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Polyamine Macrocycles Incorporating a Phenanthroline Unit: Their Synthesis, Basicity, and Cu(II) Coordination

Carla Bazzicalupi,[†] **Andrea Bencini,***[,†] **Vieri Fusi,**[‡] **Claudia Giorgi,**[†] **Piero Paoletti,***[,†] **and Barbara Valtancoli**[†]

Department of Chemistry, University of Florence, Via Maragliano 75/77, 50144 Florence, Italy, and
Institute of Chemical Sciences, University of Urbino, Urbino, Italy

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Synthesis and characterization of the two new polyamine macrocycles 2,5,8,11,14-pentaaza[15]-16,29-phenanthrolinophane (**L1**) and 8-methyl-8-aza-1(1,4),11(1,4)-dipiperazina[15]-16,29-phenanthrolinophane (**L2**) are reported. Both ligands incorporate a 2,9-phenanthroline unit as integral part of their cyclic structure. **L1** contains a pentaamine chain linking the 2,9-phenanthroline positions. **L2** contains two piperazine rings within the macrocyclic framework. The basicity constants and the formation constants of their complexes with Cu(II) have been determined by potentiometric measurements in aqueous solution (298.1 K, $I = 0.1$ mol dm^{-3}). Both **L1** and **L2** form mono- and binuclear complexes in aqueous solution. In the $[\mathrm{Cu}\mathbf{L1}]^{2+}$ and $[\mathrm{Cu}\mathbf{L2}]^{2+}$ complexes, the metal ion is coordinated by the aromatic nitrogens and one or two nitrogens adjacent to the phenanthroline moiety. The remaining polyamine chain is not coordinated. These results are confirmed by the crystal structure of $[\mathrm{H_2}\mathbf{L2}\mathrm{Cu(NCS)_2}](\mathrm{ClO_4})_2\cdot3\mathrm{H_2O}$ (space group $P\bar{1}$, $a = 9.770(10)$ Å, $b = 12.027(5)$ Å, $c = 18.006(7)$ Å, $\alpha = 106.87(3)°$, $\beta = 90.22(8)°$, $\gamma = 104.48(8)°$, $V = 1954(2)$ Å^3, $Z = 2$, $R = 0.0971$, w$R2 = 0.2553$). The metal ion is five-coordinated by the phenanthroline nitrogens, by one adjacent amine nitrogen, and by two isothiocyanate ions. The noncoordinated polyamine chain can bind a second Cu(II) ion in aqueous solution, giving binuclear $[\mathrm{Cu_2}\mathbf{L}]^{4+}$ complexes ($\mathbf{L} = \mathbf{L1}$ or $\mathbf{L2}$). In the case of **L2**, the formation of the binuclear complex leads to piperazine inversion from the chair to the boat conformation, as shown by the crystal structure of $[\mathrm{Cu_2}\mathbf{L2}(\mu\text{-OH})(\mathrm{H_2O})(\mathrm{ClO_4})](\mathrm{ClO_4})_2\cdot2\mathrm{H_2O}$ (space group $P2_1/a$, $a = 19.573(2)$ Å, $b = 9.320(10)$ Å, $c = 21.552(2)$ Å, $\beta = 108.556(9)°$, $V = 3727(4)$ Å^3, $Z = 4$, $R = 0.0835$, w$R2 = 0.2759$). This structure displays a piperazine ring unusually bridging two metal cations.

Introduction

In recent years, a variety of polyamine ligands capable of binding two metals in close proximity have appeared in the literature.[1] Special attention has been devoted to macrocyclic ligands because they can impose a high degree of preorganization on metal coordination.[2−6] Furthermore, polyamine macrocycles may constitute an excellent basis for the study of molecular recognition of different kind of substrates, such as inorganic or organic cations, anionic species, and neutral molecules.[1,7]

Binucleating macrocycles can be used to force two metals at close distance. The chemical properties of the metal centers depend on the ligational properties of the chelating sites. In particular, when the binding sites contain three or four nitrogen donors, the resulting metal complexes are characterized by unsaturated coordination spheres. These complexes can behave as receptors for molecules or anionic species, giving bimetallic assemblies containing the two metal centers bridged by substrate molecules.[2−5]

Furthermore, even without the involvement of metal cations, protonated species of polyazamacrocycles are effective receptors for negative substrates, such as carboxylate or phosphate anions, through charge−charge and hydrogen-bonding interactions and can also catalyze hydrolytic reactions and syntheses of nucleotides, such as ATP.[8−12]

[†] University of Florence.

[‡] University of Urbino.

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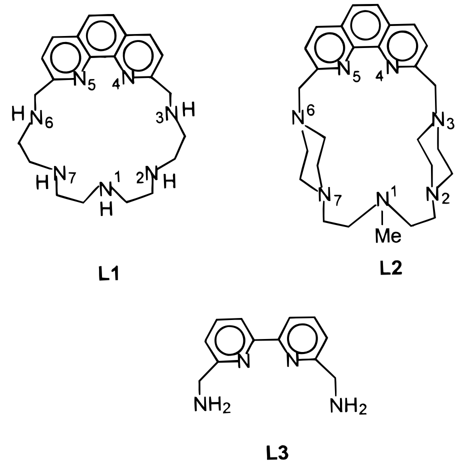
S0020-1669(97)00842-2 CCC: $15.00

Chart 1



Recently, it has been shown that the insertion of a heteroaromatic unit as a pendent arm on a polyamine macrocycle gives rise to a further binding site for a substrate molecule, such as nucleotides or nucleic bases, through hydrophobic and stacking interactions.[9,13]

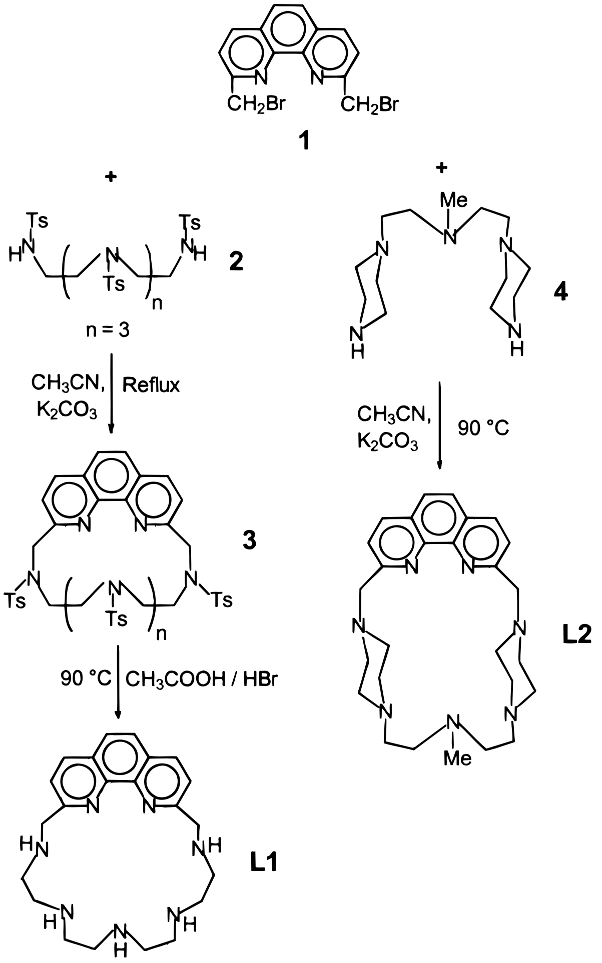
In this context, it appeared of interest to synthesize new macrocyclic receptors containing heteroaromatic moieties as an integral part of a polyamine macrocyclic structure. In particular, the insertion of a phenanthroline unit can provide a further binding site for both metal cations and nucleotide anions. This unit is rigid and provides two aromatic nitrogens whose unshared electron pairs are beautifully placed to act cooperatively in binding cations.[14−16]

Moreover, the heteroaromatic moiety may offer an optimal binding site for the coordination of nucleotide anions or nucleobases, through π-stacking and hydrophobic interactions.

In this paper we report the synthesis and characterization of two new macrocycles, **L1** and **L2** (Chart 1), incorporating a phenanthroline unit within the cyclic framework. **L1** contains a pentaamine chain linking the 2,9-phenanthroline positions. **L2** contains two piperazine rings within the macrocyclic framework and resembles in part the ligands of the family of "reinforced" polyazacycloalkanes.[17] Both ligands contain seven nitrogen donors, and the formation of binuclear complexes can be expected.

As a first investigation in the binding abilities of these macrocycles, we have tried to rationalize the relations between the binding characteristics toward H^+ (basicity) and Cu(II) and the structural features of **L1** and **L2**.

Scheme 1



Experimental Section

Synthesis. Ligands **L1** and **L2** were obtained by following the synthetic procedure reported in Scheme 1. 2,9-bis(bromomethyl)-1,10-phenanthroline (**1**),[18] 1,4,7,10,13-pentakis(*p*-tolylsulfonyl)-1,4,7,10,13-pentaazatridecane (**2**)[19] and bis(2-piperazinylethyl)methylamine triperchlorate ($\mathbf{4}\cdot 3HClO_4$)[20] were prepared as previously described.

2,5,8,11,14-Pentakis(*p*-tolylsulfonyl)-2,5,8,11,14-pentaaza[15]-16,29-phenanthrolinophane (3). A sample of **2** (2.6 g, 2.7 mmol) and K_2CO_3 (3.7 g, 27 mmol) were suspended in refluxing CH_3CN (100 mL). To this mixture, a solution of **1** (1 g, 2.7 mmol) in CH_3CN (200 mL) was added dropwise in 6 h. After the addition was completed, the suspension was refluxed for 2 h and then filtered. The solution was vacuum evaporated to yield the crude product which was chromatographated on neutral alumina (100/3 CH_2Cl_2/ethyl acetate). The eluted fractions were collected and evaporated to dryness to afford **3** as a colorless solid (0.85 g, 27%): mp 104−106 °C; ^{13}C NMR ($CDCl_3$) 47.3, 49.2, 49.3, 49.7, 55.7, 122.9, 126.5, 127.4, 127.5, 128.2, 129.7, 129.8, 134.4, 134.9, 135.9, 137.2, 143.5, 145.1, 156.6 ppm. Anal.

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Calcd for $C_{57}H_{61}N_7O_{10}S_5$: C, 58.79; H, 5.28; N, 8.42. Found: C, 58.6; H, 5.4; N, 8.3.

2,5,8,11,14-Pentaaza[15]-16,29-phenanthrolinophane Pentahydrobromide (L1·5HBr). Pentatosylated macrocycle **3** (0.85 g, 0.73 mmol) and phenol (10 g, 106 mmol) were dissolved in HBr/AcOH (33%, 80 mL). The solution was stirred at 90 °C for 18 h. The resulting suspension was filtered, and the solid was washed with CH_2Cl_2 for several times. The yellowish solid was recrystallized from a water/ethanol mixture to give **4** as pentahydrobromide salt (0.55 g, 94%). Anal. Calcd for $C_{22}H_{36}N_7Br_5$: C, 33.11; H, 4.55; N, 12.29. Found: C, 32.4; H, 4.6; N, 12.2. ^1H NMR (D_2O solution, pH 5.3) (ppm): 2.97 (m, 4H), 3.16 (m, 2H), 3.30 (m, 2H), 4.71 (s, 2H), 7.81 (d, 1H), 7.98 (s, 1H), 8.51 (d, 1H). ^{13}C NMR (D_2O solution, pH 5.3) (ppm): 45.6, 45.7, 48.1, 48.2, 52.9, 125.0, 128.3, 130.1, 140.1, 145.5, 152.8.

8-Methyl-8-aza-1(1,4),11(1,4)-dipiperazina[15]-16,29-phenanthrolinophane Triperchlorate (L2·3HClO$_4$). A sample of **4**·3HClO$_4$ (4 g, 7.2 mmol) and K_2CO_3 (7.5 g, 54 mmol) were suspended in refluxing CH_3CN (200 mL). To this mixture, a solution of **1** (2.4 g, 7.2 mmol) in CH_3CN (300 mL) was added dropwise in 7 h. After the addition was completed, the suspension was refluxed for 12 h and then filtered. The solution was vacuum evaporated to yield the crude product which was chromatographated on alumina (activity II/III, 100/1 $CHCl_3$/MeOH). The eluted fractions were collected and evaporated to dryness to afford **L2** as a colorless solid. The triperchlorate salt **L2**·3HClO$_4$ was obtained by adding 65% $HClO_4$ to an ethanolic solution of **L2** (2.5 g, 46%): ^1H NMR (D_2O solution, pD 11) 1.83 (s, 3H), 2.35 (b, 16H), 3.76 (s, 4H), 6.97 (s, 2H), 7.36 (d, 2H), 7.75 ppm (d, 2H); ^{13}C NMR (D_2O solution, pD 11) 41.76, 52.6, 54.1, 56.1, 63.4, 125.1, 126.7, 128.0, 138.1, 144.8, 156.8 ppm. Anal. Calcd for $C_{27}H_{40}Cl_3N_7O_{12}$: C, 42.61; H, 5.30; N, 12.88. Found: C, 42.4; H, 5.3; N, 12.8.

[H$_2$L2Cu(NCS)$_2$](ClO$_4$)$_2$·3H$_2$O. A solution of $Cu(ClO_4)_2\cdot6H_2O$ (3.7 mg, 0.01 mmol) in water (5 cm^3) was slowly added to an aqueous solution (15 cm^3) containing **L2**·3HClO$_4$ (7.6 mg, 0.01 mmol). The pH was adjusted at 5.5 with 0.01 M NaOH. NaSCN (3.2 mg, 0.04 mmol) was added, and the resulting solution was stirred for 2 h at room temperature. Green crystals of the complex suitable for X-ray analysis were obtained by slow evaporation at room temperature of this solution. Yield: 7 mg (83%). Anal. Calcd for $C_{29}H_{45}Cl_2CuN_9O_{11}S_2$: C, 38.95; H, 5.07; N, 14.10. Found: C, 38.9; H, 5.2; N, 14.2.

Caution: Perchlorate salts of organic ligands and their metal complexes are potentially explosive; these compounds must be handled with great caution!

[Cu$_2$L2(μ-OH)(H$_2$O)(ClO$_4$)](ClO$_4$)$_2$·2H$_2$O. A sample of $Cu(ClO_4)_2\cdot6H_2O$ (7.4 mg, 0.02 mmol) in water (5 cm^3) was slowly added to an aqueous solution (10 cm^3) containing **L2**·3HClO$_4$ (7.6 mg, 0.01 mmol). The pH was adjusted at 10 with 0.01 M NaOH. $NaClO_4\cdot H_2O$ (70 mg, 0.5 mmol) was added, and the resulting solution was stirred for 4 h at room temperature. Green crystals of the complex suitable for X-ray analysis were obtained by slow evaporation at 10 °C of this solution. Yield: 6 mg (62%). Anal. Calcd for $C_{27}H_{44}Cl_3Cu_2N_7O_{16}$: C, 33.92; H, 4.64; N, 10.25. Found: C, 33.8; H, 4.8; N, 10.1.

X-ray Structure Analysis. Analyses on prismatic green single crystals of [H$_2$**L2**Cu(SCN)$_2$]·2ClO$_4$·3H$_2$O (**a**) and of [Cu$_2$**L2**(OH)(H$_2$O)(ClO$_4$)]·2ClO$_4$·2H$_2$O (**b**) were carried out with an Enraf-Nonius CAD4 X-ray diffractometer which uses an equatorial geometry. Graphite-monochromated Mo Kα (**a**) and Cu Kα (**b**) radiations were used for cell parameter determinations and data collections. A summary of the crystallographic data is reported in Table 1.

Cell parameters for both compounds were determined by least-squares refinement of diffractometer setting angles for 25 carefully centered reflections. The intensities of two standard reflections per compounds were monitored during data collections to check the stability of the diffractometer and of the crystal; no loss of intensity was recognized.

Totals of 3804 ($2\theta_{max} = 40°$) for **a** and 3952 ($2\theta_{max} = 100°$) reflections for **b** were collected. Intensity data were corrected for Lorentz and polarization effects, and an absorption correction was applied once the structures were solved by the DIFABS method[21] (compound **a**, φ and μ correction maximum = 1.202 919, minimum = 0.869 815, θ corrections maximum = 1.052 035, minimum = 0.879 204; compound **b**, φ and μ correction maximum = 1.171 565, minimum = 0.816 830, θ corrections maximum = 1.031 990, minimum = 0.934 646).

Table 1. Crystal Data and Structure Refinement for [H$_2$**L2**Cu(NCS)$_2$]·2ClO$_4$·3H$_2$O (**a**) and of [Cu$_2$**L2**(μ-OH)(H$_2$O)(ClO$_4$)]·2ClO$_4$·2H$_2$O (**b**)

	a	**b**
empirical formula	$C_{29}H_{45}Cl_2CuN_9O_{11}S_2$	$C_{27}H_{44}Cl_3Cu_2N_7O_{16}$
fw	894.30	956.12
temp	298 K	298 K
wavelength	0.710 69 Å	1.541 78 Å
space group	$P\bar{1}$	$P2_1/a$
unit cell dimens	$a = 9.770(10)$ Å $b = 12.027(5)$ Å $c = 18.006(7)$ Å $\alpha = 106.87(3)°$ $\beta = 90.22(8)°$ $\gamma = 104.48(8)°$	$a = 19.573(2)$ Å $b = 9.320(10)$ Å $c = 21.552(2)$ Å $\beta = 108.556(9)°$
V	1954(2) Å^3	3727(4) Å^3
Z	2	4
D(calcd)	1.520 Mg/m^3	1.704 Mg/m^3
abs coeff	0.870 mm^{-1}	4.099 mm^{-1}
cryst size	0.2 × 0.17 × 0.06 mm	0.2 × 0.05 × 0.05 mm
final R indices [$I > 2\sigma(I)$]	$R1 = 0.0971$ w$R2 = 0.1832^a$	$R1 = 0.0835$ w$R2 = 0.2221^a$
R indices (all data)	$R1 = 0.2313$ w$R2 = 0.2553^a$	$R1 = 0.1583$ w$R2 = 0.2759^a$

^{a} $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; w$R2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma wF_o^4]^{1/2}$.

Both structures were solved by the heavy atom technique, which showed the metal centers for both compounds. Remaining non-hydrogen atoms were found by means of subsequent Fourier maps. Refinements were performed by means of the full-matrix least-squares method of SHELXL-93[22] programs which uses the analytical approximation for the atomic scattering factors and anomalous dispersion corrections for all atoms from ref 23 .

The function minimized was $\Sigma w(F_o^2 - F_c^2)^2$ with $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$ and $P = (F_o^2 + 2F_c^2)/3$, where a and b are refined parameters.

(a) [H$_2$L2Cu(SCN)$_2$]·2ClO$_4$·3H$_2$O. Crystals of this compound belong to the triclinic family, space group $P\bar{1}$ ($Z = 2$), with lattice constants $a = 9.770(10)$ Å, $b = 12.027(5)$ Å, $c = 18.006(7)$ Å, $\alpha = 106.87(3)°$, $\beta = 90.22(8)°$, and $\gamma = 104.48(8)°$. All the non-hydrogen atoms were anisotropically refined. The hydrogen atoms were introduced in calculated positions and their coordinates refined in agreement with those of the linked atoms. Different refined temperature factors were used for ethylenic, aromatic, and methylic hydrogen atoms. Rotational disorder, giving rise to high thermal parameters for the oxygen atoms, was found for the perchlorate anions. In particular, six electron density peaks were introduced as oxygen atoms, with population parameter 0.66, around Cl1.

The ΔF map, carried out in the last refinement step, did not allow us to localized either the acidic protons or the hydrogen atoms belonging to the water molecules.

The final agreement factors for 509 refined parameters were $R1 = 0.0971$ (for 1620 reflections with $I > 2\sigma(I)$) and w$R2 = 0.2553$ (for all data).

(b) [Cu$_2$L2(μ-OH)(H$_2$O)(ClO$_4$)]·2ClO$_4$·2H$_2$O. Crystals of this compound belong to the monoclinic family, space group $P2_1/a$ ($Z = 4$), with lattice constants $a = 19.573(2)$ Å, $b = 9.320(10)$ Å, $c = 21.552(2)$ Å, and $\beta = 108.556(9)°$. All the non-hydrogen atoms were anisotropically refined. The hydrogen atoms were introduced in calculated positions and their coordinates refined in agreement with those of the linked atoms. Different refined temperature factors were

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used for ethylenic, aromatic, and methylic hydrogen atoms. Rotational disorder, giving rise to high thermal parameters for the oxygen atoms, was found for the perchlorate anions. Double positions, introduced with population parameter 0.5, were found for O24, belonging to a perchlorate anion, and for C2, belonging to an ethylenic chain of the macrocyclic ligand.

The ΔF map, carried out in the last refinement step, did not allow us to localize the water hydrogen atoms, except for one belonging to the water molecule which coordinates the Cu1 copper ion.

The final agreement factors for 512 refined parameters were $R1 = 0.0835$ (for 2246 reflections with $I > 2\sigma(I)$ and $wR2 = 0.2759$ (for all data).

EMF Measurements. Equilibrium constants for protonation and complexation reactions with **L1** and **L2** were determined by pH-metric measurements (pH = $-\log [H^+]$) in 0.1 mol dm^{-3} NMe_4Cl at 298.1 ± 0.1 K, by using the potentiometric equipment that has been already described.[24] The combined glass electrode was calibrated as a hydrogen concentration probe by titrating known amounts of HCl with CO_2-free NaOH solutions and determining the equivalent point by Gran's method,[25] which allows to determine the standard potential $E°$ and the ionic product of water ($pK_w = 13.83(1)$ at 298.1 K in 0.1 mol dm^{-3} NMe_4Cl, $K_w = [H^+][OH^-]$). Ligand and metal ion concentrations of 1×10^{-3}–2×10^{-3} were employed in the potentiometric measurements, performing three titration experiments (about 100 data points each) in the pH ranges 2–11. The computer program SUPERQUAD[26] was used to calculate equilibrium constants from emf data. All titrations were treated either as single sets or as separated entities, for each system, without significant variation in the values of the determined constants.

NMR and Electronic Spectroscopy. ^1H (200.0 MHz) and ^{13}C NMR (50.32 MHz) spectra were recorded in D_2O solution at 298 K in a Bruker AC-200 spectrometer. In the ^1H NMR spectra peak positions are reported relative to HOD at 4.75 ppm. Dioxane was used as the reference standard in ^{13}C NMR spectra ($\delta = 67.4$ ppm). UV spectra were recorded on a Shimadzu UV-2101PC spectrophotometer.

Results and Discussion

Synthesis. The synthetic pathway to obtain **L1** and **L2** is depicted in Scheme 1. The procedure developed for synthesis of both macrocycles utilizes the simple starting material **1**. Reaction of **1** with the tosylated polyamine **2** in CH_3CN in the presence of K_2CO_3, a modification of the method of Richman and Atkins,[27] affords, after purification by chromatography, the tosylated macrocycles **3**. Finally, the removal of the tosyl groups in HBr/CH_3COOH gives the macrocycle **L1** in good yield. It is to be noted that this synthetic procedure is a promising route to produce other phenanthroline-containing polyazamacrocycles by substitution of **2** with tosylated open-chain polyamine compounds. **L2** was obtained by means of the one-pot reaction of **1** with the pentaamine **4**, by following a similar procedure reported for **3**.

Mononuclear and binuclear Cu(II) complexes can be easily isolated from aqueous solution containing ligand and metal in 1:1 and 1:2 molar ratio, respectively. The crystal structures of a mononuclear and a binuclear **L2** complex were solved.

Description of the Structure of [H$_2$L2Cu(NCS)$_2$](ClO$_4$)$_2$·3H$_2$O. The crystal structure consists of $[H_2\mathbf{L2}Cu(NCS)_2]^{2+}$ cations, perchlorate anions, and water solvent molecules. Figure 1shows an ORTEP[28] drawing of $[H_2\mathbf{L2}Cu(NCS)_2]^{2+}$, and Table 2 reports selected angles and distances.

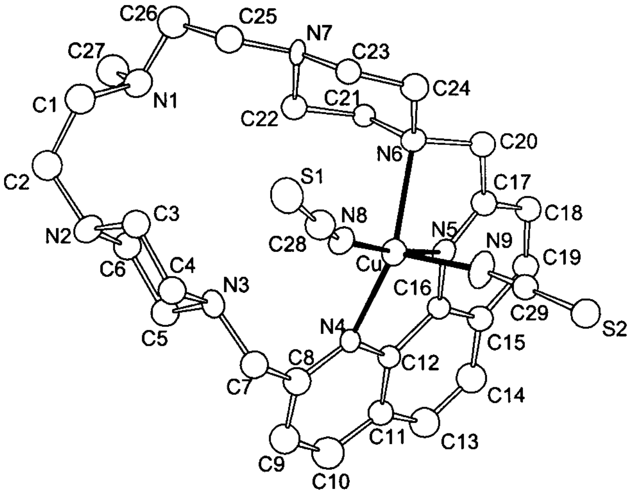

Figure 1. ORTEP drawing of the $[H_2\mathbf{L2}Cu(NCS)_2]^{2+}$ cation.

Table 2. Selected Bond Lengths (Å) and Angles (deg) for $[H_2\mathbf{L2}Cu(NCS)_2]\cdot 2ClO_4\cdot 3H_2O$

Cu–N8	1.897(14)	Cu–N4	2.187(13)
Cu–N5	1.932(13)	Cu–N6	2.312(13)
Cu–N9	2.017(14)		
N8–Cu–N5	171.8(6)	N9–Cu–N4	115.0(6)
N8–Cu–N9	92.8(6)	N8–Cu–N6	97.6(5)
N5–Cu–N9	91.4(5)	N5–Cu–N6	74.9(6)
N8–Cu–N4	105.3(6)	N9–Cu–N6	97.5(6)
N5–Cu–N4	79.1(6)	N4–Cu–N6	138.6(5)

The metal center is pentacoordinated by the phenanthroline nitrogens (N4 and N5), an amine nitrogen of the adjacent piperazine ring (N6), and two isothiocyanate anions. The geometrical arrangement of the donor atoms is intermediate between a square pyramid (with N9 in the apical position) and a trigonal bipyramid (N5 and N8 in the axial positions). The metal to donor distance for the piperazine nitrogen is 2.31(1) Å, by far longer than those found for the aromatic nitrogens (Cu–N5, 1.93(1) Å; Cu–N4, 2.19(1) Å). The Cu–N6 bond length is also significantly longer than that usually found for Cu–N bonds,[29] indicating a weak interaction between the piperazine nitrogen and the Cu(II).

The two acidic protons are located on the tetraamine moiety not involved in metal coordination. Both the piperazine rings are in the chair conformation, with the N2 and N7 lone pairs pointing outside the cavity. These two nitrogens form strong hydrogen bond contacts with the O2 and O1 water molecules (N2···O2 2.90(2) Å and N7···O1 ($1 - x, -y, 1 - z$) 2.70(2) Å). These observations may suggest that the two acidic protons are localized on N2 and N7.

The crystal packing shows that the aromatic moieties of two symmetry-related macrocyclic complexes are parallel (Figure S1, Supporting Information); *i.e.*, they exhibit π–π attractive interactions with a stacking distance of 3.66 Å.

Description of the Structure of [Cu$_2$L2(μ-OH)(H$_2$O)(ClO$_4$)](ClO$_4$)$_2$·2H$_2$O. The crystal structure consists of $[Cu_2\mathbf{L2}(\mu\text{-}OH)(H_2O)(ClO_4)]^{2+}$ cations, perchlorate anions, and water solvent molecules. Figure 2 shows an ORTEP[28] drawing of complex cation, and Table 3 reports selected angles and distances for the coordination environment.

The copper atoms Cu1 and Cu2 are 3.567(2) Å apart from each other, five-coordinated, and bridged by an oxygen donor atom. A further oxygen donor is bound to Cu1. Although the

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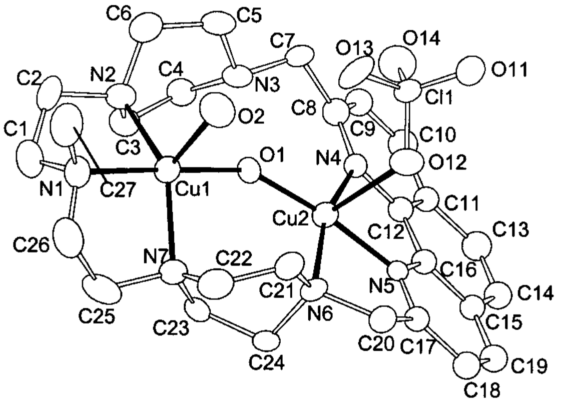

Figure 2. ORTEP drawing of the $[Cu_2\mathbf{L2}(\mu\text{-OH})(H_2O)(ClO_4)]^{2+}$ cation.

Table 3. Selected Bond Lengths (Å) and Angles (deg) for $[Cu_2\mathbf{L2}(\mu\text{-OH})(H_2O)(ClO_4)]\cdot 2ClO_4\cdot 2H_2O$

Cu1−O1	1.871(8)	O1−Cu2	1.830(8)
Cu1−N1	2.007(12)	Cu2−N5	1.889(10)
Cu1−N7	2.108(12)	Cu2−N6	2.132(11)
Cu1−N2	2.184(12)	Cu2−N4	2.246(11)
Cu1−O2	2.262(14)		
O1−Cu1−N1	176.4(5)	N2−Cu1−O2	105.9(5)
O1−Cu1−N7	92.7(4)	Cu2−O1−Cu1	149.0(5)
N1−Cu1−N7	86.2(5)	O1−Cu2−N5	172.5(4)
O1−Cu1−N2	93.9(4)	O1−Cu2−N6	93.7(4)
N1−Cu1−N2	85.0(6)	N5−Cu2−N6	81.4(5)
N7−Cu1−N2	143.8(6)	O1−Cu2−N4	104.1(4)
O1−Cu1−O2	90.0(5)	N5−Cu2−N4	79.9(5)
N1−Cu1−O2	93.6(6)	N6−Cu2−N4	160.0(4)
N7−Cu1−O2	109.6(6)		

ΔF map does not allow us to localize all the hydrogen atoms of O1 and O2, both the Cu−O1 bond distances are remarkably shorter than the Cu1−O2 one and similar to those found for other $Cu_2(\mu\text{-OH})$ assemblies.[3] As a consequence, the presence of a bridging hydroxide can be deduced.

Similarly to the mononuclear $[H_2\mathbf{L2}Cu(NCS)_2]^{2+}$ complex, the aromatic nitrogens N4 and N5 and one adjacent piperazine nitrogen N6 are involved in the coordination of the same copper atom, Cu2. The coordination environment is completed by the bridging hydroxide (O1) and an oxygen atom of a perchlorate (O12). The coordination geometry can be described as square pyramidal, with O1, N4, N5, and N6 defining the basal plane (maximum deviation from the mean plane 0.038(1) Å for N5) and O12 in the apical position. Cu2 lies 0.126(2) Å above the basal plane. The Cu2−O12 bond forms an angle of 11.5(3)° with the normal to the basal plane.

The Cu2−N6 bond length is shorter than the Cu−N6 one found in the structure of $[H_2\mathbf{L2}Cu(NCS)_2]^{2+}$ (2.13(1) Å vs 2.31(1) Å), indicating a somewhat stronger interaction between the metal and this piperazine nitrogen.

The Cu1 atom is coordinated by the methylated nitrogen N1, two nitrogens of different piperazine units, N2 and N7, the bridging O1, and a water molecule (O2). The coordination geometry can be described as intermediate between a square pyramid, with O2 in an apical position, and a trigonal bipyramid, with N1 and O1 in axial positions.

The metal centers and the coordinated oxygens O2 and O12 are almost coplanar (maximum deviation 0.09(1) Å for O2). The bridging hydroxide lies 0.489(9) Å apart from this plane, shifted toward N3. The short O1···N3 distance (2.57(2) Å) indicates a strong hydrogen bonding interaction. A further hydrogen bond contact is found between the coordinated water O2 and the perchlorate oxygen O13 (O13···O2 2.93(2) Å).

Table 4. Protonation Constants (log *K*) of **L1** and **L2** Determined by Means of Potentiometric Measurements in 0.1 mol dm^{-3} NMe_4Cl Aqueous Solution at 298.1 K

	log *K*	
reacn	**L1**	**L2**
$\mathbf{L} + H^+ = \mathbf{L}H^+$	9.38(1)[a]	9.18(2)
$\mathbf{L}H^+ + H^+ = \mathbf{L}H_2^{2+}$	8.74(1)	7.20(2)
$\mathbf{L}H_2^{2+} + H^+ = \mathbf{L}H_3^{3+}$	7.18(1)	5.57(3)
$\mathbf{L}H_3^{3+} + H^+ = \mathbf{L}H_4^{4+}$	3.85(2)	1.71(3)
$\mathbf{L}H_4^{4+} + H^+ = \mathbf{L}H_5^{5+}$	1.79(3)	

[a] Values in parentheses are standard deviations on the last significant figure.

Considering the conformation of the macrocyclic framework, it is worthy to note that both piperazine rings are in the boat conformation (torsion angles: N7−C22−C21−N6, −44°; N7−C23−C24−N6, −49°; N3−C4−C3−N2, 31°; N3−C5−C6−N2, 31°). Since in the mononuclear $[H_2\mathbf{L2}Cu(NCS)_2]^{2+}$ complex the piperazine units are in the chair conformation, such an inversion is likely due to the coordination of two Cu(II) cations within the macrocyclic cavity. It is to be noted that the two piperazine rings display different coordination features. While the piperazine N6−N7 bridges the two metals, the other one coordinates Cu1 through the N2 nitrogen, N3 being entirely noncoordinated. Mononuclear complexes containing a piperazine ring in a boat conformation to give metal chelates have been already observed.[17,30] However, to our knowledge, this is the first example of a macrocyclic complex in which piperazine inversion takes place to bridge two metal centers.

Finally, similarly to $[H_2\mathbf{L2}Cu(NCS)_2]^{2+}$, the crystal packing shows that symmetry-related macrocyclic complexes are coupled by π-stacking interactions between the phenanthroline moieties. The aromatic systems are parallel, with a plain to plain distance of 3.33 Å (Figure S2, Supporting Information).

Solution Studies. Protonation of L1 and L2. The protonation equilibria of **L1** and **L2** have been studied in 0.1 mol dm^{-3} NMe_4Cl aqueous solution at 298.1 ± 0.1 K by means of potentiometric pH ($-\log [H^+]$) measurements, and the results are reported in Table 4.

L1 and **L2** bind up to five and four protons in the pH range 2−11, respectively. Since phenanthroline nitrogens are characterized by far lower basicity than amine nitrogens, in the protonated forms of **L1** and **L2**, the acidic protons are likely located on the polyamine chains. Moreover, UV spectra recorded on solutions containing **L1** or **L2** at various pH values do not show any variations in the pH range 2−11, indicating that the aromatic nitrogens are not involved in protonation. **L1** shows higher basicity constants than **L2** for each protonation step, in accord with the less basicity of tertiary nitrogens usually found in polyamines. However, the two macrocycles show a similar protonation behavior in the pH range investigated. Considering **L1**, the first three basicity constants range between 9.38 and 7.18 logarithmic units, while the further protonation steps take place at much more acidic pH value (Figure S3, Supporting Information). A similar grouping of the protonation constants is also observed in the case of **L2**. In this case the first three protonation constants range between 9.18 and 5.57 log units, while the fourth one is by far lower (1.71 log units). This observation leads us to suggest that the acidic protons occupy alternate positions, on the N1, N3, and N6 nitrogens, separated from each other either by the aromatic moiety or the unprotonated N2 and N5 amine groups; such a disposition would

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Table 5. Logarithms of the Equilibrium Constants Determined in 0.1 mol dm^{-3} NMe_4Cl at 298.1 K for the Complexation Reactions of Cu^{2+} with **L1** and **L2**

reacn	log *K*	
	L1	**L2**
$Cu^{2+} + \mathbf{L} = Cu\mathbf{L}^{2+}$	17.91(3)[a]	11.73(3)
$Cu\mathbf{L}^{2+} + H^+ = Cu\mathbf{L}H^{3+}$	6.63(3)	7.82(3)
$Cu\mathbf{L}H^{3+} + H^+ = Cu\mathbf{L}H_2{}^{4+}$	4.53(3)	6.72(3)
$Cu\mathbf{L}^{2+} + OH^- = Cu\mathbf{L}OH^+$	3.34(1)	4.86(5)
$Cu\mathbf{L}^{2+} + Cu^{2+} = Cu_2\mathbf{L}^{4+}$	7.37(2)	5.60(5)
$Cu_2\mathbf{L}^{4+} + H^+ = Cu_2\mathbf{L}H^{5+}$		5.42(5)
$Cu_2\mathbf{L}^{4+} + OH^- = Cu_2\mathbf{L}OH^{3+}$	6.38(3)	7.0(1)

[a] Values in parentheses are standard deviations on the last significant figure.

mean a minimum in electrostatic repulsions, resulting in a stabilization of the $[H_3\mathbf{L1}]^{4+}$ species, which is prevalent in aqueous solution in a wide pH range (pH 7.5−4). The much lower affinity of the ligands for the fourth proton is due to the fact that this protonation reaction occurs at a nitrogen atom contiguous to a protonated one, leading, of course, to increased Coulombic repulsion.

These protonation features make **L1** and **L2** promising receptors for nucleotides. They give polyprotonated forms and neutral pH. These polycharged species display a polyammonium chain, potential binding site for the anionic phosphate moiety of nucleotides, and a phenanthroline unit, which may give π-stacking interactions with the nucleobase.

Cu(II) Coordination in Aqueous Solution. The formation of the Cu(II) complexes with **L1** and **L2** has been investigated by means of potentiometric measurements in aqueous solution (0.1 M NMe_4Cl, 298.1 K), and the stability constants of the complexes are reported in Table 5.

Ligands **L1** and **L2** can form both mononuclear and binuclear Cu(II) complexes. On the basis of the equilibrium data displayed in Table 5, the distribution of individual metal complexes can be calculated as a function of pH. Mononuclear complexes are largely prevalent in aqueous solutions containing ligand and Cu(II) in 1:1 molar ratio. For both ligands the formation of binuclear complexes takes place mainly for metal:ligand molar ratios greater than 1. Figure 3 displays the distribution diagrams for the system Cu(II)/**L2** in 1:1 and 2:1 molar ratio as a function of pH. As shown in Figure 3b, for 2:1 Cu(II):**L2** molar ratios, the formation of the monometallic complex is depressed and only protonated $Cu\mathbf{L2}H_x{}^{(2+x)+}$ species (x = 1, 2) are formed in low percentage at acidic pH, while binuclear species are largely prevalent in solution.

Mononuclear Complexes. As can be noted from Table 5, **L1** forms a rather stable $[Cu\mathbf{L1}]^{2+}$ complex in aqueous solution. A marked lower stability was found for the mononuclear $[Cu\mathbf{L2}]^{2+}$ species. However, the metal ion forms stable mononuclear complexes with protonated species of **L1** and **L2**. The equilibrium constants for the successive addition of H^+ to the $Cu\mathbf{L}^{2+}$ complexes (**L** = **L1** or **L2**) are significantly high, revealing that protonation occurs on a ligand moiety not involved in the coordination to the metal ion. To get further information on the role played by the phenanthroline moiety in Cu(II) coordination, the reaction of complex formation was followed by means of UV spectra recorded on aqueous solutions containing **L1** (1×10^{-2} M) and Cu(II) in various molar ratios at pH 6.5. At this pH the aromatic moiety gives a rather sharp band at 273 nm ($\epsilon = 21\,200$ M^{-1} cm^{-1}). Solutions containing **L1** and increasing amounts Cu(II), up to a 1:1 molar ratio, show a marked increase of the adsorbance. A linear correlation between the values and the Cu(II): **L1** ratio is found up to a 1:1 molar ratio (in this condition $\lambda_{max} = 274$, $\epsilon = 36\,500$ M^{-1} cm^{-1}). Since only mononuclear complexes are present in solution containing Cu(II) and **L1** in molar ratios less than 1, these data account for the involvement of the phenanthroline moiety in metal coordination in the $[Cu\mathbf{L1}]^{2+}$ complex. On the other hand, binuclear Cu(II) complexes are found in aqueous solution for Cu(II):**L1** molar ratios greater than 1; addition of further Cu(II) to a 1:1 Cu(II)/**L1** solution does not give any change for the band at 274 nm, indicating that the second metal is bound to nitrogens of the pentaamine chain. Similar results are found for the system Cu(II)/**L2** at pH 8.5, where the mononuclear $[Cu\mathbf{L2}]^{2+}$ complex is present in solution in large percentage (ca. 90%) in the 1:1 system (Figure 3a).

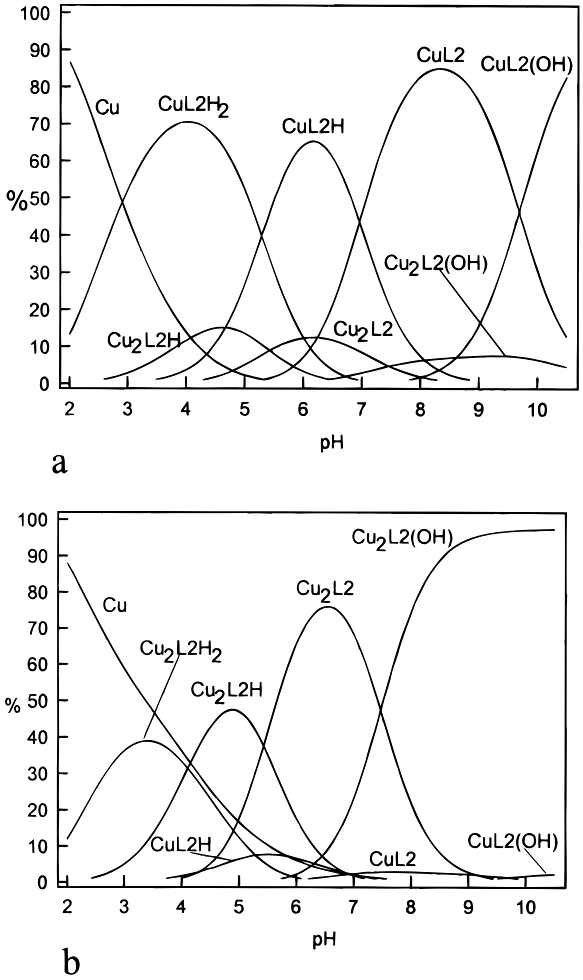

Figure 3. Distribution diagrams of the species for the systems L2/Cu(II) ([NMe_4Cl] = 0.1 mol dm^{-3}, 298.1 K, [**L2**] = 1×10^{-3} mol dm^{-3}, [Cu^{2+}] = 1×10^{-3} mol dm^{-3}) (a) and L2/Cu(II) ([NMe_4Cl] = 0.1 mol dm^{-3}, 298.1 K, [**L2**] = 1×10^{-3} mol dm^{-3}, [Cu^{2+}] = 2×10^{-3} mol dm^{-3}) (b) as a function of pH.

It is to be noted that the stability constants for the $[Cu\mathbf{L1}]^{2+}$ complex are somewhat higher than those reported by Martell and co-workers for the $[Cu\mathbf{L3}]^{2+}$ complex.[31] In this latter complex, the metal ion is coordinated by the two aromatic nitrogens and the amine groups. A similar involvement of two phenanthroline donors and the adjacent two amine nitrogen atoms N3 and N6 can be proposed also for our $[Cu\mathbf{L1}]^{2+}$ complex, as shown in Figure 4a. The higher stability of our mononuclear complex may be ascribed to the presence in **L1** of a phenanthroline group, which shows a higher affinity for

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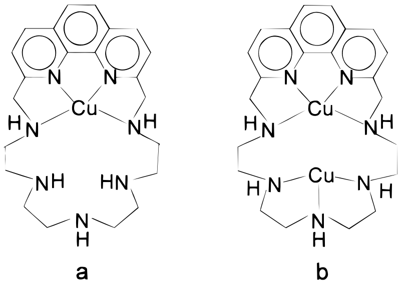

Figure 4. Proposed coordination modes of Cu(II) in the $[\mathrm{Cu}\mathbf{L1}]^{2+}$ (a) and $[\mathrm{Cu}_2\mathbf{L1}]^{4+}$ (b) complexes. The drawn structures of the complexes are only partial, and additional water molecules or hydroxide ions coordinating at the remaining sites of Cu(II) are not specified.

Cu(II) than a dipyridine moiety.[32] Considering the $[\mathrm{Cu}\mathbf{L2}]^{2+}$ complex, it is worthy to note that the complex stability is remarkably lower than that found for the $[\mathrm{Cu}\mathbf{L1}]^{2+}$ complex, indicating a lower number of nitrogens donor involved in metal coordination, as actually shown by the crystal structure of the $[\mathrm{CuH}_2\mathbf{L2}(\mathrm{NCS})_2](\mathrm{ClO}_4)_2$ complex. In this protonated complex only the two aromatic nitrogens and one piperazine nitrogen, adjacent to the phenanthroline moiety, participate in metal binding. A similar coordination for the Cu(II) ion in aqueous solution can be proposed. Most likely, the NCS anions in the $[\mathrm{CuH}_2\mathbf{L2}(\mathrm{NCS})_2](\mathrm{ClO}_4)$ solid complex are replaced by water molecules in aqueous solution.

Since in $[\mathrm{Cu}\mathbf{L1}]^{2+}$ and $[\mathrm{Cu}\mathbf{L2}]^{2+}$ the metal is coordinated by the aromatic subunit and one or two adjacent amine nitrogens, both complexes exhibit a polyamine chain, containing three or four nitrogens, not involved in metal coordination; they can bind up to two protons in slightly acidic media, giving rather stable $[\mathrm{CuH}\mathbf{L}]^{3+}$ and $[\mathrm{CuH}_2\mathbf{L}]^{4+}$ species ($\mathbf{L} = \mathbf{L1}$ or $\mathbf{L2}$). Finally, both $[\mathrm{Cu}\mathbf{L1}]^{2+}$ and $[\mathrm{Cu}\mathbf{L2}]^{2+}$ give rise to a hydroxylated $[\mathrm{Cu}\mathbf{L}(\mathrm{OH})]^{+}$ species at alkaline pH. It is to be noted that the $[\mathrm{Cu}\mathbf{L2}]^{2+}$ complex shows a higher tendency for deprotonation of the coordinated water molecules (Table 5), confirming the low number of nitrogens in the coordination environment of the metal.

The characteristics of these mononuclear complexes indicate that both ligands behave as ditopic receptors; *i.e.*, they display two different binding sites, the phenanthroline moiety and the adjacent amine nitrogens N3 and N6, where the Cu(II) is preferentially lodged, and a polyamine chain, where protons are bound at acidic pH. This further binding site can be also used for the coordination of a second metal cation.

Binuclear Complexes. Both $[\mathrm{Cu}\mathbf{L1}]^{2+}$ and $[\mathrm{Cu}\mathbf{L2}]^{2+}$ can bind an additional Cu(II) ion in aqueous solution, giving binuclear $[\mathrm{Cu}_2\mathbf{L1}]^{4+}$ and $[\mathrm{Cu}_2\mathbf{L2}]^{4+}$ complexes, respectively. In both ligands, for a 2:1 Cu(II):**L** molar ratio, binuclear complexes are largely prevalent in aqueous solution. Such a tendency to form binuclear species indicates that in the binuclear complexes the two metals are coordinated by the two different binding subunits of the ligands, as actually shown by the crystal structure of the $[\mathrm{Cu}_2\mathbf{L2}(\mu\text{-OH})(\mathrm{H}_2\mathrm{O})(\mathrm{ClO}_4)]^{2+}$ complex. For the binuclear **L1** complexes a similar metal lodging within the macrocyclic framework can be assumed. A proposed structure for the $[\mathrm{Cu}_2\mathbf{L1}]^{4+}$ is reported in Figure 4b.

If the 1:2 Cu/**L1** and Cu/**L2** systems are compared, two main differences can be outlined.

First, the $[\mathrm{Cu}\mathbf{L1}]^{2+}$ complex shows a higher tendency to bind a second Cu(II) ion than the $[\mathrm{Cu}\mathbf{L2}]^{2+}$ complex (see Table 5). The coordination of the second Cu(II) ion by the mononuclear $[\mathrm{Cu}\mathbf{L2}]^{2+}$ complex implies the inversion of both the piperazine rings from the low-energy chair conformation to the less energetically favorable boat form, as shown by the crystal structures of the mono- and binuclear **L2** complexes. The unfavorable energetic contribution of piperazine inversion in the formation of mononuclear complexes has been nicely discussed by Hancock and co-workers;[17] in the present case piperazine inversion would occur only in the binuclear complex. Furthermore, the binuclear $[\mathrm{Cu}_2\mathbf{L2}(\mu\text{-OH})(\mathrm{H}_2\mathrm{O})(\mathrm{ClO}_4)]^{2+}$ cation shows a rather strained structure, one nitrogen donor being uncoordinated to the metal. The energy loss due to piperazine inversion and the strained stucture of the binuclear complex justify the lower tendency of $[\mathrm{Cu}\mathbf{L2}]^{2+}$ to bind a second Cu(II) ion.

Second, the $[\mathrm{Cu}_2\mathbf{L2}]^{4+}$ complex can bind a proton in aqueous solution, giving rise to a rather stable monoprotonated $[\mathrm{Cu}_2\mathrm{H}\mathbf{L2}]^{5+}$ species (see Table 5 and Figure 3b). On the other hand, the binuclear **L1** complex does not form any protonated species, suggesting that in $[\mathrm{Cu}_2\mathbf{L1}]^{4+}$ all nitrogen donors are likely involved in metal coordination and giving confidence to the proposed structure for this complex (Figure 4b).

It is worth noting that both $[\mathrm{Cu}_2\mathbf{L1}]^{4+}$ and $[\mathrm{Cu}_2\mathbf{L2}]^{4+}$ complexes show a marked tendency to form monohydroxo species in aqueous solution. In both systems with a metal:ligand 2:1 molar ratio, such species are largely present in aqueous solution even at neutral or slightly alkaline pH's, as shown in Figure 3b for the system **L2**/Cu(II). The behavior of the binuclear Cu^{2+} complexes in alkaline solution is interesting in that they can give structural information on their hydroxo species. Particularly, the constants for the addition of the OH^{-} anion to the $[\mathrm{Cu}_2\mathbf{L1}]^{4+}$ or $[\mathrm{Cu}_2\mathbf{L2}]^{4+}$ complexes are very high (6.38 and 7.0 logarithmic units) in comparison with the analogous constants for the addition of hydroxo groups to the corresponding mononuclear complexes (see Table 5). This indication of a strong binding of the hydroxide ion leads one to suppose that this group is bridged between the two metal centers, as actually observed in the crystal structure of the $[\mathrm{Cu}_2\mathbf{L2}(\mu\text{-OH})(\mathrm{H}_2\mathrm{O})(\mathrm{ClO}_4)]^{2+}$ cation.

Concluding Remarks. The new macrocyclic ligands **L1** and **L2** behave as ditopic receptors for Cu(II); *i.e.*, they display two different binding sites, the phenanthroline moiety together with the adjacent amine nitrogens, where the Cu(II) is lodged in the mononuclear complexes, and a polyamine chain. This further binding site is used for the coordination of a second metal cation to form binuclear $[\mathrm{Cu}_2\mathbf{L}]^{4+}$ complexes. In the binuclear $[\mathrm{Cu}_2\mathbf{L2}]^{4+}$ the piperazine rings are in the less energetically favorable boat conformation; one of the piperazine rings displays an unusual coordination motif, bridging the two metals through its 1,4 nitrogens.

In both mono- and binuclear Cu(II) complexes the metal ions show an unsaturated coordination environment. In particular, in the binuclear complex the two metals are kept at close distance by the macrocyclic framework. These complexes are therefore promising receptors for substrate molecules, which can bridge the metal centers. Actually, the hydroxide anion, which is the simplest example of a bridge between two metal centers, forms bridging $[\mathrm{Cu}_2\mathbf{L1}(\mathrm{OH})]^{3+}$ or $[\mathrm{Cu}_2\mathbf{L2}(\mathrm{OH})]^{3+}$ complexes with great facility. It would be of interest in future work to study the binding ability of these complexes toward nucleotides or nucleobases, since the phenanthroline moiety may act as a further binding site through hydrophobic or π-stacking interactions.

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Supporting Information Available: Distribution diagrams for the systems **L1**/H^+ and **L1**/Cu^{2+} and crystal packing diagrams and tables of crystallographic and experimental data, complete atomic positional parameters, anisotropic temperature factors, and bond distances and angles for $[H_2\mathbf{L2}Cu(NCS)_2](ClO_4)_2\cdot 3H_2O$ and $[Cu_2\mathbf{L2}(\mu\text{-}OH)(H_2O)(ClO_4)](ClO_4)_2\cdot 2H_2O$ (28 pages). X-ray crystallographic data, in CIF format, are available. Ordering and access information is given on any current masthead page.

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