAL} values for Cu(II), Zn(II) and Cd(II) are 11.42, 10.67 and 9.72, respectively, at temp. = 25 °C and $\mu = 0.1\,M$ (KNO_3); the order is discussed.

(Keywords: Bipyridyl; Complex stabilities; Nitrilotriacetic acid)

Ternäre Komplexe in Lösung: Die Komplexbildung zwischen Kupfer(II), Zink(II) und Kadmium(II) mit Liganden von biologischem Interesse

Die Stabilitätskonstanten für Cu(II)-, Zn(II)- und Cd(II)-Komplexe vom Typ *MAL* wurden bestimmt. Die biologisch relevanten Liganden, die für diese Untersuchung ausgewählt wurden, waren Bipyridyl (*A*) und Nitrilotriessigsäure (*L*). Bei einer Temperatur von 25 °C und $\mu = 0{,}1\,M$ (KNO_3) sind die entsprechenden log K_{MAL}-Werte für Cu(II), Zn(II) und Cd(II) 11,42, 10,67 und 9,72; diese Reihenfolge wird ebenfalls diskutiert.

Introduction

It is known that 2-2′ bipyridyl (*bipy*) (*A*) and nitrilotriacetic acid (*NTA*) (*L*) are chelating agents and both of them have been reported to be biologically active either alone or in presence of metal ions[1].

In literature one finds few reports[2,3] on mixed ligand complexes of metal ions containing ligands which together have more than four donor sites grouped around the metal ion. It has been found that increasing the

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number of donor sites makes it difficult to determine the coordination level from evaluation of stability constants alone. Recently, *McBryde*[4] has critically reviewed the work on the evaluation of equilibrium constants of metal complexes of 2,2′ bipyridyl and other related ligands of biological importance. *Sarkar* et al.[5–7] found that the exchangeable portion of Cu(II) in blood plasma occurs mainly as a result of mixed ligand formation. These systems are becoming objects of attention because they can be taken as models for biological systems, provided there exists the prevalent number of polydentate ligands in biological fluids. Interesting observations have been made by *Sigel*[8] about the influence of primary ligands like bipyridyl which possess the capability of forming π-bonds with metals, provided the second ligand has oxygen donor sites.

These reasons prompted us to investigate the equilibria operative in the binary (1 : 1) and in the ternary (1 : 1 : 1) complexes of bipyridyl and *NTA* with Cu(II), Cd(II) and Zn(II). The equilibrium constants or rather the stability constants have been determined by potentiometric titration at temp. $= 25 \pm 0.2\,°C$, and $\mu = 0.1\,M$ (KNO_3).

Experimental

Materials

Reagent grade bipyridyl (*A*) was obtained from E. Merck and a stock solution of $5 \cdot 10^{-3}\,M$ of the same was prepared by direct weighing. Reagent grade nitrilo triacetic acid (*L*) was obtained from Hopkin and Williams Ltd. England. A stock solution of $5 \cdot 10^{-3}\,M$ strength was prepared and standardised potentiometrically against freshly prepared carbonate-free sodium hydroxide solution. The metal ion solutions were prepared from AnalaR Grade nitrates and standardised by conventional complexometric titration methods. AnalaR grade potassium nitrate was used for maintaining a ionic strength of 0.1 *M*.

Apparatus

A Toshniwal expanded scale *pH* metre Model A Type C1–44 and an Elico Digital *pH* meter Model LI-120 were used for *pH*-metric titrations. The titrations were carried out in a double-walled reactor kept at $25 \pm 0.2\,°C$ by circulation of water from a thermostated bath. A microburette provided with a sodalime tube was used for addition of carbonate-free NaOH solution into the reactor.

Procedure

Titrations against NaOH solutions were performed against the following solutions:

i) $10\,ml\ 5.0 \cdot 10^{-3}\,M$ *NTA* $+ 10\,ml\ 0.4\,M\ KNO_3 + 20\,ml\ H_2O$
ii) $10\,ml\ 5.0 \cdot 10^{-3}\,M$ Bipyridyl $+ 10\,ml\ 5.0 \cdot 10^{-3}\,M\ M(II) +$
   $+ 10\,ml\ 0.4\,M\ KNO_3 + 10\,ml\ H_2O$
iii) $10\,ml\ 5.0 \cdot 10^{-3}\,M$ Bipyridyl $+ 10\,ml\ 5.0 \cdot 10^{-3}\,M\ M(II) +$
   $+ 10\,ml\ 5.0 \cdot 10^{-3}\,M$ *NTA* $+ 10\,ml\ 0.4\,M\ KNO_3$

M(II) represents the metal ions viz. Zn^{2+}, Cd^{2+} and Cu^{2+}.

Calculations

It is assumed, for convenience, that complexation of the secondary ligand L starts after the complete formation of the M(II)-*Bipy* 1 : 1 complex denoted by MA^{2+}. The equilibrium involved in the mixed ligand complex formation for the 1 : 1 : 1 complex may be represented by

$$MA^{2+} + L^{3-} \rightleftharpoons MAL^- \tag{1}$$

So,

$$K_{MAL} = \frac{[MAL^-]}{[MA^{2+}]\,[L^{3-}]}$$

and

$$\beta_{MAL} = \frac{[MAL^-]}{[M^{2+}]\,[A]\,[L^{3-}]} = K_{MAL} \cdot K_{MA} \tag{2}$$

For calculation of stability constants of ternary complexes we have extended the method originally given by *Martell* and *Chaberek Jr.*[9]. It is outlined below:

When T_M is the total metal ion concentration and T_L is the total ligand concentration of the secondary ligand, viz. NTA, then (3) is valid.

$$T_M = [MA^{2+}] + [MAL^-] \tag{3}$$

Here the formation of ML^- has been neglected due to reasons which follow. NTA is a weakly acidic ligand and is largely protonated to start with. Bipyridyl on the other hand is not protonated and will be the first to complex with the formation of MA^{2+}. As we add more of NTA, is gets deprotonated and reacts with MA^{2+} to produce MAL^-. The second reaction also pushes the first reaction i.e., both reactions are favourably disposed to each other.

Now we account for the mass balance of the species involved (4)

$$T_L = [L^{3-}] + [H_3L] + [H_2L^-] + [HL^{2-}] + [MAL^-] \tag{4}$$

and insert the protonation constants of NTA viz., K_1, K_2 and K_3 in equation (4):

$$T_L = [L^{3-}] + \frac{[H^+]^3[L^{3-}]}{K_1 K_2 K_3} + \frac{[H^+]^2[L^{3-}]}{K_2 K_3} + \frac{[H^+][L^{3-}]}{K_3} + [MAL^-] =$$

$$= \left\{1 + \frac{[H^+]^3}{K_1 K_2 K_3} + \frac{[H^+]^2}{K_2 K_3} + \frac{[H^+]}{K_3}\right\} [L^{3-}] + [MAL^-] \tag{5}$$

$$= X\,[L^{3-}] + [MAL^-] \tag{6}$$

where X represents the collection of terms within the bracket and can be calculated from the pH and the three pK_a's of NTA.

So,

$$T_M = T_L = X\,[L^{3-}] + [MAL^-]$$

or,

$$[MAL^-] = T_M - X\,[L^{3-}].$$

Also,

$$T_{OH} + [H^+] - [OH^-] = [H_2L^-] + 2\,[HL^{2-}] + 3\,[L^{3-}] + 3\,[MAL^-] \tag{7}$$

In the pH range of interest the concentration of the hydroxy derivative of the 1 : 1 M(II)—bipyridyl complex can be neglected in comparison with the concentrations of other species present in the system. Combination of eqs. (3) and (6) gives

$$[MA^{2+}] = X[L^{3-}] \tag{8}$$

For $T_{OH} = mT_M$ eq. (7) becomes

$$mT_M + [H^+] - [OH^-] = [H_2L^-] + 2[HL^{2-}] + 3[L^{3-}] + 3[MAL^-] \tag{9}$$

Multiplying eq. (4) by (3) we get

$$3T_L = 3T_M = 3[H_3L] + 3[H_2L^-] + 3[HL^{2-}] + 3[L^{3-}] + 3[MAL^-] \tag{10}$$

Substracting eq. (9) from (10) we get

$$(3-m)T_M - [H^+] + [OH^-] = 3[H_3L] + 2[H_2L^-] + [HL^{2-}]$$

Or,
$$[L^{3-}] = \frac{(3-m)T_M - [H^+] + [OH^-]}{(X-1)} \tag{11}$$

Thus,
$$K_{MAL} = \frac{[MAL^-]}{[MA^{2+}][L^{3-}]} = \frac{[MAL^-]}{X[L^{3-}]^2} \tag{12}$$

This expression can be used for calculating the stability constants K_{MAL} of 1 : 1 : 1 mixed ligand complexes of metal ions with bipyridyl and NTA at various points of the titration curves for the ternary systems.

Results and Discussion

The pK_a's of bipyridyl and NTA used in this work have been taken from literature[10, 11] and are listed in Table 1. Fig. 1 shows the titration curves of Cu^{2+} with NTA and that of Cu^{2+} in presence of bipyridyl and NTA taken together. A sharp inflexion in case of the Cu^{2+}—NTA curve at $m = 3$ indicates the formation of a Cu—NTA complex. In case of the ternary complex the lowering of the curve after $m = 3$ indicates the formation of the ternary 1 : 1 : 1 complex.

Fig. 1 also shows the corresponding titration curves of Zn^{2+} systems. The two inflexions at $m = 3$ and $m = 4$ in case of Zn^{2+}—NTA indicate the formation of a Zn—NTA complex at lower pH but Zn (NTA) (OH)

Table 1. *Dissociation constants of ligands*

Ligand	pK_1	pK_2	pK_3	Ref.
NTA	1.75	2.47	9.71	10
Bipy	4.4	—	—	11

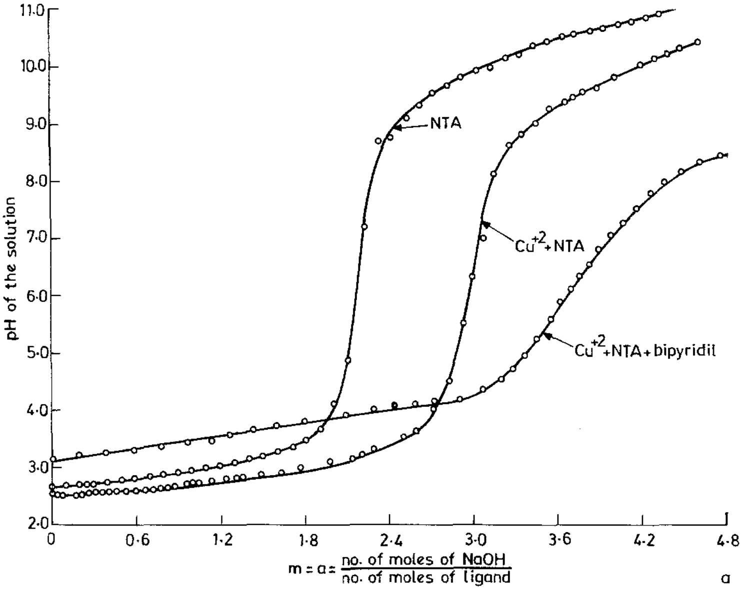

Fig. 1. Potentiometric titration curves of the Cu(II) (*a*), Zn(II) (*b*) and Cd(II) (*c*) system of 2,2′-bipyridyl and *NTA*

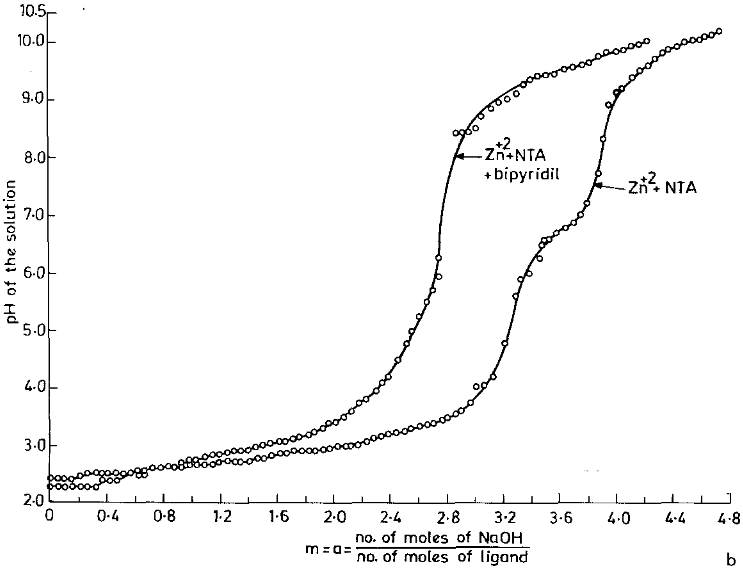

Fig. 1*b*

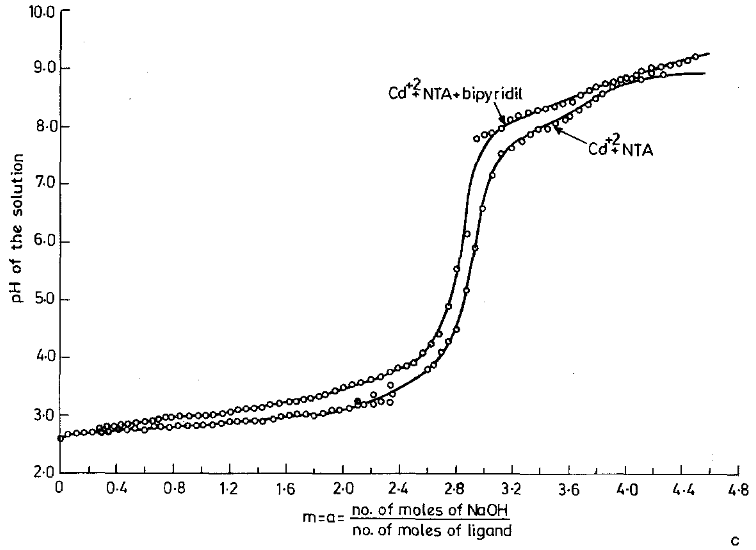

Fig. 1*c*

at higher *pH*. Interestingly the value of m ($= 3$) for the ZnAL complex is one unit less than for the ZnL complex ($m = 4$) at the inflexion points. This probably is due to a freely hanging glycinate segment of *NTA* in the ternary complex. This is not unexpected with complexes of metal ions with amino carboxylates. For example, *EDTA* has been shown to be pentacoordinated with Ni^{2+} in the octahedral complex[12]. In case of Cd(Bipyridyl) (*NTA*) and Cd(*NTA*) complexes the inflexions are close to $m = 3$ (Fig. 1). We may, therefore, infer that the binding in case of Cd^{2+} involves all the four sites of *NTA* in both complexes.

$\Delta \log K$, defined by eq. (13), is a measure of the stability of the ternary complexes with respect to the binary complexes.

$$\Delta \log K = \log K^{MA}_{MAL} - \log K^{M}_{ML} \tag{13}$$

This is found to be slightly positive or negative (Table 2) in accordance with statistical expectations[8]. In the ternary complex systems the two nitrogen atoms of the bipyridyl molecule form σ-bonds with the metals. In addition to this there exists a strong tendency of $M \rightarrow N$ π-interaction due to back donation of electrons from the metal d_{π} orbital to the vacant delocalised π-orbital over the bipyridyl molecule[13, 14]. As a result of this back donation the concentration of electrons around the metal ion in *M(bipy)* does not increase significantly and the electronegativity of the metal ion in this species remains almost the same as in M^{2+} aq. This

Table 2. *Stability constants for binary and ternary complexes; $t = 25\,°C$, $\mu = 0.1\,M$* (KNO_3)

Metal Ion	$\log K_{ML}$[a]	$\log K_{MA}$	$\log K_{MAL}$[a]	$\log \beta_{MAL}$	$\Delta \log K$
Cu^{2+}	10.78	8.15[b] (0.1 *M* KCl)	11.42	19.57	0.64
Zn^{2+}	10.65	5.04[b] (0.1 *M* KCl)	10.67	15.71	0.02
Cd^{2+}	9.78	4.12[b] (0.1 *M* KCl)	9.72	13.84	−0.06

[a] Determined in this work; A = Bipyridyl; $L = NTA$.
[b] Reference: *Irving H., Mellor D. H.*, J. Chem. Soc. **1962**, 5222.

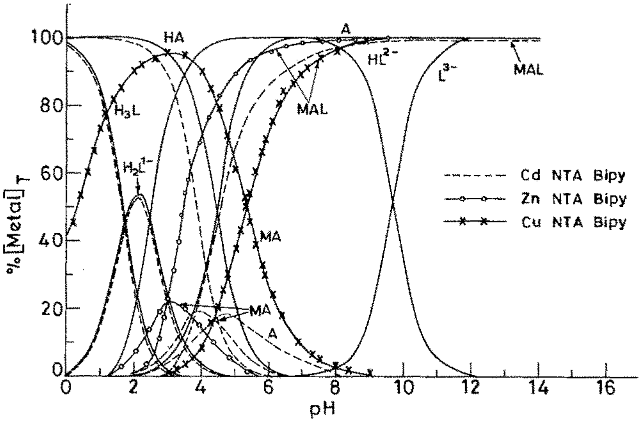

Fig. 2. Distribution of various species present in solution as a function of *pH*

justifies the very small differences in the values of $\log K^{M}_{ML}$ and $\log K^{MA}_{MAL}$. *Martell* and coworkers[13] and *Sigel*[15–19] et al. have observed that in several ternary complexing systems the value of $\log K^{MA}_{MAL}$ is slightly greater than that of $\log K^{M}_{ML}$ where the coordination is through two oxygen atoms from the secondary ligand. Our results are in agreement with their findings. It may be added that our value for the Cd(*bipy*) (*NTA*) complex is different than that reported by a group of workers ($\log K_{MAL} = 8.56$)[20].

The distribution of various species present in solution as a function of *pH* for all the three systems has been calculated by a computer program originally given by *Perrin* and *Sayce*[21] after suitable modifications (Fig. 2).

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