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Some factors affecting metal ion–monohydroxamate interactions in aqueous solution

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Abstract

The chelating properties exhibited by a series of monohydroxamic acids (propanohydroxamic acid (Pha), hexanohydroxamic acid (Hha), benzohydroxamic acid (Bha), *N*-methyl-acetohydroxamic acid (MAha), *N*-phenyl-acetohydroxamic acid (PhAha) and 2-hydroxypyridine-*N*-oxide (PYRha)) towards copper(II), nickel(II), zinc(II), calcium(II), magnesium(II) and aluminium(III) ions were studied by pH-metric, spectrophotometric and, in one case, by ^{27}Al NMR methods. The results were compared with the corresponding data for metal ion–acetohydroxamate (Aha) and metal ion–desferrioxamine B (DFB) complexes. Changes of the substituents either on the carbon or on the nitrogen of the hydroxamate moiety caused a measurable effect on the chelate stability only in the case of aluminium(III) complexes. The aromatic derivative, PYRha, formed significantly more stable complexes than expected on the basis of the ligand basicity. The higher complex-forming ability of DFB compared to monohydroxamic acids diminishes in the case of the largest calcium(II) ion. ©2000 Elsevier Science Inc. All rights reserved.

Keywords: Monohydroxamic acids; Desferrioxamine B; Stability constants; Metal complexes; Equilibrium studies

1. Introduction

Due to the special biological role of hydroxamate-based compounds in microbial siderophores which is largely determined by the iron(III) complexation of these compounds, studies on the coordination chemistry of hydroxamates have special interest. First of all, iron(III) complexes have been studied [1–6]. Essential effects on iron(III) chelating abilities associated with the structure of the ligand have been summarized in recent reviews [1,2]. Studies on ‘non-iron(III)’ metal ion–hydroxamate interactions are far less. Metal selectivity was discussed in a review by Hancock and co-workers [4] concluding that the stability of a certain hydroxamate complex depends strongly on the acidity of the metal ion ($\log K_{\text{OH}}$) under study. Some features affecting the interactions between different hydroxamate-based compounds and metal ions were also studied in our former works [5–9]. Among others, we studied the effects of different C- or N-substituents on the stability of iron(III) and a few copper(II) complexes [6]. Some other environmental metal ions (nickel(II), zinc(II), calcium(II), magnesium(II) and aluminium(III)) have also been involved in the present study.

Experiments for the copper(II) complexes have also been completed. Papers published on metalloenzyme inhibition (e.g. on nickel(II)-containing urease, zinc(II)-containing collagenase and 5-lipoxygenase [10–13]) greatly investigated this work.

2. Experimental

2.1. Chemicals

Benzohydroxamic acid (Bha), 2-hydroxypyridine-*N*-oxide (PYRha) and desferrioxamine B (DFB) were pure commercially available chemicals (Aldrich, Sigma and Ciba-Geigy). The propanohydroxamic acid (Pha), hexanohydroxamic acid (Hha), *N*-phenyl-acetohydroxamic acid (PhAha) and *N*-methyl-acetohydroxamic acid (MAha) were prepared by standard procedures from the corresponding carboxylic esters and hydroxylamine [14]. The purity of the ligands and the concentrations of the ligand stock solutions were determined by Gran’s method [15]. The metal ion stock solutions were prepared from $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, $\text{NiCl}_2 \cdot 5\text{H}_2\text{O}$, $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$, $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ (Reanal). ZnO and MgO (Reanal) were dissolved in a known amount of HCl solution. The concentrations of the copper(II), nickel(II), zinc(II)

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and aluminium(III) stock solutions were determined gravimetrically via precipitation as quinolin-8-olates. EDTA was used as a titrant to determine the concentrations of the calcium(II) and magnesium(II) stock solutions.

2.2. Potentiometric and spectrophotometric studies

All measurements were carried out at 25 °C and 0.2 mol/dm³ ionic strength (KCl). Carbonate-free KOH solution of known concentration (about 0.2 mol/dm³) was used as titrant. The pH-metric titrations were performed throughout the pH range 2.0–10.5 or below precipitation on samples of 10.00 or 25.00 cm³.

The ligand concentrations were varied in the range 2×10^{-3} – 8×10^{-3} mol/dm³; the metal to ligand ratios were in general in the range 1:1 to 1:10, but in the case of calcium(II) the ratio was increased to 20:1. Samples at five or six different ratios were measured. The pH-metric titrations were made with a Radiometer pHM84 instrument equipped with a Metrohm 6.0234.100 combined electrode. The titrant was added from a Metrohm 715 Dosimat autoburette. The electrode system was calibrated by the method of Irving et al. [16] so that the pH-meter readings could be converted into hydrogen ion concentration.

UV–Vis measurements on systems containing nickel(II) and copper(II) were performed. The metal ion to ligand ratios were 1:5 and titrations were made on samples containing copper(II) ions at 5×10^{-3} mol/dm³ or nickel(II) ions at 1×10^{-3} mol/dm³. A HP 8453 spectrophotometer was used to record the spectra in the region 300–800 nm.

The pH-metric results were utilized to establish the stoichiometry of the species and to calculate the stability constants. The calculations were performed with the computer program PSEQUAD [17]. Literature data on the aluminium(III) hydroxo complexes were incorporated into the models [18]. In the pH regions where the experimental findings indicated the possibility of hydrolysis (a continuous decrease in the pH or the formation of a precipitate) calculations were not performed. Volumes of titrant (cm³) were fitted and the accepted fittings were below 1×10^{-2} .

A Bruker DRX 500 spectrometer was used to record the ²⁷Al NMR spectra on the aluminium(III)–DFB system using 0.05 mol/dm³ AlCl₃ solution as reference. D₂O concentration in the samples was 10% (v/v). A sample of aluminium(III)–DFB with aluminium(III) at 4.8×10^{-3} mol/dm³ and the DFB at 7×10^{-3} mol/dm³ was measured at pH 2.0 and 10.0.

3. Results and discussion

3.1. Metal complexation of various monohydroxamic acids

The protonation constants of the ligands were already published in our former paper [6]. The values determined in the present work (listed in Table 1) are in good agreement with the formerly published data within ± 0.05 log units. As it is

clearly shown in Table 1 the acidity trend of the ligands which was interpreted in Ref. [6] is the following:

aromatic derivative (PYRha)

>secondary hydroxamic acids (PhAha, MAha)

≥primary hydroxamic acids (Bha, Aha, Pha, Hha)

Representative pH-metric titration curves of metal ion-aliphatic derivatives are shown in Fig. 1: in some cases there are significant differences in the pH effects caused by the complex formation with various metal ions which clearly reveal the great differences in the stability of the complexes. Whereas the complex formation starts at about pH 2 with aluminium(III) (and the extra base consumption strongly suggests the formation of mixed hydroxo species), there is no interaction up to about pH 7 with calcium(II). In the other cases, the titration curves run almost together (e.g. nickel(II)–MAha and zinc(II)–MAha).

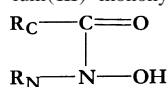
The situation is different with the aromatic and more acidic derivative (PYRha). The complex formation with this ligand starts at much lower pH than it does with the aliphatic derivatives (e.g. at somewhat below pH 2 in nickel(II)–PYRha and far below pH 2 in aluminium(III)–PYRha).

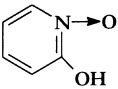
The equilibrium models yielded the best fits of the pH-metric experimental data and the calculated stability constants are shown in Table 1. (The UV–Vis spectrophotometric results relating to the different ligands did not show significant differences in λ_{\max} and ϵ values [19] (minimum λ_{\max} values for copper(II) complexes were 647 ± 3 nm, ϵ was about 40 dm³/(mol·cm), for nickel(II) complexes the λ_{\max} values assigned to the ${}^3A_{2g} \rightarrow {}^3T_{1g}$ transition occurred at 649 ± 2 nm and that of ${}^3A_{2g} \rightarrow {}^3T_{1g}(P)$ at 395 ± 2 nm) and, thus, they are not included in Table 1.) Precipitation hindered the studies on copper(II)–Bha [6] and copper(II)–Hha systems. Because of the low stabilities of the calcium(II) and magnesium(II) complexes, we were not interested in studying all of the calcium(II)- and the magnesium(II)-containing systems. Aluminium(III)–PYRha 1:1 species formed below the studied pH region and thus the corresponding stability constant could not be determined. Data for the metal ion–Aha complexes are taken from our former papers [6,19,20].

As Table 1 shows, besides MA_n-type complexes (where $1 \leq n \leq 3$), various deprotonated or mixed hydroxo species are also formed in many of the systems (not in the calcium(II)-containing ones, where the hydrolytic processes are not significant in the studied pH range [7]). Our former EPR results for copper(II)–Aha proved the deprotonation of the coordinated hydroxamate(s) in [CuA₂] resulting in the formation of [CuA₂H₋₁]⁻ at about pH 10 and [CuA₂H₋₂]²⁻ at higher pH [6]. The similar behaviour of the other primary hydroxamic acid, Pha suggests that this coordinated ligand can also release a proton in the measured pH range. Certainly, formation of [CuA₂H₋₁]⁻ does not occur with the secondary derivatives. On the contrary, [Al(Aha₂)H₋₁] and [Al(Aha₂)H₋₂]⁻ are mixed hydroxo complexes as it was

Table 1

Overall stability constants ($\log \beta$) for the complexes formed in proton-, copper(II)-, nickel(II)-, zinc(II)-, calcium(II)-, magnesium(II)- and aluminium(III)-monohydroxamic acid systems ($t = 25^\circ\text{C}$; $I = 0.2 \text{ mol/dm}^3 \text{ KCl}$)^a



	$M_p A_q H_r$		Aha	Pha	Hha	Bha	MAha	PhAha	PYRha	
R_C			–CH ₃	–C ₂ H ₅	–C ₄ H ₉	–Ph	–CH ₃	–CH ₃		
R_N			–H	–H	–H	–H	–CH ₃	–Ph		
H ⁺	0	1	1	9.27(5)	9.343(5)	9.409(9)	8.696(7)	8.70(1)	8.435(5)	5.767(6)
Cu(II)	1	1	0	7.89	7.889(7)	–	–	7.40(4)	7.31(2)	6.84
	1	2	0	13.80	14.32(3)	–	–	13.3(1)	12.90(3)	12.46
	1	2	–1	4.4	5.32(6)	–	–	–	–	–
Ni(II)	1	1	0	5.37	5.24(1)	5.15(2)	4.92(1)	4.73(2)	4.68(1)	4.844(9)
	1	2	0	9.50	9.51(2)	9.06(5)	8.73(2)	8.27(4)	8.28(1)	9.06(2)
	1	3	0	13.32	12.34(5)	–	10.7(1)	–	10.16(9)	11.91(5)
	1	2	–1	–0.87	–0.76(9)	–0.4(4)	–2.7(4)	–3.2(3)	–2.42(5)	–0.78(8)
	1	1	–1	–	–3.78(8)	–	–	–	–	–
Zn(II)	1	1	0	5.32	5.07(2)	5.29(1)	4.86(1)	4.51(6)	4.34(2)	4.87(1)
					5.08(2) ^b					
	1	2	0	9.64	9.51(3)	9.41(5)	8.77(2)	8.35(6)	8.12(3)	9.04(2)
					9.47(3) ^b					
	1	3	0	12.8	11.6(3)	–	–	–	–	11.80(6)
Ca(II)	1	2	–1	–0.32	–0.32(6)	–0.0(1)	–	–	–1.9(3)	–
					–0.44(9) ^b					
	1	1	–1	–	–3.7(2) ^b	–2.93(8)	–	–	–	–
Mg(II)	1	1	0	2.45	–	–	2.135(6)	1.59(2)	1.64(6)	2.47(3)
	1	2	0	–	–	–	–	–	–	3.5(8)
Mg(II)	1	1	0	2.96	–	–	2.67(2)	2.63(1)	2.39(1)	3.08(1)
	1	2	0	–	–	–	4.61(6)	3.9(2)	4.05(7)	5.73(2)
	1	1	–1	–7.22	–	–	–8.48(4)	–	–	–
Al(III)	1	1	0	8.15	7.97(3)	8.32(2)	7.57(5)	8.69(2)	7.84(4)	–
	1	2	0	15.77	15.59(3)	16.17(2)	14.6(1)	16.21(3)	15.10(3)	12.5(1)
	1	3	0	21.5	–	–	–	22.41(1)	–	–
	1	2	–1	10.40	10.14(2)	11.26(3)	–	–	10.77(4)	–
	1	2	–2	1.04	0.3(1)	–	–	–	–	–

^a Standard deviations are shown in parentheses. Aha results taken from Ref. [6] (Cu(II)), Ref. [7] (Ca(II), Mg(II)), Ref. [19] (Ni(II), Zn(II)), Ref. [20] (Al(III)); Cu(II)–PYRha results taken from Ref. [6].

^b Two models were accepted.

proved by our former ¹H and ²⁷Al NMR results [20] which strongly suggest the formation of hydroxo species with other monohydroxamic acids as well. It seems most likely that mixed hydroxo species are formed in the nickel(II)-, zinc(II)- and magnesium(II)-containing systems where precipitate is often formed at about pH 8.5–9.0.

Various possibilities are available to compare the metal-binding ability of the ligands. Out of them, we chose the following competition reaction for the comparison:



The higher stability constant for the above equilibrium ($\log K = \log K_{\text{MA}_n} - \text{p}K_{\text{HA}}$) means more favoured complex formation. Out of the calculated values those related to the 1:1 complexes together with the corresponding iron(III) results [6] are depicted in Fig. 2.

From Fig. 2 the following conclusions can be drawn: On the basis of the basicity of the hydroxamate moiety, the MAha is the most effective aliphatic monohydroxamate chelator of iron(III) and aluminium(III) indicating that the electron-donating R_N substituent of this ligand has a significant effect in delocalization of the lone pair of N into the C–N bond. It is evident that the delocalization of the N atom lone pair increases the electron density on the carbonyl oxygen, thus increasing the stability of the metal chelate. However, as it is demonstrated by our results, this effect is measurable only in the cases of complexes formed with 3+ metal ions and not with the 2+ ones.

The data for PYRha-containing complexes are very interesting. As seen by its $\text{p}K_{\text{HA}}$, the complexation with this ligand is unambiguously the most favoured with all the metal ions studied (Fig. 2 shows data only for the complexes formed

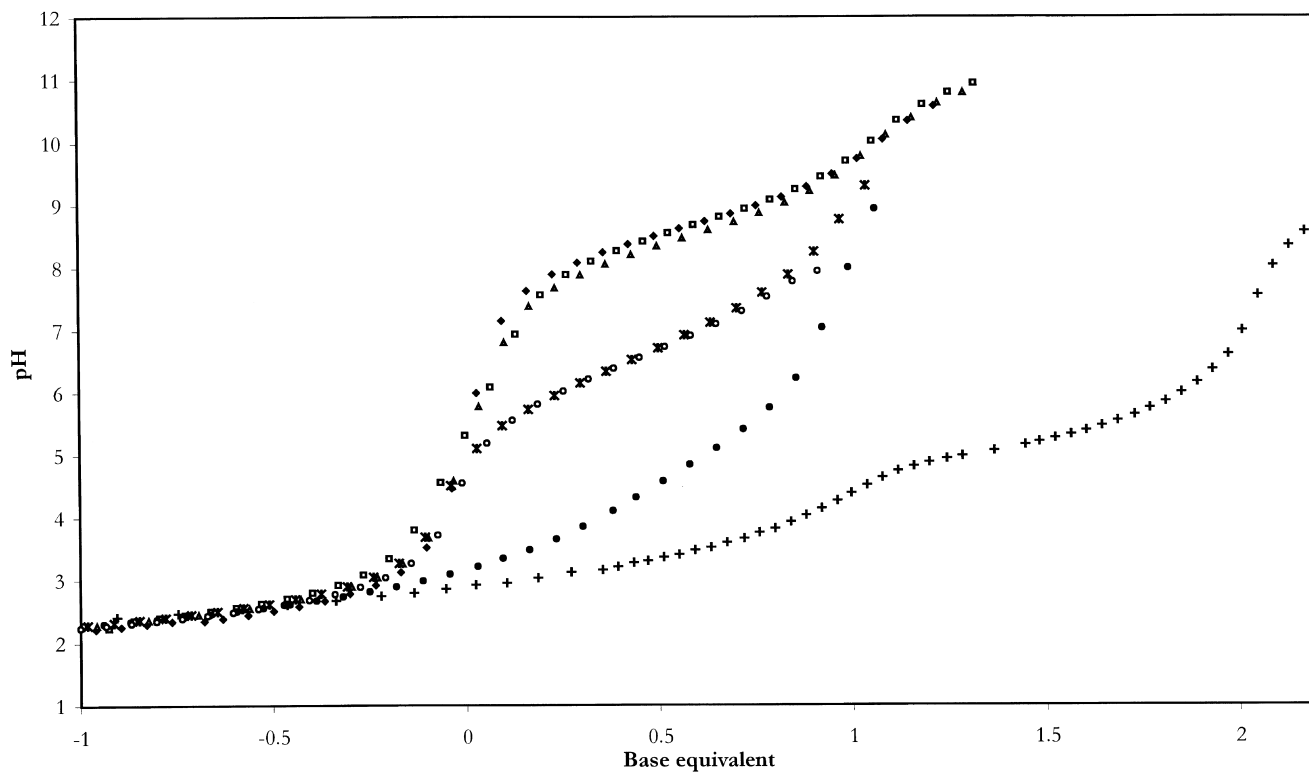


Fig. 1. The pH-metric titration curves for the MAHa (\blacklozenge) and calcium(II) (\square), magnesium(II) (\triangle), nickel(II) ($*$), zinc(II) (\circ), copper(II) (\bullet), aluminium(III) ($+$)–MAHa systems ($c_{\text{lig}} = 8 \times 10^{-3} \text{ mol/dm}^3$, metal to ligand ratio: 1:2). Negative base equivalent values mean acid excess.

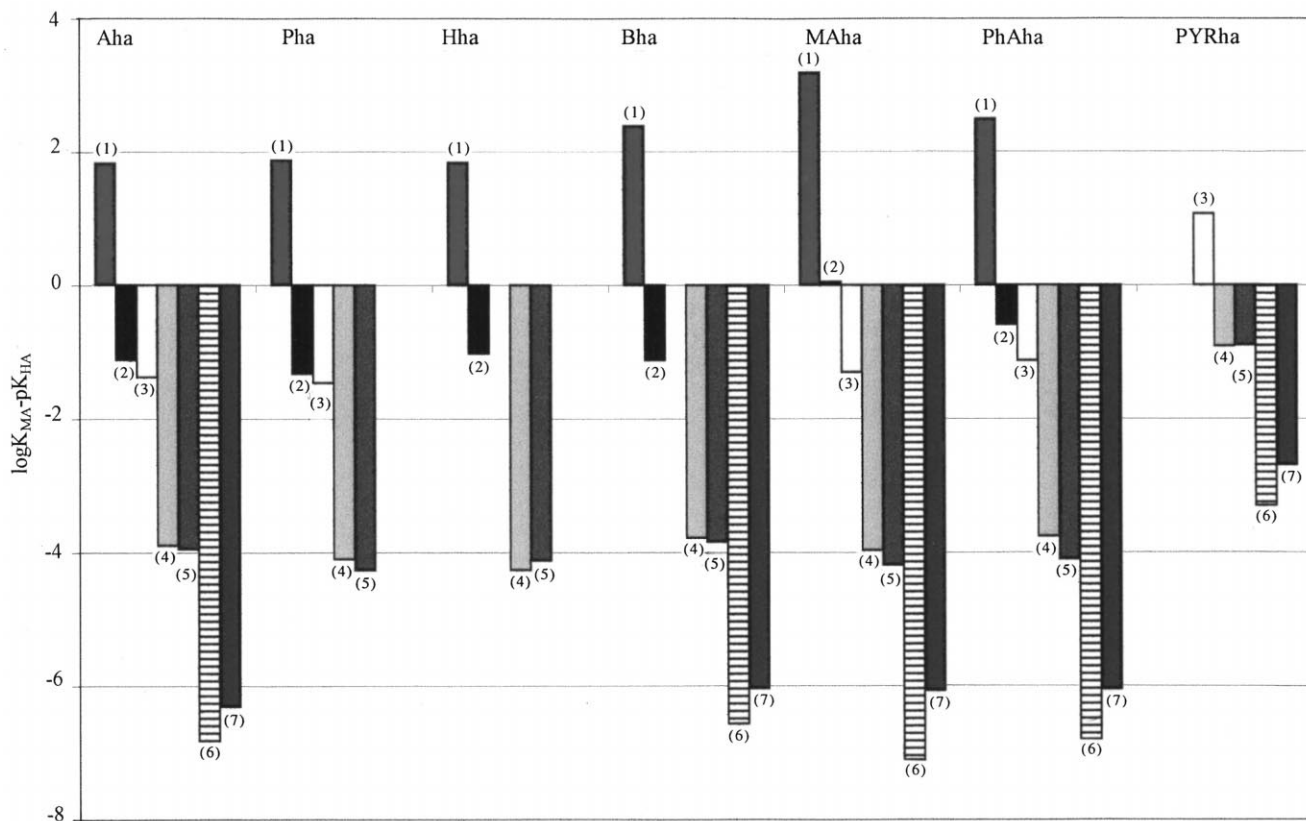


Fig. 2. Derived stability constants calculated for iron(III) (1), aluminium(III) (2), copper(II) (3), nickel(II) (4), zinc(II) (5), calcium(II) (6) and magnesium(II) (7)–monohydroxamic acid complexes according to the following equation: $M + HA \rightleftharpoons MA + H$; $\log K_{MA} - pK_{HA}$.

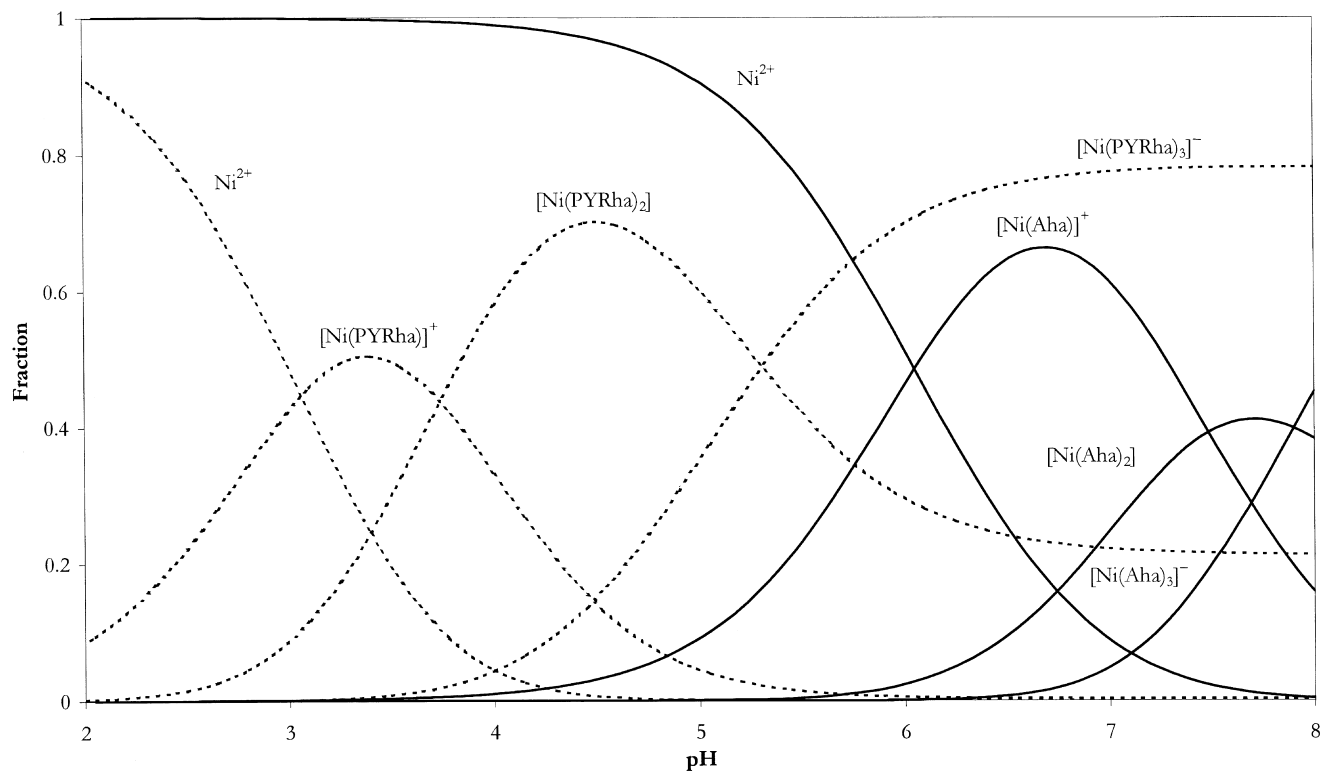


Fig. 3. Concentration distribution curves for nickel(II)–Aha (solid) and nickel(II)–PYRha (dashed) complexes ($c_{\text{Ni(II)}} = 2 \times 10^{-3} \text{ mol/dm}^3$, $c_{\text{ligand}} = 8 \times 10^{-3} \text{ mol/dm}^3$).

Table 2

Overall ($\log \beta$) and derived stability constants for metal ion–DFB complexes^a

	Cu(II) ^b	Ni(II) ^b	Zn(II) ^b	Ca(II) ^c	Mg(II) ^c	Al(III)
MAH ₃	36.99	33.20	33.40	–	–	–
MAH ₂	33.10	27.66	28.17	22.41	23.85	36.6(1)
MAH	23.98	19.71	20.40	13.25	14.66	33.8(1)
MA	13.73	8.89	10.36	3.03	2.8	23.9(1)
M ₂ AH	32.09	–	–	–	–	–
M + AH ₃	7.69	3.90	4.10	–	–	–
M + AH ₂	12.80	7.36	7.87	2.11	3.55	16.3
M + AH	13.14	8.87	9.56	2.41	3.82	23.0
M + A	13.73	8.89	10.36	3.03	2.80	23.9
pK_{MAH_3}	3.89	5.54	5.23	–	–	–
pK_{MAH_2}	9.12	7.95	7.77	9.19	9.19	2.8
pK_{MAH}	10.25	10.82	10.04	10.22	11.86	9.9

^a Stepwise dissociation constants (pK) for DFB: pK_1 : 8.30, pK_2 : 9.00, pK_3 : 9.46, pK_4 : 10.84 [7].

^b Ref. [8].

^c Ref. [7].

with 2+ metal ions because the aluminium(III)–PYRha 1:1 species is formed below the measurable pH range and the iron(III)–PYRha complexes are not soluble in water). It can be assumed that the presence of the ring π -electrons result in

a more favoured charge distribution in the chelates. In order to demonstrate the differences between the complex formation pH range of an aliphatic derivative and PYRha, concentration distribution curves of nickel(II)–Aha and nickel(II)–

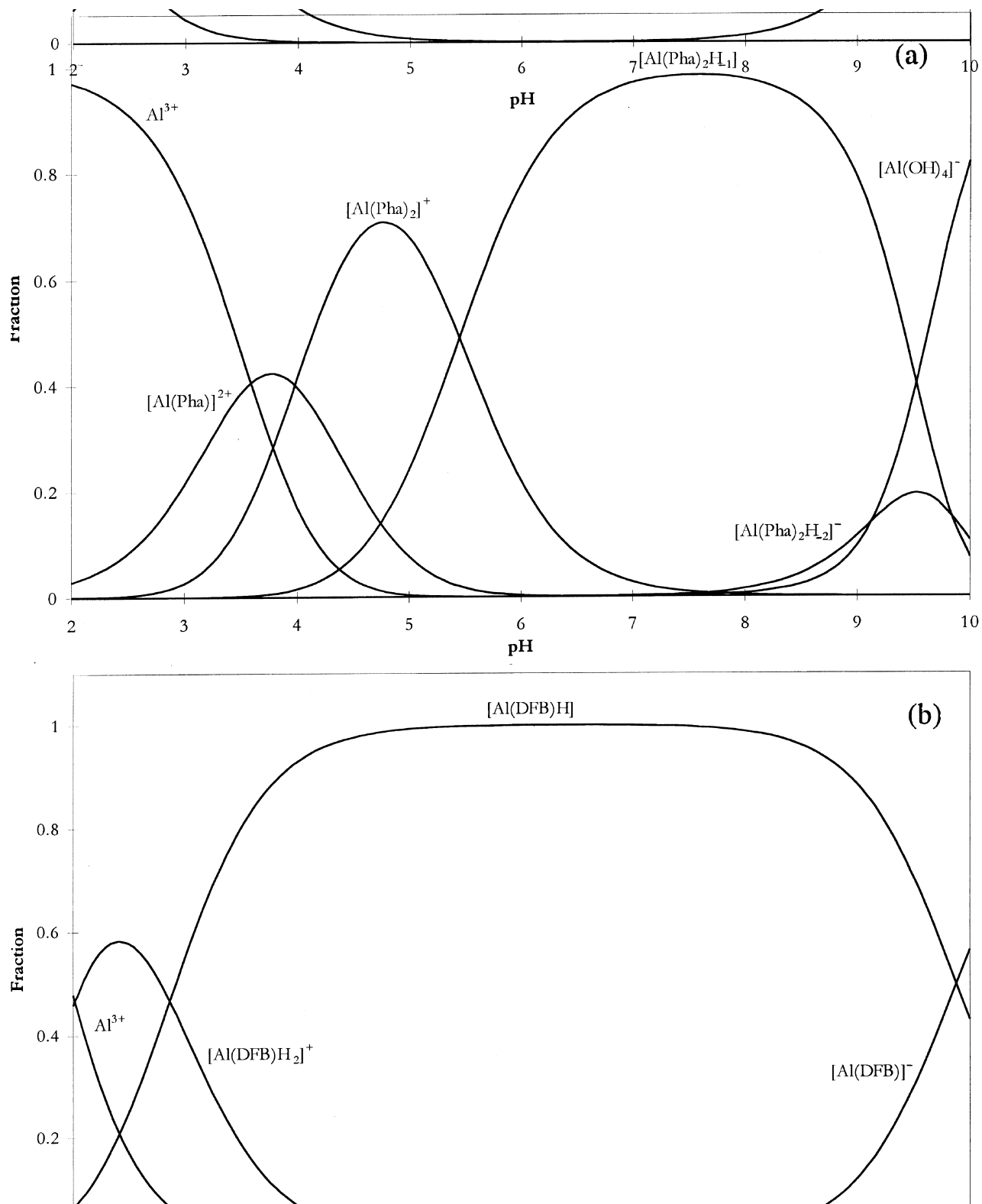


Fig. 4. Concentration distribution curves for aluminium(III)-Pha (a) and aluminium(III)-DFB (b) complexes ($c_{\text{Al(III)}} = 2 \times 10^{-3} \text{ mol/dm}^3$, $c_{\text{Pha}} = 6 \times 10^{-3} \text{ mol/dm}^3$, $c_{\text{DFB}} = 2 \times 10^{-3} \text{ mol/dm}^3$).

PYRha complexes were calculated and plotted in the same figure (see Fig. 3).

3.2. Comparison between the chelating properties of the monohydroxamic acids and DFB

The overall stability constants for the complexes with the natural trihydroxamate based DFB and some derived constants are reported in Table 2. The stability constants of aluminium(III)–DFB complexes were determined in the present work, all the others were taken from our former papers [7,8]. It can be seen in Table 2 that the various metal ion-protonated DFB complexes release the protons in a stepwise way. The lower the deprotonation constants for the complexes of $[\text{MAH}_3]$ and $[\text{MAH}_2]$ compared to the corresponding $\text{p}K$ values of the free ligand, the higher is the tendency of the chelate formation between the second and third hydroxamate and the metal ion, respectively. The non-coordinated terminal NH_3^+ -moiety releases its proton during the deprotonation of $[\text{MAH}]$.

If we compare the corresponding stepwise stability constants for the complexes with monohydroxamates (calculated from the overall constants in Table 1) and DFB (Table 2) we conclude that simultaneous coordination of the hydroxamate chelates of DFB does not result in 'extra' high values of stability constants (chelate effect). This has been explained by the relatively long connecting chain lengths between the hydroxamate binding groups of DFB, which resulted in their almost independent coordination [2]. A comparison of the corresponding concentration curves for DFB and monohydroxamates, however, shows the much more favoured metal binding ability of DFB. To illustrate this, the concentration distribution curves for the aluminium(III)–Pha and aluminium(III)–DFB are shown in Fig. 4(a) and (b), respectively.

As Fig. 4(b) shows, the $[\text{Al}(\text{DFB})\text{H}]$ species exists in a very wide pH range and its deprotonation starts at about pH 9. ^{27}Al NMR results prove that hydrolytic processes do not start in the aluminium(III)–DFB system up to pH 10 (there is only one signal at 31.54 ppm, which most probably relates to the aluminium(III)-tris-chelated species and there is no characteristic signal for $[\text{Al}(\text{OH})_4]^-$ at 80–81 ppm). In contrast, mixed hydroxo species exist already at about pH 5 in the aluminium(III)–Pha system (see Fig. 4(a)). We could not observe, however, the favoured complex formation with DFB in the case of the largest calcium(II). The most reasonable explanation for this is that the length of the connecting chains between hydroxamate binding groups allows only the monochelated coordination of DFB to the large calcium(II) ion [7].

4. Conclusions

The chelating properties of the studied aliphatic monohydroxamic acids (Aha, Pha, Hha, Bha, MAha, PhAha)

towards the 2+ metal ions follow their basicity order. This trend is somewhat modified by electronic effects of the substituents in the cases of the 3+ metal ions. The aromatic derivative, PYRha, is a real effective chelator for all the studied metal ions. Among the studied monohydroxamic acids, PYRha is the only one which forms complexes in the fairly acidic pH range with all the 2+ transition metal ions studied.

When the denticity of DFB is higher towards a certain metal ion than that of a monohydroxamic acid, its metal binding ability is also higher. This is not the case with the large calcium(II) ion where the complex-forming abilities of DFB and monohydroxamic acids are comparable.

Acknowledgements

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