DOI: 10.1002/chem.201101266

Acid/Base Controllable Molecular Recognition

Kent A. Nielsen,* Steffen Bähring, and Jan O. Jeppesen[a]

Abstract: The study of controllable molecular recognition in supramolecular receptors is important for elucidating design strategies that can lead to external control of molecular recognition applications. In this work, we present the design and synthesis of an asymmetric (TTF) tetrathiafulvalene-calix[4]pyrrole receptor and show that its recognition of 1,3,5-trinitrobenzene (TNB) can be controlled by an acid/base input. The new receptor is composed of three identical TTF units and a fourth TTF unit appended with a phenol moiety. Investigation of the host–guest complexation taking place between the TTF-calix[4]pyrrole receptor and the TNB guests was studied by means of absorption and ^{1}H NMR spectroscopy; this revealed that the conformation of the molecular receptor can be switched between locked and unlocked states by using base and acid as the input. In the unlocked state, the receptor is able to accommodate two TNB guest molecules, whereas the guests are not able to bind to the receptor in the locked state. This work serves to illustrate how external control (acid/base) of a receptor may be used to direct the molecular recognition of guests (TNBs). It has led to a new controllable molecular recognition system that functions as an acid/base switch.

Keywords: anion recognition · calix[4]pyrrole · molecular devices · receptors · self-complexation

Introduction

Allosteric change in activity is characteristic for many biological receptors.[1] In these systems an effector typically enhances or reduces the binding efficiency and eventually switches the activity fully ON or OFF. One of the ultimate challenges in supramolecular chemistry is to obtain external control of a molecular receptor, thus enabling the release and/or uptake of guest molecules to be induced at will. Pioneering work in this field has been reported by Rebek and Shinkai among others.[2] Calix[4]pyrroles[3] are well-known for their ability to bind a variety of different anions through intermolecular hydrogen-bonding interactions taking place between the four NH protons and the anion in quest. Although several groups have explored this recognition motif and used it for the synthesis of strapped calix[4]pyrroles,[4] extractants for halide anion salts,[5] colorimetric sensors,[6] ion-selective electrodes,[7] electrochemical sensors,[8] anion-pair receptors,[9] selective encapsulation systems,[10] molecular sensors,[8a,11] and catalysts,[12] the creation of unique intramolecular self-complexation[13] systems based on the calix[4]pyrrole recognition motif has to the best of our knowledge not been reported.

Herein, we report the design, synthesis, and characterization of a tetrathiafulvalene-calix[4]pyrrole receptor **1** appended (Schemes 1 and 2) with a phenol moiety and demonstrate how deprotonation/protonation at a "remote" site can be utilized to lock/unlock the molecular receptor. Deprotonation of the phenol moiety in the calix[4]pyrrole receptor **1** changes its ability to bind guest molecules as a result of a conformational change induced by a self-complexation[14] event taking place between the phenolate anion "tail"[15] and the calix[4]pyrrole "head".[16]

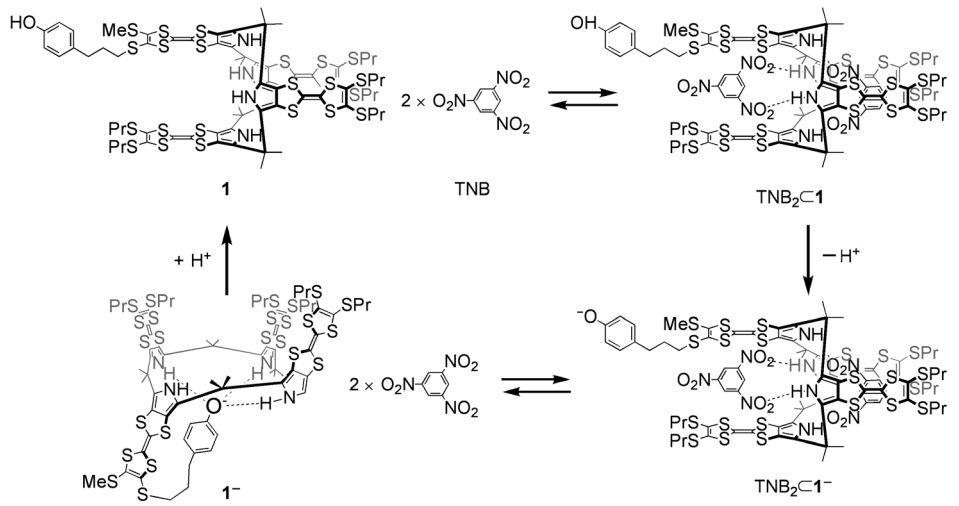
The mechanistic scheme for the proposed locking/unlocking of the molecular receptor **1** is illustrated in Scheme 1. In its neutral form, the molecular receptor **1** exists predominantly in the 1,3-alternate conformation[17] allowing electron-deficient guests, such as 1,3,5-trinitrobenzene (TNB),[11a,e,18] to access the two cavities of **1** leading to the formation of the 2:1 complex $TNB_2\subset$**1**. Deprotonation of the phenol moiety leads to the formation of $TNB_2\subset$**1**$^-$, which undergos conformational changes, from the 1,3-alternate to the self-complexing conformation **1**$^-$ with a concomitant release of the two TNB guests since no cavities in the self-complexing conformation **1**$^-$ are available for binding. Finally, protonation of **1**$^-$ regenerates the neutral 1,3-alternate conformation of the receptor. Since this receptor design allows the calix[4]pyrrole "head" to bite its own "tail" (phenolate), it seems appropriate to name it an ouroboros ("tail-eater" in Greek).

Results and Discussion

The neutral receptor **1** was synthesized in four steps as outlined in Scheme 2. Treatment of the cyanoethyl-protected monopyrrolotetrathiafulvalene[19] (MPTTF) building block **2** with one equivalent of $CsOH\cdot H_2O$ generated the corre-

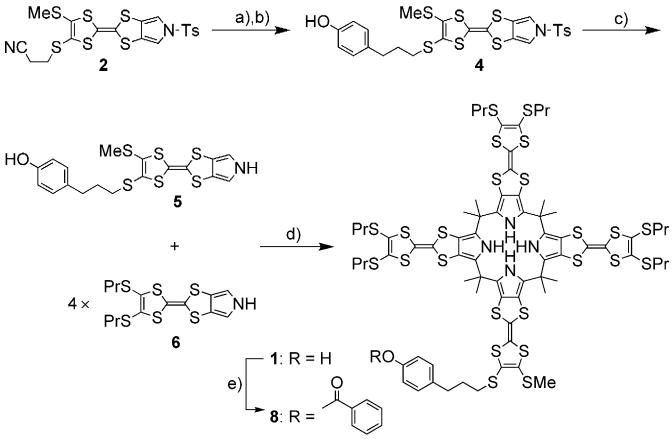
[a] Dr. K. A. Nielsen, S. Bähring, Prof. J. O. Jeppesen
Department of Physics and Chemistry
University of Southern Denmark, Campusvej 55
5230 Odense M (Denmark)
Fax: (+45) 66-15-87-80
E-mail: kan@ifk.sdu.dk

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201101266.



Scheme 1. Mechanistic scheme for the acid/base controllable conformational locking and unlocking of the molecular receptor **1**, directing decomplexation and complexation of the TNB guests.

The asymmetry of the neutral receptor **1** is clearly evident from the ^{1}H NMR spectrum (400 MHz) recorded in $CDCl_3$ at 298 K. The spectrum (Figure 1a) shows three singlets resonating at $\delta = 7.21$, 7.19, and 7.18 ppm—integrating to 1H, 1H, and 2H, respectively—which can be assigned to the three chemically nonequivalent NH protons. In agreement with the asymmetric nature, multiplets arising from the six thiopropyl and eight *meso*-methyl groups are observed (see Figure S7 in the Supporting Information) to resonate in the aliphatic part of the spectrum.



Scheme 2. Synthesis of the neutral receptor **1** and the model receptor **8**: a) 1 equiv $CsOH{\cdot}H_2O$, THF/MeOH, RT, 1 h; b) 4-(3-bromopropyl)phenol (**3**), RT, 16 h, 86%; c) 10 equiv NaOMe, THF/MeOH, 50°C, 1 h, 93%; d) TFA, TBACl, CH_2Cl_2/Me_2CO, RT, 16 h, then Et_3N, RT, 20 min, 10%; e) Et_3N, benzoyl chloride, CH_2Cl_2, RT, 30 min, 79%.

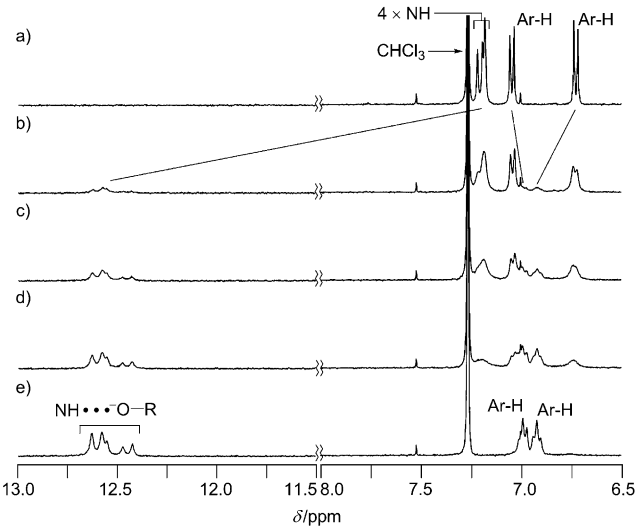


Figure 1. Partial ^{1}H NMR spectra (400 MHz, 298 K) recorded in $CDCl_3$ of a) **1** (1.5 mM), b) **1**+0.25 equiv DBU, c) **1**+0.50 equiv DBU, d) **1**+0.75 equiv DBU, and e) **1**+1.00 equiv DBU.

sponding MPTTF-thiolate, which was alkylated with 4-(3-bromopropyl)phenol[20] (**3**) affording the MPTTF derivative **4** in 86% yield. The tosyl protecting group on the MPTTF compound **4** was removed with an excellent yield (93%) by using sodium methoxide (NaOMe) in a THF/MeOH mixture. Reaction of the MPTTF derivative **5** appended with the phenol moiety and four equivalents of the MPTTF derivative[21] **6** in a CH_2Cl_2/Me_2CO mixture in the presence of tetrabutylammonium chloride (TBACl) and excess trifluoroacetic acid (TFA) afforded a mixture of the desired receptor **1** in 10% yield, and the tetraTTF-calix[4]pyrrole[8a,11] **7** (see Figure S10 in the Supporting Information) in 10% yield, after basic aqueous workup and column chromatographic purification. Reaction of the receptor **1** with benzoyl chloride in a CH_2Cl_2 solution in the presence of Et_3N afforded the model receptor tetraTTF-calix[4]pyrrole **8** in 79% yield.

Formation of the ouroboros **1**$^-$ was followed by using ^{1}H NMR spectroscopy. The base 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) was used to deprotonate the phenol moiety in the receptor **1** and the resulting self-complexing event (Scheme 1) taking place between the phenolate anion "tail" and the calix[4]pyrrole "head" is clearly evident from the ^{1}H NMR spectra (Figure 1) recorded in $CDCl_3$ at 298 K. Stepwise addition of DBU reveals that the resonances associated with the NH protons ($\delta = 7.21$–7.18 ppm) in the 1,3-alternate conformation of **1** are observed to decrease in intensity concurrent with an increase in the intensity of the NH signals associated with the ouroboros **1**$^-$. As a consequence of the inherent asymmetry of the ouroboros **1**$^-$, a multiplet of NH signals are observed to resonate between $\delta = 12.64$–12.40 ppm.[22,6a] The phenol pro-

tons are found to resonate as two doublets at $\delta = 7.04$ and 6.72 ppm in the neutral receptor **1**. Upon addition of DBU, the signals associated with these protons are also seen to decrease in intensity concurrent with the appearance of two new multiplets resonating at $\delta = 7.02$–6.95 and 6.95–6.88 ppm, respectively. These shifts ($\Delta\delta = -0.06$ and 0.20 ppm, respectively) can most likely be accounted for by the apparent proximity between the phelolate moiety and the MPTTF unit and the *meso*-methyl groups of the calix[4]-pyrrole macrocycle in the ouroboros **1**$^-$. To confirm that these shifts are associated with the formation of the self-complexing system **1**$^-$ rather than the formation of dimers or supramolecular oligomers, the complex between the *p*-cresolate anion and the model system tetraTTF-calix[4]pyrrole **8** was also investigated by using ^{1}H NMR spectroscopy. In the case of the **8**•*p*-cresolate complex (see Figure S10 in the Supporting Information), one broad NH signal is observed to resonate at $\delta = 12.6$ ppm, which indicates a higher degree of symmetry relative to the self-complexing system **1**$^-$. Furthermore, the signals corresponding to the SCH_2 and *meso*-methyl groups were found to split into different signals for the self-complexing system **1**$^-$, whereas for the **8**•*p*-cresolate complex only a shift and a broadening of the signals were observed.[23] Finally, the ^{1}H NMR spectra (400 MHz, 298 K) recorded of **1**$^-$ in $CDCl_3$ at different concentrations[13f–i,m] did not show any concentration dependence from 1.7 down to 0.12 mM. These observations indicate that the phenol "tail" and the calix[4]pyrrole macrocycle "head" of the receptor **1** upon deprotonation forms an intramolecular complex that can be ascribed as the ouroboros **1**$^-$ and it is unlikely, therefore, that supramolecular oligomers are formed to any significant extent under the conditions studied.

No significant changes appear in the ^{1}H NMR spectra recorded of the receptor **1** after addition of more than one equivalent of DBU, which indicates that the formation constant (K_f) for the ouroboros **1**$^-$ is very strong. Consequently, the K_f value cannot be determined by traditional titration techniques, because the titration plot tended towards linearity with increasing DBU concentration, which makes the nonlinear curve fitting procedure unreliable. Instead, the K_f value for the ouroboros **1**$^-$ was determined by a competitive method.[24] Initially, the binding constant (K_a) for the complexation between the neutral receptor **1** and Cl^- (as its TBA^+ salt; Table 1) was determined by using absorption spectroscopy, which gave a K_a value of $1.9 \times 10^6\,M^{-1}$ in CH_2Cl_2 at 298 K.[25] Subsequently, the K_f value for the formation of the ouroboros **1**$^-$ was determined from a competitive ^{1}H NMR spectroscopic experiment with Cl^- ions under conditions of negligible free receptor conditions. The calix[4]pyrrole receptor **1** was brought to self-complex by the addition of one equivalent of DBU; then Cl^- anions (as its TBA^+ salt) were added[26] until approximately 50% of the ouroboros **1**$^-$ was converted (see Figure S8 in the Supporting Information) into the **1**•Cl^- complex. Integration of the resonances associated with the CH_3 protons in the TBA^+ cation and the CH_3 protons in the calix[4]pyrrole receptor,

Table 1. Binding constants[a] (K_a, M^{-1}) corresponding to the interactions between the receptors **1** and **8** and the Cl^- and *p*-cresolate anions in the form of their TBA^+ salts as determined by absorption spectroscopy[b] at 298 K in CH_2Cl_2 and formation constant[a] (K_f) for the self-complexing ouroboros **1**$^-$, determined by ^{1}H NMR spectroscopy[c] at 298 K in $CDCl_3$.

Receptor	Cl^-	*p*-Cresolate	Self-complexation
1	1.9×10^6	–	1.5×10^6
8	1.3×10^6	1.4×10^5	–

[a] Estimated errors are $<15\%$. [b] Receptors **1** and **8** were titrated with a concentrated TBA•Cl or TBA•*p*-cresolate solution containing the corresponding receptor at its initial concentration to give the corresponding complexation. [c] Determined from competitive binding experiments.[24] An average K_{rel} of 1.5 for the **1**•Cl^-/**1**$^-$ was obtained by analyzing a $CDCl_3$ solution of **1** (1.5 mM) containing 0.5 equiv of Cl^- and 1.0 equiv of DBU.

respectively, allow the relative binding constant (K_{rel}) to be determined. Finally, the K_f value can be calculated by using the K_a value for the **1**•Cl^- complex. Analysis of the data gave a K_f value of 1.5×10^6 for the formation of the ouroboros **1**$^-$. For comparison, the binding constant for the intermolecular complexation between the model system tetraTTF-calix[4]pyrrole **8** and *p*-cresolate was determined by using absorption spectroscopy and gave a K_a value of $1.4 \times 10^5\,M^{-1}$ in CH_2Cl_2 at 298 K. A comparison[27] of the K_a value for the **8**•*p*-cresolate complex and the K_f value for the ouroboros **1**$^-$ revealed that the binding in the intramolecular self-complexating system **1**$^-$ is eleven times stronger than the binding in the intermolecular **8**•*p*-cresolate complex, an observation that also supports the hypothesis that **1**$^-$ is a self-complexing system.

To examine whether the receptor can be switched between its neutral 1,3-alternate conformation **1** and the self-complexing ouroboros **1**$^-$ conformation, an ^{1}H NMR spectroscopic experiment (Figure 2) was carried out that in-

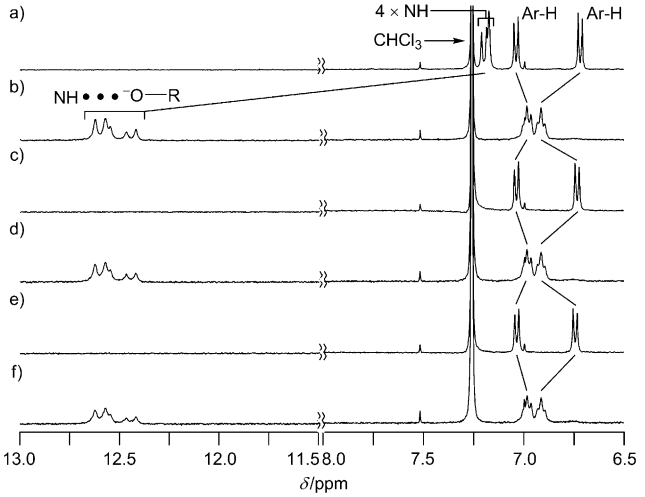


Figure 2. Partial ^{1}H NMR spectra (400 MHz, 298 K) recorded in $CDCl_3$ of a) the receptor **1** (1.5 mM), b) the mixture obtained after adding 1.0 equiv of DBU to the solution in a), c) the mixture obtained after adding 1.0 equiv of MSA to the solution in b), d) the mixture obtained after adding 1.0 equiv of DBU to the solution in c), e) the mixture obtained after adding 1.0 equiv of MSA to the solution in d), and f) the mixture obtained after adding 1.0 equiv of DBU to the solution in e).

volved the repeated addition of first base followed by acid to a solution of the receptor **1**. Initially, the neutral receptor **1** was converted (Figure 2b) to the ouroboros $\mathbf{1}^-$ by addition of one equivalent of base (DBU). Addition of one equivalent of methanesulfonic acid (MSA) to the solution of the ouroboros $\mathbf{1}^-$ reprotonates the phenolate anion. A ^{1}H NMR spectrum (Figure 2c) recorded subsequently revealed that the aromatic phenol protons reverted back to essentially their initial positions ($\delta = 7.04$ and 6.73 ppm, respectively),[28] which indicates that the neutral 1,3-alternate conformation of the receptor **1** has been regenerated. Repeated additions of base (DBU) followed by the subsequent addition of acid (MSA) resulted in the continuation of the controlled switching of the receptor **1** between its neutral 1,3-alternate (unlocked) and its ouroboros $\mathbf{1}^-$ (locked) conformations, as can be inferred from Figure 2.

After it has been established that the sequential addition of DBU and MSA to a solution of the receptor **1** can be used to switch the receptor between its neutral 1,3-alternate and ouroboros states, it was investigated how the acid/base controllable switching event affects the binding ability of the receptor **1** toward TNB. The binding between the receptor **1** and TNB was studied (Figure 3) in CH_2Cl_2 solution by using

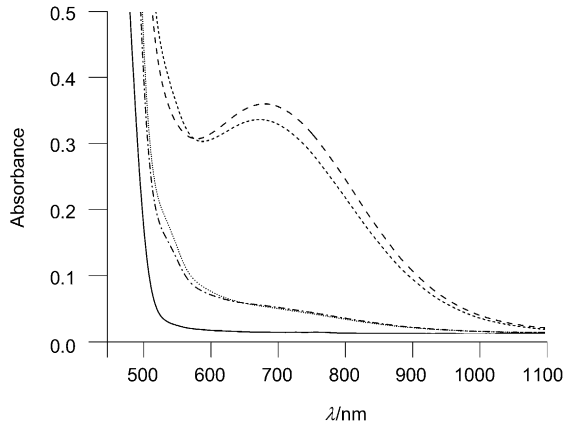


Figure 3. Absorption spectra recorded in CH_2Cl_2 at 298 K of a) the receptor **1** (0.83 mM; ——), b) **1**+2 equiv TNB (– – –), c) the mixture obtained after adding 1 equiv of DBU to the solution in b) (•••••), d) the mixture obtained after adding 1 equiv of MSA to the solution in c) (-----), and e) the mixture obtained after adding 1 equiv of DBU to the solution in d) (–•–•).

absorption spectroscopy. Neither the receptor **1** or TNB gave rise to any notable visible absorption bands at $\lambda >$ 500 nm. Addition of two equivalents of TNB to a CH_2Cl_2 solution of **1** resulted in an immediate color change from yellow to green and the appearance (Figure 3b) of a charge-transfer (CT) absorption band centered at 677 nm in the absorption spectrum, a situation that is characteristic[11c] for the inclusion of TNB guests inside the two cavities of a tetraTTF-calix[4]pyrrole receptor. The addition of one equivalent of DBU to the CH_2Cl_2 solution of the $TNB_2\subset\mathbf{1}$ complex results (vide supra) in a base-mediated conformational change of the receptor **1** to its self-complexing ouroboros $\mathbf{1}^-$ conformation. This change in conformation happens essentially instantaneously and is observed as a color change from green to yellow concomitant with the disappearance (Figure 3c) of the CT absorption band centered at 677 nm in the absorbance spectrum, which indicates that the TNB guests have been released (Scheme 1) from the receptor since no cavities are available for TNB binding in the ouroboros $\mathbf{1}^-$. Finally, addition of one equivalent of MSA to the solution of the ouroboros $\mathbf{1}^-$ and TNB resulted in a color change from yellow to green and an absorption spectrum (Figure 3d) similar to that recorded of the original mixture of the receptor **1** and TNB (Figure 3b), which suggests that the $TNB_2\subset\mathbf{1}$ complex has been regenerated in the CH_2Cl_2 solution as a result of protonation of the phenolate moiety in the ouroboros $\mathbf{1}^-$. Analyses of this sequence of events were also carried out by using ^{1}H NMR spectroscopy (Figure 4) in $CDCl_3$ at 298 K. Upon addition (Figure 4a,b) of two equivalents of TNB to a solution of the neutral receptor **1**, the signals associated with the NH protons—resonating at $\delta = 7.21$, 7.19, and 7.18 ppm—are downfield-shifted to $\delta = 7.82$ and 7.80 ppm as a result of hydrogen-bonding interactions taking place between the NH protons of the receptor **1** and the TNB guests. In this mixture, the CH protons of the TNB guests are found to resonate at $\delta =$ 9.28 ppm and are upfield-shifted relative to their initial position at $\delta = 9.37$ ppm. These observations are in complete agreement[11c] with the formation of the $TNB_2\subset\mathbf{1}$ complex in which the two TNB guests are being sandwiched between the TTF subunits. Upon addition of one equivalent of DBU (Figure 4c) to the solution of the $TNB_2\subset\mathbf{1}$ complex, the CH protons of the TNB guests are observed to revert back to essentially their initial position ($\delta = 9.38$ ppm) and the NH protons are found to resonate at $\delta = 12.64$–12.40 ppm, which clearly indicates that the self-complexing ouroboros $\mathbf{1}^-$ con-

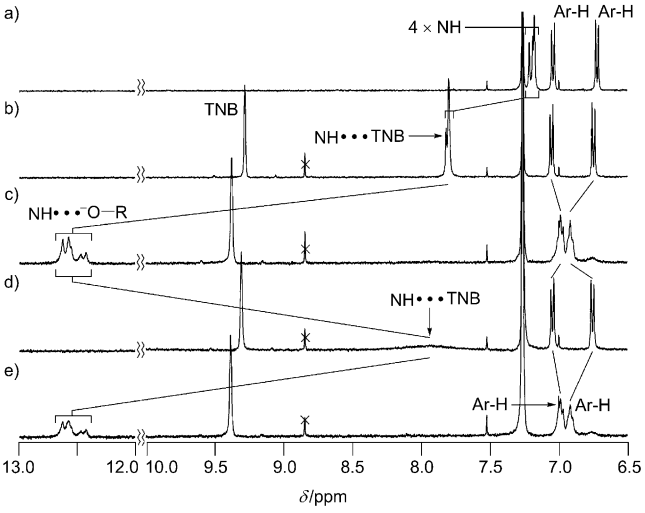


Figure 4. Partial ^{1}H NMR spectra (400 MHz, 298 K) recorded in $CDCl_3$ of a) the receptor **1** (1.5 mM), b) **1**+2 equiv TNB, c) the mixture obtained after adding 1.0 equiv of DBU to the solution in b), d) the mixture obtained after adding 1.0 equiv of MSA to the solution in c), and e) the mixture obtained after adding 1.0 equiv of DBU to the solution in d).

formation has been formed. Acidification of the ouroboros $\mathbf{1}^-$ and TNB mixture by addition of one equivalent of MSA revealed (Figure 4d) that the CH protons of the TNB guests resonate at $\delta = 9.29$ ppm signaling that the $TNB_2\subset\mathbf{1}$ complex has been re-established. In this mixture, the NH protons of the receptor are found to resonate as a broad singlet at $\delta =$ 7.94 ppm. Although the signal is broad,[29] it is clear that the NH protons have reverted back to the position expected for the $TNB_2\subset\mathbf{1}$ complex.

Conclusion

We have demonstrated the operation of a molecular receptor **1**—which through an acid/base input—adjusts its ability to complex guest molecules. In the unlocked state, the receptor is able to accommodate two TNB guest molecules, whereas the guests are not able to bind to the receptor in the locked state. The locked state of the receptor **1** is obtained by a base-mediated conformational change from a 1,3-alternate conformation to an ouroboros $\mathbf{1}^-$ conformation in which the phenolate anion "tail" and the calix[4]pyrrole "head" forms a self-complexing system. These results represent an important step towards the construction of more advanced molecular devices and to achieve control of motion at the single-molecule level. The uses of such supramolecular systems add attractive features to the construction of advanced nanoscale molecular machinery because of their potential to undergo controllable intramolecular complexation in response to a particular stimulus.

Experimental Section

General methods: Chemicals were purchased from Aldrich and used as received unless indicated otherwise. Tetrabutylammonium chloride (TBACl) was dried under vacuum at 40 °C for 24 h before use. The compounds **2**,[19e] **3**,[20] and **6**[21] were prepared according to literature procedures. All reactions were carried out under an inert N_2 atmosphere. THF was distilled from sodium-benzophenone immediately prior to use. MeOH was distilled from Mg and I_2. TLC was carried out by using aluminum 336 sheets precoated with silica gel 60F (Merck 5554). The plates were inspected under UV light (254 nm) and developed with I_2 vapor. Column chromatography was carried out by using silica gel 60F (Merck 9385, 0.040–0.063 mm). Melting points were determined with a Büchi melting point apparatus. ^{1}H NMR spectra were recorded with a Bruker Avance III 341 (400 MHz) instrument by using the residual solvent as the internal standard. ^{13}C NMR spectra were recorded at room temperature with a Bruker Avance III (100 MHz) by using the residual solvent as the internal standard. Samples were prepared by using $CDCl_3$ purchased from Cambridge Isotope Labs. Mass spectra were obtained by using a Bruker Autoflex III smart beam (MALDI-TOF) utilizing a 2,5-dihydroxybenzoic acid (DHB) matrix or by using a Thermo Finnigan MAT SSQ710 (ESI-MS). Absorption spectroscopic data was recorded by using a Shimadzu UV-1601PC apparatus. Microanalyses were performed by the Atlantic Microlab, Inc., Atlanta, Georgia.

Monopyrrolotetrathiafulvalene 4: A solution of the monopyrrolotetrathiafulvalene **2** (635 mg, 1.20 mmol) was dissolved in anhydrous THF (500 mL) and degassed (N_2, 10 min) before a solution of $CsOH{\cdot}H_2O$ (212 mg, 1.26 mmol) in anhydrous MeOH (1 mL) was added dropwise via a syringe over a period of 1 h. The mixture was stirred for 15 min and 4-(3-bromopropyl)phenol[20] **3** (212 mg, 1.32 mmol) was added in one portion. The reaction mixture was stirred overnight, after which time the solvent was evaporated in vacuo. The resulting yellow residue was dissolved in CH_2Cl_2 (200 mL), washed with H_2O (3×100 mL), and dried ($MgSO_4$). Evaporation of the solvent gave a yellow solid which was purified by column chromatography (silica gel). The yellow band was collected and concentrated to give **4** as a yellow solid (630 mg, 86%). $R_f = 0.2$ (CH_2Cl_2); m.p. 65–68 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): $\delta = 7.72$ (d, $J = 8.3$ Hz, 2H), 7.29 (d, $J = 8.3$ Hz, 2H), 7.03 (d, $J = 8.4$ Hz, 2H), 6.93 (s, 2H), 6.74 (d, $J = 8.4$ Hz, 2H), 4.82 (s, 1H), 2.77 (t, $J = 7.2$ Hz, 2H), 2.67 (t, $J = 7.2$ Hz, 2H), 2.41 (s, 3H), 2.39 (s, 3H), 1.90 ppm (p, $J = 7.2$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): $\delta = 153.8$, 145.5, 135.3, 133.1, 130.2, 129.7, 129.6, 127.3, 127.2, 127.0, 125.1, 115.3, 115.3, 114.9, 111.3, 35.4, 33.3, 31.3, 21.7, 19.2 ppm, one signal missing or overlapping; HRMS (ESI): m/z: calcd for $C_{25}H_{23}NO_3S_7 + Na^+$: 631.9616 [$M$+Na$^+$]; found: 631.9622; elemental analysis calcd (%) for $C_{25}H_{23}NO_3S_7$: C 49.23, H 3.80, N 2.30, S 36.80; found: C 49.46, H 3.85, N 2.40, S 36.51.

Monopyrrolotetrathiafulvalene 5: A solution of the monopyrrolotetrathiafulvalene **4** (1.22 g, 2.00 mmol) in anhydrous THF (300 mL) and anhydrous MeOH (100 mL) was degassed (N_2, 15 min) before sodium methoxide (25% w/w solution in MeOH, 4.0 mL, 1.08 g, 20.0 mmol) was added in one portion. The yellow mixture was heated to 50 °C for 1 h and cooled to room temperature. H_2O (200 mL) was added and the mixture extracted with CH_2Cl_2 (3×100 mL). The combined organic phases were washed with H_2O (2×100 mL) and dried ($MgSO_4$). After evaporation of the solvent, the yellow oil was purified by column chromatography (silica gel). The yellow band was collected and concentrated to give **5** as a pure yellow solid (0.85 g, 93%). $R_f = 0.4$ (CH_2Cl_2/MeOH/Et_3N 97.9:2.0:0.1); m.p. 51–54 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): $\delta = 8.21$ (brs, 1H), 7.01 (d, $J = 8.3$ Hz, 2H), 6.74 (d, $J = 8.3$ Hz, 2H), 6.60 (d, $J = 2.6$ Hz, 2H), 4.70 (s, 1H), 2.79 (t, $J = 7.2$ Hz, 2H), 2.69 (t, $J = 7.2$ Hz, 2H), 2.42 (s, 3H), 1.91 ppm (p, $J = 7.2$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): $\delta =$ 153.7, 133.3, 129.6, 125.1, 120.7, 119.9, 119.8, 115.3, 110.8, 109.8, 109.8, 35.4, 33.3, 31.3, 19.2 ppm, one signal missing or overlapping; HRMS (ESI): m/z: calcd for $C_{18}H_{17}NOS_6$: 454.9629 [M^+]; found: 454.9620; elemental analysis calcd (%) for $C_{18}H_{17}NOS_6$: C 47.44, H 3.76, N 3.07; found: C 47.61, H 3.73, N 3.05.

TetraTTF-calix[4]pyrrole 1: A solution of the monopyrrolotetrathiafulvalene **6** (1.41 g, 3.60 mmol), monopyrrolotetrathiafulvalene **5** (0.41 g, 0.90 mmol), and tetrabutylammonium chloride (1.25 g, 4.50 mmol) in a mixture of CH_2Cl_2 (600 mL) and Me_2CO (200 mL) was degassed (N_2, 20 min) before TFA (3.4 mL) was added to the yellow solution. The reaction mixture was stirred at room temperature for 16 h, whereupon Et_3N (6 mL) was added slowly. The reaction mixture was concentrated to approximately 150 mL, whereupon CH_2Cl_2 (250 mL) was added and the mixture was washed with H_2O (3×150 mL) before being dried ($MgSO_4$). After evaporation of the solvent, the yellow solid was purified by column chromatography (silica gel). The first yellow band ($R_f = 0.85$) was collected and concentrated to give the symmetric tetraTTF-calix[4]pyrrole **7** as a yellow solid. Recrystallization from CH_2Cl_2/Me_2CO gave **7** as fine yellow needles (0.20 g, 10%).[30] Subsequently, the second yellow band was collected and concentrated to give **1** as a yellow solid (0.16 g, 10%). $R_f = 0.25$ (CH_2Cl_2/hexanes 3:1); m.p. 143–145 °C (melts with decomposition); ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): $\delta = 7.21$ (brs, 1H), 7.19 (brs, 1H), 7.18 (brs, 2H), 7.04 (d, $J = 7.2$ Hz, 2H), 6.72 (d, $J = 7.2$ Hz, 2H), 4.55 (s, 1H), 2.83–2.77 (m, 14H), 2.69 (t, $J = 7.2$ Hz, 2H), 2.42 (s, 3H), 1.93 ppm (p, $J = 7.2$ Hz, 2H), 1.72–1.62 (m, 12H), 1.60–1.57 (m, 24H), 1.04–0.98 ppm (m, 18H); HRMS (MALDI): m/z: calcd for $C_{72}H_{84}N_4OS_{24}$: 1787.9937 [M^+]; found: 1787.9896; elemental analysis calcd (%) for $C_{72}H_{84}N_4OS_{24}$: C 48.28, H 4.73, N 3.13, S 42.97; found: C 48.23, H 3.82, N 3.12, S 42.69.

Synthesis of TetraTTF-calix[4]pyrrole 8: TetraTTF-calix[4]pyrrole **1** (5.0 mg, 2.8 μmol) and Et_3N (0.6 mg, 6.0 μmol) were dissolved in CH_2Cl_2 (5 mL) before a solution of benzoylchloride (0.6 mg, 4.3 μmol) in CH_2Cl_2 (0.5 mL) was added in one portion. The mixture was stirred for 30 min, after which time the reaction mixture was washed with H_2O (3×5 mL) and dried ($MgSO_4$). Evaporation of the solvent gave a yellow oil that was purified by column chromatography (silica gel). The yellow band was col-

lected and concentrated to give **8** as a yellow solid (4.2 mg, 79%). R_f = 0.4 (CH_2Cl_2/hexanes 2:1); m.p. 148–153 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 8.22–8.17 (m, 2H), 7.66–7.61 (m, 1H), 7.54–7.48 (m, 2H), 7.28–7.24 (m, 2H), 7.16–7.10 (m, 6H), 2.83–2.77 (m, 16H), 2.43 (s, 3H), 1.99 (p, J = 7.2 Hz, 2H), 1.72–1.62 (m, 12H), 1.61–1.56 (m, 24H), 1.04–0.98 ppm (m, 18H); HRMS (MALDI): m/z: calcd for $C_{79}H_{88}N_4O_2S_{24}$: 1892.0204 [M^+]; found: 1892.0170.

Acknowledgements

This work was supported by the Danish Natural Science Research Council (FNU, projects no. 272-08-0047), the Center for Fundamental Living Technology (FLinT), University of Southern Denmark (SDU), and the Villum Foundation.

[1] a) L. Stryer, *Biochemistry* 4th ed., Freeman, New York, **1995**; b) A. Livitzki, *Quantitative Aspects of Allosteric Mechanism*, Springer, Berlin, **1978**.

[2] a) J. Rebek, Jr., *Angew. Chem.* **2005**, *117*, 2104–2115; *Angew. Chem. Int. Ed.* **2005**, *44*, 2068–2078; b) L. Kovbasyuk, R. Krämer, *Chem. Rev.* **2004**, *104*, 3161–3187; c) F. Hof, S. L. Craig, C. Nuckolls, J. Rebek, Jr., *Angew. Chem.* **2002**, *114*, 1556–1578; *Angew. Chem. Int. Ed.* **2002**, *41*, 1488–1508; d) M. Takeuchi, M. Ikeda, A. Sugsaki, S. Shinkai, *Acc. Chem. Res.* **2001**, *34*, 865–873; e) S. Shinkai, M. Ikeda, A. Sugasaki, M. Takeuchi, *Acc. Chem. Res.* **2001**, *34*, 494–503; f) T. Nabeshima, *Coord. Chem. Rev.* **1996**, *148*, 151–169.

[3] a) D. Canevet, M. Sallé, G. Zhang, D. Zhang, D. Zhub, *Chem. Commun.* **2009**, 2245–2269; b) D. E. Gross, F. P. Schmidtchen, W. Antonius, P. A. Gale, V. M. Lynch, J. L. Sessler, *Chem. Eur. J.* **2008**, *14*, 7822–7827; c) J. L. Sessler, D. E. Gross, W.-S. Cho, V. M. Lynch, F. P. Schmidtchen, G. W. Bates, M. E. Light, P. A. Gale, *J. Am. Chem. Soc.* **2006**, *128*, 12281–12288; d) J. L. Sessler, P. A. Gale, W. S. Cho in *Synthetic Anion Receptor Chemistry*, RSC, London, **2006**, Chapter 5; e) P. A. Gale, P. Anzenbacher, Jr., J. L. Sessler, *Coord. Chem. Rev.* **2001**, *222*, 57–102; f) P. A. Gale, J. L. Sessler, V. Král, *Chem. Commun.* **1998**, 1–8.

[4] a) M. G. Fisher, P. A. Gale, J. R. Hiscock, M. B. Hursthouse, M. E. Light, F. P. Schmidtchen, C. C. Tonga, *Chem. Commun.* **2009**, 3017–3019; b) D.-W. Yoon, D. E. Gross, V. M. Lynch, C.-H. Lee, P. C. Bennett, J. L. Sessler, *Chem. Commun.* **2009**, 1109–1111; c) D.-W. Yoon, D. E. Gross, V. M. Lynch, J. L. Sessler, B. P. Hay, C.-H. Lee, *Angew. Chem.* **2008**, *120*, 5116–5120; *Angew. Chem. Int. Ed.* **2008**, *47*, 5038–5042; d) D.-W. Yoon, H. Hwang, C.-H. Lee, *Angew. Chem.* **2002**, *114*, 1835–1837; *Angew. Chem. Int. Ed.* **2002**, *41*, 1757–1759.

[5] a) A. Aydogan, D. J. Coady, S. K. Kim, A. Akar, C. W. Bielawski, M. Marquez, J. L. Sessler, *Angew. Chem.* **2008**, *120*, 9794–9798; *Angew. Chem. Int. Ed.* **2008**, *47*, 9648–9652; b) A. Aydogan, D. J. Coady, V. M. Lynch, A. Akar, M. Marquez, C. W. Bielawski, J. L. Sessler, *Chem. Commun.* **2008**, 1455–1457.

[6] a) S.-J. Hong, J. Yoo, S.-H. Kim, J. S. Kim, J. Yoonc, C.-H. Lee, *Chem. Commun.* **2009**, 189–191; b) G. V. Zyryanov, M. A. Palacios, P. Anzenbacher Jr., *Angew. Chem.* **2007**, *119*, 7995–7998; *Angew. Chem. Int. Ed.* **200**7, 46, 7849–7852.

[7] a) T. V. Shishkanova, R. Volf, V. Král, J. L. Sessler, S. Camiolo, P. A. Gale, *Anal. Chim. Acta* **2007**, *587*, 247–253; b) V. Král, J. L. Sessler, T. V. Shishkanova, P. A. Gale, R. Volf, *J. Am. Chem. Soc.* **1999**, *121*, 8771–8775.

[8] a) K. A. Nielsen, W.-S. Cho, J. Lyskawa, E. Levillain, V. M. Lynch, J. L. Sessler, J. O. Jeppesen, *J. Am. Chem. Soc.* **2006**, *128*, 2444–2451; b) K. A. Nielsen, J. O. Jeppesen, E. Levillain, J. Becher, *Angew. Chem.* **2003**, *115*, 197–201; *Angew. Chem. Int. Ed.* **2003**, *42*, 187–191; c) P. A. Gale, M. B. Hursthouse, M. E. Light, J. L. Sessler, C. N. Warriner, R. S. Zimmerman, *Tetrahedron Lett.* **2001**, *42*, 6759–6762; d) J. L. Sessler, A. Gebauer, P. A. Gale, *Gazz. Chim. Ital.* **1997**, *127*, 723–726.

[9] K. Kim, J. L. Sessler, D. E. Gross, C.-H. Lee, J. S. Kim, V. M. Lynch, L. H. Delmau, B. P. Hay, *J. Am. Chem. Soc.* **2010**, *132*, 5827–5836.

[10] a) G. Gil-Ramírez, M. Chas, P. Ballester, *J. Am. Chem. Soc.* **2010**, *132*, 2520–2521; b) B. Verdejo, G. Gil-Ramírez, P. Ballester, *J. Am. Chem. Soc.* **2009**, *131*, 3178–3179; c) P. Ballester, G. Gil-Ramírez, *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 10455–10459.

[11] a) J. S. Park, F. L. Derf, C. M. Bejger, V. M. Lynch, J. L. Sessler, K. A. Nielsen, C. Johnsen, J. O. Jeppesen, *Chem. Eur. J.* **2010**, *16*, 848–854; b) K. A. Nielsen, L. Martín-Gomis, G. H. Sarova, L. Sanguinet, D. E. Gross, F. Fernández-Lázaro, P. C. Stein, E. Levillain, J. L. Sessler, D. M. Guldi, Á. Sastre-Santos, J. O. Jeppesen, *Tetrahedron* **2008**, *64*, 8449–8463; c) K. A. Nielsen, W.-S. Cho, G. H. Sarova, B. M. Petersen, A. D. Bond, J. Becher, F. Jensen, D. M. Guldi, J. L. Sessler, J. O. Jeppesen, *Angew. Chem.* **2006**, *118*, 7002–7007; *Angew. Chem. Int. Ed.* **2006**, *45*, 6848–6853; d) K. A. Nielsen, W.-S. Cho, J. O. Jeppesen, V. M. Lynch, J. Becher, J. L. Sessler, *J. Am. Chem. Soc.* **2004**, *126*, 16296–16297.

[12] G. Cafeo, M. D. Rosa, F. H. Kohnke, A. Soriente, C. Talotta, L. Valenti, *Molecules* **2009**, *14*, 2594–2601.

[13] a) F. Durola, J. Rebek, Jr., *Angew. Chem.* **2010**, *122*, 3257–3259; *Angew. Chem. Int. Ed.* **2010**, *49*, 3189–3191; b) D.-H. Qu, B. L. Feringa, *Angew. Chem.* **2010**, *122*, 1125–1128; *Angew. Chem. Int. Ed.* **2010**, *49*, 1107–1110; c) I. Aprahamian, O. Miljanic, W. R. Dichtel, K. Isoda, T. Yasuda, T. Kato, J. F. Stoddart, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1856–1869; d) S. Nygaard, Y. Liu, P. C. Stein, A. H. Flood, J. O. Jeppesen, *Adv. Funct. Mater.* **2007**, *17*, 751–762; e) H. Wu, D. Zhang, L. Su, K. Ohkubo, C. Zhang, S. Yin, L. Mao, Z. Shuai, S. Fukuzumi, D. Zhu, *J. Am. Chem. Soc.* **2007**, *129*, 6839–6846; f) R. J. Hooley, J. Rebek, Jr., *Org. Lett.* **2007**, *9*, 1179–1182; g) G. Cooke, P. Woisel, M. Bria, F. Delattre, J. F. Garety, S. G. Hewage, G. Rabani, G. M. Rosair, *Org. Lett.* **2006**, *8*, 1423–1426; h) Y. Liu, A. H. Flood, R. M. Moskowitz, J. F. Stoddart, *Chem. Eur. J.* **2005**, *11*, 369–385; i) Y. Liu, A. H. Flood, J. F. Stoddart, *J. Am. Chem. Soc.* **2004**, *126*, 9150–9151; j) L. Fabbrizzi, F. Foti, M. Licchelli, P. M. Maccarini, D. Sacchi, M. Zema, *Chem. Eur. J.* **2002**, *8*, 4965–4972; k) V. Balzani, P. Ceroni, A. Credi, M. Gómez-López, C. Hamers, J. F. Stoddart, R. Wolf, *New J. Chem.* **2001**, *25*, 25–31; l) M. B. Nielsen, J. G. Hansen, J. Becher, *Eur. J. Org. Chem.* **1999**, 2807–2815; m) R. Wolf, M. Asakawa, P. R. Ashton, M. Gómez-López, C. Hamers, S. Menzer, I. W. Parsons, N. Spencer, J. F. Stoddart, M. S. Tolley, D. J. Williams, *Angew. Chem.* **1998**, *110*, 1018–1022; *Angew. Chem. Int. Ed.* **1998**, *37*, 975–979; n) L. Fabbrizzi, M. Licchelli, P. Pallavicini, L. Parodi, *Angew. Chem.* **1998**, *110*, 838–841; *Angew. Chem. Int. Ed.* **1998**, *37*, 800–802; o) M. B. Nielsen, S. B. Nielsen, J. Becher, *Chem. Commun.* **1998**, 475–476; p) P. R. Ashton, R. Ballardini, V. Balzani, S. E. Boyd, A. Credi, M. T. Gandolfi, M. Gomez-Lopez, S. Iqbal, D. Philp, J. A. Peece, L. Prodi, H. G. Ricketts, J. F. Stoddart, M. S. Tolley, M. Venturi, A. J. P. White, David J. Williams, *Chem. Eur. J.* **1997**, *3*, 152–169; q) R. Corradini, A. Dossena, R. Marchelli, A. Panagia, G. Sartor, M. Saviago, A. Lombardi, V. Pavone, *Chem. Eur. J.* **1996**, *2*, 373–381; r) M. Nakamura, A. Ikeda, N. Ise, T. Ikeda, H. Ikeda, F. Toda, A. Ueno, *J. Chem. Soc. Chem. Commun.* **1995**, 721–722.

[14] It should be mentioned that self-complexation in a calix[2]furan[4]-pyrrole receptor has been suggested in the conclusion of the following article: G. Cafeo, A. Kaledkowski, F. H. Kohnke, A. Messina, *Supramol. Chem.* **2006**, *18*, 273–279.

[15] It has previously been reported that the parent calix[4]pyrrole is able to form a 1:1 complex with the *p*-nitrophenolate anion, see: a) P. A. Gale, L. J. Twyman, C. I. Handlin, J. L. Sessler, *Chem. Commun.* **1999**, 1851–1852; b) G. Cafeo, F. H. Kohnke, L. Valenti, A. J. P. White, *Chem. Eur. J.* **2008**, *14*, 11593–11600.

[16] Conformational control of the tetraTTF-calix[4]pyrrole system **7** has previously been described with successive chloride and sodium additions, see reference [11b]. However, acid/base control of the receptor conformation and self-complexation are novel concepts.

[17] J. R. Blas, J. M. López-Bes, M. Márquez, J. L. Sessler, F. J. Luque, M. Orozco, *Chem. Eur. J.* **2007**, *13*, 1108–1116.

[18] D.-S. Kim, V. M. Lynch, K. A. Nielsen, C. Johnsen, J. O. Jeppesen, J. L. Sessler, *Anal. Bioanal. Chem.* **2009**, *395*, 393–400.

[19] a) J. O. Jeppesen, M. B. Nielsen, J. Becher, *Chem. Rev.* **2004**, *104*, 5115–5131; b) J. O. Jeppesen, J. Becher, *Eur. J. Org. Chem.* **2003**, 3245–3266; c) J. L. Segura, N. Martín, *Angew. Chem.* **2001**, *113*, 1416–1455; *Angew. Chem. Int. Ed.* **2001**, *40*, 1372–1409; d) M. R. Bryce, *J. Mater. Chem.* **2000**, *10*, 589–598; e) J. O. Jeppesen, K. Takimiya, F. Jensen, T. Brimert, K. Nielsen, N. Thorup, J. Becher, *J. Org. Chem.* **2000**, *65*, 5794–5805.

[20] Y. Sato, H. Sakakibara, *J. Organomet. Chem.* **1979**, *166*, 303–307.

[21] J. A. Hansen, J. Becher, J. O. Jeppesen, E. Levillain, M. B. Nielsen, B. M. Petersen, J. C. Petersenc, Y. Şahin, *J. Mater. Chem.* **2004**, *14*, 179–184.

[22] Splitting of the NH signal(s) for asymmetric calix[4]pyrrole systems upon complexation with anions has previously been reported; a) A. Aydogan, J. L. Sessler, A. Akar, V. Lynch, *Supramol. Chem.* **2008**, *20*, 11–21; b) G. Bruno, G. Cafeo, F. H. Kohnke, F. Nicol, *Tetrahedron* **2007**, *63*, 10003–10010; c) S.-D. Jeong, J. Yoo, H.-K. Na, D. Y. Chi, C.-H. Lee, *Supramol. Chem.* **2007**, *19*, 271–275; d) R. Nishiyabu, M. A. Palacios, W. Dehaen, P. Anzenbacher, Jr., *J. Am. Chem. Soc.* **2006**, *128*, 11496–11504; e) R. Nishiyabu, P. Anzenbacher, Jr., *Org. Lett.* **2006**, *8*, 359–362.

[23] The complex between the *p*-cresolate anion and the model system tetraTTF-calix[4]pyrrole **7** was also investigated by using ^{1}H NMR spectroscopy. The results show (see Figure S10 in the Supporting Information) that the **7**•*p*-cresolate complex has the same high degree of symmetry as observed for the **8**•*p*-cresolate complex.

[24] a) S. Liu, C. Ruspic, P. Mukhopadhyay, S. Chakrabarti, P. Y. Zavalij, L. Isaacs, *J. Am. Chem. Soc.* **2005**, *127*, 15959–15967; b) L. Fielding, *Tetrahedron* **2000**, *56*, 6151–6170; c) W. L. Mock, N.-Y. Shih, *J. Org. Chem.* **1986**, *51*, 4440–4446; d) J. A. A. de Boer, D. N. Reinhoudt, *J. Am. Chem. Soc.* **1985**, *107*, 5347–5351.

[25] The K_a value corresponding to the interaction between **1** and Cl^- anions is too strong to be determined by using ^{1}H NMR spectroscopy and was therefore determined by using absorption spectroscopy.

[26] This resulted in the appearance of a new signal in the ^{1}H NMR spectrum ($\delta = 10.9$ ppm) corresponding to formation of the **1**•Cl^- complex, see the Supporting Information. This confirms the competition between phenolate and chloride anions for the complexation to the NH protons.

[27] It should be noted that the ouroboros $\mathbf{1}^-$ are expected to be found in the partial cone conformation (Scheme 1), whereas the **7**•*p*-cresolate complexes are expected to be found in the cone conformation (see Figure S10 in the Supporting Information).

[28] The labile OH and NH protons are not observed under the acidic conditions.

[29] The fact the NH protons are observed as a broad singlet can most likely be accounted for by an exchange process taking place between the NH protons and the solvent under the acidic conditions in which the ^{1}H NMR spectrum has been recorded.

[30] Analytical data for **7** are identical with those reported in the literature, see reference [11d].

Received: April 26, 2011
Published online: August 18, 2011

