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Macrocyclic and Acyclic Molecules Synthesized from Dipyrrolylmethanes: Receptors for Anions

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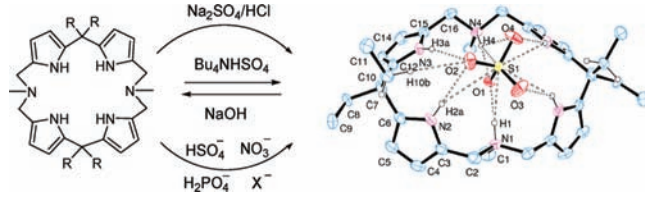
ABSTRACT



A new class of macrocyclic and acyclic molecules was synthesized by the Mannich reactions of dipyrrolylmethanes to investigate anion recognition. The X-ray structures of the macrocycle and sulfate complexes are reported.

Developing synthetic receptors that bind anions with high affinity and selectivity is an active area of research in supramolecular chemistry, as selective binding of an anion can lead to an effective remedy for problems caused by anions, which contaminate the environment and play important roles in biological systems.[1,2] For example, the sulfate anion is present in nuclear fuel waste along with other oxoanions,[3] which eventually get into the environment. Given that the sulfate anion has a large standard Gibbs energy of hydration (−1080 kJ mol^{-1}), the separation of the sulfate anion from an aqueous solution is a challenging task.[4] However, in nature, the sulfate anion is recognized and transported by the sulfate-binding protein through hydrogen bonds.[5] In an effort to mimic this natural phenomenon, several synthetic sulfate-binding receptors have been reported which can be broadly classified as receptors containing metal centers[6] and receptors without metal centers.[7] While many receptors of the former type have been reported and showed high affinity and selectivity for the sulfate anion by a

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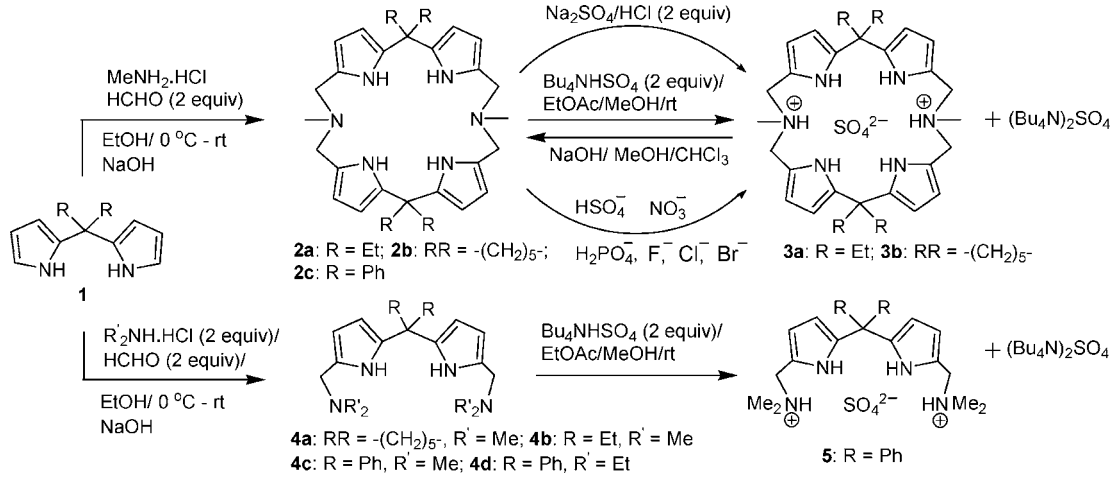
Scheme 1. Synthesis of Receptors, **2**·2H_2O and **4**·H_2O, and Their Sulfate Complexes, **3** and **5**·2H_2O·MeOH



competition crystallization experiment, very few receptors of the latter type with high affinity and selectivity for the sulfate anion in aqueous medium are known.[8]

To develop receptors containing pyrrole rings, we used Mannich reactions giving macrocycles[9] in contrast to the traditionally used condensation reactions. Applying the same strategy on dipyrrolylmethanes, herein we report yet another new class of receptors **2a**−**c** and **4a**−**d**, their sulfate complexes **3a**,**b** and **5**, selective crystallization of **3a**, and anion recognition studies.

The new macrocycles **2a**−**c**·2H_2O were synthesized in 40−75% yields by the Mannich reactions of dipyrrolylmethanes[10] in the presence of primary amine hydrochloride and formaldehyde in a 1:1:2 molar ratio, respectively. In analogy to azacalixarenes,[11] **2** can be named tetrahomodiazacalix[2]dipyrrolylmethane or diazacalix[2]dipyrrolylmethane. When the reaction was carried out with secondary amine hydrochloride and formaldehyde in a 1:2:2 molar ratio, respectively, acyclic molecules **4a**−**d**·H_2O containing two R_2NCH_2 groups in the 1,9-positions were obtained in good yields (Scheme 1). Lindsey's group reported similar types of acyclic Mannich bases of dipyrrolylmethanes by using Eschenmoser's reagent.[12]

The ^{1}H NMR spectra of **2a**−**c**·2H_2O showed a broad singlet at δ 8.55, 8.52, and 8.76, respectively, for their NH protons, which are downfield shifted as compared to the corresponding dipyrrolylmethane. The structures of the macrocycles **2a**−**c** are confirmed by the X-ray structure of **2a**·2H_2O and (+)ESI-MS spectra of **2a**−**c**, which showed the molecular ion peaks *m*/*z* at 515.3862, 539.3867, and 707.3858, respectively, corresponding to the mass of their [M + H^+] ions.

The structure of **2a**·2H_2O (Figure 1, a) reveals that the molecule consists of two dipyrrolylmethane moieties connected by two $CH_2N(Me)CH_2$ segments at 1,9-positions of the dipyrrolylmethane molecule to form a tub-shape conformation, resembling the conformation of the cot molecule, and two water molecules situated below the tub shape. While two of the alternative pyrrole NH protons (N2 and N5) are facing each other, the remaining two NH protons (N3 and N6) and both the N−Me groups are pointing downward, the direction in which the water molecules are attached. The tertiary amine nitrogen atoms, N1 and N4, as H-bond acceptor and the pyrrole N6H proton as H-bond donor are involved in trapping a water molecule, which in turn is H-bonded to another water molecule lying below the first one.

To investigate anion coordination chemistry of **2**, the sulfate anion complexes **3a** and **3b**·MeOH were synthesized in 72% and 77% yields by the reaction between **2a**·2H_2O or

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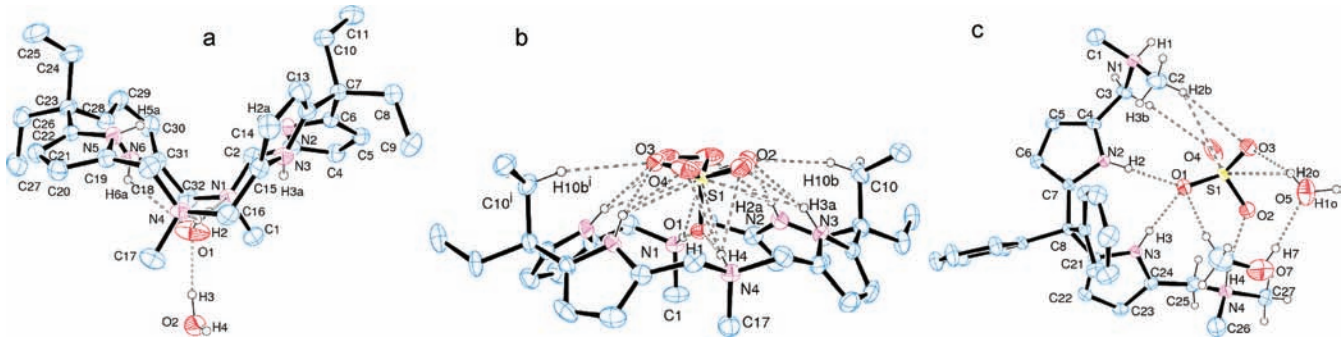

Figure 1. ORTEP diagram of **2a**·2H_2O (a), **3a** (b), and **5**·2H_2O·MeOH (c) with 30% probability ellipsoids. Most H atoms and one water molecule of **5**·2H_2O·MeOH are omitted for clarity. Selected bond lengths (Å) and angles (deg): For **2a**·2H_2O: O1···N1 2.803(3), H1···N1 2.042(19), O1−H1···N1 147(3); O1···N4 2.823(3), H2···N4 2.010(18), O1−H2···N4 157(3); O2···O1 2.736(4), H3···O1 1.824(17), O2−H3···O1 174(3). For **3a**: N1···O1 2.740(5), H1···O1 1.82, N1−H1···O1 172.4; N1···S1 3.493(4), H1···S1 2.63, N1−H1···S1 154.2; N2···O2 3.076(6), H2A···O2 2.20, N2−H2A···O2 173.6; N2···S1 3.680(3), H2A···S1 2.91, N2−H2A···S1 147.7; N3···O2 2.992(6), H3A···O2 2.14, N3−H3A···O2 162.3; N4···O1 2.833(4), H4···O1 1.92, N4−H4···O1 167.8; N4···S1 3.530(4), H4···S1 2.65, N4−H4···S1 158.4. For **5**·2H_2O·MeOH: N2···O1 2.800(2), H2···O1 1.94, N2−H2···O1 178.2; N3···O1 2.821(2), H3···O1 1.97, N3−H3···O1 171.2; N4···O2 2.773(2), H4···O2 2.02, N4−H4···O2 139.3; O5···O3, 2.832(3), H2o···O3, 1.93(2), O5−H2o···O3 165(3); O5···S1 3.700(2), H2o···S1 2.93(2), O5−H2o···S1 142(2).

2b·2H_2O and 2 equiv of Bu_4NHSO_4 in an EtOAc/MeOH mixture, respectively. The analogous reaction between the acyclic molecule **4c**·H_2O and Bu_4NHSO_4 afforded the sulfate complex **5**·2H_2O·MeOH in 87% yield. As a result of the sulfate anion coordination, the ^{1}H NMR spectra of **3a** and **3b** showed, in contrast to the sulfate free macrocycles, two different sets of resonances for the methylene groups of the $CH_2N^+H(Me)CH_2$ segment and their coupling with the N^+H proton.

The sulfate complex **3a** was also synthesized in 77% crystalline yield from the reaction between **2a**·2H_2O and sodium sulfate in the presence of 2 equiv of HCl. However, the same reaction in the absence of HCl has not yielded **3a**, suggesting geometric and electrostatic complementarities between SO_4^{2-} and [**2a**·2H]$^{2+}$ that prefers the formation of a sulfate complex rather than a chloride complex. This observation led us to investigate the affinity of **2a**·2H_2O toward the sulfate anion by a competition crystallization experiment. Interestingly, only the sulfate complex **3a** was crystallized in more than 85% yield from a solution containing a mixture of 2 equiv of each competing anion such as HSO_4^- (or SO_4^{2-}/2HCl), $H_2PO_4^-$, F^-, Cl^-, Br^-, and NO_3^- (10 equiv) in the THF/H_2O/MeOH (5:1:1, v/v) mixture and was confirmed by ^{1}H NMR and IR spectra (see the Supporting Information). Treatment of **3a** with aq NaOH gave back the receptor **2a**·2H_2O. Thus, the selective crystallization of **3a** from an aqueous−organic solvent and the recovery of the receptor form a process for separating sulfate anions present in nuclear waste.

The structure of the sulfate complex **3a** (Figure 1, b) is confirmed by X-ray and reveals that the sulfate anion is coordinated to **2a** through NH···O, NH···S, and C−H···O types of H-bonds and is further stabilized by the electrostatic interactions from the two ammonium cations formed in situ by the transfer of protons from Bu_4NHSO_4. While all the pyrrole NH and the ammonium hydrogen atoms are pointing toward the sulfate anion and hydrogen bonded, the NMe groups are facing the opposite side. All of the pyrrole N atoms, both of the *meso*-carbons of the dipyrrolylmethane moieties, and the sulfate O1 atom are in a plane, rendering a flat shape to **2a**, and the sulfur atom lies at ∼1.5 Å from this plane. Besides, **3a** has a mirror plane passing through N1, N4, C1, C17, S1, and O1 atoms; SO_4^{2-} sits on the mirror plane, and its O2, O3, and O4 atoms are disordered over two positions.

The X-ray structure of **5**·2H_2O·MeOH (Figure 1, c) reveals that one sulfate anion is bound to one molecule of **4c** by both electrostatic interactions from the ammonium cations and hydrogen bonds. The two pyrrole NH protons, in a chelated fashion, and one of the ammonium hydrogen atoms (N4H), whose methyl groups are in *gauche* and *trans* positions to the pyrrole carbon atom (C24) that is supported by the dihedral angles (C26−N4−C25−C24 = 48.9° and C27−N4−C25−C24 = 172.8°), are hydrogen bonded to O1 and O2, respectively. Conversely, the hydrogen atom of the ammonium cation (N1H), whose two methyl groups are in *gauche* positions to the pyrrole carbon atom (C1−N1−C3−C4 = −59.4° and C2−N1−C3−C4 = 68.8°), is not hydrogen bonded to the sulfate anion, but the methyl and methylene groups of this segment (N1) are involved in C−H···O type hydrogen bonds. Although the cation [**4c**·2H]$^{2+}$ has four NH protons for H-bonds, the sulfate anion utilizes only three of them and prefers H-bonds with the solvent molecules.

The anion binding study of **2a**·2H_2O was carried out by ^{1}H NMR titrations. The binding constants K_a of the complexes formed between the receptor **2a**·2H_2O and the halide anions were determined from the changes in the NH or pyrrole β-CH resonance observed upon addition of aliquots of anions as their tetra-*n*-butylammonium salts in acetone-d_6 at room temperature by the EQNMR program with a 1:1 receptor:anion model complex, which are verified by another nonlinear least-squares method.[13] As an interesting example, upon addition of aliquots of fluoride anion to a solution of **2a**·2H_2O in acetone-d_6, the NH resonance initially appeared very broad and then appeared as a doublet with J_{HF} = 27 Hz, indicating a strong interaction with the receptor. Similar coupling between pyrrole NH and F^- has been reported

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earlier.[14] Conversely, the resonance due to the pyrrole β-CH protons smoothly shifted to the upfield region for which the titration curve could be fitted rather well in comparison to the NH resonance. The fluoride anion induced change in the chemical shift of the NH proton is the largest ($\Delta\delta = 5.34$) among the halide anions.

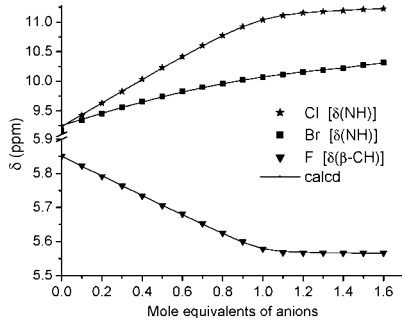

Figure 2. ^{1}H NMR titration curve fittings for **2a**·2H_2O.

The titration curve fittings are given in Figure 2. The binding constants K_a of **2a**·2H_2O for F^-, Cl^-, and Br^- are $>10^4$, 4763 (<10% error), and 317 (13% error) M^{-1}, respectively, and the binding stoichiometry 1:1 for each complex is confirmed by Job's plots, showing maxima at 0.5 mol fraction of **2a**·2H_2O (see the Supporting Information). No change in the NH resonance was observed upon addition of iodide anion. This trend of K_a, $F^- > Cl^- > Br^- > I^-$, is the same as the strength of the hydrogen bonds formed by these anions.

As ^{1}H NMR titration spectra of **2a**·2H_2O and Bu_4NHSO_4 showed a slow exchange process in $CDCl_3$ or in acetone-d_6, its K_a could not be determined. Conversely, log K_a for the sulfate complex of **4a**·H_2O or **4c**·H_2O in $CDCl_3$ was estimated to be >4 by EQNMR with a 1:2 model complex (host:guest). A similar range of log K_a has also been observed with other receptors.[15] This binding stoichiometry was confirmed by the Job's plot in $CDCl_3$ that showed a maximum at 0.33 mol fraction of **4c**·H_2O. This 1:2 complex formation in $CDCl_3$ is in constrast to the solid state structure of **5**·2H_2O·MeOH. Probably, the structure of the 1:2 complex is cleaved to form most stable $(Bu_4N)_2SO_4$ and a 1:1 complex when it crystallizes from a MeOH−EtOAc mixture. The slow exchange process and the large K_a indicate the preference of the receptors, **2**·2H_2O and **4**·H_2O, for the sulfate anion over other anions and is supported by the readily forming crystals of **3** and **5**·2H_2O·MeOH and the selective crystallization of **3a**.

In conclusion, novel macrocycles **2a**−**c**·2H_2O, representing a new class of expanded calix[4]pyrrole molecule, and acyclic molecules **4a**−**d**·H_2O are synthesized and act as receptors for anions. **2a**−**c**·2H_2O and **4a**−**d**·H_2O have both hydrogen bond donors (NH) and acceptors (tertiary amine groups) in the cleft, which make them suitable to act as an ion-pair receptor for which **3** and **5**·2H_2O·MeOH are the examples. The flexibility of the macrocycle in changing its conformation to accommodate a guest species is demonstrated through the crystal structure of **3a**. Work on other pyrrole-based receptors is under progress.

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Supporting Information Available: Synthetic procedures; NMR, IR, crystallographic data (CIF); structure refinement data;[16] X-ray structures; and details of binding constant calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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