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Coordination behaviour of new open chain and macrocyclic peptidomimetic compounds with copper(II)†

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Two valine-derived bis(amino amides) ligands have been prepared and fully characterized. Both compounds contain additional functionalities that implement their basicity and their water solubility. Besides, compound **1** is an open chain ligand, while **2** is a macrocycle. Their protonation constants as well as their stability constants for the formation of the corresponding Cu^{2+} complexes have been determined potentiometrically. Important differences are associated to the macrocyclic effect and to the additional functionalities in the spacer. The presence of an additional amine group and/or the inclusion of a carboxylic side chain in this spacer increase the stabilities of the Cu^{2+}complexes, suggesting its participation in the interaction with the metal. Thus, **2** is the first pseudopeptidic cyclophane of this family displaying the ability to form highly stable metal complexes in water. UV-Vis and ESI-MS were used for analyzing the complex species detected in the speciation diagram.

Introduction

Enzymes are essential for biological processes. In many cases their activity is associated to the presence of metalloenzymes in which metal cofactors mediate the corresponding biological transformations.[1] In particular, for enzymatic systems involving transport of electrons and dioxygen, as well as oxidation and oxygenation processes, the presence of copper is important.[2] The exact properties of those active centers are often related to the coordination geometry of copper. As a diverse family of proteins, copper proteins could be divided into several types.[1d] One classical example is that of azurins, which catalytic center harbors a type 1 copper site.[1d,3] In those systems a carboxylate group, derived from the side chains of aspartate and glutamate, is present. The involvement of a carboxyl group in the coordination environment of the metal center also takes place, moreover, in binuclear enzymes like the metalloenzyme Zn-phosphorotriesterase.[4]

The most common geometries reported for copper complexes include octahedral, tetrahedral,[5] distorted tetragonal,[6] distorted trigonal pyramidal or bipyramidal,[7] and square planar arrangements around the metal center.[8] Copper complexes with open-chain and macrocyclic polydentate amine ligands are frequently pentacoordinate.[9] With this coordination number the complexes can adopt structures that can be described as either square pyramidal (sp) or trigonal bipyramidal (tbp) depending mainly on the actual nature of the ligand. One illustrative example is that of tripodal tetradentate ligands that favour tbp coordination.[10] In this regard, the design and synthesis of ligands functionalized to achieve metal complexation in a biomimetic approach is a challenge of current interest.[11,12]

Although many model complexes use non amino acid ligands mimicking various aspects of the ligand environment in proteins, the development of new ligands based on the presence of amino acid subunits is a fundamental approach in this area.[12,13] In this context, amino acid derived open-chain and macrocyclic compounds have recently drawn much attention in very different fields like synthetic,[14] bioorganic,[15] medicinal,[16] supramolecular chemistry,[17] and catalysis,[18] and recent contributions from our group have shown how minimalistic pseudopeptides derived from simple natural amino acids can have important applications,[19] for instance in the selective recognition of carboxylic acids[20] and amino acid derivatives,[21] and for developing new self-assembled materials[22] or molecular rotors.[21a,23]

Previous studies have revealed the capacity of some C_2-symmetric open-chain pseudopeptides to form stable metal complexes in aqueous solution.[24] However, the same capacity is absent in most of the related pseudopeptidic cyclophanes studied because of their higher lipophilic character, decreasing their water solubility, and the structural strain developed for the coordination of several donor atoms in the macrocycle to the

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same metal center. Taking all this into account, the design and study of macrocyclic pseudopeptides incorporating carboxylate pendant groups coexisting with amino and amide groups is an important target. In such systems, besides the inclusion of additional donor groups, the presence of the carboxylic group can provide an important contribution to the water solubility of the resulting ligand, allowing its study under aqueous conditions of biological relevance.

Here we present our results on the acid–base and coordination properties of the macrocyclic pseudopeptide **2** containing a pendant carboxylic group. The structurally related open-chain pseudopeptide **1**, lacking the carboxylic functionality has also been studied for a better analysis of the effect of the carboxylic group and the macrocyclic nature present in **2**.

Results and discussion

The structure of the ligands (**1–3**) considered in this work is displayed in Chart 1. The synthesis of compounds **1** and **2** is presented in Scheme 1 and follows the general synthetic approaches previously developed by us.[25] The synthesis and study of the open-chain ligand **3**, containing a central spacer of the same length than **1** but lacking the additional amino group has been reported elsewhere.[24] The open-chain bis(amino amide) compound **1** can be easily prepared starting from *N*-Cbz protected valine through the initial formation of the corresponding activated *N*-hydroxysuccinimide ester, coupling with diethylenetriamine and final *N*-deprotection. The *N*-Cbz protected precursor of **1** (Cbz-protected compound **6**) was also a key intermediate for the synthesis of the macrocyclic compound **2**. Nevertheless this synthetic procedure is more complex as it requires a proper definition of the step at which the pendant group is introduced at the central nitrogen atom of the spacer. In this regard, we followed successfully the approach recently used for the preparation of related derivatives containing fluorescent subunits that can act as markers of acidic organelles within live cells.[26] Thus, the open-chain intermediate **6** was reacted with methyl-2-bromoacetate in DMF at 50 °C for 24 h, using K_2CO_3 as the base, to introduce the ester functionalized pendant arm. Then, deprotection of the Cbz group was carried out by hydrogenolysis to provide the intermediate **8**. Reaction of this compound with 1,3-bis(bromomethyl)benzene provided the macrocyclic structure **9** from which, after hydrolysis of the ester group using lithium hydroxide in a 2 : 1 THF–water mixture, the desired cyclic pseudopeptide **2** was obtained in 41% yield. The resulting pseudopeptide is a highly functional macrocycle with a relatively large and flexible cavity, which increases its potential for the interaction with metal cations and its water solubility.

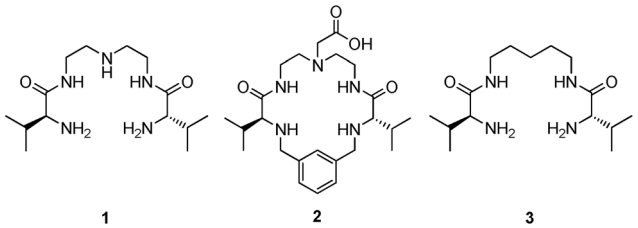
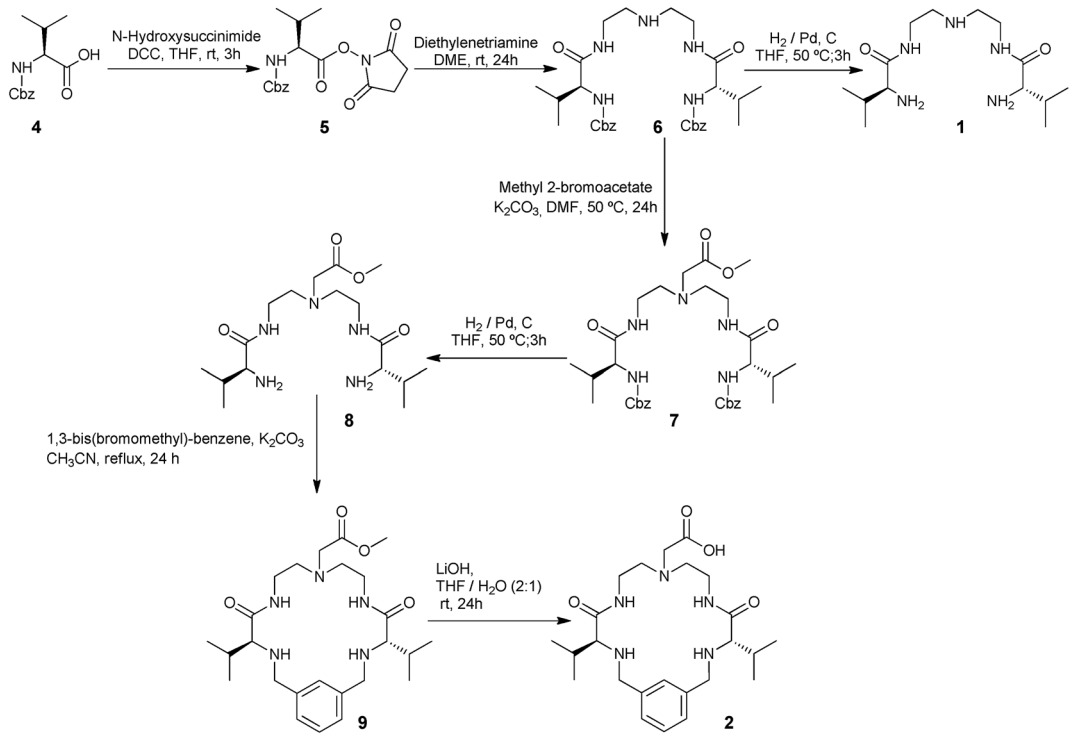


Chart 1 Bis(amino amide) ligands studied in this work.



Scheme 1 Synthetic route for the preparation of the open chain (**1**) and macrocyclic (**2**) pseudopeptidic compounds.

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Acid–base studies

The presence of the additional nitrogen atom in the central spacer, in particular the tertiary one in **2**, and the carboxylic group present in the pendant arm of the macrocyclic derivative **2** must significantly affect the acid–base properties of these compounds when compared to those of related systems (*i.e.* **3**). Thus, the acid–base properties of **1** and **2** were studied using potentiometric titrations. All the titrations were carried out as is fully described in the experimental section, at 298.1 ± 0.1 K using NaCl 0.1 M to maintain a constant ionic strength. The cumulative and stepwise stability constants for the protonation of these pseudopeptidic valine derivates obtained following this methodology are presented in Table 1, along with those for the related compound **3** previously determined.[24] According to their structure, three protonation constants are detected for **1** and four for **2**, while only two protonation constants are present in the related compound **3**. To facilitate the analysis of the data the monoanionic carboxylate derived from **2** has been considered as the L species (see Fig. 1). Charges have been omitted for clarity in the description of the different protonated and complex species.

Table 1 Logarithms of the stepwise protonation constants of pseudopeptidic compounds **1–3** determined in NaCl 0.1 M at 298.1 + 0.1 K

Reaction[a]	**1**	**2**	**3**[b]
$H + L \rightleftharpoons HL$	9.02(1)[c]	10.01(1)	8.11(4)
$H + HL \rightleftharpoons H_2L$	7.86(1)	7.95(1)	7.31(4)
$H + H_2L \rightleftharpoons H_3L$	6.93(1)	6.45(1)	
$H + H_3L \rightleftharpoons H_4L$	—	5.87(2)	

[a] Charges omitted for clarity. [b] Taken from ref. 24. [c] Values in parentheses are the standard deviations in the last significant figure. Values lower than 2 have not been considered. Charges omitted for clarity.

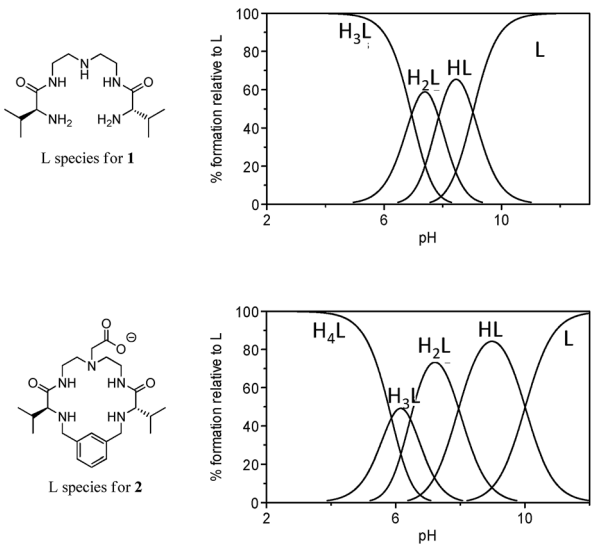


Fig. 1 Distribution diagrams for protonated species of **1** (top) and **2** (bottom) in 0.1 M NaCl at 298.1 K. Charges have been omitted for clarity.

Regarding the values of the stepwise protonation constants, data in Table 1 show that compound **2**, having three basic nitrogen atoms and one basic carboxylate, displays the higher constant ($\log K = 10.01$) for the formation of the [HL] species. This first protonation can be assigned to the carboxylate group or to one of the amine groups, leading to the formation of a neutral or a zwitterionic species. In this regard, computational calculations carried out at the PM3 level revealed a strong stabilization of the zwitterionic structures for **2** relative to the neutral species. In the same way, as could be expected, this first protonation is easier for the open-chain pseudopeptide **1** with three basic nitrogen atoms than for the reference dibasic compound **3** ($\log K = 9.02$ for **1** and 8.11 for **3**). However, the second and third protonation constants are relatively similar for **1** and **2** ($\log K = 7.86$ and 7.95 for $[H_2L]$, 6.93 and 6.45 for $[H_3L]$, respectively). Compound **3** presents a second protonation constant that is only slightly lower that the ones obtained for **1** and **2**. This seems to suggest that the $[H_2L]$ species for **1** and **2** involves the preferential protonation at the two more distant amine nitrogen atoms to reduce the electrostatic repulsion. The higher conformational freedom of the open chain compounds and the more favourable solvation of the primary ammonium groups could partly compensate the effect in **2** of the presence of the carboxylate group. For the macrocyclic ligand a fourth constant is identified, which can be associated with its full protonation, including the acid group in the pendant arm ($\log K = 5.87$).

The resulting distribution diagrams for the protonated species of **1** and **2** are shown in Fig. 1. For the open chain ligand the diagram shows the predominance of non-protonated species (L) at pH values slightly higher than 9. For compound **2**, the anionic species (L), corresponding to the presence of a carboxylate group and non-protonated amino groups, predominates in the very basic region (pH > 10), while the neutral species (HL), is prevalent at the pH range 8–10. In general, the different positively charged species of **2** appear at slightly more acidic regions that those with the same charge in **1**, in particular for the fully protonated species (H_4L for **2** and H_3L for **1**).

The location of the protons in the protonated species is not a simple matter, in particular for **2**, considering the presence of several basic fragments, which leads to the existence of a very complex set of potential protonation equilibria at most protonation steps (see ESI† for protonation equilibria). The ^{1}H NMR spectra obtained at different pH values in D_2O are in agreement with the distribution diagrams obtained and suggest that all the different nitrogen atoms are protonated, at some extent, in the different $[H_xL]$ species. Fig. 2 displays the ^{1}H NMR spectra, at different pH values, for the macrocyclic compound **2** (see ESI† for data regarding compound **1**). The coexistence of several structures for each protonated species is confirmed by the complexity of the spectra at intermediate pH values. Interestingly, the formation of the zwitterionic species seems to involve the protonation of one of the benzylic nitrogen atoms, as the corresponding signals (AB doublets at >3.6 ppm) are the ones experiencing a more significant shift when changing from pH 11.4 to pH 8.3, although the signal corresponding to proton b located in α relative to the tertiary amine group is also slightly

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shifted. On the other hand, the last protonation also seems to affect significantly to this position as shown by the additional changes observed at very acidic pH values. This is also in good agreement with the observation in fluorescent systems related to **2** that full protonation of the benzylic amine groups, required for activating the fluorescence, takes place only at the acidic regions (pK_a = 4.45–4.83).

Determination of the Cu^{2+} complexes formation constants

The interaction of Cu^{2+} and ligands **1** and **2** was systematically studied by potentiometric titrations in aqueous solution over the 2–11 pH range. The stability constants for the formation of Cu^{2+} complexes were determined in water for a 1 : 1 metal–ligand ratio, using 0.1 M NaCl to maintain a constant ionic strength and a temperature of 298.1 K. The results obtained are presented in Table 2 and the corresponding distribution diagrams are displayed in Fig. 3.

The presence of an additional nitrogen donor atom in the central spacer linking the two amino acid subunits provides, as could be expected, the formation of significantly more stable complexes. This is clearly observed when comparing the values of the constants for open chain pseudopeptides **1** and **3**. As shown in the table, these values are at least two orders of magnitude higher for the ligand **1**. This is particularly relevant for the formation of the [CuL] species. The value of this constant for **1** is higher than that reported for ethylenediamine ($\log K$ = 10.60)[27] in spite of the more favourable chelating ring that can be achieved in the case of ethylenediamine, suggesting that more than two nitrogen atoms are involved in the coordination to the metal. The existence of an additional carboxylate donor group in L for **2** provides [CuL] formation constants significantly higher for this ligand. However, if we compare the complex formation constants calculated for the neutral ligands (L for **1** and HL for **2**) the situation is different. Thus, the value of the constant for the formation of the [CuL] dicationic species for **1** ($\log K$ = 11.03) can be compared to that for the dicharged [CuHL] species for **2** (HL + Cu ⇄ CuHL, $\log K$ = 9.28). This seems to preclude a relevant contribution of the macrocyclic effect in this case, most likely for it is counterbalanced by the increase in structural stress associated to the presence of the rigid aromatic ring. As has been observed for other C_2 symmetric pseudopeptides like **3**, ligands **1** and **2** can form stable copper complex through mono- and bisdeprotonation of the N–H amide functional groups, which can be easily monitored through spectroscopic measurements.[24] Both

Table 2 Logarithms of the cumulative and stepwise formation constants for the Cu^{2+} complexes of ligands **1–3** determined in 0.1 M NaCl at 298.1 ± 0.1 K

Reaction[a]	**1**	**2**	**3**[b]
Cu + L ⇄ CuL	11.03(1)[c]	12.19(2)	6.76(1)
Cu + L + H ⇄ CuHL	16.46(1)	19.29(3)	12.51(4)
Cu + L + 2H ⇄ CuH_2L	—	23.73(3)	—
Cu + L ⇄ $CuH_{-1}L$ + H	3.052(2)	2.44(1)	−0.23(2)
Cu + L ⇄ $CuH_{-2}L$ + 2H	−6.457(2)	−7.05(1)	−9.89(3)
Cu + L ⇄ $CuH_{-3}L$ + 3H	−16.96(4)	—	—
CuL + H ⇄ CuHL	5.43(1)	7.10(2)	5.74(3)
CuHL + H ⇄ CuH_2L	—	4.44(3)	—
CuL ⇄ $CuH_{-1}L$ + H	−7.978(1)	−9.75(1)	−7.00(2)
$CuH_{-1}L$ ⇄ $CuH_{-2}L$ + H	−9.509(1)	−9.49(1)	−9.66(4)
$CuH_{-2}L$ ⇄ $CuH_{-3}L$ + H	−10.503(1)	—	—

[a] Charges omitted for clarity. [b] Taken from ref. 24. [c] Values in parentheses are the standard deviations in the last significant figure. Values lower than 2 have not been considered.

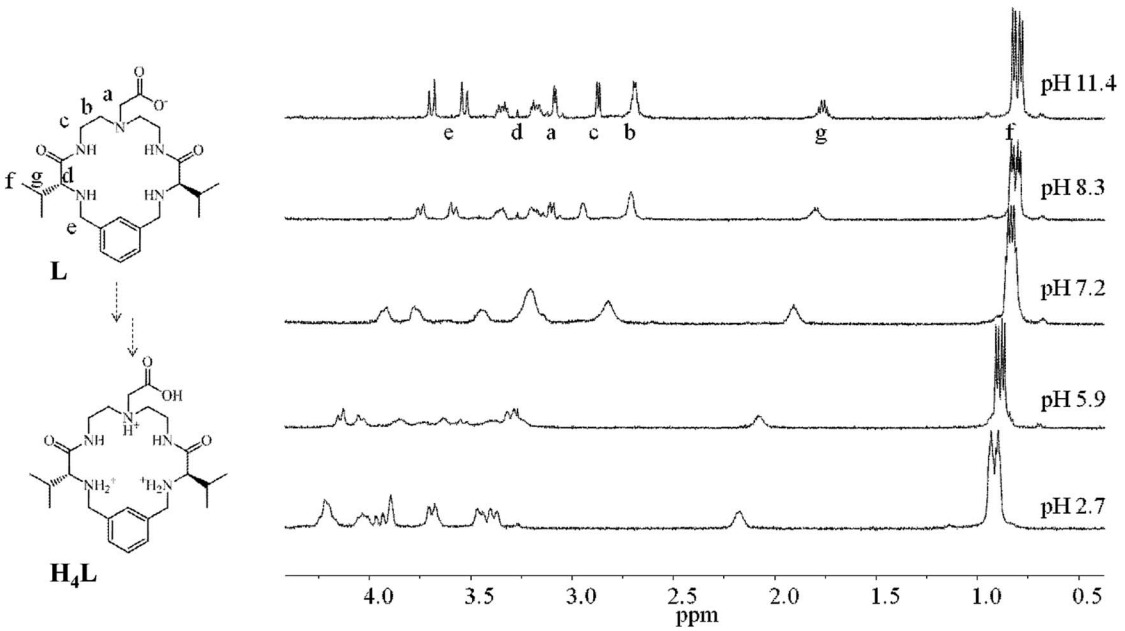


Fig. 2 ^1H NMR spectra in D_2O for the different protonated species derived from compound **2** at different pH values. Major species present according to the distribution diagrams: pH 11.4 (L); pH 8.3 (HL); pH 7.2 (H_2L); pH 5.9 (H_3L); pH 2.7 (H_4L).

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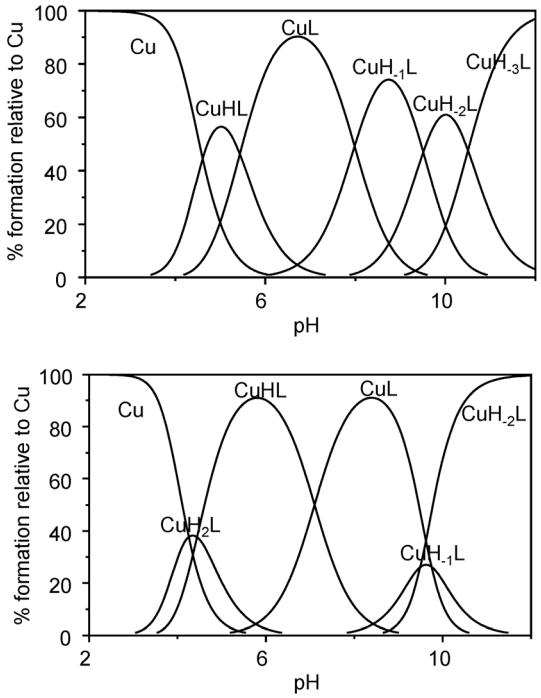


Fig. 3 Distribution diagrams for the systems Cu^{2+}-**1** (top) and Cu^{2+}-**2** (bottom) determined in 0.1 M NaCl. Charges omitted for clarity.

deprotonation steps are detected and should correspond to the formation of the monocationic [$CuH_{-1}L$] and neutral [$CuH_{-2}L$] species for **1** and the neutral [$CuH_{-1}L$] and monoanionic [CuH neutral [$CuH_{-2}L$] species$_2$L] species for **2**. Although, formally, in the case of **2** a species like [$CuH_{-1}L$] could also correspond to the complex formed by the ligand bisdeprotonated at both amide groups and protonated at the carboxyl group, the large difference between the pK_a values for both functionalities seems to preclude this possibility. The analysis of the distribution diagrams is also consistent with this situation, as this species is only present for **2** at pH values around 10 at which the carboxyl group should not be protonated.

It is worth mentioning that the presence of an additional nitrogen atom in the central spacer is not reflected in an increased basicity of the [CuL] complex for **1**, indicating a strong participation of all the amino groups in the coordination to the metal. Thus, the constants determined for the process CuL + H $\rightleftarrows$ CuHL are log $K = 5.43$ for **1** and log $K = 5.74$ for the reference compound **3**. A higher first protonation constant is detected for 2 (log $K = 7.10$), but this must correspond to the protonation of the carboxylate fragment in the monocationic [CuL] species. As a matter of fact, a second protonation for this complex, that should correspond to the protonation of a nitrogen atom, is also detected (log $K = 4.44$). Interestingly, in the case of **1**, the formation of a monoanionic complex species, [$CuH_{-3}L$] is detected, which should correspond to the deprotonation of a coordinated water molecule to form the corresponding hydroxide. Such a complex has not been detected for 3, revealing the important structural differences associated to the presence of the third amino group in the spacer. As this species starts to be present at pH values above 8 (Fig. 3), this could be of interest in the development of catalytic applications and biomimetic models, for instance as simplified HCA mimics.[28] For the macrocyclic ligand **2**, this is not observed as the carboxylate group can coordinate to the copper center instead of the hydroxide anion.

The distribution diagrams for **1** and **2** displayed in Fig. 3 show that species with similar total charge are predominant at each pH region. In both cases, the monocationic and dicationic complexes ([$CuH_{-1}L$] and [CuL] for **1** and [CuL] and [CuHL] for **2**) are the major species identified around neutral pH values. Overall, the macrocyclic ligand **2** represents the first example of this family of pseudopeptidic cyclophanes being able to display a significant capacity to form stable copper complexes in aqueous solutions and for a broad range of pH values.

The use of ESI-MS has been revealed to be of great help for the identification of supramolecular species.[29] Nevertheless, it is important to realize that the nature of the species present in purely aqueous solutions can differ from those under the conditions required for ESI-MS analysis, in particular taking into account that ESI-MS experiments require the use of methanolic solutions or water–methanol mixtures. In spite of this, its potential to detect species even at very low concentrations is a unique feature of this technique.[30] On the other hand, many different studies have shown how ESI-MS allows properly detecting the complex species observed in solution. The identification of metal–ligand species is of particular relevance as the exact nature of the complex can be efficiently confirmed by the analysis of the corresponding isotopic patterns. This has been used previously to confirm the metal complex species formed by ligands related to **3**, revealing that similar results are obtained in methanol and in aqueous solutions containing some methanol.[24] Accordingly, the ESI technique in the positive mode of analysis was used to confirm the species observed at the different pH regions in the distribution diagrams for **1** and **2**. Thus, for instance (Fig. 4), at basic pH values (pH range 9–11) a peak at 403 was clearly detectable for ligand **1** (Fig. 4). This peak can be assigned to the solvated (H_2O) sodium ion adduct of the neutral species [$CuH_{-2}L$], [$CuH_{-2}L + H_2O + Na^+]^+$. The base peak, however, appears at 363 corresponding to the monocationic species [$CuH_{-2}L + H$] obtained from the neutral complex [$CuH_{-2}L$], or directly from the monocationic species [$CuH_{-1}L$]. In addition, a peak at 385 can be assigned to [$CuH_{-2}L + Na^+]^+$, whose +H_2O and +2H_2O species are [$CuH_{-2}L + H_2O + Na^+]^+$ (403) and [$CuH_{-2}L + H_2O + Na^+]^+$ (421), respectively. Complex species formed by the monodeprotonated or bisdeprotonated ligand predominate in solution in this pH region. The second most intense peak appears at 302, corresponding to the protonated free ligand [HL]. The monoanionic [$CuH_{-3}L]^-$ species could not be observed even with the use of the ESI in negative mode.

The ESI^+ MS spectra for the Cu^{+2} complexes with **2** at pH = 11.5 presents a base peak at 545. Taking into account that L has been defined for **2** as monoanionic (see Fig. 1), this peak can be assigned to the monocationic [$CuH_{-2}L + H^+ + Na^+]^+$ species, while the peak at 561 should correspond to the monocationic [$CuH_{-2}L + H^+ + K^+]^+$ species (see ESI†), again in good agreement with the distribution diagram.

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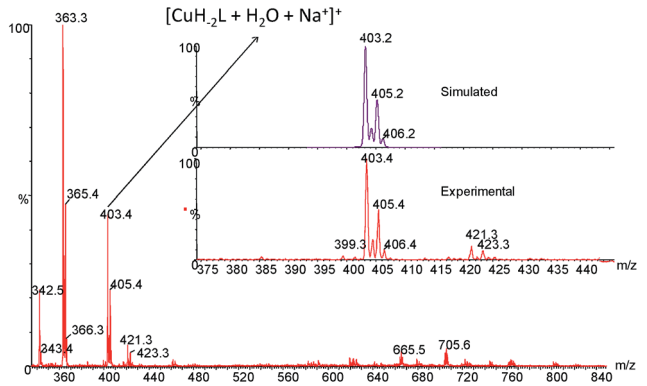


Fig. 4 ESI$^+$-MS spectra for Cu^{2+} complexes with **1** at pH = 11.0 in methanol.

Spectroscopic analyses also provided additional information on the exact nature of the complex species. As for other ligands related to **3**, FT-IR spectra of the Cu^{2+} complexes formed by **1** and **2** under basic condition revealed the participation of deprotonated amide groups, with the observation of the corresponding amide bands at *ca.* 1670 cm^{-1}.[31] Taking advantage of the distribution diagrams presented in Fig. 3, a UV-visible spectroscopic study was carried out, by selecting preferentially those pH regions at which one of the complex species is dominant. A selection of the UV-visible spectra, obtained for **1** and **2** at different pH values are gathered in Fig. 5. The spectral window selected is the region corresponding to the d–d transitions, which provides useful information on the coordination geometries of the respective copper complexes.[9h,32] The respective observed values of λ_{max} are presented in Table 3. Interestingly, the observed pH dependence patterns of the molecular spectra for **1** and **2** are very similar and clearly differ from those reported for tetradentate ligands related to **3** and having different central aliphatic spacers and amino acids side chains.[24] In the case of compounds related to **3**, significant differences are observed in the electronic spectra with changes in the pH that were associated to the presence/absence of deprotonated complexes $[CuH_{-x}L]^{(2-x)+}$. For regions involving the uncomplexed cation or complexes with the fully protonated ligands absorption maxima were observed in the 640–690 range, characteristic for octahedral copper complexes. On the contrary, for regions involving the predominant formation of complexes with deprotonated ligands, the maxima appear at the 490–560 range, corresponding to square planar to square-pyramidal geometries. In the case of ligands **1** and **2**, however, no significant shifts in the maxima are observed for most of the pH values studied, although the intensity of the bands is variable. Only at very acidic pH values, where the uncomplexed Cu^{2+} cation is the major species in solution, the appearance of a new diffuse band at much larger wavelengths and a strong decrease of the original band, accompanied by a shift in its maximum, are detected. In the case of **1**, the observed maxima range from 545 to 549 nm, except for the more acidic region, while for **2** the maxima of the spectra, for the same pH range, appear at 579–590 nm.

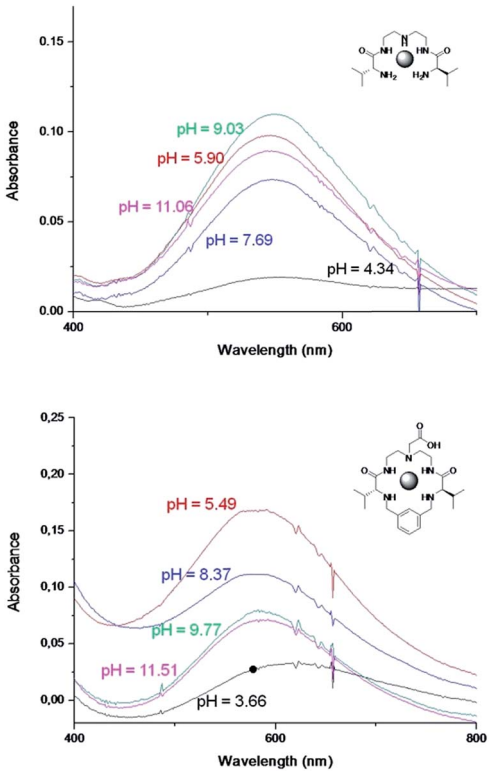


Fig. 5 UV-visible spectra obtained for 1 : 1 Cu : L mixtures for ligands **1** (top) and **2** (bottom) at different pH values.

Table 3 Observed values of λ_{max} for the UV-visible spectra of Cu complexes with **1** and **2** at different pH values

L	pH	λ_{max} (nm)	Major species from distribution diagrams (abundance in %)
1	4.3	555	Cu (45), CuHL (45), CuL (10)
	5.9	545	CuL (70), CuHL (30),
	7.7	546	CuL (60) $CuH_{-1}L$ (40)
	9.0	549	$CuH_{-1}L$ (70), $CuH_{-2}L$ (10), CuL (10)
	11.0	547	$CuH_{-3}L$ (90)
2	3.7	624	Cu (40), CuH_2L (40), CuHL (20)
	5.5	590	CuHL (90)
	8.4	579	CuL (90)
	9.8	583	$CuH_{-1}L$ (30), $CuH_{-2}L$ (30), CuL (30)
	11.5	585	$CuH_{-2}L$ (95)

This should be in good agreement with the maintenance, for the different complex species formed, of a predominant square planar to square-pyramidal geometry (500–600 nm).[9h] This last geometry is common to many complexes formed by pentadentate ligands,[33] and many five-coordinate copper(II) complexes adopt square pyramidal arrangements of the donor atoms around the metal center, in some cases with a clear distortion towards a trigonal pyramidal coordination.[34] For **1**, the square planar base can be easily formed by the two amides and two amine groups from the amino acid moieties, while the additional nitrogen atom or, in basic media, a hydroxide anion could occupy the apical position.

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A similar situation can be expected for the complexes formed by ligand **2**, although in this case we need to take into account the steric constrains imposed by the macrocyclic structure and the presence of the carboxyl/carboxylate group that could act as an additional donor group in the coordination to copper(II). This can lead to distorted square pyramidal complexes or distorted square planar complexes. In some cases, the transition from square pyramidal to trigonal bipyramidal has been observed to be associated to a bathochromic shift from around 550 to *ca.* 600 nm, as is observed here.[33]

Computational models (MMFF) reveal, in good agreement with experimental data, that distorted square planar and square pyramidal geometries can be easily achieved, for instance, for complexes of both deprotonated ligands (see ESI†). They suggest, taking also into consideration former studies with related systems, that a square planar arrangement can be achieved involving the two deprotonated amide groups and two amine nitrogen atoms. The additional coordination to the third amino group, to the carboxylate in **2** or to a water molecule could transform this square planar arrangement into square pyramidal. However, the existence of different possible structural possibilities for those arrangements and the low energy differences calculated for many of them does not allow an unambiguous definition of the coordination geometries in the absence of additional data, in particular crystal structures. Thus, different complex structures could coexist, for instance, for the $[CuH_{-2}L]$ species predominant at the basic region. The same can apply for [CuL] and the related protonated complex species for which an efficient coordination to the metal seems to take place and can involve the amino groups and the carbonyl oxygen atoms of the amide groups. Similar results are obtained in the case of the ligand **1** (see ESI†).

Conclusions

The introduction of a nitrogen atom in the central spacer linking the two amino acid subunits in C_2 symmetric pseudopeptides provides important changes in the properties of the resulting derivatives (*i.e.* **1** and **2**) relative to those of the parent compounds like **3**. The presence of this additional nitrogen atom increases the basicity of the resulting system and the number of donor atoms for coordination to metal ions like Cu(II), but besides, facilitates the building of more elaborated structures as is illustrated in the case of **2**. Overall, this modification significantly increases their solubility in water and affords pentadentate ligands that are able to form more stable Cu(II) complexes than the parent ligand **3**. Copper complex species dominate the distribution diagram for pH values above 5. The geometry of these complexes, having different protonation states, seems to be very similar, most likely from square planar to square-pyramidal, a behaviour clearly divergent from the one found for ligand **3** and related compounds. The existence of a large enough flexible cavity in the case of the macrocyclic compound **2** and the presence of the six potential donor groups in the macrocyclic structure allows the formation of strong metal complexes for this ligand, in spite of the important steric constraints often found for structures of this class like polyaza[*n*]cyclophanes.[35] Thus, the macrocyclic ligand **2** represents the first example of this family of receptors with a significant capacity to form stable copper complexes in aqueous solutions and for a broad range of pH value.

Experimental section

Materials and reagents

All reagents were obtained from commercial sources and used as received unless otherwise stated. Dimethoxyethane (DME) was dried and distilled from molecular sieves (4 Å) and then stored over molecular sieves. Deionised water was used from a Milli-Q water system by Millipore.

Synthesis and characterization of organic compounds

Synthesis of 5. To a clear solution of *N*-Cbz-L-valine **4** (25 g, 99.49 mmol) and *N*-hydroxysuccinimide (11.45 g, 99.49 mmol) at 0 °C was added DCC (20.52 g, 99.49 mmol) in anhydrous THF in a dropwise manner, and the reaction mixture was stirred at 0–5 °C for 3 h. The dicyclohexylurea formed was filtered off and the filtrate was concentrated to dryness. The crude product was recrystallized from 2-propanol to obtain the pure product. Yield 87% (49 g); m.p. 119–120 °C; $[\alpha]_D^{25} = -20.1°$ ($c = 0.1$, $CHCl_3$); IR (KBr) 3360, 1741, 1526 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (δ, ppm): 1.02 (d, 6H, $J = 7.4$ Hz), 1.06 (d, 6H, $J = 7.7$ Hz), 2.31 (m, 1H), 2.77 (s, 4H), 4.66 (dd, 1H, $J = 4.7$ Hz), 5.13 (s, 2H), 5.43 (d, 1H, $J = 9.5$ Hz), 7.28–7.41 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): (δ, ppm): 17.2, 18.7, 25.5, 31.5, 57.4, 67.2, 128.0, 128.1, 128.3, 135.8, 155.6, 167.5, 168.6; anal. calcd (%) for $C_{17}H_{20}N_2O_6$: C, 58.6; H, 5.8; N, 7.7; found: C, 58.1; H, 5.9; N, 8.0.

Synthesis of 6. To a clear solution of the *N*-hydroxysuccinimide ester of *N*-Cbz-L-valine **5** (30.0 g, 86.12 mmol) in anhydrous dimethoxyethane (DME, 250 mL) at 0 °C, diethylenetriamine (4.46 g, 43.06 mmol) dissolved in dry DME (20 mL) was added in a dropwise manner. The reaction mixture was stirred at room temperature for 18 h and then was heated to 40–50 °C for 6 h. The white solid formed was filtered and washed with cold water and cold methanol. Yield 94% (23.27 g), m.p. = 175 °C; $[\alpha]_D^{25} = 11.39°$ ($c = 0.1$, $CHCl_3$); IR (ATR) 3285, 2957, 1685, 1649, 1535, 1236 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) (δ, ppm): 7.83 (s, 2H), 7.38–7.23 (m, 8H), 7.19 (d, 2H, $J = 8.3$ Hz), 5.07–4.94 (m, 4H), 3.83–3.68 (m, 4H), 3.10 (dd, 4H, $J = 12.6$, 6.1 Hz), 1.98–1.84 (m, 2H), 0.82 (d, 12H, $J = 6.1$ Hz). ^{13}C NMR (75 MHz, DMSO-d_6) (δ, ppm): 174.7, 171.8, 156.8, 137.8, 129.0, 128.4, 128.3, 66.1, 61.1, 48.9, 30.9, 19.9, 18.9; HRMS (ESI-TOF)$^+$ Calcd for $C_{30}H_{43}N_5O_6$ (M + H^+) 570.3292. Found 570.3296 (M + H^+); anal. calcd for $C_{30}H_{43}N_5O_6$ H_2O: C, 61.3, H, 7.7, N, 11.9. Found. C, 61.4, H, 7.8, N, 11.9.

Synthesis of 7. A mixture of compound **6** (10 g, 17.55 mmol), anhydrous K_2CO_3 (24.25 g, 175.5 mmol) and methyl bromoacetate (2.68 g, 19.30 mmol) was placed in a flask containing dry dimethylformamide (DMF, 10 mL) and heated to 50 °C for 24 h under nitrogen atmosphere. The reaction was monitored by TLC. After complete consumption of the starting material, distilled water was added (30 mL). This solution was extracted by using ethyl acetate (EtOAc, 30 mL, ×3). The organic phase

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was dried over anhydrous $MgSO_4$ and evaporated under vacuum. The product was purified by silica flash chromatography using $MeOH/CH_2Cl_2$ (1 : 50) to give the white solid **7** (8.19 g, 75% yield): m.p. 156–158 °C; $[\alpha]_D^{25} = -10.45°$ (*c* 0.1, 55 $CHCl_3$); IR (ATR) 3300, 3064, 3031, 2949, 2869, 2360, 1736, 1685, 1644, 1532 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) (δ, ppm): 7.77 (s, 2H), 7.39–7.24 (m, 10H), 7.17 (d, 2H, $J = 8.8$ Hz), 5.00 (m, 4H), 3.78 (t, 2H, $J = 7.9$ Hz), 3.58 (s, 3H), 3.37 (d, 2H), 3.10 (m, 4H), 2.63 (m, 4H), 1.91 (m, 4H), 0.82 (m, 12H); ^{13}C NMR (126 MHz, DMSO-d_6) (δ, ppm): 173.7, 171.5, 139.8, 129.3, 128.6, 127.5, 67.5, 55.7, 55.0, 53.6, 51.5, 37.5, 31.2, 19.5, 18.0; HRMS $(ESI\text{-}TOF)^+$ (*m*/*z*) Calcd for $C_{33}H_{47}N_5O_8$ ($M + H^+$) 642.3503, found 642.3508. Anal. calcd (%) for $C_{33}H_{47}N_5O_8$: C, 61.8, H, 7.4, N, 10.9; found: C, 61.7, H, 7.5, N, 10.9.

Synthesis of 8. To a clear solution of compound **7** (2.00 g, 3.11 mmol) in dry tetrahydrofuran (THF), 10 mol% of the catalyst (5 wt% Pd on activated carbon) was added. The reaction mixture was stirred under an H_2 atmosphere (H_2 balloon) at 50 °C for 4 h. The reaction was monitored by TLC, and after complete consumption of the starting material the catalyst was filtered off through a Celite® bed and washed with THF. The crude product was purified by column chromatography using $MeOH/CH_2Cl_2/NH_3$ (1 : 15 : 0.01) as eluent. Evaporation of the solvent under vacuum yielded the green oil **8** (0.462 g, 80% yield): $[\alpha]_D^{25} = 6.26°$ (*c* 0.1, $CHCl_3$); IR (ATR) 3289, 3073, 2963, 2869, 1736, 1640, 1526 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (δ, ppm): 7.50 (s, 2H), 3.26 (m, 4H), 3.09 (m, 2H), 2.66 (m, 4H), 2.10 (m, 2H), 1.59 (m, 5H), 0.87 (d, 6H, $J = 6.8$ Hz), 0.74 (d, 6H, $J = 6.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm): 174.3, 171.8, 68.2, 54.8, 54.1, 51.0, 43.4, 36.9, 31.2, 19.6, 17.9, 15.2; HRMS $(ESI\text{-}TOF)^+$ (*m*/*z*) Calcd for $C_{17}H_{35}N_5O_4$ ($M + H^+$) 374.2767, found 374.2762. Anal. calcd (%) for $C_{17}H_{35}N_5O_4$: C, 49.9, H, 9.6, N, 17.1; found: C, 49.9, H, 9.7, N, 17.0.

Synthesis of 9. A mixture of compound **8** (0.50 g, 1.33 mmol), anhydrous K_2CO_3 (1.85 g, 13.38 mmol) and 9,10-bis(bromomethyl)-benzene (0.39 g, 1.47 mmol) in dry CH_3CN (175 mL) was stirred to reflux for 24 h under a nitrogen atmosphere. The reaction was monitored by TLC. After complete consumption of the starting material, the reaction mixture was filtered and the solvent was evaporated under vacuum. The crude product was purified by silica flash chromatography using $MeOH/CH_2Cl_2$ (1 : 25) as the eluent to yield the yellowish solid compound **9**. Yield 72% (0.459 g), m.p. 106 °C, $[\alpha]_D^{25} = -24.36$ (*c* = 0.1, $CHCl_3$); IR (ATR) 3323, 2947, 2922, 2856, 1741, 1651, 1592, 1198 cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$) (δ, ppm): 7.68 (s, 2H), 7.38 (s, 1H), 7.26–7.07 (m, 5H), 3.65 (dd, 4H, J = 30.0, 12.1 Hz), 3.53 (s, 3H), 3.42 (d, 2H, $J = 40.9$ Hz), 3.30 (s, 2H), 3.19 (s, 2H), 2.85 (d, 2H, $J = 3.4$ Hz), 2.73 (dd, 4H, $J = 41.5$, 34.7 Hz), 2.06 (d, 2H, $J = 5.3$ Hz), 0.82 (dt, 12H, $J = 62.3$, 31.1 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) (δ, ppm): 174.2, 171.9, 140.1, 129.3, 128.5, 127.6, 67.8, 55.6, 53.6, 51.5, 37.4, 31.3, 19.5, 18.0. HRMS $(ESI\text{-}TOF)^+$ Calcd for $C_{25}H_{41}N_5O_4$ ($M + H^+$) 476.3237. Found 476.3235 ($M + H^+$). Anal. calcd (%) for $C_{25}H_{41}N_5O_4$: C, 63.7, H, 8.7, N, 14.7; found. C, 63.5, H, 8.8, N, 14.7.

Synthesis of 2. To a clear solution of **9** (0.2 g, 0.42 mmol) in 7 mL of THF/H_2O (2 : 1), was added LiOH (0.07 g, 2.94 mmol) and the reaction was stirred at room temperature for 24 h (2 : 1, 3 mL). The reaction was monitored by using TLC; after complete consumption of the starting material, the reaction mixture was acidified (pH 6) by addition of 1 : 1 HBr/H_2O. To this solution was added washed DOWEX® ion exchange resin (4 g), and the mixture was left for 18 h at room temperature. (The standard procedure to wash the DOWEX® ion exchange resin was as follows: 50 mL deionized H_2O, 50 mL MeOH, 50 mL H_20, 50 mL THF, 50 mL H_20, 50 mL 10% NH_3 in H_2O, H_2O till neutral pH, 50 mL 2 M HCl, H_2O till neutral pH). The solvent of this mixture was evaporated under vacuum, and the resulting solid was put in a column containing 20 g washed DOWEX® ion exchange resin and deionized H_2O. The eluents used for the resin column purification were: 100 mL H_2O; 1 : 1 THF/H_2O 100 mL; 5% NH_3 in H_2O. From this resin column purification the compound was isolated by the elution with 5% NH_3 in H_2O. Then the water was evaporated under vacuum to yield the off-white solid **2**. Yield 41% (0.80 g), m.p. 83 °C, $[\alpha]_D^{25} = -31.84°$ (*c* = 0.1, $CHCl_3$), IR (ATR) 3285, 2957, 1685, 1649, 1535 cm^{-1}; ^1H NMR (500 MHz, D_2O) (δ, ppm): 7.46–7.27 (m, 3H), 7.14 (s, 1H), 3.83 (d, 2H, $J = 12.9$ Hz), 3.68 (d, 2H, $J = 13.0$ Hz), 3.44–3.31 (m, 2H), 3.19 (dd, 2H, $J = 18.6$, 8.9 Hz), 3.13 (d, 2H, $J = 19.2$ Hz), 3.07 (d, 2H, $J = 5.9$ Hz), 2.74 (d, 4H, $J = 4.8$ Hz), 1.85 (dt, 2H, $J = 11.2$, 5.6 Hz), 0.83 (dd, 12H, J = 14.6, 6.8 Hz). ^{13}C NMR (126 MHz, D_2O) (δ, ppm): 178.3, 173.7, 136.1, 131.1, 129.7, 128.8, 71.5, 65.8, 57.3, 53.9, 50.9, 37.1, 31.0, 18.4, 17.8. HRMS $(ESI\text{-}TOF)^+$ Calcd for $C_{24}H_{39}N_5O_4$ ($M + H^+$) 462.3080. Found 462.3082 ($M + H^+$). Anal. calcd (%) for $C_{24}H_{39}N_5O_4 \cdot H_2O$: C, 60.1, H, 8.6, N, 14.6; found. C, 60.0, H, 8.6, N, 14.9.

Synthesis of 1. To a clear solution of compound **6** (10.0 g, 17.55 mmol) in dry tetrahydrofuran (THF), 10 mol% of the catalyst (5 wt% Pd on activated carbon) was added. The reaction mixture was stirred under an atmosphere of H_2 (H_2 balloon) at 50 °C for 4 h. The reaction was monitored by TLC, and after complete consumption of the starting material the catalyst was filtered off through a Celite® bed and washed with THF. The crude product was purified by column chromatography using $MeOH/CH_2Cl_2$ (1 : 15 : 0.01) as eluent. Evaporation of the solvent under vacuum yielded the white solid **1**. Yield 88% (4.69 g). ^1H NMR (300 MHz, $CDCl_3$) (δ, ppm): 7.50 (s, 2H), 3.34 (d, 4H, $J = 5.7$ Hz), 3.20 (d, 2H, $J = 3.6$ Hz), 2.76 (t, 4H, $J = 5.7$ Hz), 2.30–2.19 (m, 2H), 1.52 (s, 3H), 0.96 (d, 6H, $J = 6.9$ Hz), 0.82 (d, 6H, J = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm): 174.7, 77.5, 77.0, 76.6, 60.4, 48.7, 38.8, 31.0, 19.7, 16.2; ESI-MS $m/z = 302.2$ ($M + H^+$). Anal. calcd (%) for $C_{14}H_{31}N_5O_2$: C, 55.8, H, 10.4, N, 23.3; found. C, 56.0, H, 10.5, N, 23.5.

Electromotive force measurements. The potentiometric titrations were carried out at 298.1 ± 0.1 K using NaCl 0.1 M as supporting electrolyte. The experimental procedure (burette, potentiometer, cell, stirrer, microcomputer, *etc.*) has been fully described elsewhere.[36] The acquisition of the emf data was performed with the computer program Crison Capture. The reference electrode was an Ag/AgCl electrode in saturated KCl solution. The glass electrode was calibrated as a hydrogen-ion concentration probe by titration of previously standardized amounts of HCl with CO_2-free NaOH solutions and the equivalent point determined by the Gran's method, which gives the standard potential, $E^{\circ\prime}$, and the ionic product of water [pK_w = 13.78(1)]. The computer program HYPERQUAD was used to

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calculate the protonation and stability constants,[37] and the HySS program was used to obtain the distribution diagrams.[38] The pH range investigated was 2.0–12.0 and the concentration of the metal ions and of the ligands ranged from 1×10^{-3} to 5×10^{-3} M with Cu^{2+} : L molar ratios as 1 : 1. The different titration curves for each system (at least two) were treated either as a single set or as separated curves without significant variations in the values of the stability constants. Finally, the sets of data were merged together and treated simultaneously to give the final stability constants.

NMR measurements. The ^{1}H spectra were recorded on a Varian INOVA 500 spectrometer (500 and 125 MHz for ^{1}H and ^{13}C NMR, respectively). The solvent signal was used as a reference standard. Adjustments to the desired pH were made using drops of DCl or NaOD solutions. The pD was calculated from the measured pH values using the correlation, pH = pD − 0.4.[39]

Mass spectrometry. Mass spectra were recorded on a hybrid QTOF I (quadrupole-hexapole-TOF) mass spectrometer with an orthogonal Z-spray-electrospray interface (Micromass, Manchester, UK) either by electrospray positive mode (ES+) or by electrospray negative mode (ES−). The desolvation gas as well as nebulizing gas was nitrogen at a flow of 700 L h^{-1} and 20 L h^{-1} respectively. The temperature of the source block was set to 120 °C and the desolvation temperature to 150 °C. A capillary voltage of 3.5 and 3.3 KV was used in the positive and negative scan mode, respectively. The cone voltage was typically set to 20 V to control the extent of fragmentation of the identified ions. Sample solutions were infused *via* syringe pump directly connected to the ESI source at a flow rate of 10 mL min^{-1}. The observed isotopic pattern of each intermediate perfectly matched the theoretical isotopic pattern calculated from their elemental composition using the MassLynx 4.0 program.[40]

UV spectroscopy. UV-Vis absorption spectra were recorded in MeOH, in a Hewlett-Packard 8453 apparatus, using solutions (1×10^{-3} M) at different pH values containing 1 : 1 ligand to metal molar ratios. Additional experiments were carried in NaCl 0.1 M solutions. Only minimal differences were observed in this case.

IR spectroscopy. FTIR spectra were acquired on a JASCO 6200 instrument with a MIRacle single-reflection ATR diamond/ZnSe accessory. The raw IR spectral data were processed with the JASCO spectral manager software. Solutions (2×10^{-3} M) at different pH values containing 1 : 1 ligand to metal molar ratios were used for those experiments.

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