Complexes of Peptide Hydroxamates. Complex Formation between Transition Metals and L-Prolyl-L-leucylglycinehydroxamic Acid [*N*-Hydroxy-7-methyl-4-oxo-5-(pyrrolidine-2'-carboxamido)-3-azaoctanamide] and L-Prolyl-L-leucinehydroxamic Acid [*N*-Hydroxy-4-methyl-2-(pyrrolidine-2'-carboxamido)pentanamide] †

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The systems of cobalt(II), nickel(II), copper(II), zinc(II), and iron(III) with L-prolyl-L-leucinehydroxamic acid [*N*-hydroxy-4-methyl-2-(pyrrolidine-2'-carboxamido)pentanamide] (Pro-Leu-NHOH) and L-prolyl-L-leucylglycinehydroxamic acid [*N*-hydroxy-7-methyl-4-oxo-5-(pyrrolidine-2'-carboxamido)-3-azaoctanamide] (Pro-Leu-Gly-NHOH) have been studied at metal/ligand ratios of 1:1—1:6 by means of pH-metric, spectrophotometric, and e.s.r. methods. The formation constants have been determined and the bonding modes in the species present in aqueous solutions are discussed. Complexes of moderate stability are formed in the systems containing cobalt(II) and zinc(II) ions in the approximate range pH 6.0—8.5. There is no deprotonation of the peptide amides. Stable complexes are formed in the copper(II)–Pro-Leu-NHOH and –Pro-Leu-Gly-NHOH systems at above pH 4. It can be postulated that the hydroxamate nitrogen, peptide carbonyl oxygen, and terminal amino nitrogen take part in the co-ordination at the beginning of complex formation in the copper(II)–Pro-Leu-NHOH system, but the co-ordination is primarily 'hydroxamate-like' in the copper(II)–Pro-Leu-Gly-NHOH system in that region. However, deprotonation of the peptide amides takes place in both systems, after which only the nitrogen donor atoms (amino, amide, and hydroxamate) are involved in the co-ordination. Planar complexes involving co-ordination of the above nitrogen donor atoms predominate at above pH 6 in both systems containing nickel(II). In the iron(III)–containing systems complex formation is appreciable even below pH 3. Mixed hydroxo complexes can be proposed in addition to the binary ones. In these latter complexes, co-ordination of the hydroxamate oxygens is suggested.

The biological activity of hydroxamates is known.[1–3] Results have also been published on the inhibitory activity of hydroxamic acid derivatives of amino acids and peptides on metalloproteinases.[4] With regard to the strong ability of ligands of this type to form chelates, clarification of their interactions with metal ions is of particular importance. In this decade some studies have been performed on the metal complexes of aminohydroxamic acids,[5–9] but only one paper[10] deals with metal ion–peptidehydroxamic acid systems. In this paper[10] results were published on metal complexes of the *N*-benzyloxycarbonyl derivatives of alanylglycinehydroxamic acid (5-amino-*N*-hydroxy-4-oxo-3-azahexanamide). The authors did not find any interaction with the peptide chain.

Recently, we published results on the complex-forming ability of L-α-alaninehydroxamic acid (2-amino-*N*-hydroxypropanamide).[11] In the present work, the complexes of cobalt(II), nickel(II), copper(II), zinc(II), and iron(III) with Pro-Leu-NHOH and Pro-Leu-Gly-NHOH have been studied. The special interest in Pro-Leu-Gly-NHOH is due to the fact that human collagenase [a zinc(II)-containing metalloezyme] was isolated by means of an affinity column prepared with this tripeptidehydroxamic acid.[12] pH-Metric and spectrophotometric measurements have been carried out, together with e.s.r. measurements on the copper(II)–Pro-Leu-NHOH and –Pro-Leu-Gly-NHOH systems. The formation constants and suggested bonding modes of the species present in these systems are given.

† *Non-S.I. unit employed:* G = 10^{-4} T.

Experimental

Pro-Leu-NHOH and Pro-Leu-Gly-NHOH were prepared *via* the methyl esters of the peptides, by the methods described in ref. 13. The syntheses of the unprotected peptide methyl esters were completed by the conventional peptide synthetic method.[14] The purities of the ligands and the exact concentration of their stock solutions were determined by Gran's method.[15]

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

The pH-metric and spectrophotometric measurements were carried out at an ionic strength of 0.2 mol dm^{-3} (KCl).

Carbonate-free KOH solutions of known concentrations (*ca.* 0.2 mol dm^{-3}) were used as titrants.

The pH-metric titrations were performed throughout the approximate range pH 2.0—11.0, on samples of 10.00 cm^3. The ligand concentration was varied in the range 0.004—0.001 mol dm^{-3}. The metal/ligand ratios were 1:1—1:6. Measurements were made with samples at five or six different ratios.

The pH-metric measurements were carried out with a Radiometer pHM 84 pH-meter and a GK 2301 combined electrode. 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 concentrations. The calculations on the data were performed with the PSEQUAD computer program.[17]

Visible absorption spectra were recorded on a Beckman ACTA MIV double-beam recording spectrophotometer over the range *ca.* 380—800 nm, e.s.r. spectra at liquid-nitrogen temperature on a JES-ME-3F spectrometer.

Results and Discussion

Proton Complexes.—The fully protonated form (H_2A^+) of Pro-Leu-NHOH or Pro-Leu-Gly-NHOH can release two protons in the range pH 7—10, one from the amido group of the prolyl moiety and one from the hydroxamic acid group. pH-Metric measurements were carried out to determine the pK values. The calculated values are as follows: Pro-Leu-NHOH, pK_1 = 8.17, pK_2 = 9.11; Pro-Leu-Gly-NHOH, pK_1 = 8.22, pK_2 = 9.06.

Comparison of the corresponding pK values with each other, of the pK_2 values with that of Pro-Leu (9.16),[18] and of the pK_1 values with that of Z-Ala-Gly-NHOH (8.32)[10] (Z = N-benzyloxycarbonyl), shows that the pK_2 values of the peptidehydroxamic acids are in good agreement both with each other and with that of Pro-Leu. However, the two pK_1 values differ a little from that of Z-Ala-Gly-NHOH. If we assume that Z-Ala-Gly-NHOH is an acceptable model for the comparison, we can say that there may be some overlap between the two dissociation processes for these two peptidehydroxamic acids, but the overlap is not very considerable. Moreover, the hydroxamic acid group is more acidic than the amino group in these ligands.

Metal Complexes of Pro-Leu-NHOH.—Representative pH-metric titration curves for Pro-Leu-NHOH and the metal ion–Pro-Leu-NHOH system can be seen in Figure 1. The titration curves were evaluated by assuming all feasible models. Those that provided the best fittings, together with the refined stability constants, are given in Table 1.

It can be seen from Figure 1 that the complex formation in the zinc(II)–Pro-Leu-NHOH and cobalt(II)–Pro-Leu-NHOH systems is limited to the pH ranges *ca.* 6.0—8.5 and 6.0—9.0, respectively. Precipitation (most probably an indication of hydrolysis of the metal ions) occurs even at a metal/ligand ratio of 1:6. (The beginning of the precipitation is supported by the fact that the pH-meter reading does not become constant.) As Table 1 shows, complexes of moderate stability are formed. The titration curves could be fitted well when the complexes $[M(HA)]^{2+}$, $[MA]^+$, and $[MAH_{-1}]$ were assumed. In $[M(HA)]^{2+}$ the ligand contains one dissociable proton (either on the amino or on the hydroxamic acid group); $[MAH_{-1}]$ is formed just before the precipitate occurs, so it may be a mixed hydroxo complex with composition [MA(OH)].

Species with a metal/ligand ratio of 1:2 can be assumed, with stoicheiometry $[MA_2]$ or rather $[M(HA)A]^+$, since the precipitate appears at increasingly higher pH as the metal/ligand ratio is increased in the samples. However, its concentration is quite small, especially in the system containing zinc(II).

Since the stabilities of the peptide complexes and hydroxamate complexes formed with zinc(II) and cobalt(II) ions[11,18] are comparable, several bonding modes may be supposed for the complexes formed in the cobalt(II)– and zinc(II)–Pro-Leu-NHOH systems. The most likely assumption is that both the peptide moiety and the hydroxamate group take part in the co-ordination.

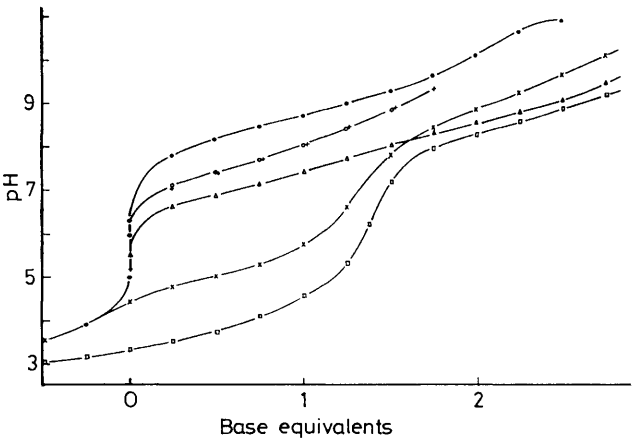


Figure 1. Titration curves for Pro-Leu-NHOH (●) and for metal ion–Pro-Leu-NHOH systems at 1:2 ratio, $c_M = 1 \times 10^{-3}$ and $c_{H_2A^+} = 2 \times 10^{-3}$ mol dm^{-3}. (+), Cobalt(II)–, (○), zinc(II)–, (△), nickel(II)–, (×), copper(II)–, and (□), iron(III)–Pro-Leu-NHOH

Table 1. Stability data for complexes present in the metal ion–Pro-Leu-NHOH systems

Metal ion	Complex	log β	pH Range of main species
Co^{II}	$[M(HA)]^{2+}$	13.06 ± 0.04	6.5—7.5
	$[MA]^+$	5.42 ± 0.02	>7.5
	$[MAH_{-1}]$	−4.7 ± 0.15	>8.5 (minor)
	$[MA_2]$	8.5 ± 0.15	>8
Zn^{II}	$[M(HA)]^{2+}$	12.95 ± 0.04	6.0—7.0 (minor)
	$[MA]^+$	5.91 ± 0.02	>7
	$[MAH_{-1}]$	−3.50 ± 0.09	>8
Ni^{II}	$[MA]^+$	6.37 ± 0.02	6—8
	$[MAH_{-1}]$		negligible
	$[MAH_{-2}]^-$ $\{[M(AH_{-1})(OH)]^-\}$	−9.99 ± 0.04	>8.5
	$[MA_2]$	11.00 ± 0.06	7.5—9.0
Cu^{II}	$[MA]^+$	10.22 ± 0.03	4.5—6.5
	$[MAH_{-1}]$	4.30 ± 0.04	6.5—9.5
	$[MAH_{-2}]^-$ $\{[M(AH_{-1})(OH)]^-\}$	−5.26 ± 0.06	>10.0
Fe^{III}	$[M(HA)]^{3+}$	17.38 ± 0.03	<3.0
	$[MA]^{2+}$	13.75 ± 0.03	3.0—4.4
	$[M(HA)A]^{2+}$	30.9 ± 0.2	4.0—7.0
	$[MA_2]^+$	23.3 ± 0.1	6.0—8.0
	$[MA_2H_{-1}]$	14.50 ± 0.2	7.5—9.0 (minor)
	$[MA_2H_{-2}]^-$	5.70 ± 0.09	>8

The interaction of Pro-Leu-NHOH with the 'nitrogenphilic' nickel(II) starts at somewhat lower pH than with cobalt(II) and zinc(II) ions (see Figure 1). The complex forms relatively slowly. The samples turn yellow at above pH *ca.* 7. This suggests the formation of square-planar complexes, as is supported by the observation that only one absorption peak can be found in the visible spectra over the range pH 7—11, with a $\lambda_{max.}$ of 400 nm.

An additional important observation was that titration of the 1:1 nickel(II)–Pro-Leu-NHOH system up to pH *ca.* 10 involved the consumption of 4 equivalents of base in overlapping processes. This means that two 'extra equivalents' of base are necessary for formation of the 1:1 complex (see the proton complexes of the ligand).

When all these observations and results are taken into account, together with earlier findings on nickel(II)–peptide

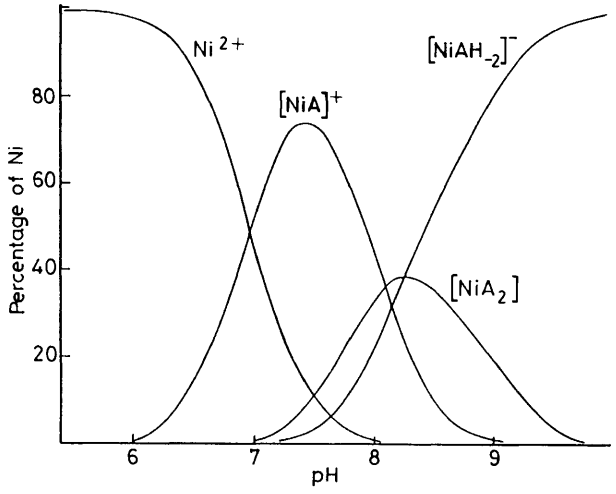
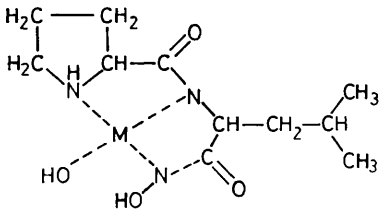
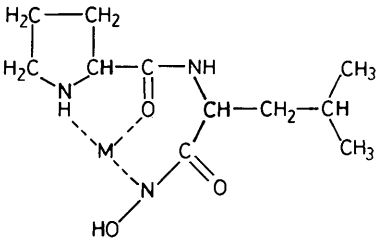


Figure 2. Concentration distribution curves for complexes present in the nickel(II)–Pro-Leu-NHOH system. $c_{Ni} = 8.6 \times 10^{-4}$, $c_{H_2A^+} = 1.8 \times 10^{-3}$ mol dm^{-3}



$[MAH_{-2}]^-$
$\{[M(AH_{-1})(OH)]^-\}$

Scheme 1.



$[MA]^+$

Scheme 2.

systems,[19,20] it can be assumed that the two 'extra equivalents' of base are consumed for deprotonation of the peptide amide and a co-ordinated water molecule, and a species $[NiAH_{-2}]^-$ {which is in fact $[Ni(AH_{-1})(OH)]^-$} is formed. The 'extra' base consumptions can also be found in the presence of a ligand excess.

The model which yielded the best fit to the titration data, together with the refined stability constants, can be found in Table 1.

As an illustration, the concentration distribution curves of complexes formed at a metal/ligand ratio of 1:2 are presented in Figure 2.

It can be seen that the complex $[MAH_{-1}]$ does not appear in measurable concentration. The main species is $[MAH_{-2}]$, for which the most possible bonding mode (based on the above facts) is given in Scheme 1.

In the copper(II)–Pro-Leu-NHOH system the complex formation starts at pH *ca.* 4. The observations relating to the base consumptions are identical to those detailed above. However, as can be seen from Figure 1, in the copper(II)–Pro-Leu-NHOH system the 'extra equivalents' of base are consumed in separate processes. Thus, the complex $[CuAH_{-1}]$ appears in measurable concentration in addition to $[CuA]^+$ and $[CuAH_{-2}]^-$. For steric reasons, the formation of 1:2 complexes is negligible.

Table 2. Some characteristic spectral data for the copper(II)–Pro-Leu-NHOH system

pH	$\lambda_{max.}$/nm	ε/dm^3 mol^{-1} cm^{-1}
4.99[a]	610	57
6.09	575	127
6.81	566	150
7.50	562	152
8.65[b]	559	152
9.00	557	156
9.54	555	160
10.01	550	160
11.01	552	160

[a] $A_{\|} = 177.0$ G, $g_{\|} = 2.252$. [b] $A_{\|} = 191.3$ G, $g_{\|} = 2.217$.

To obtain information about the bonding modes in the complexes, spectrophotometric and e.s.r. measurements were carried out, and some of the results are given in Table 2. The species $[CuA]^+$ reaches its maximum concentration at pH *ca.* 5.0. At this pH the spectral parameters correspond to co-ordination of two nitrogen atoms (2 N). The most probable arrangement of the donor atoms around the copper(II) ion can be seen in Scheme 2. Increases of the pH to *ca.* 7.0 causes $\lambda_{max.}$ to shift to *ca.* 560 nm, which corresponds well to 3 N co-ordination. This indicates that the peptide amide in $[CuAH_{-1}]$ is in deprotonated and co-ordinated form. Above pH 9, during the second 'extra' base consumption, the deprotonation of a co-ordinated water molecule can occur ($pK = 9.92$) and the complex $[CuAH_{-2}]^-$ {in fact $[Cu(AH_{-1})(OH)]^-$} is formed (see Scheme 1).

It is noteworthy that, although the copper(II) ion has a strong affinity for the hydroxamate oxygens too, the role of these donor atoms in this system appears to be insignificant. This may be explained by the fact that, according to Scheme 1, relatively stable joined chelate rings can be formed *via* the nitrogens and the peptide carbonyl oxygen, even at around pH 4.

It is well known that the hydroxamate group has a special affinity for the 'hard' iron(III) ion. Accordingly, three Pro-Leu-NHOH molecules can satisfy the octahedral configuration around the iron(III) ion. As Figure 1 shows, there is measurable complex formation in this system even below pH 3. This means that the stability of the 1:1 complex is very high. However, the model which yielded the best fitting does not contain a 1:3 complex at all, as can be seen in Table 1. Even the 1:2 complexes are formed in relatively low concentrations. [In the calculations, the effects of iron(III)–hydroxy complexes were taken into account *via* the reported[21] stability constants.] It can be assumed that, in addition to the complex $[Fe(HA)]^{3+}$ (in which the hydroxamate oxygen donors can be co-ordinated and the amino group contains the dissociable proton), primarily mixed hydroxo complexes are formed. Steric effects may mean that the formation of complexes with metal/ligand ratios of 1:2 and especially 1:3 are less favoured than in the iron(III)–L-α-alaninehydroxamic acid system.[11]

Metal Complexes of Pro-Leu-Gly-NHOH.—The terminal amino group and the hydroxamate group are more distant from each other in this peptide than in Pro-Leu-NHOH. This means that the simultaneous co-ordination of the above two donor

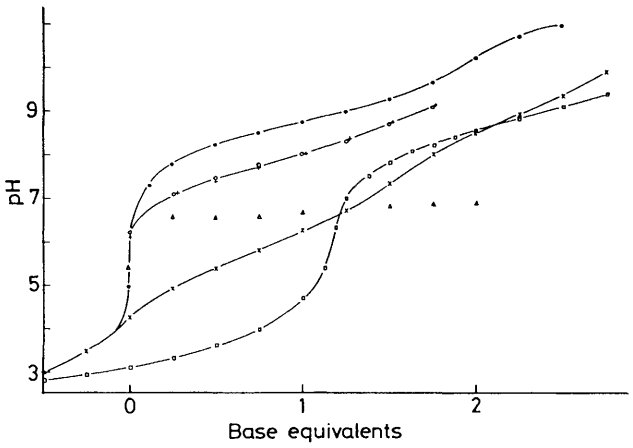


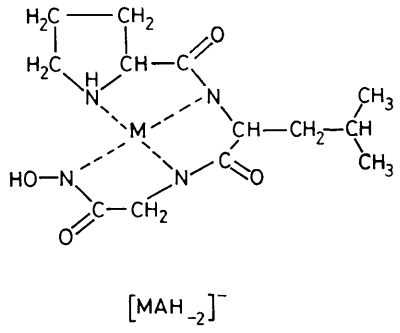
Figure 3. Titration curves for Pro-Leu-Gly-NHOH (●) and metal ion–Pro-Leu-Gly-NHOH systems at 1:2 ratio, $c_M = 1 \times 10^{-3}$ and $c_{H_2A^+} = 2 \times 10^{-3}$ mol dm^{-3}. (+), Cobalt(II)–, (○), zinc(II)–, (△), nickel(II)–, (×), copper(II)–, and (□), iron(III)–Pro-Leu-Gly-NHOH

Table 3. Stability data for complexes present in the metal ion–Pro-Leu-Gly-NHOH systems

Metal ion	Complex	log β	pH Range of main species
Co^{II}	$[M(HA)]^{2+}$	12.45 ± 0.04	6.5—7.6
	$[MA]^{+}$	4.96 ± 0.02	7.0—9.0
	$[MAH_{-1}]$		negligible
	$[MA_2]$	8.22 ± 0.08	>8.5
Zn^{II}	$[M(HA)]^{2+}$	12.50 ± 0.10	
	$[MA]^{+}$	4.75 ± 0.02	>7.0
	$[MAH_{-1}]$	−5.31 ± 0.2	>8.5
Ni^{II}	$[MAH_{-2}]^{-}$		the only species above pH 8
Cu^{II}	$[M(HA)]^{2+}$	14.92 ± 0.10	3.5—5.5
	$[MA]^{+}$	9.52 ± 0.06	5.0—6.0
	$[MAH_{-1}]$	3.44 ± 0.05	5.5—7.3
	$[MAH_{-2}]^{-}$	−3.89 ± 0.03	>7
Fe^{III}	$[M(HA)]^{3+}$	17.48 ± 0.03	<3.5
	$[MA]^{2+}$	13.69 ± 0.05	3.5—5.0
	$[MAH_{-1}]^{+}$	8.45 ± 0.07	5.0—7.0
	$[MA_2]^{+}$	21.03 ± 0.10	6.5—8.5
	$[MA_2H_{-1}]$	12.50 ± 0.11	8.0—9.5 (minor)
	$[MA_2H_{-2}]^{-}$	3.72 ± 0.09	>8.5

groups in a monomer without deprotonation of the peptide amides is much less probable than in the case of Pro-Leu-NHOH (see Scheme 2). Thus, with metal ions which do not promote the ionization of peptide amides, we can expect the formation of less stable complexes in the case of Pro-Leu-Gly-NHOH. On the other hand, with metal ions which promote the ionization, complexes of high stability may be formed, since the 'totally ionized' Pro-Leu-Gly-NHOH can satisfy a square-planar co-ordination sphere, like a macrocycle.

The results we have obtained are as follows, and some of the pH-metric titration curves are depicted in Figure 3. Table 3 contains the models that yielded the best fittings between the measured and calculated titration curves, together with the refined stability constants of the species. As can be seen from Figure 3, in the systems containing cobalt(II) and zinc(II) the formation of metal(II) ion–Pro-Leu-Gly-NHOH complexes is limited to a narrow pH range (*ca.* 6—8.5). The ionization of peptide amides does not occur. Before the precipitation, mixed hydroxo complexes can be formed in addition to 1:1 complexes. A comparison of the stability data in Tables 1 and 3 indicates that, in accordance with the above-mentioned expectations, the



Scheme 3.

complexes formed in the cobalt(II)– and zinc(II)–Pro-Leu-Gly-NHOH systems are less stable than those formed in the cobalt(II)– and zinc(II)–Pro-Leu-NHOH systems.

With nickel(II) and copper(II) ions deprotonation of the peptide amides takes place (see Figure 3). In the case of nickel(II) the ionization starts at above pH 6 and the complexes are formed at very low rates (as with polypeptides[22]). Approximate equilibrium was reached in 1 d (there was no further change in pH), so the stability constant was not calculated. A square-planar complex was found ($\lambda_{max.}$ for the single absorption peak is 410 nm). The most probable bonding mode is shown in Scheme 3.

In the case of the copper(II)–Pro-Leu-Gly-NHOH system, complex formation starts with the formation of $[Cu(HA)]^{2+}$ at above pH 3.5. The spectral characteristics ($\lambda_{max.}$ in the *d–d* absorption spectra is over 700 nm) correspond to the co-ordination of oxygen donors, which clearly indicates that the interaction between copper(II) and Pro-Leu-Gly-NHOH starts *via* hydroxamate oxygens. (The solubility of this complex is very low.) At above pH 5 totally different bonding modes start to develop. Overlapping ionization processes take place and only $[CuAH_{-2}]^{-}$ is formed above pH 8.5. The spectral data demonstrate that the bonding mode in Scheme 3 can be assumed in $[CuAH_{-2}]^{-}$. The $\lambda_{max.}$ of the *d–d* absorption spectra is 490 nm and the e.s.r. parameters correspond well to 4 N co-ordination ($g_{\|} = 2.181$, $A_{\|} = 208.5$, and $A_N = 15.6$ G).

Because of the greater bulk of Pro-Leu-Gly-NHOH, the formation of mixed hydroxo complex is more favoured in the iron(III)–Pro-Leu-Gly-NHOH system than in the iron(III)–Pro-Leu-NHOH system, and especially than in the iron(III)-L-α-alaninehydroxamic acid system.[11] While the samples in the latter system could be titrated without precipitation up to a pH of about 11, even at a metal/ligand ratio of 1:1,[11] the precipitation of metal hydroxides occurred with samples in the iron(III)–Pro-Leu-Gly-NHOH system above pH 9, even at a ligand excess.

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