



Rational design of a macrocycle-based chemosensor for anions

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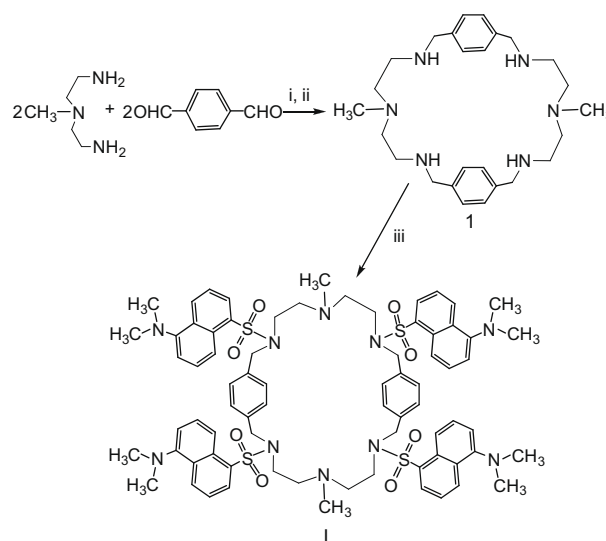
ABSTRACT

A macrocycle-based fluorescence chemosensor has been designed and synthesized from the reaction of dansyl chloride and a hexaaminomacrocycle containing four secondary and two tertiary amines. The new chemosensor has been examined for its binding ability towards phosphate, sulfate, nitrate, iodide, bromide, chloride, and fluoride by fluorescence spectroscopy in DMSO. The results indicate that the compound binds each of the anions with a 1:1 stoichiometry, showing high affinity for oxoanions, chloride, and iodide with binding constants up to four orders of magnitude. Ab initio calculations based on density functional theory (DFT) suggest that the ligand is deformed in order to encapsulate an anion, and each anion, except fluoride, is bonded to the macrocycle through two $\text{NH} \cdots \text{X}^-$ and four $\text{CH} \cdots \text{X}^-$ interactions.

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Because molecular interactions with anions are prevalent in many environmental and health-related issues, the development of new anion sensors has attracted immense interest in current research.^{1–6} In recent years, polyazamacrocycle-based receptors have been well studied for anions,^{7–9} and some of them have been proven as effective systems showing high selectivity and affinity for simple inorganic¹⁰ to biological anions.¹¹ Hexaaza-monocycles that are conveniently synthesized from the Schiff base-derived cyclization were shown to complex a variety of anions including halides and oxoanions;^{12–16} however, their application as anion sensors has not been explored yet. Indeed, compared to acyclic anion sensors, reports on cyclic anion sensors are quite limited^{1,7,16–19} which often require complicated synthetic pathways. An ideal molecular chemosensor should have active binding sites for recognizing anions along with a suitable optical or electrochemical group for sensing anions.¹⁹ In particular, fluorescence chemosensors seem to be attractive due to their simplicity in signal detection and high sensitivity for anions in solution at the parts per million level. Herein, we use a simple strategy of making an anion sensor **L** using macrocycle and dansyl groups as fluorophore units. We choose a macrocyclic precursor ligand **1** consisting of both secondary and tertiary amines, which by itself is an effective anion receptor.²⁰ This particular combination of two different amines allows the ligand to add dansyl groups at the secondary amines, leaving two tertiary amines unreacted that are available for protonation. Therefore, it is expected that the ligand will bind an anion through the protonated tertiary amines while the optical properties of the fluorophores will be changed upon complexation.

The synthesis of precursor **1** was accomplished from the reaction of *N*-methyl-2,2'-diaminodiethylamine with terephthalaldehyde in CH_3OH under high dilution condensation and the subsequent reduction of the resulting imine with NaBH_4 (Scheme 1) following the procedure previously reported by us.²⁰ The reaction of neutral **1** with four equivalents of dansyl chloride in the presence of K_2CO_3 in CH_3CN afforded the target chemosensor **L**.



Scheme 1. Synthesis of chemosensor **L**. Reagents and conditions: (i) CH_3OH , high dilution, 0°C , 24 h; (ii) CH_3OH , NaBH_4 , rt, 12 h; (iii) CH_3CN , dansyl chloride, K_2CO_3 , 25°C , 24 h.

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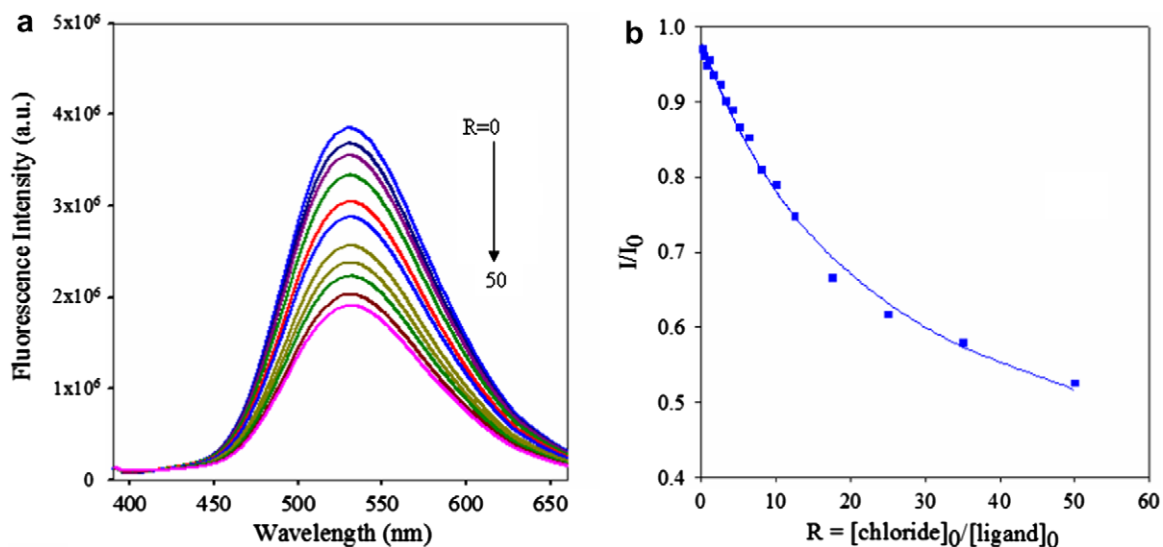


Figure 1. (a) Change in the fluorescence emission spectra of $\text{H}_2\text{L}(\text{Ts})_2$ with an increasing amount of chloride ($R = [\text{chloride}]_0/[\text{L}]_0 = 0\text{--}50$, excitation at 350 nm, 25 °C) and (b) the fluorescence titration curve as a function of R with I/I_0 .

The anion-binding ability of the chemosensor was evaluated using $[\text{H}_2\text{L}]^{2+}$ (prepared from the addition of two equivalents of tosylic acid to **L**) by fluorescence titration studies (excitation at 350 nm) with $[n\text{-Bu}_4\text{N}]^+\text{X}^-$ ($\text{X}^- = \text{F}^-, \text{Cl}^-, \text{Br}^-, \text{I}^-, \text{NO}_3^-, \text{HSO}_4^-$ and H_2PO_4^-) in DMSO. The fluorescence emission spectra of the ligand (1×10^{-6} M) showed a broad peak at 530 nm when excited at 350 nm. Upon gradual addition of an anion (1×10^{-4} M) to the ligand solution, a quenching of the fluorescence was observed in each case. Figures 1a and 2a illustrate the representative fluorescence titration spectra for chloride and phosphate, respectively, derived from the experiments with portion-wise addition of the respective anions (0–50 equiv). Such quenching is attributed to the photoinduced electron transfer (PET) process¹⁹ from the lone pair of electrons on the unprotonated nitrogens, facilitated from the formation of an anion complex that increases the charge density on the linking nitrogens. However, any spectral shift or the formation of an excimer was not observed during these studies. The ligand showed similar quenching trends in the presence of other

anions except fluoride and bromide for which only a small change in the emission was observed (Fig. 3). The relative fluorescence emission (I/I_0 , where I_0 and I are the emissions of the ligand before and after the addition of an anion, respectively) as a function of an anion concentration gave the best fit for a 1:1 association model (Figs. 1b and 2b), yielding the highest binding constants for phosphate among the oxoanions, and chloride among the halide series.²¹ As shown in Table 1, the association constants derived from the non-linear regression analysis showed the binding trend, $\text{H}_2\text{PO}_4^- > \text{HSO}_4^- > \text{Cl}^- > \text{NO}_3^- > \text{I}^- > \text{F}^- > \text{Br}^-$. The observed data clearly indicate that the binding is largely influenced by electrostatic interactions and size-compatibility between the host and the guest. The high affinity for phosphate and sulfate is perhaps due to the strong electrostatic interactions between the two species, as well as the possible contribution from $\text{CH}\cdots\text{anion}$ interactions as revealed from ab initio calculations discussed in the following section. The weak binding for fluoride is attributed to the mismatch of its size with the cavity, while the bigger anions

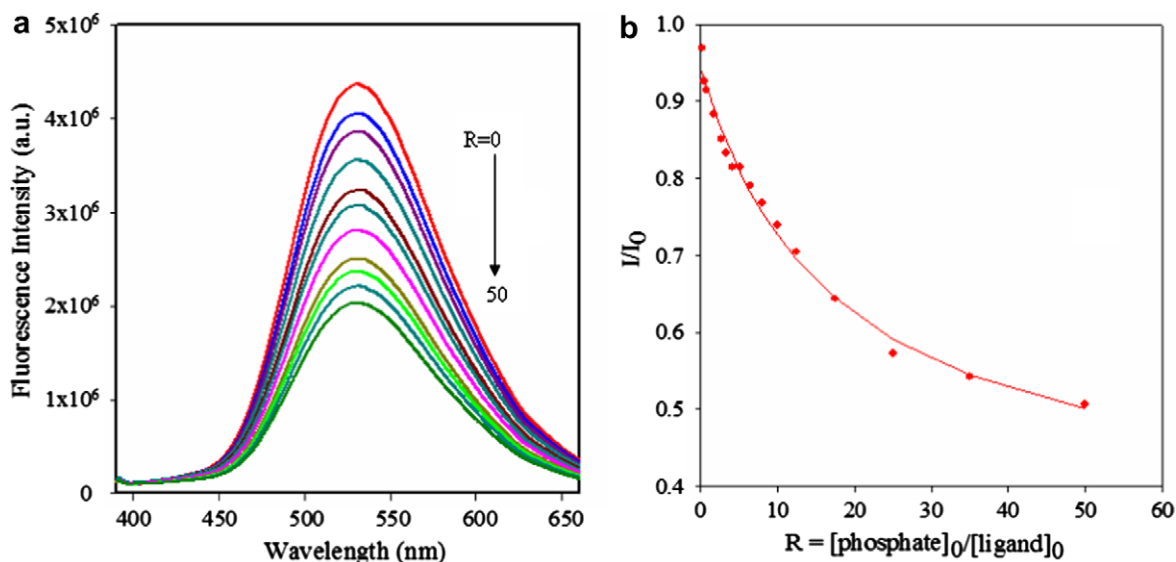


Figure 2. (a) Change in the fluorescence emission spectra of $\text{H}_2\text{L}(\text{Ts})_2$ with an increasing amount of phosphate ($R = [\text{phosphate}]_0/[\text{L}]_0 = 0\text{--}50$, excitation at 350 nm, 25 °C) and (b) the fluorescence titration curve as a function of R with I/I_0 .

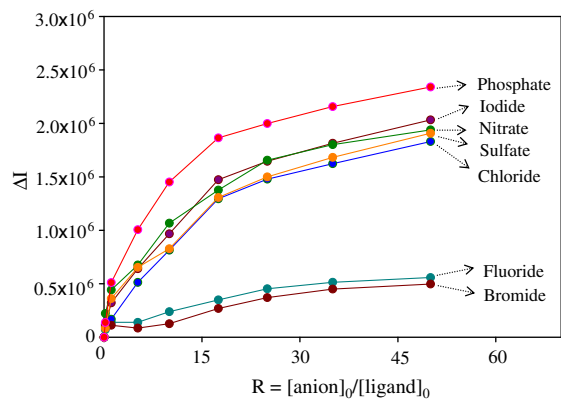


Figure 3. Plot of change in emission of $H_2L(Ts)_2$ with increasing amount of anion ($R = 0$ – 50) at 530 nm.

Table 1

Association constants (K) and binding energies (E) of the anion complexes of $[H_2L]^{2+}$

Anion	K^a (M^{-1})	E^b (kcal/mol)
Fluoride	1.3×10^4	–176.4
Chloride	4.0×10^4	–154.8
Bromide	3.6×10^3	+37.5
Iodide	3.8×10^4	^c
Nitrate	3.9×10^4	–147.8
Sulfate	4.5×10^4	–302.9
Phosphate	6.4×10^4	–590.1

^a Association constant determined by fluorescence titrations in DMSO at 25 °C (error limit is less than 20%).

^b Binding energy obtained from DFT calculations.

^c The 6-31+G(d,p) basis set is not available for iodide.

such as iodide and chloride fit into the macrocyclic cavity, showing stronger affinity under similar conditions. However, bromide was found to interact much weakly compared with other halides, which could be related to its possible bridging in the non-polar solvent leading to the formation of tribromide.²²

In order to investigate the properties of the anion-ligand complexes, with a view of estimating binding energies, we also carried out ab initio calculations based on density functional theory (DFT). Since the anion-ligand systems involve hydrogen-bonding interactions, it is important to choose an exchange-correlation functional which accurately captures these electronic effects. To this end, all DFT calculations were performed using the M06-2X²³ hybrid functional which incorporates an improved description of dispersion energies, an effect which was previously found to be necessary for describing non-covalent interactions.²⁴ The initial equilibrium geometry for the free protonated ligand with two positive charges (H_2L^{2+}) was first optimized at the M06-2X/MidiX level of theory. From this equilibrium geometry, each of the negatively charged anions was added near the two protonated amines at the center of the ligand. The geometry of the anion-ligand complex was then optimized at the M06-2X/MidiX level of theory. Single-point energies with the 6-31G(d,p) basis set (a diffuse 6-31+G(d,p) basis set was used for all the anions) were subsequently performed for each of the M06-2X/MidiX-relaxed geometries. The optimized structure of the ligand and some representative structures are shown in Figure 4. The structure of free H_2L^{2+} was optimized in a rectangular fashion (Fig. 4A) as seen in the *p*-xylyl macrocycle¹³ and forms a suitable cavity to host an anion. From our DFT-optimized complexes, we found that the ligand deformed its geometry in order to encapsulate each of the anions.

The calculated binding energies for the complexes, as shown in Table 1, roughly correlated with the charge and electronegativity of the anion. Specifically, an anion with a larger charge demonstrated

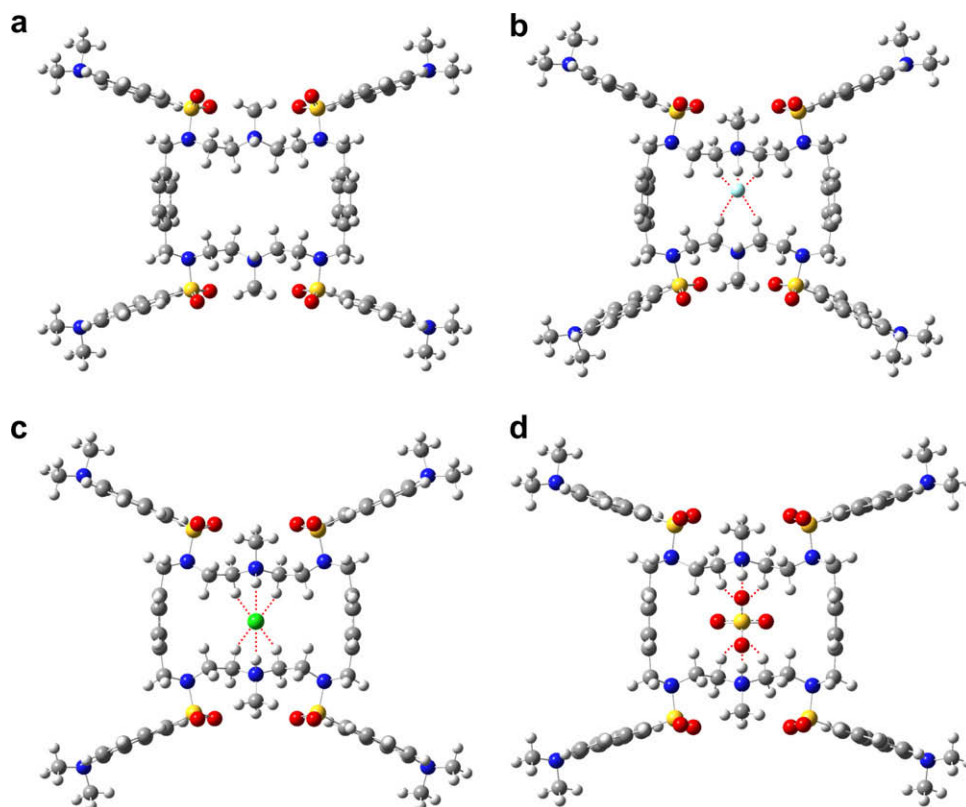


Figure 4. Optimized structures: diprotonated **L** (a), fluoride complex (b), chloride complex (c) and sulfate complex (d).

increased binding ($\text{PO}_4^{3-} > \text{SO}_4^{2-} > \text{NO}_3^-$), and an anion with a larger electronegativity showed higher binding energies ($\text{F}^- > \text{Cl}^- > \text{Br}^-$). Interestingly, each of the anions except fluoride formed two $\text{NH}\cdots\text{X}^-$ and four additional $\text{CH}\cdots\text{X}^-$ bonds from the methylene groups close to the tertiary amines. Although the attachment of dansyl groups makes the secondary amines unavailable for protonation, the ligand binds an anion strongly. As reported previously, the parent ligand **1** in its tetra-protonated form was found to show moderate binding affinity ($K = 500 \text{ M}^{-1}$) for bromide in CDCl_3 that was determined by ^1H NMR titrations.²⁰ In the present case, the observed high binding constants measured at much dilute conditions ($1 \times 10^{-6} \text{ M}$ compared with $5 \times 10^{-3} \text{ M}$) can be attributed to the decreased salt effect²⁵ as well as to the involvement of $\text{CH}\cdots$ anion interactions.^{26,27} The small fluoride, however, failed to coordinate with one of the protons on the tertiary amines. In the case of the bromide complex, a large deformation occurred after the encapsulation of the anion, resulting in a slightly positive binding energy. Thus the observed binding energy of the complex is fairly consistent with the lower binding affinity for bromide as compared to that for chloride in solution ($K = 3.6 \times 10^3$ for bromide vs $K = 4.0 \times 10^4 \text{ M}^{-1}$ for chloride). The variations in binding energies indicate a significant change in electronic structure among the anion-ligand complexes, confirming the experimental observation of fluorescence quenching for each of the complexes.

In conclusion, we report a macrocycle-based fluorescence chemosensor using an azamacrocycle and dansyl group, which effectively binds oxoanions and halides showing strong affinity for phosphate and chloride. The addition of an anion to the chemosensor did not affect the fluorescence emission wavelength (350 nm) for H_2L^{2+} , thus not allowing the direct identification of different anion species; however, it resulted in a significant quenching of fluorescence emission at a different magnitude. DFT calculations indicate that an anion is coordinated not only with the NH groups but also with CH_2 attached to the tertiary nitrogens, supporting the higher binding constants observed in solution. The complexation process leads to a significant change in the electronic density of the attached fluorophores resulting in the quenching of fluorescence emission. The unique combination of fluorescence experiments coupled with DFT calculations allows a guided understanding toward the rational design for other macrocycle-based sensors.

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Supplementary data

Supplementary data (experimental procedure for the synthesis of **L** and $\text{H}_2\text{L}(\text{Ts})_2$, figures showing the ^1H NMR peaks assignment of the ligand, experimental procedure for titrations, the change in the fluorescence emission spectra in presence of different anions, the optimized structures of the complexes and calculated hydrogen bond distances) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.004.

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