Formation Constants and Coordination in Transition Metal Complexes of Glycinehydroxamic Acid

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Abstract

Formation constants of Mn(II), Co(II), Zn(II) and Cd(II) complexes with glycinehydroxamic acid (GHA) have been determined in aqueous solution at 25.0 °C and 0.1 M ($NaClO_4$) by potentiometric measurements. The mathematical models which explained the experimental data better included the formation of mononuclear species with ligand to metal ratios 1:1 and 2:1, as well as protonated and hydrolysed species for all the systems studied. Species with ligand to metal ratio of 3:1 (for cobalt(II)) and 3:2 (for zinc(II)) are also postulated. The stability of the complexes follows the Irving–Williams order. The amino group of GHA is found not to be involved in coordination, exept in the case of the nickel(II) and copper(II) ions.

Introduction

In recent years there has been an increasing interest in the chemistry of hydroxamic acids, due mainly to the biological importance of their Fe(III) complexes [1–6].

One group of hydroxamic acids, the α aminohydroxamic derivatives, show wide applications. As $RNHCH_2CONHOH$ they have been tested as therapeutic agents for urolithiasis [7]. Anchored to Sepharose 6B support they have been proposed as a new absorbent for protein purification and for selective removal of heavy metal ions from aqueous solutions [4]. In all these applications, the interaction of these acids with metal ions is a relevant aspect to be considered.

Glycinehydroxamic acid ($NH_2CH_2CONHOH$) is the simplest of these compounds and it has been reported as having a low acute and chronic toxicity in animals [8]. There have been reports evaluating, among other aspects, its antimycobacterial properties [8], its action as inhibitor of *Aeromonas aminopeptidase,* a metalloenzyme that contains zinc [9], its inhibitory effect on DNA synthesis [10] and also its efficiency as an iron chelating agent in the therapy of iron overload [3]. On the other hand, ferric glycinehydroxamate has been proposed as a source of iron in the treatment of anemia in animals [5].

As a result of its biological importance and potential usefulness as a therapeutic agent, metal complexes of this acid have been recently investigated both in aqueous solution [6, 11, 12] and in the solid state [14–16].

One interesting question concerning the metal complexes of this acid is which atom of the –CONHOH group, the nitrogen or the oxygen atom, is involved in the coordination to the metal ion. The hydroxamate group generally behaves as a bidentate ligand, coordinating through the carbonyl oxygen and the oxygen atom of the –NHOH group [17]. However, when the hydroxamic acid contains another donor group, as the amino group in this case, the coordination could involve this group and the nitrogen or the oxygen of the –CONHOH group, forming either five or six membered rings, respectively.

The X-ray crystal structures of two complexes of nickel(II) [14, 15] and one of copper(II) [16] containing two glycinehydroxamato anions ($L = NH_2CH_2CONHO^-$) provide evidence of coordination by the nitrogen amino and the nitrogen of the hydroxamate group. Additional evidence for this type of coordination, which persists in solution, was given by potentiometric and spectrophotometric studies on nickel(II) [12, 13] and copper(II) [11] complexes. For iron(III) complexes a coordination by the nitrogen amino and the oxygen atoms has been suggested [5].

In this work we report the formation constants of the species formed in metal–glycinehydroxamic acid systems with Mn(II), Co(II), Zn(II) and Cd(II) ions. A comparison of the formation constants of the ML species with those of the acetohydroxamic acid (AHA) with the same metal ion is made to clarify the participation of the amino glycinehydroxamic acid (GHA) group in the coordination.

Experimental

Reagents and Materials

Glycinehydroxamic acid was prepared following the procedure described by Safir [18]. The solu-

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tions of this acid, prepared just before use, had their concentrations determined potentiometrically.

Metal perchlorates were prepared from their respective carbonates or oxides and perchloric acid. The metal content in the stock perchlorates solutions was determined by complexometric titrations with EDTA.

Stock sodium perchlorate solution used to adjust the ionic strength at 0.1 M was prepared by treating a sodium carbonate suspension with perchloric acid, filtering, boiling and neutralizing with sodium hydroxide solution.

Sodium hydroxide solution was prepared with carbonate-free bidistilled water and standardized with potassium hydrogen phthalate.

Apparatus and Technique

Potentiometric titrations were carried out using a Metrohm E636 Titroprocessor and an electrode arrangement consisting of a Metrohm EA 109 glass electrode and an EA 404 calomel (containing 0.1 M NaCl) electrode. The system was calibrated in terms of hydrogen ion concentrations before and after a series of measurements by titrations of perchloric acid (or sodium hydroxide) solution (0.1 M in $NaClO_4$) with standard carbonate-free sodium hydroxide (or perchloric acid) solution. The dissociation constant of water was calculated from these potential measurements and used in the determination of hydrogen ion concentration [19]. In this study the symbol pH represents $-\log[H^+]$.

The temperature during titrations was maintained at 25.0 °C and the ionic strength was adjusted to 0.1 M with $NaClO_4$. All the measurements were made under a purified nitrogen atmosphere.

Protonation constants were calculated from titration curves of the ligand in our previous work [11]. Titration curves of the ligand in the presence of metal ions were obtained in different ligand to metal ratios (9.6:1 to 2.4:1); the hydrogen ion concentration was varied by adding sodium hydroxide solution.

Calculations

The equilibria reactions for the systems investigated can be expressed (charges are omitted for simplicity) as:

$$qM + pL + rH = M_qL_pH_r$$

The overall formation constant for the species $M_qL_pH_r$ (M = metal ion, L = ligand and H = proton) is defined as:

$$\beta_{pqr} = \frac{[M_qL_pH_r]}{[M]^q[L]^p[H]^r}$$

Formation constants were refined by the corrected version of the computer program SCOGS [20]. The adequacy of a mathematical model to reproduce the experimental data was determined considering the lowest value obtained for the standard deviation in titre and the agreement between experimental and calculated titrations curves. Species distribution as a function of pH was determined with the computer program COMICS [21]. An IBM 4341 computer was used for the calculations.

Results and Discussion

Equilibrium Constants

The average number of ligands bound to each metal ion studied, $\bar{n}$, was calculated assuming that only simple mononuclear species are present. The formation curves of $\bar{n}$ *versus* $-\log[L]$ (L = free ligand), plotted for different ligand to metal ratios, are non superimposable for all metal ions studied, as shown in Fig. 1 for the Zn(II) system. This indicates the presence of protonated, hydrolysed or polynuclear species in these systems.

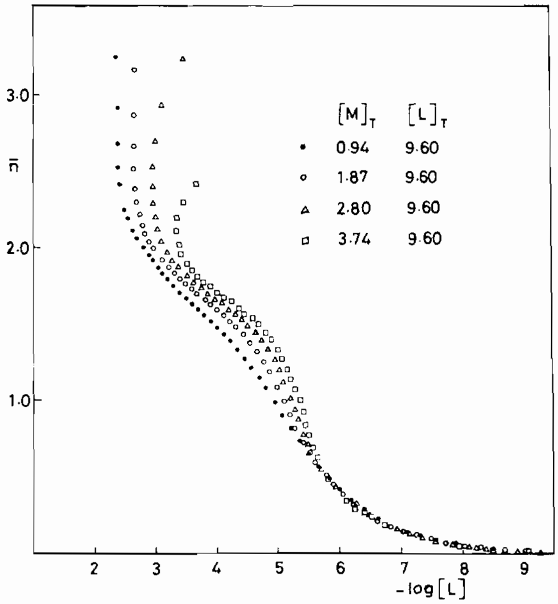


Fig. 1. Formation curves $\bar{n}$ *versus* $-\log[L]$ for zinc(II)–glycinehydroxamic acid system. Total ligand and metal concentrations in mmol/l.

As a first approximation, the formation constants for the complexes ML and ML_2 were calculated by a graphical method [22], using the data at low pH.

Our previous results for Ni(II) and Cu(II) [11] also indicated the existence, in alkaline solution, of the species $MH_{-1}L_2$ (corresponding to ML_2OH in terms of equilibrium). In addition, with the Cu(II) ion, a dimeric species, Cu_2OHL_2, was found to be significantly formed in the pH range 4–7.

Working with the computer program SCOGS, models based on these results were tested. However, they were not able to reproduce the titrations curves and other species had to be included. We then set a basic model containing the ML, ML_2 and ML_2OH species and with this model we investigated the possible formation of the species MHL, MLOH, M_2L_2, M_2L_3, $M_2L_2(OH)$, etc. The metal hydroxo species MOH [23] were included in all these models as fixed parameters, as well as the protonated ligand constants determined in the same experimental conditions [11].

Cadmium and Manganese Systems

In these systems we tried first the inclusion of a protonated species in the basic mathematical model. The formation of a polynuclear species was not confirmed and the introduction of the protonated MHL species seems to be sufficient to improve the fit. The hydroxo species ML_2OH could be, however, replaced by MLOH. A final refinement of these constants for each metal ion was done with all titrations points simultaneously and the results are presented in Table I.

TABLE I. Formation Constants of GHA–Metal Species ($L_pM_qH_r$) at I = 0.1 M and 25.0 °C[a]

Species			Mn	Co	Zn	Cd
p	*q*	*r*				
1	1	1	11.07(3)	11.90(3)	12.40(2)	11.48(3)
1	1	0	3.85(1)	5.60(1)	5.38(4)	4.81(1)
2	1	0	6.45(2)	10.03(1)	10.07(2)	8.24(2)
1	1	−1	−5.51(1)	−1.90(1)	−1.46(2)	−3.37(1)
3	1	0		12.45(4)		
3	2	0			19.45(4)	
n			234	257	242	245
pH range			5.0–10.2	4.6–10.6	4.6–10.1	4.8–10.7

[a] *n* = number of titration readings for each series. Standard deviations given in parentheses.

They suggest that the experimental data are best explained by the formation of ML, ML_2, MLOH and MHL species (Table I).

Calculated species distribution done with the aid of the computer program COMICS [21], for several ligand to metal ratios, indicates a less important contribution of protonated species, which reaches about 20% of the total metal ion in acid medium. Therefore it cannot be discarded.

Cobalt System

The inclusion of protonated species only was unable to promote a better simulation of the Co(II) system. The presence of mononuclear CoL_3 proves to be essential, and it reaches over 40% of the total metal ion concentration at the highest ligand to metal ratio used. As for Mn(II) and Cd(II) systems, CoL_2-OH could be replaced by CoLOH. As in the previous metal systems analysed, our final choice is the model which contains the MLOH species (Table I).

Zinc System

In this case, the formation of a polynuclear species besides a protonated and a hydrolysed MLOH species was confirmed. Table I shows the result for the final refinement. The species distribution in this system is shown in Fig. 2. In it, the importance of the species Zn_2L_3, which, at about pH 7.5, corresponds to almost 80% of the total zinc in solution, becomes evident. The species ZnHL is also significant and ZnLOH reaches 100% of the metal ion in solution. These findings are in agreement with the results shown in Fig. 1.

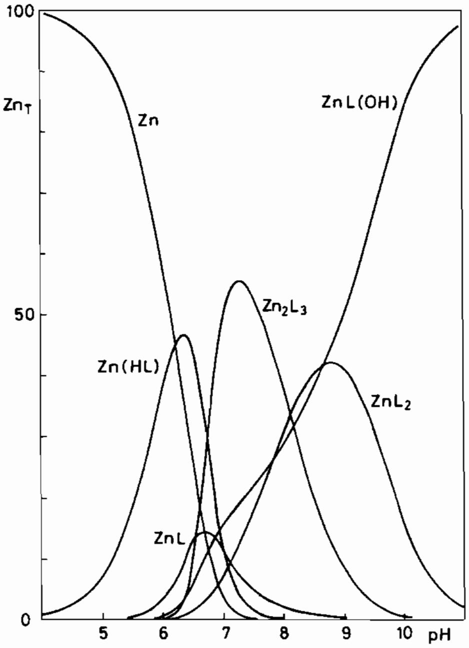


Fig. 2. Species distribution as a function of pH for zinc(II)–glycinehydroxamic acid system $[Zn(II)]_T$ = 3.0 mmol/l; $[GHA]_T$ = 10.0 mmol/l.

Coordinating Groups

The calculated stepwise equilibrium constants for all these systems are summarized in Table II together with our previously reported values for the Ni(II) and Cu(II) [11] systems. The data are in agreement with the Irving–Williams series (Fig. 3).

The hydroxamate group, –CO(NOH), usually behaves as a bidentate ligand, as shown by structure **I** for Fe(III)–hydroxamates.

TABLE II. Equilibrium Constants for Metal Hydroxamic Acid Complexes[a]

		Mn	Co	Ni	Cu	Zn	Cd
GHA	$\log K_1$	3.85	5.50	6.98	10.83	5.38	4.81
	$\log K_2$	2.60	4.43	6.70	9.06	4.69	3.43
AHA	$\log K_1$	3.80	5.01	5.30	7.90	5.37	4.50
	$\log K_2$	3.05	4.00	4.12	6.40	4.21	3.30

[a]GHA complexes: Ni, Cu = ref. 11; others = this work. AHA complexes: Cd = ref. 24a; others = ref. 24b.

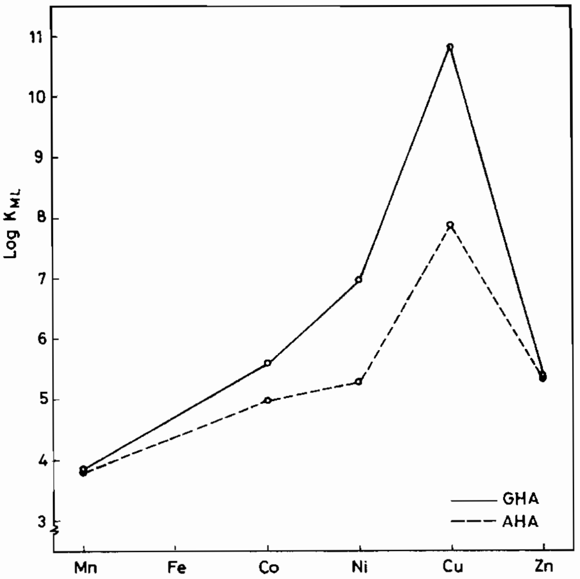
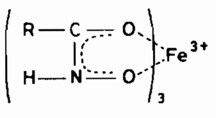


Fig. 3. Log K variation for transition metal complexes of hydroxamic acids.

Considering the amino group of glycinehydroxamic acid and the three potential donor sites in its hydroxamic acid moiety, coordination of GHA to a metal ion could form either five or six membered rings. Five membered rings would be formed in a O,O-type coordination as shown in structure **I**, in which case the amino group is left uncoordinated, or in a N,O-type coordination including a bonding to the carbonyl oxygen atom or then, in a N,N-coordination to the nitrogen of the hydroxamate group. A six membered ring would require coordination to the amino group and to the oxygen atom of the –NHOH group. This type of coordination has been proposed for Fe(III) complexes [5], but it is certainly less stable than a five membered ring.



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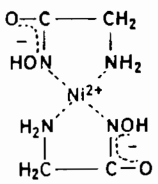

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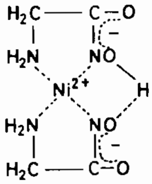

III

In the Ni(II) and Cu(II) complexes of glycinehydroxamic acid, a N,N-coordination was found, as shown by structures **II** and **III**, for NiL_2 and $NiH_{-1}L_2$ respectively. For these Ni(II) complexes in the solid state a square planar coordination was found, having *trans*-(NiL_2) [14] and *cis*-($NiH_{-1}L_2$) [15] configurations. The *trans*-copper(II) complex has a distorted octahedral structure, in which the oxygen of carbonyl groups in adjacent molecules complete the coordination [16].

In Fig. 4, log K_{ML} values from Table II are plotted against the corresponding data for acetohydroxamic acid complexes [24]. The full line has an intersection equal to the difference between the protonation constants for the two ligands ($\Delta pK_a = 9.40 - 9.12 = 0.28$) and a slope equal to unity.

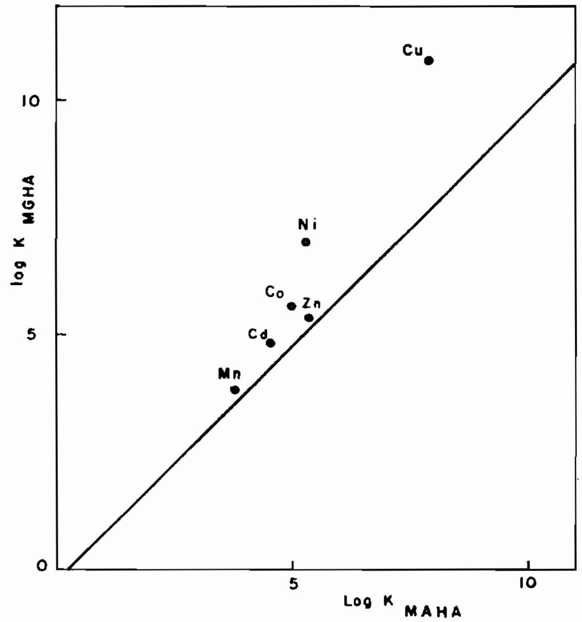

Fig. 4. Correlation between the stability constants of glycine hydroxamic and acetohydroxamic acid metal complexes.

It becomes clear that the copper(II) and nickel(II) complexes have a type of coordination different from the other ions [25]. Since the 1:2 nickel and copper complexes, according to X-ray data [14–16], are N,N-coordinated forming five membered rings, we could suggest a similar coordination for the ML species. This hypothesis is supported by a remarkable coincidence in the log K of NiL for GHA and ethylenediamine complexes [26] ($\Delta \log K = 0.01$).

The NiL_2 complex being square planar, the small difference in log K for NiL and NiL_2 species (Δ log $K = 0.28$) could be explained if we considered that it corresponds to an octahedral (NiL) to square planar (NiL_2) transformation.

For the remaining metal ions, Mn(II), Co(II), Zn(II) and Cd(II), the coordination takes place through the –CONHOH group, as in the metal acetohydroxamic acid complexes, leaving the amino group uncoordinated. In these complexes, the free amino group can be protonated forming the MHL species. The protonation constants, corresponding to the reaction

$$ML + H^+ \rightleftharpoons MHL$$

are indicated in Table III. Comparing these values with the protonation constant for the ligand itself we observed that the coordination to the metal causes a lowering of the protonation constant for the amino group (pK = 7.37), which is reasonable.

TABLE III. Equilibrium Constants (as log K) for Metal Glycinehydroxamic Complexes

Reaction	Mn	Co	Zn	Cd
$M + L = ML$	3.85	5.60	5.38	4.81
$M + H_2O = MOH + H^+$	-10.35^a	-8.65^a	-9.36^a	-9.46^a
$ML + H_2O = MLOH + H^+$	−9.36	−7.60	−6.84	−8.18
$MOH + L = MLOH$	4.84	6.75	7.90	6.09
$MOH + ML = MLOH + M$	0.99	1.15	2.52	1.28
$ML + H^+ = MHL$	7.22	6.30	7.02	6.67

[a] Ref. 23.

The ML species of the metal–GHA systems studied are also capable of losing a proton to give MLOH species. Proton ionization from the ligand hydroxy group could be responsible for these reactions and this was found to be the case with NiL_2 and CuL_2. The lost proton may also come from a coordinated water molecule, producing in this case a ternary complex.

In Table III we have included, for comparison, the log K values for the hydrolysis of both M(II) and ML ions. When we consider MLOH to be a ternary complex, the difference in stability, Δ log K, between the binary and the ternary complexes is given by:

$$\Delta \log K = \log K^{MOH}_{MOHL} - \log K^{M}_{ML}$$

$$= \log K^{ML}_{MLOH} - \log K^{M}_{MOH}$$

and it corresponds to the reaction: $ML + MOH \rightleftharpoons MLOH + M$.

The calculated values of Δ log K, listed in Table III, show MLOH to be more stable than the corresponding ML and MOH species. It is, therefore, reasonable to believe that MLOH is a ternary species, formed as result of an OH^- addition to ML.

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