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Monopicolinate Cyclen and Cyclam Derivatives for Stable Copper(II) Complexation

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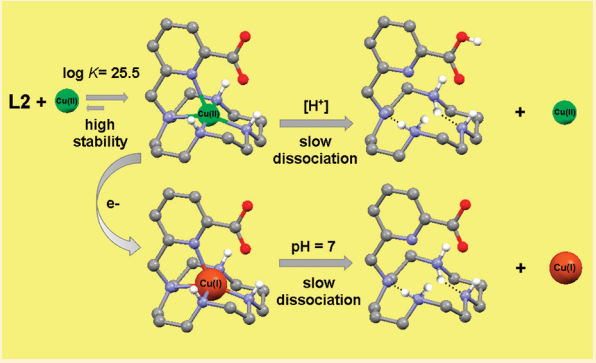
Supporting Information

ABSTRACT: The syntheses of a new 1,4,7,10-tetraazacyclododecane (cyclen) derivative bearing a picolinate pendant arm (H**L1**), and its 1,4,8,11-tetraazacyclotetradecane (cyclam) analogue H**L2**, were achieved by using two different selective-protection methods involving the preparation of cyclen-bisaminal or phosphoryl cyclam derivatives. The acid−base properties of both compounds were investigated as well as their coordination chemistry, especially with Cu^{2+}, in aqueous solution and in solid state. The copper(II) complexes were synthesized, and the single crystal X-ray diffraction structures of compounds of formula $[Cu(HL)](ClO_4)_2{\cdot}H_2O$ (L = **L1** or **L2**), $[Cu\mathbf{L1}](ClO_4)$ and $[Cu\mathbf{L2}]Cl{\cdot}2H_2O$, were determined. These studies revealed that protonation of the complexes occurs on the carboxylate group of the picolinate moiety. Stability constants of the complexes were determined at 25.0 °C and ionic strength 0.10 M in KNO_3 using potentiometric titrations. Both ligands form complexes with Cu^{2+} that are thermodynamically very stable. Additionally, both H**L1** and H**L2** exhibit an important selectivity for Cu^{2+} over Zn^{2+}. The kinetic inertness in acidic medium of both complexes of Cu^{2+} was evaluated by spectrophotometry revealing that $[Cu\mathbf{L2}]^+$ is much more inert than $[Cu\mathbf{L1}]^+$. The determined half-life values also demonstrate the very high kinetic inertness of $[Cu\mathbf{L2}]^+$ when compared to a list of copper(II) complexes of other macrocyclic ligands. The coordination geometry of the copper center in the complexes was established in aqueous solution from UV−visible and electron paramagnetic resonance (EPR) spectroscopy, showing that the solution structures of both complexes are in excellent agreement with those of crystallographic data. Cyclic voltammetry experiments point to a good stability of the complexes with respect to metal ion dissociation upon reduction of the metal ion to Cu^+ at about neutral pH. Our results revealed that the cyclam-based ligand H**L2** is a very attractive receptor for copper(II), presenting a fast complexation process, a high kinetic inertness, and important thermodynamic and electrochemical stability.



INTRODUCTION

Copper complexation is currently attracting a huge amount of research interest owing to the importance of the complexes of Cu^{2+} in numerous fields, such as the preparation of biomimetic complexes of copper-dependent enzymes,[1] cation detection and sensing,[2] or the development of metal-based imaging and therapeutic agents.[3] Indeed, significant progress has been achieved in the past years in nuclear medicine to find stable chelates of radioactive copper ions, particularly ^{64}Cu and ^{67}Cu. The use of these radioisotopes for PET (Positron Emission Tomography) imaging and RIT (RadioImmunoTherapy) requires the development of specific ligands able to form highly stable complexes with the radioactive metal ions to avoid their transchelation in biological media. Therefore, complexes of Cu^{2+} suitable for use as radiopharmaceuticals must be thermodynamically stable and kinetically inert in the highly competitive biological media. An important affinity of the ligands for Cu^+ ions is also required to prevent the complex dissociation upon reduction of the metal ion at physiological pH.[4] Besides, taking into account the relatively fast decay properties of ^{64}Cu and ^{67}Cu (12.7 and 62 h, respectively),[5] the complex formation must be fast enough to avoid significant activity losses before administration of the radiopharmaceutical. The use of ^{64}Cu- and ^{67}Cu-based radiopharmaceuticals also requires the design of bifunctional chelators allowing the labeling of monoclonal antibodies with the radionuclide of interest.[6] Consequently, there is an increasing interest in the synthesis of new chelating agents that fulfill these requirements, as well as in performing detailed investigations of the

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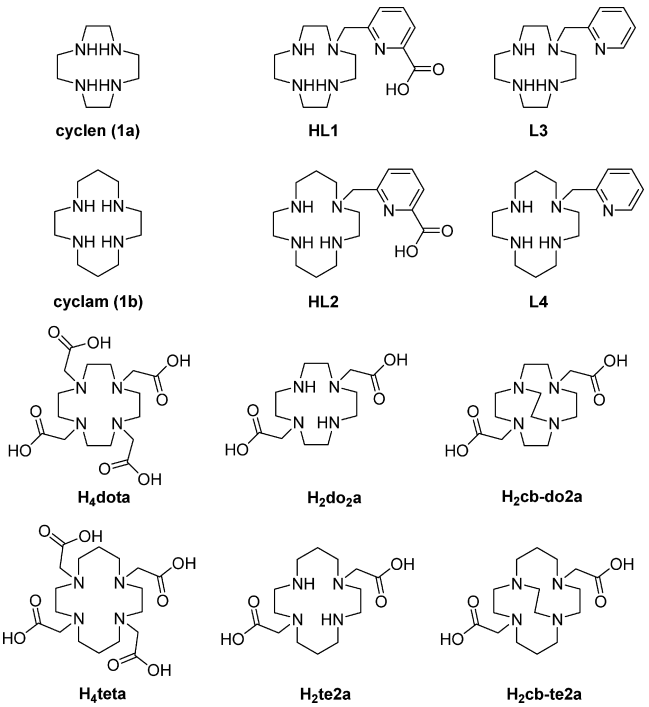
thermodynamic, kinetic, and electrochemical properties of the corresponding Cu^{2+} complexes.

Different nonmacrocyclic bifunctional chelators for Cu^{2+} radioisotopes have been reported in the literature.[7] Cage-like chelators have also been developed for successful Cu^{2+} chelation, such as the family of hexamine cages reported by Sargeson, which show intriguing properties.[8] However, among the potential chelators used for complexation of Cu^{2+}, tetraazamacrocycles continue to attract the interest of organic, inorganic, and biochemists owing to their ability to form complexes with very high thermodynamic, kinetic, and electrochemical stability with respect to metal dissociation. Cyclen (**1a**) or cyclam (**1b**) macrocyclic derivatives bearing additional coordinative pendant arms are of particular interest, as their properties and selectivity for some metal ions may be rather different from those of their nonfunctionalized parents.[9] While complexation studies of heavy metal or lanthanide ions have focused mainly on fully *N*-substituted derivatives,[10] mono-, di-, tri-, and tetra-alkylated macrocycles were all involved in transition metal coordination studies, including complexes with Cu^{2+} ions.[11]

So far, tetraazacycloalkane derivatives such as H_4dota, H_2do2a, H_4teta, and H_2te2a (Chart 1), or closely related

Chart 1. Structure of the Ligands Discussed in This Work



derivatives, have been commonly chosen as copper chelators for numerous applications including radiolabeling. These ligands have been widely used in the literature thanks to their commercial availability as well as their relatively fast complexation kinetics and their good thermodynamic stability. However, these complexes are not sufficiently inert at physiological pH, especially in their reduced Cu^{+} forms. To address this issue, cross-bridged cyclam and cyclen derivatives such as H_2cb-do2a, H_2cb-te2a, and related systems (Chart 1) were designed by us and others, and have shown to form extremely inert complexes with Cu^{2+} and Cu^{+}.[12,13] Nevertheless, these complexes are less thermodynamically stable than the parent nonbridged derivatives, and the proton-sponge properties of these constrained ligands lead to dramatic slow complexation kinetics, which constitutes an important drawback for their application as radiopharmaceuticals.[12a]

Therefore, the current challenge is to find new cyclen- or cyclam-based ligands able to combine better all the required properties. With this in mind, we decided to investigate the behavior of cyclen and cyclam ligands containing picolinate groups. We and others proved that azamacrocycles containing picolinate pendant arms provide strong binding to different metal ions, such as the Ln^{3+}, Zn^{2+}, Cd^{2+}, Pb^{2+}, or Sr^{2+}.[14,15] In addition, their complexes are soluble in water, which is highly required for biomedical applications. However, complexation studies of Cu^{2+} with ligands containing picolinate groups are scarce.[16]

We present here the syntheses and the complexation behavior toward Cu^{2+} of the macrocyclic ligands H**L1** and H**L2**, which were obtained following selective mono-*N*-alkylation of cyclen and cyclam, respectively. The structures of the complexes with Cu^{2+} in the solid state were determined by single-crystal X-ray diffraction studies. The acid−base properties of the ligands as well as the stability constants of their complexes with Cu^{2+} and Zn^{2+} were investigated by using potentiometric titrations. The behavior of the complexes in solution was studied using cyclic voltammetry (CV), UV−vis, and electron paramagnetic resonance (EPR) spectroscopic experiments. Finally, the kinetic stability of the complexes with respect to acid decomplexation was also analyzed.

RESULTS AND DISCUSSION

Syntheses of the Ligands and Their Cu^{2+} Complexes.

The synthetic protocols used for the preparation of H**L1** and H**L2** are shown in Scheme 1. The synthesis of H**L1** was achieved from cyclen (**1a**) by using the currently well-known bis-aminal chemistry.[17] Cyclen glyoxal (**2a**) was quantitatively obtained by direct condensation of glyoxal with cyclen following the literature procedure.[18] On the other hand, 6-chloromethylpyridine-2-carboxylic acid methyl ester (**3**) was obtained with an overall yield of 70% by partial reduction of dimethylpyridine-2,6-dicarboxylate with $NaBH_4$ followed by reaction of the intermediate alcohol with $SOCl_2$.[19] Alkylation of **2a** with the 6-chloromethylpyridine derivative **3** in tetrahydrofuran (THF) and in the presence of NaI afforded compound **4a** as the iodide salt. Recrystallization of **4a** from water provided single crystals of formula **4a**·$2H_2O$ suitable for X-ray diffraction (Supporting Information, Figure S1). The structure of **4a**·$2H_2O$ reveals a *cis* configuration of the central two-carbon bridge,[20] with hydrogen bonding occurring between the water of crystallization and the iodide anions [O(4)···I(1) 3.5243(16) Å, O(4)−H(4E)···I(1) 2.690(17) Å, O(4)−H(4E)···I(1) 173(3)°], and between water of crystallization and one of the oxygen atoms of the methyl ester group [O(3)···O(1) 2.944(2) Å, O(3)−H(3E)···O(1) 2.199(18) Å, O(3)−H(3E)···O(1) 155(3)°]. The reductive cleavage of **4a** with hydrazine monohydrate followed by deprotection of the methyl ester groups with 6 M HCl gave the desired ligand in 65% yield.

The synthesis of H**L2** started from cyclam **1b**, and involved the preparation of the triprotected phosphoryl derivative **2b**,[21] which was reacted with **3** to give the triprotected cyclam derivative **4b** in 74% yield. The desired ligand H**L2** was isolated with an overall yield of 55% after complete deprotection of the phosphoryl and methyl ester groups with 4 M HCl. Reaction of

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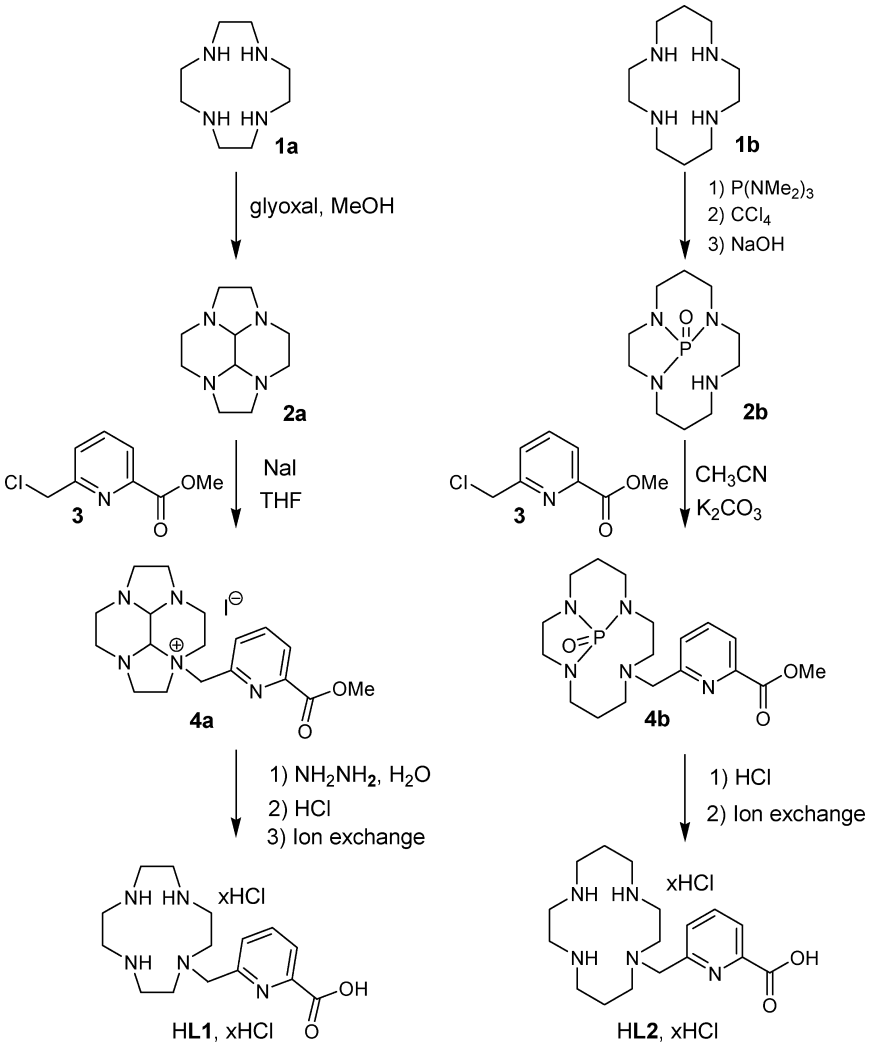
Scheme 1



HL**1** or HL**2** with $Cu(ClO_4)_2 \cdot 6H_2O$ in aqueous solution at pH ∼ 7 provided the desired complexes as the corresponding perchlorate salts in good yields (66% and 83%, respectively). The mass spectra (ESI^+) show only one intense peak corresponding to the $[CuL]^+$ (L = **L1** or **L2**) entity, thereby confirming the exclusive formation of the desired complexes.

Structure of the Complexes in the Solid State. Single crystals of complexes of Cu^{2+} with both HL**1** and HL**2** were obtained by slow evaporation of concentrated aqueous solutions at neutral pH and also at acidic pH. Crystals of formula $[Cu(HL\mathbf{1})](ClO_4)_2 \cdot H_2O$ and $[Cu(HL\mathbf{2})](ClO_4)_2 \cdot H_2O$ were found to be composed of the $[Cu(HL\mathbf{1})]^{2+}$ or $[Cu(HL\mathbf{2})]^{2+}$ cations, two perchlorate anions, and one water molecule. Views of the structures of the complex cations are shown in Figure 1, while bond distances and angles of the metal coordination environments are given in Table 1. Both complexes are protonated on an oxygen atom of the pyridylcarboxylate unit of the ligands, as previously observed for a Zn^{2+} complex with a macrocyclic ligand containing picolinate pendants.[22] The water molecule present in the crystal lattice is involved in hydrogen bonds with the protonated oxygen atom of the carboxylic function and with perchlorate anions. Perchlorate anions also form hydrogen bonds with the NH groups of the macrocyclic fragment. Intramolecular hydrogen bonding interactions also exist between one of the NH groups of the macrocyclic fragment and one of the oxygen atoms of the carboxylic acid function ($[Cu(HL\mathbf{1})]^{2+}$: N(3)···O(1) 2.808(7) Å, N(3)−H(3)···O(1) 2.16 Å, N(3)−H(3)···O(1) 126.0°; $[Cu(HL\mathbf{2})]^{2+}$: N(3)···O(1) 2.814(3) Å, N(3)−H(3)···O(1) 2.16 Å, N(3)−H(3)···O(1) 126.9°). In both complexes the metal center is pentacoordinated, being directly bound to the four nitrogen atoms of the macrocyclic unit and the nitrogen atom of the pyridyl group. The distances between the metal atom and the oxygen atom of the carboxylic group O(1) [2.85 and 2.88 Å for $[Cu(HL\mathbf{1})]^{2+}$ and $[Cu(HL\mathbf{2})]^{2+}$, respectively] are too long to be considered as bond distances. The five-membered chelate rings formed upon coordination of the ethylenediamine moieties of HL**1** adopt gauche conformations, giving rise to two possible macrocyclic conformations: ($\delta\delta\delta\delta$) and ($\lambda\lambda\lambda\lambda$).[23] Inspection of the crystal structure of $[Cu(HL\mathbf{1})]^{2+}$ shows that the enantiomeric forms ($\delta\delta\delta\delta$) and ($\lambda\lambda\lambda\lambda$) crystallize in equal amounts (racemate). In the case of $[Cu(HL\mathbf{2})]^{2+}$ the five-membered chelate rings also adopt the same conformation [($\delta\delta$) or ($\lambda\lambda$)], with the six-membered chelate rings adopting chair conformations. Upon metal coordination, cyclam-based complexes may adopt five possible configurations depending on the spatial alignment of the NH protons: *RSRS*, *RSRR*, *SSRR*, *RSSR* and *RRRR*, designed *trans*-I to *trans*-V, respectively.[24] The cyclam unit in $[Cu(HL\mathbf{2})]^{2+}$ adopts a *trans*-I configuration, which is usually

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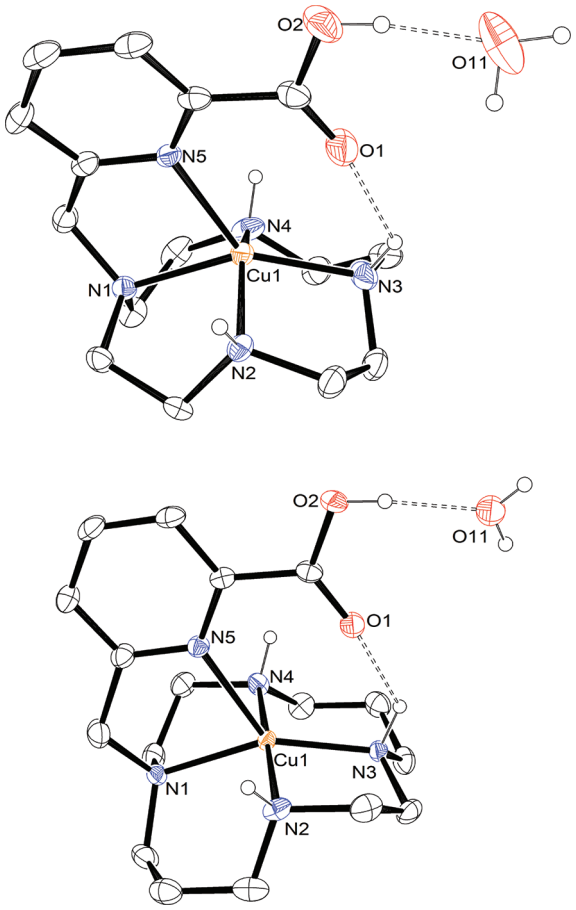

Figure 1. Views of the crystal structures of $[Cu(HL1)](ClO_4)_2 \cdot H_2O$ (top) and $[Cu(HL2)](ClO_4)_2 \cdot H_2O$ (bottom). Perchlorate anions and hydrogen atoms bound to carbon atoms are omitted for clarity. The ORTEP plots are at the 30% probability level.

favored over the *trans*-III configuration in five-coordinated Cu^{2+} complexes of ligands containing cyclam units.[25]

The coordination polyhedron around the copper center in $[Cu(HL1)]^{2+}$ and $[Cu(HL2)]^{2+}$ complexes can be defined as a heavily distorted square pyramid, in which the basal plane is defined by the four N atoms of the macrocyclic fragment, and the apical position is occupied by the nitrogen atom of the pyridyl unit N(5). The distortion of the square-pyramidal coordination is more important in the complex of H**L2** than in the H**L1** analogue, as reflected by the mean deviation from planarity of the four atoms that delineate the basal plane (0.027 and 0.210 Å for the complexes of H**L1** and H**L2**, respectively). This is also in line with the values of the index of trigonality τ, which amount to 0.06 and 0.39 for the complexes of H**L1** and H**L2**, respectively (τ = 0 for a perfect square-pyramidal geometry and τ = 1 for an ideal trigonal-bipyramidal geometry).[26] The distortion of the square pyramidal coordination is attributed to the small bite angle provided by donor atoms N(1) and N(5), which results in N(1)−Cu(1)−N(5) and N(3)−Cu(1)−N(5) angles (ca. 79° and 130°, respectively, see Table 1) that deviate considerably from the ideal value of 90°.

In both $[Cu(HL1)]^{2+}$ and $[Cu(HL2)]^{2+}$ complex cations the donor atoms of the macrocyclic fragment provide the strongest interactions with the copper center, with bond distances in the range 2.01−2.13 Å. The bond distances involving the nitrogen donor atom of the pyridyl units [2.237 and 2.289 Å for $[Cu(HL1)]^{2+}$ and $[Cu(HL2)]^{2+}$, respectively] are clearly longer than the corresponding distances to donor atoms of the macrocycle. The bond distances of the metal coordination environments in $[Cu(HL1)]^{2+}$ and $[Cu(HL2)]^{2+}$ complexes are very similar to those observed for the five-coordinated complexes of **L3** and **L4** (Chart 1).[27]

Crystals of formula $[CuL1](ClO_4)$ contain the $[CuL1]^+$ cation and one perchlorate anion involved in hydrogen bonds

Table 1. Bond Distances (Å) and Angles (deg) of the Metal Coordination Environments in Copper(II) Complexes of HL1 and HL2

	$[Cu(HL1)]^{2+}$	$[CuL1]^+$	$[Cu(HL2)]^{2+}$	$[CuL2]^+$
Cu(1)−N(1)	2.055(4)	2.523(1)	2.124(2)	2.047(2)
Cu(1)−N(2)	2.016(5)	2.1267(11)	2.010(3)	2.012(2)
Cu(1)−N(3)	2.012(5)	1.9898(10)	2.035(2)	2.003(2)
Cu(1)−N(4)	2.038(5)	2.1095(11)	2.020(3)	2.020(3)
Cu(1)−N(5)	2.237(4)	2.0270(10)	2.289(2)	2.347(2)
Cu(1)−O(1)		2.1711(9)		
N(2)−Cu(1)−N(4)	146.26(19)	141.42(4)	175.93(11)	161.52(11)
N(2)−Cu(1)−N(3)	86.10(19)	82.53(4)	86.34(11)	96.11(10)
N(4)−Cu(1)−N(3)	85.7(2)	84.03(4)	92.61(10)	84.09(10)
N(2)−Cu(1)−N(5)	96.75(16)	101.40(4)	94.38(10)	95.04(8)
N(4)−Cu(1)−N(5)	113.17(17)	98.58(4)	89.34(11)	101.95(11)
N(3)−Cu(1)−N(5)	130.99(19)	169.06(4)	128.82(9)	112.65(9)
N(1)−Cu(1)−N(5)	79.17(17)	73.77(4)	78.50(9)	77.08(8)
N(2)−Cu(1)−N(1)	86.01(17)	76.97(4)	92.86(11)	86.22(9)
N(4)−Cu(1)−N(1)	84.8(2)	77.44(4)	86.27(10)	90.50(10)
N(3)−Cu(1)−N(1)	149.56(19)	117.15(4)	152.67(10)	169.64(9)
O(1)−Cu(1)−N(5)		78.83(4)		
N(2)−Cu(1)−O(1)		109.18(4)		
N(4)−Cu(1)−O(1)		106.87(4)		
N(3)−Cu(1)−O(1)		90.24(4)		
N(1)−Cu(1)−O(1)		152.60(4)		

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with the NH groups of the ligand. Bond distances and angles of the metal coordination environment are given in Table 1 while a view of the structure of the $[CuL1]^+$ complex cation is shown in Figure 2. The deprotonation of the carboxylic acid function

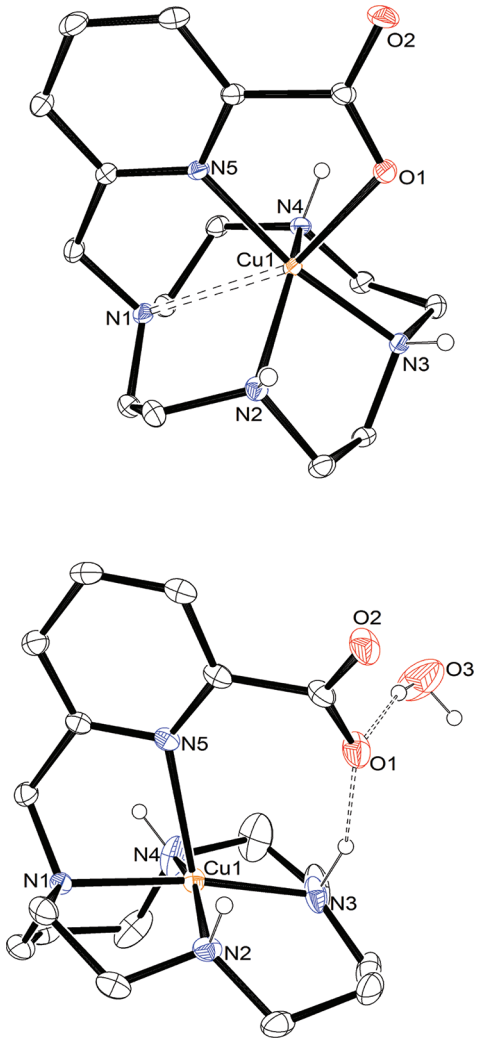

Figure 2. View of the crystal structures of $[CuL1](ClO_4)$ (top) and $[CuL2]Cl{\cdot}2H_2O$ (bottom). Anions and hydrogen atoms bound to carbon atoms are omitted for clarity. The ORTEP plot is at the 30% probability level.

of the ligand in $[Cu(HL1)]^{2+}$ to give $[CuL1]^+$ has a strong impact on the metal coordination environment around the copper center. The metal ion in $[CuL1]^+$ is five coordinated, being directly bound to three nitrogen donor atoms of the cyclen unit [N(2), N(3), and N(4)] and the two donor atoms of the picolinate pendant [N(5) and O(1)]. The distances from the metal ion and these donor atoms (ca. 2.03−2.17 Å) are considerably shorter than the Cu(1)−N(1) distance of 2.523 Å, and therefore N(1) provides a weak binding to the metal ion in this complex. The coordination polyhedron around the metal ion may be described as a distorted trigonal bipyramid, where N(2), N(4), and O(1) define the equatorial plane and N(3) and N(5) occupy the apical positions. The N(3)−Cu(1)−N(5) angle [169.06(4)°, Table 1] deviates about 11° from the ideal value expected for a regular trigonal bipyramid. The weak interaction between the Cu^{2+} and N(1) results in a N(2)−Cu(1)−N(4) angle [141.42(4)°] that deviates considerably from the ideal value of 120°, thereby providing small N(2)−Cu(1)−N(3) and N(3)−Cu(1)−N(4) angles (ca. 83°, Table 1). Alternatively, the metal coordination environment may be described as heavily distorted square-pyramid, where N(2), N(3), N(4), and N(5) define the basal plane (mean deviation from planarity 0.403 Å), with O(1) occupying the apical position. The index of trigonality τ of 0.46 points to a coordination polyhedron intermediate between square-pyramidal and trigonal-bipyramidal.

Crystals of formula $[CuL2]Cl{\cdot}2H_2O$ contain the $[CuL2]^+$ cation, one chloride anion involved in hydrogen bonds with the NH groups of the ligand and two water molecules. One of these water molecules is involved in hydrogen bonds with the chloride anion, and the second one with an oxygen atom of the carboxylate group (Figure 2). Besides, intramolecular hydrogen bonding interactions also exist between one of the NH groups of the macrocyclic fragment and one of the oxygen atoms of the carboxylate group [N(3)···O(1) 2.766(3) Å, N(3)−H(3)···O(1) 1.94 Å, N(3)−H(3)···O(1) 146.5°]. Unlike for the complexes of HL1, the deprotonation of the carboxylic acid function of the ligand in $[Cu(HL2)]^{2+}$ to give $[CuL2]^+$ has a minor impact on the metal coordination environment around the copper center (Table 1). The metal ion remains five-coordinated upon deprotonation, being directly bound to the four nitrogen donor atoms of the cyclen unit [N(1), N(2), N(3), and N(4)] and the nitrogen atom of the picolinate pendant [N(5)]. The coordination polyhedron around the metal ion may be described as square-pyramidal (τ = 0.14), where the basal plane is defined by the four N atoms of the macrocyclic fragment, and the apical position is occupied by the nitrogen atom of the pyridyl unit. The mean deviation from planarity of the four atoms that delineate the basal plane amounts to 0.077 Å, with the Cu^{2+} being placed 0.246 Å above that plane. The cyclam unit in $[Cu(L2)]^+$ adopts a *trans*-I configuration, with the six-membered chelate rings formed upon coordination of the cyclam unit adopting chair conformations. However, the five-membered chelate rings

Table 2. Stepwise Protonation Constants[a] (log K_i^H) Determined for HL1 and HL2 by Potentiometry at 25.0 °C with I = 0.10 M Using KNO_3, and of Related Ligands Taken from the Literature

equilibrium quotient[b]	HL1	HL2	L3[c]	L4[c]	cyclen[d]	cyclam[e]
[HL]/[L][H]	10.46(1)	11.55(1)	10.6	11.31	10.6	11.29
$[H_2L]/[HL][H]$	9.26(1)	10.11(1)	9.77	10.47	9.6	10.19
$[H_3L]/[H_2L][H]$	3.23(1)	2.71(1)	3.42	2.88		1.61
$[H_4L]/[H_3L][H]$		1.7(1)	<2	2.32		1.91
$[H_5L]/[H_4L][H]$			<2	1.73		

[a]Values in parentheses are standard deviations in the last significant figure. [b]L denotes the ligand in general; charges are omitted for clarity. [c]From ref 27, at 20.0 °C with I = 1 M in KNO_3. [d]From ref 28, with I = 0.1 M in $NaNO_3$. [e]From ref 29, with I = 0.1 M in KCl.

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Table 3. Stepwise Stability Constants[a] (log K_{MHiL}) Determined for the Complexes of Cu^{2+} and Zn^{2+} with the Studied Ligands at 25.0 °C with I = 0.10 M Using KNO_3, and of Related Ligands Taken from the Literature

cation	equilibrium quotient[b]	HL1	HL2	L3[c]	L4[c]	cyclen[d]	cyclam
Cu^{2+}	[ML]/[M][L]	24.0(1)	25.5(1)	21.0	23.0	23.4	28.09[e]
	[MHL]/[ML][H]	1.83(1)	2.17(1)				
	[ML]/[MLOH][H]	9.85(3)	11.15(1)				
Zn^{2+}	[ML]/[M][L]	20.39(2)	18.86(1)			16.2	15.0[f]
	[MHL]/[ML][H]	2.00(2)	2.52(4)				
	[ML]/[MLOH][H]	10.31(2)	11.02(1)				

[a]Values in brackets are standard deviations in the last significant figure. [b]L denotes the ligand in general; charges are omitted for clarity. [c]From ref 27, at 20.0 °C with I = 1 M in KNO_3. [d]From ref 28, with I = 0.1 M in $NaNO_3$. [e]From ref 35 at 25.0 °C with I = 0.1 M in KCl. [f]From ref 36, with I = 0.2 M in $NaClO_4$.

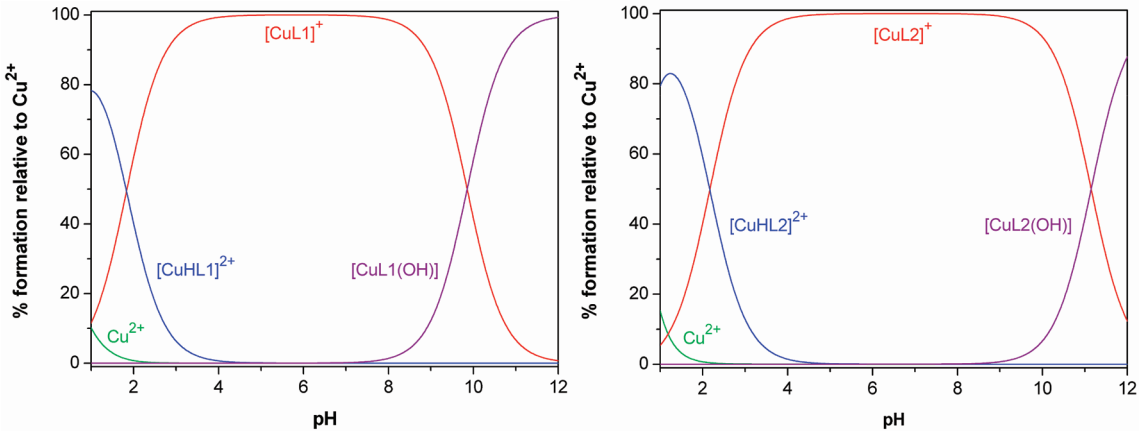

Figure 3. Speciation of Cu^{2+} in the presence of HL**1** and HL**2**. $[Cu^{2+}]_{tot} = [L]_{tot} = 10^{-3}$ M.

adopt different conformations [$(\delta\lambda)$ or $(\lambda\delta)$], in contrast to the situation observed for the protonated form of the complex.

Acid–Base Properties of the Ligands. Potentiometric titrations in aqueous solution were used to determine the protonation constants of HL**1** and HL**2** at 25.0 °C with ionic strength adjusted to 0.10 M using KNO_3. The stepwise constants determined are collected in Table 2 together with literature values for related ligands. Overall protonation constants (log β_i^H) are presented in Supporting Information, Table S1.

The first protonation constants of $L1^-$ and $L2^-$ are very similar to those determined for **L3** and **L4**, while the second ones are slightly lower in $L1^-$ and $L2^-$ in comparison to **L3** and **L4**. These protonation processes occur on the nitrogen atoms of the macrocyclic amines, and the values for $L1^-$ and $L2^-$ do not differ much from the corresponding values reported for cyclen and cyclam, showing that the picolinate pendant arm does not affect significantly the basicity of the macrocyclic amines. The third protonation process in $L1^-$ and $L2^-$ is attributed to the protonation of the pyridylcarboxylate group by comparison to related systems.[15] An additional fourth protonation constant could be determined with less accuracy for $L2^-$, corresponding to further protonation of the macrocyclic amines.

Thermodynamic Stability of the Complexes. Potentiometric titrations in aqueous solution were used to determine the stability constants of the complexes formed by HL**1** and HL**2** with Cu^{2+}, and additionally with Zn^{2+} as a bioavailable cation with coordination properties related to those of Cu^{2+}. Chelates for application as Cu^{2+}-based radiopharmaceuticals should present an important selectivity for this metal ion over Zn^{2+} to avoid the release of the radioisotope in vivo.[30] The complexes of HL**1** and HL**2** form very quickly from low pH, with almost no free metal ion found above pH 2 for Cu^{2+} or above pH 3–4 for Zn^{2+}. Consequently, for the complexes of Cu^{2+} it was not possible to determine the stability constants by direct potentiometry. Instead, competition titrations with H_4edta (ethylenediaminetetracetic acid) were used to determine the stability constant for the ML (L = **L1** or **L2**) species of each complex of Cu^{2+}, and the values obtained were then used as constants on the equilibrium model to fit the curves of direct potentiometry and obtain the remaining stability constants.

The fact that the complexation of Cu^{2+} and Zn^{2+} was quite fast may appear somewhat surprising for HL**2**. Indeed, transition metal complexes of cyclam derivatives containing coordinating pendant arms have been frequently found to form rather slowly at low pH,[31,32] including for ligands containing a single coordinating pendant arm.[33] Without a thorough study of the formation kinetics of these complexes, we can only speculate that the presence of the picolinate pendant arm in our ligands could be the cause of the fast complexation, as the picolinate function is an excellent metal binding moiety.[14−16] Indeed, it has been demonstrated that macrocycles with a pendant arm suitable to chelate cations are able to accelerate the complexation by assisting the overall complex formation mechanism.[34]

Besides the deprotonated complex species, the analysis of the potentiometric titration data of all complexes evidence formation of monoprotonated complex species at low pH, while at high pH there is a deprotonation step indicating the additional formation of monohydroxo complexes. The stability constants of the complexes of HL**1** and HL**2** with Cu^{2+} and Zn^{2+} are reported in Table 3, while speciation diagrams are

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shown in Figure 3 and Supporting Information, Figure S2. Overall stability constants (log β_{MH_iL}) determined for the complexes of Cu^{2+} and Zn^{2+} are presented in Supporting Information, Table S2. Both HL1 and HL2 show an important selectivity for Cu^{2+} over Zn^{2+}, particularly HL2, as observed for the parent cyclen and cyclam ligands (Table 3). A more accurate assessment of the complexation efficiency of the ligands can be made by determining the respective pM values ($-\log [M]_{free}$), which take into account the different basicity of the ligands and the full set of stability constants for each system. The pM values obtained at physiological pH (Table 4) show

Table 4. Calculated pM[a] Values for the Complexes of HL1 and HL2

cation	HL1	HL2	L3	L4	cyclen	cyclam
Cu^{2+}	19.08	18.64	15.43	16.02	18.00	21.41
Zn^{2+}	15.47	12.00			10.80	8.32

[a]Values calculated at pH = 7.4 for 100% excess of ligand with $[M^{2+}]_{tot} = 1 \times 10^{-5}$ M, based on the constants of Tables 2 and 3.

that the stability of the complexes of Cu^{2+} with HL1 and HL2 is considerably higher than with L3 and L4, but it is lower than with cyclam. Conversely, the complexes of Zn^{2+} with HL1 and HL2 are significantly more stable than those of cyclen and cyclam. Importantly, these values also demonstrate that while HL1 and HL2 have a high and approximately equivalent efficiency for Cu^{2+} complexation, HL2 has a much better selectivity for Cu^{2+} over Zn^{2+}. This selectivity is frequently verified for cyclam derivatives as a consequence of the size of the Cu^{2+} cation matching that of the macrocyclic cavity, thus yielding complexes were the metal is invariably coordinated in the plane formed by the four nitrogen donors of the macrocycle.[10]

The speciation diagrams shown in Figure 3 highlight the strong complexation ability of both HL1 and HL2 for Cu^{2+}, which is clearly higher than for Zn^{2+} (Supporting Information, Figure S2). Indeed, the complexes of HL1 and HL2 with Cu^{2+} are almost totally formed at pH ~ 2, while the same is true for Zn^{2+} only above pH ~ 3 or pH ~ 5, respectively for HL1 and HL2. These diagrams evidence the formation of hydroxo complexes above pH ~ 8 for the complexes of HL1 and above pH ~ 9 for the complexes of HL2, while protonated forms of the complexes are observed below pH ~ 4.

Spectroscopic Study of the Complexes. UV−vis spectra of the Cu^{2+} complexes of HL1 and HL2 were recorded in aqueous solution at neutral pH, and additionally at acidic pH for HL1 because of the pH dependence of the absorption spectrum of this complex. The UV region of the spectrum is dominated by a relatively intense band centered at 268−270 nm that is typical of the picolinate chromophore (Table 5).[37] The absorption spectra of the complexes exhibit a weaker band with maxima at 626 or 648 nm in $[CuL1]^+$, depending on the pH of the solution, and at 556 in $[CuL2]^+$ nm. These bands are characteristic of the d−d transitions centered on the Cu^{2+} ion. The maximum of the d−d absorption band in $[CuL2]^+$ is considerably shifted to the blue when compared to that of $[CuL1]^+$ (70−92 nm). This is in agreement with the coordination environment around the copper center observed in the X-ray crystal structures (see above), which show that the carboxylate group of the ligand binds to copper at neutral pH in $[CuL1]^+$ and simultaneously one of the macrocyclic amines is only weakly bound to the metal center . On the other hand, the

Table 5. UV-vis Spectroscopic Data of Complexes of HL1 and HL2 with Cu^{2+} in Water Solutions

complex	pH	color	λ_{max} /nm	ε /M^{-1} cm^{-1}
$[Cu(HL1)]^{2+}$	1.7	blue	218 sh	8549
			263 sh	7849
			270	8586
			277 sh	7436
			626	151
$[CuL1]^+$	7.5	turquoise	218 sh	9180
			263 sh	8260
			269	8890
			276 sh	7667
			648	117
$[CuL2]^+$	7.3	violet	214	8563
			268	11571
			302	2941
			556	197

carboxylate group of the ligand is uncoordinated at acidic pH in $[Cu(HL1)]^{2+}$, while in CuL2 it remains uncoordinated in the entire pH range.

The X-band EPR spectra of the complexes of Cu^{2+} in frozen aqueous solutions were obtained for various samples from very low to neutral pH (Figure 4). For CuL2 the spectra showed no

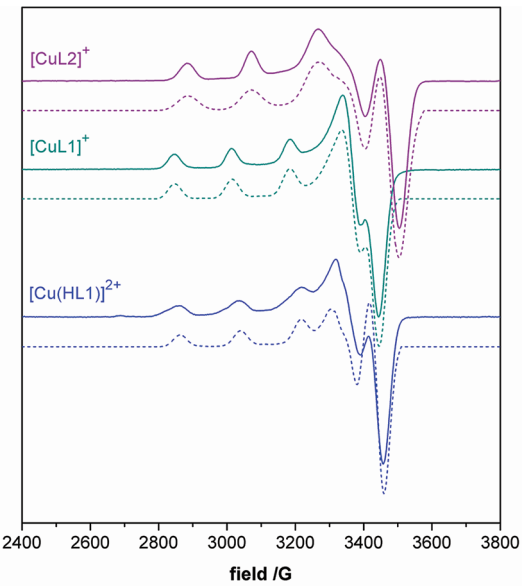

Figure 4. EPR spectra of the complexes $[CuL2]^+$ (pH = 7.8), $[Cu(HL1)]^{2+}$ (pH = 1.3), and $[CuL1]^+$ (pH = 7.1). Dashed lines represent the simulated spectra in each case.

pH dependence, indicating that the metal coordination environment in the paramagnetic complex does not change in the pH range 1−7. Thus, EPR parameters were determined from a spectrum obtained around neutral pH where the complex exists only in the deprotonated form (Table 6). For CuL1, however, the spectra show clear pH dependence, as the increase in pH causes a noticeable change in the spectral bands in a similar way to what was found for the visible spectrum. Although a single paramagnetic complex species was found at neutral pH, in the acidic range there is a mixture of two different species in variable proportion where one of the species corresponds to the one observed at neutral pH. In this case parameters were determined from two different spectra, one

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Table 6. EPR Parameters Determined for the Cu^{2+} Complexes of HL1 and HL2 in Frozen Aqueous Solutions (88 K)

complex	pH	g_x	g_y	g_z	A_x[a]	A_y[a]	A_z[a]
$[Cu(HL1)]^{2+}$ [b]	1.3	2.053	2.053	2.209	21.8	21.8	182.0
$[CuL1]^{+}$	7.1	2.041	2.067	2.229	0.8	15.9	175.0
$[CuL2]^{+}$	7.8	2.036	2.041	2.184	1.6	44.7	188.5

[a] In 10^{-4} cm^{-1}. [b] The complex species determined at pH = 7.1 is also present at pH = 1.3.

around neutral pH and the other at very acidic pH where the complex exists as a mixture of $[Cu(HL1)]^{2+}$ and $[CuL1]^{+}$. The parameters for the less abundant (and never exclusive) $[Cu(HL1)]^{2+}$ species could be obtained by inserting the parameters previously determined for the $[CuL1]^{+}$ species (exclusive around neutral pH) as constants in a system containing two distinct paramagnetic species.

All the spectra exhibit the four expected lines at low field, and no superhyperfine splitting. The simulation of the spectra, using the SpinCount software,[38] indicated three different principal values of the g parameter for all complexes, except for $[Cu(HL1)]^{2+}$ that appears to possess a less distorted structure. Additionally, $g_z > (g_x + g_y)/2$ (or $g_{\parallel} > g_{\perp}$), while the lowest g value is ≥ 2.04, which is characteristic of mononuclear copper(II) complexes in $d_{x^2-y^2}$ ground state and elongation of the axial bonds. Distorted square pyramidal stereochemistry is, therefore, consistent with these data.[39] Consequently, the EPR parameters of the complexes of both ligands at low pH and of HL2 at neutral pH, being similar for all three complexes, point to solution structures in agreement with those observed in the crystal X-ray structures (see above). On the other hand, $[CuL1]^{+}$ exhibits a larger g_z value, a smaller A_z value, and simultaneously its d−d absorption band in the electronic spectra is red-shifted in comparison with the other three complexes. These features are in agreement with a weaker equatorial ligand field, following the ligand field theory.[40] This is also in accordance with that found on the corresponding crystal structure (see above). Therefore, it is possible to conclude that in all complexes the copper centers adopt very similar coordination geometries in the solid state and in aqueous solution.

Kinetic Stability of the Copper(II) Complexes. The kinetics of the acid-assisted dissociation of the complexes of Cu^{2+} was studied under pseudo-first order conditions in aqueous solution at 25.0 °C. The dissociation of the complexes was monitored by following the changes in the d−d absorption bands of the complexes. For the complex of HL1, the half-life values found were 1.4 min in 2 M HCl and 1.8 min in 5 M $HClO_4$. In contrast, the half-life values found for the complex of HL2 were 32 min in 1 M HCl and 144 min in 5 M $HClO_4$. This clearly shows that the complex of HL2 is much more inert than that of HL1. But more importantly, these half-life values also demonstrate the very high kinetic inertness of the complex of HL2 when compared to a list of complexes of Cu^{2+} with other macrocyclic ligands,[31] and even compare reasonably well with those recently found for the complex of a dipyridyl cross-bridged cyclen ligand.[12a] Additionally, the significant difference between the half-lifes of the complex of HL2 in Cl^{-} and in ClO_4^{-} medium is a clear evidence of the important role played by the anion in the dissociation mechanism, as it has occasionally been found for similar complexes.[41]

Electrochemical Studies. It has been shown that an important pathway for the dissociation of complexes of Cu^{2+} with macrocyclic ligands is the reduction of Cu^{2+} to Cu^{+} followed by the demetalation of the Cu^{+} complex.[4] Thus, we have investigated the electrochemical behavior of the $[CuL1]^{+}$ and $[CuL2]^{+}$ complexes by using CV in aqueous solutions of the complexes at pH values of 6.4 for $[CuL1]^{+}$ and 7.3 for $[CuL2]^{+}$ (Figure 5). These experiments were carried out with a glassy-carbon working electrode in solutions containing 0.1 M $Na(ClO_4)$ as supporting electrolyte. For the $[CuL1]^{+}$ complex, a quasireversible reduction system was observed at $E_{1/2}^{red}$ = −0.93 V versus Fc/Fc^{+} (ΔE_p = 159 mV), together with a negligible oxidation peak of free Cu^{+} ions to Cu^{2+} at −0.14 V. The corresponding complex of HL2 showed a similar behavior, with a quasireversible reduction process at $E_{1/2}^{red}$ = −1.05 V versus Fc/Fc^{+} (ΔE_p = 87 mV), together with the oxidation peak of free Cu^{+} ions to Cu^{2+}.[42] These data indicate that the electrogenerated complex species of Cu^{+} are reasonably stable on the CV time scale, although a certain degree of demetalation is observed upon reduction of Cu^{2+} to Cu^{+}. In contrast, when the CV experiments were carried out in aqueous solution of $[Cu(HL2)]^{2+}$ at pH 2.8 (Figure 5) the Cu^{2+}/Cu^{+} reduction process appeared irreversible (−0.95 V), while the quasireversible reduction system at $E_{1/2}^{red}$ = −1.05 V nearly disappears. Besides, a high oxidation current is observed at −0.13 V because of the oxidation of free Cu^{+} to Cu^{2+}. The cyclic voltammogram obtained for $[Cu(HL1)]^{2+}$ at pH 1.5 is virtually identical to that obtained for $[Cu(HL2)]^{2+}$ at low pH. These results imply that both ligands hold most of the Cu^{+} ion in the coordination cage at about physiological pH, and that the demetalation is quite suppressed upon reduction of Cu^{2+} to Cu^{+}. However, at lower pH values the dissociation of the Cu^{+} complexes appears to be very important. A comparison of the $E_{1/2}^{red}$ values determined for the complexes of HL1 and HL2 shows that $[CuL1]^{+}$ is more vulnerable to the reduction by a factor of 120 mV than $[CuL2]^{+}$. A similar trend was previously observed for the complexes of L3 and L4 in acetonitrile solution (Chart 1).[27]

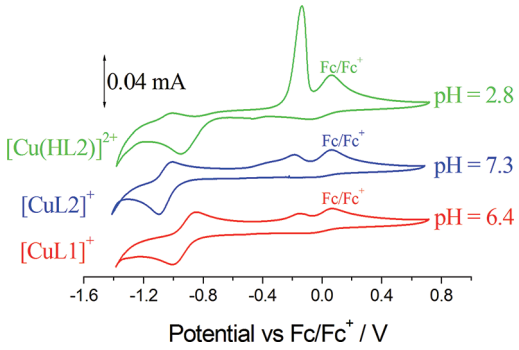

Figure 5. Cyclic voltammograms (scan rate 150 mV/s) of $[CuL1]^{+}$ and $[CuL2]^{+}$ recorded at different pH values.

CONCLUSIONS

We have presented here the synthesis of two new ligands HL1 and HL2, which are based on cyclen and cyclam frameworks functionalized with a picolinate pendant arm, and were

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designed for stable complexation of Cu^{2+} in aqueous solution. Selective monofunctionalization of the macrocyclic skeletons was obtained following two different easy-to-run procedures involving the preparation of either cyclen-bisaminal or phosphoryl cyclam derivatives. The final receptors were obtained in only three steps with very good overall yields. The introduction of the picolinate group does not influence significantly the basicity of the nitrogen atoms of the macrocycle. The process of complexation of Cu^{2+} with the two ligands was found to be very fast, including in acid medium. Besides, the thermodynamic stability of the complexes of Cu^{2+} was found to be very high, with a good selectivity for this metal ion over Zn^{2+} being observed in both cases but especially for H**L2**. A detailed investigation of the structure of the complexes of Cu^{2+} by using X-ray crystallography and EPR and UV−vis spectroscopies revealed that the protonation of the carbonyl function of the ligand may condition the metal ion coordination environment. Upon deprotonation, the carboxylic function of H**L1** was found to be coordinated to Cu^{2+}, while at low pH values the ligand binds to the metal ion by using its five nitrogen donor atoms as a result of the protonation of the carboxylic group. However, the carboxylic acid function of H**L2** remains uncoordinated in both its protonated and its unprotonated form.

The investigation of the kinetic stability of the complexes in acidic solutions underlines a significantly higher kinetic inertness of the $[Cu\mathbf{L2}]^+$ complex compared to that of $[Cu\mathbf{L1}]^+$ and other copper(II) complexes of macrocyclic ligands reported in the literature. In addition, CV experiments performed in aqueous solution emphasized a good stability of the complexes with respect to metal ion dissociation upon reduction of the metal ion to Cu^+ at about neutral pH. Consequently, the ligands reported here appear to be very attractive candidates for the design of Cu^{2+}-based radiopharmaceuticals for application in PET imaging or RIT, especially the cyclam derivative H**L2**. In the latter case the carbonyl group of the ligand is not involved in coordination to Cu^{2+}, and therefore can be used as a coupling function for conjugation with biomolecules. Currently, we are investigating the behavior of $[^{64}Cu\mathbf{L2}]^+$ to evaluate its stability with this radionuclide. In parallel, works are also in progress with the aim to increase the kinetic and electrochemical inertness of the complexes by proper modification of the macrocyclic ring.

EXPERIMENTAL SECTION

Materials and Methods. Reagents were purchased from ACROS Organics and from Aldrich Chemical Co. Cyclen was purchased from Chematech (Dijon, France). Cyclen glyoxal (**2a**),[18] 6-chloromethylpyridine-2-carboxylic acid methyl ester (**3**),[19] cyclam (**1b**),[43] and phosphoryl cyclam (**2b**)[21] were synthesized as previously described. Elemental analyses were performed at the Service de Microanalyse, CNRS, 69360 Solaize, France. NMR and MALDI mass spectra were recorded at the "Services communs" of the University of Brest, while ESI mass spectra were obtained at the Analytical Services Unit of ITQB-UNL. ^1H, ^{31}P, and ^{13}C NMR spectra were recorded with Bruker Avance 500 (500 MHz), Bruker Avance 400 (400 MHz), or Bruker AMX-3 300 (300 MHz) spectrometers. MALDI mass spectra were recorded with an Autoflex MALDI TOF III LRF200 CID spectrometer, while high resolution ESI-TOF mass spectra were recorded using a LC-Q-q-TOF Applied Biosystems QSTAR Elite spectrometer in the positive mode.

Syntheses. Compound 4a. A solution of 6-chloromethylpyridine-2-carboxylic acid methyl ester (**3**) (0.991 g, 5.34 mmol) was slowly added dropwise to a solution of sodium iodide (2.40 g, 16.01 mmol) and cyclenglyoxal **2a** (1.037 g, 5.34 mmol) in 10 mL of freshly distilled THF. The mixture was stirred at room temperature during 5 days. After filtration and washing with diethylether, the white powder containing compound **4a** and inorganic salts (NaI and NaCl) was used for the next step without further purification. ^1H NMR (D_2O, 300 MHz): 2.62−2.86 (m, 2H); 2.83−3.22 (m, 4H); 3.25−3.60 (m, 6H); 3.64−3.72 (m, 1H); 3.74−3.86 (m, 2H); 4.06 (s, 3H); 4.19 (s, 2H); 4.45−4.65 (m, 1H); 4.68−4.89 (m, 1H); 5.18−5.31 (m, 1H); 7.89 (d, 1H); 8.19 (t, 1H); 8.34 (d, 1H). ^{13}C NMR (D_2O, 75.5 MHz): 47.2 ; 51.0 ; 51.2 ; 51.5 ; 51.7 ; 54.7 ; 56.8 ; 62.1 ; 64.6 ; 66.0 ; 75.0 ; 129.8 ; 134.2 ; 143.4 ; 151.0 ; 151.7 ; 169.6. MALDI-TOF (DHB): m/z = 345.21 (M^+).

HL1·4HCl·3H$_2$O. A solution containing 2 g of compound **4a** as previously obtained and hydrazine monohydrate (10 mL) was refluxed and stirred overnight. After cooling to room temperature, the colorless solid obtained was filtered and dissolved in ethanol and evaporated. This was repeated 4 times, and a solution of 6 M hydrochloric acid (20 mL) was added. The mixture was stirred at 80 °C overnight, the solvent was evaporated, and the residue was dissolved in a minimum amount of water. Successive workups on anion-exchange (DOWEX 1X2-200) and cation-exchange (DOWEX 50WX4−400) resins afforded the desired compound H**L1** as a pale yellow solid (1.75 g, 65% calculated from **2a**). ^1H NMR (D_2O, 300 MHz): 2.87−3.06 (m, 4H); 3.15−3.38 (m, 12H); 4.06 (s, 2H); 7.69 (dd, 1H, ^3J = 7.5 Hz, ^3J = 7.6 Hz); 8.07 (2d, 2H, 3J = 7.6 Hz). ^{13}C NMR (D_2O, 75.5 MHz): 44.8; 45.7; 45.9; 52.6; 59.1; 128.2; 131.3; 144.4; 148.6; 159.6; 169.2. MALDI-TOF (2,5-dihydroxybenzoic acid, DHB): m/z = 308.23 [M +1$^+$]. HR−MS (ESI$^+$): m/z 308.2079; calcd. for $[C_{15}H_{26}N_5O_2]^+$ 308.2081. Elem. Anal. Calcd. for $C_{15}H_{25}N_5O_2{\cdot}4HCl{\cdot}3H_2O$: C, 35.51; H, 6.95; N, 13.81%. Found: C, 35.15; H, 6.65; N, 14.18%.

Compound 4b. Phosphoryl cyclam **2b** (1.037 g, 4.244 mmol) was dissolved in 20 mL of dry CH_3CN and K_2CO_3 (2.933 g, 21.22 mmol) was added. The mixture was heated at 40 °C under argon while a solution of compound **3** (0.787 g, 4.244 mmol) in 20 mL of dry CH_3CN was added dropwise. Once the addition was completed the reaction mixture was stirred for another 5 h. The suspension was cooled down, filtered, and the solution was evaporated to dryness. The crude product was purified by column chromatography in silica gel ($CHCl_3$/MeOH 95:5) to yield compound **4b** as a white solid (1.241 g, 74%). ^1H NMR ($CDCl_3$, 400 MHz): 1.38−1.41 (m, 2H); 1.45−1.57 (m, 1H); 1.58−1.69 (m, 1H); 2.10 (m, 1H); 2.26−2.49 (m, 5H); 2.56−2.75 (m, 2H); 2.76−2.87 (m, 2H); 2.88−2.95 (m, 1H); 3.00−3.15 (m, 3H); 3.26−3.38 (m, 1H); 3.53−3.62 (m, 1H); 3.60 (AB system, 2H); 3.71 (s, 3H); 7.64 (dd, 1H, ^3J = 8.0 Hz, ^3J = 7.6 Hz); 7.71 (d, 1H, ^3J = 7.6 Hz); 8.12 (d, 1H, ^3J = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 21.4; 26.0; 40.4; 41.3; 41.7; 43.9 (d, $^2J_{C-P}$ = 10.9 Hz); 45.3 (d, $^2J_{C-P}$ = 15.6 Hz); 51.2; 52.2 (CH_3); 52.6; 53.1; 59.9; 123.0; 126.6; 137.4; 146.3; 160.5; 165.3. ^{31}P NMR ($CDCl_3$, 162.0 MHz): 25.95. MALDI-TOF (2,5-dihydroxybenzoic acid, DHB): m/z = 393.23 [M+1$^+$]. Elem. Anal. Calcd. for $C_{18}H_{28}N_5O_3P$: C, 54.95; H, 7.17; N, 17.80%. Found C, 55.05; H, 7.39; N, 18.21%.

HL2·4HCl·EtOH. Hydrochloric acid (30 mL, 4 M) was slowly added to compound **4b** (1.241 g, 3.15 mmol), and the mixture was stirred and heated at 80 °C overnight. After cooling to room temperature and solvent evaporation the residue was dissolved in the minimum amount of water. After usual workup on ion-exchange resin DOWEX 1X2-200, H**L2** is obtained as a colorless oil (830 mg, 78%). ^1H NMR (D_2O, 300 MHz): 1.65−1.74 (m, 2H); 1.79−1.96 (m, 2H); 2.62−2.74 (m, 4H); 2.75−2.89 (m, 8H); 2.90−3.02 (m, 4H); 3.68 (s, 2H); 7.38 (d, 1H, ^3J = 7.5 Hz); 7.70 (d, 1H, ^3J = 7.6 Hz); 7.83 (dd, 1H, ^3J = 7.5 Hz, ^3J = 7.6 Hz). ^{13}C NMR (D_2O, 75.5 MHz): 26.0; 27.3; 47.4; 48.2; 49.0; 49.8; 52.3; 52.5; 55.6; 57.2; 60.2; 125.1; 128.6; 141.3; 157.3; 160.1; 176.3. MALDI-TOF (dithranol): m/z = 335.23 [M+1$^+$]. Hydrochloric acid (12 M) was slowly added dropwise to a solution of the free amine $\mathbf{L2}^-$ dissolved in the minimum amount of absolute ethanol. The resulting precipitate was filtered off and washed with warm ethanol (3 × 10 mL). Hydrochloric acid (1 M) was added to the residue, the solvent was evaporated, and the solid was dried under vacuum at 80 °C during 24 h to give the expected compound as the hydrochloride salt. ^1H NMR (D_2O, 300 MHz): 1.95−2.12 (m, 2H) ; 2.20−2.37 (m, 2H) ; 3.00−3.11 (m, 2H); 3.12−3.25 (m, 4H); 3.27−

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Table 7. Crystal Data and Refinement Details of the Complexes

	4a·2H$_2$O	[Cu(H**L1**)](ClO$_4$)$_2$·H$_2$O	[Cu**L1**](ClO$_4$)	[Cu(H**L2**)](ClO$_4$)$_2$·H$_2$O	[Cu**L2**]Cl·2H$_2$O
formula	$C_{18}H_{30}IN_5O_4$	$C_{15}H_{27}Cl_2CuN_5O_{11}$	$C_{15}H_{24}ClCuN_5O_6$	$C_{17}H_{31}Cl_2CuN_5O_{11}$	$C_{34}H_{62}Cl_2Cu_2N_{10}O_7$
MW	507.37	587.86	469.38	615.91	920.92
crystal system	monoclinic	monoclinic	triclinic	orthorhombic	monoclinic
space group	$P2_1/c$	$P2_1/c$	$P\bar{1}$	*Pbca*	$C2/c$
T/K	170(2)	170(2)	170(2)	170(2)	170(2)
a/Å	9.3035(2)	11.8699(5)	8.0688(2)	15.5459(3)	32.746(3)
b/Å	23.0310(4)	11.6792(5)	9.5667(2)	14.7640(3)	8.0014(4)
c/Å	10.0613(2)	16.8272(7)	12.2122(3)	21.8188(4)	17.6495(14)
α/deg	90	90	96.883(2)	90	90
β/deg	93.173(2)	90.399(4)	96.800(2)	90	120.138(11)
γ/deg	90	90	98.919(2)	90	90
V/Å^3	2152.52(7)	2332.71(17)	915.51(4)	5007.84(17)	3999.3(5)
F(000)	1032	1212	486	2552	1936
Z	4	4	2	8	4
λ, Å (MoK$_\alpha$)	0.71073	0.71073	0.71073	0.71073	0.71073
D_{calc}/g cm^{-3}	1.566	1.674	1.703	1.634	1.529
μ/mm^{-1}	1.521	1.231	1.385	1.151	1.257
θ range/deg	3.03 to 30.51	2.98 to 26.37	2.88 to 30.51	2.91 to 28.28	2.80 to 28.28
R_{int}	0.0381	0.0663	0.0161	0.0525	0.0391
reflns measd	41732	17589	17100	42075	17145
unique reflns	6564	4765	5519	6214	4946
reflns obsd	5235	2780	4975	4453	3460
GOF on F^2	1.049	0.967	1.102	1.065	0.979
R_1[a]	0.0393	0.0667	0.0262	0.0477	0.0449
wR_2 (all data)[b]	0.0653	0.1874	0.0745	0.1375	0.1196
Largest differences peak and hole/eÅ^{-3}	1.232 and −0.546	1.105 and −0.769	0.578 and −0.227	0.923 and −0.395	1.335 and −0.614

[a] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $wR_2 = \{\sum w(F_o^2 - F_c^2)^2/\sum w(F_o^4)\}^{1/2}$.

3.62 (m, 10H); 4.18 (s, 2H); 7.78 (d, 1H, ^3J = 7.7 Hz); 8,17 (dd, 1H, ^3J = 7.5 Hz, ^3J = 7.6 Hz); 8.22 (d, 1H, ^3J = 7.6 Hz). ^{13}C NMR (D_2O, 75.5 MHz): 23.4; 24.7; 41.8; 43.7; 45.1; 45.7; 46.0 (2C); 52.0; 55.0; 60.0; 128.0; 130.6; 144.0; 149.5; 158.9; 169.6. Elem. Anal. Calcd. for $C_{17}H_{29}N_5O_2$·4HCl·EtOH: C, 43.27; H, 7.45; N, 13.28. Found: C, 43.10; H, 7.06; N, 13.24. HR-MS (ESI$^+$): m/z 336.2380; calcd. for $[C_{17}H_{30}N_5O_2]^+$ 336.2394.

Preparation of [CuL1]ClO$_4$. Cu(ClO$_4$)$_2$·6H$_2$O (0.049 g, 0.132 mmol) was added to a solution of **L1**·4HCl·3H$_2$O (0.065 g, 0.128 mmol) in 10 mL of water, and the pH of the solution was adjusted to ≈7 with an aqueous KOH solution. The mixture was heated to 80 °C for 2 h and then stirred overnight at room temperature. Solid impurities were filtered off, and the solution was evaporated to dryness. The solid was dissolved in the minimum volume (ca. 20 mL) of boiling ethanol, and the solution was left standing overnight. The insoluble colorless crystals formed were filtered off, and the filtrate was evaporated to dryness; this procedure was repeated until no more colorless crystals could be separated. A powdery turquoise solid of [Cu**L1**]ClO$_4$·KCl·EtOH was obtained after drying under vacuum (0.050 g, 66%). Elem. Anal. Calcd. for $C_{17}H_{28}ClCuN_5O_6$·KCl·C_2H_5OH: C, 34.61; H, 5.13; N, 11.87. Found: C, 34.40; H, 5.00; N, 11.59. ESI-MS: (m/z) 369.0 ([CuL1]$^+$, 100%). UV−vis (water): λ_{max} (ε) 218 sh (9180), 263 sh (8260), 269 (8890), 276 sh (7667), 648 nm (117 M^{-1} cm^{-1}).

Preparation of [CuL2]ClO$_4$. Cu(ClO$_4$)$_2$·6H$_2$O (0.061 g, 0.165 mmol) was added to a solution of **L2**·4HCl·EtOH (0.073 g, 0.138 mmol) in 10 mL of water, and the pH of the solution was adjusted to ≈7 with an aqueous KOH solution. The solution was heated to 80 °C for 2 h, and then stirred overnight at room temperature. Solid impurities were filtered off, and the solution was evaporated to dryness. The solid was treated with 20 mL of a hot CH$_3$CN/CH$_3$OH (10:1) mixture, the insoluble colorless salt formed was separated by filtration, and the solution evaporated to dryness; this procedure was repeated until no more colorless salt could be separated. A powdery violet solid of [Cu**L2**]ClO$_4$·2H$_2$O·CH$_3$OH was obtained after drying under vacuum (0.065 g, 83%). Elem. Anal. Calcd. for $C_{17}H_{28}ClCuN_5O_6$·2H$_2$O·CH$_3$OH: C, 38.23; H, 6.42; N, 12.38. Found: C, 38.30; H, 6.75; N, 12.66. ESI-MS: (m/z) 397.0 ([CuL2]$^+$, 100%). UV−vis (water): λ_{max} (ε) 214 sh (8563), 268 (11571), 302 sh (2941), 556 nm (197 M^{-1} cm^{-1}).

X-ray Diffraction Measurements. Single-crystal X-ray diffraction data were collected at 170 K on an X-CALIBUR-2 CCD 4-circle diffractometer (Oxford Diffraction) with graphite-monochromatized MoK$_\alpha$ radiation (λ = 0.71073). Crystal data and structure refinement details are given in Table 7. Unit-cell determination and data reduction, including interframe scaling, Lorentz, polarization, empirical absorption and detector sensitivity corrections, were carried out using attached programs of Crysalis software (Oxford Diffraction).[44] Structures were solved by direct methods and refined by full matrix least-squares method on F^2 with the SHELXL[45] suite of programs. The hydrogen atoms were identified at the last step and refined under geometrical restraints and isotropic U-constraints.[46] CCDC 876182 to 876186 contain 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.

Potentiometric Studies. All experiments were carried out in aqueous solutions thermostatized at 25.0 ± 0.1 °C under inert atmosphere. Protonation and complexation titrations were performed in a glass-jacketed titration cell, using a Metrohm 702 SM Titrino titration stand connected to a Metrohm 6.0233.100 combined glass electrode. Competition titrations were performed on a setup consisting of a glass-jacketed titration cell and a separate reference cell connected by a Wilhelm-type salt bridge filled with 0.1 M KNO$_3$ electrolyte, using a Metrohm 665 Dosimat buret and an Orion 720A potentiometer fitted with a Metrohm 6.0150.100 glass electrode and a Metrohm 6.0733.100 reference electrode. Titrants were KOH solutions prepared at about 0.1 M from a commercial ampule of analytical grade, and their accurate concentration was obtained by titration of a standard HNO$_3$ solution. Ligand solutions were prepared

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at about 2×10^{-3} M, and the Cu^{2+} and Zn^{2+} solutions were prepared from analytical grade chloride salts and standardized by complexometric titrations with H_4edta (ethylenediaminetetraacetic acid). Sample solutions for titration contained approximately 0.04 mmol of ligand in a volume of 30 mL where the ionic strength was kept at 0.10 M using KNO_3 as background electrolyte. In complexation titrations metal cations were added at 0.9 equiv of the ligand amount, while in competition titrations Cu^{2+} was added at 1 equiv and H_4edta was added at 5 equiv as a competitor ligand. The electromotive force of the sample solutions was measured after calibration of the electrode by titration of a standard HNO_3 solution at 2×10^{-3} M. The $[H^+]$ of the solutions was determined by measurement of the electromotive force of the cell, $E = E^{o\prime} + Q \log [H^+] + E_j$. The term pH is defined as $-\log [H^+]$. $E^{o\prime}$ and Q were determined by titrating a solution of known hydrogen-ion concentration at the same ionic strength. The liquid-junction potential, E_j, was found to be negligible under the experimental conditions used. A value of $K_w = [H^+][OH^-]$ equal to $10^{-13.778}$ was taken from the literature for our ionic strength conditions.[47] The protonation constants of H_4edta and the thermodynamic stability constants of its copper(II) complex used in competition titration refinements were taken from the literature.[48] Each titration consisted of 100−150 equilibrium points in the range of pH 2.0−11.5, and at least two replicate titrations were performed for each particular system. The potentiometric data were refined with the Hyperquad software,[49] and speciation diagrams were plotted using the Hyss software.[50] The overall equilibrium constants β_i^H and $\beta_{M_mH_hL_l}$ are defined by $\beta_{M_mH_hL_l} = [M_mH_hL_l]/[M]^m[H]^h[L]^l$ and $\beta_{MH_{-1}L} = \beta_{ML(OH)} \times K_w$. Differences, in log units, between the values of protonated (or hydrolyzed) and nonprotonated constants provide the stepwise (log K) reaction constants (being $K_{M_mH_hL_l} = [M_mH_hL_l]/[M_mH_{h-1}L_l][H]$). The errors quoted are the standard deviations calculated by the fitting program from all the experimental data for each system.

Cyclic Voltammetry. Cyclic voltammograms were measured using Autolab equipment with a PGSTAT20 potentiostat at room temperature. All measurements were made by using a three-electrode system: a glassy-carbon electrode as a working electrode, a platinum wire as a counter-electrode, and a silver wire as a pseudoreference electrode, calibrated with ferrocene as internal standard. All the potentials reported in this work are referenced to the classical Fc/Fc^+ standard couple.[51] All electrochemical experiments were performed under an Ar atmosphere with $NaClO_4$ (0.1 M) as the supporting electrolyte. From the initial potential of the analysis (−0.5 V), the voltage was ramped to −1.4 V, then to 0.7 V, and back to −0.5 V at a scan rate of 150 mV/s. After each measurement, ferrocene (6.7 mM in acetonitrile) was added to the sample (0.13 mM ferrocene after addition) and the measurement was repeated to enable referencing to Fc/Fc^+.[52]

Spectroscopic Studies. UV−vis spectra were measured on a Unicam UV4 spectrometer in aqueous solutions at $1.6-1.8 \times 10^{-3}$ M and 25.0 °C. EPR spectra were measured on a Bruker EMX 300 spectrometer operating in the X-band and equipped with a continuous-flow cryostat for liquid nitrogen, in frozen aqueous solutions (88 K) at about 1 mM of complex and 1 M of $NaClO_4$. Selected EPR spectra were simulated with the SpinCount software[38] to determine the relevant parameters.

Kinetic Inertness of the Complexes of Cu^{2+} in Acidic Media. The measurement of the acid-assisted dissociation of the complexes of Cu^{2+} with both ligands was performed under pseudo-first order conditions by addition of concentrated aqueous solutions of the relevant acid to an aqueous solution of the preformed complex. Sample solutions containing each complex at 1.0×10^{-3} M and either 1 M HCl, 2 M HCl, or 5 M $HClO_4$ were used. Dissociation was followed by the decrease with time in the intensity of the complex d−d transition band in the visible range (616 nm for Cu**L1** and 550 nm for Cu**L2** in Cl^- medium, or 615 nm for Cu**L1** and 547 nm for Cu**L2** in ClO_4^- medium), at 25.0 °C, and without control of ionic strength. The experimental data were processed by exponential regression, after correction for background absorbance due to the weakly absorbing free Cu^{2+} in the presence of excess Cl^- anions, to calculate the half-life of each complex in the two acidic media.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Crystal structure of **4a**·$2H_2O$, overall protonation constants (log β_i^H) determined for H**L1** and H**L2**, overall stability constants (log β_{MH_iL}) determined for the complexes of Cu^{2+} and Zn^{2+}, speciation of Zn^{2+} in the presence of H**L1** and H**L2**, and X-ray crystal structures in cif format. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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