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Synthesis and Anion Binding Properties of 2,5-Diamidothiophene Polypyrrole Schiff Base Macrocycles

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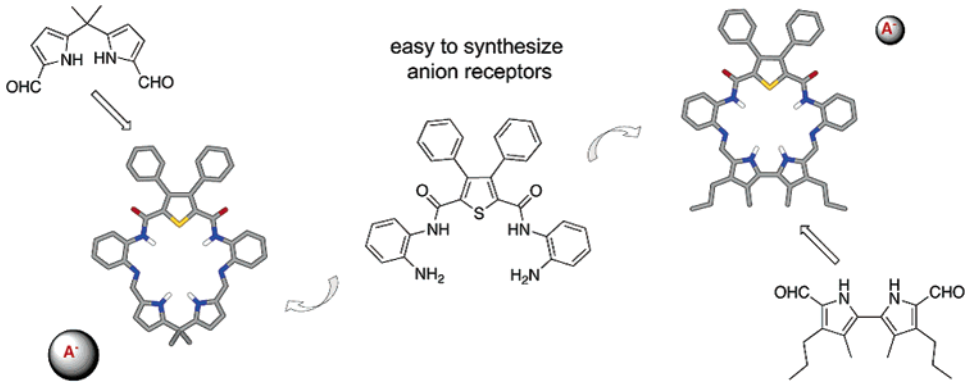
ABSTRACT



Two easy-to-synthesize polypyrrolic 2,5-diamidothiophene Schiff base macrocycles are reported, along with their anion binding properties as determined via UV–vis spectroscopic titrations carried out in dichloroethane. There is a striking difference between the interactions with anions of the two macrocycles, a finding ascribed to differences in their rigidity. For example, the more flexible dipyrromethane-derived macrocycle displays a 1.2:1 hydrogen sulfate versus nitrate selectivity, while its more rigid bipyrrole-derived congener shows a 7.4:1 selectivity in favor to hydrogen sulfate.

The ubiquity of anions in nature makes an understanding of biological anion-receptor interactions a topic of considerable current interest.[1] It is also inspiring the synthesis of synthetic anion receptors, systems whose potential utility could span the full spectrum of applications from separations and waste remediation to biomedical analysis and therapy.[2] Indeed, the field of synthetic anion receptor chemistry is one of the fastest growing disciplines within the general context of supramolecular chemistry.[3] One of the problems that has attracted the attention of our groups[6] and others[4] is the design of systems that effect the specific recognition of hydrogen sulfate in nitrate-rich mixtures. The reason for this interest is that such mixtures are surrogates for nuclear tank waste, whose remediation is made difficult by the presence of small

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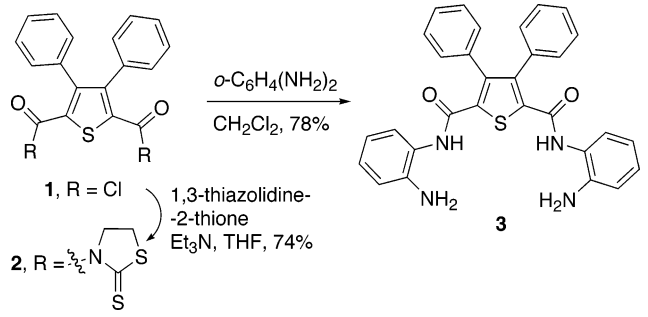
amounts of sulfate.[5] Recently, we reported the synthesis of a 2,6-diamidopyridine-dipyrromethane hybrid macrocycle[6] and several congeners based on bipyrole[7] that displayed high selectivity for HSO_4^- over NO_3^-. In an effort to understand more completely the determinants of this selectivity, we have sought to replace the central 2,6-diamidopyrridine moiety by another known anion receptor subunit, namely, 2,5-diamidothiophene.[8] Such a substitution was expected to result in a more flexible macrocyclic receptor and one that would interact with a wider range of anions.[9]

We now wish to report the synthesis and anion binding properties of the first members of this potentially large series of receptors, as well as their anion binding properties. As compared to the corresponding pyridine-based systems, these new agents display affinities for a broader range of anions. They also differ in terms of selectivity. In particular, while the pyridine-based macrocycles display a preference for tetrahedral anions, the thiophene-based systems permit a discrimination based on size rather than specific geometry.

The bis(2-aminophenyl)-thiophene-2,5-dicarboxamide **3** (Scheme 1) is the central precursor for the synthesis of

Scheme 1. Synthesis of Precursor **3**



macrocycles **6** and **7** (Scheme 2). It was prepared using an extension of the procedure introduced by Picard et al.[10] Specifically, 2,5-thiophene dicarboxylic acid was converted into the corresponding diacid dichloride, **1**, by treatment with $SOCl_2$.[8] Compound **1** was then condensed with 1,3-thiazolidine-2-thione to give the diamide **2** in 74% yield. Reaction of **2** with *o*-phenylenediamine in dichloromethane then afforded compound **3** in 78% yield. In analogy to what was done previously,[6,7] precursor **3** was condensed with the diformyldipyrromethane **4** in the presence of 2.5 equiv of H_2SO_4 to give **6**·H_2SO_4 in 90% yield.[11] In a similar manner, macrocycle **7**·HCl was synthesized in 83% yield via the condensation of **3** with diformylbipyrrole **5** in the presence of 2.5 equiv of HCl. Both macrocycles were converted to their respective "free base" forms by treating methylene chloride solutions of the corresponding acid salts with triethylamine. The overall yields for the deprotonation steps were 81% and >99% for **6** and **7**, respectively.

Proof for the proposed structures of macrocycles **6** and **7** came from single-crystal X-ray diffraction analyses carried out using their neutral forms. On this basis it was determined that compound **6** adopts a conformation in the solid state in which the two phenyl groups in the β-positions of the thiophene are held above the effective macrocyclic cavity. Presumably as a consequence, the sulfur atom of the thiophene is forced to point out from the central macrocyclic core. The presence of several solvent molecules (acetone) is also seen in this structure. One of these is bound within the central cavity of the macrocycle via an N4H−O3 (2.92 Å, 175°) hydrogen bond from one of the pyrrole rings, as well as a weak C37H−O3 (3.33 Å, 141°) hydrogen bond from one of the β-phenyl rings of the thiophene. A second bound acetone molecule is coordinated via a hydrogen bond

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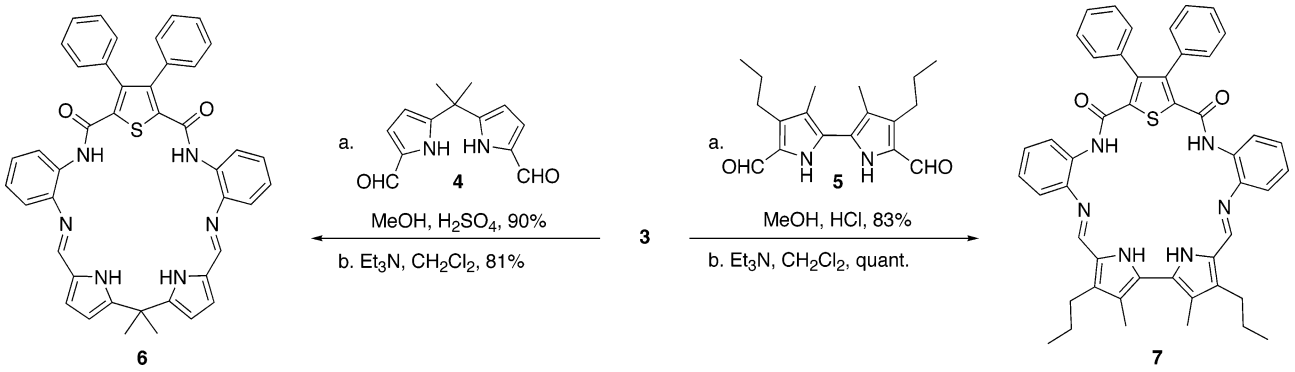
(11) Efforts to prepare an analogue of **6** lacking the β-phenyl substituents were stymied by a lack of solubility.

Scheme 2. Synthesis of Macrocycles **6** and **7**



involving the other pyrrole moiety (i.e., N3H−O4 = 3.18 Å, 127°). Finally, a third acetone molecule is coordinated through two weak C22H−O5 (3.57 Å, 168°) and C24H−O5 (3.59 Å, 135°) hydrogen bonds involving the imine CH and an *o*-phenylene CH proton. In addition to these effects, the structure reveals that both amide NH protons are hydrogen bound to the Schiff base nitrogen atoms N1H−N2 (2.68 Å, 111°) and N6H−N5 (2.66 Å, 113°). The X-ray structure of **7** provides support for the notion that it contains a framework more rigid than that of **6**. In this case, the bipyrrole unit forces the macrocycle to adopt an "all-in" structure, wherein all of the N and S atoms point in toward the center of the ring. There are two internal hydrogen bonds in this structure, between the amide NHs and the Schiff base nitrogen atoms: N1H−N2 (2.66 Å, 109°) and N6H−N5 (2.72 Å, 97°). Also to be noted is the twist (dihedral angle = 53°) present in the bipyrrole moiety. This twisting could reflect unfavorable steric interactions between the 4,4′-methyl groups but mostly likely is due to presence of intramolecular hydrogen bonding interactions involving the pyrrole NH protons and the amide carbonyl oxygen atom of another molecule. A second X-ray structure of **7** was solved from single crystals obtained via slow evaporation of a methylene chloride−acetone mixture. In this case, macrocycle **7** exists in the form of a solvent-bridged dimer in the solid state (cf. Supporting Information).

Table 1. Affinity Constants (M^{-1}) for Binding of Anions by Receptors **6** and **7** As Determined from UV−vis Spectroscopic Titrations[d]

anion	**6**	**7**	anion volume (Å^3)[b]
Cl^-	16 600 ± 900	3 300 ± 300	24.8
Br^-	7 100 ± 1000	7 100 ± 900	31.5
AcO^-	3 200 ± 600	3 600 ± 300	17.8
NO_3^-	15 400 ± 2100	1 000 ± 300	24.0
HSO_4^-	18 900 ± 1000	7 400 ± 800	28.7
$H_2PO_4^-$	9 500 ± 400	*c*	33.5

[a] The R^2 values for the curves fits used to determine the affinity constants range between 0.989 and 0.998. [b] From ref 8. [c] No clean fit to the binding profile could be made. [d]Titrations were carried out in $C_2H_4Cl_2$ at 23 °C. The anions were studied in the form of their tetrabutylammonium salts. Binding stoichiometries are 1:1 unless otherwise noted.

Macrocycles **6** and **7** were investigated as potential anion binding agents. Toward this end, their interactions with various tetrabutylammonium salts were studied via UV−vis spectrophotometric titrations. For reasons of solubility, involving both the anion salts and the macrocycles themselves, these studies were conducted in dichloroethane. Binding stoichiometries were determined using Job plots. Table 1 summarizes the associated findings.

A quick inspection of this table reveals that, as a general rule, macrocycle **6** displays a higher affinity for the various test anions studied than does **7**. There are two notable exceptions, namely, bromide and acetate anion. In the case of these two anions, the association constants were found to be very similar (e.g., for acetate, $K_a = 3200 \pm 600$ and 3600 ± 300 M^{-1} for **6** and **7**, respectively). In attempting to rationalize these findings, it is useful to note that macrocycle **6** displays the strongest interaction with hydrogen sulfate, chloride, and nitrate anions, followed by dihydrogenphosphate, bromide, and acetate, respectively.

This selectivity, as well as the generally higher affinity this system displays relative to that of **7**, is ascribed to its greater inherent flexibility. This flexibility allows it to interact with anions of very different geometry, such as hydrogen

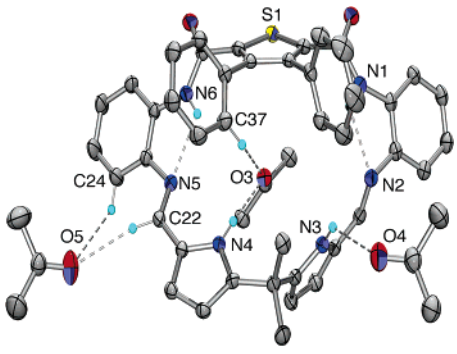


Figure 1. ORTEP-POVray rendered view of **6** showing three bound acetone molecules. Most hydrogen atoms have been removed for clarity. Thermal ellipsoids are scaled to the 50% probability level.

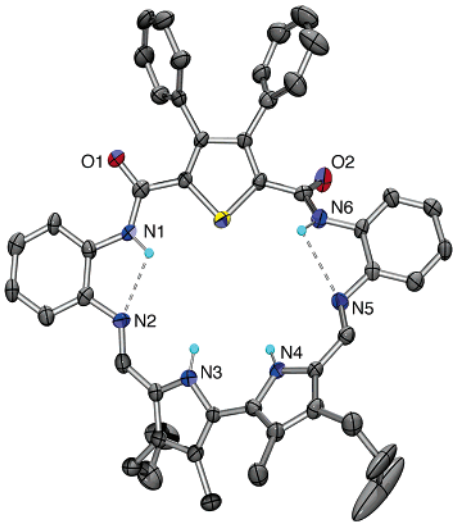


Figure 2. ORTEP-POVray rendered view of **7**. Most hydrogen atoms have been removed for clarity. Thermal ellipsoids are scaled to the 50% probability level.

sulfate (tetrahedral), nitrate (trigonal planar), and chloride (spherical), while showing, naturally, a preference for those it can best accommodate. A comparison of the anion affinities with anion volume[12] leads to the conclusion that macrocycle **6** favors anions with volumes ranging between 24.0 and 28.7 Å^3. In contrast, macrocycle **7** interacts most strongly with the larger anions considered in this study. For instance, the ca. 2:1 selectivity for chloride over bromide seen in the case of **6**, is essentially reversed in the case of **7**. Such observations are considered consistent with the fact macrocycle **7** contains a core that is large and fairly rigid, as inferred from the X-ray structural analysis. In other words, receptor **7**, in contrast to **6**, possesses a well-defined cavity that cannot change its size easily to interact with anions of higher charge density and smaller dimensions. In conclusion, two thiophene-containing polypyrrolic Schiff base macrocycles have been prepared. To the best of our knowledge they are the first members of a potentially large class of easy-to-synthesize anion receptors. Studies of the anion binding behavior of these systems revealed a dramatic difference between the more flexible macrocycle (**6**) and an otherwise similar rigid analogue, **7**. This work thus serves to highlight further how subtle changes in design can be translated into useful differences in anion selectivity.

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Supporting Information Available: General methods and materials, synthetic experimental, representative Job plots, UV−vis titrations, corresponding binding isotherms, details of affinity constant determinations, and X-ray crystallographic information including CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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