Mono- and Dinuclear Cu^{II} and Zn^{II} Complexes of Cyclen-Based Bis(macrocycles) Containing Two Aminoalkyl Pendant Arms of Different Lengths

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Keywords: Copper / Coordination modes / Macrocyclic ligands / N ligands / Zinc

The basicity and coordination properties towards Cu^{II} and Zn^{II} of the bis(macrocycles) **L1**, **L2** and **L3** have been investigated by means of potentiometric, ^1H NMR and UV/Vis spectroscopic titrations in aqueous solutions. The synthesis of **L1** and **L3** is also described. The three ligands are composed of two [12]aneN_4 units separated by a *p*-phenylene spacer and differ in the length of the aminoalkyl pendant arms linked to each macrocyclic unit. **L1**–**L3** form mono- and dinuclear complexes in aqueous solutions; in the dinuclear species each metal ion is coordinated by one of the two identical [12]aneN_4 ligand moieties, as shown by the crystal structures of the complexes $[Cu_2\mathbf{L1}]Cl_4\cdot 8H_2O$, $[Zn_2\mathbf{L2}](ClO_4)_4$ and $[Zn_2\mathbf{L3}](ClO_4)_4\cdot H_2O$. In all structures the metal ion is pentacoordinate, and is bound to the four nitrogen donors of the cyclic unit and to the amine group of the side arm. The stability of both the $[ML]^{2+}$ and $[M_2L]^{4+}$ complexes in aqueous solution decreases in the order **L1** > **L2** > **L3**. At the same time, both the $[Cu_2L]^{4+}$ and $[Zn_2L]^{4+}$ complexes show a different ability in proton binding among the three ligands, with the $[M_2\mathbf{L1}]^{4+}$ complexes displaying the highest basicity. These results are explained in terms of the decreasing number of nitrogen donors involved in Cu^{II} or Zn^{II} binding on passing from **L1** to **L3**; in other words, while in the **L1** dinuclear complexes each metal ion is coordinated to the four amine groups of a [12]aneN_4 moiety and to the amine group of the side arm, in the **L3** ones the metal cations are bound only to the four donor atoms of a cyclic moiety, the aminobutyl group not being coordinated.

Introduction

There is a continuing interest in the chemistry of polyazamacrocycles because of their ability to form chelates in aqueous solutions and to act as selective complexing agents for metal cations. Structural factors, such as ligand rigidity and the electron-donor properties of the nitrogen atoms and their disposition, have been shown to play significant roles in determining the binding features of macrocycles toward metal cations.[1–17]

Among polyazamacrocycles, the investigations have been focused on tetraazamacrocycles owing to their proven ability in binding biologically relevant metal ions. For example, cyclen and cyclam and their derivatives have been studied as carriers of metal ions in antitumour and imaging applications.[18–22] Furthermore, metal complexes with these polyazamacrocyclic ligands can behave as metallo-receptors for organic and inorganic anions (similar to thymidine mono- and diphosphate nucleotides).[23,24]

From this point of view the introduction of structural features that impart high selectivity in the recognition of different guests into the molecular framework is one of the goals in the design of synthetic receptors. Aromatic subunits are often introduced into the host molecules. The presence of rigid aromatic systems gives particular coordination properties to the ligands defining distinct preorganized binding sites for the metal ions within the ligand itself. Furthermore, the attachment of an aminoalkyl side arm can strongly effect the coordination properties of the ligand,[25–48] depending on the nature of the donors of the pendant arms.

To gain further insight into the coordination chemistry of cyclen derivatives, we have now synthesised the two homoditopic ligands **L1** and **L3**, which are composed of two [12]aneN_4 units separated by a rigid *p*-phenylene spacer; each tetraazamacrocyclic moiety bears an aminoalkyl pendant arm (an aminoethyl pendant arm in the case of **L1** and an aminobutyl one in the case of **L3**).

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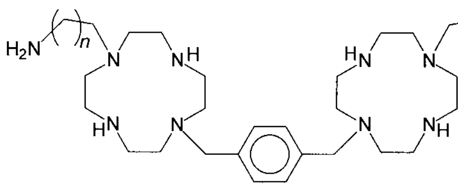
DOI: 10.1002/ejic.200400896



$n = 1$, **L1**
$n = 2$, **L2**
$n = 3$, **L3**

With the aim of making a comparative study of the coordination properties of these homoditopic ligands, the proton binding and Cu^{II} and Zn^{II} complexation with **L1**, **L3** and **L2**,[49] which displays a similar molecular architecture but contains two aminopropyl side arms, were studied in the solid state by X-ray diffraction methods and in aqueous solution by potentiometric and ^{1}H NMR measurements.

Results and Discussion

Ligand Protonation

The protonation equilibria of **L1**–**L3** were studied by means of potentiometric measurements in 0.1 M Me$_4$NCl aqueous solution at 298.1 K; the corresponding basicity constants are reported in Table 1.

Table 1. Logarithms of the protonation constants of ligands **L1**, **L2** and **L3** determined by means of potentiometric measurements in 0.1 M Me$_4$NCl at 298.1 K.

Reaction	log*K*		
	L1	**L2**	**L3**
$LH^+ + H^+ \rightleftharpoons LH_2^{2+}$	9.74(3)[a]	10.07(2)	10.30(2)
$LH_2^{2+} + H^+ \rightleftharpoons LH_3^{3+}$	8.88(5)	9.24(3)	9.54(3)
$LH_3^{3+} + H^+ \rightleftharpoons LH_4^{4+}$	8.39(4)	8.87(2)	9.08(2)
$LH_4^{4+} + H^+ \rightleftharpoons LH_5^{5+}$	7.33(6)	7.69(3)	7.80(4)
$LH_5^{5+} + H^+ \rightleftharpoons LH_6^{6+}$	6.67(6)	7.22(3)	7.40(3)

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

Ligands **L1**–**L3** behave as hexaprotic bases, at least in the pH range investigated (2–11). **L1**–**L3** display almost equal basicity constants for the first protonation step (10.07–10.34 log units). Similar high values for the first protonation constant are often found in polyamine macrocycles and are generally attributed to the simultaneous involvement of two or more amine groups in proton binding.[50] The data in Table 1 also show that the first six basicity constants range between about 10 and 7 log units. Further protonation steps are not detectable by potentiometry under our experimental conditions. This behaviour can be rationalised in terms of minimisation of the electrostatic repulsion between the positive charges in the protonated species of polyazamacrocycles. In other words, the first six protons can occupy alternate positions in the macrocycles, separated by a non-protonated amine group and/or by the *p*-phenylene linkage, while three or more protonated nitrogen atoms would necessarily be contiguous in the species with a protonation degree greater than six. For this reason, the $[H_xL]^{x+}$ species with $x > 6$ (L = **L1**, **L2** and **L3**) are not formed, at least in the pH range investigated (2–11).

To shed further light on the basicity properties of these ligands, we carried out ^{1}H NMR titrations in aqueous solutions. The spectral features of **L1** at pH = 11.0, where the free amine predominates in solution, account for a D_{2h} time-averaged symmetry of the ligand, which is preserved over all the pH range investigated. The pH dependence of the ^{1}H NMR signals is shown in Figure 1, together with the distribution diagram of the protonated species of **L1**.

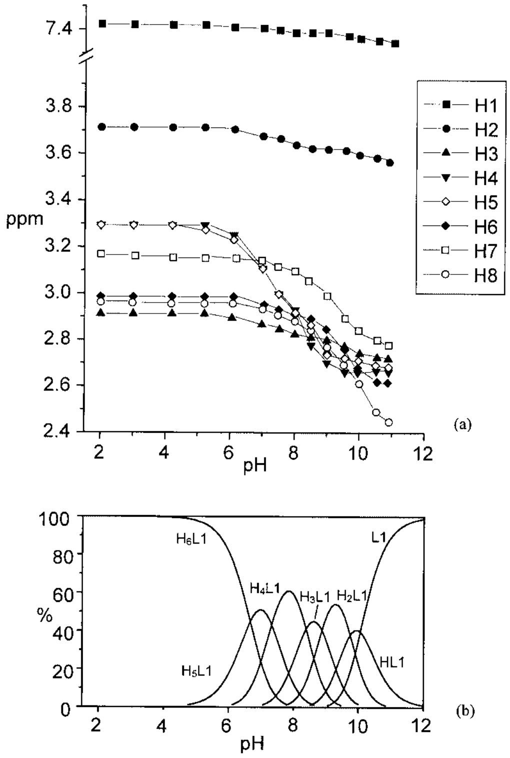
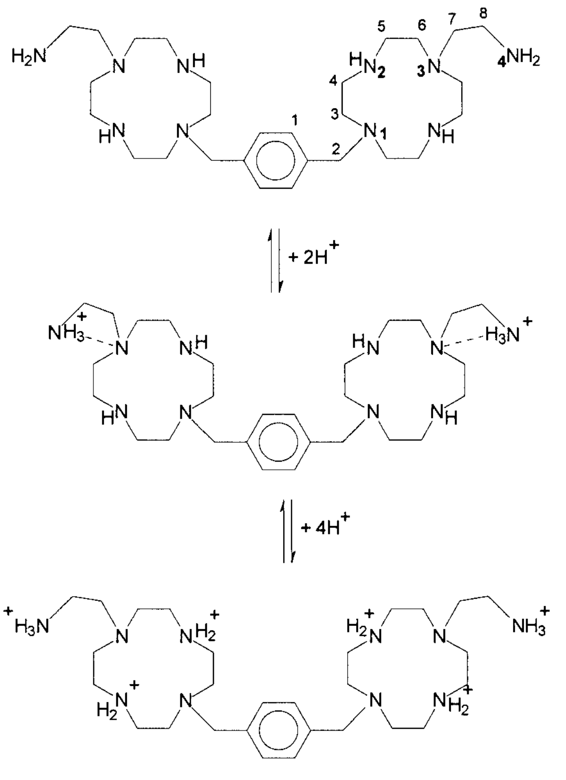


Figure 1. (a) pH dependence of the ^{1}H NMR signals of **L1**. (b) Distribution diagram of protonated species formed by **L1** as a function of pH (0.1 M Me$_4$NCl, 298.1 K, [L] = 1×10^{-3} M).

At first glance, Figure 1a shows an overall downfield shift of the resonances of all the methylene groups, with the exception of the signals of H2 and H3, which are adjacent to the tertiary amine group N1, in the pH range 11.0–6.0. This clearly indicates that the tertiary nitrogen atoms N1 are not involved in proton binding over the pH range investigated. A more accurate analysis of the pH dependence of the signals in Figure 1a shows that in the pH range 11.0–9.0, where the first two protons bind to the ligand, the resonance of H8, in the α-position with respect to N4, gives rise to the highest downfield shift (ca. 0.4 ppm), which shows that the first two protonation steps take place on the primary amine groups of the pendant arms. In the same pH range, however, a marked downfield shift (almost 0.3 ppm) is also observed for the H6 and H7 signals, which are adjacent to N3, thereby suggesting the presence of a hydrogen bond between the protonated N4 nitrogen atom and N3 and/or to a partial localisation of the acidic proton on the N3 tertiary nitrogen atom (Scheme 1).



Scheme 1.

The signals of H4 and H5, which are adjacent to the N2 nitrogen atoms, do not shift remarkably (less than 0.1 ppm) up to pH = 9. In the pH range 9–6, however, these signals give rise to a remarkable downfield shift, thus indicating that the further four protonation steps occur on the secondary amine groups of the macrocyclic ring.

Similar protonation patterns, involving initial protonation of the aminoalkyl function and then proton binding to the secondary amine groups of the macrocycle, are also found for **L2** and **L3**.

Metal Coordination

Crystal Structure of [{Cu_2L1}Cl_4]·$8H_2O$

The molecular structure consists of centrosymmetric [Cu_2**L1**]$^{4+}$ complex cations, chloride anions and water molecules. An ORTEP[51] drawing of the [Cu_2**L1**]$^{4+}$ cation is shown in Figure 2, and Table 2 reports selected distances and angles for the coordination environment of the metals.

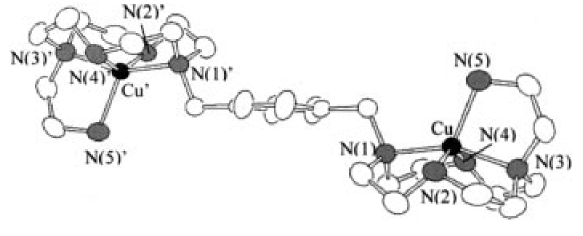


Figure 2. ORTEP drawing of the [Cu_2**L1**]$^{4+}$ cation.

Each metal ion is lodged in a cyclic tetraaza moiety and the coordination sphere is completed by the nitrogen atom of the side arm, giving rise to an overall pentacoordination which can best be described as a distorted square pyramid. The axial position is occupied by the N5 nitrogen atom of the side arm, while N1, N2, N3 and N4 define the basal plane [maximum deviation from the mean plane of 0.075(1) Å for N4]. The Cu atom lies 0.512(1) Å above this plane and is shifted toward the apical position, with an angle of 16.65(1)° between the Cu–N5 bond and the normal to the basal plane. The Cu–N bond lengths range between 2.004(6) and 2.127(6) Å (Table 2).

Table 2. Bond lengths [Å] and angles [°] for the metal-ion coordination environments in the [Cu_2**L1**]$^{4+}$ cation.

Cu–N1	2.040(6)	N4–Cu–N1	86.1(2)
Cu–N2	2.027(6)	N2–Cu–N1	86.9(2)
Cu–N3	2.049(6)	N4–Cu–N3	86.8(2)
Cu–N4	2.004(6)	N2–Cu–N3	86.0(2)
Cu–N5	2.127(6)	N1–Cu–N3	155.3(3)
		N4–Cu–N5	107.4(2)
		N2–Cu–N5	104.9(3)
		N1–Cu–N5	119.0(2)
		N3–Cu–N5	85.7(2)

Considering the overall conformation of the complex, the ligand presents a rather flat conformation, with the two symmetry-related tetraazamacrocycles lying on two parallel planes and forming an angle of 7.20(1)° with the plane defined by the aromatic unit. In consequence of this flat conformation of the ligand the two Cu^{II} ions lie at a rather long distance [11.447(1) Å].

Crystal Structures of [{Zn_2L2}$(ClO_4)_4$] and [{Zn_2L3}$(ClO_4)_4$]·H_2O

The molecular structures consist of centrosymmetric [Zn_2L]$^{4+}$ (L = **L2** and **L3**) complex cations, perchlorate anions and, in the case of the **L3** complex, water molecules. ORTEP[51] drawings of the [Zn_2**L2**]$^{4+}$ and [Zn_2**L3**]$^{4+}$ cations are shown in Figure 3a and 3b, respectively, and Table 3 reports selected distances and angles for the metal-ion coordination environments.

The coordination sphere of the Zn^{II} ions is almost equal in the two structures. Each metal ion, in fact, is five-coordinate to the four nitrogen atoms of a cyclic [12]aneN_4 moiety and the nitrogen atom of the side arm. The coordination geometry can be described as a distorted square pyramid; the basal planes are defined by the four amine groups of the [12]aneN_4 units, with maximum deviations from the mean planes being 0.0587(2) Å for N3 (**L2**) and 0.0398(2) Å for N1 (**L3**). The axial positions are occupied by a nitrogen atom of the side arm, with angles of 7.70(1)° (for **L2**) and 4.10(1)° (for **L3**) between the Zn1–N5 bond and the normal to the corresponding basal planes. Finally, the two Zn^{II} cations lie 0.783(2) Å (**L2** complex) and 0.786(2) Å (**L3** complex) above the basal plane, shifted toward the apical position.

The Zn–Zn distances are 11.776(1) and 11.770(1) Å in the Zn^{II} complexes with **L2** and **L3**, respectively.

As far as the overall conformation of the ligand is concerned, it adopts an overall flat conformation in both struc-

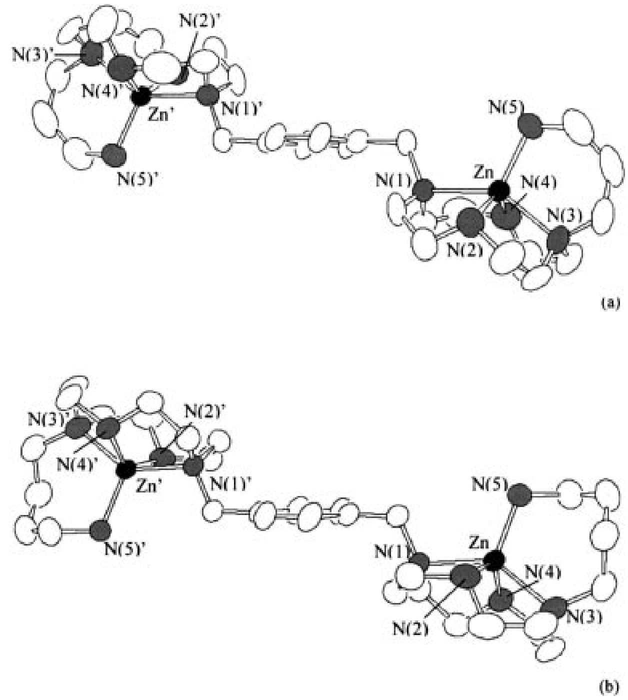


Figure 3. ORTEP drawings of the $[Zn_2\mathbf{L2}]^{4+}$ (a) and $[Zn_2\mathbf{L3}]^{4+}$ (b) cations.

tures. The two symmetry-related [12]aneN_4 units form an angle of 18.83(2)° (**L2** complex) and 22.52(1)° (for **L3** complex) with the plane defined by the aromatic unit. The two zinc ions are lodged within a symmetry-related cyclic unit at each extremity of the ligand, and the nitrogen atoms of the side arms lie *trans* with respect to the plane of the benzene unit.

Cu^{II} and Zn^{II} Coordination in Aqueous Solution

The coordination properties of **L1**–**L3** were studied by means of potentiometric measurements in aqueous solution. Table 4 lists the stability constants of the Cu^{II} and Zn^{II} complexes determined in 0.1 M NMe_4Cl at 298.1 K.

Table 3. Bond lengths [Å] and angles [°] for the metal-ion coordination environments in the $[Zn_2\mathbf{L2}]^{4+}$ and $[Zn_2\mathbf{L3}]^{4+}$ cations.

	$[Zn_2\mathbf{L2}]^{4+}$		
Zn1–N1	2.215(8)	N5–Zn1–N2	111.6(4)
Zn1–N2	2.085(9)	N5–Zn1–N4	115.4(4)
Zn1–N3	2.153(9)	N2–Zn1–N4	132.7(4)
Zn1–N4	2.115(1)	N5–Zn1–N3	102.3(4)
Zn1–N5	2.004(9)	N2–Zn1–N3	83.7(5)
		N4–Zn1–N3	82.0(4)
		N5–Zn1–N1	116.5(3)
		N2–Zn1–N1	81.8(4)
		N4–Zn1–N1	82.0(4)
		N3–Zn1–N1	141.2(4)
	$[Zn_2\mathbf{L3}]^{4+}$		
Zn1–N1	2.206(4)	N5–Zn1–N4	117.73(18)
Zn1–N2	2.110(4)	N5–Zn1–N2	109.10(17)
Zn1–N3	2.197(5)	N4–Zn1–N2	133.17(17)
Zn1–N4	2.092(5)	N5–Zn1–N3	109.68(18)
Zn1–N5	2.004(4)	N4–Zn1–N3	82.6(2)
		N2–Zn1–N3	82.53(18)
		N5–Zn1–N1	109.76(17)
		N4–Zn1–N1	82.14(18)
		N2–Zn1–N1	81.77(16)
		N3–Zn1–N1	140.43(17)

The data in Table 4 clearly outline that all ligands display similar binding features toward Cu^{II} and Zn^{II}, above all a marked ability to form both mono- and dinuclear complexes. Furthermore, the mononuclear $[ML]^{2+}$ complexes show a high tendency to protonate in solution, the three first protonation constants being only slightly lower than the corresponding basicity constants of the free ligands. The rather high values of the equilibrium constants for the protonation of the $[ML]^{2+}$ species can be reasonably ascribed to the protonation of nitrogen atoms not bound to the metal cation in the mononuclear Zn^{II} and Cu^{II} complexes the metal ion is most likely coordinated to a single macrocyclic unit, while the second one is not involved in metal-ion binding and can easily be protonated.

Considering the mononuclear complexes, it was of interest to compare the stability of the present complexes with

Table 4. Stability constants (log *K*) of the Cu^{II} and Zn^{II} adducts with **L1**, **L2** and **L3**, determined by means of potentiometric measurements in 0.1 M Me_4NCl at 298.1 K.

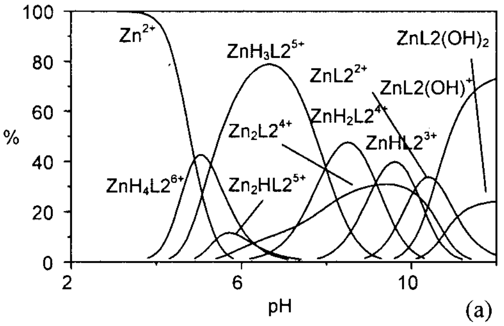
Reaction	log *K*					
	L1		**L2**		**L3**	
	Cu	Zn	Cu	Zn	Cu	Zn
$L + M^{2+} \rightleftharpoons ML^{2+}$	20.16(1)	16.45(5)	18.60(2)	14.35(7)	16.09(5)	13.40(5)
$ML^{2+} + H^+ \rightleftharpoons MHL^{3+}$	10.02(2)[a]	9.88(4)	9.55(3)	10.09(8)	10.06(5)	10.16(4)
$MHL^{3+} + H^+ \rightleftharpoons MH_2L^{4+}$	8.53(3)	8.44(4)	9.15(3)	9.16(7)	9.64(7)	9.30(7)
$MH_2L^{4+} + H^+ \rightleftharpoons MH_3L^{5+}$	7.00(3)	6.81(3)	7.76(5)	7.98(6)	8.92(7)	8.49(7)
$MH_3L^{5+} + H^+ \rightleftharpoons MH_4L^{6+}$	3.90(3)	4.32(6)	6.14(5)	5.28(7)	7.60(5)	7.44(6)
$ML^{2+} + OH^- \rightleftharpoons ML(OH)^+$	3.7(1)	4.10(4)	3.41(3)	3.26(8)	2.91(6)	3.26(6)
$ML^{2+} + M^{2+} \rightleftharpoons M_2L^{4+}$	19.77(2)	14.20(3)	17.19(4)	13.18(6)	14.66(6)	10.72(5)
$M_2L^{4+} + H^+ \rightleftharpoons M_2HL^{5+}$	4.28(1)	4.92(3)	6.07(8)	6.26(5)	9.40(6)	8.31(5)
$M_2HL^{5+} + H^+ \rightleftharpoons M_2H_2L^{6+}$			5.73(8)		9.04(6)	
$M_2L^{4+} + OH^- \rightleftharpoons M_2L(OH)^{3+}$			3.0(1)		4.86(4)	3.73(4)
$M_2L(OH)^{3+} + OH^- \rightleftharpoons M_2L(OH)_2{}^{2+}$						3.44(5)
$M_2L^{4+} + 2OH^- \rightleftharpoons M_2L(OH)_2{}^{2+}$	5.87(1)			6.11(5)		7.17(5)

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

that of the corresponding complex with 1,7-dimethyl-1,4,7,10-tetraazacyclododecane (**L4**), which contains two secondary and two tertiary nitrogen donors. The stability of the [Cu**L3**]$^{2+}$ complex is somewhat lower than those of [Cu**L4**]$^{2+}$ (log K = 16.09 and 17.89 for the equilibrium $Cu^{2+} + L \rightleftharpoons [CuL]^{2+}$, with L = **L3** and **L4**, respectively), while the **L1** complex displays a higher affinity for Cu^{II} than **L4** (log K = 20.16 and 17.89 for the equilibrium $Cu^{2+} + L \rightleftharpoons [CuL]^{2+}$, with L = **L1** and **L4**, respectively). These data suggest that in the [Cu**L3**]$^{2+}$ complex the amine group of the side arm is not involved in metal-ion coordination, while in [Cu**L1**]$^{2+}$ the amine pendant arm is coordinated to the metal ion. In the case of ligand **L2**, the stability constant of the [Cu**L2**]$^{2+}$ complex is intermediate between those observed for the corresponding **L1** and **L3** complexes, suggesting that in [Cu**L2**]$^{2+}$ the amine group of the pendant arm is weakly involved in metal-ion coordination.

Considering the formation of the dinuclear complexes, the equilibrium constant for the addition of a second metal ion to the mononuclear [ML]$^{2+}$ complexes is similar to that found for the formation of the corresponding [ML]$^{2+}$ species (for instance, log K = 20.16 for the equilibrium Cu^{2+} + **L1** $\rightleftharpoons$ [Cu**L1**]$^{2+}$, and log K = 19.77 for the equilibrium [Cu**L1**]$^{2+}$ + Cu^{2+} $\rightleftharpoons$ [Cu$_2$**L1**]$^{4+}$). This is in agreement with the involvement of the two identical ligand moieties in the coordination of each metal ion in the dinuclear complexes, as shown by the crystal structures of the dinuclear complexes [Cu$_2$**L1**]Cl$_4$·8H$_2$O, [Zn$_2$**L2**](ClO$_4$)$_4$ and [Zn$_2$**L3**](ClO$_4$)$_4$·H$_2$O (see above). This behaviour is clearly depicted by the distribution diagrams of the complexes, as shown in Figure 4 for the system Zn^{II}/**L2**. Both mononuclear and dinuclear complexed species are present in solutions containing the ligand and the metal ion in an equimolecular ratio (Figure 4a). On the other hand, for a 2:1 Zn^{II}/L molar ratio, the formation of monometallic complexes is depressed and only minor percentages of protonated mononuclear complexes are formed at acidic pH (Figure 4b).

The process of Zn^{II} coordination was also monitored by means of ^{1}H NMR titrations in D$_2$O at pH = 10, carried out by successive addition of Zn(ClO$_4$)$_2$ to a ligand solution. Figure 5 displays the ^{1}H NMR spectra of **L1** in the absence and presence of different amounts of Zn^{II}. Upon adding 0.25 equiv. of Zn^{II} to a solution of **L1**, a different set of signals appears in the ^{1}H NMR spectrum, together with the resonances of the ligand alone. Although the signals of the ethylenic chains of **L1** are affected by a certain degree of fluxionality in the presence of the metal ion and cannot be confidently attributed, the appearance of a new singlet for the aromatic protons (H1A) and of a doublet for the benzylic hydrogen atoms (H2A) is clearly recognisable, pointing out the formation in solution of a metal complex (**A** species) that is slowly exchanging on the NMR timescale with the free ligand. On addition of further Zn^{II}, the signals of this species are enhanced, while the resonances of L decrease in intensity. With an M^{II}/L molar ratio of 0.5:1, however, a third set of signals (H1B and H2B) appears in the spectrum, due to the formation of a second complexed species (**B** com-



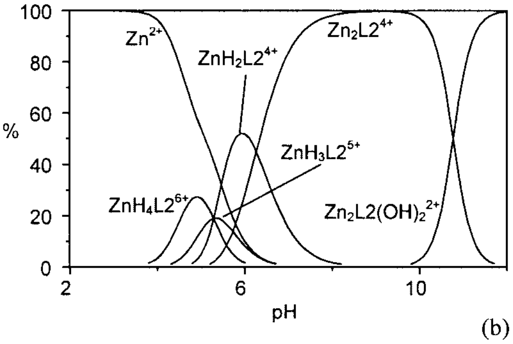


Figure 4. Distribution diagrams of the species for the system Zn^{2+}/**L2** in 1:1 (a) and 2:1 (b) molar ratios ([L] = [Zn^{2+}] = 1×10^{-3} M, 0.1 M Me$_4$NCl 298.1 K) as a function of pH.

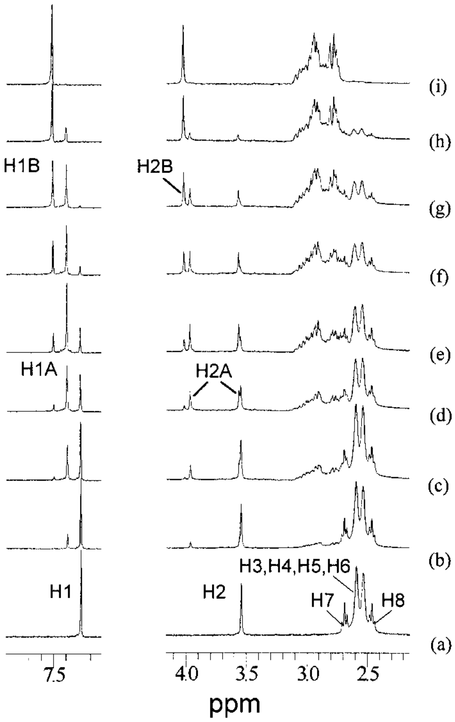


Figure 5. ^{1}H NMR spectra of **L1** in D$_2$O in the absence (a) and presence of Zn^{II} in different molar ratios: (b) R = 0.25; (c) R = 0.5; (d) R = 0.75; (e) R = 1.0; (f) R = 1.25; (g) R = 1.5; (h) R = 1.75; (i) R = 2.0; R = [Zn^{II}]/[**L1**].

plex) that is slowly exchanging with the **A** complex on the NMR timescale. When a 1:1 M^{II}/L molar ratio is reached, the predominant species in solution is the **A** complex, most likely the mononuclear Zn^{II} complex. Further additions of Zn^{II} lead to the progressive enhancement of the signals of the **B** complex, accompanied by the disappearance of the signals of the mononuclear complex and of the free ligand. Finally, with a 1:2 **L1**/Zn^{II} molar ratio the $[Zn\mathbf{L1}]^{2+}$ subspectrum disappears and the resulting spectrum can be attributed to a unique dinuclear $[Zn_2\mathbf{L1}]^{4+}$ complex. A similar behaviour is also found for **L2** and **L3**.

A more accurate analysis of the data in Table 4 shows some relevant differences in the coordination properties of the three ligands. First of all, the stability of both the $[ML]^{2+}$ and $[M_2L]^{4+}$ complexes (M = Cu^{II}, Zn^{II}) decreases in the order **L1** > **L2** > **L3** (for instance, $\log K$ = 19.77, 17.19 and 14.66 for the equilibrium $Cu^{2+} + [CuL]^{2+} \rightleftharpoons [Cu_2L]^{4+}$ with L = **L1**, **L2** and **L3**, respectively). Second, both the $[Cu_2L]^{4+}$ and $[Zn_2L]^{4+}$ complexes show a different ability in proton binding among the three ligands. The equilibrium constant for the addition of an acidic proton to the $[M_2L]^{4+}$ complexes, in fact, increases in the order **L1** < **L2** < **L3**. In particular, the protonation constants of the $[M_2\mathbf{L1}]^{4+}$ complexes are rather low, less than 5 log units, as expected in the case of protonation of metal-ion-bound amine groups. On the contrary, the protonation constants of the $[M_2\mathbf{L3}]^{4+}$ dinuclear complexes are remarkably high (ca. 9 log units), just slightly lower than the corresponding constants of the "free" ligand, as generally found in the case of nitrogen atoms not involved in metal-ion binding. Finally, the ability of $[M_2L]^{4+}$ complexes to form hydroxylated species decreases from **L3** to **L1** (for instance, $\log K$ = 7.17 and 6.11 for the equilibrium $[Zn_2L]^{4+} + 2\ OH^- \rightleftharpoons [Zn_2L(OH)_2]^{2+}$ with L = **L3** and **L2**, respectively, while the $[Zn_2\mathbf{L1}]^{4+}$ complex does not form any hydroxo complex). In polyamine complexes, an increasing tendency to form hydroxo complexes is generally related to a lower number of metal-ion-bound nitrogen donors.

These experimental observations suggest that a decreasing number of nitrogen donors is involved in Cu^{II} or Zn^{II} binding on passing from **L1** to **L3**; in other words, while in the **L1** dinuclear complexes each metal ion is coordinated to the four amine groups of a cyclen moiety and the amine group of the side arm, in the **L3** ones the metal cations are bound only to the four donor atoms of the cyclic moieties. The amine group of the pendant arms seems not to be involved in metal-ion coordination, at least in aqueous solution. In the **L3** complexes a water molecule most likely occupies the apical position in the coordination sphere of both metal ions. In the case of **L2**, the stability constants of the $[M_2\mathbf{L2}]^{4+}$ complexes as well as the equilibrium constants for proton addition to the $[M_2\mathbf{L2}]^{4+}$ species are intermediate between those observed for the corresponding **L1** and **L3** complexes, suggesting that in $[M_2\mathbf{L2}]^{4+}$ the amine groups of the pendant arms are weakly involved in metal-ion coordination.

These hypotheses are confirmed by the UV/Vis spectral features of the dinuclear Cu^{II} complexes. The $[Cu_2L]^{4+}$ complexes display a single band at 610 (ε = 805), 640 (ε = 836) and 693 nm (ε = 888 $cm^{-1} mol^{-1} L$) for L = **L1**, **L2** and **L3**, respectively (Figure 6). The observed red shift of the absorption maximum on passing from $[Cu_2\mathbf{L1}]^{4+}$ to $[Cu_2\mathbf{L3}]^{4+}$ suggests a decreasing ligand-field splitting at the Cu^{II} centres, in agreement with an increasing number of coordinated nitrogen atoms from the **L3** dinuclear complex to the **L1** one.[52,53]

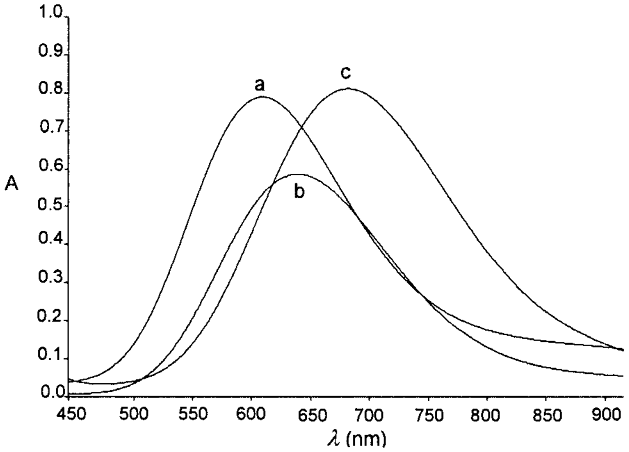


Figure 6. Absorption spectra of $[Cu_2L]^{2+}$: (a) L = **L1**, pH = 8.04; (b) L = **L2**, pH = 8.75; (c) L = **L3**, pH = 10.91 in aqueous solution.

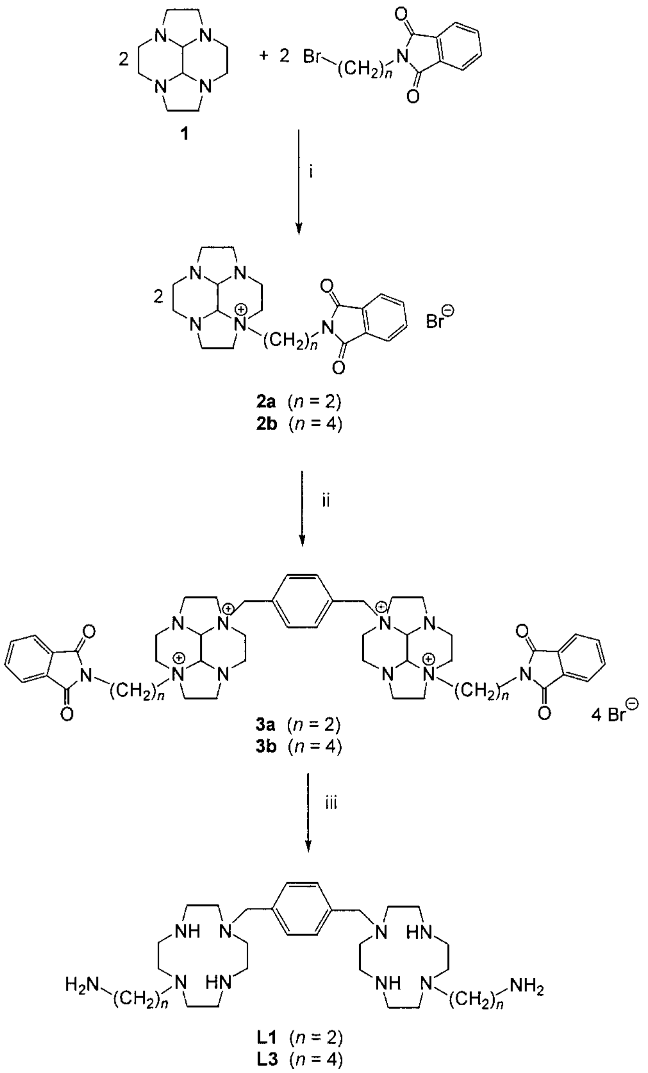
In the case of the dinuclear Zn^{II} complexes, the involvement of the amine group of the pendant arm in metal-ion binding can be determined by analysis of the pH dependence of the ^1H NMR signal of the adjacent methylene group. In the case of $[Zn_2\mathbf{L1}]^{4+}$ and $[Zn_2\mathbf{L2}]^{4+}$ protonation of the complexes gives rise to an upfield shift of this signal (0.2 and 0.15 ppm in the case of the **L1** and **L2** complexes, respectively). This strongly suggests that the formation of protonated complexes implies detachment of the ethyl- or propylamino groups from the metal ion due to protonation of a primary amine function.[54] On the contrary, protonation of the $[Zn_2\mathbf{L3}]^{4+}$ complex is accompanied by a downfield shift of the signal of the methylene group in the α-position with respect to the primary nitrogen atom, as generally observed (see above) in the case of proton binding by amine groups not involved in metal-ion coordination.

The crystal structure of the complex $[Cu_2\mathbf{L1}]Cl_4\cdot 8H_2O$ shows each metal ion coordinated to the nitrogen atoms of the cyclen unit and to the amine group of a pendant arm, in agreement with the structural hypothesis made on the basis of the solution data. Interestingly, the reflectance spectrum of solid $[Cu_2\mathbf{L1}]Cl_4\cdot 8H_2O$ shows a single band with λ_{max} = 615 nm, which is very similar to that found for the $[Cu_2\mathbf{L1}]^{4+}$ complex in aqueous solution (λ_{max} = 610 nm), thereby supporting the hypothesis of a similar coordination sphere of the metal ion in the solid state and in solution. In the case of **L3**, however, the crystal structure of $[Zn_2\mathbf{L3}](ClO_4)_4\cdot H_2O$ shows that each metal ion is pentacoordinate by the four nitrogen donors of the macrocycle and by the nitrogen donor of the side arm, in contrast to the conclusions derived from the solution study. Although no Cu^{II} complex with **L3** was structurally characterised, it is of interest to note that the reflectance spectrum of solid $[Cu_2\mathbf{L3}](ClO_4)_4$ shows a band at 620 nm, which is blue-shifted by 70 nm with respect to that of the $[Cu_2\mathbf{L3}]^{4+}$ complex in solution. This experimental result may suggest a higher number of coordinated nitrogen donors in solid $[Cu_2\mathbf{L3}](ClO_4)_4$. While in the solid state the NH_2 group of the pendant arm is coordinated to the metal ion in a similar fashion to that found in $[Zn_2\mathbf{L3}](ClO_4)_4\cdot H_2O$, in the $[Cu_2\mathbf{L3}]^{4+}$ species in solution the alkylamino pendant would most likely not be involved in metal-ion coordination.

In conclusion, in the case of $[M_2\mathbf{L1}]^{4+}$ and $[M_2\mathbf{L2}]^{4+}$ all nitrogen donors are coordinated to the metal ions; the solution data, however, suggest a weaker interaction of the amine group of the pendant arm in the **L2** complex. Protonation of the $[M_2L]^{4+}$ species takes place on the aminoethyl or aminopropyl side arms, with consequent detachment of the primary nitrogen donor from the metal ion. In other words, the coordination sphere of the two metal ions is modulated by the pH of the medium. On the contrary, in the $[M_2\mathbf{L3}]^{4+}$ complexes the butylamino side arms are not involved in metal-ion coordination and facile protonation of the primary nitrogen atoms occurs. This different behaviour can be ascribed to the different length of the chelate ring formed by coordination of the aminoalkyl pendant arm to Cu^{II} or Zn^{II}. In the case of $[M_2\mathbf{L1}]^{4+}$, coordination of the primary nitrogen atom gives rise to a stable five-membered chelate ring, whereas in the $[M_2\mathbf{L3}]^{4+}$ complexes coordination of the NH_2 group would lead to the formation of a less stable seven-membered chelate ring. As a consequence, binding of a water molecule in the apical position of the coordination sphere of the metal ion in the $[M_2\mathbf{L3}]^{4+}$ complexes would be energetically more favoured, and, therefore, the aminoalkyl side arm would not be involved in metal-ion coordination in aqueous solution.

Experimental Section

General Procedures: 3-[7-{4-[{7-(3-Aminopropyl)-1,4,7,10-tetraazacyclododecan-1-yl}methyl]benzyl}-1,4,7,10-tetraazacyclododecan-1-yl]propylamine (**L2**) was prepared as previously reported,[49] recrystallised from an ethanol/water mixture and isolated as $\mathbf{L2}\cdot 6HCl\cdot 2H_2O$. **L1**–**L3** require a suitable protection of two opposite nitrogen atoms of cyclen and, moreover, the control of the two successive steps of N-1 and N-7 alkylations. The bis(aminal) resulting from the reaction of cyclen with aqueous glyoxal proved to be an excellent tool for the synthesis of such dissymmetrical dialkylated macrocyclic adducts.[49,55] The synthetic route used for the synthesis of **L1** and **L3** is depicted in Scheme 2. Cyclen reacts with glyoxal in methanolic solution to give *cis*-decahydro-2a,4a,6a,8a-tetraazacyclopenta[*fg*]acenaphthylene (**1**) quantitatively.[56] The reaction with an electrophilic moiety leads to a stable quaternary ammonium salt; the use of an appropriate solvent in which the solubility of this salt is low prevents further alkylation and allows the control of the monoalkylation of **1**. Salts **2** were found to precipitate in CH_3CN and were subsequently isolated by filtration; salts **3** were obtained in a second step by reaction of the monosalts **2** with 0.5 equiv. of the bis(electrophile) (α,α′-dibromo-*p*-xylene) in DMF, in which salts **2** are partially soluble. Subsequent refluxing of **3** in hydrazine monohydrate according to a previously described procedure[49] afforded ligands **L1**–**L3** in good yields.



Scheme 2. (i) Stirring in CH_3CN for 2 d at 50°C or at room temp. for **2a** and **2b**, respectively; (ii) α,α′-dibromo-*p*-xylene in DMF at room temp.; (iii) H_2NNH_2, H_2O, reflux overnight.

2a-[3-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]decahydro-4a,6a,8a-triaza-2a-azoniacyclopenta[*fg*]acenaphthylene Bromide (2a): A solution of *N*-(bromoethyl)phthalimide (2.9 g, 11 mmol) in dry acetonitrile (5 mL) was added to a stirred solution of **1** (2.0 g, 10 mmol) in 5 mL of dry acetonitrile,. The mixture was stirred at 50 °C for 2 d. The precipitate was collected by filtration, washed with acetonitrile and dried in vacuo to give the monosalt as a white powder. Yield: 1.79 g (40%). ^{13}C NMR (D_2O): δ = 172.3 (CO), 138.0, 133.9, 126.6 (C_{ar}), 87.0, 74.4 (C_{aminal}), 65.1, 60.1, 57.4, 54.1, 51.2, 50.9, 50.7, 50.4, 46.4 (CH_2N), 34.6 ($N^+CH_2CH_2N_{pht}$) ppm. $C_{20}H_{26}BrN_5O_2$ (448.36): calcd. C 53.58, H 5.84, Br 17.82, N 15.62; found C 53.26, H 5.89, Br 17.73, N 15.51.

2a-[3-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)butyl]decahydro-4a,6a,8a-triaza-2a-azoniacyclopenta[*fg*]acenaphthylene bromide (2b): Compound **2b** was obtained from **1** (2.0 g, 10 mmol) and *N*-(bromobutyl)phthalimide (3.2 g, 11 mmol) at room temperature by applying the same procedure as for **2a**. Yield: 4.43 g (93%). ^{13}C

NMR (D_2O): δ = 173.4 (CO), 137.7, 134.0, 126.2 (C_{ar}), 86.6, 74.6 (C_{aminal}), 64.9, 60.6, 59.7, 54.1, 51.3, 51.0, 50.6, 50.5, 46.5 (CH_2N), 39.5 ($N^+CH_2CH_2CH_2CH_2N_{pht}$), 27.7, 22.9 ($N^+CH_2CH_2CH_2CH_2N_{pht}$) ppm. $C_{22}H_{30}BrN_5O_2$ (476.41): calcd. C 55.46, H 6.35, Br 16.77, N 14.70; found C 55.19, H 6.37, Br 16.64, N 14.61.

2a-[4-{[6a-{2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl}decahydro-4a,8a-diaza-2a,6a-diazoniacyclo-penta[*fg*]acenaphthylen-2a-yl]methyl}benzyl]-6a-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl] decahydro-4a,8a-diaza-2a,6a-diazoniacyclopenta[*fg*]acenaphthylene Tetrabromide (3a): A solution of α,α′-dibromo-*p*-xylene (0.6 g, 2.38 mmol) in 50 mL of dry DMF was added dropwise to a suspension of **2a** (2.1 g, 4.75 mmol) in 100 mL of dry DMF. The mixture was stirred at room temperature for 2 weeks. The solvent was evaporated, 10 mL of dry acetonitrile was added to the residue and the mixture was stirred for some minutes. The precipitate was collected by filtration, washed with acetonitrile and dried in vacuo. The white crude product was used without further purification. Yield: 2.45 g (89%). ^{13}C NMR (D_2O): δ = 172.4 (CO), 138.3, 136.7, 134.2, 132.4, 126.9 (C_{ar}), 82.1, 80.9 (C_{aminal}), 64.9, 64.3, 63.5, 59.0, 58.2, 57.6, 49.5, 49.0, 45.6 (NCH_2), 34.8 (CH_2N_{pht}) ppm.

2a-[4-{[6a-{2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)butyl}decahydro-4a,8a-diaza-2a,6a-diazoniacyclopenta[*fg*]acenaphthylen-2a-yl]methyl}benzyl]-6a-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)butyl]decahydro-4a,8a-diaza-2a,6a-diazoniacyclopenta[*fg*]acenaphthylene Tetrabromide 3b: Compound **3b** was obtained from α,α′-dibromo-*p*-xylene (0.6 g, 2.38 mmol) and **2b** (2.3 g, 4.75 mmol) by the same procedure as **3a**. The white crude product was used without further purification. Yield: 2.63 g (91%). ^{13}C NMR (D_2O): δ = 173.4 (CO), 137.7, 136.5, 134.1, 132.2, 126.2 (C_{ar}), 81.3, 80.8 (C_{aminal}), 64.5, 64.0, 63.2, 60.2, 58.2, 49.1, 45.5 (NCH_2), 39.6 (CH_2N_{pht}), 27.6, 24.3 ($CH_2CH_2CH_2CH_2$) ppm.

2-[7-{4-[{7-(2-Aminoethyl)-1,4,7,10-tetraazacyclododecan-1-yl}-methyl]benzyl}-1,4,7,10-tetraazacyclododecan-1-yl]ethylamine Hexahydrochloride Dihydrate (L1·6HCl·2H$_2$O): Compound **3a** (2.3 g, 2 mmol) and 6 mL of hydrazine monohydrate were heated at 120 °C overnight. After cooling, the solid was filtered off, dissolved in ethanol and the solvent was evaporated. The resulting oil was dissolved in 10 mL of ethanol and 10 mL of concentrated HCl was added dropwise. The precipitate was filtered off, dissolved in 3 M HCl and the solvent was evaporated. The white solid was recrystallised from an ethanol/water mixture (1:1). Yield: 1.12 g (72%). ^{13}C NMR (D_2O): δ = 137.2, 133.5, 58.7, 52.0, 50.0, 49.7, 45.5, 43.9, 37.2 ppm. $C_{28}H_{66}Cl_6N_{10}O_2$ (787.61): calcd. C 42.70, H 8.45, Cl 27.01, N 17.78; found C 42.45, H 8.53, Cl 26.89, N 17.54.

4-[7-{4-[{7-(4-Aminobutyl)-1,4,7,10-tetraazacyclododecan-1-yl}-methyl]benzyl}-1,4,7,10-tetraazacyclododecan-1-yl]butylamine Hexahydrochloride Dihydrate (L3·6HCl·2H$_2$O): Compound **3b** was treated as above to give a white solid. Yield: 1.48 g (93%). ^{13}C NMR (D_2O): δ = 137.7, 133.4, 58.8, 54.5, 50.0, 49.9, 45.4, 45.3, 42.2, 27.5, 23.0 ppm. $C_{32}H_{74}Cl_6N_{10}O_2$ (843.71): calcd. C 45.55, H 8.84, Cl 25.21, N 16.60; found C 45.81, H 8.87, Cl 25.57, N 16.68.

Synthesis of [{Cu$_2$L1}Cl$_4$]·8H$_2$O: A solution of $Cu(ClO_4)_2\cdot 6H_2O$ (14 mg, 0.038 mmol) in water (5 mL) was slowly added to an aqueous solution (10 mL) containing **L1**·6HCl·2H$_2$O (15 mg, 0.019 mmol). The pH was adjusted to 8.0 with 0.01 M NaOH and then $NaClO_4$ (30 mg) was added. Blue crystals of the complex suitable for X-ray analysis were obtained by slow concentration at room temperature. Yield: 11 mg (61%) $C_{28}H_{72}Cl_4Cu_2N_{10}O_8$ (945.85): calcd. C 35.56, H 7.67, N 14.81; found C 35.45, H 7.60, N 14.78.

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

Synthesis of [Zn$_2$L2](ClO$_4$)$_4$: Crystals of [{Zn$_2$**L2**}(ClO$_4$)$_4$] suitable for X-ray analysis were obtained by slow concentration, at room temperature, of an aqueous solution containing **L2**·6HCl·2H$_2$O (11 mg, 0.013 mmol) and $Zn(ClO_4)_2$ (10 mg, 0.027 mmol) at pH = 9.0. Yield: 11.72 mg (80%). $C_{30}H_{60}Cl_4N_{10}O_{16}Zn_2$ (1089.4): calcd. C 33.07, H 5.55, N 12.86; found C 33.40, H 5.45, N 12.93.

Synthesis of {[Zn$_2$L3](ClO$_4$)$_4$}·H$_2$O: This complex was synthesised according to the procedure reported for **L2** adjusting the solution pH to 9.3. Yield: 9.45 mg (64%). $C_{32}H_{66}Cl_4N_{10}O_{17}Zn_2$ (1135.5): calcd. C 33.85, H 5.86, N 12.33; found C 33.80, H 5.90, N 12.37.

X-ray Structure Analyses: Analyses on prismatic, blue single crystals of [{Cu$_2$**L1**}Cl$_4$]·8H$_2$O (a), prismatic colourless crystals of [{Zn$_2$**L2**}(ClO$_4$)$_4$] (b) and [{Zn$_2$**L3**}(ClO$_4$)$_4$]·H$_2$O (c) were carried out with CCD SMART 1K (**L1**) and SIEMENS P4 (**L2** and **L3**) diffractometers. A summary of the crystallographic data is given in Table 5. Empirical absorption corrections (SADABS for **L1** and ψ-scan methods for **L2** and **L3**) were applied. No loss of intensity was observed during data collection. Both structures were solved by direct methods with the SIR97 program.[57] Refinements were performed by the full-matrix least-squares method with the SHELXL-97 program.[58] All non-hydrogen atoms were refined anisotropically while hydrogen atoms, except those of the water molecules, were introduced in calculated positions and their coordinates refined according to the linked atom. As is common for perchlorate ligands, in the structure of [{Zn$_2$**L3**}(ClO$_4$)$_4$]·H$_2$O the perchlorate anion Cl1 exhibits disorder (six oxygen peaks, three assigned 33% and three 66% occupancy). CCDC-240959, -240960 and -240961 (**L1**–**L3**, respectively) 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 Measurements: All the pH-metric measurements (pH = –log [H$^+$]) were carried out in degassed 0.1 M Me_4NCl, with CO_2-free solutions, at 298.1 K, with equipment and procedures that have already been described.[59] The combined Ingold 405 S7/120 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,[60,61] which allows the determination of the standard potential, E^o, and the ionic product of water [pK_w = 13.83(1) at 298.1 K in 0.1 M Me_4NCl]. A ligand concentration, [L], of 1×10^{-3} M and metal-ion concentration, [M], from 0.5•[L] to 1.8•[L] were adopted in the complexation experiments. The emf data were treated with the computer program HYPERQUAD[62] which furnished the equilibrium constants reported in Table 1 and Table 4. 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. In the HYPERQUAD[62] program the sum of the weighted square residuals of the observed emf values is minimised. The weights were derived from the estimated errors in emf (0.2 mV) and titrant volume (0.002 mL). The most probable chemical model was selected by using a strategy based on the statistical inferences applied to the variance of the residuals, σ^2. The sample standard deviation should be 1 in the absence of systematic errors and when a corrected weighting scheme is used. However, the agreement is considered good for standard deviation values smaller than 3 ($\sigma^2 < 9$). Values of σ^2 lower than 6 were obtained for all the refined equilibrium models in the present work. If more than one model gave an acceptable σ^2 value the reliability of the proposed specia-

Table 5. Crystal data and structure refinement for $\{[Cu_2\mathbf{L1}]Cl_4\}\cdot 8H_2O$, $[Zn_2\mathbf{L2}](ClO_4)_4$ and $\{[Zn_2\mathbf{L3}](ClO_4)_4\}\cdot H_2O$.

	$\{[Cu_2\mathbf{L1}]Cl_4\}\cdot 8H_2O$	$[Zn_2\mathbf{L2}](ClO_4)_4$	$\{[Zn_2\mathbf{L3}](ClO_4)_4\}\cdot H_2O$
Empirical formula	$C_{28}H_{72}Cl_4Cu_2N_{10}O_8$	$C_{30}H_{60}Cl_4N_{10}O_{16}Zn_2$	$C_{32}H_{66}Cl_4N_{10}O_{17}Zn_2$
Formula weight	945.83	1089.4	1135.5
Crystal system	triclinic	monoclinic	monoclinic
T [K]	298	298	298
λ [Å]	1.54180	1.54180	1.54180
Space group	$P\bar{1}$	$P2_1/n$	$P2_1/n$
a [Å]	8.993(5)	9.180(5)	10.193(5)
b [Å]	9.214(5)	18.05(5)	14.353(5)
c [Å]	14.093(5)	13.58(5)	16.113(5)
α [°]	95.000(5)		
β [°]	91.000(5)	99.00(5)	97.89(5)
γ [°]	111.000(5)		
V [Å^3]	1084.6(9)	2222.5(2)	2335.0(2)
Z	1	2	2
μ [mm^{-1}]	3.929	4.218	4.056
F(000)	484	1132	1180
Reflections collected	4042	3645	4392
Independent reflections	2412	2759	3363
Final R indices [$I > 2\sigma(I)$]: R_1, wR_2[a]	0.0801, 0.2497	0.0842, 0.2084	0.0625, 0.1730
R indices (all data)	0.0858, 0.2566	0.1353, 0.2441	0.0698, 0.1810

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

tion models was checked by performing F tests at the 0.05 confidence level, using the method reported in ref.[63] and ref.[64] for two different proposed models, A and B. Assuming that the minimum value of the sample variance, σ_A^2, has been reached for the proposed model A, an alternative model B, which supplies a value of the variance σ_B^2, was rejected if $\sigma_B^2/\sigma_A^2 > F$, where σ_A and σ_B are given directly by data treatment with the HYPERQUAD[62] program. The F values were taken from ref.[63] For all the systems investigated this method provided only one acceptable system.

NMR Spectroscopy: 300.0 MHz ^{1}H, 75.46 MHz ^{13}C NMR spectra in D_2O solutions at different pH values were recorded at 298 K with a Varian 300 MHz spectrometer. In the ^{1}H NMR spectra the peak positions are reported relative to HOD at $\delta = 4.75$ ppm. Dioxane was used as reference standard in ^{13}C NMR spectra ($\delta = 67.4$ ppm). ^{1}H-^{1}H and ^{1}H-^{13}C 2D correlation experiments were performed to assign the signals. Small amounts of 0.01 M NaOD or DCl solutions were added to a solution of the three ligands to adjust the pD. The pH was calculated from the measured pD values using the relationship pH = pD – 0.40.[65]

Electronic Spectroscopy: Absorption spectra were recorded with a Perkin–Elmer Lambda 25 spectrophotometer. HCl and NaOH were used to adjust the pH values, which were measured with a Metrohm 713 pH meter.

Acknowledgments

Financial support by the Italian Ministero dell'Università e della Ricerca Scientifica e Tecnologica, within the program COFIN 2002, is acknowledged.

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Received: October 25, 2004