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Interaction of rare earth metal ions with nucleosides—a study of binary and ternary systems in solution

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Abstract. Studies on interaction of La(III), Pr(III), Nd(III), Sm(III), Gd(III), Dy(III) and Er(III) with inosine and xanthosine in a 1:1 ratio have been carried out by potentiometric equilibrium measurements at 35 ± 0·1°C and 0·1 M (KNO_3) ionic strength. Investigations were also made for the interaction of these metal ions and nucleosides with the biologically important secondary ligands glycine and histidine. These investigations were undertaken with a view to assess the influence of charge on the structure and stability of 1:1 metal-inosine/xanthosine systems.

Keywords. Lanthanide-nucleoside complexes; metal-inosine/xanthosine systems.

1. Introduction

Although the biological importance of nucleoside and nucleotide metal complexes has been recognised for long, we have only recently begun to understand the structural chemistry operating at biological sites where metal ions are found. A study of the specific mode and site of interaction of metal ions with nucleosides could provide useful information in understanding the nature of such interactions in biological systems. Such endeavours have yielded fruitful results earlier (Fritzsche 1970; Eichorn 1973; Rabindra Reddy *et al* 1976, 1978, 1979, 1983, 1984, 1985; Orenberg *et al* 1980; Rabindra Reddy and Harilatha Reddy 1983, 1985; Rabindra Reddy and Venugopal Reddy 1983; Bruce Martin 1985). However, data on complexes of metal ions of higher oxidation states are not available in the literature. Therefore, it was considered important to investigate the interaction of trivalent rare earth metal ions with nucleosides in both binary and ternary systems.

In the present paper, we report the stability constants of both binary and ternary complexes of inosine and xanthosine with La(III), Pr(III), Nd(III), Sm(III), Gd(III), Dy(III) and Er(III) and the biologically important secondary ligands, glycine and histidine. The interaction of these metal ions with secondary ligands has been attempted for the first time. The stabilities of trivalent metal-nucleoside

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complexes were found to be higher than those of the complexes of bivalent metal ions. The extra stabilization in the lanthanide metal complexes is attributed to the increased charge on the metal ions. We hope that this type of study will help in elucidating the various factors responsible for the stabilization of trivalent metal-nucleoside complexes in solution.

2. Experimental

Inosine, xanthosine, glycine and histidine were obtained from Sigma Chemical Company, St. Louis, USA. All the metal ions were of AnalaR grade and were used without further purification. For every titration fresh solid ligand was weighed out to avoid hydrolysis, which may take place when stock solutions are employed. The lighter rare earth metal ions were standardised volumetrically by titration with disodium salt of EDTA in the presence of a suitable indicator as described by Schwarzenbach (1957). Heavier rare earth metal ions were estimated gravimetrically (Kolthoft and Elving 1963). Carbonate-free sodium hydroxide was prepared by the method of Schwarzenbach and Biedermann (1948) and was standardised by titration with potassium hydrogen phthalate. The experimental method consisted of potentiometric titration of the metal ions and inosine, xanthosine, glycine and histidine in 1:1 and 1:1:1 ratios at $35 \pm 0{\cdot}1$°C with standard sodium hydroxide solution. The experimental conditions maintained were the same as those described earlier (Rabindra Reddy *et al* 1984).

3. Calculations

The acid dissociation constants of ligands, inosine, xanthosine, histidine and glycine calculated by the usual algebraic method are presented in table 1.

Stability constants

The stability constants of 1:1 metal-inosine complexes were calculated using (1) (charges omitted for clarity).

$$K^{M}_{ML} = \frac{T_M - [M]}{[M][L]}. \qquad (1)$$

Table 1. Acid dissociation constants* of the ligands at $35 \pm 0{\cdot}1$°C and $\mu = 0{\cdot}1$ M (KNO_3).

Ligand	pK_{a_1}	pK_{a_2}
Inosine	$8{\cdot}48 \pm 0{\cdot}02$	–
Xanthosine	$5{\cdot}46 \pm 0{\cdot}02$	$9{\cdot}70 \pm 0{\cdot}02$
Glycine	$2{\cdot}33 \pm 0{\cdot}02$	$9{\cdot}75 \pm 0{\cdot}02$
Histidine	$6{\cdot}00 \pm 0{\cdot}04$	$9{\cdot}00 \pm 0{\cdot}04$

* From Rabindra Reddy *et al* 1985.

To calculate the stability constants of 1:1 protonated complexes of metal-xanthosine equation (2) was employed.

$$K^{M}_{MHL} = \frac{T_M - [HL]X}{[HL]^2 \times [H^+]/K_{2a}}, \tag{2}$$

where $X = ([H^+]^2/K_a K_{2a}) + ([H^+]/K_a K_{2a})$

and $$[HL] = \frac{(1-a)\,T_L - [H^+] + [OH^-]}{[H^+]^2/K_a K_{2a}}.$$

Equation (2) was also used for obtaining the stability constants of 1:1 metal-glycine/histidine complexes.

For calculating the stability constants of ternary complexes of La(III), Pr(III), Nd(III), Sm(III), Gd(III), Dy(III) and Er(III) with inosine (HL) and glycine/histidine (H_2A) in 1:1:1 ratio eq. (3) was employed.

$$K^{M(HA)}_{MLA} = \frac{T_M - [M]}{[M][L][A]} \tag{3}$$

The stability constants of the ternary complexes of La(III), Pr(III), Nd(III), Sm(III), Gd(III), Dy(III) and Er(III) with xanthosine (H_2L) and histidine/glycine (H_2A) in a 1:1:1 ratio were calculated using

$$K^{M}_{M(HL)(HA)} = \frac{T_M - [HL]X}{[HL]^3[X]^2} \tag{4}$$

This equation was described earlier (Rabindra Reddy and Harilatha Reddy 1985).

All calculations were made using the experimental data depicted in figures 1 and 2 on a Casio PB 100 personal computer employing suitable programmes.

4. Results

(i) *Metal-inosine (1:1) system*: The formation constants for the normal 1:1 metal inosine complexes calculated using (1) are listed in table 2.
(ii) *Metal-xanthosine (1:1) system*: The constants for the monoprotonated 1:1 metal-xanthosine complexes calculated using (2) are shown in table 2.
(iii) *Metal-glycine and metal-histidine (1:1) systems*: The stability constants of 1:1 metal glycine/histidine complexes calculated using (2) are presented in table 2.
(iv) *Metal-inosine-glycine/histidine (1:1:1) systems*: The stability constants of 1:1:1 metal-inosine-glycine/histidine complexes calculated using (3) are given in table 3.
(v) *Metal-xanthosine-glycine/histidine (1:1:1) systems*: The interaction of rare earth metal ions with xanthosine and glycine/histidine in a 1:1:1 ratio resulted in the formation of diprotonated complexes. The constants were calculated using (4) and are also listed in table 3.

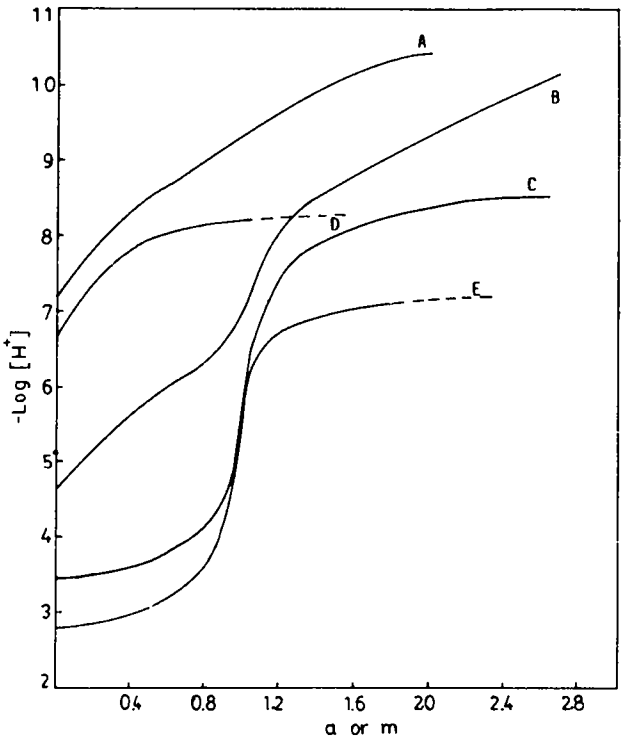


Figure 1. Potentiometric titration curves for La(III):inosine (1:1) and Dy(III):inosine:glycine (1:1:1) systems at 35°C and μ = 0·1 M (KNO_3). *a* or *m*, moles of base added per mple of ligand for curves A, B, C: *m*, moles of base added per mole of metal ion for curves D and E. A, free inosine; B, free glycine; C, free histidine; D, La(III):inosine; E, Dy(III):inosine:glycine.

Table 2. Stability constants* for the interaction of rare earth metal ions with inosine, xanthosine, glycine and histidine in a 1:1 ratio at 35 ± 0·1°C and μ = 0·1 M (KNO_3).

Metal ion (III)	Metal:inosine K^M_{ML}	Metal:xanthosine $K^M_{M(HL)}$	Metal:glycine $K^M_{M(HA)}$	Metal:histidine $K^M_{M(HA)}$
La	4·10	3·50	3·23	3·41
Pr	4·21	4·24	3·53	3·56
Nd	4·29	4·35	3·71	3·79
Sm	4·39	4·52	3·82	3·85
Gd	4·41	3·62	3·72	3·76
Dy	4·52	4·58	3·86	3·99
Er	4·71	4·63	3·93	4·06

* The constants are accurate to the extent of 0·06 log *K* units.

5. Discussion

The stability constants of metal-inosine and metal-xanthosine complexes decrease in the order: Er(III) > Dy(III) > Gd(III) > Sm(III) > Nd(III) > Pr(III) > La(III). The stability constants are inversely proportional to their ionic radii, a trend observed for a variety of ligands combining with the rare earth metals

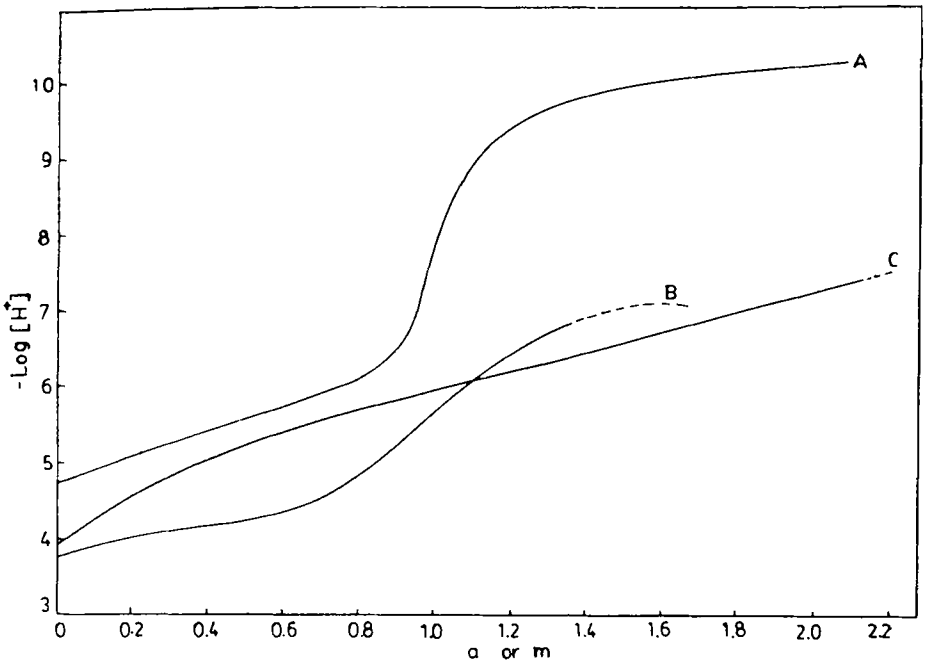


Figure 2. Potentiometric titration curves for Sm(III):xanthosine (1:1) and Er(III):xanthosine:histidine (1:1:1) at 35°C and 0·1 M (KNO_3) ionic strength. *a* or *m* = moles of base added per mole of ligand for curve A; *m*, moles of base added per mole of metal ion for curves B and C. A, free xanthosine; B, Sm(III):xanthosine (1:1); C, Er(III):xanthosine:histidine (1:1:1).

Table 3. Stability constants for the ternary rare earth chelates of inosine and xanthosine with glycine/histidine in a 1:1:1 ratio at 35 ± 0·1°C and μ = 0·1 M (KNO_3).

Metal ion (III)	Metal:inosine: glycine $K^{M(HA)}_{MLA}$	Metal:inosine: histidine $K^{M(HA)}_{MLA}$	Metal:xantho: glycine $K^{M}_{M(OH)(HA)}$	Metal:xantho: histidine $K^{M}_{M(OH)(HA)}$	Δ log *K* M: xantho: gly	Δ log *K* M: xantho: histidine
Lr	9·32 ± 0·03	10·11 ± 0·05	5·00 ± 0·01	5·62 ± 0·06	− 2·33	− 1·89
Pr	9·51 ± 0·02	10·45 ± 0·06	5·10 ± 0·01	5·65 ± 0·06	− 2·64	− 2·04
Nd	9·90 ± 0·04	10·56 ± 0·02	5·16 ± 0·06	5·81 ± 0·09	− 2·90	− 2·22
Sm	10·22 ± 0·01	10·89 ± 0·05	5·28 ± 0·04	5·95 ± 0·08	− 3·60	− 2·30
Gd	10·52 ± 0·07	10·96 ± 0·02	5·36 ± 0·04	4·72 ± 0·08	− 1·98	− 3·04
Dy	10·58 ± 0·02	11·02 ± 0·04	5·42 ± 0·04	6·07 ± 0·04	− 3·02	− 2·39
Er	10·86 ± 0·04	11·09 ± 0·06	5·55 ± 0·01	6·49 ± 0·04	− 3·01	− 2·02

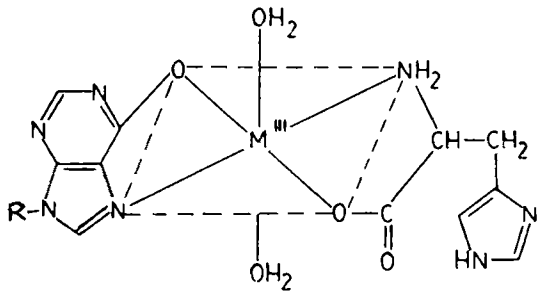
(Rabindra Reddy and Madhusudan Reddy 1985). It is of interest here to compare the stabilities of bivalent metal-inosine/xanthosine complex binary systems (Rabindra Reddy *et al* 1976, 1983) with those of the lanthanides. The lanthanone complexes are found to be more stable than the bivalent metal complexes. The higher stability of the rare earth metal-nucleoside complexes can be explained on the basis of the differences in the charge on the metal ions. The rare earth metal

ions have smaller ionic radii as compared to bivalent metal ions because of their positive charge. This enables ligands to come closer to the central metal ion paving the way for better electrostatic attractions, which in turn result in stronger metal-ligand interactions. However, the types of complexes formed and the magnitudes of the stability constants suggest that the nature of bonding in both bivalent and trivalent metal complexes may be similar.

Interaction of the metal ions with glycine and histidine resulted in the formation of monoprotonated complexes. The closeness in the stabilities of 1:1 metal-glycine and metal-histidine complexes indicates that the mode of binding in metal-glycine and metal-histidine complexes is the same, i.e., histidine acts like glycine with the involvement of mixed N/O donor sites in metal coordination. This is different from the situation in transition metal complexes (Rabindra Reddy and Harilatha Reddy 1985) where histidine behaves as a terdentate ligand involving all its available donor sites in metal binding.

The ternary complexes of histidine in the case of both inosine and xanthosine are more stable than the ternary complexes of glycine. This is due to the fact that histidine, being an aromatic ligand, can participate in an additional interaction with inosine and xanthosine. This explanation is similar to that given for the transition metal complexes (Rabindra Reddy and Harilatha Reddy 1985). The Δ log K values (the differences in the overall 1:1:1 ternary stability constants and the corresponding binary constants) for the xanthosine system are shown in table 3. The corresponding data for the inosine system could not be computed because of the formation of different types of complexes in both binary and ternary systems. The data for the xanthosine system show negative values. This suggests that protonated xanthosine complexes are less favoured. The normal complexes could not be observed because of the formation of precipitates. A comparison of even these negative Δ log K values shows that histidine forms more stable complexes as compared to glycine even though the donor atoms involved in bonding are similar (N/O). This may be due to the aromaticity of histidine. Based on this observation we have proposed the tentative structure of metal-inosine-histidine (1:1:1) as shown in figure 3.

When the Δ log K values of the ternary complexes of rare earth metal ions are compared with those of the corresponding ternary systems of transition metal ions,



R = Ribose

Figure 3. Tentative structure of M(III)-inosine-histidine (1:1:1) in solution.

we find that the rare earth mixed chelates are less stable than the transition metal complexes (Rabindra Reddy and Harilatha Reddy 1983, 1985). The lower stability of the ternary rare earth chelates may be due to the high stability of their 1:1 metal-inosine or 1:1 metal-xanthosine complexes. The higher stability of binary complexes of rare earth metal ions may disfavour the formation of ternary complexes in solution. A better understanding of these interactions can be obtained with a knowledge of thermodynamic parameters like ΔH_f^0 and ΔS_f^0. Studies involving these parameters are presently being carried out.

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