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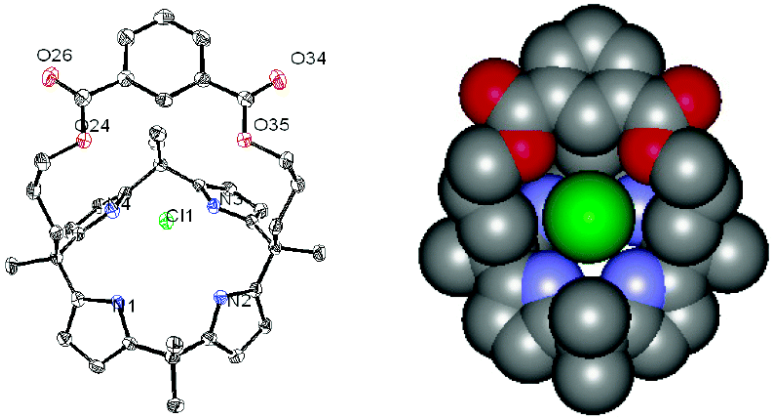

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Single Side Strapping: A New Approach to Fine Tuning the Anion Recognition Properties of Calix[4]pyrroles

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Abstract: Three calix[4]pyrroles bearing *m*-orcinol-derived diether straps of different lengths on one side of the tetrapyrrolic core have been synthesized and characterized. Structural information for an analogous diester bridged strapped system reported previously (Yoon, D. W.; Hwang, H.; Lee, C. H. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1757−1759) is also provided as are bromide and chloride anion affinities for all four systems determined by Isothermal Titration Calorimetry (ITC) in acetonitrile. Although both sets of the strapped calix[4]pyrroles displayed enhanced affinities for chloride and bromide anion, differences were seen among the various receptors that support the conclusion that the anion binding ability of calixpyrrole-type systems can be effectively tuned by modifying the length and nature of the bridging straps. In the specific case of the diether systems, the largest chloride affinity was seen with the shortest strap, whereas the largest affinity for bromide anion was recorded in the case of the longest strap. On the basis of these findings, as well as supporting ^{1}H NMR spectroscopic studies, it is postulated that not only cavity size per se, but also the ability of the aryl portion of the strap to serve as a C*H* hydrogen bond donor site are important in regulating the observed anion affinities.

Introduction

The synthesis of anion receptors possessing high affinity and adequate selectivity for various targeted substrates represents an ongoing challenge in the area of supramolecular chemistry. Appreciated as being more difficult to achieve than cation recognition, this challenge continues to attract the attention of researchers within the molecular recognition community due to the important role anions play in various biological systems.[1] Among the various neutral anion receptors described in the literature, calix[4]pyrroles, possess several attributes that make them attractive. They are, for instance, easily produced, being the product of the acid catalyzed condensation of pyrrole and acetone (or other readily available ketones), and have been shown to bind fluoride, chloride, and phosphate anion in organic media. Because their anion recognition characteristics were first reported by Sessler et al. in 1996,[2] various modifications have been made in an effort to tune the binding characteristics of the parent, acetone-derived system **5**. To date, these modifications have included the synthesis of systems bearing electron donating or withdrawing substituents in the β-pyrrolic positions **6**,[3] covalently linked dimers,[4] functionalized derivatives bearing chromophore attached to one of the β-pyrrolic or meso-like positions,[5] as well as so-called deep cavity models (e.g., ref 7), wherein bulky substituents are used to either lock the conformation of the inherently flexible calix[4]pyrrole core or provide ancillary recognition motifs.[6] Although remarkable enhancements in the binding affinities and useful modulations of the

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(1) (a) Chakrabarti, P. *J. Mol. Biol*. **1993**, *234*, 463−482, (b) Van Kuijck, M. A.; Van Aubel, R. A. M. H.; Busch, A. E.; Lang, F.; Russel, G. M.; Bindels, R. J. M.; Van Os, C. H.; Deen, P. M. T. *Proc. Natl. Acad. Sci. U. S. A*. **1996**, *93*, 5401, (c) Calnan, B. J.; Tidor, B.; Biancalana, S.; Hudson, D.; Frankel, A. D. *Science* **1991**, *252*, 1167.

(2) (a) Gale, P. A.; Sessler, J. L.; Kral, V.; Lynch, V. *J. Am. Chem. Soc*. **1996**, *118*, 5140−5141. (b) Sessler, J. L.; Gale, P. A.; Genge, J. W. *Chem. Eur. J*. **1998**, *4*, 1095−1099. (c) Sessler, J. L.; Gale, P. A. Calixpyrroles: Novel Anion and Neutral Substrate Receptors. In *The Porphyrin Handbook*; Kadish, K. M.; Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, CA, Burlington, MA, 2000. (d) Sessler, J. L.; Anzenbacher Jr. P.; Miyaji, H.; Jursikova, K.; Bleasdale, E. R.; Gale, P. A. *Ind. Eng. Chem. Res*. **2000**, *39*, 3471−3478. (e) Sessler, J. L.; Genge, J. W.; Gale, P. A.; Kral, V. *ACS Symp. Series*. **2000**, 757. (*Calixarenes for Separations*) 238−254. (f) Gale, P. A.; Anzenbacher Jr. P.; Sessler, J. L. *Coord. Chem. Rev*. **2001**, *222*, 57−102. (g) Bucher, C.; Zimmerman, R. S.; Lynch, V.; Sessler, J. L. *J. Am. Chem. Soc*. **2001**, *123*, 9716−9717.

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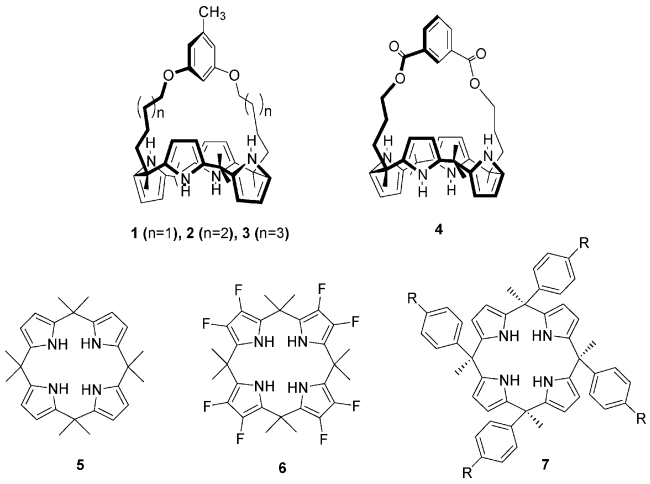
inherent anion selectivities have been achieved as the result of these efforts, further fine-tuning of these features would be desirable.



One way of achieving this goal, outlined in a recently preliminary communication,[7] would involve the construction of systems wherein a bridging strap is used not only to pre-organize the calix[4]pyrrole binding domain but also, in the limit, adjust its inherent electronic features. In this article we report the design and synthesis of several new calix[4]pyrrole-type anion receptors based on this paradigm (compounds **1**−**3**) and show how the use of appropriately chosen, functionalized straps does indeed allow the inherent anion affinities of calix[4]pyrroles to be modulated significantly. Also reported is the solid-state structure of the chloride complex of a diester strapped system, **4**, reported previously,[7] as well as further details of the solution phase anion binding characteristics of this latter first generation system.

In the design of the first generation receptor **4**, a flexible strap bearing an aromatic diester was used as the bridging element. This strap was expected to allow for the isolation of the binding site from solvent and encapsulation of a bound anionic substrate target. It was also expected to provide additional hydrogen bonding sites and thus allow for the specific modulation of the inherent anion affinities. Although marked changes in the chloride anion affinity relative to the parent, acetone-derived calix[4]pyrrole **5** were observed, it was appreciated that by using straps of different sizes or by introducing other functional groups into the straps, further modifications in the inherent properties of the system could be engendered, including ultimately the production of sensor systems (Structure **A**, Figure 1).

On a different level, it was recognized that by varying the nature of the strap, fundamental insights into the relationship between receptor structure, anion size and shape, and binding affinities might be obtained. It was in an effort to address this latter issue that the present study was undertaken. Specifically, we sought to address how the use of phenyl-containing, ether bridged straps of varying lengths would effect the chloride and bromide anion binding properties of calix[4]pyrrole relative both to the parent system **5** and the ester strapped material **4** whose synthesis and binding properties were recently described.[7]

(6) (a) Anzenbacher, Jr., P.; Jursikova, K.; Lynch, V. M.; Gale, P. A.; Sessler, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 11 020−11 021. (b) Camiolo, S.; Gale, P. A. *Chem. Comm.* **2000**, 1129−1130.
(7) Yoon, D. W.; Hwang, H.; Lee, C. H. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1757−1759.

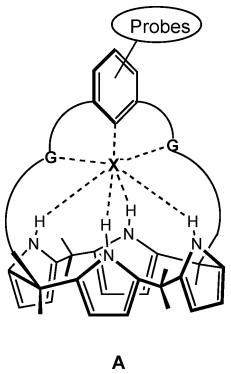
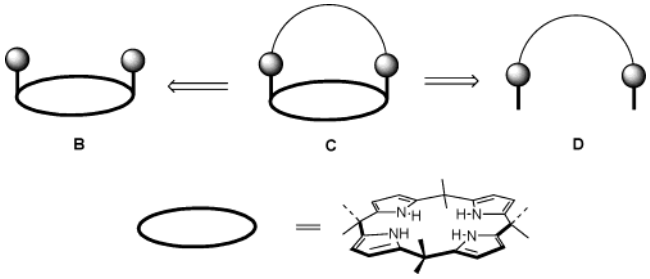


Figure 1. Schematic representation of strapped calix[4]pyrroles showing how the properties of the parent system can modified. Here, X^- represents an anion, G indicates an ancillary binding motif, and Probes refers to any of a range of species that could be used to provide a readout of the putative anion binding event.

Scheme 1. Retrosynthetic Analysis Showing Two Generalized Approaches to Strapped Calix[4]pyrroles, Convergent and Divergent (represented by the right and left arrows, respectively).

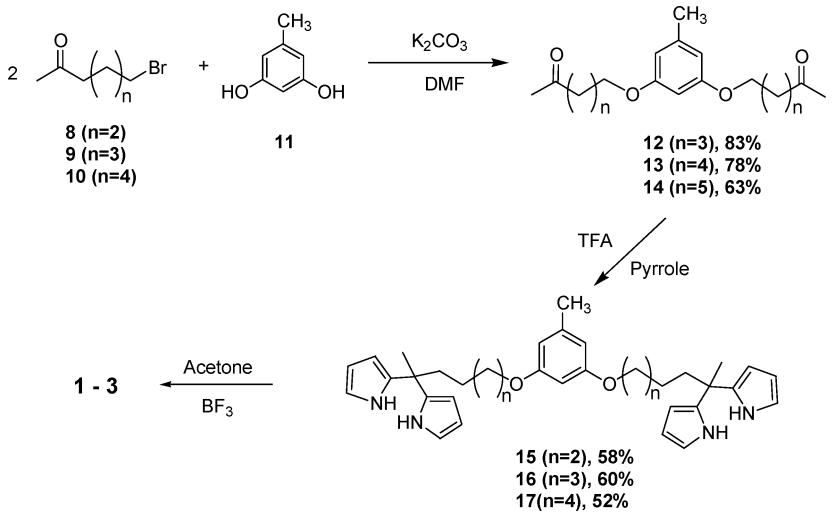


Results and Discussions

In an effort to generate strapped systems represented by generalized structure **C** in Scheme 1 (a schematic version of structure **A** in Figure 1), two limiting approaches, convergent and divergent, can be easily conceived. There are pros and cons associated with each one. In principle, the coupling of a calix[4]pyrrole such as **B** with a functionalized strap should give rise to the desired product **C**. However, the synthesis of precursors represented by structure **B** is challenging since it would likely require the generation and separation of isomeric mixtures regardless of the specific synthetic route chosen (e.g., condensation of pyrrole with two different ketones or condensing a preformed dipyrromethane with a ketone). Confounding the problem is the fact that isolating and assigning the structure of the desired cis, as opposed to trans, configuration in a product such as **B** might not be easy. Given this, we considered that a convergent approach, involving the intramolecular cyclization of a precursor such as **D** with a ketone, would be more efficacious. For the present study, we chose *m*-orcinol (3,5-dihydroxytoluene) as the "keystone" of the strap as shown in Scheme 2.

This choice represented a balance between precursor availability and the desire to have a strap that would enhance, or at least not diminish, the solubility of the resulting product in solvents such as dichloromethane and acetonitrile that have been traditionally used to study calix[4]pyrroles. We were also keen to explore whether C*H* hydrogen bonding interactions, considered to be important in the case of **4**,[6] could play a role in regulating the halide anion affinities of the resulting products **1**−**3**.

Scheme 2



The requisite precursor bromoketones, **8**−**10** were synthesized in accord with literature procedures,[8] and were subsequently condensed with *m*-orcinol in DMF/K_2CO_3 to give the corresponding diketones **12**−**14** in high yields. Treatment of these diketones **12**−**14** with an of excess pyrrole in the presence of 1 equivalent of trifluoroacetic acid then afforded the corresponding bisdipyrromethanes **15**−**17** as one of several condensation products. Although the yields were moderate, purification and isolation of the bisdipyrromethanes proved straightforward, requiring simply column chromatography over silica gel.

With the bisdipyrromethanes **15**−**17** in hand, the desired strapped calix[4]pyrroles **1**−**3** were obtained in yields of 8−11% by condensing with acetone in the presence of a catalytic amount of BF_3. Proton NMR spectra of all three new receptors were consistent with the proposed structure and symmetry, with the aromatic protons, in particular, being sufficiently well resolved to permit a straightforward first-order structural analysis.

Efforts to obtain single crystals of **1**−**3**, or their halide anion complexes, suitable for X-ray diffraction analysis proved unsuccessful. However, such crystals were obtained in the case **4** when crystallization was carried out in the presence of excess triethylammonium chloride. The resulting structure, shown in Figure 2, reveals a cone-like conformation for the calix[4]pyrrole core and the presence of a chloride anion encapsulated within the 3-dimensional binding cavity. The distance between the central phenyl carbon atom and the chloride anion is 3.793 Å, a finding that is consistent with the presence of a strong aryl CH- - -Cl^- hydrogen bond. The average distance between the pyrrolic nitrogens and the bound chloride anion center is 3.285 ± 0.0005 Å. The phenyl group of the strap is tilted off the perpendicular drawn through the RMS center of the four calix[4]pyrrole nitrogen atoms by about 70° as the result, perhaps, of a need to accommodate an interaction between the chloride anion and the countercation (not shown in Figure 1). Despite this deviation, it is clear that the use of a 5 atom linker between the meso-like positions of an otherwise normal calix[4]pyrrole core and a capping tolyl group provides a cavity that is suitable for anion recognition, at least in the solid state.

(8) Zhang, W.; Li, C. *J. Org. Chem.* **2000**, *65*, 5831−5833.

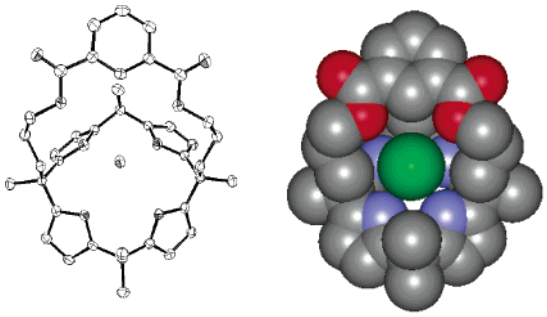


Figure 2. Ortep (left) and CPK (right) representations of the chloride complex of receptor (**4**) deduced from an X-ray diffraction analysis. Hydrogen atoms and the countercation (triethylammonium ion) have been omitted for clarity. The complex adopts a cone conformation and clearly shows a hydrogen bond interaction between Ar−H and Cl^- (C—Cl distance = 3.793 Å).

Attempts to study the anion binding properties of systems **1**−**3** were carried out in CD_3CN using proton NMR spectroscopy. No quantitative estimates of anion affinities could be made on the basis of these studies due to the fact that extremely strong binding with slow complexation/decomplexation kinetics was observed. On the other hand, these spectroscopic studies did provide good qualitative evidence for halide anion binding. For example, titration of receptor **2** with chloride anion (studied in the form of its tetrabutylammonium salt) gave rise to a completely new set of signals, including ones for both (i) the pyrrole N*H* protons at 11.11 ppm that were shifted to dramatically lower field than what was observed in the absence of anions (δ = 8.11 ppm), (ii) the central aromatic C*H* proton, a singlet at 6.27 ppm was shifted to lower field at 6.78 ppm, and (iii) the methylene protons adjacent to the phenolic oxygen that were shifted from 3.92 to 4.11 ppm. On the other hand, the β-pyrrolic protons, which appeared originally at 5.78 ppm, were found to be shifted upfield to 5.51 ppm as expected. Smaller upfield shifts (ca. ∼0.05 ppm) were also observed in the case of the two upper aromatic *CH* signals. This appearance of completely new peaks, coupled with a corresponding disappearance in the original signals, was fully complete by the time ca. ∼1 equivalent of chloride anion had been added. Similar trends were observed with the other two new receptors, **1** and **3**, as well as when bromide anion was substituted for chloride anion. Taken together, these observations are consistent with a

Table 1. Association Constants for the Binding of Chloride and Bromide by Compound **1**−**6** as Measured by ITC (isothermal titration calorimetry) at 30 °C Using the Corresponding Alkylammonium and Cryptand Salts[f]

	TBA–Cl	K–Cryptand–Cl	TBA–Br	TBA–Cl
	CH_3CN			DMSO
1	3 630 000	4 270 000	30 000	340 000
2	1 370 000	1 810 000	31 000	11 000
3	1 370 000	1 810 000	120 000	7400
4	1 380 000	1 620 000	∼0	110 000[a]
5	96 000[b]	190 000[b]	2 800[b]	
5	140 000		3 400	1300
5	55 000[c]			
5	5000[d]			1025[e]
6	530 000	760 000	8500	1500

[a] Data from Ref 7. [b]Measured using tetraethylammonium as the counter cation; data from ref 9. [c]Measured in acetonitrile-d_3 (0.5% v/v D_2O) at 22 °C; association constant determined by ITC. [d]Data from ref 3b; association constant determined by ^{1}H NMR spectroscopic titration. [e]Data from ref 6b; association constant determined by ^{1}H NMR spectroscopic titration. The CH_3CN was rigorously dried simply by passage over two columns of activated molecular sieves using a solvent dispensing system ($[H_2O] < 10$ ppm). The DMSO was spectral grade (Aldrich) but not otherwise dried. Estimated error <10%. [f] TBA = tetrabutylammonium; cryptand = [2,2,2]-cryptand.

strong 1:1 binding motif and a rate of complexation-decomplexation that is slow on the NMR time scale.

Quantitative analyses of the solution phase chloride and bromide anion binding properties of strapped compounds **1**−**3**, as well as the unstrapped "control" systems octamethylcalix[4]pyrrole **5** and octafluorocalix[4]pyrrole **6**, were made using isothermal titration calorimetry (ITC). The advantages of this method for studying the anion recognition properties of the parent calix[4]pyrrole **3** in acetonitrile, particularly in the case when organic soluble salts of chloride and bromide are used for analysis, have recently been presented by Schmidtchen.[9] In the case of K_a values that are on the order of 10^3 M^{-1} or less, we have found that ITC gives K_a values that are concordant with those obtained using more classic ^{1}H NMR spectroscopic titration methods. However, we have found that for K_a values larger than this, ITC routinely gives rise to calculated affinity constants that are larger, often substantially larger, than those determined by ^{1}H NMR spectroscopic means.[10] We ascribe this difference to limitations in the range of useful affinities that may be determined by ^{1}H NMR spectroscopic means, rather than to inherent problems associated with ITC as applied to anion recognition. Indeed, we have found similar disparities in calculated affinity constants when fluorescence-based, rather than ^{1}H NMR spectroscopic, methods are used to determine large (i.e., $> 10^3$ M^{-1}) K_a values.[5,6a] Moreover, we have found that our own ITC measurements involving simple calix[4]pyrrole gave rise to K_a values that are coincident with those of Schmidtchen when essentially identical experimental protocols were used (cf., Table 1). We thus feel confident that ITC permits a relatively precise comparison between the compounds of this study, even though the K_a values in question are exceptionally high.

Table 1 summarizes the equilibrium association constants measured by ITC for the binding of chloride and bromide anion to various calix[4]pyrroles as determined in dry acetonitrile or in spectral grade DMSO that was not subject to any special drying. Inspection of this table underscores the obvious advantage that accrues as the result of using a strap. Even as compared to the previous "best" calix[4]pyrrole system, the octafluoro derivative **6**, a large increase in association constants is engendered by the use of a "strap".[11] In the case of the C-4(ether) **1**, where the effect is most dramatic, an enhancement factor of almost 7 relative to this earlier benchmark is achieved in the case of chloride in acetonitrile. This means that well over an order in magnitude in K_a increase has been engendered relative to the parent system **5**. In DMSO, the effect appears to be even more dramatic, as a comparison of the K_a values for the C-4(ether) **1** and normal calix[4]pyrrole **5** will confirm.

Table 2. Themodynamic Parameters Determined by ITC for the Binding of Various Anion Salts by the Indicated Receptors in Dry Acetonitrile at 30 °C[a]

host	guest	[H] (mM)	[G] (mM)	ΔH	$T\Delta S$	ΔG
1	TBA−Cl	0.12	1.64	−12.65	−3.55	−9.10
1	Cryptand−Cl	0.24	2.43	−11.27	−2.07	−9.20
2	TBA−Cl	0.23	3.03	−7.43	1.08	−8.51
2	Cryptand−Cl	0.23	2.43	−7.08	1.60	−8.68
3	TBA−Cl	0.22	3.06	−7.73	0.77	−8.50
3	Cryptand−Cl	0.23	2.43	−7.53	1.14	−8.67
3	TBA−Br	0.45	1.77	−7.46	−0.45	−7.01
3		0.23	3.53	−6.88	0.09	−6.97
4	TBA−Cl	0.19	2.99	−9.17	−0.65	−8.52
4	Cryptand−Cl	0.19	2.45	−8.83	−0.22	−8.61
6	TBA−Cl	0.26	3.31	−7.78	0.16	−7.94
6	Cryptand−Cl	0.25	2.91	−7.13	1.03	−5.45

[a] The error for the fitting is estimated to be < 0.08 kcal/mol.

Although for the most part, the effect of the strap appears to be a "simple" increase in anion affinity, in the case of the C-6 (ether) strap system **3**, an appreciable increase in the bromide anion affinity relative to the chloride anion affinity appears to have been achieved. Presumably, this result reflects the more open binding cavity present in this latter system and the fact that its size better complements that of the larger bromide anion. Although further studies, involving the synthesis and analysis of other systems, will be required to substantiate such a hypothesis, to the extent it stands, it leads to the suggestion that the use of straps to define further the size and nature of the binding pockets in elaborated calix[4]pyrroles provides a way of fine-tuning both anion affinities and selectivities.

Table 2 shows the thermodynamic parameters for selected compounds involved in the chloride anion-receptor binding process. An interesting conclusion that results from an inspection of this table is that changing the countercation from an alkylammonium to a potassium cryptand[2,2,2] complex did not change the experimental enthalpy significantly in the case of strapped calixpyrroles **1**−**3**. Such an observation is consistent with the two cations in question acting as essentially innocent

(9) Schmidtchen F. P. *Org. Lett.* **2002**, *4*, 431−434.
(10) Sessler, J. L.; An, D.; Cho, W.-S.; Lynch, V. *Angew. Chem.*, in press.

(11) Attempts to estimate the association constants of the strapped systems by ^{1}H NMR methods using competition experiments proved unsuccessful. Under conditions where an equimolar amount of the receptor **1** and octafluorocalix[4]pyrrole **6** are mixed with a stiochiometric limiting amount of TBACl (0.7−1.2 equivalents) in CD_3CN, such experiments indicate that there is almost no change is observed in the chemical shift of the *NH* protons for **6**, whereas a completely new sets of signals were observed for the N*H* signals of **1**. Upon adding >1.1 equiv of the anion, shifts in the resonance ascribed to **6** began to be observed. Although such observations provide important qualitative support for the notion that **6** is a stronger chloride anion receptor than **1** under these experimental conditions, the large differences in apparent affinity constants, coupled with the slow nature of the exchange observed in the case of **6**, precludes calculation of an equilibrium constant for the exchange of chloride anion between **1** and **6**. This, in turn, makes it impossible to calculate a competition-derived K_a value for **6**.

observers.[9] Another noteworthy feature highlighted by this table is that receptors **4** and **1** display the largest enthalpy changes, possibly due to the presence of an additional hydrogen bonding motif provided by the C*H* proton of the bridging phenyl ring. On the other hand, these species, wherein binding presumably most strongly benefits from a cryptand effect, are characterized by the most negative entropic terms. The resulting enthalpy−entropy compensation, which appears to be structure, as opposed to solvent,[9] based serves to reduce somewhat the affinity values of **1** and **4** below what might expect based on an extrapolation of those measured for **2** and **3**. Nonetheless, it is important to appreciate that system **1**, in particular, displays an absolute chloride anion affinity that is remarkably high, exceeding by a large margin the value seen for any other neutral pyrrole-based anion binding receptor.

Conclusions

In summary, we have demonstrated that by strapping the calix[4]pyrrole core, substantial increases in chloride and bromide binding affinity in acetonitrile and DMSO may be achieved. This approach also appears to allow for a modification of the inherent anion selectivity of calix[4]pyrroles, in that the larger strapped system show an increased affinity for bromide relative to chloride, albeit at an absolute affinity value that is still substantially reduced as compared to this latter anion. A further benefit of the present strapping strategy is that it should be amenable to future modification through, e.g., the introduction of electron withdrawing atoms on the β-pyrrolic positions or the use of straps that contain ancillary hydrogen bond donor groups. Possibilities involving the use of straps containing built-in chromophores are also attractive and may allow for the construction of new sensors that exhibit dynamic ranges or inherent selectivities that are superior to existing systems. Also attractive is the use of modified strapped systems to create clefts that might allow for the specific targeting of nonspherical anions such as, e.g., oxalate or pyrophosphate, that have obvious biological importance. Work along these lines is currently in progress.

Experimental Section

Proton NMR spectra (400 MHz, Bruker IFS 48) were recorded in $CDCl_3$ using TMS as the internal standard. High and Low resolution FAB mass spectra were obtained on AUTO SPEC M-363 high-resolution mass spectrometer. Column chromatography was performed over silica gel (Merck, 230−400 mesh). Pyrrole was distilled at atmospheric pressure from CaH_2. Both CH_2Cl_2 and $CHCl_3$ (reagent grade) were distilled from K_2CO_3 to eliminate traces of acid. All other reagents were obtained from Aldrich and used as received unless noted otherwise. Compounds **8**−**10** were prepared by a Retro-Barbier procedure.[8] The ester-strapped receptor **4** was prepared using the procedure reported recently.[7] The acetonitrile used for the ITC studies was dried simply by passage over two columns of activated molecular sieves using a solvent dispensing system designed by J. C. Meyer ("$[H_2O]$ < 10 ppm"), whereas the DMSO was spectral grade (Aldrich) but used without further purification.

6-[3-Methyl-5-(5-oxo-hexyloxy)phenoxy]-2-hexanone (12). A solution of DMF (150 mL), K_2CO_3 (7.46 g, 54.0 mmol), and orcinol (**11**, 0.67 g, 5.4 mmol) was stirred for 10 min at room temperature and then compound **8** (4.8 g, 27.0 mmol) was added. The whole mixture was heated to 60 °C and stirred for 30 min. The mixture was combined with water (20 mL) and extracted with methylene chloride (2 × 50 mL). The organic layer was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The remaining solid was purified by column chromatography on silica gel (eluent: CH_2Cl_2/EtOAc = 19/1). Collection of the appropriate fraction and drying produced **12** in the form of a yellow solid (1.44 g; 83%). Mp 42−44 °C; ^{1}H NMR ($CDCl_3$) δ 1.74−1.77 (m, 8H, CH_2), 2.15 (s, 6H, CH_3), 2.28 (s, 3H, tolyl), 2.51 (m, 4H, CH_2), 3.92(t, 4H, J = 5.79 Hz, OCH_2), 6.24 (m, 1H, Ar−H), 6.30(m, 2H, Ar−H). ^{13}C NMR ($CDCl_3$), δ 208.72, 160.02, 140.13, 107.65, 98.44, 67.41, 43.24, 29.92, 28.67, 21.79, 20.46. HRMS (CI+): Calcd for $C_{19}H_{28}O_4$ 321.206585, Found 321.207465.

7-[3-Methyl-5-(6-oxo-heptyloxy)phenoxy]-2-heptanone (13). Orcinol (0.1 g, 0.81 mmol), K_2CO_3 (1.1 g, 8.05 mmol), and compound **9** (0.78 g, 4.03 mmol) were subject to reaction under conditions identical to those used for the synthesis of **12**. Column chromatography over silica gel (eluent: CH_2Cl_2/EtOAc = 19/1) gave product **13** in 78% yield (0.22 g). Mp 48−49.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.42−1.49 (m, 4H, CH_2), 1.60−1.68 (m, 4H, CH_2), 1.73−1.80 (m, 4H, CH_2), 2.14 (s, 6H, CH_2), 2.28 (s, 3H, tolyl-H), 2.46 (m, 4H, CH_2), 3.91 (t, 4H, J = 6.40 Hz, OCH_2), 6.25 (m, 1H, Ar−H), 6.30(m, 2H, Ar−H). ^{13}C NMR ($CDCl_3$), δ 209.38, 160.50, 140.49, 108.01, 98.80, 67.94, 44.01, 30.33, 29.49, 26.09, 23.90, 22.18. HRMS (CI+): Calcd for $C_{21}H_{32}O_4$ 349.237885, Found 349.238106.

7-[3-Methyl-5-(6-oxo-heptyloxy)phenoxy]-2-heptanone (14). Orcinol (240 mg, 1.7 mmol), K_2CO_3 (2.4 g, 17 mmol), and compound **10** (1.06 g, 5.1 mmol) were subject to reaction under conditions identical to those used for the synthesis of **12**. Column chromatography over silica gel (eluent: CH_2Cl_2/EtOAc = 19/1), gave product **14** in 63% yield (0.41 g). Mp 40−41 °C; ^{1}H NMR ($CDCl_3$) δ 6.31 (s, 2H, ArH), 6.26 (s, 1H, ArH), 3.91 (t, 4H, J = 6.4 Hz, CH_2), 2.44 (t, 4H, J = 7.4 Hz, CH_2), 2.28 (s, 3H, $ArCH_3$), 2.14 (s, 6H, *meso*-CH_3), 1.79−1.72 (m, 4H, CH_2), 1.64−1.57 (m, 4H, CH_2), 1.50−1.42 (m, 4H, CH_2), 1.39−1.31 (m, 4H, CH_2). ^{13}C NMR ($CDCl_3$), δ 209.54, 160.55, 140.46, 107.98, 98.81, 68.10, 44.05, 30.29, 29.52, 29.30, 26.29, 24.12, 22.19. HRMS (CI+): Calcd for $C_{23}H_{36}O_4$ 377.269185, Found 377.269217.

1,3-Bis[5,5-di(pyrrol-2-yl)hexyloxy]-5-methylbenzene (15). To a solution of pyrrole (4.3 mL, 62.4 mmol) and compound **12** (0.5 g, 1.56 mmol) was added TFA (120 μL, 1.56 mmol) and the solution was stirred for 10 min at 60 °C. Then the reaction mixture was combined with aqueous NaOH (0.1 N, 20 mL) and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and the solvent was removed in vaccuo. The remaining oily solid was purified by column chromatography over silica gel (eluent: CH_2Cl_2) to give 0.5 g of **15** (58% yield). This product was then used directly to the next step without further purification.

1,3-Bis[6,6-di(pyrrol-2-yl)heptyloxy]-5-methylbenzene (16). Compound **13 (**1.0 g, 2.87 mmol), pyrrole (4 mL, 57.4 mmol), and TFA (0.22 mL, 2.87 mmol) were reacted in accord with the procedure used in synthesis of **15**. Column chromatography over silica gel (eluent: CH_2Cl_2) gave product **16** in 60% yield (1.03 g, oily solid); ^{1}H NMR ($CDCl_3$) δ 1.23−0.29 (m, 5H, CH_2), 1.38−1.43 (m, 4H, CH_2), 1.58 (s, 6H, CH_3), 1.67−1.73 (m, 4H, CH_2), 1.96−2.00 (m, 4H, CH_2), 2.27 (s, 3H, CH_3), 3.86 (t, 4H, J = 6.42 Hz, CH_2), 6.07−6.08 (m, 4H, pyrrole-H), 6.12−6.14 (m, 4H, pyrrole-H), 6.22 (m, 1H, Ar−H), 6.28 (m, 2H, Ar−H), 6.62−6.64 (m, 4H, pyrrole-H), 7.77 (brs, 4H, NH). FAB MS Calcd for $C_{37}H_{48}N_4O_2$ 580.38, Found 580.30.

1,3-Bis[7,7-di(pyrrol-2-yl)octyloxy]-5-methylbenzene (17). Compound **14 (**0.40 g, 1.06 mmol), pyrrole (2.9 mL, 42.5 mmol) and TFA (82 μL, 1.06 mmol) were reacted in accord with the procedure used in synthesis of **15**. Column chromatography over silica gel (eluent: CH_2Cl_2) gave desired product in 52% yield (0.33 g, oily solid). ^{1}H NMR ($CDCl_3$) δ 7.75 (br s, 4H, NH), 6.63 (m, 4H, pyrrole-H), 6.29 (s, 2H, Ar−H), 6.24 (s, 1H, Ar−H), 6.14−6.12 (m, 4H, pyrrole-H), 6.07 (m, 4H, pyrrole-H), 3.87 (t, 4H, J = 6.40 Hz, CH_2), 2.27 (s, 3H, Ar−CH_3), 1.98−1.94 (m, 4H, CH_2), 1.74−1.67 (m, 4H, CH_2), 1.58 (s, 6H, CH_3), 1.45−1.37 (m, 4H, CH_2), 1.35−1.22 (m, 8H, CH_2). CI−MS Calcd for $C_{39}H_{52}N_4O_2$ 608.41, Found 609 (M^++1).

C4−Strapped calix[4]pyrrole (1). To a solution of **15** (0.5 g, 0.9 mmol) and acetone (100 mL) was added BF_3·OEt_2 (34 μL, 0.26 mmol). The resulting solution was stirred for 20 min at room temperature before being combined with aqueous NaOH (0.1 N, 20 mL). The mixture obtained as the result of this addition was extracted twice with CH_2Cl_2 and the organic layer was dried over Na_2SO_4. The solvent was removed in vacuo and the resulting solid was purified by column chromatography over silica gel (eluent: CH_2Cl_2). Recrystallization from methanol afforded product **1** in pure form. Yield: 0.055 g (10%). Mp 213 °C decomp.; ^{1}H NMR ($CDCl_3$) δ 1.38−1.44 (m, 4H, CH_2), 1.47 (m, 12H, CH_2), 1.54(s, 6H, CH_3) 1.73(m, 4H, CH_2), 1.91 (m, 4H, CH_2), 2.34 (s, 3H, tolyl), 4.04 (t, 4H, J = 5.50 Hz, OCH_2), 5.83 (m, 4H, pyrrole-H), 5.88 (m, 4H, pyrrole-H), 6.27 (m, 1H, Ar−H), 6.36 (m, 2H, Ar−H) 7.07 (br s, 4H, NH). ^{13}C NMR ($CDCl_3$), δ 160.16, 140.28, 138.07, 136.25, 107.35, 104.34, 102.83, 101.75, 67.80, 40.83, 39.14, 35.42, 30.98, 28.77, 28.46, 27.38, 22.14, 22.03. FAB−MS Calcd for $C_{41}H_{52}N_4O_2$ 632.41, Found 632.59 (M^+).

C5-strapped Calix[4]pyrrole (2). Compound **16** (0.2 g, 0.344 mmol), acetone (34 mL), and BF_3·OEt_2 (12 μL, 0.1 mmol) were reacted in accord with the procedure used for the synthesis of **1**. Column chromatography over silica gel (eluent: CH_2Cl_2) and recrystallization from methanol gave the strapped calixpyrrole product (0.025 g; 11%) in pure form. Mp 205 °C decomp.; ^{1}H NMR ($CDCl_3$) δ 1.22−1.36 (m, 6H, CH_2), 1.46 (m, 12H, CH_2), 1.49−1.50 (m, 16H, CH_2), 1.76−1.83 (m, 8H, CH_2), 2.33 (s, 3H, tolyl), 3.99 (t, 4H, J = 6.11 Hz, OCH_2), 5.84(m, 4H, pyrrole-H), 5.88 (m, 4H, pyrrole-H), 6.30 (s, 1H, Ar−H), 6.39 (s, 2H, Ar−H), 7.32 (br s, 4H, NH). ^{13}C NMR ($CDCl_3$), δ 160.27, 140.09, 138.16, 136.34, 107.75, 104.13, 102.69, 99.17, 67.73, 41.92, 39.19, 35.38, 31.18, 29.71, 28.78, 28.26, 27.25, 26.59, 24.92, 21.87. FAB−MS Calcd for $C_{43}H_{56}N_4O_2$ 660.44, Found 660.47 (M^+).

C6-Strapped Calix[4]pyrrole (3). Compound **17 (**0.33 g, 0.542 mmol), acetone (50 mL) and BF_3·OEt_2 (21 μL, 0.16 mmol) were reacted in accord with the procedure used for the synthesis of **1**. Column chromatography over silica gel (eluent: CH_2Cl_2) and recrystallization from methanol gave the strapped calixpyrrole product in 8% yield (30 mg). Mp 204 °C decomp.; ^{1}H NMR ($CDCl_3$) δ 7.13 (br s, 4H, NH), 6.39 (s, 1H, Ar−H), 6.37 (s, 2H, Ar−H), 5.86 (m, 4H, pyrrole-H), 5.85 (m, 4H, pyrrole-H), 4.01 (t, 4H, J = 5.7 Hz, CH_2), 2.33 (s, 3H, Ar−CH_3), 1.84−1.80 (m, 4H, CH_2), 1.76−1.70 (m, 4H, CH_2), 1.55 (s, 6H, CH_3), 1.55−1.47 (m, 4H, CH_2), 1.47 (s, 6H, CH_3), 1.44 (s, 6H, CH_3), 1.40−1.33 (m, 4H, CH_2), 1.24−1.19 (m, 4H, CH_2). ^{13}C NMR ($CDCl_3$), δ 160.32, 140.09, 138.16, 137.28, 106.74, 103.85, 102.83, 100.74, 67.41, 39.93, 38.86, 35.45, 35.31, 30.82, 28.15, 27.67, 27.63, 26.91, 24.57, 23.36, 22.05. HRMS (CI^+) Calcd for $C_{45}H_{60}N_4O_2$ 689.479453, Found 689.478151.

ITC and ^{1}H NMR Spectroscopic Binding Studies. Isothermal Titration Calorimetery (ITC) measurements were performed as follows: Solutions of the chosen receptor in rigorously dry acetonitrile or spectral grade DMSO were made up so as to provide a receptor concentration range of 0.1−1 mM. These solutions were then individually titrated with the appropriate alkylammonium or potassium cryptand salts at 30 ± 0.01 °C, unless indicated otherwise. The original heat pulses were normalized using reference titrations carried out using the same salt solution but pure solvent, as opposed to a solution containing the receptor. The values recorded in Table 1 are the average result of at three separate titrations carried out at least two different concentrations.

X-ray Experimental. Crystal structure analyses were measured on a Nonius Kappa CCD diffractometer using a graphite monochromator with $Mo_{K\alpha}$ radiation (λ = 0.71073 Å). The data were collected at 153K using an Oxford Cryostream low-temperature device. Data reduction were performed using DENZO−SMN.[12] The structure was solved by direct methods using SIR92[13] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[14] The hydrogen atoms were calculated in ideal positions with isotropic displacement parameters set to 1.2 × Ueq of the attached atom (1.5 × Ueq for methyl hydrogen atoms). The hydrogen atoms bound to nitrogen were located in a ΔF map and refined with isotropic displacement parameters. The function, $\Sigma w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.0317P)^2 + (2.8372P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_w(F^2) = \{\Sigma w(|F_o|^2 - |F_c|^2)^2/\Sigma w(|F_o|)^4\}^{1/2}$ where w is the weight given each reflection. $R(F) = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|\}$ for reflections with $F_o > 4(\sigma(F_o))$. S = $[\Sigma w(|F_o|^2 - |F_c|^2)^2/(n - p)]^{1/2}$, where n is the number of reflections, and p is the number of refined parameters. The data were corrected for secondary extinction effects. The correction takes the form: $F_{corr} = kF_c/[1 + (3.1(6) \times 10^{-6})F_c^2\lambda^3/(\sin 2\theta)]^{0.25}$ where k is the overall scale factor. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[13]

4·$(C_2H_5)_3$NHCl. $C_{46}H_{62}N_5O_4Cl$; Crystals grew as colorless prisms and lathes. The data crystal was cut from a long needle and had approximate dimensions 0.20 × 0.15 × 0.11 mm; triclinic, space group *P-1*, a = 9.5568(2) Å, b = 11.0858(3) Å, c = 20.6450(6) Å, α = 76.832(1)°, β = 77.413(1)°, γ = 84.170(1)°, V = 2075.43(9) Å^3, Z = 2, ρ_{calc} = 1.255 gcm^{-3}, μ = 0.142 mm^{-1}, $F(000)$ = 844; a total of 461 frames of data were collected using ω-scans with a scan range of 1° and a counting time of 123 s per frame. A total of 15232 were measured, 9255 unique (R_{int} = 0.0812). The structure was refined on F^2 to 0.156, with $R(F)$ equal to 0.0857 and a goodness of fit, S, = 0.994.

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Supporting Information Available: Spectra, tables of experimental data, ITC plots of **1**−**6**, and an X-ray crystallographic data file. This material is available free of charge via the Internet at http://pubs.acs.org.

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