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COMMUNICATION

A calix[2]phenol[2]pyrrole and a fused pyrrolidine-containing derivative†‡

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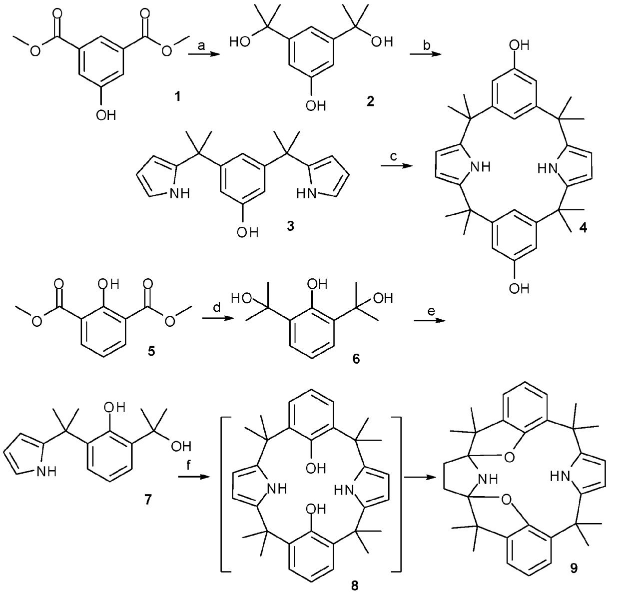
The hybrid calix[2]phenol[2]pyrrole 4 and the fused pyrrolidine-containing macrocycle 9 were synthesized from two different isomeric starting materials, namely dimethyl 2-hydroxyisophthalate and 5-hydroxyisophthalate, respectively. The fused species 9 is devoid of obvious substrate binding properties. In contrast, the heterocalix system 4 displays the fluoride-induced conformational changes characteristic of the parent system.

Calixarenes, synthesized from phenol and formaldehyde, continue to play a central role in supramolecular chemistry due to their unique vessel-like structures and recognized ability to act as receptors for a wide-range of ionic and small molecule neutral substrates. The structural diversity embodied within this family of compounds has made them of further interest for the construction of self-assembled materials, as well as a wide range of functionalized hosts.[1] It has also inspired efforts to make new analogues wherein one or more of the constituent phenols is replaced by a different aromatic subunit. Among the most extensively studied of these latter analogues are the calix[4]pyrroles, a class of compounds first reported by Baeyer in 1886[2] that have recently attracted attention as simple-to-prepare anion binding agents. As in the case of calixarenes, efforts have been devoted to the preparation of new calix[4]pyrrole derivatives, with modified structure and function. To this end, the calix[4]pyrrole core has been extensively modified by varying the β-pyrrolic substituents,[3] incorporating *meso* carbon substituents other than CH_3,[4] or expanding the size of the ring (calix[*n*]pyrroles; $n > 4$).[5] Work has also been devoted to replacing the pyrroles by other heterocyclic building blocks (*e.g.* pyridine).[6] However, to the best of our knowledge, calixarene–calixpyrrole hybrid systems that contain both pyrrolic and phenolic building blocks are unknown. Here, we report the synthesis and characterization of a new chimera system, specifically the calix[2]phenol[2]pyrrole **4**, as well as a related hybrid system (**9**) that incorporates a fused pyrrolidine subunit.

Two distinct calix[2]phenol[2]pyrroles of relatively high symmetry with a basic phenol–pyrrole–phenol–pyrrole sequence of subunits can be conceived depending on whether the phenolic subunits are attached *via* the 2,6 or 3,5 positions. We thought that these two putative products (**4** and **8**) could be synthesized from the two isomeric intermediates **2** and **6** as shown in Scheme 1. Starting from dimethyl 5-hydroxyisophthalate, compound **2** was prepared in 73% yield *via* a Grignard reaction. Substitution with pyrrole in acetonitrile then afforded compound **3** in 73% yield. Reaction of **3** and **2** in the presence of *p*-TsOH then gave the target calix[2]phenol[2]pyrrole (**4**) in 13% yield. Attempts to react **2** with pyrrole directly in the presence of acetone were not fruitful; under these conditions, calix **4** was only obtained in 2% yield.

In an attempt to prepare isomer **8**, a similar synthetic protocol was employed. Interestingly, the same conditions used to obtain the dipyrrole substituted phenol (**3**) failed to



Scheme 1 Synthesis of macrocycles **4** and **9**. *Reagents and conditions*: (a) MeMgCl, ether, 73%; (b) pyrrole, *p*-TsOH, CH_3CN, 43%; (c) *p*-TsOH, **2**, CH_3CN : DCM (7 : 10 v/v), 13%; (d) MeMgCl, ether, 62%; (e) pyrrole, *p*-TsOH, CH_3CN, 68%; (f) methane sulfonic acid, CH_3CN, 10%.

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‡ Electronic supplementary information (ESI) available: Synthetic procedures and characterization data for all new compounds, X-ray data for **4**, **4**·TBAF, and **9**,[10] and NMR spectra provided in support of the results presented in the main text. CCDC 858002 (**9**), 858003 (**4**) and 858004 (**4**·TBAF). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc17888e

provide the expected disubstituted product. Rather, what was obtained in 68% yield was the monopyrrole substituted phenol **7**. A subsequent acid catalyzed reaction afforded the unexpected fused calix[2]phenol[2]pyrrole (fused calix **9**) in 10% yield. The desired target, the putative calix **8** (and isomer of **4**), was thus not obtained.

The unique fused calix **9** was characterized by standard spectroscopic techniques, as well as by single-crystal X-ray diffraction analysis (Fig. 2a). In the solid state, there are two molecules of the fused calix **9** in each asymmetric unit. One is hydrogen bonded to a molecule of acetonitrile (Fig. S6, ESI‡). The second one is disordered by an approximately 180° rotation about the mean plane through the two orientations of the molecule (Fig. S7, ESI‡).

The unusual fused nature of product **9**, as well as the disorder revealed in the solid state structure, led us to consider whether this particular calix derivative might not have fluxional character. Specifically, we speculated that it might exist in the form of two identical tautomeric structures that could interconvert *via* **8**, as shown in Fig. 1. To test whether interconversion between these proposed tautomers took place, deuterium exchange studies were carried out in CD_2Cl_2 at 298 K.[7] These studies involved adding CD_3OD to an initial solution of **9** and recording the changes in the ^{1}H-NMR spectrum as a function of time. It was found that the protons on C14 and C15 underwent exchange and were replaced by deuterium. In contrast, the protons on C2 and C3 did not exchange (Fig. 1 and Fig. S2, ESI‡). These results provide support for the conclusion that, once formed, compound **9** is stable; it exists in the fused form and is not a labile species that is in effective equilibrium with the proposed calix intermediate **8** or the labeled tautomer of **9** shown in Fig. 1.

Calix[4]arenes generally exist in the cone conformation as long as strong intramolecular hydrogen bonds are maintained between the phenolic OH subunits. In contrast, anion-free calix[4]pyrroles are generally conformationally flexible and exist predominantly in the 1,3-alternate conformation in the absence of a bound anion. On the other hand, the addition of suitable anionic guests generally serves to lock calix[4]pyrroles into the corresponding cone conformation. Given this disparity in conformational behavior for the two "parent" systems from which it is formally derived, efforts were made to analyze the conformational features of calix **4**. These analyses were carried out primarily in the solid state as detailed below.

Single crystals of **4** suitable for X-ray diffraction analysis were grown by slow diffusion of *n*-hexane into an acetone solution of **4**. The resulting structure, shown in Fig. 2b, reveals that one of the two phenolic OH and one of the pyrrolic NH groups point in one direction, while the other set points in the opposite direction. Calix **4** thus exists in a unique alternate form, and one that differs from what is typically seen for either calixarenes or calix[4]pyrroles in the solid state.

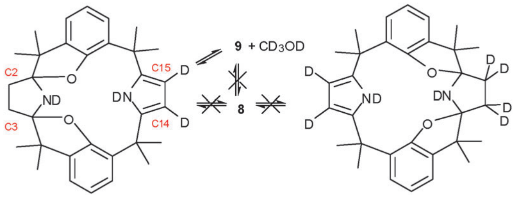

Fig. 1 Summary of deuterium exchange experiments with **9** carried out in CD_2Cl_2/CD_3OD.

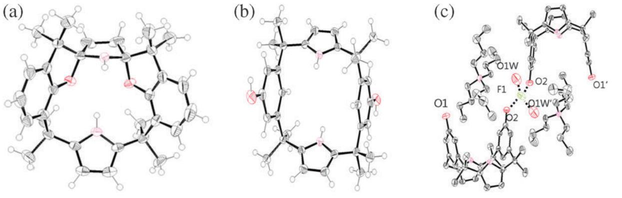

Fig. 2 X-Ray crystal structures. (a) Top view of **9**. (b) Top view of **4**. (c) Cone conformation of **4** stabilized in the presence of F$^-$ anions. Thermal ellipsoids are scaled to the 50% probability level. Most hydrogen atoms and the disordered solvent molecules have been omitted for clarity.

Within the crystal lattice, the calix[2]phenol[2]pyrrole macrocycle acts to create a what can be considered to be a rectangular container wherein the *meso* carbons are separated by distances of 5.081 and 5.101 Å, respectively (*cf.* Fig. 2b). This container-like structure is presumably stabilized by six hydrogen bonds per unit of calix **4**. These hydrogen bonds involve two phenolic oxygen centers and two pyrrole NH protons per calix molecule (*cf.* Fig. S8 and S9, ESI‡). These interactions are thought to underlie the formation of molecular columns in the solid state, as seen in the unit cell packing diagram. They are also responsible, presumably, for the low solubility of this prototypic calix[2]phenol[2]pyrrole observed in solvents of low dielectric constant, such as CH_2Cl_2, $CHCl_3$, and CH_3CN. Unfortunately, this low solubility precluded a detailed analysis of the conformational properties in solution, at least using standard ^{1}H-NMR spectroscopic methods.

The addition of TBAF salts to a heterogeneous suspension of **4** in CH_2Cl_2 results in formation of a clear solution. Diffusion of *n*-hexane into a solution produced in this way afforded single crystals suitable for X-ray diffraction analysis. As can be seen from an inspection of Fig. 2c, calix[2]phenol[2]pyrrole **4** adapts a cone conformation in the solid state in the presence of fluoride anions, a species that is bound in a 2 : 1 (receptor : anion) stoichiometry in the solid state. The bound fluoride ion is hydrogen bonded to two phenolic OH protons arising from two different receptor molecules, as well as by two water molecules (Fig. 2c). In marked contrast to what is seen in the case of calix[4]pyrroles, the NH protons do not participate in hydrogen bond interactions with the fluoride anion and play no obvious role in stabilizing the overall complex or the observed cone conformation.

The bound fluoride ion resides on a crystallographic two-fold rotation axis. Two TBA ions are seen per anion equivalent. These cations are bound within the cavity produced by the association of the two anion-tethered units of **4**. The net result is an apparent charge imbalance at the level of the co-bound anions. This imbalance is accommodated by a negative charge that arises from deprotonation of one of the phenolic OH protons at O1 and O1′.

Phenolic hydrogen bond donors[8] have not been widely used for the construction of synthetic anion receptors due to their susceptibility to deprotonation in the presence of basic anions, such as carboxylic and fluoride anions. On the other hand, phenolic OH motifs are present in the naturally occurring, structurally characterized chloride anion channel.[9] Calix **4** is thus of interest because it contains two phenol OH and two pyrrole NH moieties that could act as hydrogen bonding donors. The number of hydrogen bonding donors is thus the same as present in the calix[4]pyrroles. However, the phenolic OH proton (pK_a *ca.* 10) is more acidic than the pyrrole NH proton (pK_a *ca.* 23 in DMSO), and *a priori* might be considered to be the better anion recognition motif. Moreover, the X-ray diffraction analyses described above revealed no interaction between the pyrrole NH groups and the bound fluoride anion in the solid state. We were thus curious to see if this selectivity in favor of OH hydrogen bond donors over NH donors was maintained in solution. In an effort to probe this issue, preliminary ^{1}H-NMR spectroscopic binding experiments were carried out using the chloride anion (chosen in preference to fluoride due to its lower basicity). These experiments, conducted at room temperature in CD_2Cl_2/DMSO-d_6 (20/1, v/v) using tetrabutylammonium chloride (TBACl) as the chloride anion source, revealed an upfield shift in the pyrrolic NH proton resonance and little change in the pyrrolic CH signal (Fig. S3, ESI‡). In contrast, downfield shifts were observed for the *ortho*-CH proton of the phenolic ring. A broadening of the OH proton signal was also seen as the titration progressed (*cf.* Fig. S3 and S4, ESI‡). Such changes are consistent with the OH, rather than the NH, serving as the primary donor group. The unusual upfield shifts seen for the pyrrolic NH protons can be explained by the fact that in the absence of a bound anion the pyrrolic NH protons are tied up in hydrogen bonds, involving either the phenolic OH protons or the DMSO solvent. These bonds become reduced in strength upon conversion to the cone conformation and concomitant formation of a more protected cavity-like structure.

Finally, it was noted that the dimethyl protons of calix **4** appear as a singlet peak in the absence or presence of TBACl. Such a finding is consistent with the rate of conformational change being fast on the NMR time scale, as is true for calix[4]pyrroles.

The affinity constant for chloride ions ($K_{Cl} = 46 \pm 3\ M^{-1}$) deduced from the above titration is relatively low (Fig. S5, ESI‡). This result is rationalized in terms of the hydrogen bond donors present in **4** not acting in a cooperative fashion, as is typically the case for calix[4]pyrroles. Nevertheless, the fact that anion recognition is achieved serves to underscore the role that OH, rather than NH, hydrogen bond donor groups could have in the design of future anion receptor systems.

In summary, two new hybrid calixarene–calixpyrrole systems have been prepared. These consist of the *bona fide* calix[2]phenol[2]pyrrole **4** and a fused derivative calix **9**. These two macrocyclic products were synthesized from two different isomeric starting materials, namely dimethyl 2-hydroxyisophthalate and 5-hydroxyisophthalate, respectively. The fused calix **9** was fully characterized in solution and in the solid state. Deuterium exchange experiments disclosed that fused calix **9** maintains its structural integrity in solution. The calix **4** was also fully characterized in solution and in the solid state. It was found to act as a weak anion receptor as the result of OH, rather than NH, hydrogen bond donor-anion interactions. The present study has thus demonstrated a possibly general approach to the creation of new hybrid receptor systems. It has also permitted a direct comparison between two ostensibly related hydrogen bond donor motifs (OH *vs.* NH) and has provided evidence that OH hydrogen bonds can be used to support anion recognition in suitably designed receptor systems.

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10 Crystal data for **9** (CCDC 858002): $C_{66}H_{79}N_5O_4$, $M = 1005.61$, orthorhombic, $a = 24.3554(10)$ Å, $b = 11.3368(3)$ Å, $c = 20.2929(4)$ Å, $\alpha = 90.00°$, $\beta = 90.00°$, $\gamma = 90.00°$, $V = 5603.1(3)$ Å^3, $T = 153(2)$ K, space group $Pna2_1$, $Z = 4$, 12 374 reflections measured, 6597 independent reflections ($R_{int} = 0.0527$). The final R_1 values were 0.0519 ($I > 2\sigma(I)$). The final w$R(F^2)$ values were 0.1218 ($I > 2\sigma(I)$). The final R_1 values were 0.0972 (all data). The final w$R(F^2)$ values were 0.1394 (all data). Crystal data for **4** (CCDC 858003): $C_{32}H_{38}N_2O_2$, $M = 482.64$, monoclinic, $a = 7.3075(2)$ Å, $b = 17.5050(4)$ Å, $c = 9.9498(3)$ Å, $\alpha = 90.00°$, $\beta = 91.307(1)°$, $\gamma = 90.00°$, $V = 1272.43(6)$ Å^3, $T = 153(2)$ K, space group $P2_1/n$, $Z = 2$, 5334 reflections measured, 2892 independent reflections ($R_{int} = 0.0184$). The final R_1 values were 0.0417 ($I > 2\sigma(I)$). The final w$R(F^2)$ values were 0.1076 ($I > 2\sigma(I)$). The final R_1 values were 0.0555 (all data). The final w$R(F^2)$ values were 0.1164 (all data). Crystal data for **4**·TBAF (CCDC 858004): $C_{99}H_{155}Cl_6FN_6O_5$, $M = 1740.99$, monoclinic, $a = 29.8044(8)$ Å, $b = 10.3800(5)$ Å, $c = 31.855(2)$ Å, $\alpha = 90.00°$, $\beta = 95.290(2)°$, $\gamma = 90.00°$, $V = 9813.1(8)$ Å^3, $T = 153(2)$ K, space group $I2/a$, $Z = 4$, 18 633 reflections measured, 10 914 independent reflections ($R_{int} = 0.0493$). The final R_1 values were 0.0831 ($I > 2\sigma(I)$). The final w$R(F^2)$ values were 0.2221 ($I > 2\sigma(I)$). The final R_1 values were 0.1623 (all data). The final w$R(F^2)$ values were 0.2553.