Complex Formation between Transition Metals and DL-Aspartic Acid-β-hydroxamic Acid (*N*-Hydroxyasparagine)

Etelka Farkas* and Péter Buglyó
Department of Inorganic and Analytical Chemistry, Lajos Kossuth University, H-4010 Debrecen, Hungary

Formation constants and assumptions concerning the bonding mode are reported for the complexes present in aqueous solution in the cobalt(II)–, nickel(II)–, copper(II)–, zinc(II)–, and iron(III)–DL-aspartic acid-β-hydroxamic acid (*N*-hydroxyasparagine, hasn) systems. The amino nitrogen, the hydroxamate nitrogen, and the carboxylate oxygen are the main co-ordinating donor atoms in the cobalt(II)– and nickel(II)–hasn complexes. The hydroxamate oxygens may also take part in co-ordination in the zinc(II)–hasn system. Very stable 1 : 1 and 1 : 2 binary complexes are formed in the iron(III)–hasn system, with tridentate co-ordination (hydroxamate and carboxylate oxygens) of the ligand. Mixed hydroxo complexes are proposed at pH > 5. A polymeric species, with composition $[Cu_4A_4H_{-2}]^{2-}$, is the most stable complex in the copper(II)–hasn system.

Since the possible biological activity of the aminohydroxamic acids must be correlated with the formation of their metal complexes,[1,2] interest in these systems has increased extensively over the past decade.[3–7] Most of the investigations relate to the complexes of simple aminohydroxamates. Other publications are rather limited in number. For example, only one[8] reports results on DL-aspartic acid-β-hydroxamic acid (*N*-hydroxyasparagine, hasn). Recently, Leporati[8] studied the cobalt(II), nickel(II), and copper(II) complexes of hasn. In all of the systems investigated he found polymers in which the monomer units were joined *via* carboxylate groups. The formation of 1:2 complexes involving co-ordination of amino and hydroxamate nitrogens was also found. These results are very interesting, but at the same time very surprising. For example, it is not clear why hasn co-ordinates to the metal ions only as a bidentate ligand and why the monomers are joined by the carboxylate oxygens.

We have previously studied transition-metal complexes of L-α-alaninehydroxamic acid (2-amino-*N*-hydroxypropanamide) (ahpr)[9] and peptide hydroxamic acids.[10] In the present work, an equilibrium and structural study has been performed on the cobalt(II), nickel(II), copper(II), zinc(II), and iron(III) complexes of hasn, using pH-metric, spectrophotometric, and e.s.r. methods.

Experimental

The compound hasn was purchased from Sigma (St. Louis). Its purity and the exact concentration of its stock solution were determined by the Gran method.[11] The metal-ion stock solutions were made as before[9,10] and their concentrations checked gravimetrically *via* precipitation of the quinolin-8-olate and oxide. The pH-metric titrations were performed at five or six different metal ion/ligand ratios in the range 1:1—1:6. The concentration of hasn in the samples was varied between 4×10^{-3} and 1×10^{-2} mol dm^{-3}. All measurements were made at 25 °C, at an ionic strength of 0.2 mol dm^{-3} KCl. The pH-metric procedure and the evaluation of the titration data were described previously;[9] the pH-meter readings were converted into hydrogen-ion concentrations.[12] The calculations on the pH-metric data were performed with the aid of the PSEQUAD computer program.[13]

Visible absorption spectra were recorded on a Beckman Acta MIV double-beam recording spectrophotometer over the range *ca.* 350—800 nm. E.s.r. spectral measurements were made at liquid-nitrogen temperature on a JES-ME-SF spectrometer.

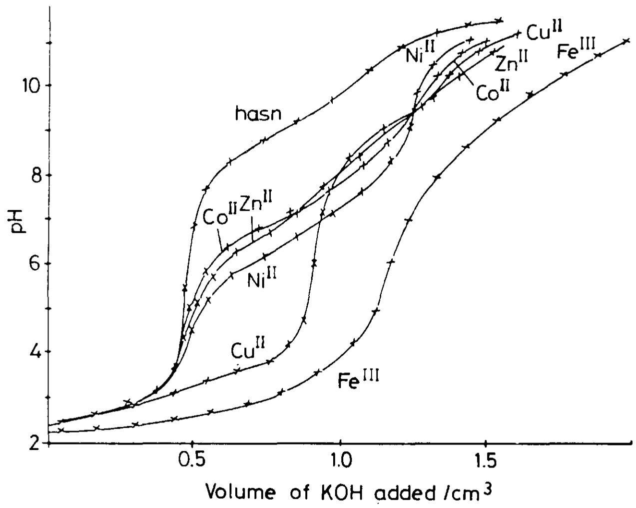


Figure 1. Titration curves for hasn (4×10^{-3} mol dm^{-3}) and metal ion (2×10^{-3} mol dm^{-3})–hasn systems at 1:2 metal/ligand ratio

Results and Discussion

The fully protonated form of hasn [$H_3A^+ = HO_2CCH(\overset{+}{N}H_3)CH_2CONHOH$] can release three protons in the pH range 1.5—11.0. The determined dissociation constants are $pK_1 = 2.12 \pm 0.01$, $pK_2 = 8.29 \pm 0.01$, and $pK_3 = 9.42 \pm 0.01$. These values are in fairly good agreement with those published by Leporati,[8] and we also assign pK_1 to deprotonation of the carboxylate group. However, there is some contradiction in the assignments of pK_2 and pK_3. Leporati assigns these values to the hydroxamic acid group and amino group, respectively. On the other hand these two dissociation processes overlap with each other. This means that pK_2 and pK_3 are macroconstants and the deprotonation microconstants have to be determined in order to get information about the basicities of the hydroxamic acid and amino groups.

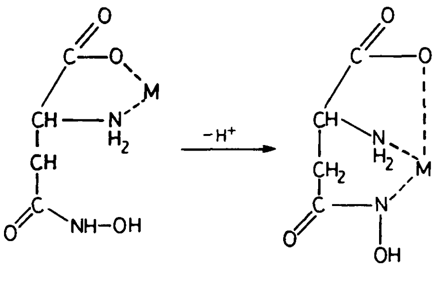
The titration curves registered for hasn and for the cobalt(II)–, nickel(II)–, zinc(II)–, copper(II)–, and iron(III)–hasn systems can be seen in Figure 1. The models yielding the best fits between the measured and calculated titration curves, together with the refined stability constants, are compiled in Table 1. As can be seen in Figure 1, each of the samples with 1:2 metal/ligand ratio

Table 1. Stability data (log β) for complexes present in the metal ion–hasn systems at 25 °C and $I = 0.2$ mol dm^{-3} (KCl)

Complex	Co^{II}	Ni^{II}	Zn^{II}	Cu^{II}	Fe^{III}
[M(HA)]	13.71 ± 0.02	14.45 ± 0.03	13.91 ± 0.02	16.41 ± 0.16	18.82 ± 0.05
[MA]	7.10 ± 0.01	8.38 ± 0.02	7.44 ± 0.01	13.24 ± 0.05	
[M(HA)$_2$]					36.35 ± 0.05
[MA(HA)]	19.92 ± 0.03	21.74 ± 0.06	20.30 ± 0.03		31.63 ± 0.06
[MA$_2$]	12.00 ± 0.02	14.41 ± 0.03	11.72 ± 0.03		24.25 ± 0.07
[MA$_2$H$_{-1}$]	1.87 ± 0.02	4.56 ± 0.10	2.11 ± 0.03		15.32 ± 0.07
[M$_4$A$_4$H$_{-2}$]				52.82 ± 0.16	
[M$_4$A$_4$H$_{-3}$]				42.30 ± 0.20	

Table 2. Derived constants for nickel(II) and zinc(II) systems

	Ni^{II}				Zn^{II}			
Equilibria	hasn	Asp	Asn	daba	hasn	Asp	Asn	daba
$M^{2+} + HA^- \rightleftharpoons [M(HA)]^+$	5.03	4.05		4.66	4.49			3.74
$M^{2+} + A^{2-} \rightleftharpoons [MA]$	8.38	7.05	5.59	8.97	7.44	5.73	4.49	6.70
$[MA] + HA^- \rightleftharpoons [MA(HA)]^-$	3.94			3.92	3.44			3.39
$[MA] + A^{2-} \rightleftharpoons [MA_2]^{2-}$	6.03	5.29	4.54	7.37	4.28	4.47	3.67	5.60



$[M(HA)]^+$ $[MA]$

Scheme 1.

can be titrated without precipitation up to pH 11. Especially the cobalt(II)– and zinc(II)–hasn systems appear to behave strangely from this point of view, because the hydrolysis of these two metal ions occurs even at high ligand excesses (up to a metal/ligand ratio of 1 : 6) in systems containing ahpr or peptide hydroxamic acids.[9,10]

As Table 1 shows, the experimental data for the cobalt(II)–, zinc(II)–, and nickel(II)–hasn systems can be fitted with the same model. This model, in contrast with a recently published one,[8] does not involve polymeric species at all, but does include various protonated complexes. The refined stability data (Table 1) have been compared with those for the following analogous ligands (the totally protonated forms are depicted): aspartic acid (asp), $HO_2CCH(\overset{+}{N}H_3)CH_2CO_2H$;[14] asparagine (asn), $HO_2CCH(\overset{+}{N}H_3)CH_2CONH_2$;[14] and 2,4-diaminobutyric acid (daba), $HO_2CCH(\overset{+}{N}H_3)CH_2CH_2\overset{+}{N}H_3$.[15] Table 2 contains stepwise equilibrium constants for the nickel(II) and zinc(II) complexes of hasn and the reference ligands. The corresponding values for the reference cobalt(II) complexes are not available.

When the differences in the dissociation constants of the ligands are taken into account, Table 2 shows that the derived constants for the complexes formed in the nickel(II)–hasn system approximate well to the corresponding data for daba. The octahedral geometry of the complexes was consistent with the visible spectra. Therefore, the data are strongly suggestive of the 'daba-like' co-ordination of hasn. The most likely bonding mode in the species $[M(HA)]^+$ and [MA] is given in Scheme 1. (The same co-ordination mode can be assumed for the HA^- and A^{2-} forms of hasn in the bis complexes.)

The results for the cobalt(II)–hasn complexes (Table 1) are in good agreement with those proposed on the basis of the Irving–Williams series with the assumption of 'daba-like' co-ordination (see Scheme 1). The stability of the zinc(II)–hasn complexes is somewhat higher. This may be explained if (considering that, of these three metal ions, zinc has the strongest ability to form complexes with O donors) it is assumed that complexes involving both 'daba-like' and 'hydroxamate-like' co-ordination are formed in this system.

The interaction of hasn with copper(II) starts at *ca.* pH 3. The model yielding the best fit between the measured and calculated titration curves is different from those for the nickel(II)–, cobalt(II)–, and zinc(II)–hasn systems, and those published earlier for the copper(II)–daba [16] and copper(II)–ahpr [9] systems. Moreover, there is some difference between the models presented here and that described previously [8] for the copper(II)–hasn system. To validate the model given in Table 1, formation curves were calculated and evaluated from pH-metric data, and e.s.r. and visible spectrophotometric measurements were performed. Some of the formation curves are depicted in Figure 2. They reach a long plateau at $\bar{n} = 1.16$, which indicates that bis complexes are not formed. A rapid increase in $\bar{n}$ can be seen only at high ligand concentration (high pH). This may indicate deprotonation of the co-ordinated ligand or hydrolytic processes. The e.s.r. spectra confirmed that species involving a strong copper(II)–copper(II) interaction start to form at pH >4 and there is no e.s.r.-active species at all at pH >6.

The above-mentioned results and considerations strongly suggest the formation of 1 : 1 complexes at pH <6, but at pH >6 polymers are the only species in this system. Since the plateau in the $\bar{n}$ curves occurs at 1.16, it must be assumed for the polymeric species that the metal/ligand ratio = 1 : 1.16 or the metal/ligand/proton ratio = 1 : 1 : −0.5. The best fit of the titration data was given in the latter case. The simplest formula reflecting this is $[Cu_2A_2H_{-1}]^-$. This species was demonstrated previously in the copper(II)–ahpr system,[9] and mixed N,N and O,O co-ordination of the ligands was found. In the copper(II)–hasn system the spectral characteristics ($\lambda_{max.} = 615$ nm in the *d–d* absorption spectra in the pH interval 5.0—11.0) also indicate that both nitrogen and oxygen donors are co-ordinated to the copper(II) ion. However, the formation of bis complex(es) is not hindered in the presence of $[Cu_2A_2H_{-1}]^-$.[9] The only species

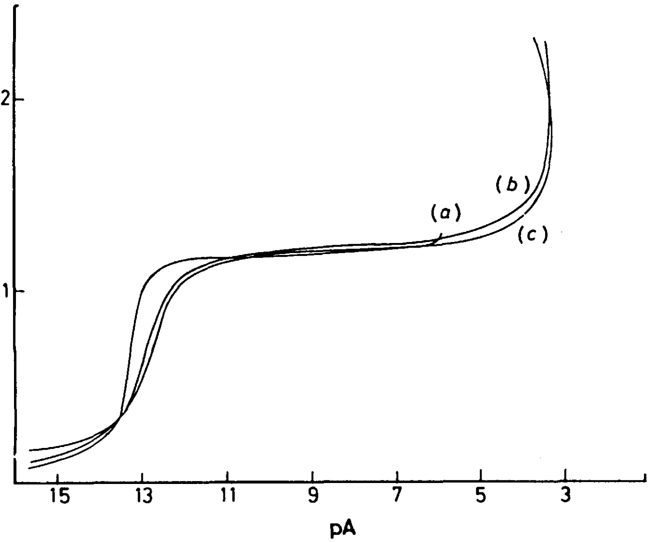
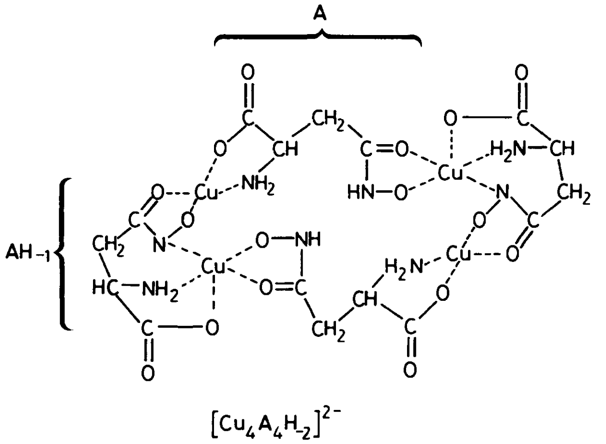


Figure 2. Formation curves for the copper(II)–hasn system calculated at an hasn concentration of 4 × 10^{-3} mol dm^{-3}. Copper(II) ion/hasn ratio: 1:1 (*a*), 1:2 (*b*), or 1:5 (*c*)



Scheme 2.

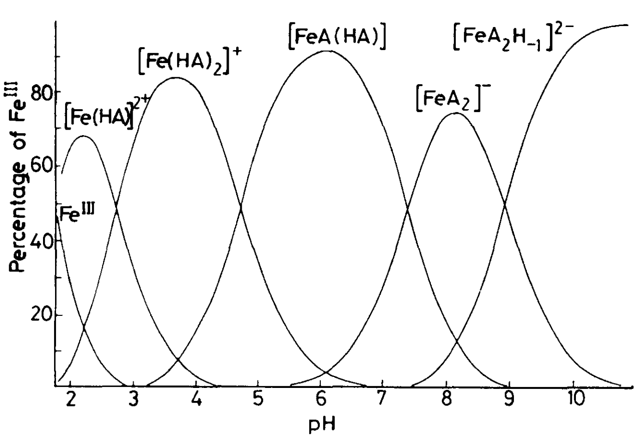


Figure 3. Concentration distribution curves for iron(III)–hasn (4 × 10^{-3} mol dm^{-3}) complexes formed at 1:2 metal/ligand ratio

which corresponds well to the above-mentioned results and observations is $[Cu_4A_4H_{-2}]^{2-}$, with the suggested bonding mode as depicted in Scheme 2. The stabilities of the complexes formed between copper(II) and α-amino acids, daba, or aliphatic hydroxamic acids are thus comparable.

Measurable complex formation occurs between iron(III) and hasn even at pH <2 (see Figure 1). This is in agreement with earlier findings on the iron(III)–ahpr system.[9] However, there are some disagreements between the results for the two systems: mixed hydroxo complexes were found in measurable concentration in the iron(III)–ahpr system (with composition FeA) at around pH 3, but in the iron(III)–hasn system only 1:1 and 1:2 protonated complexes are formed at pH <4, as can be seen in Figure 3. (Metal-ion hydrolysis was taken into account, as in ref. 9.)

Since iron(III) is a typical hard ion, the hydroxamate oxygens can be presumed to be the main co-ordinating donor atoms and the amino nitrogen must contain the dissociable proton in the protonated complexes. Deprotonation of the $\overset{+}{N}H_3$ group of the co-ordinated ligands may overlap with deprotonation of the co-ordinated water (the formation of mixed hydroxo complexes) at pH >4. When the refined stability constants of the iron(III)–hasn complexes (Table 1) are compared with the corresponding data in ref. 9 it can be seen that the iron(III)–hasn complexes are more stable and the differences in the constants are *ca.* 2 log units. These data and the above-mentioned considerable hindrance to hydrolytic processes are strongly suggestive of the tridentate co-ordination of the ligand in the iron(III)–hasn complexes. Co-ordination of the carboxylate group in addition to the hydroxamate oxygens can be assumed.

Acknowledgements

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