Inorganica Chimica Acta, 125 (1986) 191–195

Rare Earth Metal Complexes of Cytidine

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(Received March 6, 1986; revised July 5, 1986)

Abstract

The interactions of La(III), Pr(III), Nd(III), Sm(III), Gd(III), Dy(III) and Er(III) and cytidine with glycine, histidine and oxalic acid for the formation of binary (1:1) and ternary complexes (1:1:1) have been investigated by potentiometric equilibrium measurements at 35 °C and 0.10 mol dm^{-3} (KNO_3) ionic strength. These investigations were undertaken to assess the influences of charge on the structure and stability of metal nucleoside complexes in solution. Cytidine forms more stable complexes with trivalent lanthanones compared to bivalent transition metal ions. This is explained on the basis of the differences in the charge of the metal ions concerned. The ternary complexes of these systems are more stable than the corresponding binary complexes. This enhanced stability is measured in terms of $\Delta \log K$ (difference between the stability of overall (1:1:1) and binary (1:1)). Based on the trends in $\Delta \log K$ values, various factors that affect the stability of these complexes have been explained.

Introduction

The interactions of metal ions with nucleosides and nucleotides have received considerable attention during the last fifteen years [1–6] with an aim to develop suitable model systems for metal nucleic acid interactions which subsequently lead to a more comprehensive understanding of the reactions that occur *in vivo*. We have been involved for some time in the study of metal nucleic acid interactions, in particular with nucleosides and nucleotides [7–16]. In two of our recent publications [17, 18] we have emphasized the role of secondary ligands in the structure and stability of metal–cytidine complexes. The metal ions involved were Cu(II), Ni(II), Co(II), Zn(II), Mn(II), Mg(II) and Ca(II). The present manuscript is the extension of the above investigations to trivalent lanthanones. The purpose of such studies is to assess the influence of charge on the cytidine complexes. Such studies will be helpful in identifying the specific contributions of metal ions having different charges, especially where multi-metal equilibria are involved.

In this publication a detailed investigation on the interactions of La(III), Pr(III), Nd(III), Sm(III), Gd(III), Dy(III) and Er(III) with cytidine and the biologically important secondary ligands glycine, histidine and oxalic acid have been carried out both in binary and ternary systems. The results from this investigation are compared with the literature data of related systems for a critical review of various aspects that affect the metal nucleoside binding.

Experimental

Cytidine, glycine and histidine were obtained from Sigma (U.S.A.) and oxalic acid from Fluka (Switzerland). For every titration, fresh solid ligands were weighed out into the reaction cell to avoid possible hydrolysis. All rare earth oxides are of Johnson Mathey's spectral grade, and a stock solution was prepared by dissolving a known weight of the oxide in pure nitric acid. The lighter lanthanides were standardized with the disodium salt of EDTA [19]. The heavier lanthanides were estimated gravimetrically as oxides [20]. Carbonate-free sodium hydroxide was prepared and was standardized by titration with potassium acid phthalate.

The experimental method consisted of the potentiometric titration of the ligand with a standard sodium hydroxide solution in the absence and presence of the above metal ions being investigated. The ionic strength of the solution was maintained constant in the course of titration by the use of a medium containing 0.10 M KNO_3 and a relatively low concentration of ligand and metal ion (1×10^{-3} M). Presaturated nitrogen was passed through the solution during the course of titration to eliminate the adverse effect of atmospheric carbon dioxide, and the temperature was maintained at 35 ± 0.1 °C. The experimental details are given elsewhere [12].

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0020-1693/86/$3.50

Calculations

Dissociation Constants

The acid dissociation constants of the primary ligand cytidine and the protonated secondary ligands, glycine and histidine, were calculated by the usual algebraic method [21]. However, for the secondary ligand oxalic acid the constants were calculated with the aid of the graphical method [22].

Formation constants

In order to calculate the stability constants of the binary complexes of La(III), Pr(III), Nd(III), Sm(III), Gd(III), Dy(III) and Er(III) with cytidine in a 1:1 ratio, the following equations were used (excluding the charges):

$$M + HL \overset{K'}{\rightleftharpoons} ML + H^+ \tag{1}$$

together with related equilibria

$$M + L \overset{K^M_{ML}}{\rightleftharpoons} ML \tag{2}$$

$$K^M_{ML} = \frac{[ML]}{[M][L]} \tag{3}$$

To calculate the stability constants of the ternary complexes of rare earth metal ions with cytidine and histidine or glycine in a 1:1:1 ratio, the following equations were employed [eqns. (4)–(14)] (charges are omitted for clarity):

$$M + HL + H_2A \overset{K'_2}{\rightleftharpoons} [M(HA)L] + 2H^+ \tag{4}$$

$$M + HA + L \overset{K^M_{M(HA)L}}{\rightleftharpoons} [M(HA)L] \tag{5}$$

$$K^M_{M(HA)L} = \frac{T_M - [M]}{[M][HA][L]} \tag{6}$$

$$[M] = QL \ \text{(or)} \ PA \tag{7}$$

$$L = \frac{P\alpha}{QX + PY} \tag{8}$$

$$A = \frac{Q\alpha}{QX + PY} \tag{9}$$

$$\alpha = AX + LY \tag{10}$$

$$\left.\begin{aligned} X &= \frac{2[H]^2}{K_a K_{2a}} + \frac{[H]}{K_{2a}} && (11)\\ P &= \frac{[H]^2}{K_a K_{2a}} + \frac{[H]}{K_{2a}} && (12)\end{aligned}\right\} \text{using } K_a \text{ and } K_{2a} \text{ values of histidine}$$

$$\left.\begin{aligned} Y &= \frac{2[H]}{K_a} + 1 && (13)\\ Q &= \frac{[H]}{K_a} + 1 && (14)\end{aligned}\right\} \text{using } K_a \text{ values of cytidine}$$

where HL = monoprotonated cytidine, H_2A = monoprotonated histidine or glycine and T_M = total metal ion species present in solution.

For the ternary complexes of rare earth metal ions with cytidine and oxalic acid in a 1:1:1 ratio the following equations are used (charges are omitted for clarity):

$$M + HL + H_2A \overset{K'_3}{\rightleftharpoons} MLA + 3H^+ \tag{15}$$

$$M + L + A \overset{K^M_{MLA}}{\rightleftharpoons} MLA \tag{16}$$

$$K^M_{MLA} = \frac{T_M - [M]}{[M][L][A]} \tag{17}$$

$$[M] = QL \ \text{or} \ PA \tag{18}$$

$$[L] = \frac{P\alpha}{QX + PY} \tag{19}$$

$$[A] = \frac{Q\alpha}{QX + PY} \tag{20}$$

$$\alpha = AX + LY \tag{21}$$

$$\left.\begin{aligned} X &= \frac{3[H]^2}{K_a K_{2a}} + \frac{2[H]}{K_{2a}} && (22)\\ P &= \frac{[H]^2}{K_a K_{2a}} + \frac{[H]}{K_{2a}} + 1 && (23)\end{aligned}\right\} \text{using } K_a \text{ and } K_{2a} \text{ values of oxalic acid}$$

$$\left.\begin{aligned} Y &= \frac{3[H]}{K_a} + 2 && (24)\\ Q &= \frac{[H]}{K_a} + 1 && (25)\end{aligned}\right\} \text{using } K_a \text{ values of cytidine}$$

where H_2A is oxalic acid.

All calculations were undertaken with a Casio PB100 Personal Computer with appropriate programs.

Results

The proton dissociation constants of the ligands cytidine, glycine, histidine and oxalic acid are presented in Table I.

TABLE I. Acid Dissociation Constants of the Ligands. Temperature = 35 °C, μ = 0.10 mol dm^{-3} (KNO_3)

Ligand	pK_a	pK_{2a}
Cytidine	4.15 ± 0.04	
Glycine	2.50 ± 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

Metal:Cytidine System (1:1)

The potentiometric titration curve of La(III)–cytidine in a 1:1 ratio (Fig. 1b′) resulted in an inflection at $a = 1$, indicating the formation of a normal 1:1 complex in the buffer region between $a = 0$ and $a = 1$. The stability constant K^{M}_{ML} was calculated using eqn. (3). Similar trends were observed for the other metal ions studied. The constants thus calculated are presented in Table II.

Metal:Cytidine:Glycine System (1:1:1)

The mixed ligand titration curve of La(III)–cytidine–glycine given in Fig. 1c′ shows an inflection at $m = 2$ (where m = mol of base added per mol of metal ion), indicating the formation of a monoprotonated mixed ligand complex. The constant $K^{M}_{M(HA)L}$ was calculated using eqn. (6). Similar results were obtained for other metal ions studied, and the calculated constants are listed in Table II. However, the precipitate was observed after $m = 2.2$.

Metal:Cytidine:Histidine (1:1:1) System

This system is exactly the same as the metal–cytidine–glycine system. The constants thus calculated are presented in Table II.

Metal:Cytidine:Oxalic Acid System (1:1:1)

The titration curve of all the metal ions showed an inflection at $m = 3$, indicating the simultaneous formation of 1:1:1 mixed ligand complex in the entire buffer region between $m = 0$ and $m = 3$. The constants were calculated using eqn. (17) and are presented in Table II.

Discussion

The stability constants of cytidine with rare earth metal ions 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 that is observed for a variety of ligands with lanthanones.

Cytidine forms more stable complexes with lanthanones compared to its bivalent complexes except for Cu(II) [17]. The higher stability of rare earth complexes of cytidine may be explained on the basis of differences in the charge of the metal ions.

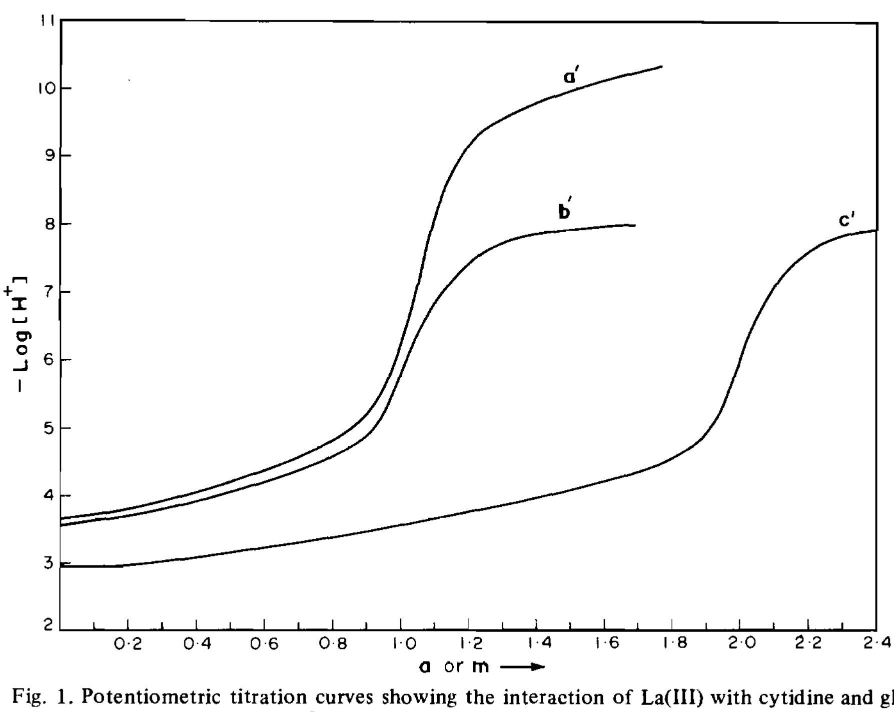

Fig. 1. Potentiometric titration curves showing the interaction of La(III) with cytidine and glycine (1:1:1) in solution. Temperature = 35 °C, μ = 0.10 mol dm^{-3} (KNO_3). (a′) = free cytidine; (b′) = La(III):cytidine (1:1); (c′) = La(III):cytidine:glycine (1:1:1). a or m = mol of base added per mol of ligand or metal ion, respectively.

TABLE II. Stability Constants[a] of the Binary and Ternary Complexes of Cytidine (cyti, HL) with Glycine (gly, H_2A), Histidine (histi, H_2A) and Oxalic Acid (oxalic, H_2A). Temperature = 35 °C, μ = 0.10 mol dm^{-3} (KNO_3)

Metal ion (III)	Metal:cyti (1:1) K^M_{ML}	Metal:gly (1:1) $K^M_{M(HA)}$	Metal:cyti:gly (1:1:1) $K^M_{M(HA)L}$	Metal:histi (1:1) $K^M_{M(HA)}$	Metal:cyti:histi (1:1:1) $K^M_{M(HA)L}$	Metal:oxalic (1:1) K^M_{MA}	Metal:cyti:oxalic (1:1:1) K^M_{MLA}
La	2.90	3.23	8.27	3.41	8.47	6.20	9.74
Pr	2.96	3.53	8.37	3.56	8.50	6.29	9.81
Nd	3.03	3.71	8.41	3.79	8.54	6.45	9.89
Sm	3.10	3.82	8.51	3.85	8.63	6.61	9.98
Gd	3.13	3.72	8.49	3.76	8.57	6.56	9.94
Dy	3.17	3.86	8.59	3.99	8.76	6.72	10.09
Er	3.21	3.93	8.64	4.06	8.81	6.85	10.22

[a]Deviations are omitted for clarity.

The high positive charge on the lanthanones permits a closer approach of the ligands and better electrostatic attractions. This results in the formation of more stable complexes with cytidine compared to the less positively charged transition and alkaline earth metal ions. However, the magnitude of the stability data suggests that in both cases (tri- and bivalent metal cytidine complexes) the nature of bonding may be similar, *i.e.*, through N-3 of the base. The stability data for ternary complexes of cytidine with glycine, histidine and oxalic acid are compiled in Table II. In the ternary systems there are two types of complexes: (i) complexes in which interligand interaction occurs, and (ii) complexes in which there is no such interaction. These interligand interactions have been found to be most effective in deciding the stability of the ternary complexes in solution along with other factors, such as the nature of the metal ion, the geometry of the metal complex and the solvent effects. Further, these interactions become more pertinent when the ligands participate in stacking interactions which, however, vary from ligand to ligand and metal ion to metal ion.

Table III presents the $\Delta\log K$ values for various systems studied. The $\Delta\log K$ is the difference between the overall 1:1:1 ternary complexes and the corresponding 1:1 binary complexes. Thus, if $\Delta\log K$ values are positive, the ternary complexes are more stable than the corresponding binary complexes. If they are negative, the binary are more stable than the ternary. However, negative values of $\Delta\log K$ do not preclude the formation of ternary complexes in solution. It can be seen from Table III that the $\Delta\log K$ values are positive for all the systems studied. In a previous study, we have suggested various reasons for the positive values of $\Delta\log K$ [17]. These included charge neutralization through the π-accepting capacity of the secondary ligands and stacking interactions. Stacking interaction is a phenomenon that occurs between the two aromatic moieties of different ligands in a ternary system. Therefore, the same factors can be expected to be operating in explaining the positive $\Delta\log K$ values of various systems studied in this investigation.

TABLE III. $\Delta\log K$ Values for Various Metal–Ligand Systems in Solution. Temperature = 35 °C, μ = 0.10 mol dm^{-3} (KNO_3)

Metal ion (III)	Metal:cytidine: glycine (1:1:1)	Metal:cytidine: histidine (1:1:1)	Metal:cytidine: oxalic acid (1:1:1)
La	+2.14	+2.16	+0.64
Pr	+1.88	+1.98	+0.56
Nd	+1.67	+1.72	+0.41
Sm	+1.59	+1.68	+0.27
Gd	+1.64	+1.68	+0.25
Dy	+1.56	+1.60	+0.20
Er	+1.50	+1.54	+0.16

The $\Delta\log K$ values of glycine and oxalic acid systems, where interligand interactions are absent, are compared first. The $\Delta\log K$ values of glycine complexes are more positive compared to the corresponding complexes of oxalic acid, although both are aliphatic ligands. This may be due to the involvement of hetero-donor atoms in metal coordination in the case of glycine system. The enhancement of the stability when mixed donor atoms are involved has also been reported for other related systems [17, 23]. These conclusions are further supported by electrostatic molecular potential calculations [24]. The $\Delta\log K$ values for histidine complexes (where interligand interactions are possible) are slightly more positive than the corresponding values for glycine complexes for all the metal ions investigated. This closeness in the $\Delta\log K$ values suggests that the mode of binding in ternary complexes is most probably similar in both ligands. That is, in ternary complexes histidine is acting like glycine, involving only amino and carboxylate groups. It is important to note here that histidine acts like glycine if there is only one histidine; if there are two histidines, the first may act like glycine and the second like histamine [25]. Histidine also acts like glycine in binary complexes, as is clearly evident from their stability data. This is further exemplified by the fact that both the ligands form protonated complexes in both binary and ternary systems.

The Δlog K values of ternary complexes of rare earth metal ions are compared with the corresponding values for transition metal ions [17]. It is found that the values for rare earth metal ion complexes are less positive than the transition metal complexes. This indicates that the trivalent ternary complexes are less stable than the bivalent ternary complexes. The lower stability of ternary complexes of rare earth metal ions is due to the formation of more stable binary 1:1 complexes. Conversely, the more stable binary complexes of rare earth metal ions may disfavour the formation of ternary complexes in solution.

Based on the conclusions arrived at in this investigation, we propose the following tentative structure for metal–cytidine–histidine (Fig. 2) complex.

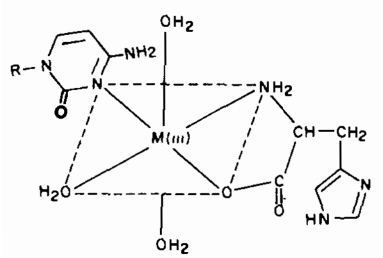

Fig. 2. Tentative structure of 1:1:1 M(III)–cytidine–histidine showing the glycine-like coordination. R = ribose; M(III) = rare earth metal ion.

Acknowledgement

V.B.M.R. is grateful to the CSIR (New Delhi) for financial support.

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