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Cooperative NH···O and CH···O interactions for sulfate encapsulation in a thiophene-based macrocycle

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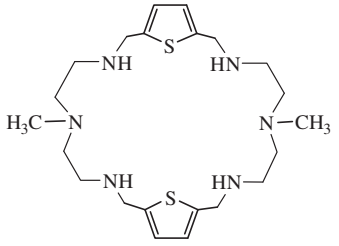
ABSTRACT

A thiophene-based macrocycle containing four secondary and two tertiary amines has been synthesized and its binding affinity has been investigated toward sulfate anion in solution and solid states. Structural analysis of the sulfate salt suggests that the ligand in its hexaprotonated form is capable of encapsulating one sulfate within the cavity through cooperative NH···O and CH···O interactions. As investigated by ^{1}H NMR titrations, the ligand forms a 1:1 complex with sulfate in water at pH 2.1, showing a binding constant (K) of 3200 M^{-1}. The formation of the complex has been further confirmed by ESI-MS, indicating that the complex can exist in solution with considerable stability.

Anion binding is a natural process that occurs in numerous biochemical systems.[1] In biology, sulfate is known to play a key role in biosynthesis.[2] A protein-bound sulfate complex has been structurally identified in which all of the sulfate oxygens except one are held by two hydrogen bonds with adjacent amino acid residues, resulting in a seven coordinate anion complex.[3] Because of the directionality of the lone pairs on the oxygens, sulfate is an attractive anion as a potential template in the formation of a number of molecular devices including macrocycles, helixes, and molecular capsules.[4] Sulfate is also prevalent in environment that is a known contaminant in water and soil.[5] Therefore, the design of new hosts capable of encapsulating sulfate anion still remains an important area of research in supramolecular chemistry.

It is known that sulfate can form up to 12 coordination bonds via hydrogen bonding or the combination of hydrogen bonding and electrostatic interactions with synthetic receptors.[6] The first structural evidences of encapsulated sulfate complexes were observed with cryptand-based receptors in which the divalent sulfate was held by five hydrogen bonds with a polyamine cryptand or eight hydrogen bonds with a polyamide cryptand.[7] Sulfate encapsulation was also observed in the crystal lattice of metal–organic framework,[6] self-assembled metal–organic cage host,[8] or monocyclic polyamide.[9] Although, azamacrocycles are good hosts for a variety of inorganic anions,[10] forming monotopic to ditopic complexes with different binding modes,[11] to the best of our knowledge, there is no structural report of encapsulated sulfate within monocycle-based polyamines. Herein, we report a new receptor with thiophene spacers that encapsulates sulfate through NH···O as well as CH···O interactions.



L

The ligand **L** was synthesized from the reaction of an equimolar amount of *N*-methyl-2,2′-diaminodiethylamine and 2,5-thiophenedicarbaldehyde under high dilution condensation in CH_3OH followed by the reduction with $NaBH_4$. The sulfate salt of **L** was obtained as a white powder from the reaction of the ligand (20 mg, 0.044 mM) with a few drops of concentrated H_2SO_4 in CH_3OH (2 mL). X-ray quality crystals were grown from the sulfate salt dissolved in H_2O/CH_3OH (5:1, v/v) under slow evaporation at room temperature.

Single-crystal X-ray diffraction analysis[12] of the sulfate salt reveals that the macrocycle is hexaprotonated with encapsulated sulfate within the macrocycle. In the macrocycle two protons on tertiary amines (N1 and N14) and two protons on secondary amines (N11 and N11^i) are pointed toward the cavity and are involved in hydrogen-bonding interactions with the internal sulfate via short NH···O bonds (<3 Å).[7] As shown in Figure 1A and Table 1, the encapsulated sulfate is coordinated with the macrocycle with relatively strong four NH···O bonds (2.633(7)–2.852(7) Å) and also with one CH···O (3.10 Å).[13]

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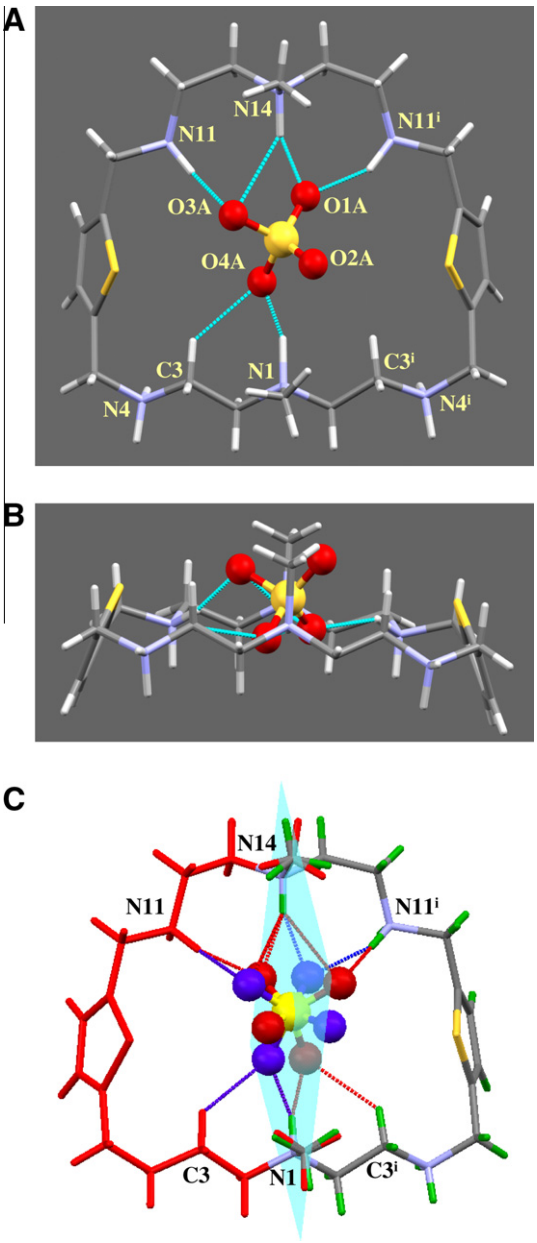

Figure 1. Crystal structure of $[H_6\mathbf{L}(SO_4)]^{4+}$ motif showing encapsulated sulfate: (A) side view, (B) view along the tertiary *N*–*N* axis, and (C) two symmetry-related mirror images with disordered sulfate ion. External sulfates and water molecules are not shown for clarity.

Table 1
Hydrogen-bonding parameters (A, °) for SO_4^{2-} binding in **L**

D—H···O	H···O	D···O	∠DHO
N1—H1···4OA	1.53	2.633(7)	159.7
C3—H3A ···O4A	2.325	3.10	134.3
$N11^i$—H11B^i ···O1A	1.82	2.644(7)	137.7
N14—H14···O1A	1.69	2.716(7)	157.8
N14—H14···O3A	2.557	3.366	156
N11—H11B··O3A	1.87	2.852(7)	165.7

The distance of H···O in CH···O bond is 2.325 Å which is much shorter than the sum of van der Waals radii for H and O (2.72 Å), suggesting a strong CH···anion interactions.[14] Indeed, the CH···O bond is known to be prevalent in many natural systems, playing an important role in protein–nucleic acid interactions and drug binding.[13] In addition, the contact between N14 and O3A (3.36 Å) which is less than the upper limit (3.5 Å) for hydrogen bonding could be considered as a weak hydrogen bond.[6] Therefore, except one oxygen atom (O2A) which is directed outside the cavity, each oxygen atom accepts two hydrogen bonds from either two NH or one NH and one CH groups. This is in agreement to the SO_4^{2-} binding by the two macrocyclic amides, in which each oxygen atom acts as an acceptor of two hydrogen bonds.[15]

A close inspection of the structure suggests that the macrocyclic cation lies almost on a plane with N1···N14 distance of 7.218 Å (Fig. 1B).[16] The methyl groups on the tertiary amines sit on the same side of the macrocycle. The macrocycle, the encapsulated sulfate, and three of the water molecules lie on a crystallographic mirror plane. The orientation of oxygens of the internal sulfate is such that they are disordered in a 50:50 ratio at mirror symmetry-related positions (Fig. 1C). The water O4S is too close to one oxygen of the sulfate, so the occupancy of O4S was set to 1/2, the same occupancy as that of the oxygens in internal sulfate. The protons on (N4 and $N4^i$) are directed outside the cavity and involved in coordinating two external sulfates (see Supplementary data).

In order to compare the sulfate binding in solution with that in solid state, ^{1}H NMR titrations were performed using $[H_6\mathbf{L}]\cdot 6Ts$ (5 mM) with an increasing amount of sodium sulfate solution (50 mM) in D_2O at pH 2.1 (see Supplementary data for the synthetic procedure of $[H_6\mathbf{L}]\cdot 6Ts$). As shown in Figure 2, the addition of the anion resulted in a significant downfield shift of the macrocyclic protons. It is remarkable that the large shifts were observed for the aliphatic protons, on CH_2 (b, $\Delta\delta = 0.73$ ppm) and CH_3 (a, $\Delta\delta = 0.69$ ppm) which are directly linked to the tertiary nitrogen centers. The observation suggests the possible interactions between sulfate and central nitrogens, supporting the results obtained in the crystal structure. The involvement of the protons on tertiary amines was previously reported in a thiophene-based cryptand binding one chloride[17a] and three nitrate[17b] ions in solid states. The protons (c and d, see the Fig. 2) on the methylene groups linked with secondary amines shifted downfield by 0.25 and 0.08 ppm, respectively. On the other hand, there was no significant shift observed in the aromatic resonances of **L**. We also assume that the large shift in the aliphatic protons as compared to the related compounds[7,11,17] could be due to the effect of the added charge in the divalent sulfate. The observed shift changes for several protons were plotted against the anion concentration which provided the best fit for a 1:1 binding model[18] (Fig. 3), yielding a binding constant (K) of 3200 M^{-1} which is considerably higher than that reported for other receptors in polar solvents, for example, 30–170 M^{-1} with tren-based amides or sulfonamides in acetonitrile,[19] or 68 M^{-1} with an amide-based cryptand in DMSO-d_6[7] determined by NMR titrations. Clearly, the binding of **L** with sulfate is enhanced by electrostatic interactions of the charged ligand.

The evidence of the complex formation between **L** and sulfate was also further confirmed by ESI-MS experiments. As shown in Figure 4, the complex displays a cationic peak at m/z 549.0 for the monovalent $[H_3\mathbf{L}SO_4]^+$ and m/z 274.8 for the divalent $[H_4\mathbf{L}SO_4]^{2+}$. The peak at m/z 451.2 corresponds to monovalent free ligand $[H\mathbf{L}]^+$ while the peak at m/z 226.3 for divalent $[H_2\mathbf{L}]^{2+}$. These data further support that sulfate is tightly held with the macrocyclic ligand, which is consistent with the 1:1 complexation observed in the solid and solution states.

In conclusion, we have synthesized a new thiophene-based azamacrocycle containing both secondary and tertiary amines which is found to encapsulate sulfate anion via strong NH···O and CH···O interactions. Although the conventional hydrogen bonds are the primary binding forces, the involvement of CH···O bond provides enhanced stability of the sulfate complex. To the best of our knowledge, structural evidence of an encapsulated sulfate in polyamine-based macrocycle has not been reported before. The results from

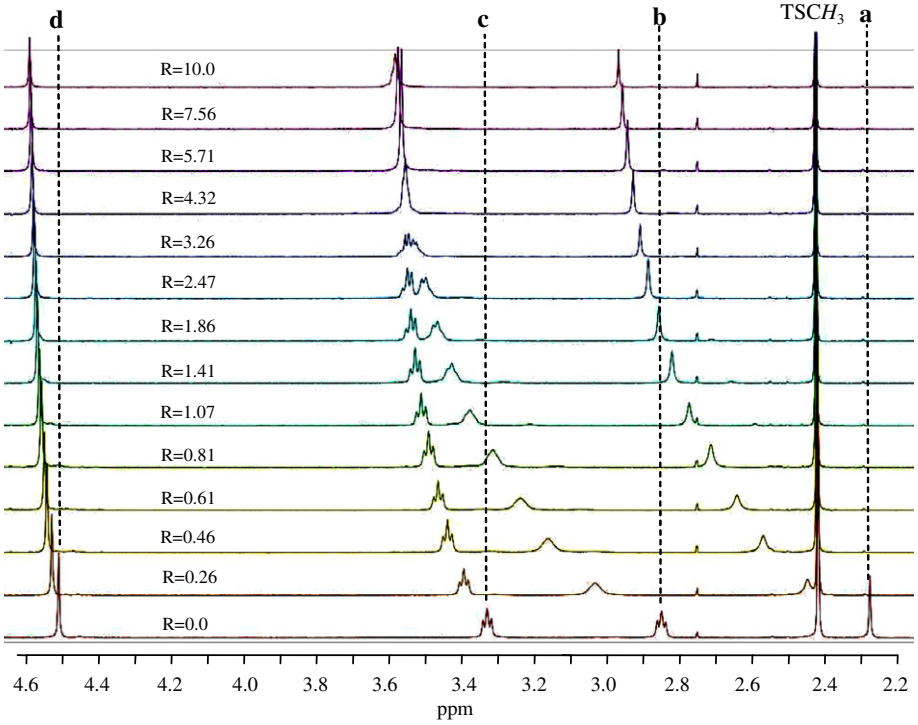

Figure 2. Partial ^{1}H NMR spectra of tosylated salt of **L** (5 mM) with the increasing amount of sodium sulfate (50 mM) in D_2O at pH 2.1. *a* = NCH_3, *b* = NCH_2, *c* = NCH_2CH_2, and *d* = $ArCH_2$.

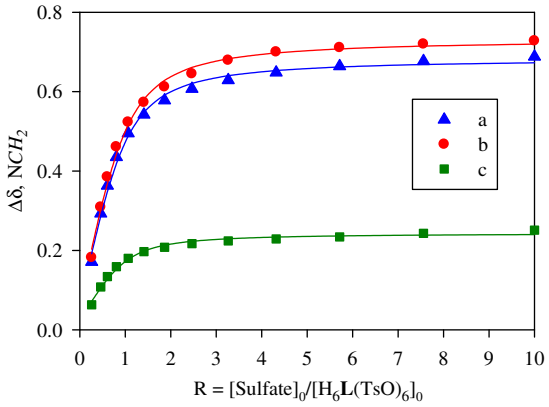

Figure 3. ^{1}H NMR titration curves for sulfate binding with $H_6\mathbf{L}(OTs)_6$ in D_2O at pH 2.1. Net changes in the chemical shifts of *a* = NCH_3, *b* = NCH_2, and *c* = NCH_2CH_2 are shown against the anion concentration.

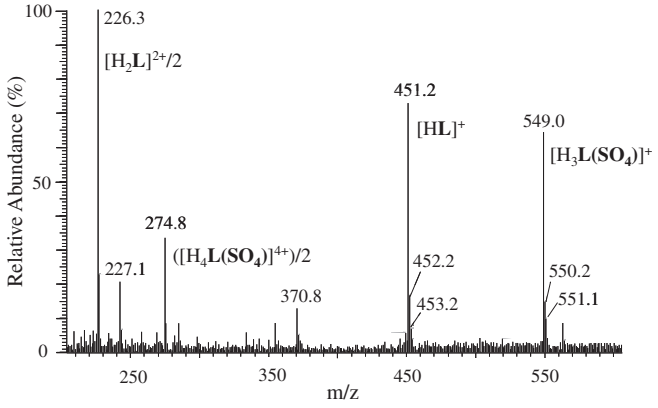

Figure 4. ESI-MS (positive ion mode) spectrum of the sulfate complex. The solution was prepared from the sulfate salt of **L** (1.0×10^{-5} M) in $MeOH/H_2O$ (50:50).

^{1}H NMR and ESI-MS studies further confirmed the formation of the sulfate complex which can exist in solution with considerable stability.

Acknowledgments

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Supplementary data

Supplementary data (crystallographic file in CIF format and synthetic procedures) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.036.

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