Binary and Ternary Metal Complexes of Guanosine: Stability and Thermodynamic Parameters

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The stability constants of the binary and ternary complexes of Cu^{II}, Ni^{II}, Zn^{II}, Co^{II}, Mn^{II}, Mg^{II}, and Ca^{II} with guanosine as a primary ligand and 2,2′-bipyridyl, 1,10-phenanthroline, and 5-sulphosalicylic acid as secondary ligands were determined from potentiometric titrations at 45, 35, 25, and 15 °C at $I = 0.10$ mol dm^{-3} (KNO_3). The stability of 1 : 2 metal–guanosine and ternary metal complexes was characterized by the $\Delta \log K$ values (difference in stabilities of the 1 : 2 and 1 : 1 complexes and difference between the 1 : 1 : 1 and the corresponding binary systems). These values are positive for the 1 : 2 metal–guanosine and 1 : 1 : 1 metal–bipyridyl–guanosine systems. This is attributed to stacking of guanosine. The $\Delta \log K$ values are negative for the ternary phenanthroline and 5-sulphosalicylic acid systems. The thermodynamic parameters ΔH_f°, ΔS_f°, and ΔG_f° are reported for all the systems.

Interaction of nucleosides and nucleotides with metal ions has been a subject matter of much recent interest. Because of the role of bivalent metal ions in many biochemical processes[1–8] attempts are being made to elucidate the mode of interaction of metal ions with vital molecules like DNA and RNA. We have recently reported[9,10] the interaction of cytidine and uridine with bivalent metal ions in solution. Mössbauer, ^{13}C and ^{1}H n.m.r., i.r. and electronic spectral studies of the metal complexes of guanosine [2-amino-9-β-D-ribofuranosyl-9*H*-purin-6(1*H*)-one] with Sn^{IV}, Pd^{II}, Pt^{II}, Au^{I}, Au^{II}, Ru^{III}, and Rh^{I} and spectrophotometric and conductometric studies of complexes of Cu^{II} and Pb^{II} have been reported,[11–19] but very little is known about the interaction of metal ions with guanosine in aqueous solution. Mixed-ligand metal complexes of nucleosides and nucleotides have attracted the attention of many investigators because they serve as models for metalloenzyme reactions in biological systems.[20–22] They also provide useful information in understanding the specific and selective interactions that take place in many biochemical processes.

In the present paper we report the formation of binary 1 : 1 metal guanosine complexes at four different temperatures and the influence of secondary ligands such as 2,2′-bipyridyl (bipy), 1,10-phenanthroline (phen), and 5-sulphosalicylic acid (ssa) on their stability. The enthalpy and entropy changes associated with the formation of 1 : 2 and ternary complexes of guanosine in solution were compared with the help of these parameters, the extra stability of the 1 : 2 metal complexes being explained in terms of their $\Delta(\Delta H)$ and $\Delta(\Delta S)$ values.

Results and Discussion

The potentiometric titration curve of monoprotonated guanosine shown in Figure 1 shows a steep inflection at $n = 1$ followed by a buffer region at higher pH, where n is the number of moles of base added per mol of metal ion. The acid dissociation constants K_a and K_{2a} for guanosine were calculated at 15, 25, 35, and 45 °C by a direct algebraic method[23] and the values are listed in Table 1.

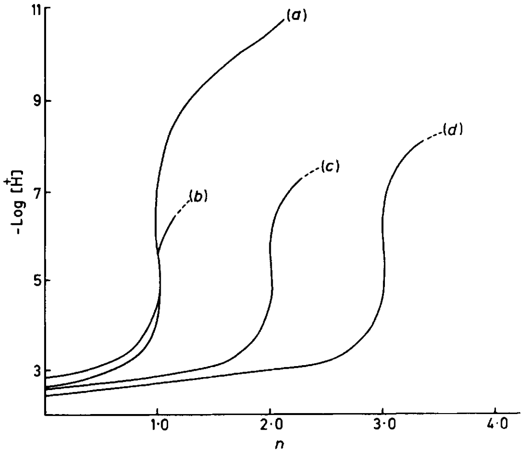


Figure 1. Potentiometric titration curves of (*a*) free guanosine, (*b*) 1 : 1 copper(II)–guanosine, (*c*) 1 : 2 manganese(II)–guanosine, and (*d*) 1 : 1 : 1 nickel(II)–bipy–guanosine at 35 °C and $I = 0.10$ mol dm^{-3} (KNO_3)

1 : 1 and 1 : 2 Binary Systems.—The titration curve for a 1 : 1 ratio of guanosine to Cu^{II} at 35 °C is shown in Figure 1. Similar titration curves were obtained for the 1 : 1 complexes of guanosine with Ni^{II}, Co^{II}, Zn^{II}, Mn^{II}, Mg^{II}, and Ca^{II} and at other temperatures studied. In all these cases an inflection was obtained at $n = 1$ followed by precipitation. This indicates the dissociation of one proton from the protonated guanosine. The stability constants of the guanosine (HL) complexes were calculated with the help of equation (3) (see Experimental section) and are presented in Table 1. The corresponding thermodynamic parameters were computed at the temperatures studied and are presented in Table 2.

The potentiometric titration curve of a 1 : 2 ratio of Mn^{II} to guanosine (Figure 1) gives a steep inflection at $n = 2$ followed by precipitation. It was assumed that two protons are lost from the protonated ligands H_2L^+. The stability constants were calculated by using equation (4) in the buffer region before the inflection. Similar titration curves were obtained for Cu^{II}, Ni^{II}, Co^{II}, Zn^{II}, and Mg^{II} at 15, 25, and 45 °C. The stability constants and corresponding thermodynamic parameters are given in Tables 1 and 2, respectively.

1 : 1 : 1 Ternary Systems.—The potentiometric titration curves for M–A–HL (M = bivalent metal ion; A = 2,2′-bipyridyl, 1,10-phenanthroline, or 5-sulphosalicylic acid; HL = guanosine) show inflections at $n = 3$ indicating mixed-ligand complex formation in a single step. The titration curve of nickel(II)–guanosine–bipyridyl in a 1 : 1 : 1 ratio at 35 °C is presented in Figure 1. Similar titration curves were obtained at the other

Table 1. Stability constants and $\Delta \log K$ values of 1:1 and 1:2 metal–guanosine complexes at $I = 0.10$ mol dm^{-3} (KNO_3)[a]

	$\log K^{M}_{M(HL)}$ [b]				$\log K^{M(HL)}_{MH_2L_2}$ [b]				$\Delta \log K$			
Metal ion	45	35	25	15 °C	45	35	25	15 °C	45	35	25	15 °C
Cu^{II}	4.10	4.20	4.31	4.39	3.20	3.09	3.16	3.25	−1.08	−1.11	−1.15	−1.14
Ni^{II}	3.70	3.79	3.89	4.00	4.01	4.12	4.23	4.34	+0.31	+0.33	+0.34	+0.34
Co^{II}	3.34	3.40	3.47	3.55	4.10	4.18	4.27	4.37	+0.76	+0.78	+0.80	+0.82
Zn^{II}	3.02	3.07	3.13	3.20	3.21	3.28	3.36	3.45	+0.19	+0.21	+0.23	+0.25
Mn^{II}	2.58	2.61	2.65	2.70	3.39	3.44	3.49	3.55	+0.81	+0.83	+0.84	+0.85
Mg^{II}	2.51	2.40	2.31	2.22	3.87	3.80	3.71	3.62	+1.36	+1.40	+1.40	+1.40
Ca^{II}	1.89	1.82	1.75		3.65	3.60	3.54	3.49	+1.76	+1.78	+1.79	

[a] For guanosine: $pK_a = 2.41, 2.57, 2.68$, and 2.81; $pK_{2a} = 9.15, 9.21, 9.29$, and 9.36 at 45, 35, 25, and 15 °C respectively. [b] The values are accurate to ±0.05 log K units.

Table 2. Thermodynamic parameters* for the 1:1 and 1:2 metal–guanosine systems

	$\log K^{M}_{M(HL)}$			$\log K^{M(HL)}_{MH_2L_2}$				
Metal ion	$\Delta H^{\ominus}_f$	$\Delta G^{\ominus}_f$(25 °C)	$\Delta S^{\ominus}_f$(25 °C)	$\Delta H^{\ominus}_f$	$\Delta G^{\ominus}_f$(26 °C)	$\Delta S^{\ominus}_f$(25 °C)	$\Delta(\Delta H^{\ominus}_f)$	$\Delta(\Delta S^{\ominus}_f)$
Cu^{II}	−17	−24.6	25	−13.0	−18.0	17	+4.2	−8
Ni^{II}	−18	−22.2	16	−19.3	−24.1	16	−1.8	0
Co^{II}	−12	−19.8	25	−15.6	−24.4	29	−3.4	+4
Zn^{II}	−11	−17.9	25	−13.9	−19.21	18	−3.4	−7
Mn^{II}	−7	−15.1	27	−9.3	−19.9	35	−2.3	+9
Mg^{II}	+17	−13.2	101	+14.7	−21.2	120	−2.3	+19
Ca^{II}	+13	−7.0	76	+9.5	−20.2	100	−3.2	+24

* The $\Delta H^{\ominus}_f$ values are accurate to ±1 kJ mol^{-1}, the $\Delta S^{\ominus}_f$ values to ±4 J K^{-1} mol^{-1}.

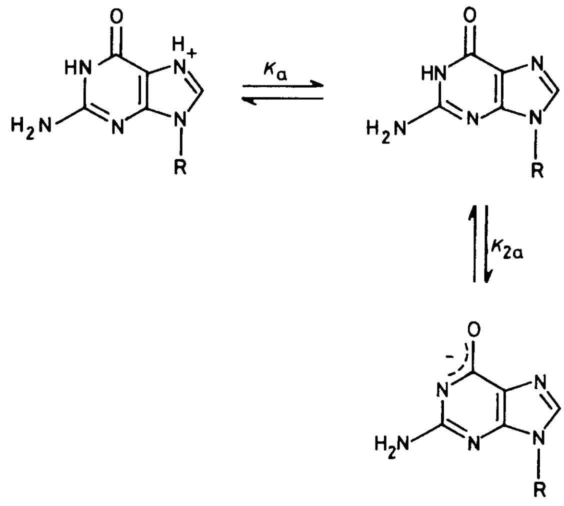
Table 3. Stability constants* of the ternary metal complexes of guanosine with 2,2′-bipyridyl, 1,10-phenanthroline, or 5-sulphosalicylic acid at $I = 0.10$ mol dm^{-3} (KNO_3)

	bipy, $\log K^{M}_{M(HL)A}$				phen, $\log K^{M}_{M(HL)A}$				ssa, $\log K^{M(HL)}_{M(HL)(HA)}$			
Metal ion	45	35	25	15 °C	45	35	25	15 °C	45	35	25	15 °C
Cu^{II}	11.01	11.16	11.30	11.42	7.05	7.15	7.26	7.35	3.02	3.05	3.09	3.14
Ni^{II}	11.51	11.70	11.85	12.02	7.27	7.36	7.45	7.55	3.21	3.26	3.33	3.40
Co^{II}	10.60	10.74	10.89	11.01	7.11	7.20	7.28	7.34	3.09	3.15	3.22	3.30
Zn^{II}	9.19	9.28	9.39	9.50	6.73	6.83	6.89	6.93	2.99	3.03	3.07	3.00
Mn^{II}	5.98	6.06	6.16	6.23	6.87	6.93	6.99	7.05	2.67	2.71	2.75	2.80
Mg^{II}	6.10	6.02	5.96	5.88	5.72	5.66	5.59	5.50	2.39	2.32	2.24	2.15
Ca^{II}	4.98	5.04	5.11	5.20	4.63	4.58	4.52	4.49				

* The values are accurate to ±0.07 log K units.

temperatures and for the other systems studied. The stability constants of these ternary complexes were calculated by using equations (5)—(7) and are given in Table 3. The corresponding thermodynamic parameters are presented in Table 4.

Guanosine is a weak base and exists in keto and enolic forms depending on the pH of the solution. In equimolar solutions of guanosine and hydrochloric acid, N^7 is the only site available for protonation.[24] This has been confirmed by *X*-ray diffraction studies of guanine hydrochloride,[25] i.r. studies of the guanosine cation,[26] and a comparison of the u.v. spectra of the cations of 7,9-dimethyl- and 1,7,9-trimethyl-guanine with those of 9-methyl- and 1,9-dimethyl-guanine.[27] The pK_a value of guanosine is very close to those of guanine [2-amino-9*H*-purin-6(1*H*)-one] and hypoxanthine [9*H*-purin-6(1*H*)-one].[28] The $\Delta S^{\ominus}_f$ and $\Delta H^{\ominus}_f$ values corresponding to the ionization constants of these ligands suggest that the dissociation site is the N^7H^+ group. The proton-dissociation steps involved in the titration of guanosine can be represented as in the Scheme. The second proton dissociation takes place from the N^1HC^6O site. On the basis of potentiometric data for hypoxanthine, Taqui Khan and Khrishnamoorthy[29] proposed a chelate formation involving



Scheme. R = Ribose

Table 4. Thermodynamic parameters[a] for the ternary complexes at I = 0.10 mol dm^{-3} (KNO_3)

	bipy[b]			phen[b]			ssa[c]		
Metal ion	ΔH_f°	ΔG_f°(25 °C)	ΔS_f°(25 °C)	ΔH_f°	ΔG_f°(25 °C)	ΔS_f°(25 °C)	ΔH_f°	ΔG_f°(25 °C)	ΔS_f°(25 °C)
Cu^{II}	−24	−64.5	137	−18	−41.4	79	−7	−17.6	36
Ni^{II}	−30	−67.6	127	−17	−42.5	86	−8	−19.0	37
Co^{II}	−24	−62.1	127	−15	−41.5	90	−12	−18.4	20
Zn^{II}	−18	−53.6	120	−12	−39.3	92	−7	−17.5	34
Mn^{II}	−15	−35.1	69	−11	−39.9	98	−8	−15.7	27
Mg^{II}	+13	−33.9	157	+13	−31.9	150	+14	−12.8	90
Ca^{II}	−13	−29.2	55	+8	−25.8	155			

[a] The ΔH_f° values are accurate to ±1 kJ mol^{-1}, the ΔS_f° values to ±4 J K^{-1} mol^{-1}. [b] Calculated from the temperature dependence of log $K^{M}_{M(HL)A}$ (Table 3). [c] Calculated from the temperature dependence of log $K^{M(HL)}_{M(HL)(HA)}$ (Table 3).

Table 5. Values of Δ log K for the ternary complexes at I = 0.10 mol dm^{-3} (KNO_3)

	bipy[a]		phen[a]		ssa[b]			
Metal ion	45	35 °C	45	35 °C	45	35	25	15 °C
Cu^{II}	−0.12	−0.99	−5.07	−4.54	−1.08	−1.15	−1.22	−1.25
Ni^{II}	+1.16	+0.97	−3.60	−1.33	−0.49	−0.53	−0.56	−0.60
Co^{II}	+0.61	+1.27	−3.77	−1.07	−0.25	−0.25	−0.25	−0.25
Zn^{II}	+0.76	+0.80	−3.14	−2.18	−0.03	−0.04	−0.06	−0.09
Mn^{II}	+0.88	+0.85	+0.28	+0.11	+0.99	+0.10	+0.10	+0.10
Mg^{II}	−0.05	+3.62	+0.38	+1.05	−0.12	−0.08	+0.07	−0.07
Ca^{II}		+3.22	+0.40	+0.51				

[a] Δ log K = log $K^{M}_{M(HL)A}$ − (log $K^{M}_{M(HL)}$ + logK_{MA}). The value of log K^{M}_{MA} for bipy and phen were obtained from ref. 36. [b] Δ log$K$ = log $K^{M(HL)}_{M(HL)}$ log $K^{M}_{M(HL)}$.

C^6O and N^7. In our work the involvement of these sites is confirmed in the case of guanosine also.

The stability constants of the 1:1 metal–guanosine complexes M(HL) follow the Irving–Williams order. They increase with decreasing temperature, except in the case of Mg^{II} and Ca^{II} (Table 1). The corresponding enthalpy changes are exothermic. The positive enthalpy for the magnesium complex is due to the high heat of hydration of Mg^{II} as compared to other alkaline-earth metal ions. The heats of hydration of metal ions are in general inversely proportional to the ionic radii, accordingly Mg^{II} with the smallest ionic radius of 0.65 Å has the highest value for ΔH_f°. The entropy change for the 1:1 metal–guanosine complexes is positive in all the cases. However, there is no regular trend in the values. Relatively more negative enthalpy values coupled with the positive entropy values provides evidence for the primary role of enthalpy in the formation of the metal complexes of guanosine.

The stability constants for the mixed-ligand 1:1:1 systems metal–bipy–guanosine and metal–phen–guanosine (Table 3) decrease in the order: Ni^{II} > Co^{II} > Cu^{II} > Zn^{II} > Mn^{II} > Mg^{II} > Ca^{II}. The Δ log K values for metal–phen–guanosine and metal–ssa–guanosine are negative (Table 5) indicating that in these ternary systems the stabilities are lower than in the corresponding binary systems. This is in accord with statistical considerations, but the Δ log K values for metal–bipy–guanosine are however positive and these complexes are more stable than the corresponding binary systems. The enhanced stability in this case may be explained in terms of stacking interactions, which are less extensive than in the 1:2 metal–guanosine system.

The stability constants for the 1:2 metal–guanosine systems are higher than those for the corresponding 1:1 systems, contrary to statistical considerations. The Δ log K values (log $K^{M(HL)}_{MH_2L_2}$ − log $K^{M}_{M(HL)}$) are all positive Table 1. The only exception to this is with Cu^{II} where the 1:2 is less stable than the 1:1 guanosine complex. The enthalpy changes for the formation of the 1:2 metal–guanosine complexes are more negative (*i.e.* more exothermic) than those for the 1:1 corresponding metal complexes (Table 2). The entropy values are however more positive for the 1:2 than for the corresponding 1:1 systems, but there is no regular trend in the values. Thus enthalpy seems to be the driving force for the formation of 1:2 metal–guanosine complexes. It was shown earlier that the Δ log K values are all positive for 1:2 metal–guanosine complexes. More important than the Δ log K values, which often vary with temperature, are $\Delta(\Delta H) = H_f^\circ$(log $K^{M(HL)}_{MH_2L_2}$) − H_f°(log $K^{M}_{M(HL)}$) and $\Delta(\Delta S) = \Delta S_f^\circ$(log $K^{M(HL)}_{MH_2L_2}$) − ΔS_f°(log $K^{M}_{M(HL)}$) (Table 2). The $\Delta(\Delta H)$ values for the guanosine complexes are all exothermic (1.8—3.4 kJ mol^{-1}), except for Cu^{II} (Table 2), and represent the extra stabilization of the 1:2 as compared to the 1:1 system. High exothermic $\Delta(\Delta H)$ may be explained in terms of stacking interactions of the aromatic rings[30–36] which confer extra stability on the 1:2 complexes by long-range weak bonding of the order of 8—17 kJ mol^{-1}. The $\Delta(\Delta H)$ observed values may thus be roughly correlated with the extent of stacking in the 1:2 complexes of guanosine. The structure of the stacked complex is shown in Figure 2. The $\Delta(\Delta S)$ values seem to have little significance, being positive or negative and indicating that there are solvation differences in the 1:2 and 1:1 systems.

Experimental

Potentiometric titration of the ligand was carried out with a standard carbonate-free sodium hydroxide solution in the absence and in the presence of the metal ion investigated. The ionic strength was maintained constant by using 0.10 mol dm^{-3} (KNO_3) as the supporting electrolyte and relatively low concentrations of ligand and metal ion. A stream of purified nitrogen was passed throughout the experiment in order to exclude the adverse effect of atmospheric carbon dioxide. A Digisun pH meter with combination glass and calomel electrodes was used to measure the hydrogen-ion concentration.

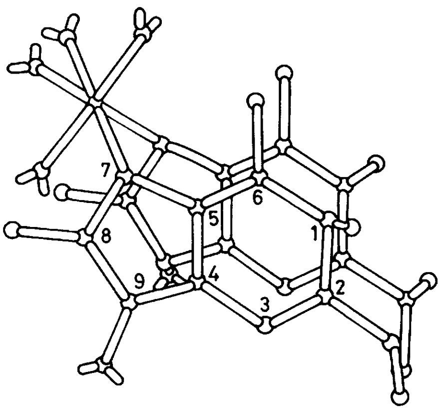


Figure 2. Stacking interaction in 1:2 metal–guanosine complexes

The electrode system was calibrated by direct titration with acetic acid, and the pH meter reading observed was compared with the actual hydrogen-ion concentration as calculated from the data tabulated by Harned and Owen.[37] The regions below pH 3.5 and above 10.5 were calibrated by direct measurement of the hydrogen-ion concentration in hydrochloric acid and sodium hydroxide solutions, respectively.

Reagents.—Chromatographically pure guanosine was obtained from Sigma Chemical Company, 2,2′-bipyridyl, 1,10-phenanthroline, and 5-sulphosalicyclic acid from E. Merck, Darmstadt. Fresh solid ligand was weighed out for each titration to exclude loss by hydrolysis or photochemical decomposition. The metal salt solutions were standardized by titration with the disodium salt of ethylenediaminetetra-acetate (edta) as described by Schwarzenbach.[38] Carbonate-free sodium hydroxide was prepared by the method of Schwarzenbach and Biedermann[39] and was standardized by titration with pure potassium hydrogenphthalate.

Calculations.—The acid dissociation of monoprotonated guanosine is described by the equilibria (1) and (2). The pK_a

$$H_2L^+ \underset{}{\overset{K_a}{\rightleftharpoons}} HL + H^+ \qquad (1)$$

$$HL \overset{K_{2a}}{\rightleftharpoons} H^+ + L^- \qquad (2)$$

values of guanosine were calculated by a direct algebraic method.[23]

The equilibrium (3) is involved in the formation of 1:1 metal–guanosine complexes where $K^{M}_{M(HL)} = [M(HL)]/[M][HL]$,

$$M + HL \overset{K^{M}_{M(HL)}}{\rightleftharpoons} M(HL) \qquad (3)$$

$[HL] = K_a\{(1 - n)c_M - [H^+] + [OH^-]\}/[H^+]$, $[M] = [HL](K_a^{-1}[H^+] + 1)$, $[M(HL)] = c_M - [M]$, and c_M = total metal-ion concentration. In solutions containing a 1:2 molar ratio of metal to guanosine equilibria (3) and (4) are involved

$$M(HL) + HL \overset{K^{M(HL)}_{M(HL)_2}}{\rightleftharpoons} M(HL)_2 \qquad (4)$$

where $K^{M(HL)}_{M(HL)_2} = [M(HL)_2]/[M(HL)][HL]$, [HL] is defined as above, $[M(HL)] = K_1[M][HL]$, $[M] = [HL](K_a^{-1}[H^+] + 1)/(2 + K_1[HL])$, $[M(HL)_2] = c_M - [M](1 + K_1[HL])$, and $K_1 = K^{M}_{M(HL)}$ is the stability constant of the 1:1 protonated complex.

For the calculation of stability constants of ternary complexes having 1:1:1 molar ratios of metal ion–guanosine–2,2′-bipyridyl or –1,10-phenanthroline the equilibria (5) were

$$M + HL + A \overset{K^{M}_{M(HL)A}}{\rightleftharpoons} M(HL)A \qquad (5)$$

considered where $K^{M}_{M(HL)A} = X_L(c_M - [L]X_A/[L]^3{X_A}^2$, $[L] = \{6c_M - (2nc_M + 2[H^+] - 2[OH^-])\}/[\alpha_M + (3\alpha_L X_A/X_L) + (X_A/X_L)]$, $X_A = [H^+]^2/K_aK_{2a} + ([H^+]/K_{2a}) + 1$, $\alpha_A = (3[H^+]^2/K_aK_{2a}) + ([H^+]/K_{2a}) - 1$, $\alpha_L = [H^+]/K_a$, and $X_L = ([H^+]/K_a) + 1$. For the bipy system equation (6) is applicable,

$$K^{M}_{M(HL)A} = \frac{c_M - [L]X}{[L]^3X^2} \cdot Y \qquad (6)$$

where $[L] = \{(3 - n)c_M - [H^+] + [OH]\}/({K_{2a}}^{-1}[H^+] + {K_a}^{-1}[H^+]XY^{-1})$ with K_{2a} for bipy and K_a for guanosine, $X = {K_{2a}}^{-1}[H^+] + 1$, and $Y = {K_a}^{-1}[H^+] + 1$. In case of ssa the equilibria (7) were considered, where $K^{M(HA)}_{M(HL)(HA)} = [M(HL)(HA)]/[M(HA)][HL]$.

$$M(HA) + HL \overset{K^{M(HA)}_{M(HL)(HA)}}{\rightleftharpoons} M(HL)(HA) \qquad (7)$$

The stability constant $K^{M(HA)}_{M(HA)(HL)}$ was calculated in a manner similar to that described for the 1:1 metal–guanosine system.

The values of $\Delta H_f^{\ominus}$, $\Delta G_f^{\ominus}$, and $\Delta S_f^{\ominus}$ were calculated by using the usual relationships as described in an earlier paper.[24] All calculations were done on a Casio FX-702P personal computer. The formation of hydrolysed species can be ruled out as the inflections in the titration curves do not indicate any protons to be liberated except those of the ligands. Moreover, the buffer regions lie in a pH range where free metal ion is not hydrolysed. Since the titration curves were independent of concentration, the formation of dimers can also be ruled out.

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