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Charge-assisted encapsulation of two chlorides by a hexaprotonated azamacrocycle

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Abstract

A chloride complex of a hexaprotonated azamacrocycle has been isolated, and its structure has been determined by X-ray crystallography showing two encapsulated chloride anions in the cavity. The two internal guests are coordinated at two binding sites on the opposite side of the macrocycle through trigonal recognition by hydrogen-bonding interactions. The other four chlorides are located outside the cavity, each with a single hydrogen bond from secondary amines. *Ab initio* calculations based on density functional theory (DFT) suggest that the encapsulation of two chlorides inside the cavity leads to a significant charge transfer from the anions to the protonated amines.

Because of the critical roles played by anions in biological and environmental systems, there is an immense interest in the scientific community to understand molecular recognition of anions with synthetic receptors.[1] Among the various systems,[2] synthetic azamacrocyles with multiple binding sites are particularly interesting since they mimic many biological polyamines[3] and are attractive hosts for binding a diverse variety of inorganic and biological anions,[4] as well as transition metal ions.5 A number of azamacrocycles with variable spacers have been reported to bind anionic guests in solution, and their interactions in the solid state have been characterized crystallographically showing the formation of both monotopic and ditopic complexes.6,7 Because of their structural flexibility, monocycles often undergo a conformational change in order to bind anions[8]; for instance, [24]N_6O_2 was found to adopt a cleft-like conformation in its hexachloride,8a or tetranitrate salt.8b A similar conformational change was observed in tetraamido macrocycle with perrhenate[9] and pentaprotonated [26] $phen_2N_4O_2$ with halide (chloride and bromide) complexes.[10]

In the case of ditopic complexation, an azamacrocyclic ligand is found to interact with anions from one or both sides of the macrocycle in different fashions (Chart 1) such as face (**a**), bipyramidal (**b**) or cross binding (**c**), without complete encapsulation.[11] Small macrocycles comprising multiple binding sites preferentially bind two anions from both sides in a binding fashion **b**, as observed earlier in the nitrate complex of [18]N_4O_2 reported by Bowman-James. A similar binding was also reported by Spiccia for [18]N_6[11a] and by Steed for metacyclophanes[11b] complexing chloride, bromide, or iodide. On the other hand, a *p*-xylyl-based macrocycle with a slightly larger cavity was reported to form ditopic complexes in a "cross binding" with 3,5-dinitrobenzoate,[12] "bipyramidal binding" with tosylate[13] and "face

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Supporting Information available: Crystallographic file in CIF format, ^{1}H NMR titration spectra, hydrogen bonding interactions, and full list of the authors in Ref [20]. This material is available free of charge via the Internet at http://pubs.acs.org.

binding" with perchlorate.[14] However, to the best of our knowledge, complete encapsulation of two anions (fashion **d**) in an azamacrocycle-based ligand has not been reported before, although such binding is present in neutral ligands coordinating two transition metal ions.[5, 15] In an attempt to explore selective binding partners for simple azamacrocycles, we synthesized a ligand **L** and isolated a crystal of its chloride salt (Figure 1). In this communication, we present the structural report of two encapsulated chlorides in $H_6[\mathbf{L}]^{6+}$, the results of ^{1}H NMR binding studies, and density functional theory (DFT) calculations.

The ligand **L** was prepared from the high-dilution condensation of an equimolar amount of *N*-methyl-2,2′-diaminodiethylamine and terephthalaldehyde in methanol followed by the reduction with $NaBH_4$, as reported by us previously.[16] The chloride complex was obtained as a white powder from the reaction of neutral **L** (50 mg) with a few drops of concentrated HCl in methanol. Crystals suitable for X-ray analysis were grown from the chloride salt dissolved in H_2O/CH_3OH (5:1, v/v) under the slow diffusion of Et_2O.[17]

Structural analysis of the chloride complex reveals that the macrocycle in its hexaprotonated state crystallizes with 6 chloride anions and 2.34 water molecules, and lies on an inversion center. All charged nitrogen centers are involved in hydrogen-bonding interactions with chloride anions. As shown in Figure 2, two chlorides are completely encapsulated inside the cavity (Chart 1d) in close contact with two binding units on the opposite side of the macrocycle. The encapsulation occurs through trigonal recognition with three hydrogen bonds at distances ranging from 3.0674 (18) to 3.146 (2) Å (Table 1). These distances are comparable to 3.048 (3) or 3.10 Å observed for the NH···Cl^- distance in the thiophene-based azacryptand[18a] or tiny octaazacryptand,[18b] respectively.

The two symmetry-related encapsulated chlorides are separated by 4.433 Å and lie at 0.588 Å from the axis of the two central nitrogen atoms. The position of two internal chlorides nearly on the macrocyclic plane is indicative of negligible chloride-chloride repulsion inside the cavity which can be attributed to the reduction of charges on the encapsulated chlorides caused by the formation of three hydrogen bonds. The remaining chlorides are outside the cavity, each with a single hydrogen bond from protonated secondary amines. The macrocyclic unit in the complex is essentially flat rather than a chair conformation observed in the *p*-xylyl macrocycle[19] or in the chloride complex of the larger *m*-xylyl analogue.[8b] In the chloride complex of **L**, two aromatic units are parallel to each other at a distance of 7.842 Å (centroid-to-centroid), while the distance between the two central nitrogens is 10.338 Å, providing an oval-shaped cavity suitable for two chlorides (Figure 3). The six protons from the nitrogen centers at both sides are directed toward the center, making the ligand ideal to anchor the two chlorides inside the cavity.

Water molecules in the crystal lattice are located outside the cavity and are not involved in hydrogen-bonding interactions with the macrocycle. However, they are coordinated with the two symmetry-related *trans*-chlorides located outside the cavity. In extending view, the water molecules play an important role in linking the neighboring macrocyclic units through chloride anions, forming an intermolecular chain viewed along the *c* axis (Figure 4).

In order to understand the binding interactions of **L** with chloride anions, a series of DFT calculations were carried out using the Gaussian 09 software codes.20 Since the macrocycle and chlorides are involved in hydrogen bonding interactions, it was necessary to choose a functional which accurately captures these effects on the potential energy surface. To this end, all DFT calculations were performed using the M06-2X21 hybrid functional which incorporates an improved description of dispersion energies, an effect which was previously found to be necessary (compared to other hybrid functionals) for describing noncovalent interactions.[22] The initial equilibrium geometry for the free protonated macrocycle with six

positive charges was first optimized at the M06-2X/6-31G(d,p) level of theory. From this equilibrium geometry, two chloride anions were added to the center of the macrocycle, and the geometry of the complex was fully re-optimized at the same M06-2X/6-31G(d,p) level of theory. Harmonic frequencies were also computed to verify all structures were true minima. Single-point properties with the 6-311G(d,p) basis set (a diffuse 6-311+G(d,p) basis set was used for the chloride anions) were subsequently performed for each of the relaxed geometries. The calculated binding energy was found to be −756.5 kcal/mol for the two chlorides encapsulated within the protonated macrocycle, while the binding energy for a single anion was significantly less (−394.6 kcal/mol), confirming the experimental observation of two chloride anions internally bound to the macrocycle. The resulting binding energies obtained from the DFT calculations are large and do not take into account solvent effects. However, incorporation of explicit solvent molecules to understand their effect on binding energies would be extremely computationally demanding, especially for this large macrocycle. Our DFT results should thus be considered as upper bounds for both the binding energy and charge transfer between the chloride ions and the macrocycle. In a related work, the group of Bowman-James calculated binding energies of −364 and −668 kcal/mol for 1:1 and 1:2 nitrate binding in hexaprotonated *m*-xylyl-based cryptand.[23] In the optimized structure of $[H_6\mathbf{L}(Cl)_2]^{4+}$ shown in Figure 5a, each encapsulated chloride is coordinated with three NH···Cl^- bonds at each binding unit of the macrocycle in good agreement with the experimental crystal structure (Table 1). From the DFT-optimized geometry, we also computed the total electrostatic potential from the self-consistent density matrix. As shown in Figure 5(b), the chloride ions have the most (negatively-charged) electron density of the entire complex and, therefore, have the lowest electrostatic potential. However, since the protonated macrocycle has a very large positive charge, there is significant charge transfer between the chlorides and the protonated amines, and the resulting potential on the chlorides is slightly positive.

In solution, the binding affinity of **L** for chloride was evaluated by ^{1}H NMR titration studies using $H_6\mathbf{L}(OTs)_6$ in DMSO-d_6. Tetrabutyl ammonium chloride was used as a source for chloride ions. The titration of $H_6\mathbf{L}(OTs)_6$ (5 mM) with chloride anion (50 mM) resulted in a downfield shift of macrocyclic protons (Figure 6 and supporting materials). The largest shift was observed for NH protons, demonstrating the participation of NH in chloride binding, as seen in the solid state. The change in the chemical shift with an increasing amount of chloride solution at room temperature gave the best fit for a 1:1 complex, yielding a binding constant $K = 70\ M^{-1}$. The obtained 1:1 binding mode, however, is not consistent with the results observed in crystal structure. This inconsistency is most likely due to the effect of polar solvent used in the titration which tends to highly solvate the ligand, resulting in reduced populations of binding sites.[14,16] We were, therefore, interested in examining the binding studies in a non-polar solvent like $CDCl_3$. However, in $CDCl_3$, the titration of $H_6\mathbf{L}(OTs)_6$ (5 mM) with tetrabutyl ammonium chloride was hampered due to precipitation that occurred after an addition of guest solution, resulting in the gradual disappearance of ligand resonances. Further dilution (up to 2 mM) of the initial concentration of the ligand solution also did not allow us to complete the full titration. However, this observation indicates that the ligand interacts strongly with chloride in chloroform forming a complex that is poorly soluble in non-polar solvent, as expected.

In summary, we have demonstrated an elegant example of an azamacrocycle capable of encapsulating two chlorides inside its cavity, a phenomenon commonly observed in macrocyclic systems which bind two transition metal ions.[5,15] All nitrogens in the anion complex are protonated, and the two chlorides remain within the cavity in close contact with binding units at opposite sides. The six protons on the nitrogen centers point towards the cavity, making an attractive cavity for encapsulating two chlorides within the macrocyclic ring. Each of the remaining four chlorides binds outside the cavity with a single hydrogen bond from four secondary amines. In the complex, all ten protons (eight from secondary and two from tertiary

nitrogens) on the charged nitrogen centers are effectively utilized in coordinating chloride anions. The water molecules that are present in the lattice play an important role in linking the neighboring macrocyclic frameworks through the external chlorides. *Ab initio* calculations performed on the ligand-chloride complex not only support the stabilization of two chlorides inside the highly charged cavity, but also suggest that the complex with two encapsulated chlorides is energetically more favorable than that with one chloride. While there are many examples of ditopic binding of anions in different fashions (Chart 1a–c),[6,7,11–14] the complete encapsulation of two anionic guests has not been previously shown in an azamacrocycle-based ligand. The presence of two methyl groups coupled with fully-charged nitrogens makes the ligand ideal for fitting two compatible chlorides inside the cavity through trigonal recognition with three hydrogen bonds. We are currently pursuing further work on related ligands for designing other charge-assisted encapsulated complexes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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17. Crystallographic data: $C_{26}H_{48}N_6Cl_6{\cdot}2.34H_2O$, M = 699.47, crystal size 0.25 × 0.18 × 0.17 mm^3, Monoclinic, *P*21/*c*, *a* = 10.925 (3), *b* = 12.736 (2), *c* = 12.453 (3) Å, β = 98.413 (9)°, *V* = 1714.1 (7) $Å^3$, Z = 2, d_{calc} = 1.355 Mg m^{-3}, *T* = 90 K, F(000) = 743, , μ(Mo-*Kα*) = 50.54 mm^{-1}, 4083 independent reflections (18451 measured), R_{int} = 0.066, *R*[*F*2 > 2σ(*F*2)] = 0.054, wR2 = 0.122. Structural data were collected on a Nonius KappaCCD (with Oxford Cryostream) diffractometer. The structure was solved by direct methods and refined with the full-matrix least-squares technique. Selected bond lengths and angles for hydrogen bonding interactions in the complex are listed in Table S1.
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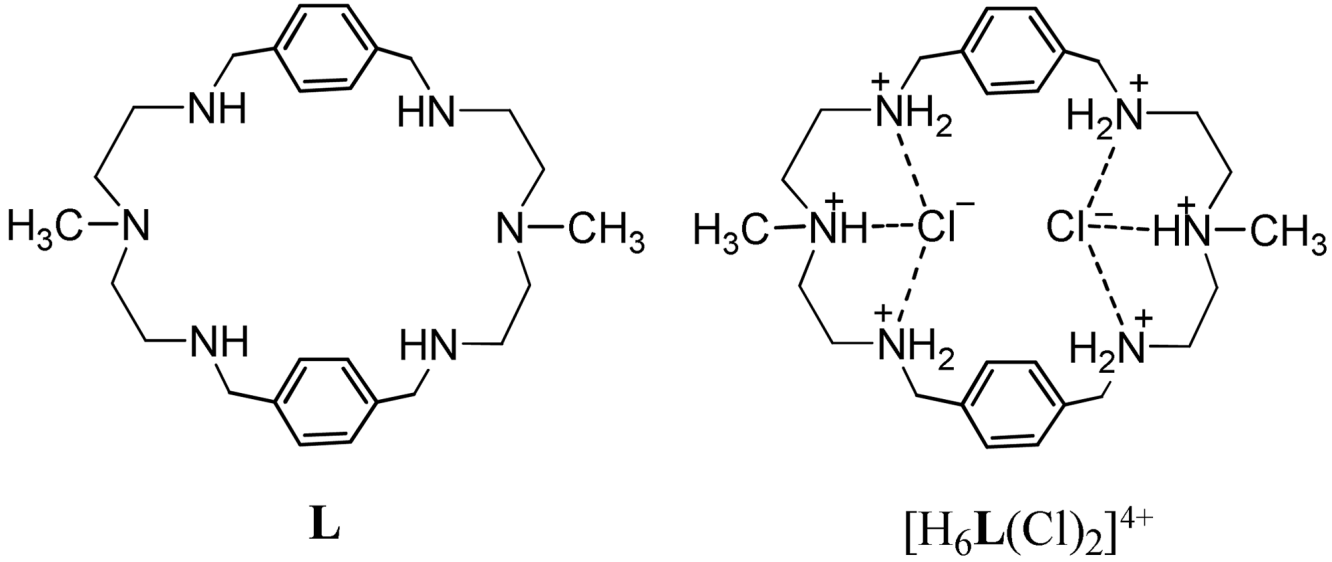


L $[H_6\mathbf{L}(Cl)_2]^{4+}$

Figure 1.
Hexaprotonated macrocyle (**L**) and its chloride salt ($[H_6\mathbf{L}(Cl)_2]^{4+}$).

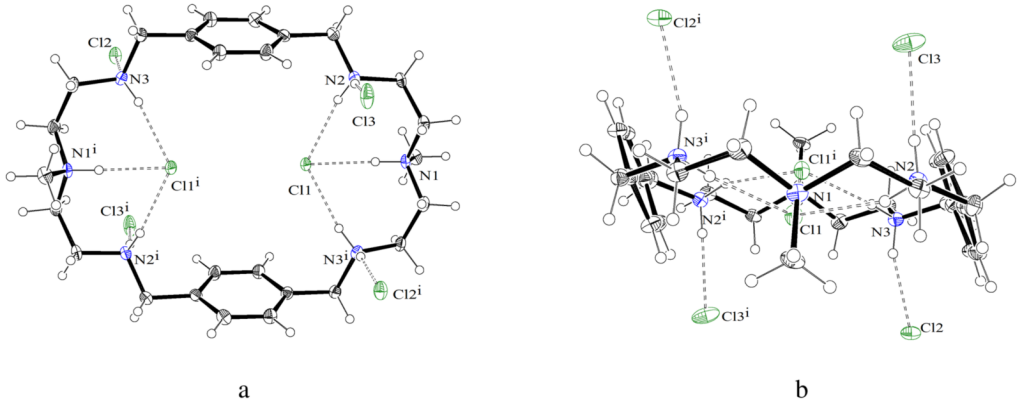


Figure 2.
Crystal structure of the chloride complex **L** showing two chlorides bonded through trigonal recognition. (a) side view (b) perspective view down the two central amines (water molecules are omitted for clarity).

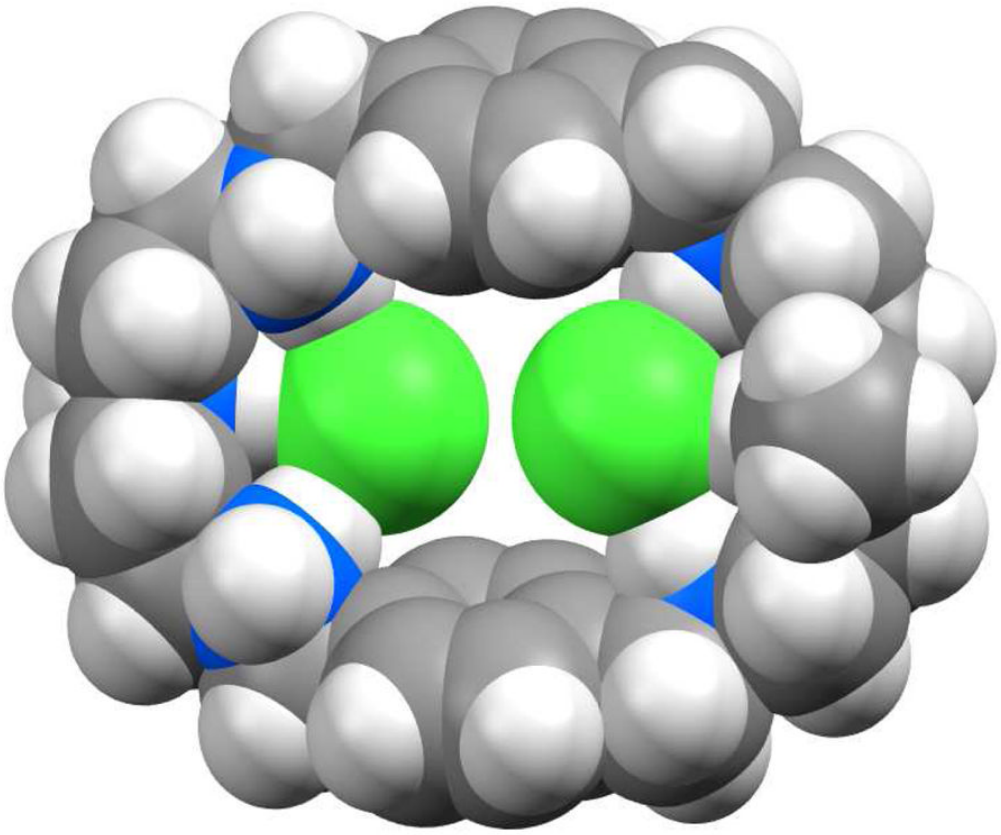


Figure 3.
Space-filling representation of $[H_6\mathbf{L}(Cl)_2]^{4+}$ showing two encapsulated chlorides in the cavity. Color code: white = hydrogen; gray = carbon; blue = nitrogen; green = chloride.

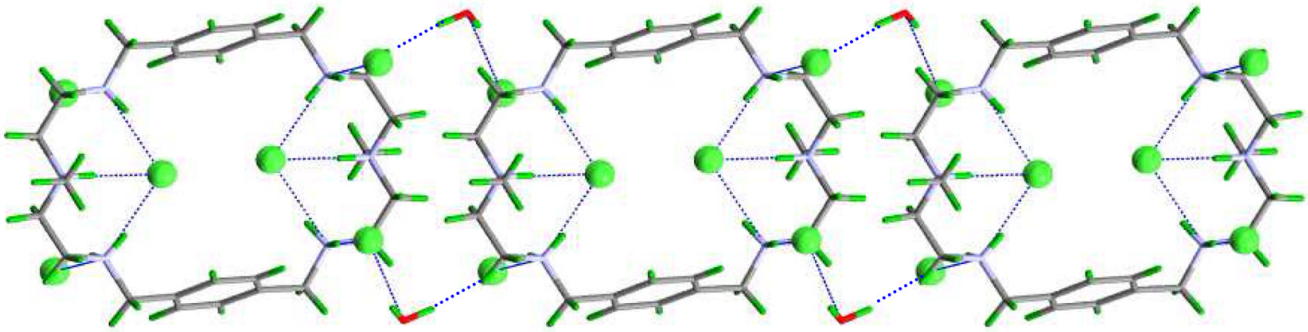
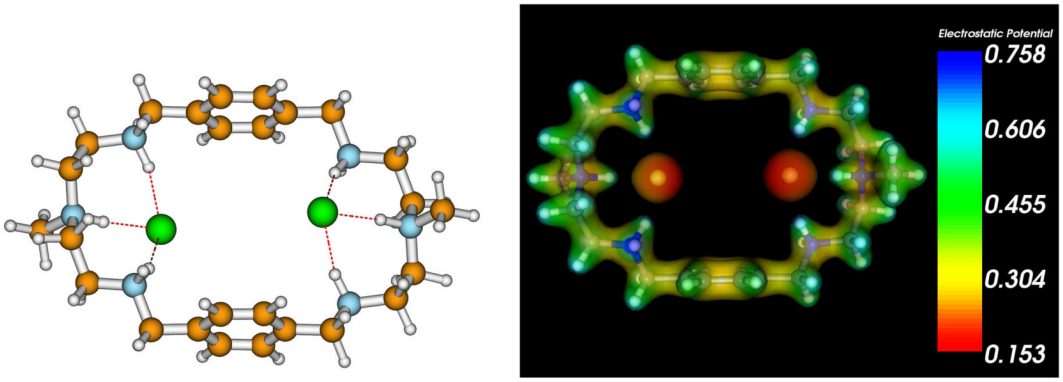


Figure 4.
View of hydrogen-bonded chain of the chloride complex of **L** (viewed along the *c* axis). Water molecules are shown to link two macrocycles via chloride anions in the crystal lattice.



a b

Figure 5.
(a) Optimized geometry of $[H_6\mathbf{L}(Cl)_2]^{4+}$ at the M06-2X/6-31G(d,p) level of theory. (b) Electrostatic potential of $[H_6\mathbf{L}(Cl)_2]^{4+}$.

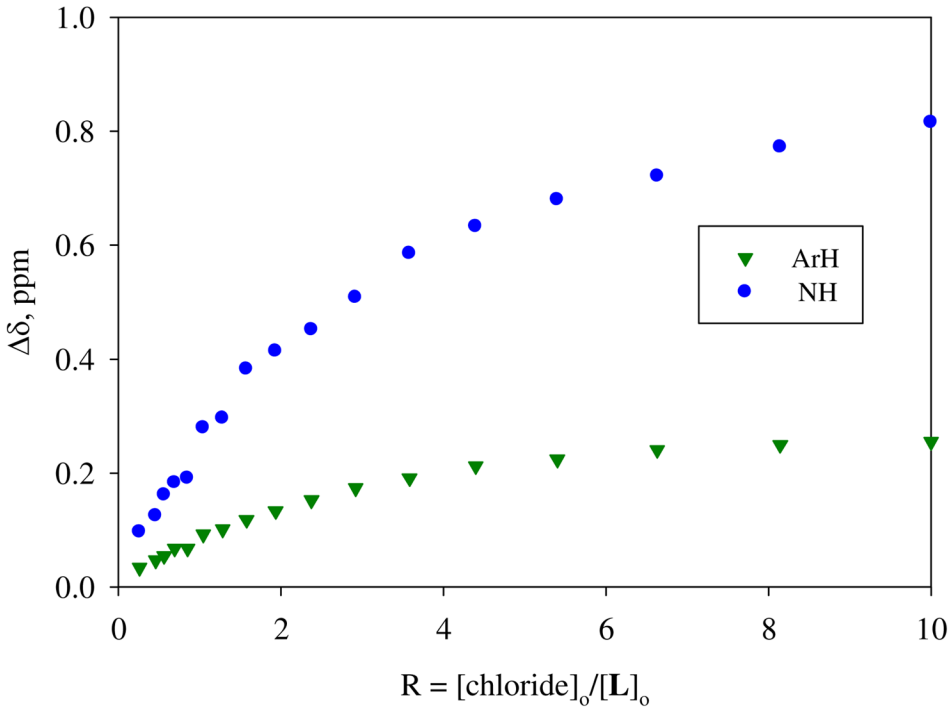


Figure 6.
^{1}H NMR titration curves of $H_6L(OTs)_6$ with chloride in DMSO-d_6 at room temperature.

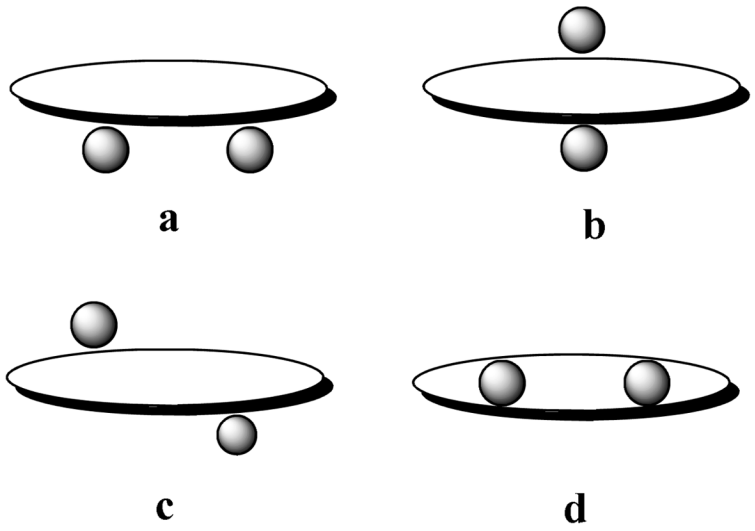


Chart 1.
Classification of ditopic binding of anions by a macrocyclic ligand: (a) face binding, (b) bipyramidal binding, (c) cross binding, and (d) encapsulation.

Table 1

Hydrogen bonding interactions of symmetry-related encapsulated chlorides within the crystal and the DFT-optimized structure

Atoms	Experimental bond distance (Å)	DFT-optimized bond distance (Å)
N1···Cl1	3.0674 (18)	2.986
N2···Cl1	3.126 (2)	3.062
N3···Cl1	3.146 (2)	3.062