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FULL PAPER

A ferrocene functionalised macrocyclic receptor for cations and anions

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The isolation and characterisation of a new macrocyclic hexaamine *trans*-6,13-bis(ferrocenylmethylamino)-6,13-dimethyl-1,4,8,11-tetraazacyclotetradecane (L^2) bearing two ferrocenyl groups appended to its exocyclic amines is reported. The crystal structures of L^2 and its dihydrochloride salt $L^2{\cdot}2HCl{\cdot}2H_2O$ have been determined. In the latter case cation–anion hydrogen bonding is observed in the solid state. Substrate binding by the electroactive L^2 in $MeCN–CH_2Cl_2$ solution has been examined by cyclic voltammetry and reveals the receptor electrochemically to recognise benzoate and chloride anions. The macrocyclic N-donors may also bind transition metal cations such as Cu^{II} and Zn^{II}.

Introduction

The fourteen-membered macrocycle 1,4,8,11-tetraazacyclotetradecane (cyclam) is an ideal host for metal ions as it may bind in either a planar or folded conformation as a tetradentate forming complexes of exceptional stability. Much effort has been devoted to the elaboration of the basic cyclam unit to more sophisticated assemblies.[1,2] Less attention has been given to the ability of cyclam to act as a host for anionic guests through hydrogen bonding interactions. A particularly useful technique for detecting weak, reversible host–guest interactions is cyclic voltammetry whereby the shift in redox potential of the host or guest is perturbed by complex formation. Very few anions are redox active, so the host ideally should possess a functional group proximate to the guest binding site with well behaved electrochemistry.

The ferrocenyl group continues to be a versatile redox probe in electrochemically responsive receptors for charged and neutral guests.[3,4] Communication between the redox active signalling unit and the binding site may be achieved in a variety of ways.[5] For charged guests electrostatic forces are most important and oxidation or reduction of the receptor may significantly affect the binding strength. Receptor design usually involves the combination of a functionalised ferrocene with a ligand suited to binding a guest of a certain type. A balance must be maintained between strong ferrocene–guest interaction and efficient host–guest binding.

We have now synthesized a novel bis-ferrocene substituted cyclam receptor where the macrocyclic N-donors remain unaffected by covalently appending the redox active signalling units to the exocyclic amines of the macrocyclic ring. We will demonstrate that this molecule has the ability to bind both cations or anions and that these interactions may be detected electrochemically.

Experimental

Syntheses

The macrocycle *trans*-6,13-dimethyl-1,4,8,11-tetraazacyclotetradecane-6,13-diamine hexahydrochloride ($L^1{\cdot}6HCl$) was synthesized as described previously.[6] All other regents were obtained commercially.

***trans*-6,13-Dimethyl-1,4,8,11-tetraazacyclotetradecane-6,13-diamine (L^1).** A solution of $L^1{\cdot}6HCl$ (5.12 g) in NaOH solution (50 cm^3, 5 mol dm^{-3}) was cooled to room temperature then extracted (3 × 50 cm^3) with CH_2Cl_2. The extracts were combined, dried over Na_2SO_4, filtered and evaporated to dryness (2.10 g). ^1H NMR ($CDCl_3$): δ 1.04 (s, 6H), 1.78 (s (br), 8H), 2.47–2.71 (m, 16H).

***trans*-6,13-Bis(ferrocenylmethylamino)-6,13-dimethyl-1,4,8,11-tetraazacyclotetradecane (L^2).** Ferrocenecarbaldehyde (0.90 g) was melted with stirring at 130 °C. Solid *trans*-6,13-dimethyl-1,4,8,11-tetraazacyclotetradecane-6,13-diamine (0.54 g) was added gradually over about 2 min. After cooling, MeOH (60 cm^3) and $NaBH_4$ (0.9 g) were added and the mixture was stirred for 2 h at room temperature, then evaporated to dryness. The residue was suspended in water (60 cm^3) and extracted with CH_2Cl_2 (3 × 50 cm^3). Column chromatography (SiO_2, MeOH–NH_3(aq) 9 : 1) gave four bands in the order: (i) ferrocene (impurity in starting material); (ii) hydroxymethylferrocene; (iii) L^2 (0.45 g) [^1H NMR ($CDCl_3$): δ 1.08 (s, 6H), 2.48 (d, 4 H), 2.59 (d, 4H), 2.71 (m, 8H), 3.41 (s, 4H), 4.09 (t, 4H), 4.16 (s, 10H), 4.20 (t, 4H)] and (iv) L^3 (0.03 g) [^1H NMR ($CDCl_3$): δ 1.06 (s, 3H), 1.08 (s, 3H), 2.48–2.73 (m, 16 H), 3.41 (s, 2H), 4.08 (t, 2H), 4.15 (s, 5H), 4.21 (t, 2H)]. Recrystallisation of L^2 from the minimum amount of hot MeCN afforded crystals suitable for X-ray work.

***trans*-6,13-Bis(ferrocenylmethylamino)-6,13-dimethyl-1,4,8,11-tetraazacyclotetradecane dihydrochloride dihydrate ($L^2{\cdot}2HCl{\cdot}2H_2O$).** To a solution of L^2 (0.05 g) in chloroform (*ca.* 1 cm^3) was added trifluoroacetic acid (0.01 cm^3) in a small glass vial. The vial was sealed and, on standing, yellow crystals suitable for X-ray work formed and were collected by filtration.

Physical methods

NMR spectra were measured with a Bruker AC200 spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. Cyclic voltammetry experiments were performed at a sweep rate of 0.1 V s^{-1} with an EG&G PAR 362 potentiostat employing a glassy carbon working electrode, a platinum wire

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auxiliary electrode and a non-aqueous $Ag–Ag^+$ electrode (0.01 mol dm^{-3} $AgNO_3$) in MeCN–CH_2Cl_2 (2 : 1) with tetrabutylammonium tetrafluoroborate (0.1 mol dm^{-3}) as supporting electrolyte. All samples were made up with distilled solvents and each solution was purged with Ar before measurement. Electrochemical titrations were carried out by the addition of concentrated aliquots of the tetrabutylammonium salt of each anion. The data were fitted by eqn. (1) where E is the observed

$$\Delta E = E - E^\circ = \frac{RT}{nF} \ln\left[\frac{1 + K_{red}[A]}{[1 + K_{ox}[A]}\right] \qquad (1)$$

redox potential as a function of the anion (A) concentration and K_{ox} and K_{red} are association constants for the oxidised and reduced forms of the host respectively. This equation applies in the situation where so-called 'shifting' behaviour of the redox potential is observed upon titration of substrate.[7] This behaviour is observed when the stability constants are not large. In the limit where strong substrate binding is observed (*i.e.* $K_{red}[A]$ and $K_{ox}[A] \gg 1$) 'two-wave' behaviour results where two separate redox responses appear at potentials that are independent of substrate concentration.

Structure determinations

Unique data sets were measured at 296 K on an Enraf-Nonius CAD4 diffractometer employing graphite monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å). Data reduction[8] and absorption corrections (ψ scans)[9] were applied. Both structures were solved by Patterson methods with SHELXS and refined by full matrix least squares with SHELXL 97.[10] Views of the two molecules were drawn with PLATON.[11] All calculations were performed within the integrated WINGX suite of programs.[12]

Crystal data. L^2. $C_{34}H_{50}Fe_2N_6$, $M = 654.50$, triclinic, space group $P\bar{1}$ (no. 2), $a = 7.679(4)$, $b = 10.914(4)$, $c = 11.027(5)$ Å, $\alpha = 115.07(3)$, $\beta = 100.90(4)$, $\gamma = 99.74(3)°$, $U = 789.0(6)$ Å^3, $Z = 1$, μ(Mo-Kα) = 9.53 cm^{-1}, $N = 2762$ (R_{int} 0.0477), N_o ($I > 2\sigma(I)$) = 2428, $R1 = 0.0526$ ($I > 2\sigma(I)$), $wR2 = 0.1458$ (all data).

$L^2 \cdot 2HCl \cdot 2H_2O$. $C_{34}H_{56}Cl_2Fe_2N_6O_2$, $M = 763.45$, monoclinic, space group $C2/c$ (no. 15), $a = 14.967(5)$, $b = 7.4043(8)$, $c = 33.06(1)$ Å, $\beta = 90.55(2)°$, $U = 3664(2)$ Å^3, $Z = 4$, μ(Mo-Kα) = 9.77 cm^{-1}, $N = 3204$ (R_{int} 0.0528), N_o ($I > 2\sigma(I)$) = 2509, $R1 = 0.0386$ ($I > 2\sigma(I)$), $wR_2 = 0.1191$ (all data).

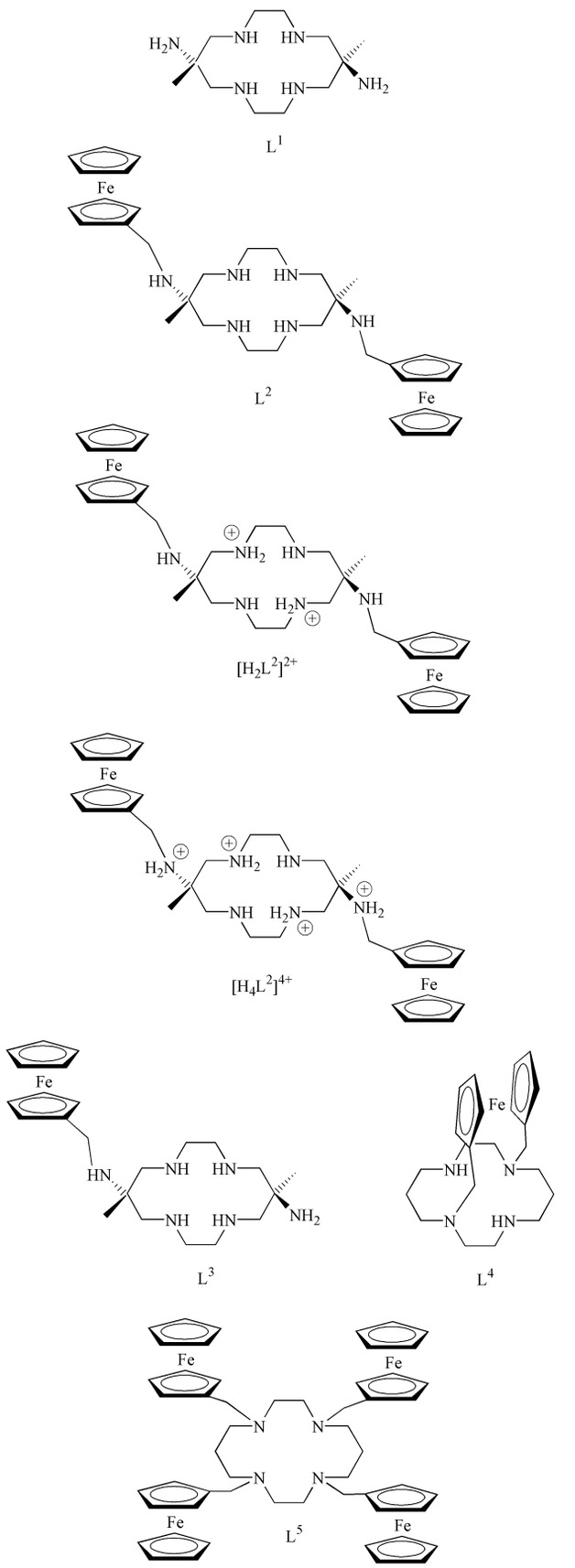
CCDC reference numbers 156422 and 156423.

See http://www.rsc.org/suppdata/dt/b1/b100439p/ for crystallographic data in CIF or other electronic format.

Results and discussion

The macrocycle *trans*-6,13-dimethyl-1,4,8,11-tetraazacyclotetradecane-6,13-diamine (L^1) was functionalised with two ferrocenylmethyl groups by condensing the exocyclic primary amines with ferrocenecarbaldehyde then reduction with $NaBH_4$. Given that no protection of the macrocyclic secondary amines was undertaken, the 33% yield of the disubstituted macrocycle was satisfactory. Previously we have found[13] that cyclisation of the intermediate imine to form a five-membered imidazolidine ring fused to the macrocycle is a very competitive reaction when the aldehyde (and hence imine) is relatively free of steric bulk. In this case no such complex was identified, and the only by-product was a very small amount of monosubstituted macrocycle (L^3), which was identified by ^1H NMR.

The crystal structure of L^2 (Fig. 1) revealed a centrosymmetric molecule comprising ferrocenylmethyl groups attached to each exocyclic amine. The coordination geometry of the unique ferrocene group is not unusual. All Fe–C bond distances lie within the range 2.040(3)–2.059(3) Å and the cyclopentadienyl rings are twisted by *ca.* 8° from an ideal eclipsed conformation. The intramolecular Fe · · · Fe separation is 15.695(6) Å. Hydrogen bonding interactions are surprisingly few given the six donor and six acceptor sites on the macrocyclic hexaamine; indeed no N · · · H contact is closer than 2.40 Å. Notably, the H atom attached to N1 points away from the adjacent amine N2. In all other crystal structures of cyclam or



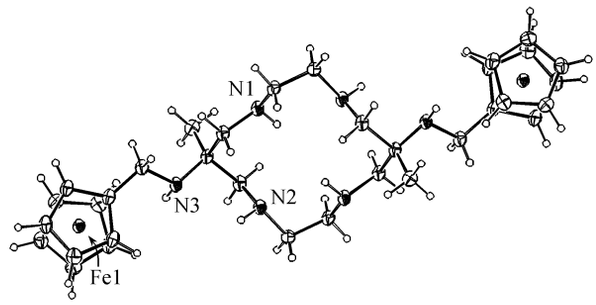


Fig. 1 View of the L^2 molecule showing 30% probability ellipsoids.

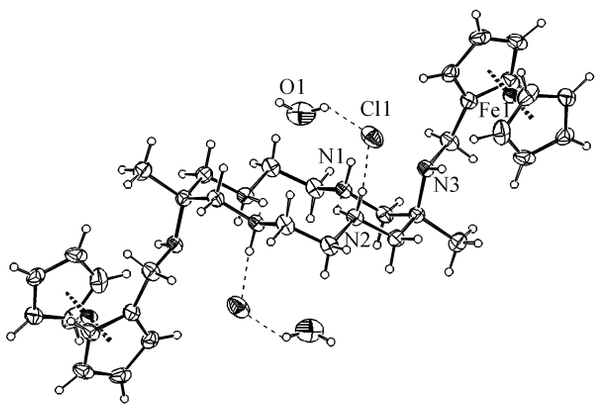


Fig. 2 View of the $[H_2L^2]Cl_2{\cdot}2H_2O$ molecule showing 30% probability ellipsoids.

L^1 in their diprotonated or free base forms a six-membered cyclic hydrogen-bond between this donor–acceptor pair is found,[14,15] but the unusual conformation of the macrocycle in L^2 prevents a similar interaction in the present case.

There are only three reports of structurally characterised examples of ferrocene-substituted cyclam ligands in the literature, comprising L^4 as its nickel(II) complex,[16] and L^5 in its free base[17] and complexed forms ($[CuL^5]^{2+}$ and $[NiL^5]^{2+}$).[18] The sterically crowded tertiary amines L^4 and L^5 are poorer ligands than the parent secondary amine cyclam. By contrast, L^2 retains the basic cyclam unit of four secondary amines and no steric crowding of the binding site is enforced.

An unexpected observation was the spontaneous crystallisation of $L^2{\cdot}2HCl$ from a $CHCl_3$ solution of L^2 acidified with CF_3CO_2H. It is known[19] that chloroform may be deprotonated by strong bases to generate the CCl_3^- anion which dissociates to $:CCl_2$ and Cl^-. In the presence of Cl^- ions the macrocycle $[H_2L^2]^{2+}$ precipitates from chloroform solution. We did not identify any secondary reactions involving dichlorocarbene, which presumably decomposes to CO and HCO_2^- in the presence of trace amounts of water thus further liberating chloride ions.

The crystal structure of the adduct $L^2{\cdot}2HCl{\cdot}2H_2O$ (Fig. 2) reveals a centrosymmetric cation with hydrogen bonds between the macrocyclic amines and the chloride anions being a feature. The sites of protonation were identified unequivocally and the Cl1 · · · H2D–N2 contact (H2D · · · Cl1 2.31, Cl1 · · · N2 3.185(3) Å) is found at the site of protonation. The conformation of the macrocycle in $L^2{\cdot}2HCl{\cdot}2H_2O$ is different to that found in the free base L^2. The diprotonated macrocycle adopts the so-called *trans*-III conformation[20] reminiscent of that found in tetradentate coordinated square planar complexes of cyclam and L^1.[21] Indeed we have reported isomorphous pairs of protonated or metallated macrocycles where the conformation remains unaffected by replacement of two ammonium protons by a divalent metal ion.[22] In this conformation a strong intramolecular hydrogen-bond is found (N1 · · · H2C–N2 2.02 Å, N1 · · · N2 2.759(3) Å). The intramolecular Fe · · · Fe separation (14.518(4) Å) is shorter than that seen in the free base L^2. The cyclopentadienyl rings are twisted by *ca.* 5° from an eclipsed conformation.

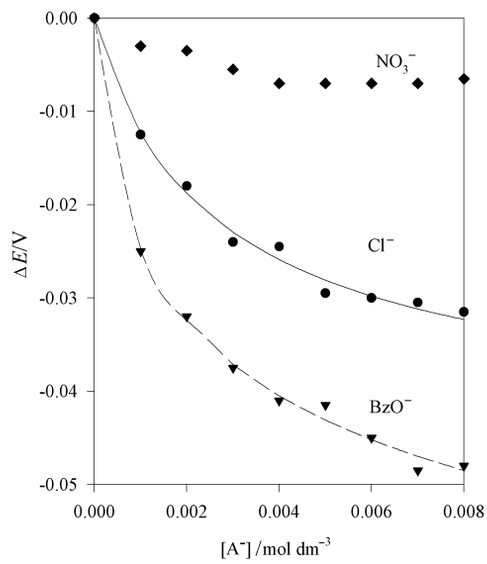


Fig. 3 Electrochemical titrations of L^2 with NO_3^- (◆), Cl^- (●) and BzO^- ($PhCO_2^-$) (▼). Curves show the fit to each set of experimental data.

Cyclic voltammetry of L^2 ($MeCN–CH_2Cl_2$ 2 : 1, 0.1 mol dm^{-3} NBu_4BF_4) identified a single reversible oxidation wave at +0.11 V *vs.* $Ag–Ag^+$, which suggests the two ferrocenyl centres are oxidised in one step, undergoing independent one electron transfer at the same potential. Significant cathodic shifts (>40 mV) in the ferrocenium–ferrocene redox potential were found upon titration of tetrabutylammonium benzoate and chloride (Fig. 3), and the anion association constants with the receptor in its oxidised and reduced forms were determined from a fit by a Nernstian model for a 1 : 1 host–guest complex. Other stoichiometries (*e.g.* 1 : 2 host : guest) gave worse fits to the data and these models were rejected.

The following binding constants were determined: $K_{ox}(Cl^-)$ $8.6(8) \times 10^2$ and $K_{red}(Cl^-)$ $1.5(3) \times 10^2$ dm^3 mol^{-1}; $K_{ox}(BzO^-)$ $2.0(3) \times 10^2$ and $K_{red}(BzO^-)$ $2.1(2) \times 10^2$ dm^3 mol^{-1}. The association constant enhancement upon oxidation is attributable to the electrostatic attraction between the dicationic bis-ferrocenium receptor and the anionic guest. Electrostatic effects are absent in the neutral host L^2 and weaker binding in this case arises from hydrogen-bonding forces alone. These anion association constants are comparable with those reported for other ferrocene-based receptors measured under similar conditions.[23] The small shift (<0.01 V) in the L^2 redox potential in the presence of NO_3^- ions did not allow the anion binding stability constant to be determined.

The receptor L^2 is also capable of binding metal ions or protons within the confines of its macrocyclic ring as seen previously for the parent ligand L^1.[15,24] Titration of $Cu(ClO_4)_2{\cdot}6H_2O$ into a solution of L^2 shows the gradual emergence of a reversible $Cu^{II/I}$ response at −1.33 V *vs.* $Ag–Ag^+$ (Fig. 4). Although the appearance of the redox response of the guest is obvious, it is notable that the potential of the ferrocenium–ferrocene couple is virtually unchanged upon incorporation of the divalent metal into the macrocycle. When the amount of added Cu^{II} exceeds one equivalent, a cathodic response at −1.0 V *vs.* $Ag–Ag^+$ due to free Cu^{II} is observed with an anodic stripping wave at −0.5 V (data not shown). When $Zn(ClO_4)_2{\cdot}6H_2O$ is added to a solution of L^2 again no significant shift in the ferrocenium–ferrocene redox couple is observed and no cathodic responses due to reduction of complexed zinc are seen. However, when the amount of added Zn^{II} exceeds one equivalent, a cathodic response at −1.4 V *vs.*

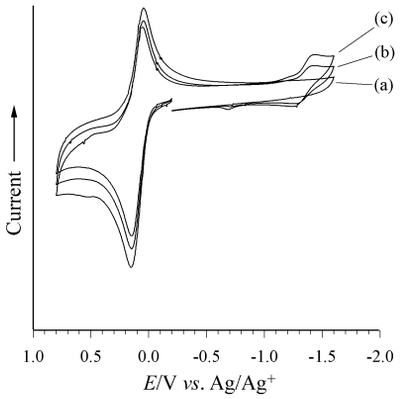


Fig. 4 Cyclic voltammograms of (a) L^2, (b) $L^2 + \frac{1}{2}$ equivalent of $Cu(ClO_4)_2 \cdot 6H_2O$ and (c) L^2 + 1 equivalent of $Cu(ClO_4)_2 \cdot 6H_2O$ (sweep rates all 100 mV s^{-1}).

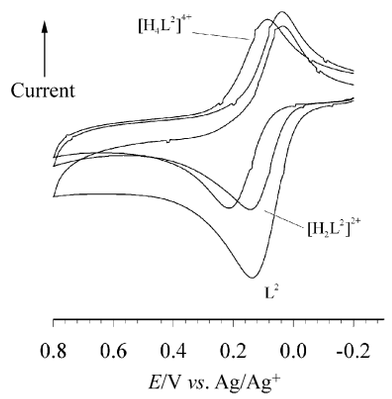


Fig. 5 Cyclic voltammograms of L^2, $[H_2L^2]^{2+}$ and $[H_4L^2]^{4+}$ (sweep rates all 100 mV s^{-1}).

$Ag–Ag^+$ due to uncomplexed Zn^{II} is found in addition to an anodic stripping wave at −0.6 V.

When two equivalents of trifluoroacetic acid are added to the receptor L^2 to generate the cation $[H_2L^2]^{2+}$ (Fig. 5) there again is no significant shift to the ferrocenium–ferrocene redox potential. However, the addition of four equivalents of acid does shift this couple anodically by *ca.* 40 mV (Fig. 5). This suggests that the third and fourth equivalents of acid are taken up by the proximate exocyclic amines as discussed below.

In water the two most basic sites of the parent amine L^1 lie within the macrocyclic ring (pK_a 11.0 and 9.9), whereas the next two protonation steps take place at the exocyclic amines (pK_a 6.3 and 5.5).[15,25] Although insolubility did not allow a potentiometric titration of L^2 in water, the order of protonation of L^2 in $CDCl_3$ was found to be the same by ^1H NMR titration with trifluoroacetic acid. The electrochemistry results demonstrate that the binding of dipositively charged guests within the macrocyclic ring of L^2 does not perturb the host redox couple significantly as the binding site is too remote (more than 6 Å) from the signalling group. However, the exocyclic amines *ca.* 3.6 Å from the ferrocenyl moieties are sufficiently close to produce a significant anodic shift in the ferrocenium–ferrocene redox potential upon protonation.

Conclusion

Significant redox potential shifts were found upon addition of anions to the neutral host L^2, which implicates the exocyclic amines in anion binding. The cyclam moiety is well suited to bind transition metals, but is too small to encircle anions. Therefore, anion binding presumably involves hydrogen-bonding contacts between the host and the anionic guest perched above the macrocyclic plane. The anion–receptor hydrogen-bonding identified in the crystal structure of $L^2 \cdot 2HCl \cdot 2H_2O$ is suggestive of the interaction in solution between L^2 and its guest anions. We are currently exploring further the coordination chemistry and host–guest interactions of this novel macrocyclic receptor.

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