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Encapsulated chloride coordinating with two *in-in* protons of bridgehead amines in an octaprotonated azacryptand

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Abstract

An encapsulated chloride in a thiophene-based cryptand is bridged with the two *in-in* protons of tertiary amines with a N…Cl^- distance of 3.048(3) Å, similar to that observed in the chloride complex of Park and Simmons' *katapinand*.

Nearly forty years ago, anion coordination chemistry emerged with the discovery by Park and Simmons of diazabicyclic compounds, known as *katapinands*.[1] These compounds were shown to form inclusion complexes with halide anions by hydrogen bonding interactions in acidic solution. Time-dependent NMR studies suggested that the protons on the nitrogen atoms of the ligand H_2**[L1]**$^{2+}$ changed their direction from *out-out* to *in-in* conformation in the presence of chloride anion. Seven years later of this discovery, Bell *et al.* isolated crystals of **L1** in the presence of hydrochloric acid in water, thereby confirming by X-ray structure analysis that one chloride was encapsulated in the cavity.[2] The anion was located along the axis of two apical NH groups with N^+…Cl^- distance of 3.10(1) Å, where the two protons are oriented with *in-in* conformation.

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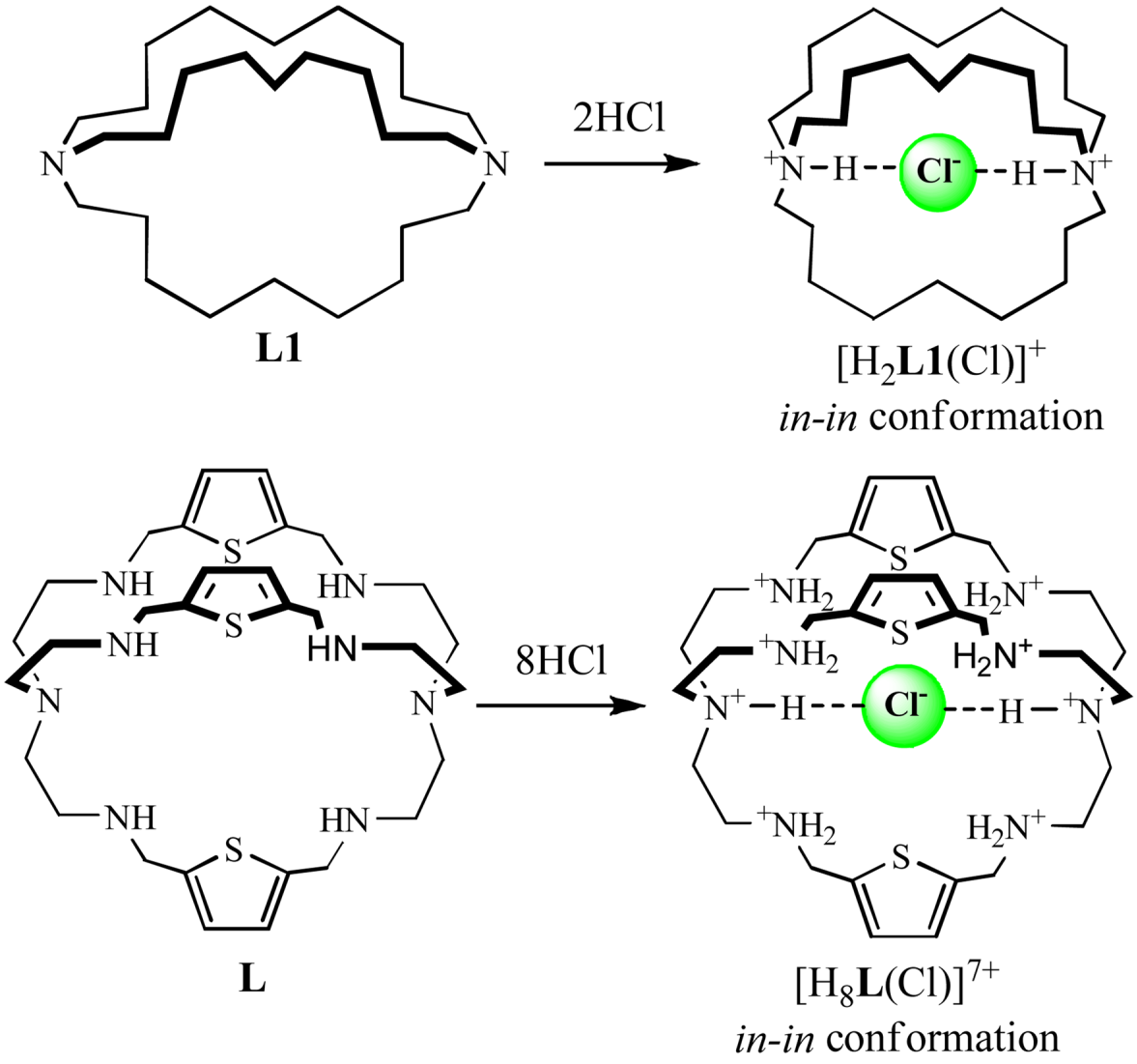
†Electronic Supplementary Information (ESI) available: ^{1}H NMR titration spectra and details of the Job plot in pdf format. See DOI: 10.1039/b000000x/



During the period of last thirty years, substantial progress has been made on anion binding with polyammonium-based receptors,[3] particularly with the Schiff based derived[4] biclyclic cryptands containing rigid spacers, e.g., *m*-xylyl[5] and *p*-xylyl,[6] furan[7] and pyridine[8] in both solution and solid states. This type of ligands provides a well defined cavity which is often suitable for hosting a spherical halide anion. For example, Bowman-James *et al.* reported that an hexaprotonated azacryptand containing *m*-xylyl was capable to encapsulate one fluoride and one water molecule in its cavity.[5c] In a recent work of Ghosh *et al.*, this ligand was shown to form a monotopic complex with iodide, and a ditopic complex with chloride.[5d] The *p*-xylyl analogue with a larger cavity was found to form a tritopic (cascade) complex with two fluorides bridging with a water molecule,[6a] but it was shown to complex chloride and bromide with both ditopic6b and monotopic6c binding modes in the solid phase. The internal anionic guest described above, however, binds to the secondary amino groups in the linking arms of macrocycles. To the best of our knowledge, there has been no structural report that an encapsulated anion is bridged with only protonated bridgehead nitrogens in the presence of secondary amines, unless the protonation ability of the latter sites is blocked by a protecting group, e.g., tosyl9 or imidazole group.[10] Herein we report the structural evidence of an encapsulated chloride that is coordinated with *only* two *in-in* protons on bridgehead nitrogens

in an unprotected octaazacryptand, showing a similar *in-in* conformation observed in the chloride complex of Park and Simmons' *katapinand*.

The cryptand **L** was first synthesized by Nelson as dicopper and disilver complexes[11] and later by Fabbrizzi as dinuclear copper complex.[12] To our knowledge, the free ligand has not been previously investigated for anion binding. In an effort to examine the influence of linking spacers on anion binding, we prepared the ligand **L**[13] from high dilution condensation of tren and 2,5-thiophenedicarboxaldehyde followed by reduction using the method that was employed to synthesize other cryptands.[4] The chloride complex was obtained by dissolving **L** (20 mg) in methanol (2 mL) and adding 6N HCl (100 μL). The white precipitate which formed was redissolved in methanol with a few drops of water. Crystals suitable for X-ray analysis were obtained from slow diffusion of methanol.

Single crystal analysis reveals that the crystal is hexagonal, and the molecule has its full C_{3h} symmetry in the crystal.‡ In the complex, all eight nitrogen atoms are protonated and the charges are balanced by eight chloride anions. Fig. 1 shows the perspective views looking into the cavity (**A**) and down the three-fold axis (**B**). The macrocyclic moiety contains a 3-fold rotation axis and exhibits a remarkable anion chelating geometry in which the protons on the terminal nitrogen atoms are pointed toward the cavity center with *in-in* conformation. As shown in the crystal views, one chloride is linearly coordinated to both axial NH groups, and located at the midpoint of the two bridgehead nitrogen atoms with N…Cl^- distances of 3.048(3) Å, half the N…N distance, 6.096(4) Å. The N…Cl^- distance is much shorter than the sum of the Van der Waals radii of nitrogen and chloride atoms, 3.30 Å[14] indicating strong hydrogen bonding interactions.

Although the encapsulated chloride in $[H_8\mathbf{L}]^{8+}$ is encrypted by a highly positively charged cage, surprisingly the coordination pattern is similar to that observed in the *katapinand* **L1**, where the chloride was bound at the center of the two axial nitrogens with N…N = 6.2 Å as compared with N…N = 6.096(4) Å in $[H_8\mathbf{L}(Cl)]^{7+}$. The encapsulated chloride in $[H_8\mathbf{L}]^{8+}$ does not form a hydrogen bond with the secondary amine protons, and is equidistant (4.886(3) Å) from the six nitrogen atoms. Through the hydrogen bonding interactions with axial protons, the internal chloride strongly pulls the terminal nitrogen groups towards the cavity center. As a result, all the secondary nitrogen groups move away from the central anion. However, six out of seven extracavity chlorides are singly coordinated with the secondary nitrogen atoms with N…Cl distance of 3.0425(17) Å (Fig. 2). The remaining chloride does not interact with the macrocycle and is located at 5.551 Å from the nearest nitrogen.

The structural results were confirmed by ^{1}H NMR studies in D_2O at pH 2, in which hexatosylated salt of **L**[15] (2 mM) was titrated with an increasing amount of NaCl solution (20 mM), providing the best fit for a 1:1 binding model (Fig. 3), yielding a log *K* 3.60.[16] The 1:1 stoichiometry of the complex was further confirmed by the Job plot, showing a maximum at the 0.5 mole fraction of **L** in D_2O at pH 2 (see supplementary information). The addition of chloride anion to the ligand solution at pH 4.5, however, did not result in an appreciable change in proton signals. While measured at pH 2, the methylene protons (3.17 ppm) adjacent to tertiary amines were shifted downfield by 0.10 ppm in the presence of one equivalent of anion. Very little change was observed in the chemical shift of other protons under the same conditions. These results suggest that the binding occurs when the tertiary amines are protonated, as expected at the low pH. A similar binding pattern was reported previously for

‡Crystal data: For $[H_8\mathbf{L}(Cl)]Cl_7\cdot 2.5H_2O$: $C_{30}H_{61}N_8S_3Cl_8O_{2.5}$, M = 953.65, crystal size 0.30 × 0.25 × 0.20 mm^3, hexagonal, $P6_3/m$, a = 12.7445 (10), c = 19.393 (2) Å, V = 2727.9 (4) Å^3, Z = 2, d_{calc} = 1.161 g cm^{-3}, T = 100.0 (5) K, Nonius KappaCCD diffractmeter, μ(Mo−K α) = 0 . 5 6 mm^{-1}, 2241 independent reflections (1864 observed), 77 parameters, R_{int} = 0.028, $R[F2>2\sigma(F2)]$ = 0.039, $wR(F^2)$ = 0.100. CCDC 710863.

a tiny cryptand in chloride binding at pH 2.5.[17] The solution studies thus indicate a direct bond between the NH of the tertiary amines and the encapsulated species, as seen in the X-ray structure. The calculated binding constant in **L** is comparable to that observed in the bigger *p*-xylyl analogue with a log *K* of 3.37, which was measured at pH 5.[6b]

In conclusion, by X-ray crystallography we have shown that an octaprotonated ligand **L** encapsulates a single chloride in its cavity though hydrogen bonding interactions with two NH protons on tertiary amines, adopting an '*in-in*' conformation that was seen in the first synthetic anion receptors '*katapinands*' in the chloride binding. In the chloride complex of $H_8L(Cl)]^{7+}$, the encapsulated chloride anion is linearly coordinated with the two bridgehead protons, *not* to the protons on secondary amines. The binding pattern of this ligand differs from its analogues, e.g. *m-xylyl* cryptand in nitrate5a,b or fluoride binding,[5c] *p-xylyl* cryptand in halide binding6b,c and furan cryptand in perchlorate binding,[7] in which the secondary NH donor groups are involved in binding process. But in the present structure, the protons on the secondary amines point outside the cavity and are involved in coordinating external chlorides. We are currently investigating the binding mechanism, and selectivity aspects of this and related ligands which will be reported elsewhere.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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13. The ligand **L** was prepared from high dilution condensation of tren and 2,5-thiophenedicarboxaldehyde followed by diborane reduction using the literature method[4]. A solution of *tris*(2-aminoethyl)amine (1.00 g, 6.84×10^{-3} mol) in 200 mL of CH_3OH and 2,5-thiophenedicarboxaldehyde (1.44 g, 10.26×10^{-3} mol) in 200 mL of CH_3OH were added dropwise to 400 mL of CH_3OH over 3 h. The resulting mixture was stirred at room temperature for 24 h and the solvent was evaporated under reduced pressure. The oily Schiff base product was redissolved in 100 mL of CH_3OH and $NaBH_4$ (1.73 g, 45.7 mmol) was added. After stirring at room temperature for 24 h, the solvent was removed in vacuo. The resulting yellowish residue was dissolved in 1 M a q N a O H solution (100 mL), and the aqueous phase was extracted by CH_2Cl_2 (3×50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give a light yellowish oil. The crude product was purified by column chromatography (neutral alumina, 2% CH_3OH in CH_2Cl_2). Yield: 0.85 g, 40%. FAB-MS: *m/z* 617 $[H\mathbf{L}]^+$. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): 2.61 (t, 12H, NCH_2), 2.72 (t, 12H, NCH_2CH_2), 3.85 (s, 12H, $ArCH_2$), 6.62 (d, 6H, Ar*H*). Anal. Calcd. for ($C_{30}H_{45}N_8S_3$): C, 58.40; H, 7.84; N, 18.16. Found: C, 58.53; H, 7.97; N, 18.61.
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15. The protonated ligand, $H_6\mathbf{L}$·6Ts, was prepared by reacting 100 mg **L** with 8-fold *p*-toluenesulfonic acid in methanol. The addition of diethyl ether resulted in a white microcrystalline product that was filtered and washed by diethyl ether. The ligand was found to be hexaproptonated as supported by NMR and elemental analysis. Yield: 85 mg, 40 %. ^{1}H NMR (300 MHz, D_2O, TSP): δ 2.32 (s, 18H, CH_3,), 2.69 (t, 12H, NCH_2,), 3.05 (t, 12H, NCH_2CH_2), 4.31 (s, 12H, $ArCH_2$), 7.10 (d, 6H, Ar*H*), 7.29 (d, 12H, $TsCH_2$,), 7.60 (d, 12H, $TsCH_2$,). Anal. Calcd. for ($C_{72}H_{90}N_8S_9O_{18}$): C, 52.60; H, 5.52; N, 6.82. Found.: C, 52.90; H, 5.45; N, 6.55.
16. Binding constants were obtained by ^{1}H NMR (300 MHz Bruker) titrations of $H_6\mathbf{L}$ · 6Ts with NaCl in D_2O at pH 2. Initial concentrations were $[\text{ligand}]_0$ = 2 mM, and $[\text{anion}]_0$ = 20 mM. Sodium salt of 3-(Trimethylsilyl)propionic-2,2,3,3,-d4 acid (TSP) in D_2O was used as an external reference in a capillary tube. The pH was adjusted with a concentrated solution of TsOH and NaOH in D_2O. Each titration was performed by 12 measurements at room temperature. The association constant *K* was calculated by fitting of several independent NMR signals with a 1:1 association model using Sigma Plot software, from the following equations: $\Delta\delta = ([A]_0 + [L]_0 + 1/K - (([A]_0 + [\mathbf{L}]_0 + 1/K)_2 - 4[\mathbf{L}]_0[A]_0)^{1/2}) \Delta\delta max/2[\mathbf{L}]_0$ (where **L** = ligand and A = chloride). Error limit in K was less that 15%.
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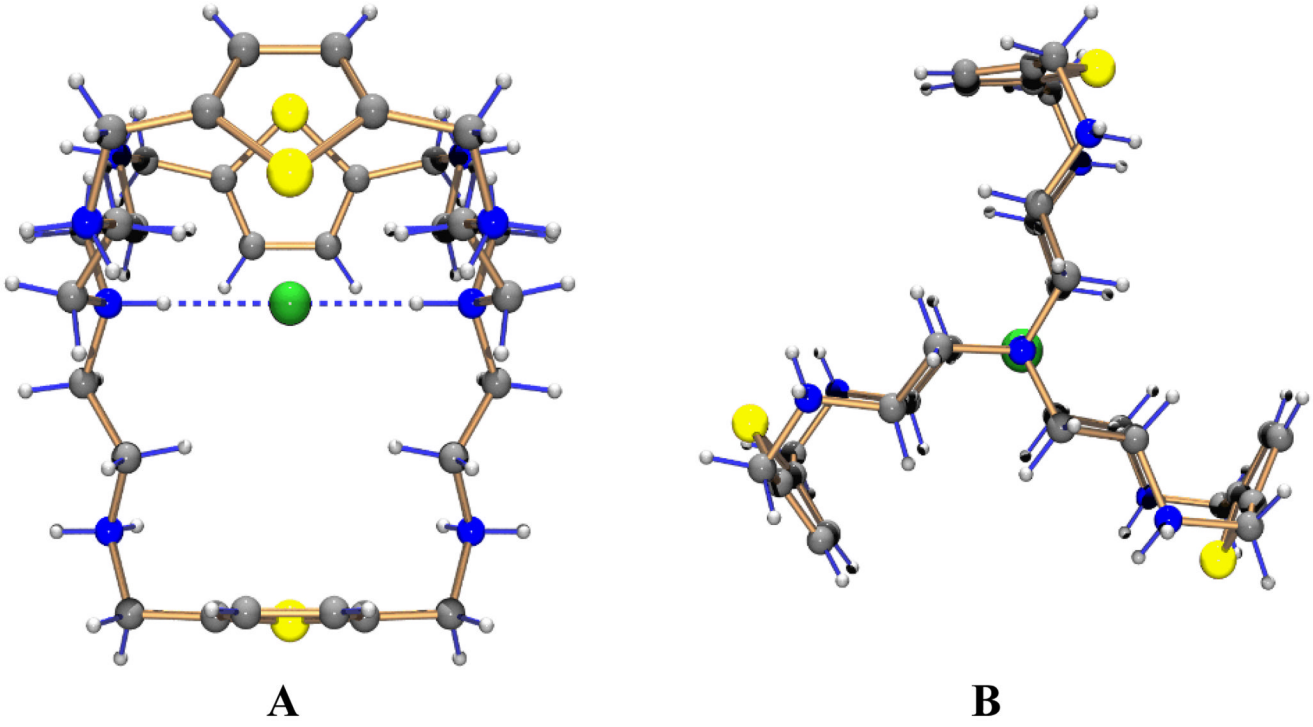

Fig. 1.
Perspective views of $[H_8\mathbf{L}(Cl)]^{7+}$: (**A**) Side view. (**B**) 3-fold axis view (seven external chloride anions and water molecules of crystallization are omitted for clarity).

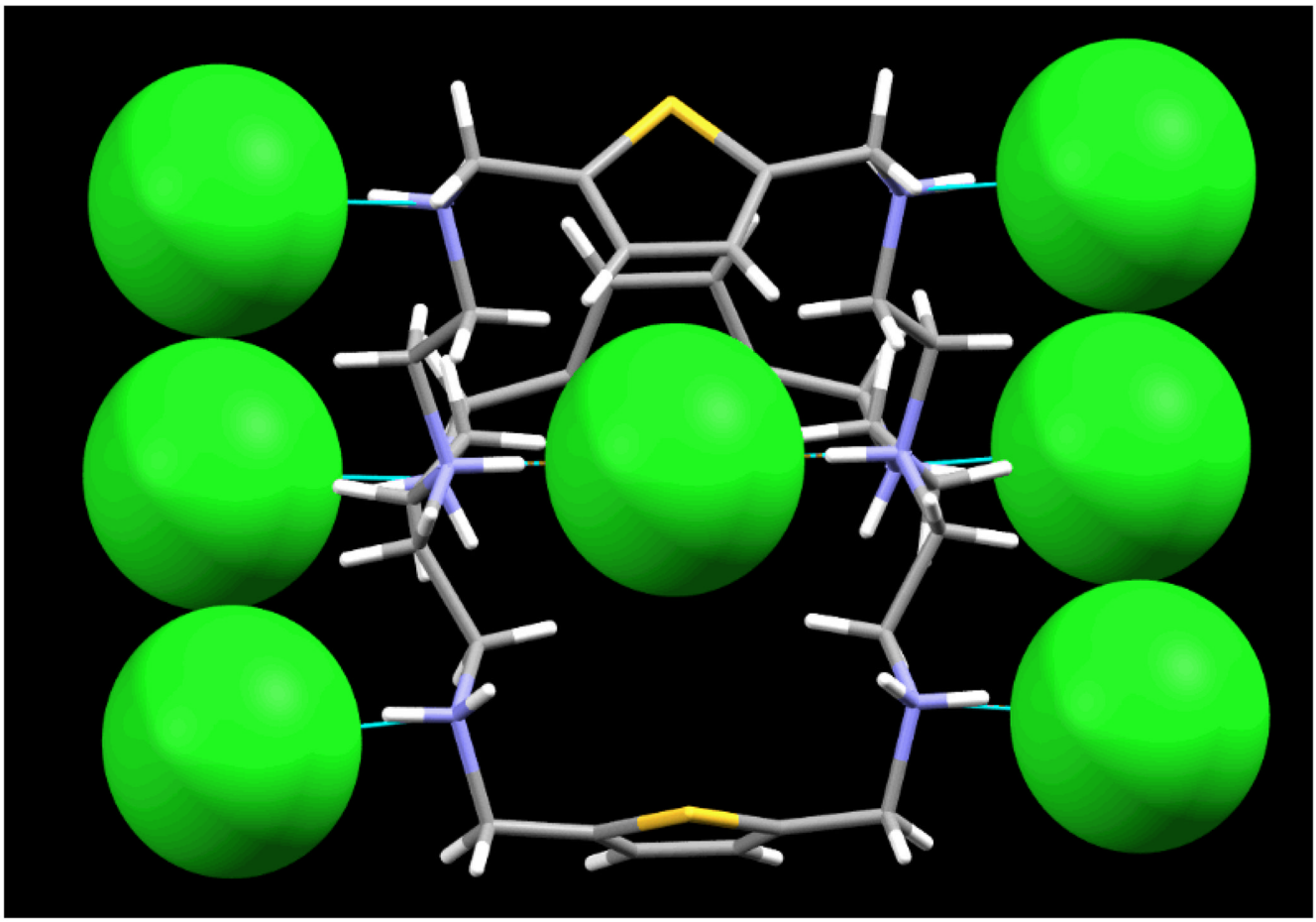

Fig. 2.
Space filling views of the coordinated internal and external chlorides in $[H_8\mathbf{L}(Cl)](Cl)_6^+$ motif. The cryptand is shown in capped sticks.

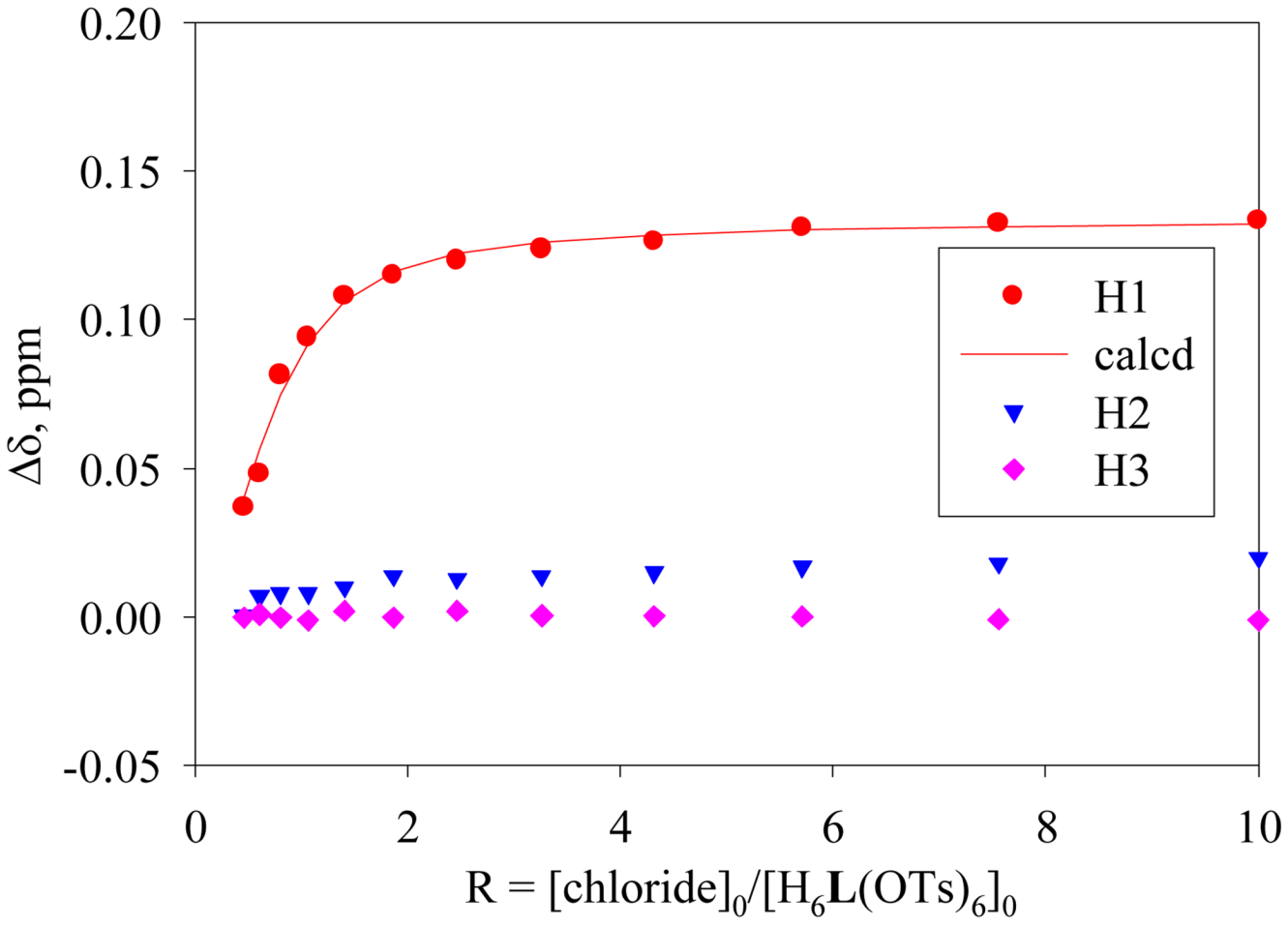

Fig. 3.

^{1}H NMR titration curves for chloride binding with H_6**L**$(OTs)_6$ in D_2O at pH = 2. Net changes in the chemical shifts of NCH_2 (H1), NCH_2CH_2 (H2) and $ArCH_2$ (H3) are shown against the anion concentration.