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Article

Spherical versus Linear Anion Encapsulation in the Cavity of a Protonated Azacryptand

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Grams scale synthesis of an octaaminocryptand $\mathbf{L}^2$ with high yield is obtained in one-pot by low-temperature [2 + 3] condensation of tris(2-aminoethyl)amine with isophthalaldehyde, followed by sodium borohydride reduction. Structural aspects of octaaminocryptand $\mathbf{L}^2\cdot$MeOH, binding of iodide (spherical) and bichloride (linear) in $\mathbf{L}^2$, (1,4,11,14,17,24,29,36-octa-azapentacyclo-[12.12.12..$2^{6,9}$.$2^{19,22}$.$2^{31,34}$]-tetratetraconta 6(43),7,9(44),19(41),20,22(42), 31(39),32,34(40)-nonane, $N(CH_2CH_2NHCH_2$-*m*-xylyl-$CH_2NHCH_2CH_2)_3N$), in the hexaprotonated and tetraprotonated states, respectively, are examined. Crystallographic results show binding of single iodide $[H_6\mathbf{L}^2I](I)_5\cdot 4H_2O$, (**2**), in a hexaprotonated cryptand $\mathbf{L}^2$. Monotopic recognition of iodide is observed via $(N-H)^+\cdots$iodide interactions. The tetraprotonation of $\mathbf{L}^2$ by hydrochloric acid showed the formation and encapsulation of a bichloride inside the cavity, which is examined from the single-crystal X-ray study. Encapsulation and binding of a proton-bridged linear bichloride inside the cavity of tetraprotonated $\mathbf{L}^2$, $[H_4\mathbf{L}^2(ClHCl)](Cl)_3\cdot nH_2O$ (**3**), via $(N-H)^+\cdots$chloride interactions is observed in the structural investigation. This study shows that degree of protonation and its distribution in the receptor architecture play an important role in guest encapsulation. Further, it represents the first example of an encapsulated bichloride inside the cavity of an organic host.

Introduction

Protonated amines and quaternary ammonium functions incorporated into a suitable ligand topology make attractive receptors for anions mainly because of a balanced combinations of both the electrostatic and hydrogen-bonding interactions with the anion of interest.[1] In protonated azamacrobicycles, it is important to know the actual degree of protonation and also the distribution of the positively charged centers for guest encapsulation/binding.[2] The azamacrobicycle $\mathbf{L}^1$ (Chart 1) has shown a fluoride-based cascade complex,[3] chloride/bromide, and a water molecule,[4] and monotopic chloride/bromide,[5] encapsulation inside the cavity of $[H_6\mathbf{L}^1]^{6+}$. Further, $[H_7\mathbf{L}^1]^{7+}$ has also shown a monotopic encapsulation of chloride where external undecameric water clusters participate in the hydrogen bonding with the encapsulated guest.[6] Whereas, $\mathbf{L}^2$, upon hexaprotonation with HF, showed encapsulation of one fluoride ion and a molecule of water (Chart 1, **1**), which is the only structural evidence known to date on halide encapsulation in $\mathbf{L}^2$,[7] although $\mathbf{L}^2$

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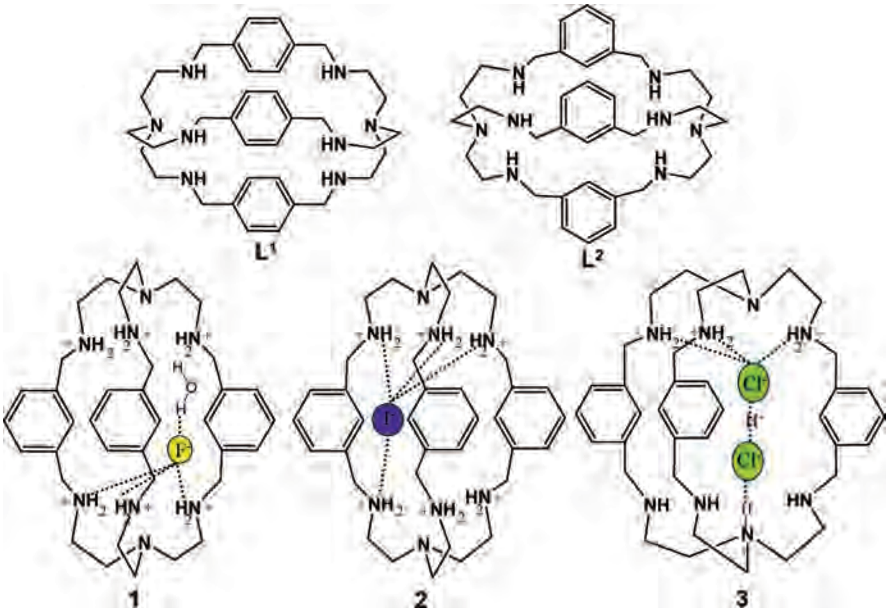
10.1021/ic702056y CCC: $40.75

Chart 1. Octaaminocryptand with *p*-Xylyl Spacers $\mathbf{L}^1$, with *m*-Xylyl Spacers $\mathbf{L}^2$, $\mathbf{L}^2$ Containing a Fluoride Ion and Water, Monotopic Iodide Complex of $[H_6\mathbf{L}^2]^{6+}$ (**2**), and Receptor $[H_4\mathbf{L}^2]^{4+}$Encapsulating a Bichloride (**3**)



as host has been extensively used for oxoanion binding.[8] In this study, we are interested in investigating the encapsulation of higher homologue halides in $\mathbf{L}^2$ in its different degree of protonated states. Herein, we show a monotopic encapsulation of the largest halide, iodide (spherical), inside the hexaprotonated cryptand $\mathbf{L}^2$ via four $(N-H)^+\cdots$iodide interactions (Chart 1, **2**) and bichloride (linear) inside the tetraprotonated $\mathbf{L}^2$ (Chart 1, **3**). Though in case of chloride complex **3**, we expected either a monotopic or ditopic encapsulation in its protonated state, but the single crystal X-ray structure of the complex revealed encapsulation of two chlorides in the cavity of $[H_4\mathbf{L}^2]^{4+}$, separated by a distance less than the sum of their ionic radii (3.60 Å), along with three chlorides in the lattice. The shorter separation between the encapsulated chlorides and compensation for the extra negative charge in the salt lead us to notice the formation of $[HCl_2]^-$ species (linear) inside the cavity of $[H_4\mathbf{L}^2]^{4+}$.

Linear triatomic bihalides, HX_2^-, where X is F, Cl, Br, and I, have been the subject of numerous studies, and they participate in important chemical processes.[9] Encapsulation of first linear triatomic anion, azide is reported by Lehn et al. in 1978 in a hexaprotonated bicyclic cryptand.[10] After three decades, recently Bowman-James et al. have structurally demonstrated the encapsulation of a bifluoride within a tricyclic receptor.[11] Though, the anion coordination chemistry began in 1968 with the discovery of a chloride encapsulated katapinand by Park and Simmons,[12a] and first structural proof of chloride encapsulation came out in 1975.[12b] Later a number of reports on chloride encapsulated systems have been appeared in the literature.[4−6,13] To the best of our knowledge, the crystallographic corroboration of an encapsulated bichloride has remained elusive to date despite the finding of bichloride in a number of crystal lattices.[14]

Experimental Section

Materials. Isophthalaldehyde, tris(2-amino ethyl)amine (tren), *p*- toluenesulfonic acid, tetrabutylammonium chloride, tetrabutylammonium bromide, tetrabutylammonium iodide, and sodium borohydride were purchased from Sigma-Aldrich and were used

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as received. HCl, HI and solvents were purchased from SD Fine Chemicals, India. All the solvents were purified prior to use.

Synthesis of Macrobicyclic Receptor, $\mathbf{L^2}$. The cryptand $\mathbf{L}^2$ was synthesized after modification of the literature procedure and isolated as the free base.[15] Isophthalaldehyde (5.04 g, 37.57 mmol) and 500 mL dry of MeOH were added to a 2-neck 1-L round-bottom flask equipped with a magnetic stirrer. Isophthalaldehyde was dissolved at rt; then the solution was cooled to 5−10 °C using an ice bath. A dropping funnel containing diluted tren (3.65 g, 25 mmol) with 100 mL of dry MeOH was fitted in to the 2-neck round-bottom flask. Tris(2-amino ethyl)amine solution was added dropwise (2−3 drops/min), allowing for complete dispersion of each drop between the additions with constant stirring under N_2 atmosphere. Tren solution was added over approximately 4 h, and addition was continued at a temperature of 5−10 °C with constant stirring. After all of the tren solution was added; the yellow solution was allowed to stir at room temperature for another 8 h. Reduction of the Schiff base thus formed was achieved by hydrogenation with with excess $NaBH_4$ (portion-wise) for 2−3 h at room temperature followed, by refluxing for an hour. The MeOH was evaporated to dryness under reduced pressure, and the residue was treated with cold distilled water (200 mL). The desired cryptand was extracted with $CHCl_3$ (100 × 3 mL). The organic layer was further washed with (500 × 3 mL) distilled water, and then it was dried over anhydrous Na_2SO_4 and evaporated to obtain a colorless semisolid. The semisolid product was redissolved in a binary solvent system MeCN/MeOH (1:1) and was allowed to crystallize at rt. Colorless crystals of single crystal X-ray diffraction quality $\mathbf{L}^2$ were obtained within 2 days.

Complex **2** was obtained by dissolving $\mathbf{L}^2$ (60 mg, 100 μmol) in MeOH (10 mL) and adding 55% of HI. The solid formed was filtered and redissolved by adding about 4 mL of water, and the solution was further filtered and kept for crystallization. Crystals suitable for X-ray analysis were obtained by slow evaporation of the solution at rt.

Complex **3** was obtained by dissolving $\mathbf{L}^2$ (60 mg, 100 μmol) in EtOH/water (1:2, 10 mL) and adding 2 mL of 37% HCl (pH = 4.42) in warm conditions. No precipitate was formed, but the solution was filtered, and filtrate was allowed to evaporate at rt. Few crystals suitable for X-ray analyses were obtained by slow evaporation of the solution after a month when the resultant mass was about to dry.

$[H_6\mathbf{L}^2][TsO]_6$, **4** was obtained by following the literature procedure with high yield.[7b,24] The ^{1}H NMR data of the product matched with the literature values.[7b]

$\mathbf{L^2}$. Yield: 80−90%. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ 2.54 (t, 12H, NCH_2), 2.63 (t, 12H, NCH_2CH_2), 3.74 (s, 12H, ArCH_2), 7.15 (s, 3H, ArH), 7.29 (d, 6H, ArH), 7.80 (t, 3H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 48.85 (NCH_2), 52.51 (NCH_2CH_2), 53.44 (ArCH_2), 126.34, 129.78, 131.71, 139.04 (C_{Ar}). HRMS (ESI): m/z 599.7241 $[H\mathbf{L}^2]^+$.

$[H_6L^2(I)](I)_5\cdot 4H_2O$, 2. ^{1}H NMR (200 MHz, D_2O): δ 2.62 (t, 12H, NCH_2), 2.71 (t, 12H, NCH_2CH_2), 3.72 (s, 12H, $ArCH_2$), 7.15 (s, 3H, ArH), 7.24 (d, 6H, ArH), 7.77 (t, 3H, ArH). ^{13}C NMR (50 MHz, D_2O): δ 48.35 (NCH_2), 54.07 (NCH_2CH_2), 54.73 ($ArCH_2$), 128.02, 130.54, 130.94, 137.49 (C_{Ar}). HRMS (ESI): m/z 599.4476 $[H\mathbf{L}^2]^+$.

$[H_4L^2(HClH)](Cl)_3\cdot nH_2O$, 3. ^{1}H NMR (200 MHz, D_2O): δ 2.77 (t, 12H, NCH_2), 3.21 (t, 12H, NCH_2CH_2), 4.22 (s, 12H, ArCH_2), 7.23 (s, 3H, ArH), 7.31 (d, 6H, ArH), 7.73 (t, 3H, ArH).. ^{13}C NMR (50 MHz, D_2O): δ 44.72 (NCH_2), 51.26 (NCH_2CH_2), 53.61 (ArCH_2), 124.49, 129.78, 131.67, 141.52 (C_{Ar}). HRMS (ESI): m/z 599.6725 $[H\mathbf{L}^2]^+$.

Physical Measurements. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 300 and 75 MHz FT-NMR spectrometers (model Advance DPX200) instrument. HRMS measurements were carried out on QTof-Micro YA 263 instruments.

^{1}H NMR Titration Studies. The binding constant was obtained by ^{1}H NMR (300 MHz Bruker) titrations of $[H_6\mathbf{L}^2][OTs]_6$ with $[n\text{-}Bu]_4N^+Cl^-$ in DMSO-d_6 at 25 °C. The initial concentration of $[H_6\mathbf{L}^2][OTs]_6$ was 20 mM. Aliquots of anion were added from two different stock solutions, 25 and 50 mM of anion (host/guest = up to 1:1, 25 mM stock solution was used, and above 1:1 ratio higher concentration of anion was used). Tetramethylsilane (TMS) in DMSO-d_6 was used as an internal reference, and titration was performed upon 15 measurements at room temperature. All proton signals were referred to TMS. The association constant, K, was calculated by fitting the change in the $-NH_2^+$ chemical shift with a 1:1 association model with nonlinear least-squares analysis using EQNMR.[25] The error limit in K was less than 10%. There was no detectable chemical shift of $-NH_2^+$ resonance in case of Br^- and I^- as guest, which indicates no host−guest complex formation with the $[H_6\mathbf{L}^2][OTs]_6$.

X-ray Crystallography. The crystallographic data and details of data collection for $\mathbf{L}^2\cdot$MeOH and complexes **2** and **3** are given in Table 1. In each case, a crystal of suitable size was selected from the mother liquor, immersed in paratone oil, then mounted on the tip of a glass fiber, and cemented using epoxy resin.

X-ray single-crystal diffraction data for all the three compounds $\mathbf{L}^2$, **2**, and **3** were collected on a Bruker SMART Apex CCD diffractometer at 100 K with Mo Kα radiation (0.71073 Å). There was no evidence of crystal decay during data collection. Semiempirical absorption corrections were applied (SADABS), and program SAINT was used for integration of the diffraction profiles.[16a] The structures were solved by direct methods using the SHELXS program of the SHELXTL package and refined with SHELXL.[16b] For complex **2**, after location of the complete ligand moiety and three iodide anions, closely associated high intensity peaks started appearing in the difference Fourier map. Three sets of clustered peaks appeared with each cluster having two peaks which are closely associated. These peaks are assigned as the disordered iodide anions. Thus the three iodide anions present in the unit cell were disordered at two positions each, and the occupancy factor for each peaks within the cluster is assigned using the FVAR command in the SHELXL program. Refinement of these disordered peaks with partial occupancy factor has been carried out isotropically until convergence. The difference Fourier map showed the presence of four lattice water molecules. All the non-hydrogen atoms including the three disordered iodide of **2** were refined anisotropically until convergence was attained. Hydrogen atoms of the ligand moiety

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Table 1. Crystallographic Data for $\mathbf{L}^2\cdot CH_3OH$, $[H_6\mathbf{L}^2(I)](I)_5\cdot 4H_2O$ (**2**), and $[H_4\mathbf{L}^2(HCl_2)](Cl)_3\cdot nH_2O$ (**3**)

	$\mathbf{L}^2\cdot$MeOH	**2**	**3**
empirical formula	$C_{38}H_{60}N_8O_6$	$C_{36}H_{60}I_6N_8O_4$	$C_{72}H_{116}Cl_{10}N_{16}O_{34}$
fw	724.94	1430.22	2104.31
cryst syst	hexagonal	monoclinic	cubic
space group	$P6_3/a$	$P2_1/c$	$P2_13$
a (Å)	8.9953(4)	17.4641(19)	22.8080(7)
b (Å)	8.9953(4)	17.4260(18)	22.8080(7)
c (Å)	27.457(3)	17.1392(18)	22.8080(7)
α (deg)	90.00	90.00	90.00
β (deg)	90.00	101.465(2)	90.00
γ (deg)	120.00	90.00	90.00
V (Å^3)	1924.0(2)	5111.9(9)	11864.8(6)
Z	2	4	4
d_{calcd} (g/cm^3)	1.251	1.858	1.080
cryst size (mm^3)	0.58 × 0.43 × 0.38	0.30 × 0.22 × 0.12	0.64 × 0.45 × 0.33
diffractometer	Smart CCD	Smart CCD	Smart CCD
λ (Å)	0.71073	0.71073	0.71073
F(000)	784	2728	4408
abs corr	SADABS	SADABS	SADABS
T (K)	100(2)	100(2)	100(2)
Θ range	1.48−28.20	1.67−25.00	1.79−28.30
reflns collected	7797	8940	9558
independent reflns	1499	5958	8019
R(int)	0.0601	0.0572	0.0719
data/restraints/params	1499/0/97	8940/0/514	8019/0/416
R1, wR2	0.0584, 0.1531	0.0658, 0.1477	0.0763, 0.1977
GOF (F^2)	1.035	1.036	1.080

were positioned geometrically and treated as riding atoms, whereas the water hydrogen atoms cannot be located from the difference Fourier map.

For complex **3**, in addition to twelve water molecules located in the compound from difference Fourier map, a large number of diffused scattered peaks with electron density ranging from 3.2 to 2.5 Å^{-3} was observed, which can be attributed to the disordered solvent present in this compound. Attempts were made to model this, but were unsuccessful because the residual electron density peaks obtained were diffused, and there was no obvious major site occupation for the solvent molecules. PLATON/SQUEEZE[16c] was used to correct the data for the presence of the disordered solvent. A potential solvent volume of 727.1 Å^3 was found; 208 electrons per unit cell worth of scattering was located in the void. This electron counts corresponds to approximately 10 more water molecules in the unit cell. Thus, the structure of the compound revealed that there are two molecules of tetraprotonated $\mathbf{L}^2$, 8 Cl^- counterions, two HCl molecules(for which the H-atom is not located), and 12 molecules of water in the asymmetric unit, along with tentatively 10 molecules of disordered waters in the lattice, whose contribution is removed by the PLATON/SQUEEZ program. For complex **3**, the full-matrix least-squares refinement of all non-hydrogen atoms with isotropic temperature factors was carried out until the convergence was reached. All the H atoms for **3** were positioned geometrically and treated as riding atoms. With the modified data set using SQUEEZ program, the final cycles of least-squares refinements improved both the *R*-values and goodness of fit significantly. Graphics are generated using PLATON[16d] and MERCURY 1.3.[16e]

Results and Discussion

Synthesis. The cryptand $\mathbf{L}^2$ is prepared in grams scale with a very high yield of above 80%, following the modified literature procedure.[15] The key step in the multi-gram synthesis of the octaazacryptand is the condensation of tris(2-aminoethyl) amine (tren) with isophthalaldehyde at 5−10 °C and slow addition of tren solution to the aldehyde solution. Low-temperature syntheses of other cryptand molecules are known in the literature.[17] The condensation reaction is carried out in dry MeOH, and in situ reduction of Schiff base is done with $NaBH_4$. Higher temperature (40−50 °C) and fast addition rates lead to mostly polymeric product in this high scale synthesis. In Nelson's synthesis, Schiff base is isolated from MeCN and recrystallized from MeOH with 40−60% yield; then disilver or dilead complexes are prepared from the Schiff base with ~90% yield,[15b] and finally disilver or dilead metal cryptate is reduced by tetrahydroborate with 70% yield. Therefore, the overall yield of the cryptand with respect to the starting material is not more than 30−50%. Synthesis by Chen and Martell yielded 40% of cryptand by direct reduction of the free Schiff base, which is obtained by a non-template method in MeCN solvent.[15a] In an attempt to synthesize $\mathbf{L}^2$, in a multigram scale following modified literature procedure, we obtained single crystal of the ligand suitable for X-ray diffraction study from a binary solvent mixture methanol/acetonitrile (1:1).

Complexes **2** and **3** are obtained by titration of $\mathbf{L}^2$ with 55% of HI and 37% HCl in methanol and ethanol, respectively. In the case of **2**, a colorless precipitate is obtained after addition of hydroiodic acid to the methanolic solution of $\mathbf{L}^2$, whereas the solution became turbid in **3**. In complex **2**, the precipitate is isolated from the reaction mixture, and the solids are dissolved by adding appropriate amount of distilled water. In complex **3**, the turbid solution is filtered and allowed to crystallize.

Description of the Crystal Structure, $\mathbf{L}^2\cdot$MeOH. Arnaud-Neu et al. has reported the crystal structure of the free ligand moiety obtained from hexane−ether mixture in

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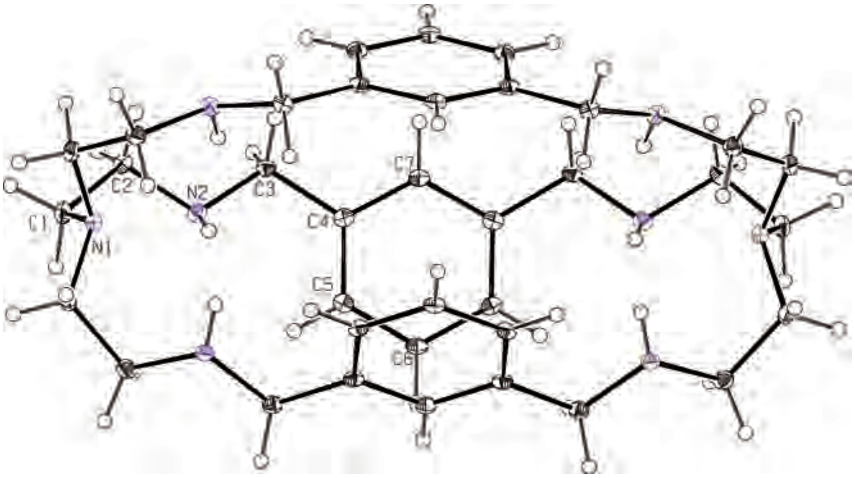

Figure 1. ORTEP diagram of $L^2 \cdot$MeOH with atom numbering scheme (40% probability factor for the thermal ellipsoid and lattice methanol molecule is omitted for clarity), $N_{bridgehead}-N_{bridgehead}$ distance = 10.913 Å, and the distance between any two secondary nitrogen centers of the tren cavities is 4.033 Å.

triclinic system,[18] with two independent molecules in the asymmetric unit (2 L^2), although structure of parent Schiff base of L^2 has been known for long time.[19] No intramolecular interaction is observed within the L^2 moiety, but weak $C-H \cdots \pi$ interaction exists between the molecules present in the asymmetric unit. Later, Clifford et al. also isolated the free ligand as water complex $L^2 \cdot 12\ H_2O$, comprising an intricate water network.[20]

In our study, the crystal turned out to be $L^2 \cdot$MeOH. The crystal structure of $L^2 \cdot$MeOH showed high degree of symmetry (Figure 1), and the compound crystallizes in hexagonal system, with $P6_3/m$ space group.

Along with the L^2, one molecule of MeOH is located in the lattice, and the carbon atom of the methanol molecule is occupying the 3-fold axis. In an attempt to understand the various intermolecular interactions and the interaction of the ligand moiety with the lattice methanol, we have analyzed the crystal structure in detail including the packing arrangement. The L^2 moiety also possesses a 3-fold symmetry passing through the apical nitrogen atoms and an additional C_2 symmetry bisecting the carbon atoms C6 and C7 of the phenyl ring. $L^2 \cdot$MeOH shows a strong intermolecular $C-H \cdots \pi$ interaction between the phenyl hydrogen and the centroid of the symmetrically disposed phenyl ring. The packing diagram and details of the intermolecular interaction are given in the Supporting Information.[21]

Description of the Crystal Structure, $[H_6L^2(I)][I]_5 \cdot 4H_2O$, (2). Complex **2** crystallizes in monoclinic space group $P2_1/c$. All the six secondary amino groups of the ligand moiety are protonated and four molecules of water are located in the lattice. As depicted in Figure 2, one of the iodide anions, I1, is encapsulated within the $[H_6L^2]^{6+}$ moiety via four strong $(N-H)^+ \cdots I^-$ interactions. Thus, hydrogen atoms H2A and H3A of two protonated nitrogen atoms from one of the three strands and two other hydrogen atoms H6A and H8B of protonated nitrogen centers from rest of the three strands are involved in four $(N-H)^+ \cdots I^-$ interactions with the encapsulated iodide. Details of these intramolecular hydrogen bonding interactions are shown in Table 2.

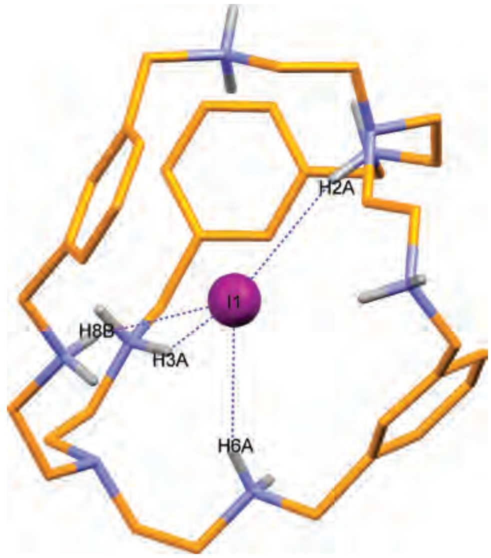

Figure 2. Mercury diagram depicting the encapsulation of Iodide inside the cryptand moiety via intramolecular $(N-H)^+ \cdots I-$ interactions (dotted blue lines). $N_{bridgehead}-N_{bridgehead}$ distance = 8.349 Å.

Table 2. Hydrogen Bonding Interactions of I1 of **2**

interactions	HA (Å)	DA (Å)	∠D−HA (deg)
N(2)−H(2A)···I(1)	2.97	3.8442	164
N(3)−(3A)···I(1)	2.93	3.6811	142
N(8)−H(8B)···I(1)	2.79	3.5789	148
N(6)−H(6A)···I(1)	2.70	3.5187	142

The encapsulated iodide, I1, does not reside exactly at the center of the apical nitrogen atoms with I1···N1/N4 distances of 4.030 and 4.348 Å, respectively. The $[H_6L^2]^{6+}$ moiety is compressed along the bridgehead N1/N4 axis compared to the cryptand base, which is reflected in the distance between the apical nitrogen atoms of the cryptand moieties (N1···N4 = 8.349 Å in complex **2** and N1···N4 = 10.913 Å in

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[21] See Supporting Information.

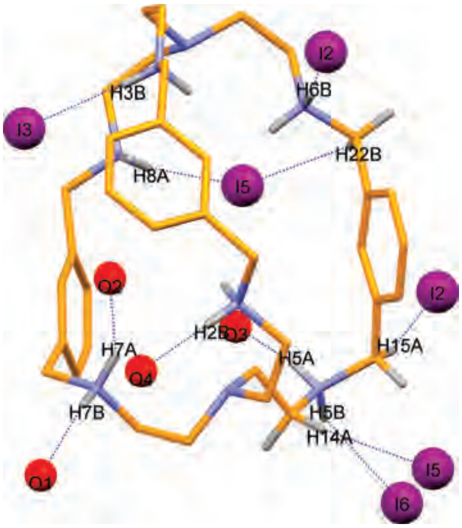

Figure 3. Interaction of the surrounding iodide anions and lattice water molecules with the $[H_6\mathbf{L}^2]^{6+}$ moiety (encapsulated iodide anion I1, iodide I4, H-atoms of $\mathbf{L}^2$ that are not involved in H-bonding interactions are omitted for clarity; only one of the disordered positions of I5 and I6 is shown).

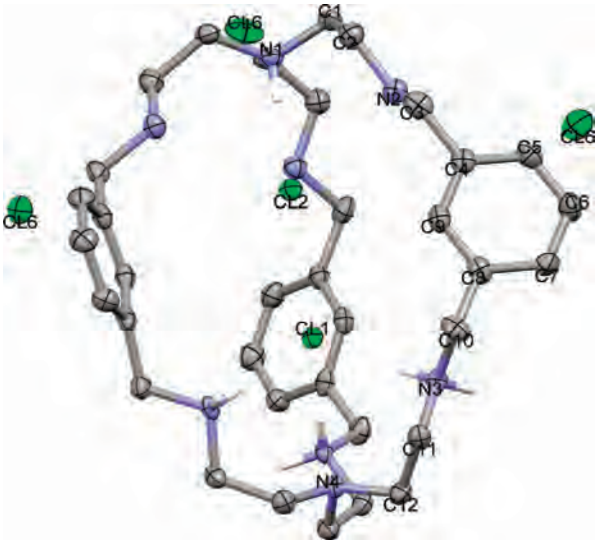

Figure 4. ORTEP diagram with atom numbering for one of the $[H_4\mathbf{L}^2]^{4+}$ in the asymmetric unit with the encapsulated and surrounding chlorides (40%probability factor for the thermal ellipsoids and only the hydrogens attached to the protonated nitrogen atoms are shown in the figure for clarity). Average $N_{bridgehead}-N_{bridgehead}$ distance = 9.761 Å.

$\mathbf{L}^2\cdot$MeOH). Because of the flexibility of the cryptand structure, after hexaprotonation the $[H_6\mathbf{L}^2]^{6+}$ moiety undergoes compression along the bridgehead nitrogen atoms, thus the cavity bulged in the other direction and made effective binding with the encapsulated iodide.

In an attempt to understand various intra- and intermolecular interactions between the $[H_6\mathbf{L}^2]^{6+}$ moiety with the surrounding anions and lattice water molecules, we have analyzed the packing and various weak molecular interactions in detail. Figure 3 represents the various molecular interactions of the hexaprotonated cryptand with the surrounding iodide anions and lattice water molecules. Except I4, all four iodide anions, surrounding the cryptand moiety are involved in various hydrogen bonding interactions. Thus, I2 is involved in intermolecular $C-H\cdots I^-$ interactions with the methylenic hydrogen atom H15A and one intermolecular $(N-H)^+\cdots I^-$ contact with the ammonium hydrogen atom H6B, respectively, at a $C\cdots I^-$ distance of 3.935 Å and a $N\cdots I^-$ distance of 3.538 Å where $\angle C-H\cdots I$ and $\angle N-H\cdots I$ are 162 173°. Whereas, I3 is involved in one strong intermolecular $N-H\cdots I^-$ contact with amino hydrogen H3B ($N\cdots I$ distance 3.4796 Å and $\angle N(3)-H(3B)\cdots I = 178°$). Disordered iodide ion I5 is involved in three hydrogen bonding contacts (one $(N-H)^+\cdots I^-$ and two $C-H\cdots I^-$ interactions) with H8A, H14A, and H22B, whereas I6 is involved in one intermolecular $(N-H)^+\cdots I^-$ contact with amino hydrogen H5B ($N(8)\cdots I(5) = 3.4853$, $\angle N(8)-H(8A)\cdots I(5) = 169°$; $C(14)\cdots I(5) = 3.9657$ Å, $\angle C(14)-H(14A)\cdots I(5) = 166°$; $C(22)\cdots I(5) = 3.766$ Å, $\angle C(22)-H(22B)\cdots I(5) = 132°$, $N(5)\cdots I(6) = 3.7558$, $\angle N(5)-H(5B)\cdots I(6) = 150°$). Even though the hydrogen atoms attached to water molecules could not locate from the difference Fourier map, all the four water molecules act as an acceptor in $(N-H)^+\cdots O$ interactions with the protonated amino nitrogen atoms. Details of these $N-H\cdots O$ interaction with symmetry code are given in the hydrogen bonding table. All the lattice water molecules are involved in short contacts with the iodide ions, where the water hydrogen atoms may be acting as donors. Thus O1 makes short contacts with I6 ($O1\cdots I6 = 3.397$ Å) oxygens, O2 with I1 ($O2\cdots I1 = 3.372$ Å), O3 with I5 ($O3\cdots I5 = 3.408$ Å), and O4 in a bifurcated short contact with I4 at distances of 3.398 and 3.205 Å, respectively. The packing diagram viewed down the *a*-axis with various H-bonding interactions is depicted in the Supporting Information, which shows that the hexaprotonated cryptand moiety along with the various molecular interactions are aligned along *b*-axis in layers in *bc*-plane.[18]

Description of the Crystal Structure, $[H_4\mathbf{L}^2(HCl_2)]3Cl\cdot nH_2O$ (3). X-ray crystallographic analysis shows that the compound **3** crystallizes in the cubic space group $P2_13$ with two independent tetraprotonated $\mathbf{L}^2$ moieties $(H_4\mathbf{L}^2)^{4+}$, counteranions, along with water molecules as solvent of crystallization. As depicted in the Figure 4, each $(H_4\mathbf{L}^2)^{4+}$ moiety in the asymmetric unit is associated with five Cl^-, in which two of them are inside the cavity and three chlorides (which are symmetrically disposed surrounding the cryptand) are outside. To compensate for the one extra negative charge in the tetraprotonated receptor, one proton per $(H_4\mathbf{L}^2)^{4+}$ moiety must be available in the crystal system, for which we could not locate the hydrogen atom from the difference Fourier map. The lattice water hydrogen atoms also could not be located from the difference Fourier map. Although the data collection for the compound is carried out under liquid-nitrogen temperature conditions (100 K), in addition to the twelve located water molecules in the lattice, the presence of residual electron density indicated some more lattice water molecules, which are highly diffused, and the SQUEEZ program is used to eliminate the contribution from these atoms for the structure.

The crystal structure of the compound revealed a high degree of symmetry. Cl1, Cl2 and Cl3, Cl4 are encapsulated inside the $(H_4\mathbf{L}^2)^{4+}$moieties present in the asymmetric unit, which occupy the special positions with C_3 symmetry. Both the $(H_4\mathbf{L}^2)^{4+}$moieties also possess 3-fold symmetry, with the

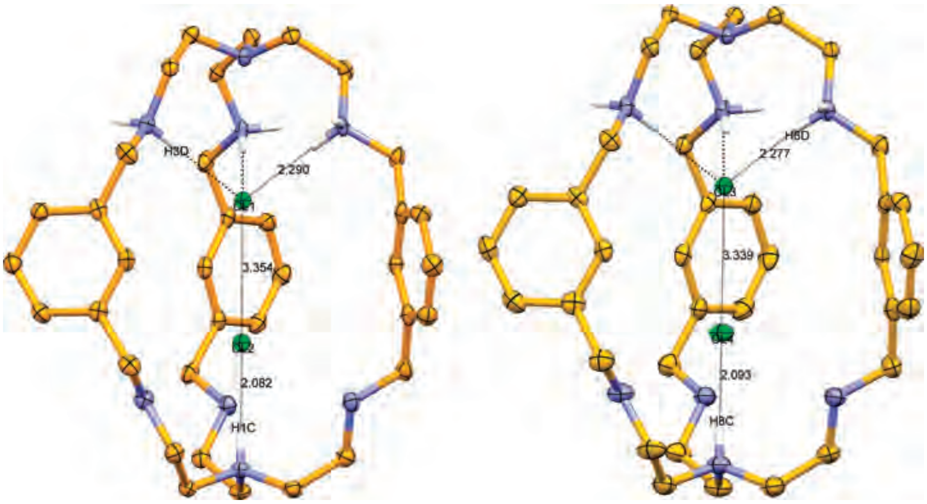

Figure 5. ORTEP diagram depicting the interactions of the encapsulated halides with the $[\mathrm{H_4}\mathbf{L}^2]^{4+}$ moieties present in the asymmetric unit.

C_3 axis bisecting the apical nitrogen atoms and the encapsulated chlorides (N1, H1C, Cl1, Cl2, and N4) for the first and (N5, Cl3, Cl4, N8, and H8C) second molecules. Therefore, Cl1 and Cl2, which are encapsulated within the cryptand cavity, are positioned exactly in the plane of N1, H1C, N4, and are involved in a linear orientation within the cavity (Figure 4). A similar mode of arrangement is also observed in the case of second $(\mathrm{H_4}\mathbf{L}^2)^{4+}$ moiety with Cl3 and Cl4 encapsulation. Even though, the conformation of the $(\mathrm{H_4}\mathbf{L}^2)^{4+}$ moieties are almost identical, intramolecular N−H···Cl− interaction distances show slight variation. Bridgehead nitrogen atoms N1 and N8 of both molecules are protonated (N1−C1 = 1.524(4) Å, N8−C24 = 1.522(5) Å), whereas N4 and N5 bridgehead nitrogen atoms are nonprotonated (N4−C12 = 1.473(4) Å, N5−C13 = 1.487(9) Å). Upon analysis of the N−C distance of bridgehead nitrogen centers of $\mathbf{L}^2$, $\mathbf{L}^1$, and most of their different hexaprotonated salts reported in literature; it is also observed that in case of nonprotonated bridgehead nitrogen center, average N−C distance ranges from 1.46 to 1.48 Å.[3,4,8b,c,e,18,20] In cases of bridgehead nitrogen atom's protonation, the average bridgehead N−C distance ranges from 1.50 to 1.51 Å.[6,8g] In addition to the bridgehead nitrogen atoms N1 and N8, secondary amino nitrogen atoms N3 and N6 from symmetrically disposed strands of both the molecules in the asymmetric unit are also protonated with the average N−C distance 1.50 Å account for the tetraprotonation in each ligand moiety.

Figure 5 shows the various intramolecular interactions between the chlorides with cryptand moiety for both the molecules present in the asymmetric unit. Thus, Cl1 is involved in three N−H···Cl$^-$ interactions with the amino hydrogen H3D from the symmetrically disposed C_3 arms of the cryptand. These hydrogen bonding interactions are N3−H3D···Cl1/H3D···Cl1 = 2.29 Å, N3···Cl1 = 3.190(3) Å, ∠N3−H3D···Cl1 = 178°. Cl2 is involved in only one strong N−H···Cl− interaction with the protonated apical amino hydrogen H1C (N1−H1C···Cl2/H1C···Cl2 = 2.08 Å, N1···Cl2 = 2.993 Å, ∠N1−H1C···Cl2 = 180°). A similar mode of binding is observed in the encapsulated Cl3 and Cl4 with the second receptor moiety, having a slight deviation in the H-bonding parameters. These pertinent N−H···Cl− interactions are N6−H6D···Cl3/H6D···Cl3 = 2.28 Å, N6···Cl3 = 3.170(3) Å, ∠N6−H6D···Cl3 = 172° and N8−H8C···Cl4/H8C···Cl4 = 2.09Å, N8···Cl4 = 3.003(4) Å, ∠N8−H8C···Cl4 = 180°. In both of these encapsulated units, Cl1, Cl2 and Cl3, Cl4 are in a very short contact distances, Cl1···Cl2 = 3.354 Å and Cl3···Cl4 = 3.339 Å (Figure 5), which are less than the twice chloride ionic radii (r_{Cl^-} = 1.81 Å).[22] This indicates that the extra proton takes the position between the two closely situated negative charges as a curtain. This leads to the formation and encapsulation of $[\mathrm{HCl_2}]^-$ species inside the cavity of $(\mathrm{H_4L^2})^{4+}$. The structure of the anion [Cl−H−Cl]$^-$ has been determined in several salts.[13] The Cl···Cl separation ranges from 3.110 to 3.315 Å.[14,23] The slightly higher Cl···Cl separation observed in complex **3**, where the chlorides are encapsulated, is caused by the strong and linear N−H···Cl− interaction between the protonated apical nitrogen with one of the encapsulated Cl$^-$ (Cl2 and Cl4 of the different receptor moiety) and strong trifurcated hydrogen bonding interactions of other encapsulated chloride (Cl1 and Cl3 from different moiety).

Solution States Studies. The protonation constants of $\mathbf{L}^2$ are determined separately by Martell et al.,[8a] Nelson et al.,[18] and Bowman-James et al.[7b] In the Martell and Nelson studies, protonation of six secondary nitrogen centers of $\mathbf{L}^2$ are observed, whereas the bridgehead amines are undetectable. In the work of Bowman-James et al., protonation constants up to six are similar to the previously reported data,[8a,18] but they could also observe seventh protonation. These data show that in case of $\mathbf{L}^2$, after the protonation of six secondary nitrogen centers, bridgehead nitrogen atoms participate in protonation in their experimental conditions. In complex **2**, the crystal structure shows encapsulation of iodide in

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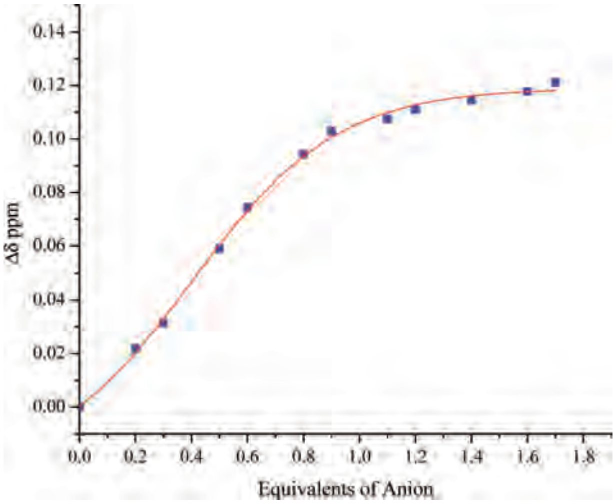

Figure 6. Chemical shift of the $-NH_2^+$ protons of $[H_6L^2]^{6+}$ **3** (20 mM) with increasing amount of n-$Bu_4N^+Cl^-$ in DMSO-d_6 at 25 °C.

$[H_6\mathbf{L}^2]^{6+}$, where all the protonation sites are at the secondary nitrogen centers. Surprisingly, in complex **3**, the protonation pattern in solid state is quite unusual, that is, three secondary nitrogen centers of one tren unit and one tertiary nitrogen center of the other tren unit is protonated, which encapsulates two chloride ions inside the cryptand cavity. To understand the solution binding of halides we have undertaken ^1H NMR solution studies in DMSO-d_6 with the hexatosylated cryptand $[H_6\mathbf{L}^2][OTs]_6$ and tetrabutylammonium salts of halides. It is important to mention that the binding constants for fluoride and oxyanions like perchlorate, nitrate, and sulfate with the $[H_6\mathbf{L}^2][OTs]_6$ were determined earlier.[3,7a,8c,20] To investigate the solution state binding of higher homologue halides with the $[H_6\mathbf{L}^2][OTs]_6$, we have protonated $\mathbf{L}^2$ with p-toluene sulfonic acid following literature procedure.[20] ^1H NMR studies revealed that addition of tetrabutylammonium chloride to $[H_6\mathbf{L}^2][OTs]_6$ in DMSO-d_6 showed a significant downfield shift of the $-NH_2^+$ resonances ($\Delta\delta = 0.12$ ppm), which indicates the participation of the receptor in anion binding via hydrogen bonding interactions of $-NH_2^+$ protons. Both the benzylic $-CH_2$ singlet and $-NH_2^+$ resonances are selected for NMR monitoring for bromide and iodide anions. There is no change in chemical shift of $-NH_2/-CH_2$ resonances upon addition of either Br^- or I^- as their tetrabutylammonium salts to the $[H_6\mathbf{L}^2][OTs]_6$ in DMSO-d_6 at 25 °C, although the solid-state X-ray crystal structure showed encapsulation of iodide inside the $[H_6\mathbf{L}^2]^{6+}$ when $\mathbf{L}^2$ is treated with HI.[7a] This could be the result of the interactions of tosyl groups with the $[H_6\mathbf{L}^2]^{6+}$ moiety, which is evident from the reported crystal structure of complex **4**,[20] and lower nucleophilicity of iodide and bromide anions than chloride. In case of solution study with tetrabutylammonium chloride and complex **4** in DMSO-d_6 titration data gave the best fit for 1:1 association of host to guest (Figure 6). It means that this solution study does not support information about a 2:1 chloride complex observed in crystal structure analysis of complex **3**, which was obtained upon crystallization from ethanol−water binary system. This may be the result of the difference in degree of protonation and sites of protonation in complexes **3** and **4**. The evaluation of titration data by EQNMR revealed that the host binds to the chloride anion with a binding constant (log K in M^{-1}) of 3.32. In case of fluoride guest binding to the $[H_6\mathbf{L}^2]^{6+}$ receptor (having TsO^- counterion) is higher (log $K = 3.64\ M^{-1}$) than the chloride guest.[7a] Although these data have no direct relevance to signify the solid state structural results obtained in this work, but this will definitely strengthen the halide binding properties of $\mathbf{L}^2$ in the hexaprotonated state.

Conclusions

We have succeeded in encapsulating higher homologue halides (I^- and HCl_2^-) inside the cavity of an azacryptand $\mathbf{L}^2$ in its different protonated states. Monotopic iodide recognition inside the cavity of $[H_6\mathbf{L}^2]^{6+}$ receptor in complex **2** is preferred over the ditopic recognition of a molecule of water and a fluoride ion in case of complex **1**. In **2**, the encapsulated iodide resides in distorted square pyramidal fashion with four intramolecular $(N-H)^+\cdots I^-$ interactions and one intermolecular $O-H\cdots I^-$ interaction from lattice water molecule (where hydrogen atom could not be located), although it is important to note that in case of halides four- and six-coordination numbers are common. Iodide being the largest member in the halide family, its encapsulation inside the $[H_6\mathbf{L}^2]^{6+}$ does not allow further entry of solvent guest. In complex **2**, the bridgehead nitrogen atoms distance is 8.349 Å, whereas this distance in **1** is 9.217 Å, and in $\mathbf{L}^2\cdot$MeOH the bridgehead nitrogen atoms distance is 10.913 Å. These results indicate that partial protonation (less than hexaprotonation) of $\mathbf{L}^2$ might stretch the cavity having bridgehead nitrogen atoms distance even greater than 9.217 Å to encapsulate two halide guests. In **3**, $\mathbf{L}^2$ is in tetraprotonated state having one bridgehead protonated nitrogen center in one side tren cap and three protonated secondary nitrogen centers on the other side of the tren cap, encapsulating the linear bichloride via four coordination with a distorted tetrahedral geometry. The resulting average distance between bridgehead nitrogen atoms in $(H_4\mathbf{L}^2)^{4+}$ receptor is 9.761 Å for the two molecules present in the asymmetric unit. This fine-tuning of the cavity dimension upon lowering the degree of protonation on $\mathbf{L}^2$ helped us to succeed for encapsulation of two chloride ions bridged by a proton.

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Supporting Information Available: Three crystallographic files in CIF format of complexes $\mathbf{L}^2$, **2**, and **3**, a table of hydrogen bonding parameters, and packing diagrams. This material is available free of charge via the Internet at http://pubs.acs.org.

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