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Lithiation of *meso*-Octamethylcalix[4]pyrrole: A General Route to *C*-Rim Monosubstituted Calix[4]pyrroles

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Lithiation and subsequent addition of an electrophile to *meso*-octamethylcalix[4]pyrrole provides a straightforward synthetic route to new, *C*-rim monosubstituted calix[4]pyrroles. A variety of electrophiles were used, resulting in calix[4]pyrroles with appended functional groups including carboxyl, ester, iodo, and formyl. This method was optimized to give maximum yields of the monosubstituted derivatives with lowest possible contamination by di- and trisubstituted congeners. Solid-state studies, performed for a number of these derivatives, showed unexpected supramolecular interactions involving both solvents and the monosubstituted calix[4]pyrrole derivatives themselves.

Introduction and Background

The production of new receptors for anions and neutral species which are easy to synthesize and yet effective and selective in their guest binding properties is an area of supramolecular chemistry that provides a continuing challenge to our groups[1,2] and others.[3] Calix[4]pyrroles (*meso*-octaalkylporphyrinogens) are stable tetrapyrrolic macrocycles first synthesized in the 19th century by Baeyer via acid-catalyzed condensation of pyrrole with acetone to produce *meso*-octamethylcalix[4]pyrrole **1**.[4] The discovery that these species act as receptors for anions and neutral molecules[5,6] has been used in the production of fluorescent,[7] colorimetric,[8] and electrochemical[9] sensors for anions, in addition to new solid supports capable of separating mixtures of anions (including oligonucleotides).[10] Encouraged by the facile synthesis of calix[4]pyrroles in high yield,[11,12] via the acid-catalyzed condensation of pyrrole with a ketone, we decided to investigate whether it was possible to functionalize selectively the periphery of the macrocycle;[13,14] this, we thought, would allow for the production of new species that could be used in the fabrication of anion receptors or sensors. Our previous strategy to synthesize functionalized calix[4]pyrroles had relied upon statistical syntheses from mixtures of two different ketones. This produced a variety of *meso*-substituted products that were separable by column chromatography.[15] Other attempts at producing selectively substituted calix[4]pyrroles by reacting mixtures of two different pyrroles with a single ketone have given low yields of monosubstituted products (<2%), presumably due to the different reactivity of the pyrroles used and the consequent selective formation of calix[4]pyrroles derived from only one of pyrroles actually used (homo-calix[4]pyrroles).[16]

We report here the synthesis of monosubstituted calix[4]pyrrole derivatives containing acid (**3**), ester (**4**), iodo (**5**), and formyl (**6**) as well as calix[4]pyrrole-2-ethanol (**8**); these species were obtained by reaction of lithiated calix-

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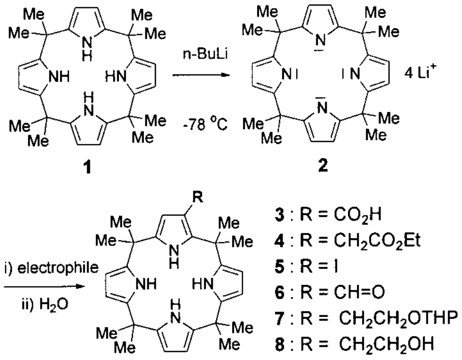
Table 1. The Effect of Electrophile Equivalents Employed on Isolated Yield of Monosubstituted Calix[4]pyrrole Derivatives. All Syntheses Were Carried out Using Method A except Entry 5 (method B)

entry	product	electrophile	equiv of electrophile	yield (%) of monosubstituted product	yield (%) of disubstituted derivatives
1	**3**	solid CO_2	excess	17	<4
2	**4**	ethyl bromoacetate	3	35	11
3	**4**	ethyl bromoacetate	2	21	<5
4	**5**	chloroiodide (ICl)	2	13	<5
5	**5**[a]	chloroiodide (ICl)	1	7	traces
6	**6**[b]	*N*-formylpiperidine	2	7	<3
7	**7**	2-(2-bromoethoxy)tetrahydro-2*H*-pyran	5	12[c]	none

[a] Lithiation of the starting calix[4]pyrrole **1** was performed using only 3 equiv of n-BuLi. [b] Although higher yields of the formyl derivative **6** may be achieved by using 3 equiv of *N*-formylpiperidine (yields up to 15%), such an enhanced yield is accompanied by an increased presence of unwanted doubly functionalized material (ca. 5−7%). [c] Assumes deprotection of the intermediate tetrahydropyranyl derivative is quantitative.

Scheme 1. Synthetic Procedure



[4]pyrrole **2**[17,18] with carbon dioxide, ethyl bromoacetate, *N*-formylpiperidine, chloroiodide (ICl), and 1-bromo-2-(tetrahydropyranyloxy)ethane, respectively (Scheme 1). A preliminary account of this work, describing the synthesis of **3** and **4**, has recently appeared.[7,13]

Discussion

The starting material, *meso*-octamethylcalix[4]pyrrole **1,** was prepared according to previously published procedures.[11] This material was then lithiated with 4 equiv of *n*-butyllithium in hexanes in THF at −78 °C (method A) (Scheme 1) to give a polyanion **2**, of undetermined structure.[17,18] The reaction mixture was stirred for 1−2 h at −78 °C, and the calix[4]pyrrole anion was then treated with a suitable electrophile and quenched by addition of water.

Carbon dioxide, ethyl bromoacetate, chloroiodide (iodine monochloride), *N*-formylpiperidine, and 2-(2-bromoethoxy)tetrahydro-2*H*-pyran were successfully employed as electrophiles. Halogens such as bromine or iodine were found relatively ineffective for generating the monosubstituted calix[4]pyrroles via the reaction with calix[4]pyrrole polyanion **2**. However, octabrominated calix[4]pyrroles have already been reported as being formed by more direct routes.[13] Similarly, some other less reactive electrophiles such as derivatives of aromatic carboxylic acids such as benzoyl chloride, benzonitrile, and ethyl benzoate did not give satisfactory results.

The quantity of n-BuLi used in these reactions was altered in order to give an optimum yield of monosubstituted product. Although the 1:4 calix[4]pyrrole to n-BuLi molar ratio (method A, $n = 4$, Scheme 1) proved generally optimal, in the case of chloroiodide (Table 1, entry 5) it was found advantageous to use fewer equivalents of n-BuLi (method B, $n = 3$, Scheme 1). Using method A, optimum yields of monosubstituted calix[4]pyrrole products were obtained in the case of the carboxylic acid, ester, formyl, and THP protected 2-hydroxyethyl derivatives (**3**, **4**, **6**, and **7**, respectively) (Table 1, entries 1, 2, 3, 5, and 6).

Using method A, a statistical distribution of mono-, di-, tri- and tetrasubstituted calix[4]pyrroles was often observed for the more reactive electrophiles. This is particularly true in the case of chloroiodide, where significant formation of monosubstituted derivative could only be achieved by using just 3 equiv of n-BuLi (method B). Thus, in this and other cases, the reaction conditions were specifically optimized for each electrophile in order to give the monosubstituted product with lowest possible contamination of di- and trisubstituted derivatives.[19] Unfortunately, the price of increased production of the monosubstituted derivative was a lower overall conversion of the starting material. In this study, an optimized procedure was considered one wherein the highest yield of monosubstituted derivatives was obtained so long as the contamination by disubstituted products was less than 5% (based on the starting macrocycle **1**). This was usually achieved by using a lower than stoichiometric amount of electrophile (Table 1). Presumably, the effectiveness of this particular optimization strategy is a direct reflection of the high reactivity of ethyl bromoacetate and ICl, respectively.

Both acidic and basic workup procedures were explored. In the acidic workup, the pH was adjusted to 3−4 by addition of dilute mineral acid (aqueous perchloric acid, sulfuric acid, or HCl) to hydrolyze the remaining lithium salts. The acidic workup procedure using aqueous perchloric acid proved to be particularly advantageous in preparing the calix[4]pyrrole monocarboxylic acid **4**. In this case, the calix[4]pyrrole dicarboxylic acid dissolves in the aqueous medium, while the desired monocarboxylic acid **4** and the unreacted starting material (**1**) precipitate from the solution. Similarly, a mildly basic workup procedure, involving the use of either water or water containing ammonium chloride solution (pH ≃ 8−9), proved advantageous in the preparation of derivatives bearing acid-sensitive functionalities, such as the tetrahydropyranyl-protected hydroxyl system **8**.

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(19) With exception of the monoiodocalix[4]pyrrole **5**, all the products can be separated from unreacted starting material **1** by crystallization from mixture of dichloromethane and methanol. This provides the required monoderivatives in 80% purity before chromatography.

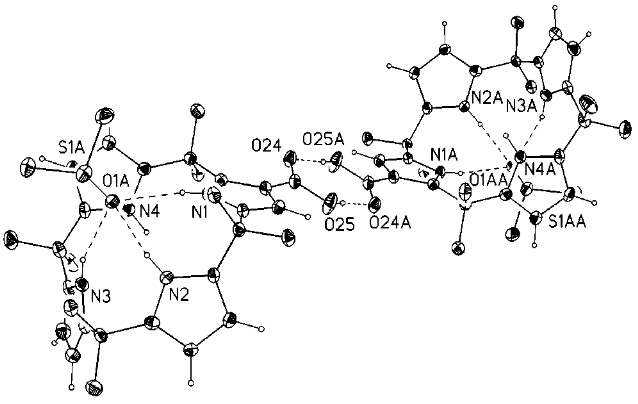

Figure 1. View of the hydrogen bound dimer of compound **3**. Molecules labeled with A are related by $-x$, $1 - y$, $1 - z$. Thermal ellipsoids are scaled to the 30% probability level. Dashed lines are indicative of H-bonding interactions. The geometry of these interactions are: N1−H1N···O1a, N···O 3.108(4) Å, H···O 2.32(4) Å, N−H···O 168(3)°; N2−H2N···O1a, N···O 2.845(4) Å, H···O 2.01(4) Å, N−H···O 161(4)°; N3−H3N···O1a, N···O 2.990(4) Å, H···O 2.18(5) Å, N−H···O 159(4)°; O25−H25···O24 (related by $-x$, $1 - y$, $1 - z$), O···O 2.632(4) Å. H···O 1.77(5) Å, O−H···O 171(5)°.

The solid state studies not only confirmed the proposed structure of the monofunctionalized derivatives reported here, but also revealed the presence of supramolecular interactions involving calix[4]pyrrole derivatives **3**, **4**, and **6**. As such, these structures help rationalize previous observations made in the context of solution-phase studies. For instance, the X-ray crystal structure of **3** (Figure 1) revealed the presence of a DMSO molecule bound to the calix[4]pyrrole core. In addition, the carboxylic acid functionalities were seen to form intermolecular hydrogen bonds, thereby stabilizing calix[4]pyrrole dimers within the crystal lattice. This structural motif differs from that seen for the carboxylic acid derived from ester **4** by hydrolysis.[15] In the latter case, the carboxyl function is seen to interact directly with the pyrrole NHs of a separate calix[4]pyrrole receptor.[15] In other words, it acts as an anion-like substrate. By contrast, in the case of the **3**, this same functionality is found to be tied up in the form of carboxylic acid dimers in the crystal lattice.

By contrast, the X-ray crystal structure of **4** reveals the ester carbonyl oxygen forming a hydrogen bond to an adjacent pyrrole NH group (Figure 2). Perhaps as a result of this narcissistic interaction, no substrate or solvent is found bound within the calix[4]pyrrole cavity in the solid state. This finding seems to be in accord with the fact that fluorescent sensors for anions derived from **4** show substantially lower affinity for common anions than analogous sensors derived from **3**.[7] This decrease in anion affinity may now be rationalized in terms of the solid-state structure of **4** which reveals that the 1,3-alternate conformation is stabilized by a hydrogen bond between N2 and O23; this latter conformation is less effective than the cone conformation in terms of allowing for optimized anion−receptor interactions.

An absence of bound guest is also seen in the crystal structure of **6**. In this instance, intersubunit hydrogen bonding interactions serve to stabilize a dimer structure in the solid state (Figure 3).

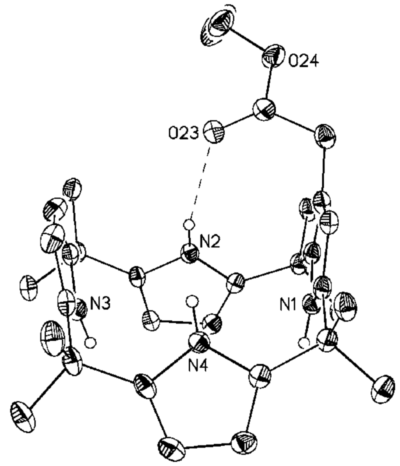

Figure 2. View of **4** showing a partial atom labeling scheme. Thermal ellipsoids are scaled to the 30% probability level. Hydrogen atoms shown are drawn to an arbitrary scale. Dashed lines indicate an intramolecular H-bonding interaction with geometry: N2−H2N···O23, N···O 3.000(3) Å, H···O 2.23(3) Å, N−H···O 155(2)°.

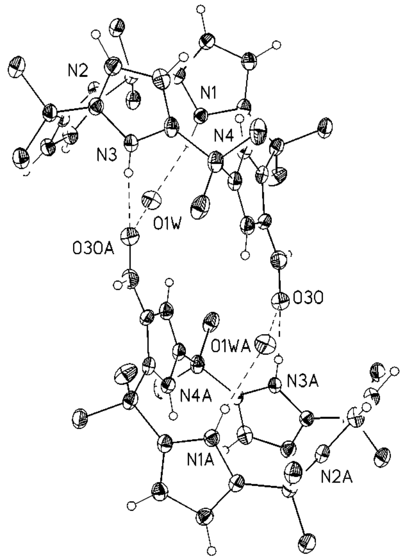

Figure 3. View of the hydrogen-bonded dimer of **6** formed in the unit cell. This dimer spans a crystallographic inversion center. The H-bonding interactions are shown with dashed lines. The geometry of these interactions are: N1−H1N···O1W, N···O 2.918(4) Å, H···O 2.097(4) Å, N−H···O 151.0(1)°; N3−H3N···O30 (related by 1-x, -y, 1-z), N···O 2.909(4) Å, H···O 2.011(4) Å, N−H···O 174.5(1)°. Atoms with labels appended by A are related by $1 - x$, $-y$, $1 - z$.

The presence of hydrogen bond donating and accepting moieties in these receptors, and the observation of various hydrogen bonding interactions in the solid state, leads us to suggest that functionalized calix[4]pyrroles may act as receptors for a variety of substrates under solution-phase conditions. The binding and aggregation properties of these systems are thus being studied currently in several different solvent systems.

Conclusion

In conclusion, a general method for preparing monofunctionalized derivatives of *meso*-octamethylcalix[4]pyrrole **1** has been developed. This method, illustrated with five specific examples, provides a variety of elaborated calix[4]pyrroles that could prove useful in the construction of calix[4]pyrrole-based anion sensors[7,8,14] and chromatographic stationary phases. Although the exclusive monofunctionalization process reported here is not particularly high yielding (typical yields are on the order of 10%), the fact that the starting *meso*-octamethylcalix[4]pyrrole **1** may be made in ca. 80% yield in one step from inexpensive starting materials, namely pyrrole and acetone, without recourse to chromatography, makes this functionalization method superior to those based on mixed condensation-type approaches.

Experimental Section

General Procedures. All solvents were purchased from EM Science. THF was redistilled from sodium−benzophenone. Dichloromethane was filtered through a short column of potassium carbonate before using. Melting points of all calix[4]pyrroles compounds were higher than 250 °C. Thin-layer chromatography data (R_f values) were obtained with KSF Silica 60 Å (Whatman; layer thickness 0.25 mm), using the mobile phases described below. Column chromatography was carried out on Silica gel 60 Å, 230−400 mesh (Whatman). *n*-Butyllithium (1.6 M in hexane) was purchased from Aldrich. All chemicals and reagents were used as received. All reactions were carried out under dry nitrogen. The reaction yields represent true isolated yields and represent the average from three independent runs. All NMR solvents were purchased from Cambridge Isotope Laboratories, Inc. Chemical shifts are reported in ppm and are referenced to solvent. Proton and ^{13}C NMR spectra used in the characterization of products were recorded on Varian Unity 300 MHz and Varian 500 MHz spectrometers. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA, and Canadian Microanalytical Service, Ltd., Delta, British Columbia.

Lithium Salt of *meso*-Octamethylcalix[4]pyrrole Tetraanion 2. Method A. *meso*-Octamethylcalix[4]pyrrole[5,11] (4.0 g, 9.34 mmol) was dissolved in 250 mL of dry THF in a round-bottomed flask with stirring. The solution was then cooled to −78 °C in a CO_2/acetone bath under nitrogen. n-BuLi (25 mL, 1.6M in hexane, 40.0 mmol) was added dropwise to the reaction mixture. Once the addition was complete, the reaction mixture was stirred for additional 30 min. The resulting solution was then used directly in the next step.

Calix[4]pyrrole Monocarboxylic Acid 3. The reaction vessel containing calix[4]pyrrole tetraanion **2** was quickly filled with excess dry ice, the cooling bath was refilled with dry ice, and the reaction was left to stand overnight. The THF was removed in vacuo and the residue suspended in water (300 mL) and stirred for 15 min. The slurry formed was then filtered to remove starting material **1**. Acidification to pH = 3−4 (as judged by indicator paper) of the filtrate with perchloric acid (35%) produced a precipitate that was isolated by filtration. The precipitate was dissolved in dichloromethane (25 mL), dried over $MgSO_4$, and passed through a filter funnel. The filtrate was then taken to dryness in vacuo and the residue crystallized from acetone/water by slow evaporation. This yielded the monoacid **3** (310 mg, 7%) in the form of colorless crystals.

Alternatively, the aqueous filtrate obtained after removal of unreacted **1** was acidified to pH = 3−4 (indicator paper) and evaporated in vacuo, and the solid residue was extracted by a warm dichloromethane−methanol mixture (9:1, 3 × 50 mL). After concentration of the extract in vacuo, the crude monoacid (80−85% according to TLC) was purified using flash-chromatography over silica gel (4% methanol in dichloromethane, eluent). In this case, the first UV-active fraction (TLC R_f = 0.45) was collected to yield product **3** as a white powder (750 mg, 17%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.53 (s, 1 H, CO_2H), 9.93 (apparent s, 2H, NH), 8.96 (s, 1H), 8.72 (s, 1H), 6.16 (m, 1H, pyrrole CH), 5.96 (m, 2H, pyrrole CH), 5.69 (m, 2H, pyrrole CH), 5.63 (m, 2H, pyrrole CH), 1.71 (s, 6H, CH_3), 1.55 (s, 6H, CH_3), 1.52 (apparent s, 12H, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.5, 143.7, 138.97, 138.88, 138.3, 138.0, 136.9, 136.7, 136.2, 109.1, 107.0, 103.9, 103.2, 102.2, 101.8, 101.4, 101.3, 36.9, 34.9, 34.3, 33.9, 30.7, 29.6, 29.0, 28.4, 28.3, 27.0. Anal. Calcd for $C_{29}H_{36}N_4O_2 \cdot 0.5H_2O$: C, 72.32; H, 7.74; N, 11.63. Found: C, 72.48; H, 7.81; N, 11.34. MS (FAB+, *m/z*): 472 (M^+, 100), 495 (MNa^+, 25). High-resolution TOF MS ES+ Calcd for $C_{29}H_{36}N_4O_2Na^+$: 495.2736. Found 495.2712.

Crystallographic summary for **3**: small, colorless prisms were grown from DMSO, triclinic, $P\bar{1}$, $Z = 2$ in a cell of dimensions: $a = 9.8040(5)$, $b = 10.3870(6)$, 19.2570(12) Å, $\alpha = 93.281(3)$, $\beta = 100.996(3)$, $\gamma = 117.143(3)°$, $V = 1689.5(2)$ Å^3, $\rho_{calcd} = 1.22$ g·cm^{-3}, $F(000) = 656$. A total of 10332 reflections were measured (5916 unique reflections) on a Nonius Kappa CCD using graphite monochromatized Mo Kα radiation ($\lambda = 0.71073$ Å) at −150 °C. The structure was refined on F^2 to an $R_w = 0.159$, with a conventional $R = 0.0747$ (3480 reflections with $F_o > 4[\sigma(F_o)]$), and a goodness of fit = 1.112 for 574 refined parameters.

Ethyl *meso*-Octamethylcalix[4]pyrrole Acetate 4. Ethyl bromoacetate (3.10 mL, 28.00 mmol) in THF (20 mL) was added dropwise to the reaction vessel containing lithiated calix[4]pyrrole **2**, and the resulting mixture was stirred for 2 h. The reaction was then removed from the cooling bath and allowed to warm to room temperature. After 90 min, the solvent was removed in vacuo, and EtOH (100 mL) was added to the flask. Water (100 mL) was slowly added with stirring, causing a white precipitate to form. The precipitate was collected by filtration, dried under high vacuum, and then purified by column chromatography on silica gel eluting with hexanes−dichloromethane (2:3). The second fraction (R_f = 0.40) containing monoester **4** (1.585 g, 33%) was collected. A mixture of diester derivatives, with an R_f = 0.30−0.33, could also be isolated.

^{1}H NMR (500 MHz, dichloromethane-d_2) δ 8.55 (s, 1H, NH), 7.15 (s, 1H, NH), 7.04 (s, 1H, NH), 7.00 (s, 1H, NH), 5.94−5.88 (m, 5H, pyrrole CH), 5.83 (m, 1H, pyrrole CH), 5.72 (m, 1H, pyrrole CH), 4.24 (q, 2H, J = 7.15 Hz, ethyl CH_2), 3.65 (s, 2H, CCH_2), 1.62−1.47 (overlapping singlets, 24H, meso CH_3), 1.33 (t, 3H, J = 7.15 Hz, ethyl CH_3). ^{13}C NMR (125 MHz, dichloromethane-d_2) δ 174.9, 140.4, 139.7, 139.3, 138.9, 138.5, 138.0, 137.2, 134.1, 109.95, 107.1, 103.4, 103.1, 102.9, 102.7, 101.4, 61.4, 37.2, 35.5, 35.4, 35.2, 34.0, 29.2, 29.1, 28.9, 28.7, 14.5. High-resolution FABMS Calcd for $C_{32}H_{42}N_4O_2$ 514.3308; found 514.3302 (Δ1.2 ppm).

Crystallographic summary for **4**: Colorless lathes were grown from dichloromethane−methanol mixture, triclinic, $P\bar{1}$; $Z = 2$ in a cell of dimensions: $a = 10.0508(9)$, $b = 10.2303(9)$, 15.276(1) Å, $\alpha = 102.527(5)$, $\beta = 94.157(5)$, $\gamma = 108.305(4)°$, $V = 1438.9(2)$ Å^3, $\rho_{calcd} = 1.19$ g·cm^{-3}, $F(000) = 556$. A total of 10354 reflections were measured at −150 °C, 6488 unique ($R_{int} = 0.077$) on a Nonius Kappa CCD diffractometer using graphite monochromatized Mo Kα radiation ($\lambda = 0.71073$ Å). The structure was refined on F^2 to an $R_w = 0.171$, with a conventional $R = 0.0800$ for 3673 reflections with $F^2 > 4(\sigma(F^2))$, with a goodness of fit = 1.05 for 360 refined parameters.

Formyl *meso*-Octamethylcalix[4]pyrrole 6. *N*-Formylpiperidine (2.22 mL, 20.00 mmol) in THF (20 mL) was added dropwise to the reaction vessel containing lithiated calix[4]pyrrole **2**, and the resulting mixture was stirred for 2 h. The reaction was then removed from the cooling bath and allowed to warm to room temperature and stirred for additional 2 h. The reaction mixture was cooled to 0 °C in ice−water bath and carefully quenched by 0.25 N HCl (200 mL) and diluted by ethyl acetate−hexane (1:1, 200 mL). The organic layer was separated off, washed with aqueous saturated $NaHCO_3$, dried over $MgSO_4$, and evaporated in vacuo. The dark brown residue was quickly flash-chromatographed (2% methanol in dichloromethane). The second UV-active fraction (R_f = 0.70) contained 298 mg (7%) of product **6**. Compound **6** rapidly decomposed in solution (50% after 1 day) and in the solid state at room temperature (80% after 2 days).

^{1}H NMR (300 MHz, chloroform-d) δ: 10.09 (s, 1H, CHO), 7.43 (bs, 2H, NH), 7.29 (bs, 1H, NH), 7.00 (bs, 1H, NH), 6.46 (d, 1H, J = 2.8 Hz, pyrrole CH), 5.86−6.03 (m, 6H, pyrrole CH), 1.75 (s, 6H, CH_3), 1.56 (s, 12H, CH_3), 1.51 (s, 6H, CH_3). ^{13}C NMR (75 MHz, chloroform-d) δ 181.4, 142.2, 135.3, 134.9, 133.7, 133.6, 132.9, 132.6, 131.6, 116.6, 100.8, 100.0, 99.6, 99.4, 98.5, 98.4, 96.9, 33.1, 30.7, 30.6, 30.5, 25.1, 24.8, 24.1, 24.0. LR MS (CI+, *m*/*z*): 457 (MH^+); High-resolution MS(CI+) Calcd for $C_{29}H_{37}N_4O$ 457.296737; found 457.295944 (Δ1.7 ppm).

Crystallographic summary for **6**: pale yellow lathes were grown from CH_2Cl_2, triclinic, $P\bar{1}$; $Z = 2$ in a cell of dimensions: $a = 10.097(2)$, $b = 10.351(2)$, 13.079(3) Å, $\alpha = 78.72(1)$, $\beta = 82.44(1)$, $\gamma = 89.97(1)°$, $V = 1328.4(5)$ Å^3, $\rho_{calcd} = 1.19$ g·cm^{-3}, $F(000) = 1116$. A total of 10016 reflections were measured at −150 °C, 6007 unique ($R_{int} = 0.065$) on a Nonius Kappa CCD diffractometer using graphite monochromatized Mo Kα radiation ($\lambda = 0.71073$ Å). The structure was refined on F^2 to an $R_w = 0.207$, with a conventional $R = 0.0887$ for 2865 reflections with $F^2 > 4(\sigma(F^2))$, with a goodness of fit = 1.13 for 316 refined parameters.

2-(Hydroxyethyl)-*meso*-octamethylcalix[4]pyrrole 8 (via intermediate 7). 2-(2-Bromoethoxy)tetrahydro-2*H*-pyran (7.49 mL, 46.70 mmol) in THF (20 mL) was added dropwise to the reaction vessel containing lithiated calix[4]pyrrole **2**, and the resulting mixture was stirred for 2 h. The reaction was then removed from the cooling bath and allowed to warm to room temperature. After 90 min, the solvent was removed in vacuo and EtOH (100 mL) added to the flask. Water (100 mL) was slowly added with stirring causing a white precipitate to form. The precipitate, crude compound **7**, was collected by filtration and dried under high vacuum. Methanol (250 mL) and *p*-toluenesulfonic acid (10.00 g, 52.63 mmol) were added and allowed to stir at ambient temperature for 3 h. Dichloromethane (250 mL) and saturated $NaHCO_3$(aq) (250 mL) were added, and the organic phase was dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure. Purification by column chromatography on silica gel eluting with 1% methanol in dichloromethane resulted in the isolation of **8** (0.53 g, 1.13 mmol) in 12% yield. It displayed an R_f of 0.25 under these conditions.

^{1}H NMR (300 MHz, dichloromethane-d_2) δ 7.60 (bs, 1H, NH), 7.53 (bs, 1H, NH), 7.52 (bs, 1H, NH), 7.50 (bs, 1H, NH), 5.90−5.88 (m, 6H, pyrrole CH), 5.76 (d, 1H, $J = 3.12$ Hz, pyrrole CH), 3.78 (bq, 2H, $J = 4.22$ Hz, CH_2OH), 2.82 (t, 2H, $J = 6.31$ Hz, CCH_2), 1.58 (s, 6H, CH_3), 1.53 (s, 1H, OH), 1.49 (s, 6H, CH_3), 1.48 (s, 6H, CH_3), 1.46 (s, 6H, CH_3). ^{13}C NMR (75 MHz, dichloromethane-d_2) δ 147.5, 139.9, 139.1, 138.9, 138.8, 137.1, 133.4, 114.8, 105.9, 103.6, 103.1, 102.9, 102.8, 102.7, 102.5, 102.4, 64.4, 37.3, 35.6, 35.5, 35.4, 30.7, 29.6, 29.1, 29.0, 28.9. High-resolution MS(CI+) Calcd for $C_{30}H_{41}N_4O_1$ 473.3271; found 473.3280 (Δ1.9 ppm).

Lithiation of *meso*-Octamethylcalix[4]pyrrole. Method B. *meso*-Octamethylcalix[4]pyrrole (4.0 g, 9.35 mmol) was dissolved in 250 mL of dry THF in a 500 mL of round-bottomed flask with stirring under an argon atmosphere. The solution was cooled to −78 °C using a dry ice/acetone bath. *n*-Butyllithium (18 mL, 28.8 mmol) was added dropwise to the solution of *meso*-octamethylcalix[4]pyrrole, and the resulting mixture was stirred for an additional 1 h.

Monoiodo-*meso*-octamethylcalix[4]pyrrole 5. Chloroiodide (4.5 g, 28 mmol) was added into the solution of lithiated *meso*-octamethylcalix[4]pyrrole, and the reaction mixture was stirred at −78 °C for additional 15 min, before being allowed to warm to room temperature. After 1 h, the reaction mixture was cooled to 0 °C and quenched by slow addition of water (50 mL) and saturated aqueous $Na_2S_2O_3$ solution (50 mL). The resulting mixture was treated with ethyl acetate (250 mL) and washed with brine. The organic layer was separated and dried over Na_2SO_4. The solvents were removed in vacuo, and the residue was purified by column chromatography (silica gel, CH_2Cl_2/hexane 1:1, eluent). The first fraction ($R_f = 0.55$) contained the desired product **5** (the starting material **1** has an $R_f = 0.50$). Yield: 354 mg (7%). ^{1}H NMR (500 MHz, dichloromethane-d_2) δ 7.28 (s, 2H, NH), 6.93 (s, 2H, NH), 6.06 (d, 1H, $J = 3.06$ Hz, pyrrole CH), 5.97−5.82 (m, 6H, pyrrole CH), 1.67 (s, 6H, CH_3), 1.52−1.45 (overlapping singlets, 18H, CH_3). ^{13}C NMR (125 MHz, dichloromethane-d_2) δ 139.5, 139.3, 139.1, 138.8, 138.7, 137.94, 137.6, 136.1, 114.4, 104.5, 104.3, 104.0, 103.2, 103.1, 102.1, 54.9, 37.1, 35.6, 35.5, 35.4, 29.5, 28.9, 28.8, 28.7, 28.5. HRMS (FAB$^+$): calcd mass = 554.190649, found mass = 554.189579 (Δ1.9 ppm). Anal. Calcd for $C_{28}H_{35}N_4I$: C, 60.65%; H, 6.36%; N, 10.10%; I, 22.89%. Found: C, 60.46%; H, 6.40%; N, 9.89%; I, 22.66%.

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Supporting Information Available: Crystallographic data for octamethylcalix[4]pyrrole monocarboxylic acid **3**, octamethylcalix[4]pyrrole monoester **4**, and monoformyloctamethylcalix[4]pyrrole **6**. This material is available free of charge via Internet at http://pubs.acs.org.

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