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N-Tosylpyrrolidine Calix[4]pyrrole: Synthesis and Ion Binding Studies

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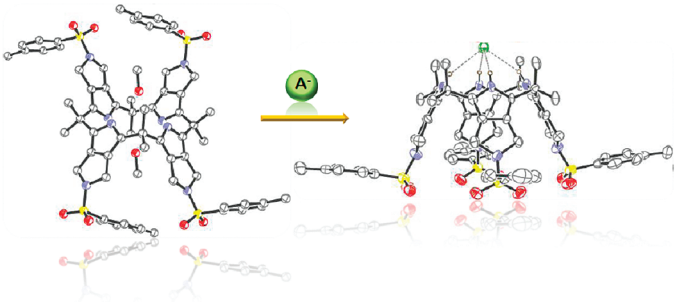

The synthesis and preliminary solution phase ion binding properties of the *N*-tosylpyrrolidine calix[4]pyrrole **2** are reported. This *β*-octaalkyl-substituted calix[4]pyrrole, the first to be prepared via a direct condensation reaction, was obtained by reacting the 3,4-alkyl-functionalized pyrrole **8** with acetone in the presence of an acid catalyst. On the basis of ^{1}H NMR spectroscopic analyses and isothermal titration calorimetry, it was concluded that, compared with the parent, *β*-unsubstituted calix[4]pyrrole (**1**), compound **2** possesses significantly enhanced binding ability for halide anions in chloroform. Furthermore, **2** proved capable of solubilizing in chloroform solution the otherwise insoluble salts, CsF and CsCl. These effects are ascribed to the interactions between the four tosyl groups present in **2** and the counter cations of the halide anion salts.

Introduction

A century after it was first synthesized in 1886 by Baeyer,[1] *meso*-octamethylcalix[4]pyrrole **1**, a tetrapyrrolic macrocycle, was found in 1996 by Sessler and co-workers to act as an efficient receptor for specific anions, such as halides, carboxylates, and phosphates.[2,3] Since that time, increasing attention has been paid to calix[4]pyrrole **1** as an anion receptor,[4] with considerable effort having been devoted to enhancing the binding affinity and selectivity for specific anionic guests. These efforts have led, inter alia, to the development of calix[4]pyrrole-based anion receptors, such as strapped calix[4]pyrroles[5] and *β*-substituted calixpyrroles.[6] In addition, calix[4]pyrrole derivatives equipped with various chromogenic, fluorogenic, or redox-active units have been synthesized for anion sensing.[6,7] As a general rule, calix[4]pyrrole derivatives with improved anion recognition features have been obtained by modifying either the

(1) Baeyer, A. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 2184–2185.
(2) (a) Gale, P. A.; Sessler, J. L.; Král, V.; Lynch, V. *J. Am. Chem. Soc.* **1996**, *118*, 5140–5141. (b) Allen, W. E.; Gale, P. A.; Brown, C. T.; Lynch, V. M.; Sessler, J. L. *J. Am. Chem. Soc.* **1996**, *118*, 12471–12472.
(3) Gale, P. A.; Sessler, J. L.; Král, V. *Chem. Commun.* **1998**, 1–8.
(4) (a) Sessler, J. L.; Gale, P. A.; Cho, W.-S. *Anion Receptor Chemistry*; Monographs in Supramolecular Chemistry; Stoddart, J. F., Ed.; RSC Publishing: Cambridge, U.K., 2006. (b) Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 486–516. (c) Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 191–221. (d) Gale, P. A.; Quesada, R. *Coord. Chem. Rev.* **2006**, *250*, 3219–3244. (e) Gale, P. A.; García-Garrido, S. E.; Garric, J. *Chem. Soc. Rev.* **2008**, *37*, 151–190.
(5) (a) Lee, C.-H.; Miyaji, H.; Yoon, D.-W.; Sessler, J. L. *Chem. Commun.* **2008**, 24–34. and references cited therein. (b) Yoon, D.-W.; Gross, D. E.; Lynch, V. M.; Sessler, J. L.; Hay, B. P.; Lee, C.-H. *Angew. Chem., Int. Ed.* **2008**, *47*, 5038–5042.
(6) (a) Sessler, J. L.; Anzenbacher, P., Jr.; Shriver, J. A.; Jursíková, K.; Lynch, V. M.; Marquez., M. *J. Am. Chem. Soc.* **2000**, *122*, 12061–12062. (b) Sessler, J. L.; Cho, W.-S.; Gross, D. E.; Shriver, J. A.; Lynch, V. M.; Marquez, M. *J. Org. Chem.* **2005**, *70*, 5982–5986. (c) Nielsen, K. A.; Jeppesen, J. O.; Levillain, E.; Becher, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 187–191. (d) Nielsen, K. A.; Cho, W.-S.; Lyskawa, J.; Levillain, E.; Lynch, V. M.; Sessler, J. L.; Jeppesen, J. O. *J. Am. Chem. Soc.* **2006**, *128*, 2444–2451.

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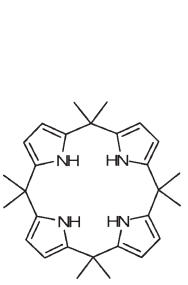
meso-positions or the β-pyrrolic positions with various functional groups.[5−8] However, in both cases the underlying syntheses are subject to limitations. For instance, the use of asymmetric ketones leads to a mixture of configurational isomers, which complicates purification efforts.[8] In contrast, functionalization of the pyrrolic β-positions leads to unfavorable steric interactions with the methyl groups on the *meso*-carbon atoms.[9] Therefore, only relatively small groups such as halogen, oxygen, and sulfur atoms, but not methylene ($-CH_2-$), can be introduced directly into the β-pyrrolic positions via the standard acid-catalyzed pyrrole + ketone condensation strategy typically used to prepare calix[4]pyrroles.[6,9] In some cases, the introduction of β-pyrrolic substituents decreases the anion affinity, presumably as the result of destabilizing the cone conformation that favors calix[4]pyrrole−anion interactions.[9,10] Nevertheless, we consider β-carbon functionalized calix[4]pyrroles bearing methylene substitutents to be worthy synthetic targets. In particular, we suggest that, if appropriately elaborated, such species could prove useful as ion pair receptors. Ion pair receptors, species capable of forming simultaneously a complex with both a cation and an anion, are interesting in that they generally display higher selectivities and affinities than do simple ion receptors.[4b,11] We recently reported that calix[4]pyrrole **1** can form a complex with cesium halide ion pairs in the solid state where anions are bound to the pyrrolic NH protons through hydrogen bonds and the Cs^+ cation is held within the cone-like cavity of the calix[4]pyrrole via apparent π-cation interactions.[12] Here, we report that the introduction of *N*-tosylpyrrolidine units, specifically when fused onto the β-pyrrolic positions, gives rise to a system, **2**, that displays anion affinities that are enhanced relative to calix[4]pyrrole **1**. We also show that this new β-octaalkyl-substituted calix[4]pyrrole acts as an effective receptor for cesium halide ion pairs in chloroform solution.



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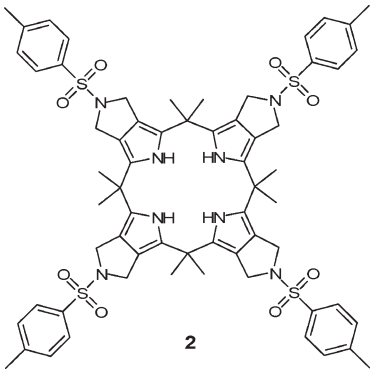


2

Results and Discussion

The synthesis of **2** is outlined in Scheme 1. It starts with diethyl pyrrole-3,4-dicarboxylate **3**,[13] which was subjected to N-protection by treating with tosyl chloride. The diester groups were then reduced with LAH to afford *N*-*p*-toluenesulfonylpyrrole-3,4-dimethanol (**5**). Bromination of this latter diol with PBr_3, followed by cyclization with TsNHNa, gave the bicyclic pyrrole (**7**) in moderate yield. Treatment of this ditosyl pyrrole (**7**) with excess sodium methoxide (30 equiv) in a mixture of THF/methanol (3/1) served to remove only the tosyl group on the pyrrole moiety leaving that on the pyrrolidine moiety untouched; this gave *N*-*p*-toluenesulfonylpyrrolidinylpyrrole **8** in 91% yield. Condensation of this latter pyrrole with acetone in the presence of 1 equiv of trifluoroacetic acid (TFA) then gave the desired β-octaalkyl-substituted calix[4]pyrrole derivative **2** in 20% yield.

Calix[4]pyrrole **2** was characterized by standard spectroscopic techniques as well as by single-crystal X-ray diffraction analysis. Two crystals of the anion-free form of **2** suitable for such analyses were obtained. They were grown by slow evaporation of solutions of **2** made up in chloroform/methanol (1/1) and dichloromethane/DMF (10/1). In both cases, the resulting structures revealed that calix[4]pyrrole **2** adopts the so-called 1,2-alternate conformation in the solid state with two solvent molecules bound to the pyrrolic NH protons (Figures 1 and 2). In the single-crystal structure of $\mathbf{2}\cdot(MeOH)_2$, two tosyl groups are directed in toward the inside of the calix[4]pyrrole cavity, while the other two point toward the outside of the macrocycle. In contrast, in the case $\mathbf{2}\cdot(DMF)_2$ all of four tosyl groups point toward the outside of the cavity; such a finding is consistent with the expected steric repulsion between the tosyl groups and the two bound DMF molecules.

The first evidence that compound **2** is capable of forming a complex with an anion came from a single-crystal X-ray diffraction analysis of the presumed chloride anion complex, $\mathbf{2}\cdot Cl^-$ (Figure 3). The resulting structure confirmed that in this complex calix[4]pyrrole adopts the cone conformation and that the four pyrrolic NH protons participate in hydrogen bonding

(7) (a) Miyaji, H.; Anzenbacher, P., Jr.; Sessler, J. L.; Bleasdale, E. R.; Gale, P. A. *Chem. Commun.* **1999**, 1723–1724. (b) Anzenbacher, P., Jr.; Jursíková, K.; Sessler, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 9350–9351. (c) Miyaji, H.; Sato, W.; Sessler, J. L. *Angew. Chem., Int. Ed.* **2000**, *39*, 1777–1780. (d) Miyaji, H.; Sato, W.; Sessler, J. L.; Lynch, V. M. *Tetrahedron Lett.* **2000**, *41*, 1369–1373. (e) Miyaji, H.; Sato, W.; An, D.; Sessler, J. L. *Collect. Czech. Chem. Commun.* **2004**, *69*, 1027–1049. (f) Nishiyabu, R.; Anzenbacher, P., Jr. *J. Am. Chem. Soc.* **2005**, *127*, 8270–8271. (g) Nishiyabu, R.; Palacios, M. A.; Dehaen, W.; Anzenbacher, P., Jr. *J. Am. Chem. Soc.* **2006**, *128*, 11496–11504. (h) Palacios, M. A.; Nishiyabu, R.; Marquez, M.; Anzenbacher, P., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 7538–7544.

(8) (a) Anzenbacher, P., Jr.; Jursíková, K.; Lynch, V. M.; Sessler, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 11020–11021. (b) Bonomo, L.; Solari, E.; Toraman, G.; Scopelliti, R.; Floriani, C.; Latronico, M. *Chem. Commun.* **1999**, 2413–2414. (c) Gil-Ramírez, G.; Benet-Buchholz, J.; Escudero-Adán, E. C.; Ballester, P. *J. Am. Chem. Soc.* **2007**, *129*, 3820–3821. (d) Gil-Ramírez, G.; Escudero-Adán, E. C.; Benet-Buchholz, J.; Ballester, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4114–4118. (e) Verdejo, B.; Gil-Ramírez, G.; Ballester, P. *J. Am. Chem. Soc.* **2009**, *131*, 3178–3179. (f) Ballester, P.; Gil-Ramírez, G. *Proc. Natl. Acad. Sci.* **2009**, *106*, 10455–10459. (g) Chas, M.; Gil-Ramírez, G.; Escudero-Adán, E. C.; Ballester, P. *Org. Lett.* **2010**, *12*, 1740–1743. (h) Gil-Ramírez, G.; Chas, M.; Ballester, P. *J. Am. Chem. Soc.* **2010**, *132*, 2520–2521.

(9) Gale, P. A.; Sessler, J. L.; Allen, W. E.; Tvermoes, N. A.; Lynch, V. *Chem. Commun.* **1997**, 665–666.

(10) Sessler, J. L.; Roznyatovskiy, V. V.; Lynch, V. M. *J. Porphyrins Phthalocyanines* **2009**, *13*, 322–355.

(11) (a) Smith, B. D. In *Ion-pair Recognition by Ditopic Receptors, Macrocyclic Chemistry: Current Trends and Future Prospectives*; Gloe, K., Antonioli, B., Eds.; Kluwer: London, U.K., 2005; pp 137−152. (b) Kirkovits, G. J.; Shriver, J. A.; Gale, P. A.; Sessler, J. L. *J. Inclusion Phenom. Macrocyclic Chem.* **2001**, *41*, 69–75. (c) Kim, S. K.; Sessler, J. L. *Chem. Soc. Rev.* **2010**, *39*, 3784–3809. and references cited therein.

(12) Custelcean, R.; Delmau, L. H.; Moyer, B. A.; Sessler, J. L.; Cho, W.-S.; Gross, D.; Bates, G. W.; Brooks, S. J.; Light, M. E.; Gale, P. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 2537–2542.

(13) Bush, L. C.; Heath, R. B.; Feng, X. U.; Wang, P. A.; Maksimovic, L.; Song, A. I.; Chung, W.-S.; Berinstain, A. B.; Scaiano, J. C.; Berson, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 1406–1415.

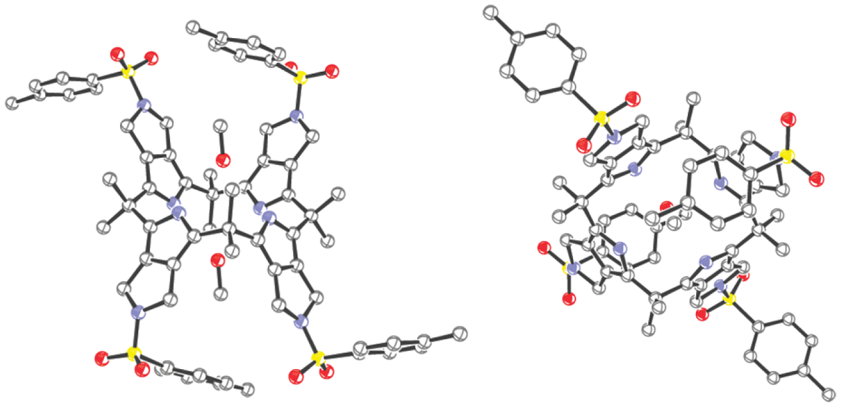


FIGURE 1. Two different views of the single crystal structure of **2**·$(MeOH)_2$. Displacement ellipsoids are scaled to the 30% probability level. Hydrogen atoms have been removed for clarity. The macrocycle lies on a crystallographic inversion center at $^1/_2$, $^1/_2$, $^1/_2$.

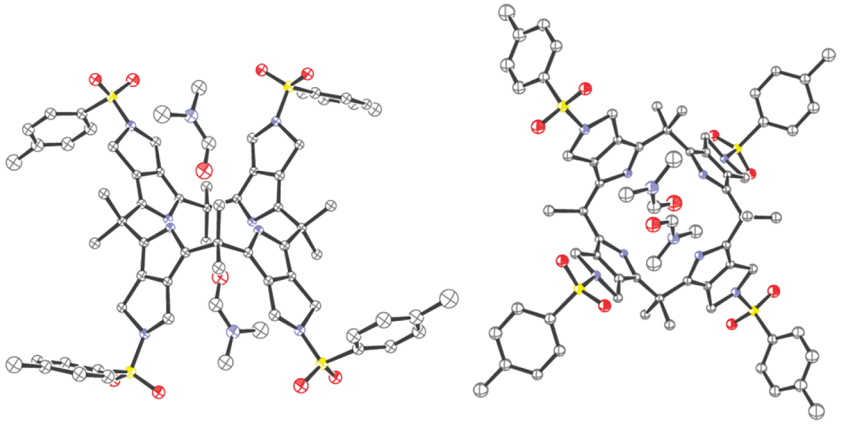
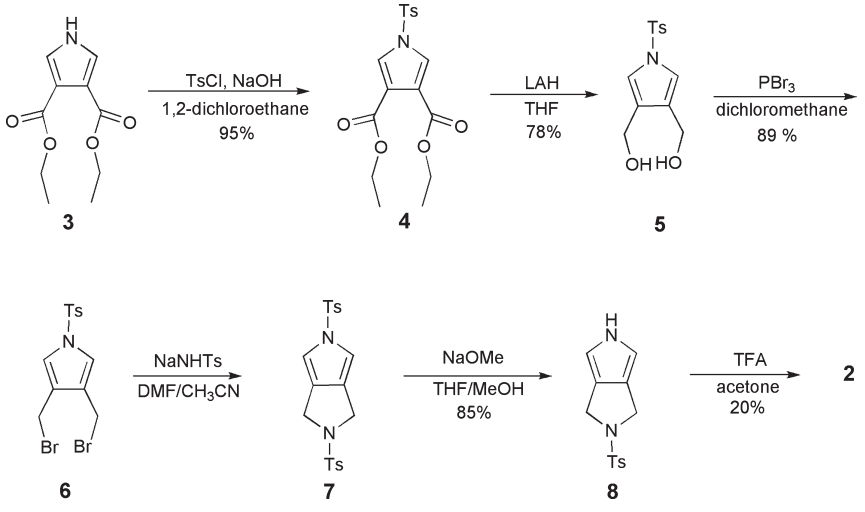


FIGURE 2. Two different views of the single crystal structure of **2**·$(DMF)_2$. Displacement ellipsoids are scaled to the 50% probability level. Hydrogen atoms have been removed for clarity. The macrocycle lies on a crystallographic inversion center at $^1/_2$, $^1/_2$, $^1/_2$.

SCHEME 1. Synthesis of Compound 2



interactions with the chloride anion (Figure 3). The distance between the chloride anion and nitrogen atoms is 3.372 Å and the N−H···Cl^- angle is ca. 155°.

Initial evidence that calix[4]pyrrole **2** could bind halide anions in solution came from ^{1}H NMR spectroscopic analyses carried out in $CDCl_3$. As shown in Figure 4, the anion-free form of **2** displays a singlet peak for the H_a and H_b protons at 4.27 ppm. Such a finding is consistent with the rate of conformation change being fast on the NMR time scale, as is true for most other anion-free calix[4]pyrrole derivatives. However, upon the addition of increasing quantities of tetrabutylammonium fluoride (TBAF), the singlet peak of H_a and H_b first becomes

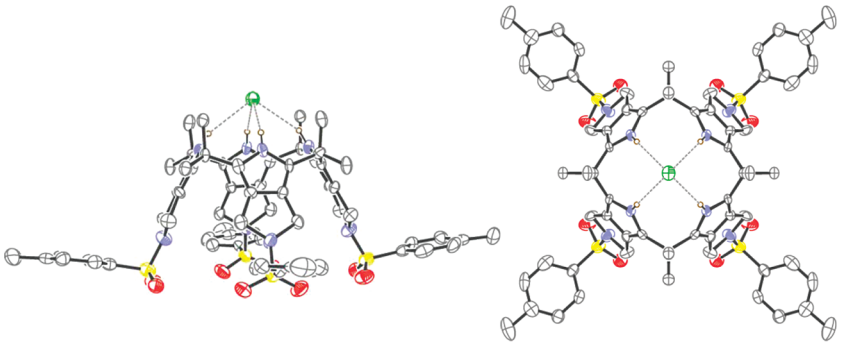


FIGURE 3. Two different views of the single crystal structure of **2**·Cl^-. Displacement ellipsoids are scaled to the 30% probability level. Compound **2** in this complex lies around a crystallographic 4-fold rotation axis at $^1/_2$, $^1/_2$, *z*. Most hydrogen atoms have been removed for clarity. Dashed lines are indicative of H-bonding interactions. The countercation, TBA^+, sitting in the cavity formed by four sulfonyl groups, is disordered and is not shown.

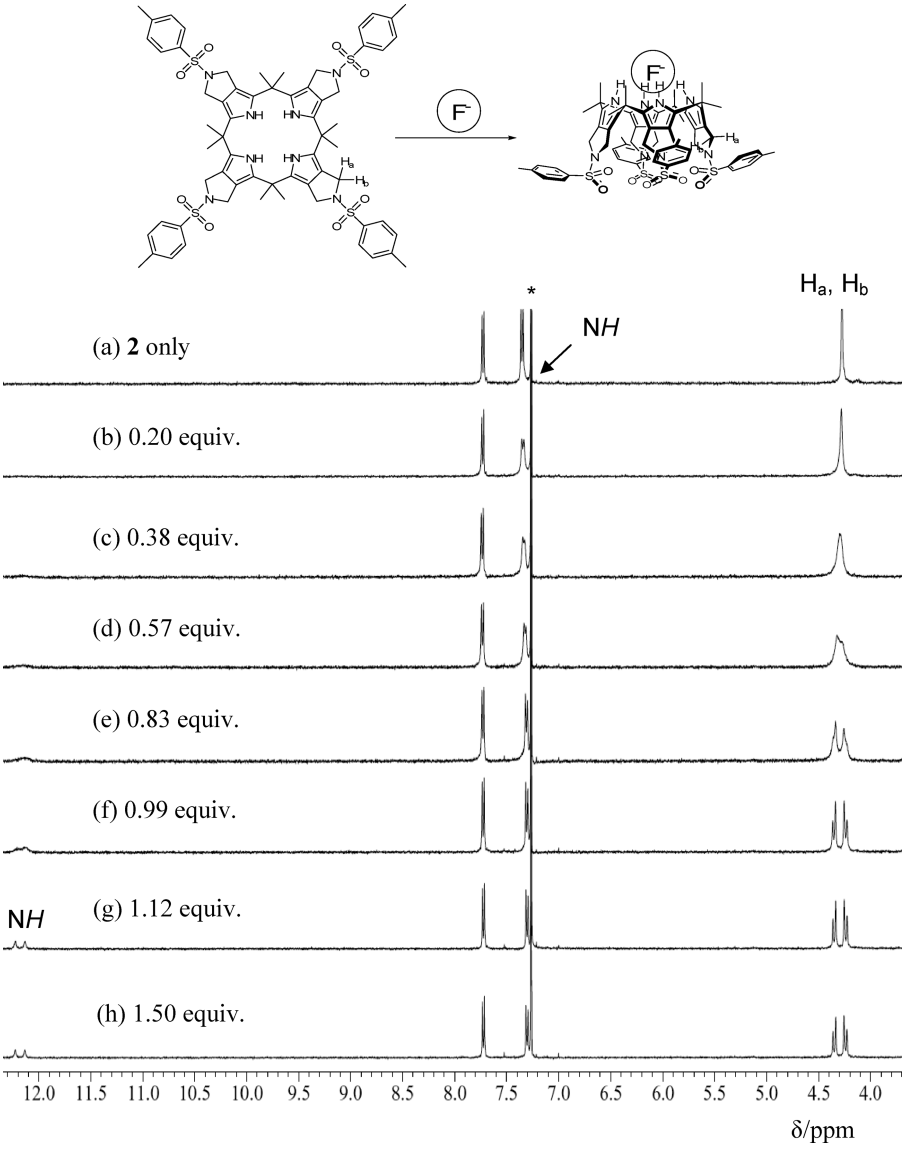


FIGURE 4. Partial ^{1}H NMR spectra recorded during the titration of receptor **2** with TBAF (tetrabutylammonium fluoride) in $CDCl_3$. The asterisk denotes peaks due to the NMR solvent.

broadened, something that is apparent after the addition of fewer than 0.38 equiv, and then becomes split. This splitting gives rise to two doublets (J = 10.8 Hz) in an AB pattern, and is consistent with the conformation of **2** becoming fixed in the cone conformation as the result of fluoride anion binding (Figures 4 and 5).

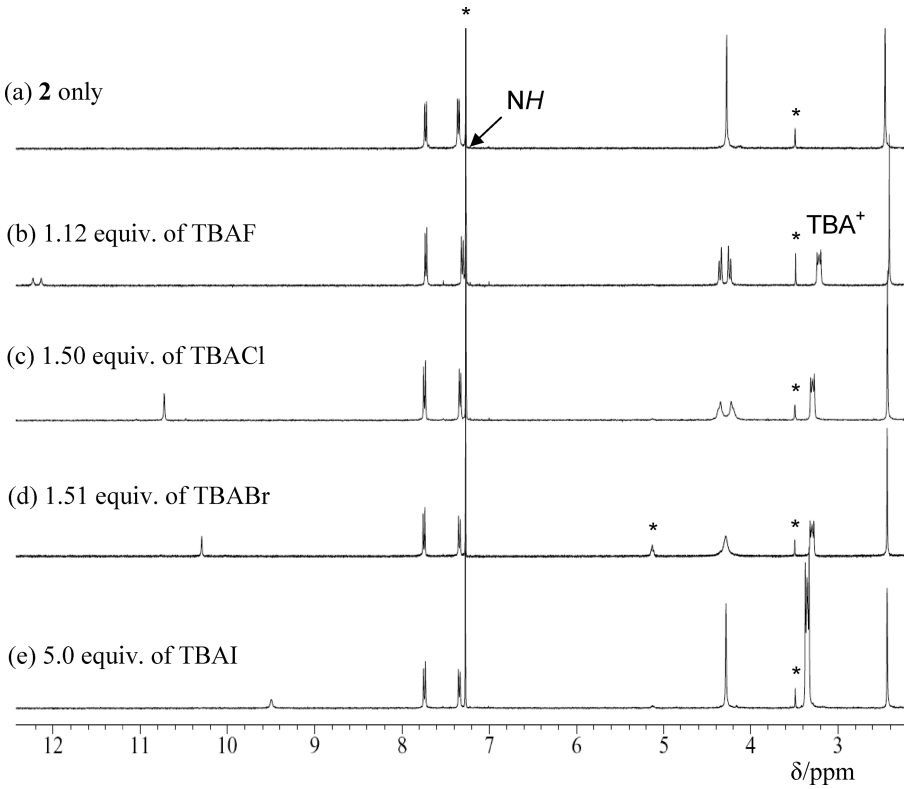


FIGURE 5. Proton NMR spectra of **2** recorded in $CDCl_3$ after adding quantities of TBAX (tetrabutylammonium halide) sufficient to induce no further observable spectral changes. Note the position of the NH signal. An asterisk denotes peaks due to the NMR solvent and other residual impurities.

This anion-induced conformational locking stands in contrast to what is seen in the case of calix[4]pyrrole **1**; at room temperature in $CDCl_3$, the conformation of this latter system is not fixed via fluoride anion binding, as evidenced by the fact that the *meso* carbons of **1** still appear as a singlet in the ^{1}H NMR spectrum after the addition of excess TBAF (Figure S1, Supporting Information). This difference led us to postulate that the new calix[4]pyrrole derivative, **2**, binds fluoride anion more strongly than does the parent system **1**.

In an effort to test the above assumption, more detailed titrations were carried out. As shown in Figures 4 and 5, these titrations revealed that the changes in the spectrum are essentially complete after receptor **2** is treated with ca. 1.0 equiv of TBAF, whereas ca. 2.8 equiv is required to achieve saturation in the case of calix[4]pyrrole **1**. Further support for the conclusion that **2** is a better fluoride anion receptor under these solution phase conditions came from the observation that the NH proton resonance of **2** is split into a doublet (J_{HF} = 29.6 Hz) at room temperature in the presence of the fluoride anion, presumably as the result of coupling between the bound fluoride anion and the NH protons.[14] A significant downfield shift in the NH proton peak (by roughly 5 ppm; final $\delta \approx 12.7$ ppm) was also seen in the presence of TBAF (Figure 4).

In analogy to what is seen in the case of fluoride, the singlet corresponding to the meso H_a and H_b resonances of **2** was found to split into two doublets upon the addition of TBACl ($CDCl_3$ solution; room temperature). As above, this was taken as evidence that the chloride anion binds strongly to **2** thus fixing the conformation on the NMR time scale. This binding also serves to lock the calix[4]pyrrole framework into the cone conformation, which places protons H_a and H_b in a diastereotopic environment (Figure 5, as well as Figure S2 in the Supporting Information). Such an interpretation is fully consistent with the crystal structure of the chloride anion complex of **2** discussed above (cf. Figure 3). The observation that the changes in the NH proton chemical shift of **2** become saturated upon the addition of ca. 1.0 equiv of TBACl provides, as above, further support for the notion that the chloride anion is strongly bound by **2** (Figure S2, Supporting Information). In contrast to what was seen with TBAF and TBACl, when **2** was subject to the titration with the TBA salts of bromide and iodide, the H_a and H_b signals did not split, but rather remained in the form of a singlet at room temperature. This lack of change is ascribed to the fact that the bromide and the iodide anions are bound only weakly and that calix[4]pyrrole undergoes fast conformational "flipping" in the presence of these two anions. Support for this conclusion comes from the fact that only relatively small downfield shifts in the NH proton resonance are seen upon the addition of TBABr or TBAI (Figure 5 and Figures S3 and S4 in the Supporting Information).

Unfortunately, in the case of the fluoride and chloride anions, kinetics and difficulties associated with integrating the signals for the separate species precluded the use of ^{1}H NMR spectroscopic methods to obtain quantitative measures of the anion affinities in the case of **2**. Therefore, isothermal titration calorimetry (ITC) analyses were carried out. In contrast to NMR spectroscopic methods, ITC analyses provide direct access to the energetics of the binding event without the necessity of a structural probe (e.g., an NMR spectroscopic signal).

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

TABLE 1. Selected Thermodynamic Data Derived from Isothermal Titration Calorimetry (ITC) for the Interactions of Receptors 1 and 2 with Tetraalkylammonium Halides[a]

					data obtained after adjusting host concn to obtain a value of 1 for N (stoichiometry)[b]			
	salt (mM)	host (mM)	original N	original K_a (M^{-1})	ΔG (kcal·mol^{-1})	ΔH (kcal·mol^{-1})	$T\Delta S$ (kcal·mol^{-1})	K_a (M^{-1})
TBA-Cl								
1	23.1	1.1	–[c]	$< 10^2$	–[c]	–[c]	–[c]	$< 10^2$
2	2.71	0.21	0.83	2.5×10^6	−8.70	−8.27	0.43	2.4×10^6
2	0.09	1.57	1.19	1.6×10^6	−8.65	−8.96	−0.30	2.2×10^6
TEA-Cl								
1	21.0	1.64	0.99	7.0×10^3	−5.26	−8.60	−3.34	7.0×10^3
2	4.74	0.21	0.83	1.8×10^7	−9.89	−8.97	0.92	1.8×10^7
TBA-Br								
2	10.3	1.0	0.85	2.2×10^5	−7.29	−6.38	0.91	2.2×10^5
TEA-Br								
2	16.4	1.0	0.75	8.9×10^5	−8.11	−5.01	3.10	8.9×10^5
TBA-I								
2	11.9	1.0	0.77	4.4×10^2	−3.60	−5.21	−1.61	4.4×10^2
TEA-I								
2	12.2	1.0	0.85	1.5×10^4	−5.70	−1.86	3.84	1.5×10^4

[a]Titrations were performed in $CHCl_3$ at 25 °C. [b]See ref 15. [c]Unable to determine the energetics of the presumed interaction due to weak binding.

While these two techniques necessarily probe different aspects of the presumed binding event, we have recently demonstrated, in collaboration with Gale and Schmidtchen, that NMR spectroscopic titrations and ITC analyses give rise to concordant results when the conditions for the measurements are comparable.[15] Accordingly, ITC methods were explored in an effort to quantify the anion affinities of calixpyrrole **2**.

ITC experiments were carried out under conditions chosen to given an N value (calculated stoichiometry) close to 1. Under varying host−guest ratios, different N values between 0.5 and 2.0 could be obtained depending on the exact salt and concentration. This variation, which in all cases remained within a factor of less than two, is thought to reflect ion-pairing effects. Such effects are significant in this system as noted below. Nevertheless, the possibility of forming complexes of non-1:1 stoichiometry, especially under conditions where either the host or guest is present in great excess, cannot be eliminated. Therefore, in order to allow intercomparisons between different anion binding processes the host concentration (i.e., concentration of **2**) was adjusted to obtain an N value of 1. The uncorrected K_a values are, however, also shown in Table 1 for purpose of reference.

Interestingly, the interactions of **2** with halide anions are driven almost entirely by enthalpy. For example, the chloride complex is formed with ΔH contributing >95% to the interaction energy. In conjunction with a modest entropic term, this gives rise to a favorable (negative) ΔG and a K_a of $2.4 \times 10^6\ M^{-1}$ in $CHCl_3$ (Table 1). This represents a considerable increase in affinity relative to the parent, unsubstituted calix[4]pyrrole **1** ($K_a < 10^2\ M^{-1}$ in $CHCl_3$). This ca. 4 orders of magnitude difference can be noted qualitatively from an inspection of the associated titration plots (Figure 6).

The affinities of receptor **2** for other halide anions, such as bromide and iodide, are also substantially enhanced as compared with calix[4]pyrrole **1**. Whereas no appreciable interaction with these latter anions could be discerned under the conditions of ITC analysis, binding constants (K_a) of 8.9×10^5 for TEABr and 1.5×10^4 for TEAI, respectively, could be derived in the case of **2**. As detailed further below, the relatively high affinities seen in the case of **2** are ascribed in part to additional interactions between the countercations and the four tosyl groups. Such interactions are not possible in the case of the unsubstituted system **1**. Additional evidence for the interactions between the countercation and the tosyl groups came from the ^{1}H NMR spectroscopic titrations of receptor **2** with TEACl (tetraethylammonium chloride) (Figure S13, Supporting Information). In the presence of less than 1.0 equiv of TEACl ([**2**] > [TEACl]), the ethyl peak of the tetraethylammonium cation appears to be significantly shifted downfield, which is attributable to the encapsulation of the cation by the tosyl group forming an ion pair complex. For instance, adding 0.59 equiv of TEACl to **2** gives rise to a spectrum with two sets of distinguishable resonances for the H_a and H_b proton signals. This splitting, which is not seen in the absence of TEACl, is ascribed to the presence of both ion pair-free and TEACl-bound forms of **2** and is thus consistent with the ion pair binding/decomplexation equilibrium being slow on the ^{1}H NMR time scale. This splitting becomes enhanced up to the point where 1.0 equiv of TEACl is added. After this point, the addition of further equivalents results in no appreciable change in these resonances. Conversely, the signals corresponding the tetraethylammonium cation continue to move downfield as the number of equivalents increases. This is consistent with the cation being bound within the cavity via an equilibrium process.

The ability of calix[4]pyrrole **2** to act as an ion pair receptor was tested and compared with that of normal calix[4]pyrrole **1**. This was done via solid−liquid extraction experiments using the chloroform-insoluble salts, CsF and CsCl, as test ion pairs. After subjecting $CDCl_3$ solutions of **1** and **2** to sonication for 1 h in the presence of 5.0 equiv of CsF and CsCl, the soluble portion of the samples was monitored by ^{1}H NMR spectroscopy. Under these experimental conditions, two sets of distinguishable peaks, corresponding to the free calix[4]pyrroles and their ion pair complexes, were seen in the ^{1}H NMR spectra of **1**·CsF, **2**·CsF, and **2**·CsCl (cf. Figure 7 and in the Supporting Information Figure S14). Such findings are consistent with the formation of ion pair complexes, albeit under conditions of slow equilibrium. Comparison of the peak integral ratios for the free form of calix[4]pyrrole **1** and its corresponding ion pair complexes

(15) Sessler, J. L.; Gross, D. E.; Cho, W.-S.; Lynch, V. M.; Schmidtchen, F. P.; Bates, G. W.; Light, M. E.; Gale, P. A. *J. Am. Chem. Soc.* **2006**, *128*, 12281–12288.

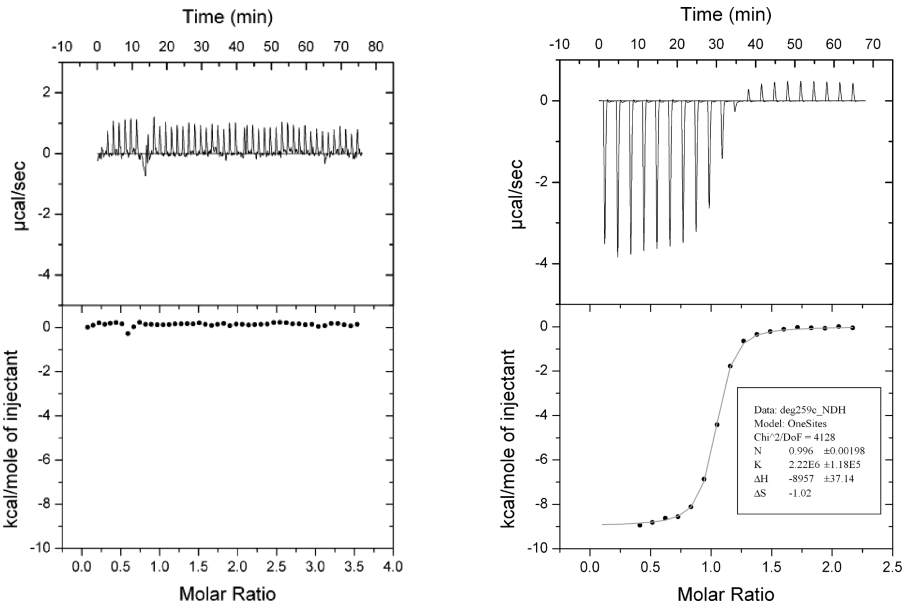


FIGURE 6. ITC plots showing the titration of TBACl into chloroform solutions of calixpyrroles **1** (left, 10 mM) and **2** (right, 0.1 mM). A high concentration was used in the former case in an attempt to obtain a discernible binding isotherm.

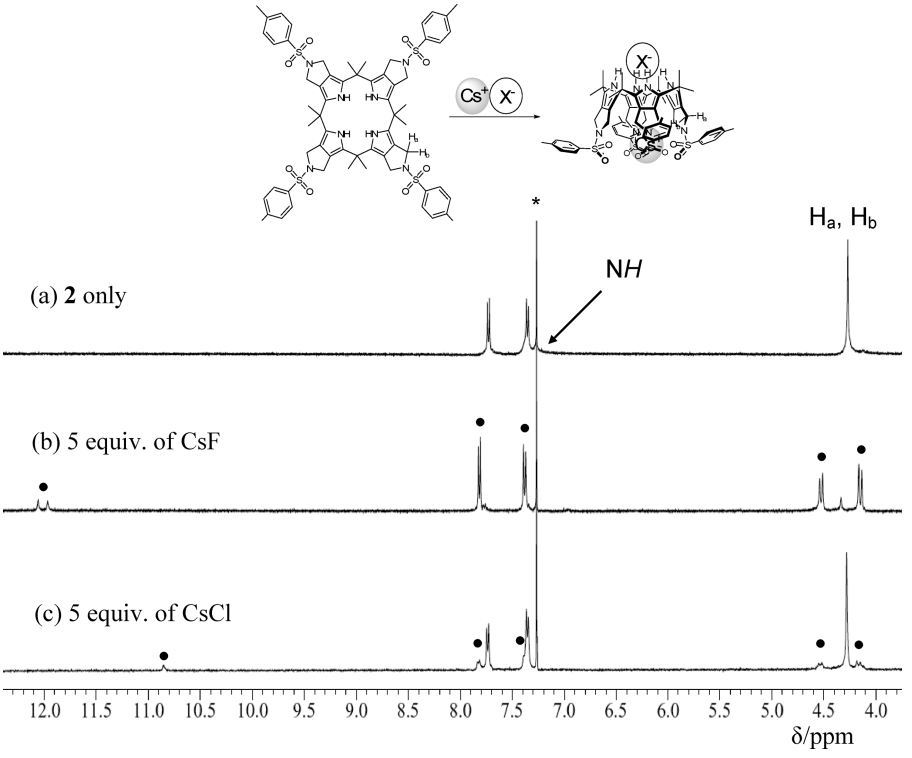


FIGURE 7. Proton NMR spectra of **2** recorded at room temperature in $CDCl_3$ before and after the addition of CsF and CsCl. The asterisk and dots denote the peaks of the NMR solvent and complexes **2**·CsF and **2**·CsCl, respectively. Note the position of the NH signals.

(cf. Figure S14 in the Supporting Information) revealed that <10% of the receptor was involved in ion pair recognition in the case of CsF and essentially none in the case of CsCl. In contrast, under these solid-to-solution extraction conditions ca. 95% and ca. 15% of the available calix[4]pyrrole **2** in solution was tied up in the form of CsF and CsCl ion pairs, respectively (Figure 7). These results lead us to suggest that receptor **2** acts as an ion pair receptor and is even more effective for this purpose than calix-[4]pyrrole **1**. This, we propose, reflects participation of the tosyl groups of **2** in the cesium cation binding process. Support for this supposition comes from the observation that relatively larger downfield shifts are seen for the signals of the aromatic protons of the tosyl groups upon complexation of CsF and CsCl than are observed upon treatment with TBAF and TBACl. Relatively larger splittings in the H_a and H_b proton peaks are also seen.

In conclusion, we have shown that it is possible to obtain a β-substituted calix[4]pyrrole, in this case one bearing fused

N-tosyl pyrrolidine subunits (i.e., **2**), via a direct condensation of an appropriately chosen pyrrolic precursor and acetone under conditions of acid catalysis (TFA in the present instance). Taken in concert, ^{1}H NMR spectroscopic titration experiments and isothermal titration calorimetry (ITC) analyses provide support for the conclusion that calix[4]pyrrole **2** recognizes halide anions much more effectively than normal calix[4]pyrrole **1**. In particular, receptor **2** is a good receptor for certain chloride salts, with a strong dependence on the countercation being seen. Likewise, compound **2** appears to be a considerably better ion pair receptor for cesium salts than **1**. For instance, the *N*-tosyl pyrrolidine functionalized calix[4]pyrrole **2** is able to extract solid cesium fluoride and cesium chloride into chloroform solution well under conditions where calix[4]pyrrole **1** is not particularly effective. This latter increase in efficacy, as well as the enhancement in anion affinities, is ascribed at least in part to ancillary interactions between the tosyl groups present in receptor **2** and the countercations in question. These interactions appear particularly favorable in the case of cesium cations.

Experimental Section

Diethyl *N*-*p*-Toluenesulfonylpyrrole-3,4-dicarboxylate (4). To a mixture of diethyl pyrrole-3,4-dicarboxylate (**3**)[13] (3.00 g, 14.2 mmol) and NaOH (0.68 g, 17.0 mmol) in 1,2-dichloroethane (250 mL) was added dropwise *p*-toluenesulfonyl chloride (5.51 g, 28.9 mol) dissolved in 1,2-dichloroethane (20 mL) at 0 °C. After being stirred for 48 h at room temperature, the reaction mixture was extracted with dichloromethane and washed with water two times. The organic layer was separated off and then dried over anhydrous $MgSO_4$. The solvent was removed in vacuo to give a colorless oily solid. The crude product was purified by column chromatography over silica gel (eluent: ethyl acetate/hexane (1/3)) to give 5.0 g (96.3% yield) of **4** as a white solid. All spectroscopic data for this compound proved consistent with those reported in the literature.[13]

***N*-*p*-Toluenesulfonylpyrrole-3,4-dimethanol (5).** To a suspension of $LiAlH_4$ (1.56 g, 41.2 mmol) in THF (30 mL) was added a solution of **4** (5.00 g, 13.7 mmol) in THF (30 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C and then a small amount of water was added to quench the reaction. The reaction mixture was extracted with dichloromethane (30 mL) twice. The organic layer was collected, washed with water, and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo to give a white solid. The resulting solid was crystallized from dichloromethane/hexane (1/10) and filtered to give compound **5** (3.01 g, 78% yield) as a white solid. All spectroscopic data for this compound proved consistent with those reported in the literature.[13]

***N*-*p*-Toluenesulfonyl-3,4-bis(bromomethy)pyrrole (6).** A solution of **5** (4 g, 14.2 mmol) in dry CH_2Cl_2(40 mL) was cooled to 0 °C under an argon atmosphere. To the resulting suspension was added phosphorus tribromide (3.21 mL, 34.1 mmol) via syringe. The reaction mixture was warmed to room temperature and stirred for 2 h. At this point, 30 mL of aqueous Na_2CO_3 solution (sat.) was added slowly to the reaction mixture to quench the reaction. The organic phase was separated off, washed with water three times, and dried over anhydrous $MgSO_4$. Evaporation of the solvent in vacuo, followed by crystallization from dichloromethane/hexane (1/10), afforded the desired compound **6** (5.15 g, 89% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, 2H, Ar*H* (tosyl), J = 8 Hz), 7.33 (d, 2H, Ar*H* (tosyl), J = 8 Hz), 7.18 (s, 2H, Ar*H* (pyrrole)), 4.45 (s, 4H, pyrrole-CH_2Br), 2.43 (s, 3H, ArCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 135.6, 130.5, 127.4, 124.2, 121.1, 23.7, 21.9; HRMS (CI) m/z 405.9112 $(M + H)^+$ calcd for $C_{13}H_{14}NO_2SBr_2$, found 405.9111.

***N*-*p*-Toluenesulfonylpyrrolidinyl-*N*-*p*-toluenesulfonylpyrrole (7).** To a suspension of TsNHNa (3.35 g, 17.3 mmol) in dry CH_3CN (75 mL) was added dropwise a solution of **6** (3.00 g, 7.37 mmol) in dry DMF (25 mL) at 80 °C. After the reaction mixture was stirred for a further 30 min, the hot mixture was filtered through Celite and the filter was washed with DMF. The filtrate was evaporated in vacuo to give a white solid, which was extracted with dichloromethane and washed with water three times. The organic phase was separated off and dried over anhydrous $MgSO_4$. Crystallization from diethyl ether, following evaporation of solvents in vacuo, gave compound **7** (2.10 g, 68% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (m, 4H, Ar*H* (tosyl)), 7.31 (d, 2H, Ar*H* (tosyl), J = 4 Hz), 7.28 (d, 2H, Ar*H* (tosyl), J = 5 Hz), 6.83 (s, 2H, Ar*H* (pyrrole)), 4.29 (s, 4H, pyrrole-CH_2N), 2.40 (s, 6H, ArCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 144.0, 136.0, 134.1, 130.3, 130.1, 128.2, 127.7,127.1, 112.0, 47.4, 21.9, 21.7; HRMS (CI) m/z 417.0943 $(M + H)^+$ calcd for $C_{20}H_{21}N_2O_4S_2$, found 417.0941.

***N*-*p*-Toluenesulfonylpyrrolidinylpyrrole (8).** To a solution of **7** (1.50 g, 1.20 mmol) in dry THF/MeOH (3:1 v/v) was added NaOMe (30% solution in MeOH, 30 equiv) via syringe. The resulting solution was heated at reflux for 20 min and then cooled to room temperature. After the solvent was removed in vacuo, the resulting crude product was extracted with dichloromethane and washed with water twice. The organic phase was separated off and dried over anhydrous $MgSO_4$. Crystallization from hexane, following evaporation of solvents in vacuo, gave compound **8** (0.86 g, 91% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (broad s, 1H, N*H*), 7.76 (d, 2H, Ar*H* (tosyl), J = 8 Hz), 7.23 (d, 2H, Ar*H* (tosyl), J = 8 Hz), 6.45 (s, 2H, Ar*H* (pyrrole)), 4.42 (s, 4H, pyrrole-CH_2N), 2.40 (s, 3H, ArCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 134.5, 129.9, 127.7, 122.9, 109.0, 48.3, 21.7; HRMS (CI) m/z 263.0854 $(M + H)^+$ calcd for $C_{13}H_{15}N_2O_2S$, found 263.0854.

***N*-*p*-Toluenesulfonylpyrrolidinecalix[4]pyrrole (2).** To compound **8** (1.2 g, 4.57 mmol) in acetone (150 mL) was added TFA (0.52 g, 4.57 mmol) in one portion. The resulting solution was stirred for 24 h at room temperature and taken to dryness in vacuo to give a brownish solid. To the crude product were added dichloromethane (100 mL), water (100 mL), and triethylamine (5 mL). The organic phase was then separated off and washed three times with water (100 mL). The organic layer was dried over anhydrous $MgSO_4$ and evaporated in vacuo to give a yellowish solid. Column chromatography over silica gel (eluent: ethyl acetate/dichloromethane (99/1)), followed by crystallization from methanol, gave the target compound **2** (0.28 g, 20% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, 8H, Ar*H* (tosyl), J = 8 Hz), 7.35 (d, 8H, Ar*H* (tosyl), J = 8 Hz), 4.27 (s, 16H, pyrrole-CH_2N), 2.46 (s, 12H, ArCH_3), 1.32 (s, 24H, pyrrole-C(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 134.3, 130.2, 127.7, 127.5, 118.1, 48.5, 36.4, 29.9, 21.9; HRMS (CI) m/z 1209.4434 $(M + H)^+$ calcd for $C_{64}H_{73}N_8O_8S_4$, found 1209.4435. The results of an HPLC analysis are given in the SI. This compound was further characterized by X-ray diffraction analysis.

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Supporting Information Available: NMR spectroscopic data, CI-HRMS, HPLC analysis of **2**, ITC analyses, and X-ray structural data and CIF files for **2**·(DMF)$_2$ (CCDC 794361), **2**·(CH$_3$OH)$_2$ (CCDC 794362), and **2**·TBACl (CCDC 794363). This material is available free of charge via the Internet at http://pubs.acs.org.