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Polyaza metacyclophanes as ditopic anion receptors

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Five macrocyclic polyaza metacyclophanes L^1–L^5 prepared by dipode coupling of the tosylated precursors have been studied. The basicity of the ligands has been measured potentiometrically and their ability to complex halides and perchlorate has been studied in the solid state by X-ray crystallography. The results reveal that the ligands generally act as ditopic halide receptors with even the largest, L^5, being too small to envelop the anion. The ligand's basicity behaviour parallels that observed for related *para*-analogues. Despite the ready crystallisation of fluoride, HF_2^-, chloride, bromide, iodide and triiodide salts in the solid state, there appears to be little affinity for halides in aqueous solution in the pH range accessible *via* potentiometry. The results do give a detailed insight into the role of the aryl ring in restricting the conformational flexibility of the ligands and, hence, the ability to chelate perching anions.

Introduction

Azacorands (the nitrogen analogues of crown ethers)[1] and azaoxacorands are possibly the most well studied class of macrocyclic polyamine receptors for anionic species. They have attracted the interest of researchers since the early 1980's as these substances are cyclic analogues of biological polyamines such as histamine, spermidine and putrescine and could therefore interact with biomolecules. Indeed, the molecular recognition of nucleotides and other biological phosphates, along with phosphoryl transfer catalysis, has been the theme for much of the work regarding protonated azamacrocycles.[2–9] In the case of catalytic dephosphorylation of adenosine triphosphate, it was found that the ring size plays a crucial role. The 21-membered polyamine ring was found to be superior to larger macrocycles. Moreover, rates of dephosphorylation were found to increase with increasing number of nitrogen atoms in the ring. In an effort to obtain further insight into the mechanism of the dephosphorylation reaction, the crystal structure of the pentahydrobromide salt of $[21]N_5O_2$ was determined.[10] In contrast to $[22]N_6{\cdot}6HCl$,[11] the macrocycle ring crystallizes in a boat form (which is also the case for the tetrachloride salt of $[21]N_7$,[12] as well as $[24]N_6O_2$[13]), maintaining an ellipsoidal shape.[14] However, no bromide is incorporated in the macrocyclic cavity, although Br^- does perch on one face of the macrocycle, interacting with four NH_2^+ units to form a square pyramid.

Incorporation of aromatic rings within the macrocycle increases rigidity and hence potentially preorganisation. A range of *ortho*-, *meta*- and *para*-azacyclophanes have been studied for both their cation binding behaviour (as model sites for metal-containing enzymes) and as anion hosts,[15–20] as have non-cyclophane azamacrocycles.[21–23] For example, triprotonated 2,6,9,13-tetraaza[14]paracyclophane is an effective host for anionic species as ATP^{4-} and $P_2O_7^{4-}$ at around neutral pH.[20] With the exception of the picrate complex of 2,5,9,12-orthocyclophane,[15] however, little structural information exists on azacyclophane–anion complexes. As part of our own work we have shown that bicyclic azametacyclophanes include anions in a way that is limited by anion–π repulsion and thus exhibit sharp selectivity for fluoride.[24] A smaller analogue acts as a highly basic proton host.[25] We have also shown that a large metacyclophane, 2,9,16-triaza[17]metacyclophane, acts as a ditopic host for polyiodides with anion binding occuring on each face of the macrocycle.[26] We now report the extension of this later work to a series of metacyclophanes of varying ring size and heteroatom placement and examine the protonation and anion binding behaviour of the compounds. Anion coordination geometries are compared to work on model, acyclic systems.[27,28]

Results and discussion

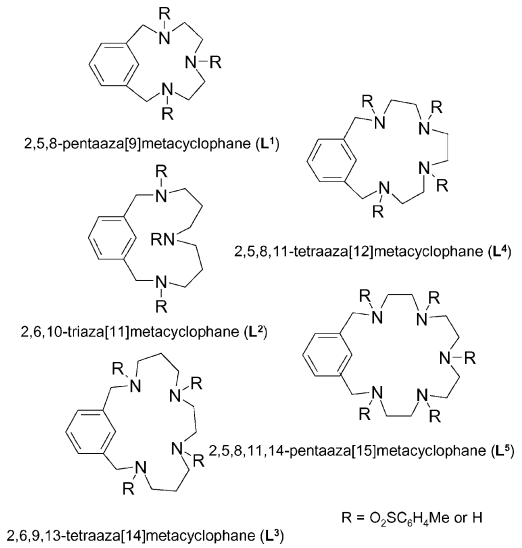
Synthesis

Macrocycles L^1–L^5 (of which only L^5 is novel) were all prepared by K_2CO_3 templated cyclisation of the appropriate linear tosylamide precursors with 1,3-bis(bromomethyl)benzene, to give tosylated macrocycles L^1–L^5 (R = $SO_2C_6H_4Me$). A 20-fold excess of base was required in order to obtain satisfactory yields, which were in the region of 60–75%. Detosylation to give L^1–L^5 (R = H) was achieved by either three day reflux with aqueous HBr and phenol, or by a milder and faster procedure involving 2 h reflux of the tosylated macrocycle in a toluene suspension of metallic sodium with gradual additon of ethanol (see Experimental). Ligand L^4 has been prepared independently during the course of this work in slightly better yield by the same procedure.[15] Ligands L^1 and L^3 have also been prepared by a similar macrocyclisation procedure as ligand systems for enzyme mimics[29] and in CO_2 activation and sulfate binding,[30,31] respectively. The interaction of L^3 with DNA and RNA has been studied.[32] Ligand L^2 has been prepared using β-trimethylsilylethanesulfonamides.[33] The cyclometallated *N*-methyl analogue of L^2 is also known as a ligand for Cu(III) and Rh(III) from intramolecular CH activation.[34,35]

The tosylated precursor macrocycles L^1–L^5 (R = $SO_2C_6H_4Me$) were all characterised by X-ray crystallography in addition to the usual techniques (see Experimental). The tosylated L^1 and L^4 include disordered dichloromethane in pockets formed by aryl rings while the other compounds do not co-crystallise with solvent. The principal crystal packing interaction appears to be aryl CH···O=S hydrogen bonds.[36–38] The conformations of tosylated L^1–L^4 are relatively open while L^5 is folded in on itself, minimising empty space. Therefore, there is very little open space within the macrocyclic cavity in any of the compounds. Full coordinates have been deposited with the CCDC.†

† CCDC reference numbers 272024–272042. See http://dx.doi.org/10.1039/b506828b for crystallographic data in CIF or other electronic format.

DOI: 10.1039/b506828b



Free ligand structures

Two of the detosylated free ligands, L^1 and L^3, were also characterised by X-ray crystallography. The remaining free ligands were all waxy solids or oils. Amine L^1 forms offset dimeric pairs comprised of two crystallographically independent molecules (Fig. 1). These pairs then form further interactions linking them in helical chains resulting in chiral crystal packing, space group $P2_12_12_1$. The structure of L^3 exhibits an open conformation for the macrocycle with the molecular cavity held open by intramolecular NH $\cdots$ N interactions across the propyl spacers, giving an S(6) motif.[39] Macrocycles are linked together by two hydrogen bonds on each side giving an infinite stack (Fig. 1b). The open conformation of the free amine is a marked contrast to the tosylated precursor in which there is very little free cavity volume.

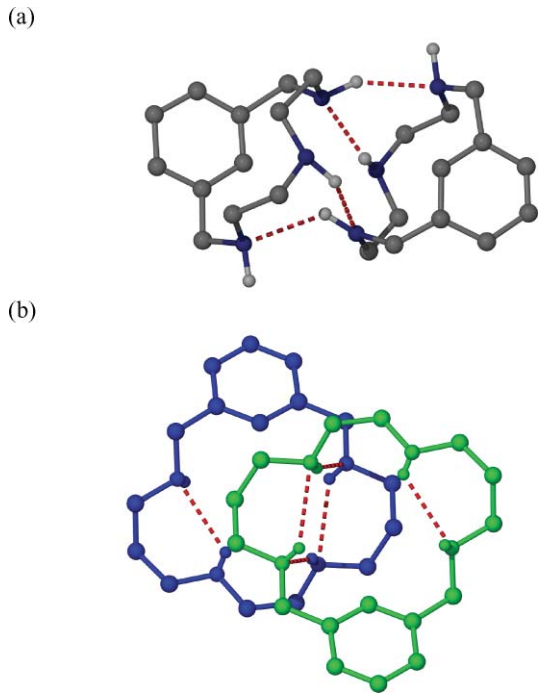


Fig. 1 (a) Offset hydrogen bonded dimers in the structure of L^1; (b) intra- and inter-molecular hydrogen bonding in L^3. Two molecules that form an infinite stack are shown in different shades (CH hydrogen atoms omitted for clarity).

Anion complexes

Attempts were made to structurally characterise each ligand as a series of hydrohalide salts obtained either by slow evaporation of solutions of the ligands in dilute acid or by diffusion of acetone into aqueous acid solutions. This resulted in the isolation of the ten halide complexes of the protonated macrocycles listed below.

Ligand L^2: (i) $L^2{\cdot}HF{\cdot}2H[HF_2]{\cdot}H_2O$, (ii) $L^2{\cdot}3HCl$ and (iii) $L^2{\cdot}3HBr$;

ligand L^3: (i) $L^3{\cdot}3HF{\cdot}H[HF_2]{\cdot}3H_2O$ and (ii) $L^3{\cdot}4HBr$;

ligand L^4: (i) $L^4{\cdot}4HCl{\cdot}1\frac{1}{2}H_2O$;

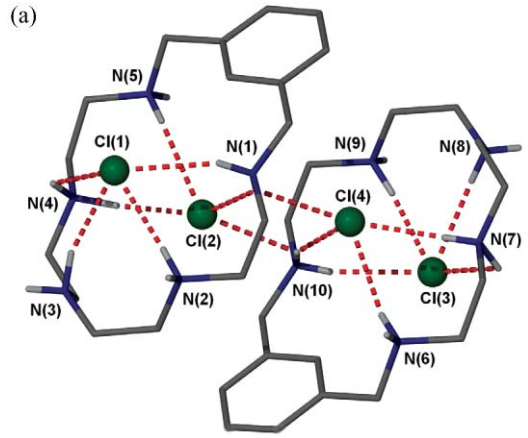
ligand L^5: (i) $L^5{\cdot}5HCl{\cdot}H_2O$, (ii) $L^5{\cdot}5HCl{\cdot}2\frac{1}{2}H_2O$, (iii) $L^5{\cdot}5HBr{\cdot}2H_2O$ and (iv) $L^5{\cdot}4HI{\cdot}HI_3$.

In addition the hydroperchlorate complex of L^2, $L^2{\cdot}3HClO_4{\cdot}H_2O$ was isolated as part of the purification of L^2 and a mixed hydroperchlorate–hydrobromide complex of L^3, $L^3{\cdot}3HClO_4{\cdot}HBr{\cdot}H_2O$ was obtained by serendipitous incorporation of HBr vapour into a crystallisation of the perchlorate salt. Unfortunately no anion complexes were isolated for the smallest macrocycle, L^1.

Halide complexes. 2,5,8,11,14-Pentaaza[15]metacyclophane (L^5) is the largest macrocycle studied. The crystal structures of two pseudopolymorphic chloride salts, $L^5{\cdot}5HCl{\cdot}H_2O$ and $L^5{\cdot}5HCl{\cdot}2\frac{1}{2}H_2O$, were analyzed and in both cases L^5 acts as a ditopic receptor for chloride with anions hydrogen bonding to both faces of the macrocycle *via* charge assisted $NH^+ \cdots Cl^-$ interactions. In the monohydrate the macrocycle adopts a boat conformation, wrapping around the anion, which is a conformation observed in other systems.[11–13,40] This has the effect of preventing one NH_2^+ group, N(5), from interaction with the perching Cl^- anions and it interacts with extra-cavity Cl^- instead. In the more hydrated form the macrocycle adopts a flatter, more extended conformation in order to span the portion of the lattice parallel to the included water. This results in a shorter inter-halide separation across the macrocycle, and an increased number of hydrogen bonds to the included chloride (see Fig 3 caption for inter-halide distances). The structure of the macrocycle in both forms is very different from the folded conformation observed in the tosylated precursor. The flatter conformation of the macrocycle in $L^5{\cdot}5HCl{\cdot}2\frac{1}{2}H_2O$ allows increased interaction to the included anions and deeper penetration (Fig. 3). The added interactions apparently lower the symmetry to give two independent macrocycles instead of one in the monohydrate. In both cases, the macrocycles form dimers sandwiching a pair of chloride anions (Fig. 2). This basic structural type comprising a stack of dimers sandwiching included anions is the fundamental building block of most of the compounds studied and reflects the polyiodide structures observed for 2,9,16-triaza[17]metacyclophane in which I_4^{2-} is sandwiched as part of a related stack.[26]

A common feature revealed in these structures is the existence of several CH $\cdots$ X^- interactions, depending on the size of the complexed anion and its proximity to the macrocyclic cavity. For the crystal structure of $L^5{\cdot}5HCl{\cdot}H_2O$ these interactions vary between C $\cdots$ Cl = 3.457(10) and 3.549(10) Å. Interestingly, in all the structures of polyammonium macrocyclic salts studied there is an Ar–H $\cdots$ X^- short contact between the hydrogen of the 2 position of the aromatic ring and the anion nesting at the bottom side of the macrocycle, C(1) $\cdots$ $Cl(1)^-$ 3.457(10) Å for $L^5{\cdot}5HCl{\cdot}H_2O$, while the closer approach of the chloride anions to the amino groups of the macrocyclic rings leads to longer Ar–H $\cdots$ Cl^- interactions in $L^5{\cdot}5HCl{\cdot}2\frac{1}{2}H_2O$ C $\cdots$ Cl^-: 3.740(6) and 3.763(6) Å.

In previous work on acyclic polyammonium species we have adopted a simple arithmetic approach to the analysis of the hydrogen bonded network.[27,28] In the case of the two L^5 hydrochloride hydrates there is a total of 12 or 15 acidic protons, one or 2.5 water oxygen atom acceptors and five chloride ions. Thus, each Cl^- should accept 2 or, at the most, 3 (in the absence of water–water interactions) non-bifurcated hydrogen bonds. The observation of up to 5-coordinate chloride is evidence for the operation of a macrocyclic enhancement of the binding of the intra-cavity anions.



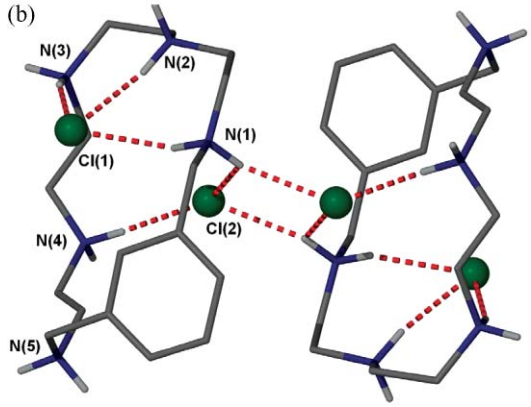


Fig. 2 (a) Interaction of four independent anions with an independent pair of macrocycles in $L^5 \cdot 5HCl \cdot 2\frac{1}{2}H_2O$; (b) the more symmetrical arrangement in $L^5 \cdot 5HCl \cdot H_2O$.

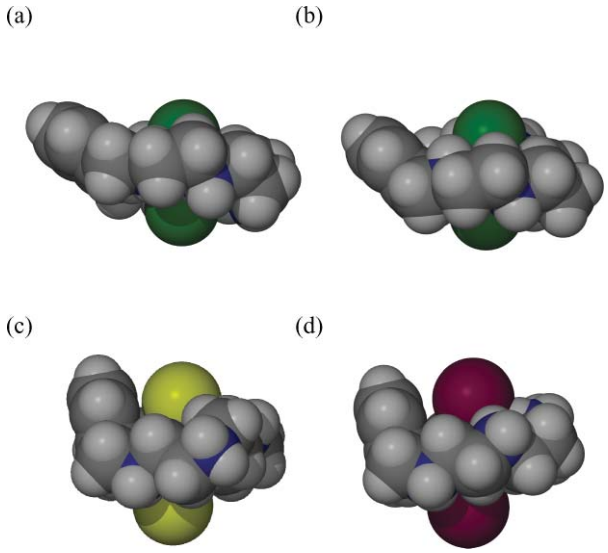


Fig. 3 Space filling plots of the Cl^- binding in (a) $L^5 \cdot 5HCl \cdot 2\frac{1}{2}H_2O$, (b) $L^5 \cdot 5HCl \cdot H_2O$, (c) $L^5 \cdot 5HBr \cdot 2H_2O$ and (d) $L^5 \cdot 4HI \cdot HI_3$. The Cl^- is more tightly bound in $L^5 \cdot 5HCl \cdot 2\frac{1}{2}H_2O$ than in the monohydrate. The macrocycle conformation is much more upright in the bromide and iodide complexes. Inter-halide distances: (a) 3.51, (b) 3.85, (c) 5.01 and (d) 4.60 Å.

The hydrobromide and hydroiodide/hydrotriiodide complexes of L^5 have also been isolated; $L^5 \cdot 5HBr \cdot 2H_2O$ and $L^5 \cdot 4HI \cdot HI_3$ (Fig. 4). In both cases the macrocycle behaves as a ditopic receptor as in the chloride complexes. The bromide case is unusual in that the water, which forms a linear hydrogen bonded chain[41] through the structure, draws the anions out of the cavity giving the largest inter-halide separation (Fig 3c, see caption for inter-halide distances). In both bromide and iodide

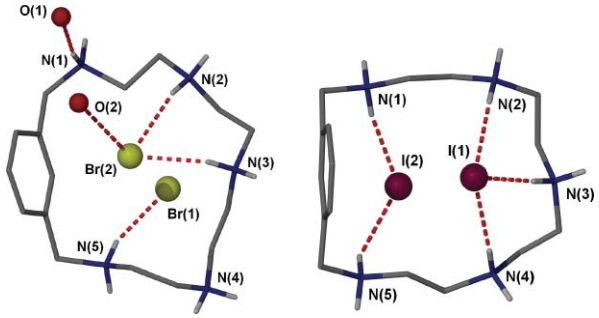


Fig. 4 Hydrogen bonding in $L^5 \cdot 5HBr \cdot 2H_2O$ and $L^5 \cdot 4HI \cdot HI_3$. While there are fewer $NH^+ \cdots Br^-$ interactions to the macrocycle compared to the chloride and iodide cases, the environment around Br(2) is completed by interactions to water and CH_2 groups.

complexes, however, the macrocycle adopts a conformation in which the aromatic ring is much more perpendicular to the plane of the macrocycle, resulting in relatively short anion $\cdots$ centroid distances of 3.77 and 4.22 Å for the bromide and iodide complexes, respectively. These distances are longer than the almost constant figure of *ca.* 3.65 Å observed for a series of anion-encapsulating cryptand structures.[24] Work by Kochi *et al.*[42] has shown that anions form stable charge transfer complexes with a variety of electron deficient aromatic rings. The crystal structures reveal that the anion sits in an offset fashion at the edge of the aromatic rings rather than above the centroid, with anion–carbon distances as short as 2.93 Å for tetrachloro-*o*-quinone and Br^-, compared to a van der Waals radius of 3.55 Å. In the present case, however, there does not seem to be a significant anion–π interaction. Surprisingly, and despite their expected large coordination sphere, I(1) and I(2) do not form any hydrogen bonds with other amine moieties, apart from those belonging to the host macrocyclic ring. A short $Ar–H \cdots I^-$ contact is also observed ($C(1) \cdots I(2)^-$ 3.820(13) Å). The I_3^- anion participates in a single $NH_2^+ \cdots I^-$ hydrogen bond. However, there are several short contacts between I_3^- and the CH_2 moieties of the aliphatic chains.

Conceptually removing one binding site and ethylene linker from L^5 gives the smaller homologue L^4, 2,5,8,11-tetraaza[12]-metacyclophane. Only a hydrochloride salt $L^4 \cdot 4HCl \cdot 1\frac{1}{2}H_2O$ was isolated for this material. The complex highlights the steric constraints on the macrocycle induced by the arene ring, with only three of the NH_2^+ groups being able to interact with the Cl^- anion perching on the opposite face of the cavity to the arene ring, (Fig. 5). The remaining NH_2^+ group is turned out from the cavity and interacts with other chloride anions in the lattice. This L^4 complex is also unique in not acting as a ditopic halide receptor. There is a second halide anion on the opposite face of the molecule but it is situated above the aliphatic chain and only forms long and very non-linear $CH \cdots Cl^-$ interactions, suggesting little significant interaction.

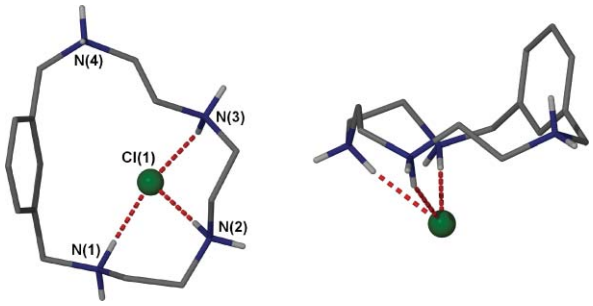


Fig. 5 Partial structure of $L^4 \cdot 4HCl \cdot 1\frac{1}{2}H_2O$ showing the perching chloride anion interacting with three NH_2^+ groups. Selected hydrogen bond distances: $N(2) \cdots Cl(1)$ 3.148(5), $N(1) \cdots Cl(1)$ 3.123(5), $N(3) \cdots Cl(1)$ 3.167(5) Å.

The tetraaza[14]metacyclophane L^3 is slightly larger than L^4 and thus might be expected to be better able to wrap around individual anions and exhibit a ditopic coordination mode as observed for all structure of L^5. Two complexes of L^3 were isolated, $L^3{\cdot}3HF{\cdot}H(HF_2){\cdot}3H_2O$ and $L^3{\cdot}4HBr$. The hydrobromide salt exhibits a similar conformation to the iodide complex of L^5 with two anions bound one to either side of the receptor, each *via* two $NH\cdots Br^-$ hydrogen bonds in this case. Anion Br(2) is actually three coordinate and forms a cyclic interaction with an adjacent host molecule (Fig. 6), while Br(1) appears to be genuinely two-coordinate with no other particularly close interactions. The structure is of overall poor precision due to persistent crystal twinning but the key structural features are unambiguous.

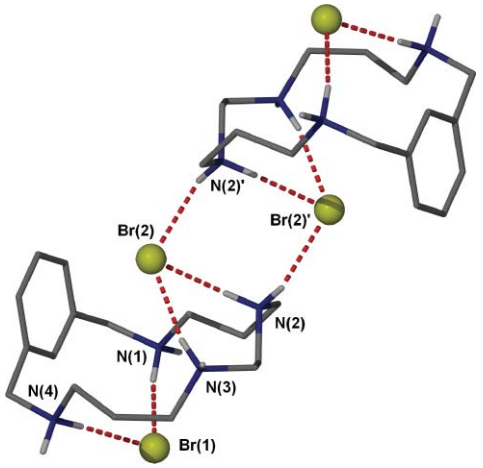


Fig. 6 Dimeric arrangement and ditopic Br^- binding by protonated L^3 in the tetrahydrobromide salt. Hydrogen bond distances: $N\cdots Br(1)/Br(2)$ 3.279(16)–3.437(17) Å.

The hydrogen fluoride salt of L^3 also exhibits ditopic anion binding. Fluoride ion F(1) is held by three hydrogen bonds to the upper face of the macrocycle (the same side as the aryl ring) (Fig. 7). The macrocycle conformation is reminiscent of that observed for L^4 (Fig. 5), in which one NH_2^+ group turns out from the macrocycle cavity and interacts in this case with F(4) and thence a discrete, well resolved water trimer in which each of the water hydrogen atoms interacts with fluoride. On the opposite, 'lower' face of the macrocycle there is a single interaction to a fluorine atom of an HF_2^- anion based on F(2), one of two symmetry independent hydrogen difluoride ions in the structure (the other is based on F(5)). The $F\cdots F$ distances are 2.261(10) and 2.152(10) Å, respectively, and in each case the central proton is located on a two-fold rotation axis in *C*2/*c*. The proton is thus positioned in the exact centre of the HF_2^- ions by symmetry, although minor unresolved disorder of the proton cannot be ruled out in X-ray data. The $F\cdots F$ distance of 2.15 Å is extremely short, even for HF_2^- ions. A CSD search[43,44] reveals the normal range to be *ca.* 2.20–2.30 Å. Examination of the thermal ellipsoids for F(5) reveal them to be somewhat enlarged, whereas those for F(2) are normal. It is likely therefore, that the very short distance is an artefact of a minor unresolved disorder. In terms of $NH\cdots F$ interactions, the $N(1)\cdots F(2)$ interaction (to the HF_2^- ion as opposed to F^-) is significantly longer at 2.913(5) Å than the distances to F^- (2.60–2.73 Å) and presumably reflects the lower negative charge density per fluorine in HF_2^-, along with the fact that the proton involved on N(1) also interacts with F(1), $N\cdots F$ 2.734(5) Å.

Turning to the smallest ligand studied crystallographically, 2,6,10-triaza[11]metacyclophane (L^2) the hydrofluoride, hydrochloride and hydrobromide salts, $L^2{\cdot}HF{\cdot}2H[HF_2]{\cdot}H_2O$, $L^2{\cdot}3HCl$ and $L^2{\cdot}3HBr$ were isolated. Despite the small size of this ligand's cavity, the crystal structure of $L^2{\cdot}HF{\cdot}2H[HF_2]{\cdot}H_2O$ shows that two crystallographically equivalent fluoride anions approach the ring from the 'top' and the 'bottom' side. There is only one hydrogen bond between an NH_2^+ moiety and the fluoride anion at the 'top' side of the ring ($N(2)\cdots F(1)^-$), as well as one hydrogen bond between an NH_2^+ moiety and the fluoride anion at the 'bottom' side of the ring ($N(1)\cdots F(1)^-$, Fig. 8). Numerous $CH\cdots F^-$ contacts from methylene groups and one from an aryl CH group complete the coordination sphere of the 'bottom' fluoride anion, possibly because of the large negative charge density on the surface of the fluoride. $C\cdots F^-$ contacts range from 3.174(5) to 3.214(6) Å. The NH_2^+ group N(2) interacts with a single fluoride and one water molecule while N(1) interacts with F^- and HF_2^- and N(3) binds to an HF_2^- anion and foms a bifurcated interaction to water and the second HF_2^-. There is thus no anion chelate effect. The HF_2^- ions both exhibit slightly longer $F\cdots F$ distances (2.32–2.33 Å) than in $L^3{\cdot}3HF{\cdot}H(HF_2){\cdot}3H_2O$ and the X-ray determined H-atom positions suggest that the ions are slightly bent and unsymmetrial.

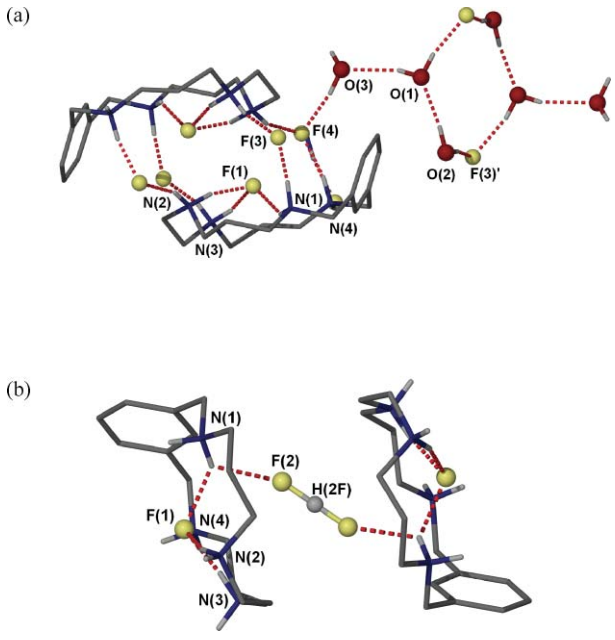


Fig. 7 (a) Fluoride F(1) binding on the 'upper' face of L^3 in $L^3{\cdot}3HF{\cdot}H(HF_2){\cdot}3H_2O$, including details of the water network and (b) HF_2^- inclusion, sandwiched between the lower faces of a pair of macrocycles.

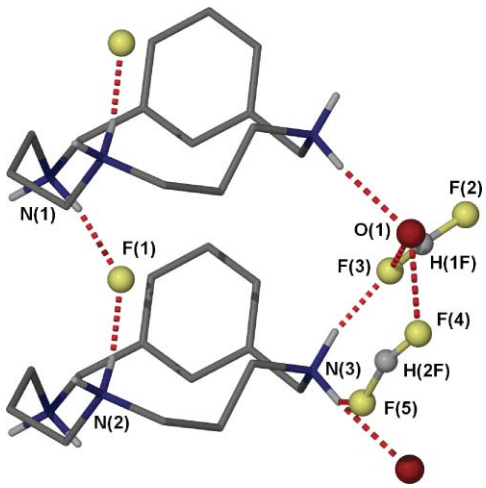


Fig. 8 . Anion coordination environment for $L^2{\cdot}HF{\cdot}2H(HF_2){\cdot}H_2O$. Selected hydrogen bond lengths (Å): $N(1)\cdots F(1)$ 2.625(5), $N(1)\cdots F(4)$ 2.652(4), $F(3)\cdots F(2)$ 2.330(4), $N(2)\cdots O(1)$ 2.814(4), $N(2)\cdots F1$ 2.569(5), $N(3)\cdots F(3)$ 2.601(4), $N(3)\cdots O(1)$ 2.847(5), $N(3)\cdots F(5)$ 2.939(4), $F(4)\cdots F(5)$ 2.322(4).

In the case of $L^2 \cdot 3HCl$, the large size of chloride in comparison with the small size of the cavity result in no anion being at the 'top' side of the macrocyclic ring. Oddly, however, the aromatic group of another ring approaches the macrocyclic ring, thus giving rise to a C–H $\cdots \pi$ interaction[45–47] shown in Fig. 9 (C(11) $\cdots$ centroid: 3.89 Å). There is a chloride at the 'bottom' side of the ring accepting only one hydrogen bond from an NH_2^+ moiety (N(2) $\cdots$ $Cl(2)^-$: 3.183 Å). This chloride is involved in three weak C–H $\cdots$ Cl^- interactions with distances typical for this type of binding (3.645(2)–3.794(2)Å for the corresponding C $\cdots$ Cl(2) distances). Fig. 9 also shows the overall NH $\cdots$ chloride connectivity.

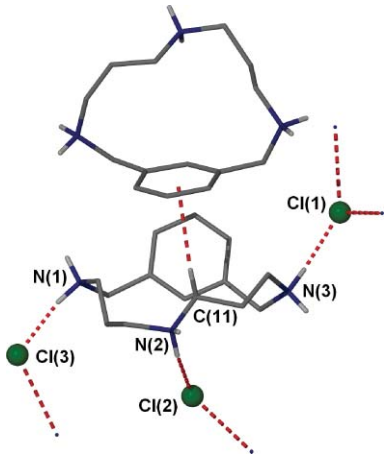


Fig. 9 Hydrogen bond network in the proximity of the ligand for the crystal structure of $L^2 \cdot 3HCl$.

For $L^2 \cdot 3HBr$ there is a bromide anion at the bottom of the macrocyclic cavity forming an NH $\cdots$ Br^- hydrogen bond as well as four C–H $\cdots$ Br^- weak interactions, more than those seen for the fluoride and the chloride complexes apparently due to the larger size of the bromide anion. A very short NH $\cdots$ Br^- hydrogen bond is also formed between an amine moiety and the bromide anion at the 'top' of the macrocyclic ring (N(2) $\cdots$ Br(2): 3.216(4) Å). The small size of the cavity as well as the fact that the aromatic ring 'faces' the bromide anion (centroid–Br: 4.200(5) Å) disfavour any further interactions between the bromide and the macrocycle. The macrocycle cavity appears to be closed by an intramolecular C–H $\cdots \pi$ interaction. A somewhat longer contact is also observed in the chloride case (C(12) $\cdots$ centroid: 3.819(7) Å, Fig. 10).

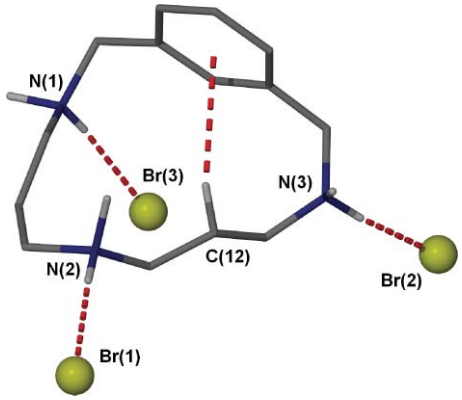


Fig. 10 Hydrogen bond network in the proximity of the ligand for the crystal structure of $L^2 \cdot 3HCl$ showing intramolecular CH $\cdots \pi$ interaction.

Perchlorate complexes. In addition to pure halide complexes, the perchlorate salts $L^3 \cdot 3HClO_4 \cdot HBr \cdot H_2O$ and $L^2 \cdot 3HClO_4 \cdot H_2O$ were isolated as part of this study (*vide supra*). The immediate environment of the macrocycle in the L^3 mixed bromide/perchlorate salt (Fig. 11) is highly reminiscent of the ditopic bromide salt $L^3 \cdot 4HBr$ (*cf.* Fig. 6), with one bromide anion occupying one face of the macrocycle and a perchlorate anion on the other. The two anions are held to the host by both NH $\cdots$ anion and CH $\cdots$ anion interactions. The perchlorate anion occupies the more sterically hindered face near the aryl ring, possibly because of the smaller size of the anion oxygen atom that makes the closest approach, in comparison to Br^-.

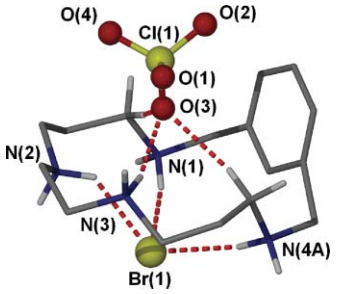


Fig. 11 Macrocycle–anion interactions in the mixed salt $L^3 \cdot 3HClO_4 \cdot HBr \cdot H_2O$.

The structure of $L^2 \cdot 3HClO_4 \cdot H_2O$ is shown in Fig. 12. The perchlorate anions above and below the macrocycle are held only by CH $\cdots$ anion interactions, with distances similar to those reported in the literature.[38] For example, O(12) comes in close contact with three C–H protons that belong to the macrocyclic system. One of the interactions is rather short (C(11) $\cdots$ O(12): 3.304(9) Å) but the other two are longer (C(1) $\cdots$ O(12): 3.481(10) Å, C(9) $\cdots$ O(12): 3.654(10) Å). All of the NH_2^+ groups are directed away from the cavity. Two NH groups interact with two symmetry equivalent water molecules which, in turn, hydrogen bond to the perchlorate anion situated over the cavity on the same side as the aryl ring. The remaining NH units all interact directly with perchlorate anions, forming both non-bifurcated and bifurcated hydrogen bonds, Fig. 12.

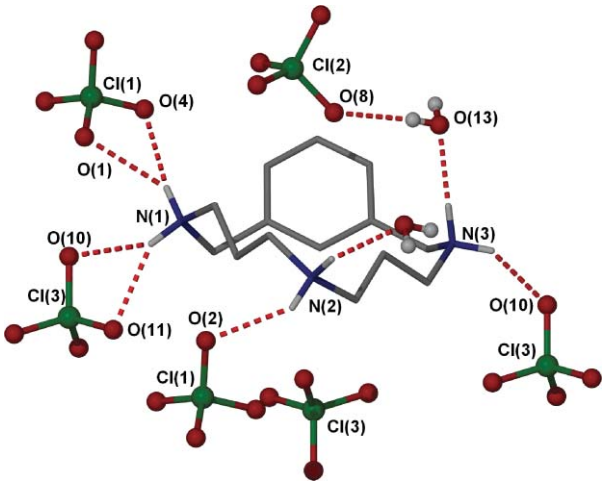


Fig. 12 View of $L^2 \cdot 3HClO_4 \cdot H_2O$ showing that NH $\cdots$ anion interactions are directed away from the cavity. Anions situated above and below the macrocycle are held solely by CH $\cdots$ anion interactions and one hydrogen bond to the included water molecule.

Potentiometric measurements

The reaction involving the transfer of a proton from one atom to another has been described as 'the most general and important reaction in chemistry'.[48] The complexation properties of polyazamacrocycles towards anionic and cationic species depend largely on their basicity behaviour. Hydrogen bonding

Table 1 Logarithms of the stepwise protonation constants for the *meta*-cyclophanes synthesized. Conditions: 0.001 M ligand, 0.01 M HCl, 0.1 M $NaNO_3$, 293 K

	Log K_1	Log K_2	Log K_3	Log K_4	Log K_5	Σ log K_i
L^1	9.58(14)	7.69(11)	3.51(13)	—	—	20.78(38)
L^2	10.09(4)	8.74(3)	6.55(4)	—	—	23.92(10)
L^4	9.33(5)	8.65(4)	5.76(3)	2.71(4)	—	26.45(16)
L^3	9.80(5)	9.02(4)	7.13(3)	3.49(4)	—	29.44(16)
L^5	10.97(3)	9.18(6)	8.81(4)	7.35(4)	4.10(5)	40.41(22)

in anion coordination, although not clearly understood, seems to be crucial in water.[49,50] Also, the positive charge imparted to protonated macrocyclic polyamines in aqueous solutions is obviously an important factor in stabilizing a host–anion guest complexes. Therefore, the basicity of the monocyclic metacyclophanes was studied in aqueous solutions, in the presence of 0.1 M $NaNO_3$ as supporting electrolyte, Table 1. The metacyclophanes reported herein follow trends similar to those observed for 1 : 1 and 2 : 2 polyazacyclophanes.[51] As observed for paracyclophanes, the overall basicity of these compounds increases in an almost linear fashion as a function of the number of atoms in the polyamine chain bridging the arene unit.[52] The stepwise basicity constants depend on the number of amine moieties present in the macrocycle, as well as on the aliphatic spacers between the amine moieties. In general, minimum electrostatic repulsion between charges of the same sign explains the protonation trends observed.

Of interest are the marked differences in the stepwise protonation constants between the metacyclophanes studied and the 'parent' linear chain aliphatic amines. These differences imply a greater conformational freedom of the 'parent' amines in comparison with the macrocyclic compounds and the fact that primary rather than secondary amines are involved in some cases. Indeed, with the exception of the pair L^5/tetraethylenepentammine, the overall basicities, as well as each stepwise basicity constant, for the macrocycles studied are lower than the corresponding basicity of the 'parent' aliphatic amine. Similar trends have also been observed for the paracyclophane analogues.[52] For example, the *para*-analogue of L^5 displays larger basicity constants (10.68, 9.29, 8.66, 7.23, 3.83, Σ log K_i = 39.7) than its parent amine, tetraethylenepentammine, which is not much different to those observed for L^5. It is also of practical interest to inspect the protonation state of these molecules at neutral pH. For the first three macrocycles, the diprotonated form is the predominant species, with relative concentrations at around 90% or more. For the larger and more basic species L^3 and L^5 at neutral pH, the triprotonated ligands are the predominant species, with relative concentrations 60–70%. This is indicative of that fact that, despite the strong basicity of these species, it is rather difficult to protonate two adjacent amine groups.[51,53]

Starting with L^1, two large stepwise protonation constants are observed and one much lower. The two NH moieties next to the aromatic ring are protonated first. The last protonation steps is a lot more unfavourable and involves the binding of a proton on a nitrogen atom between two amine moieties that are already protonated. The situation is different in L^2, however, which is much more basic because of reduced repulsion between protonated nitrogen atoms due to the presence of the propylenic chains. The increased log K_1 value may relate to inductive effect and decreased intramolecular hydrogen bonding. These simple trends are also reflected in the marked difference to the overall basicity of L^1.

The same considerations explain the basicity constants of L^4. Again, the first two protonation constants are attributed to the nitrogen atoms close to the arene ring. This time the first protonation constant is particularly low compared to the other macrocycles. A similar trend was found for the *para*-analogue of this compound and it was attributed to the effects of a particular solvation promoted by the arene ring.[52] The third protonation constant is considerably higher than the corresponding log K value of L^1 that also has ethylene units in its spacer. This is because the third proton does not enter the macrocycle between two nitrogen atoms already protonated but between one nitrogen that is protonated and one nitrogen that is not. The last protonation constant of L^4 is very low, as protonation takes place between amine moieties already protonated.

Moving to L^3, the trend is very similar to that observed for L^4. This time however, the existence of two propylene units increases the basicity constants in comparison with L^4. The impact of the propylene units is particularly shown in the third protonation constant which is larger by 1.37 logarithmic units as compared with that of L^4. It is clear that the introduction of the propylene units makes protonation of the middle amine groups much more favourable. The present data for L^3 are comparable to that obtained for the compound in the presence of NMe_4Cl.[30]

Even larger basicity constants were found for L^5 because of the large size of the macrocycle. It is interesting, however, that the basicity constants of this macrocycle are larger than the basicity constants of its 'parent' amine, TEP. It is also remarkable that the fourth protonation constant is quite large despite that the protonation takes place next to at least one nitrogen atom that is already protonated. Exactly the same trend was found in the *para*-analogue of L^5 and implies that the fourth protonation step for this species involves a reorganization of the protonation sites within the molecule such that the middle nitrogen remains unprotonated and each protonated nitrogen has only one adjacent protonated site.[53]

The basicity constants of L^5 were redetermined in the presence of TsOH/TsONa (Ts = $MeC_6H_4SO_2$; values obtained log K_1 = 9.63(7), log K_2 = 8.19(5), log K_3 = 4.65(6) and log ($K_4 \times K_5$) = 4.91(42)). There is a remarkable difference between the values observed in this medium and with $HNO_3/NaNO_3$, apparently because the basicity of L^5 is enhanced as a result of stronger anion binding in the presence of NO_3^-. In order to probe the macrocycles' anion binding in aqueous solution, pH titrations were conducted in this medium in the presence of NaF and NaCl but no difference was observed with the results of the pH titration in the presence of TsOH/TsONa only. A possible explanation for this result could be the fact that pH titrations is the least sensitive method for the determination of binding constants, thus making the measurement of low log K values difficult. It is also likely that the affinity of these macrocycles for halides is insignificant for pH >2.5. What is observed in the solid state by means of X-ray crystallography does not necessarily reflect what happens in solution. All polyammonium halide crystals were grown from a very acidic solution, whereas pH titrations are considered to be accurate only for 2.5 < pH < 11. A similar effect is observed in the crystal structures of polyammonium salts of cryptand analogues.[24]

Conclusions

A total of twelve X-ray structure determinations of hydrohalide and perchlorate salts of ligands L^2–L^5 have been undertaken. In the case of the larger macrocycles, particularly L^5, ditopic binding is normal, with anions positioned both above and below the macrocyclic cavity engaging in multiple chelate NH···anion interactions with the same macrocycle. As the macrocycle gets smaller the tendency towards ditopic binding and towards anion chelation diminish. They are replaced by CH···π and intermolecular NH···anion interactions. Even the largest macrocycle, L^5, is insufficiently large to encapsulate halides in a 1 : 1 fashion, as observed for fluoride complexes of sapphyrin, for example.[54–56] Macrocyclic *meta*-azaphanes studied by pH potentiometry possess a protonation behaviour not different from that observed for macrocyclic *para*-azaphanes and related compounds.[51] Unfortunately, we have not been able

to detect the binding constants of any halide species probably due to the low affinity of these species for halides at pH >2.5.

Experimental

Instrumental

NMR Spectra. ^{1}H and ^{13}C NMR spectra were measured with a Bruker Avance NMR spectrometer, operating at 360 MHz and 90 MHz, respectively, and the chemical shifts are reported in ppm relative to tetramethylsilane. Fast atom bombardment (low resolution) mass spectra were obtained with a Kratos MS 890 Mass Spectometer. High resolution mass spectra were obtained with a Bruker Apex III Mass Spectrometer by electrospray ionization. Elemental analysis for carbon, hydrogen and nitrogen was carried out by the Elemental Analysis Service at the London Metropolitan University.

Potentiometric titrations

All potentiometric titrations were performed at rt, using carbonate-free NaOH. A Titrino model 736 GP along with a Metrohm combined glass electrode was used. The protonation constants were determined from titrations of an approximately 10^{-3} M ligand solution containing an excess of HCl or HNO_3 or TsOH (0.01 M) in the presence of $NaNO_3$, Me_4NCl or TsONa to maintain ionic strength at 0.1 M. The range of accurate pH measurements was considered to be 2.5–11. Stability constants were calculated with the program HYPERQUAD.[57]

X-Ray crystallography

Crystal data and data collection parameters are summarised in Table 1. Crystals were mounted using silicone grease on a thin glass fibre. All crystallographic measurements were carried out with a Nonius KappaCCD diffractometer, equipped with graphite monochromated Mo–Kα radiation using wide ϕ and ω-scans. Data collection temperature was 120 K, maintained using an Oxford Cryosystem low temperature device. Integration was carried out by the Denzo-SMN package.[58] Data sets were corrected for Lorentz and polarization effects and for the effects of absorption (Scalepack[58]) and crystal decay where appropriate. Structures were solved using the direct methods option of SHELXS-97[59] and developed using conventional alternating cycles of least-squares refinement (SHELXL-97)[60] and difference Fourier synthesis with the aid of the program XSeed.[61] In all cases non-hydrogen atoms were refined anisotropically except for some disordered, while C–H hydrogen atoms were fixed in idealised positions and allowed to ride on the atom to which they were attached. Hydrogen atom thermal parameters were tied to those of the atom to which they were attached. Where possible, non C–H hydrogen atoms were located experimentally and their positional and isotropic displacement parameters refined. Otherwise a riding model was adopted. All calculations were carried out on an IBM–PC compatible personal computer. Some structural data is not of high precision due to frequent crystal twinning or generally poor crystal quality, but does establish the gross structural features of the compounds. Specific issues relating to each refinement are detailed below.

In the crystal structure of L^1–Ts_3 a disordered chloroform molecule was refined by assigning a site occupancy factor of 0.333 to the atoms C(1S), Cl(1S), Cl(2S), Cl(3S).

In the crystal structure of L^4–Ts_4 there are two disordered dichloromethane molecules. In one of them, C(43), C(43A), Cl(2) and Cl(2A) were assigned a site occupancy factor of 0.5 each. In the other, Cl(3), Cl(3A), Cl(3B), Cl(4), Cl(4A), and Cl(4B) were assigned a site occupancy factor of 0.333 each.

In the crystal structure of L^3 the atoms H(31A), H(31B), H(41A), and H(41B) were assigned with an occupancy factor of 0.5 each.

In the crystal structue of $L^3 \cdot 3HF \cdot H[FHF] \cdot 3H_2O$ the HF_2^- ion based on F(5) proved only partially occupied (58%) with disordered atom F(5A) substituted into the H-atom special position in 42% of unit cells. Thus the true formula of the crystal studied is $L^3 \cdot 3.21HF \cdot 0.79H[FHF] \cdot 3H_2O$.

In the crystal structure of $L^5 \cdot 5HCl \cdot H_2O$ atom O(1) that belongs to a partially occupied solvated water molecule site, was refined isotropically.

Syntheses

Materials were obtained from standard commercial sources.

***N*,*N*′,*N*″-Tritosyl-1,5,9-triazanonane.** Dipropylenetriamine (5.25 g, 40 mmol), and K_2CO_3 (11.06 g, 80 mmol) were suspended in water (600 mL) at 80 °C. To this mixture, tosyl chloride (23.00 g, 121 mmol) was added in batches over a period of 1 h. After addition was complete, vigorous stirring and heating were continued overnight. The tosylated macrocycle precipitated as a white solid which was filtered under a reduced pressure, washed thoroughly with 500 mL of water and quickly with 50 mL of methanol and dried under a high vacuum to give a white solid (16.16 g, 27.2 mmol, 68% yield). ^{1}H NMR ($CDCl_3$): 7.72 (d, J = 8.2, 4H), 7.63 (d, J = 8.2, 2H), 7.29 (d, J = 8.2, 4H), 7.27 (d, J = 8.2, 4H), 3.10 (t, J = 6.7, 4H), 2.95 (pt, J = 6.2, 4H), 2.42 (s, 3H), 2.41 (s, 6H), 1.71 (m, J = 6.4, 4H); ^{13}C NMR ($CDCl_3$): 144.16, 144.83, 137.15, 135.77, 130.31, 130.16, 127.48, 127.41, 47.18, 40.46, 29.60, 21.96; MS m/z (FAB) 594 ([M + H]$^+$); anal. calcd for $C_{27}H_{35}S_3O_6N_3$: C, 54.61%; H, 5.94%; N, 7.08%. Found: C, 54.75%; H, 5.83%; N, 6.94%.

***N*,*N*′,*N*″,*N*‴-Tetratosyl-1,5,8,12-tetraazadodecane.** 1,2-Bis-(3-aminopropyl)diaminoethane (6.97 g, 40 mmol), tosyl chloride (23.00 g, 121 mmol) and K_2CO_3 (11.06 g, 80 mmol) were reacted by following the same procedure as that for the synthesis of *N*,*N*′,*N*″-tritosyl-1,5,9-triazanonane. After work-up, the product was isolated as a white solid (23.41 g, 29.6 mmol, 74% yield). ^{1}H NMR (DMSO-d_6): 7.74 (d, J = 8.2, 4H), 7.68 (d, J = 8.2, 4H), 7.34 (d, J = 8.2, 4H), 7.31 (d, J = 8.2, 4H), 5.35 (b, 2H), 3.24 (s, 4H), 3.17 (t, J = 6.8, 4H), 2.99 (b, 4H), 2.46 (s, 6H), 2.43 (s, 6H), 2.26 (pt, 4H); ^{13}C-{^{1}H} NMR ($CDCl_3$): 144.32, 143.83, 137.12, 135.47, 130.39, 130.16, 127.62, 127.41, 49.29, 47.52, 40.36, 29.39, 21.96, 21.92; MS m/z (FAB) 791 ([M + H]$^+$); anal. cCalcd for $C_{36}H_{46}S_4O_8N_4$: C, 54.66%; H, 5.86%; N, 7.08%. Found: C, 54.60%; H, 5.85%; N, 6.88%.

***N*,*N*′,*N*″,*N*‴,*N*⁗-Pentatosyl-1,4,7,10,13-pentaazadecatriane.** Tosyl chloride (40 g, 0.211 mol), H_2O (40 mL) and diethyl ether were stirred and cooled to 0 °C in an ice bath. To this mixture, a solution of tetraethylenepentamine (7.97 g, 42 mmol) and NaOH (10 g, 0.25 mol) in H_2O (80 mL) was added dropwise over a period of 1 h. The reaction mixture was stirred further for 3 h at rt. The precipitate was filtered and then washed with diethyl ether and water. Recrystallization from hot $CHCl_3$–MeOH afforded the product as white powder (16.55 g, 17 mmol, 41% yield). ^{1}H NMR ($CDCl_3$): 7.79 (d, J = 8.3, 2H), 7.75 (d, J = 8.3, 4H), 7.72 (d, J = 8.3, 4H), 7.38 (d, J = 8.3, 2H), 7.34 (d, J = 8.3, 4H), 7.29 (d, J = 8.3, 4H), 5.54 (b, 2H), 3.38 (b, 8H), 3.20 (b, 8H), 2.48 (s, 3H), 2.45 (s, 6H), 2.42 (s, 6H); ^{13}C-{^{1}H} NMR ($CDCl_3$): 144.41, 144.34, 143.87, 136.92, 135.13, 134.88, 130.46, 130.38, 130.16, 127.92, 127.86, 127.55; MS m/z (FAB) 961 ([M + H]$^+$); anal. calcd for $C_{43}H_{53}S_5O_{10}N_5$: C, 53.79%; H, 5.56%; N, 7.29%. Found: C, 53.85%; H, 5.45%; N, 7.18%.

***N*,*N*′,*N*″-Tritosyl-2,5,8-triaza[9]metacyclophane (L^1–Ts_3).** *N*,*N*′,*N*″-Tritosyl-1,4,7-triazaheptane[62] (10.70 g, 18.9 mmol) and K_2CO_3 (52.24 g, 378 mmol) were suspended in refluxing CH_3CN (700 mL). To this mixture, a solution of 1,3-bis(bromomethyl)-benzene (5.00 g, 18.9 mmol) in CH_3CN (700 mL) was added dropwise. After the addition was complete, the suspension was refluxed and stirred for 36 h and then

filtered. The solvent was removed and the crude product was purified by column chromatography on silica (toluene–AcOEt, 85 : 15). The product was obtained as a white solid (9.36 g, 14.0 mmol, 74% yield). Suitable crystals for X-ray analysis were obtained as colourless blocks after slow diffusion of hexane into a solution of the product in chloroform for a few days. ^{1}H NMR ($CDCl_3$): 7.72 (d, J = 8.2, 4H), 7.64 (d, J = 8.2, 2H), 7.14–7.40 (m, 4H), 7.35 (d, J = 8.2, 4H), 7.28 (d, J = 8.2, 2H), 4.21 (s, 4H), 3.04 (t, 4H), 2.58 (t, 4H), 2.46 (s, 6H), 2.42 (s, 3H); ^{13}C-{^{1}H} NMR ($CDCl_3$): 142.55, 142.35, 134.93, 134.45, 133.83, 129.87, 129.52, 129.07, 128.71, 128.60, 125.96, 125.88, 53.19, 52.22, 49.17, 46.06, 20.32, 20.29; MS m/z (FAB) 668 ([M + H]$^+$); anal. calcd for $C_{33}H_{37}S_3O_6N_3$: C, 59.37%; H, 5.59%; N, 6.29%. Found: C, 59.50%; H, 5.47%; N, 6.26%.

***N*,*N*′,*N*″-Tritosyl-2,6,10-triaza[11]metacyclophane (L^2–Ts_3).** By following a procedure similar to that described for the synthesis of L^1–Ts_3, *N*,*N*′,*N*″-tritosyl-1,5,9-triazanonane (11.23 g, 18.9 mmol), K_2CO_3 (52.24 g, 378 mmol) and 1,3-bis(bromomethyl)-benzene (5.00 g, 18.9 mmol) yielded the product as a white solid (9.87 g, 14.2 mmol, 75% yield). Suitable crystals for X-ray analysis were obtained as colorless blocks in the same manner as for L^1–Ts_3. ^{1}H NMR ($CDCl_3$): 7.72 (d, J = 8.2, 4H), 7.58 (d, J = 8.2, 2H), 7.14–7.47 (m, 4H), 7.35 (d, J = 8.2, 4H), 7.16 (d, J = 8.2, 2H), 4.18 (s, 4H), 3.07 (t, J = 6.8, 4H), 2.86 (t, J = 7.3, 4H), 2.45 (s, 6H), 2.41 (s, 3H), 1.35 (m, 4H); ^{13}C-{^{1}H} NMR ($CDCl_3$): 143.87, 143.53, 137.57, 135.59, 130.12, 129.93, 129.76, 129.71, 129.69, 129.24, 127.41, 127.27, 54.46, 47.97, 47.94, 29.34, 21.74, 21.68; MS m/z (FAB) 696 ([M + H]$^+$); anal. calcd for $C_{35}H_{36}S_3O_6N_3$: C, 60.42%; H, 5.94%; N, 6.04%. Found: C, 60.37%; H, 5.88%; N, 5.94%.

***N*,*N*′,*N*″,*N*‴-Tetratosyl-2,5,8,11-tetraaza[12]metacyclophane (L^4–Ts_4).** By following a procedure similar to that described for the synthesis of L^1–Ts_3, *N*,*N*′,*N*″,*N*‴-tetratosyl-1,4,7,10-tetraazadecane[62] (14.42 g, 18.9 mmol), K_2CO_3 (52.24 g, 378 mmol) and 1,3-bis(bromomethyl)benzene (5.00 g, 18.9 mmol) yielded the product as a white solid (11.11 g, 12.9 mmol, 68% yield). Suitable crystals for X-ray analysis were obtained as colorless blocks in the same manner as for L^1–Ts_3. ^{1}H NMR ($CDCl_3$): 7.75 (d, J = 8.2, 4H), 7.69 (d, J = 8.2, 4H), 7.11–7.38 (m, 4H), 7.37 (d, J = 8.2, 4H), 7.31 (d, J = 8.2, 4H), 4.13 (s, 4H), 2.98 (t, J = 5.3, 4H), 2.89 (t, J = 5.6, 4H), 2.68 (s, 4H), 2.47 (s, 6H), 2.44 (s, 6H); ^{13}C-{^{1}H} NMR ($CDCl_3$): 144.37, 144.12, 137.03, 135.90, 134.80, 130.40, 130.25, 129.99, 129.31, 127.88, 127.81, 54.82, 50.15, 49.21, 48.28, 21.98, 21.97; MS m/z (FAB) 865 ([M + H]$^+$); anal. calcd for $C_{42}H_{48}S_4O_8N_4$: C, 58.31%; H, 5.59%; N, 6.48%. Found: C, 58.39%; H, 5.54%; N, 6.43%.

***N*,*N*′,*N*″,*N*‴-Tetratosyl-2,6,9,13-tetraaza[14]metacyclophane (L^3–Ts_4).** By following a procedure similar to that described for the synthesis of L^1–Ts_3, *N*,*N*′,*N*″,*N*‴-tetratosyl-1,5,8,12-tetraazadodecane (14.95 g, 18.9 mmol), K_2CO_3 (52.24 g, 378 mmol) and 1,3-bis(bromomethyl)-benzene (5.00 g, 18.9 mmol) yielded the product as a white solid (11.98 g, 13.42 mmol, 71% yield). Suitable crystals for X-ray analysis were obtained as colorless blocks in the same manner as for L^1–Ts_3. ^{1}H NMR ($CDCl_3$): 7.72 (d, J = 8.2, 4H), 7.65 (d, J = 8.2, 4H), 7.11–7.54 (m, 4H), 7.37 (d, J = 8.2, 4H), 7.33 (d, J = 8.2, 4H), 4.17 (s, 4H), 3.11 (t, J = 7.2, 4H), 2.94 (t, J = 7.0, 4H), 2.66 (s, 4H), 2.46 (s, 6H), 2.44 (s, 6H), 1.41 (m, 4H); ^{13}C-{^{1}H} NMR ($CDCl_3$): 144.24, 144.10, 138.09, 135.65, 135.05, 130.45, 130.27, 129.46, 128.58, 127.92, 127.72, 54.68, 48.66, 48.59, 48.50, 29.50, 22.03; MS m/z (FAB) 893 ([M + H]$^+$); anal. calcd for $C_{44}H_{52}S_4O_8N_4$: C, 59.17%; H, 5.87%; N, 6.27%. Found: C, 59.06%; H, 5.63%; N, 6.05%.

***N*,*N*′,*N*″,*N*‴,*N*⁗-Pentatosyl-2,5,8,11,14-pentaaza[15]metacyclophane (L^5–Ts_5).** By following a procedure similar to that described for the synthesis of L^1–Ts_3, *N*,*N*′,*N*″,*N*‴,*N*⁗-pentatosyl-1,4,7,10,13-pentaazadecatriane (18.16 g, 18.9 mmol), K_2CO_3 (52.24 g, 378 mmol) and 1,3-bis(bromomethyl)-benzene (5.00 g, 18.9 mmol) yielded the product as a white solid (8.77 g, 8.25 mmol, 69% yield). Suitable crystals for X-ray analysis were obtained as colorless blocks in the same manner as for L^1–Ts_3. ^{1}H NMR ($CDCl_3$): 7.76 (d, J = 8.3, 4H), 7.70 (d, J = 8.3, 4H), 7.64 (d, J = 8.3, 2H), 7.48 (d, J = 8.2, 2H), 7.36 (d, J = 8.3, 4H), 7.34 (d, J = 8.3, 4H), 7.24 (m, 1H), 7.17 (d, J = 8.5, 2H), 7.04 (s, 1H), 4.25 (s, 4H), 3.18 (b, 4H), 3.13 (b, 4H), 3.02 (b, 8H), 2.47 (s, 6H), 2.46 (s, 3H), 2.45 (s, 6H); ^{13}C-{^{1}H} NMR ($CDCl_3$): 144.49, 144.21, 144.14, 136.95, 135.89, 135.31, 134.14, 130.32, 130.01, 128.68, 128.60, 128.00, 127.89, 127.82, 53.91, 51.17, 50.26, 49.99, 47.75, 21.97; MS m/z (FAB) 1063 ([M + H]$^+$); anal. calcd for $C_{51}H_{59}S_5O_{10}N_5$: C, 57.66%; H, 5.60%; N, 6.59%. Found: C, 57.81%; H, 5.73%; N, 6.70%.

2,6,9,13-Tetraaza[14]metacyclophane (L^3). A mixture of tosylated amine L^3–Ts_3 (2.00 g, 2.24 mmol), phenol (4.0 g, 42.50 mmol) and 60 mL of 48% aqueous HBr was stirred and heated to reflux for 72 h. After cooling to rt, the mixture was repeatedly washed with chloroform. The aqueous phase was cooled to 0 °C and sodium hydroxide was added slowly until the pH of the solution became at least 12. The product was extracted in chloroform which was removed under a high vacuum to afford the free amine as a waxy solid (0.32 g, 1.16 mmol, 52% yield). Suitable cystals for X-ray analysis of the fluoride, chloride and bromide salts of L^3 were obtained in two ways: Either from a solution of this material in the corresponding diluted acid after a few days by slow evaporation or by slow diffusion of acetone into a concentrated solution of the macrocycle in the corresponding diluted acid. The species $L^3 \cdot 3HClO_4 \cdot HBr \cdot H_2O$ was synthesized after a mixture of L^3 and perchloric acid was accidentally treated with fumes of hydrobromic acid inside a fume cubpoard (for crystal data, see Table 2). Suitable cystals for X-ray analysis of the free amine L^3 were obtained by slow evaporation of a concentrated solution of the compound in chloroform. ^{1}H NMR ($CDCl_3$): 7.34 (s, 1H), 7.18 (t, J = 7.4, 1H), 7.04 (d, J = 7.6, 2H), 3.73 (s, 4H), 2.62–2.66 (m, 4H), 2.61 (s, 4H), 1.73 (s, b, 4H), 1.60–1.67 (m, 4H); ^{13}C-{^{1}H} NMR ($CDCl_3$): 140.78, 128.79, 127.70, 127.30, 54.48, 50.38, 50.00, 48.79, 29.87; HRMS calcd for $C_{16}H_{29}N_4$ [M]$^+$ 277.2387, found 277.2363. Ligand L^3 has previously been prepared ina similar way.

2,5,8,11,14-Pentaaza[15]metacyclophane (L^5). By following a procedure similar to that described for the synthesis of L^3, L^5–Ts_5 (2.00 g, 1.88 mmol), phenol (4.0 g, 42.50 mmol) and 60 mL of 48% aqueous HBr afforded the product as a waxy solid (0.43 g, 1.47 mmol, 78% yield). Suitable cystals for X-ray analysis of the chloride (two structures), bromide and iodide salts of the macrocycle were obtained in a similar manner as for L^3. ^{1}H NMR ($CDCl_3$): 7.54 (s, 1H), 7.12 (t, J = 7.4, 1H), 7.00 (d, J = 7.3, 2H), 3.73 (s, 4H), 2.65–2.76 (m, 16H), 2.32 (b, 5H); ^{13}C-{^{1}H} NMR ($CDCl_3$): 141.16, 128.26, 127.23, 126.84, 53.96, 49.65, 49.53, 49.52, 48.99; HRMS calcd for $C_{16}H_{30}N_5$ [M]$^+$ 292.2496, found 292.2491.

2,5,8-Triaza[9]metacyclophane (L^1). By following a procedure similar to that described for the synthesis of L^3, L^1–Ts_3 (2.00 g, 2.99 mmol), phenol (4.0 g, 42.50 mmol) and 60 mL of 48% aqueous HBr afforded the product as a waxy solid (0.40 g, 1.94 mmol, 65% yield). Suitable crystals for X-ray analysis of this material were obtained by slow diffusion of *n*-hexane into a solution of the compound in chloroform after a few days. ^{1}H NMR ($CDCl_3$): 8.20 (s, 1H), 7.08 (t, J = 7.5, 1H), 6.95 (d, J = 7.3, 2H), 3.83 (s, 4H), 2.66 (t, J = 5.1, 4H), 2.45 (s, b, 3H), 2.06 (s, b, 4H); ^{13}C-{^{1}H} NMR ($CDCl_3$): 142.28, 127.60, 126.31, 125.80, 53.40, 48.27, 47.67; HRMS calcd for $C_{12}H_{19}N_3$ [M]$^+$ 206.1652, found 206.1654. Ligand L^1 has previously been prepared by a very similar method.[29]

2,6,10-Triaza[11]metacyclophane (L^2). By following a procedure similar to that described for the synthesis of L^3, L^2–Ts_3 (2.00 g, 2.87 mmol), phenol (4.0 g, 42.50 mmol) and 60 mL of

Table 2 Crystallographic parameters for new compounds

Compound	L^1–Ts_3	L^2–Ts_3	L^3–Ts_4	L^4–Ts_4	L^5–Ts_5	L^1	L^3	L^5·5HCl·H_2O	L^5·5HCl·2.5H_2O
Formula	$C_{34}H_{38}Cl_3N_3O_6S_3$	$C_{35}H_{41}N_3O_6S_3$	$C_{44}H_{52}N_4O_8S_4$	$C_{44}H_{50}Cl_4N_4O_8S_4$	$C_{51}H_{59}N_5O_{10}S_5$	$C_{12}H_{19}N_3$	$C_{16}H_{28}N_4$	$C_{16}H_{36}Cl_5N_5O$	
M	787.25	695.89	893.14	1032.92	1062.39	205.30	276.42	491.76	518.79
System	Triclinic	Monoclinic	Triclinic	Monoclinic	Monoclinic	Orthorhombic	Monoclinic	Triclinic	Triclinic
Space group	$P\bar{1}$	$P2_1/c$	$P\bar{1}$	$P2_1/n$	$P2_1/n$	*Pbca*	*C*2/*c*	$P\bar{1}$	$P\bar{1}$
a/Å	10.0306(11)	16.6393(8)	11.8732(12)	10.0881(10)	13.925(2)	10.8052(12)	12.5482(8)	9.862(2)	10.5378(8)
b/Å	13.5130(13)	12.0999(7)	13.1219(10)	30.6387(9)	16.012(2)	10.8631(15)	14.9721(11)	10.5252(2)	11.8423(6)
c/Å	14.3379(15)	18.0854(11)	15.1537(11)	15.8038(10)	22.880(2)	19.5021(17)	17.2980(14)	12.113(2)	20.8415(12)
α/°	108.817(5)		88.451(7)					97.6535(19)	81.025(4)
β/°	104.119(7)	115.568(3)	86.682(6)	94.292(3)	98.651(8)		91.735(3)	100.990(2)	78.116(4)
γ/°	103.132(6)		68.424(6)					103.968(3)	87.769(4)
V/Å^3	1682.0(6)	3284.6(11)	1682.0(6)	4870.9(17)	5043.5(18)	2289.1(8)	3248.3(11)	1176.3(4)	2513.9(9)
Z	2	4	2	4	4	8	8	2	4
Measured rflns.	8530	26 070	8530	17 287	21 828	13 345	5174	3946	22 586
Unique rflns.	4608	7513	4608	8547	8431	2012	2494	2333	10 628
*R*1 (on *F*, $I > 2\sigma(I)$)	0.0619	0.0549	0.0988	0.0526	0.1870	0.1280	0.0572	0.0942	0.1078
w*R*2 (on F^2, all data)	0.1598	0.1234	0.1583	0.1294	0.3184	0.2049	0.1485	0.2683	0.2058

Table 2 (*Contd.*)

Compound	L^3·3HF·H[FHF]·3H_2O	L^5·4HI·HI_3	L^2·HF·2H[FHF]·H_2O	L^2·3HCl	L^2·3HBr	L^4·4HCl·1.5H_2O	L^3·4HBr	L^5·5HBr·2H_2O	L^2·3$HClO_4$·H_2O	L^3·3$HClO_4$·HBr·H_2O
Formula	$C_{16}H_{39}N_4F_5O_3$	$C_{16}H_{34}I_7N_5$	$C_{14}H_{30}F_5N_3O$	$C_{14}H_{26}Cl_3N_3$	$C_{14}H_{26}Br_3N_3$	$C_{14}H_{31}Cl_4N_4O_{1.5}$	$C_{16}H_{32}Br_4N_4$	$C_{16}H_{38}Br_5N_5O_2$	$C_{14}H_{28}Cl_3N_3O_{13}$	$C_{16}H_{32}BrCl_3N_4O_{13}$
M	430.50	1184.78	351.41	342.73	476.11	421.24	600.10	732.03	552.74	662.72
System	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Triclinic	Triclinic	Triclinic	Orthorhombic
Space group	*C*2/*c*	*C*2/*c*	$P2_1/c$	$P2_1/n$	$P2_1/n$	*C*2/*c*	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$Pna2_1$
a/Å	21.1356(8)	33.7945(18)	5.4382(3)	9.5996(3)	11.0558(5)	29.725(3)	9.4815(8)	8.4897(9)	8.7647(4)	14.8930(4)
b/Å	11.3701(5)	11.5702(8)	16.5549(9)	10.1003(4)	11.6209(5)	6.3480(7)	11.0386(10)	11.1914(11)	11.2725(6)	18.0550(6)
c/Å	19.3306(7)	15.8028(9)	19.6525(13)	17.1572(6)	15.1984(7)	22.054(3)	11.4504(10)	14.9026(10)	12.7812(8)	10.0567(9)
α/°							88.574(2)	82.708(6)	82.1469(24)	
β/°	111.392(4)	103.859(5)	91.581(2)	93.850(2)	107.8422(26)	93.999(4)	68.2659(19)	81.857(5)	71.7511(23)	
γ/°							86.071(2)	69.501(6)	69.0389(32)	
V/Å^3	4324.9(15)	5999(2)	1768.6(6)	1659.7(6)	1858.6(6)	4151.2(14)	1110.6(4)	1308.3(5)	1119.5(4)	2704.2(3)
Z	8	8	4	4	4	8	2	2	2	4
Measured rflns.	8370	12 929	14 435	10 814	10 798	2138	7106	9218	3311	15 138
Unique rflns.	3449	5536	3628	3784	4242	1599	4839	5930	2214	5068
*R*1 (on *F*, $I > 2\sigma(I)$)	0.0523	0.0555	0.0713	0.0313	0.0555	0.0457	0.1621	0.0707	0.0662	0.0924
w*R*2 (on F^2, all data)	0.1087	0.1306	0.1605	0.0681	0.1371	0.1099	0.3011	0.1597	0.1571	0.2051

48% aqueous HBr afforded the product as a viscous oil (0.48 g, 2.07 mmol, 72% yield). Suitable cystals for X-ray analysis of the chloride, bromide and iodide salts of the macrocycle were obtained in a similar manner as for L^3. Ligand L^2 is difficult to handle because of its viscous nature. Thus, for analytical purposes its perchlorate salt was prepared by dropwise addition of perchloric acid into a concentrated solution of the compound in ethanol. The resulting solution was left in the refrigerator overnight and the resulting precipitate filtered and dried under a high vacuum. ^{1}H NMR ($CDCl_3$): 7.62 (s, 1H), 7.13 (t, J = 7.5, 1H), 6.97 (d, J = 7.5, 2H), 3.81 (s, 4H), 2.71 (t, J = 5.6, 4H), 2.47 (t, J = 5.9, 4H), 1.79 (s, b, 3H), 1.64 (m, 4H); ^{13}C-{^{1}H} NMR for $L^2 \cdot 3HClO_4 \cdot 3H_2O$ (D_2O): 131.92, 131.76, 131.66, 49.93, 42.58, 42.33, 20.84; MS m/z (FAB) 234 ([M + H]$^+$); anal. calcd for the perchlorate salt $C_{14}H_{28}N_3Cl_3O_{15}$: C, 28.76%; H, 4.83%; N, 7.19%. Found: C, 28.64%; H, 4.87%; N, 7.17%. Ligand L^2 has been previously prepared by a modified Richman–Atkins method.[33]

2,5,8,11-Tetraaza[12]metacyclophane (L^4). By following a procedure similar to that described for the synthesis of L^3, L^4–Ts_4 (2.00 g, 2.31 mmol), phenol (4.0 g, 42.50 mmol) and 60 mL of 48% aqueous HBr afforded the product as a waxy solid (0.40 g, 1.62 mmol, 70% yield). Suitable cystals for X-ray analysis of the chloride and bromide salts were obtained in a similar manner as for L^3. ^{1}H NMR ($CDCl_3$): 7.75 (s, 1H), 7.22 (t, J = 7.4, 1H), 7.09 (d, J = 7.8, 2H), 3.84 (s, 4H), 2.77–2.80 (m, 4H), 2.71–2.73 (m, 8H), 1.99 (s, b, 4H);^{13}C-{^{1}H} NMR ($CDCl_3$): 141.59, 128.32, 127.23, 127.11, 53.12, 49.03, 49.01, 48.23; HRMS calcd for $C_{14}H_{25}N_4$ [M]$^+$ 249.2074, found 249.2077. Ligand L^4 has been prepared independently by asimilar method.[15]

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