Stabilities and Thermodynamic Parameters of 1:2 Metal–Xanthosine Complexes in Solution

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Potentiometric equilibrium measurements were made at 5, 25, 35 and 45 °C to determine the stability constants of Cu(II), Ni(II), Zn(II), Co(II), Mn(II), Mg(II) and Ca(II) with xanthosine in a 1:2 ratio (μ = 0.10 M KNO_3). The enthalpy and entropy changes associated with the above interactions were also calculated using temperature coefficient data. The stability constants of these 1:2 metal–xanthosine complexes are higher than the corresponding complexes of 1:1 systems (Δ log K positive). This enhanced stability is measured in terms of $\Delta\Delta H_f^\circ$ (ΔH_2 – ΔH_1), a quantity which directly measures the extent of extra interaction. This enhanced interaction in the 1:2 system is attributed to a favourable 'stacking' interaction between two xanthosine moieties in solution.

Introduction

We have been involved for some time in the study of metal–xanthosine complexes in solution. In our earlier [1–4] publications we reported the stability constants of binary and ternary complexes of xanthosine in solution with various metal ions. In this paper, we report the stability constants and also the thermodynamic quantities associated with the 1:2 metal–xanthosine system. We have undertaken these studies to see the effect of a secondary ligand (here xanthosine itself) on the 1:1 metal–xanthosine system. Such studies are important to understand the driving forces that lead to the formation of ternary complexes in biological systems, since the 1:2 system can also be considered as a ternary system having two similar ligands. Usually, as expected from statistical considerations [5], the stability constant for the stepwise formation of a 1:2 metal–ligand complex is smaller than that for the 1:1 metal complex. But, for the 1:2 metal–xanthosine system the stability constants are much higher than those of the corresponding 1:1 metal–xanthosine system. This extra stability is reflected not only in the more positive values of Δ log K ($\log^{M}_{MH_2L_2} - 2\log^{M}_{MHL}$) but also in the more exothermic values of ΔH_2. The enhanced stability of the complex is measured in terms of $\Delta\Delta H_f^\circ$ (ΔH_2 – ΔH_1), a quantity which directly measures the extent of extra interaction in this system. This enhanced interaction is attributed to a favourable 'stacking' interaction of xanthosine in the 1:2 system.

The stacking interaction has been observed as the most important phenomenon in natural systems and explains the extra stability found in biological systems.

Experimental

Xanthosine was obtained from Sigma Chemical Company (U.S.A.). Transition and alkaline earth metal ions were of Analar grade and were standardised volumetrically by titration with the disodium salt of EDTA in the presence of a suitable indicator as outlined by Schwarzenbach [6].

The experimental method consisted of a potentiometric titration of metal ions and xanthosine in a 1:2 ratio with standard NaOH solution. All titrations were carried out at 5, 25, 35 and 45 ± 0.1 °C. The experimental conditions maintained were similar to those described in our earlier work [7].

For this investigation as well as for a large number of similar investigations in the literature, the standard state is defined as 0.10 *M* (KNO_3) solution, so that the activity of any species becomes unity when it is highly dilute in 0.10 *M* (KNO_3).

Calculations

The acid dissociation constants of xanthosine were calculated by the usual algebraic method.

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TABLE I. Stability Constants of Complexes Containing 1:2 Ratio of Metal Ions with Xanthosine.[a] $\mu = 0.10\,M$ (KNO_3).

Metal ion	5 °C		25 °C		35 °C		45 °C	
	$\log K^{M}_{MH_2L_2}$	$\log K_2$	$\log K^{M}_{MH_2L_2}$	$\log K_2$	$\log K^{M}_{MH_2L_2}$	$\log K_2$	$\log K^{M}_{MH_2L_2}$	$\log K_2$
Cu(II)	6.66 ± 0.08	3.55 ± 0.07	6.24 ± 0.04	3.33 ± 0.05	6.36 ± 0.05	3.30 ± 0.06	5.96 ± 0.10	3.13 ± 0.08
Ni(II)	6.58 ± 0.04	3.61 ± 0.05	5.84 ± 0.07	2.96 ± 0.06	5.90 ± 0.07	2.98 ± 0.06	5.88 ± 0.10	3.08 ± 0.08
Zn(II)	6.15 ± 0.07	3.81 ± 0.07	5.21 ± 0.06	2.95 ± 0.06	5.25 ± 0.11	3.04 ± 0.08	5.53 ± 0.10	3.37 ± 0.08
Co(II)	6.03 ± 0.08	3.39 ± 0.07	5.32 ± 0.07	3.09 ± 0.07	5.38 ± 0.06	2.87 ± 0.06	5.53 ± 0.10	3.31 ± 0.08
Mn(II)	6.36 ± 0.05	3.47 ± 0.06	5.31 ± 0.09	2.83 ± 0.07	5.76 ± 0.06	2.89 ± 0.06	5.61 ± 0.10	3.12 ± 0.08
Mg(II)	5.60 ± 0.08	3.16 ± 0.07	5.00 ± 0.10	2.78 ± 0.08	5.07 ± 0.08	2.84 ± 0.07	5.47 ± 0.10	2.98 ± 0.08
Ca(II)	6.01 ± 0.10	3.59 ± 0.08	5.16 ± 0.08	2.79 ± 0.07	5.15 ± 0.07	2.94 ± 0.06	5.56 ± 0.10	3.17 ± 0.08

[a] $\log K_2 = \log K^{M}_{MH_2L_2} - \log K^{M}_{MHL}$.

TABLE II. Thermodynamic Parameters Associated with the Interaction of Metal Ions with Xanthosine (1:2). $\mu = 0.10\,M$ (KNO_3).

Metal ion	ΔH°_f (Kcal/mol) $K^{M}_{MH_2L_2}$	ΔG°_f (25 °C) (Kcal/mol) $K^{M}_{MH_2L_2}$	ΔS°_f (25 °C) (e.u.) $K^{M}_{MH_2L_2}$
Cu(II)	−6.3 ± 0.9	−8.51 ± 0.04	+7.4 ± 2.9
Ni(II)	−4.6 ± 0.9	−7.97 ± 0.7	+11.3 ± 2.8
Zn(II)	−2.8 ± 1.1	−7.10 ± 0.06	+14.4 ± 3.2
Co(II)	−2.2 ± 0.7	−7.26 ± 0.07	+16.9 ± 2.2
Mn(II)	−2.8 ± 0.5	−7.24 ± 0.09	+15.0 ± 1.2
Mg(II)	+1.9 ± 0.1	−6.82 ± 0.10	+29.3 ± 0.3
Ca(II)	−0.9 ± 0.3	−7.04 ± 0.08	+20.7 ± 0.7

In order to determine the stability constants of diprotonated 1:2 complexes, the following equations were used:

$$M^{2+} + 2HL^- \rightleftharpoons MH_2L_2 \tag{1}$$

$$K^{M}_{MH_2L_2} = \frac{T_M - [M^{2+}]}{[M^{2+}]\{(2-a)T_M - [H^+] + [OH^-])Ka/[H^+]^2\}} \tag{2}$$

where

$$M^{2+} = \frac{(2-m)T_M - [H^+] + [OH^-])(1 + Ka/[H^+])}{2 + K_1(2-m)T_M - [H^+] + [OH^-])Ka/[H^+]}$$

K_1 = protonated 1:1 stability constant of metal xanthosine; T_M = total concentration of metal ion species; Ka = dissociation constant of xanthosine and m = moles of base added per mole of metal ion.

Values of enthalpy of complex formation ΔH°_f were obtained at each temperature interval by the relationship:

$$\Delta H^\circ_f = \frac{2.303\,RT_1T_2\log(K_2/K_1)}{(T_2 - T_1)} \tag{3}$$

and values of ΔG°_f and ΔS°_f for the various reactions involved were calculated by the relationships

$$\Delta G^\circ_f = -RT\ln K \tag{4}$$

$$\Delta S^\circ_f = \frac{\Delta H^\circ_f - \Delta G^\circ_f}{T} \tag{5}$$

respectively.

Results and Discussion

The potentiometric titration curves of Cu(II), Ni(II), Zn(II), Co(II), Mn(II), Mg(II) and Ca(II) with xanthosine in a 1:2 ratio at 5, 25 and 35 °C are similar [3] to those at 45 °C. The diprotonated 1:2 complex, $K^{M}_{MH_2L_2}$, was calculated by using eqn. (2). The stability constants obtained at various temperatures are presented in Table I. The thermodynamic constants pertaining to the interaction of

TABLE III. Comparison of the Stability Constants of 1:1 Metal–Xanthosine and 1:2 Metal–Xanthosine Complexes.

Metal ion	Δ log K (log $K^M_{MH_2L_2}$ – 2 log K^M_{MHL})a			
	5 °C	25 °C	35 °C	45 °C
Cu(II)	+0.44	+0.42	+0.24	+0.30
Ni(II)	+0.54	+0.08	+0.06	+0.28
Zn(II)	+1.47	+0.69	+0.83	+1.21
Co(II)	+0.75	+0.86	+0.36	+1.09
Mn(II)	+0.58	+0.35	+0.02	+0.63
Mg(II)	+0.72	+0.56	+0.61	+0.59
Ca(II)	+1.17	+0.42	+0.73	+0.88

[a]The values are taken from ref. (2).

TABLE IV. Differences in the Enthalpies of Formation Associated with the Interaction of Metal Ions with Xanthosine (1:1 and 1:2). μ = 0.10 *M* (KNO_3).

Metal ion	ΔH_2 (Kcal/mol) (1:2)	ΔH_1 (Kcal/mol) (1:1)[a]	$\Delta\Delta H^\circ_f$
Cu(II)	–6.3 ± 0.9	–1.9 ± 0.1	–4.4
Ni(II)	–4.6 ± 0.9	–1.8 ± 0.1	–2.8
Zn(II)	–2.8 ± 1.1	–2.2 ± 0.1	–0.6
Co(II)	–2.2 ± 0.7	–0.5 ± 0.1	–1.7
Mn(II)	–2.8 ± 0.5	+0.5 ± 0.1	–2.3
Mg(II)	+1.9 ± 0.1	+3.7 ± 1.0	+1.8
Ca(II)	–0.9 ± 0.3	–1.6 ± 0.1	–0.7

[a]The values are taken from ref. (2).

TABLE V. Differences in the Entropies of Formation Associated with the Interaction of Metal Ions with Xanthosine (1:1 and 1:2). μ = 0.10 *M* (KNO_3).

Metal ion	ΔS°_f (25 °C) (e.u.) (1:2)	ΔS°_f (25 °C) (e.u.) (1:2)	$\Delta\Delta S^\circ_f$ (e.u.)
Cu(II)	+7.4 ± 2.9	+6.9 ± 0.4	+0.5
Ni(II)	+11.3 ± 2.8	+7.1 ± 0.3	+0.4
Zn(II)	+14.4 ± 3.2	+3.1 ± 0.2	+11.3
Co(II)	+16.9 ± 2.2	+8.6 ± 0.5	+8.3
Mn(II)	+15.0 ± 1.2	+10.9 ± 0.2	+4.1
Mg(II)	+29.3 ± 0.3	+22.8 ± 3.0	+6.5
Ca(II)	+20.7± 0.7	+5.4 ± 0.2	+15.3

*The values are taken from ref. (2).

the above mentioned metal ions with xanthosine are given in Table II.

The stability constants of 1:2 metal–xanthosine complexes are higher than the 1:1 metal–xanthosine complexes as is evident from Table III. This is contrary to the statistical considerations [5], according to which the stability constant for the stepwise fomation of the 1:2 metal–ligand complex should be smaller than that for the 1:1 complex.

This is also in accord with Pearson's HSAB Principle and is observed in most of the cases where the ligand is a neutral or negatively charged species. Then, what are the factors that are responsible for the extra stability of 1:2 complexes as compared to 1:1 complexes ? This extra stability cannot be explained merely on the basis of charge neutralization. Therefore, we have evaluated various parameters associated with the 1:2 metal–xanthosine system like Δ log K, $\Delta\Delta H^\circ_f$, $\Delta\Delta S^\circ_f$ etc. to account for this extra stability.

First, let us see how the Δ log K varies and what information one can get from it. The Δ log K values for the 1:2 system are quite high and are positive for all the metal ions studied. However, the Δ log K values obtained for Cu(II)–bipyridyl (1:2 and 1:1) and Cu(II)–glycine (1:2 and 1:1) are negative [8]. These differences in Δ log K values may be explained on the following basis. Although the Δ log K values are helpful, to certain extent, to explain the differences in stabilities between 1:2 and 1:1 systems, it is not an absolute means of measuring the enhanced stability, since it varies with temperature. So we have measured this enhanced stability in terms of $\Delta\Delta H^\circ_f$ ($\Delta H_2 - \Delta H_1$) where ΔH_2 and ΔH_1 are the enthalpies corresponding to the formation of 1:2 and 1:1 complexes, respectively.

It may be seen from Table IV that the enthalpies associated with the formation of 1:2 metal–xanthosine complexes are fairly exothermic and are of the order of about 2–6 Kcal/mole. The more exothermic enthalpy values in the formation of a 1:2 complex are also reflected in the $\Delta\Delta H^\circ_f$ values, which vary from 1–4 Kcal/mole within the series of metal ions studied. A positive enthalpy value for Mg(II) is due to the very high heat of hydration of Mg(II) as compared to the other metal ions. These exothermic values of $\Delta\Delta H^\circ_f$ can be associated with the energy of 'stacking' interaction which is purely a van der Waals type of interaction and is expected to have a low value of energy of interaction. This interaction is much smaller than a hydrogen bond formation which has energies in the range of 5–10 Kcal/mole. Thus the 'stacking' interaction seems to favor the formation of 1:2 metal–xanthosine complexes in solution.

The entropy also seems to favour the formation of the 1:2 metal complex over the 1:1 metal complex, to a small extent, as is seen from Table V. This is attributed to the release of solvated water molecules by the anion during complex formation and charge neutralization with the metal ion.

To conclude, it has been established that purine and pyrimidine bases, nucleosides and nucleotides

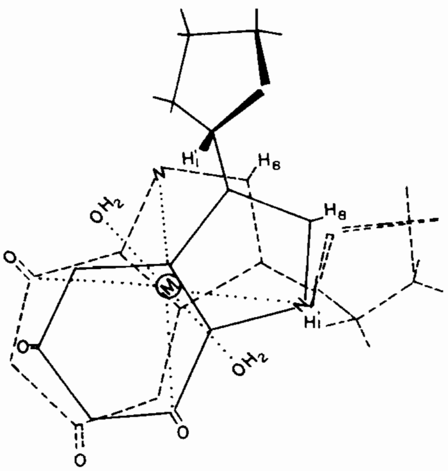

Fig. 1. Model illustrating the proposed arrangements for two xanthosines in stacks (alternate stack) along with the metal ion.

associate extensively in aqueous solution by a mechanism involving vertical stacking of bases. The importance of stacking in the hydrolysis of nucleoside phosphates has been observed by Sigel [9, 10] recently where it was shown that the system undergoes hydrolysis in a ML_2 type of system with parallel configuration of adenosine residues. Sigel has also reported [11], in a very recent article, the influence of divalent metal ions on the self association tendency of nucleoside 5'-triphosphates and concluded that the divalent metal ions like Mg(II) and Zn(II) promote stacking by a factor of about 4 in these systems. Therefore, in the case of nucleoside xanthosine also, the stacking is expected to be promoted by divalent metal ions, though to a lesser extent, compared with the nucleotides. So it is clear that the extra stability of 1:2 metal xanthosine complexes is due to the 'stacking' interaction between the two xanthosine moieties. This agrees well with the earlier observations [12, 13] that 'stacking' is far more effective in purine bases than in pyrimidine bases.

Based on our conclusions we propose the following tentative and simplified stacking model (alternate stack) for the metal xanthosine system. Although we have an oxo group in xanthosine these stacks will have a partially overlapped orientation so that the H-8 and H-1' can both be shielded to a similar extent. In this model not only the steric hindrance of the ribosyl group is reduced but also the repulsion between the dipole moments of the adjacent bases expected in the straight stack.

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