Influence of Secondary Ligands on the Stability of Metal–Xanthosine Complexes in Solution

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Potentiometric equilibrium measurements have been carried out at 35 °C for the formation of ternary complexes of xanthosine and Cu^{II}, Ni^{II}, Zn^{II}, Co^{II}, Mn^{II}, Mg^{II}, and Ca^{II} with histidine, catechol, and oxalic acid in a 1 : 1 : 1 ratio. The ternary complexes of these systems are more stable than the corresponding binary complexes. This increased stability is measured in terms of $\Delta\log K$. The $\Delta\log K$ values for the 1 : 1 : 1 complexes of metal–xanthosine with aromatic ligands were found to be more positive (*i.e.* more stable) than those of the corresponding complexes with aliphatic ligands. This has been attributed to the 'stacking phenomenon' that occurs between the two aromatic moieties of the ligands in solution.

Ternary complexes are gaining importance because they provide models for metalloenzyme reactions. Ternary complexes of biomolecules in general, and nucleosides and nucleotides in particular, have received much attention during the last decade because of their importance in biological systems.[1–10] These studies have explained to some extent the specific and selective interactions that take place in biological systems. However, much more information is needed before clear conclusions about the reactions that occur *in vivo* can be obtained. In a ternary system, the probability of formation of mixed-ligand complexes is greater than that of binary complexes.[11,12] This is especially true when the chelate rings formed by the individual ligands are similar in nature.[13] The difference in stability constants between a binary and a ternary complex is usually explained in terms of $\Delta\log K$. In ternary complexes (MLA), the secondary ligands (A) are known to influence the structure and stability of many metal–ligand complexes (ML) in solution. Conversely, metal–ligand complexes (ML) are known to have discriminating tendencies toward the secondary ligands (A).[14] Hence the stability of ternary complexes is influenced mainly by the nature of the secondary ligand. The extra stabilization in ternary complexes has been attributed to interligand π interactions[15] and electronic repulsion.[16] We have observed in earlier investigations[17,18] that stacking interactions, which are expected to occur between two aromatic ligands (a situation encountered in many biochemical processes), are most effective for accounting for this extra stability.

In the present work we have investigated the interactions leading to the formation of ternary complexes of xanthosine and Cu^{II}, Ni^{II}, Zn^{II}, Co^{II}, Mn^{II}, Mg^{II}, and Ca^{II} with various biologically important ligands like glycine, histidine, catechol, and 2,2′-bipyridyl (bipy). We have also included oxalic acid and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (tmen) for effective comparison. This kind of study, we hope, will assist in elucidating the role of secondary ligands in the formation and stabilization of ternary complexes in solution.

Experimental

Xanthosine and histidine were obtained from Sigma (U.S.A.) and catechol and oxalic acid from Fluka (Switzerland). Transition and alkaline-earth metal ions were of AnalaR grade and were standardized volumetrically by titration with the disodium salt of ethylenediaminetetra-acetate in the presence of a suitable indicator as outlined by Schwarzenbach.[19]

The experimental method employed consisted of a potentiometric titration of metal–xanthosine and the secondary ligands histidine, catechol, or oxalic acid in a 1:1:1 ratio at 35 ± 0.1 °C with standard NaOH solution. The experimental conditions maintained were similar to those described in our previous work.[5]

Calculations and Results

Calculation of Dissociation Constants.—The acid dissociation constants of the diprotonated ligands such as histidine, catechol, and oxalic acid were calculated by the usual algebraic method and are presented in Table 1.

Equations (1)—(7) were employed to calculate the stability constants of the ternary complexes of Cu^{II}, Ni^{II}, Zn^{II}, and Co^{II} with xanthosine and histidine in a 1:1:1 ratio (charges are omitted for clarity).

$$M + H_2L + H_2A \rightleftharpoons[K_{M(HL)A}^{M}] [M(HL)A] + 3\,H^+ \quad (1)$$

$$M + HL + A \rightleftharpoons[K_{M(HL)A}^{M}] [M(HL)A] \quad (2)$$

$$K_{M(HL)A}^{M} = \frac{T_M - [L]X_A}{[L]^3(X_A)^2} \cdot X_L \quad (3)$$

$$[L] = \frac{6T_M - (2mT_M - 2[H^+] + 2[OH^-])}{\alpha_A + 3\alpha_L(X_A/X_L) + (X_A/X_L)} \quad (4)$$

$$X_A = \frac{[H^+]^2}{K_aK_{2a}} + \frac{[H^+]}{K_{2a}} + 1 \quad (5)$$

$$\alpha_A = \frac{3[H^+]^2}{K_aK_{2a}} + \frac{[H^+]}{K_{2a}} - 1 \quad (6)$$

$$\alpha_L = \frac{[H^+]}{K_a};\ X_L = \frac{[H^+]}{K_a} + 1 \quad (7)$$

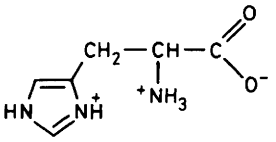
For the ternary complexes of Mn^{II}, Ca^{II}, and Mg^{II} with xanthosine and histidine in a 1:1:1 ratio equations (8)—(10) were used.

$$MA + H_2L \rightleftharpoons^{K_{M(HL)A}^{MA}} [M(HL)A] + H^+ \quad (8)$$

$$MA + HL \rightleftharpoons^{K_{M(HL)A}^{MA}} [M(HL)A] \quad (9)$$

$$K_{M(HL)A}^{MA} = \frac{T_M - [M]}{[MA][HL]} \quad (10)$$

For equations (1)—(10), H_2L = neutral xanthosine, H_2A = monoprotonated histidine (A = monoanion of histidine), T_M = total metal ion species present in solution, m = moles of base added per mole of metal ion, and subscripts A and L represent histidine and xanthosine respectively.



H_2A

The concentrations of the various species involved in the above equations were obtained by setting up suitable material balanced equations and solving for the unknowns and the constant $K_{M(HL)A}^{MA}$, which is similar to the method employed for the 1:1 metal–xanthosine complex described earlier.[6]

The stability constants of the ternary complexes of Cu^{II}, Ni^{II}, Zn^{II}, Co^{II}, Mn^{II}, Mg^{II}, and Ca^{II} with xanthosine and oxalic acid in a 1:1:1 ratio were calculated with the help of equation (3). The same equation was also used for the ternary complex of Cu^{II} with xanthosine and catechol.

In the case of ternary complexes of Ni^{II}, Zn^{II}, Mn^{II}, Co^{II}, Ca^{II}, and Mg^{II} with xanthosine (H_2L) and catechol (H_2A) in a 1:1:1 ratio equations (11)—(15) were employed.

$$M + HL + HA \rightleftharpoons^{K_{M(HL)(HA)}^{M}} [M(HL)(HA)] \quad (11)$$

$$K_{M(HL)(HA)}^{M} = \frac{T_M - [HL]X}{[HL]^3X^2} \quad (12)$$

$$[HL] = \frac{(2 - m)T_M - [H^+] + [OH^-]}{([H^+]/K_{aL}) + (X/Y)([H^+]/K_{aA})} \quad (13)$$

$$X = \frac{[H^+]}{K_{aL}} + 1 \text{ (using } K_a \text{ value of xanthosine)} \quad (14)$$

$$Y = \frac{[H^+]}{K_{aA}} + 1 \text{ (using } K_a \text{ value of catechol)} \quad (15)$$

The constants pertaining to various reactions associated with the above systems are presented in Table 2.

Table 1. Acid dissociation constants of the ligands; T = 35 °C, I = 0.10 mol dm^{-3} (KNO_3)

Ligand	pK_a	pK_{2a}
Xanthosine	5.46 × 0.02	9.90 ± 0.02
Glycine	2.33 ± 0.02	9.75 ± 0.02
Histidine	6.00 ± 0.04	9.00 ± 0.04
Oxalic acid	2.18 ± 0.05	4.20 ± 0.05
Catechol	9.21 ± 0.05	11.00 ± 0.05
2,2′-Bipyridyl		4.36 ± 0.02
tmen	5.83 ± 0.01	9.03 ± 0.03

Discussion

Although the dissociation and stability constants of histidine with transition-metal ions are available in the literature[20,21] we have remeasured them, since it is preferable to determine the stability constants of binary and ternary complexes under identical experimental conditions as experimental differences might affect the Δlog K values. Our results agree well with those given in the literature, the slight deviations observed being due

Table 2. Stability constants* of the binary and ternary complexes of xanthosine (xan, H_2L) with glycine (gly, HX), histidine (hist, HX), oxalic acid (ox, H_2X), and catechol (cat, H_2X) (X = L or A depending on binary or ternary reaction); T = 35 °C, I = 0.10 mol dm^{-3} (KNO_3)

	M:xan (1:1)	M:gly (1:1)	M:xan:gly (1:1:1)		M:hist (1:1)		M:xan:hist (1:1:1)	
M^{II}	$K_{M(HL)}^{M}$	K_{ML}^{M}	$K_{M(HL)A}^{M}$	$K_{M(HL)A}^{MA}$	$K_{M(HL)}^{M}$	K_{ML}^{M}	$K_{M(HL)A}^{M}$	$K_{M(HL)A}^{MA}$
Cu	3.06	8.61	12.8			10.02	13.19	
Ni	2.92	5.92	10.9			8.42	11.84	
Zn	2.21	5.22		2.8		6.35	9.05	
Co	2.51	5.50		3.0		7.00	10.11	
Mn	2.57	3.85		2.8		6.26		2.9
Mg	2.23	3.40		2.5	3.35			2.79
Ca	2.21	3.58		2.6	3.10			2.76

	M:cat (1:1)		M:xan:cat (1:1:1)		M:ox (1:1)	M:xan:ox (1:1:1)
M^{II}	$K_{M(HL)}^{M}$	K_{ML}^{M}	$K_{M(HL)A}^{M}$	$K_{M(HL)(HA)}^{M}$	K_{ML}^{M}	$K_{M(HL)A}^{M}$
Cu		11.95	16.36		6.16	10.25
Ni	4.57			10.13	5.23	9.38
Zn	5.08			10.28	5.31	8.46
Co	4.40			9.08	4.97	9.33
Mn		6.55		8.94	5.14	8.70
Mg		4.12		7.27	4.65	8.30
Ca		3.64		5.45	4.85	8.22

*The standard deviations are omitted for clarity.

Table 3. Δlog K values for various metal–ligand systems in solution; T = 35 °C, I = 0.10 mol dm^{-3} (KNO_3)

M^{II}	M:xan:gly (1:1:1)	M:xan:hist (1:1:1)	M:xan:cat (1:1:1)	M:xan:ox (1:1:1)	M:xan:bipy (1:1:1)
Cu	+1.13	+0.11	+1.25	+1.03	+0.02
Ni	+2.06	+0.50	+2.64	+1.23	−0.11
Zn	+0.59	+0.49	+2.99	+1.80	+0.37
Co	+0.49	+0.60	+2.17	+0.98	+0.01
Mn	+0.23	+0.33		+0.99	+1.24
Mg	+0.27	+0.56		+1.42	
Ca	+0.39	+0.55		+1.16	

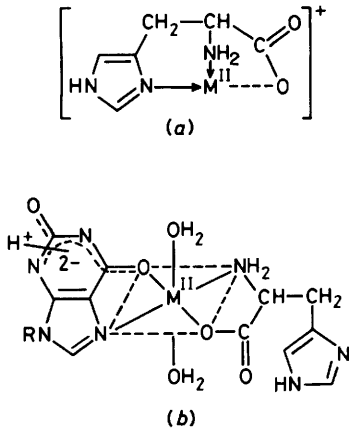


Figure 1. Tentative structure of 1:1 metal–histidine (*a*) and 1:1:1 metal–xanthosine–histidine (*b*) systems in solution; R = ribose

to differences in experimental conditions like temperature and ionic strength.

Before we discuss the contribution of Δlog K to understanding the nature of the ternary complexes in solution, it is worthwhile, in the interest of clarity, to briefly mention the algebraic definition of Δlog K and its origin. In a ternary system containing a metal ion and two bidentate ligands, A and L, with significantly different complexing capabilities, a simple complex forms with the ligand which has the greater complexing tendency compared to the other. However, if the complexing tendencies of the two ligands differ only slightly the following type of complex will result [equation (i)].

$$M + A + L \rightleftharpoons MLA \qquad (i)$$

The reaction may proceed by either of the following sets of equilibria [(ii) and (iii), or (iv) and (v)].

$$M + A \rightleftharpoons MA \qquad (ii)$$

$$MA + L \rightleftharpoons MAL \qquad (iii)$$

$$M + L \rightleftharpoons ML \qquad (iv)$$

$$ML + A \rightleftharpoons MLA \qquad (v)$$

In dilute solutions the possibility of other species present (hydroxo, polymeric *etc.*) can be ignored. Therefore, the equilibrium constants represent the overall or stepwise mixed-ligand complex formation, depending upon the system under investigation. The difference in stability between a binary and a ternary complex is usually explained in terms of Δlog K, *i.e.*, Δ log K = log $K_{MAL}{}^{MA}$ − log $K_{ML}{}^{M}$ or log $K_{MLA}{}^{ML}$ − log $K_{MA}{}^{M}$.

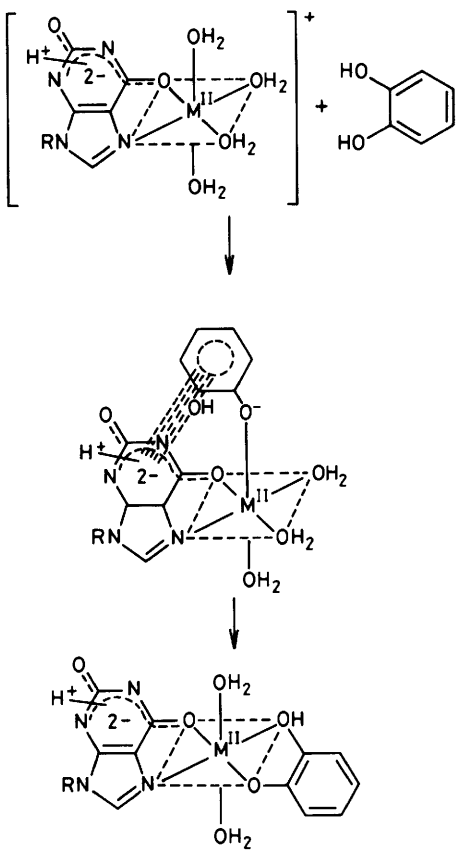


Figure 2. Model illustrating the stacking interaction followed by co-ordination in H_2O; R = ribose

Thus, if Δlog K values are positive the ternary complexes are more stable than the corresponding binary complexes and if they are negative the binary are more stable than the ternary. However, negative values of Δlog K do not preclude the formation of ternary complexes in solution.

Table 3 presents the Δlog K values for the systems studied. It can be seen that the Δlog K values are positive for all the systems except for Ni^{II}–xanthosine–2,2′-bipyridyl. Various factors have been attributed to account for this extra stability found in ternary complexes of xanthosine in solution.[7,11,17,18] These include charge neutralization through the π-accepting capacity of the secondary ligands and also stacking interactions.

It is important to consider the role of histidine as a ligand. It has been reported earlier that histidine acts as glycine-like if there is only one histidine, and if there are two histidines, the first may act as glycine-like and the second as histamine-like.[22] Our values [Cu^{II}–histidine (log K = 10.02) and Cu^{II}–glycine

(log K = 8.61)], however, suggest that histidine acts as a terdentate ligand in the binary complex Cu^{II}–histidine, involving the amino, imidazole, and carboxylate groups [Figure 1(*a*)]. If histidine had acted as glycine-like the differences in stability constants for the 1:1 Cu^{II}–glycine and 1:1 Cu^{II}–histidine systems would not have been of this order of magnitude (1.4 log K units).

The difference between the stability constants of the 1:1:1 Cu^{II}–xanthosine–glycine and 1:1:1 Cu^{II}–xanthosine–histidine systems, however, is reduced to 0.4 log K units, suggesting that the mode of binding in both ternary complexes may be similar [Figure 1(*b*) and Figure 1 of ref. 11].

For the Cu^{II}– and Ni^{II}–xanthosine–glycine systems in a 1:1:1 ratio the values of $\Delta\log K$ are more positive than the corresponding values for the Cu^{II}– and Ni^{II}–xanthosine–histidine systems (Table 3). This reduced stability of the Cu^{II}– and Ni^{II}–xanthosine–histidine ternary complexes compared to the glycine complexes may be due to the lower co-ordination number of these metal ions, where histidine may act as a bidentate ligand, co-ordinating either histamine-like or glycine-like. However, for the other metal ions studied, the $\Delta\log K$ values for the 1:1:1 metal–xanthosine–histidine complexes are more positive than those of the corresponding 1:1:1 metal–xanthosine–glycine complexes. In these cases, the metal ions might possess higher co-ordination numbers and, therefore, the histidine may act as a terdentate ligand involving all its available donor atoms for metal binding. This results in a stronger interaction between the 1:1 metal–xanthosine complex and the histidine, as the imidazole group will be able to form π bonds. No such interaction can be expected in the case of the glycine complexes.

In addition, the ternary complexes of xanthosine with histidine and glycine can be compared to the 1:2 metal–xanthosine system, since these ligands have similar donor atoms (mixed N/O) available for metal co-ordination. The $\Delta\log K$ values for the ternary complexes of xanthosine with histidine and the 1:2 metal–xanthosine complexes are more positive than those for the ternary complexes of xanthosine with glycine (ref. 17, Table 3). This is expected because glycine, being an aliphatic ligand, cannot take part in stacking interactions, whereas such an interaction is possible in the former case. It may be added that there is evidence that the purine part of xanthosine and the imidazole moiety of histidine will participate in stacking interaction.[17,23]

When the $\Delta\log K$ values of the ternary complexes of histidine and the 1:2 complexes of xanthosine, where stacking interaction is possible in both the systems, are compared, the $\Delta\log K$ values are more positive for the former except for the metal ions Zn^{II}, Mg^{II}, and Ca^{II}. Other factors being equal, repulsion between the primary and secondary ligands in the 1:2 xanthosine system may result in lower values of $\Delta\log K$ compared to the ternary histidine system. However, in the case of Ca^{II}, Mg^{II}, and Zn^{II} the data suggest that the stacking interaction prevails over other factors. Incidentally, these are the metal ions which are very important in biological systems. Thus, it is clear that for biologically important ligands and metal ions, the stacking phenomenon contributes significantly to the stabilization of mixed-ligand complexes.

The ligands catechol and oxalic acid have O,O′ donor atoms, although one is aromatic and the other is aliphatic in nature. The $\Delta\log K$ values for the catechol systems (Table 3) are more positive than those of the oxalic acid system. These results are in line with the explanation given earlier that aromatic ligands which take part in 'stacking interactions' will form more stable ternary complexes. These results confirm our earlier observations for the tmen and 2,2′-bipyridyl systems.[7] Thus the ability to participate in stacking interactions can be attributed solely to the aromaticity of the ligands concerned. A model illustrating such 'stacking interaction' is shown in Figure 2.

Finally, the above investigations clearly emphasize the role of the secondary ligands in the stabilization of the ternary complexes in solution.

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References

1 H. Sigel, in 'Metal Ions in Biological Systems,' Marcel Dekker, New York, 1973, vol. 2, ch. 2 and refs. therein.
2 M. M. Taqui Khan and P. Rabindra Reddy, *J. Inorg. Nucl. Chem.*, 1972, **34**, 967.
3 M. M. Taqui Khan and P. Rabindra Reddy, *J. Inorg. Nucl. Chem.*, 1973, **35**, 2821.
4 H. Sigel, *J. Am. Chem. Soc.*, 1975, **97**, 3209.
5 P. Rabindra Reddy, K. Venugopal Reddy, and M. M. Taqui Khan, *J. Inorg. Nucl. Chem.*, 1976, **38**, 1923.
6 P. Rabindra Reddy, K. Venugopal Reddy, and M. M. Taqui Khan, *J. Inorg. Nucl. Chem.*, 1978, **40**, 1265.
7 P. Rabindra Reddy, K. Venugopal Reddy, and M. M. Taqui Khan, *J. Inorg. Nucl. Chem.*, 1979, **41**, 423.
8 J. B. Orenberg, B. E. Fischer, and H. Sigel, *J. Inorg. Nucl. Chem.*, 1980, **42**, 785.
9 B. E. Fischer and H. Sigel, *J. Am. Chem. Soc.*, 1980, **102**, 2998.
10 H. Sigel, B. E. Fischer, and E. Farkas, *Inorg. Chem.*, 1983, **22**, 925.
11 P. Rabindra Reddy and M. Harilatha Reddy, *Polyhedron*, 1983, **2**, 1171.
12 H. Sigel, *Angew. Chem., Int. Ed. Engl.*, 1975, **14**, 394.
13 H. C. Freeman and R. P. Martin, *J. Biol. Chem.*, 1969, **244**, 4823.
14 R. Griesser and H. Sigel, *Inorg. Chem.*, 1970, **9**, 1238.
15 F. A. Walker, H. Sigel, and D. B. McCormick, *Inorg. Chem.*, 1972, **11**, 276.
16 K. Gopalkrishnan and P. K. Bhattacharya, *J. Chem. Soc., Dalton Trans.*, 1981, 543.
17 P. Rabindra Reddy and K. Venugopal Reddy, *Inorg. Chim. Acta*, 1983, **80**, 95.
18 P. Rabindra Reddy, H. Harilatha Reddy, and K. Venugopal Reddy, *Inorg. Chem.*, 1984, **23**, 974.
19 G. Schwarzenbach, in 'Complexometric Titrations,' Interscience, New York, 1957, p. 77.
20 A. Chakravorthy and F. A. Cotton, *J. Phys. Chem.*, 1963, **67**, 2878.
21 D. D. Perrin and V. S. Sharma, *J. Chem. Soc. A*, 1967, 724.
22 H. Sigel and D. B. McCormick, *J. Am. Chem. Soc.*, 1971, **93**, 2041.
23 P. H. Haffner and J. H. Wang, *Biochemistry*, 1973, **12**, 1608.

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