Complex-forming Properties of L-α-Alaninehydroxamic Acid (2-Amino-*N*-hydroxypropanamide)

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The systems of manganese(II), cobalt(II), nickel(II), copper(II), zinc(II), cadmium(II), iron(III), and aluminium(III) with L-alaninehydroxamic acid (2-amino-*N*-hydroxypropanamide) (ahpr) have been investigated in the metal–ligand ratio range 1 : 1—1 : 10 by means of pH-metric and spectrophotometric methods. Formation constants and assumptions concerning the bonding modes in the species present in aqueous solution are reported. There is appreciable complex formation between iron(III) and ahpr even below pH 3. Mixed hydroxo complexes can be proposed in addition to the binary iron(III)–ahpr complexes. The aluminium(III)–ahpr complexes are formed in the range pH *ca.* 3—9. There is no significant complex formation below pH 3, and $[Al(OH)_4]^-$ is the only species present in measurable concentration above pH 9. Co-ordination of the hydroxamate oxygens is suggested in both the iron(III)– and aluminium(III)–ahpr systems. Of the metal ions in the 2+ oxidation state, copper(II) forms the most stable complexes with ahpr. It can be postulated that both the oxygen and the nitrogen donor atoms of the ligand (H_2A^+) are involved in the co-ordination complexes $[CuA]^+$ and $[Cu_2A_2H_{-1}]^+$, but in the species $[CuA_2]$ and $[CuA_2H_{-1}]^-$ only the nitrogens are co-ordinated. Co-ordination of the nitrogen atoms is proposed in the planar complexes present in the nickel(II)–ahpr system. Complexes of medium stability are formed in the cobalt(II)– and zinc(II)–ahpr systems in the range pH 5.0—8.5. Complex formation only occurs to a small extent with manganese(II) and cadmium(II) ions.

Interest in hydroxamic acids has increased over the past few decades, since their biological importance has been proved beyond doubt.[1,2] However, investigations of hydroxamic acid derivatives of amino acids were very limited up until the 1970s, at which time the first results were published in connection with their inhibitory activity on metalloproteinases.[3] With regard to the significant complex-forming ability of both the hydroxamic acid and amino groups, the biological activity of the ligands must be closely correlated with the formation of their metal complexes. In spite of this, few studies have been made on the metal complexes of aminohydroxamic acids,[4–17] primarily the complexes of glycinehydroxamic acid (2-amino-*N*-hydroxyacetamide) (aha).[4–11] Publications on other aminohydroxamic acids are rather limited in number.[12–17] A survey of the relevant publication[4–17] reveals numerous unsolved questions, even for the systems containing aha and 2-amino-*N*-hydroxypropanamide (ahpr). Contradictions exist even as regards the acid–base chemistry of these ligands. Recently, we reported the dissociation macro- and micro-constants of ahpr,[18] and the present paper reports the formation constants of the species present in the systems of ahpr with iron(III), aluminium(III), manganese(II), cobalt(II), nickel(II), copper(II), zinc(II), and cadmium(II). Spectrophotometric and pH-metric measurements have been carried out, together with circular dichroism (c.d.) measurements on the copper(II)–ahpr system.

Experimental

L-α-Alaninehydroxamic acid (ahpr) was prepared *via* the methyl ester of L-α-alanine as described in ref. 19. The purity of the ligand and the exact concentrations of the ahpr stock solutions were determined by Gran's method.[20]

Metal ion solutions were prepared from the metal chlorides, or zinc(II) oxide, or cadmium(II) nitrate (Reanal) by dissolving an appropriate amount in doubly distilled water or in hydrochloric acid of known concentration. The iron(III) and aluminium(III) chloride stock solutions contained an excess of HCl (0.1 mol dm^{-3}). Metal ion concentrations in the stock solutions were determined gravimetrically *via* precipitation of the quinolin-8-olate or oxide.

For samples used in pH-metric and spectrophotometric measurements, the ionic strength was adjusted to 0.2 mol dm^{-3} with KCl [KNO_3 was used for the cadmium(II) nitrate-containing systems]. Titrations were carried out with carbonate-free KOH solutions of known concentrations (*ca.* 0.2 mol dm^{-3}).

The pH-metric titrations were performed throughout the approximate range pH 2.0—11.0, using 25.00-cm^3 samples. The ligand concentration in the samples was varied within the range 3×10^{-2}—2×10^{-3} mol dm^{-3}. The metal–ligand ratios were adjusted in the range 1:1—1:10 and measurements were made with samples at 6—10 different ratios.

The pH-metric measurements were carried out on a computer-controlled system consisting of a Radiometer pHM 84 pH-meter with a GK 2322C combined electrode, an ABU 80 burette, and a Commodore 64. The calculations were performed with the aid of the PSEQUAD computer program.[21] The electrode system was calibrated by the method of Irving *et al.*[22] so that the pH-meter readings could be converted into hydrogen-ion concentrations.

The visible absorption spectra were recorded on a Beckman ACTA MIV double-beam recording spectrophotometer over the range *ca.* 350—800 nm. The concentration of nickel(II) ion in the samples was 1×10^{-2} mol dm^{-3} and that of copper(II) and iron(III) ion was 5×10^{-3} mol dm^{-3}. The metal–ligand ratios were 1:1, 1:2, 1:2.5, or 1:5.

C.d. measurements were performed on the copper(II)–ahpr system. The spectra were recorded on an automatic recording spectropolarimeter, Jasco-J-20, in the 800—200 nm region.

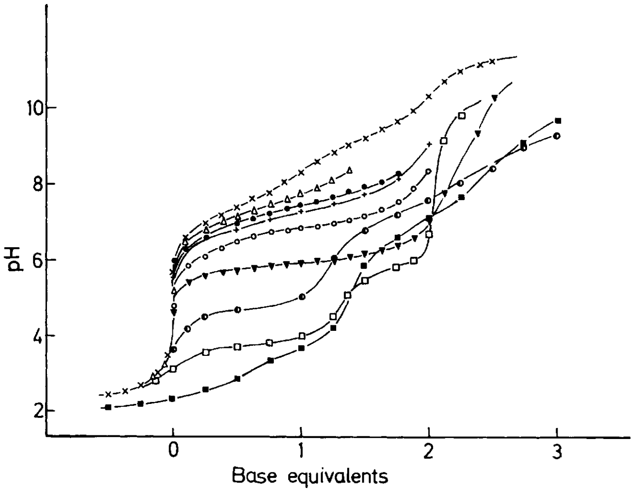


Figure 1. Titration curves for ahpr and for metal ion–ahpr systems (1:2). Concentrations (mol dm^{-3}): metal ion, 5×10^{-3}; ahpr, 1×10^{-2}. (×) ahpr, (△) manganese(II)–ahpr, (○) zinc(II)–ahpr, (□) copper(II)–ahpr, (●) cadmium(II)–ahpr, (▲) nickel(II)–ahpr, (■) iron(III)–ahpr, (+) cobalt(II)–ahpr, (◐) aluminium(III)–ahpr

Results and Discussion

In the measurable pH range, the fully protonated form of ahpr [$H_2A^+ = CH_3CH(NH_3^+)CONHOH$] can release two protons, one from the amino group and one from the hydroxamic acid group. We determined the macroscopic and microscopic dissociation constants of ahpr in a former study;[18] in the present work, only the macroscopic constants have been determined ($pK_1 = 9.16$, $pK_2 = 7.34$).

Representative pH-metric titration curves for ahpr alone and the metal ion–ahpr systems are shown in Figure 1. The titration curves for the metal ion–ahpr systems were evaluated by assuming all the presumable models. Models that provided the best fit, and the refined formation constants together with results previously published for metal ion–aha and copper(II)–ahpr systems, are given in Table 1.

Manganese(II)*–and Cadmium*(II)*–ahpr Systems.*—It can be seen from Figure 1 that in these systems the formation of metal(II)–ahpr complexes is limited to the range pH *ca.* 6.0—8.5. The experimental data are best fitted with models shown in Table 1. These models are in good agreement with those reported by Paniago and Carvalho[7] for manganese(II)– and cadmium(II)–aha. However, the stability of the complexes is somewhat lower in the case of ahpr. In addition, because of the higher stability of cadmium-chloro complexes, the formation of cadmium(II)–ahpr complexes is favourable in the presence of NO_3^- rather than Cl^-. The species [MAH_{-1}] is formed just before the metal hydroxide precipitates, so it may in fact be a mixed hydroxo complex with the composition [MA(OH)].

Zinc(II)*– and Cobalt*(II)*–ahpr Systems.*—As Figure 1 shows, the extent of complex formation is quite similar in these systems. It begins above pH 5.5, but at above pH 8.5 metal(II) hydroxide is precipitated even at a metal–ligand ratio of 1:5.

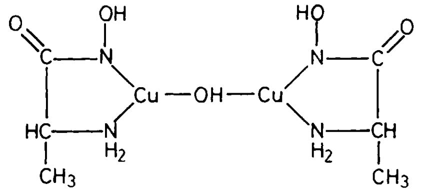
Our experimental data could be fitted with the model published by Paniago and Carvalho[7] for zinc(II)–aha. However, in the cobalt(II)–aha system they found [CoA_3]$^-$ and not [Co_2A_3]$^+$.

According to our experimental results the cobalt(II)–ahpr system is very sensitive to oxygen above pH 7. This suggests that there are nitrogen atoms around the cobalt(II) ion. At the same time the formation of a polynuclear complex suggests the hydroxamate moiety has a role in co-ordination, since the formation of this species can be conceived as the joining of two monomer species [MA]$^+$ through a ligand A, co-ordinating *via* its amino N atom to one monomer and *via* its hydroxamate group to the second monomer.

Nickel(II)*–ahpr System.*—Our results concerning this system are in good agreement with those reported earlier for nickel(II)–aha.[5,7,8]

The titration data can be fitted satisfactorily assuming the complexes [NiA]$^+$, [NiA_2], and [NiA_2H_{-1}]$^-$ are formed. The complex [NiA]$^+$ is formed in low concentration and only at a metal–ligand ratio of 1:1. The pH dependence of the absorption spectra (in agreement with earlier observations[8]) suggests the formation of square planar complexes with N,N co-ordination of ahpr above pH 6.

Copper(II)*–ahpr System.*—Several investigations have been performed on the copper(II)–aha[6–8] and –ahpr[12] systems. In both systems, the complexes [CuA]$^+$, [CuA_2], [$Cu_2A_2H_{-1}$]$^+$, and [CuA_2H_{-1}]$^-$ were found in solution, in the approximate range pH 3—11. The amino and the deprotonated hydroxamate nitrogen atoms were suggested to co-ordinate in all these complexes. The binuclear complex was considered to be a mixed hydroxo species in which two [CuA]$^+$ units are joined *via* one OH^- [(I)].

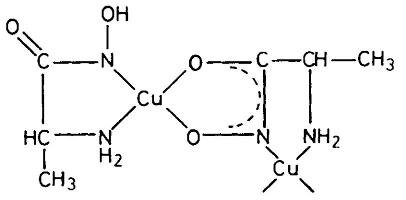


(I)

As regards the compositions and stability constants of the complexes, our results are in good agreement with the above-mentioned ones. However, there is some disagreement with co-ordinating groups in cases.

In agreement with earlier findings,[6–8,12] our spectroscopic results shown in Table 2 strongly suggest that four nitrogen atoms occupy the equatorial positions in [CuA_2] and [CuA_2H_{-1}]$^-$. The maximum concentration of [CuA_2] is reached at pH ≈6.5. At this pH in the charge transfer (c.t.) region (see Table 2) the two bands correspond well to transitions from amino and hydroxamic nitrogens to copper(II). The $\lambda_{max.}$ is *ca.* 535—540 nm which corresponds to 4 N co-ordination. Increasing the pH to above 9, $\lambda_{max.}$ shifts to *ca.* 495 nm. This indicates deprotonation of a co-ordinated hydroxamate moiety in [CuA_2], and not the hydrolysis of this species.

The contradiction between the assumptions reported earlier[6–9] and in the present paper is in respect of the complexes [CuA]$^+$ and [$Cu_2A_2H_{-1}$]$^+$. Our results indicate that it is not only the nitrogen atoms of ahpr that are involved in co-ordination in these two complexes; it can be assumed that the hydroxamate oxygen(s) also take(s) part. We assume the bonding mode (**II**) instead of (**I**) in [$Cu_2A_2H_{-1}$]$^+$. This assumption is supported by the c.d. spectroscopic results. The



(**II**)

Table 1. Stability data (log β) for complexes present in the metal ion–ahpr and –aha systems

Metal ion	Complex	Log β	pH Range (main species)	Literature data[a]
Mn^{II}	$[M(HA)]^{2+}$	10.92 ± 0.05	5—8 (minor)	11.07
	$[MA]^{+}$	3.47 ± 0.01	Above 7.5	3.85
	$[MAH_{-1}]$	−5.99 ± 0.02	Above 8	−5.51
	$[MA_2H]^{+}$	14.30 ± 0.07	Above 7.5	
	$[MA_2]$	5.97 ± 0.03	Above 8 (minor)	6.45
Co^{II}	$[M(HA)]^{2+}$	12.12 ± 0.01	6—7	11.90
	$[MA]^{+}$	4.74 ± 0.04	6.8—7.3 (minor)	5.60
	$[MAH_{-1}]$	−2.64 ± 0.01	Above 9	−1.90
	$[MA_2]$	9.39 ± 0.01	8—9.5	10.03
	$[M_2A_3]^{+}$	17.69 ± 0.03	6.8—8.3	
	$[MA_3]^{-}$			12.45
Ni^{II}	$[MA]^{+}$	6.76 ± 0.01	(Minor)	6.80[b] 6.768[c]
	$[MA_2]$	14.13 ± 0.01	6—8.5	13.50[b] 13.378[c]
	$[MA_2H_{-1}]^{-}$	5.47 ± 0.01	Above 9	5.061[c]
Cu^{II}	$[MA]^{+}$	10.89 ± 0.02	3.2—5.0	10.90[d]
	$[MA_2]$	19.87 ± 0.01	5.0—9.5	19.65[d]
	$[MA_2H_{-1}]$	9.98 ± 0.02	Above 9	9.74[d]
	$[M_2A_2H_{-1}]^{+}$	20.89 ± 0.02	3—6	21.41[d]
Zn^{II}	$[M(HA)]^{2+}$	12.27 ± 0.01	6—7	12.40
	$[MA]^{+}$	5.29 ± 0.01	6.5—7 (minor)	5.38
	$[MAH_{-1}]$	−2.26 ± 0.02	Above 9	−1.46
	$[MA_2]$	9.32 ± 0.04	8.5—9.5 (minor)	10.07
	$[M_2A_3]^{+}$	18.77 ± 0.02	7—9	19.45
Cd^{II}	$[M(HA)]^{2+}$	11.40 ± 0.01	5.8—7.5 (minor)	11.48
	$[MA]^{+}$	4.25 ± 0.01	6.5—8.5 (minor)	4.81
	$[MAH_{-1}]$	−3.93 ± 0.02	Above 7 (minor)	−3.37
	$[MA_2]$	7.11 ± 0.04	7.7—9 (minor)	8.24
Cd^{II}[f]	$[M(HA)]^{2+}$	11.52 ± 0.00		
	$[MA]^{+}$	4.52 ± 0.01		
	$[MAH_{-1}]$	−3.30 ± 0.02		
	$[MA_2]$	7.85 ± 0.04		
Al^{III}	$[M(HA)]^{3+}$	14.35 ± 0.03	3—6	
	$[M_2A_2]^{4+}$	22.21 ± 0.06	4—5.5 (minor)	
	$[M_2A_2H_{-1}]^{3+}$	17.59 ± 0.09	4.5—6.0	
	$[M_2A_2H_{-2}]^{2+}$	12.63 ± 0.02	4.5—8.0	
	$[M_2A_2H_{-3}]^{+}$	5.85 ± 0.03	5.5—9	
	$[M_2A_2H_{-4}]$	−2.44 ± 0.29	7—9.5 (minor)	
	$[MA_2]^{+}$	16.7 ± 0.1	6—9 (minor)	
	$[MA_2H_{-1}]$	9.62 ± 0.05	7—9	
	$[MA_2H_{-2}]^{-}$	−0.16 ± 0.20	8—10 (minor)	
Fe^{III}	$[M(HA)]^{3+}$	17.15 ± 0.01	2—4	16.450[g] 17.36[h]
Fe^{III}	$[MA]^{2+}$	13.92 ± 0.01	2—5	13.388[g] 14.14[h]
	$[MA_2H]^{2+}$	28.36 ± 0.05	3—7	27.558[g] 28.94[h]
	$[MA_2]^{+}$	21.99 ± 0.04	5—8	21.868[g] 22.72[h]
	$[MA_2H_{-1}]$	14.54 ± 0.03	Above 6	
	$[MA_3H]^{+}$	33.90 ± 0.05	6.5—8	33.856[g]
	$[MA_3H_3]^{3+}$			48.28[i]
	$[MA_3]$			26.501[g]
	$[MA_3H_{-1}]^{-}$			17.225[g]
	$[MA_3H_{-2}]^{2-}$			6.891[g]

[a] From ref. 7 unless stated otherwise. [b] Ref. 5. [c] Ref. 8. [d] Ref. 12. [e] Measured in KCl. [f] Measured in KNO_3. [g] Ref. 4. [h] Ref. 10, model (**I**). [i] Ref. 10, model (**II**).

Table 2. Spectroscopic data for copper(II)–ahpr complexes

Species[a]	Absorption spectra,[b] λ/nm	C.d. spectra[c] λ/nm
$[Cu_2A_2H_{-1}]^{+}$	635 (84) 338 (857)	660 (+0.008), 612 (−0.042), 538 (+0.005), 432 (+0.059), 355 (−0.35), 315 (−0.227), 265 (+2.02)
$[CuA_2]$	536 (86)	558 (−0.28), 320 (+0.20), 290 (+0.26)
$[CuA_2H_{-1}]^{-}$	495 (109)	558 (−0.28), 320 (+0.29), 280 (+0.24)

[a] The concentration of [CuA] was too low to get correct spectroscopic data. [b] Approximate absorption coefficients in parentheses (ε/dm^3 mol^{-1} cm^{-1}). [c] Δε Values in parentheses (dm^3 mol^{-1} cm^{-1}).

concentration of [CuA] is too low to be seen well in the c.d. spectra. The formation of the dimeric $[Cu_2A_2H_{-1}]^{+}$ species, however, results in very rich sets of Cotton effects both in the *d–d* region and the c.t. region. In the *d–d* region the major band is at 612 nm with two weaker effects at 660 and 538 nm. These three *d–d* bands can be assigned as $B + E(\gamma_1)$, A, and $E(\gamma_2)$ transitions and they correspond well to a species in which the metal ion is bound to two nitrogen donors.[23] The c.t. region consists of four ligand to metal transitions. Although the lack of data for analogous species does not allow ready assignment of the respective bands, their number indicates clearly diversity of the metal-bound donor set. The band at 265 nm corresponds most likely to the $NH_2 \longrightarrow Cu^{II}$ c.t. transition as is the case in copper(II)–amino acid systems.[23,24]

The NOH nitrogen is involved in the π system originated on the carbonyl unit and the c.t. transition to Cu^{II} should be of lower energy than the previous one ($NH_2 \longrightarrow Cu^{II}$). Thus, it is reasonable to assign the bands at 355 and 315 nm to the transitions from NOH and NO^- nitrogens to the metal ion (a similar range of energy is found for the transitions from the amide nitrogen which is also involved in the carbonyl π bond system).

These two different bands clearly indicate that the two bound hydroxamic nitrogens are different (*i.e.* NOH and NO^-) as assumed in (**II**).

The lowest-energy c.t. band observed only for the binuclear species is centred at 432 nm. This energy corresponds to the c.t. transitions of the phenolate oxygen to Cu^{II}. The low energy of this transition is caused by the coupling of the oxygen donor with the π system of the aromatic ring. In the case discussed here the NO^- oxygen is also coupled with the strongly delocalized π-orbital system of $O{=}C{-}NO^-$ and hence the band at 432 nm

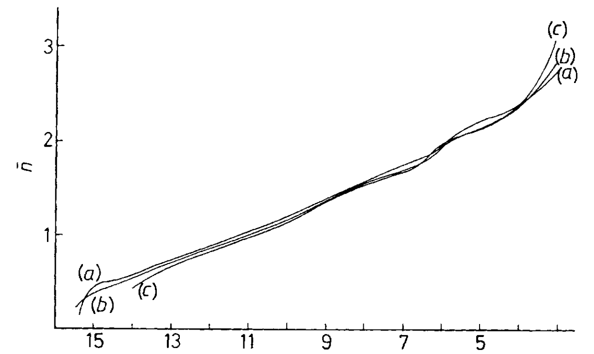


Figure 2. Formation curves for the iron(III)–ahpr system. Concentrations (mol dm^{-3}): Fe^{II}, 2.0 × 10^{-3} (*a*), and (*c*), 4.0 × 10^{-3} (*b*); ahpr, 1.9 × 10^{-2} (*a*), 1.8 × 10^{-2} (*b*), and 9.5 × 10^{-3} (*c*)

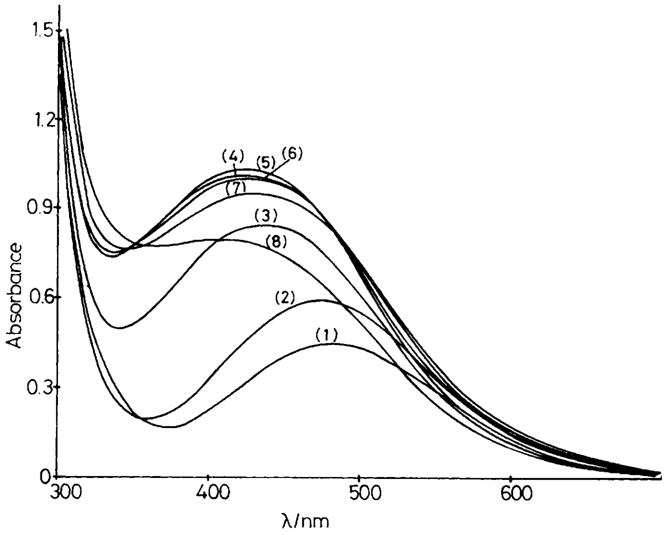


Figure 3. Visible absorption recorded in the iron(III)–ahpr system at various pH values: 2.49 (1), 3.00 (2), 4.80 (3), 7.02 (4), 8.28 (5), 9.48 (6), 10.55 (7), and 11.10 (8). Concentrations (mol dm^{-3}): Fe^{III}, 2 × 10^{-3}; anpr, 1 × 10^{-2}

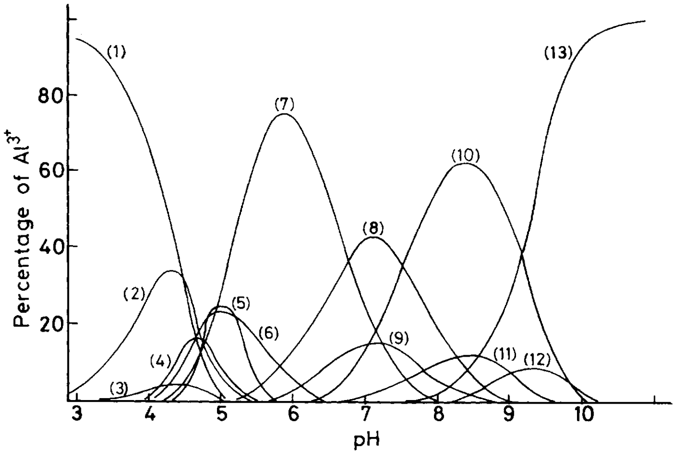


Figure 4. Concentration distribution curves for complexes present in the aluminium(III)–ahpr system. Concentrations (mol dm^{-3}): Al^{III}, 2 × 10^{-3}; ahpr, 6 × 10^{-3}. (1) Al^{III}, (2) $[Al(HA)]^{3+}$, (3) $[Al(OH)]^{2+}$, (4) $[Al_2A_2]^{4+}$, (5) $[Al_{13}(OH)_{32}]^{7+}$, (6) $[Al_2A_2H_{-1}]^{3+}$, (7) $[Al_2A_2H_{-2}]^{2+}$, (8) $[Al_2A_2H_{-3}]^{+}$, (9) $[AlA_2]^{+}$, (10) $[AlA_2H_{-1}]$, (11) $[Al_2A_2H_{-4}]$, (12) $[AlA_2H_{-2}]^{-}$, and (13) $[Al(OH)_4]^{-}$

could be assigned as the c.t. transition NO$^-$ (oxygen) ⟶ Cu^{II}. The latter assignment seems to be the only one possible for the studied system. Although more c.d. studies are needed for the copper(II)–hydroxamic acid system to make the proposed assignment more reliable, to explain the four c.t. bands of the dimeric complex the only possibility for the bonding mode is that suggested in (**II**).

Iron(III)*–ahpr System.*—Figure 1 shows that there is measurable complex formation between iron(III) and ahpr even below pH 2. Typical formation curves are given in Figure 2 from which it can be seen that the 1:1 complex appears at very low [A] values. This means that the stability of this complex is very high. However, the average number of ligands co-ordinated to the metal ion ($\bar{n}$) increases slowly. Three hydroxamate groups can satisfy the octahedral configuration around iron(III), but $\bar{n} = 3$ can be reached only at very high A concentration, *i.e.* below pA 4. Moreover, there are no points of inflection in the formation curves. All of these observations indicate that the 1:2 and particularly the 1:3 iron(III)–ahpr complexes are much less stable than the 1:1 species. Additionally, the formation of protonated, deprotonated, and/or mixed hydroxo complexes can be assumed.

It was also necessary to take into account hydrolysis of the metal ion. Recently, Khoe *et al.*[25] described the formation of $[Fe(OH)]^{2+}$, $[Fe(OH)_2]^{+}$, $[Fe_2(OH)_2]^{4+}$, and $[Fe_3(OH)_4]^{5+}$ in freshly made Cl$^-$-containing solutions. These hydroxo complexes were taken into consideration with the reported stability constants.[25] From numerous models, the one which yielded the best fit of the titration data is given in Table 1.

Our model is only in partial agreement with those given by Brown *et al.*[4] and El-Ezaby and Hassan[10] for the iron(III)–aha system. The most surprising feature in these earlier publications is that the amino N atom is assumed to play an important role in the co-ordination. This assumption was based on the result that the totally deprotonated species [MA] was found in a quite acidic pH range.

Since iron(III) is a typical hard ion, we presume the co-ordination of O atoms of ahpr. Accordingly, $[FeA]^{2+}$ is in fact a mixed hydroxo complex and has the composition $[Fe(HA)(OH)]^{2+}$, *i.e.* it contains the amino group in its protonated form. This assumption is supported by the spectrophotometric results (see Figure 3). The absorption spectra of the iron(III)–ahpr system do not differ substantially from those recorded for iron(III)–acetohydroxamic acid.[1] In the latter system, the co-ordination of hydroxamate oxygen atoms is beyond doubt.

Aluminium(III)*–ahpr System.*—In this system, complex formation begins only about pH 3. However, in this pH region hydrolysis of the metal(III) ion is also possible.[26,27] Nevertheless, we find that ahpr suppresses the precipitation, even at metal–ligand ratio of 1:1, up to pH ≈6.

To establish the best equilibrium model, we have relied on our earlier findings concerning the aluminium(III)–L-3-(3′,4′-dihydroxyphenyl)alanine and related systems[28] as well as results on the hydrolysis of aluminium(III),[26,27] which suggest that the most probable aluminium(III)–hydroxo complexes are $[Al(OH)]^{2+}$, $[Al_2(OH)_2]^{4+}$, $[Al_3(OH)_4]^{5+}$, $[Al_{13}(OH)_{32}]^{7+}$, and $[Al(OH)_4]^{-}$. Their effects were taken into account *via* the reported[26,27] stability constants.

The model providing the best fit of the titration data is given in Table 1. Concentration distribution curves can be seen in Figure 4. These data demonstrate that hydroxo complexes play an important role in the aluminium(III)–ahpr system. Their concentration is measurable even at a ratio of 1:3, and only $[Al(OH)_4]^{-}$ is formed above pH 9.

Since aluminium(III) is also a typical hard ion, it is evident that primarily the oxygen donor atoms of ahpr are involved in the co-ordination. Consequently, it can be assumed that the amino group is in its protonated form in $[Al(HA)]^{3+}$.

The complex $[Al_2A_2]^{4+}$ reaches its maximum concentration at pH ≈4.5. It is most probably a hydrolysed binuclear complex, $[Al_2(HA)_2(OH)_2]^{4+}$. When the pH is increased, deprotonation of ammonium groups and that of water take place in overlapping processes in $[Al_2A_2]^{4+}$. Moreover, 1:2 mixed hydroxo complexes are also formed below pH 9.

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