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A new functionalized hexaazamacrocycle. Effect of pyridine pendants on cation and anion binding

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The macrocyclic ligand 1,4,7,13-tetramethyl-10,16-bis(*o*-pyridylmethyl)-1,4,7,10,13,16-hexaazacyclooctadecane (L) has been prepared and its protonation studied by means of potentiometric measurements. It binds up to five protons in aqueous solution above pH 2. The ^{1}H and ^{13}C NMR spectra at different pH values allowed the determination of the stepwise protonation sites. The first three protonation steps take place on amine groups of the macrocyclic structure, the fourth and fifth on the pyridine nitrogens. Co-ordination of Cu^{II}, Zn^{II}, Cd^{II} and Pb^{II} in aqueous solution has been studied by means of potentiometric, ^{1}H NMR and/or UV-vis measurements (0.1 M $NaClO_4$, 298.1 K). The $[ML]^{2+}$ complexes show unusually low stabilities, which are considered due to the low σ-donating properties of tertiary nitrogens as well as to the formation of large chelate rings containing unbound amine groups. The ligand behaves as a ditopic receptor for Cu^{II}. The $[CuL]^{2+}$ complex exhibits a marked tendency to bind a second Cu^{2+} ion, giving binuclear complexes. Protonated forms of L are efficient receptors for ATP and ADP. The binding properties toward these anions are influenced by the presence of the two heteroaromatic moieties, which lead to a higher efficiency in ATP binding at acidic pH.

There is a continuing interest in the chemistry of polyazamacrocycles because of their ability to interact with both metal cations and anionic species.[1] Cyclic polyamines containing six or more nitrogen donors, namely large polyazacycloalkanes, are able to form very stable metal complexes, containing one or more metal ions, due to their large number of nitrogens.[2,3] Furthermore, these ligands undergo extensive protonation in solution, forming highly charged polyammonium cations, which give rise to strong interactions with both inorganic phosphate and nucleotide anions, such as ATP. It has been shown that polyammonium macrocycles are effective recognizers of nucleotides and may catalyse ATP hydrolysis at physiological pH.[4]

The presence in such molecules of large numbers of amine groups may allow the modulation of their co-ordinative properties through nitrogen functionalization.[5–10] It has been shown that nitrogen methylation produces significant changes in cation and anion binding features of polyazamacrocycles.[11–14] In particular, methylation of secondary nitrogens leads to a decrease of the thermodynamic stability of their metal complexes, due to the poorer σ-donor ability of tertiary amine groups.[11,13] Ligands 1,4,7,13-tetramethyl-1,4,7,10,13,16-hexaazacyclooctadecane (L^1) and 1,4,7,10,13,16-hexaazacyclooctadecane (L^2) form mononuclear complexes with transition metals.[15,16] The stabilities of the complexes with the tetramethylated hexaazamacrocycle L^1 are lower than those of the analogous unmethylated ligand L^2.[16]

Hexaazaalkanes are also strong ATP binders in aqueous solution. N-Methylation affects the binding ability and the hydrolytic properties toward ATP.[11] Macrocycle L^1 interacts more strongly with inorganic phosphates and ATP than does L^2, but the latter is a better catalyst in ATP hydrolysis.

Earlier it had been shown that the attachment of a pyridine moiety to N_4[17,18] or N_2O_4[19] macrocycles strongly affects the thermodynamic stability and the structural features of their metal complexes, due to the binding characteristics of the heteroaromatic nitrogens. Aiming to get further insight on the binding properties of macrocycles containing a large number of nitrogen donors, we have now appended two pyridine moieties to a hexaazamacrocyclic structure, having synthesized the new octadentate ligand L. In this paper we report the results of a thermodynamic study on the binding of H^+ (basicity), metal cations and nucleotide anions, such as ATP or ADP, in aqueous solutions.

Results and discussion

Ligand protonation

The protonation equilibria of L have been studied in 0.1 mol dm^{-3} $NaClO_4$ aqueous solution at 298.1 ± 0.1 K by means of potentiometric pH (−log $[H^+]$) measurements and the results are reported in Table 1. The protonation constants of $L^{1\,5b}$ are also given for comparison. The distribution diagram for the species present in solution as a function of pH for the system L/H^+ is given in Fig. 1.

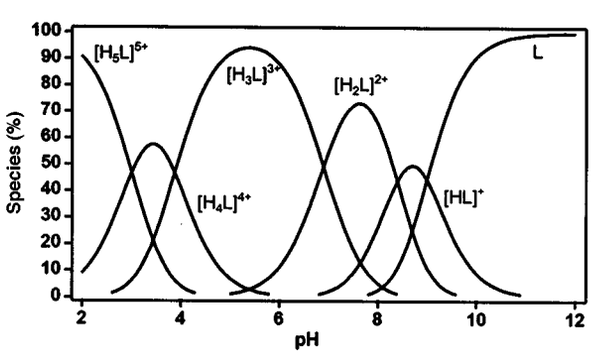
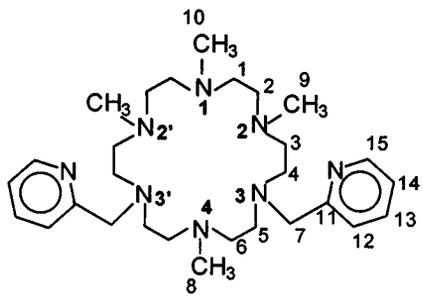


Fig. 1 Distribution diagram of the protonated species formed by L as a function of pH ([L] = 1 × 10^{-3} mol dm^{-3}) at 298.1 K.

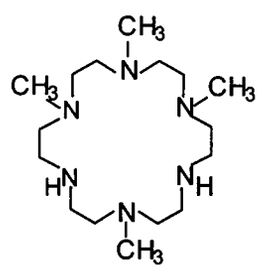
Table 1 Protonation constants (log K) of L and L^1 determined by means of potentiometric measurements in 0.1 mol dm^{-3} $NaClO_4$ aqueous solution at 298.1 K

	log K	
	L	L^1
$L + H^+ \rightleftharpoons HL^+$	9.00(1)[a]	9.75
$HL^+ + H^+ \rightleftharpoons H_2L^{2+}$	8.41(2)	9.11
$H_2L^{2+} + H^+ \rightleftharpoons H_3L^{3+}$	6.89(2)	7.53
$H_3L^{3+} + H^+ \rightleftharpoons H_4L^{4+}$	3.88(2)	2.59
$H_4L^{4+} + H^+ \rightleftharpoons H_5L^{5+}$	3.01(3)	—

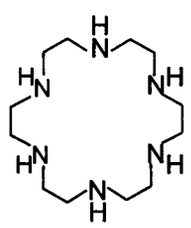
[a] Values in parentheses are standard deviations on the last significant figure.



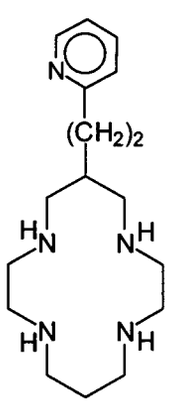
L



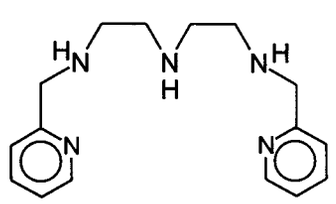
L^1



L^2



L^3



L^4

In the case of L^1 a sharp decrease in basicity is observed between the third and the fourth stepwise protonation constant. The difference between the first and the third protonation constants is only 2.2 logarithm units while that between the third and the fourth is 4.9 logarithm units. As previously reported,[5b] this behavior can easily be rationalized by taking into account that the first three protons can bind the macrocycle in alternative positions while the fourth has to be necessarily placed between two already protonated nitrogen atoms. Such a grouping of the protonation constants is less marked for ligand L. The attachment of the pyridine moieties causes a lowering of basicity in the first three protonation steps of L. On the contrary, L shows a higher fourth protonation constant than L^1 and can also give rise to the formation of a pentaprotonated $[H_5L]^{5+}$ species, while, in the same pH range, L^1 behaves at most as a tetraprotic base. Since tertiary amine groups as well as pyridine nitrogens are less basic than secondary nitrogens, the lower values of the first protonation constants of L can simply be ascribed to the presence of only tertiary or heteroaromatic nitrogen atoms as proton binding sites. On the other hand, the higher fourth and fifth protonation constants of L require a more accurate investigation to be explained. The protonation mechanism of L can be clarified by recording ^1H and ^{13}C NMR spectra in aqueous solution at various pH values. All the assignments have been made on the basis of ^1H–^1H homonuclear and ^1H–^{13}C heteronuclear correlation experiments at the different pH values studied.

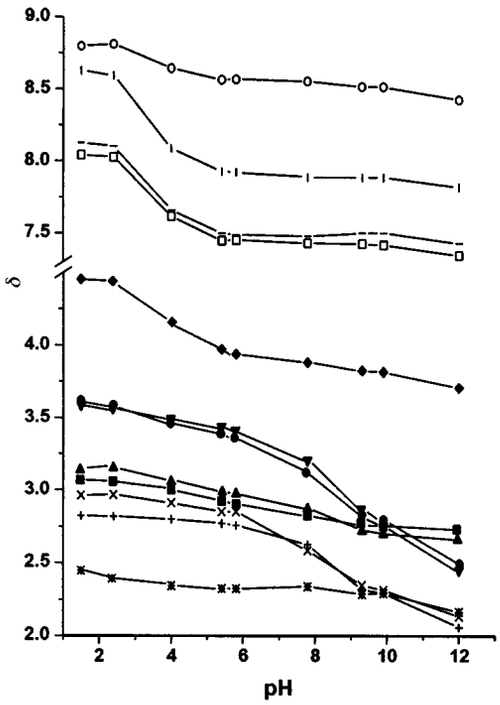


Fig. 2 Experimental ^1H chemical shifts of L as a function of pH: ■, H1; ●, H2, H3; ▲, H4, H5; ▼, H6; ◆, H7; +, H8; ×, H9; ∗, H10; – – –, H11; –|–, H13; □, H14; ○, H15.

The ^{13}C NMR spectrum of L at pH 12.0, where the unprotonated amine predominates in solution, exhibits fifteen peaks, at δ 43.6, 43.4, 43.8 (the methyl groups C8, C9 and C10, respectively), 54.0, 54.1, 54.2, 51.8, 51.6, 54.7 (the ethylenic chains, C1, C2, C3, C4, C5 and C6, respectively), 61.4 (C7), 124.7, 126.1, 139.5, 149.7 and 158.3 (the aromatic carbons C14, C12, C13, C15 and C11, respectively). The ^1H spectrum at this pH shows three singlets at δ 2.05, 2.13 and 2.19 (integrating 3, 6 and 3 protons and attributed to the hydrogens of the methyl groups, H8, H9 and H10, respectively), a multiplet at δ 2.50 (12 protons, the hydrogen H2, H3 and H6), a multiplet at δ 2.80 (12 protons, H4, H5 and H1), a singlet at δ 3.71 (4 H, H7), and the signals of the pyridine moiety at δ 7.34 (dd, 2 H, attributed to H14), 7.43 (d, 2 H, H12), 7.82 (dd, 2 H, H13) and 8.42 (d, 2 H, H15). These spectral features indicate a C_{2v} time averaged symmetry and this is preserved throughout the pH range investigated.

Figs. 2 and 3 show respectively the ^1H and ^{13}C NMR chemical shifts of L as a function of pH. In the pH range 12–5.8, where the first three protons bind to the ligand, the signals of the hydrogens H2, H3 and H6, in α position with respect to

N2 and N4, as well as those of the methyl groups H8 and H9, exhibit a marked downfield shift, while the other signals do not shift appreciably (see, for instance, H1, H4, H7 and the methyl H10, Fig. 2). This suggests that the three protons bind to the three methylated nitrogens N2, N2′, and N4. This hypothesis is confirmed by the ^{13}C spectra recorded in the same pH range, which show that the resonances of the carbon atoms C1 and C4, in β position with respect to N2, as well as the signal of C5, in β position with respect to N4, shift upfield (Fig. 3), in good agreement with the β shift reported for protonation of polyamines.[20] Such a disposition of the protons in the $[H_3L]^{3+}$ species would mean a minimum in electrostatic repulsions, since the protons occupy alternate positions, separated from each other by the unprotonated N1 and N3 nitrogens. It is to be noted that in the pH range 12–5.8 the resonances of the aromatic protons do not exhibit significant changes in their chemical shift, indicating that the aromatic nitrogens are not involved in the binding of the first three protons. In the pH range 5.8–2, where the tetra- and penta-protonated $[H_4L]^{4+}$ and $[H_5L]^{5+}$ species are formed in aqueous solution, the signals of the aromatic protons exhibit a remarkable downfield shift, while those of the protons of the macrocyclic framework do not shift appreciably (Fig. 2), thus indicating that the fourth and fifth protonations take place on pyridine nitrogens. The ^{13}C NMR spectra in the same pH range show a marked upfield shift of the resonances of the benzylic carbon C7, in β position with respect to the aromatic nitrogens, and of the aromatic carbons C11 and C15, confirming this protonation pathway.

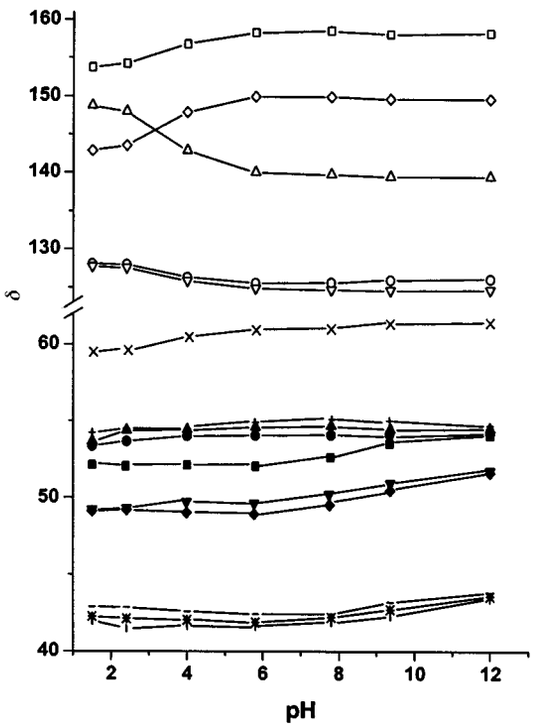


Fig. 3 Experimental ^{13}C NMR chemical shifts of L as a function of pH: ■, C1; ●, C2; ▲, C3; ▼, C4; ◆, C5; +, C6; ×, C7; ∗, C8; –·–, C9, –|–, C10; □, C11; ○, C12; △, C13; ▽, C14; ◇, C15.

Protonation of the pyridine nitrogens is also confirmed by the analysis of UV spectra recorded at different pH values. The aromatic moieties give a rather sharp band at 260 nm ($\varepsilon = 6400$ dm^3 mol^{-1} cm^{-1}). The spectra do not show any variation in the pH range 10–5.8, where the first three protons bind to the macrocycle. On the other hand a marked increase of the absorbance is observed at more acidic pH (5.8–2), due to protonation of the pyridine nitrogens ($\varepsilon = 8300$ dm^3 mol^{-1} cm^{-1} at pH 3).

Metal co-ordination in aqueous solution

As a first investigation of the co-ordination properties of L toward metal cations, the formation of the complexes of Cu^{II}, Zn^{II}, Cd^{II} and Pb^{II} has been studied by means of potentiometric measurements in aqueous solution (0.1 mol dm^{-3} $NaClO_4$, 298.1 K). The stability constants of the complexes are reported in Table 2, together with those of L[1,11] The distribution diagrams for the systems L/Cu^{II} (in 1:1 and 1:2 molar ratios), L/Zn^{II} and L/Cd^{II} are in Fig. 4.

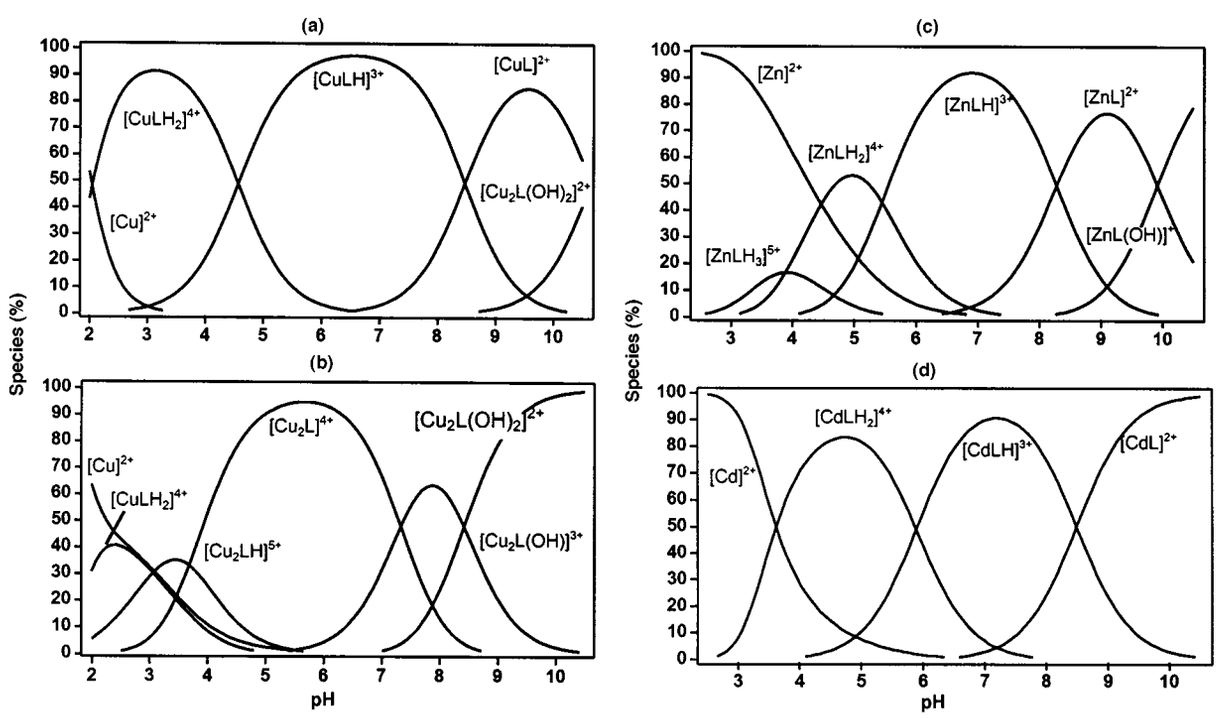


Fig. 4 Distribution diagrams of the species for the systems (a) L/Cu^{II} ($[L] = [Cu^{2+}] = 1 \times 10^{-3}$ mol dm^{-3}), (b) L/Cu^{II} ($[L] = 1 \times 10^{-3}$, $[Cu^{2+}] = 2 \times 10^{-3}$ mol dm^{-3}), (c) L/Zn^{II} ($[L] = [Zn^{2+}] = 1 \times 10^{-3}$ mol dm^{-3}) and (d) L/Cd^{II} ($[L] = [Cd^{2+}] = 1 \times 10^{-3}$ mol dm^{-3}) as a function of pH (0.1 mol dm^{-3} $NaClO_4$, 298.1 K).

Table 2 Logarithms of the equilibrium constants determined in 0.1 mol dm^{-3} $NaClO_4$ at 298.1 K for the complexation reactions of Cu^{2+}, Zn^{2+}, Cd^{2+}, Pb^{2+} with L and L^1

	log *K*	
Reaction	L	L^{1a}
$Cu^{2+} + L \rightleftharpoons CuL^{2+}$	15.36(3)[b]	20.49
$CuL^{2+} + H^+ \rightleftharpoons CuLH^{3+}$	8.47(2)	2.97
$CuLH^{3+} + H^+ \rightleftharpoons CuLH_2^{4+}$	4.57(3)	2.90
$CuL^{2+} + Cu^{2+} \rightleftharpoons Cu_2L^{4+}$	9.19(2)	—
$Cu_2L^{4+} + H^+ \rightleftharpoons Cu_2LH^{5+}$	3.69(2)	—
$Cu_2L^{4+} + OH^- \rightleftharpoons [Cu_2L(OH)]^{3+}$	6.40(3)	—
$[Cu_2L(OH)]^{3+} + OH^- \rightleftharpoons [Cu_2L(OH)_2]^{2+}$	5.85(2)	—
$Zn^{2+} + L \rightleftharpoons ZnL^{2+}$	9.59(3)	13.29
$ZnL^{2+} + H^+ \rightleftharpoons ZnLH^{3+}$	8.28(2)	—
$ZnLH^{3+} + H^+ \rightleftharpoons ZnLH_2^{4+}$	5.45(3)	—
$ZnLH_2^{4+} + H^+ \rightleftharpoons ZnLH_3^{5+}$	3.89(2)	—
$ZnL^{2+} + OH^- \rightleftharpoons [ZnL(OH)]^+$	3.81(3)	—
$Cd^{2+} + L \rightleftharpoons CdL^{2+}$	10.12(3)	16.75
$CdL^{2+} + H^+ \rightleftharpoons CdLH^{3+}$	8.49(2)	—
$CdLH^{3+} + H^+ \rightleftharpoons CdLH_2^{4+}$	5.89(2)	—
$Pb^{2+} + L \rightleftharpoons PbL^{2+}$	11.01(2)	13.37
$PbL^{2+} + H^+ \rightleftharpoons PbLH^{3+}$	5.92(2)	—
$PbLH^{3+} + 2H^+ \rightleftharpoons PbLH_3^{5+}$	10.74(3)	—
$PbL^{2+} + OH^- \rightleftharpoons [PbL(OH)]^+$	3.29(2)	—

[a] From ref. 11(*a*). [b] Values in parentheses are standard deviations on the last significant figure.

Considering the data in Table 2, some main features can be outlined. (i) Compound L forms mononuclear complexes with the metals under investigation which show a marked tendency to protonate. They can form mono- and di-protonated species at neutral or slightly alkaline pH, as shown in Fig. 4. In the case of the Zn^{II} and Pb^{II} a triprotonated species is also formed at acidic pH values. (ii) The stability constants of the mononuclear complexes with L are unusually low for a hexaamine macrocycle. For instance, the complexes are less stable than the L^1 ones, although L contains two heteroaromatic nitrogens as potential sites for metal binding. (iii) Hexaazamacrocycles, such as L^1 and L^2, do not form binuclear complexes in aqueous solution with the metal ions investigated herein.[5] On the contrary, the mononuclear $[CuL]^{2+}$ complex can add a second copper(II) ion forming binuclear complexes in aqueous solutions; this is reasonably due to the introduction of the two pyridine units.

Considering proton binding, it should be noted that only extensive protonation of the ligand inhibits the formation of metal complexes. In fact, as can be noted from Table 2 and Fig. 4, all the metal ions under investigation form complexes with protonated species of L. The equilibrium constants for the successive addition of H^+ to the $[ML]^{2+}$ complexes are significantly high, suggesting that protonation occurs on nitrogen atoms not involved in metal co-ordination. On the contrary, the L^1 complexes with Zn^{II}, Cd^{II} and Pb^{II}, in which the metals are six-co-ordinated,[5] do not show any tendency to protonate (Table 2). Only $[CuL^1]^{2+}$ binds two protons and the values of the corresponding protonation constants are very low. It is also of interest that the protonation constants of the L complexes are higher than those for protonation of the pyridine nitrogens in the uncomplexed ligands and even higher than that of pyridine itself ($pK_a = 5.3$). This observation strongly suggests that protonation of the complexes takes place on the amine groups of the macrocyclic framework, and does not involve the pyridine moieties.

Further information about the co-ordination features of this ligand in its mononuclear complexes can be obtained by means of ^1H NMR spectra recorded on aqueous solutions at different pH values containing ligand and metal ions (Zn^{II}, Cd^{II} or Pb^{II}) in equimolar ratios. Fig. 5 shows the ^1H NMR chemical shifts for selected protons of the zinc(II) complex as a function of pH.

Table 3 Differences of chemical shift (ppm) between the resonances of the $[ML]^{2+}$ complexes (M = Zn^{II}, Cd^{II} or Pb^{II}) and those of ligand L

	$\delta_{[ML]} - \delta_L$							
Complex	H7	H8	H9	H10	H12	H13	H14	H15
$[ZnL]^{2+}$	0.68	0.60	0.02	0.04	0.30	0.32	0.20	−0.14
$[CdL]^{2+}$	0.72	0.68	0.02	0.04	0.34	0.36	0.18	−0.17
$[PbL]^{2+}$	0.75	0.65	0.03	0.00	0.32	0.35	0.24	−0.18

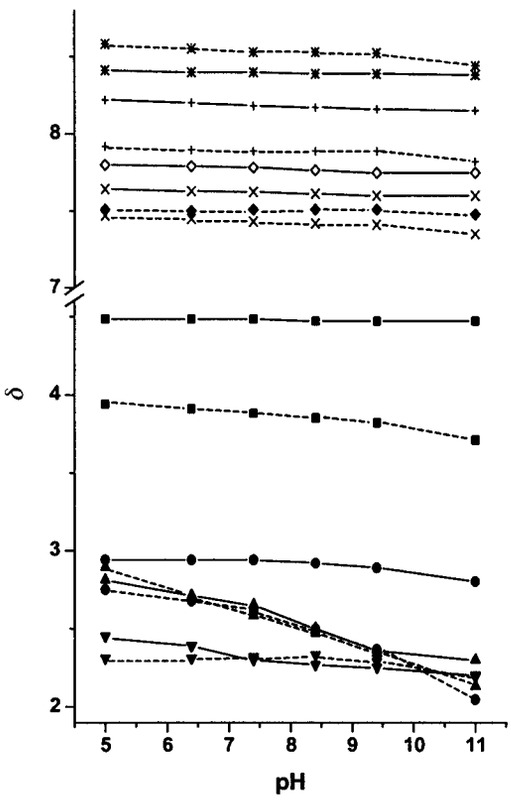
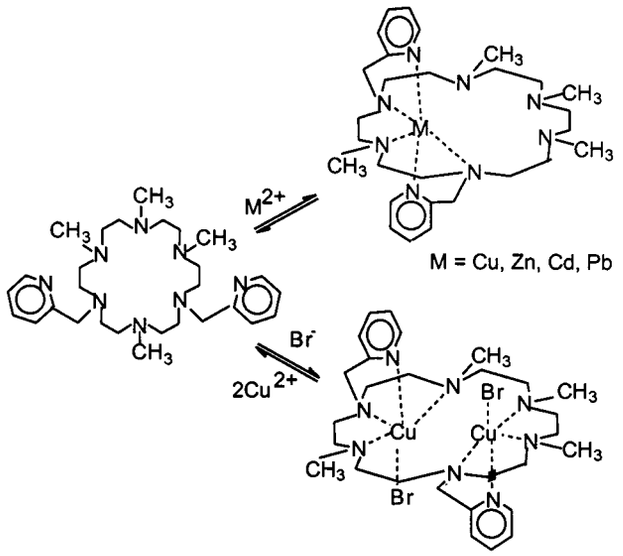


Fig. 5 Selected ^1H chemical shifts of the Zn–L complexes (solid lines) and of L (dashed lines) as a function of pH: ■, H7; ●, H8; ▲, H9; ▼, H10; ◆, H12; +, H13; ×, H14; ∗, H15.

The chemical shifts of the corresponding protons of free L are also reported for comparison. Although the signals of the protons of the ethylenic chains cannot be confidently attributed, the analysis of the ^1H NMR chemical shifts of the methyl groups 8, 9 and 10, the benzylic protons 7 and the aromatic protons 12–15 can give useful information about the co-ordination environment of the metal ions and the structural features of their protonated complexes. Actually, in the ^1H spectrum recorded at pH 9.5, where the $[ZnL]^{2+}$ complex is prevalent in solution, the resonances of the methyl protons 8, the benzyl protons 7 and the aromatic hydrogens 12, 13 and 14 show a marked downfield shift with respect to the corresponding resonances of free L at the same pH value. On the contrary, the chemical shifts of the methyl groups 9 and 10 are almost the same for $[ZnL]^{2+}$ and free L. Almost equal spectral characteristics are also found for the $[CdL]^{2+}$ and $[PbL]^{2+}$ complexes and are summarized in Table 3, where the differences of chemical shifts between the resonances of the $[ML]^{2+}$ complexes and those of ligand L are reported. The spectral features of the $[ML]^{2+}$ complexes reveal that the tertiary amine groups N3, N3′, N4 and the pyridine nitrogens are involved in metal co-ordination, while N1, N2 and N2′ are not. A proposed structure for the $[ML]^{2+}$ complexes is sketched in Scheme 1. Co-ordination of the aromatic nitrogens to the metals is also confirmed by the UV spectra recorded on aqueous solutions of the complexes, which show an increase in absorbance of the π–π* band at 260 nm of pyridine upon co-ordination (for



Scheme 1 Metal co-ordination environments in the mononuclear L complexes and in the binuclear copper(II) one.

instance, $\varepsilon = 7300$ dm^3 mol^{-1} cm^{-1} for Zn^{II}, while $\varepsilon = 6400$ dm^3 mol^{-1} cm^{-1} for free L). Fig. 5 also shows that the ^{1}H NMR signal of methyl group 9 of the zinc(II) complex bears a remarkable downfield shift in the pH range 8–5, where protonation of the $[ZnL]^{2+}$ complex takes place to give $[ZnLH]^{3+}$ and $[ZnLH_2]^{4+}$. A lower downfield shift is also observed for methyl 10 in the same pH range. On the contrary, the resonances of the benzyl group 7 and those of methyl 8, in α position to the co-ordinated nitrogens, do not shift significantly in the same pH range. Similar results were also obtained for the complexes of Cd^{II} and Pb^{II}. Therefore, protonation of ligands occurs on the N2′, N1, N2 polyamine chain not involved in metal co-ordination, as previously hypothesized on the basis of the equilibrium data. Although such an NMR study cannot be carried out on the copper(II) complexes, a similar co-ordination environment can also be proposed for this metal ion. Actually, the UV-vis spectrum of the $[CuL]^{2+}$ complex shows a band at 560 nm ($\varepsilon = 180$ dm^3 mol^{-1} cm^{-1}) with a shoulder at 700 nm, which may be reasonably ascribed to a five-co-ordinated copper(II) ion.[21]

As previously observed, the thermodynamic stability of the L complexes is unusually low for a polyamine macrocycle. The stability constants of the $[ML]^{2+}$ complexes are several orders of magnitude less stable than those with the precursor L[1,5b] and with tetraamine macrocycles containing a co-ordinating pyridine moiety as side arm, such as L^3.[17] It should be pointed out that the $[ML]^{2+}$ complexes also show a lower stability than those with L^4,[22] which contains three secondary amine groups and two pyridine nitrogens and behaves as a pentadentate ligand in its complexes, as actually proposed for L.

The low stability of the L complexes can be ascribed to two main reasons. (1) It contains only tertiary amine groups within the macrocyclic framework. Tertiary nitrogens are poorer σ donors than secondary ones, since nitrogen functionalization prevents the formation of hydrogen bonds between water and amine groups, which contribute, *via* the $H_2O\cdots H$–N interaction, to the σ-donating ability of amine groups in aqueous solution.[13] Furthermore, the presence of methyl groups and two *o*-pyridylmethyl subunits leads to a molecular crowding and stiffening of the macrocycle and reduces the ability of the ligand to adapt to the steric requirements of metals. Both these electronic and steric factors may contribute to reduce the binding ability toward metal cations exhibited by L. (ii) It is known that the formation of large chelate rings in metal ion binding decreases the stability of complexes.[1] In the $[ML]^{2+}$ complexes a triamine chain does not participate in metal co-ordination, thus leading to the formation of a 14-membered chelate ring containing the unbound N2–N1–N2′ nitrogens.

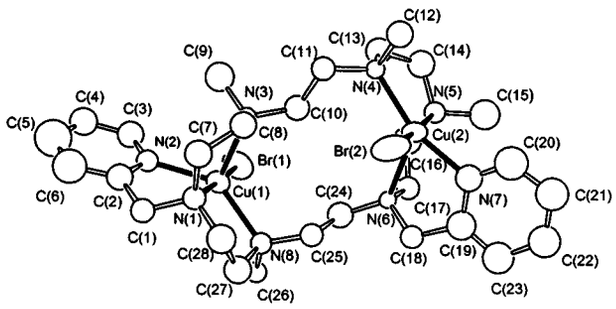


Fig. 6 An ORTEP drawing of the $[Cu_2Br_2L]^{2+}$ cation.

The characteristics of these mononuclear complexes indicate that L contains two different binding sites, the N3–N4–N3′ moiety, with the pyridine pendant arms, where the metal ions are preferentially lodged, and the polyamine chain N2–N1–N2′, where protons are bound even at slight alkaline pH.

Actually, the $[CuL]^{2+}$ complex also exhibits a good ability to bind an additional Cu^{II} in aqueous solution, giving binuclear complexes. As shown in Fig. 4(b), for a 2:1 Cu^{II}:L molar ratio, binuclear complexes are the only species in aqueous solution from slight acidic to alkaline pH. The formation of a stable copper(II) binuclear complex may suggest that in $[Cu_2L]^{4+}$ the metals are co-ordinated by a similar set of donors. To establish the co-ordination environment of the copper(II) ions in the binuclear complex attempts were made to grow crystals suitable for structural analysis by X-ray diffraction. These attempts were only partially successful and because of disorder in all the crystals examined led only to a less than optimum solution of the crystal and molecular structures of $[Cu_2Br_2L][BPh_4]_2$. While the structure cannot be reported in full, it was sufficiently well refined to establish the atom connectivity, the gross structure, and interatomic distances to ±0.1 Å. The ORTEP[23] drawing in Fig. 6 shows that each Cu^{II} is co-ordinated by the same set of donors (three tertiary amine groups, a pyridine nitrogen and a bromide anion). Since in the mononuclear complex the metal seems to be five-co-ordinated by three amine groups and two pyridine nitrogens, addition of a second copper ion to the $[CuL]^{2+}$ complex leads to a change of the nitrogen donors involved in the co-ordination environment of the first copper ion and, therefore, to a rearrangement of the macrocyclic framework, as in Scheme 1.

Most likely, the two bromide anions in the $[Cu_2Br_2L]^{2+}$ binuclear complex are replaced by water molecules in aqueous solutions and facile deprotonation should take place to give hydroxo-complexes. Actually, the $[Cu_2L]^{4+}$ complex shows a marked tendency to form mono- and di-hydroxo species in aqueous solutions. With a metal:ligand 2:1 molar ratio, such species are largely present in aqueous solution at neutral or slight alkaline pH, as shown in Fig. 4(b). It is to be noted that the values of the constants for the addition of the first and the second OH^- to the $[Cu_2L]^{4+}$ complex, *i.e.* the pK_a for the dissociation of two co-ordinated water molecules, are similar. This observation suggests that in the $[Cu_2L(OH)_2]^{2+}$ complex each hydroxide anion is bound to a different Cu^{II}, in a similar fashion to that shown by the bromide anions in the $[Cu_2Br_2L]^{2+}$ cation.

Anion co-ordination

It was found that, among hexaazacycloalkanes, L^1 is the most efficient receptor for phosphate anions and nucleotides.[11] With the purpose to analyse the effects of the insertion of pyridine side arms on anion binding, species selection (speciation) and equilibrium constant in the L/ATP and L/ADP systems have been determined by means of potentiometric measurements.

Table 4 Logarithms of the equilibrium constants determined in 0.1 mol dm^{-3} $NaClO_4$ at 298.1 K for the complexation reactions of ATP and ADP with L, L^1 and L^2

Reaction	log *K*		
	L	L^1	L^2
$L + 3H^+ + ATP^{4-} \rightleftharpoons [H_3L(ATP)]^-$	27.80(1)[a]	29.66[b]	30.99[b]
$L + 4H^+ + ATP^{4-} \rightleftharpoons [H_4L(ATP)]$	34.37(1)	36.41	38.70
$L + 5H^+ + ATP^{4-} \rightleftharpoons [H_5L(ATP)]^+$	39.62(1)	40.93	43.92
$L + 6H^+ + ATP^{4-} \rightleftharpoons [H_6L(ATP)]^{2+}$	42.89(9)	44.18	—
$L + 7H^+ + ATP^{4-} \rightleftharpoons [H_7L(ATP)]^{3+}$	46.59(7)	—	—
$H_3L^{3+} + ATP^{4-} \rightleftharpoons [H_3L(ATP)]^-$	3.10	3.26	2.47
$H_4L^{4+} + ATP^{4-} \rightleftharpoons [H_4L(ATP)]$	6.59	7.42	5.91
$H_4L^{4+} + HATP^{3-} \rightleftharpoons [H_5L(ATP)]^+$	5.20	5.70	4.90
$H_4L^{4+} + H_2ATP^{2-} \rightleftharpoons [H_6L(ATP)]^{2+}$	4.47	5.0	—
$H_5L^{5+} + H_2ATP^{2-} \rightleftharpoons [H_7L(ATP)]^{3+}$	5.16	—	—
$L + 3H^+ + ADP^{3-} \rightleftharpoons [H_3L(ADP)]$	—	29.04(8)	—
$L + 4H^+ + ADP^{3-} \rightleftharpoons [H_4L(ADP)]^+$	33.40(5)	35.83(4)	33.81(4)
$L + 5H^+ + ADP^{3-} \rightleftharpoons [H_5L(ADP)]^{2+}$	37.23(5)	39.98(4)	38.67(5)
$L + 6H^+ + ADP^{3-} \rightleftharpoons [H_6L(ADP)]^{3+}$	—	42.93(3)	—
$L + 7H^+ + ADP^{3-} \rightleftharpoons [H_7L(ADP)]^{4+}$	—	—	—
$H_3L^{3+} + ADP^{3-} \rightleftharpoons [H_3L(ADP)]$	—	3.14	—
$H_4L^{4+} + ADP^{3-} \rightleftharpoons [H_4L(ADP)]^+$	5.22	6.83	4.82(5)
$H_4L^{4+} + HADP^{2-} \rightleftharpoons [H_5L(ADP)]^{2+}$	3.86	4.83	3.52(5)
$H_4L^{4+} + H_2ADP^- \rightleftharpoons [H_6L(ADP)]^{3+}$	—	3.85	—

[a] Values in parentheses are standard deviations in the last significant figure. [b] From ref. 11.

Table 4 reports the constants determined for L, together with those previously obtained for ligands L^1 and L^2.[13] From these results we can observe that all the anion complexes formed present 1:1 stoichiometry. This seems to be the preferred binding mode for highly charged anions, in particular this is true for bulky nucleotides, presenting many sites for hydrogen bonding anchorage to the macrocycles.[4,13] Nevertheless, electrostatic attraction is the main force in determining the nucleotide–receptor interaction. Indeed for each ligand the stability of the ATP or ADP complexes increases with the degree of protonation, and for a given charge on the macrocycle the more charged ATP forms more stable complexes than ADP.

As far as the effect of the two pyridine pendants on the binding of nucleotides is concerned, Table 4 shows that for a given protonation degree of the ligand the equilibrium constants for nucleotide binding ($H_nL + H_mA = H_{(n+m)}LA$, A = ATP or ADP) are lower for L than for L^1. On the contrary, the L complexes show somewhat higher stabilities than those of L^2. On the other hand, the stability constants in Table 4 may be misleading in the analysis of selectivity in anion binding by polyamines, since the different basicity features may give an important contribution to the selectivity patterns. As discussed above, ligand L exhibits a much higher basicity than L^1 in the last protonation steps, due to protonation of the pyridine nitrogens. It forms $[H_4L]^{4+}$ and $[H_5L]^{5+}$ species below pH 5 which strongly interact with ATP, while L^1 forms only a $[H_4L]^{4+}$ species at strongly acidic pH values. It has been suggested that an appropriate way to overcome this problem is to consider a ternary system containing the nucleotide and the two ligands in equimolar concentrations and calculate the overall percentages of complexed ATP or ADP over a wide pH range.[13,16] Plots of the percentages *vs.* pH produce species distribution diagrams from which the binding ability of both receptors can be interpreted in terms of selectivity. In Fig. 7 are reported similar diagrams calculated for the ATP/L/L^1 and ATP/L/L^2 systems. As can be seen, in the former the formation of ATP adducts with L prevails at acidic pH (pH < 6), while the complexes with L^1 prevail at neutral or slight basic pH values. This is ascribed to the higher basicity of L^1 in the first three protonation steps. The preferential binding of ATP by receptor L at pH < 6 is related to the higher basicity of L in the fourth and fifth protonation steps, which take place on pyridine nitrogens. Similar considerations can explain the much higher percentages of ATP complexes with L in the ATP/L/L^2 system at acidic pH values.

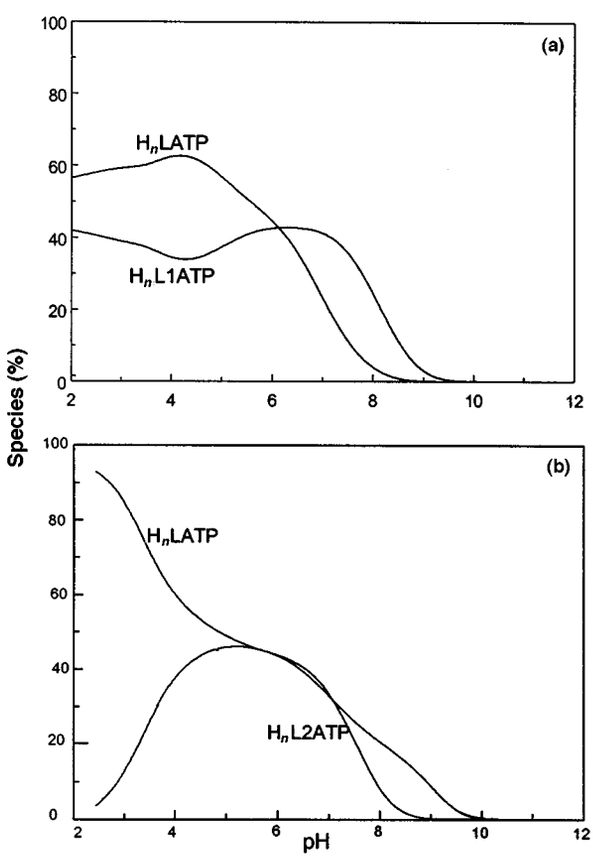


Fig. 7 Overall percentages of ATP complexed species formed as a function of pH in competing systems containing L and L^1 (a) and L and L^2 (b). Percentages are calculated with respect to ATP.

Concluding remarks

The insertion of two pyridine side arms on an hexaazamacrocyclic structure markedly affects its binding feature toward metal cations and nucleotide anions. Ligand L presents a

triamine chain bearing the two pyridine moieties, which is the preferred binding site for metal cations and a triaza subunit, where protons can be bound. These structural features lead to the low stability of the mononuclear complexes. On the other hand, considering copper(II) binding, the mononuclear complex shows a marked tendency to bind a second Cu^{II}, giving binuclear complexes which are usually not formed by 18-membered hexaamines. Therefore, the attachment of two pyridine moieties to an hexaazamacrocyclic structure reduces the thermodynamic stability of the mononuclear complexes, but enhances its ability to form binuclear complexes. As far as anion complexation is concerned, the insertion of the pyridine moieties enhances ATP binding at acidic pH. This result can be explained considering the higher basicity of L in its fourth and fifth protonation equilibria with respect to L^1 and L^2, due to the involvement of pyridine nitrogens.

Experimental

Synthesis of the compounds

The macrocycle 1,4,7,13-tetramethyl-10,16-bis(*o*-pyridylmethyl)-1,4,7,10,13,16-hexaazacyclooctadecane (L) was obtained by reaction of 1,4,7,13-tetramethyl-1,4,7,10,13,16-hexaazacyclooctadecane (L^1) with 2-methylpyridine chloride hydrochloride; L^1 was synthesized as previously described.[24]

1,4,7,13-Tetramethyl-10,16-bis(*o*-pyridylmethyl)-1,4,7,10,13,16-hexaazacyclooctadecane (L). Compound L^1 (0.98 g, 3.11 mmol) was dissolved in a suspension of K_2CO_3 (14 g, 0.1 mol) in anhydrous CH_3CN (100 ml). To this mixture a solution of 2-methylpyridinechloride hydrochloride (1.22 g, 7.44 mmol) in 50 cm^3 of CH_3CN was added dropwise in 1 h at room temperature under a nitrogen atmosphere. After the addition was completed the solution was refluxed for 4 h and then filtered. The filtrate was vacuum evaporated to yield the crude product as a red oil which was chromatographed on neutral alumina (70–230 mesh, activity II-III) eluting with $CHCl_3$. The eluted fractions were collected and evaporated to dryness to afford a colorless oil. Yield: 0.24 g (15.5%) (Found: C, 67.95; H, 10.05; N, 22.45. Calc. for $C_{28}H_{48}N_8$: C, 67.70; H, 9.74; N, 22.56%).

L·5.5HClO$_4$. This compound was obtained in almost quantitative yield by addition of 66% of $HClO_4$ to a solution of L in ethanol (Found: C, 31.9; H, 5.2; N, 10.4. Calc. for $C_{28}H_{53.5}Cl_{5.5}N_8O_{22}$: C, 32.05; H, 5.14; N, 10.68%).

[Cu$_2$Br$_2$L][BPh$_4$]$_2$. A solution of $Cu(ClO_4)_2·6H_2O$ (7.2 mg, 0.021 mmol) in MeOH (10 cm^3) was slowly added to a methanol solution (5 cm^3) containing L (5.3 mg, 0.011 mmol). Sodium bromide (2.2 mg, 0.021 mmol) and $NaBPh_4$ (7.2 mg, 0.021 mmol) were added. To the resulting solution butanol was added. By slow evaporation of the solution a blue powder crystallized, which was filtered off and dried in vacuum. Yield: 8 mg (54%) (Found: C, 64.1; H, 6.3; N, 7.7. Calc. for $C_{38}H_{44}BBrCuN_4$: C, 64.19; H, 6.24; N, 7.88%). The complex was recrystallized twice from a methanol–butanol (2:1) to give crystals suitable for X-ray analysis.

NMR and electronic spectroscopy

The 200.0 MHz ^1H and 50.32 MHz ^{13}C NMR spectra in D_2O solutions at different pH values were recorded at 298 K in a Bruker AC-200 spectrometer. In ^1H NMR spectra peak positions are reported relative to HOD at δ 4.75. 1,4-Dioxane was used as reference standard in ^{13}C NMR spectra (δ 67.4). The ^1H–^1H and ^1H–^{13}C 2-D correlation experiments were performed to assign the signals. Small amounts of 0.01 mol dm^{-3} NaOD or DCl solutions were added to a solution of the ligand to adjust the pD. The pH was calculated from the measured pD values using the relationship pH = pD − 0.40.[25] The UV spectra were recorded on a Shimadzu UV-2101PC spectrophotometer.

Potentiometric measurements

Equilibrium constants for protonation and complexation reactions with L were determined by pH-metric measurements (pH = −log [H^+]) in 0.1 mol dm^{-3} $NaClO_4$ at 298 ± 0.1 K, by using potentiometric equipment that has been described.[26] 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 equivalence point by Gran's method[27] which allows one to determine the standard potential $E°$, and the ionic product of water [pK_w = 13.73(1) at 298.1 K in 0.1 mol dm^{-3} $NaClO_4$]. 1×10^{-3}–2×10^{-3} mol dm^{-3} ligands and metal ion concentrations were employed in the potentiometric measurements performing three titration experiments (about 100 data points each) in the pH range 2–11. For anion complexation, the concentration of ATP or ADP [A] was varied in the range [L] ≤ [A] ≤ 2[L]. The computer program HYPERQUAD[28] 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.

X-Ray crystallography

Crystal data. $[Cu_2LBr_2][BPh_4]_2$, $C_{76}H_{88}B_2Br_2Cu_2N_8$, M = 1422.06, monoclinic, space group $P2_1/a$, a = 21.562(4), b = 10.564(3), c = 30.628(8) Å, β = 90.19(2)°, V = 6976(3) Å^3, Z = 4, D_c = 1.354 Mg m^{-3}, μ(Mo-Kα) = 1.804 mm^{-1} (approximate crystal size 0.2 × 0.2 × 0.2 mm), h = −22 to 22, k = 0–11, l = 0–27, Enraf-Nonius CAD4 diffractometer, reflections 5661 up to θ = 22°, T = 298 K, refined parameters 285, final agreement factors $R(F)$ = 0.1384 for 2497 reflections with $I > 2\sigma(I)$. Goodness of fit on F^2 = 1.035, largest difference peak and hole = 0.998 and −0.907 e Å^{-3}.

Solution and refinement. The structure was solved by direct methods using SIR 92.[29] An absorption correction was applied, once the structure had been solved, by means of the Stuart and Walker methods[30] (minimum and maximum corrections in φ and μ, 0.73 and 1.48; in θ, 0.95 and 1.07). Refinement was performed on F^2 by means of SHELXL 93.[31] Heavy atoms were refined with anisotropic displacement parameters, and lighter atoms with isotropic displacement parameters. Hydrogen atoms included at calculated positions and refined with an overall constant thermal parameter (U = 0.05 Å^2). Some degree of disorder and high thermal parameters for several carbon atoms were found in the phenyl rings of the BPh_4^- anions, which were refined as rigid groups.

Crystals of this compound were of extremely poor quality. Several attempts to obtain those of better quality did not give good results. The Laue group was verified by comparing several equivalent reflections, excluding the possibility of a crystal system of higher symmetry, such as orthorhombic. The analysis of our crystallographic data also excludes the possibility of crystal twinning. Direct methods automatically identified all the non-hydrogen atoms in the structure (except for some carbon atoms of the BPh_4^- anions); the atoms of the macrocycle were all correctly linked as expected and the co-ordination around the copper atoms was plausible. We therefore contend that, even though the final R value is large by today's expectations, the molecular structure is essentially correct and shows the stereochemistry in the solid state. However, while this 'structure determination' is useful in the context of this paper the results should be treated with caution and details should not heedlessly be used to extrapolate to other conclusions.

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