Published in final edited form as:

Comments Mod Chem A Comments Inorg Chem. 2016 ; 36(6): 305–326. doi:
10.1080/02603594.2016.1171216.

Experimental and Theoretical Aspects of Anion Complexes with a Thiophene-Based Cryptand

Syed A. Haque, Musabbir A. Saeed, Afsana Jahan, Jing Wang, Jerzy Leszczynski, and Md. Alamgir Hossain

Department of Chemistry and Biochemistry, Jackson State University, Jackson, MS 39217

Graphical abstract

Abstract

Selective recognition of anions has received a tremendous attention in recent years because of their significant importance in biology and environment. This article highlights our recent research on a thiophene-based azacryptand that has been shown to effectively bind anions including iodide, bromide, chloride, nitrate and sulfate. Structural studies indicate that the ligand forms inclusion complexes with chloride and iodide. On the other hand, it forms cleft-like complexes with nitrate and sulfate, where three anions are bound between the cyclic arms. The ligand binds each anion with a 1:1 binding mode in water, exhibiting strong selectivity for sulfate; which is further supported by ESI-MS and DFT calculations.

Keywords

Anion receptor; host-guest chemistry; association constant; DFT calculation; binding energy

1. INTRODUCTION

Anion recognition with synthetic molecules has become a major field of research because of the critical role played by an anion in chemistry, biology and environment.^{1–3} The first synthetic anion receptors which are diazabicyclic compounds (known as *katapinands*) were discovered by Park and Simmons in 1968, showing inclusion complexes with halides through hydrogen bonding interactions from two *endo*-oriented protons on the bridgehead nitrogens.⁴ The encapsulation was further confirmed from the structural characterization of a chloride complex, where the anion was held within the cavity with two $\text{NH}\cdots\text{Cl}^-$ bonds.⁵ After this milestone discovery, a variety of anion receptors have been reported based on

different functional groups including amine,^{6,7} amide,^{8–11} thioamide,^{12,13} urea,^{14–16} thiourea,^{17,18} pyrrole,^{19–21} and indole.^{22–24} Among these receptors, amine-based receptors tend to bind anions strongly in solution and solid state.^{25–27} In particular, bi- or polycyclic multidentate ligands termed as *cryptands*, which were originally designed to encapsulate and discriminate cations and neutral molecules,²⁸ are also useful to form inclusion complexes exhibiting strong affinity and selectivity in an acidic medium.²⁹ The most common cryptant in the field of anion binding chemistry is azamacrobicyclic compounds.^{26–29} Because of the presence of amine groups, these compounds are capable to add up to eight positive charges under an acidic condition, thereby making them versatile to form complexes with anions *via* hydrogen bonding and electrostatic interactions. For example, an octaazacryptand with ethylene-chains reported by Lehn and coworkers was shown to be highly selective for fluoride with a binding constant in the range of 10^{10} to 10^{11} M⁻¹ in water.^{30,31} Structural characterization of the fluoride complex showed that the anion was encapsulated with a total of six NH...F⁻ bonds.³¹ Bowman-James and coworkers identified similar coordination for a larger chloride at low pH.³² A *m*-xylyl based cryptand was reported to encapsulate two nitrates in solid state,³³ while it was shown to bind one nitrate in solution.³⁴ The same ligand was also found to form a ditopic complex with one fluoride and one water,³⁵ as well as a monotopic complex with a larger iodide.³⁶ The *p*-xylyl analogue with a slightly larger cavity was reported to form a cascade complex with two fluorides bridged by one water.³⁷ However, with chloride or bromide it formed both a ditopic complex with one halide and one water³⁸ and a monotopic complex with one halide,³⁹ depending on crystallization conditions. This host was also shown to bind perchlorate and hydrogen sulfate in solid state.⁴⁰ The cryptands containing pyridine and pyrrole spacers were reported as effective hosts to bind carboxylate anions including oxalate, malonate, acetate and lactate.⁴¹ Steed and coworkers have reported a macrobicyclic azaphane, showing halide binding through C–H...X⁻ and N–H...X⁻ interactions.⁴² Recently, Guchhait and Mani synthesized a pyrrole-based diazacryptand which was specially suitable for selective binding of fluoride;⁴³ while penta- and tetra-azacryptands with expanded cavities were proven as effective anion receptors for larger inorganic anions.⁴⁴

We recently isolated an octahydrochloride complex of the cryptand L, in which a chloride was found to be encapsulated inside the cavity by two *in-in* protons of bridgehead nitrogens.⁴⁵ Upon further investigation on nitrate anions, it was shown to complex three nitrates in solid state.⁴⁶ In particular, the thiophene rings in the bridging chains can act as better electron-withdrawing groups than the corresponding aromatic analogues, thereby enhancing hydrogen bonding ability of the protons on ammonium groups. This assumption was further supported by the electrostatic potential surfaces of L calculated at the B3LYP/6-311G(d,p) level of theory (discussed later), showing the highest electron density on thiophene groups (Scheme 1). Herein is the highlight of the anion binding properties of the cryptand L, using ¹H NMR titrations, X-ray crystallography, mass spectrometry and DFT calculations.

2. RESULTS AND DISCUSSION

2.1. SYNTHESIS

The synthesis of L was readily accomplished from the Schiff base condensation of dialdehyde and tren, followed by the reduction with sodium borohydride.⁴⁷ The tosylate complex (**1**) was obtained from the recrystallization of $[\text{H}_6\text{L}]\cdot(\text{TsO})_6$ in water, while the chloride (**2**), iodide (**3**), nitrate (**4**) and sulfate (**5**) complexes were made by mixing of the free ligand with respective inorganic acids in water/methanol mixture. All the salts gave good quality of crystals from the slow evaporation of the solution. However, attempts to prepare crystals of the free ligand and other anions were unsuccessful. All the isolated crystals were fairly stable at room temperature, and were characterized by single crystal structure analysis.

2.2. NMR BINDING STUDIES

The binding properties of the ligand were investigated for different anions (Cl^- , Br^- , I^- , SO_4^{2-} and NO_3^-) by ^1H NMR titrations using the hexatosylated salt of L in D_2O at $\text{pD} = 2.0$. The composition of $\text{H}_6\text{L}\cdot 6\text{Ts}$ salt (Scheme 2) was confirmed by ^1H NMR showing the correct intensities of the respective protons on tosylate ions and cryptand moiety. The choice of hexatosylated $\text{H}_6\text{L}\cdot 6\text{Ts}$ salt in the NMR titration was due to assumption that the bulky tosylate groups would remain outside the cavity and would have poor interactions with the ligands.^{45,46} As shown in Figure 1, the addition of one equivalent of respective anion to $\text{H}_6\text{L}(\text{Ts})_6$ resulted in a significant downfield shift of NCH_2CH_2 (b) proton for all anions, allowing us to evaluate the binding constants by NMR titrations. The other aliphatic protons of NCH_2CH_2 (c) slightly shifted downfield only in the case of nitrate. On the other hand, the protons of ArCH_2 (a) shifted upfield in the presence of sulfate, chloride and bromide, while these protons shifted slightly downfield in the case of nitrate and almost remained unchanged for iodide. Such a contrast in the chemical shift of ArCH_2 (a) with nitrate and sulfate could be due to the structural as well as charge difference of these two anions.

Figure 2 and Figure 3 show two representative examples of ^1H NMR titration spectra obtained from the portion-wise additions of chloride and sulfate, displaying a gradual shift change in the aliphatic protons. There are also noticeable change in the chemical shifts of H_a and H_c during the titration of the ligand with sulfate and chloride (Figure 2 and Figure 3), further indicating the formation of the complexes in the solution. The changes in the chemical shift (H_b) of the ligand were plotted with the increasing amount of each anion at room temperature, giving the best fit for 1:1 binding model (Figure 4). The binding constants were determined from non-linear regression analysis of chemical shifts, showing strong affinity for sulfate ($\log K = 5.26$), and nitrate ($\log K = 4.32$). The ligand exhibited moderate binding affinity of 3.70, 3.65 and 3.55 and (in $\log K$) for chloride, bromide, and iodide, respectively (Table 1), which might be the reflection of the relative basicity of halides (chloride > bromide > iodide). The slightly larger *p*-xylyl analogue was found to complex chloride and bromide with the binding constants (in $\log K$) of 3.37 and 3.34, respectively, measured at $\text{pH} = 5$.³⁸ Clearly, the high binding of the sulfate to $[\text{H}_6\text{L}]^{6+}$ is due to the fact that the sulfate is the strongest basic species among the anions investigated as well as the presence of two negative charges, which interacts strongly with the cationic ligand *via*

hydrogen bonding and electrostatic interactions. This observation is also consistent with the results of DFT calculations displaying the highest binding energy for sulfate (discussed later). In a recent communication, we reported similar binding pattern of a furan-based hexaaza macrocycle for anions, where both hydrogen-bonding and electrostatic interactions play an important role in selective binding of sulfate in water.⁴⁹ The binding constant of L for nitrate anion is considerably higher than that found in *m*-xylyl (log K = 3.63) and furan (Log K = 3.74) analogues measured by ¹H NMR titrations,³⁴ which could be the effect of electron-withdrawing thiophene groups on aromatic rings as also demonstrated by DFT calculations (discussed later).

2.3. MASS SPECTROMETRY

Mass spectrometry can be employed as a direct method to identify non-covalent interactions in a gaseous phase.⁵⁰ We recently used ESI-MS to probe a sulfate complex with a thiophene-based monocycle⁵¹ and an octameric phosphate cluster with a tren-based amine.⁵² This is a direct method to examine the stability and stoichiometry of a complex in a gaseous state.

The ¹H NMR titrations indicated that the ligand formed a 1:1 complex with anions in water when the ligand was positively charged under acidic medium. In order to correlate the solution data, we applied an ESI-MS in positive ion detection mode using their anion salts in water and methanol mixture (1:1, v/v). All the peaks were designated on the basis of mass-to-charge ratios in the range of m/z 200 to 1000. As shown in Figure 5, each complex including chloride, iodide, nitrate or sulfate complex, provides a strong peak at m/z 617.3 that corresponds to the singly charged free ligand [HL]⁺ (the mass number of the neutral ligand is 616.3). Additional peaks were observed at m/z 653.3 for chloride complex, 745.2 for iodide complex, 680.3 for nitrate complex and 715.3 for sulfate complex, corresponding to [H₂L(Cl)]⁺, [H₂L(I)]⁺, [H₂L(NO₃)]⁺ and [H₃L(SO₄)]⁺, respectively. These peaks correspond to 1:1 complexes of the ligand with the respective anions, which are in agreement with the results of NMR titrations in solution. It is also noted that the relative abundance of [H₃L(SO₄)]⁺ is higher compared to other ligand-anion peaks, which is possibly due to the strong interaction of the sulfate with ligand. We also observed the 1:1 species for bromide complex. Although, this observation does not necessarily warrant to form an inclusion complex; the results from ESI-MS, however, suggest that the noncovalent interactions persist in the gaseous phase, and solution-phase complexes can be transferred into gas-phase complexes without disrupting the binding stoichiometry.

2.4. CRYSTAL STRUCTURE ANALYSIS

2.4.1. CHLORIDE COMPLEX—Single crystal X-ray diffraction analysis of the chloride complex reveals that it crystallizes as [H₈L(Cl)]Cl₇·2.5H₂O (**1**). The cryptand is fully protonated and adopts an ideal C_{3h} symmetry, with one chloride anion encapsulated within the cavity. This binding mode is thus consistent with a 1:1 binding observed in solution discussed in the preceding section. Figure 6 shows the perspective view of the complex looking into the cavity. The encapsulated chloride sits at the center of the cavity, being bonded with the two bridgehead ammonium groups with an equidistance (NH⁺⋯Cl[−] = 3.048(3) Å). The bridgehead protons are pointed to the center of the cavity, exhibiting an *in-in* conformation, as observed in Park and Simmons' *katapinands* – the first synthetic anion

receptor, where the chloride was held at the center of the two axial nitrogens with a distance of $\text{NH}\cdots\text{Cl}^- = 3.10(1) \text{ \AA}$.⁴ The cationic $[\text{H}_8\text{L}(\text{Cl})]^{7+}$ moiety is anchored by symmetrically arranged six chlorides that interact with secondary nitrogen atoms with an equal $\text{NH}\cdots\text{Cl}^-$ bond of $3.0425(17) \text{ \AA}$. In the complex of $[\text{H}_8\text{L}(\text{Cl})]^{7+}$, the distance between the bridgehead nitrogens is $6.096(4) \text{ \AA}$ which is just twice of the distance for $\text{NH}\cdots\text{Cl}^-$ ($3.048(3) \text{ \AA}$). In contrast, the encapsulated chloride is considerably far from the six secondary ammonium groups with equidistance of ($4.886(3) \text{ \AA}$). Through the hydrogen bonding interactions with axial protons, the internal chloride strongly pulls the terminal nitrogens towards the cavity center. As a result, the secondary nitrogen groups lie at considerable distance from the central anion in order to avoid the steric strain of the cryptand. The remaining chloride anion ($\text{Cl}3$) lies at a considerable distance ($5.551 \text{ \AA}$) from the nearest secondary nitrogen.

2.4.2. BROMIDE COMPLEX—The complex crystallizes as $[\text{H}_6\text{L}(\text{Br})(3\text{H}_2\text{O})] \cdot \text{Br}_5 \cdot 12.33\text{H}_2\text{O}$ (**2**), where the cryptand is hexaprotonated with one bromide encapsulated within the cavity. The cationic unit sits on a crystallographic 3-fold rotation axis, whereas all six secondary nitrogen atoms are protonated. In contrast to the chloride complex shown in Figure 6, the encapsulated bromide in this complex is involved in three ($\text{NH}\cdots\text{Br} = 3.472(4) \text{ \AA}$) bonds with three secondary ammonium groups and three $\text{OH}\cdots\text{Br}$ with three water molecules. The X-ray structure of the hexaprotonated cryptand moiety with the encapsulated bromide is shown in Figure 7. Three water molecules are present in the clefts between the arms involving hydrogen bonding interactions with the encapsulated bromide and macrocyclic units. Other five bromides and the remaining water molecules present in the crystal lattice are outside the cavity. The bridgehead nitrogen atoms in the complex are unprotonated with a distance of $9.661 \text{ \AA}$, which is much longer than that observed in the chloride complex ($6.096(4) \text{ \AA}$). Such a large difference is due to the presence of protons on the bridgehead nitrogen atoms in the octaprotonated chloride complex, which are involved in coordinating the encapsulated chloride (Figure 6). In the bromide complex, the hexaprotonated cryptand moiety assumes an elliptical shape due to the elongated distance between the bridgehead nitrogen atoms. This observation suggests that depending upon the protonation and the nature of hydrogen bonding, the cavity could be readjusted to fit a specific guest.

2.4.3. IODIDE COMPLEX—The structure of the iodide complex ($[\text{H}_6\text{L}(\text{I})(3\text{H}_2\text{O})] \cdot \text{I}_5 \cdot 4.6\text{H}_2\text{O}$, **3**) is similar to that of the bromide complex. In the iodide complex, the cryptand is hexaprotonated, where the two tertiary nitrogen atoms are unprotonated. The cationic moiety adopts a non-crystallographic C_3 symmetric conformation. One iodide is found inside the cavity lying on the bridgehead N1-N14 axis. However, the encapsulated anion shifts slightly from the cavity center to one bridgehead nitrogen (N1), and the distance between the iodide and N1 is $4.127 \text{ \AA}$. The encapsulated iodide is bonded with three secondary ammonium groups of the N1-linked tren unit (Figure 8). The bridgehead nitrogens in **3** are separated by a distance of $9.645 \text{ \AA}$. This distance is comparable to that observed in the bromide complex ($9.661 \text{ \AA}$), but much longer than the corresponding distance in the chloride complex ($6.096(4) \text{ \AA}$), which could be the reflection of the absence of protons on bridgehead nitrogens. Three iodides (I3, I4 and I5) out of the remaining five external iodides are linked directly with secondary ammonium protons (N29, N24, and N4)

of the same tren unit. Two other iodides are found outside the cavity without any interaction with L. Three water molecules are bound to the other tren unit, resulting in a cyclic hydrogen bonding network through six $\text{NH}\cdots\text{O}$ bonds (2.74(7) Å to 2.91(7) Å). Two water molecules are involved in H-bonding with the internal iodide ($\text{NH}\cdots\text{I}^- = 3.37(5)$ and $3.44(5)$ Å).

2.4.4. NITRATE COMPLEX—The nitrate complex crystallizes as $[\text{H}_8\text{L}(\text{NO}_3)_3](\text{NO}_3)_5 \cdot (\text{HNO}_3) \cdot 5\text{H}_2\text{O}$ (**4**), where the ligand is octaprotonated, exhibiting the similar *in-in* conformation as observed in the chloride complex. The two bridgehead nitrogens in **4** are separated with a relatively short distance of 5.528(6) Å as compared to that in the chloride complex of L (6.096(4) Å). The *in-in* protons on N1 and N4 are involved in bridging three nitrates from both sides with the $\text{NH}\cdots\text{O}$ distances in the range of 3.099(10) to 3.370 (8) Å, forming two trifurcated^{53–55} H-bonds on the both tren units (Figure 9). Each nitrate is bridged with two hydrogen bonds donated by two bridgehead nitrogens and is located at almost perfect cleft position between each pair of arms. Because of the sharing of one H-bond donor by the three acceptors in the trifurcated complex, the observed bond distances in $\text{NH}\cdots\text{O}$'s are somewhat longer than those observed in the $\text{NH}\cdots\text{O}$ with a single acceptor.^{33,34} Except one proton on N7, which is involved in H-bonding with one cleft bound nitrate, all other protons on the remaining ammonium groups are pointed outward the cavity and are linked with external nitrates. The bridging oxygens are very close to each other 2.494(12), 2.602(11), and 3.000(8) Å, which are almost encapsulated in the cavity, and are positioned at the corner of a triangle bisecting the $\text{N}\cdots\text{N}$ axis. There are several examples reporting cleft bound anions stabilized by the secondary ammonium groups including nitrate,²⁷ perchlorate⁵⁶ and perrhenates⁵⁷ complexes of a pyridine-based cryptand. The other nitrates remain outside the cavity with one to four $\text{NH}\cdots\text{O}$ bonds in the range of 2.763(7) to 3.113(9) Å. The $\text{N}=\text{O}$ bonds in the nitrate groups range from 1.2041 (13) to 1.294 (8) Å, agreeing with an even negative charge distribution as expected.⁵⁸

2.4.5. SULFATE COMPLEX—The complex crystallizes as $2[\text{H}_6\text{L}(\text{CH}_3\text{OH})] \cdot 3\text{SO}_4 \cdot 6\text{HSO}_4 \cdot 11\text{H}_2\text{O}$ (**5**), with the two bridgehead nitrogen atoms unprotonated. However, the cavity is occupied by one molecule of neutral methanol (used for the crystallization) instead of sulfate. As shown in Figure 10, the encapsulated methanol is held in the cavity *via* two hydrogen bonds ($\text{N17H}\cdots\text{O1S} = 2.947(5)$ and $\text{N36H}\cdots\text{O1S} = 2.832(5)$ Å) with secondary amines of the one tren unit. The secondary ammonium groups of other tren unit are involved in coordinating one HSO_4^- and two SO_4^{2-} , each being located in a cleft between the arms *via* two $\text{NH}\cdots\text{O}$ bonds. The overall shape of the cavity is ellipsoidal and the bridgehead nitrogen atoms are separated by 9.457 Å. This distance is comparable to that for the bromide (9.661 Å) or iodide complex (9.645 Å), but longer than that observed for the chloride (6.096 Å) or nitrate (5.528 Å) complex. Even though the cavity is highly charged, the encapsulation of methanol was unanticipated in the presence of sulfates and water molecules. The present mode of binding of sulfate is quite different than the sulfate structure reported by Bowman-James and coworker with the *m*-xylyl analogue⁵⁹ and Nelson and coworker with the furan analogue,⁶⁰ where the sulfate was found to be encapsulated in both cases. As reported previously, the complex with an encapsulated methanol is energetically more favorable than that with water molecule.⁶¹ Similar encapsulation of methanol with

three cleft bound sulfate anions was also observed in the *p*-xylyl based cryptand.⁶¹ The remaining sulfate anions are involved in an extensive H-bonding network with water molecules outside the cavity.

We have presented structural aspects of five anion complexes including chloride, bromide, iodide, nitrate and sulfate complexes of the cryptand L. In the chloride complex ([H₈L(Cl)]Cl·2.5H₂O, **1**), one chloride sits at the center of the ligand cavity linking the two bridgehead amines *via* two NH···Cl⁻ bonds (3.048(3) Å). However, for both bromide ([H₆L(Br)(3H₂O)]·Br₅·12.33H₂O, **2**) and iodide ([H₆L(I)(3H₂O)]·I₅·4.6H₂O, **3**) complexes, the encapsulated anion is coordinated with three secondary ammonium groups (NH···Br = 3.472(4) Å and NH···I⁻ = 3.69(5) to 3.72(5) Å) and three water molecules. In each case, water molecules sit between the arms of the ligand *via* hydrogen bonding interactions with the encapsulated anion and other three secondary ammonium groups of the ligand. In the nitrate complex ([H₈L(NO₃)₃]·5NO₃·HNO₃·6H₂O, **4**), three nitrates are bridged in a cleft fashion to both *in-in* protons of the bridgehead amines *via* six NH···O bonds (3.099(10) to 3.370(8) Å), exhibiting two trifurcated hydrogen bonds. For the sulfate complex (2[H₆L(CH₃OH)]·3SO₄·6HSO₄·11H₂O, **5**), two sulfates and one hydrogen sulfate are bound in a cleft mode between the arms, where the cavity is occupied by a methanol molecule.

2.5. DFT CALCULATIONS

In order to understand the binding properties of L, density functional theory (DFT) calculations were carried out on its interactions with anions including Cl⁻, Br⁻, I⁻, SO₄²⁻ and NO₃⁻. The DFT approach through Becke's three parameter (B3) exchange functional along with the Lee-Yang-Parr(LYP) nonlocal correlation functional with an optimized weight of the exact HF exchange was applied in this study.⁶²⁻⁶⁴ The LanL2DZ pseudopotential basis set was applied for iodine. The standard valence triple zeta basis set, augmented with d-type polarization functions for heavy elements and p-type polarization functions for H, namely 6-311G(d,p),⁶⁵ was applied for all the other elements. The geometries of ligand-anion complexes H₆L(X) were fully optimized at the above described theoretical level. Due to the multiple charges carried out by anion-binding complexes, the Barone-Tomasi polarizable continuum model (PCM)⁶⁶ with the standard dielectric constant of water ($\epsilon = 78.39$) was also applied for the optimization of the systems in order to eliminate the strong static electronic interactions within the complexes. The local minima of the molecular structures both in gas phase and with PCM models on the considered potential energy surface were verified by the harmonic frequency analysis. All the calculations were carried out using Gaussian 09 package of programs.⁷⁴ The geometries of the considered models are similar in gas phase and in solvent. As depicted in Scheme 1, the optimized structure of [H₆L]⁶⁺ adopts a perfect *C*_{3h} symmetry calculated at the B3LYP/6-311G(d,p) level of theory,⁶⁵ showing the highest electron density on the sulfur of thiophene units and the most positive potential on the NH₂⁺ groups. This observation suggests that the thiophene groups act as electron-withdrawing groups, enhancing the binding ability of L for anions. In order to correlate binding strengths, the binding energy for each structure was calculated as $E_b = E(L) + E(A) - E(L + A)$ (where L = ligand, A = anion). After the inclusion of a chloride anion in the cavity, the *C*_{3h} symmetry of L remains in the optimized [H₆L(Cl)]⁵⁺ complex, as seen in the crystal structure of the chloride complex. The calculated binding

data for the complexation of L with anions is given in Table 2. The binding energy is predicted to be -371.8 kcal/mol for chloride ion in gas phase. However, this binding energy is mainly covered by the strong static electronic interactions between the L and the anions. In order to reveal the more realistic binding properties, the binding energies more suitable for the description for the models were obtained in solvent through the PCM model calculations. Hence, the binding between chlorine anion and $[\text{H}_6\text{L}]^{6+}$ is predicted to be -33.4 kcal/mol. The similar geometric structures are predicted for $[\text{H}_6\text{L}(\text{Br})]^{5+}$ and $[\text{H}_6\text{L}(\text{I})]^{5+}$, but there are weaker hydrogen bonds with longer atomic distances for the HBs (by $0.2 \sim 0.4$ Å). The binding energy using PCM model amount to -31.3 kcal/mol and -26.1 kcal/mol for $[\text{H}_6\text{L}(\text{Br})]^{5+}$ and $[\text{H}_6\text{L}(\text{I})]^{5+}$, respectively. Hence among the three halogen anions the chloride ion shows the strongest binding with $[\text{H}_6\text{L}]^{6+}$, which agrees with the experimental results performed by NMR titrations. For nitrate and sulfate complexes, each structure is characterized by a single anion locating in the cavity, which agrees with a 1:1 complex in solution observed by ^1H NMR titration studies.

Figure 11 shows the representative optimized structure of a 1:1 complex of $[\text{H}_6\text{L}]^{6+}$ with sulfate where the sulfate is fully encapsulated within the host's cavity. Interestingly, the encapsulated sulfate is H-bonded *via* six $\text{NH}\cdots\text{O}$ and two $\text{CH}\cdots\text{O}$ bonds, each oxygen of the sulfate being bonded with two hydrogen bonds. The involvement of $\text{NH}\cdots\text{O}$ and $\text{CH}\cdots\text{O}$ bonds for sulfate binding was previously reported in a furan-based macrocycle.⁶⁶ The hydrogen bonding distances of $\text{NH}\cdots\text{O}$ ($2.664 - 3.195$ Å) and $\text{CH}\cdots\text{O}$ (3.353 and 3.477 Å) are comparable to those observed in crystals.^{49,67} However, three cleft bound anions were seen in the crystal structures of both sulfate and nitrate complexes crystallized with additional water molecules. The calculated binding energies of $[\text{H}_6\text{L}(\text{NO}_3)]^{5+}$ and $[\text{H}_6\text{L}(\text{SO}_4)]^{4+}$ in solvent are -44.0 and -68.3 kcal/mol, respectively. As shown on Table 2, the binding energy of L for various anions are in the order of sulfate > nitrate > chloride > bromide > iodide, which fairly correlates with the experimental binding constants (Table 1), showing the highest binding affinity for sulfate. The observed data from the theoretical and spectroscopic studies, suggest that the ligand provides binding sites as electrostatic positive charges and acidic H-bonding donors in anion binding, thereby the binding trend of anions to L is influenced by the relative basicity of respective anions.⁶⁸

3. Experimental Section

3.1. Synthesis

L. The synthesis of free ligand L was carried out from the reaction of tris(2-aminoethyl)amine and 2,5-thiophenedicarboxaldehyde under high dilution conditions in CH_3OH , followed by diborane reduction, as reported earlier.⁴⁷ The protonated ligand, $[\text{H}_6\text{L}] \cdot (\text{TsO})_6$, was prepared by reacting L with 8-fold *p*-toluenesulfonic acid in methanol.⁴⁷

3.3. X-ray Crystallography

The crystallographic data and details of data collection for the crystals (**1** – **5**) are given in Table 1. Intensity data for **1**, **2** and **4** were collected using Nonius KappaCCD diffractometer, λ ($\text{MoK}\alpha$) = 0.71073 Å, at 90.0 (5) or 100.0 (5) K. For **1**, six sites (36 per macrocycle) with diffuse residual electron density $>0.5\text{e}\text{\AA}^{-3}$ were interpreted as indicative of solvent water

disordered outside the cavity. Attempts to model these sites as water O atoms with various populations were not very successful in revealing a reasonable hydrogen-bonding pattern nor providing a good fit to the diffraction data. Consequently, their contribution in the crystal was removed using SQUEEZE,⁶⁹ amounting to 99 electrons per unit cell. With $Z = 2$, this was approximately 2.5 H₂O molecules per macrocycle. For **4**, hydrogen atoms on the water molecules could not be reliably located, and were not included in the model. The nitrate ion containing N11 is disordered into two orientations, each of which was assigned half occupancy. The six N-O distances in the disordered nitrate were restrained to 1.25(2) Å. The water molecule nearest to the disordered nitrate, O6W, is also disordered into two sites separated by 1.81 Å. Their populations were constrained to sum to unity, and they refined to 0.638(13) and 0.362(13). Intensity data for **3** and **5** were collected using a diffractometer with a Bruker APEX ccd area detector and graphite-monochromated CuK α radiation ($\lambda = 1.54178$ Å).⁷⁰ The samples were cooled to 100(2) K. The structure was solved by direct methods and refined by full-matrix least-squares methods on F^2 .⁷¹ The positions of the hydrogens bonded to carbons were refined by a riding model, while those of hydrogens bonded to nitrogens were located on a difference map, and their positions were refined independently. Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atom displacement parameters were set to 1.2 times the isotropic equivalent displacement parameters of the bonded atoms.

Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 863934, 863935, 983552, 983553 and 1033622. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre (CCDC) via www.ccdc.cam.ac.uk/data_request/cif and are available free of charge upon request to CCDC, 12 Union Road, Cambridge, UK (fax: +44-(0)1223-336033, deposit@ccdc.cam.ac.uk).

3.4. NMR studies

Binding constants were obtained by ¹H NMR (500 MHz Varian) titrations of H₆L-6Ts with the anions (Cl⁻, Br⁻, I⁻, SO₄²⁻ and NO₃⁻) as their sodium salts in D₂O. The composition of H₆L-6Ts salt was confirmed by ¹H NMR as well as single crystal structure determination. All titrations were performed at pD = 2.0. The pD of the solution was adjusted with a concentrated solution of TsOH and NaOD. Initial concentrations were [ligand]₀ = 2 mM, and [anion]₀ = 20 mM. Sodium salt of 3-(trimethylsilyl)propionic-2,2,3,3-*d*₄ acid (TSP) in D₂O was used as an external reference in a sealed capillary tube. Each titration was performed by 15 measurements at room temperature, and repeated three times. The association constants (K) were calculated by fitting several independent NMR signals with a 1:1 association model using Sigma Plot.⁷² Error limit in K was less than 10% which was based on the standard deviation from three titrations for each anion.

3.5. DFT calculations

In order to understand the binding properties of L, density functional theory (DFT) calculations were carried out on anions including Cl⁻, Br⁻, I⁻, SO₄²⁻ and NO₃⁻. The DFT approach through Becke's three parameter (B3) exchange functional along with the Lee-Yang-Parr (LYP) nonlocal correlation functional with an optimized weight of the exact HF

exchange was applied in this study.^{62–64} The standard valence triple zeta basis set, augmented with *d*-type polarization functions for heavy elements and *p*-type polarization functions for H, namely 6–311G(*d,p*),⁶⁵ was applied. The geometries of ligand-anion complexes H₆L(X) were fully optimized at the above described theoretical level. The local minima of the molecular structures on the considered potential energy surface were verified by the harmonic frequency analysis. All the calculations were carried out using Gaussian 09 package of programs.⁷³

4. CONCLUSIONS

The results from the solution studies suggest that the ligand serves as an effective host for a wide range of anions including chloride, bromide, iodide, nitrate and sulfate in water. In particular, the strong selectivity was observed for both nitrate and sulfate over halide anions, while the ligand consistently shows a 1:1 binding mode for each of the anions studied. The binding stoichiometry in solution is fully consistent with the observation from ESI-MS with a positive mode, indicating that the non-covalent interactions have not been perturbed in the gaseous phase. However, in the solid state, the ligand forms a 1:1 inclusion complex with a spherical halide, and 1:3 complex with nitrate in a cleft fashion, which could be the effect of crystallization forces leading to the formation of crystals, and additional intermolecular interactions in the solid state. Even though the solid state binding modes are different in the chloride and nitrate complexes, the interesting feature is the participation of only two bridgehead protons in coordinating one chloride or three nitrates, even the ligand is fully protonated in the both cases. For the nitrate complex, two trifurcated hydrogen bonds are formed, which exist in natural systems including enzyme-peptides⁷⁴ and protein α -helices.⁷⁵ In the bromide or iodide complex, the encapsulated anion was also accompanied by three cleft bound water molecules bonded to three secondary ammonium groups, suggesting that water can readily be incorporated with protonated amines especially in the presence of weakly basic anion. The observed highest affinity of the ligand for sulfate as compared to other anions is the effect of both hydrogen bonding and electrostatic interactions.

Acknowledgments

FUNDING

The National Science Foundation is acknowledged for a CAREER award (CHE-1056927) to MAH. NMR core facility at Jackson State University was supported by the National Institutes of Health (G12MD007581). The computation work described in this paper was supported by the National Science Foundation under award number EPS 0903787.

REFERENCES

1. Bianchi, A., Bowman-James, K., García-España, E. Supramolecular chemistry of anions. New York: Wiley-VCH; 1997.
2. Gale PA, Gunnlauugsson T. Chem. Soc. Rev. 2010; 39:3595–3596.
3. Wenzel M, Hiscock JR, Gale PA. Chem. Soc. Rev. 2012; 41:480–520. [PubMed: 22080279]
4. Park CH, Simmons HE. J. Am. Chem. Soc. 1968; 90:2431–2433.
5. Bell RA, Christoph GG, Fronczek FR, Marsh RE. Science. 1975; 190:151–152.
6. Llinares JM, Powell D, Bowman-James K. Coord. Chem. Rev. 2003; 240:57–75.

7. Bazzicalupi C, Bencini A, Bianchi A, Borsari L, Danesi A, Giorgi C, Mariani P, Pina F, Santarellia S, Valtancolia B. Dalton Trans. 2006:5743–5752. [PubMed: 17146539]
8. Bondy CR, Loeb SJ. Coord. Chem. Rev. 2003; 240:77–99.
9. Hossain MA, Llinares JM, Powell D, Bowman-James K. Inorg. Chem. 2001; 40:2936–2937. [PubMed: 11399156]
10. Kang SO, Day VW, Bowman-James K. Org. Lett. 2009; 11:3654–3657. [PubMed: 19640003]
11. Begum R, Kang SO, Bowman-James K. Angew. Chem. Int. Ed. 2006; 45:7882–7894.
12. Hossain MA, Kang SK, Llinares LM, Powell D, Bowman-James K. Inorg. Chem. 2003; 42:5043–5045. [PubMed: 12924873]
13. Inoue Y, Kanbara T, Yamamoto T. Tetrahedron Lett. 2003; 44:5167–5169.
14. Amendola V, Fabbrizzi L, Mosca L. Chem. Soc. Rev. 2010; 39:3889–3915. [PubMed: 20818452]
15. Custelcean R. Chem. Commun. 2008:295–307.
16. Carroll CN, Berryman OB, Johnson CA, Zakharov LN II, Haley MM, Johnson DW. Chem. Commun. 2009:2520–2522.
17. Zhang Z, Schreiner PR. Chem. Soc. Rev. 2009; 38:1187–1198. [PubMed: 19421588]
18. Li A-F, Wang J-H, Wang F, Jiang Y-B. Chem. Soc. Rev. 2010; 39:3729–3745. [PubMed: 20737072]
19. Sessler JL, Camiolo S, Gale PA. Coord. Chem. Rev. 2003; 240:17–55.
20. Custelcean R, Delmau LH, Moyer BA, Sessler JL, Cho W-S, Gross D, Bates GW, Brooks SJ, Light ME, Gale PA. Angew. Chem. Int. Ed. 2005; 44:2537–2542.
21. Sessler JL, Gross DE, Cho W-S, Lynch VM, Schmidtchen FP, Bates GW, Light ME, Gale PA. J. Am. Chem. Soc. 2006; 128:12281–12288. [PubMed: 16967979]
22. Bates GW, Triyanti LME, Albrecht M, Gale PA. J. Org. Chem. 2007; 72:8921–8927. [PubMed: 17939724]
23. Chang K-J, Moon D, Lah MS, Jeong K-S. Angew. Chem. Int. Ed. 2005; 44:7926–7929.
24. Chang K-J, Chae M-K, Lee C, Lee J-Y, Jeong K-S. Tetrahedron Lett. 2006; 47:6385–6388.
25. Dietrich B, Lehn J-M, Sauvage JP. Tetrahedron Lett. 1969; 10:2889–2892.
26. McKee V, Nelson J, Town RM. Chem. Soc. Rev. 2003; 32:309–325. [PubMed: 14518184]
27. Hossain MA. Curr. Org. Chem. 2008; 12:1231–1256.
28. Lehn, JM. Supramolecular Chemistry: Concepts and Perspectives. VCH: Weinhiem; 1995.
29. Kang SO, Llinares JM, Day VW, Bowman-James K. Chem. Soc. Rev. 2010; 39:3980–4003. [PubMed: 20820597]
30. Dietrich B, Lehn J-M, Guilhem J, Pascard C. Tetrahedron Lett. 1989; 30:4125–4128.
31. Dietrich B, Dilworth B, Lehn J-M, Souchez J-P, Cesario M, Guilhem J, Pascard C. Helv. Chim. Acta. 1996; 79:569–587.
32. Hossain MA, Llinares JM, Miller C, Seib L, Bowman-James K. Chem. Commun. 2000:2269–2270.
33. Mason S, Seib L, Bowman-James K. J. Am. Chem. Soc. 1998; 120:8899–8900.
34. Hynes MJ, Maubert B, McKee V, Town RM, Nelson J. Dalton Trans. 2000:2853–2859.
35. Mason S, Llinares JM, Morton M, Clifford T, Bowman-James K. J. Am. Chem. Soc. 2000; 122:1814–1015.
36. Ravikumar I, Lakshminarayanan PS, Suresh E, Ghosh P. Inorg. Chem. 2008; 47:7992–7999. [PubMed: 18710222]
37. Hossain MA, Llinares JM, Mason S, Morehouse P, Powell D, Bowman-James K. Angew. Chem. Int. Ed. Engl. 2002; 41:2335–2338. [PubMed: 12203584]
38. Hossain MA, Morehouse P, Powell PD, Bowman-James K. Inorg. Chem. 2005; 44:2143–2149. [PubMed: 15792448]
39. Lakshminarayanan PS, Kumar DK, Ghosh P. Inorg. Chem. 2005; 44:7540–7546. [PubMed: 16212380]
40. Nelson J, Nieuwenhuyzen M, Pál I, Raewyn M, Town RM. Dalton Trans. 2004:229–235. [PubMed: 15356717]

41. Ilioudis CA, Tocher DA, Steed JW. *J. Am. Chem. Soc.* 2004; 126:12395–12402. [PubMed: 15453773]
42. Ravikumar I, Lakshminarayanan PS, Suresh E, Ghosh P. *Beilstein J. Org. Chem.* 2009; 5:1–8. [PubMed: 19259337]
43. Guchhait T, Mani G. *J. Org. Chem.* 2011; 76:10114–10121. [PubMed: 22059925]
44. Jana D, Mani G, Schulzke C. *Inorg. Chem.* 2013; 52:6427–6439. [PubMed: 23662741]
45. Saeed MA, Fronczek FR, Hossain MA. *Chem. Commun.* 2009:6409–6411.
46. Saeed MA, Fronczek FR, Huang M-J, Hossain MA. *Chem. Commun.* 2010; 46:404–406.
47. Wu H, Saeed MA, Hwang H-M, Zhao S, Liu Y-M, Hossain MA. *J. Phys. Org. Chem.* 2011; 24:1–5. [PubMed: 21218124]
48. Saeed MA, Wong BM, Fronczek FR, Venkatraman R, Hossain MA. *Cryst. Growth Des.* 2010; 10:1486–1488.
49. Rhaman MA, Ahmed L, Wang J, Powell D, Leszczynski J, Hossain M. *Org. Biomol. Chem.* 2014; 12:2045–2048. [PubMed: 24554233]
50. Kavallieratos K, Sabucedo AJ, Pau AT, Rodriguez JM. *J. Am. Soc. Mass Spectrom.* 2005; 16:1377–1383. [PubMed: 27035012]
51. Saeed MA, Fronczek FR, Powell DR, Hossain MA. *Tetrahedron Lett.* 2010; 51:4233–4236. [PubMed: 20640221]
52. Hossain MA, Iklán M, Pramanik A, Saeed MA, Fronczek FR. *Cryst. Growth Des.* 2012; 12:567–571.
53. Taylor R, Kennard O, Versichel W. *J. Am. Chem. Soc.* 1984; 106:244–248.
54. Steiner T. *Angew. Chem. Int. Ed.* 2002; 41:48–76.
55. Fabbrizzi L, Foti F, Taglietti A. *Org. Lett.* 2005; 7:2603–2606. [PubMed: 15957901]
56. McKee V, Morgan GG. *Acta Crystallogr. Sec. C.* 2003; 59:o150–o152.
57. Farrell D, Gloe K, Gloe K, Goretzki G, McKee V, Nelson J, Nieuwenhuyzen M, Pal I, Stephan H, Town RM, Wichmann K. *Dalton Transactions.* 2003:1961–1968.
58. Housecroft, A., Sharpe, AG. *Inorganic Chemistry*. 3rd. Prentice Hall; 2008. p. 450
59. Kang SO, Hossain MA, Powell D, Bowman-James K. *Chem. Commun.* 2005:328–329.
60. Nelson J, Nieuwenhuyzen M, Pal I, Town RM. *Dalton Trans.* 2004:2303–2308. [PubMed: 15278122]
61. Hossain MA, Saeed MA, Gryn'ova G, Powell DR, Leszczynski J. *CrystEngComm.* 2010; 12:4042–4044.
62. Becke AD. *Phys. Rev. A.* 1988; 38:3098.
63. Lee CT, Yang WT, Parr RG. *Phys. Rev. B.* 1988; 37:785–789.
64. Becke AD. *J. Chem. Phys.* 1993; 98:5648–5652.
65. Casida ME, Jamorski C, Casida KC, Salahub DR. *J. Chem. Phys.* 1998; 108:4439–4449.
66. Cossi M, Barone V, Cammi R, Tomasi J. *Chem. Phys. Lett.* 1996; 255:327–335.
67. Rhaman MM, Fronczek FR, Powell DR, Hossain MA. *Dalton Trans.* 2014; 43:4618–4621. [PubMed: 24419223]
68. Valiyaveetil S, Engbersen JFJ, Verboom W, Reinhoudt DN. *Angew. Chem. Int. Ed. Engl.* 1993; 32:900–901.
69. Van der Sluis P, Spek AL. *Acta Crystallogr. Sect. A.* 1990; 46:194–201.
70. Data Collection: SMART Software Reference Manual. Bruker-AXS, 5465 E. Cheryl Parkway, Madison, WI 53711–5373, USA. 1998
71. Sheldrick GM. *Acta Cryst.* 2008; A64:112–122.
72. Schneider HJ, Kramer R, Simova S, Schneider U. *J. Am. Chem. Soc.* 1988; 110:6442–6448.
73. Frisch, MJ., et al. *Gaussian 09, Revision A.1.* Wallingford CT: Gaussian, Inc; 2009.
74. Betzel C, Singh TP, Visanji M, Peters K, Fittkau S, Saenger W, Wilson KS. *J. Biol. Chem.* 1993; 268:15854–15858. [PubMed: 8340410]
75. Fain AV, Ukrainskii DL, Dobkin SA, Galkin AV, Esipova NG. *Biophysics.* 2008; 53:125–133.

Figure 1. Partial ^1H NMR spectra (500 MHz) of $\text{H}_6\text{L}(\text{Ts})_6$ in the presence of one equivalent of various anions in D_2O at $\text{pD} = 2.0$. [a = ArCH_2 , b = NCH_2CH_2 , c = NCH_2CH_2].

Figure 2.
 ^1H NMR titrations of $\text{H}_6\text{L}(\text{Ts})_6$ (2 mM) with an increasing amount of NaCl ($R = [\text{NaCl}]_0/[\text{L}]_0$) in D_2O at $\text{pD} = 2.0$.

Figure 3.
 ^1H NMR spectra of $[\text{H}_6\text{L}](\text{Ts})_6$ (2 mM) with an increasing amount of Na_2SO_4 ($R = [\text{Na}_2\text{SO}_4]_0/[\text{host}]_0$) in D_2O at pD 2.0.

Figure 4.

¹H NMR titration curves of [H₆L](Ts)₆ with anions in D₂O. The changes in chemical shifts of NCH₂CH₂ are shown against the increasing ratio of an anion to [H₆L]⁶⁺.

Figure 5. ESI-MS (positive ion mode) spectrum of the (a) chloride, (b) iodide, (c) nitrate and (d) sulfate complexes. Each solution was prepared from the respective anion salt of L (1.0×10^{-6} M) in MeOH/H₂O (1:1, v/v).

Figure 6. Crystal structure of $[\text{H}_8\text{L}(\text{Cl})](\text{Cl})_6^+$ motif in **1** showing one encapsulated and six external chlorides.

Figure 7.
Crystal structure of $[H_6L(Br)(H_2O)_3]^{5+}$ motif in **2** showing one encapsulated bromide and three cleft bound water molecules.

Figure 8.
Crystal structure of $[H_6L(I)(H_2O)_3]I_3^{2+}$ motif in **3** showing one encapsulated iodide and three cleft bound water molecules.

Figure 9.
Crystal structure of $[\text{H}_8\text{L}(\text{NO}_3)_3]^{5+}$ motif in **4** showing three cleft bound nitrates.

Figure 10.
Crystal structure of $[H_6L(CH_3OH)(HSO_4)(SO_4)_2]^+$ motif in **5** showing the encapsulated methanol and three cleft bound sulfates.

Figure 11.

Optimized structure of the encapsulated sulfate in [H₆L]⁶⁺: perspective view and space filling model calculated at the B3LYP/6-311G(d,p) level of theory. Selected H-bond lengths (Å) of D...O [H...O]: O1...N2, 2.79 [1.649]; O1...C2, 3.477 [3.153]; O2...N3, 2.907 [1.887]; O2...N6, 2.880 [1.835]; O3...N5, 2.664 [1.598]; O3...N6, 3.195 [2.681]; O4...N7, 2.744 [1.690]; O4...C3, 2.744 [2.379].

Scheme 1.

The ligand L and the electrostatic potential map for [H₆L]⁶⁺ calculated at the B3LYP/6-311G(d,p) level of theory (red: negative potential, blue: positive potential).

Scheme 2.

The L and the electrostatic potential map for [H₆L]⁶⁺ calculated at the M06-2X/6-31G(d,p) level of theory (red: negative potential, blue: positive potential).

Table 1Association constants (K) of the anion complexes of $[\text{H}_6\text{L}](\text{Ts})_6$

Anion	$\text{Log } K^a$
Cl^-	3.70
Br^-	3.65
I^-	3.55
NO_3^-	4.32
SO_4^{2-}	5.26

^aEstimated deviations are less than 10%.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2

Binding energies for the calculated models at B3LYP/6-311G(d,p) level both in gas phase and solvent.

Complex	E (kcal/mol)	E(PCM) (kcal/mol)
$[\text{H}_6\text{L}(\text{Cl})]^{5+}$	-371.83	-33.4
$[\text{H}_6\text{L}(\text{Br})]^{5+}$	-368.51	-31.3
$[\text{H}_6\text{L}(\text{I})]^{5+}$	-361.82	-26.1
$[\text{H}_6\text{L}(\text{SO}_4)]^{4+}$	-806.57	-68.3
$[\text{H}_6\text{L}(\text{NO}_3)]^{5+}$	-382.58	-44.0