DALTON

Mono- and bi-nuclear copper(II) complexes with polyazacyclophane receptors containing two different binding sites

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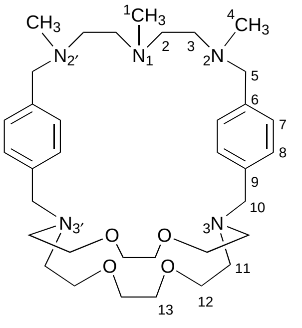
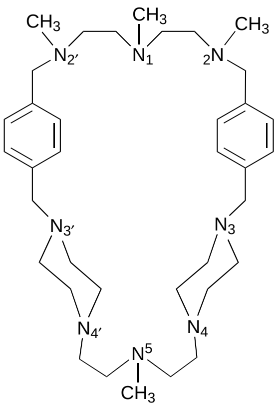
The macrobicyclic compound 1,4,7,-trimethyl-19,22,28,31-tetraoxa-1,4,7,14,23-pentaaza[9.25]-*p*-cyclophane (L^1) has been prepared. It comprises a N_3 and a cyclic N_2O_4 subunit, connected by *p*-phenylene spacers. Protonation of L^1 (and L^2, in which the N_2O_4 unit is replaced by a N_5 moiety) has been studied by means of potentiometric measurements. The compounds L^1 and L^2 bind up to five and six protons in aqueous solution above pH 2, respectively. Proton and ^{13}C NMR spectra at different pH values allow the determination of the stepwise protonation sites. Considering the $[H_4L^1]^{4+}$ species, the acidic protons are located on the benzylic nitrogens. Copper(II) co-ordination by L^1 and L^2 has been potentiometrically studied (298.1 K, 0.1 mol dm^3 NMe_4Cl aqueous solution): L^1 forms only a mononuclear complex, while L^2 gives both mono- and bi-nuclear species in aqueous solution. In the $[CuL^1]^{2+}$ complex the metal is co-ordinated by the three tertiary nitrogens of the N_3 unit, while the N_2O_4 moiety shows a high tendency to protonation. These solution data are confirmed by the crystal structure of $[Cu(HL^1)Cl(H_2O)][ClO_4]_2$. In the $[Cu(HL^1)Cl(H_2O)]^{2+}$ cation the metal is co-ordinated by the three amine groups of the triaza moiety and by a chloride anion, in a rather unusual square-planar geometry. A water molecule is encapsulated by the N_2O_4 moiety, held by a hydrogen-bond network. In the mononuclear $[CuL^2]^{2+}$ complex the Cu^{II} is preferentially lodged inside the pentaaza moiety. Such a complex can add a further copper(II) ion, which is co-ordinated by the N_3 binding unit.

In the last few years the design and synthesis of macrocyclic molecules containing two binding subunits linked by two bridges have received much attention;[1] these compounds are known to form stable binuclear complexes and the metal–metal distance can be modulated by varying the length and flexibility of the bridges. The chemical properties of the metal centres depend on the ligational properties of the two chelating sites. In particular, when the binding sites contain three or four amine groups, the macrocycle can bind a variety of transition-metal ions leaving binding sites accessible on the metal ion. Consequently, these complexes behave as receptors for molecules of anionic species, forming 'cascade' complexes.[2–4]

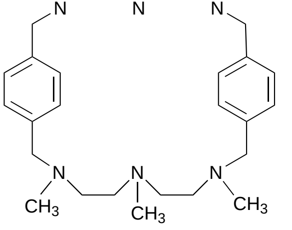
Aromatic systems are often introduced as integral parts of the macrocycle. Much effort has been devoted to the synthesis of macrocyclic or macropolycyclic receptors containing two aromatic moieties as rigid spacers to link two binding subunits, such as polyamine chains or a polyazacrown structure, to form ditopic macrocycles or cryptands.[5–13] In particular, several ditopic macrocycles containing two equal polyamine moieties have been synthesized, by using 2 + 2 cyclization reactions. Their binuclear metal complexes have been shown to react with various molecules or ions and several assemblies containing two metal centres bridged by anionic species have been reported.[2–4,12] Fewer efforts have been devoted to the study of macrocyclic systems containing two different metal binding sites within the same macrocyclic framework, mainly due to synthetic difficulties. Recently we communicated a general procedure to produce ligands with two different binding sites linked by 1,4-phenylene spacers.[14] In this paper we report the synthesis of compound ligand L^1 which contains N_3 and cyclic N_2O_4 moieties. Protonation and copper(II) co-ordination by L^1 and L^2 have been studied where L^2 has the same N_3 binding moiety as that of L^1, while the N_2O_4 site is replaced by a N_5 'chain' containing two piperazine rings. Compound L^2 resembles in part the 'reinforced' polyazacycloalkanes,[15] due to the presence of the two piperazine rings within the macrocyclic framework.



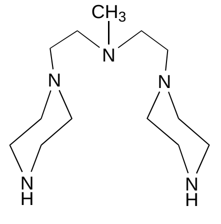
L^1



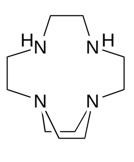
L^2



L^3



L^4



L^5

Table 1 Protonation constants (log *K*) of L^1 and L^2 determined by means of potentiometric measurements in 0.1 mol dm^{-3} NMe_4Cl aqueous solution at 298.1 K

Reaction	log *K** L^1	log *K** L^2
$L + H^+ \rightleftharpoons HL^+$	8.96(3)	9.36(3)
$HL^+ + H^+ \rightleftharpoons H_2L^{2+}$	8.26(3)	8.53(3)
$H_2L^{2+} + H^+ \rightleftharpoons H_3L^{3+}$	6.95(3)	7.53(3)
$H_3L^{3+} + H^+ \rightleftharpoons H_4L^{4+}$	5.81(5)	6.41(3)
$H_4L^{4+} + H^+ \rightleftharpoons H_5L^{5+}$	1.7(1)	5.87(3)
$H_5L^{5+} + H^+ \rightleftharpoons H_6L^{6+}$	—	2.36(4)

* Values in parentheses are standard deviations on the last significant figure.

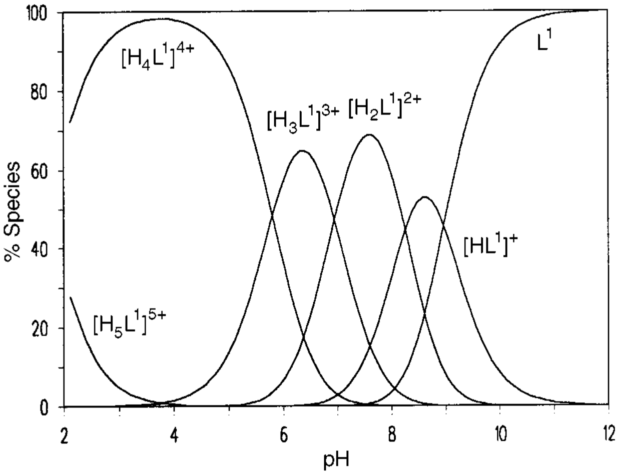


Fig. 1 Distribution diagram of the protonated species formed by L^1 as a function of pH ($[L^1] = 1 \times 10^{-2}$ mol dm^{-3}) at 298.1 K

The present work tries to rationalize the relations between the co-ordination characteristics toward H^+ (basicity) and Cu^{2+} and the structural features of L^1 and L^2, as a preliminary investigation on the reactivity of their mono- and bi-nuclear complexes toward neutral or anionic substrates.

Results and Discussion

Protonation of L^1 and L^2

The protonation equilibria of L^1 and L^2 have been studied in 0.1 mol dm^{-3} NMe_4Cl solution at 298.1 ± 0.1 K by means of potentiometric pH ($-\log[H^+]$) measurements and the results are reported in Table 1. The distribution diagram for the species present in solution as a function of pH for the system $L^1 + H^+$ is given in Fig. 1

Compounds L^1 and L^2 bind up to five and six protons in aqueous solution above pH 2, respectively. However, the two macrocycles show a similar protonation behaviour in the pH range investigated (2–11). Considering L^1, the first four basicity constants range between 8.96 and 5.81 logarithmic units, while the last is less than 2. A similar grouping of the protonation constants is observed in the case of L^2. In this case, the first five range between 9.36 and 5.87 logarithmic units, while the sixth is far lower (2.36). As a consequence, the tetraprotonated $[H_4L^1]^{4+}$ and the pentaprotonated $[H_5L^2]^{5+}$ species are largely prevalent in aqueous solution over a wide pH range (2–6, as shown in Fig. 1 for L^1).

Further information on the protonation mechanism of L^1 and L^2 can be obtained 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. The ^{13}C spectrum of L^1 at pH 12.0, where the unprotonated amine predominates in solution, exhibits twelve peaks, at δ 42.9 (C^1 and C^4), 52.2 (C^3), 52.3 (C^{11}), 53.6 (C^2), 58.3 (C^{10}), 61.5 (C^5), 69.3 (C^{12}), 70.8 (C^{13}), 130.7 (C^8), 130.8 (C^7), 136.8 (C^9) and 137.2 (C^6). The ^1H spectrum of L^1 at this pH shows two singlets at δ 2.09 and 2.22 (integrating for three and six protons and attributed to the hydrogens of the methyl groups, H^1 and H^4, respectively), a mutiplet at δ 2.42 (eight protons, the hydrogen atoms of the ethylenic chain H^2 and H^3), a triplet at δ 2.78 (eight protons, H^{11}), three singlets at δ 3.49, 3.60 and 3.69 (integrating for four, eight and four protons, attributed to H^5, H^{13} and H^{10}, respectively), a triplet at δ 3.64 (eight protons, H^{12}) and two doublets at δ 7.29 and 7.34 (each integrating for four protons, H^7 and H^8). These spectral features indicate a C_{2v} time-averaged symmetry, which is preserved throughout the pH range investigated.

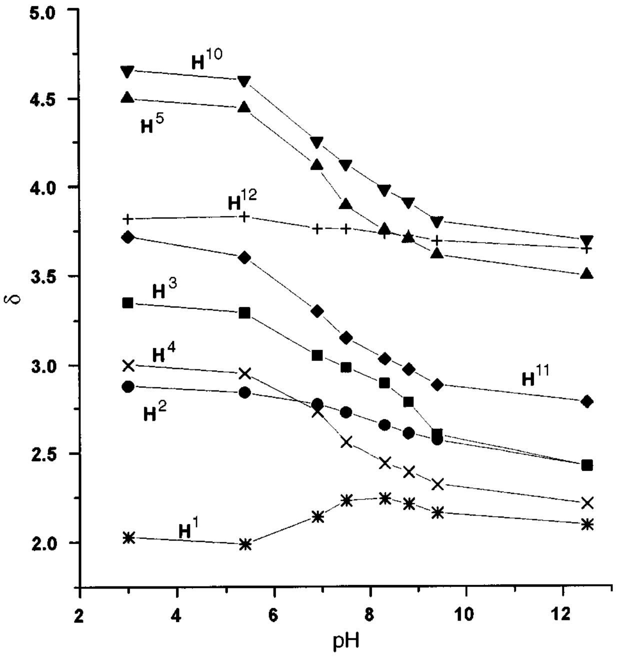


Fig. 2 Experimental ^1H chemical shifts of L^1 as a function of pH (the signals of the aromatic protons, as well as the resonance of H^{13}, have been omitted for clarity; their chemical shifts do not change significantly in the pH range investigated)

Figs. 2 and 3 show respectively the ^1H and ^{13}C NMR chemical shifts of L^1 as a function of pH. In the range pH 9.5–4, where the first four protons bind to the ligand, the signals of the hydrogens H^{3-5}, in α position with respect to N^2, as well as those of H^{10} and H^{11}, in α position with respect to N^3, exhibit a marked downfield shift, while the other signals do not shift appreciably (see, for example, H^1 and H^2, Fig. 2). This suggests that the four protons bind to the four benzylic nitrogen atoms N^2, $N^{2'}$, N^3 and $N^{3'}$. This hypothesis is confirmed by ^{13}C NMR spectra recorded in the same pH range which show that the resonances of the carbon atoms C^2 and C^6, in β position with respect to N^2, as well as the signals of C^9 and C^{12}, in β position with respect to N^3 shift upfield (Fig. 3), in good agreement with the β shift reported for protonation of polyamines.[16]

It can be concluded that the benzylic nitrogens of L^1 display a higher basicity than does the N^1 amine group. π-Ammonium interaction, *i.e.*, a stabilizing effect of the π cloud of the aromatic rings, could be invoked to explain such behaviour.[17]

Moreover, since the protons occupy alternate positions, separated from each other either by the aromatic rings, the unprotonated N^1 nitrogen or the polyoxa chains, such a disposition would mean a minimum in electrostatic repulsion, resulting in a stabilization of the $[H_4L^1]^{4+}$ species which is prevalent in aqueous solution over a wide pH range (2.5–6).

Considering compound L^2, the analysis of the ^1H and ^{13}C NMR spectra recorded at different pH values evidences a

Table 2 Selected bond lengths (Å) and angles (°) for $[Cu(HL^1)Cl(H_2O)][ClO_4]_2$

Molecule A		Molecule B	
Cu(1)–N(2)	1.984(10)	Cu(2)–N(7)	1.987(10)
Cu(1)–N(1)	2.094(10)	Cu(2)–N(6)	2.036(10)
Cu(1)–N(3)	2.095(11)	Cu(2)–N(8)	2.051(9)
Cu(1)–Cl(1)	2.208(4)	Cu(2)–Cl(2)	2.232(4)
N(2)–Cu(1)–N(1)	86.1(4)	N(7)–Cu(2)–N(6)	86.1(4)
N(2)–Cu(1)–N(3)	84.8(4)	N(7)–Cu(2)–N(8)	84.7(4)
N(1)–Cu(1)–N(3)	155.7(4)	N(6)–Cu(2)–N(8)	155.3(4)
N(2)–Cu(1)–Cl(1)	173.5(3)	N(7)–Cu(2)–Cl(2)	172.3(3)
N(1)–Cu(1)–Cl(1)	95.2(3)	N(6)–Cu(2)–Cl(2)	96.3(3)
N(3)–Cu(1)–Cl(1)	96.4(3)	N(8)–Cu(2)–Cl(2)	95.9(3)

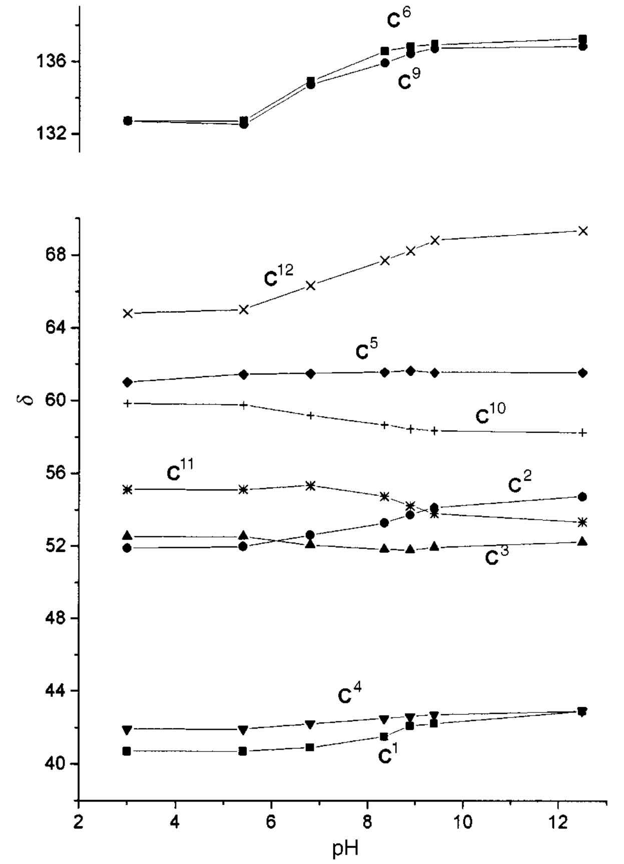


Fig. 3 Experimental ^{13}C NMR chemical shifts of L^1 as a function of pH (the signals of the aromatic carbons C^7 and C^8 as well as that of C^{13} have been omitted for clarity; their chemical shifts do not change significantly in the pH range investigated)

similar protonation mechanism; in the $[H_5L^2]^{5+}$ species four protons are located on the four benzylic nitrogens (N^2, N^3, $N^{2'}$ and $N^{3'}$) and the fifth is positioned on N^5.

Crystal structure of $[Cu(HL^1)Cl(H_2O)][ClO_4]_2$

The molecular structure consists of complex cations $[Cu(HL^1)Cl(H_2O)]^{2+}$ and perchlorate anions. The asymmetric unit contains two independent molecules (herein indicated with A and B). Their ORTEP[18] drawings are shown in Fig. 4(*a*) and 4(*b*), respectively. Table 2 lists selected bond angles and distances for the co-ordination sphere of Cu^{II}. The co-ordination environments of the metal are very similar in the two molecules. The copper atom is localized in the N_3 subunit, co-ordinated by the three methylated nitrogen atoms and a chloride ion, in a square-planar arrangement. Considering the mean plane determined by the four donors [maximum deviation 0.36(1) Å for N(3) in A and 0.38(1) Å for N(6) in B] the metal is shifted toward the cavity described by the benzyl units and the N_2O_4 moiety [0.061(1) Å for Cu(1) and 0.055(1) Å for Cu(2)]. The aromatic rings linking the N_3 and the N_2O_4 subunits are not coplanar to each other, and form a dihedral angle of 39(1) and 40(2)° for A and B, respectively.

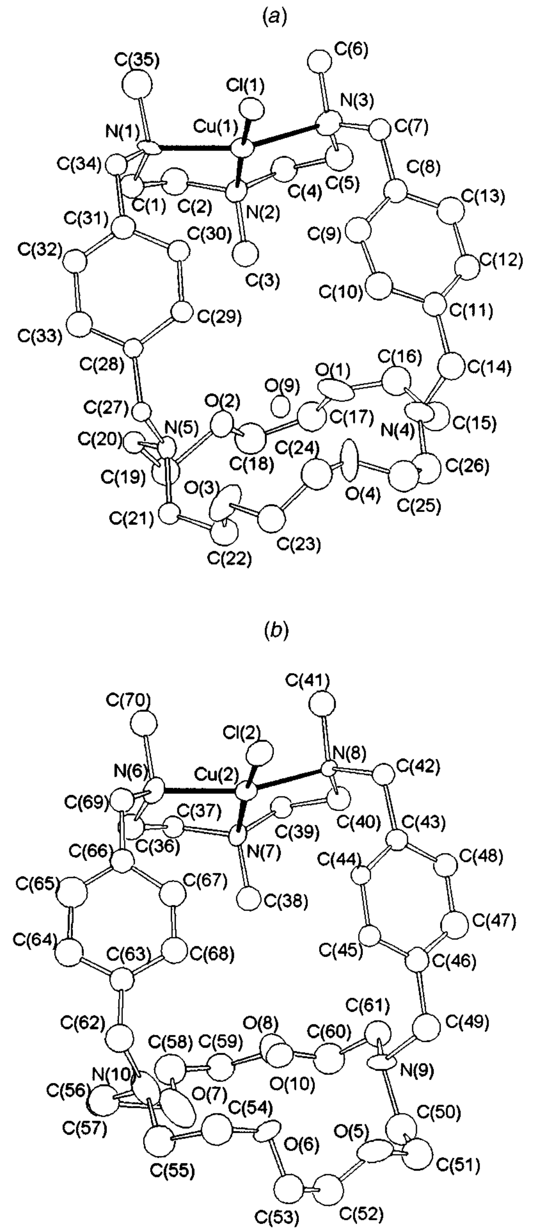


Fig. 4 The ORTEP drawings of the cation $[Cu(HL^1)Cl(H_2O)]^{2+}$ for the two independent molecules A and B

As far as the protonated N_2O_4 moiety is concerned, both A and B molecules show some degree of disorder; two positions were assigned to O(1) , O(2) and C(16) (A molecule) and to C(57) (B molecule). Moreover, the conformations of the two N_2O_4 macrocyclic rings are quite different, as evidenced by the different values for the corresponding torsion angles in the two N_2O_4 rings.† As a consequence, the least-square planes defined by the N_2O_4 heteroatoms in the A and B molecules [maximum deviation 0.81(2) Å for O(2′) in A and 0.81(1) Å for O(7) in B] form dihedral angles of 36.8(2) (A molecule) and 43.5(2)° (B molecule) with the corresponding mean planes defined by the co-ordination environment of the metal ion. The different conformations of the N_2O_4 moiety justify the lack of

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† The different conformations of the N_2O_4 rings in A and B can be deduced by comparing the values of the corresponding torsion angles relative to this moiety. Several torsion angles are significantly different. A complete list of the torsion angles for the N_2O_4 unit in both molecules has been deposited.

Table 3 Logarithms of the equilibrium constants determined in 0.1 mol dm^{-3} NMe_4Cl at 298.1 K for the complexation reactions of Cu^{2+} with L^1 and L^2

	log *K**	
Reaction	L^1	L^2
$Cu^{2+} + L \rightleftharpoons [CuL]^{2+}$	10.22(3)	11.03(3)
$[CuL]^{2+} + H^+ \rightleftharpoons [Cu(HL)]^{3+}$	7.51(3)	7.82(3)
$[Cu(HL)]^{3+} + H^+ \rightleftharpoons [Cu(H_2L)]^{4+}$	6.83(3)	6.72(3)
$[Cu(H_2L)]^{4+} + H^+ \rightleftharpoons [Cu(H_3L)]^{5+}$		5.79(3)
$[CuL]^{2+} + OH^- \rightleftharpoons [CuL(OH)]^+$	5.5(1)	4.4(1)
$[CuL(OH)]^+ + OH^- \rightleftharpoons [CuL(OH)_2]$	2.8(1)	3.8(1)
$[CuL]^{2+} + Cu^{2+} \rightleftharpoons [Cu_2L]^{4+}$		5.31(5)
$[Cu_2L]^{4+} + OH^- \rightleftharpoons [Cu_2L(OH)]^{3+}$		6.1(1)
$[Cu_2L(OH)]^{3+} + OH^- \rightleftharpoons [Cu_2L(OH)_2]^{2+}$		5.1(1)

* Values in parentheses are standard deviations on the last significant figure.

crystallographic symmetry between the two independent molecules A and B.

The monoprotonated N_2O_4 subunit binds through hydrogen bonds a water molecule, which lies 0.886(8) Å in the A molecule [0.98(1) Å in the B molecule] above the mean plane defined by the N_2O_4 heteroatoms. In the A molecule the O(9) atom of the water forms two hydrogen bonds with N(4) and N(5). The shorter O(9)···N(5) distance [2.72(1) *vs.* 3.16(1) Å for O(9)···N(4)] leads us to suppose that the acidic proton is located on the N(5) nitrogen. The water molecule forms further short contacts with some oxygens of the N_2O_4 moiety [O(9)···O(1) 2.88(2), O(9)···O(1′) 2.78(2), O(9)···O(2) 2.86(2) and O(9)···O(4) 2.83(1) Å]. A hydrogen-bond network involving the O(10) water molecule is also found in the B molecule [O(10)···N(9) 2.71(1), O(10)···N(10) 3.33(1), O(10)···O(6) 2.74(1) and O(10)···O(8) 2.91(1) Å]. The different arrangements in the hydrogen-bond network involving the encapsulated water in A and B further confirm the lack of crystallographic symmetry between the two molecules.

Examples of water molecules encapsulated in macrocyclic structures and held by hydrogen-bond networks have been reported.[19,20] Closest comparison can be found in the water clathrates formed by oxaaza macrobicyclic ligands which contain the same N_2O_4 moiety. Similarly to the present complex, in both cases a water molecule is encapsulated in the macrobicyclic cavity, interacting *via* hydrogen bonds with the N_2O_4 unit.[20]

Copper(II) co-ordination in aqueous solution

The formation of the copper(II) complexes with L^1 and L^2 has been investigated by means of potentiometric measurements in aqueous solution (0.1 mol dm^{-3} NMe_4Cl, 298.1 K). The stability constants of the complexes are reported in Table 3.

As far as L^1 is concerned, only mononuclear copper(II) complexes are observed in aqueous solution. The features of the complexes are strongly influenced by the ditopic structure of L^1, which presents two different binding subunits. Only extensive protonation of the ligand inhibits the formation of the complexes. As can be noted from Table 3 and Fig. 5(*a*), the metal ion forms stable complexes with mono- and diprotonated L^1. The equilibrium constants for the successive addition of H^+ to the $[CuL^1]^{2+}$ are significantly high, revealing that protonation occurs on a ligand moiety not involved in the co-ordination. In other words, the copper(II) ion and the protons occupy two almost independent binding sites. Thus, protonation of the $[CuL^1]^{2+}$ complex strongly competes with formation of binuclear species in aqueous solution. Such complexes have not been detected in aqueous solution and separation of copper(II) hydroxide is observed from slightly alkaline solutions containing Cu^{II} and L^1 in molar ratios greater than 1:1.

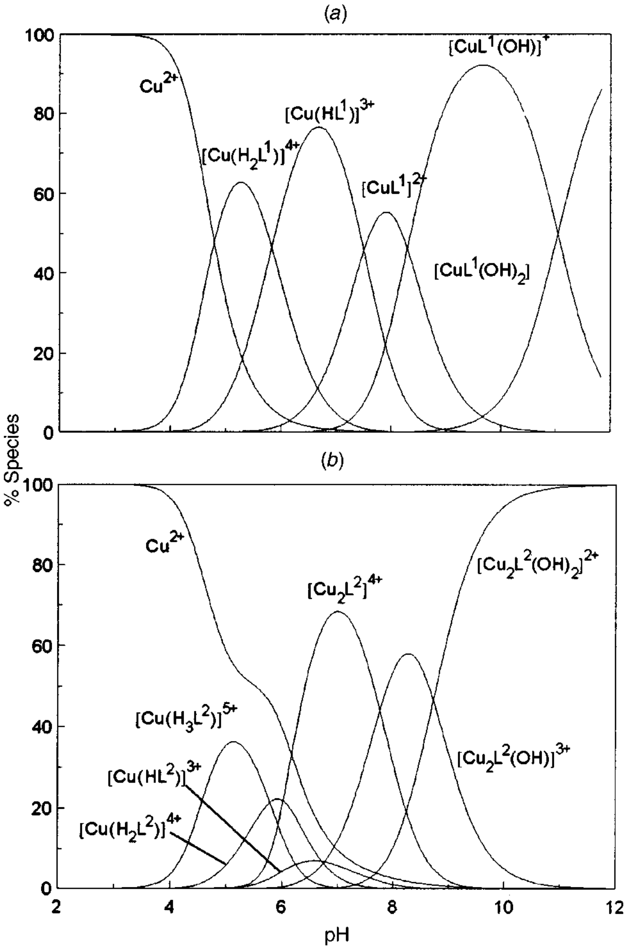


Fig. 5 Distribution diagram of the species for the systems (*a*) L^1–Cu^{II} (0.1 mol dm^{-3} NMe_4Cl, 298.1 K, $[L^1] = 1 \times 10^{-3}$, $[Cu^{2+}] = 1 \times 10^{-3}$ mol dm^{-3}) and (*b*) L^2–Cu^{II} (0.1 mol dm^{-3} NMe_4Cl, 298.1 K, $[L^2] = 1 \times 10^{-3}$, $[Cu^{2+}] = 2 \times 10^{-3}$ mol dm^{-3}) as a function of pH

The stability constant of the $[CuL^1]^{2+}$ complex (log $K = 10.22$) is very similar to that previously found for the mononuclear copper(II) complex with the ligand L^3 (log $K = 10.03$),[4b] where the metal ion is co-ordinated by three adjacent nitrogens of one N_3 unit. This observation indicates that the metal ion is bound by the triaza subunit of L^1, while the N_2O_4 moiety is not involved in co-ordination and can bind up to two protons at neutral or slightly acidic pH. Since in the $[CuL^1]^{2+}$ complex only three nitrogen donors bind to the metal ion, facile deprotonation of the co-ordinated water molecules occurs at slightly alkaline pH, producing mono- and di-hydroxylated species $[CuL^1(OH)]^+$ and $[CuL^1(OH)_2]$ [see Table 3 and Fig. 5(*a*)].

These conclusions about metal and proton binding by L^1 in aqueous solution are confirmed by the crystal structure of the $[Cu(HL^1)Cl]^{2+}$ cation, which shows the metal co-ordinated by the triaza moiety, while the acidic proton is located on the N_2O_4 subunit. Furthermore, the electronic spectrum of the $[CuL^1]^{2+}$ complex in aqueous solution (pH 7), which shows two absorptions at 630 ($\varepsilon = 169$) and 510 nm ($\varepsilon = 140$ dm^3 mol^{-1} cm^{-1}) is almost the same as that found for the $[Cu(HL^1)Cl(H_2O)][ClO_4]_2$ solid complex (two bands at 628 and 505 nm), suggesting a similar co-ordination for the copper(II) ion in aqueous solution and in the solid complex. Most likely, the chloride anion in the solid complex is replaced by a water molecule in aqueous solution.

It is to be noted that the macrocycle 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (L^6), which resembles the N_2O_4 moiety inserted in L^1, can bind Cu^{II} (log $K = 7.59$)[1d] as well as alkali-metal ions in aqueous solution. In the present case this unit does not show any binding ability toward such metals. This may be due to the presence of the benzyl groups bound to the two nitrogen atoms. Although alkyl groups have electron σ-donating properties, their presence prevents the formation of hydrogen bonds between solvating water and amine groups, which contribute, *via* the $H_2O\cdots HN$ interaction, to the σ-donating ability of amine groups in aqueous solution.[21] Furthermore, the benzyl groups lead to a molecular crowding and stiffening of the receptor. Both these electronic and steric factors explain the low binding ability toward metal cations exhibited by the N_2O_4 moiety of L^1.

On the other hand, it is well known that receptors containing the L^6 unit can also bind small molecules or ions, such as ammonium salts, through the formation of hydrogen bonds.[1a,f,h,9] In the present case, the crystal structure of the $[Cu(HL^1)Cl(H_2O)]^{2+}$ cation, a water molecule is encapsulated inside the N_2O_4 moiety of L^1, held by a hydrogen-bond network.

It seems likely that L^1 is a promising ditopic receptor, containing a N_3 subunit for metal co-ordination and a N_2O_4 moiety able to bind, *via* hydrogen bonding, substrate molecules.

In the macrocycle L^2 the N_2O_4 subunit of L^1 is replaced by a pentaamine binding site containing two piperazine rings. Both the piperazine rings are in the chair conformation, as shown by the crystal structure of its pentaperchlorate salt.[22] Considering copper(II) binding, L^2 can form both mono- and bi-nuclear complexes in aqueous solution (see Table 3). Similarly to $[CuL^1]^{2+}$, the mononuclear $[CuL^2]^{2+}$ complex exhibits a marked tendency to protonation, forming mono-, di- and tri-protonated species. The equilibrium constants for successive protonation of this complex are high indicating that protonation involves nitrogen atoms not involved in metal co-ordination. Actually, the metal ion can be co-ordinated by the triaza moiety or by the pentaaza subunit containing the two piperazine rings. On the other hand, the electronic spectrum of the $[CuL^2]^{2+}$ species, which shows only one absorbance at 650 nm ($\varepsilon = 135$ dm^3 mol^{-1} cm^{-1}), remarkably differs from that of the $[CuL^1]^{2+}$ complex, indicating a different co-ordination environment for the metal. The spectrum of $[CuL^2]^{2+}$ is very similar to that reported for the copper(II) complex of the ligand L^4 ($\lambda_{max} = 645$ nm, $\varepsilon = 145$ dm^3 mol^{-1} cm^{-1}).[23] Furthermore, the stability constant for the $[CuL^2]^{2+}$ species is larger (log $K = 11.03$) than that found for $[CuL^1]^{2+}$ and similar to that of $[CuL^4]^{2+}$ (log $K = 10.8$).[23] These spectroscopic and thermodynamic data suggest that in the $[CuL^2]^{2+}$ complex the metal is co-ordinated by the N_5 binding unit, while the N_3 moiety seems to be not involved in metal binding.

The values of the stability constants for both the $[CuL^2]^{2+}$ and $[CuL^4]^{2+}$ complexes seem to indicate that only a few nitrogens of the N_5 unit are involved in co-ordination. Actually, the stability constants for these complexes are similar or lower than those reported for triaza ligands (for instance, log $K = 12.16$ for the copper(II) complex of 2,5,8-trimethyl-2,5,8-triazanonane, where the metal is co-ordinated by three tertiary nitrogens connected by ethylenic chains),[24] while it is far lower than that found for L^5 (log $K = 21.5$), where two nitrogens of a piperazine unit are bound to the metal.[15] It seems likely that in the $[CuL^2]^{2+}$ complex the metal is co-ordinated by the methylated nitrogen N^5 and by one nitrogen of each adjacent piperazine ring (N^4 and $N^{4'}$). Binding of the other nitrogens (N^3 and $N^{3'}$) of the piperazine group would involve the interconversion of the piperazine rings from the chair to the boat conformation and would be not favoured from an energetic point of view. The low co-ordination number of the metal in the $[CuL^2]^{2+}$ complex is confirmed by the formation of stable mono- and di-hydroxo complexes at alkaline pH (see Table 3).

The $[CuL^2]^{2+}$ complex can bind a second metal ion, giving binuclear complexes. For 2:1 Cu^{II}:L^2 molar ratios, the formation of the monometallic complex is depressed and only protonated $[Cu(H_xL^2)]^{(2+x)+}$ species ($x = 1$–3) are formed in low percentage at acidic pH [see Fig. 5(*b*)], while binuclear species are largely prevalent in solution. Such a marked tendency to form binuclear species leads us to propose that in these the two metals are co-ordinated by the two different binding subunits of the ligand, in order to minimize the electrostatic repulsion between the two metal centres. Proposed co-ordination arrangements of L^2 in the $[CuL^2]^{2+}$ and $[Cu_2L^2]^{4+}$ complexes are depicted in Fig. 6. It seems likely that in $[Cu_2L^2]^{4+}$ both metals are co-ordinated by three nitrogens and facile deprotonation of the co-ordinated water molecules produces mono- and di-hydroxylated species. The equilibrium constants for the addition of the first and the second OH^- anions to $[Cu_2L^2]^{4+}$ are similar (see Table 3) suggesting that the hydroxide anions in $[Cu_2L^2(OH)_2]^{2+}$ are located on two separate metal centres.

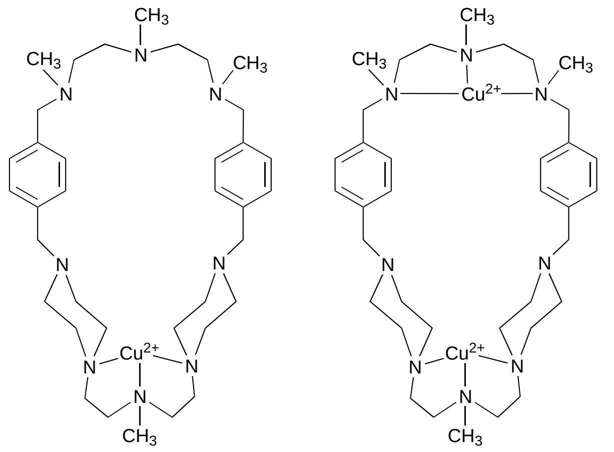
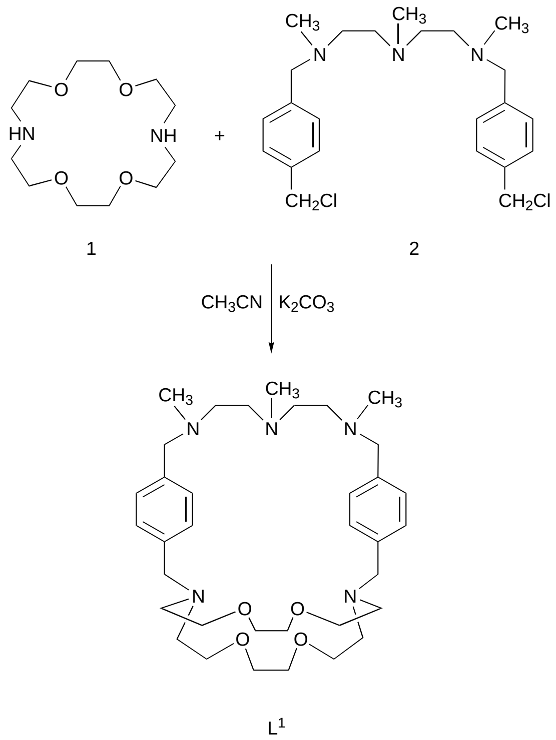


Fig. 6 Proposed co-ordination modes of Cu^{2+} in the $[CuL^2]^{2+}$ and $[Cu_2L^2]^{4+}$ complexes. The structures drawn are only partial, and additional water molecules or hydroxide ions at the remaining sites of Cu^{2+} are not specified



Scheme 1

Experimental

Syntheses

The macrocycle 1,4,7,-trimethyl-19,22,28,31-tetraoxa-1,4,7,14,23-pentaaza[9.25]paracyclophane (L^1) was obtained by following the synthetic procedure depicted in Scheme 1. 2,8-Bis(*p*-chloromethylbenzyl)-5-methyl-2,5,8-triazanonane (**2** in

Scheme 1) and L^2 were synthesized as previously described.[4b,22] 1,4,10,13-Tetraoxa-7,16-diazacyclooctadecane **1** was obtained from Aldrich Chemical Co.

1,4,7-Trimethyl-19,22,28,31-tetraoxa-1,4,7,14,23-pentaaza-[9.25]paracyclophane (L^1). Compound **1** (9 g, 0.026 mol) and K_2CO_3 (36.1 g, 0.26 mol) were suspended in refluxing CH_3CN (300 cm^3). To this mixture was added a suspension of **2** (13.9 g, 0.026 mol) in CH_3CN (250 cm^3) in small portions (*ca.* 5 cm^3 each) over 7 h. Upon completion of the addition, the suspension was refluxed for 8 h and then filtered. The solution was vacuum evaporated to yield the crude product which was chromatographed on neutral alumina (70–230 mesh, activity I, length 25 cm, diameter 4 cm) eluting with $CHCl_3$–CH_3OH (100 : 1.5). After elution with 500 cm^3, L^1 began to leave the column. Further elution (500 cm^3) gave unchanged **1** (2.5 g). The fractions containing L^1 were collected and evaporated to dryness to afford pure L^1 as a colourless oil. Yield: 3.3 g (18%). ^1H NMR ($CDCl_3$): δ 2.15 (s, 3 H), 2.17 (s, 6 H), 2.44 (m, 8 H), 2.88 (t, 8 H), 3.43 (s, 4 H), 3.56 (s, 8 H), 3.60 (t, 8 H), 3.64 (s, 4 H), 7.17 (d, 4 H) and 7.27 (d, 4 H). ^{13}C NMR ($CDCl_3$): δ 43.0, 43.3, 54.5, 54.7, 55.3, 59.8, 62.4, 70.0, 70.9, 128.6, 128.9, 137.4 and 138.6. FAB mass spectrum: *m/z* 613 ($M + H^+$) (Found: C, 68.5; H, 9.5; N, 11.3. Calc. for $C_{35}H_{57}N_5O_4$: C, 68.70; H, 9.39; N, 11.44%).

L^1·5HClO$_4$. This compound was obtained in almost quantitative yield by adding 37% $HClO_4$ to an ethanolic solution of L^1 (Found: C, 37.6; H, 5.6; N, 6.2. Calc. for $C_{35}H_{62}Cl_5N_5O_{24}$: C, 37.73; H, 5.61; N, 6.29%).

[Cu(HL^1)Cl(H$_2$O)][ClO$_4$]$_2$. A solution of $Cu(ClO_4)_2·6H_2O$ (11.1 mg, 0.03 mmol) in water (5 cm^3) was slowly added to an aqueous solution (5 cm^3) containing L^1 (18.3 mg, 0.03 mmol) and NaCl (20 mg). The pH was adjusted to 7 with 0.1 mol dm^{-3} HCl. To the resulting solution $NaClO_4$ (100 mg) was added. Blue crystals of the complex suitable for X-ray analysis were obtained by slow evaporation of this solution at room temperature. Yield: 20 mg (72%) (Found: C, 45.3; H, 6.5; N, 7.6. Calc. for $C_{35}H_{60}Cl_3CuN_5O_{13}$: C, 45.26; H, 6.51; N, 7.54%). **CAUTION:** Perchlorate salts of metal complexes with organic ligands are potentially explosive; these compounds must be handled with great care.

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 on a Bruker AC-200 spectrometer. For ^1H spectra the peak positions are reported relative to HOD at δ 4.75. 1,4-Dioxane was used as reference for ^{13}C NMR spectra (δ 67.4). The ^1H–^1H and ^1H–^{13}C two-dimensional 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 macrocycle to adjust the pD. The pH was calculated from the measured pD values using the following relationship:[25] pH = pD − 0.40. The UV spectra were recorded on a Shimadzu UV-2101PC spectrophotometer.

Crystallography

Crystal data and data collection parameters. Two independent molecules of [Cu(HL^1)Cl(H$_2$O)][ClO$_4$]$_2$ were found in the asymmetric unit (A and B). $C_{35}H_{60}Cl_3CuN_5O_{13}$, $M = 928.79$ for A and B, orthorhombic, $a = 30.249(10)$, $b = 12.136(4)$, $c = 23.920(7)$ Å, $U = 8781(5)$ Å^3 (by least-squares refinement on diffractometer angles from 25 centred reflections, $16 < 2\theta < 25°$), 298 K, space group $Pca2_1$, graphite-monochromated Mo-Kα radiation, $\lambda = 0.71069$ Å, $Z = 4$, $D_c = 1.405$ Mg m^{-3}, $F(000) = 3912$, blue prism with approximate dimensions 0.05 × 0.1 × 0.2 mm, μ(Mo-Kα) = 0.745 mm^{-1}, absorption correction performed by the Stuart and Walker method (DIFABS),[26] φ and μ correction, maximum = 1.195 916, minimum = 0.615 109; θ correction maximum = 1.018 156, minimum = 0.821 900; transmission factors 0.86–0.91. Enraf-Nonius CAD4 X-ray diffractometer, θ–2θ scan mode, data-collection range 2.63–24.97°, *h,k,l*; two standard reflections showed no significant variation in intensity; 7908 reflections measured.

Structure solution and refinement. The structure was solved by the Patterson method and subsequent Fourier-difference technique, and refined anisotropically, by full-matrix least squares on F^2 (programs SHELX 76 and SHELXL 93).[27] Atomic scattering factors and anomalous dispersion corrections were from ref. 28. Hydrogen atoms were included in calculated position. The final Δ*F* map did not localize the acidic protons nor the hydrogens of water molecules. Rotational disorder was found for two perchlorate anions: seven peaks around Cl(4) and five around Cl(5) were introduced as oxygen atoms with partial population factors. Double positions were solved for O(1), O(1′), O(2), O(2′), C(16), C(16′) (population parameter 0.5) and C(57), C(57′) (population parameters 0.6, 0.4 respectively). The weighting scheme was $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]^{\frac{1}{2}}$ where $3P = F_o^2 + 2F_c^2$ and *a* and *b* are constants adjusted by the program. The final $wR(F^2) = 0.3168$, with conventional $R[F, I > 2\sigma(I)] = 0.0985$ $\{R(F) = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, $wR(F^2) = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma wF_o^4]^{\frac{1}{2}}\}$, for 1106 refined parameters, goodness of fit = 1.025, maximum $\Delta\rho = 0.417$ e Å^{-3}. The absolute configuration was confirmed by an *x* refinement; $x = 0.01(5)$. The rather low number of observed reflections with respect to the collected ones and, consequently, the poor quality of the structure determination, with unusually high estimated standard deviations for the refined parameters, are related to the high degree of disorder and/or thermal motion found for the perchlorate anions and the N_2O_4 moieties.

CCDC reference number 186/634.

Potentiometric measurements

Equilibrium constants for protonation and complexation reactions with L^1 and L^2 were determined by pH-metric measurements (pH = −log [H$^+$]) in 0.1 mol dm^{-3} NMe_4Cl at 298.1 ± 0.1 K, by using potentiometric equipment described previously.[29] 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[30] which allows one to determine the standard potential $E^\ominus$, and the ionic product of water [pK_w = 13.83(1) at 298.1 K in 0.1 mol dm^{-3} NMe_4Cl]. Concentrations 1×10^{-3} – 2×10^{-3} mol dm^{-3} of ligands and metal ion were employed in the potentiometric measurements, performing three titration experiments (about 100 data points each) in the ranges pH 2–11. The computer program SUPERQUAD[31] was used to calculate equilibrium constants from electromotive force data. All titrations were treated either as single sets or as separate entities, for each system, without significant variation in the values of the constants determined.

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References

1 (*a*) J. S. Bradshaw, *Aza-crown Macrocycles*, Wiley, New York, 1993; (*b*) R. M. Izatt, J. S. Bradshaw, S. A. Nielsen, J. D. Lamb, J. D. J. J. Christensen and D. Sen, *Chem. Rev.*, 1985, **85**, 271;

(*c*) K. E. Krakowiak, J. S. Bradshaw and D. J. Zamecka-Krakowiak, *Chem. Rev.*, 1989, **89**, 929; (*d*) R. M. Izatt, K. Pawlak, J. S. Bradshaw and R. L. Bruening, *Chem. Rev.*, 1991, **91**, 1721; (*e*) J. S. Bradshaw, K. E. Krakowiak and R. M. Izatt, *Tetrahedron*, 1992, **48**, 4475; (*f*) J. M. Lehn, *Angew Chem.*, *Int. Ed. Engl.*, 1988, **27**, 89; (*g*) J. J. Christensen and R. M. Izatt (Editors), *Synthesis of Macrocycles, the Design of Selective Complexing Agents*, Wiley, New York, 1987; (*h*) G. W. Gokel, *Crown Ethers and Cryptands*, Monographs in Supramolecular Chemistry, ed. J. F. Stoddart, The Royal Society of Chemistry, Cambridge, 1992.

2 D. J. Marrs, J. Hunter, C. Harding, M. G. B. Drew and J. Nelson, *J. Chem. Soc., Dalton Trans.*, 1992, 3235; Q. Lu, C. Harding, V. McKee and J. Nelson, *Inorg. Chim. Acta*, 1993, **255**, 195; Q. Lu, M. McCann and J. Nelson, *J. Inorg. Biochem.*, 1993, **51**, 633; Q. Lu, V. McKee and J. Nelson, *J. Chem. Soc.*, *Chem. Commun.*, 1994, 649; G. Morgan, V. McKee and J. Nelson, *Inorg. Chem.* 1994, **33**, 4427; D. J. Marrs, J. Hunter, C. Harding, M. G. B. Drew and J. Nelson, *J. Chem. Soc.*, *Dalton Trans.*, 1992, 3235; C. J. Harding, F. E. Mabbs, E. J. L. MacInnes, V. McKee and J. Nelson, *J. Chem. Soc., Dalton Trans.*, 1996, 3227.

3 J. Comarmond, B. Dietrich, J. M. Lehn and R. Louis, *J. Chem. Soc.*, *Chem. Commun.*, 1985, 74; R. J. Motekaitis and A. E. Martell, *J. Chem. Soc.*, *Chem. Commun.*, 1988, 915; *J. Am. Chem. Soc.*, 1988, **110**, 8059; R. J. Motekaitis, A. E. Martell, I. Murase, J. M. Lehn and M. H. Hosseini, *Inorg. Chem.*, 1988, **27**, 3630; R. J. Motekaitis and A. E. Martell, *Inorg. Chem.*, 1991, **30**, 694; 1992, **31**, 5534; 1994, **33**, 1032; P. E. Jurek, A. E. Martell, R. J. Motekaitis and R. D. Hancock, *Inorg. Chem.*, 1995, **34**, 1823; Q. Lu, J. J. Reibenspies, A. E. Martell and R. J. Motekaitis, *Inorg. Chem.*, 1996, **35**, 2630; D. A. Nation, A. E. Martell, R. I. Carroll and A. Clearfield, *Inorg. Chem.*, 1996, **35**, 7246.

4 (*a*) C. Bazzicalupi, A. Bencini, A. Bianchi, V. Fusi, P. Paoletti and B. Valtancoli, *J. Chem. Soc., Chem. Commun.*, 1994, 881; (*b*) C. Bazzicalupi, A. Bencini, A. Bianchi, V. Fusi, C. Giorgi, P. Paoletti, S. Stefani and B. Valtancoli, *Inorg. Chem.*, 1995, **34**, 3003; (*c*) C. Bazzicalupi, A. Bencini, A. Bianchi, V. Fusi, M. Mazzanti, P. Paoletti and B. Valtancoli, *Inorg. Chem.*, 1995, **34**, 3003; (*d*) C. Bazzicalupi, A. Bencini, A. Bianchi, V. Fusi, P. Paoletti, G. Piccardi and B. Valtancoli, *Inorg. Chem.*, 1995, **34**, 5622.

5 F. Diederich, *Cyclophanes*, Monographs in Supramolecular Chemistry, ed. J. F. Stoddart, The Royal Society of Chemistry, Cambridge, 1992.

6 B. Dietrich, T. M. Fyles, J. M. Lehn, L. G. Pease and D. L. Fyles, *J. Chem. Soc.*, *Chem. Commun.*, 1978, 934; J. Jazwinski, J. M. Lehn, M. Meric, J.-P. Vigneron, M. Cesario, J. Guilhem and C. Pascard, *Tetrahedron Lett.*, 1987, **42**, 3489.

7 F. Vögtle and W. M. Muller, *Angew Chem.*, *Int. Ed. Engl.*, 1984, **23**, 712; F. Vögtle, W. M. Muller, V. Werner and H. W. Losensky, *Angew. Chem.*, *Int. Ed. Engl.*, 1987, **26**, 901.

8 Y. Murakami, J. KiKuchi, T. Ohno, T. Hirayama, Y. Hisaeda, Y. Nishimura, J. P. Snyder and K. Steliou, *J. Am. Chem. Soc.*, 1991, **113**, 8229.

9 A. Kumar, S. Mageswaran and I. O. Sutherland, *Tetrahedron*, 1986, **42**, 3291; E. A. Pratt, I. O. Sutherland and R. F. Newton, *J. Chem. Soc.*, *Perkin Trans. 1*, 1988, 13; I. O. Sutherland, *Chem. Soc. Rev.*, 1986, **15**, 63; *Pure Appl. Chem.*, 1989, **61**, 1547.

10 M. Pietraszkiewicz and R. Gasiorowki, *Chem. Ber.*, 1990, **123**, 405.

11 R. J. Motekaitis, A. E. Martell, J. P. Lecomte and J. M. Lehn, *Inorg. Chem.*, 1983, **22**, 609; D. Chen and A. E. Martell, *Tetrahedron*, 1991, **34**, 6895; R. Menif, A. E. Martell, P. J. Squattrito and A. Clearfield, *Inorg. Chem.*, 1990, **29**, 4723; D. A. Rockcliffe, A. E. Martell and J. H. Reibenspies, *J. Chem. Soc.*, *Dalton Trans.*, 1996, 167.

12 D. McDowell and J. Nelson, *Tetrahedron Lett.*, 1988, 385; J. Hunter, J. Nelson, M. McCaan and V. McKee, *J. Chem Soc.*, *Chem. Commun.*, 1990, 1148; Q. Lu, J. M. Latour, C. J. Harding, N. Martin, D. J. Marrs, V. McKee and J. Nelson, *J. Chem. Soc.*, *Dalton Trans.*, 1994, 1471; C. J. Harding, Q. Lu, J. F. Malone, D. J. Marrs, N. Martin, V. McKee and J. Nelson, *J. Chem. Soc.*, *Dalton Trans.*, 1995, 1739; M. G. B. Drew, C. J. Harding, O. W. Howarth, Q. Lu, D. J. Marrs, G. G. Morgan, V. McKee and J. Nelson, *J. Chem. Soc.*, *Dalton Trans.*, 1996, 3021.

13 J. A. Aguilar, E. Garcia-España, J. A. Guerrero, J. M. Llinares, J. A. Ramirez, C. Soriano, S. V. Luis, A. Bianchi, L. Ferrini and V. Fusi, *J. Chem. Soc.*, *Dalton Trans.*, 1996, 239.

14 C. Bazzicalupi, A. Bencini, A. Bianchi, V. Fusi, G. Giorgi, M. Micheloni, P. Paoletti and B. Valtancoli, *Tetrahedron Lett.*, 1994, **35**, 8469.

15 R. D. Hancock, A. Evers, M. P. Ngwenya and P. W. Wade, *J. Chem. Soc.*, *Chem. Commun.*, 1987, 1129; R. D. Hancock, S. M. Dobson, A. Evers, P. W. Wade, M. P. Ngwenya, J. C. A. Boeyens and K. P. Wainwright, *J. Am. Chem. Soc.*, 1988, **110**, 2788; R. D. Hancock and A. E. Martell, *Chem. Rev.*, 1989, **89**, 1875; R. D. Hancock and P. W. Wade, *J. Chem. Soc.*, *Dalton Trans.*, 1990, 1323; R. D. Hancock, M. P. Ngwenya, A. Evers, P. W. Wade, J. C. A. Boeyens and S. M. Dobson, *Inorg. Chem.*, 1990, **29**, 264.

16 J. C. Batchelor, J. H. Prestegard, R. J. Cushley and S. R. Lipsy, *J. Am. Chem. Soc.*, 1973, **95**, 6558; A. R. Quirt, J. R. Lyerla, I. R. Peat, J. S. Cohen, W. R. Reynold and M. F. Freedman, *J. Am. Chem. Soc.*, 1974, **96**, 570; J. C. Batchelor, *J. Am. Chem. Soc.*, 1975, **97**, 3410; J. E.Sarnessky, H. L. Surprenant, F. K. Molen and C. N. Reilley, *Anal. Chem.*, 1975, **47**, 2116.

17 A. Andres, M. I. Burguete, E. Garcia-España, S. V. Luis, J. F. Miravet and C. Soriano, *J. Chem. Soc.*, *Perkin Trans. 2*, 1993, 749 and refs. therein.

18 C. K. Johnson, ORTEP, Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, TN, 1971.

19 G. R. Newkome, F. R. Fronczek and D. K. Kohli, *Acta. Crystallogr.*, *Sect. B*, 1981, **37**, 2114; J. P. Behr, P. Dumas and D. Moras, *J. Am. Chem. Soc.*, 1982, **104**, 4540; S. Buøen, J. Dale, P. Groth and J. Krane, *J. Chem. Soc.*, *Chem. Commun.*, 1982, 1172; P. D. J. Grootenhuis, C. J. van Staveren, H. J. der Hertog jun., D. N. Reinhoudt, M. Bos, J. W. H. M. Uiterwijk, L. Kruise and S. Harkema, *J. Chem. Soc.*, *Chem. Commun.*, 1984, 1412; P. D. J. Grootenhuis, C. J. van Staveren, D. N. Reinhoudt, M. Bos, J. W. H. M. Uiterwijk, L. Kruise, S. Harkema, E. J. R. Sudhölter, J. van Eerden and W. T. Klooster, *J. Am. Chem. Soc.*, 1986, **108**, 780; P. J. Dijkstra, H. J. der Hertog, jun., D. N. Reinhoudt and S. Harkema, *Acta. Crystallogr.*, *Sect. C*, 1991, **47**, 225; M. J. Grannas, B. F. Hoskins and R. Robson, *Inorg. Chem.*, 1994, **33**, 1071.

20 P. Clarke, J. M. Gulbis, S. F. Lincoln and E. R. T. Tiekink, *Inorg. Chem.*, 1992, **31**, 3398; N. Lahrahar and P. Marsau, *Acta Crystallogr.*, *Sect. C*, 1995, **51**, 1218.

21 G. Golub, H. Cohen, P. Paoletti, A. Bencini, L. Messori, I. Bertini and D. Meyerstein, *J. Am. Chem. Soc*., 1995, **117**, 8353.

22 C. Bazzicalupi, A. Bencini, A. Bianchi, V. Fusi, A. Granchi, C. Giorgi, P. Paoletti and B. Valtancoli, *J. Chem. Soc.*, *Perkin Trans. 2*, 1997, 775.

23 C. Bazzicalupi, A. Bencini, V. Fusi, M. Micheloni, R. Pontellini and B. Valtancoli, *Inorg. Chim. Acta*, in the press.

24 G. Golub, H. Cohen, P. Paoletti, A. Bencini and D. Meyerstein, *J. Chem. Soc.*, *Dalton Trans.*, 1996, 2055.

25 A. K. Covington, M. Paabo, R. A. Robinson and R. G. Bates, *Anal. Chem.*, 1968, **40**, 700.

26 N. Walker and D. D. Stuart, *Acta. Crystallogr.*, *Sect. A*, 1983, **39**, 158.

27 G. M. Sheldrick, SHELX 76, Program for Crystal Structure determination, University of Cambridge, 1976; G. M. Sheldrick, SHELXL 93, University of Göttingen, 1993.

28 *International Tables for X-Ray Crystallography*, Kynoch Press, Birmingham, 1974, vol. 4.

29 A. Bianchi, L. Bologni, P. Dapporto, M. Micheloni and P. Paoletti, *Inorg. Chem.*, 1984, **23**, 1201.

30 G. Gran, *Analyst* (*London*), 1952, **77**, 661; F. J. Rossotti and H. Rossotti, *J. Chem. Educ.*, 1965, **42**, 375.

31 P. Gans, A. Sabatini and A. Vacca, *J. Chem. Soc.*, *Dalton Trans.*, 1985, 1195.

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