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Mixed Metal Complexes in Solution. Part I. Potentiometric Study of Heterobinuclear Copper(II)–l-Histidinate Complexes with Nickel(II), Zinc(II) and Cadmium(II) Ions in Aqueous Solution

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Introduction

Formation, stability and thermodynamic studies of mixed ligand complexes of metal ions have been reported, although to a lesser extent with respect to the binary ones [1]. The complexation of metal ions with ligands of biological interest has been in particular investigated [2], in relation to the relevance of the ternary complexes in biofluids. On the basis of the results obtained, the factors determining the stabilization of mixed complexes with respect to the parent binary ones have been pointed out [3].

On the contrary, although some heteronuclear mixed complexes of common biofunctional ligands have been synthesized [4, 5] and the analytical importance of this kind of ternary compounds has been shown [6–8], the driving forces for mixed-metal complex formation remain obscure. In spite of the contribution of thermodynamic approach to elucidating the characteristics of coordination of two different ligands around one metal ion, only recently have the formation constants of ternary complexes of glutathionate containing two dissimilar metal ions been determined [9].

In this work we report the stability constants of heterobinuclear copper(II)–l-histidinate (his) complexes with nickel(II), zinc(II) and cadmium(II) in aqueous solution at 25 °C and $I = 0.1$ mol dm^{-3} ($K[NO_3]$).

Experimental

The measurements were carried out as previously described [10]. The stock solutions of metal nitrates were prepared and standardized as reported in the literature [11]. The l-histidine (Aldrich) was used without further purification. The types of species present in solution were evidenced by graphical methods [12, 13]; the approximate values of stability constants so obtained were then refined by two different least-squares computer programs [13–15]. Computations relative to the purity of the ligand, to the E° determination and to the standardization of the stock solutions were made by means of the least-squares computer program ACBA [16]. Experimental details of potentiometric titrations are reported in Table I.

Results

The protonation constants of l-histidine (as pK_i^H values) and the stability constants of binary complexes are collected in Table II. In solutions containing Cu(II), l-histidine and another metal ion (Ni(II), Zn(II) or Cd(II)) it is possible to show that, for suitable concentration ratios (see Table I), besides the binary species, mixed-metal complexes are present as well. For the three ternary systems the species $[CuM(his)_2]^{2+}$ was first evidenced (M = Ni(II), Zn(II) or Cd(II)). Moreover, by considering only the acid buffer region (pH = 3–6) of alkalimetric titration curves the protonated species $[CuM(his)_2H]^{3+}$ was also found: Hamilton statistical tests [17, 18] confirm this view, in fact the calculated $R([CuM(his)_2]^{2+})/R([CuM(his)_2]^{2+}, [CuM(his)_2H]^{3+})$ values are 1.22, 1.41 and 1.23 for M = Ni(II), Zn(II) and Cd(II) respectively, which means that the formation of the protonated species is highly probable. In the alkaline range (pH > 6.5) there is displacement of hydrogen ion in excess of the dissociation of amino group of l-histidine, and then the deprotonated species form. The complex $[CuM(his)_2H_{-1}]^+$ is present in all the ternary systems here reported, while small quantities of the species further deprotonated form, before precipitation, only in presence of Ni(II) and Zn(II) ($R([CuM(his)_2H_{-1}]^+/R([CuM(his)_2H_{-2}]^\circ) > 1.2$ both for M = Ni(II) and Zn(II)). The values of the stability constants for heterobinuclear species are collected in Table III, with their ranges. In Table I the values of formation percentages (referred to l-histidine) for the different heterobinuclear species are collected as well.

Discussion

The $[CuM(his)_2]^{2+}$ complex is by far the more relevant at pH < 7, while for higher pH values the most important mixed species is $[CuM(his)_2H_{-1}]^+$ (Fig. 1).

The values of stability constants of $[CuM(his)_2]^{2+}$ show that the Ni(II) complex is more stable than those of Zn(II) and Cd(II), which have a very similar

TABLE I. Concentrations in mmol dm^{-3}[a], Total Number of Points[b], Percentages (Referred to 1-Histidine) at Indicated Values of pH[c].

Metal	C_{Cu}[a]	C_M[a]	C_{his}[a]	pH-range	N[b]	%$[CuM(his)_2]^{2+}$[c] pH 5.0	%$[CuM(his)_2H]^{3+}$[c] pH 4.5	%$[CuM(his)_2H_{-1}]^{+}$[c] pH 7, 8	%$[CuM(his)_2H_{-2}]^{0}$[c] pH 7.5, 8
Ni(II)	3.0	4.0	4.0	3.5–7.0	17	10	4	7, –	–, –
	3.5	5.0	6.0	3.6–7.1	18	15	5	10, –	–, –
	3.0	4.0	5.0	3.5–7.2	14	13	4	9, –	–, –
	4.0	5.0	5.0	3.5–6.8	16	14	4	7, –	–, –
	3.0	5.0	4.5	3.6–7.0	15	14	5	8, –	–, –
	3.0	3.0	6.0	5.3–8.1	64	–	–	7, 20	1, 7
	4.0	5.0	9.0	5.3–7.9	46	–	–	8, 20	2, 7
	2.3	7.5	10.0	3.2–8.0	28	8	4	7, 19	1, 7
	3.0	3.0	6.0	3.2–7.9	29	11	3	7, 20	1, 7
						pH 5.5	pH 4.5	pH 6.8, 7.2	pH 7.2, 7.5
Zn(II)	3.0	6.0	4.4	3.1–7.2	33	27	10	4, 9	6, –
	2.5	5.0	3.5	3.0–7.2	28	24	7	4, 7	5, –
	3.5	7.0	4.9	3.1–7.1	33	27	10	3, –	–, –
	4.0	8.0	6.1	3.1–7.2	33	34	12	5, 10	5, –
	3.0	7.0	5.0	3.1–7.2	30	34	11	5, 11	7, –
	3.5	6.0	4.5	3.0–7.3	31	21	7	3, 7	5, –
	2.0	7.7	10.0	5.2–7.6	52	14	–	1, 3	2, 8
	2.5	7.5	9.9	3.1–7.5	20	17	8	2, 4	2, 6
	3.0	3.0	5.9	3.2–7.3	20	20	6	1, 6	5, –
						pH 5.5	pH 4.5	pH 7, 8	
Cd(II)	2.5	5.1	2.9	3.4–8.0	29	16	4	1, 10	
	3.0	6.1	3.9	3.2–8.2	33	22	6	2, 14	
	3.5	8.2	5.0	3.2–8.0	36	29	9	3, 21	
	3.0	8.2	3.9	3.3–8.1	35	26	8	2, 15	
	3.5	7.2	4.4	3.3–8.1	34	22	7	2, 15	
	2.5	7.5	15.0	5.6–8.4	75	–	–	1, 3	
	2.5	7.5	10.0	3.3–8.3	29	20	7	1, 11	
	3.0	3.0	6.0	3.2–7.6	23	20	5	2, –	

TABLE II. Values of Protonation Constants (as pK_i^H) and of Stability Constants of Binary Complexes Metal–1-Histidine at t = 25 °C and I_c = 0.1 *M* (KNO_3).

	$lg\beta_{1,1,0}$	$lg\beta_{1,1,1}$	$lg\beta_{1,2,0}$	
Copper(II) [25]	10.15	14.17	18.13	$lg\beta_{1,2,1} = 23.87; lg\beta_{1,2,2} = 27.10$ $lg\beta_{1,1,-1} = 2.00; lg\beta_{2,2,-2} = 8.03$ $lg\beta_{1,2,-1} = 6.80$
Nickel(II) [26]	8.67		15.52	
Zinc(II)	6.53(27)	11.37(21)	11.92(27)	
Cadmium(II) [28]	5.74	11.17	9.96	
	$pK_1^H = 1.8; pK_2^H = 6.03; pK_3^H = 9.09$			
	$lg\beta_{p,q,r}$: $pM + q\,his + rH \rightleftharpoons M_p his_q H_r$			

TABLE III. Values of lgβ for Heterobinuclear Ternary Complexes. t = 25.0 ± 0.2 °C, I_c = 0.1 *M* (KNO_3).

Reaction	lgβ
$Cu^{2+} + Ni^{2+} + 2\,his \rightleftharpoons [CuNi(his)_2]^{2+}$	21.20 ± 0.04
$Cu^{2+} + Zn^{2+} + 2\,his \rightleftharpoons [CuZn(his)_2]^{2+}$	20.78 ± 0.04
$Cu^{2+} + Cd^{2+} + 2\,his \rightleftharpoons [CuCd(his)_2]^{2+}$	20.73 ± 0.04
$Cu^{2+} + Ni^{2+} + H^+ + 2\,his \rightleftharpoons [CuNi(his)_2H]^{3+}$	25.56 ± 0.07
$Cu^{2+} + Zn^{2+} + H^+ + 2\,his \rightleftharpoons [CuZn(his)_2H]^{3+}$	25.69 ± 0.06
$Cu^{2+} + Cd^{2+} + H^+ + 2\,his \rightleftharpoons [CuCd(his)_2H]^{3+}$	25.45 ± 0.10
$Cu^{2+} + Ni^{2+} + 2\,his \rightleftharpoons [CuNi(his)_2H_{-1}]^+ + H^+$	14.00 ± 0.13
$Cu^{2+} + Zn^{2+} + 2\,his \rightleftharpoons [CuZn(his)_2H_{-1}]^+ + H^+$	13.02 ± 0.12
$Cu^{2+} + Cd^{2+} + 2\,his \rightleftharpoons [CuCd(his)_2H_{-1}]^+ + H^+$	12.65 ± 0.25
$Cu^{2+} + Ni^{2+} + 2\,his \rightleftharpoons [CuNi(his)_2H_{-2}]^0 + 2H^+$	5.45 ± 0.15
$Cu^{2+} + Zn^{2+} + 2\,his \rightleftharpoons [CuZn(his)_2H_{-2}]^0 + 2H^+$	5.48 ± 0.15
$Cu^{2+} + Cd^{2+} + 2\,his \rightleftharpoons [CuCd(his)_2H_{-2}]^0 + 2H^+$	<3.9

stability. This trend is the same as was found for the complexes of the above metal ions with imidazole ($lg\beta_2$ = 5.50, 4.82 and 4.90 for Ni(II), Zn(II) and Cd(II) respectively [19]). It is possible therefore to put forth the hypothesis that l-histidine coordinates glycine-like to the Cu(II) ion, with the other metal ion bonded to the imidazole nitrogen atoms.

It was verified that in the complex formation between transition metal ions and compounds containing an imidazole ring, the pyrrole group can dissociate at pH values much lower than the pK^H value of the pyrrole group in the free ligand [20, 21]; such a decrease can even reach four pH units [19]. By supposing that also in the ternary complexes here reported the dissociation of pyrrole group takes place in the considered pH range, l-histidine might behave as a tetradentate ligand; if the aminoacid binds Cu(II) ion in the same way as in the $[Cu(his)_2]^0$ complex, it is likely that, in this case, pyrrole nitrogen binds the other metal ion. The formation in solution of l-histidine deprotonated species in presence of two different metal ions is very interesting, taking into account that recently the imidazolate anion has been proposed as bridging ligand in a number of biological systems. In particular crystallographic evidence confirms the presence of imidazolate as a bridge between copper and zinc in bovine superoxide dismutase [22] and Palmer [23] has also postulated the involvement of bridging imidazolate between iron and copper in cytochrome *c* oxidase, implying the participation of the histidyl imidazolate in the electron-transfer process of oxygen reduction.

The different 'soft' and 'hard' character of metal ions may explain the trend of stability constants, since Ni(II), Zn(II) and Cd(II) respond in a different way to the double σ- and π-bonding character of l-histidine imidazole.

On the basis of formation of heterobinuclear l-histidine species here reported, it can be asserted that the existence of this type of complexes does not need the presence of two complexing sites of different donor properties (*e.g.* S and N), as previously

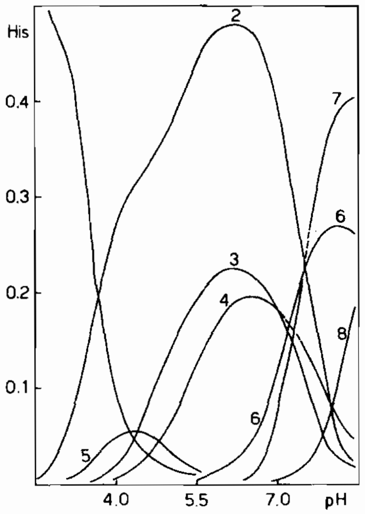

Fig. 1. Distribution diagram of the system Cu(II)–Ni(II)–l-histidine, referred to l-histidine. $C_{Cu} = C_{Ni} = 4.00$ mmol dm^{-3}; $C_{his} = 8.00$ mmol dm^{-3}. 1: his$^-$; 2: $[Cu(his)]^+$; 3: $[CuNi(his)_2]^{2+}$; 4: $[Cu(his)_2]^{\circ}$; 5: $[CuNi(his)_2H]^{3+}$; 6: $[CuNi(his)_2H_{-1}]^+$; 7: $[Cu_2(his)_2H_{-2}]^{\circ}$; 8: $[CuNi(his)_2H_{-2}]^{\circ}$.

suggested [9], and that probably the species distribution relative to complexes of essential metal ions with low molecular weight ligands in biofluids [24] may be affected by the presence of heteronuclear ternary species.

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