CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200601035

Synthesis, Solution Thermodynamics, and X-ray Study of Cu^{II} [12]Metallacrown-4 with GABA Hydroxamic Acid: An Unprecedented Crystal Structure of a [12]MC-4 with a γ-Aminohydroxamate**

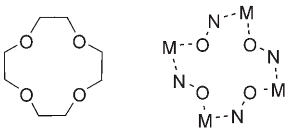
Matteo Tegoni,[a] Luca Ferretti,[a] Francesco Sansone,[b] Maurizio Remelli,[c] Valerio Bertolasi,[d] and Francesco Dallavalle*[a]

Abstract: The solution equilibria of γ-aminobutanehydroxamic acid (GABAha) with H^+ and Cu^{2+} were investigated by potentiometry, titration calorimetry, spectrophotometry, NMR spectroscopy, and ESI-MS. The thermodynamic parameters of the Cu^{II} [12]metallacrown-4 obtained for GABAha were compared with those of the corresponding complexes of (*S*)-α-Alaha and β-Alaha. The stability ($-\Delta G^0$) sequence was β-Alaha ⩾ α-Alaha > GABAha, whereas the order of formation enthalpies ($-\Delta H^0$) was β-Alaha ⩾ GABAha > α-Alaha. These data were interpreted on the basis of the dimensions of the chelate rings and the planarity of the metallamacrocycles. The Cu^{II} [12]metallacrown-4 ([12]MC-4) complex of GABAha was isolated and its crystal structure, which is the first reported for a [12]MC-4 of a γ-aminohydroxamic acid, fully supports the structural features interpreted from the thermodynamic data.

Keywords: aminohydroxamic acids • crown compounds • metallacycles • structure elucidation • thermodynamics

Introduction

Metallacrowns (MC) are a class of compounds belonging to the large family of metallamacrocycles.[1] The molecular architecture of metallamacrocycles (e.g., metallacryptates,[2] molecular squares,[3] metallacalixarenes,[4] metallahelicates,[5] and metallacrowns[1,6]) resembles that of related organic compounds (cryptates, cyclophanes, calixarenes, helicates, and crown ethers, respectively), and is obtained by conceptually replacing the carbon atoms of the organic macrocycle backbone with a metal–heteroatom coordination unit. Thus, topological analogues of [12]crown-4 ligands ([12]C-4) can be constructed, for example, by replacing the two methylene groups of each macrocycle arm with −M−N− coordination units (Scheme 1 and ref. [1]). This structure, called [12]metallacrown-4 ([12]MC-4), is a 12-membered macrocycle capable of encapsulating a core metal ion into a four-oxygen-atom cavity. While [12]MC-4 complexes generally contain Cu^{2+} as a core cation,[1,7,8] for [15]MC-5 complexes, the five-oxygen cavity is of suitable dimensions to encapsulate lanthanide(III),[9] calcium(II),[10] or uranyl(II) ions.[10]



Scheme 1. Macrocyclic backbone of the [12]crown-4 ether and its inorganic analogue, [12]metallacrown-4.

---

[a] Dr. M. Tegoni, Dr. L. Ferretti, Prof. F. Dallavalle
Dipartimento di Chimica Generale ed Inorganica
Chimica Analitica, Chimica Fisica
Università degli Studi di Parma
Viale G.P. Usberti 17A, 43100 Parma (Italy)
Fax: (+39) 0521-905-557
E-mail: francesco.dallavalle@unipr.it

[b] Dr. F. Sansone
Dipartimento di Chimica Organica e Industriale
Università degli Studi di Parma
Viale G.P. Usberti 17A 43100 Parma (Italy)

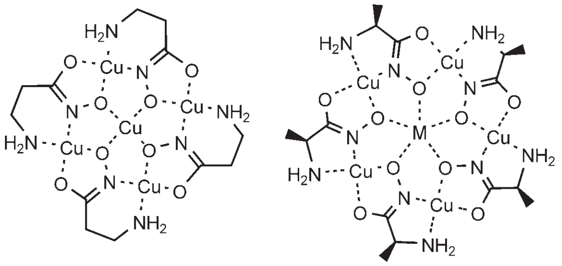
[c] Prof. M. Remelli
Dipartimento di Chimica, Università di Ferrara
Via L. Borsari 46, 44100 Ferrara (Italy)

[d] Prof. V. Bertolasi
Centro di Strutturistica Diffrattometrica
Dipartimento di Chimica, Università di Ferrara
Via L. Borsari 46, 44100 Ferrara (Italy)

[**] GABA = γ-aminobutanoic acid

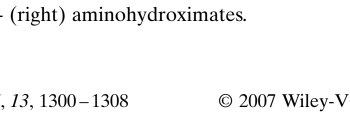
Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author.

Several Cu^{II} metallacrown complexes have been synthesized during the last decade by using aminohydroxamic acids (HL), which can act as (O,O^-)–(NH_2,N^-) bridging bischelating ligands. In particular, [12]MC-4 complexes $[Cu_5L_4H_{-4}]^{2+}$ were synthesized by using β-aminohydroxamic acids (e.g., β-alanine- and β-phenylalaninehydroxamic acids), whereas [15]MC-5 complexes $[M[Cu_5L_5H_{-5}]]^{n+}$ were synthesized by using α-aminohydroxamates (e.g., α-alanine- and α-phenylalaninehydroxamic acids) in the presence of lanthanides(III) or uranyl(II).[1] The structures of [12]metallacrown-4 and [15]metallacrown-5 complexes with β- and α-aminohydroxamates are presented in Scheme 2. Notably, Cu^{II} metallacrowns are only structural, and not functional, analogues of the parent organic compounds, because vacant metallacrowns (with no metal ions in the cavity) have not yet been isolated.[1]



Scheme 2. Structures of the Cu^{II} [12]metallacrown-4 (left) and [15]metallacrown-5 (right) complexes with β- and α-alaninehydroxamate, respectively ($M^{n+} = Ln^{3+}, Ca^{2+}, UO_2^{2+}$).

β- and α-Aminohydroxamic acids satisfy the topological requirements for the synthesis of planar [12]MC-4 and [15]MC-5, respectively. The [12]MC-4 complexes are topologically related to squares in which the metals (or the ligands) are at the vertices, whereas [15]MC-5 complexes are related to pentagons. The theoretical internal angles at the vertices in pentagons are 108°, and in squares, 90°. By bisecting the chelate rings of β-Alaha, we obtain an angle close to 90°, whereas the same angle for α-Alaha is close to 108° (Scheme 3 and ref. [1]). Thus, these units can be considered conceptual building blocks of the metallacrown ensemble. In the case of α derivatives, the wider angle leads to a 15-membered ring to obtain a planar arrangement of the structure. As a result, a [12]MC-4 contains both five- and six-membered rings, whereas a [15]MC-5 contains only five-membered rings. The many publications dealing with this concept constitute the basis of this "metallacrown structural paradigm".[1]



Scheme 3. Structures of the conceptual building blocks of metallacrowns of β- (left) and α- (right) aminohydroximates.

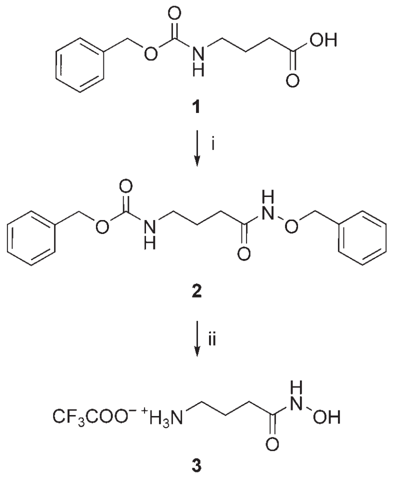
However, since 2001 it has been established that also α-aminohydroxamates can form Cu^{II} [12]MC-4 complexes in solution and a tensioned-cup structure has been proposed.[11,12] More recently, solid pentacopper complexes of (*S*)-α-phenylalanine- and 2-picoline-hydroxamic acids were isolated and characterized,[13] and metallahelicates containing 28 copper(II) atoms were synthesized with D- and L-norvalinehydroxamic acids and characterized by X-ray diffraction.[5] Moreover, we have demonstrated that also the (*S*)-glutamic-γ-monohydroxamic acid, which gives rise to seven-membered (NH_2,N^-) chelate rings, can form a Cu^{II} [12]metallacrown-4 in solution.[14] These results demonstrate that the formation of metallacrowns is also possible in solution by using conceptual building blocks different to those expected by the "metallacrown structural paradigm". In addition, recent papers have reported results of NMR studies on the conversion of α-aminohydroxamates [12]MC-4 into [15]MC-5 induced by lanthanide ions,[13,15] from studying in detail the capability of an appropriate central metal ion to rearrange the building blocks with an expansion of the metallacrown ensemble, as predicted by Pecoraro and co-workers.[9] These data, together with thermodynamic studies, have proved that a metallacrown is a real self-assembly, in which the building blocks are only conceptually defined and not present in solution prior to the metallacrown formation.[12,14] In other words, under favorable experimental conditions, the metal ions and the ligand molecules can directly arrange to form the supramolecular structure.

The aim of the present work was the evaluation of the effect of the $(N_{amine},N_{hydroximate})$ chelate ring dimensions on the thermodynamic parameters (ΔG^0, ΔH^0, ΔS^0) of the [12]MC-4 Cu^{II} complexes of pure α-, β-, and γ-aminohydroxamic acids. For this purpose, we synthesized the γ-aminobutanehydroxamic acid (GABAha, HL) and performed a complete characterization of its protonation and Cu^{II}-complexation equilibria, by means of potentiometry, calorimetry, spectrophotometry, ^1H NMR spectroscopy, and ESI-MS. The structural hypothesis put forward for the $[Cu_5L_4H_{-4}]^{2+}$ metallacrown found in solution was confirmed by X-ray diffraction analysis on a single crystal.

Results and Discussion

Synthesis of γ-aminobutanehydroxamic acid (GABAha): For ligand synthesis, we followed a published procedure that describes as starting point the preparation of *N*-Cbz-protected methyl γ-aminobutanoate. This is then reacted with hydroxylamine and, finally, the Cbz group is removed by catalytic hydrogenation in the presence of HCl.[16] Several attempts to reproduce this synthesis were not completely successful. In fact, in our hands, all of these steps gave yields much lower than those reported, and difficulties were encountered in the purification of both intermediates and the γ-aminobutanehydroxamic acid hydrochloride.

Better results were obtained by exploiting a method based on the use of trichlorotriazine (TCT) as a convenient coupling reagent to obtain hydroxamic acids of *N*-protected amino acids, as described by Giacomelli and co-workers.[17] Under these conditions, the reaction of **1** with *O*-benzyl-hydroxylamine resulted in the isolation of **2** in good yields (Scheme 4, procedure a). A further improvement in the reaction of **1** to **2** was achieved by using ethylchloroformiate as activating agent (Scheme 4, procedure b).[18] Due to the shorter reaction time and the higher yields (>90%), this second route proved to be particularly convenient. The subsequent simultaneous removal of benzyl groups was performed by using hydrogen gas (H_2) and Pd/C (10%) in the presence of trifluoroacetic acid to give 4-aminobutanehydroxamic acid as the trifluoroacetate salt (**3**, GABAha·CF_3COOH) in 60–65% overall yield (Scheme 4 procedure ii). Attempts to remove the protecting groups without acid or in the presence of HCl led to the cyclization of the compound or to hydrolysis of the hydroxamate function, respectively.



Scheme 4. i) Procedure a: NH_2OBn hydrochloride, *N*-methylmorpholine, DMAP, trichlorotriazine, dry CH_2Cl_2, 0°C then RT, 48 h; Procedure b: NH_2OBn hydrochloride, *N*-methylmorpholine, ethylchloroformate, dry CH_2Cl_2, 0°C, 1 h; ii) H_2 (1 atm), Pd/C (10%), CF_3COOH, CH_3OH, RT, 12 h.

Protonation equilibria of GABAha: The thermodynamic parameters (ΔG^0, ΔH^0, ΔS^0) obtained for the protonation of GABAha (HL) and for acetohydroxamic acid (Acha, HL) are listed in Table 1. Acetohydroxamic acid was chosen as a reference for a pure (O,O^-) hydroxamate chelator: the protonation equilibria of this were reinvestigated and gave results in excellent agreement with recent literature data ($\log K = 9.30$, $\Delta H^0 = -22.2\,\mathrm{kJ\,mol^{-1}}$, $\Delta S^0 = 98.3\,\mathrm{J\,K^{-1}mol^{-1}}$).[19] The two protonation processes of the GABAha anion (L^-) overlap and cannot be distinguished by potentiometry.[20]

To elucidate the protonation microequilibria, GABAha was studied by conducting ^1H NMR titrations in D_2O solution. Three sets of chemical-shift values, corresponding to the signals of the three methylene groups, were recorded at appropriate pH values and were processed together in the calculations. The resulting macroconstants (Table 1) are not significantly different from those determined by potentiometry. Figure 1 shows the experimental chemical-shift values of the three groups as a function of pH, superimposed on the species-distribution diagram.

The chemical-shift values of the γ-methylene group, being the closest one to the amino group, were used to determine the protonation microconstants. The χ_p^γ values (the molar fraction of the ligand with the amino group in the protonated form) as a function of pH was computed by using the equation of Szakács and Noszál [Eq. (1)]:[21]

$$\chi_p^\gamma = \frac{\delta^\gamma - \delta_d^\gamma}{\delta_p^\gamma - \delta_d^\gamma} = \frac{1 + (K_{a1} - K_{aA})[H]^{-1}}{1 + K_{a1}[H]^{-1} + K_{a1}K_{a2}[H]^{-2}} \tag{1}$$

Table 1. Overall thermodynamic parameters for protonation and Cu^{2+}-complex formation of GABAha and Acha in aqueous solution. $T = 298.15$ K, $I = 0.1$ M (KCl). Standard deviations on the last figure are given in parentheses.

	GABAha (HL)					Acha (HL)			
	Potentiometry/calorimetry				NMR	Potentiometry/calorimetry			
Species	$\log\beta$	$-\Delta G^0$ [kJ mol^{-1}]	$-\Delta H^0$ [kJ mol^{-1}]	ΔS^0 [J K^{-1} mol^{-1}]	$\log\beta$	$\log\beta$	$-\Delta G^0$ [kJ mol^{-1}]	$-\Delta H^0$ [kJ mol^{-1}]	ΔS^0 [J K^{-1} mol^{-1}]
HL	10.22(1)	58.3	44.2(5)	47(2)	10.19(1)	9.35(1)	53.4	22.4(2)	104.0(6)
H_2L^+	18.92(1)	108.0	67.6(5)	136(2)	18.95(2)	–	–	–	–
σ[a]	1.78	–	–	–	0.01	1.13	–	–	–
U[b]	–	–	9.4×10^{-4}	–	–	–	–	6.1×10^{-4}	–
n[a]	174	–	280	–	75	156	–	248	–
$[CuL]^+$	–	–	–	–	–	7.85(2)	44.8	13.5(3)	105(1)
$[CuL_2]$	–	–	–	–	–	14.01(5)	80.0	27.0(3)	178(1)
$[CuLH]^{2+}$	17.25(1)	98.4	60.2(3)	128(1)	–	–	–	–	–
$[CuL_2H_2]^{2+}$	33.28(3)	189.9	108.0(4)	275(1)	–	–	–	–	–
$[Cu_5L_4H_{-4}]^{2+}$	36.72(6)	209.6	93(2)	391(6)	–	–	–	–	–
σ[a]	2.89	–	–	–	–	3.06	–	–	–
U[b]	–	–	2.0×10^{-4}	–		–	–	7.4×10^{-4}	–
n[a]	275	–	306	–	–	49	–	144	–

[a] $\sigma = [\Sigma w_i(E_i^0 - E_i^c)^2/(n-m)]^{1/2}$ = sample standard deviation; $w_i = 1/\sigma_i^2$, in which σ_i is the expected error on each experimental electromotive force value or chemical-shift value (E_i^0); n = number of observations, m = number of parameters refined. [b] $U = \Sigma w_i(Q_i^0 - Q_i^c)^2$, in which w_i is the statistical weight (unitary in the present work), and Q_i^0 and Q_i^c are the experimental and calculated heats, respectively.

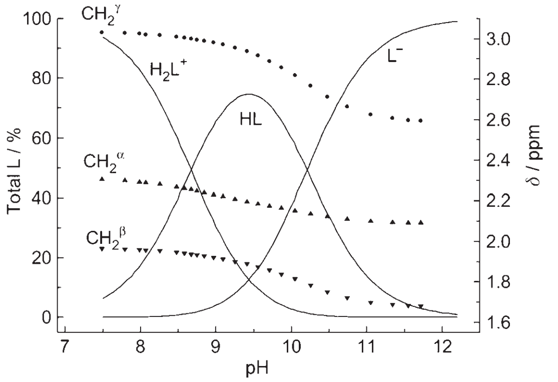
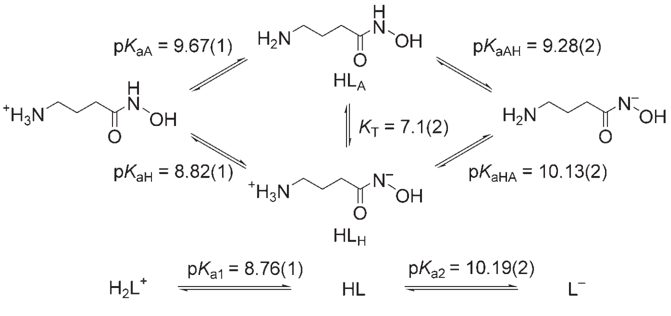


Figure 1. ^{1}H NMR chemical-shift values of the methylene groups for the titration of GABAha in D_2O ($[L]_{tot}=1.66\times10^{-2}$ M).

in which K_{a1} and K_{a2} are the dissociation macroconstants of the ligand obtained by NMR titrations, [H] is the free-proton concentration ($[H]=10^{-pH}$), δ^γ is the observed chemical shift of the methylene group in the γ position at the considered pH value, and δ_p^γ and δ_d^γ are the corresponding chemical-shift values for the γ-methylene group in the H_2L^+ and L^- species, respectively, as determined by using the HypNMR2004 program ($\delta_p^\gamma=3.031(6)$; $\delta_d^\gamma=2.579(8)$).[22] K_{aH}, K_{aA}, K_{aAH}, K_{aHA}, and K_T are the dissociation microconstants, as described in Scheme 5. The observed and expected chemical-shift values for the ^{1}H NMR titration of GABAha, together with the calculated values of δ_p and δ_d for the three methylene groups, are reported in the Supporting Information. Nonlinear least-squares regression on the observed and calculated χ_p^γ gave a $pK_{aA}=9.67(1)$. The other four microconstants were calculated by using Equations (2)–(5):



Scheme 5. Microscopic dissociation equilibria of GABAha. The pK_a values determined by ^{1}H NMR titration are reported, with standard deviations in parentheses.

$$pK_{aH} = -\log(K_{a1}-K_{aA}) \tag{2}$$

$$pK_{aAH} = -\log\left(\frac{K_{a1}K_{a2}}{K_{aA}}\right) \tag{3}$$

$$pK_{aHA} = -\log\left(\frac{K_{a1}K_{a2}}{K_{aH}}\right) \tag{4}$$

$$K_T = \frac{K_{aH}}{K_{aA}} = \frac{[HL_H]}{[HL_A]} = \frac{\chi_H}{\chi_A} \tag{5}$$

in which χ_A and χ_H are the molar fractions of the HL_A and HL_H species, respectively (Scheme 5). The K_T constant indicates that the hydroxamic group is the most acidic ($\chi_H=0.877(3)$), so that the 87.7 % of the HL species is in the zwitterionic HL_H form. It has been reported that the ammonium group is the most acidic in α-Alaha, whereas the most acidic group in β-Alaha is the hydroxamic function.[20] In GABAha, as the length of the spacer between the two groups increases, the pK_a values become closer to those of acetohydroxamic acid and an alkylamine (see below).

Taking into account the protonation microequilibria, the protonation enthalpies for the amino and hydroxamate groups can be calculated by using the Equations (6) and (7):

$$\Delta H_1^0 = \chi_A\Delta H_H^0 + \chi_H\Delta H_A^0 \tag{6}$$

$$\Delta H_2^0 = \Delta H_A^0 + \Delta H_H^0 \tag{7}$$

in which ΔH_1^0 and ΔH_2^0 are the experimental global protonation enthalpies for L^- and HL (Table 1), and ΔH_A^0 and ΔH_A^0 are the protonation enthalpies for the amino and hydroxamate functions, respectively. The same equations can be used for the ΔS_A^0 and ΔS_H^0 calculations. Both enthalpy and entropy values for the protonation of the amino group ($\Delta H_A^0=-47.6(7)$ kJ mol^{-1}, $\Delta S_A^0=40(3)$ J K^{-1}mol^{-1}) are in good agreement with those reported for the amino group of 4-aminobutanoic acid ($\Delta H^0=-51.0$ kJ mol^{-1}, $\Delta S^0=30$ J K^{-1}mol^{-1}).[23] Those of the hydroxamate group ($\Delta H_H^0=-20.0(9)$ kJ mol^{-1}, $\Delta S_H^0=95(3)$ J K^{-1}mol^{-1}) are close to the values of Acha ($\Delta H^0=-22.4$ kJ mol^{-1}, $\Delta S^0=104.0$ J K^{-1}mol^{-1}).

Cu^{2+}/GABAha mononuclear complexes: Table 1 shows the speciation model proposed to interpret the potentiometric data concerning the Cu^{2+}/GABAha system. This model consists of three complexes: $[CuLH]^{2+}$, $[CuL_2H_2]^{2+}$, and $[Cu_5L_4H_{-4}]^{2+}$. Our proposed hypothesis for the coordination of GABAha to Cu^{2+} involves an (O,O$^-$) chelation in both $[CuLH]^{2+}$ and $[CuL_2H_2]^{2+}$, which was confirmed by calorimetric and spectroscopic data, as discussed below. A representative distribution diagram is shown in Figure 2 and the calculated visible spectra of the complex species are reported in Figure 3.

ESI-MS measurements confirmed the presence of $[Cu_5L_4H_{-4}]^{2+}$ and $[CuL_2H_2]^{2+}$ together with peaks attributable to the $[CuL]^+$ and $[CuL_2H]^+$ ions (see Table 2). The latter two species are most likely derived from the deprotonation of $[CuLH]^{2+}$ and $[CuL_2H_2]^{2+}$, respectively. If the two $[CuL]^+$ and $[CuL_2H]^+$ complexes are added to the speciation model previously employed to process the potentiometric data, only the former is successfully retained in the refinement, with a negligible improvement of the curve fitting. In the corresponding distribution diagram (not shown), $[CuL]^+$ is present in the pH range 4.8–6.5, (max. 30 % if Cu/

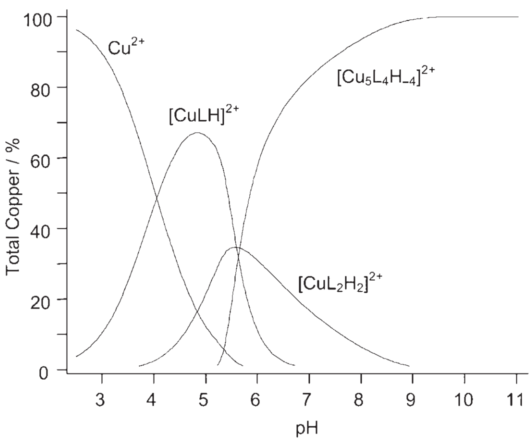


Figure 2. Representative distribution diagram of the system Cu^{2+}/GABAha (Cu/L = 1:2, $[Cu^{2+}]_{tot} = 3.0 \times 10^{-3}$ M).

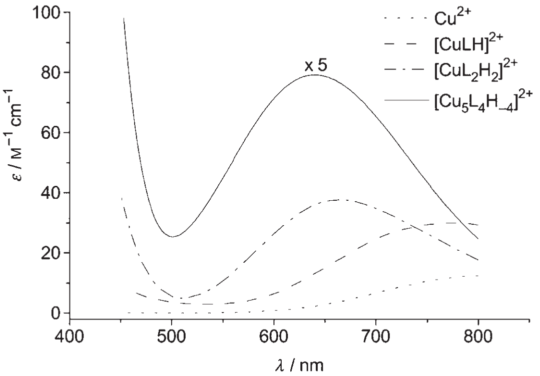


Figure 3. Calculated visible spectra for the Cu^{II} complexes of GABAha.

Table 2. Detected ESI-MS ions for Cu^{2+} complexes with GABAha. The *m/z* values were calculated on the basis of the most abundant peak of the multiplet.

Species	*m/z*	Species	*m/z*
$[[CuL]]^+$	180	$[[Cu_5L_4H_{-4}]]^{2+}$	391
$[[CuL_2H_2]CF_3COO]^+$	294	$[[Cu_5L_4H_{-4}]Cl]^+$	818
$[[CuL_2H]]^+$	298	$[[Cu_5L_4H_{-4}]CF_3COO]^+$	894

L = 1:4). The $[CuL]^+$ stoichiometry requires the deprotonation of the NH_3^+ group at pH ≈ 5, and this can only happen if the proton is displaced by Cu^{2+}. However, a tridentate behavior of the ligand with an additional coordination of NH_2 is prevented by the shortness of the alkyl chain. On the other hand, an alternative bidentate chelation mode with formation of a (NH_2,N^-) seven-membered chelate ring is inconsistent with the behavior of β-alaninehydroxamate, for which a six-membered (NH_2,N^-) chelation was not observed.[7,12] Moreover, if the spectrophotometric data are processed with the inclusion of the $[CuL]^+$ species, meaningless results (negative molar-absorbance values for $[CuL_2H_2]^{2+}$) are produced. In conclusion, only the speciation model reported in Table 1 appears to be reliable. This means that $[CuL]^+$ and $[CuL_2H]^+$ ions observed in the ESI-MS spectra are formed during the ionization process.

Calorimetric results reported in Table 1 show that the formation of mononuclear complexes is both enthalpically and entropically favored. The enthalpic effect for the reaction $Cu^{2+} + LH \rightarrow [CuLH]^{2+}$ can be estimated by subtracting the neat contribution due to the amino-group protonation (−47.6 kJ mol^{-1}, see above) from the ΔH^0 value of $[CuLH]^{2+}$ (−60.2 kJ mol^{-1}, Table 1). The calculated value (−12.6 kJ mol^{-1}) is in very good agreement with the enthalpy of formation of $[CuL]^+$ of Acha (−13.5 kJ mol^{-1}, Table 1), thus, confirming the (O,O$^-$) chelation of GABAha on Cu^{2+}. The bis complexes, $[CuL_2H_2]^{2+}$ of GABAha and $[CuL_2]$ of Acha, give overall enthalpy of formation values (−108.0 and −27.0 kJ mol^{-1}, respectively) that are almost double those for the corresponding 1:1 species (see Table 1), supporting the (O,O$^-$) chelation hypothesis for both ligands.

The same suggestion arises from the inspection of the spectrophotometric parameters obtained for the protonated complexes ($\lambda_{max} = 778$ and 664 nm for $[CuLH]^{2+}$ and $[CuL_2H_2]^{2+}$, respectively, see Figure 3), which are in good agreement with the literature data for ligands behaving as simple hydroxamates (Acha, $[CuL_2]$: $\lambda_{max} = 653$ nm;[24] (*S*)-*N*-(3-hydroxycarbamoyl-propionyl)-proline, [CuL]: $\lambda_{max} = 760$ nm; $[CuL_2]^{2-}$, $\lambda_{max} = 656$ nm[18]).

Cu^{2+}/GABAha [12]MC-4 complex: Both potentiometric results (Table 1 and Figure 2) and ESI-MS spectra (Table 2) agree with the formation of high amounts of the [12]metallacrown-4 $[Cu_5L_4H_{-4}]^{2+}$ at pH > 6.5. The ESI-MS spectra of a Cu^{2+}/GABAha solution at pH 8.10 were recorded at different cone voltages and are reported in the Supporting Information. The most abundant ions are either $[Cu_5L_4H_{-4}]^{2+}$ or $[[Cu_5L_4H_{-4}]CF_3COO]^+$ (*m/z* = 391 or 894, respectively). As the cone voltage increases from 30 to 200 V, a decrease in the intensity of the doubly charged ion in favor of an increasing intensity of the single-charged ions $[[Cu_5L_4H_{-4}]CF_3COO]^+$ and $[[Cu_5L_4H_{-4}]Cl]^+$ was observed. No other significantly intense peaks were observed. Notably, at a cone voltage as high as 200 V, the peak corresponding to the metallacrown complex is still present, whereas significant peaks attributable to fragments of the supramolecular ensemble are absent.

It is interesting to compare the thermodynamic parameters referring to the GABAha metallacrown formation ($\log\beta = 36.72$; $\Delta H^0 = -93$ kJ mol^{-1}, $\Delta S^0 = 391$ J K^{-1} mol^{-1}, Table 1) with those of the corresponding compounds formed by α-Alaha ($\log\beta = 40.16$;[12] $\Delta H^0 = -85$ kJ mol^{-1}, $\Delta S^0 = 484$ J K^{-1} mol^{-1}),[25] and β-Alaha ($\log\beta = 49.39$;[12] $\Delta H^0 = -166$ kJ mol^{-1}, $\Delta S^0 = 388$ J K^{-1} mol^{-1})[25]. $\log\beta$ values indicate that the stability order for the [12]MC-4 is β-Alaha ≫ α-Alaha > GABAha, which is reflected in the starting formation pH of 2.5, 4.5, 6.5, respectively (ref. [12] and Figure 2). Given the constant (O,O$^-$) chelation enthalpy to Cu^{2+} for all metallacrowns, the differences in $-\Delta H^0$ values mainly represent the strength of the (N_{amine},$N_{hydroximate}$) chelation rings. In the case of α-Alaha, this is affected by the nonplanar, tensioned structure of the metallamacrocycle. This determines the $-\Delta H^0$ sequence β-Alaha ≫ GABAha > α-

Alaha, which is different from the stability order. Absorption maxima of β-Alaha, GABAha, and α-Alaha metallacrowns ($\lambda_{max}=611$,[12] 640, 648 nm,[12] respectively) correspond to $\tilde{\nu}_{max(d-d)}=1.637$, 1.563, and $1.543\times10^4\,cm^{-1}$, and represent a decreasing field strength to which less-negative ΔH^0 values (−166, −93, −85 kJ mol^{-1}) correspond. This behavior is in agreement with that reported for Cu^{II} complexes of tetraamines, both linear and cyclic, for which a linear relationship between $\tilde{\nu}_{max(d-d)}$ and ΔH^0 was found.[26]

X-ray data for [12]MC-4 of β-Alaha[7,25] and GABAha (see below) demonstrated the planarity of both complexes; therefore, the principal differences in their structures are the dimensions of the peripheral (N_{amine},$N_{hydroximate}$) chelation rings. Thus, the lower logβ value determined for GABAha [12]MC-4 reflects the weakness of its seven-membered rings with respect to the six-membered rings of β-Alaha. By contrast, even if a tensioned-cup configuration was proposed for the [12]MC-4 of α-Alaha,[12] accounting for its lowest formation enthalpy, the formation of stronger five-membered rings with a more favorable chelate effect accounts for the higher stability of this metallacrown relative to that of GABAha. Thus, the stability of the [12]MC-4 of α-Alaha is determined by mainly entropic factors.

Table 3. Selected bond lengths [Å] and angles [°].

Cu1−O1	1.932(2)	Cu1−O3	1.913(2)
Cu2−Cl1	2.774(1)	Cu3−O1w	2.349(3)
Cu2−O1	1.958(2)	Cu3−O3	1.928(2)
Cu2−O2	1.958(2)	Cu3−O4	1.950(3)
Cu2−N3′	1.996(3)	Cu3−N1	1.961(3)
Cu2−N4′	2.021(3)	Cu3−N2	2.005(3)
O1-Cu1-O1′	180.0	O1-Cu1-O3	91.3(2)
O1-Cu1-O3′	88.7(2)	O3-Cu1-O3′	180.0
Cl1-Cu2-O1	103.0(1)	O1w-Cu3-O3	96.3(1)
Cl1-Cu2-O2	91.3(1)	O1w-Cu3-O4	94.7(1)
Cl1-Cu2-N3′	96.1(1)	O1w-Cu3-N1	92.3(1)
Cl1-Cu2-N4′	88.2(1)	O1w-Cu3-N2	88.8(1)
O1-Cu2-O2	81.2(1)	O3-Cu3-O4	81.2(1)
O1-Cu2-N3′	88.9(1)	O3-Cu3-N1	85.8(1)
O1-Cu2-N4′	165.6(1)	O3-Cu3-N2	173.1(1)
O2-Cu2-N3′	164.8(1)	O4-Cu3-N1	165.8(1)
O2-Cu2-N4′	88.6(1)	O4-Cu3-N2	93.8(1)
N3′-Cu2-N4′	99.0(1)	N1-Cu3-N2	98.7(1)

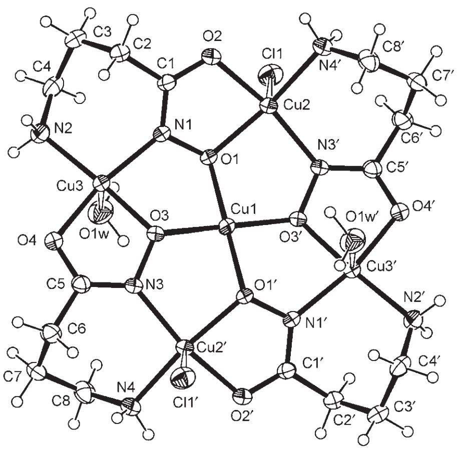


Figure 4. An ORTEP view of the $[[Cu_5L_4H_{-4}]Cl_2(H_2O)_2]$ complex of GABAha showing the thermal ellipsoids at 40 % probability level.

Crystal structure of $[[Cu_5L_4H_{-4}]Cl_2(H_2O)_2]\cdot9\,H_2O$: An ORTEP view of the Cu^{II} metallacrown $[[Cu_5L_4H_{-4}]Cl_2(H_2O)_2]$ with GABAha is shown in Figure 4. Selected interatomic distances and angles are given in Table 3. The complex lies on a crystallographic center of symmetry situated on the central Cu1 atom and assumes a "flattened chair" conformation. The structure consists of 12 chelate rings, from which eight are five-membered, and the (NH_2,N^-) chelation leads to the formation of four puckered seven-membered rings at the corners of the metallacrown complex. The binucleating anionic ligands connect the four peripheral Cu^{II} cations through the hydroximate oxygen atoms and the amino and hydroximate nitrogen atoms. The Cu1 cation is encapsulated in the central cavity and is coordinated in a square-planar mode to four hydroximate oxygen atoms. The Cu2 and Cu3 atoms display a square-pyramidal geometry in which the fifth ligand consists of a Cl$^-$ anion and a water O1w molecule, respectively. The Cu–O and Cu–N distances are in agreement with those of other similar Cu^{II} metallamacrocycles.[7,8,27–30]

The Cu2−Cl1 and Cu3−O1w apical-bond lengths, 2.774(1) and 2.349(3) Å, respectively, are significantly greater than the average Cu−Cl and Cu−Ow bond lengths, 2.323 and 2.189 Å, respectively, in pentacoordinated Cu^{II} complexes.[31] These data are consistent with the Cu−Cl and Cu−Ow apical-bond elongation, due to the Jahn–Teller effect, observed in Cu^{II} complexes.

In the crystal packing, the complexes are arranged in a herring-bone mode (Figure 5) interacting with each other by means of O1w···Cl hydrogen bonds (O1w···Cl1 = 3.155(3) Å). The other water molecules surrounding the metallamacrocycle are linked by hydrogen bonds with N, O,

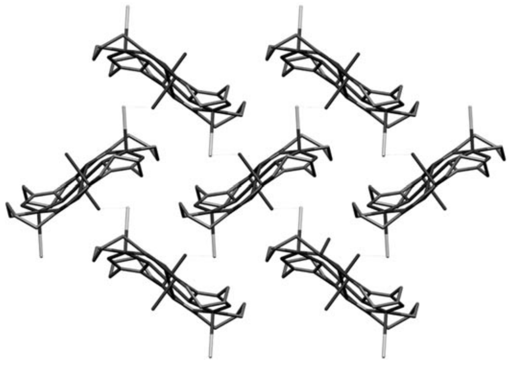


Figure 5. Stick representation of the metallacrown units in the crystal, projected down the crystallographic *a* axis. The neutral complexes are arranged in a herringbone mode and interact with each other by means of O1w···Cl1 hydrogen bonds.

and Cl atoms, stabilizing the crystal packing. The remaining uncoordinated water molecules are in disordered positions.

Conclusion

Comparison of the thermodynamic parameters (ΔG^0, ΔH^0, and ΔS^0) of GABAha and β-Alaha [12]MC-4 complexes showed that the overall stability of the metallamacrocycle of the latter ligand is greatest, which is due to a more favorable enthalpic effect, as the entropic contributions are similar. This confirms the observations of Pecoraro and co-workers that β-aminohydroamates are appropriate for the synthesis of the most stable [12]metallacrown-4 compounds. However, we have demonstrated that γ- and α-aminohydroxamic acids are also capable of forming $\mathrm{Cu^{II}}$ metallacrowns and we have measured their thermodynamic properties in solution. Metallacrowns of γ-aminohydroxamates are the less stable, although their formation is slightly more exothermic than that of α-aminohydroxamates. However, the stability of [12]MC-4 with α-aminohydroxamates is higher than that of γ-aminohydroxamates on the basis of a more favorable formation entropy, determined in particular by a stronger chelate effect for the α derivatives.

The crystal structure of the first $\mathrm{Cu^{II}}$ [12]MC-4 of a γ-aminohydroxamate is reported; it fully supports the structural hypothesis proposed to interpret the thermodynamic data in aqueous solution.

Experimental Section

Materials and instrumentation: Acetohydroxamic acid was purchased from Sigma (St. Louis, MO) and its purity was checked by potentiometry and NMR spectroscopy. Dichloromethane was dried over molecular sieves (4 Å). If not otherwise specified, all solvents were reagent grade and were used without further purification. ^{1}H NMR spectra were collected by using a Bruker Avance 300 MHz spectrometer (partially deuterated solvents were used as internal standards). FTIR spectra (4000–400 $\mathrm{cm^{-1}}$) were recorded by using a Nicolet Nexus FT spectrometer. Electrospray mass spectra were recorded by using a single quadrupole ZMD Mass Spectrometer (Micromass, Manchester, UK) fitted with a pneumatically assisted electrospray probe. Data were processed by using the spectrometer software (MassLynx NT Version 3.4). Elemental analyses (C, H, N, S) were performed by using a Carlo Erba EA 1108 automated analyzer. Visible absorption spectra were recorded by using a Perkin–Elmer Lambda 25 spectrophotometer. Enthalpy values were determined by titration calorimetry using a Tronac model 450 isoperibol calorimeter equipped with a 25-mL reaction vessel.

Synthesis of *N*-carbobenzyloxy-γ-aminobutanoic acid: Benzylchloroformiate (16.7 mL, 50 % mol/mol solution in toluene, 0.05 mol) was added to an aqueous solution (20 mL) of γ-aminobutanoic acid (GABA, 4 g, 0.04 mol) and NaOH (3.1 g, 0.08 mol) cooled at −5°C. The reaction mixture was stirred at this temperature for 1 h and at RT for 3 h, then diethyl ether (20 mL) was added and the organic phase was separated to remove the excess benzylchloroformiate and toluene. The aqueous phase was then acidified with HCl (30 mL, 1 M) and extracted with diethyl ether (20 mL, 3×). The combined organic phases were evaporated at reduced pressure and the product was obtained without further purification as a white solid in 80 % yield. M.p. 63.5–66.3°C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 300 K): $\delta = 12.05$ (s, 1H; OH), 7.32 (m, 6H; Ar and NH), 5.00 (s, 2H; $\mathrm{PhC}H_2$), 3.07–2.92 (m, 2H; $\mathrm{NHC}H_2$), 2.21 (t, $J = 7.2$ Hz, 2H; $\mathrm{C}H_2\mathrm{COOH}$), 1.70–1.57 ppm (m, 2H; $\mathrm{CH_2C}H_2\mathrm{CH_2}$); ^{13}C NMR (75 MHz, [D]CHCl$_3$, 300 K): $\delta = 178.3$ (s; COOH), 156.6 (s; CONH), 136.2 (s; Ar), 128.4, 128.0 (d; Ar), 66.6 (t; $\mathrm{Ph}C\mathrm{H_2}$), 40.1 (t; $\mathrm{NHCH_2}$), 31.0 (t; $C\mathrm{H_2CO}$), 24.7 ppm (t; $\mathrm{CH_2}C\mathrm{H_2CH_2}$); IR (KBr pellet): $\tilde{\nu} = 3333$ (N−H), 1689 (C=O(OH) and C=O(urethane), overlapped), 1549 $\mathrm{cm^{-1}}$ (δN−H); MS (ESI): m/z (%): 260 (85) $[M+\mathrm{Na}]^+$, 282 (100) $[M-\mathrm{H}+\mathrm{Na}]^+$; elemental analysis calcd (%) for $\mathrm{C_{12}H_{15}NO_4}$ (237.26): C 60.75, H 6.37, N 5.90; found: C 60.87, H 6.46, N 5.81.

Synthesis of benzyl *N*-carbobenzyloxy-γ-aminobutanehydroxamate (2): Procedure a: Acid **1** (1.50 g, 6.33 mmol), *N*-methylmorpholine (2.15 mL, 1.96 mmol), dimethylaminopyridine (DMAP, catalytic), and *O*-benzylhydroxylamine hydrochloride (1.3 g, 8.23 mmol) were dissolved in dry $\mathrm{CH_2Cl_2}$ (20 mL) and the solution was cooled at 0°C. 2,4,6-Trichloro-[1,3,5]-triazine (cyanuric chloride, TCT, 0.580 g, 3.16 mmol) was added to the mixture and the reaction was kept at RT for 48 h. The color of the solution changed from bright- to pale-yellow. The reaction mixture was filtered on Celite and washed with HCl (20 mL, 1 M, 3×), 4 % $\mathrm{NaHCO_3}$ aqueous solution (20 mL, 2×), and brine (20 mL). The organic phase was dried with $\mathrm{Na_2SO_4}$, was evaporated to dryness in vacuo, and the solid obtained was triturated with ethyl ether to give the product as a white powder in 70 % yield (1.51 g). Procedure b: Ethylchloroformiate (0.800 mL, 8.40 mmol) and *N*-methylmorpholine (0.922 mL, 8.39 mmol) were added to a solution of acid **1** (2.00 g, 8.39 mmol) in dry $\mathrm{CH_2Cl_2}$ (60 mL) at 0°C and under a $\mathrm{N_2}$ stream. In a separate flask, *N*-methylmorpholine (1.016 mL, 9.24 mmol) was added to a suspension of *O*-benzylhydroxylamine hydrochloride (1.48 g, 9.24 mmol) in dry $\mathrm{CH_2Cl_2}$ (20 mL) at 0°C and under a $\mathrm{N_2}$ stream. The suspension obtained was added to the reaction mixture and the flask was kept at 0°C for 1 h. The solvent was removed in vacuo and the crude material was dissolved in ethyl acetate (200 mL). The organic phase was washed with HCl (100 mL, 1 M, 1×), 4 % $\mathrm{NaHCO_3}$ water solution (100 mL, 1×), and brine (100 mL, 2×), and the solvent was removed in vacuo. The crude white solid obtained was suspended in cold diethyl ether (10 mL) and the product was collected by filtration in 92 % yield. TLC (silica): $\mathrm{CH_2Cl_2}$/methanol 9:1, $R_\mathrm{f} = 0.75$; m.p. 105.1–106.0°C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 300 K): $\delta = 10.97$ (s, 1H; $\mathrm{C(O)N}H\mathrm{OBn}$), 7.32 (m, 11H; Ar and $\mathrm{CbzN}H$), 5.00 (s, 2H; $\mathrm{PhC}H_2\mathrm{OCO}$), 4.77 (s, 2H; $\mathrm{PhC}H_2\mathrm{ONH}$), 3.01–2.93 (m, 2H; $\mathrm{OC(O)NHC}H_2$), 1.96 (t, 2H; $J = 7.8$ Hz, $\mathrm{CH_2C}H_2\mathrm{C(O)NH}$), 1.70–1.58 ppm (m, 2H; $\mathrm{CH_2C}H_2\mathrm{CH_2}$); ^{13}C NMR (75 MHz, [D]CHCl$_3$): $\delta =$ 170.5 (s; CONHOBn), 157.1 (s; OC(O)NH), 136.5, 135.3 (s; Ar), 129.1, 128.5, 128.1, 128.06 (d; Ar), 78.0 ($\mathrm{O}C\mathrm{H_2Ph}$), 66.8 ($C\mathrm{H_2OCO}$), 39.8 (t; $\mathrm{NHCH_2}$), 30.2 (t; $C\mathrm{H_2CO}$), 26.1 ppm (t; $\mathrm{CH_2}C\mathrm{H_2CH_2}$); IR (KBr pellet): $\tilde{\nu} = 3312$ (N−H), 3222 (N−H), 1685 (C=O (urethane)), 1653 (C=O (hydroxamate)), 1553 $\mathrm{cm^{-1}}$ (δN−H); MS (ESI): m/z (%): 365 (100) $[M+\mathrm{Na}]^+$, 707 (10) $[2M+\mathrm{Na}]^+$; elemental analysis calcd (%) for $\mathrm{C_{19}H_{22}N_2O_4}$ (342.40): C 66.65, H 6.47, N 8.18; found: C 66.34, H 6.82, N 8.31.

Synthesis of γ-aminobutanehydroxamic acid trifluoroacetate salt (3): Trifluoroacetic acid (TFA, 0.400 mL, 0.006 mol) was added to a solution of **2** (1.70 g, 0.006 mol) in methanol (30 mL) in which Pd/C (10 %, 300 mg) was previously suspended under nitrogen. Hydrogenation was performed with a Parr apparatus by using $p(\mathrm{H_2}) = 1$ atm. After 2 h, the catalyst was filtered off, the solvent was evaporated in vacuo, and a slightly rubbery product was isolated in 90 % yield, corresponding to the trifluoroacetate salt of **3**. M.p. 85.2–86.9°C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 300 K): $\delta =$ 8.33 (br s, 1H), 2.76 (t, $J = 7.5$ Hz, 2H; $\mathrm{NHC}H_2$), 2.04 (t, $J = 7.5$ Hz, 2H; $\mathrm{CH_2CO}$), 1.73 ppm (q, $J = 7.5$ Hz, 2H; $\mathrm{CH_2C}H_2\mathrm{CH_2}$); IR (KBr pellet): $\tilde{\nu} = 3175$ (N−H), 1642 $\mathrm{cm^{-1}}$ (C=O); MS (ESI): m/z (%): calcd for $\mathrm{C_4H_{10}N_2O_2}$: 118 $[M]^+$; found: 119 (100) $[M+\mathrm{H}]^+$, 102 (10) $[M+\mathrm{H}-\mathrm{OH}]^+$, 86 (5) $[M+\mathrm{H}-\mathrm{NHOH}]^+$; elemental analysis calcd (%) for $\mathrm{C_6H_{11}O_4F_3N_2}$ (232.16): C 31.04, H 4.78, N 12.07; found C 31.22, H 4.75, N 11.99.

Synthesis of $\mathbf{[[Cu_5L_4H_{-4}]Cl_2(H_2O)_2]\cdot 9\,H_2O}$ (HL = GABAha): Solid $\mathrm{CuCl_2\cdot 2\,H_2O}$ (0.63 mmol) was added with stirring to a solution of GABAha (0.50 mmol) in water (10 mL). The solution was then neutralized by adding a KOH solution. Green crystals of the compound $\mathrm{[[Cu_5L_4H_{-4}]Cl_2(H_2O)_2]\cdot 9\,H_2O}$ suitable for X-ray analysis were obtained by slow evaporation of the solvent. IR (KBr pellet): $\tilde{\nu} = 1642\ \mathrm{cm^{-1}}$ (C=O, shoulder at 1638 $\mathrm{cm^{-1}}$), 1557 $\mathrm{cm^{-1}}$ (N−H); MS (ESI): m/z (%): 818 (55)

$[M-11\,H_2O-Cl]^-$; elemental analysis calcd (%) for $C_{16}H_{54}Cl_2Cu_5N_8O_{19}$ (1051.27): C 18.28, H 10.66, N 28.92; found C 18.52, H 10.45, N 28.59.

Potentiometric measurements: Stock solutions of GABAha (ca. 0.03 M) were prepared by weight and their titre was checked by potentiometric titration with standard KOH solutions. Acetohydroxamic acid was dried in vacuo and its solutions prepared by weight. KOH and HCl aqueous solutions (ca. 0.2 M) were prepared by diluting concentrated Merck Titrisol ampoules and were standardized by using the usual procedure of this laboratory.[32] All solutions were prepared by using freshly boiled, doubly distilled water. The titrations were carried out in aqueous solution at $T=298.15\pm0.1$ K and $I=0.1$ M (KCl) under a N_2 stream, using 25-cm^3 samples. The potentiometric apparatus for the automatic data acquisition was described previously.[32] A Hamilton combined glass electrode (P/N 238000) was employed and was calibrated in terms of $[H^+]$ concentration by titrating HCl solutions with KOH ($pH=-\log[H^+]$), as reported previously.[32] The pK_w value was 13.77(1). The protonation constants of GABAha were determined by alkalimetric titration of four samples (4.7–7.1×10^{-3} M). For the Cu^{II} complexation equilibria, eight titrations were carried out by using ligand/copper molar ratios of 0.84:1 to 4:1 and $[Cu^{2+}]_{tot}$ ranging between 1.5 and 4.0×10^{-3} M. The pH range explored was 2.8–11.1. The protonation constants of acetohydroxamic acid were determined by alkalimetric titration of six samples (5.0×10^{-3} M). For the Cu^{II}-complexation equilibria, four titrations were performed using ligand/copper molar ratios of 1:6 and 1:7, with $[Cu^{2+}]_{tot}=1.0\times10^{-3}$ M. The pH range explored was 3.5–6.5; at higher pH values, a precipitate was observed.

Calorimetric measurements: Enthalpy values for both protonation and Cu^{2+} complexation of the ligands were determined by titration calorimetry at $T=298.15\pm0.02$ K and $I=0.1$ M (KCl). The measurements were recorded by titrating in duplicate 25-mL aliquots of solutions, of composition similar to those employed in potentiometry, with standard HNO_3. The reaction heats were corrected for nonchemical contributions[33] and for the dilution heats computed from literature data.[34]

Spectrophotometric and ESI-MS measurements: Cu^{II}-complexation equilibria of GABAha were studied by conducting visible spectrophotometric titrations by recording 17 spectra in the range 400–800 nm (Cu/L = 1:2, $[Cu^{2+}]_{tot}=3.0\times10^{-3}$ M, pH 2.6–10.1). Visible absorption spectra were recorded by using matched quartz cells of 5-cm pathlength and a 0.1 M KCl solution as a reference. The solutions examined were passed from the potentiometric vessel to the thermostatted cuvette by means of a peristaltic pump. Electrospray-assisted mass spectrometric studies were performed on Cu^{2+}/GABAha solutions at appropriate pH values between 3.5 and 9.0 (Cu/L = 1:2.5, $[Cu^{2+}]_{tot}=2.3\times10^{-3}$ M) without the addition of KCl, to avoid the formation of KCl clusters. Samples were analysed by direct infusion at 10 μL min^{-1}. In the positive-ion mode, the conditions were: ES capillary, 3.0 kV; cone, 25–200 V; extractor, 2 V; RF lens, 0.15 V; source block temperature, 80 °C; desolvation temperature, 130 °C; cone and desolvation gas (N_2), 1.6 and 8 L min^{-1}, respectively. Scanning was performed from $m/z=100$–1800. In the negative-ion mode, the conditions were: ES capillary, 3.08 kV; cone, 22 V; extractor, 4 V; RF lens, 0.26 V; source block temperature, 80 °C; desolvation temperature, 130 °C; cone and desolvation gas (N_2), 1.6 and 8 L min^{-1}, respectively. Scanning was performed from $m/z=100$–1800.

^{1}H NMR titration: ^{1}H NMR titration of GABAha was performed by collecting 25 spectra of GABAha in D_2O, at appropriate pH, at 298.15 K. A 0.75-mL sample of **3** in D_2O (1.66×10^{-2} M) was prepared by weight and the pH* was adjusted within the range 7.5–12.1 by addition of small amounts of concentrated NaOD (approximately 0.9 M). No KCl was added to the solution. A Mettler–Toledo U402M3-S7/200 glass microelectrode was calibrated by potentiometric titration in aqueous solution, as described above. The pH-meter reading in D_2O solutions (pH*) was converted into pH as proposed in the literature.[35] NMR spectra were calibrated by using sodium [2,2,3,3-D_4]-3-(trimethylsilyl)propionate (TSP).

Calculations: Protonation and Cu^{2+} complexation constants for GABAha and Acha were calculated from potentiometric data by using the HYPERQUAD2003 program.[36] For each system, the data of different titrations were treated together. Visible spectrophotometric data were treated with the SPECFIT32 program[37] to calculate the molar absorptivity (ε) of the various species, by using the $\log\beta$ values obtained by potentiometry as fixed parameters. The ^{1}H NMR data were treated by using the HypNMR2004 program.[22] Nonlinear least-squares regression calculations were performed by using SPSS 14.[38] ΔH^0 values were computed from the calorimetric data by means of the least-squares program DOEC,[39] which minimizes the function: $U=\Sigma w_i(Q_i^0-Q_i^c)^2$, in which w_i are statistical weights (unitary in the present work), and Q_i^0 and Q_i^c are the experimental and calculated heats, respectively. A literature ΔH_w^0 value of 56.4 kJ mol^{-1} was used in the calculations.[40] Throughout, the precision of each thermodynamic parameter was reported as the standard deviation given by the corresponding least-squares program. This is shown in parentheses as uncertainty on the last significant figure (Table 1).

Crystal structure analysis: The crystal data of compound $[[Cu_5L_4H_{-4}]Cl_2(H_2O)_2]\cdot9\,H_2O$ of GABAha were collected at RT by using a Nonius Kappa CCD diffractometer with graphite-monochromated $Mo_{K\alpha}$ radiation. The data sets were integrated by using the Denzo-SMN package[41] and were corrected for Lorentz, polarization, and absorption effects (SORTAV)[42]. The structures were solved by direct methods (SIR97)[43] and were refined by using full-matrix least-squares with all non-hydrogen atoms anisotropically and hydrogen atoms included on calculated positions, riding on their carrier atoms. Some hydrogen atoms of the water molecules were found in the difference Fourier maps and were taken in fixed position during the refinements. The remaining unidentified hydrogen atoms were not included in the refinement process. The water molecule O6w was disordered and was refined over two positions with occupancies 0.5. All calculations were performed by using SHELXL-97[44] and PARST[45] implemented in the WINGX[46] system of programs. Crystal data are reported in Table 4. CCDC 608266 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

Financial support by the University of Parma (FIL 2005) and the University of Ferrara (ex-60 %) is gratefully acknowledged.

Table 4. Summary of crystal data, intensity measurements, and structure refinement.

formula	$C_{16}H_{36}Cl_2Cu_5N_8O_{10}\cdot9\,H_2O$
M_W	1051.27
crystal size [mm^3]	$0.55\times0.36\times0.10$
crystal system	monoclinic
space group	$C2/c$
a [Å]	28.5625(7)
b [Å]	12.3687(3)
c [Å]	10.7403 (3)
β [°]	96.1564(9)
V [Å^3]	3772.5(2)
Z	4
ρ_{calcd} [g cm^{-3}]	1.851
θ range for data collection [°]	$3.2\leq\theta\leq28.0$
limiting indices	$-37\leq h\leq36$
	$-16\leq k\leq16$
	$-11\leq l\leq14$
T [K]	295
μ [cm^{-1}]	29.95
T_{min}/T_{max}	0.310/0.744
$\Delta\rho_{min}$; $\Delta\rho_{max}$ [e Å^{-3}]	−1.22; 1.33
independent reflections measured	4516
observed reflections [$I\leq2\sigma(I)$]	3605
refinement against	$\lvert F^2\rvert$
final R index (observed reflns)	0.0467
wR (all reflections)	0.1426
S	1.034

---

[1] a) V. L. Pecoraro, A. J. Stemmler, B. R. Gibney, J. J. Bodwin, H. Wang, J. W. Kampf, A. Barwinski, *Prog. Inorg. Chem.* **1997**, *45*, 83–177; b) J. J. Bodwin, A. D. Cutland, R. G. Malkani, V. L. Pecoraro, *Coord. Chem. Rev.* **2001**, *216–217*, 489–516.

[2] M. S. Lah, B. R. Gibney, D. L. Tierney, J. E. Penner-Hahn, V. L. Pecoraro, *J. Am. Chem. Soc.* **1993**, *115*, 5857–5858.

[3] a) M. Fujita, J. Yazaki, K. Ogura, *J. Am. Chem. Soc.* **1990**, *112*, 5645–5647; b) D. H. Cao, K. Chen, J. Fan, J. Manna, B. Olenyuk, J. A. Whiteford, P. J. Stang, *Pure Appl. Chem.* **1997**, *69*, 1979–1986.

[4] H. Rauter, E. G. Hillgeris, A. Erxleben, B. Lippert, *J. Am. Chem. Soc.* **1994**, *116*, 616–624.

[5] J. A. Johnson, J. W. Kampf, V. L. Pecoraro, *Angew. Chem.* **2003**, *115*, 564–567; *Angew. Chem. Int. Ed.* **2003**, *42*, 546–549.

[6] M. S. Lah, V. L. Pecoraro, *J. Am. Chem. Soc.* **1989**, *111*, 7258–7259.

[7] B. Kurzak, E. Farkas, T. Gløwiak, H. Kozłowski, *J. Chem. Soc. Dalton Trans.* **1991**, 163–167.

[8] B. R. Gibney, D. P. Kessissoglou, J. W. Kampf, V. L. Pecoraro, *Inorg. Chem.* **1994**, *33*, 4840–4849.

[9] A. J. Stemmler, T. W. Kampf, M. L. Kirk, B. H. Atasi, V. L. Pecoraro, *Inorg. Chem.* **1999**, *38*, 2807–2817.

[10] A. J. Stemmler, J. W. Kampf, V. L. Pecoraro, *Angew. Chem.* **1996**, *108*, 3011–3013; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2841–2843.

[11] F. Dallavalle, M. Tegoni, *Polyhedron* **2001**, *20*, 2697–2704.

[12] M. Careri, F. Dallavalle, M. Tegoni, I. Zagnoni, *J. Inorg. Biochem.* **2003**, *93*, 174–180.

[13] S. H. Seda, J. Janczak, J. Lisowski, *Inorg. Chim. Acta* **2006**, *359*, 1055–1063.

[14] M. Tegoni, F. Dallavalle, B. Belosi, M. Remelli, *Dalton Trans.* **2004**, 1329–1333.

[15] A. Pacco, T. N. Parac-Vogt, E. Van Besien, K. Pierloot, C. Görller-Walrand, K. Binnemans, *Eur. J. Inorg. Chem.* **2005**, 3303–3310.

[16] H. Hjeds, T. Honoré, *Acta Chem. Scand. B* **1978**, *32*, 187–192.

[17] G. Giacomelli, A. Porcheddu, M. Salaris, *Org. Lett.* **2003**, *5*, 2715–2717.

[18] M. Tegoni, F. Dallavalle, M. A. Santos, *J. Inorg. Biochem.* **2004**, *98*, 209–218.

[19] M. L. Senent, A. Nino, C. Munoz Caro, S. Ibeas, B. Garcia, J. M. Leal, F. Secco, M. Venturini, *J. Org. Chem.* **2003**, *68*, 6535–6542.

[20] E. Farkas, T. Kiss, B. Kurzak, *J. Chem. Soc. Perkin Trans. 2* **1990**, 1255–1257.

[21] Z. Szakács, B. Noszál, *J. Math. Chem.* **1999**, *26*, 139–155.

[22] C. Frassineti, S. Ghelli, P. Gans, A. Sabatini, M. S. Moruzzi, A. Vacca, *Anal. Biochem.* **1995**, *231*, 374–382.

[23] A. E. Martell, R. M. Smith, NIST Standard Reference Database 46, Version 7.0, Gaithersburg (MD, USA), **2003**.

[24] E. Farkas, E. A. Enyedy, G. Micera, E. Garribba, *Polyhedron* **2000**, *19*, 1727–1736.

[25] F. Dallavalle, M. Tegoni, L. Ferretti, F. Sansone, M. Remelli, V. Bertolasi, unpublished results.

[26] L. Fabbrizzi, P. Paoletti, A. B. P. Lever, *Inorg. Chem.* **1976**, *15*, 1502–1506.

[27] M. Orama, H. Saarinen, J. Korvenranta, *Acta Chem. Scand.* **1994**, *48*, 127–133.

[28] J. J. Bodwin, V. L. Pecoraro, *Inorg. Chem.* **2000**, *39*, 3434–3435.

[29] Y. Song, J.-C. Liu, Y.-J. Liu, D.-R. Zhu, J.-Z. Zhuang, X.-Z. You, *Inorg. Chim. Acta* **2000**, *305*, 135–142.

[30] D. Gaynor, Z. A. Starikova, S. Ostrovsky, W. Haase, K. B. Nolan, *Chem. Commun.* **2002**, 506–507.

[31] A. G. Orpen, L. Brammer, F. H. Allen, O. Kennard, D. G. Watson, R. Taylor, *J. Chem. Soc. Dalton Trans.* **1989**, S1–S83.

[32] F. Dallavalle, G. Folesani, R. Marchelli, G. Galaverna, *Helv. Chim. Acta* **1994**, *77*, 1623–1630.

[33] L. D. Hansen, T. E. Jensen, S. Mayne, D. J. Eatough, R. M. Izatt, J. J. Christensen, *J. Chem. Thermodyn.* **1975**, *7*, 919–926.

[34] V. B. Parker, *Thermal Properties of Aqueous Uni-Univalent Electrolytes*, Natl. Stand. Ref. Data Ser. (US Natl. Bur. Stand.) 2, US Government Printing Office, **1965**.

[35] A. Krezel, W. Bal, *J. Inorg. Biochem.* **2004**, *98*, 161–166.

[36] P. Gans, A. Sabatini, A. Vacca, *Talanta* **1996**, *43*, 1739–1753.

[37] R. A. Binstead, B. Jung, A. D. Zuberbühler, SPECFIT Global Analysis System, Version 3.0, Spectrum Software Associates, Marlborough (MA, USA), **2004**.

[38] SPSS 14, SPSS Inc., Chicago (IL, USA), **2006**.

[39] C. Rigano, E. Rizzarelli, S. Sammartano, *Thermochim. Acta* **1979**, *33*, 211–216.

[40] A. Sabatini, A. Vacca, L. Bologni, *J. Chem. Soc. Dalton Trans.* **1981**, 1246–1250.

[41] Z. Otwinowski, W. Minor in *Methods in Enzymology, Vol. 276, Part A* (Eds.: C. W. Carter, R. M. Sweet), Academic Press, London, **1997**, pp. 307.

[42] R. H. Blessing, *Acta Crystallogr. Sect. A* **1995**, *51*, 33–38.

[43] A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. Moliterni, G. Polidori, R. Spagna, *J. Appl. Crystallogr.* **1999**, *32*, 115–119.

[44] G. M. Sheldrick, SHELX-97, Program for Crystal Structure Refinement, University of Göttingen, Göttingen (Germany), **1997**.

[45] M. Nardelli, *J. Appl. Crystallogr.* **1995**, *28*, 659.

[46] L. J. Farrugia, *J. Appl. Crystallogr.* **1999**, *32*, 837–838.

Received: July 18, 2006