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A New Macrocyclic Cryptand with Squaramide Moieties: An Overstructured Cu^{II} Complex That Selectively Binds Halides: Synthesis, Acid/Base- and Ligational Behavior, and Crystal Structures

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Abstract: The synthesis and characterization of the novel 24,29-dimethyl-6,7,15,16-tetraoxotetracyclo-[19.5.5.$0^{5,8}$.$0^{14,17}$]-1,4,9,13,18,21,24,29-octaazaenatriaconta-$\Delta^{5,8}$,$\Delta^{14,17}$-diene (**L**) are reported. Molecule **L** incorporates two squaramide functions in a overstructured chain connecting two opposite nitrogen atoms of the Me_2[12]aneN_4 polyaza macrocyclic base to obtain a cage topology. The basicity and binding properties of **L** towards Cu^{II} were determined by means of potentiometric measurements in aqueous solution (298.1 ± 0.1 K, I = 0.15 mol dm^{-3}). Molecule **L** behaves as a diprotic base under the experimental conditions employed and forms only mononuclear Cu^{II} complexes in which the squaramide moieties are not involved in the stabilization of the metal ion that is stabilized by the amine functions of the polyaza base inside the three-dimensional cavity. The $[Cu\mathbf{L}]^{2+}$ species was tested as a host for the series of halide anions. UV-visible spectrophotometric experiments permitted the determination of the addition constants of halides to the Cu^{II}-complexed species. The $[Cu\mathbf{L}]^{2+}$ species binds the anions F^-, Cl^-, and Br^- by forming the $[Cu\mathbf{L}X]^+$ species, but does not bind the biggest I^- anion. A trend of selectivity as a function of the hydrogen-bonding capability as well as the dimensions of the anion were established; the maximum value of selectivity was for addition of the F^- anion (log K = 4.8). This selectivity is due to the presence of the overstructured chain containing the squaramide groups up to the Me_2[12]aneN_4 macrocyclic base. The squaramide groups, by providing hydrogen-bond contacts, permit the $[Cu\mathbf{L}]^{2+}$ species to selectively bind these anions through the formation of a hydrogen-bond network with F^- and Cl^-. The crystal structures of the $[Cu\mathbf{L}F]^+$ and $[Cu\mathbf{L}Cl]^+$ cations support the results obtained in aqueous solution.

Keywords: copper · cryptands · halides · squaramides · synthetic methods

Introduction

There has been a continuous effort to develop synthetic receptors able to bind and recognize anions and cations in aqueous solution.[1–5] In this field, the ditopic receptors are an important class of molecules that can bind two species simultaneously. Many ditopic molecular systems have been synthesized and characterized for various purposes in the last decade; one of the most common is the formation of dinuclear metal receptors able to bind, recognize, activate, and/or transport guests with the aim of mimicking biological functions.[6–10]

In this context, macrocyclic molecules containing two binding subunits have received much attention as these compounds are known to form stable binuclear complexes and the metal–metal distance can be modulated. In particular, several ditopic macrocycles containing two identical binding moieties were synthesized.[11,12] In contrast, little effort has been devoted to synthesizing macrocyclic systems containing two different metal-binding sites, and even less to producing systems with two different sites for the simultaneous binding of cations and anions.[13–15] Two means of binding anions can be explored; the anion guest can be coordinated to a metal-

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loreceptor to saturate the coordination environment of the metal center,[16] or it can interact through mainly electrostatic forces, but also hydrogen bonds, with the binding sites of the host.[17]

The latter interaction, which is fundamental in biological environments, has given rise to many synthetic receptors with the aim of selectively recognizing biologically important anions and guests with which to detect, quantify, and regulate the guest or to mimic biological functions. The studies to date have been performed mainly in lipophilic solvents because of the strong solvation of the interacting groups in polar media. In fact, these interactions are not easily achieved in polar solvents, especially in aqueous solution, due to the strong solvent–guest and solvent–host interactions that compete with the process of selective host–guest recognition.

For this reason, the design of host molecules that recognize anions in aqueous solution and the relative studies in this medium are important in view of the biological relevance of many anions.[18]

Due to the central role that they play in both inorganic and biological processes, inorganic anions are often the substrates targeted for binding by the synthetic host. For instance, a large majority of substrates and cofactors engaged in biological processes are anions and many of them are inorganic. Among these, halides are of special interest due to their ubiquitous presence in biological systems. Their selective detection in aqueous solution is of great interest and many efforts have been made to selectively bind them, although this is often achieved in organic and mixed solvents.[19–23] In fact, the main difficulty in discerning them in aqueous solution is caused by their spherical symmetry, which does not permit selective spatial recognition; in addition, the strong solvation power of the solvent in halides, as well as receptor salvation, prevent the interaction that occurs better in other solvents.

With these considerations in mind, we planned the synthesis of a novel macrocyclic molecule **L** (24,29-dimethyl-6,7,15,16-tetraoxotetracyclo-[19.5.5.$0^{5,8}$.$0^{14,17}$]-1,4,9,13,18,21,24,29-octaazaenatriaconta-$\Delta^{5,8}$,$\Delta^{14,17}$-diene) that has two separate binding sites (Figure 1) and, thus, is able to simultaneously host cations and anions. Preorganization of the host has been recognized as a key condition for better host–guest interactions; in addition to electrostatic charge–charge interactions, hydrogen bonds between host and guest can further contribute to stabilization of the complex. In this case, we chose to use a macrobicyclic molecular skeleton to build two distinct binding areas. One is formed by the tetra-aza macrocyclic base in which the four amine functions can act as coordination sites for metal cations or hydrogen-bond-donor or -acceptor sites, depending on the pH of the medium. The other binding area is formed by two squaramide moieties present in the long chain that connects two opposite amine functions of the base to form a cage topology. The latter are able to behave as hydrogen-bond donors through the two amide functions and are, thus, able to interact only with hydrogen-bond-acceptor guests.[24] In fact, the squaramide group has been demonstrated to be a good hydrogen-bond donor through the two amide functions, permitting it to interact with many simple anions, such as chloride, phosphate, carboxylate, and others.[25]

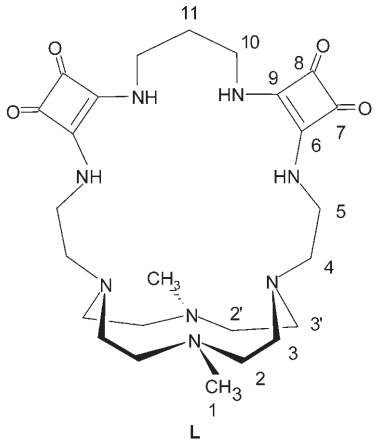
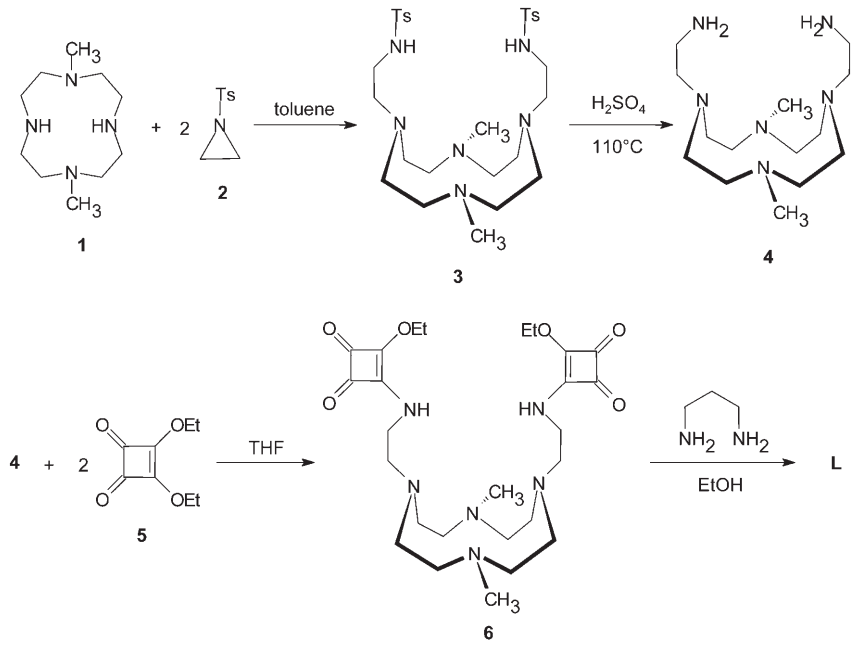


Figure 1. Ligand **L** with atom labeling used in the NMR assignments.

As well as investigating the synthesis, acid–base properties, and preliminary coordination behavior towards a transition-metal ion, such as Cu^{II}, in aqueous solution, we also studied the use of this molecular topology to form a selective Cu^{II} metalloreceptor towards halides, given the presence of the overstructured bridging chain containing squaramide groups able to preorganize an area rich in hydrogen-bond sites. The X-ray crystal structures of the $[Cu\mathbf{L}F]^+$ and $[Cu\mathbf{L}Cl]^+$ species are reported.

Results and Discussion

Synthesis: The synthetic pathway used to obtain ligand **L** is depicted in Scheme 1. The first step involved attaching two pendant arms to the macrocyclic base **1**. The new polyamine **4** was obtained by reacting **1** with two equivalents of *N*-(*p*-toluenesulfonyl)aziridine (**2**) in toluene and the subsequent removal of the *p*-toluenesulfonyl groups of **3** in H_2SO_4. Compound **4** was reacted with 3,4-diethoxy-3-cyclobutene-1,2-dione (**5**); the reaction, carried out in THF, allowed the replacement of only one of the ethoxyl groups of each molecule of **5** with the amine group of **4**.[26] Under these conditions, cyclization and polymerization were avoided, obtaining **6** in high yield. Both compounds **4** and **6** can be used as building blocks for new molecular ligands of various topologies. In this case, **6** was reacted in a cyclization scheme with one equivalent of 1,3-diaminopropane, affording the macrocyclic cryptand **L** (Figure 1) in a high yield. The ^{13}C and ^{1}H NMR spectra of **L** recorded at pH 3 in D_2O (see Experimental Section) showed a higher number of resonances than for the expected C_{2v} symmetry. The signals were fully assigned on the basis of $^{1}H\{^{1}H\}$ and $^{1}H\{^{13}C\}$ two-dimensional correlation experiments. The ^{13}C NMR spectrum shows eleven peaks: at $\delta = 30.5$ (ascribed to the carbon atom of the propyl chain C(11), at 41.8 (C1), 43.1 (C3), 43.2 (C3′), 48.0



Scheme 1. Synthesis of ligand **L**.

(C4), 54.2 (C2, C2′), 55.9 (C5), 168.5 (C9), 169.4 (C6), 182.9, and 183.1 ppm (C7, C8). The ^{1}H NMR spectrum recorded at the same temperature and pH shows a quintet at $\delta = 2.44$ (integrating for two protons and assigned to the hydrogens of the propyl chain H11), a triplet at $\delta = 3.30$ (four protons, H4), a singlet at $\delta = 3.41$ (six protons, H1), a multiplet at $\delta = 3.43$ (eight protons, H2 and H2′), a multiplet at $\delta = 3.78$ (four protons, H3), a multiplet at $\delta = 4.00$ (four protons, H3′), a triplet at $\delta = 4.19$ (four protons, H10), and a triplet at $\delta = 4.26$ ppm (four protons, H5). Analysis of both the ^{13}C and ^{1}H NMR spectra showed a reduced C_s symmetry in solution at this pH on the NMR timescale with respect to the expected C_{2v} symmetry. Analysis of the spectra revealed that the symmetry element lost is the plane passing through the bridgehead nitrogen atoms of the Me_2[12]aneN_4 macrocyclic base, whereas the other plane containing the nitrogen atoms bearing both the methyl groups and the central group of the propyl chain is preserved. This reduced symmetry is attributed to the presence of the squaramide groups that stiffen the molecule on the NMR timescale.

Description of structures [(CuLF)(ClO_4)·(C_2H_5OH)·0.5H_2O] (7) and [(CuLCl)(ClO_4)·H_2O] (8): The asymmetric unit of **7** contains the cation [Cu**L**F]$^+$, a perchlorate anion, a molecule of ethanol, and half a water molecule, whereas that of **8** contains one complex cation [Cu**L**Cl]$^+$, a water molecule, and a perchlorate anion. In both complexes the metal ion is surrounded by the four nitrogen atoms of the tetra-aza macrocyclic base and a halide ion in a distorted square-pyramidal fashion, with the halide ion at the apex of the pyramid (Table 1, Figure 2). In both metal complexes the four nitrogen donor atoms define clearly a plane with the copper ion slightly shifted towards the fluoride ion (0.5422(4) Å) in **7** and the chloride ion (0.5620(6) Å) in **8**. The Cu–donor atom bond lengths (Table 1) are in the range usually observed for analogous Cu^{II} complexes, obtained by searching the Cambridge Structural Database (CSD), Version 5.26.[27]

The macrocyclic ring has the typical [3333]C corners conformation, as described by the sequence of its dihedral angles:[28] C(3), C(5), C(8), and C(10) being the corner atoms.

The overall shape of the [Cu**L**F]$^+$ cation appears quite symmetrical and a pseudosymmetrical C_2 axis, passing through Cu(1), F(1), and C(18), can be recognized (Figures 2a and 3a). In fact, the ethyl chains connecting the

Table 1. Selected bond lengths [Å] and angles [°] of the coordination sphere for compounds **7** and **8**.

	7	**8**
Cu(1)–N(1)	2.043(3)	2.043(4)
Cu(1)–N(2)	2.091(3)	2.094(4)
Cu(1)–N(3)	2.033(3)	2.061(4)
Cu(1)–N(4)	2.118(3)	2.086(4)
Cu(1)–X[a](1)	2.008(2)	2.374(1)
N(1)-Cu(1)-N(2)	86.1(1)	85.3(2)
N(1)-Cu(1)-N(3)	149.8(1)	146.6(2)
N(2)-Cu(1)-N(3)	86.4(1)	86.1(2)
N(1)-Cu(1)-N(4)	86.6(1)	85.5(2)
N(2)-Cu(1)-N(4)	149.5(1)	150.3(2)
N(3)-Cu(1)-N(4)	85.2(1)	86.2(2)
N(1)-Cu(1)-X[a](1)	102.7(1)	107.6(1)
N(2)-Cu(1)-X[a](1)	104.13(9)	101.7(1)
N(3)-Cu(1)-X[a](1)	107.5(1)	105.7(1)
N(4)-Cu(1)-X[a](1)	106.4(1)	108.0(1)

[a] X = F in **7**, X = Cl in **8**.

atom pairs N(4)–N(5) and N(2)–N(8) show the same conformation (i.e., *trans*), whereas the propyl chain connecting N(6)–N(7) takes a *gauche–gauche* conformation. The hydrogen atoms bound to the nitrogen atoms N(6) and N(7) point inside the macrocyclic cavity (*in*), and H(5) and H(8) (bound to N(5) and N(8), respectively) point outside (*out*).

In the [Cu**L**Cl]$^+$ species the overall disposition of the ligand around the metal ion is quite asymmetrical (Figure 2b), at variance with the regular shape observed for the fluoride complex. This different three-dimensional disposition could be ascribed to the bulkier chloride ion in **8**, as suggested by the fact that the overstructured squaramide moiety is rather shifted with respect to the core metal com-

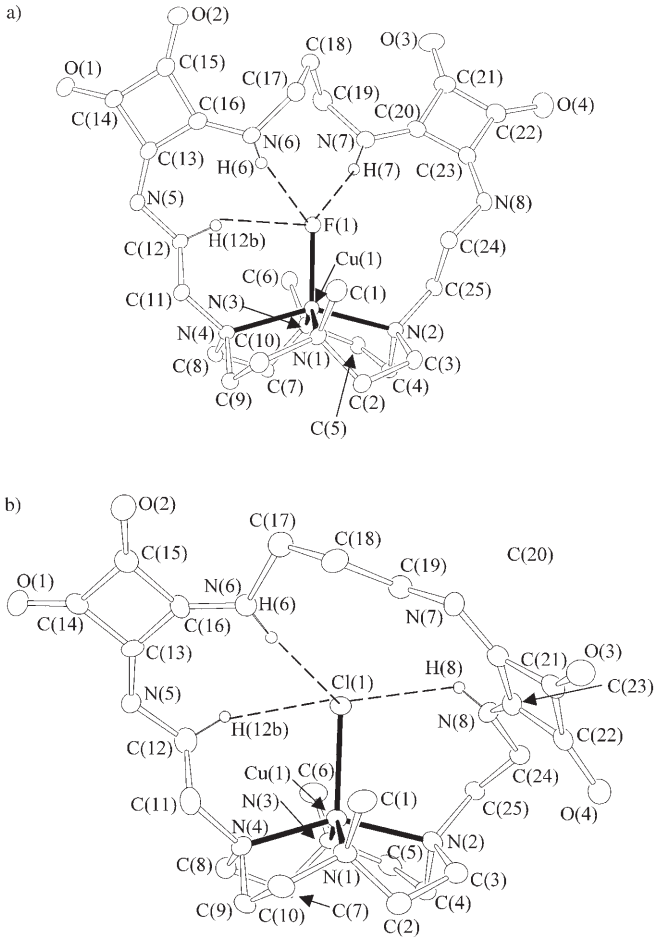


Figure 2. ORTEP3 view of the complex cations $[(Cu\mathbf{L}F)]^+$ (a) and $[(Cu\mathbf{L}Cl)]^+$ (b), highlighting contacts involving the halide ions. Thermal ellipsoids are drawn at 30% probability.

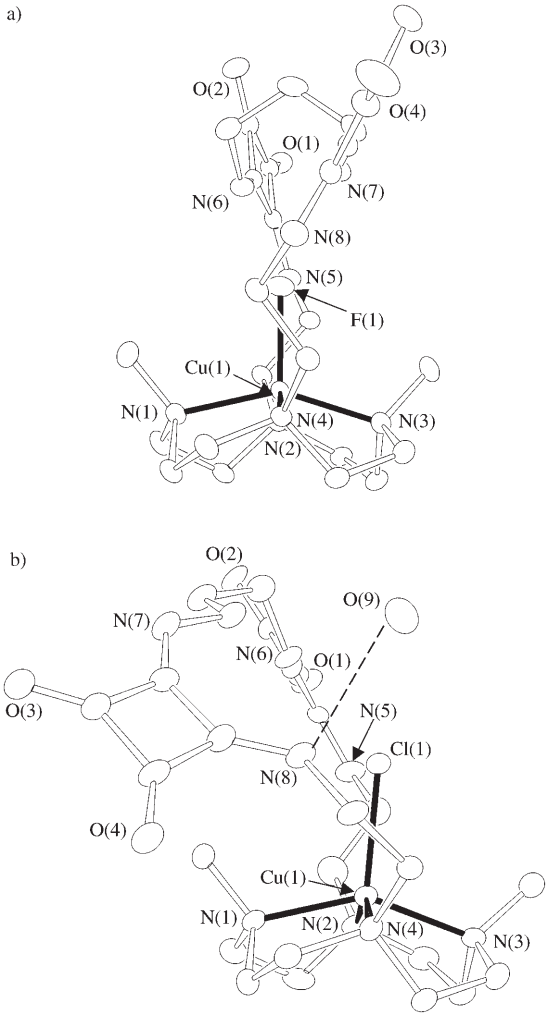


Figure 3. ORTEP3 side views of the complex cations $[(Cu\mathbf{L}F)]^+$ (a) and $[(Cu\mathbf{L}Cl)]^+ \cdot H_2O$ (b). The latter highlights the contact with the oxygen-water molecule. Thermal ellipsoids are drawn at 30% probability.

plex (Figure 3b). As a matter of fact, in the crystal lattice of **8** the empty space between the core and the squaramide units is occupied by a water-of-crystallization molecule held in place by a hydrogen-bond interaction with the nitrogen atom N(8) (O(9)···H(8), 2.20(6) Å, angle at H(8) is 133(5)°).

In **8**, the propyl chain between the two squaramide moieties has a *gauche–trans* conformation (*gauche–gauche* in **7**) and the ethyl chain connecting N(2)–N(8) has a *gauche* conformation (*trans* in $[Cu\mathbf{L}F]^+$). The relative disposition of the hydrogen atoms bound to N(5)–N(8) with respect to the macrocyclic cavity can be described as *out-in-out-in* (Figure 2b, *out-in-in-out* is the sequence in **7**). Notably, in both complexes the Nsp^2–H hydrogen atoms, classified as *in*, contribute through hydrogen bonds[29] to the recognition and stabilization of the metal–halide adduct.[30] In fact, this latter acts as a bifurcated acceptor with respect to H(6) and H(7) in **7**, and H(6) and H(8) in **8** (Table 2). Moreover, in both complexes an auxiliary contact between the halide ion and the hydrogen atom H(12b) provided by a methylene group can be observed (Figure 2). In both cases the two atoms are closer than the sum of their van der Waals radii (2.42(5) vs. 2.67 Å[31] in **7** and 2.455(3) vs. 2.95 Å in **8**) and the angles at the hydrogen atom are greater than 150°.

Finally, in the crystal lattice of **7**, pairs of complex cations are associated through hydrogen bonds: the *out* hydrogen atom H(5) (bound to N(5)) interacts with the squaramide oxygen atom O(1)′ of an image cation reported by the sym-

Table 2. Bond lengths [Å] and angles [°] for the intramolecular hydrogen bonds in compounds **7** and **8**.

	7			**8**		
	H···X	N···X	N–H···X	H···X	N···X	N–H···X
N(6)–H(6)···X[a]	2.02(5)	2.709(4)	161(5)	2.41(6)	3.345(5)	173(5)
N(7)–H(7)···X[a]	1.85(4)	2.698(3)	166(5)			
N(8)–H(8)···X[a]				2.61(5)	3.271(5)	133(5)

[a] X = F in **7**, X = Cl in **8**.

metry operation $-x+1$, $-y$, $-z$ (2.18(4) Å). Naturally, the opposite holds for O(1), which accepts a hydrogen bond from N(5)′. Thus, doubly bonded dimers arise in the crystal lattice. Concerning **8**, each complex cation interacts with three different symmetry-related complexes; through the *out* N–H groupings N(5) and N(7), which are hydrogen-bond donors, and through O(3) and O(4) of a squaramide unit, which work as acceptors. In particular, H(5) is bound to O(4)′ of a symmetry-related species (H(5)···O(4)′ 1.95(6) Å, $x+1$, $-y+1/2$, $z+1/2$) and the opposite holds for O(4), which accepts a hydrogen bond from H(5)″ ($x-1$, $-y+1/2$, $z-1/2$). In contrast, H(7) and O(3) are hydrogen bonded to the same image complex ($-x$, $-y+1$, $-z$) through O(3)‴ and H(7)‴, respectively (H(7)···O(3)‴ 1.93(3) Å).

Solution studies: Basicity: The values of the protonation constants are reported in Table 3. Although there are many nitrogen atoms within the molecular framework of **L**, only two protonation constants can be measured under the experimental conditions employed in this study. As expected, the four nitrogen atoms belonging to the two squaramide moieties did not show any basicity; moreover, they also did not show any acidic behavior, in that no deprotonation processes of squaramides were detected. Only the tertiary nitrogen atoms forming the tetra-aza macrocyclic moieties are involved in the protonation. The relatively high basicity ($\log K = 11.02$, see Table 3) is comparable with that of twelve-membered tetra-aza macrocyclic precursors.[32,33] The drop in stepwise basicity that occurs as the degree of protonation increases is also usual and is due to the repulsion of positive charges that occurs as the number of protonated, close nitrogen atoms increases.

Table 3. Logarithms of the protonation constants of **L** determined by potentiometric measurements in 0.15 M NMe_4NO_3 at 298.1 K. [a]

Reaction	$\log K$
$\mathbf{L} + H^+ = [H\mathbf{L}]^+$	11.02(1)
$[H\mathbf{L}]^+ + H^+ = [H_2\mathbf{L}]^{2+}$	5.59(1)

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

Coordination of metal ions: The coordination properties of **L** were studied in two different ionic media, 0.15 M NMe_4NO_3 and NMe_4Cl aqueous solution at 298.1 K. The stability constants for the equilibrium reactions with Cu^{II} in 0.15 M NMe_4NO_3 aqueous solution were potentiometrically determined and are reported in Table 4; the distribution diagram of the complexed species is reported in Figure 4.

Molecule **L** forms only mononuclear species with Cu^{II} (see Table 4); the $[Cu\mathbf{L}]^{2+}$ species, depending on pH, forms a protonated species or binds up to two hydroxide anions. The value of the formation constant of the $[Cu\mathbf{L}]^{2+}$ species ($\log K = 10.28$) is lower than that given for the macrocyclic base alone[32] and is similar to those reported for cryptand ligands possessing the Me_2[12]aneN$_4$ base, in which the bridging chain does not participate in the coordination of the metal, which is nevertheless located inside the three-dimensional cavity.[34] The addition of a proton to the $[Cu\mathbf{L}]^{2+}$ is quite unfavourable (5.0 logarithmic units), denoting that all four amine functions are involved in the coordination of the metal in the $[Cu\mathbf{L}]^{2+}$ species. Consequently, we can hypothesize that the squaramide moieties of the bridging chain of **L** are not involved in the coordination of Cu^{II}, which is located inside the macrocyclic three-dimensional cavity and stabilized by the four amine functions of the Me_2[12]aneN$_4$ base only. In contrast, mainly the addition of the first, but also of the second OH^- anion, is favorable ($\log K = 6.5$ and 4.5 for the first and second OH^- addition, respectively), suggesting an easy access of the small guest at least to the fifth coordination position of the metal.

Table 4. Logarithms of the equilibrium constants determined in 0.15 mol dm^{-3} NMe_4NO_3 at 298.1 K for the complexation reactions of **L** with the Cu^{II} ion ($M = Cu^{2+}$). [a]

Reaction	$\log K$
$M^{2+} + \mathbf{L} = [M\mathbf{L}]^{2+}$	10.28(1)
$M^{2+} + \mathbf{L} + H^+ = [MH\mathbf{L}]^{3+}$	15.32(2)
$M^{2+} + \mathbf{L} + H_2O = [M\mathbf{L}OH]^+ + H^+$	2.98(1)
$M^{2+} + \mathbf{L} + 2H_2O = M\mathbf{L}(OH)_2 + 2H^+$	−6.27(4)
$[M\mathbf{L}]^{2+} + H^+ = [MH\mathbf{L}]^{3+}$	5.04(3)
$[M\mathbf{L}]^{2+} + OH^- = [M\mathbf{L}OH]^+$	6.48(2)
$[M\mathbf{L}OH]^+ + OH^- = M\mathbf{L}(OH)_2$	4.53(5)

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

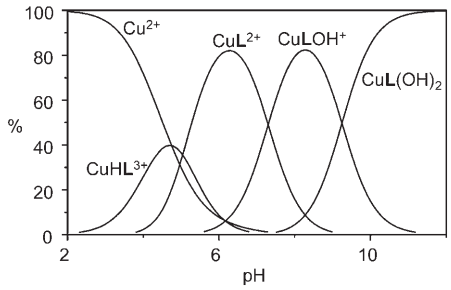


Figure 4. Distribution diagrams of the species for the Cu^{II}/**L** systems as a function of pH in aqueous solution. $I = 0.15$ mol dm^{-3} NMe_4NO_3 at 298.1 K, $[\mathbf{L}] = [Cu^{2+}] = 1 \times 10^{-3}$ mol dm^{-3}.

The same potentiometric experiments were also carried out in 0.15 M NMe_4Cl as the ionic medium. The stability constants obtained in the two media were different, although calculated by using the same model. The main difference is the addition of Cu^{II} to the free **L** to form the $[Cu\mathbf{L}]^{2+}$ species; this is about 3.4 logarithmic units higher in NMe_4Cl than in NMe_4NO_3 (13.63 vs. 10.28 logarithmic units, respectively). The reason for this large difference in $\log K$ can be justified by considering the crystal structure of the metal-complex species reported in Figures 2b and 3b that was obtained in aqueous solution at pH 6 in the presence of Cl^-. The structure shows the Cu^{II} lodged inside the three-dimensional cavity of the cage stabilized by the four amine functions of the macrocyclic base, with a fifth coordination posi-

tion occupied by a chloride interacting through a hydrogen-bond network with an amide function of each squaramide moiety (see above). This stable situation is likely to be absent in NMe_4NO_3 medium because NO_3^- is not able to occupy the fifth position of the metal interacting simultaneously with the squaramide groups. In other words, the $[CuL]^{2+}$ species probably shows a coordinated Cl^- guest interacting simultaneously with the copper ion and with the overstructured chain of the cryptand through a hydrogen bond in NMe_4Cl, whereas it does not show a coordinated NO_3^- in NMe_4NO_3 because of its poorer coordination properties and its unfavorable geometry with respect to the spherical Cl^-. In other words, the $[CuL]^{2+}$ species seems to form more readily in NMe_4Cl than in NMe_4NO_3, however, the model used in NMe_4Cl is not correct and the speciation in the presence of Cl^- must be related to the formation of the $[CuLCl]^+$ and not to the $[CuL]^{2+}$ species. Attempts to determine potentiometrically the value of the addition of Cl^- to the $[CuL]^{2+}$ species did not give reliable values; however, considering the values for the formation of the $[CuL]^{2+}$ in the two ionic media, a value of 3.4 logarithmic units for the reaction $[CuL]^{2+} + Cl^- = [CuLCl]^+$ could be hypothesized. This value is similar to that calculated from spectrophotometric measurements (Table 5), supporting the previous hypothesis.

Table 5. Logarithms of the addition constants of the guest X to the $(CuL)_{tot}$ species [Eq. (1)], determined in 0.05 M MES buffer solution at pH 6.1 and 298.1 K (X = F^-, Cl^-, Br^-, and I^-).[a]

Reaction	log*K*			
	F^-	Cl^-	Br^-	I^-
$X^- + [CuL]^{2+} = [CuLX]^+$	4.8(1)	3.9(1)	2.7(1)	–

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

To verify if the squaramide moieties are involved in coordination of the copper ion, UV spectra were recorded in 0.15 M NMe_4NO_3 aqueous solutions containing **L** and Cu^{II} at different pH values. As an example, the spectrum recorded at pH 6.1, in which the $[CuL]^{2+}$ species is prevalent in solution, shows two main bands, one at $\lambda_{max} = 283$ nm ($\varepsilon = 48000\ cm^{-1}mol^{-1}dm^3$) and a large one at 683 nm ($\varepsilon = 270\ cm^{-1}mol^{-1}dm^3$). The first band is due to the n–π* transitions of the squaramide group, the other to the d–d transition bands of the metal. The absorption band due to the squaramide chromophores shows a similar profile for all pH ranges, in either the presence or absence of Cu^{II}; the data indicate that the squaramides are not perturbed by the presence of Cu^{II}, supporting the hypothesis that they are not involved in the coordination of the metal.

Halide bonding: To detect and quantify the addition of halides and to highlight if the chain containing the squaramide groups affected the binding properties of the $[CuL]^{2+}$ species towards the halides series, the systems $X/Cu^{II}/L$ with Cu^{II}/L^{-1} in a 1:1 molar ratio were studied by conducting UV-visible experiments in a 0.05 M MES (2-(*N*-morpholino)ethanesulfonic acid) buffer solution at pH 6.1 (X = F^-, Cl^-, Br^-, I^-). A pH value of 6.1 was chosen because at this pH the $[CuL]^{2+}$ species is virtually the only species existing in solution (see Figure 4) and, thus, the addition of X to the Cu^{II}/L system can be interpreted mainly as an addition to this species. For comparison, the addition of X anions to the $Cu^{II}/Me_2[12]aneN_4$ system (that is, the macrocyclic base) was also performed under the same experimental conditions. The $[CuMe_2[12]aneN_4]^{2+}$ species was the only species existing at pH 6.1;[32] therefore, it can be compared to the $[CuL]^{2+}$ species. In fact, the two species show the same metallohost unit and the main difference between them is caused by the presence of the overstructured squaramides chain over the metal in the $[CuL]^{2+}$ species. Electron paramagnetic resonance (EPR) spectra of the species present at pH 6.1 in the various systems of **L** were recorded.

The UV-visible spectra in the range 450–900 nm, obtained by adding increasing amounts of a buffer pH 6.1 solution containing Cl^- as sodium salt to a buffer pH 6.1 solution of the Cu^{II}/L system in a 1:1 molar ratio, are reported in Figure 5b. Within this range, the absorption is due to the Cu^{II}-complexed chromophore. As shown in Figure 5b, the spectral profile of the Cu^{II}/L system changes by adding increasing amounts of Cl^- up to the addition of two equivalents of

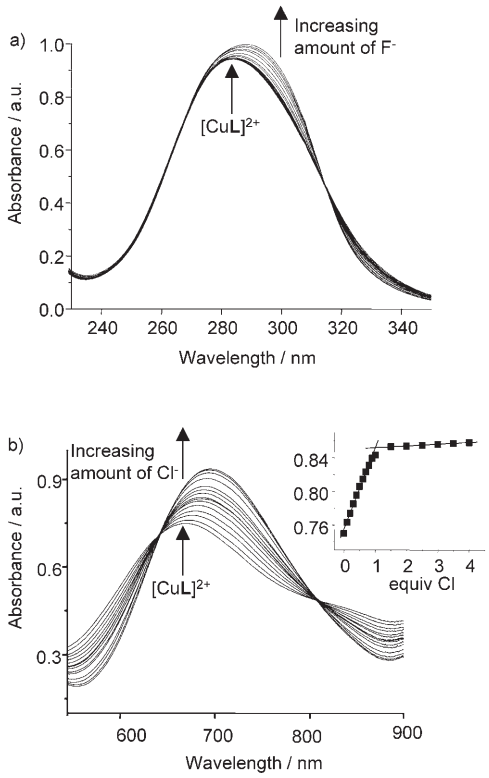


Figure 5. Absorption spectra of the Cu^{2+}/L system in aqueous buffer solution (MES, 0.05 M) at pH 6.1 by adding up to five equivalents of X^- halide with respect to Cu^{II}. a) Within the range 500–900 nm, $X^- = Cl^-$, $[Cu^{2+}] = [L] = 2.8 \times 10^{-3}$ M; b) within the range 230–350 nm, $X^- = F^-$, $[Cu^{2+}] = [L] = 2.0 \times 10^{-5}$ M. Inset: variation in the absorbance at $\lambda = 711$ nm as a function of the Cl^-/L molar ratio.

the anion; this change denotes the coordination of Cl^- to the metal center. The final spectrum obtained shows that the λ_{max} of the band shifts towards lower energy, with respect to that recorded in the absence of Cl^-, as the absorptivity of the species increases (see above paragraph and Figure 5b). The band shifts from 683 ($\varepsilon = 270\ cm^{-1}mol^{-1}dm^3$) in the absence of Cl^- to 711 nm ($\varepsilon = 330\ cm^{-1}mol^{-1}dm^3$) in the presence of Cl^-. The job plot of the absorption at 711 nm versus the equivalents of chloride added shows the formation of a chloride-complexed species of 1:1 stoichiometry, in agreement with the solid-state structure. Similar spectral features were also obtained for the addition of F^- and Br^- anions, whereas the addition of I^- did not affect the spectrum at pH 6.1, even after the addition of 20 equivalents of I^-, revealing that I^- is not bound by the metal center.

The progress of the spectrophotometric curves for each $X/Cu^{II}/\mathbf{L}$ system allowed the relationship of the association constant of X to the total amount of Cu^{II}-complexed species present in solution at this pH to be evaluated by using Equation (1):

$$X + (Cu\mathbf{L})_{tot} = [(Cu\mathbf{L})_{tot}X] \quad (1)$$

in which $(Cu\mathbf{L})_{tot}$ is the sum of the several complexed species present in solution ($(Cu\mathbf{L})_{tot} = [CuH\mathbf{L}]^{3+} + [Cu\mathbf{L}]^{2+} + [Cu\mathbf{L}OH]^{+} + [Cu\mathbf{L}(OH)_2]$).

Table 5 reports the value ($\log K$) of the addition of X to $(Cu\mathbf{L})_{tot}$. At pH 6.1 the $[Cu\mathbf{L}]^{2+}$ species is present at over 83% with respect to the other species; thus, it can be safely assumed that the addition of X to $[Cu\mathbf{L}]^{2+}$ occurs by forming the $[Cu\mathbf{L}X]^{+}$ species, the same as those reported in the crystal structures for $X = F^-$, Cl^-. In other words, the halides F^-, Cl^-, and Br^- are bound by the $[Cu\mathbf{L}]^{2+}$ species and not by the other species present at this pH value. The same experiments carried out in a 3-[tris(hydroxymethyl)methylamino] 1-propanesulfonic acid (TAPS) buffer (0.05 M) at pH 8.4, in which the $[CuLOH]^{+}$ species is almost the only existing species (see Figure 4), did not show evidence of binding halides, supporting the idea that the $[Cu\mathbf{L}]^{2+}$ species is the host species for halides. The addition of the X series to the $Cu^{II}/Me_2[12]aneN_4$ system under the same experimental conditions did not affect the spectral profile of the $[Cu\text{-}Me_2[12]aneN_4]^{2+}$ species (the only species existing at this pH), suggesting that the overstructured chain containing the two squaramide moieties plays a key role in the formation of the $[Cu\mathbf{L}X]^{+}$ species. The value of the addition constant of X to the $(Cu\mathbf{L})_{tot}$ shows a trend $F^- \rightarrow Cl^- \rightarrow Br^-$, with a decrease of more than two logarithmic units from F^- to Br^-. Usually, the thermodynamic stability of the halide–metal complexes follows this trend, even if it is not a general rule. In this case, we must consider two things; the presence of the overstructured chain in **L** and the hydrogen-bonding capability of both the anion and the squaramide moieties. In fact, the chain can discriminate in terms of the best fitting between the dimensions of the macrocyclic cavity and that of the anion, and also by the hydrogen-bonding interactions between the amide groups of the squaramides and the X anions. Taking into account that the hydrogen-bonding capability of the halide series is highest for F^- and decreases in the series, with no hydrogen bonding at all for I^-, the formation of a hydrogen-bond network between the amide groups of the chain and X seems to play the key role in the halide addition to the $[Cu\mathbf{L}]^{2+}$ species, as also suggested by the two crystal structures reported here. In the above experiments, the UV-visible spectra obtained between 230 and 350 nm (the range in which the squaramide groups absorb) reveal changes in the spectral profile upon addition of F^- and Cl^-, whereas the profile remains largely unchanged by adding Br^- to the $Cu^{II}/\mathbf{L}$ system. Figure 5a shows the UV-visible spectra within this range obtained by adding increasing amounts of F^- to a solution of the $Cu^{II}/\mathbf{L}$ system in a 1:1 molar ratio under the above experimental conditions. As depicted, addition of the anion shifts the λ_{max} of the band towards lower energy, with a small increase in the absorptivity with respect to that recorded in the absence of F^- (from 283 nm in absence of F^- to 291 nm after addition of F^-). Furthermore, in this case the final spectrum is obtained by adding two equivalents of F^-. The spectral change indicates that the coordination of F^- to the $[Cu\mathbf{L}]^{2+}$ species affects also the squaramide chromophore; this can be explained by the formation of strong hydrogen-bonding interactions between the amide groups of the squaramides and the fluoride, which have an effect on the absorption properties of the groups. A similar spectral feature was obtained with Cl^-, but not with the Br^- anion, indicating formation of hydrogen bonds also with Cl^-. Thus, the hydrogen-bond contacts evidenced in the solid-state structures of **7** and **8** are also maintained in solution.

To obtain further information about the Cu^{II} coordination environment in the $[Cu\mathbf{L}X]^{+}$ species, EPR spectra of these and the $[Cu\mathbf{L}]^{2+}$ species were recorded in aqueous solution at pH 6.1 and 298.1 K. The EPR spectrum of the $[Cu\mathbf{L}]^{2+}$ species shows a four-line resolution typical of a distorted square-planar coordination of Cu^{II} complexes with nitrogen ligands, and a water molecule occupies the apical position.[35] The hyperfine coupling constant (for the coupling between the unpaired electron spin and the copper nuclear spin), $<A>$, was evaluated to be 64.5 G for the $[Cu\mathbf{L}]^{2+}$, which is consistent with four equatorial nitrogen ligands.[35] The addition of the Cl^- ion to this species produces a slight increase in $<A>$ of up to 67.0 G, due to an increased spin density at the copper nucleus. This effect can be attributed to the replacement of a water molecule at the apical position of the pentacoordinated copper environment with the chloride ion. A similar effect was also found for the fluorinated and (to a lesser degree) for the brominated complexes, with $<A> =$ 66.9 and 65.5 G, respectively. These data once again support the conclusion that the coordination environment of Cu^{II} observed in both crystal structures is also preserved in solution.

In conclusion, the $[Cu\mathbf{L}]^{2+}$ species in aqueous solution binds the anions F^-, Cl^-, and Br^- of the halide series by forming a $[Cu\mathbf{L}X]^{+}$-complexed species, but does not bind the largest I^- anion. A trend of selectivity with a maximum

towards F^- can be determined. The properties necessary to bind these anions and the trend of selectivity are attributed to the presence of the overstructured chain up to the $Me_2[12]aneN_4$ macrocyclic base, which furnishes further favorable contacts with the coordinated halide that permit the $[Cu\mathbf{L}]^{2+}$ species to bind these anions although they are not bound by the $[CuMe_2[12]aneN_4]^{2+}$ complex of the base. In particular, the trend of selectivity is due to the hydrogen-bond-donor properties of the amide groups of the squaramides, which form the strongest interaction with the best hydrogen-bond acceptor F^- and the weakest with Br^-, in which only a dipolar interaction between the amide groups and the anion can be invoked. The analysis of the crystal structures of the $[Cu\mathbf{L}F]^+$ and $[Cu\mathbf{L}Cl]^+$ species support this hypothesis. The best fitting of the dimensions of the macrocyclic cavity and the anionic radius of the halide can be also considered mainly in the case of Br^- and could be the reason for the lack of interaction with I^-.

Conclusion

The novel ligand **L** was synthesized and characterized; it can be derived from the $Me_2[12]aneN_4$ macrocyclic base in which two opposite nitrogen atoms are bridged by a chain containing two squaramide moieties in a 1+1 cyclization scheme forming a macrocyclic ligand with a cage topology. Ligand **L** behaves as a diprotic base in aqueous solution and any deprotonation process of the squaramide groups was observed under these experimental conditions. The coordination behavior towards the Cu^{II} ion was studied in aqueous solution by performing potentiometric and UV-visible experiments. The former, carried out in two different ionic media (NMe_4NO_3 and NMe_4Cl), highlight the formation of a $[Cu\mathbf{L}]^{2+}$ species of differing stability, in that the presence of Cl^- favors the formation of the $[Cu\mathbf{L}Cl]^+$ adduct in NMe_4Cl. The Cu^{II} ion lodges inside the macrocyclic three-dimensional cavity, stabilized by the four amine functions of the $Me_2[12]aneN_4$ base; the squaramide functions do not participate directly in the coordination of the metal ion and, thus, in the $[Cu\mathbf{L}]^{2+}$ species, the chain containing the squaramides forms an overstructure over the metal center rich in hydrogen-bond-donor groups. This overstructure can interact with hydrogen-bond acceptors, as demonstrated by results of UV-visible experiments in the case of the spherical halide series. The $[Cu\mathbf{L}]^{2+}$ species can bind one anion of the series in aqueous solution at pH 6.1, with the exception of the iodide, and forms a $[Cu\mathbf{L}X]^+$ species. A trend of selectivity was obtained that depends on the hydrogen-bonding properties of the anion, giving the highest addition constant for the fluoride (over 100 times higher than that of the bromide). For comparison, the same experiments with **L** were also performed with the $Me_2[12]aneN_4$ macrocyclic base. The results showed that the $[CuMe_2[12]aneN_4]^{2+}$ species does not bind any halide anion, once more highlighting the key role played by the overstructured chain in stabilizing the anion mainly through the formation of a hydrogen-bond network. The solid-state structures of the $[Cu\mathbf{L}F]^+$ and $[Cu\mathbf{L}Cl]^+$ species, showing the Cu^{II} ion inside the cavity of **L** stabilized by the four amine functions of the macrocyclic base and by the halide ion that interacts through a hydrogen-bond network with the amide functions of each squaramide moiety, supports this hypothesis.

In conclusion, **L** has a molecular structure that can interact with metal cations and anions simultaneously; the cation is stabilized by the amine functions, and the anion is stabilized by the squaramide moieties rich in hydrogen-bond donors provided by the amide groups. The anion is also coordinated by the metal cation, as in this case, however, the interaction of the anion with the overstructured chain determines the selectivity towards the anionic guest. This suggests that it might be possible to extend the hosting properties of the $[Cu\mathbf{L}]^{2+}$ species towards other anionic guests of biological relevance that are able to bind Cu^{II} and simultaneously form hydrogen-bond contacts with squaramide groups, such as citrate, phosphate, and carboxylate anions. It would be also interesting to replace Cu^{II} with another metal center to investigate the role played by the metal and by its coordination requirement; for example, Zn^{II}, which usually shows a pentacoordination pattern similar to that of Cu^{II}, or Ni^{II}, which preferentially shows a hexacoordination environment. Moreover, a coordination bond between cation and anion, even if important, should not be essential to give interaction between **L** and the anion. In other words, the presence of positive charges in the amine groups, together with the squaramide chain, should contribute to stabilization of an anion. Following this concept, the presence of the protonated ammonium group of the macrocyclic base can produce a positively charged area and, thus, a suitably preorganized host for anions. In addition, the study of different couples of cation (not only metal cations) and anion that can interact simultaneously with each other and with the several donor groups present in **L** makes this molecule attractive and suitable for further studies in the host–guest field. These aspects are under investigation and will be the subject of future publications.

Experimental Section

IR spectra were recorded by using a Shimadzu FTIR-8300 spectrometer. Melting points were determined by using a Büchi melting point B 540 apparatus and are uncorrected. EI-MS spectra (70 eV) were recorded by using a Fisons Trio 1000 spectrometer; ESI mass spectra were recorded by using a ThermoQuest LCQ Duo LC/MS/MS spectrometer. ^1H and ^{13}C NMR spectra were recorded by using a Bruker Avance 200 instrument, operating at 200.13 and 50.33 MHz, respectively, and equipped with a variable-temperature controller. The temperature of the NMR probe was calibrated by using 1,2-ethanediol as calibration sample. For the spectra recorded in D_2O, the peak positions are reported with respect to HOD (4.75 ppm) for ^1H NMR spectra, and dioxane was used as reference standard in ^{13}C NMR spectra ($\delta = 67.4$ ppm). For the spectra recorded in $CDCl_3$ the peak positions are reported with respect to TMS. The EPR spectra were recorded by using an EMX-Bruker spectrometer operating at the X band (9.5 GHz) and interfaced to a PC computer (Bruker software) for data acquisition and handling. The temperature was controlled by means of a Bruker ST3000 variable-temperature assembly.

Synthesis: Ligand **L** was obtained according to the synthetic procedure reported in Scheme 1. 1,7-Dimethyl-1,4,7,10-tetra-azacyclododecane (**1**),[32] *N*-(*p*-toluenesulfonyl)aziridine (**2**),[36] and 3,4-diethoxy-3-cyclobutene-1,2-dione (**5**)[26] were prepared as described previously. All other chemicals were purchased at the highest quality commercially available. The solvents were of RP grade unless otherwise indicated.

4,10-Bis[2-(*p*-toluenesulfonyl)aminoethyl]-1,7-dimethyl-1,4,7,10-tetra-azacyclododecane (3): A solution of *N*-(*p*-toluensulfonyl)aziridine (**2**) (3.55 g, 0.018 mol) in anhydrous toluene (75 cm^3) was added dropwise at RT in a nitrogen atmosphere to a stirred solution of **1** (3.60 g, 0.018 mol) in anhydrous toluene (500 cm^3) over a period of 7 h. The resulting solution was kept at RT for approximately 12 h and then **2** (3.55 g, 0.018 mol) in anhydrous toluene (75 cm^3) was added under the same conditions. After 12 h, the resulting mixture was filtered and evaporated under reduced pressure to give crude **3** as a yellow solid, which was purified by crystallization from a chloroform/ethanol (1:1) mixture (7.4 g, 69%). ^{1}H NMR ($CDCl_3$): $\delta = 2.01$ (s, 6H), 2.38 (s, 6H), 2.41 (br, 16H), 2.53 (t, 4H), 2.90 (t, 4H), 7.30 (d, 4H), 7.88 (d, 4H), 8.65 ppm (br, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 21.4$, 41.2, 42.9, 51.0, 54.7, 55.5, 127.4, 129.5, 137.5, 142.4 ppm; elemental analysis calcd (%) for $C_{28}H_{46}N_6O_4S_2$ (594.8): C 56.54, N 14.13, H 7.79; found: C 56.62, N 14.18, H 7.83.

4,10-Bis(2-aminoethyl)-1,7-dimethyl-1,4,7,10-tetra-azacyclododecane (4): Compound **3** (6.5 g, 0.011 mol) was dissolved in 98% H_2SO_4 (13 cm^3) and the resulting solution was kept at 100 °C for 72 h. The solution was cooled to RT and added dropwise into diethyl ether (200 cm^3) with stirring. The colorless solid that precipitated was filtered off, washed with diethyl ether, and was then dissolved in a minimum amount of water. The aqueous solution was made alkaline by adding concentrated NaOH and was then extracted with chloroform (5×50 cm^3). The combined extracts were dried with anhydrous Na_2SO_4 and evaporated under reduced pressure, affording compound **4** as a colorless oil (3.10 g, 98%). ^{1}H NMR ($CDCl_3$): $\delta = 2.17$ (s, 6H), 2.41 (t, 4H), 2.50 (br, 16H), 2.69 ppm (t, 4H); ^{13}C NMR ($CDCl_3$): $\delta = 39.5$, 43.6, 53.0, 55.9, 57.7 ppm; MS (ESI): *m*/*z*: 287.3 $[M+H]^+$; elemental analysis calcd (%) for $C_{14}H_{34}N_6$ (286.5): C 58.70, N 29.34, H 11.96; found: C 58.47, N 29.16, H 12.10.

4,10-Bis[2-(2-ethoxyl-3,4-dioxocyclobut-1-en-1-ylamino)ethyl]-1,7-dimethyl-1,4,7,10-tetra-azacyclododecane (6): A solution of 3,4-diethoxy-3-cyclobutene-1,2-dione (**5**) (6.60 g, 38.8 mmol) in anhydrous THF (15 cm^3) was added dropwise at RT to a stirred solution of **4** (5.55 g, 19.4 mmol) in THF (400 cm^3) over a period of 3 h. The reaction mixture was maintained at RT with stirring for 48 h, after which it was filtered and the organic layer was evaporated under reduced pressure to obtain an orange oil. The crude product was purified by chromatography on alumina eluting with a $CHCl_3/CH_3OH$ (10:1) mixture and **6** was obtained as a white solid (6.4 g, 62%). M.p. 124–125 °C; ^{1}H NMR ($CDCl_3$): $\delta = 1.42$ (t, 6H), 2.26 (s, 6H), 2.39–2.58 (br, 20H), 3.39 (br, 4H), 4.71 (q, 4H), 9.01 ppm (br, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 15.7$, 15.9, 43.1, 45.1, 51.6, 53.9, 69.4, 172.4, 177.3, 182.9, 189.0 ppm; FTIR (KBr): $\tilde{\nu} = 1608.6$, 1705.0, 1793.7 cm^{-1}; MS (ESI): *m*/*z*: 535 $[M+H]^+$; elemental analysis calcd (%) for $C_{26}H_{42}N_6O_6$ (534.7): C 58.41, N 15.72, H 7.92; found: C 58.52, N 15.78, H 8.03.

24,29-Dimethyl-6,7,15,16-tetraoxotetracyclo-[19.5.5.0^{5,8}.0^{14,17}]-1,4,9,13,18,21,24,29-octaazaenatriaconta-$\Delta^{5,8}$,$\Delta^{14,17}$-diene (L): 1,3-Diaminopropane (0.14 g, 1.87 mmol) in dried ethanol (100 cm^3) was added dropwise at RT to a stirred solution of **6** (1.0 g, 1.87 mmol) in anhydrous ethanol (250 cm^3) over a period of 6 h. The solution was kept at RT with stirring for a further 72 h, then was cooled at 0 °C. The yellow precipitate that formed was filtered, washed with cold ethanol, and was recrystallized from hot ethanol to obtained **L** as a white solid (0.81 g, 84%). M.p. 258 °C, dec; ^{1}H NMR (D_2O, pH 3): $\delta = 2.44$ (quin, 2H), 3.30 (t, 4H), 3.41 (s, 6H), 3.43 (m, 8H), 3.78 (m, 4H), 4.00 (m, 4H), 4.19 (t, 4H), 4.26 ppm (t, 4H); ^{13}C NMR (D_2O, pH 3): $\delta = 30.5$, 41.8, 43.1, 43.2, 48.0, 54.2, 55.9, 168.5, 169.4, 182.9, 183.1 ppm; FTIR (KBr): $\tilde{\nu} = 1577.7$, 1679.9, 1793.7 cm^{-1}; MS (ESI): *m*/*z*: 517 $[M+H]^+$; elemental analysis calcd (%) for $C_{25}H_{40}N_8O_4$ (516.6): C 58.12, N 21.69, H 7.80; found: C 58.21, N 21.73, H 7.91

[(CuLF)(ClO$_4$)·(C$_2$H$_5$OH)·0.5H$_2$O] (7): A sample of $Cu(ClO_4)_2 \cdot 6H_2O$ (37 mg, 0.1 mmol) in water (10 mL) was added to an aqueous solution (20 mL) containing **L** (52 mg, 0.1 mmol) and NaF (6.3 mg, 0.15 mmol). The pH of the resulting solution was adjusted to 6 with NMe_4OH (0.1 M). After a few minutes, **7** precipitated as a microcrystalline blue solid (60 mg, 79%). Crystals suitable for X-ray analysis were obtained by slow diffusion of ethanol in a pH 6 aqueous solution containing **7**. Elemental analysis calcd (%) for $C_{27}H_{47}ClFCuN_8O_{9.5}$ (753.7): C 43.03, H 6.28, N 14.87; found: C 42.86, H 6.43, N 14.75.

[(CuLCl)(ClO$_4$)·H$_2$O] (8): This compound was synthesized from **L** (52 mg, 0.1 mmol), $Cu(ClO_4)_2 \cdot 6H_2O$ (37 mg, 0.1 mmol) and NaCl (9 mg, 0.15 mmol) by following the same procedure reported for **7**, giving **8** as blue microcrystals (56 mg, 77%). Crystals suitable for X-ray analysis were obtained by slow diffusion of ethanol in a pH 6 aqueous solution containing **8**. Elemental analysis calcd (%) for $C_{25}H_{42}Cl_2CuN_8O_9$ (733.11): C 40.96, H 5.77, N 15.28; found: C 41.06, H 5.63, N 15.34. Crystals suitable for X-ray analysis were obtained by slow diffusion of an aqueous solution containing **8**.

Caution: Perchlorate salts of organic compounds are potentially explosive; these compounds must be prepared and handled with great care!

X-ray crystallography: Intensity data for compounds **7** and **8** were collected by using an Oxford Diffraction Excalibur diffractometer using $Mo_{K\alpha}$ radiation ($\lambda = 0.71070$ Å) for **7** and $Cu_{K\alpha}$ radiation ($\lambda = 1.5418$ Å) for **8**. For both compounds the diffractometer was equipped with a cryo-cooling device used to set the temperatures at 150 and 100 K for **7** and **8**, respectively. Data collection was performed by using the program CrysAlis CCD.[37] For **7**, 594 frames of data were collected by using six settings of ω scan. For **8**, several sets of ω scan were used and data "frames" were collected for 1° increments in ω. A total of 725 frames of data were collected, providing a sphere of data. Data reduction for both structures was carried out by using the program CrysAlis RED.[38] Absorption correction was applied by using the ABSPACK[39] program for both **7** and **8**.

The structures were solved by using the SIR-97 package[40] and were subsequently refined on the F^2 values by the full-matrix least-squares program SHELXL-97.[41]

Concerning compound **7**, all the non-hydrogen atoms were refined anisotropically, but the hydrogen atoms of ligand **L**, which were found in the Fourier syntheses and whose positions were refined, were treated isotropically. The perchlorate ion, the ethanol, and the water-of-crystallization molecules in the asymmetric unit are affected by disorder. Two models for the perchlorate anion and for the ethanol molecule were proposed. A population factor of 0.5 was assigned to the water molecule. All the non-hydrogen atoms in **8** were refined anisotropically. The hydrogen atoms belonging to N(5), N(6), N(7), and N(8) were found in the Fourier map and were refined isotropically. All the other hydrogen atoms of the ligand were set in calculated positions and were refined with an isotropic thermal parameter depending on the atom to which they are bound.

Geometrical calculations were performed by using PARST97[42] and molecular plots were produced by using the ORTEP3 program.[43]

Crystallographic data and refinement parameters are reported in Table 6.

CCDC 297159 and 297160 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.

Electromotive force (EMF) measurements: Equilibrium constants for protonation and complexation reactions with **L** were determined by taking pH-metric measurements ($pH = -\log[H^+]$) in 0.15 M NMe_4NO_3 or 0.15 M NMe_4Cl at 298.1 ± 0.1 K by using the fully automatic equipment described previously.[44] The EMF data were acquired by using the PASAT computer program.[45] The combined glass electrode was calibrated as a hydrogen-concentration probe by titrating known amounts of HNO_3 with CO_2-free NMe_4OH solutions and determining the equivalent point by Gran's method,[46] which gives the standard potential $E^\ominus$ and the ionic product of water ($pK_w = 13.78(1)$ and 13.73(1) at 298.1 K in 0.15 M NMe_4NO_3 and NMe_4Cl, respectively, $K_w = [H^+][OH^-]$). At least three potentiometric titrations were performed for each system within the pH range 2–11 by using different molar ratios of Cu^{II}/**L** ranging from 1:1 to 2:1. All titrations were treated either as single sets or as separate entities for each system; no significant variations were found in the values of the

Table 6. Crystallographic data and refinement parameters for compounds **7** and **8**.

	7	**8**
empirical formula	$C_{27}H_{47}ClFCuN_8O_{9.5}$	$C_{25}H_{42}Cl_2CuN_8O_9$
formula weight	753.47	733.11
T[K]	150	100
λ[Å]	0.7107	1.5418
crystal system	triclinic	monoclinic
space group	$P\bar{1}$	$P2_1/c$
a[Å]	9.043(1)	10.6889(8)
b[Å]	10.747(1)	20.487(2)
c[Å]	17.414(2)	14.488(1)
α[°]	82.42(1)	–
β[°]	79.852(9)	100.729(6)
γ[°]	68.74(1)	–
V[Å^3]	1548.3(3)	3117(4)
Z, ρ_{calcd}[mg cm^{-3}]	2, 1.613	4, 1.560
μ[mm^{-1}]	0.867	3.124
F(000)	790	1528
crystal size[mm^3]	0.5×0.4×0.3	0.35×0.3×0.28
θ range[°]	4.25–28.33	4.73–50.48
reflns collected/unique	16140/6596	13618/3238
data/parameters	5541/600	2549/422
GOF on F^2	1.098	1.091
final R indices [$I>2\sigma(I)$]	$R1=0.0540$, $wR2=0.1288$	$R1=0.0558$, $wR2=0.1560$
R indices (all data)	$R1=0.0627$, $wR2=0.1335$	$R1=0.0694$, $wR2=0.1660$

constants determined. The HYPERQUAD computer program was used to process the potentiometric data.[47]

UV/Vis experiments: UV absorption spectra were recorded at 298 K by using a Varian Cary-100 spectrophotometer equipped with a temperature-control unit. The interaction of halides with the $[Cu\mathbf{L}]^{2+}$ species was studied in aqueous 0.05 M MES (2-(*N*-morpholino)ethanesulfonic acid) buffer solution at pH 6.1. Buffered MES solution containing up to five equivalents of inorganic ions (F^-, Cl^-, Br^-, or I^-), relative to the amount of Cu^{II} complex, was added to the buffer solution containing the $[Cu\mathbf{L}]^{2+}$ species. ($[Cu^{2+}]=[\mathbf{L}]=2.8\times10^{-3}$ or 2.0×10^{-5} M.). At least three sets of spectrophotometric titration curves for each $X^-/Cu^{2+}/\mathbf{L}$ system were performed. All sets of curves were treated either as single sets or as separate entities for each system; no significant variations were found in the values of the constants determined. The HYPERQUAD computer program was used to process the spectrophotometric data.[47]

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[1] a) H. J. Schneider, A. K. Yatsimirsky, *Principles and Methods in Supramolecular Chemistry*, John Wiley & Sons, **2000**; b) J. W. Steed, J. L. Atwood, *Supramolecular Chemistry*, John Wiley & Sons, **2000**; c) F. Voegtle, *Comprehensive Supramolecular Chemistry: Molecular Recognition: Vol. 2, Receptors for Molecular Guests*, Pergamon, **1996**; d) G. W. Gokel, *Comprehensive Supramolecular Chemistry, Vol. 1: Molecular Recognition: Receptors for Cationic Guests*, Pergamon, **1996**.

[2] a) A. Zelewsky, *Stereochemistry of Coordination Compounds*; John Wiley & Sons, **1996**; b) E. C. Constable, *Coordination Chemistry of Macrocyclic Compounds*, Oxford University Press, **1999**.

[3] a) R. D. Hancock, *Metal Complexes in Aqueous Solution; Modern Inorganic Chemistry*, Plenum Press, New York, **1996**; b) J.-S. Bradshaw, *Aza-Crown Macrocycles*, Wiley, New York, **1993**; c) P. Dietrich, P. Viout, J.-M. Lehn, *Macrocyclic Chemistry*, VCH, Weinheim, **1993**.

[4] a) G. W. Gokel, *Crown Ethers and Cryptands (Monographs in Supramolecular Chemistry)* (Ed.: J. F. Stoddart), The Royal Society of Chemistry, Cambridge, **1992**; b) A. Bianchi, K. Bowman-James, E. Garcia-España, *Supramolecular Chemistry of Anions*, Wiley-VCH, New York, **1997**.

[5] a) M. Formica, V. Fusi, M. Micheloni, P. Pontellini, P. Romani, *Coord. Chem. Rev.* **1999**, *184*, 347; b) G. W. Gokel, W. M. Leevy, M. E. Weber, *Chem. Rev.* **2004**, *104*, 2723.

[6] a) C. A. Ilioudis, J. W. Steed, *Org. Biomol. Chem.* **2005**, *3*, 2935; b) Y. Mulyana, C. J. Kepert, L. F. Lindoy, A. Parkin, P. Turner, *Dalton Trans.* **2005**, 1598; c) L. Kovbasyuk, H. Pritzkow, R. Kraemer, *Eur. J. Inorg. Chem.* **2005**, 894; d) E. R. Sanchez, M. T. Caudle, *J. Biol. Inorg. Chem.* **2004**, *9*, 724.

[7] a) A. L. Gavrilova, B. Bosnich, *Chem. Rev.* **2004**, *104*, 349; b) C. Miranda, F. Escarti, L. Lamarque, M. J. R. Yunta, P. Navarro, E. Garcia-España, M. L. Jimeno, *J. Am. Chem. Soc.* **2004**, *126*, 823; c) L. Lamarque, P. Navarro, C. Miranda, V. J. Aran, C. Ochoa, F. Escarti, E. Garcia-España, J. Latorre, S. V. Luis, J. F. Miravet, *J. Am. Chem. Soc.* **2001**, *123*, 10560.

[8] A. Bencini, A. Bianchi, V. Fusi, C. Giorgi, A. Masotti, P. Paoletti, *J. Org. Chem.* **2000**, *65*, 7686.

[9] a) A. Mizukami, T. Nagano, Y. Urano, A. Odani, K. Kikuchi, *J. Am. Chem. Soc.* **2002**, *124*, 3920; b) G. Xue, J. S. Bradshaw, N. K. Dalley, P. B. Savage, K. E. Krakowiak, R. M. Izatt, L. Prodi, M. Montalti, N. Zaccheroni, *Tetrahedron* **2001**, *57*, 7623.

[10] a) B. Verdejo, J. Aguilar, A. Domenech, C. Miranda, P. Navarro, H. R. Jimenez, C. Soriano, E. Garcia-España, *Chem. Commun.* **2005**, 3086; b) M. Cangiotti, M. Formica, V. Fusi, L. Giorgi, M. Micheloni, M. F. Ottaviani, S. Sampaolesi, *Eur. J. Inorg. Chem.* **2004**, 2853.

[11] a) V. Amendola, L. Fabbrizzi, C. Mangano, P. Pallavicini, *Acc. Chem. Res.* **2001**, *34*, 488; b) M. Suzuki, H. Furutachi, H. Okawa, *Coord. Chem. Rev.* **2000**, *200–202*, 105; c) K. Bowman-James, *Acc. Chem. Res.* **2005**, *38*, 671.

[12] a) S. O. Kang, D. Powell, K. Bowman-James, *J. Am. Chem. Soc.* **2005**, *127*, 13478; b) B. Bauer-Siebenlist, S. Dechert, F. Meyer, *Chem. Eur. J.* **2005**, *11*, 5343; c) A. D. Bond, S. Derossi, C. J. Harding, E. J. L. McInnes, V. McKee, C. McKenzie, J. Nelson, J. Wolowska, *Dalton Trans.* **2005**, 2403; d) A. E. Martell, R. J. Motekaitis, D. Chen, R. D. Hancock, *Supramol. Chem.* **1996**, *6*, 333.

[13] a) S. L. Murphy, S. J. Loeb, G. K. H. Shimizu, *Tetrahedron* **1998**, *54*, 15137; b) P. Ghosh, S. S. Gupta, P. K. Bharadwaj, *J. Chem. Soc. Dalton Trans.* **1997**, 935; c) F. Oton, A. Tarraga, M. D. Velasco, P. Molina, *Dalton Trans.* **2005**, 1159; d) P. K. Panda, C.-H. Lee, *J. Org. Chem.* **2005**, *70*, 31; e) V. A. Koulov, J. M. Mahoney, B. D. Smith, *Org. Biomol. Chem.* **2003**, *1*, 27.

[14] a) P. D. Beer, S. W. Dent, *Chem. Commun.* **1998**, 825; b) D. M. Rudkevich, Z. Brzozka, M. Palys, H. C. Viser, W. Verboon, D. N. Reinhoudt, *Angew. Chem.* **1994**, *106*, 480; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 467; c) D. J. White, N. Laing, H. Miller, S. Parsons, S. Coles, P. A. Tasker, *Chem. Commun.* **1999**, 2077.

[15] a) P. D. Beer, S. R. Bayly, *Top. Curr. Chem.* **2005**, 255; b) M. Cametti, M. Nissinen, A. Dalla Cort, L. Mandolini, K. Rissanen, *Chem. Commun.* **2003**, 2420.

[16] a) C. Bazzicalupi, A. Bencini, A. Bianchi, V. Fusi, P. Paoletti, B. Valtancoli, *J. Chem. Soc. Chem. Commun.* **1995**, 1555; b) C. Bazzicalupi, A. Bencini, A. Bencini, A. Bianchi, F. Corona, V. Fusi, C. Giorgi, P. Paoli, P. Paoletti, B. Valtancoli, C. Zanchini, *Inorg. Chem.* **1996**, *35*, 5540.

[17] J. M. Mahoney, A. M. Beatty, B. D. Smith, *J. Am. Chem. Soc.* **2001**, *123*, 5847.

[18] a) E. Gouaux, R. MacKinnon, *Science* **2005**, *310*, 1461; b) A. W. J. W. Tepper, L. Bubacco, G. W. Canters, *J. Biol. Chem.* **2002**, *277*, 30436.

[19] M. Cametti, M. Nissinen, A. Dalla Cort, L. Mandolini, K. Rissanen, *J. Am. Chem. Soc.* **2005**, *127*, 3831.
[20] a) M. Baiocchi, L. Del Boca, D. Esteban-Gòmez, L. Fabbrizzi, M. Licchelli, E. Monzani, *Chem. Eur. J.* **2005**, *11*, 3097; b) A. F. Danil de Namor, M. Shehab, *J. Phys. Chem. B* **2003**, *107*, 6462; c) V. Amendola, M. Boiocchi, L. Fabbrizzi, A. Palchetti, *Chem. Eur. J.* **2005**, *11*, 5648; d) O. B. Berryman, F. Hof, M. J. Hynes, D. W. Johnson, *Chem. Commun.* **2006**, 506.
[21] a) P. D. Beer, P. A. Gale, *Angew. Chem.* **2001**, *113*, 502; *Angew. Chem. Int. Ed.* **2001**, *40*, 486; b) M. R. Sambrook, P. D. Beer, J. A. Wisner, R. L. Paul, A. R. Cowley, F. Szemes, M. G. B. Drew, *J. Am. Chem. Soc.* **2005**, *127*, 2292; c) M. D. Lankshear, A. R. Cowley, P. D. Beer, *Chem. Commun.* **2006**, 612; d) P. D. Beer, S. W. dent, G. S. Hobbs, T. J. Wear, *Chem. Commun.* **1997**, 99.
[22] a) J. L. Sessler, D. An, W.-S. Cho, V. Lynch, M. Marquez, *Chem. Commun.* **2005**, 540; b) M. Shionoya, H. Furuta, V. Lynch, A. Harryman, J. L. Sessler, *J. Am. Chem. Soc.* **1992**, *114*, 5714.
[23] a) C. J. Woods, S. Camiolo, M. E. Light, S. J. Coles, M. B. Hursthouse, M. A. King, P. A. Gale, J. W. Essex, *J. Am. Chem. Soc.* **2002**, *124*, 8644; b) P. A. Gale, S. Camiolo, G. J. Tizzard, C. P. Chapman, M. E. Light, S. J. Coles, M. B. Hursthouse, *J. Org. Chem.* **2001**, *66*, 7849.
[24] a) D. Quinonero, R. Prohens, C. Garau, A. Frontera, P. Ballester, A. Costa, P. M. Deyà, *Chem. Phys. Lett.* **2002**, *351*, 115; b) C. Garau, D. Quinonero, A. Frontera, A. Costa, P. Ballester, P. M. Deyà, *Chem. Phys. Lett.* **2003**, *370*, 7.
[25] a) R. Prohens, G. Martorell, P. Ballester, A. Costa, *Chem. Commun.* **2001**, 1456; b) M. N. Pina, C. Rotger, A. Costa, P. Ballester, P. M. Deyà, *Tetrahedron Lett.* **2004**, *45*, 3749; c) K. Sato, K. Seio, M. Sekine, *J. Am. Chem. Soc.* **2002**, *124*, 12715.
[26] M. C. Rotger, M. N. Pina, A. Frontera, G. Martorell, P. Ballester, P. M. Deyà, A. Costa, *J. Org. Chem.* **2004**, *69*, 2302.
[27] F. H. Allen, *Acta Cryst. Sect. B* **2002**, *B58*, 380.
[28] *Stereochemical and Stereophysical Behaviour of Macrocycles, Vol. 2* (Ed.: I. Bernal), Elsevier, **1987**.
[29] The N–H···X$^-$ distances (as well as the N···X$^-$ distances) are only slightly longer (Table 2) than the average lengths for Nsp^2–H hydrogen bonds with angles at H > 140°: 1.64(1) Å (2.64(1) Å), X = F) and 2.221(7) Å (3.181(6) Å, X = Cl). See T. Steiner, *Acta Cryst. Sect. B* **1998**, *B54*, 456.
[30] Z. Shirin, J. Thompson, L. Liable-Sands, G. P. A. Yap, A. L. Rheingold, A. S. Borovik, *J. Chem. Soc. Dalton Trans.* **2002**, 1714.
[31] A. J. Bondi, *J. Chem. Phys.* **1964**, *68*, 441.
[32] M. Ciampolini, P. Dapporto, M. Micheloni, N. Nardi, P. Paoletti, F. Zanobini, *J. Chem. Soc. Dalton Trans.* **1984**, 1357.
[33] R. Hancock, P. Wade, M. Ngwenya, *Inorg. Chem.* **1990**, *29*, 1968.
[34] C. Bazzicalupi, A. Bencini, A. Bianchi, V. Fusi, C. Giorgi, P. Paoletti, B. Valtancoli, *J. Chem. Soc. Dalton Trans.* **1994**, 3581.
[35] M. F. Ottaviani, S. Bossmann, N. J. Turro, D. A. Tomalia, *J. Am. Chem. Soc.* **1994**, *116*, 661.
[36] A. E. Martin, T. M. Ford, J. E. Bulkowski, *J. Org. Chem.* **1982**, *47*, 412.
[37] CrysAlis CCD, Oxford Diffraction Ltd., Version 1.171.pre23 10 beta (release 21.06.2004 CrysAlis171.NET), (compiled Jun 21, **2004**, 12:00:08).
[38] CrysAlis RED, Oxford Diffraction Ltd., Version 1.171.pre23 10 beta (release 21.06.2004 CrysAlis171.NET), (compiled Jun 21, **2004**, 12:00:08).
[39] ABSPACK in CrysAlis RED, Oxford Diffraction Ltd., Version 1.171.29.2 (release 20.01.2006 CrysAlis171.NET), (compiled Jan 20, **2006**, 12:36:28).
[40] A. Altomare, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1999**, *32*, 115.
[41] G. M. Sheldrick, SHELXL-97, University of Göttingen, Göttingen (Germany) **1997**.
[42] M. Nardelli, *J. Appl. Crystallogr.* **1995**, *28*, 659.
[43] L. J. Farrugia, *J. Appl. Crystallogr.* **1997**, *30*, 565.
[44] P. Dapporto, M. Formica, V. Fusi, M. Micheloni, P. Paoli, R. Pontellini, P. Rossi, *Inorg. Chem.* **2000**, *39*, 4663.
[45] M. Fontanelli, M. Micheloni, *I Spanish–Italian Congr. Thermodynamics of Metal Complexes*, June 3–6, **1990**, Peñiscola, University of Valencia, Spain, p. 41.
[46] a) G. Gran, *Analyst* **1952**, *77*, 661; b) F. J. Rossotti, H. Rossotti, *J. Chem. Educ.* **1965**, *42*, 375.
[47] P. Gans, A. Sabatini, A. Vacca, *Talanta* 1996, 43, 1739.

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