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Published on Web 01/25/2006

Tetrathiafulvalene-Calix[4]pyrroles: Synthesis, Anion Binding, and Electrochemical Properties

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Abstract: The syntheses of monotetrathiafulvalene-calix[4]pyrrole **5** and bistetrathiafulvalene-calix[4]pyrrole **6**, prepared from the acid-catalyzed condensation of monopyrrolo[3,4-*d*]tetrathiafulvalene (MPTTF, **7**) with acetone in the presence of tripyrrane **8** and dipyrromethane **9**, respectively, are described. Compound **5** and the previously reported tetrathiafulvalene-calix[4]pyrrole **4** both adopt a 1,3-alternative conformation in the solid state, as determined from X-ray crystallographic analysis. The anion binding properties of the tetrathiafulvalene-calix[4]pyrroles **5** and **6**, as well as those of the parent *meso*-octamethylcalix[4]pyrrole (**1**), were investigated in acetone using ^{1}H NMR spectroscopic and isothermal titration calorimetry (ITC) techniques and, within the error limits of the methods, were generally found to give concordant results. On the basis of the results of the ITC studies carried out in 1,2-dichloroethane, increasing the number of tetrathiafulvalene units annulated to the calix[4]pyrrole system serves to enhance the anion binding affinities substantially but at the price of lowered selectivity. Cyclic voltammetry (CV) studies, carried out in 1,2-dichloroethane, provided evidence of an anion-dependent electrochemical response with Cl^- and Br^- ions. This response was particularly dramatic in the case of the monotetrathiafulvalene-calix[4]pyrrole **5**, with a ΔE_{max} of −145 mV being seen after the addition of approximately 1 equiv of Cl^- ion.

Introduction

Anion binding chemistry has attracted considerable attention in supramolecular chemistry because of the unique function of anions in biological systems.[1] For example, 70% of enzymatic binding and reactions are related to anions, while oligonucleotides, such as DNA and RNA, are polyanions.[2] In addition, it is believed that many diseases—such as cystic fibrosis[3] and Alzheimer's disease[4]—are induced by the malfunction of natural anion regulation processes. Environmentally, the eutrophication of water is caused by phosphate[5] and nitrate[6] ions used in agricultural fertilizers, while considerable risk is posed by pertechnetate anion,[7] a key radioactive component of nuclear waste. Given this importance, it is not surprising that extensive study has been dedicated to the design of simple artificial anion receptors and sensors. One of the most elegant anion receptors, calix[4]pyrrole **1** (Figure 1), first made in 1886 by Baeyer[8] and reinvestigated by Sessler and Gale[9a] in 1996 as an anion binding agent, not only exhibits good anion binding affinity and selectivity in apolar solvents, it can also be easily prepared in a one-step reaction. Continued efforts to improve anion binding ability and selectivity have resulted in various structural modifications of the basic calix[4]pyrrole skeleton.[10,11] One of the best examples (Figure 1) is the *meso*-octamethyl-β-octafluorocalix[4]pyrrole[12] (**2**) which display a dramatic improvement in the anion binding affinity. This latter feature can most likely be accounted for by the presence of eight electron-withdrawing fluoro substituents in the β-pyrrolic positions, which increase the acidity of the pyrrolic NH protons in **2** as compared to the parent calix[4]pyrrole **1**.

Derivatives of calix[4]pyrroles have been extensively studied in the search for chemosensors capable of recognizing specific

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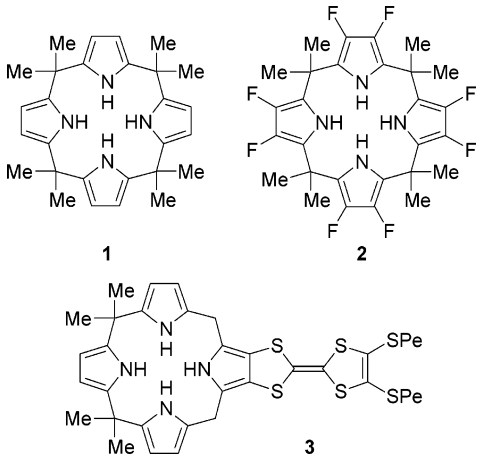

Figure 1. Structural formulas of *meso*-octamethylcalix[4]pyrrole (**1**), *meso*-octamethyl-*β*-octafluorocalix[4]pyrrole (**2**) and pseudomonoTTF-calix[4]-pyrrole **3**.

chemical species, and a large number of optically active calix-[4]pyrrole-based sensors has been reported.[13] Although some efforts have been carried out to combine calix[4]pyrroles with redox-active units, such as ferocene,[14] in order to generate electrochemically active sensors, such efforts were not fully successful until 2003[15] when a chemosensor based on a redox-active tetrathiafulvalene[16,17] (TTF) unit in combination with a pseudocalix[4]pyrrole[18] system was reported. Attaching one redox-active TTF unit directly to the pseudocalix[4]pyrrole core produced (Figure 1) a receptor **3** with strong binding affinities toward Br^-, Cl^-, and F^- ions. However, the inherent instability[19] of the underlying pseudocalix[4]pyrrole system precluded further studies of this system. Accordingly, it was considered desirable to prepare new TTF oligopyrroles that are based on the *meso*-octamethylcalix[4]pyrrole core. To the extent such systems could be made, they would provide insights into the effect that annulation of more than one TTF unit to the upper rim of the *meso*-octamethylcalix[4]pyrrole core can have on the anion binding properties of the calix[4]pyrrole core. They would also allow the presence of an anionic analyte to be monitored through changes in the cyclic voltammetry (CV) response.

In a recent communication,[20] we reported how the complexation and decomplexation of electron-deficient guests with a tetraTTF-calix[4]pyrrole host **4** (Figure 2) could be controlled through the complexation of Cl^- ions. In this follow-up full paper, we describe the synthesis of this system in detail, as well as the preparation and characterization of two new TTF-calix-[4]pyrroles, namely, (i) the monoTTF-calix[4]pyrrole **5** (Figure 2) bearing one fused TTF unit and (ii) the bisTTF-calix[4]pyrrole **6** (Figure 2) incorporating two such TTF units. We also describe the anion binding behavior of these systems, as inferred from quantitative ^{1}H NMR spectroscopic titration and isothermal titration calorimetry (ITC) studies and qualitative electrochemical analyses.

Results and Discussion

Synthesis. The routes employed in the synthesis of the three TTF-calix[4]pyrroles are outlined in Scheme 1. They are based on the use of three key precursors already reported in the literature, namely, (i) the monopyrrolo-TTF[21] (MPTTF) derivative[22] **7**, (ii) the tripyrrane[11] **8**, and (iii) the dipyrromethane[23] **9**. Reaction of the MPTTF derivative **7** with 1 equiv of the tripyrrane **8** in a mixture of Me_2CO and CH_2Cl_2 in the presence of excess trifluoroacetic acid[24] (TFA) afforded a mixture of the expected product monoTTF-calix[4]pyrrole **5** in 23% yield, as well as the bisTTF-calix[4]pyrrole **6** in 14% yield after aqueous workup and column chromatographic purification. The surprisingly high yield of the bisTTF-calix[4]pyrrole **6** can be attributed to the low stability of the tripyrrane **8**, which most likely breaks down to give dipyrromethane **9** under the acidic reactions

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(24) TTF in normally considered not to be stable under strong acidic conditions, however, addition of excess TFA to a solvent mixture of Me_2CO and CH_2Cl_2 did not affect the stability of the MPTTF **7** significantly, even over longer periods of time.

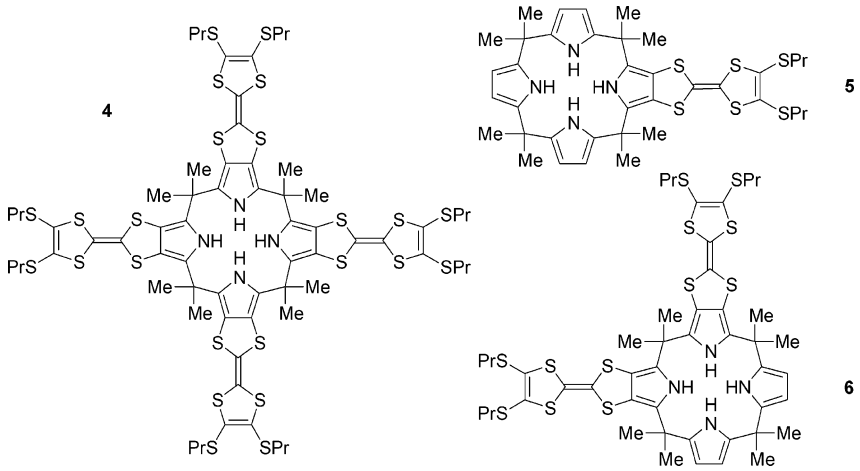
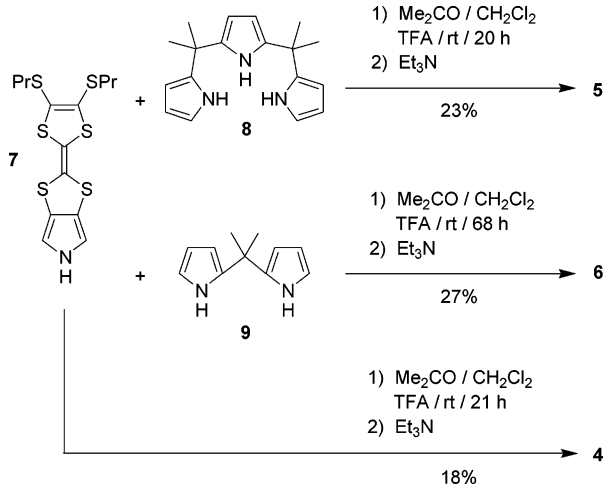


Figure 2. Structural formulas of tetraTTF-calix[4]pyrrole **4**, monoTTF-calix[4]pyrrole **5**, and bisTTF-calix[4]pyrrole **6**.

Scheme 1. Synthesis of MonoTTF-calix[4]pyrrole **5**, BisTTF-calix[4]pyrrole **6**, and TetraTTF-calix[4]pyrrole **4**



conditions applied. The bisTTF-calix[4]pyrrole **6** could also be prepared directly in 27% yield by reacting the MPTTF derivative **7** with 2 equiv of dipyrromethane **9** in a mixture of Me_2CO and CH_2Cl_2 containing an excess of TFA. In this case, no evidence for the formation of other TTF-calix[4]pyrroles, such as monoTTF- or trisTTF-calix[4]pyrrole, was observed during column chromatographic purification. The tetraTTF-calix[4]-pyrrole[20] **4** was synthesized by adding an excess of TFA to a solution of the MPTTF derivative **7** in a mixture of Me_2CO and CH_2Cl_2. After column chromatographic purification and recrystallization from CH_2Cl_2 and Me_2CO, the tetraTTF-calix-[4]pyrrole **4** was obtained in 18% yield.

Structural Characterization of TTF-Calix[4]pyrroles by Mass Spectrometry and ^{1}H NMR Spectroscopy. All three TTF-calix[4]pyrroles were isolated as yellow solids. High-resolution matrix-assisted laser-desorption/ionization mass spectrometric (MALDI-MS) analysis of monoTTF-calix[4]pyrrole **5**, bisTTF-calix[4]pyrrole **6**, and tetraTTF-calix[4]pyrrole **4** revealed signals with $m/z = 752.2222$, 1076.1514, and 1723.9921, respectively, corresponding to the molecular ion $M^{\bullet+}$ as the major peak in all cases (calcd mass $M^{\bullet+}$ 752.2198, 1076.1461, and 1723.9988 for **5**, **6**, and **4**, respectively).

The ^{1}H NMR spectrum of **5** (cf. Figure 3a and Supporting Information) recorded in $CDCl_3$ at 298 K showed three broad singlets resonating at $\delta = 6.67$, 6.93, and 7.23 ppm, integrating to 1H, 1H, and 2H, respectively, that can be assigned to the three chemically nonequivalent NH protons. The ^{1}H NMR spectrum of **6** (cf. Figure 3b and Supporting Information) revealed only two broad singlets resonating at $\delta = 6.98$ and 7.23 ppm, integrating to 2H and 2H, respectively. These results support the assignment of the pyrrolic NH resonance observed for receptor **5** at $\delta = 6.67$ ppm to the pyrrolic NH proton opposite the MPTTF unit since this signal is absent in the spectrum of **6**. The two remaining NH signals, at $\delta = 6.93$ and 7.23 ppm, in receptor **5** are assigned to the MPTTF NH proton and the two chemically equivalent pyrrolic NH protons, respectively. This assignment is in agreement with the one made in the case of the monoTTF-pseudocalix[4]pyrrole **3** (i.e., three chemically nonequivalent NH protons).[15] Further support for the proposed structure of **6**, namely one where the two MPTTF units are located next to each other and not opposite one another (Figure 2) came from an analysis of the ^{1}H NMR spectrum (See Supporting Information). For instance, the signals for the SCH_2 protons are split into two triplets; the CH_2 protons appear as two sextets, while the propyl CH_3 signals appear as two triplets. Furthermore, the resonances for the CH_3 groups attached to the calix[4]pyrrole ring system are split into three singlets integrating to 6H, 12H, and 6H, respectively. On this basis, these signals are assigned to three sets of chemically nonequivalent CH_3 protons. If the two MPTTF units in **6** had been located opposite to one another, there would have been a higher degree of symmetry in the molecule, and as a consequence thereof, a more simple ^{1}H NMR spectrum would have been observed.

The ^{1}H NMR spectrum of **4** (cf. Figure 3c and Supporting Information) is very simple; it is characterized by one broad singlet resonating at $\delta = 7.15$ ppm and integrating to 4H, that can be assigned to the MPTTF NH protons. Also seen are the

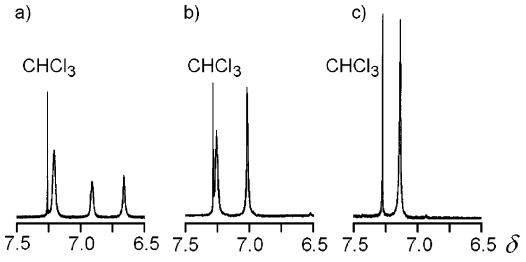


Figure 3. Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$) of: (a) monoTTF-calix[4]pyrrole **5**; (b) bisTTF-calix[4]pyrrole **6**; and (c) tetraTTF-calix[4]-pyrrole **4**.

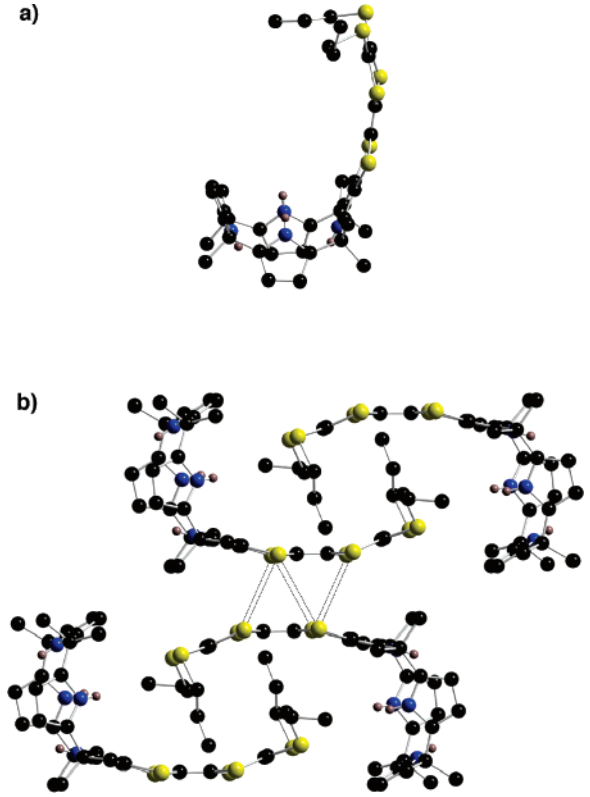


Figure 4. Single X-ray crystal structure of; (a) monoTTF-calix[4]pyrrole **5**; and (b) view showing the short S···S interactions observed in the packing diagram.

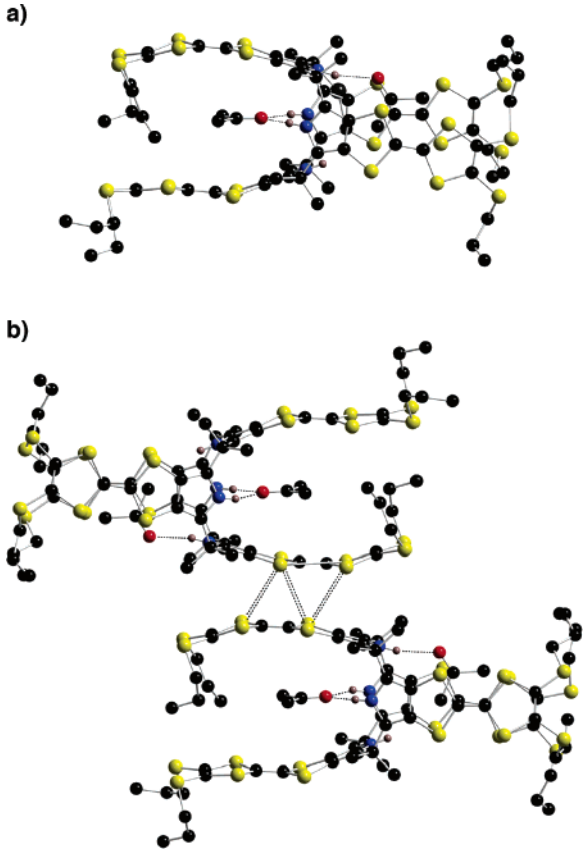


Figure 5. Single X-ray crystal structure of; (a) tetraTTF-calix[4]pyrrole **4**; and (b) view showing the short S···S interactions observed in the packing diagram. The lower occupancy atoms of the disordered thiopropyl groups have been removed for clarity.

expected signals from the propyl chains and the methyl groups attached to the calix[4]pyrrole ring system.

X-ray Crystallography. Further characterization of the monoTTF- and tetraTTF-calix[4]pyrrole products **5** and **4** came from single-crystal X-ray structure analyses. Diffraction quality single crystals of **5** were obtained as thin yellow plates by slow diffusion of a pentane layer into a solution of **5** in CH_2Cl_2. The resulting structure, depicted in Figure 4a, reveals that **5** adopts a 1,3-alternate conformation in the solid-state, in analogy to what is observed for most other calix[4]pyrroles.[9a,25] The four pyrrolic NH protons are oriented in a up/down/up/down pattern relative to the mean plane of the macrocycle. The pyrrolic NH proton located in a 'trans' position is thus oriented in just the opposite direction of the neighboring pyrrolic NH proton. Several short S···S interactions are observed (Figure 4b) within the crystal lattice. The short S···S contacts involve molecules related by a crystallographic inversion center. In **5**, the center is at 1/2, 0, 1/2. The short contacts shown (Figure 4b) in the packing diagram of **5** are: S21···S26 (related by 1-x, -y, 1-z), 3.590(1) Å and S23···S24 (related by 1-x, -y, 1-z), 3.660(1) Å. A slightly longer contact is seen in the packing diagram of **5**, namely a separation of 3.673(1) Å between S21···S23 (related by 1-x, -y, 1-z).

Single crystals of **4** were obtained as yellow needles by slow diffusion of an Me_2CO layer into a solution of **4** in CH_2Cl_2. In this case, the resulting X-ray crystal analysis revealed that **4** also adopts (Figure 5a) a 1,3-alternate conformation in the solid-state, where two Me_2CO molecules take up the space between sets of MPTTF units, forming hydrogen bonds from the carbonyl unit in Me_2CO to the pyrrole NH proton(s) from the second set of MPTTF units. In analogy to what proved true in the case of **5**, short intermolecular S···S interactions are also found (Figure 5b) in the solid-state structure of **4**. There are six short S···S contacts, but because of the symmetry involved, only three are unique. The short contacts involve two molecules related by a crystallographic inversion center at 0, 1/2, 1/2. The contacts are: S77···S84 (related by -x, 1-y, 1-z), 3.645(1) Å and S79···S81 (related by -x, 1-y, 1-z) 3.692(1) Å as shown in Figure 5b. A third shorter contact is: S77···S79 (related by -x, 1-y, 1-z) 3.525(1) Å. A comparison of the S···S contacts observed in the packing diagrams of compounds **4** and **5** reveal that where the S77···S79 contact is the shortest one (3.525(1) Å) in the case of **4**, the corresponding contact (i.e., S21···S23) is the longest one (3.673(1) Å) in the case of **5**.

Anion Binding Investigations. ^{1}H NMR spectroscopic and isothermal titration calorimetry (ITC) methods were used to determine the binding constants (K_a) corresponding to the interaction of the monoTTF-calix[4]pyrrole **5**, bisTTF-calix[4]-pyrrole **6**, and tetraTTF-calix[4]pyrrole **4** receptors with Br^-, Cl^-, CN^-, NO_2^-, and CH_3COO^- ions, respectively. As part of this general analysis, initial studies of the anion binding properties of receptor **5** were carried out at 298 K in CD_2Cl_2, CD_3COCD_3, and CD_3CN using ^{1}H NMR spectroscopic titration methods. As expected, addition of excess Br^- ions to a CD_3COCD_3 solution of the monoTTF-calix[4]pyrrole **5** caused a large downfield shift ($\Delta\delta = 2.0-3.0$ ppm) for the resonances associated with the pyrrolic NH protons (Figure 6a). For the resonances associated with the β-pyrrolic protons (Figure 6b),

(25) Gale, P. A.; Sessler, J. L.; Král, V. *Chem. Commun.* **1998**, 1−8.

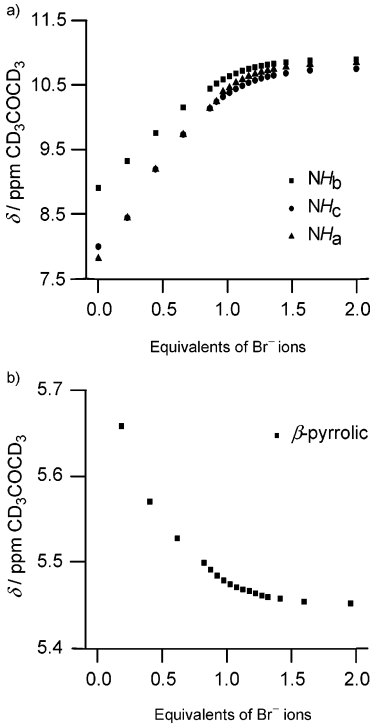


Figure 6. ^{1}H NMR titration curves for monoTTF-calix[4]pyrrole **5** in CD_3COCD_3 observed upon addition of an increasing amount of *n*-Bu_4NBr; (a) Downfield shift for the pyrrolic NH protons; (b) Upfield shift for the β-pyrrolic protons.

a smaller upfield shift ($\Delta\delta = 0.24$ ppm) was observed. To obtain the K_a value for the 1:1 complex of Br^- ions and receptor **5** in CD_3COCD_3, a ^{1}H NMR titration experiment was carried out. This involved monitoring (Figure 6) the changes in the resonances associated with the three nonequivalent pyrrolic NH protons and the β−pyrrolic protons as increasing quantities[26] of *n*-Bu_4NBr were added to the receptor **5** at 298 K. From the changes observed, the binding constant could be derived using the Wilcox[27] nonlinear method (see Supporting Information) by fitting the binding profiles to a 1:1 complex; this gave an average K_a value of 7.1×10^3 M^{-1} for the **5**·Br^- complex. Similar titration experiments were carried out in CD_2Cl_2 and CD_3CN, respectively. The results obtained from these analyses are summarized in Table 1, together with the corresponding values for calix[4]pyrrole **1**. The K_a values listed in Table 1 reveal a significant trend. As the polarity of the solvent increases, the K_a values increase. This seemingly counter-intuitive finding is rationalized in terms of initial cation−anion (e.g., *n*-Bu_4NBr) ion pairing. In less polar solvents even soluble salts can be appreciably ion-paired,[28] which serves to lower the effective concentration of free anion available for interaction with the calixpyrrole receptor. Solvents that are more polar, but still not particular competitive (e.g., Me_2CO; MeCN, as opposed to, e.g., Me_2SO; MeOH), permit a greater level of pre-dissociation of the added salt, a phenomenon that is manifest in terms of higher effective binding affinities. While far from being established unequivocally, such rationales are consistent with the emerging,

(26) The solution of *n*-Bu_4NBr also contained the receptor **5** at the initial concentration to counter dilution effects.
(27) Wilcox, C. S. In *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H.-J., Dürr, H., Eds.; VCH: Weinheim, 1991; p 123.
(28) Alunni, S.; Pero, A.; Reichenbach, G. *J. Chem. Soc., Perkins Trans 2*, **1998**, 1747−1750.

Table 1. Binding Constants[a] (K_a, M^{-1}) Corresponding to the Interaction between Br^- Ion and Receptors **1**, **5**, and **6** as Determined by ^{1}H MMR Spectroscopic[b] Titrations and by ITC Measurements[c] Carried out at 298 K in Different Solvents

method	solvent	1	5	6
^{1}H NMR	CD_2Cl_2	1.0×10^1 [d]	9.6×10^1	5.3×10^2
	CD_3COCD_3	3.6×10^3	7.1×10^3	1.2×10^4
ITC	CD_3CN	5.9×10^3 [e]	1.2×10^4	*f*
	CH_3COCH_3	2.9×10^3	6.0×10^3	9.3×10^3

[a] Estimated errors are <30%. [b] The receptors **1**, **5**, and **6** were titrated by adding a concentrated solution of *n*-Bu_4NBr which also contained the receptors at the initial concentration to account for dilution effects. Receptors **1**, **5**, and **6** were titrated with a *n*-Bu_4NBr solution to obtain the heat effects corresponding to complexation. [c] The net heat effect was determined by subtracting the heat traces for the appropriate background titration. [d] See ref 9a. [e] See ref 9b. [f] Receptor **6** was not soluble in CD_3CN.

but still currently limited, body of experimental data germane to this issue.[29]

To confirm the reliability of the binding constants obtained using ^{1}H NMR spectroscopy, receptors **1**, **5**, and **6** were also titrated with Br^- ions in Me_2CO, monitoring the putative anion binding process by ITC at 298 K. The results obtained from these experiments are also summarized in Table 1. A comparison of the results obtained from ^{1}H NMR spectroscopy and ITC reveal that they match reasonably well.

A quantitative study of the binding properties of the tetraTTF-calix[4]pyrrole **4** proved impossible to carry out in Me_2CO/CD_3COCD_3 and MeCN/CD_3CN on account of the poor solubility of **4** in these solvents. Instead, ^{1}H NMR spectroscopic titration experiments involving the bisTTF-calix[4]pyrrole **6** and the tetraTTF-calix[4]pyrrole **4** were carried out in CD_2Cl_2. This choice of solvents allowed the Br^- ion binding constants for receptors **1**, **5**, **6**, and **4** to be compared. In all cases the change in the NH proton chemical shifts was used to monitor the binding events. The K_a values obtained in this way (cf. Table 2) provide support for the conclusion that synthetic annulation of TTF units onto the upper rim of the calix[4]pyrrole system serves to enhance the anion binding affinity as compared to the corresponding model system *meso*-octamethylcalix[4]pyrrole (**1**). In fact, a detailed look at the numbers reveals that substitution of two TTF units increases the binding constant by roughly 1 order of magnitude and substitution of four TTF units increases the binding constants by 3 orders of magnitude relative to *meso*-octamethylcalix[4]pyrrole (**1**). To our knowledge, **4** displays one of the strongest Br^- ion binding affinities yet recorded for a calix[4]pyrrole-based receptor. As expected, receptor **4** displays the highest affinity for Br^- among the series of receptors, **1**, **5**, **6**, and **4**, with the actual affinity trend being **1** < **5** < **6** < **4**.

Another series of titrations were performed in CD_2Cl_2 using receptors **5** and **6**, looking at Cl^- ion binding. The binding

Table 2. Binding Constants[a] (K_a, M^{-1}) Corresponding to the Interaction of Br^- and Cl^- Ions with Receptors **1**, **5**, **6**, and **4** as Determined by ^{1}H MMR Spectroscopic[b] Titrations Carried out at 298 K in CD_2Cl_2

anion	1	5	6	4
Br^-	1.0×10^1 [c]	9.6×10^1	5.3×10^2	6.0×10^4
Cl^-	3.5×10^2 [c]	2.9×10^3	4.3×10^4	*d*

[a] Estimated errors are <30%. [b] The receptors **1**, **5**, **6**, and **4** were titrated by adding a concentrated solution of *n*-Bu_4NBr or *n*-Bu_4NCl which also contained the receptors at the initial concentration to account for dilution effects. [c] From ref 9a. [d] The binding constant was to high to be measured by NMR titrations techniques.

Table 3. Binding Constants[a] (K_a, M^{-1}) Corresponding to the Interactions between Receptors **1**, **5**, **6**, and **4** and Different Anions as Determined by ITC[b] at 298 K in CH_2ClCH_2Cl

anion	**1**	**5**	**6**	**4**
Cl^-	3.5×10^4	1.2×10^5	6.6×10^5	2.5×10^6
Br^-	$< 1.0 \times 10^3$	2.2×10^3	8.3×10^3	5.8×10^4
CN^-	2.8×10^4	8.5×10^4	2.6×10^5	1.1×10^6
NO_2^-	4.3×10^3	6.9×10^4	2.8×10^5	1.2×10^6
$CH_3CO_2^-$	4.7×10^4	6.5×10^4	3.9×10^5	1.3×10^6

[a] Estimated errors are <10%. [b] The receptors **1**, **5**, **6**, and **4** were titrated with the tetrabutylammonium salts of the anion in question so to obtain the heat effects corresponding to complexation. The net heat effect was determined by subtracting the heat traces for the appropriate background titration.

constants obtained from these studies are listed in Table 2. In the case of receptors **5** and **6** the maximum chemical shifts ($\Delta\delta$) of the NH protons were found to be 3.8 and 3.7 ppm, respectively, in the presence of Cl^- ions. As expected, the Cl^- ion affinities for receptors were again found to follow the trend **1** < **5** < **6**. However, the interaction between receptor **4** and Cl^- ions proved too high to measure accurately using NMR titration methods and, therefore, more systematic anion binding studies were carried out in 1,2-dichloroethane (DCE) using ITC.

Isothermal Titration Calorimetry. The advantage of ITC for monitoring the recognition of anionic guests by calix[4]-pyrroles was highlighted by Schmidtchen[29] in 2002. Table 3 summarizes the K_a obtained from ITC experiments for the series of receptors **1**, **5**, **6**, and **4**, with the series of test anions Cl^-, Br^-, CN^-, NO_2^-, and CH_3COO^- in DCE. An inspection of Table 3 illustrates that TTF substituted calix[4]pyrrole receptors exhibit better anion binding properties (i.e., higher affinities) that does the parent system calix[4]pyrrole **1**. As can be seen from an inspection of Table 3, receptor **4** containing four TTF units is the most effective anion binding agent among the compounds considered in this study. For instance, the Cl^- and NO_2^- anion binding affinities of **4** ($K_a = 2.5 \times 10^6$ and 1.2×10^6 M^{-1}, respectively) are roughly 70 and 280 times higher than those of calix[4]pyrrole **1** ($K_a = 3.5 \times 10^4$ and 4.3×10^3 M^{-1}, respectively) when studied under identical conditions. Overall, the ITC-derived anion binding affinities of these receptors and the selectivity order (**1** < **5** < **6** < **4**) given in Table 3 matches well with the corresponding ^1H NMR titration results (Tables 1 and 2). Interestingly, the three TTF receptors were found to show a lower level of overall selectivity than the parent system **1**, with a differentiation in favor of only Cl^- being seen relative to CN^-, $CH_3CO_2^-$, or NO_2^-. The order of affinities of all three TTF containing receptors is thus $Cl^- > CN^- \approx CH_3CO_2^- \approx NO_2^- > Br^-$, whereas in the case of calix[4]pyrrole **1** not only is a higher level of inherent selectivity observed, but also a different anion binding trend is observed, namely $CH_3CO_2^- > Cl^- > CN^- > NO_2^- > Br^-$. Presumably, these results reflect the fact that the bulky TTF units present in compounds **5**, **6**, and **4** provide a source of steric hindrance in the full cone-conformation (i.e., the one considered optimal for interaction with most anionic targets) and that these unfavorable interactions provide a certain leveling effect. On the other hand − presumably for electronic reasons − the three TTF-calix[4]pyrroles show higher overall binding affinities, especially in the case of anions having relatively small, negative charged surface areas, such as the Cl^- and CN^-, and NO_2^- ions.

(29) Schmidtchen, F. P. *Org. Lett.* **2002**, *4*, 431−434.

Table 4. Thermodynamic Parameters[a] Corresponding to the Binding of Different Anions to Receptors **1**, **5**, **6**, and **4** as Determined by ITC[b] at 298 K in CH_2ClCH_2Cl

anion	kcal/mol	**1**	**5**	**6**	**4**
Cl^-	ΔH	−10.63	−9.92	−9.23	−9.27
	$T\Delta S$	−4.41	−3.01	−1.29	−0.54
	ΔG	−6.22	−6.91	−7.94	−8.73
Br^-	ΔH	*c*	−7.20	−7.17	−7.88
	$T\Delta S$	*c*	−2.65	−1.82	−1.38
	ΔG	*c*	−4.55	−5.35	−6.50
CN^-	ΔH	−8.45	−9.43	−8.35	−9.51
	$T\Delta S$	−2.38	−2.71	−0.97	−1.25
	ΔG	−6.07	−6.69	−7.38	−8.26
NO_2^-	ΔH	−10.94	−6.79	−5.87	−7.49
	$T\Delta S$	−5.96	−0.19	−1.56	+0.82
	ΔG	−4.98	−6.60	−7.43	−8.31
$CH_3CO_2^-$	ΔH	−7.88	−8.50	−7.78	−9.27
	$T\Delta S$	−1.51	−1.93	−0.16	−0.91
	ΔG	−6.37	−6.57	−7.62	−8.36

[a] Estimated errors are <10%. [b] Receptors **1**, **5**, **6**, and **4** were titrated with the tetrabutylammonium salts of the anion in question so to obtain the heat effects corresponding to complexation. The net heat effect was determined by subtracting the heat traces for the appropriate background titration. [c] Association constant too low to be determined by ITC.

According to Table 4, the anion binding interactions of all four neutral receptors in DCE are mainly enthalpy-driven exothermic processes. In the case of Cl^- and NO_2^- ions, slightly more favorable enthalpy changes were seen with receptor **1** than with the TTF functionalized systems, **5**, **6**, and **4**. However, more favorable entropy effects contributed to the higher anion binding affinities observed for these receptors. In contrast, the interaction of **4** with CN^- and $CH_3CO_2^-$ anions is driven not only by a more favorable enthalpy contribution but also by more favorable entropy values as compared to compound **1**. In general, the anion binding interactions of receptor **1** are characterized by highly negative entropy contribution, while the corresponding entropy contributions for the interaction of TTF-calix[4]pyrroles are relatively small, i.e., slightly negative or even positive values are observed.

Cyclic Voltammetry. ^1H NMR spectroscopy and ITC studies revealed that the receptors **5**, **6**, and **4** are able to complex anions in solution. However, these receptors were further designed to allow the anion-binding events to be detected via anion-induced changes in the electrochemical properties of the appended TTF units.[30] Cyclic voltammetry (CV) was used to probe the changes in the redox potentials of the receptors upon complexation with anions. As can be seen by inspection of Figure 7, the progressive addition of Br^- ions to a solution of **6** in DCE at 298 K resulted in a negative shift of the first oxidation potential ($E_{1/2}^1$) associated with the TTF units. It should be noted (Figure 7) that the current intensity associated with the second oxidation wave increases when the concentration of Br^- ions increases. This unexpected growth in current intensity can be explained by oxidation of the Br^- ions to Br_2. As a consequence of the overlapping nature of these two processes, it is not possible to obtain any information as to whether complexation of this particular anion to the receptor **6** also affects the second oxidation process associated with the TTF units in **6**. From an inspection of Figure 8 it can be seen that the displacement of the first oxidation potential reaches a limit ($\Delta E = -70$ mV) at

(30) For examples of redox-active chemosensors, see: a) Beer, P. D.; Gale, P. A.; Chen, G. Z. *Coord. Chem. Rev.* **1999**, *185−186*, 3−36. (b) Beer, P. D.; Cadman, J. *Coord. Chem. Rev.* **2000**, *205*, 131−155. (c) Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 486-526.

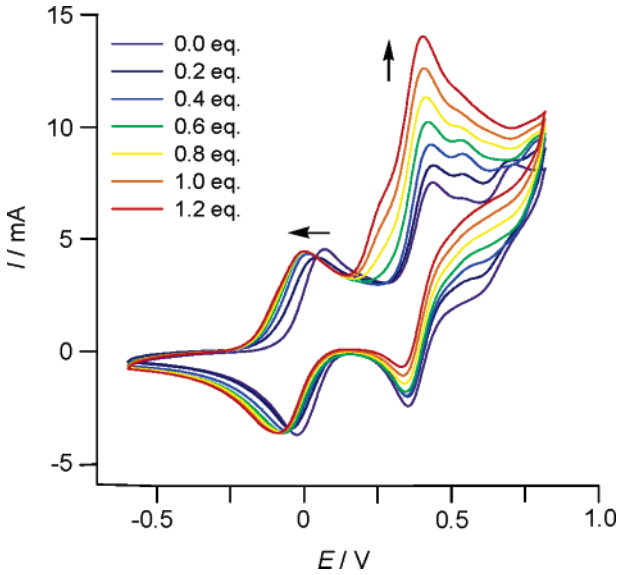


Figure 7. CVs of receptor **6** (DCE, 0.25 mM) obtained by adding in increasing quantities of a concentrated DCE solution of *n*-Bu_4NBr that also contained receptor **6** at the initial concentration, to counter the dilution effects (Reference electrode: Fc^+/Fc, supporting electrolyte: *n*-Bu_4NPF_6 (0.1 M)).

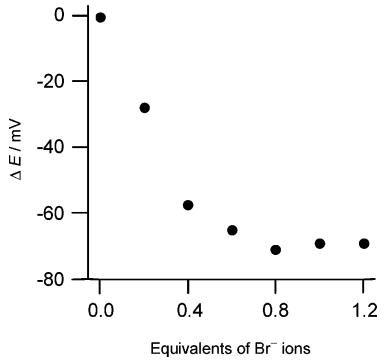


Figure 8. CV titration curves (DCE, 0.25 mM) showing the negative shift of the first oxidation potential of receptor **6** observed upon the addition of *n*-Bu_4NBr (Reference electrode: Fc^+/Fc, supporting electrolyte: *n*-Bu_4NPF_6 (0.1 M)).

the point where approximately one stoichiometric equiv[31] of Br^- ion had been added to the receptor **6**.

The progressive addition of Cl^- ions to a solution of receptor **5** in DCE at 298 K (Figure 9), did not result in the expected negative shift of the first oxidation potential. Instead, an analysis revealed that the monoTTF-calix[4]pyrrole **5** binds Cl^- ion with an exchange rate that is slow on the CV time scale. For instance, the addition of 0.2 equiv of Cl^- ions to a solution of the monoTTF-calix[4]pyrrole **5** in DCE was observed to give rise to a new peak in the region corresponding to the first oxidation process. This new peak, at $E_{1/2}^1 = -0.11$ V, is ascribed to oxidation of the complex (i.e., **5**•Cl^-) between the monoTTF-calix[4]pyrrole **5** and Cl^-. Further addition of Cl^- ions caused the intensity of the peak at $E_{1/2}^1 = +0.032$ V, corresponding to oxidation of the uncomplexed monoTTF-calix[4]pyrrole **5**, to decrease along with a concurrent increase in the intensity of the peak at $E_{1/2}^1 = -0.11$ V. The total displacement (Table 5) of the first oxidation potential is $\Delta E = -145$ mV. Such changes are considered to reflect a simultaneous decrease in the amount of uncomplexed **5** and an increase in the **5**•Cl^- complex. After addition of ca. 1 equiv[32] of Cl^- ions, the peak at $E_{1/2}^1 = +0.03$ V could no longer be observed and only the peak at $E_{1/2}^1 = -0.11$ V was seen in the voltammogram. From this point forward, further addition of Cl^- ions resulted in little observable change. The changes in these two peaks as a function of Cl^- concentration are plotted in Figure 10, from which the tight correlation between the growth (Figure 10a) in the intensity of the peak at $E_{1/2}^1 = -0.11$ V and the decrease (Figure 10b) in that at $E_{1/2}^1 = +0.03$ V can clearly be observed.

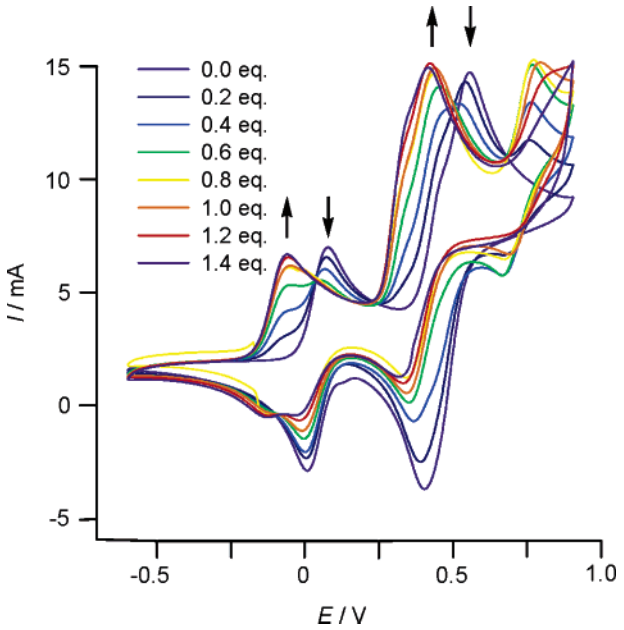


Figure 9. CVs of receptor **5** (DCE, 0.25 mM) obtained by adding in increasing quantities of a concentrated DCE solution of *n*-Bu_4NCl that also contains receptor **5** at the initial concentration to counter the dilution effects (Reference electrode: Fc^+/Fc, supporting electrolyte: *n*-Bu_4NPF_6 (0.1 M)).

In the case of receptor **4** being "titrated" with Cl^- ions, a limiting shift in the first oxidation potential of $\Delta E = -30$ mV was observed after approximately one stoichiometric equivalent of Cl^- had been added. Similar negative shifts (See Supporting Information) were observed when receptors **5**, **6**, or **4** were titrated with increasing amounts of either Br^- or Cl^- ions. While the largest shift in the first oxidation potential ($\Delta E = -145$ mV) was observed when receptor **5** was titrated with Cl^-, it is

Table 5. Maximum Displacement (ΔE, mV) in the First Oxidation Potential of the Receptors **5**, **6**, and **4** Observed upon the Addition of 1.2 Equiv of the Tetrabutylammoniums Salt of the Anion in Question in CH_2ClCH_2Cl

anion	5	6	4
Cl−	−145[b]	−70[a]	−30[a]
Br−	−70[a]	−70[a]	−20[a]

[a] The anion is in fast exchange with the receptors on the CV time scale. [b] The anion undergoes slow exchange on the CV time scale.

(31) Based on a K_a value of 8.3×10^3 M^{-1} for the complexation of the receptor **6** with Br^- ion, one can calculate that the fraction of the complex **6**•Br^- is only 51% in a DCE solution containing 0.25 mM of **6** and one equivalent of *n*-Bu_4NBr. This value is somewhat in contradiction to the extent of complexation indicated by the CV experiments which reveal that the fraction of **6**•Br^- is much lager (>90%) since no significant change in ΔE was observed after addition of more than 1 equiv of Br^- ions. However, one should bear in mind that the CV experiments were carried out in a DCE solution also containing a substantial amount of *n*-Bu_4NPF_6 (0.1 M) which increases the polarity of the medium substantial. The values listed in Table 1 show that the polarity of the medium has a strong influence on the K_a value between the receptor **6** and Br^- ions. Consequently, it is not unlikely that a change in the medium from neat DCE to DCE containing 0.1 M of *n*-Bu_4NPF_6 will increase the K_a value by one or 2 orders of magnitude.

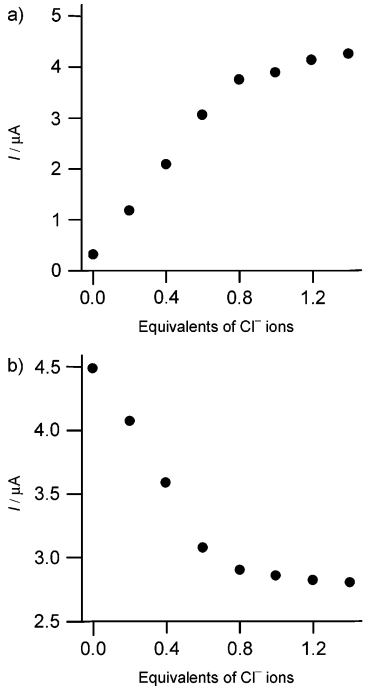


Figure 10. CV titration curves obtained upon the addition of increasing concentrations of *n*-Bu_4NCl to DCE solutions of receptor **5** (DCE, 0.25 mM) showing; (a) the increase in the intensity at $E = -0.11$ V corresponding to the monoTTF-calix[4]pyrrole **5** bound with Cl^- ion; (b) a decrease in the intensity at $E = +0.03$ V corresponding to the uncomplexed monoTTF-calix[4]pyrrole **5** (Reference electrode: Fc^+/Fc, supporting electrolyte: *n*-Bu_4NPF_6 (0.1 M)).

nonetheless clear that all three systems appear to function as effective electrochemical sensors, at least for these two anionic guests.

In an effort to test for selectivity, CV titration experiments were also carried out with solutions containing CN^-, NO_2^-, or $CH_3CO_2^-$ ions. However, in the presence of these anions the redox events become irreversible, meaning that no reliable results (or sensing effects) could be obtained for these species.

The results from the electrochemical titration experiments are summarized in Table 5. From the values listed, it is apparent that the monoTTF-calix[4]pyrrole **5** and bisTTF-calix[4]pyrrole **6** systems give rise to a larger shift in the first oxidation potential associated with the MPTTF unit(s) upon complexation with either Br^- or Cl^- ions than is true for the tetraTTF-calix[4]-pyrrole **4**. This smaller shift in the first oxidation potential associated with the MPTTF units in **4** is rationalized in terms of electron sharing effects. In **4**, the four MPTTF units act to share the negative charge from the bound anion, whereas the extent of this sharing is necessarily lower in the case of **5** and **6**, respectively. To the extent that such a rationalization can be generalized, it leads to the conclusion that calixpyrroles or other receptor systems bearing a limited number of redox-active groups may be more effective as sensors than those containing multiple electrochemical signaling subunits.

(32) Based on a K_a value of 1.2×10^5 M^{-1} for the complexation of the receptor **5** with Cl^- ion, one can calculate that the fraction of the complex **5**•Cl^- is only 80% in a DCE solution containing 0.25 mM of **5** and 1 equiv of *n*-Bu_4NCl. This value is somewhat in contradiction to the extent of complexation indicated by the CV experiments which reveal that the fraction of **5**•Cl^- is lager (>95%) since no significant changes were observed for the peaks at $E_{1/2}^1 = +0.03$ V and $E_{1/2}^1 = -0.11$ V after addition of more than 1 equiv of Cl^- ions. However, one should bear in mind that the CV experiments were carried out in a DCE solution also containing a substantial amount of *n*-Bu_4NPF_6 (0.1 M) which increases the polarity of the medium substantial. The values listed in Table 1 show that the polarity of the medium has a strong influence on the K_a value between the receptor **6** and Br^- ions, a situation which also can be expected to be true for K_a value between the receptor **5** and Cl^- ions Consequently, it is not unlikely that a change in the medium from neat DCE to DCE containing 0.1 M of *n*-Bu_4NPF_6 will increase the K_a value by one or 2 orders of magnitude.

Conclusions

In conclusion, a series of TTF substituted calix[4]pyrrole receptors, **5**, **6**, and **4** were prepared and tested as potential electrochemical sensors. In the case of compounds **4** and **5**, predicative X-ray crystallographic structures confirmed that, in the absence of an added anionic guest, the systems adopt a 1,3-alternate conformation. Anion binding studies were carried out using ^1H NMR spectroscopic and ITC methods in organic solution; these studies provide support the notion that the incorporation of one or more electron rich TTF subunits into the calix[4]pyrrole backbone improves the anion binding abilities of the receptors, while also effecting the selectivity. It was also demonstrated that halide anion complexation can be monitored by electrochemical means, in particular by observing the shifts in the TTF-based redox waves as a function of Cl^- or Br^- concentration. This ability to effect electrochemical sensing, along with this increased affinity and selectivity that results, underscores the advantage that accrues from the introduction of TTF subunits into the calix[4]pyrrole scaffold. Currently, efforts are being made to modify further the constituent TTF units so as to improve the anion binding and sensing ability of TTF-functionalized, calix[4]pyrrole-based sensor systems.

Acknowledgment. This work was funded in part by a Ph.D. Scholarship from the University of Southern Denmark to K.A.N and by the Danish Natural Science Research Council (SNF, projects #21-03-0317 and #21-02-0414) in Denmark and by the National Science Foundation (NSF grant CHE 0515670) in the USA.

Supporting Information Available: Syntheses of all compounds and spectral data for **5**, **6**, and **4**. ^1H NMR spectroscopic and ITC titration binding studies for **1**, **5**, **6**, and **4**. Cyclic voltammetry titration studies for **5**, **6**, and **4**. X-ray crystallographic data for **5** and **4**•$(Me_2CO)_2$ (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA057367U