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Highly Selective Fluorescent Recognition of Sulfate in Water by Two Rigid Tetrakisimidazolium Macrocycles with Peripheral Chains

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Supporting Information

ABSTRACT: The reinforced molecular recognition of two rigid tetrakisimidazolium macrocycles resulted in highly selective fluorescent recognition of sulfate dianion in water with an unprecedentedly high association constant of 8.6×10^9 M^{-2}. Besides the electrostatic interaction, the single crystal X-ray analysis revealed that sulfate was encapsulated in a pseudohexahedral cavity of a sandwich structure by two orthogonally packed macrocycles via eight hydrogen bonds between the C2 hydrogen atoms of the imidazolium units and the oxygen atoms of sulfate. This sandwich structure was reinforced by the $\pi-\pi$ stacking between the phenyl and the triazinonide rings and multiple charge-assisted hydrogen bonds between the peripheral chains and the rigid backbones. Notably, these peripheral-backbone hydrogen bonds rendered the flexible peripheral chains to coil around the sandwich structure to shield sulfate inaccessible to water. This binding process was visible by fluorescence enhancement, which was attributed to a restrained rotation and better conjugation of the macrocycle backbone upon binding to sulfate.

Sulfate dianion is of vital importance in biology and the environment. For example, it is commonly involved in sulfate metabolism in animal bodies.[1] It is a main component of acid rain[2] and also a problem for the disposure of nitrate-rich nuclear waste.[3] Therefore the recognition and separation of sulfate dianion have attracted much attention.[4] Synthetic receptors with tripodal, macrocyclic, cage-like, and metal-based structures have been built commonly using amine, amide, urea, pyrrole, and indole, etc. as the binding functionalities during the past decade.[5] To date, anion recognition in water is probably one of the most challenging tasks in supramolecular chemistry.[6] Among various anions, sulfate recognition is even more difficult because of its high hydration energy ($\Delta G_h = -1080$ kJ/mol vs -300 kJ/mol for nitrate)[7] and extreme hydrophilicity according to the Hofmeister series.[8] Recently, the association constant (log $K_a = 8.67$) for sulfate binding of record high was achieved in CH_3CN/H_2O (2:1, v/v) by Kubik and Otto et al. using bis(cyclopeptide)s.[9] However, while in nature sulfate binding proteins (SBP) bind sulfate very efficiently with a K_a of $\sim 10^6$ M^{-1},[10] the binding constants of synthetic receptors have never exceed 10^4 in neutral water.[5f,11] The X-ray analysis by Pflugrath and Quiocho in 1988 revealed that the polypeptides precisely fold to form a neutral cavity and tightly hold sulfate ~8 Å deep inside by seven hydrogen bonds in a capped octahedral geometry.[12] It suggests that an efficient synthetic receptor for sulfate should be soluble in water, have a large and preorganized cavity with multiple hydrogen-bond donors in a proper geometry, and be able to shield sulfate inaccessible to water.

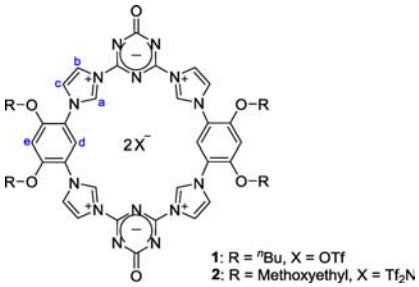

Figure 1. Chemical structures of macrocycle **1** and **2**.

Imidazolium unit is known as an ideal motif for anion recognition due to its inherently cationic and hydrogen-bond donating characteristics. To date, its wide applications in anion recognition have been well documented in the literature.[13] We recently synthesized a fully rigid tetrakisimidazolium macrocycle **1** (Figure 1), which posed in a saddle conformation and emitted blue fluorescence.[14] This shape persistent macrocycle (SPM) was expected to take advantage of its preorganized cyclic backbone, multiple hydrogen-bond donors, and cationic characteristics for highly selective anion recognition, which could be detected via fluorescence variation. Due to its insolubility in water, we replaced the four butoxy groups with four methoxyethoxy chains to afford the macrocycle **2**. Herein, we report that the tetrakisimidazolium macrocycle **2** selectively binds sulfate dianion in a 2:1 manner over other anions in water with fluorescence enhancement, and the binding constant was calculated to be as high as 8.6×10^9 M^{-2}.

The macrocycle **2** was synthesized as a white solid in 62% yield. The $^1H/^{13}C$ NMR spectra were in accordance with its analogue **1**. The synthetic details and characterization of **2** are given in the Supporting Information. The macrocycle **2** could be slightly dissolved in water and emit blue fluorescence when excited at 304 nm (Figure S1). This fluorescence was attributed

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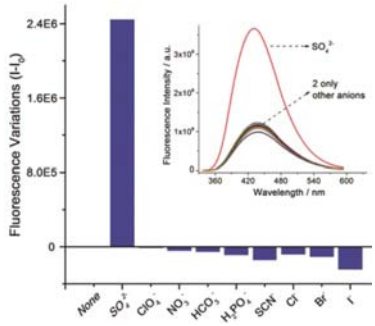

Figure 2. Fluorescence variations and fluorescence spectra (inset) of **2** (10 μM) upon addition of 20 equiv of anions in 10 mM HEPES buffer at pH 7.0, excited at 304 nm. I and I_0 are the fluorescence intensity of **2** at 433 nm with and without anions, respectively. The anions are SO_4^{2-}, ClO_4^-, NO_3^-, HCO_3^-, $H_2PO_4^-$, SCN^-, and halides.

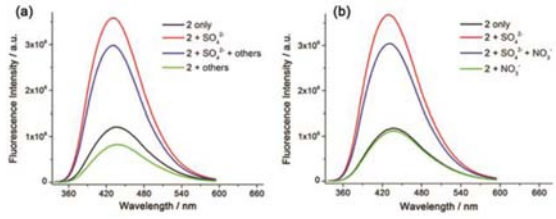

Figure 3. Fluorescence spectra of **2** (10 μM) (a) with and without all anions (20 equiv each) of SO_4^{2-}, ClO_4^-, NO_3^-, HCO_3^-, $H_2PO_4^-$, SCN^- and halides in 10 mM HEPES buffer at pH 7.0, excited at 304 nm; and (b) in the presence of sulfate (20 equiv) and nitrate (400 equiv) in the same buffer, excited at 304 nm.

to an intramolecular charge transfer (ICT) process based on the partially conjugated backbone in a saddle conformation and the donor−acceptor structure from methoxyethoxy groups and the negatively charged triazinonides to the positively charged imidazolium moieties.[14]

The anion recognition experiment was first conducted by measuring the fluorescence variation of the 10 μM aqueous solution of **2** upon addition of 20 equiv of a variety of anions under neutral conditions (10 mM HEPES buffer at pH 7.0). Figure 2 clearly shows that sulfate dianion caused ~3-fold fluorescence enhancement without shift in wavelength, indicating that no excimer was formed. Other anions, such as perchlorate, nitrate, bicarbonate, dihydrophosphate, thiocyanate, and halides caused no change or just slight fluorescence quenching of **2** (Figures 2, S2). The job's plot measurement in pure water revealed that **2** and sulfate dianion formed a 2:1 complex (Figure S3). The fluorescence titration of the 10 μM solution of **2** in water using sodium sulfate (Na_2SO_4) from 0.2 to 50 equiv resulted in a gradual fluorescence increase, and the association constant K_a was calculated to be as high as 8.6×10^9 M^{-2} by a nonlinear least-squares analysis[15] of the fluorescence intensity vs the sulfate concentration (Figure S4). The most striking is that this high affinity was obtained in 100% water!

The competitive recognition experiment showed that sulfate dianion caused ~2.4-fold enhancement of the fluorescence of **2** in the presence of all tested anions (Figure 3a). Moreover, ~2.6-fold enhancement was observed when 20 equiv of sulfate dianion were added into a solution of **2** with 400 equiv of nitrate anion (sulfate/nitrate, 1:20), while such a large amount of nitrate anion hardly caused any fluorescence change (Figure 3b). These

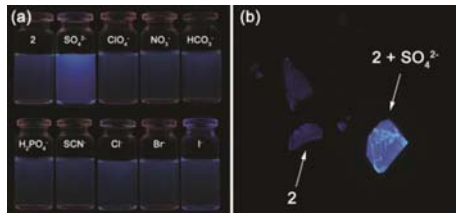

Figure 4. Under UV irradiation, (a) fluorescence photograph of **2** (5 μM) upon addition of 20 equiv of various anions in 10 mM HEPES buffer at pH 7.0; and (b) fluorescence microscopy image of the crystals of **2** itself and grown with Na_2SO_4 under the same ocular.

observations demonstrated that **2** could be used to detect sulfate dianion in either complex anion or nitrate-rich environment.

The fluorescence enhancement caused by sulfate dianion over other anions in aqueous solutions was easily discriminated by naked eyes under UV light. The dim blue fluorescence of a 5 μM solution of **2** in HEPES buffer at pH 7.0 was lightened up upon addition of 20 equiv of Na_2SO_4, whereas no visible changes were observed in the vials with the other anions (Figure 4a). In addition, the crystals grown from an aqueous solution of **2** with Na_2SO_4 emitted intensified blue fluorescence compared with the crystals of **2** itself under a fluorescence microscope (Figures 4b, S5 and S6), which rendered these two crystals to be easily differentiated under UV light.

The ESI-TOF MS analysis of **2** showed a main peak at 452.1672, which was assigned to the m/z of the cationic macrocycle ($[M\text{-}2Tf_2N]^{2+}$) with loss of two Tf_2N anions (Figure S7, calcd 452.1677). The solution of **2** in the presence of 10 equiv of Na_2SO_4 gave rise to a main peak at 952.3124, which was in accordance with $[2M\text{-}4Tf_2N{+}SO_4]^{2+}$ (Figure S8, calcd 952.3118). The mass spectrum data suggested that the 2:1 complex of **2** with sulfate dianion was stable in the gas phase.

After numerous attempts, single crystals of the complex suitable for XRD analysis were luckily obtained in $CH_3CN/CH_3OH/H_2O$ (1:1:4, v/v/v) in the presence of **2** and an excess amount of Na_2SO_4. The single crystal structure[16] showed that the complex of **2** with sulfate dianion adopted a sandwich geometry in a 2:1 ratio.[17] Sulfate dianion was immobilized in the center between two macrocycles by eight C−H···O hydrogen bonds (Figure 5a). Two Tf_2N anions located aside to balance the charges (Figure S9). Each oxygen atom of the sulfate formed two hydrogen bonds with the C2−H of two imidazolium moieties on the same triazinonide ring of one macrocycle. The bond lengths (H···O) ranged from 1.977−2.236 Å, and the bond angles ranged from 160−174° (Table S2), which demonstrated strong hydrogen bonding interactions[18] between the imidazoliums and sulfate. While the four imidazolium C2 hydrogen atoms of the upper macrocycle displayed a rectangular arrangement and all pointed downward, those hydrogen atoms of the lower macrocycle arranged in the same shape but pointed upward (Figure 5b). These two "rectangles" packed orthogonally in space and formed a twisted pseudohexahedral cavity with 3.039 Å depth, which firmly encapsulated the tetrahedral sulfate dianion inside. Otherwise, the intra-annular hydrogen atoms on the two phenyl rings pointed away from the sulfate dianion and made no contribution to the binding.[19] Additionally, it should not be neglected that the sulfate dianion was closely surrounded by eight imidazolium cations and four triazinonide anions which were yet relatively farther. The net effect resulted in a positively charged pocket comfortably accommodating the sulfate dianion in the center through the electrostatic interactions.

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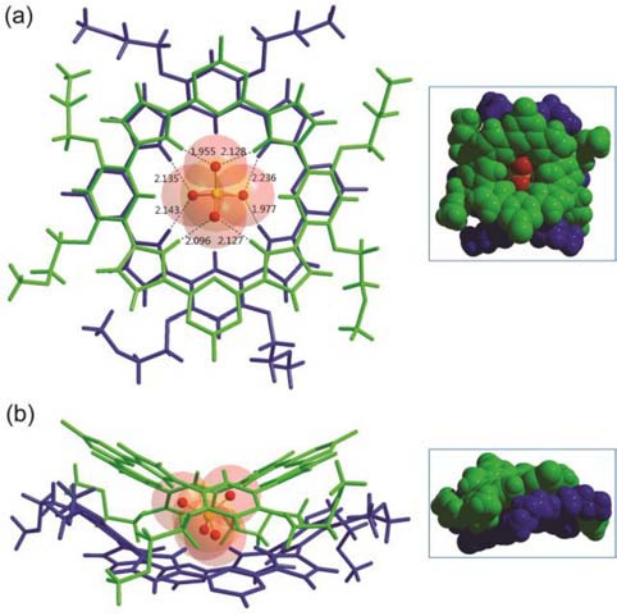

Figure 5. X-ray crystal structure of $[\mathbf{2}\text{-}Tf_2N]_2{\cdot}SO_4$: (a) top and (b) side views. Insets are the spacefilling models. The Tf_2N anions are omitted for clarity.

Besides the host−guest interactions, the interactions between two macrocycles contributed significantly to the stability of the sandwich complex. The two rigid macrocycles with alternative up and down conformation of the bisimidazolium moieties and phenyl rings orthogonally packed each other. Meanwhile, the triazinonide and phenyl rings of the two macrocycles slightly overlapped with the centroid distances of 3.8−4.0 Å and the dihedral angles of 8.4−13.5°, suggesting $\pi-\pi$ stacking between them (Table S3). This complementary packing structure with $\pi-\pi$ interactions to some extent stabilized the complex.

It is noteworthy that the methoxyethoxy peripherals not only increased the aqueous solubility of the macrocycle but also played an important role for the sandwich binding of sulfate dianion in water through two kinds of charge-assisted peripheral-backbone hydrogen bonds[20] (Table S4). The first is 9 intermacrocycle hydrogen bonds including 8 between the ethoxy hydrogen atoms and the 2 anionic triazinonide nitrogen atoms located on the outer rim of the macrocycle (H···N, 2.590−2.918 Å) and one between the cationic imidazolium C4(5) hydrogen atom H50 and the methoxy oxygen atom O8 (H···O, 2.426 Å). The second is 13 intramacrocycle hydrogen bonds between the oxygen atoms on the peripheral chains and the cationic imidazolium C4(5) hydrogen atoms on the backbone (O···H, 2.522−2.821 Å). The intermacrocycle hydrogen bonds fastened the sandwich structure of the complex. In addition, both the inter- and intramacrocycle hydrogen bonds assisted the peripheral chains to closely coil around the seam between the sandwich complex and thus completely shielded the inner cavity (Figure 5 insets), which prevented the encapsulated sulfate from being attacked by the highly competitive solvent molecules. The existence of these charge-assisted hydrogen bonds were supported by the NMR titration experiment (vide post).

Based on the above single crystal analysis, it is clear that the high affinity observed in the present system could be partly interpreted as reinforced molecular recognition.[21] The host−guest interactions (strong hydrogen bonding and electrostatic attraction between imidazolium and sulfate) on one hand

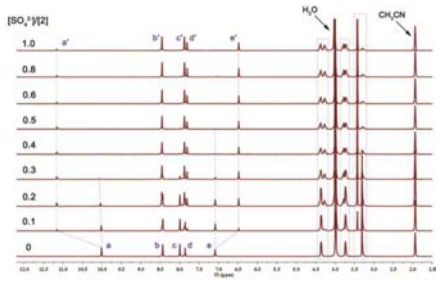

Figure 6. ^{1}H NMR spectra of **2** (5 mM) upon titration of Na_2SO_4 in CD_3CN/D_2O (2:1, v/v) at room temperature.

enveloped sulfate in the center of two macrocycles and on the other hand brought these two macrocycles spatially and geometrically well-arranged to induce host−host interactions (backbone $\pi-\pi$ stacking and peripheral-backbone hydrogen bonding). These two interactions were mutually reinforcing to enhance the sulfate binding in water.

The fluorescence enhancement of **2** could be attributed to the enhanced ICT effect upon binding to sulfate. Sulfate was stabilized in a shielded pseudocavity formed by two rigid macrocycles **2** via host−guest and host−host interactions. In return, these interactions restrained the rotation of the phenyl, imidazolium and triazinonide rings on the backbone, which reduced the nonradioactive energy loss. Moreover, although **2** was in a less conjugated saddle conformation, these interactions induced a better conjugation of the macrocyclic backbone, which was considered to partially contribute to the fluorescence enhancement. It was evidenced in the single crystal structure of the complex that the dihedral angles of the phenyl rings and imidazolium rings were 35−47° (Table S5), while 52−61° were found in the monomer analogue **1**.[22] However, the limited free movements due to the rigidity of the macrocycle should be responsible for the limited fluorescence enhancement.

Finally, ^{1}H NMR titration experiment was performed to follow the recognition process of macrocycle **2** toward Na_2SO_4. Because the fast deuterium−proton exchange of the imidazolium C2 hydrogen made the titration in pure D_2O impossible, we had to conduct this experiment in CD_3CN/D_2O (2:1, v/v) (Figure 6). In the absence of sulfate, all the signals of the backbone of **2** were sharp singlets, suggesting the rigid macrocycles as monomers with no aggregation. These signals gradually reduced in step with the emergence of a set of new signals upon addition of increasing amounts of sulfate. When the amount of sulfate reached 0.5 equiv, all the signals of the monomer vanished.[23] Therefore, the new set of signals could be attributed to the complex of **2** with sulfate formed in a 2:1 ratio. The signal of the imidazolium C2 protons dramatically shifted to low field by 1.15 ppm due to the formation of strong hydrogen bonds with sulfate. Meanwhile, the signal of the phenyl protons on the outer rim of **2** was significantly high-field shifted ∼0.6 ppm, probably because these protons were located in the shielded area of the triazinonide rings in the complex. Interestingly, the methylene and methyl hydrogen atoms on the peripheral chains split into two sets of signals with addition of sulfate, respectively (Figure 6). It suggested that the hydrogen atoms on the same carbon were in different NMR environments and a relatively fixed conformation of the peripheral chains in the complex was formed after binding. This should be ascribed to the charge-assisted hydrogen bonds as we observed in the single crystal analysis. The coexistence of the macrocycle monomers and the sulfate complexes manifested a slow dynamic interaction of **2** with sulfate on the NMR time

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scale.[5c,f,24] Further increasing sulfate to 10 equiv caused no signal variation, indicating that the formation of the 1:1 complex is thermodynamically less favored in the titration solution (Figure S10). The titration experiments with other anions did not show formation of 2:1 complexes (Figure S11).

In conclusion, the rigid tetrakisimidazolium macrocycle **2** selectively bound highly hydrophilic sulfate dianion over other anions by forming a 2:1 complex in water with a large association constant of 8.6×10^9 M^{-2} and exhibited perceptible fluorescence enhancement. This highly selective binding is attributed to: (1) the electrostatic interactions and the eight strong hydrogen bonds between the cationic imidazoliums and anionic sulfate; (2) a pseudo "geometric fit" cavity suitable for sulfate formed by two orthogonally packed rigid macrocycles; (3) the $\pi-\pi$ stacking and charge-assisted hydrogen bonds between two host macrocycles, which further stabilized the complex; and (4) the flexible peripheral chains serving as the shield around the seam of the complex to protect the sulfate from being attacked by the highly competitive solvents. The macrocycle **2** could be used as a fluorescence detector for sulfate dianion in aqueous environment with complex anions. Other applications as an extractant[4a] and a transporter[25] for sulfate dianion are expected. The combination of a rigid macrocycle and flexible peripheral chains might provide a new strategy for the design of anion receptors in highly competitive solvents especially in water.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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