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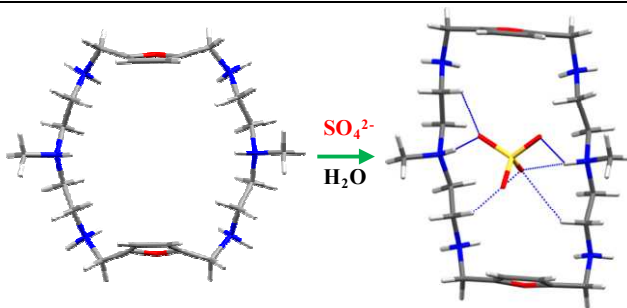
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Encapsulation and selectivity of sulfate with a furan-based hexaaza macrocyclic receptor in water



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ARTICLE TYPE

Encapsulation and selectivity of sulfate with a furan-based hexaaza macrocyclic receptor in water

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A furan-based hexaazamacrocycle encapsulates a sulfate anion in its cavity showing strong affinity and selectivity for sulfate in water over a wide range of inorganic anions. The DFT calculations demonstrate that the receptor provides binding sites as hydrogen bonding donors and electrostatic positive charges for the strong binding of sulfate.

Sulfate plays a key role in many environmental and biological processes.^{1,2} In particular, this anion has been of significant concerns with respect to the nuclear waste management in the USA, interfering the vitrification process used for waste disposal.¹ Additionally, the presence of an excess amount of sulfate in drinking water is related to several health related problems including diarrhea³ and laxative effects.⁴ In biological system, sulfate has an important role in biosynthesis^{2a} and protein binding.^{2b} For example, sulfate is known to selectively bind with sulfate binding proteins and its structure was crystallographically characterized, showing that sulfate is hepta-coordinated with the amino acid residues *via* hydrogen bonding interactions.⁵ Because of the ubiquitous presence of sulfate and its significant impact in nature, there are growing interests in developing synthetic receptors for selective binding of sulfate.⁶ However, due to the large hydration energy of sulfate ($\Delta G = -1080$ kJ/mol),⁷ this anion tends to be highly solvated by water. Therefore, the binding of sulfate with synthetic receptors is often hampered in an aqueous phase.

Polyammonium-based molecules which are soluble in water, have been shown to be effective hosts for a variety of anions in both solution and solid state;⁸ surprisingly, there are only few structural reports of sulfate encapsulated in polyammonium-based hosts.⁹ The first encapsulated sulfate with a polyammonium-based host was reported in 2005, where the sulfate was held within the cavity of a *m*-xylyl-based cryptand *via* five NH...O bonds.^{9a} Recently, there have been reported several types of neutral hosts including metal-organic cage hosts,¹⁰ polyamides,¹¹ ureas,¹² thioureas,¹³ and indoles,¹⁴ which provide remarkable selectivity and binding affinity for sulfate in organic solvents. For example, Loeb *et al.* reported an encapsulated sulfate within a metal-organic framework containing urea-functionalized quinoline ligands.^{10a} Bowman-James *et al.* isolated a sulfate sandwich stabilized between two macrocyclic tetramides with eight hydrogen bonds.^{11a} A tren-based urea linked with Ag₂SO₄ reported by Custelcean *et al.* was shown to bind a sulfate *via* twelve hydrogen bonds.^{12a} An encapsulated sulfate within a pentafluoro substituted thiourea was reported by Gale *et al.*, showing high selectivity for sulfate in DMSO-*d*₆.^{15a} A *m*-nitro

substituted tripodal urea synthesized by Das *et al.* was found to form a capsular complex with sulfate.^{12c} Similar capsular complex with sulfate was reported for a *p*-cyano substituted tripodal thiourea.^{15b} A hexaurea-based tripodal receptor synthesized by Wu, Li and coworkers was shown to form a sulfate complex *via* twelve hydrogen bonds.^{12d} Because of the lessened tendency of these neutral molecules to be dissolved in water, their uses are mostly limited in organic solvents. Further, such molecules use their H-bonds as primarily binding components to complex an anion; therefore, their binding is hampered in a competitive polar solvent. In an effort to expand our continuous interests in anion binding chemistry,¹⁶ we have synthesized a simple water soluble macrocyclic polyamine L incorporated with furan groups as linkers, showing significantly strong selectivity for sulfate in water. The electrostatic potential surfaces of [H₆L]⁶⁺ calculated at the M06-2X/6-311G(d,p) level of theory, shows the strong electrostatic positive potential inside the cavity (Fig. 1b), making the cavity potential for anion binding. Herein, we report a simple macrocycle that exhibits strong selectivity for sulfate over other anions in water, and encapsulates a sulfate as characterized by X-ray analysis and DFT calculations.

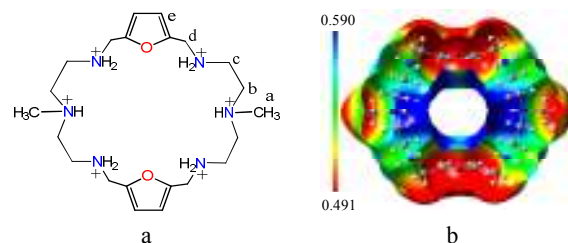


Fig. 1 (a) The macrocyclic receptor, [H₆L]⁶⁺, and (b) electrostatic potential map for [H₆L]⁶⁺ calculated at the M06-2X/6-311G(d,p) level of theory showing minimum (red) and maximum (blue) potential.

The ligand L was synthesized from the reaction of an equimolar amount of *N*-methyl-2,2'-diaminodiethylamine and 2,5-diformylfuran in CH₃OH, followed by the reduction with NaBH₄. The tosylate salt [H₆L](Ts)₆ was obtained by mixing of L with six equivalents of TsOH in water. Crystals of the sulfate salt were grown from slow evaporation of a water solution of L in the presence of H₂SO₄ at pH 2.0.

X-ray diffraction analysis[†] of the sulfate complex reveals that it crystallized in the triclinic *P*-1 space group with two crystallographically independent macrocycles (A and B). Each macrocycle is fully protonated and its cavity is occupied by a sulfate, providing an almost identical structure to each other. Fig.

2 shows the encapsulated sulfate in the unit A, where the sulfate is held *via* two NH \cdots O bonds (2.660 and 2.670 Å) with tertiary NH $^+$ groups and three CH \cdots O bonds (3.165(3) - 3.341(3) Å) with CH $_2$ groups attached to secondary NH $_2^+$ groups. The observed 5 NH \cdots O bonds distances are much stronger than that reported for an encapsulated sulfate in a *p*-xyly-based macrocycle (average NH \cdots O = 2.89 Å).^{9a} The CH \cdots O-anion bonds are well documented in the literature.^{8c,9c} Further, a recent report of Hay demonstrates that C-H groups attached to NR $_2^+$ groups are strong H-bond donors in anion binding.¹⁷ Therefore, it is assumed that H-bonding from both NH \cdots O and CH \cdots O interactions contribute to the strong binding for sulfate. Although the secondary ammonium protons are not involved in H-bonding with the internal sulfate, it is possible that the charged NR $_2^+$ cations 15 interact with the sulfate *via* electrostatic interactions, adding further stability of the encapsulated sulfate.

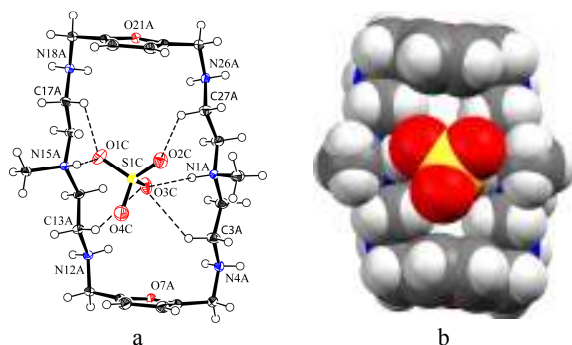


Fig. 2 Encapsulated sulfate in [H $_6$ L] $^{6+}$. (a) ORTEP view and (b) space filling model showing encapsulated sulfate in the unit A. External sulfates and water are not shown for clarity. Selected H-bond lengths (Å) of D \cdots O [H \cdots O]: N1A \cdots O3C, 2.673(2) [1.778(14)]; N15A \cdots O1C, 2.660(2) [1.764(14)]; C3A \cdots O3C, 3.341(3) [2.62]; C13A \cdots O3C, 3.302(2) [2.58]; C17A \cdots O1C, 3.165(3) [2.48].

In an asymmetric unit, two macrocycles are interconnected through two external sulfates bonded to secondary NH $_2^+$ groups 25 *via* NH \cdots O interactions in each unit. In addition to the sulfates, there are well refined 15 water molecules, with extensive hydrogen-bonding networks connecting both internal and external sulfate anions through water bridges (Fig. S6 in ESI). It is noteworthy that water molecules are not involved in interacting 30 directly with the macrocycle, thereby making the NH groups available for H-bonding and electrostatic interactions for sulfate. An inspection of the peripheral environment of a macrocycle shows that each secondary NH $_2^+$ group is H-bonded to an external sulfate, not to water (Fig. S6 in ESI), suggesting that the 35 host has strong affinity for sulfate.

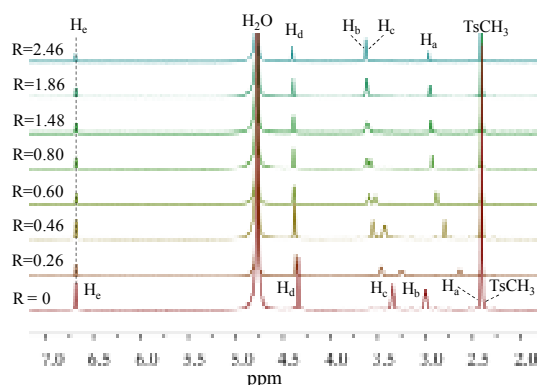


Fig. 3. Partial ^1H NMR spectra of [H $_6$ L](Ts) $_6$ (2mM) with an increasing amount of Na $_2$ SO $_4$ in D $_2$ O at pH = 2.1 ($R = [\text{SO}_4^{2-}]_0/[\text{1}]_0$, H $_a$ = NCH $_3$, H $_b$ = NCH $_2$, H $_c$ = NCH $_2$ CH $_2$, H $_d$ = NCH $_2$ Ar and H $_e$ = ArH).

40 Solution binding properties of [H $_6$ L] $^{6+}$ were evaluated by ^1H NMR titrations for different anions using their sodium salts in D $_2$ O at pH = 2.1 (adjusted with TsOH and NaOD). As shown in Fig. 3, the addition of SO $_4^{2-}$ to the receptor causes the highest downfield shift ($\Delta\delta = 0.455$ ppm) for CH $_2$ protons (H $_b$) followed 45 by CH $_3$ protons (H $_a$) connecting with the tertiary nitrogen centers ($\Delta\delta = 0.399$ ppm), indicating strong interactions of the tertiary NH $^+$ groups for this anion. Evidently, the CH protons exhibit major shifts in the NMR while the aromatic protons remain almost unchanged during the titration, suggesting the possible 50 involvement of CH protons in sulfate binding as also observed in the X-ray structure. The variation in the chemical resonances for several protons against the anion concentration gave almost similar binding constants providing the best fit for a 1:1 binding model,¹⁸ which was further supported by a Job's plot. For other 55 anions, the binding profile was also in agreement with a 1:1 association model. The results show that the host exhibits strong selectivity for sulfate over other anions (Table 1). It shows moderate affinity for nitrate ($\log K = 3.0$); however, weak binding is observed for other anions. The binding constant for sulfate, 60 which is 4.65 (in $\log K$), is higher than the previously reported data with *p*-xylyl macrocycle ($\log K = 3.6$),^{9b} or *m*-xylyl cryptand ($\log K = 4.43$)^{9a}. The strong affinity for SO $_4^{2-}$ could be the net effect of hydrogen bonding capability of the ligand *via* NH \cdots O and CH \cdots O interactions and the electrostatic positive potential of 65 the cavity provided by NH $^+$ /NH $_2^+$ groups, agreeing with the crystallographic data. Increasing the pH from 2.1 to 4.0, the ligand did not show any change of the NMR signals, indicating that the complete protonation of the macrocycle is required to bind an anion (Fig. S20 in ESI).

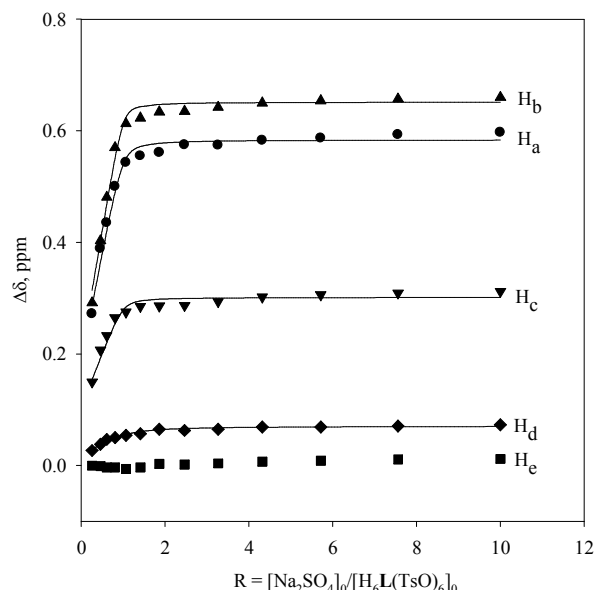


Fig. 4 ^1H NMR titration curves for sulfate binding with [H $_6$ L](Ts) $_6$ (2mM) in D $_2$ O at pH = 2.1. The chemical shifts of different protons are shown against the increasing amount of Na $_2$ SO $_4$ (20 mM) at pH 2.1. H $_a$ = NCH $_3$, H $_b$ = CH $_3$ NCH $_2$, H $_c$ = CH $_3$ NCH $_2$ CH $_2$, H $_d$ = NCH $_2$ Ar and H $_e$ = 75 ArH.

Table 1. Association constants (in $\log K$)^[a] of the anion complexes determined by ^1H NMR titration at pH 2.1.

F $^-$	Cl $^-$	Br $^-$	I $^-$	ClO $_4^-$	NO $_3^-$	SO $_4^{2-}$
1.5	1.6	2.0	1.8	2.2	3.0	4.65

[a]: at room temperature (error < 15%).

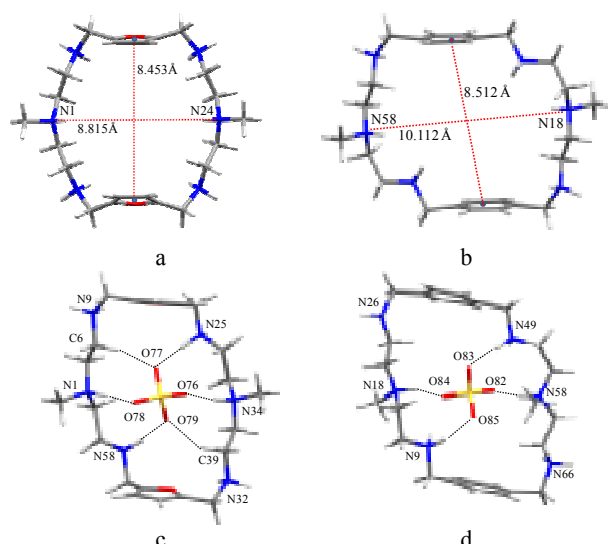


Fig. 5. Optimized structures of (a) $[H_6L]^{6+}$, (b) $[H_6L^p]^{6+}$, (c) $[H_6L(SO_4)]^{2+}$ and (d) $[H_6L^p(HSO_4)]^{2+}$.

The binding profile of $[H_6L]^{6+}$ for sulfate was further evaluated by the density functional theory (DFT) with the hybrid meta exchange-correlation functional M06-2X¹⁹ calculations using the Gaussian 09 package of programs.²⁰ Atomic coordinates from crystal structure were used as initial input to optimize structures. The relative binding energies were calculated with inclusion of zero-point correction in gas phase. From the DFT-optimized geometry, the total electrostatic potential was computed from the self-consistent density matrix. As shown in Fig. 1b, a strong electrostatic positive potential is created inside the cavity, making the macrocycle effective for anion binding. In the optimized structure, the charged macrocycle adopts an elliptical conformation (Fig. 5a) with the distances of 8.815 Å (N1...N24) and 8.453 Å (Ar...Ar). As noted earlier, this receptor as compared to its slightly larger *p*-xylyl analogue $[H_6L^p]^{6+}$, shows significantly higher affinity for sulfate. In order to compare the structural conformations between the two hosts, we also optimized the $[H_6L^p]^{6+}$ in gas phase using its crystal structure atomic coordinates.^{9b} As shown in Fig. 5b, the optimized structure is twisted, with a cavity of 10.112 (N18...N58) and 8.512 Å (Ar...Ar) distance, which is larger than that observed in $[H_6L]^{6+}$. Thus, the large difference in binding affinities between the two hosts could be in part due to the effect of size and conformation.

Using the X-ray data of the sulfate complex, the macrocycle with one encapsulated sulfate was fully optimized at M06-2x/6311G(d,p) level. Fig. 5c illustrates the complex $[H_6L(SO_4)]^{4+}$ showing that the sulfate is encapsulated *via* four NH...O and two CH...O bonds (Tables S1 and S2 in SI). The hydrogen bonding distances of NH...O (2.552 – 2.720 Å) and CH...O (3.338 and 3.431 Å) are comparable to NH...O (2.660(2) and 2.673(2) Å) and CH...O bonds (3.02(2) – 3.473 Å), respectively, observed in the crystal. In the optimized complex, the macrocycle readjusts its geometrical conformations in order to utilize secondary NH_2^+ groups for the encapsulation of sulfate. The involvement of NH_2^+ groups in H-bonding with the anion could be due to fact that a single sulfate was included in the DFT calculations, while the macrocycle in the crystal contains three sulfates including two external sulfates. On the other hand, the paraxylyl-based macrocycle deforms significantly in optimized sulfate complex of $[H_6L^p]^{6+}$ (Fig. 5d). The major difference in the later case is the absence of the involvement of CH groups in

45 binding the internal sulfate, supporting the high stability of the complex $[H_6L(SO_4)]^{4+}$ in water. The binding energy of $[H_6L]^{4+}$ for sulfate, as calculated from $\Delta E_b = E(HA) - [E(H) + E(A)]^{21}$ (where, H = ligand, A = anion), was found to be -890.7 kcal/mol. However, the binding energy of $[H_6L^p]^{4+}$ for sulfate was lower (-867.7 kcal/mol) which could be due to the effect of slightly larger cavity of $[H_6L^p]^{6+}$.

Conclusions

A simple water soluble macrocycle has been developed providing an excellent selectivity for sulfate in water. The solid state structure described herein is one of the few examples of structurally characterized encapsulated sulfates with polyamines. The hydrogen bonding capability of both NH^+ and CH_2 groups in the ligand coupled with the strong electrostatic positive potential of the cavity, makes the host suitable for strong selectivity for sulfate over a wide range of inorganic anions. The results from DFT calculations further suggest that the unique conformation of the host along with electrostatic and H-bonding interactions plays the key role in stabilizing the sulfate complex. We are currently exploring the application of this and related hosts for extraction of the sulfate.

Acknowledgements

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Notes and references

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- † Electronic Supplementary Information (ESI) available: [Crystallographic file in CIF format, synthetic procedures, additional crystal drawings, NMR titrations, and list of H-bonding and Cartesian coordinates for optimized structures in PDF formats]. See DOI: 10.1039/b000000x/
- ‡ Crystal data: $2(C_{22}H_{44}N_6O_2).6(SO_4).15(H_2O)$, $M = 1695.86$, $a = 13.0481(5)$ Å, $b = 13.2273(5)$ Å, $c = 23.4746(8)$ Å, $\alpha = 102.934(2)^\circ$, $\beta = 93.491(2)^\circ$, $\gamma = 100.629(3)^\circ$, $V = 3858.8(3)$ Å³, $T = 100(2)$ K, space group $P\bar{1}$, $Z = 2$, $\mu(MoK\alpha) = 0.280$ mm⁻¹. $R_{int} = 0.0279$. $R_1(I > 2\sigma(I)) = 0.0502$. CCDC 981557.
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