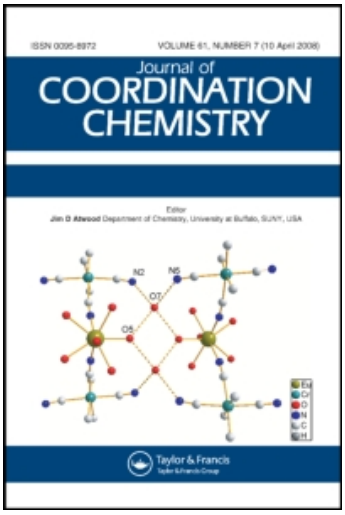

Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455674

Cu(II) Binding By 8-Substituted-Imidazo[1,2-a]Pyridines

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To cite this Article Decock, Patrick , Dubois, Bernard , Blondeau, Dominique , Sliwa, Henri and Kozlowski, Henryk(1989) 'Cu(II) Binding By 8-Substituted-Imidazo[1,2-a]Pyridines', Journal of Coordination Chemistry, 20: 1, 1 — 10
To link to this Article: DOI: 10.1080/00958978909408842
URL: http://dx.doi.org/10.1080/00958978909408842

J. Coord. Chem. 1989, Vol. 20, pp. 1–10
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Cu(II) BINDING BY 8-SUBSTITUTED-IMIDAZO[1,2-a]PYRIDINES

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(Received July 13, 1988)

Potentiometric and spectroscopic studies on complexes with 8-hydroxy and 8-methoxyimidazo[1,2-a]-pyridine are discussed. One major complex species, CuL_2, is formed. In the hydroxy substituted molecule two ligands are chelated to the copper ion *via* (NH,O^-) donor sets.

Keywords: Copper(II), imidazo[1,2–a]pyridines, complexes, stability constants

INTRODUCTION

8-hydroxyquinoline (oxine) is a very effective chelating agent for variety of metal ions and forms poorly soluble complexes. As such it has been primarily used in analytical chemistry.[1] The chelating power of oxine, as well as its relatively low toxicity, has inspired various applications in bacteriology, pharmacology, zoology and pathology.[1]

The copper complex of oxine is one of the longest used fungicides for wood, plastics, adhesives and paints.[1] The wide industrial use of the copper oxine complex derives not only from its low toxicity and its particular stability but also its very low cost. The intensive green colour, however, severly limits its applications. The oxine ligand has also been used as a corrosion inhibitor for copper and copper alloys by forming protective layer on the metal surface.

8-hydroxy substituted imidazo[1,2-a]pyridines[2a,b] are structural analogues of oxines and studies on their coordination ability could help to develop a family of useful chelating agents. On the other hand, the behaviour of the complexes formed can help in an understanding of the metabolism and degradation processes of copper oxine whose biocidic properties in the natural environment are still unclear.

In this work we present potentiometric and spectroscopic results obtained for

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copper complexes with 8-hydroxyimidazo[1,2-a]pyridine and its 8-methoxy derivative. Since the ligand solubility in water is poor we have used water-dimethylsulfoxide (DMSO) and water-dioxane mixed solvents.

EXPERIMENTAL

Materials

8-hydroxyimidazo[1,2-a]pyridine and 8-methoxyimidazo[1,2-a]pyridine were synthesized according to the method described earlier.[2] The purity of the products was checked by potentiometry. Puratronic cupric chlorides were used to prepare metal ion solutions. The ligand stock solutions were prepared under an argon atmosphere in 80/20 deionized and bidistilled water and dimethylsulfoxide (Merck), 0.15 M in NaCl and 2×10^{-3} M in HCl.

Potentiometric Titrations

The potentiometric titrations were performed with an automatic titration assembly consisting of a Tacussel Isis 20000 pH meter, an automatic Electroburex burette, a stirrer and a 50 cm^3 titration vessel thermostated at 25.00 ± 0.03°C. An Apple IIe microcomputer controlled the titrations and handled data acquisition. The pH meter and electrodes (TB/HA for the glass electrode and C8 for the calomel electrode saturated in KCl) were adjusted in terms of activity against standard buffers (pH = 4.66 and 6.88 at 25°C).

The 0.0750 M sodium hydroxyde was prepared carbonate-free in 0.15 M NaCl and stored under an argon atmosphere. It was standardized against phthalate (N.B.S.). Puratronic copper(II) chloride was dissolved to give 0.2 M solution in 3×10^{-3} M HCl and standardized against EDTA. All the solutions contained 0.15 M NaCl and a known amount of HCl to fully protonate the ligands and to lower the starting pH. The concentrations of Cu(II) and ligands in each sample are listed in Tables I and II.

Spectroscopic Studies

The electronic absorption spectra were recorded on a Beckman Acta VII spectrophotometer. E.S.R. measurements were carried out at liquid nitrogen temperature on a Varian E-9 spectrometer operating at the X-band frequency (9.30 GHz). For the spectroscopic measurements, a Cu(II) concentration of 10^{-3} M in a mixture of H_2O/DMSO (80/20) 0.15 M in $NaClO_4$ (visible) and in a mixture of H_2O/dioxane (60/40) with ethylenglycol (E.S.R.), was used.

RESULTS AND DISCUSSION

Determination of Species Distribution and Stability Constants

Due to the high insolubility of complexes, the potentiometric measurements were carried out with particular care. First, a stock solution (S) of mixed solvent DMSO/H_2O (20/80), 0.15 M NaCl and 2×10^{-3} M HCl was prepared. The exact concentration of HCl, as well as the relation between pH and p[H] and the value of pK_s were

checked by potentiometric titrations of the stock solution. Secondly, a stock solution of ligand (L1) was prepared by dissolving a weighed amount of ligand in the stock solution. The exact ligand and free proton concentrations in this solution were estimated by potentiometric titrations. By dilution of the ligand stock solution (L1) with the stock solution (S), two other stock solutions of ligand, (L2) and (L3), were prepared.

From the titrations of L1, L2 and L3, the ionization constants were determined using the PKASIMPLEX program[3] written for the Apple II and the SUPERQUAD program[4] (Table III). The latter has been adapted for an IBM–PC microcomputer equipped with an 8087 maths coprocessor. Following this preliminary step, at least five titrations were performed for which the metal/ligand ratios are indicated in Tables I and II. The electrode response was verified frequently and eventually corrected by checking S solution titrations.

TABLE I

Sample composition (micromolar) in 50 cm^3 of Cu(II)-8-hydroxyimidazo[1,2-a]pyridine solution (20/80 solvent mixture of DMSO/H_2O; 0.15 M in NaCl) for the titration experiments.

Cu(II)	Ligand		
0	16.27(2)	21.70(2)	27.12(3)
6		21.70(2)	
10	16.27(2)	21.70(2)	27.12(2)
14		21.70(2)	

TABLE II

Sample composition (micromolar) in 50 cm^3 of Cu(II)-8-methoxyimidazo[1,2-a]pyridine solution (20/80 solvent mixture of DMSO/H_2O; 0.15 M in NaCl) for the titration experiments.

Cu(II)	Ligand		
0	16.7(2)	21.5(2)	26.0(3)
3		21.5(2)	
6	16.7(2)	21.5(2)	26.0(2)
9		21.5(2)	

The F.I.C.S. program applied in this study represents a modified version of the previously used approach.[5] The major features are as follows. The complexation reaction involving metal ion M, proton H and at least one ligand A, can be represented as

$$pM + qH + rA = M_pH_qA_r$$

where p, q, and r are the stoichiometric coefficients of the complexes.

The equilibria are expressed by the mass balance equations in terms of stoichiometric equlibrium constants β_{pqr} and concentrations at each pH

$$T_i = C_i + \sum_l \beta_l q_{l,i} \pi_i C_i^{l,i}$$

where i labels either metal, proton or ligand. The term $q_{l,i}$ refers to the stoichiometric coefficients of species l, and C_i is the "free concentration".

In analytical potentiometry, it is possible to access an average value of the free concentrations C_i at each pH = v. The basic relationship for complex equilibria is

$$pC_i^v = pC_i^o - \int_{pH^o}^{pH} \left(\frac{\partial T_{i,j}^{*v}}{\partial T_{i,j}^{v}}\right) T_{s,j}^{v}{}_{(s \neq i)}, pH, \theta. \, v^*.dpH$$

where C_i^o is the average free concentration of i ions at the initial pH (pH^o). $T_{i,j}^v$ and $T_{i,j}^{*v}$ are the analytical concentrations of ion i and the concentration of protons liberated, respectively, for each metal ligand ratio j at each pH = v.[6-9] The mathematical analysis of the titration data has been described earlier.[10]

When free ion concentrations are obtained it is possible to propose an extensive set of stoichiometric coeeficients of species and to calculate for each an approximate β_l value and the pH of its maximum concentration. The program calculates the Jacobian elements $J_{l,i=l}^v$ of each species as a function of pH (i = 1 for metal). Examination of the variation of $J_{l,l}^v$ on the pH range reflects the probability of the existence of the species l.

In the following stage a least-squares minimization is performed to refine β_l values. The mass balance equation can be written as the matrix equation JB = Δ where J is the Jacobian matrix and each β_l forms the B matrix.

The elements of matrix Δ are $\delta^v = T_{l,m}^v - C_l^v$. B is decomposed into two matrices B = ξ M. M has the mantissa elements of β_l and the diagonal ξ matrix has the exponents of β_l.

A scale factor is calculated by the relation $S = 1/\sum_{v=1}^{NN} \delta^v$ where NN is the number of pH values considered; $M = [(SJ\xi)^T(SJ\xi)]^{-1} S (SJ\xi)^T$.

Finally β_l values are given in log form by $\log \beta_l = \log m_l + e_l$. A description of the minimization is given in reference 10.

SUPERQUAD is an extremely powerful general purpose computer program which differs distinctly from the F.I.C.S. method. It solves simultaneously the β_l and C_i values using a non linear least-squares algorithm in strict respect to the mass balance equations.[4] It includes some model selection criteria and does not reject negative β_l values during a refinement.

When a new complexation system is studied, the major difficulty which arises when the SUPERQUAD program is applied, is the evaluation of a proper set of species formed. Since the modified F.I.C.S. approach outlined above usually allows the real set of complex species to be predicted easily. The potentiometric results were treated first by F.I.C.S. programs and the obtained model was used in subsequent SUPERQUAD calculations.

Cu(II)-8-hydroxyimidazo[1,2-a]pyridine

The titration curves and the proton liberation as a function of pH are presented in Figures 1 and 2. The 8-hydroxy derivative has two measurable deprotonation constants $pK_1 = 9.25$ and $pK_2 = 5.59$ (Table III). These values correspond to the deprotonation of the 8-hydroxy group and the heterocyclic imidazol nitrogen atom, respectively. Both constants were estimated earlier for aqueous solution[2b] and the

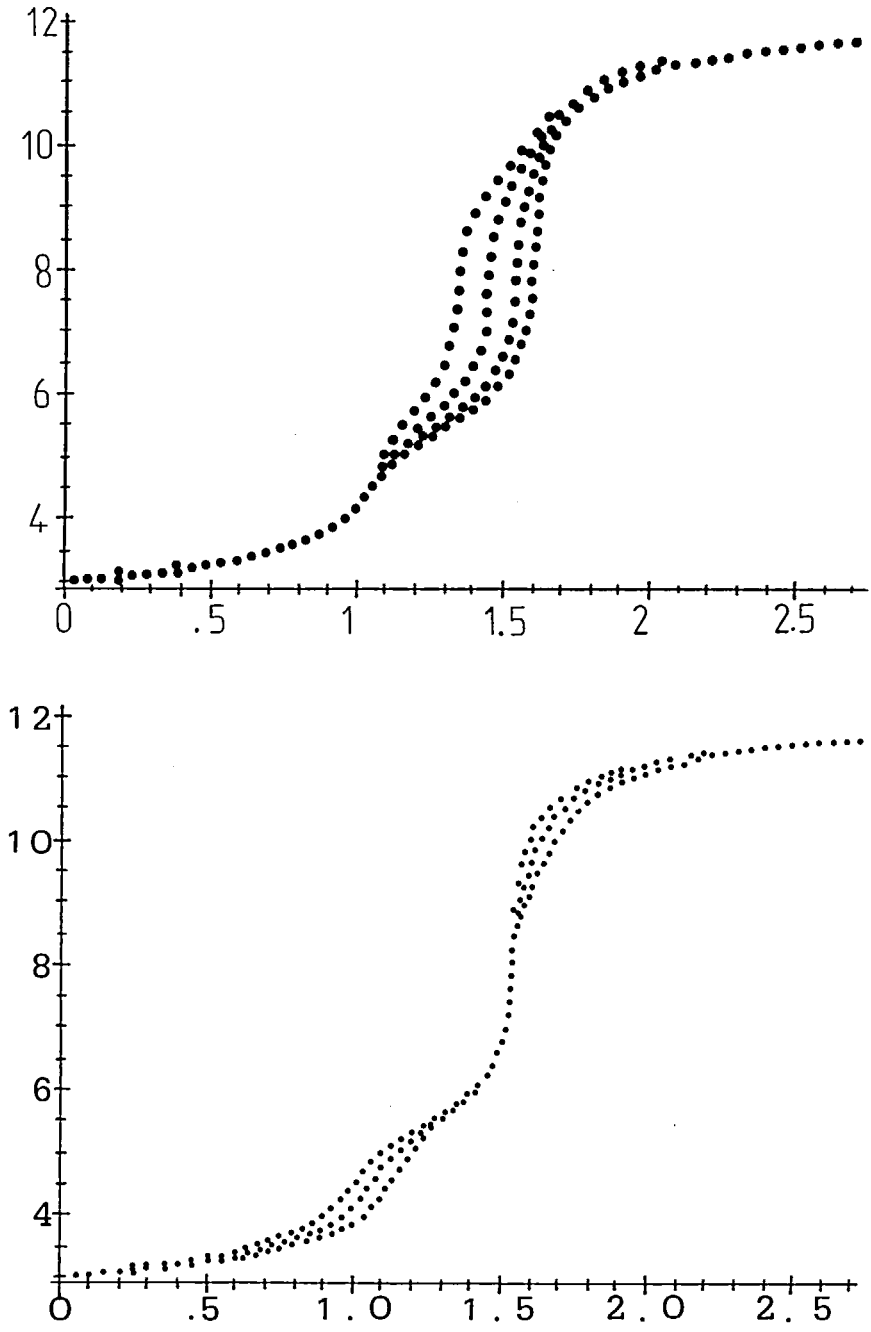

FIGURE 1 Titration curves for the system Cu-H-A (AH_2 = 8-hydroxyimidazo[1,2-a]pyridine); (a): Metal variation: $C_A = 4.34 \times 10^{-4}$M; curve 1, $C_{Cu} = 0$; curve 2, $C_{Cu} = 8 \times 10^{-5}$M; curve 3, $C_{Cu} = 1.4 \times 10^{-4}$M; curve 4, $C_{Cu} = 2 \times 10^{-4}$M; (b): Ligand (A) variation: $C_{Cu} = 1.4 \times 10^{-4}$M; curve 1, $C_A = 3 \times 10^{-4}$M; curve 2, $C_A = 4.34 \times 10^{-4}$; curve 3, $C_A = 5.42 \times 10^{-4}$M.

values obtained are close to those presented in Table III. The I.U.P.A.C. recommended dissociation constants values for oxine, in aqueous solution, are 9.70 and 5.03, respectively.[13]

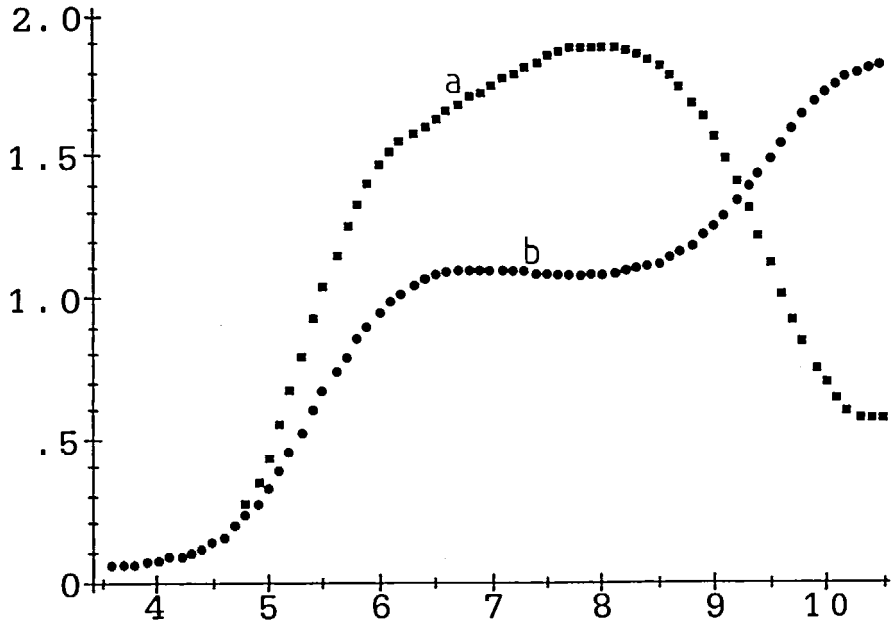

FIGURE 2 Proton liberation as a function of pH for the system Cu-H-A (AH_2 = 8-hydroxyimidazo[1,2-a]pyridine); $C_{Cu} = 1.4 \times 10^{-4}$M, $C_A = 4.34 \times 10^{-4}$M; Curve a: SH^+_1/SC_M; curve b: SH^+/SC_A.

TABLE III

Log values of stability constants (β pqr) for the complex species $Cu_pH_qA_r$ (AH_2 = 8-methoxyimidazo-[1,2-a]pyridine; 20/80 solvent mixture of DMSO/H_2O; 0.15 M in NaCl) at 25°C.

	log β pqr	
Chemical species	F.I.C.S.	SUPERQUAD
HA		9.25 (0.02)
H_2A		14.84 (0.04)
CuHA	13.05	13.35 (0.07)
CuH_2A_2	26.54	
$CuHA_2$	21.22	21.42 (0.03)
CuA_2	15.81	15.47 (0.04)
$CuH_{-1}A_2$	5.49	

Potentiometric calculations indicate the formation of one major species CuA_2 (Figures 3 and 4). The complexation begins at pH 3 by formation of CuAH complex ($\log\beta$ = 13.35, Table III) and reaches a maximum concentration at a pH around 5 (Fig. 3). The value obtained for the stability constant of the latter complex is close to that obtained for the copper mono-oxinate species, *i.e.*, 13.49[11], 13.03[12] or 12.12.[13]

However, the possible binding modes were not discussed in these papers.[11-13] The results presented in Table III for 8-hydroxy and 8-methoxy derivatives (*vide infra*) clearly indicate the formation of a monodentate metalimidazo nitrogen bond in the CuAH species. The value of the equilibrium constant (Cu + AH = CuHA), log k = 4.10, is almost identical to that obtained for a corresponding species (Cu-methyl-2-amino-2-deoxy-*D*-glucose)[14] (log K = 4.13) where metal nitrogen coordination was proposed. This again supports the above assumption about the binding mode in the CuAH species.

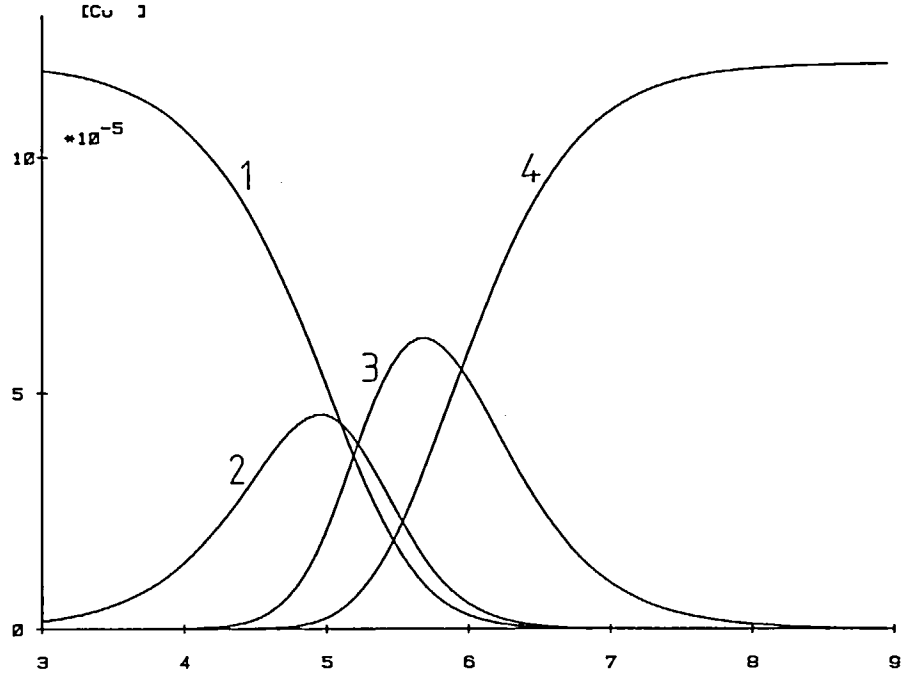

FIGURE 3 Species distribution in the system Cu-H-A (AH_2 = 8-hydroxyimidazo[1,2-a]pyridine) as a function of pH; curve 1: Cu; curve 2: CuHA; curve 3: $CuHA_2$; curve 4: CuA_2.

The species distribution, presented in Fig. 3, also indicates the formation of the CuA_2H complex around pH = 5.7, followed by the CuA_2 complex. The F.I.C.S. calculations also detect in the narrow pH range between 5 and 5.7 the formation of the species CuA_2H_2 which is eliminated by SUPERQUAD refinements, due to its very low concentration (see *e.g.*, refs. 15 and 16). The log K_1 value for CuA_2H_2 (8.04) corresponds well to two monodentate ligands bound *via* their nitrogen donors[14-20] (*vide infra*).

The binding of nitrogen donors to the cupric ion is clearly seen in the absorption spectra which show a considerable shift of the d-d transitions of copper from 800 to 700 nm when the pH increases from 2 to about 6.[14-18] Results strongly suggest cupric ion binding involving one then two nitrogen atoms. It is reasonable that the deprotonation process involves CuH_2A_2 species before the formation of the chelate (N,O) ring as expected in CuH_2A_2, by deprotonation of the phenolic group of one of

the two ligands complexed by nitrogen to copper. The β value for CuH_2A_2 ($\log \beta = 26.54$) can be compared with the values found for the equivalent copper dioxinate species, 26.22,[11] 25.38[12] or 23.[13]

TABLE IV

Log values of stability constants (β pqr) for the complex species $Cu_pH_qA_r$ (AH_2 = 8-methoxyimidazo[1,2-a]-pyridine; 20/80 solvent mixture of DMSO/H_2O; 0.15 M in NaCl) at 25°C.

	log β pqr	
Chemical species	F.I.C.S.	SUPERQUAD
HA		6.025 (0.009)
CuA	3.98	4.26 (0.07)
CuA_2	8.11	7.60 (0.12)

At pH values above 6 the major species formed is the CuA_2 complex in which the chelate ring with the (N,O^-) donor set is most likely present. Thus, this major complex could correspond to that found for the oxine ligand by X-ray structure determinations,[21,22] despite the fact that in the literature no potentiometric data related to this species are available.

The formation of two (N,O^-) chelate rings in Cu(II)-8-hydroxy-imidazo[1,2-a]-pyridine solution is identified by both absorption and E.P.R. spectra. The A// and g// values vary from g// = 2.340 to 2.278 and A// = 145 to 167. The five lines of hyperfine structure (A_N = 15 gauss) observed for the complex solutions at pH > 6 derive from two nitrogen donors bound to the cupric ion. This strongly supports binding modes presented above in CuA_2 or CuA_2H_2 species.

Cu(II)-8-methoxyimidazo[1,2-a]pyridine

The results obtained for the methoxy-derivative (AH) strongly support the conclusion drawn above for the 8-hydroxy compound. The titration curves (Fig. 4) and the calculations show one deprotonation site with a pK value of 6.025 which corresponds to the dissociation of the heterocyclic nitrogen of the imidazole ring.

The methylation of the 8-hydroxyl oxygen is responsible for its poor donor ability towards proton or metal ion. Thus the major species formed between this ligand and cupric ion contain a monodentate metal–imidazole nitrogen bond in mono or bis ligand complexes. The potentiometric and the spectroscopic results show formation of both complex species (Table III) below pH 7. At higher pH precipitation occurs. The CuA species is formed at pH > 3 and reaches a maximum around pH 6. The log K value (4.26) corresponds very well to that found for the corresponding complex of 8-hydroxyimidazo[1,2-a]pyridine (CuAH, 4.10) in which Cu–N monodentate coordination was proposed. The value for the stability constant of the CuA_2 complex of the 8-methoxy derivative (log K = 8.11, Table III) is very close to that found by the F.I.C.S. method for the 8-hydroxy ligand in the CuA_2H_2 species (log K = 8.01, *vide supra*). Thus the results obtained for the 8-methoxy derivative support the findings concerning the minor CuA_2H_2 species mentioned above and clearly indicate the formation of one or two monodentate metal–nitrogen bonds in CuAH and CuA_2H_2 (AH_2 = 8-hydroxyimidazo[1,2-a]pyridine), respectively.

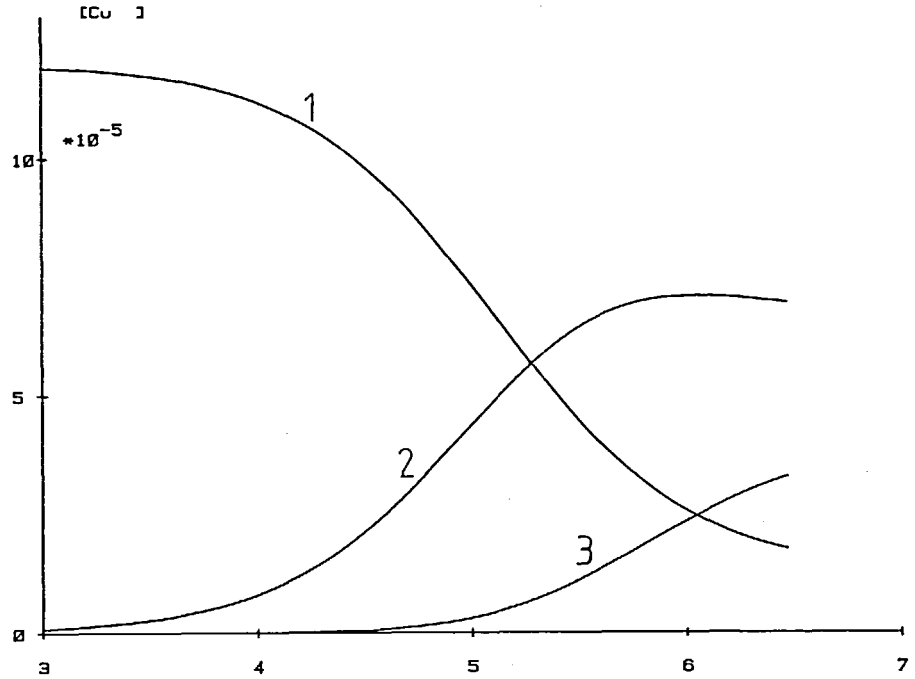

FIGURE 4 Species distribution in the system Cu-H-A (AH = 8-methoxyimidazo[1,2-a]pyridine) as a function of pH; curve 1: Cu; curve 2: CuA; curve 3: CuA_2.

It is clear from this study that CuA_2 species formed by proton dissociation from the CuAH and CuA_2H_2 (*via* CuA_2H) complexes (AH_2 = 8-hydroxyimidazo[1,2-a]-pyridine) are chelated by Cu(II) bound to a (N,O^-) donor set. CuA_2H_2 appears as a minor species which has a slightly higher stability than that proposed for oxine. The stability constant of the major species, CuA_2, described in this work is very high (15.47). This value cannot be compared with the corresponding value for copper oxine system which is not found in the literature.[13]

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