Polyamine Macrocycles Incorporating a Phenolic Function: Their Synthesis, Basicity, and Coordination Behavior toward Metal Cations. Crystal Structure of a Binuclear Nickel Complex

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The synthesis and characterization of two new polyazamacrocycles, 1,4,7,10-tetraaza[12](2,6)phenolphane (**L1**) and 1,4,7,10,13-pentaaza[15](2,6)phenolphane (**L2**), are reported. Both ligands incorporate the 2,6-phenolic unit within the cyclic framework. The basicity behavior and the ligational properties of **L1** and **L2** toward Ni(II), Zn(II), and Cu(II) were determined by means of potentiometric measurements in aqueous solution (298.1 ± 0.1 K, $I = 0.15$ mol dm^{-3}). UV spectra were used to understand the role of the phenolic function in the stabilization of the cations. **L1** and **L2** behave as pentaprotic bases under the experimental conditions used. The UV spectra showed that the deprotonation of the phenolic function occurs at low pH values for both ligands, giving rise to the simultaneous presence of positive and (one) negative charges on the macrocycle. While **L1** forms only mononuclear complexes, **L2** can also form binuclear species with all the metal ions investigated. In the mononuclear species of both ligands, one nitrogen atom close to the phenol remains unbound. The UV spectra reveled that the phenol, bridging the two metal ions in phenolate form, plays an important role in the stabilization of the binuclear complexes of **L2**. The coordination sphere of the two metals is completed by adding a secondary ligand such as water molecules or OH$^-$, in any case preferring substrates able to bridge the two close metal ions. These results are confirmed by the crystal structure of $[Ni_2(C_{16}H_{28}ON_5)(H_2O)_2Cl_2]Cl\cdot H_2O\cdot CH_3OH$ (space group $P2_1/a$, $a = 14.821(5)$ Å, $b = 10.270(4)$ Å, $c = 17.663(6)$ Å, $\beta = 108.87(3)°$, $V = 2544(2)$ Å^3, $Z = 4$, R1 = 0.0973, wR2 = 0.2136). This structure displays a Ni(II) binuclear complex of **L2** in which the phenolic oxygen and a chlorine ion bridge the two close Ni(II) ions.

Introduction

Ligands able to selectively bind a specific metal ion and undergo a concomitant color change are important in host−guest chemistry. Much effort has been devoted to the design and synthesis of macrocycles able to coordinate metal ions into their macrocyclic cavity,[1] with the aim of using them as selective complexing agents and ionophores.[2−11] The presence of a photosensitive group makes such compounds potentially suitable for use as simple optical sensors.[12−14] Many of them contain the phenolic function in the macrocyclic framework as the base of chromoionophores;[15] in fact, this aromatic moiety assembles both the photoactive and coordinative properties. Furthermore, this group could be employed as a building block of more sensitive azo-dye.

Ligands that also have the capability to form binuclear metal complexes in which the two metal centers are forced to stay close to each other by the molecular topology are of great

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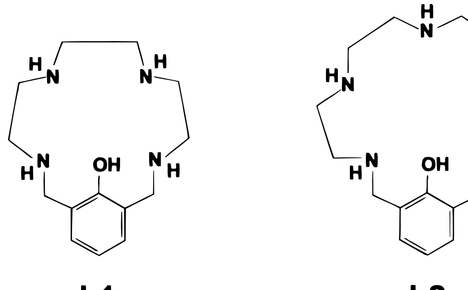
Chart 1



L1 **L2**

interest.[16] When the metal centers of the binuclear complexes present an unsaturated coordination requirement, they can be employed as receptors for new species. Moreover, if they are close to each other, they can cooperate in the assembly of a secondary ligand from the medium,[17,18] as for example in oxygen receptors and carriers.[19]

Macrocycles bearing a phenolic group based upon crown ether or oxa-aza-crown ether derivatives have been studied, and particular attention has been given to their coordination property toward alkali-metal ions.[15] In this context, it appears of interest to synthesize new receptors deriving from the polyazamacrocycles containing the phenolic ionophores, which can be utilized to extend the coordination range of metal ions and to increase the water solubility of the metal complex. Moreover, polyamine macrocycles may constitute an excellent base for the studies of molecular recognition of different kinds of substrates, such as inorganic or organic cations, anionic species, and neutral molecules.[20] The presence of an aromatic optical sensor group in the ligand can extend its capability to control the host−guest interaction.

The interest in synthesizing polyazamacrocyclic receptors characterized by different cavity sizes and bearing a chromogenic group has led us to develop a new synthetic strategy producing simple azamacrocycles incorporating the phenolic function. The number of amine nitrogen atoms, as well as the dimension of the macrocyclic ring, can be varied to modulate the coordination properties. In this paper we report the synthetic strategy and the characterization of two new macrocycles, **L1** and **L2** (Chart 1), incorporating a phenolic unit within the cyclic framework. **L1** contains a three-ethylene tetraamine chain linking the 2,6-phenol position, while **L2** is a larger molecule, presenting five amine nitrogen atoms and four ethylenic chains. To investigate the binding capabilities of these macrocycles and the role of the phenolic function, we first analyzed their acid−base behavior and coordination capabilities toward the transition-metal ions Ni(II), Cu(II), and Zn(II).

Experimental Section

Synthesis. Ligands **L1** and **L2** were obtained following the synthetic procedure reported in Scheme 1. 2,6-Dibromomethylanisole (**1**),[13] 1,4,7,-10-tetrakis(*p*-tolylsulfonyl)-1,4,7,10-tetrazadecane (**2**),[21] and 1,4,7,10,-13-pentakis(*p*-tolylsulfonyl)-1,4,7,10,13- pentaazatridecane (**3**)[22] were prepared as previously described. Solvents and starting materials were used as purchased.

1,4,7,10-Tetrakis(*p*-tolylsulfonyl)-1,4,7,10-tetraaza[12](2,6)-anisolephane (4). Over a period of 4 h, a solution of **1** (2.9 g, 0.01 mol) in 100 cm^3 of acetonitrile was added to a refluxing suspension of **2** (7.6 g, 0.01 mol) and of Na_2CO_3 (5.3 g, 0.05 mol) in 250 cm^3 of acetonitrile. The reaction mixture was maintained under reflux for a further 5 days. Subsequently, the mixture was cooled to room temperature and the resulting suspension was evaporated under reduced pressure. The crude product was suspended in chloroform (150 cm^3), and the suspension was filtered. The organic layer was evaporated under reduced pressure, giving a white solid, which was recrystallized in a minimum amount of hot acetonitrile. Yield: 7.1 g (79%). Anal. Calcd for $C_{43}H_{50}N_4O_9S_4$: C, 57.70; H, 5.63; N, 6.26. Found: C, 57.9; H, 5.7; N, 6.4. MS (FAB): 896 ($M + H^+$). ^1H NMR ($CDCl_3$, 25 °C): 2.23 (s, 12H), 2.38 (s, 4H), 2.51 (m, 8H), 4.26 (d, 2H), 4.39 (s, 4H), 4.58 (d, 2H), 7.21 (t, 1H), 7.36 (d, 8H), 7.79 (d, 4H), 7.83 (d, 4H), 7.96 (d, 2H) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): 21.8, 46.2, 47.2, 49.2, 63.8, 125.9, 127.5, 127.6, 129.4, 130.0, 130.2, 131.9, 135.6, 135.9, 143.8, 144.0, 156.9 ppm.

1,4,7,10-Tetraaza[12](2,6)phenolphane (L1·4HCl). Ammonia (300 cm^3) was condensed on a suspension of **4** (4.5 g, 5.0 mmol) in diethyl ether (30 cm^3) and methanol (1 cm^3), cooled at −70 °C. Little bits of lithium were added to the mixture until the suspension became blue. Thirty minutes after the suspension turned blue, NH_4Cl (12 g, 0.2 mol) was added. The white solid obtained after the evaporation of the solvents was treated with 3 mol dm^{-3} HCl (300 cm^3) and the resulting solution washed with $CHCl_3$ (3×100 cm^3). The acidic solution was filtered and then evaporated to dryness. The resulting solid was dissolved in the minimum amount of water necessary and the solution made alkaline with concentrated NaOH. The liquid was extracted with $CHCl_3$ (6×50 cm^3). The organic layer was dried over Na_2SO_4 and vacuum-evaporated to obtain a solid that was dissolved in ethanol and treated with 37% HCl until complete precipitation of a white solid that was filtered off to achieve **L1** as a tetrahydrochloride salt (1.5 g, 73%). Anal. Calcd for $C_{14}H_{28}N_4OCl_4$: C, 40.99; H, 6.88; N, 13.66. Found: C, 41.1; H, 6.9; N, 13.8. MS (FAB): 411 ($M + H^+$). ^1H NMR (D_2O, pH 3, 25 °C): 3.24 (s, 4H), 3.39 (m, 8H), 4.43 (s, 4H), 7.02 (t, 1H), 7.51 (d, 2H) ppm. ^{13}C NMR: 43.1, 43.6, 44.5, 47.0, 123.3, 125.2, 135.4, 155.2 ppm.

1,4,7,10,13-Pentakis(*p*-tolylsulfonyl)-1,4,7,10,13-pentaaza[15](2,6)-anisolephane (5). Over a period of 4 h, a solution of **1** (2.9 g, 0.01 mol) in 100 cm^3 of acetonitrile was added to a refluxing suspension of **3** (9.6 g, 0.01 mol) and of Na_2CO_3 (5.3 g, 0.05 mol) in 250 cm^3 of acetonitrile. The reaction mixture was maintained under reflux for a further 7 days. The mixture was then cooled to room temperature, and the resulting suspension was evaporated under reduced pressure. The crude product was suspended in chloroform (250 cm^3), and the suspension was filtered. The organic layer was evaporated under reduced pressure, giving a crude product which was chromatographed on neutral alumina ($CHCl_3$−ethyl acetate, 100:5). The eluted fractions were collected and evaporated to dryness, affording **5** as a white solid. Anal. Calcd for $C_{52}H_{61}N_5O_{11}S_5$: C, 57.18; H, 5.63; N, 6.41. Found: C, 57.2; H, 5.7; N, 6.4. MS (FAB): 1093 ($M + H^+$). ^1H NMR ($CDCl_3$, 25 °C): 2.22 (s, 12H), 2.23 (s, 3H) 2.52 (m, 16H), 4.28 (d, 2H), 4.36 (s, 4H), 4.62 (d, 2H), 7.24 (t, 1H), 7.29 (d, 4H), 7.35 (d, 6H), 7. 77 (d, 6H), 7.86 (d, 4H), 7.96 (d, 2H) ppm. ^{13}C NMR: 21.0, 21.6, 46.0, 46.2, 49.0, 49.1, 62.7, 125.3, 127.4, 127.5, 129.2, 129.9, 130.5, 134.0, 135.0, 136.1, 143.6, 143.8, 144.0, 157.0 ppm.

1,4,7,10,13-Pentaaza[15](2,6)phenolphane (L2·5HCl). This compound was synthesized from **5** (5.5 g, 5.0 mol) following the same

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Scheme 1

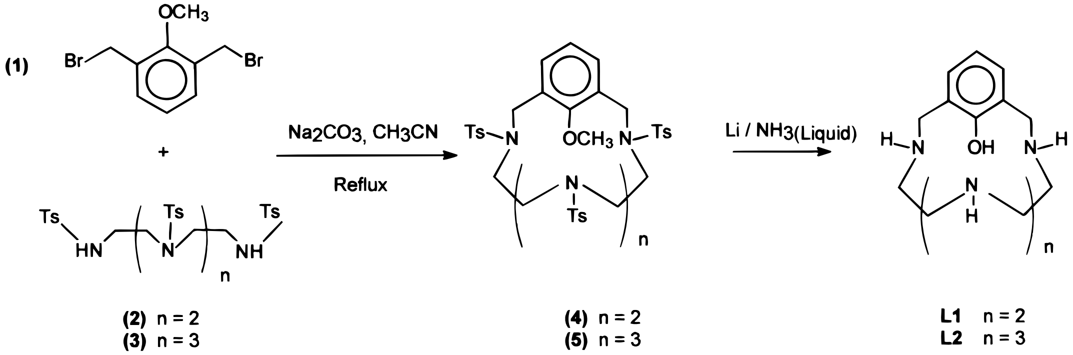

Table 1. Crystal Data and Structure Refinement for **6**

empirical formula	$C_{17}H_{38}C_{13}N_5Ni_2O_5$	V, Å^3	2544(2)
fw	616.29	Z	4
temp, K	293	D_c, Mg/m^3	1.596
wavelength, Å	0.71069	abs coeff, mm^{-1}	1.832
cryst syst	monoclinic	cryst size, mm	0.35 × 0.40 × 0.55
space group	$P2_1/a$	R [$I > 2\sigma(I)$]	0.0973
unit cell dimensions, Å, deg	$a = 14.821(5)$	$R_w{}^2$	0.2136
	$b = 10.270(4)$	a, b (weighting scheme)[a]	0.1185, 0
	$c = 17.663(6)$		
	$\beta = 108.87(3)$		

[a] $w = 1/[\sigma^2(F_o{}^2) + (aP)^2 + bP]$; $P = (F_o{}^2 + 2F_c{}^2)/3$.

procedure reported for **L1**. Anal. Calcd for $C_{16}H_{34}N_5OCl_5$: C, 39.24; H, 7.00; N, 14.3. Found: C, 38.88; H, 7.9; N, 15. MS (FAB): 491 (M + H$^+$). ^{1}H NMR (D_2O, pH 3, 25 °C): 3.17 (t, 4H), 3.19 (t, 4H), 3.39 (m, 8H), 4.40 (s, 4H), 7.17 (t, 1H), 7.48 (d, 2H) ppm. ^{13}C NMR: 44.5, 44.6, 46.4, 47.2, 48.0, 122.5, 124.3, 135.2, 157.8 ppm.

$[Ni_2(H_{-1}L2)(H_2O)_2Cl_2]Cl\cdot H_2O\cdot CH_3OH$ (6). A sample of $NiCl_2\cdot 2H_2O$ (6.6 mg, 0.04 mmol) in methanol (5 cm^3) was slowly added to a methanol solution (10 cm^3) of **L2** (9.8 mg, 0.02 mmol). The resulting solution was stirred for 30 min at room temperature and evaporated to 3 cm^3. Addition of butanol (10 cm^3) led to crystallization of compound **6** as a green solid. Anal. Calcd for $C_{17}H_{33}Cl_3N_5Ni_2O_5$: C, 33.41; H, 5.44; N, 11.46. Found: C, 33.1; H, 5.3; N, 11.5.

A crystal suitable for X-ray analysis was obtained by slow evaporation of a methanol/butanol solution of **6**.

X-ray Structure Analysis. $[Ni_2(C_{16}H_{28}ON_5)(H_2O)_2Cl_2]Cl\cdot H_2O\cdot CH_3OH$ (6). Cell parameters were determined from the setting angles of 25 reflections, measured on a Nonius CAD4 automatic diffractometer (Mo Kα radiation) using a pale green crystal of the compound with approximate dimensions 0.35 × 0.40 × 0.55 mm. Crystals are monoclinic, space group $P2_1/a$, with $a = 14.821(5)$ Å, $b = 10.270(4)$ Å, $c = 17.663(6)$ Å, $\beta = 108.87(3)°$, $V = 2544(2)$ Å^3, $Z = 4$, $D_c = 1.596$ g/cm^3, and λ(Mo Kα) = 0.710 69 Å. Intensities were collected, on the same diffractometer, in the range $5° < 2\theta < 40°$ using graphite-monochromated Mo Kα radiation and the $\theta - 2\theta$ technique. The intensity data were collected only to a limit of 2θ of 40° because besides this angular reflection observed reflections are practically absent. This feature is probably due to the presence of the methanol molecule which is disorderly disposed around a center of symmetry. For this same reason the number of observed reflections [$F_o \geq 4\sigma(F_o)$] is about 0.5 with respect to the total independent collected reflections. Three standard reflections were measured periodically to check the stability of the crystal and of the diffractometer. A total of 2451 reflections were collected, 2354 of which had $I > 2\sigma(I)$.

Intensities were corrected for Lorentz and polarization effects, and an absorption correction was applied once the structure was solved by using the Walker and Stuart method.[23] The structure was solved by direct methods, using the SIR-97 program,[24] and subsequently refined by the full-matrix least-squares program SHELXL-93.[25] ΔF Fourier synthesis showed the presence of a molecule of methanol in a disordered position around a center of symmetry. As a consequence, the carbon and oxygen atoms (C17 and O5, respectively) were introduced with population parameters of 0.5. Table 1 collects crystallographic refinement data. The hydrogen atoms of the macrocycle were introduced in calculated positions and their coordinates refined in agreement with those of the linked atoms. Their overall isotropic thermal displacement parameters converged to U values of 0.02(1) and 0.11(6) Å^2 for the methylenic and aromatic hydrogens, respectively. Carbon atoms were refined isotropically, as was oxygen atom O5; the four nitrogen atoms, the three chlorine atoms, and the remaining four oxygens were refined anisotropically. Atomic scattering factors and anomalous dispersion corrections for all the atoms were taken from ref 26. Geometrical calculations were performed by PARST93.[27] The molecular plots were produced by the ORTEP program.[28]

EMF Measurements. Equilibrium constants for protonation and complexation reactions with **L1** and **L2** were determined by pH-metric measurements (pH = $-\log [H^+]$) in 0.15 mol dm^{-3} Me_4NCl at 298.1 ± 0.1 K, using the fully automatic equipment that has already been described; the EMF data were acquired with the PASAT computer program.[29] The combined glass electrode was calibrated as a hydrogen concentration probe by titrating known amounts of HCl with CO_2-free Me_4NOH solutions and determining the equivalent point by Gran's method,[30] which gives the standard potential $E°$ and the ionic product of water (pK_w = 13.73(1) at 298.1 K in 0.15 mol dm^{-3} Me_4NCl, $K_w = [H^+][OH^-]$). Ligand and metal ion concentrations of 1×10^{-3} to 2×10^{-3} were employed in the potentiometric measurements, performing at least three measurements in the pH range 2−11. Due to the long time required for the equilibrium reactions between **L2** and Ni(II) to

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be reached, a batchwise potentiometric procedure was employed to determine the stability constants of the complexes formed. A preliminary set of 20 solutions containing different amounts of Ni(II) and **L2** in 0.15 mol dm^{-3} NMe_4Cl aqueous media in the pH range 4−10 were prepared in separate bottles and maintained at 298 K. The value of pH for each solution was measured periodically until a constant value was reached. Further solutions were prepared, once a first estimation of the stability constants was obtained, to better define the chemical model and improve and verify the values of the constants. The HYPERQUAD computer program was used to process the potentiometric data.[31] All titrations were treated either as single sets or as separate entities, for each system, without significant variation in the values of the determined constants.

NMR and Electronic Spectroscopy. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 instrument, operating at 200.13 and 50.33 MHz, respectively. For the ^1H NMR experiment, the peak positions are reported with respect to HOD (4.75 ppm); dioxane was used as the reference standard in ^{13}C NMR spectra ($\delta = 67.4$ ppm). For the spectra recorded in $CDCl_3$, the peak positions are reported with respect to TMS. $^1H-^1H$ and $^1H-^{13}C$ correlation experiments were performed to assign the signals. UV absorption spectra were recorded at 298 K on a Varian Cary-100 spectrophotometer equipped with a temperature control unit.

Results and Discussion

Synthesis. The synthetic pathway used to obtain the ligands **L1** and **L2** is depicted in Scheme 1. The reaction used to obtain the tosylated macrocycles **4** and **5**, a modification of the Richman−Atkins method, involves the cyclization of the polytosylated polyamines **2** and **3**, respectively, with 1 equiv of the 2,6-bis(bromomethyl)anisole (**1**), in the presence of an alkaline carbonate base. The final compounds were obtained by a 1 + 1 cyclization scheme. **L1** is easily obtained by recrystallization from CH_3CN, while to achieve **L2** the crude product must be purified by chromatography. The cleavage reactions of the *p*-toluensulfonic groups of the tosylated compounds were carried out with lithium in liquid ammonia. The reducing conditions of the treatment also led to the demethylation reaction of the ethereal methyl group of the anisole, obtaining, after the described workup, the ligands **L1** and **L2**. Both compounds were further purified as hydrochloride salts. Other cleavage reactions of the tosyl groups, using PBr_3 or an acetic acid−48% aqueous HBr mixture, led to an uncontrolled reaction. In these cases it was possible to isolate, in very low yield, the product derived by the bromuration of the phenolic function in the *para* position, as reported by Kimura et al.[32]

Description of the Structure of $[Ni_2(H_{-1}L2)(H_2O)_2Cl_2]Cl\cdot H_2O\cdot CH_3OH$ (6). The crystals of complex **6** are made up of $[Ni_2(C_{16}H_{28}ON_5)(H_2O)_2Cl_2]^+$ cations, chloride counterions, crystallization water, and methanol molecules. The macrocyclic ligand acts as hexadentate. Every Ni atom has octahedral coordination geometry. The metal ion Ni1 is coordinated by two nitrogens [N4, N5], by the oxygen atom [O1] of the macrocycle, by two oxygen atoms of two water molecules [O2, O3], and by one chloride [Cl1], while Ni2 is coordinated by three nitrogens [N1, N2, N3], by the oxygen of the macrocycle [O1], and by two chlorine anions [Cl1, Cl2]. Table 2 reports selected bonds and angles found in compound **6** (Table 2, Figure 1).

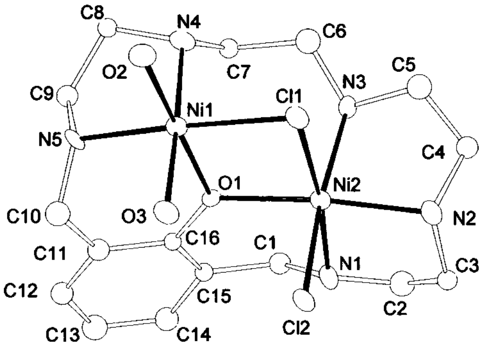

Figure 1. ORTEP view of compound **1**.

Table 2. Selected Bond Distances and Angles for **6**

Bond Distances(Å)			
Ni(1)−O(1)	2.03(1)	Ni(2)−O(1)	2.08(1)
Ni(1)−N(5)	2.06(2)	Ni(2)−N(1)	2.09(2)
Ni(1)−N(4)	2.10(2)	Ni(2)−N(2)	2.11(2)
Ni(1)−O(2)	2.15(2)	Ni(2)−N(3)	2.12(2)
Ni(1)−O(3)	2.21(2)	Ni(2)−Cl(1)	2.472(7)
Ni(1)−Cl(1)	2.429(7)	Ni(2)−Cl(2)	2.552(6)
Nickel−Nickel Distance (Å)			
Ni(1)−Ni(2)	3.209(4)		
Bond Angles (deg)			
O(1)−Ni(1)−N(5)	89.3(6)	O(1)−Ni(2)−N(1)	88.1(6)
O(1)−Ni(1)−N(4)	93.9(7)	O(1)−Ni(2)−N(2)	171.8(6)
N(5)−Ni(1)−N(4)	85.5(7)	N(1)−Ni(2)−N(2)	83.7(7)
O(1)−Ni(1)−O(2)	176.0(6)	O(1)−Ni(2)−N(3)	97.7(6)
N(5)−Ni(1)−O(2)	92.6(7)	N(1)−Ni(2)−N(3)	101.6(8)
N(4)−Ni(1)−O(2)	89.7(7)	N(2)−Ni(2)−N(3)	83.6(7)
O(1)−Ni(1)−O(3)	89.8(6)	O(1)−Ni(2)−Cl(1)	86.5(4)
N(5)−Ni(1)−O(3)	93.8(6)	N(1)−Ni(2)−Cl(1)	172.4(6)
N(4)−Ni(1)−O(3)	176.2(7)	N(2)−Ni(2)−Cl(1)	101.7(5)
O(2)−Ni(1)−O(3)	86.6(6)	N(3)−Ni(2)−Cl(1)	84.5(6)
O(1)−Ni(1)−Cl(1)	88.9(4)	O(1)−Ni(2)−Cl(2)	90.2(4)
N(5)−Ni(1)−Cl(1)	177.2(5)	N(1)−Ni(2)−Cl(2)	87.5(6)
N(4)−Ni(1)−Cl(1)	96.8(6)	N(2)−Ni(2)−Cl(2)	89.9(5)
O(2)−Ni(1)−Cl(1)	89.0(5)	N(3)−Ni(2)−Cl(2)	168.1(5)
O(3)−Ni(1)−Cl(1)	84.0(4)	Cl(1)−Ni(2)−Cl(2)	87.2(2)

As can be seen in Figure 1, the atoms O1 and Cl1 bridge the two nickel atoms. The Ni−N bond distances, which span between 2.06(2) and 2.12(2) Å, and the Ni−O bond distances, comprised in the range 2.03(2)−2.22(2) Å, are comparable with those previously reported for nickel(II) complexes with macrocycles acting as ligands, as found by an analysis carried out using the Cambridge Structural Database (CSD) V5.16.[33] Ni−Cl distances have values in the range of 2.429(7)−2.551(7) Å, but no analogous structures were found in the CSD. The distance from the two nickel atoms Ni1 and Ni2 is 3.209(4) Å, and they are on the same side of the mean plane described by all the non-hydrogen atoms defining the macrocyclic ring, with Ni1 at a longer distance than Ni2. The mean planes N5, O1, O2, Cl1 and N1, N2, O1, Cl1 form angles of 19.2(6)° and 20.7(6)°, respectively, with the aromatic ring. Finally, some H-bond contacts (<3.0 Å) involving the crystallization water molecule, the chloride anions, and various hydrogen and nitrogen atoms of the ligand are present (see Table 3).

Solution Studies. Basicity. Table 4 summarizes the basicity constants of **L1** and **L2** potentiometrically determined in 0.15 mol dm^{-3} NMe_4Cl aqueous solution at 298.1 K. Due to the presence of the phenolic function, if the ligands lose the hydroxyl proton, they can be present in solution as anionic species $H_{-1}L^-$. Examining the stepwise addition of the protons starting from this species, both compounds can bind up to five protons in the pH range 2−11 investigated. In this way, **L1** gives rise to the fully protonated ligand that is not achieved for **L2** in the pH-potentiometric range investigated.

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Table 3. Intra- and Intermolecular N−H···X Bond Distances (Å) and Angles (deg)

	H···X bond distance	angle		H···X bond distance	angle
N1−H1···Cl2^{a}	2.82(2)	109(1)	N_2−H_2···Cl2^{b}	2.55(2)	145(2)
N5−H5···O2^{a}	2.76(2)	99(1)	N5−H5···Cl3^{c}	2.46(2)	155(2)
N4−H4···O2^{a}	2.82(2)	92(2)			

^{a} *x, y, z.* ^{b} $-x + 1, -y + 1, -z + 1$. ^{c} $x, y - 1, z$.

L1 and **L2** show high basicity in the first three protonation steps, with the first constants log $K_1 = 11.10$ and 11.40 for **L1** and **L2**, respectively. The remarkably high first value can be explained taking into account that the addition of the proton occurs on an anionic species. The fully azamacrocycles of the [3*k*]N$_k$ series or the polyazacyclophane ligands of analogous dimensions show in fact a lesser basicity in the first and in all other protonation steps.[34]

L1 shows similar basicity constants in the first two protonation steps with log $K_2 = 10.73$, while the values decrease in the third proton addition (log $K_3 = 8.05$), and there is a real gap of 4.02 logarithm units for the fourth step (log $K_4 = 4.03$); the last constant is only barely detectable. Considering the number of the protonation sites and their localization, this trend in the constant values can be rationalized in terms of minimization of the electrostatic repulsion between positive charges in the protonated species. In other words, the first two protons can occupy alternate positions in the macrocycle separated by unprotonated sites; the much lower affinity of the ligand for the third and mainly for the fourth proton is due to the fact that these protonation reactions occur on positions having other close protonated sites.

L2 shows a greater grouping of the log *K* values for the addition reactions of the first three protons, which range between 11.40 and 9.78 logarithm units; again, a gap of approximately four logarithm units occurs in the fourth step (log $K_4 = 5.83$). These data too can be analyzed in terms of minimization of electrostatic repulsion in the largest **L2**. Lastly, although the two macrocycles have a similar protonation trend in the pH range investigated, **L2** shows higher basicity constants than **L1** in almost all the proton additions, in accordance with the greater dimensions and number of protonatable sites of such a ligand, which better minimizes the electrostatic repulsion.

UV−vis absorption electronic spectra of **L1** and **L2** in aqueous solution at different pH values were carried out to understand the role of the phenolic function in the acid−base behavior of such ligands. The involvement of the phenolic group in the protonation steps is well depicted by these spectra, as shown for **L2** in Figure 2, which depicts the trend of the absorbance values at $\lambda = 298$ nm and the distribution diagram of the protonated species of **L2** (3×10^{-4} mol dm^{-3}) as a function of pH. The full spectra show different wavelength maxima ($\lambda_{\max}$) in the opposite pH field. At acidic pH, a $\lambda_{\max}$ at 277 nm is observable, while at alkaline pH the spectra exhibit two $\lambda_{\max}$'s at 242 and 298 nm, respectively. This different behavior of the chromophore in the opposite pH fields can be attributed to the deprotonation of the phenolic group, in agreement with data reported in the literature. In other words, the change in $\lambda_{\max}$ is due to the presence of the phenol hydroxyl form at low pH values and to the phenolate form at high pH values. Monitoring the spectra from acidic to basic pH, the band with $\lambda_{\max} = 298$ starts to appear from pH 5 and reaches its maximum in absorbance at pH 8 for **L2**, where the triprotonated species [H$_2$**L2**]$^{2+}$ is prevalent in solution (see Figure 2). This means that the deprotonation of the hydroxyl function occurs in this pH range involving the [H$_2$**L2**]$^{2+}$ species. The species has the chromophore in its anionic form starting from pH values ≥ 7. Moreover, at pH values higher than 11 there is a drop in the molar absorptivity of the spectra, preserving the same wavelength maxima. These data can be explained by the involvement of the phenolate group in the stabilization, *via* hydrogen bonding, of the acidic protons in the protonated species, which increases the populations in the excited state without changing the energy of the state. **L1** shows a similar UV−vis absorption spectrum, suggesting that also in this case the deprotonation of the phenol function occurs in the [H$_2$**L1**]$^{2+}$ species. The negative charge is present on **L1** at pH values >6. The triprotonated species [H$_2$**L**]$^{2+}$ are the most prevalent at neutral pH for both ligands (Figure 2). In comparison with the free phenol, which shows log $K = 9.77$ under the same experimental conditions, it is clear that the insertion of the aromatic function in a polyamine macrocycle favors the deprotonation of the hydroxyl function which occurs at lower pH. It is of interest that, in this way, **L1** and **L2** are able to display separate positive and negative charges at the same time on the macrocycle; this situation is present only from neutral to alkaline, pH values. For example, in the [H$_2$L]$^{2+}$ species there are three positive charges localized on the polyammonium centers and one negative charge on the phenolic oxygen. Considering this aspect, this type of ligand shows promise for use in host−guest chemistry not only as a host for anionic substrates, as the polyammonium receptors are usually employed, but above all for substrates presenting a simultaneous separation of negative and positive charges such as the simple amino acids in zwitterionic form.

Coordination of Metal Ions. The coordination characteristics of **L1** and **L2** were studied in 0.15 mol dm^{-3} NMe$_4$NCl aqueous solution at 298.1 K. The stability constants for the equilibrium reactions of the two macrocycles with Ni(II), Cu(II), and Zn(II) were potentiometrically determined and are reported in Tables 5 and 6 for **L1** and **L2**, respectively. **L1** forms only mononuclear M(II) species, while **L2** can also form binuclear complexes with all the M(II) ions examined. Nevertheless, the mononuclear species is largely prevalent in aqueous solution also for **L2** when the metal ion to ligand ratio is close to 1:1. When the **L2**/M(II) molar ratio is 1:2, the binuclear species are instead prevalent. This behavior is depicted in parts a and b of Figure 3, which show the distribution diagram of the species for the system **L2**/Cu(II) in 1:1 and 1:2 molar ratios, respectively, as a function of pH.

Mononuclear Complexes. **L1** and **L2** form rather stable mononuclear complexes with the metal ions here examined. The Cu(II) complexes show higher stability than Ni(II) and Zn(II) complexes for both ligands. Comparing the stability constants of the complexation reactions $M^{2+} + H_{-1}L^{-} \rightleftarrows [MH_{-1}L]^{+}$ for the two ligands with Ni(II), Cu(II), and Zn(II), it can be noted that the addition of all three metal ions to the species H$_{-1}$L^{-} is moderately favored for the larger ligand **L2**. These data can be reasonably explained taking into account the greater flexibility and number of donor atoms of **L2**, which can better stabilize the mononuclear species formed. Both ligands show a similar tendency to add the metal ions either to the anionic H$_{-1}$L^{-} species or to the neutral species L (see Tables 5 and 6). These data can be interpreted in consideration of the fact that all the donor atoms are not involved in the stabilization of the ion. In fact, the additions of the first proton to the species [MH$_{-1}$L]$^{+}$ have values ranging from 8.96 to 10.22 logarithm units; these values are close to the values of the first proton addition to the

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Table 4. Protonation Constants (log *K*) of **L1** and **L2** Determined by Means of Potentiometric Measurements in 0.15 mol dm^{-3} NMe$_4$Cl Aqueous Solution at 298.1 K[a]

	log K			log K	
reaction	**L1**	**L2**	reaction	**L1**	**L2**
$H_{-1}L^- + H^+ \rightleftarrows L$	11.10(1)	11.40(1)	$H_2L^{2+} + H^+ \rightleftarrows H_3L^{3+}$	4.03(2)	5.83(2)
$L + H^+ \rightleftarrows HL^+$	10.73(1)	10.49(1)	$H_3L^{3+}\ H^+ \rightleftarrows H_4L^{4+}$	1.4(1)	3.21(3)
$HL^+ + H^+ \rightleftarrows H_2L^{2+}$	8.05(1)	9.78(1)			

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

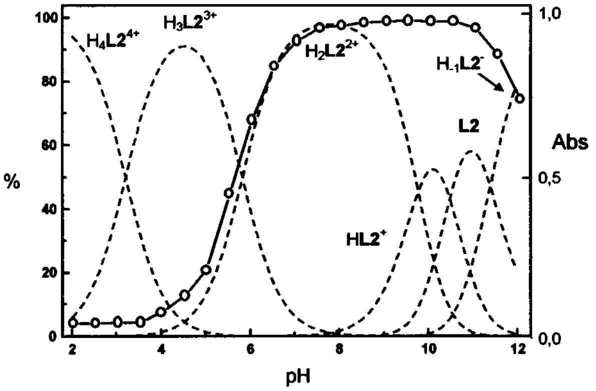

Figure 2. Absorbance values at λ = 298 nm (○) and distribution diagram of the protonated species (- - -) of **L2** as a function of pH, in aqueous solution at 298.1 K in 0.15 mol dm^{-3} NMe$_4$Cl.

Table 5. Logarithms of the Equilibrium Constants Determined in 0.15 mol dm^{-3} NMe$_4$Cl at 298.1 K for the Complexation Reactions of **L1** with Ni(II), Cu(II), and Zn(II) Ions[a]

	log K		
reaction (L = **L1**)	Ni(II)	Cu(II)	Zn(II)
$M^{2+} + H_{-1}L^- \rightleftarrows MH_{-1}L^+$	14.66(1)	21.47(1)	13.53(1)
$M^{2+} + L \rightleftarrows ML^{2+}$	13.79(1)	19.64(1)	11.39(1)
$MH_{-1}L^+ + H^+ \rightleftarrows ML^{2+}$	10.22(1)	9.27(1)	8.96(1)
$ML^{2+} + H^+ \rightleftarrows MLH^{3+}$	3.75(2)	1.99(3)	4.38(1)
$MH_{-1}L^+ + OH^- \rightleftarrows MH_{-1}LOH$	2.47(3)	2.45(3)	3.45(2)

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

Table 6. Logarithms of the Equilibrium Constants Determined in 0.15 mol dm^{-3} NMe$_4$Cl at 298.1 K for the Complexation Reactions of **L2** with Ni(II), Cu(II), and Zn(II) Ions[a]

	log K		
reaction (L = **L2**)	Ni(II)	Cu(II)	Zn(II)
$M2^+ + H_{-1}L^- \rightleftarrows MH_{-1}L^+$	17.74(1)	23.14(2)	15.99(2)
$M^{2+} + L \rightleftarrows ML^{2+}$	15.84(1)	21.64(2)	14.06(1)
$MH_{-1}L^+ + H^+ \rightleftarrows ML^{2+}$	9.50(1)	9.90(1)	9.47(2)
$ML^{2+} + H^+ \rightleftarrows MLH^{3+}$	5.12(2)	4.71(2)	5.09(1)
$MH_{-1}L^+ + OH^- \rightleftarrows MH_{-1}LOH$	3.32(2)	3.09(1)	
$2M^{2+} + H_{-1}L^- \rightleftarrows M_2H_{-1}L^{3+}$	23.55(3)	31.54(4)	20.43(3)
$M^{2+} + H_{-1}LM^+ \rightleftarrows M_2H_{-1}L^{3+}$	5.81(3)	8.41(3)	4.44(2)
$M_2H_{-1}L^{3+} + OH^- \rightleftarrows M_2H_{-1}LOH^{2-}$	6.04(3)	6.32(3)	

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

free ligands. In conclusion, it can be stated that, in all the metal-complexed species $[MH_{-1}L]^+$ of **L1** and **L2**, the ligands present a donor atom not bound to the metal ions. Moreover, diprotonated complexes also were observed. The addition constants of the second proton to the monoprotonated complexes [ML] are lower than the first one, indicating that the protonation must involve a donor atom bound to the metal ions; the additions are higher for the species of **L2** than for those of **L1**. All the $[MH_{-1}L]^+$ complexes give rise to hydroxylated $[MH_{-1}LOH]$ species at alkaline pH, except the $[ZnH_{-1}\mathbf{L2}]^+$ species in which all the coordination sites of the metal are probably saturated by the ligand. To obtain further information about the involvement of the phenolic function in the coordination of the metal ion, the complex formation reactions were followed by means of UV electronic spectra recorded in aqueous solution under the same conditions of the potentiometric measurements. The metal complexes of **L1** ([M] = [L] = 2 × 10^{-4} mol dm^{-3}) show over the entire pH range a rather sharp band attributed to the phenolic moiety, at λ_{max} = 275, 277, and 275 nm for the Ni(II), Cu(II), and Zn(II) complexes, respectively. Moreover, the molar absorptivities (ϵ) approximately maintain their value throughout the pH range for all three metal complexes (ϵ = 5700, 5900, and 5600 cm^{-1} mol^{-1} dm^3 for the Ni(II), Cu(II), and Zn(II) complexes, respectively). Such behavior indicates that the oxygen of the phenolic group is involved in the stabilization of the complex. This occurs also for the protonated complexed species at acidic pH, and due to the maintenance of the same λ_{max} and ϵ also at alkaline pH, the group involved is in the phenolate form. The UV spectra recorded on solutions containing **L2** and 1 equiv of one of the metal ions, in which only the mononuclear species are present (see Figure 3a), show similar behaviors. In conclusion, in the mononuclear metal complexes of both ligands, the phenolic group always participates in the coordination in its phenolate form; for this reason, the unbound donor atom present in all the species must be a

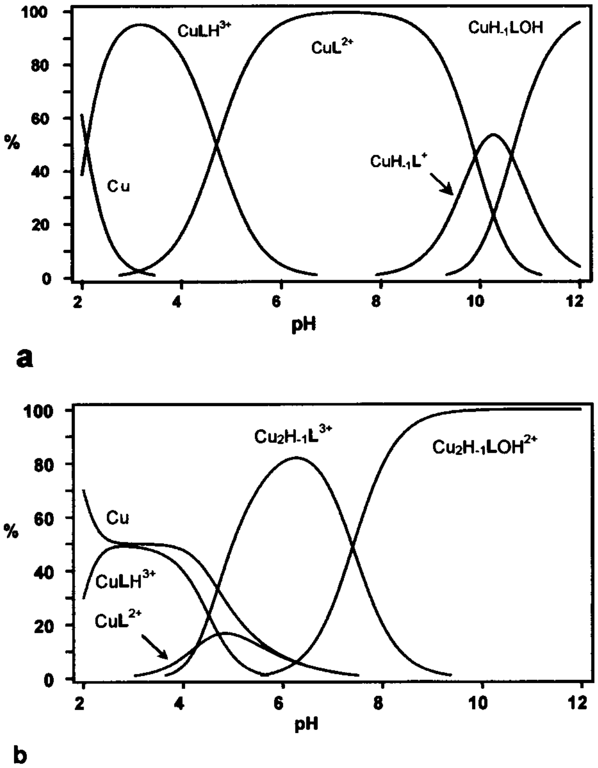

Figure 3. Distribution diagrams of the species for the systems **L2**/Cu(II) as a function of pH in aqueous solution, *I* = 0.15 mol dm^{-3} NMe$_4$Cl, at 298.1 K. (a) [**L2**] = 1 × 10^{-3} mol dm^{-3}, [Cu^{2+}] = 1 × 10^{-3} mol dm^{-3}. (b) [**L2**] = 1 × 10^{-3} mol dm^{-3}, [Cu^{2+}] = 2 × 10^{-3} mol dm^{-3}.

nitrogen atom. Examining the molecular structure of **L1** and **L2**, which shows a crowding and stiffening of the macrocyclic cavity near the aromatic group, and comparing it with that of the metal complexes of analogous ligands such as the polyazacyclophanes reported by Garcia-España,[35] led us to suppose that this unbound atom is one of the nitrogen atoms close, to the phenolic group. In other words, the bulk of the aromatic part prevents the simultaneous involvement of all the nitrogens in the coordination to the metal ions in the mononuclear species, leaving one unbound nitrogen atom in the benzylic position.

Binuclear Complexes. Only **L2** forms binuclear complexes with the three metal ions. In fact, the $[MH_{-1}\mathbf{L2}]^+$ species can coordinate another M(II) ion in aqueous solution, giving the binuclear species with stoichiometry $[M_2H_{-1}\mathbf{L2}]^{3+}$. The addition of the second cation gave lesser stability constants than the first one, due to the low number of donor atoms present in the ligand. A considerable value was found for the addition of the second Cu(II); in this case, for a 2:1 Cu(II):**L2** molar ratio, the binuclear species are largely prevalent in aqueous solution at pH values higher than 6 (Figure 3b). For the Ni(II) and Cu(II) complexes it was possible to detect a hydroxylated species, which are prevalent at alkaline pH. The constant values for the addition of the OH^- anion to the $[M_2H_{-1}\mathbf{L2}]^{3+}$ complex are very high (6.04 and 6.32 logarithmic units for the Ni(II) and Cu(II) complexes, respectively) in comparison with the analogous constants for the addition of the hydroxo group to the corresponding mononuclear complexes (see Table 6). This is indicative of a strong binding of the hydroxide ion in the binuclear complex, leading us to suppose that this species is bridged between the two metal ions, as observed for one of the chlorine ions in the crystal structure. The low addition constant of the second zinc ion (log $K = 4.44$) produces the precipitation of the zinc hydroxide at alkaline pH, preventing the potentiometric measurements for molar ratio **L2**:Zn(II) higher than 1:1; nevertheless, a binuclear species, $[Zn_2H_{-1}\mathbf{L2}]^{3+}$, was detected.

It is important to underline that the ligational properties of **L2** are profoundly different from those of the polyazamacrocycles of the $[3k]N_k$ series.[36] In fact, such ligands do not exhibit binuclear complexes in aqueous solution with the metal ions. Moreover, binuclear complexes with the more stable Cu(II) ion are observable only with the ligands containing at least seven donor atoms.

UV spectra were recorded in aqueous solution containing **L2** (1×10^{-4} mol dm^{-3}) and M(II) in various molar ratios and different pH values to understand the role played by the phenolic function in the formation of the binuclear complexes. The UV spectra recorded for the system **L2**/Cu(II) at pH 6.5 at different molar ratios show an increase in the absorbance at the formation of the binuclear species, preserving the same λ_{max} at 277 nm. In particular, at this pH, for molar ratios L:Cu(II) of 1:1 only the mononuclear species $[Cu\mathbf{L2}]^{2+}$ is prevalent in solution ($\epsilon = 5400$ cm^{-1} mol^{-1} dm^3), while for the molar ratio 1:2 almost exclusively binuclear species exist (see Figures 3a and 3b). Such binuclear species do not change their molar absorptivities ($\epsilon = 8400$ cm^{-1} mol^{-1} dm^3) also at pH greater than 6.5, indicating that the phenol participates in the complexation in the same manner in all the binuclear species. Similar features were found for the other two metal complexes. Lastly, changing its spectral characteristics at various L:M(II) molar ratios, the phenolic function in phenolate form must contribute also to the stabilization of the second metal ion. These experimental data support the hypothesis that the phenol plays an important role in the formation of the binuclear species with **L2**, due to the capacity of the phenolic oxygen to bridge two metal ions, permitting the ligand to assemble two metal ions very close together with just a low number of donor atoms. A proposal for the coordination sites in the mono- and binuclear complexes is shown in parts a and b of Figure 4. In the binuclear species, the metal ions do not have all the binding sites saturated by the donor atoms of **L2**, and thus they complete their coordination sphere by adding new species such as water molecules, OH^-, and Cl^- as in the crystal structure, preferring substrates having the possibility to bridge the two metal ions.

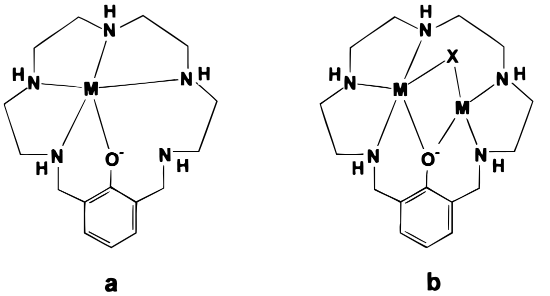

Figure 4. Proposed coordination models of the Ni(II), Cu(II), and Zn(II) ions in $[MH_{-1}\mathbf{L2}]^+$ (a) and $[M_2H_{-1}\mathbf{L2}]^{3+}$ (b) complexes. The drawings of the complexes are only partial, as other species coordinating at the remaining sites of M(II) are not specified. X = bridging ligands.

Concluding Remarks

The two new macrocycles **L1** and **L2** present the phenolic function in a polyaza skeleton. This moiety produces an increase in the basicity of the macrocycles as compared to analogous ligands. The phenol is present in its deprotonated form starting from neutral pH, giving rise to a separation of the negative and positive charges in the ligands. This makes this type of ligand attractive as a receptor for amino acids and other substrates characterized by internal separation of charge opposites. **L1** forms stable mononuclear complexes with Ni(II), Cu(II), and Zn(II) ions, in which a nitrogen atom in the benzylic position remains unbound. **L2** shows a similar behavior in the mononuclear complexes with the involvement of the phenolate group in the stabilization of the species starting from the acidic pH. Binuclear complexes were also achieved with **L2**, giving the opportunity to assemble two metal ions such as Ni(II), Cu(II), and Zn(II) very close to each other. This is possible using macrocycles with a relatively low number of donor atoms, such as **L2**. This possibility is ascribed to the presence of the phenolate function, the oxygen of which bridges two metal ions. In the binuclear species the metal ions show an unsaturated coordination environment. The solution studies highlighted the great tendency to bind the hydroxide ion to the $[M_2H_{-1}\mathbf{L2}]^{3+}$ species of Ni(II) and Cu(II), suggesting that the OH^- probably bridges the two metal centers. A similar disposition of one substrate that bridges the two metal ions is shown in the crystal structure of the binuclear nickel complex. Due to the short distance in which the two metal ions are kept by the macrocyclic framework, such binuclear species are promising receptors for substrate molecules, which can bridge the metal centers. It would be of interest to extend the binding properties of **L2** to the other transition M(II) ions such as Co(II), the binuclear complexes

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of which could be used in studies of oxygen addition and carriers.

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Supporting Information Available: Tables of crystallographic data, positional parameters, isotropic and anisotropic thermal factors, and bond distances and angles. This material is available free of charge via the Internet at http://pubs.acs.org.

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