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Hydroxamic and aminohydroxamic acids and their complexes with metal ions

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CONTENTS

ABBREVIATIONS

Aha	acetohydroxamic acid
α-Alaha	α-alaninehydroxamic acid
β-Alaha	β-alaninehydroxamic acid
Argha	argininehydroxamic acid
Asp-β-ha	aspartic acid-β-hydroxamic acid
Bha	benzohydroxamic acid
Dopaha	3,4-dihydroxyphenylalaninehydroxamic acid
Fha	formohydroxamic acid
Glu-γ-ha	glutamic acid-γ-hydroxamic acid

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Glyha	glycinehydroxamic acid
Hisha	histidinehydroxamic acid
n-Leuha	norleucinehydroxamic acid
Leuha	leucinehydroxamic acid
Pha	propionohydroxamic acid
Pheha	phenylalaninehydroxamic acid
Sarha	sarcosinehydroxamic acid
Serha	serinehydroxamic acid
Thrha	threoninehydroxamic acid
Trpha	tryptophanehydroxamic acid
Tyrha	tyrosinehydroxamic acid
n-Valha	norvalinehydroxamic acid
Metha	methioninehydroxamic acid

A. INTRODUCTION

Hydroxamic acid-containing compounds are ubiquitous and are intimately associated with iron-transport phenomena. The selectivity of this mechanism is critical since numerous other metal ions, which may not be essential or which may have a toxic effect on the organism, are present in the environment [1]. Hydroxamic acid is also known as a constituent of growth factors, food additives, antibiotics, antibiotic antagonists, tumor inhibitors, antifungal agents and cell-division factors; several of them have been used as drugs [2–8]. Hydroxamic acids are also potent and specific inhibitors of urease activity [9], thermolysin [10,11], elastase [12] and aminopeptidases [13,14]. These enzymes are metalloproteinases and the mechanism of inhibition appears to involve chelation of metals at their active sites [15].

Hydroxamic acids have also received considerable attention as reagents in analytical chemistry for gravimetric analysis [16] and for the solvent extraction and spectrophotometric determination of metals [17]. The reagents are also useful in the analysis of trace metals by flow injection analysis [18] and high-performance liquid chromatography [19]. The properties and behaviour of hydroxamic acid resins have been studied [20]. Discovery of oscillation phenomena in the fluorescence intensity of some aromatic hydroxamic acids [21] suggests that they can undergo photochemical reactions [22,23].

With regard to the ability of these ligands to form chelates, one interesting question concerning the metal complex is whether the nitrogen or oxygen atom of the hydroxamic group (CONHOH) is involved in coordination to the metal ion.

In 1978, a review [24] on hydroxamic acid complexes finished with the statement: "It is to be expected that future extensive studies will establish the donor properties of hydroxamic acids to a greater extent". During the last 12 years, much more detailed information has been published, primarily involving the first metal transition series.

These new discoveries are addressed in this contribution.

B. THE HYDROXAMIC ACID GROUP AND ITS METAL-BINDING SITES

Hydroxamic acids may be regarded as derivatives of both hydroxylamines and carboxylic acids. The acyl portion of naturally occurring derivatives is usually simple and is often acetyl or originates biogenetically from acetate. In solution, hydroxamic acid exists in the two tautomeric forms shown in Scheme 1.

If there is restricted rotation about the C–N bond, then both the *Z*- and *E*-isomers of the keto form (see Scheme 2) exist [25]. NMR spectra confirm [26] that both *Z* and *E* forms exist in solution, as do the enol forms (the *Z*–*E* isomer ratio is solvent-dependent). The stabilities of the different forms of isolated and hydrated hydroxamic acids were examined using ab initio molecular orbital calculations [25]. The calculations show that the isolated *E*-keto forms of Fha and Aha have the lowest energy. However, on hydration, the *Z*-keto isomers become the more stable forms due to hydrogen bonding. The X-ray crystal structures of Aha hemihydrate reveal that, in its crystals, the *Z*-keto form is present [27], similar to the Pha molecule [25].

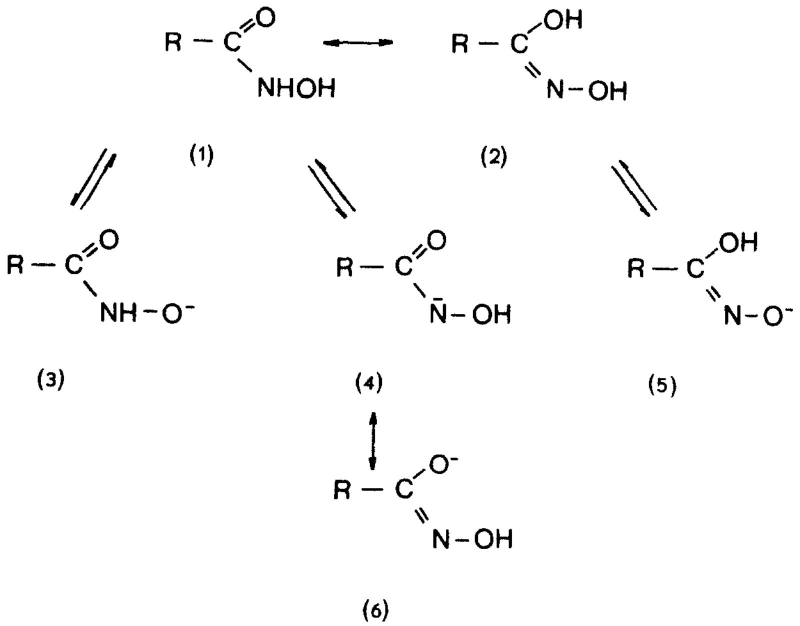
Structure **1** (Scheme 1) contains one easily replaceable proton (monobasic acid), while structure **2** may dissociate two protons, thus behaving as a dibasic acid. This keto–enol tautomerism provides a number of sites which are available for metal ion coordination. The keto form predominates in acidic solutions, while the enol is the dominant form in alkaline medium [28]. There are several possibilities for the mode of dissociation and these have been summarized [2,29,30]. The mono-anions of these forms give rise to quite complex equilibria. Proton dissociation may follow the paths shown in Scheme 3. The possibility for the existence of the several different monoionic

(1) (2)

Scheme 1.

(Z) (E)

Scheme 2.



Scheme 3.

forms depends on the ligand concerned. It was suggested [2,29,30], for example, that, for benzohydroxamic acid, structures **3** and **4** occur in essentially equal concentrations. Exner and Simon [29] concluded from IR and UV spectra that hydroxamic acids with common substituents form N-acids practically exclusively.

The existence of such forms in a complex may depend on the metal ion [31–33].

The IR spectra of hydroxamic acids and their complexes [33–35] are generally very complex, though some characteristic bands for different ligand structures were suggested. For example, the band around 3200 cm^{-1} was assigned as the NH valence frequency, while those observed in the 3080–3060 cm^{-1} region were attributed to the NH deformation and the CO valence vibrations [33–35]. The broad band around 1610–1585 cm^{-1} observed in metal-free ligands is assigned to the ketonic carbonyl vibration. Its broadening originates from intramolecular hydrogen bonding and it undergoes an energy shift of 40–60 cm^{-1} when ketonic oxygen coordinates to the metal ion [35]. The band containing the NH planar deformation (60%) and CN valence (40%) frequencies is centred at 1570 cm^{-1} [33]. There is also a band around 1400–1440 cm^{-1} which is also assigned to the deformation of the NH moiety [33–35]. When hydroxamic acids are dissolved in an inert solvent, the band at 2770 cm^{-1} disappears and a new one is observed at 3420 cm^{-1}; also, the band at 3280 cm^{-1} is shifted to 3220 cm^{-1} [33]. These variations suggest that there are considerable changes in the hydrogen bonding system during the dissolution process.

These IR results are supported in several cases by NMR spectra. The NMR spectra of Aha exhibits the signals of both NH and OH protons while, in the case of sodium acetohydroxamate, only the NH proton is observed in the spectrum [33]. This result supports the existence of the form **3**. In contrast, the NMR spectra of the Sn(III)–Aha complex show the presence of only the OH proton [32,33]. Thus, the NMR results seem to exclude structure **3** in the complex system, while the IR measurements suggest the formation of **6** in the Sn(III)–Aha species.

Hydroxamic acid derivatives of amino acids have even more complicated acid–base properties than the monohydroxamic acids. The most simple aminohydroxamic acids (alkyl aminohydroxamic acids) can liberate two protons. One from the protonated amino group and one from the hydroxamic acid group. Some contradictions concerning the acid–base chemistry of aminohydroxamic acids are found in papers published during the 1980s [35–50]. Some [46–49] have concluded that the NH_3^+ group is more acidic than the hydroxamic function, while others [35,36,39–45] have taken the opposite view. A very recent paper [51] suggests, however, that the two protons of aminohydroxamic ligand are liberated in overlapping processes. This means that the pK values determined by pH-metric titrations (Table 1) cannot be unambiguously assigned to either of the proton dissociating groups. Instead, only the dissociation microconstants are characteristic for the real acidity of the individual ligand functions. The dissociation microconstants were determined for L-α-Alaha and β-Alaha [51] by pH-^{13}C NMR spectrometric titrations. The data obtained, together with the possible dissociation processes, are shown in Table 2. According to these results, the NH_3^+ group of the α-derivative is somewhat more acidic than the CONHOH function, while the acidity sequence is opposite for the β-derivative. These results are in good agreement with the results obtained for Glyha by Karlicek and Polasek [56] from UV absorption curves. Recently, the ^1H NMR measurements published for Sarha [63] indicated that the CONHOH group may be more acidic than the amino function. According to this work, in the first deprotonation process ca. 40% of the protons derive from NH_3^+, while 60% come from the CONHOH group, respectively. The difference in the results published for α-Alaha [51] and Sarha [63] (both of which are α-derivatives) can be explained by the electron-donating effect of the methyl group.

X-ray results indicate that the above situation is not the same in the solid state. Namely, the structure of Glyha [64] reveals that a molecule crystallized from neutral solutions contains a deprotonated hydroxamic nitrogen, while its amino group and hydroxyl oxygen remain protonated.

There are aminohydroxamic acids where the dissociation of the side-chain donor can overlap with that of the NH_3^+ and NHOH groups (e.g. Tyrha, Dopaha and Hisha). The determination of the microconstants for these systems is expected to be much more complicated than that discussed above. No details about this group of compounds have been published until now.

TABLE 1

Proton dissociation constants of aminohydroxamic acids

Ligand	pK_1	pK_2	pK_3	Medium	Ref.
α-Alaha	7.34	9.16		0.2(KCl)	50
	7.19(2)	9.15(1)		0.1($NaClO_4$)	48
	7.44(1)	9.18(1)		0.5(KCl)	44
β-Alaha	8.38(1)	9.59(1)		0.2(KCl)	51
Argha	6.876(2)	8.832(1)	13.23(8)	0.5(KCl)	52
Asp-β-ha	2.18(1)	8.15(1)	9.37(1)	0.5(KCl)	43
	2.12(1)	8.29(1)	9.42(1)	0.2(KCl)	53
Dopaha	6.94(1)	8.78(1)	9.61(1)	0.2(KCl)	54
Glu-γ-ha	2.21(1)	8.55(1)	9.50(1)	0.2(KCl)	55
Glyha	7.50(1)	9.26(5)		0.1($NaClO_4$)	56
	7.373(3)	9.118(2)		0.1($NaClO_4$)	46
	7.518	9.184		0.15(NaCl)	57
	7.484(2)	9.096(1)		0.5(KCl)	39
Hisha	5.40	7.22	9.11	0.15(NaCl)	38
	5.24(2)	7.17(2)	9.17(1)	0.1($NaClO_4$)	58
	5.43(1)	7.14(1)	9.07(1)	0.2(KCl)	59
	5.391(3)	7.067(2)	8.942(2)	0.5(KCl)	41
Leuha	7.141(6)	9.104(5)		0.1($NaClO_4$)	49
n-Leuha	7.375(2)	9.172(1)		0.5(KCl)	42
Pheha	6.91(1)	9.08(2)		0.2(KCl)	54
	6.886(6)	9.013(5)		0.5(KCl)	60
Sarha	7.62(1)	9.20(1)		0.1($NaClO_4$)	61
Serha	6.795	8.953		0.15(NaCl)	35
Thrha	6.773(2)	8.868(1)		0.5(KCl)	60
Trpha	7.042(6)	9.088(5)		0.5(KCl)	42
Tyrha	6.956(3)	8.919(2)	9.931(2)	0.5(KCl)	40
	6.81(1)	8.90(1)	9.91(2)	0.2(KCl)	54
n-Valha	7.34(2)	9.125(1)		0.5(KCl)	39
Metha	6.77	9.033		0.15(NaCl)	62

No standard deviations in papers published by Brown et al.

C. COMPLEXES OF HYDROXAMIC ACIDS

(i) Monohydroxamic acids as ligands

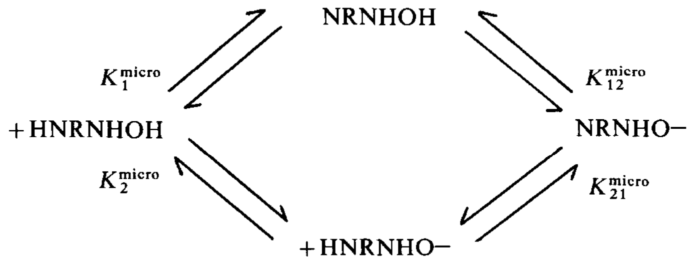
The single hydroxamic acid group behaves as a typical bidentate donor towards various metal ions.

Monohydroxamic acids form octahedral complexes with a number of metal ions coordinating via two oxygen atoms of the deprotonated hydroxamic acid group. This has been proved, e.g. in the X-ray studies of tris(Bha)iron(III) dihydrate [65] and tris(Bha)chromium(III) [66]. Brown et al. [34] also studied solid-state complexes

TABLE 2

Dissociation macroconstants (pK) and microconstants (pK^{micro}) of the ligand at 25 °C

$$H_2L^+ \xrightarrow{K_1} HL \xrightarrow{K_2} L^-$$



	α-Alaha		β-Alaha	
I/mol dm^{-3}	0.2(KCl)	1.0(KCl)	0.2(KCl)	1.0(KCl)
pK_1	7.34(1)	7.40(1)	8.32(1)	8.37(1)
pK_2	9.16(1)	9.19(1)	9.59(1)	9.63(1)
K_1^{micro}/K_2^{micro}	2.7(1)	2.7(1)	0.42(5)	0.42(5)
pK_1^{micro}	7.48(2)	7.54(2)	8.85(2)	8.90(2)
pK_2^{micro}	7.90(3)	7.96(3)	8.47(2)	8.52(2)
pK_{12}^{micro}	9.02(2)	9.05(2)	9.06(2)	9.10(2)
pK_{21}^{micro}	8.60(3)	8.63(3)	9.44(2)	9.48(2)

of Fe(III), Co(II), Cu(II) and Ni(II) with monohydroxamic acids. In the case of the bis(Aha)nickel(II) dihydrate and bis(Pha)nickel(II) dihydrate [34,35], infrared spectra show shifts of about 40–60 cm^{-1} in the broad bands at 1619–1583 cm^{-1} when compared with the metal-free ligand. This strongly suggests the complexation of the ketonic oxygen atom. Bands in the 1445 cm^{-1} region can be assigned qualitatively to the N–C stretching vibration with contributions from C–O and C–R modes, those at about 1300 cm^{-1} to C–R stretches and that at about 1100 cm^{-1} to a practically pure N–O stretching mode. The general pattern of the infrared spectra supports normal coordination via the ketonic oxygen atom and the oxygen atom of the deprotonated NHO$^-$ group. The solid-state magnetic moments and the electronic spectra provide further support for an octahedral structure in the case of Fe(III), Co(II) and Ni(II) complexes and close to tetragonal geometry for the Cu(II) complexes [34]. The higher stabilities of the Pha complexes in comparison with those obtained for the Aha complexes (Table 3), presumably reflect the greater inductive effect of the ethyl group compared with the methyl group [35].

In solution, equilibrium studies of monohydroxamic acids with Ni(II) [32,35,67], Cu(II), [32,67], Zn(II) [32,67] and Fe(III) [32,57,67–70] have shown the existence of different species. Except for Cu(II), the Aha, Pha and Bha ligands were

TABLE 3

Stability data (log β) for complexes in the metal ion–aminohydroxamic acid systems

Ligand/ species	Mn(II)	Co(II)	Ni(II)	Cu(II)	Zn(II)	Cd(II)	Fe(III)
Aha							
[ML]			$5.15(1)^{A}$	$7.89(1)^{A}$	$5.18(1)^{A}$		11.42^{D}
			5.4^{B}	7.9^{B}	5.4^{B}		$10.38(6)^{E}$
			5.369^{C}				
$[ML_2]$			$9.18(1)^{A}$	$14.06(1)^{A}$	$9.45(2)^{A}$		21.10^{D}
			9.3^{B}	14.3^{B}	9.6^{B}		$20.28(10)^{E}$
			9.597^{C}				
$[ML_3]$			$11.68(3)^{A}$		$11.57(4)^{A}$		28.3^{D}
			12.107^{B}				$27.9(15)^{E}$
$[MLH_{-1}]$			$-4.35(3)^{A}$		$-3.40(3)^{A}$		
$[ML_2H_{-1}]$				$4.44(3)^{A}$			
Bha							
[ML]							11.06^{D}
$[ML_2]$							20.43^{D}
$[ML_3]$							27.83^{D}
Pha							
[ML]			5.498^{C}				
$[ML_2]$			9.734^{C}				
$[ML_3]$			12.189^{C}				
Glyha							
[MLH]	$11.07(3)^{a}$	$11.90(3)^{a}$			$12.40(2)^{a}$	$11.48(3)^{a}$	16.450^{d}
							$17.36(3)^{f}$
							$17.36(3)^{g}$

$[ML]$	3.85(1)[a]	6.493(14)[b]	6.768(7)[b]	10.83(4)[c]	5.38(4)[a]	4.81(1)[a]	13.388[d]
		5.60(1)[a]	6.800[e]	10.682(16)[b]			14.14(9)[f]
			7.043(05)[h]				13.14(9)[g]
$[MLH_{-1}]$	−5.51(1)[a]	−1.90(1)[a]	−0.232(13)[h]		−1.46(2)[a]	−3.37(1)[a]	
$[MLH_{-2}]$			−8.692(17)[h]				
$[ML_2H]$							27.558[d]
							28.94(6)[f]
$[ML_2]$	6.45(2)[a]	11.144(11)[b]	13.378(4)[b]	19.89(2)[c]	10.07(2)[a]	8.24(2)[a]	21.868[d]
		10.03(1)[a]	13.495[e]	19.772(12)[b]			22.72(9)[f]
			13.651(15)[h]				22.62(8)[g]
$[ML_2H_{-1}]$		1.708(16)[b]	5.061(9)[b]	9.95(3)[c]			
				10.064(22)[b]			
$[ML_3H]$							33.856[d]
$[ML_3H_3]$							48.28(6)[g]
$[ML_3]$		12.45(4)[a]					26.501[d]
$[ML_3H_{-1}]$							17.225[d]
$[ML_3H_{-2}]$							6.891[d]
$[M_2L_2H_{-1}]$				20.91(3)[c]			
$[M_2L_3]$					19.45(4)[a]		
$[M_4L_5]$				61.763(21)[b]			
α-Alaha							
$[MLH]$	10.92(5)[i]	12.12(1)[i]			12.27(1)[i]	11.40(1)[i]	17.15(1)[i]
					12.41(2)[m]	11.52(0)[j]	
$[ML]$	3.47(1)[i]	4.74(4)[i]	6.76(1)[i]	10.89(2)[i]	5.29(1)[i]	4.25(1)[i]	13.92(1)[i]
		6.08(1)[k]	6.92(1)[k]	10.32(6)[k]	5.25(2)[m]	4.52(1)[j]	
			6.54(3)[n]	10.90(8)[l]			
$[MLH_{-1}]$	−5.99(2)[i]	−2.64(1)[i]			−2.26(2)[i]	−3.93(2)[i]	
					−2.31(2)[m]	−3.30(2)[j]	
$[ML_2H]$	14.30(7)[i]						28.36(5)[i]
$[ML_2]$	5.97(3)[i]	9.39(1)[i]	14.13(1)[i]	19.87(1)[i]	9.32(4)[i]	7.11(4)[i]	21.99(4)[i]
		10.69(1)[k]	14.06(1)[k]	19.65(2)[l]	9.26(3)[m]	7.85(4)[j]	
			13.31(2)[n]	20.04(1)[k]			

TABLE 3 (continued)

Ligand/ species	Mn(II)	Co(II)	Ni(II)	Cu(II)	Zn(II)	Cd(II)	Fe(III)
$[ML_2H_{-1}]$		1.59(4)[k]	5.47(1)[i] 5.82(2)[k] 4.76(1)[n]	9.98(2)[i] 9.74(3)[i] 11.11(6)[k]			14.54(3)[i]
$[ML_3H]$							33.90(5)[i]
$[M_2L]$		8.91(3)[k]					
$[M_2L_2H_{-1}]$				20.89(2)[i] 21.41(3)[j] 20.90(1)[k]			
$[M_2L_3]$		17.69(3)[i]			18.77(2)[i] 18.03(7)[m]		
n-Valha							
$[ML]$		6.185(15)[b]	6.825(12)[b]	10.609(18)[b]			
$[ML_2]$		10.593(17)[b]	13.948(5)[b]	19.699(11)[b]			
$[ML_2H_{-1}]$		1.266(21)[b]	5.620(11)[b]	9.838(20)[b]			
$[M_4L_5]$				62.616(22)[b]			
n-Leuha							
$[ML]$		6.423(25)[o]	6.571(35)[o]	10.29(14)[o]			
$[ML_2]$		10.964(35)[o]	13.902(8)[o]	19.695(26)[o]			
$[ML_2H_{-1}]$		1.77(7)[o]	6.17(9)[o]	9.877(43)[o]			
$[M_2L_2H_{-1}]$				20.767(18)[o]			
Leuha							
$[ML]$			6.18(2)[n]	10.83(9)[p]	12.03(2)[m]		
$[ML_2]$			13.150(4)[n]	19.51(3)[p]	4.21(6)[m]		
$[ML_2H_{-1}]$			4.70(1)[n]	9.98(6)[p]	8.83(5)[m]		
$[M_2L_2H_{-1}]$				21.09(5)[p]	−2.97(2)[m]		
$[M_2L_3]$					17.44(4)[m]		

Trpha				
[ML_2]		14.383(19)[o]	20.31(6)[o]	
[ML_2H_{-1}]		5.53(7)[o]	10.52(7)[o]	
[$M_2L_2H_{-1}$]			21.469(38)[o]	
Serha				
[ML]	5.807(21)[r]	7.430[C] 6.574(12)[r]		
[ML_2]	10.536(20)[r]	14.080[C] 13.478(4)[r]	19.648(14)[r]	
[ML_2H_{-1}]	1.741(47)[r]	6.240[C] 5.362(13)[r]	10.093(31)[r]	
[M_2L]	8.757(47)[r]			
[$M_2L_2H_{-1}$]			20.432(12)[r]	
[ML_2H_2]		−2.795[C]		
Thrha				
[ML]	5.787(16)[s]	6.476(7)[s]		
[ML_2]	10.299(16)[s]	13.300(4)[s]	19.507(10)[s]	
[ML_2H_{-1}]	1.429(36)[s]	5.115(13)[s]	9.918(10)[s]	
[M_2L]	8.807(36)[s]			
[$M_2L_2H_{-1}$]			20.377(28)[s]	
Pheha*				
[MLH]	11.82(2)[t]			11.69(3)[t]
[ML]	5.05(2)[t]	6.53(3)[t]	10.7(8)[t]	4.84(5)[t]
[ML_2]	9.75(5)[t]	13.89(7)[t]	19.783[s]	9.5[t]
[$M_2L_2H_{-1}$]			20.750[s]; prec[t]	
Tyrha				
[MLH_2]				20.8(3)[t]

TABLE 3 (continued)

Ligand/ species	Mn(II)	Co(II)	Ni(II)	Cu(II)	Zn(II)	Cd(II)	Fe(III)
[MLH]		14.41(6)^{t}	16.01(9)^{t}	19.78(9)^{t} 20.162(22)^{u}	14.28(5)^{t}		
[ML_2H]		28.55(6)^{t}	33.94(4)^{t} 33.668(14)^{u}	39.17(5)^{t} 33.123(59)^{u}	29.2(4)^{t}		
[ML_2H]			24.69(9)^{t} 25.700(46)^{u}	30.07(9)^{t}			
[ML_2]			15.12(8)^{t} 16.186(58)^{u}	20.21(9)^{t} 14.064(50)^{u}			
[ML_2H_{-1}]			5.15(8)^{t}	9.95(8)^{t}			
[M_2L_2H]			6.646(48)^{u}	39.4(2)^{t}			
Dopaha*							
[MLH_2]		20.97(5)^{t}			21.19(5)^{t}		
[MLH]		14.51(2)^{t}	16.25(7)^{t}	19.81(2)^{t}	14.90(3)^{t}		
[ML_2H_2]		28.76(5)^{t}	33.08(9)^{t}	prec^{t}	28.9(2)^{t}		
[ML_2H]			25.02(9)^{t}				
[ML_2]			16.28(8)^{t}				
[M_2L_2H]				prec^{t}			
Hisha							
[MLH_2]				20.4(1)^{y}			22.148$^{(ax)}$
[MLH]		14.036(23)^{w}	15.68(1)^{n} 15.009(7)^{w}	17.46(3)^{y} 17.75(3)^{x} 16.916(12)^{w}	13.68(3)^{m}		18.070$^{(ax)}$
[ML]			9.27(7)^{w}	10.698(38)^{w}	26.80(4)^{m}		13.389$^{(ax)}$
[MLH_{-1}]					$-0.64(6)^{m}$		
[ML_2H_2]		26.633(45)^{w}	29.89(1)^{n} 28.821(17)^{w}	33.53(3)^{y} 33.36(7)^{x} 29.15(9)^{w}			31.372$^{(ax)}$

$[ML_2H]$	20.861(30)^{w}	23.77(1)^{n}	27.36(4)^{y}	20.21(4)^{m}	25.885$^{(ax)}$
		22.793(12)^{w}	28.58(6)^{x}		
			22.08(9)^{w}		
$[ML_2]$	12.784(50)^{w}	16.99(1)^{n}	20.23(4)^{y}		18.984$^{(ax)}$
		15.644(13)^{w}	21.46(5)^{x}		
			13.73(8)^{w}		
$[ML_2H_{-1}]$		6.80(4)^{n}	10.31(6)^{y}	11.91(4)^{m}	
		4.961(17)^{w}	10.85(8)^{x}		
			3.34(8)^{w}		
$[M_2L_2H]$			34.03(3)^{y}		
$[M_2L_2]$			29.45(6)^{y}		
$[M_2L_2H_{-1}]$			23.07(6)^{y}		
			27.27(11)^{x}		
$[ML_3]$					21.606$^{(ax)}$
$[ML_3H_{-1}]$					12.441$^{(ax)}$
Sarha					
$[MLH]$				12.58(2)^{m}	
$[ML]$		6.21(2)^{n}	10.39(9)^{z}	5.27(1)^{m}	
$[MLH_{-1}]$				−2.79(1)^{m}	
$[ML_2]$		12.18(1)^{n}	18.52(3)^{z}	9.65(1)^{m}	
$[ML_2H_{-1}]$		2.66(3)^{n}	8.77(4)^{z}		
$[M_2L_2H_{-1}]$			20.22(3)^{z}		
$[M_2L_3]$				17.91(8)^{m}	
Metha					
$[MH_{-1}]$					−3.05$^{(ay)}$
$[MH_{-2}]$					−6.31$^{(ay)}$
$[ML]$					12.730(3)$^{(ay)}$
$[MLH]$					16.260(7)$^{(ay)}$
$[ML_2H]$					26.12(18)$^{(ay)}$
$[ML_2H_2]$					30.94(8)$^{(ay)}$
$[M_2L_3]$					38.24(12)$^{(ay)}$

TABLE 3 (continued)

Ligand/ species	Mn(II)	Co(II)	Ni(II)	Cu(II)	Zn(II)	Cd(II)	Fe(III)
β-Alaha							
[MLH]			14.12(2)[a]		14.16(5)[a]		
[ML]				12.85(3)[b]			
[ML_2H_2]					27.59(7)[a]		
[ML_2H]			20.26(2)[a]		19.65(5)[a]		
[ML_2]			11.57(4)[a]		10.85(6)[a]		
[ML_2H_{-1}]			1.99(3)[a]		1.05(6)[a]		
[$M_5L_4H_{-4}$]				46.66(7)[b]			
Asp-β-ha							
[MLH_2]							18.82(5)[c]
[MLH]		13.91(2)[d]	14.25(3)[d]	16.41(16)[c]	13.91(2)[c]		
		13.71(2)[c]	14.45(3)[c]				
[ML]		7.56(2)[d]	8.38(3)[d]	13.24(5)[c]	7.44(1)[c]		
		7.10(1)[c]	8.38(2)[c]	12.60(1)[d]			
[ML_2H_2]							36.35(5)[c]
[ML_2H]		19.92(3)[c]	21.74(6)[c]		20.30(3)[c]		31.63(6)[c]
[ML_2]		12.86(3)[d]	14.73(6)[d]	19.07(4)[d]			
		12.00(2)[c]	14.41(3)[c]	9.08(4)[d]	11.72(3)[c]		
[ML_2H_{-1}]		2.46(7)[d]	4.56(10)[c]		2.11(3)[c]		24.25(7)[c]
		1.87(2)[c]					
[ML_3]							15.32(7)[c]
[M_2L_3]		23.43(3)[d]	25.78(4)[d]	37.45(5)[d]			
[M_3L_4]				53.43(9)[d]			
[$M_4L_4H_{-2}$]				52.82(16)[c]			
[$M_4L_4H_{-3}$]				42.30(20)[c]			

Argha					
[MLH]					16.057(8)(cy)
[ML]	5.48(4)(cy)	5.81(4)(cy)			
[ML_2H_2]	24.03(4)(cy)				31.040(6)(cy)
[ML_2H]					26.69(2)(cy)
[ML_2]	9.87(5)(cy)	13.093(4)(cy)	18.87(2)(cy)		21.10(8)(cy)
[MLH_{-1}]	−1.72(6)(cy)				
[ML_2H_{-1}]		4.87(1)(cy)	9.16(4)(cy)		
[$M_2L_2H_{-1}$]		9.73(2)(cy)	19.88(1)(cy)		
[$M_2L_2H_{-2}$]					20.27(2)(cy)
[$M_2L_2H_{-4}$]					7.53(5)(cy)
[ML_3]					26.90(1)(cy)
[ML_3H]					33.78(1)(cy)
[ML_3H_2]					39.72(2)(cy)
[ML_3H_{-1}]					18.35(2)(cy)
[$M_2L_3H_{-1}$]					33.34(4)(cy)
Glu-γ-ha					
[MLH]	14.00(2)(cz)	14.44(2)(cz)		14.22(1)(cz)	18.92(7)(cz)
[ML]	6.82(1)(cz)	7.84(2)(cz)		7.34(1)(cz)	
[ML_2H_2]					36.65(7)(cz)
[ML_2H]	19.41(4)(cz)	20.51(4)(cz)		19.97(2)(cz)	31.70(8)(cz)
[ML_2]	10.28(4)(cz)	11.54(4)(cz)		10.90(2)(cz)	24.10(8)(cz)
[ML_2H_{-1}]	−0.8(1)(cz)			0.48(3)(cz)	14.70(9)(cz)

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* Only the pK values could be determined for most of the complexes formed in Cu(II)-Pheha, Cu(II)-Dopaha systems.

[A] Ref. 67. [B] Ref. 32. [C] Ref. 35. [D] Ref. 68. [E] Ref. 71. [a] Ref. 47. [b] Ref. 39. [c] Ref. 53. [d] Ref. 43. [e] Ref. 37. [f] Ref. 72, model (I). [g] Ref. 72, model (II). [h] Ref. 62. [i] Ref. 50, measured in KCl. [j] Ref. 50, measured in KNO_3. [k] Ref. 44. [l] Ref. 48. [m] Ref. 63. [n] Ref. 74. [o] Ref. 42. [p] Ref. 49. [r] Ref. 45. [s] Ref. 60. [t] Ref. 54. [u] Ref. 40. [w] Ref. 41. [x] Ref. 58. [y] Ref. 59. [z] Ref. 61. (ax) Ref. 38. (ay) Ref. 62. (by) Ref. 75. (cy) Ref. 52. (cz) Refs 55, 76.

No standard deviations in papers published by Brown et al. and Schwarzenbach.

assumed to form octahedral complexes, as found in the solid state. Analogous coordination, via two oxygen atoms also occurs in the Cu(II)–Aha system [67,69]. The stability constants for all species existing in an aqueous solution for M–Aha systems with a range of metal ions are summarized in Table 3.

According to the Irving–Williams series, nickel(II) complexes should have higher stability constants than those for Zn(II) complexes [57]. The stability constants of nickel(II) hydroxamate complexes, however, are about the same or somewhat lower than those of the respective zinc(II) species (Table 3).

(ii) Aminohydroxamic acids as ligands

(a) Derivatives of α-amino acids (α-derivatives) ($R–CH(NH_2)CONHOH$)

The NH_2 group and the hydroxamic acid group are in an α-position with respect to each other. These compounds possess the ability to form two types of five-membered chelate either via their nitrogen atoms or through the hydroxamate oxygens, and consequently they are good ligands for various metal ions.

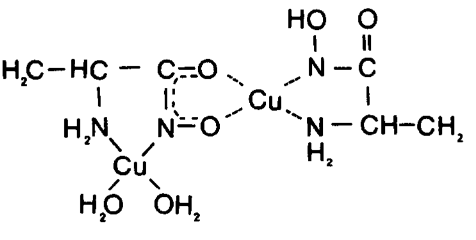
Most papers dealing with complexes of aminohydroxamic acids relate to α-derivatives [39,42,49,63,61,74] and especially to derivatives of simple amino acids, such as Glyha [36,39,46,47,56,72,73] and α-Alaha [49,50,63,74,77]. Iron(III) was involved in most of the investigations [34,36,38,50,69,72] because of the well-known biological importance of the iron(III)–hydroxamate complexes. Complexes of copper(II) [39,42, 44,46–51,56,61,77], nickel(II) [35,39,42,50,74], cobalt(II) [39,42,44,47,50] and zinc(II) [47,50,63] have also been investigated. Very few papers contain results on manganese(II) and cadmium(II)–Glyha and α-Alaha [47,50] complexes. Complexes of the latter metal ion were found to be rather weak and precipitation usually occurred at pH values around 8. Aluminium(III) was involved in a single paper [50] with α-Alaha. In this paper, the existence of mixed hydroxo complexes was proposed in the pH range ca. 3–9, while above pH 9, $[Al(OH)_4]^-$ was found to be the only species in measurable concentration.

(b) Copper(II), nickel(II), zinc(II), cobalt(II) and iron(III) complexes of simple α-aminohydroxamic acids

As Table 3 shows, Glyha and α-aminohydroxamic acids which contain alkyl side chains (α-Alaha, n-Valha, n-Leuha, Leuha, Sarha), form complexes with identical stoichiometry and almost the same stability. The lower stability of the Sarha complexes may be due to the steric hindrance caused by the N-methyl group but the lower stability of complexes with Pheha, which contains an aryl side chain [54], is due to its low solubility and is even lower than most other related complexes.

Copper complexes. Glyha complexes of Cu(II) were investigated by several authors [70–80]. However, the first reliable results were obtained by Paniago and Carvalho [46] who reported the formation of four different complexes, including a dimeric species (Table 3) whose existence was supported by ESR spectra [46]. Potentiometric data were used to evaluate the stability constants for the four proposed species. The authors suggest that, in the dinuclear complex $[Cu_2L_2H_{-1}]$, the OH^- group acts as the bridging group between two metal ions. Leporati, in his later work, suggested an even more complicated equilibrium containing a tetrameric $[Cu_4L_5]$ complex [39]. However, in most papers published recently [40–42,44–46,48,49], the authors have returned to the suggestion of a hydroxo-bridged binuclear species. Although the fact that the dimeric species exists as low pH (around 4.5–5.5) is a strong argument against a hydroxo-bridged species, none of the work reported above presented any convincing evidence, e.g. spectroscopic data, for the proposed structures. This assumption has now been corrected in a recent paper [50] and the coordination mode shown in Scheme 4 has been derived from well-documented CD results obtained for the $[Cu_2L_2H_{-1}]$ species (see Table 4). A similar bonding mode was suggested earlier by Karlicek and Polasek [56] for the Cu_2L species formed in the Cu(II)–Glyha system for which spectroscopic measurements were used to study the solutions with a copper(II) excess. Both of the latter reports indicate that the complexation of copper(II) to α-aminohydroxamic acid starts via the (N,N) as well as the (O,O) donor sets. This mixed bonding mode changes at pH ca. 4.5–5, and above pH 6 the only species is the $[CuL_2]$ complex, with 4N coordination (Tables 4 and 5) [48–50]. This latter coordination was supported by X-ray studies in the solid state [73,77,81] and in solution by visible absorption (λ_{max} ca. 535 nm) and ESR spectra ($g_{\parallel} = 2.212$; $A_{\parallel} = 195$ G) [48–50,61]. Increasing the pH up to ca. 9–10 in these systems causes a new consumption of base. This process can lead either to the formation of a mixed hydroxo species or to the deprotonation of the bound hydroxamic group (NOH) in the $[CuL_2]$ species. Both processes were suggested but only the latter has received any experimental support [48–50,61].

According to spectroscopic data, this proton release does not change the 4N coordination mode although the d–d transitions shift from 535 to ca. 500 nm (Table 4). The results suggest that the stoichiometry of the $[CuL_2H_{-1}]$ species formed is most possibly as that given in Scheme 5.



$[Cu_2L_2H_{-1}]^+$

Scheme 4.

TABLE 4

Spectroscopic data for copper(II)–L-α-Alaha complexes

Species[a]	VIS	CD	Coordination mode
	$\lambda(\varepsilon)$	$\lambda(\Delta\varepsilon)$	
$[Cu_2L_2H_{-1}]$	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)	$\{NH_2,N\}\{CO,O^-\}$
$[CuL_2]$	536(86)	558(−0.28) 320(+0.20) 290(+0.26)	$2 \times \{NH_2,N^-\}$
$[CuL_2H_{-1}]$	495(109)	558(−0.28) 320(+0.29) 280(+0.24)	$2 \times \{NH_2,N^-\}$

[a] The concentration of [CuL] species was too low to obtain correct spectroscopic data.

λ units are nanometers, ε and $\Delta\varepsilon$ are expressed in $dm^3\ mol^{-1}\ cm^{-1}$.

TABLE 5

The parameters of the ESR spectra of the Cu(II)–α-Alaha system

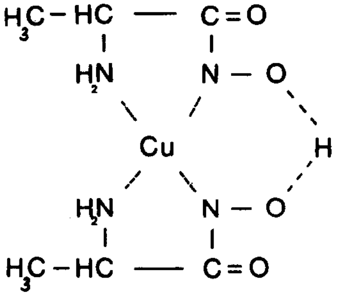
	pH						
	2.75	4.32			5.67	6.64	10.35
	$Cu^{2+}aq$	[CuL]	X[a]	$[Cu_2L_2H_{-1}]$	$[Cu_2L_2H_{-1}]$, $[CuL_2]$	$[CuL_2]$	$[CuL_2H_{-1}]$
$g_{\parallel}$	2.401	2.326	2.283	–	2.185	2.185	2.178
$\lvert A_{\parallel} \rvert$ $[10^{-4}\ cm^{-1}]$	146	167	168	–	213	213	215

[a] Additional N_2O_2 coordination sphere.

Charges are omitted for simplicity.

Hydrogen bonding was also found in the $[NiL_2H_{-1}]$ complex with L = Glyha by X-ray studies [82].

Nickel complexes. Due to the nature of the nickel(II) ion, one can expect some preference for the formation of an (N,N)-chelate. This prediction has been widely confirmed, both in the solid state [35,37,77,82,83] and in solution [39,42,47,50,74].



$[CuL_2H_{-1}]^-$

Scheme 5.

This coordination mode is especially favoured when square-planar complexes are formed.

Brown and Roche have made a comparison between the complexes formed in the Ni(II)–alkylhydroxamic acid systems with those created in the Ni(II)–aminohydroxamic acid systems, both in the solid state and in solution [35]. Aha, Pha, Glyha and Serha ligands were all involved in this review. Obvious differences were found in the solid state, e.g. in colours and in solubility properties. For instance, the bis(aminohydroxamato)nickel(II) complexes were red or orange in colour and diamagnetic (planar species), while the bis(alkylhydroxamato)nickel(II) dihydrates were green (octahedral). The complexes formed in the former system were insoluble in most solvents while those of the latter system were freely soluble in polar solvents. The infrared spectra of both bis(aminohydroxamato)nickel(II) complexes in the 3000–3500 cm^{-1} region were very similar to those of the corresponding amino acid complexes [84]. Three bands assigned to N–H stretching modes are observed to shift on deuteration. These results suggest the coordination of the amino group to the nickel ion. In contrast to the bis(alkylhydroxamato)nickel(II) dihydrates, the carbonyl frequency in bis(aminohydroxamato)nickel(II) remains unchanged at 1604 cm^{-1} when compared with the free ligand, i.e. the ketonic oxygen is not involved in coordination to the nickel atom. X-ray crystallographic studies of the bis(Glyha) nickel(II) complex [37,83] and bis(Alaha)nickel(II) complex [77], showed that these complexes are square-planar with *trans* geometry and coordination via both the amino and hydroxamic nitrogens. The inter-ligand hydrogen bonds between a CO group of one molecule and the uncoordinated oxygen atom of an adjacent NOH^- group additionally stabilizes the complex structure. There is strong theoretical evidence [85] that the central nickel atom is strongly involved in the π system of hydroxamato nitrogen atoms. In solution, depending on pH, different species are formed [39,50,64,74]. The spectroscopic results [86] (Table 6) show a square-planar environment to be present in all complexes except the NiL species.

TABLE 6

Spectroscopic data for Ni(II)–α-aminohydroxamic acid systems

Species	Alaha		Leuha		Sarha
	VIS	CD	VIS	CD	VIS
	λ ε	λ $\Delta\varepsilon$	λ ε	λ $\Delta\varepsilon$	λ ε
[NiL]			sh390(33)^a		600(5)^a 395(17)^a
[NiL$_2$]	505(150)^a 415(160)^a	505(−0.4)^a 402(−0.4)^a 295(+0.3)^b 252(+1.5)^b		507(−0.24)^a 407(−0.18)^a 285(+0.44)^b 247(+0.58)^b 220(−0.1)	490(53)^a 415(61)^a
[NiL$_2$H$_{-1}$]	sh485(160)^a 430(220)^a	504(−0.5)^a 403(−0.4)^a sh290(+0.7)^b 265(+1.1)^b	sh485(115)^a 420(135)^a	515(−0.2)^a 430(+0.06)^a 318(+0.45)^b 241(+0.53)^b 217(−0.39)	sh485(100)^a 427(108)^a

The data presented in this table actually reflect the optical properties of solutions in which the given form is the major species [74]; sh denotes shoulder.

[a] d–d transition in a square-planar complex.

[b] ligand-to-metal CT transition from the hydroxamic group.

λ units are nanometers, ε and $\Delta\varepsilon$ are expressed in dm^3 mol^{-1} cm^{-1}.

Charges are omitted for simplicity.

Spectroscopic and pH-metric results strongly suggest that the bis-complex, with 4N coordination and planar geometry, which is found in the solid state, is especially favoured [74]. Calculations from the complex stabilities (Table 3) show that the formation of octahedral [NiL] in these systems is unfavourable (log $K_{\mathrm{NiL}}/K_{\mathrm{NiL}_2}$ values are zero or negative in all cases).

At high pH (ca. 9), a new base consumption process, similar to that above for copper(II)-containing systems, begins. Deprotonation of the [NiL$_2$] complex leads to the formation of the [NiL$_2$H$_{-1}$] species. The results assigned to this complex strongly suggest the same type of second deprotonation of the hydroxamic group as found in the copper(II) complex. This was supported by X-ray studies of the [NiL$_2$H$_{-1}$] species, which shows that the coordination mode is the same as for the [NiL$_2$] complex [37,83]. However, [NiL$_2$H$_{-1}$] possess a cis geometry [82] around the metal ion.

Zinc(II) and cobalt(II) complexes. Both metal ions begin complex formation with α-aminohydroxamic acids at pH 5.5. Precipitation, however, occurs at pH ca. 8, even at a metal–ligand ratio of 1:5 [47,50,63]. The species most generally found are the [ML], and $[ML_2]$ complexes. However, formation of the polynuclear species $[M_2L_3]$ [47,50,63] or the $[CoL_3]$ complex in the case of the Co(III)–Glyha system [50] has been reported (see Table 3). The species formed just before precipitation, i.e. ($[MLH_{-1}]$ and $[ML_2H_{-1}]$), were suggested to be mixed hydroxo complexes. A possible bonding mode for these complexes was proposed [47,50] but until recently, no real experimental support has been reported. In a new study [63], proton NMR spectra were used to establish the binding mode in the zinc(II)–Glyha, –α-Alaha, –Leuha, –Sarha and –Hisha systems. It was shown that, with all of these ligands, the zinc(II) ion initiates its coordination via the two oxygens of the hydroxamic group. An increase in pH leads to deprotonation of an amino group and the formation of a binuclear $[Zn_2L_3]$ species (except the zinc(II)–Hisha system) together with [ZnL] and $[ZnL_2]$ complexes. A mixed type of coordination, via both nitrogens and oxygens, was found in the $[Zn_2L_3]$ and $[ZnL_2]$ species [63].

Iron(III) complexes. The pH-metric and spectrophotometric results [36,50,62,72] agree that there is measurable complex formation between iron(III) and α-aminohydroxamic acids even below pH 2. Moreover, freshly made samples can be titrated without precipitation.

Oligomerization has been suggested [62], although the magnetic susceptibility measurements showed the absence of any polymeric species in the iron(III)–Glyha system at physiological pH, if the metal-to-ligand ratio is above 1:10 [36]. Exactly the same results were obtained with the iron(III)–α-Alaha system [50]. However, polynuclear $[M_2L_3]$ species were suggested for the iron(III)–Metha solutions for the 1:10 ratio, even at pH values below 5 [62].

The models published by two groups for iron(III)–Glyha [36,72] differ somewhat from each other and both differ from that published for iron(III)–α-Alaha [50]. These disagreements show that the equilibria existing in iron(III)-containing systems are rather complicated, i.e. different species may exist in freshly prepared solutions and in those samples kept overnight [62]. Moreover, the different iron(III)–hydroxo complexes may coexist with iron(III)–α-aminohydroxamato species [50,62,72].

Very surprising bonding modes were presented for the iron(III)–Glyha and iron(III)–Metha complexes [36,62,72]. Instead of bonding by the two hydroxamate oxygens (as suggested in ref. 50), the involvement of the amino nitrogen and the OH oxygen of the hydroxamate groups coordinated to the iron(III) has been proposed. This proposal was based on the formation of an unprotonated species [ML] in the acidic region. However, it seems more likely that the iron(III), as a typical hard acid, would favour an oxygen donor rather than the very basic nitrogen. On this basis, it is clear that [ML] is in fact a [M(HL)(OH)] complex, i.e. a mixed hydroxo species with the amino group in its protonated form [50]. This assumption is supported by the spectrophotometric results. The absorption spectra of the iron(III)–Alaha system do not differ substantially from those recorded for iron(III)–Alaha system [87]. In the latter system, coordination of hydroxamate oxygen atoms is beyond doubt. This clearly indicates that the stoichiometries in Table 3 are rather "formal" and do not exclude the formation of the mixed hydroxo species very characteristic of the iron ion.

(c) The effect of side chain donors on the coordination of α-aminohydroxamic acids

The results obtained for Serha and Thrha (both containing an alcoholic OH group), Tyrha and Dopaha (with one and two phenolic OH groups, respectively), Metha (with a thioether sulphur), and Hisha (containing an imidazole nitrogen atom) have shown that there is no involvement of the side chain donor in Serha [34,45], Thrha [60], Tyrha [40,54] and Metha [62]. These ligands coordinate in a manner similar to the simple α-aminohydroxamic acids. Dopaha contains two phenolic OH groups in the ortho positions, which leads to the possibility of the formation of a catechol-like {O,O} chelates, in addition to the "normal" aminohydroxamate-like chelates. Results published recently [54] for the nickel(II)– and cobalt(II)–Dopaha systems indicate that phenolic groups do not affect the coordination equilibria throughout whole pH region studied. There is also no direct proof for phenolate binding in the case of the zinc(II)–Dopaha system, although some experimental observations have led to the assumption that there may be coordination of phenolate oxygen at high pH [54].

EPR measurements performed on the copper(II)–Dopaha complex indicated the formation of a 4N species at pH 6–9.5. A new species, however, with less than 4N coordination was formed above pH 9.5. Comparison of these results with those obtained for the copper(II)–Dopa system [89] suggest the formation of a catecholate-type {O,O} chelate. The comparison also shows that, in the case of copper(II)–Dopa, the catecholate type of chelation begins to form at pH ca. 5–6, while in the copper(II)–Dopaha system, this happens only above pH 9.5. This difference indicates that copper(II) ions form much more stable species when bound to aminohydroxamate moieties than in the parent amino acid donors.

One of the most effective side chains for binding of metal ions is certainly the imidazole moiety of a histidine residue [38,41,58,59,63,74]. Studies on the coordination modes of Hisha with Cu(II) ions were recently reported by three different groups, Leporati [41], Kurzak et al. [58], and Farkas and Kurzak [59]. The results obtained in the latter two studies suggest the formation of dimeric species. Kurzak et al. [58] have proposed the formation of a $[Cu_2L_2H_{-1}]$ species while Farkas and Kurzak [59] have also indicated two additional polymeric species $[Cu_2L_2H]$ and $[Cu_2L_2]$. Some differences in the values of stability constants obtained in both cases are observed (see Table 3).

ESR spectra [58] of liquid and frozen solutions of Hisha in the presence of copper(II) at pH 2.15 are typical for copper(II) ions surrounded by aqueous molecules (Table 7). The anisotropic ESR parameters of the species which exist at pH 2.75, are similar to those stated for copper(II)–α-Alaha [48], Leuha [49] or Sarha [61] (see

TABLE 7

The parameters of the ESR spectra of Cu(II)-Hisha System

	ph					
	2.12	2.70	4.00	4.50–7.00	8.54	11.50
	$Cu^{2+}aq$	[CuLH]	$[Cu_2L_2H_{-1}]$	$[Cu(LH)_2]$, [Cu(LH)L]	$[CuL_2]$	$[CuL_2H_{-1}]$
g_0		2.214	–	2.110	2.104	2.090
A_0		62		90	90	100
$g_\parallel$	2.400	2.325	–	2.200	2.176	2.168
$\lvert A_\parallel \rvert$ $[10^{-4}\,cm^{-1}]$	146	173	–	207	210	218

A_0 and g_0 were measured at 295 K. $A_\parallel$ and $g_\parallel$ were measured at 150 K.
Charges are omitted for simplicity.

Table 5). The remarkable fact that coordination of Hisha begins at a lower pH in comparison with the three previously mentioned aminohydroxamic acid ligands, suggests a different coordination pattern, i.e. also involving the imidazole nitrogen owing to its favourable pK_3 value. The binding of an imidazole nitrogen to a copper(II) ion at low pH (2.00) has also been observed for copper(II)–histidine complexes [89]. The apparent loss of ESR signals for liquid and frozen solutions between pH 3.5 and 4.7 strongly indicates the formation of dimeric complexes, postulated on the basis of potentiometric titration studies [58]. Strong spectra with well-resolved copper hyperfine structure are seen once again at pH ca. 5. Their ESR parameters quite closely resemble the value for CuN_4 centres ($g_\parallel = 2.212$; $A_\parallel =$ 195 G [58]). The characteristic change of the ESR parameters [58] of the spectra observed above pH 11 is consistent with formation of the new $[CuL_2H_{-1}]$ complex.

The complexes formed below pH 9 in the nickel(II)–Hisha system [74] are octahedral or pseudo-octahedral. Only the deprotonation of the uncoordinated hydroxamic hydroxyl group at strongly basic pH values leads to formation of the square-planar $[NiL_2H_{-1}]$ species [74] based upon spectra and CD (Table 8). Previous work, based mostly on potentiometric data [41], suggested the formation of the $[ML_2OH]$ species in which out-of-plane coordination was assumed. The spectroscopic data [74] indicated clearly that this assumption is unrealistic and that the square-planar species is clearly formed.

Below pH 9, octahedral complexes with different stoichiometries are formed (see Table 3). The first species, [MHL] starts to form at pH ca. 3. This is a chelate complex with $\{N_{im},NH_2\}$ coordination mode and octahedral geometry. This $\{N_{im},NH_2\}$ coordination mode was also proposed for the $[NiL_2H_2]$ complex, which is the second species assigned in the Ni(II)–Hisha system. Deprotonation of this complex leads to formation of $[NiL_2H]$ and $[NiL_2]$ species, which are also octahe-

TABLE 8

Spectroscopic data for the Ni(II)–Hisha system

Species	Hisha	
	VIS	CD
	λ ε	λ Δε
[$NiLH$]	600(7)[c]	606(+0.02)[c]
	350(20)[c]	520(+0.03)[c]
		397(−0.01)[c]
		342(−0.02)[c]
		251(+0.1)[c]
[NiL_2H_2]	565(12)[c]	623(+0.05)[c]
	345(32)[c]	520(+0.02)[c]
		339(−0.02)[c]
[NiL_2H]	555(12)[c]	625(+0.06)[c]
	345(32)[c]	520(+0.02)[c]
		415(−0.01)[c]
		339(−0.02)[c]
		293(−0.02)[c]
		254(+0.3)[c]
[NiL_2]	515(14)[c]	sh610(+0.02)[c]
	sh415(17)[c]	500(−0.02)[c]
		360(−0.04)[c]
		275(−0.1)
[NiL_2H_{-1}]	sh490(100)[a]	495(−0.18)[a]
		400(−0.12)[a]
		297(+0.23)[b]
		250(+2.5)[b]

The data presented in this table actually reflect the optical properties of solution in which the given form is the major species [74]; sh denotes shoulder.

[a] d–d transition in a square-planar complex.

[b] ligand-to-metal CT transition from the hydroxamic group.

[c] d–d transition in an octahedral complex.

λ units are nanometers, ε and Δε are expressed in $dm^3\ mol^{-1}\ cm^{-1}$.

Charges are omitted for simplicity.

dral but with differing coordination modes. The ligand molecule becomes tridentate with the $\{NH_2,N_{im},N^-\}$ binding set. Again, the octahedral symmetry of the [NiL_2] complex is favoured by the presence of the competitive side-chain donors, the required stability being provided by the involvement of the imidazole nitrogen. Deprotonation of this complex, however, forces a change in its geometry. An increase of electron density on the hydroxamic nitrogen, due to deprotonation of the vicinal hydroxyl group, causes the [NiL_2H_{-1}] complex to become square planar with the (NH_2,N^-)

donor set involved in the metal ion coordination. Influence of the hydroxamic hydroxyl deprotonation on the increase of binding ability of the bound hydroxamic nitrogen has also been observed in the Cu(II)–Hisha system (vide supra).

pH-metric and proton NMR measurements performed on the zinc(II)–Hisha system [63] have shown that zinc ion coordination begins in a similar manner to the simple α-derivatives [47,50,63], i.e. via two hydroxamic oxygens and with the formation of [ZnLH] and [Zn(LH)$_2$] species. Above pH 6, when one of the bound ligand molecules becomes completely deprotonated to form [ZnL$_2$H], the proton NMR spectra indicate the presence of the other binding mode which exhibits its own spectrum (Table 9), which is present until precipitation occurs at around pH 9 [63]. The proton chemical shift strongly suggests the involvement of an amino nitrogen in the binding of the metal ion. The changes in the chemical shift of the imidazole protons indicate the additional involvement of the imidazole nitrogen. Strong support for the tridentate coordination of the ligand with the involvement of both amino and imidazole nitrogens, plus one of the hydroxamic group donors, is obtained from consideration of the rotamer populations of free and bound ligands [63]. The strong stabilization of the rotational isomer, in which three donors (N_{im}, N-amino and the hydroxamic group) are in the gauche position with respect to each other, may be used as strong evidence for the tridentate coordination of a His residue to a Zn(II) ion. The NMR spectra also suggest that, in the ZnL$_2$ species, only one Hisha molecule binds the metal ion via a three-donor set, while the other molecule coordinates only as a bidentate ligand.

(d) Derivatives of β-amino acids

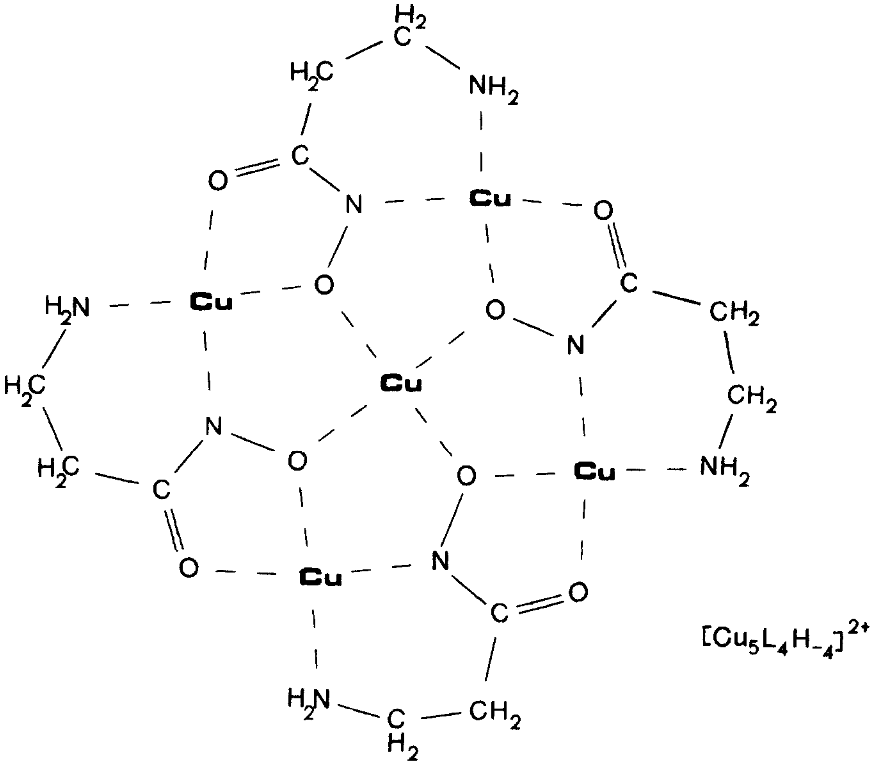
When the NH$_2$ group and the hydroxamic acid group are in the β-position with respect to each other, then the amino and hydroxamic nitrogens may form a six-membered chelate ring. Its formation is usually less favourable than that of the five-membered ring possible in the case of α-derivatives. Thus, the five-membered chelate ring created by two hydroxamic oxygens may be more competitive to (N,N) coordination in complexes with β-analogues. This fact can be clearly seen in the Cu(II)–β-Alaha system [91] (Scheme 6).

TABLE 9

^{1}H NMR parameters and rotamer populations (P_i)[a] for metal-free and complexed Hisha at pH 8.5

Hisha	δ_A	δ_B	δ_C	J_{AB}	J_{AC}	J_{BC}	P_1	P_2	P_3
Metal-free	3.001	3.048	3.681	14.67	7.35	7.22	43	42	15
Complexed	3.288 (0.287)	3.380 (0.332)	4.204 (0.523)	17.9	3.4	3.5	6	7	86

[a] Rotamer populations evaluated according to the Pachler approximation (see Ref. 90). The chemical shift differences caused by metal ion coordination are given in parentheses.



Scheme 6.

Above pH 5, the solution becomes green in colour. Taking into account the results obtained previously for copper(II)–α-Alaha [48,50] and copper(II)–Asp-β-ha [53], then in addition to the nitrogen atoms, the oxygen atoms of the hydroxamate moiety must also be involved in metal ion coordination in the copper(II)–β-Alaha system. Above pH 4.5, the d–d band at 616 nm increases in intensity until pH 9 without any change in energy. This indicates that the major species in the pH range 4.5–9 remains the same. In this pH range, the major complex does not show any EPR spectrum at liquid-nitrogen temperature or above. Thus, the coupling of the cupric centres through a NO^- group is very strong and it is now evident that the earlier suggestions for its involvement in dimer formation in the Cu(II)–α-aminohydroxamic acid system were correct. It is obvious from the potentiometric results that only one complex species exists at measurable concentration in the pH range 4.5–9. From the considerations presented earlier [91], it is possible that the major species in solution at pH 4.5–9 is a pentanuclear species $[Cu_5L_4H_{-4}]$ and this is confirmed by an X-ray structure determination (Scheme 6).

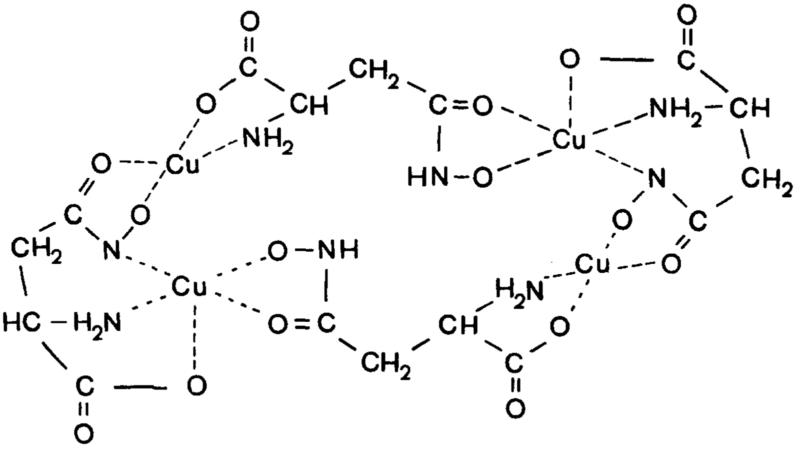
The coordinating power of ligands which form complexes with a sequence of alternating five- and six-membered rings is greater than that of ligands forming complexes with all five-membered or all six-membered chelate rings.

The unusually stable pentanuclear species exists in solution with a very high stability constant, log = 46.66, and contains 12 five- and six-membered rings of different conformations (see Scheme 6).

A similar situation to that discussed above also exists in the aspartic derivative having a hydroxamic group placed at the β-carboxylate (Asp-β-ha). Copper(II) coordination starts at around pH 3 [53]. The ESR species clearly indicate the formation of an oligomeric structure with strong metal–metal antiferromagnetic coupling. Above pH 6, the only oligonuclear complex present in solution is the $[Cu_4L_4H_{-2}]$ species. Its bonding mode is deduced from the potentiometric and spectroscopic data presented in Scheme 7. The stability of this complex is very high (log $\beta = 52.82$). In addition to {N,N} and {O,O} coordination, "glycine-type" chelates can also be formed in the stable oligomeric structure. The earlier work of Leporati [43] also suggested an oligomeric structure for the Cu(II)–Asp-β-ha complex, but the involvement of only carboxylate as the bridging group was supposed.

Evidently in copper(II)–β-aminohydroxamate systems, the formation of oligomeric species is strongly favoured.

Some very interesting results were obtained with the nickel(II)–β-Alaha system [75]. Complex formation begins at ca. pH 5 with the formation of an octahedral species. However, visible spectra show the geometry to be planar above pH 7 when the species $[NiL_2H]$, $[NiL_2]$ and $[NiL_2H_{-1}]$ are formed (see Table 3). The most probable bonding mode in the latter complexes is 4N coordination. Steric factors



$[Cu_4L_4H_{-2}]^{2-}$

Scheme 7.

may additionally favour the planar geometry with the two six-membered (N,N) chelate rings.

The Asp-β-ha ligand can also form a glycine-type chelate in addition to those created with the {N,N} and {O,O} donors. This leads to a different type of complex formation compared with that found for the β-Alaha ligand [91]. The visible absorption spectra indicated that the nickel(II)–Asp-β-ha complexes have octahedral geometry and the stability constants of these complexes (which correspond well to those obtained for the nickel(II)–2,4-diaminobutyric acid complexes) strongly suggest tridentate coordination through the carboxylate oxygen, amino nitrogen and hydroxamic nitrogen of the Asp-β-ha.

Among the divalent metal ions discussed in this review, zinc(II) forms the strongest complexes with hydroxamic oxygen donors. Taking this into account, the different protonated complexes formed in the zinc(II)–β-Alaha and –Asp-β-ha systems contain the protonated amino group [53,75].

An interesting bonding mode was proposed for the complexes formed in iron(III)–Asp-β-ha solutions [53]. The higher stability of the complexes and the considerable resistance to the hydrolytic processes suggested the presence of {O,O,O} type coordination via hydroxamate and carboxylate oxygens.

(e) Complexes of glutamic acid-γ-hydroxamic acid

Glu-γ-ha can form the same type of coordination as that found for Asp-β-ha. The resulting {N,N} chelate, however, is a seven-membered ring. As the seven-membered chelate is much less stable than the six-membered one, the Glu-γ-ha essentially has two separate metal binding sites, i.e. the glycine-like and the hydroxamate-like. Despite this separation, {O,O,O} coordination with the hard iron(III) was found to be likely [55,76]. Nickel(II) and cobalt(II) ions, on the other hand, were found to prefer a glycine type of coordination, which is stabilized by the weak coordination of the hydroxamate nitrogen.

The stabilities of the zinc(II) complexes are higher than those proposed on the basis of the Irving–Williams series (see Table 3). This may be explained by assuming that both "glycine-type" and "hydroxamate-type" chelate complexes are formed in the Zn(II)–Glu-γ-ha system.

D. TERNARY COMPLEXES OF AMINOHYDROXAMIC ACIDS

Taking into account the biological importance of aminohydroxamic acids (their possible application in chemotherapy and in chemical modelling of the transport and storage of some metal ions [92]), the fact that the ternary systems are somewhat better models for complicated biological systems, the importance of the studies on ternary complexes containing aminohydroxamic acid is beyond doubt. Despite this intrinsic interest, study on ternary complexes of aminohydroxamic acids has been initiated only recently [62,92,93].

TABLE 10

Stability data for ternary complexes formed in the cobalt(II)-, copper(II)- and zinc(II)-α-Alaha-"B" ligand as well as the copper(II)-Hisha-Histidine systems

	α-Alanine	Histidine	Glycyl-glycine	Pyrocatechol
α-Alaha				
[CoAB]	9.50	–	8.54	12.90
[CoABH$_{-1}$]	−0.35	–	0.56	–
[CuABH]	–	24.67	–	–
[CuAB]	18.33	19.28	–	22.93
[CuABH$_{-1}$]	8.63	8.75	7.73	11.97
[ZnABH]	–	18.41	–	–
[ZnAB]	–	11.28	8.77	14.19
[ZnABH$_{-1}$]	–	1.54	0.73	3.36
Hisha				
[CuABH$_2$]		31.20		
[CuABH]		26.36		
[CuAB]		19.79		
[CuABH$_{-1}$]		9.50		

El-Ezaby et al. [62,92] studied the interactions of nickel(II) as well as iron(III) with vitamin B_6 and Glyha ligands. Based on kinetic results, the formation of intermediate ternary complexes was assumed. More recently, results obtained for the modification of metal ion binding ability of L-α-Alaha by different "B" ligands have been published [93]. pH-metric and spectrophotometric measurements were performed for cobalt(II), nickel(II), copper(II), and zinc(II) ions with α-Alaha and the "B" ligands were L-α-alanine, L-histidine, glycyl-glycine and pyrocatechol. The results indicated that ternary complexes are not formed at all in systems containing a nickel(II) ion. The reason for such behaviour may derive from the different geometries of the parent complexes formed in the nickel(II)-α-Alaha and nickel(II)-B ligands. Square-planar complexes are formed in the former system (see Sect. B(ii) (b)), while octahedral complexes are created in the latter case. The majority of nickel(II) ions are bound to α-Alaha, except when the "B" ligand is histidine. In the latter system, the major species contains the amino acid ligand.

Ternary complexes were found in systems containing cobalt(II), copper(II) or zinc(II) ion. Stability constants relating to the ternary complexes formed in metal ion-α-Alaha ternary systems [93] and copper(II)-Hisha-histidine [59] systems are summarized in Table 10. L-α-Alanine and glycyl-glycine were found to play a secondary role with respect to α-Alaha [93]. In systems containing histidine as the "B" ligand, however, the formation of binary complexes with histidine and the formation of ternary complexes was favoured [59,93].

As discussed above, the hydroxamic group is a very specific donor system able to effectively bind a variety of metal ions. The delocalization of the double bond system within the set of the hydroxamic group atoms makes its binding ability unique and metal coordination very strong. The presence of the amino group in the amino-hydroxamic acid ligands increases the coordination effectiveness due to the possibility for $\{NH_2,N^-\}$ chelate formation, which favours such metal ions as Cu(II) or Ni(II) in planar complexes. The presence of two different donor sets able to form chelates via the {N,N} or {O,O} donor set very often leads to the formation of very stable oligonuclear complexes involving both the donor pairs referred to.

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