Communication

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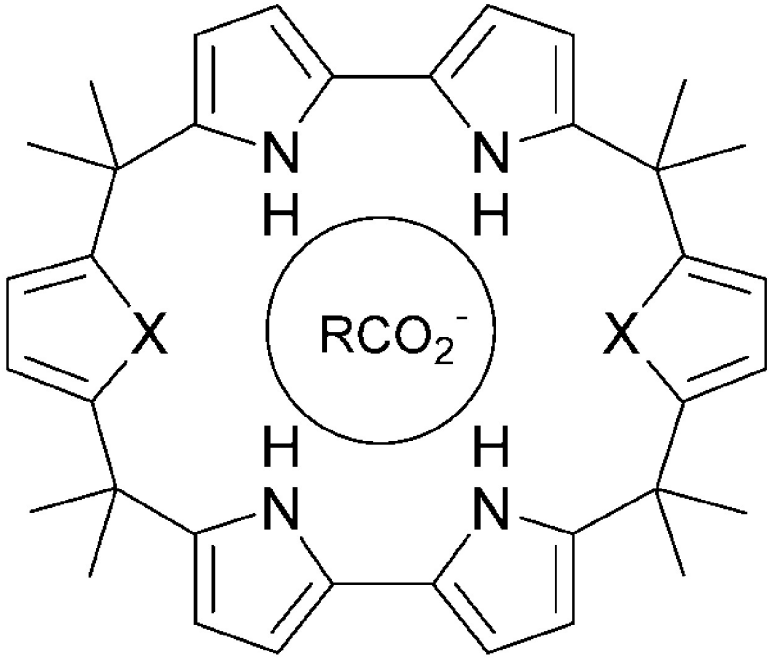

X = O, S

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Calix[2]bipyrrole[2]furan and Calix[2]bipyrrole[2]thiophene: New Pyrrolic Receptors Exhibiting a Preference for Carboxylate Anions

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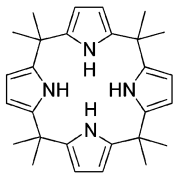
Although initially reported in the 1880s,[1] calix[4]pyrroles (e.g., **1**) were only first studied as anion binding agents in 1996.[2−4] These simple-to-make, conformationally flexible macrocycles were found to bind small anions, such as fluoride, chloride, and dihydrogen phosphate, in common aprotic solvents. However, the relatively small binding "cavities" of the calix[4]pyrroles prevented them from binding effectively most of the larger anions such as bromide, iodide, and hydrogen sulfate that were looked at in the early studies.[2−4] Recently, Gale and co-workers demonstrated that a calix[4]pyrrole bearing a fifth pyrrole in one of the *meso* positions bound carboxylate anions (acetate, benzoate) with selectivities of ≥10:1 relative to chloride anion, as opposed to the roughly 1:1−2:1 ratios seen in the case of **1**.[5] Effective binding of appropriately sized dicarboxylate anions was also observed in the case of a dialkyne-linked calix[4]pyrrole dimer.[6] To date, however, no evidence of selective carboxylate anion binding has been observed in simple, unfunctionalized calix[*n*]pyrroles, including various "higher-order" systems where $n > 4$.[7−9] These findings triggered our interest in designing novel receptors for carboxylates, "Y-shaped" anions which are important elements in many biological and synthetic organic molecules.[10] Recently, two bipyrrole-based macrocycles, calix[3]bipyrrole **2** and calix[4]bipyrrole **3**, were reported by our group.[11] Anion-binding studies revealed that compound **2** binds large halide anions (e.g., Br^-) with affinities that are substantially enhanced relative to those of calix[4]pyrrole **1**. Subsequent unpublished studies revealed a significant (roughly 9-fold) benzoate-to-chloride anion selectivity in the case of **2**. This led us to consider that analogues of these systems might serve as useful carboxylate anion receptors. In this communication, we report two new anion receptors, **9** and **10**, that are based on the use of bipyrrole and furan or thiophene "building blocks".[12] Anion binding studies, carried out using isothermal titration calorimetry (ITC) in acetonitrile, reveal that these compounds display good affinities for Y-shaped anions, such as benzoate and acetate, while binding such classic spherical anions as chloride and bromide only weakly.



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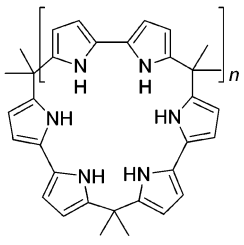
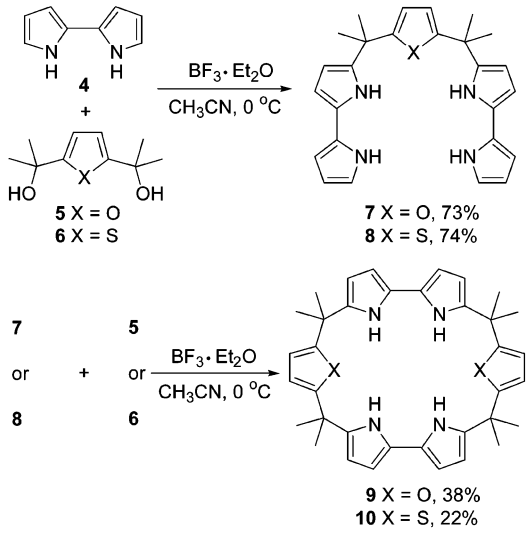


2 $n = 1$
3 $n = 2$

The synthesis of **9** and **10** is shown in Scheme 1. Efforts to obtain these targets in one step by condensing bipyrrole **4** directly with **5** or **6** proved unproductive, producing a hard-to-separate mixture of compounds. Accordingly, we adopted a stepwise procedure method

Scheme 1. Synthesis of **9** and **10**



that we[14] and others[7,13] have employed previously. Specifically, reacting **5** with excess **4** (10 equiv or more) in acetonitrile in the presence of a catalytic amount of borontrifluoride diethyl etherate at 0 °C afforded **7** in 73% yield. Condensation of **7** with **5** in a 1:1 ratio, under the same reaction conditions as those above, then produced the target macrocycle **9** in 38% yield. Using an analogous procedure, target **10** was also synthesized in two steps and in good yield (the yields for the two steps were 74% and 22%, respectively). In both cases, small amounts of various "higher-order" condensation products were formed in the final step (as revealed by TLC and mass spectrometric analysis). However, these products were not separated.

Compounds **9** and **10** were characterized by standard spectroscopic techniques (see Supporting Information). They were also characterized by X-ray diffraction analysis. Diffraction-grade crystals of **9** were grown from chloroform/hexanes. X-ray structural analysis revealed that no solvent molecules are trapped in the lattice and that the two pyrroles in each bipyrrole unit are orientated in opposite directions. Diffraction-grade crystals of **10** were grown from a tetrahydrofuran solution of the macrocycle layered with water on the bottom and methanol on the top. X-ray structural analysis revealed that, in contrast to what proved true in the case of **9**, the two pyrroles in each bipyrrole unit are faced in the same direction and that each bipyrrole unit is bound to a tetrahydrofuran molecule via two NH (pyrrole)−O (THF) hydrogen-bonding interactions. The observation of the latter interactions provides support for the notion that this system could bind other hydrogen bond acceptors, including anions (see Figure 1).

Preliminary anion binding studies were carried out using standard ^{1}H NMR spectroscopic titrations in dry acetonitrile-d_3 as well as

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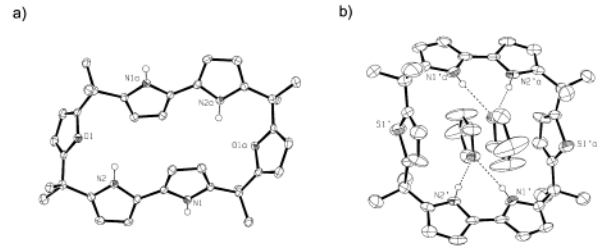

Figure 1. ORTEP view of the molecular structures of: (a) **9**; (b) **10**·2THF. In **10**·2THF, the two bipyrrole units are bound to two tetrahedron molecule via two NH−O hydrogen bonding interactions (indicated by dashed lines).

Table 1. Binding Constants (M^{-1}) for the Interaction of Anion Receptors with Different Anion in Acetonitrile

anion	**9**	**10**	**1**	**2**	**4**
Cl^-	1 100[b]	935[b]	140 000[d]	110 000[d]	246[b]
	960[c]	1 540[c]			
Br^-	37[c]	103[c]	3 400[d]	100 000[d]	53[c]
HSO_4^-	125[c]	28[c]	N.D.	N.D.	35[c]
$PhCO_2^-$	63 000[b]	99 600[b]	115 000[b]	937 000[b]	4 090[b]
$MeCO_2^-$	78 000[b]	139 000[b]	290 000[b]	N.D.	3 650[b]

[a] Anions used in this assay were in the form of their tetrabutylammonium salts; values are the average of at least three separate measurement and are considered reproducible to ±15%; N.D.: not determined. [b] Value obtained from ITC titrations at 30 °C. [c] Value obtained from ^{1}H NMR titrations at 25 °C. [d] From ref 11.

via ITC carried out in dry acetonitrile. As shown in Table 1, the ^{1}H NMR spectroscopic titrations confirmed that both **9** and **10** bind chloride, bromide, and hydrogen sulfate anions only weakly, as was expected given the size mismatch between the anions and the receptor binding cavities. On the other hand, when similar ^{1}H NMR spectroscopic titration methods were used to study the binding of benzoate anion, it was found that the interactions were so strong that the exact binding constants could not be determined. Therefore, ITC methods were used. However, to ensure that the binding constants obtained from the two methods are comparable, the binding of chloride anion was also studied via ITC. As shown in Table 1, there is no substantial difference between the affinity values obtained using these two methods. The affinity constants for benzoate binding to **9** and **10** were thus determined by ITC and found to be 63 000 and 99 600 M^{-1}, respectively. These values are 15 and 20 times larger than those displayed by bipyrrole **4**. Acetate, a close "structural relative" of benzoate, showed even stronger interactions with these two receptors than did benzoate.

As can be inferred from an inspection of Table 1, receptors **9** and **10** display good selectivity for benzoate over chloride (both over 60-fold). On the other hand, calix[4]pyrrole **1**, while displaying an absolute affinity for benzoate that was slightly enhanced relative to **9** and **10**, showed no benzoate−chloride anion selectivity, while calix[3]bipyrrole **2**, displayed intermediate selectivity behavior. This system, with a chloride anion affinity that was similar to that of **1**, showed a selectivity for benzoate over chloride that was approximately 9-fold, as noted above. Taken in concert, these findings support the notion that "fine-tuning" of the internal cavity size and overall shape of calixpyrrole-type receptors can lead to systems whose selectivities are optimized for certain classes of anions. The present findings are also noteworthy because they illustrate how changes in calix[*n*]pyrrole core design, as opposed to external ring functionalization, may be used to generate receptors for species that are relatively weak hydrogen bond acceptors. This perturbation in inherent selectivities is also important in a more general sense since it shows how appropriate receptor design may be used to generate neutral receptors for carboxylate anions, a chemically and biologically ubiquitous class of anions whose selective recognition is currently attracting the attention of many researchers within the supramolecular chemical community.[10]

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Supporting Information Available: Synthetic experimental data for calix[2]bipyrrole[2]furan **9** and calix[2]bipyrrole[2]thiophene **10**, and anion binding data for **9** and **10** (PDF). Crystallographic data for **9** and **10** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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