JOC Article

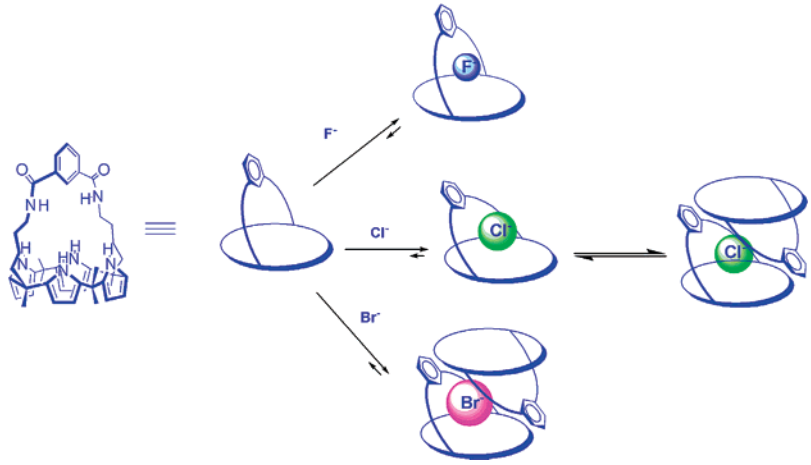
Cis- and Trans-Strapped Calix[4]pyrroles Bearing Phthalamide Linkers: Synthesis and Anion-Binding Properties

Chang-Hee Lee,*,† Jin-Suk Lee,† Hee-Kyung Na,† Dae-Wi Yoon,† Hidekazu Miyaji,† Won-Seob Cho,‡ and Jonathan L. Sessler*,‡

Department of Chemistry and Institute of Basic Science, Kangwon National University, Chun-Chon 200−701 Korea, and Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, Texas 78712

chhlee@kangwon.ac.kr; sessler@mail.utexas.edu

Received July 27, 2004



New cis-strapped calix[4]pyrrole derivatives **12**, **13**, and **19** and trans-strapped systems **14** and **15** bearing isophthalate-derived diamide spacers linked to the tetrapyrrolic core have been synthesized and characterized by spectroscopic means. The anion-binding behavior of these receptors was investigated by proton NMR spectroscopy and isothermal titration calorimetry (ITC). A 2:1 binding stoichiometry was observed under the conditions of NMR analysis but not at the lower concentration regime used for ITC. As gauged from both sets of analyses, these new strapped systems display affinities for halide anions that are enhanced compared to those of normal, unstrapped calix[4]-pyrrole. However, contrary to expectations, no size-dependent selectivity for anions is observed as the length of the bridging strap is varied. Such results are interpreted in terms of anion-binding processes that occur outside the central pocket defined by the strap but that still favor strong associations as the result of the increased number of hydrogen-bonding donors the amide groups provide.

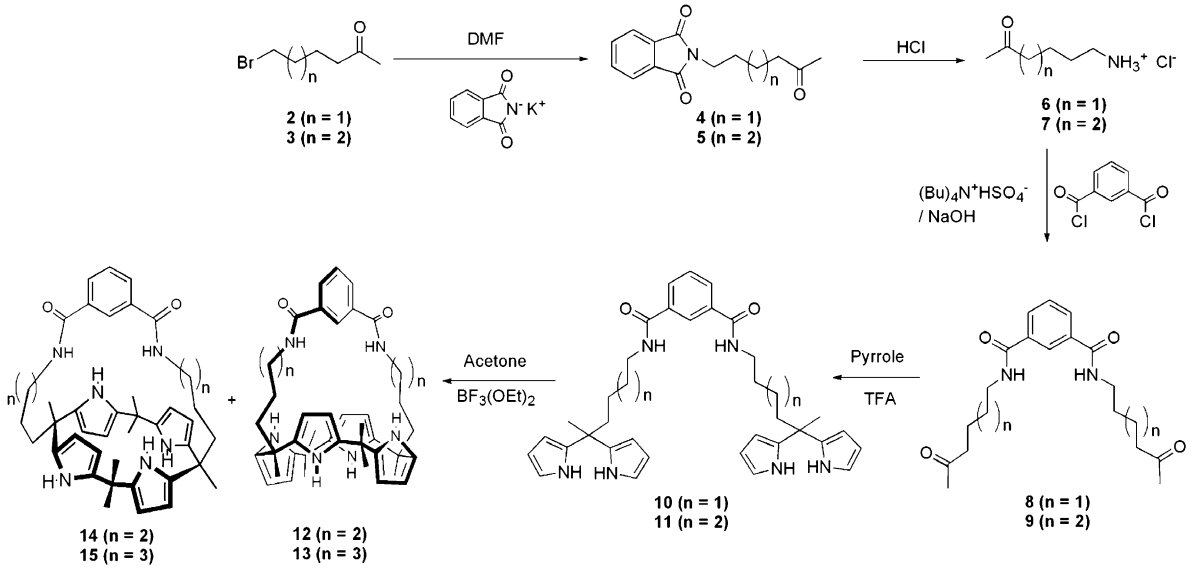
The design and synthesis of anion receptors possessing high affinity and selectivity represents a challenge that continues to attract considerable attention within the molecular recognition and supramolecular chemistry communities due to the important role anions play in areas as diverse as the environment and medicine.[1] Calix-[4]pyrroles (e.g., **1**) represent a set of readily accessible receptors for various anions whose affinity toward fluoride, chloride, and phosphate anion in organic media has been well documented since their anion recognition characteristics were first reported by Sessler and co-workers in 1996.[2] Recently, we reported that strapping one face of a calix[4]pyrrole could significantly enhance the affinity and selectivity for appropriately sized anions and that the anion recognition specifics could be "fine-tuned" by modifying the length and nature of the bridging straps.[3] As a general rule, greatly enhanced anion affinities were seen, and in the best of cases, binding

† Kangwon National University.
‡ University of Texas at Austin.

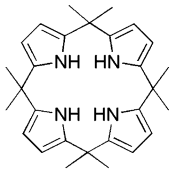
(1) (a) Chakrabarti, P. *J. Mol. Biol*. **1993**, *234*, 463−482. (b) Van Kuijck, M. A.; Van Aubel, R. A. M. H.; Busch, A. E.; Lang, F.; Russel, G. M.; Bindels, R. J. M.; Van Os, C. H. and Deen, P. M. T. *Proc. Natl. Acad. Sci. U.S.A*. **1996**, *93*, 5401. (c) Calnan, B. J.; Tidor, B.; Biancalana, S.;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

10.1021/jo0487146 CCC: $30.25
Published on Web 02/18/2005

SCHEME 1



constants for halide anions were obtained that far surpassed those achieved using alternative modification approaches, including those based on the introduction of electron withdrawing substituents in the β-pyrrolic positions,[4] the use of covalently linked dimers,[5] functionalization with chromophores,[6] or the synthesis of so-called deep cavity systems.[7]



1

To date, we have relied on straps that contain either ether or ester functionality. However, such systems represent but a small subset of what might be possible in the context of the generalized strapping paradigm. Accordingly, we are currently seeking to develop new systems based on other types of bridging motifs and in this paper wish to report the design, synthesis, and anion-binding properties of a new set of strapped-calix[4]pyrroles that contain amide functionality within the caplike strap. These systems stand in contrast to the earlier ones in that they possess additional hydrogen-bonding donor sites with the straps. They also differ from the earlier ones in that they have been isolated, at least in the case of the larger straps, in two different configurations, the "cis" and "trans" isomeric forms.

In the design of the present generation of strapped calix[4]pyrrole receptors, a flexible, *m*-phthalate-derived strap containing two amide groups was chosen as the strapping element. The presence of these amide groups was expected to provide additional hydrogen bonding sites for anion recognition, while, as in the past, the choice of strap size was expected to impart a degree of anion selective recognition. As it turned out, these expectations were only partly met.

Results and Discussion

The synthesis of the larger strapped systems, compounds **12**−**15**, is shown in Scheme 1. Starting with potassium phthalimide, reaction with 6-bromohexan-2-one (**2**) or 7-bromoheptan-2-one (**3**)[8] gives the corresponding *N*-alkyl phthalimides **4** and **5**. Acid-catalyzed hydrolysis then afforded the aminoketone hydrochloride salts **6** and **7**, respectively, in almost quantitative yields. These amine salts were not isolated or subject to further purification. Rather, they were converted directly into the corresponding bis-ketones, **8** and **9**, by reacting with isophthaloyl chloride. Treatment of diketones **8** and **9** with pyrrole in the presence of trifluoroacetic acid (1.0 molar equiv) then afforded the corresponding bisdipyrromethanes **10** and **11**, respectively.

Once intermediates**10** or **11** were in hand, they were condensed with acetone in the presence of a catalytic amount of BF_3 to produce the desired strapped calix[4]-

(2) (a) Gale, P. A.; Sessler, J. L.; Kràl, V. and 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, and Burlington, MA, 2000. (d) Sessler, J. L.; Anzenbacher, P., Jr.; 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.; Kràl, V. *ACS Symp. Series*. **2000**, 757 (Calixarenes for Separations) 238−254. (f) Gale, P. A.; Anzenbacher, P., Jr.; 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.

(3) Yoon, D. W.; Hwang, H.; Lee, C. H. *Angew. Chem., Int. Ed*. **2002**, *41*, 1757−1759.

(4) (a) Gale, P. A.; Sessler, J. L.; Allen, W. E.; Tvermoes, N. A.; Lynch, V. *Chem. Commun.* **1997**, 665−666. (b) Anzenbacher, P., Jr.; Try, A. C.; Miyaji, H.; Jurisíková, K.; Lynch, V. M.; Marquez, M.; Sessler, J. L. *J. Am. Chem. Soc*. **2000**, *122*, 10268−10272. (c) Miyaji, H.; An, D.; Sessler, J. L. *Supramol. Chem.* **2001**, *13*, 661−669.

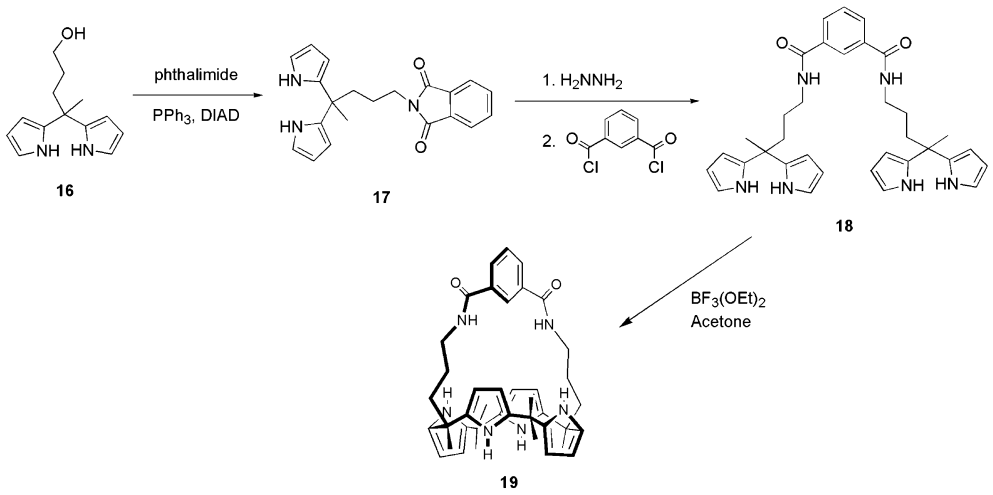
(5) Sato, W.; Miyaji, H.; Sessler, J. L. *Tetrahedron Lett*. **2000**, *41*, 6731−6736.

(6) (a) Miyaji, H.; Sato, W.; Sessler, J. L.; Lynch, V. M. *Tetrahedron Lett*. **2000**, *41*, 1369−1373. (b) Miyaji, H.; Sato, W.; Sessler, J. L. *Angew. Chem., Int. Ed*. **2000**, *39*, 1777−1779. (c) Anzenbacher, P., Jr.; Jursikova, K.; Sessler, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 9350−9351.

(7) (a) Anzenbacher, P., Jr.; Jursikova, K.; Lynch, V. M.; Gale, P. A.; Sessler, J. L. *J. Am. Chem. Soc*. **1999**, *121*, 11020−11021. (b) Camiolo, S.; Gale, P. A. *Chem. Comm*. **2000**, 1129−1130.

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

SCHEME 2



pyrroles **12** and **13** in yields of 18% and 19%, respectively. Interestingly, calix[4]pyrroles such as **14** and **15**, which represent configurational isomers of **12** and **13**, were unexpectedly isolated in relatively lower yield (~6% for **14** and ~17% for **15**). Receptors **14** and **15** have a trans junction for the diametrically positioned strap. The identity of the two compounds was confirmed unambiguously by proton NMR spectroscopy, while their isomeric nature was supported by mass spectroscopic analyses. Although the yields of these new strapped systems were moderate, the synthesis, purification, and isolation of the key bisdipyrromethane intermediates **10** and **11** proved to be straightforward, requiring only simple column chromatography over silica. As a result, systems **12**−**15** could be obtained in sufficient quantities so as to allow for detailed anion-binding studies.

Analogue **19**, bearing a shorter strap, could not be obtained readily using the procedure of Scheme 1. Therefore, it was synthesized using an alternative method as shown in Scheme 2. Briefly, the known dipyrromethane intermediate **16**[3] was converted into its phthalimide derivative **17** in high yield (87%) in the presence of $P(Ph)_3$ and diisopropyl azodicarboxylate (DIAD). After conversion to the corresponding amine by treatment with hydrazine, immediate reaction with isophthaloyl dichloride afforded the bis-dipyrromethane **18**. Acid-catalyzed condensation of **18** with acetone in the usual way then provided the desired product **19** in 16% yield. In this case, no evidence for the formation of the isomeric trans-strapped system was seen. Presumably, this reflects the fact that the strap is too short to permit the formation of such an inherently strained species.

The proton NMR spectra of the "cis" systems **12**, **13**, and **19** in chloroform-*d* were found to be in accord with the proposed structures. For example, in the case of **13**, the amide N*H* resonances appeared at 6.70 ppm in the form of a triplet, while the signals for the pyrrolic N*H*s were observed as a singlet at 7.84 ppm in a singlet. By contrast, the amide N*H* signals in **12** appeared at 6.48 ppm, while the pyrrolic N*H* signal appeared as a singlet at 7.92 ppm. These observations support the intuitively appealing notion that the tetrapyrrolic core present in the more tightly strapped system **12** is more distorted than that present in **13**.

As can be seen from an inspection of Figure 1, dramatically different proton NMR spectroscopic behavior was seen in the case of the "trans" systems **14** and **15**. For example, the resonance of the amide N*H* protons in **15** appeared at 6.37 and 6.13 ppm as two distinctive singlets and those of the pyrrolic N*H*s were also observed at 6.97 and 6.78 ppm in the form of two distinct singlets. The two Ar*H* protons at positions 4 and 6 of the phthaloyl group were found to be split into two distinct doublets appearing at 8.10 and 7.70 ppm. In addition, the shielded resonance of the methylene protons next to the meso position appeared at 0.47 ppm indicated that the compound was unusually distorted compared to the corresponding cis-strapped system, where the methylene proton signals appeared at 1.26 ppm. In the ^{13}C NMR spectrum of compound **15**, two sets of signals were observed for all the carbon atoms, including those of the carbonyl group. Unfortunately, the trans-strapped compounds **14** and **15** proved rather unstable in organic solvents and slow decomposition was observed, as evidenced by a general degradation of the NMR spectral features.

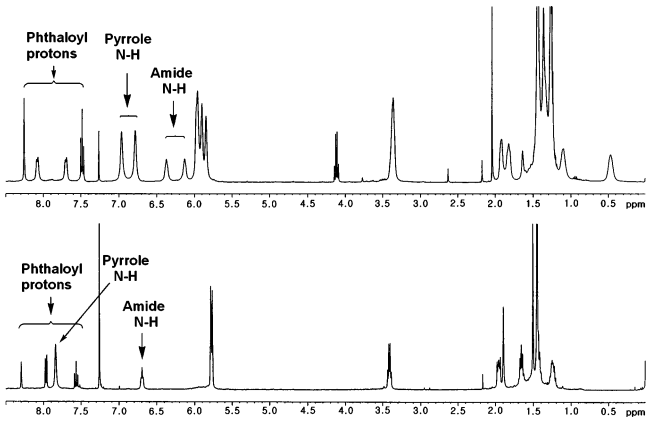


FIGURE 1. Typical proton NMR spectra at cis-strapped (**13**) (bottom trace) and trans-strapped (**15**) (top trace) calix[4]-pyrroles in $CDCl_3$ at 25 °C.

Initial studies of the anion-binding properties of systems **12**, **13**, and **19** were carried out in acetonitrile-d_3 using proton NMR spectroscopy. Unfortunately, slow

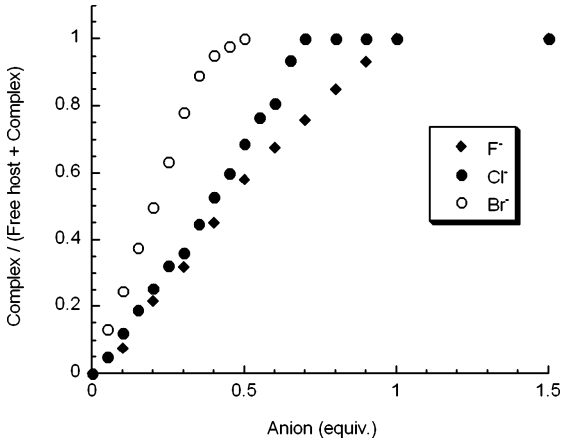


FIGURE 2. Titration of compound **12** with halide anions (as their corresponding tetrabutylammonium (TBA) salts) in CD_3CN (1.0 mM). In the case of fluoride anion, the saturation point in the binding curve is seen after the addition of 1 stoichiometric equivalent of the anion; in the case of bromide anion, saturation is seen after the addition of 0.5 molar equiv; in the case of chloride it is seen after the addition of ~0.7 molar equiv.

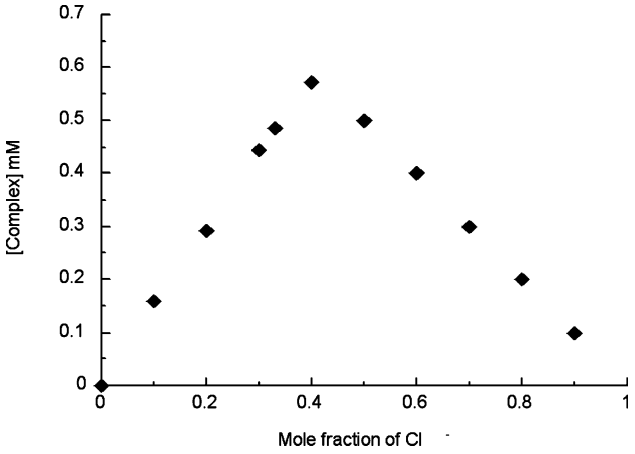


FIGURE 3. Job plot corresponding to the titration of compound **12** with chloride anion (as TBACl) in CD_3CN.

complexation/decomplexation kinetics was observed for all host systems, meaning no quantitative anion affinity information could be deduced from these studies. On the other hand, these ^{1}H NMR spectroscopic studies did provide good qualitative evidence for the proposed halide anion binding. For example, when receptor **12** (containing straps with four methylene units) was subjected to titration with TBAF in acetonitrile-d_3, dramatic changes in the ^{1}H NMR signals were observed. In particular, the integrated intensity of the pyrrole N*H* proton signals, originally observed at 8.37 ppm in the absence of any anion, was seen to diminish as the titration progressed. Meanwhile, a new signal was observed to appear at 11.84 ppm, with an integrated intensity that increased as the titration was allowed to run its course. Complete disappearance of the original signal at 8.37 ppm was observed with the addition of 1.0 equiv of TBAF.

In the titration with chloride anion, the integrated intensity of the pyrrole N*H* protons, again observed at 8.37 ppm in the absence of the added anion, was found to decrease upon the addition of small quantities of TBACl with noticeable changes being seen even after the addition of ~0.05 equiv. Concurrently, a new signal was seen to grow in at 10.30 ppm. In the case of bromide anion, a complete shift in the pyrrole N*H* signal, from 8.37 to 10.02 ppm, was observed upon the addition of only 0.5 equiv of TBABr. While these differences in shift behavior have important implications in terms of assigning binding stoichiometry under solution-phase conditions, they also lead us to the intriguing proposal that anion discrimination could be effected by analyzing changes in the pyrrole N*H* signal.

Information about the anion-binding process can also be inferred from the changes observed for several of the other signals seen in the ^{1}H NMR spectrum of **12**, **13**, and **19**. For instance, in the case of receptor **12**, the amide N*H* protons, initially appearing at 7.04 ppm, were seen to shift to 8.22 ppm upon titration with TBACl. Moreover, the signal for the aromatic C*H* proton at position 2 (i.e., between the two carbonyl groups) was found to shift from 8.23 to 8.44 ppm. The signals for the methylene protons next to the amide subunits underwent a shift from 3.45 to 3.49 ppm. In all cases, an essentially complete disappearance of the original signals, along with the appearance of the new signals, was observed after the addition of only ~0.7 molar equiv of chloride anion. This is reflected in the saturation point seen in the binding profile curve for this anion−receptor pair (Figure 2).

In contrast to the above, saturation in the binding profile curve was seen after the addition of 1 molar equiv of anion in the case of fluoride anion (added as TBAF·$3H_2O$) and after the addition of ca. 0.5 anion equiv in the case of bromide anion. Such findings are consistent with a single fluoride anion being bound by a single strapped calix[4]pyrrole host but bromide being bound by two such receptor species. They also provide a strong "hint" that the binding stoichiometry in the case of chloride is less "clean". Further analyses involving this anion were thus carried out as described below.

In accord with the finding that greater than 0.5 molar equiv but fewer than one full stoichiometric equivalent of TBACl was required to effect a considerable change in the overall spectral features, the maximum of the Job plot (Figure 3), corresponding to the binding of chloride anion to **12**, was observed when the Cl^- mole fraction was 0.4. Such a mole fraction value, which was found to be entirely reproducible, is not completely consistent with the formation of a 2:1 (receptor:anion) binding stoichiometry (for which a maximum in the Job plot at a mole fraction of 0.33 would be expected) under the relatively high (e.g., 1.0 mM in **12**) concentrations of the NMR studies. Nor is it consistent with the formation of a 1:1 complex. However, it may indicate the existence of equilibrium between a 1:1 (**20**) and 2:1 (receptor/anion) complex (**21**) as shown in Scheme 3. In particular, it is suggested that at high relative receptor concentrations (i.e., after the addition of only a small amount of TBACl), a species such as **21** forms that then dissociates to form a 1:1 complex (**20**) as the relative concentration of the anion substrate increases. In the case of fluoride, it is a complex of 1:1 stoichiometry (e.g., **22**) that is formed at most receptor:anion ratios, whereas in the case of bromide it is the 2:1 species, **23**, that predominates.

The low temperature (−50 °C; CD_3CN) proton NMR spectrum of free host **12** shows only a single peak for the pyrrolic N*H* resonances at 8.84 ppm, while the compa-

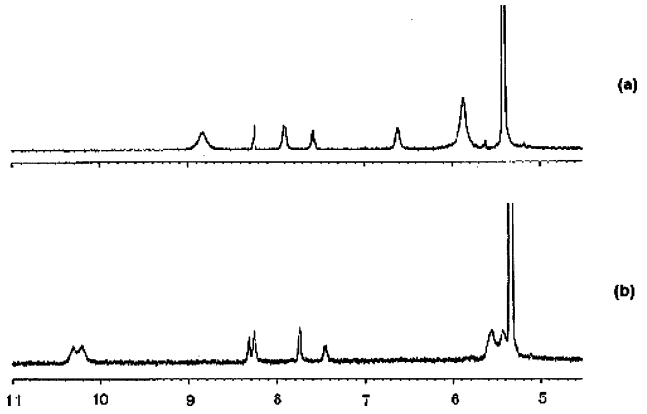
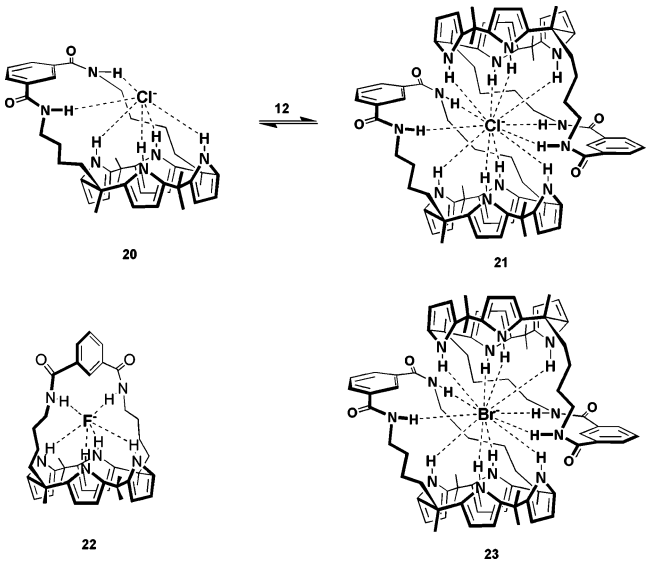


FIGURE 4. Low-temperature (−50 °C; CD_3CN) proton NMR spectrum of free receptor **12** (trace a). Notice the presence of a single pyrrolic N*H* resonance. Trace b shows the spectrum recorded at a 3:2 stoichiometric ratio of **12**/TBACl (a ratio corresponding to the saturation point seen in Figure 2) under analogous conditions. Here, attention is drawn to the split nature of the pyrrolic N*H* signal.

SCHEME 3



rable spectrum recorded at the point where the stoichiometric ratio of **12** to TBACl was 3:2, revealed two separate pyrrolic N−H resonances at 10.32 and 10.20 ppm (Figure 4). These distinct N−H signals are assigned to the 1:1 and 2:1 complexes, respectively. This splitting is not observed at room temperature, presumably as the result of a rapid equilibrium between what is predominantly a mixture of the 1:1 and 2:1 (receptor:anion) complexes (cf. Scheme 3).

To provide more support for the proposed binding modes, a so-called reverse titration was performed with bromide anion. This experiment was carried out by adding small portions of host **12** to a solution of tetrabutylammonium bromide (1.0 mM) in CD_3CN (Figure 5). At the beginning of this "titration" (i.e., when 0.1 molar equiv of **12** had been added), the complex ratio (i.e., [complex]/([free calixpyrrole] + [complex]) determined from integration of the ^{1}H NMR spectrum showed that essentially every host molecule added to the solution was bound to a bromide anion, as would perhaps be expected given the relatively high excess of bromide anion present

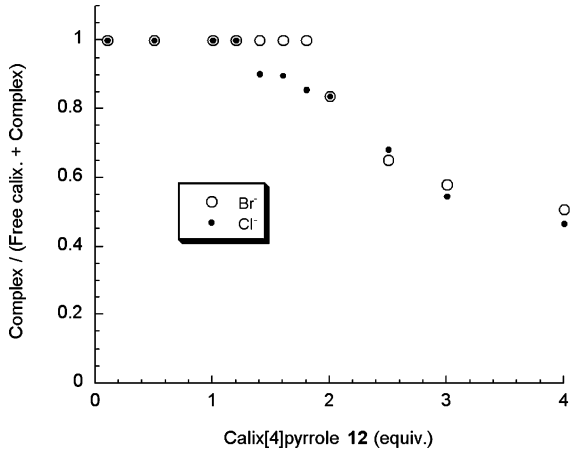


FIGURE 5. Plot showing the results of a reverse proton NMR spectroscopic titration: The strapped calix[4]pyrrole **12** was added to solutions of tetrabutylammonium bromide (TBABr) and tetrabutylammonium chloride (TBACl) (1.0 mM in CD_3CN), respectively. The 2:1 (receptor/anion) complex ratio was maintained up to the point where roughly ∼2 molar equivalents of the calixpyrrole had been added in the case of bromide. In the case of chloride anion, a 2:1 (receptor/anion) complex ratio was maintained up to the point where ∼1.3 molar equiv of the host had been added.

at this stage. The nature of the spectral features, and hence complex ratio, remained unchanged until ∼2 molar equiv of host **12** had been added. Such an invariance is consistent with the formation of a 2:1 (receptor/Br^-) complex in the solution under these conditions. After the addition of >2 molar equiv of receptor **12**, the complex ratio started to decrease, as reflected in the appearance of peaks ascribed to the uncomplexed free host (i.e., **12**). Taken in concert, these results provide important support for the proposal that the receptor is binding with bromide anion in a clean 2:1 (receptor to anion) fashion under most solution phase conditions, including those of Figure 2. The results also indicate that receptors such as **12** might be useful systems for effecting the quantitative analysis of anions under various "real life" scenarios.

Additional quantitative studies of the anion-binding properties of **12**, **13**, and **19** were made using isothermal titration calorimetry (ITC). An advantage of this method is that it allows for the study of recognition events, including those involving calix[4]pyrroles,[9,10] at concentrations that are lower than those required for NMR spectroscopic analyses. ITC also permits the determination of much higher binding affinities than do NMR-based methods. Unfortunately, to date, we have been unable to obtain reliable binding constant data for fluoride anion for any receptor, including **1**, by ITC. This anion was, therefore, excluded from the present study.

Table 1 summarizes the equilibrium association constants K_a, measured by ITC for the binding of various halide anions to receptors **12**, **13**, and **19** as determined in dry acetonitrile.[11] The sum total of the data leads us to propose that the binding mode observed with these new systems may be different from that seen in the

(9) Schmidtchen F. P. *Org. Lett.* **2002**, *4*, 431−434.
(10) Lee, C. H.; Na, H. K.; Yoon, D. W.; Won, D. H.; Cho, W. S.; Lynch, V. M.; Shevchuk, S. V.; Sessler, J. S. *J. Am. Chem. Soc.* **2003**, *125*, 7301−7306.

TABLE 1. Association Constants, K_a, and Thermodynamic Parameters for the Binding of Chloride, Bromide, and Iodide Anions by Hosts 12, 13, and 19 As Measured by ITC (Isothermal Titration Calorimetry) at 30 °C Using the Corresponding Alkylammonium Salts (TBA = Tetrabutylammonium)

	19 (C_3)			**12** (C_4)			**13** (C_5)		
anion	TBA-Cl	TBA-Br	TBA-I	TBA-Cl	TBA-Br	TBA-I	TBA-Cl	TBA-Br	TBA-I
solvent[a]	CH_3CN	CH_3CN	CH_3CN	CH_3CN	CH_3CN	CH_3CN	CH_3CN	CH_3CN	CH_3CN
ΔH	−9.75	−7.11		−9.79	−8.39	−4.89	−10.00	−8.13	−4.85
ΔG	−9.14	−8.53		−9.75	−8.46	−4.65	−9.03	−8.10	−4.83
$T\Delta S$	−0.61	1.42		−0.74	0.07	−0.24	−0.97	−0.03	−0.02
K_a	3.89×10^6	1.41×10^6	ND	3.35×10^6	1.25×10^6	2.30×10^3	3.24×10^6	7.0×10^5	3.0×10^3

[a] The CH_3CN was rigorously dried by passage over two columns of activated molecular sieves using a solvent dispensing system ([H_2O] < 10 ppm).

previously reported strapped calix[4]pyrrole systems.[10] Although a large increase in across-the-board anion affinity, relative to the unstrapped "control" calix[4]-pyrrole **1**, is seen for all three of the test anions considered, no size discrimination is observed. Rather, in contrast to what was found in the case of the analogous ether linked strapped systems,[10] all three new receptors give rise to more or less the same binding behavior and thus do not show any kind of anion-to-receptor size matched selectivity. Such a result was entirely unexpected and, in our view, is one that is most easily rationalized in terms of a binding process that takes place outside of the strap-derived binding pocket. On the other hand, the dramatic increase in affinity observed relative to **1** indicates that, in the case of **19**, **12**, and **13**, anion binding likely benefits from interactions involving both the amide N*H* and pyrrolic N*H* protons.

Structures **20** and **21** show schematic representations of the proposed binding modes of receptor **12** with chloride anion and are designed to illustrate the equilibrium between 1:1 and 2:1 (receptor/anion) complexes that are formed from **12**. The moderate size of chloride anion does not permit it to fit into the cavity well and, accordingly, interactions involving slight out-of-cavity binding may be preferred. On the other hand, in the case of fluoride anion it is the 1:1 complex (structure **22**) that is formed to near exclusion, while its larger congener, bromide anion, forms a 2:1 complex (structure **23**) almost exclusively. The fact that the nature of the binding modes for **12** and these three halide anions shifts from 1:1 to 2:1 in a monotonic fashion depending on the size of the anion, means that both the size of the anion and the tightness of the strap lay key roles in regulating the recognition process and that the latter "variable" provides a potentially versatile "tool" for fine-tuning the anion affinities and selectivities of cis-configured calix[4]pyrrole systems. On the other hand, this choice of spacer enforces an orientation for the two amide-derived N*H* donor groups that are necessarily oriented parallel to the phenyl ring. As a consequence, a strap orientation where the *m*-phthalamide "cap" is perpendicular to the calix-[4]pyrrole cone leads to a pocket that is too small to accommodate readily even the smallest of the test anions considered in this study, i.e., chloride anion. By contrast, opening up the cavity, to provide structures such as **20** allows for a full complement of anion−receptor binding interactions while at the same defining avenues of approach that permit dimerization, as per structure **21**. This latter form, which provides for multiple receptor-anion hydrogen bonding interactions, is expected to be particularly stable, especially at high receptor:anion ratios. While no independent structural proof for this model currently exists (e.g., from X-ray diffraction analysis), it is very much in accord with the experimental observations.

No substantial changes in the proton NMR spectrum were observed when compound **8** (the calix[4]pyrrole-free, bis-amide "strap" intermediate) was titrated with tetrabutylammonium chloride under conditions analogous to those used in the study of **12**, **13**, and **19**. This lack of appreciable change is consistent with the proposal made above, namely that receptor−anion interactions involving both the two amide N*Hs* and the pyrrolic N*H* protons are responsible for the high anion binding affinities seen in the case of this cis-configured receptor systems.

Further support for this generalized conclusion came from studies of the trans-configured receptor **14**. In this case, evidence for fast complexation/decomplexation kinetics was observed, as evidenced by the gradual downfield shifts of the two amides N*H* proton signals seen in the ^{1}H NMR spectrum of **14** upon the addition of increasing quantities of TABCl (measurements made, as above, in acetonitrile-d_3). Interestingly, the chemical shift of the pyrrolic N*H* protons remained almost unchanged throughout the course of the titration. From this latter observation, we infer that there is, at best, minimal participation of the pyrrolic N*H*s in the binding event; presumably, this reflects the high conformational rigidity imposed by the trans configuration of the calixpyrrole−strap junctions. Calix[4]pyrrole **14** and its congener **15**, are constrained to a rigid conformation as the result of these strap-bearing junctions and are thus probably unable to adopt the cone conformation that is known to favor the binding of anions in receptors of this type.

Conclusion

In summary, we have shown that strapping a calix[4]-pyrrole core with amide-containing linkers increases the binding affinity for halide anions in acetonitrile solution. However, in contrast to what is true for the corresponding ester or ether strapped systems, these newer *m*-phthalimide-derived systems failed to show an appreciable size-

(11) Isothermal titration calorimetery (ITC) measurements were performed as follows: Solutions of the chosen receptor in rigorously dry acetonitrile 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 salts at 30 ± 0.01 °C. 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 least three separate titrations carried out using at least two different concentrations.

based selectivity among the three test anions studied, namely chloride, bromide, and iodide. This is rationalized in terms of a binding mode that does not involve complexation of the anionic substrate within a well-defined central pocket established by the bridging strap. Rather, it is proposed that the strap tilts to one side so as to allow both amide- and pyrrole N*H*-based hydrogen bonding interactions. A consequence of this is the possibility of facile dimerization to form 2:1 receptor/anion complexes, something that is seen in the case of bromide anion in acetonitrile-d_3 and for chloride anion at high receptor/anion ratios in this same solvent. To the extent such a hypothesis is correct it leads to the suggestion that the choice of strap could play a profound role not only in increasing the intrinsic anion affinities of calix[4]pyrroles but also in modulating the receptor:anion stoichiometry, thereby modifying potentially the inherent anion binding selectivity. Current work is focused on preparing other strapped systems and extending this control paradigm into the realm of other receptor systems. Particular emphasis is being placed on the construction of systems containing straps with built-in chromophores that could act as new colorimetric anion sensors, as well as the generation of new receptors with preorganized clefts that might allow for the specific targeting of nonspherical anions, such as oxalate anion or pyrophosphate anion, that are of obvious biological importance.

Experimental Section

Proton NMR spectra (400 MHz) were recorded using TMS as the internal standard. High- and low-resolution FAB mass spectra were obtained on a high-resolution mass spectrometer. Column chromatography was performed over silica gel (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 a commercial supplier and used as received unless noted otherwise. Isothermal titration calorimetery (ITC) measurements were performed as follows: Solutions of the chosen receptor in rigorously dry acetonitrile were made up so as to provide a receptor concentration range of 0.1∼1.0 mM. These solutions were then individually titrated with the appropriate alkylammonium salts at 30 ± 0.01 °C. 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 represent the average of at least three separate titrations carried out using at least two at different concentrations.

***N*-(6-Oxohexyl)phthalimide (4).** Phthalimide (1.55 g, 8.36 mmol) and 6-bromo-2-hexanone (1.14 g, 6.39 mmol) were subjected to reaction as in the synthesis of **5**: yield 1.47 g (94%); ^{1}H NMR ($CDCl_3$) δ 7.85−7.82 (m, 2H), 7.73−7.70 (m, 2H), 3.71 (t, 2H, J = 6.9), 2.51−2.48 (t, 2H, J = 7.1 Hz), 172−1.60 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 208.3, 168.4, 133.9, 132.1, 123.2, 42.9, 37.5, 30.0, 27.9, 20.8; HRMS calcd for $C_{14}H_{15}NO_3$ 245.1052, found 245.1045.

***N*-(6-Oxoheptyl)phthalimide (5).** A mixture of phthalimide potassium salt (1.60 g, 8.72 mmol), 7-bromo-2-heptanone (1.10 g, 5.70 mmol), and DMF (10 mL) was stirred for 4 h at 65 °C. The mixture was cooled to room temperature and combined with water (50 mL). The mixture was then extracted with $CHCl_3$, and the organic layer was washed with aqueous NaOH (∼40%) and water successively. The solvent was removed in vacuo, and the resulting solid was recrystallized in water: yield 1.34 g (91%); ^{1}H NMR ($CDCl_3$) δ 7.86−7.82 (m, 2H), 7.73−7.69 (m, 2H), 3.68 (t, 2H, J = 7.22 Hz), 2.43 (t, 2H, J = 7.4 Hz), 2.13 (s, 3H), 1.73−1.58 (m, 4H), 1.39−1.31 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 209.2, 168.8, 134.3, 132.9, 123.6, 43.8, 38.1, 30.3, 28.8, 26.7, 23.6; HRMS calcd for $C_{15}H_{17}NO_3$ 259.1208, found 259.1208.

***N*,*N*′-Bis(6-oxohexyl)isophthalamide (8).** Compound **4** (1.19 g, 4.86 mmol) was subjected to hydrolysis using concentrated aqueous HCl (35%, 3.5 mL) affording **6** in essentially quantitative yield. At this point, compound **6** (0.87 g, 5.25 mmol), NaOH (2.0 g, 50.0 mmol), tetrabutylammonium hydrogensulfate (0.165 g, 0.047 mmol), and isophthaloyl dichloride (0.494 g, 2.40 mmol) were subjected to reaction in a manner analogous to that used to prepare **9**. Purification was effected by column chromatography over silica gel (THF/EtOAc = 3:7, eluent): yield 0.339 g (39%); ^{1}H NMR ($CDCl_3$) δ 8.26 (bs, 1H), 7.99−7.97(m, 2H), 7.50 (t, 1H, J = 7.7 Hz), 6.98−6.92 (m, 2H), 3.45−3.40 (m, 4H), 2.51 (t, 4H, J = 6.5 Hz), 1.68−1.58 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 209.7, 167.1, 135.2, 130.5, 129.3, 125.3, 43.4, 40.1, 30.8, 29.2, 20.9; HRMS calcd for $C_{20}H_{28}N_2O_4$ 360.209, found 360.2050.

***N*,*N*′-Bis(6-oxoheptyl)isophthalamide (9).** A mixture of *N*-(6-oxoheptyl)phthalimide (1.0 g, 3.86 mmol) and concentrated HCl (3 mL) was heated for 60 h at 100 °C. After the mixture was allowed to cool to room temperature, water (20 mL) was added. The solid precipitate that formed was removed by filtration and discarded, and the aqueous layer was washed with diethyl ether twice, with these washings also being discarded. The water was removed in vacuo, and the remaining solid was dried. The resulting 6-amino-2-heptanone−HCl salt was then used to the next step without further purification due to its instability. Specifically, this salt (6-amino-2-heptanone−HCl; 0.87 g, 5.25 mmol) was dissolved in aqueous NaOH (0.527 M, 100 mL), and the resulting mixture was combined with tetrabutylammonim hydrogen sulfate (0.179 g, 0.527 mmol) and CH_2Cl_2 (40 mL). It was then stirred for 1 h before isophthaloyl dichloride (0.508 g, 2.50 mmol) dissolved in CH_2Cl_2 (10 mL) was added dropwise over a period of 5 min. The mixture produced in this way was stirred for 1 h and extracted with CH_2Cl_2. The organic layer was dried (anhydrous Na_2SO_4), and the solvent was removed in vacuo. The remaining solid was purified by column chromatography over silica gel (THF/EtOAc = 3:7, eluent): yield 0.709 g (73%); ^{1}H NMR ($CDCl_3$) δ 8.19−8.19 (m, 1H), 7.98 (dd, 2H, J_{a-b} = 7.8 Hz, J_{a-c} = 0.1 Hz), 7.53 (t, 1H, J_{a-b} = 7.8 Hz), 6.60 (bs, 2H), 3.49 (q, 4H, J = 6.6 Hz), 2.48 (t, 4H, J = 7.1 Hz), 2.15 (s, 6H), 1.68−1.58 (m, 8H), 1.43−1.37 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 209.9, 167.0, 135.2, 130.6, 129.4, 125.1, 43.8, 40.0, 30.5, 29.4, 26.6, 23.3; HRMS calcd for $C_{22}H_{32}N_2O_4$ 388.24, found 389.18 (MH^+).

Isophthalic Acid Bis[5,5-bis(1*H*-pyrrol-2yl)hexyl]-amide (10). Compound **8** (0.298 g, 0.827 mmol), pyrrole (5 mL, 72.07 mmol), and TFA (63.7 μL, 0.827 mmol) were subjected to reaction under conditions identical to those used for the synthesis of **11**. Column chromatography over silica gel (EtOAc/CH_2Cl_2 = 3:7, eluent) was used to effect purification: yield 0.384 g (78%); ^{1}H NMR ($CDCl_3$) δ 8.05 (bs, 1H), 7.92 (bs, 4H), 7.85−7.83 (m, 2H), 7.49 (t, 1H, J = 7.7), 6.60−6.58 (m, 4H), 6.19 (bs, 2H), 6.11−6.09 (m, 4H), 6.06−6.05 (m, 4H), 3.44−3.40 (m, 4H), 2.04−2.01 (m, 4H), 1.58−1.55 (m, 4H), 1.58 (s, 6H), 1.29−1.26 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 167.3, 138.4, 135.3, 130.2, 129.3, 125.7, 117.4, 108.1, 104.9, 40.8, 39.9, 39.5, 30.2, 26.8, 21.8; HRMS calcd for $C_{36}H_{44}N_6O_2$ 592.35, found 592.40.

Isophthalic Acid Bis[6,6-bis(1*H*-pyrrol-2yl)heptyl]-amide (11). To a mixture of *N*,*N*′-bis(6-oxoheptyl)isophthalamide (0.56 g, 1.44 mmol) and pyrrole (10 mL, 141.25 mmol) was added trifluoroacetic acid (111.4 μL, 1.44 mmol). The mixture was then stirred for 1.5 h at 60 °C before being quenched with aqueous NaOH (0.1 N, 20 mL) and extracted with CH_2Cl_2. The organic layer was collected and dried (anhydrous Na_2SO_4) before the solvent was removed in vacuo. The resulting solid was purified by column chromatography over silica gel (EtOAc/CH_2Cl_2 = 3:7, eluent): yield 0.742 g (83%); ^{1}H NMR ($CDCl_3$) δ 8.13 (bs, 1H), 8.00 (bs, 4H), 7.82−7.80 (m, 2H), 7.38 (t, 1H, J = 7.8 Hz), 6.66 (bs, 2H), 6.54−

6.53 (m, 4H), 6.08−6.06 (m, 4H), 5.99 (bs, 4H), 3.30−3.23 (m, 4H), 1.90−1.86 (m, 4H), 1.52 (s, 6H), 1.49−1.42 (m, 4H), 1.25−1.20 (m, 4H), 1.18−1.13 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 167.4, 138.6, 135.2, 130.3, 129.3, 125.8, 117.4, 107.9, 104.9, 41.4, 40.5, 39.3, 29.8, 27.7, 26.5, 24.5; HRMS calcd for $C_{38}H_{48}N_6O_2$ 620.38, found 620.39.

(C_4)-Strapped Calix[4]pyrrole (12). Compound **10** (0.27 g, 0.46 mmol), acetone (300 mL), and $BF_3{\cdot}OEt_2$ (28.6 μL, 0.23 mmol) were reacted together in a manner identical to that used in the synthesis of **13**. Column chromatography over silica gel (EtOAc/CH_2Cl_2 = 3:7, eluent) gave two fractions identified as **12** and **14**. For **12**: yield 56 mg (18%); ^{1}H NMR ($CDCl_3$) δ 8.20−8.19 (m, 1H), 7.94−7.91 (m, 6H), 7.54 (t, 1H, J = 7.7), 6.49−6.46 (m, 2H), 5.90−5.89 (m, 4H), 5.83−5.82 (m, 4H), 3.56−3.52 (m, 4H), 1.92−1.88 (m, 4H), 1.61−1.58 (m, 4H), 1.52 (s, 6H), 1.49 (s, 6H), 1.47 (s, 6H), 1.42−1.37 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 166.4, 138.9, 137.1, 134.6, 129.7, 128.9, 126.0, 103.4, 103.0, 40.3, 39.9, 39.4, 35.4, 30.6, 29.7, 28.9, 28.6, 23.6; HRMS (FAB) calcd for $C_{42}H_{52}N_6O_2$ 672.40, found 672.60. For **14**: ^{1}H NMR ($CDCl_3$) δ 8.26 (s, 1H), 7.99 (d, 1H), 7.72 (d, 1H), 7.51 (t, 1H, J = 7.7 Hz), 7.00 (bs, 2H), 6.71 (bs, 2H), 6.02 (bs, 1H), 5.91−5.90 (m, 4H), 5.83−5.82 (m, 2H), 5.67−5.66 (m, 2H), 5.59 (bs, 1H), 3.68−3.67 (m, 2H), 3.17−3.15 (m, 2H), 1.84−0.80 (m, 30H); ^{13}C NMR ($CDCl_3$) δ 167.7, 139.2, 138.0, 136.3, 136.2, 135.2, 134.9, 130.8, 128.2, 127.9, 126.9, 104.8, 103.7, 102.9, 102.8, 43.5, 40.9, 40.1, 39.6, 38.6, 35.6, 35.5, 30.9, 30.8, 29.9, 28.9, 26.8, 24.4, 24.0, 21.4; FAB MS calcd for $C_{42}H_{52}N_6O_2$ 672.40, found 672.64

(C_5)-Strapped Calix[4]pyrrole (13). To a solution of isophthalic acid bis[6,6-bis(1*H*-pyrrol-2-yl)]heptylamide (0.266 g, 0.43 mmol) in acetone (200 mL) was added $BF_3{\cdot}OEt_2$ (27.2 μL, 0.215 mmol). The mixture was then stirred for 30 min at room temperature before being quenched with aqueous K_2CO_3 (saturated, 20 mL) and extracted with CH_2Cl_2. The organic layer was collected and dried, and the resulting solid was purified by column chromatography over silica gel (EtOAc/CH_2Cl_2 = 3:7, eluent) to afford two fractions that were identified as **13** and its isomer **15**. For **13**: yield 0.058 g (19%); ^{1}H NMR ($CDCl_3$) δ 8.30 (bs, 1H), 7.98−7.96 (m, 2H), 7.84 (bs, 4H), 7.57 (t, 1H, J = 7.8 Hz), 6.71−6.68 (m, 2H), 5.78 (m, 8H), 3.44−3.39 (m, 4H), 1.98−1.94 (m, 4H), 1.68−1.64 (m, 4H), 1.51 (s, 6H), 1.46 (s, 6H), 1.45(s, 6H), 1.45−1.40 (4H), 1.26−1.23 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 166.9, 138.8, 138.3, 134.4, 129.6, 128.9, 126.7, 103.1, 102.8, 39.1, 38.9, 38.7, 35.3, 29.9, 29.1, 28.2, 27.2, 25.0, 22.2; HRMS calcd for $C_{44}H_{56}N_6O_2$ 700.45, found 700.40. For **15:** ^{1}H NMR ($CDCl_3$) δ 8.26 (s, 1H), 8.08 (d, 1H), 7.70 (d, 1H), 7.48 (t, 1H, J = 7.7 Hz), 6.96 (bs, 2H), 6.78 (bs, 2H), 6.37 (bs, 1H), 6.13 (bs, 1H), 5.96−5.85 (m, 8H), 3.36 (m, 4H), 1.92 (m, 2H), 1.82 (m, 2H), 1.44−1.19 (m, 32H), 1.10 (m, 2H), 0.47 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 167.0, 166.5, 138.9, 137.6, 137.2, 136.5, 135.3, 135.0, 131.5, 128.9, 128.0, 125.5, 104.6, 103.8, 102.5, 40.8, 39.3, 39.1, 38.8, 38.1, 30.8, 30.4, 29.4, 27.0, 25.9, 25.7, 25.3, 24.5, 23.7, 23.4; FAB MS calcd for $C_{44}H_{56}N_6O_2$ 700.45, found 700.60.

2-[4,4-Bis(1*H*-pyrrol-2-yl)pentyl]isoindole-1,3-dione (17). To a mixture of 4,4-bis(1*H*-pyrrol-2-yl)pentan-1-ol (**16**) (1.3 g, 6 mmol), phthalimide (2.63 g, 3 equiv, 17.9 mmol), PPh_3 (4.7 g, 3 equiv, 17.9 mmol), and THF (100 mL) was added dropwise diisopropyl azodicarboxylate (DIAD; 3.5 mL, 3 equiv, 17.8 mmol) over a period of 15 min. This reaction mixture was stirred for 12 h at room temperature and then combined with water (100 mL). It was then extracted with methylene chloride, and the organic extracts were dried over Na_2SO_4. The solvent was removed in vacuo, and the resulting solid was purified by column chromatography over silica gel (CH_2Cl_2/EtOAc = 19:1, eluent): yield 1.66 g (80%); ^{1}H NMR ($CDCl_3$) δ 7.82−7.80 (m, 2H), 7.72 (bs, 2H), 7.71−7.69 (m, 2H), 6.57 (m, 2H), 6.08 (m, 2H), 6.05 (m, 2H), 3.60 (t, J = 7.2 Hz, 2H), 2.04−1.99 (m, 2H), 1.63−1.59 (m, 2H), 1.56 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 168.4, 137.5, 133.9, 132.1, 123.2, 117.2, 107.8, 104.7, 38.8, 38.2, 38.1, 26.3, 23.9; EI MS calcd for $C_{21}H_{21}N_3O_2$ 347.16, found 347.16.

***N*,*N*′-Bis[4,4-bis(1*H*-pyrrol-2-yl)pentyl]isophthalamide (18).** Compound **17** (1.66 g, 4.77 mmol) was dissolved in ethanol (50 mL), and then hydrazine monohydrate (0.93 mL, 19 mmol) was added. The resulting mixture was heated at reflux for 24 h and then cooled to room temperature. The mixture then was combined with aqueous NaOH (50 mL) and extracted with CH_2Cl_2. The solvent was removed in vacuo, and the resulting solid was used directly in the next step without further purification. The *meso*-(3-aminopropyl, methyl)dipyrromethane (1.0 g, 3.94 mmol) obtained as the result of this operation and isophthaloyl dichloride (0.374 g, 1.84 mmol) were dissolved in CH_2Cl_2 (40 mL). Triethylamine (1.03 mL, 7.37 mmol) was then added, and the mixture was stirred for 12 h at room temperature. At this point, the mixture was combined with water (50 mL) and extracted with CH_2Cl_2. The organic layer was collected and taken to dryness in vacuo. The resulting dark solid was purified by column chromatography over silica gel (CH_2Cl_2/EtOAc = 1:1): yield 1.02 g (76%); ^{1}H NMR ($CDCl_3$) δ 8.07 (bs, 4H), 7.98 (m, 1H), 7.76−7.74 (m, 2H), 7.38−7.34 (m, 1H), 6.53 (m, 4H), 6.50 (t, J = 5.3 Hz, 2H), 6.06−6.04 (m, 4H), 5.99 (m, 4H), 3.26−3.22 (m, 4H), 1.98−1.94 (m, 4H), 1.52 (s, 6H), 1.41−1.39 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 166.9, 137.7, 134.7, 129.9, 128.8, 125.4, 117.2, 107.7, 104.7, 40.4, 38.9, 38.2, 26.2, 24.8; EI MS calcd for $C_{34}H_{40}N_6O_2$ 564.32, found 564.32.

C_3-Strapped Calix[4]pyrrole (19). Compound **18** (1.0 g, 1.77 mmol) was dissolved in acetone (200 mL), and $BF_3{\cdot}OEt_2$ (0.09 mL, 0.71 mmol) was added. The resulting mixture was stirred for 30 min at room temperature and then combined with aqueous NaOH (10%, 20 mL). The mixture produced in this way was extracted with CH_2Cl_2. The organic extracts were collected and taken to dryness in vacuo, and the resulting solid was purified by column chromatography over silica gel (CH_2Cl_2/EtOAc = 1:1, eluent): yield 0.12 g (11%); ^{1}H NMR ($CDCl_3$) δ 8.17 (m, 1H), 8.07 (bs, 4H), 7.80−7.77 (m, 2H), 7.51−7.47 (m, 1H), 6.18 (t, J = 5.7 Hz, 2H), 5.96−5.90 (m, 4H), 5.85−5.83 (m, 4H), 3.52−3.48 (m, 4H), 2.17−2.11 (m, 4H), 1.54 (s, 6H), 1.48 (s, 6H), 1.45−1.40 (m, 4H), 1.18 (s, 6H); ^{13}C NMR ($CDCl_3$) 168.2, 138.7, 137.7, 135.7, 129.5, 129.3, 126.6, 103.9, 103.1, 39.4, 38.7, 38.2, 34.9, 30.6, 27.6, 25.5, 24.9; HRMS calcd for $C_{40}H_{48}N_6O_2$ 644.3839, found 644.8918.

Acknowledgment. This work was supported by a grant (R05-2003-000-11220-0) from the Basic Research Program of the Korea Science and Engineering Foundation (KOSEF) and by the National Institutes of Health (Grant No. GM 589907 to J.L.S.). NMR and Mass Spectra were recorded at the Central Instrumentation Facility in KNU. The Vascular System Research Center (VSRC) at KNU is also acknowledged for support.

Supporting Information Available: Spectroscopic data and ITC plots. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0487146