Calix[6]pyrrole and Hybrid Calix[*n*]furan[*m*]pyrroles ($n + m = 6$): Syntheses and Host – Guest Chemistry

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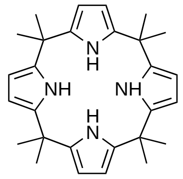
Abstract: Calix[6]pyrrole **2** and the "hybrid systems" calix[3]furan[3]pyrrole **12**, calix[2]furan[4]pyrrole **13**, and calix[1]furan[5]pyrrole **14**, have been synthesized by increasing conversion of the furan units present in the readily accessible calix[6]furan **3** to pyrroles. The host – guest chemistry of these novel macrocycles towards a number of anions, including halogen ions, dihydrogen phosphate, hydrogen sulfate, nitrate, and cyanide has been investigated in solution by ^{1}H NMR titration techniques and/or phase transfer experiments. The solid-state structures of the free receptors **2**, **12**, and **13**, the 1:1 complexes of calix[6]pyrrole **2** with chloride and bromide, and the 1:1 complex of **14** with chloride are also reported.

Keywords: anions · calixarenes · N ligands · structure elucidation

Introduction

The extensive development of the supramolecular chemistry of calixarenes[1] has promoted, over recent years, a growing interest in exploring the synthesis and host – guest chemistry of analogues of these macrocycles in which the benzo rings are replaced by heterocyclic units.[2] In particular, following the discovery by Sessler et al. that calix[4]pyrroles such as **1** are capable of binding a range of anions and neutral molecules,[3] the supramolecular chemistry of this class of macrocycles has become a rapidly expanding field of research. The anion binding properties of calix[4]pyrrole derivatives have been exploited in the development of optical sensors,[4] for the construction of ion selective electrodes,[5] and for applications in chromatographic separation techniques.[3b, 6] However, the extension of these studies to include calixpyrroles containing more than four pyrrole units was severely hampered by the very low yields with which they are formed in the crude mixtures obtained by the acid-promoted condensation of pyrrole and ketones.[7] Moreover, larger calixpyrroles undergo a "molecular mitosis"[8] reaction, even under mild acidic conditions, to form the more thermodynamically stable tetramer, and this in part accounts for the difficulties encountered in their separation. Only recently has a way to overcome this limitation been found[8a] by the direct condensation of 3,4-difluoro-1*H*-pyrrole and acetone under kinetic control to yield the corresponding *β*-fluorinated calix[*n*]pyrroles ($n = 5$, 8). Other routes to the synthesis of large calix[*n*]pyrroles include the assembly of a calix[5]pyrrole onto a calix[5]arene framework, which in turn also acts as a template for the assembly process[9] (though, this bis-macrocycle could not subsequently be separated into its two macrocyclic components), and the synthesis of a calix[6]pyrrole by the use of intermediate 1:2 condensation products of arylketones and pyrrole.[10a] A study on the host – guest chemistry of the latter compound bearing pairs of phenyl groups at the 1,3,5-*meso*-positions has recently been published[10b] subsequent to our preliminary account of some of the results which are now fully described in this paper.[11]



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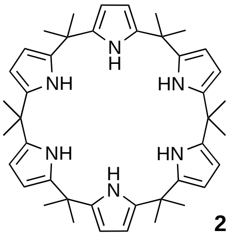

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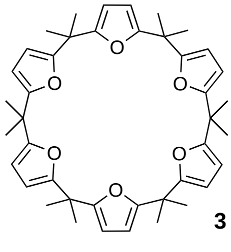

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Calix[4]pyrroles bind anions and neutral molecules by means of multiple hydrogen bonds between the pyrrole NH units of the host and electron-rich binding sites in the guests.

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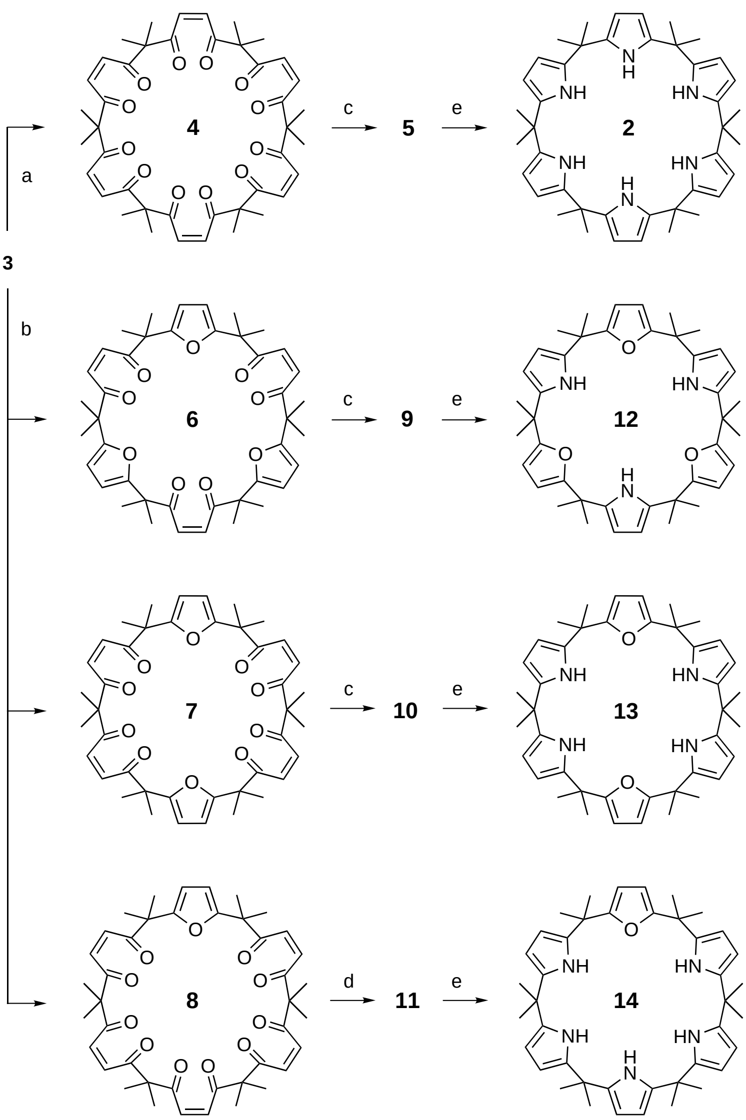
Anions, which are electron-rich species, are therefore ideal guests.[12] Moreover, a prerequisite for the efficient use of the NH units in the binding process is that the macrocycle is able to adopt a conformation in which these can converge towards the guest. However, calix[4]pyrroles are too small to accommodate any anion by inclusion, but they achieve complexation through a perching conformation wherein the NH units are oriented towards the anion which is positioned on one face of the macroring. These features have been clearly demonstrated in the work of Sessler et al. and are also consistent with the results of computational studies.[13] We therefore anticipated that the calix[6]pyrrole **2** would exhibit enhanced anion binding abilities with respect to **1** as it has: 1) the potential to form two more NH hydrogen bonds, and 2) a larger cavity that should be able to accommodate guests such as chloride and bromide by inclusion. Inclusion of guest species may also provide the means for selectivity by size discrimination.[14]

In view of these considerations, we decided to investigate the synthesis of calix[6]pyrrole **2** by conversion of the furan units present in the readily accessible calix[6]furan **3** to pyrroles.[15] Furthermore, it was anticipated that the conversion of only some of the furan units to pyrroles would yield "hybrid" calix[*n*]furan[*m*]pyrroles ($m + n = 6$) which were also likely to exhibit interesting host–guest chemistry (vide infra).[16]

Results and Discussion

Syntheses and X-ray structures of calix[6]pyrrole (2) and calix[*n*]furan[*m*]pyrroles: Our synthetic strategy is based on the use of the furan units as masked 1,4-diketones which can then be subjected to the Pall–Knorr pyrrole synthesis[17] (Scheme 1). Following the procedure described by Le Goff and Williams,[18] calix[6]furan **3** was converted into the corresponding eneketone **4** by oxidative ring-opening of the furan units with *m*-chloroperbenzoic acid (MCPA), and selective reduction of the olefinic double bonds gave the dodecaketone **5**.[19] Treatment of this compound with excess ammonium acetate in refluxing ethanol gave calix[6]pyrrole **2**. The yield of this reaction (42%) is remarkably good considering that the formation of **2** from **5** requires six cyclization steps.

Crystals of **2** suitable for X-ray analysis were obtained from ethanol. The X-ray crystal structure of **2** showed the crystals to be solvated with both water and ethanol; the former is located within the macrocycle cavity whilst the latter is disordered and lies outside. The macrocycle has a distinctly folded tennis-ball seam-like conformation (Figure 1), which is almost certainly derived from the maximization of the possible host–guest interactions. Thus here, contrary to expectations for a spherical anionic species, only three of the six pyrrole NH groups are directed inwards; the remaining three point outwards. Despite this arrangement, the water molecule is involved in no fewer than six host–guest interactions, three N–H···O hydrogen bonds and three O–H···π interactions.[11a] The binding of the water molecule observed here is in accord with that predicted theoretically[20a] and demonstrated experimentally[20b] for the solvation of water by pyrrole.



Scheme 1. The conversion of calix[6]furan **3** to calix[6]pyrrole **2**, calix[3]furan[3]pyrrole **12**, calix[2]furan[4]pyrrole **13**, and calix[1]furan[5]pyrrole **14**. Reaction conditions: a) 6 equiv MCPA, $CHCl_3$; b) 4 equiv MCPA, $CHCl_3$; c) Zn/AcOH; d) H_2, Pd/C; e) $AcONH_4$, EtOH.

The synthesis of "hybrid" calix[*n*]furan[*m*]pyrroles from calix[6]furan **3** can be achieved through its initial treatment with less than six equivalents of MCPA. In principle, the oxidation of three or four furan units could in either case lead to two sets of three isomeric products. These may differ with respect to the relative regiochemistry of the rings affected by the oxidation. However, treatment with four moles of MCPA (Scheme 1) gave the "1,3,5" and the "1,2,4,6" oxidation products **6** (24%) and **7** (52%), respectively, together with a minor amount of the eneketone **8** (14%) containing just one furan ring. No other oxidation products could be isolated from the crude mixture. Whilst the origin of the regioselectivity of these oxidations is not clear, it enhanced the yields and considerably simplified the isolation of the intermediates, which were converted into the corresponding calix[3]furan[3]pyrrole **12**, calix[2]furan[4]pyrrole **13**, and calix[1]furan[5]pyrrole **14**, as described above for calix[6]pyrrole **2**. The

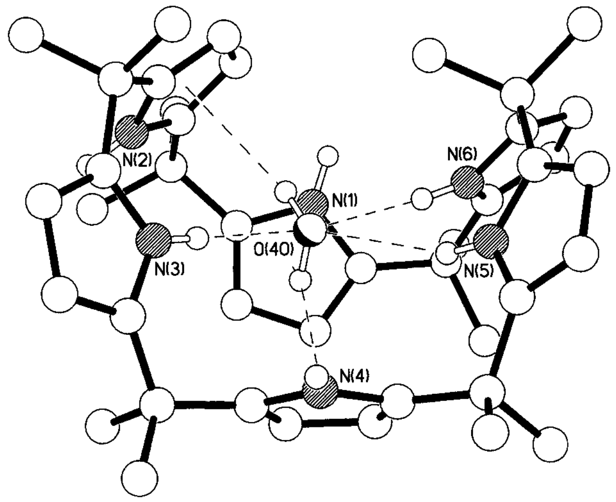


Figure 1. The solid-state structure of **2** showing the tennis-ball seam-like conformation, the encapsulated water molecule, and the host–guest N$-$H$\cdots$O and O$-$H$\cdots\pi$ interactions.

accomplishment of the cyclization reactions producing **12**, **13**, and **14** was immediately evident on the bases of their ^{1}H NMR spectra. These had resonances consistent with time-averaged planar conformations and with consequent D_{3h}, D_{2h}, and C_{2v} symmetries, respectively.

Single crystals of **12** were obtained from EtOH. The X-ray structure, in contrast to **2**, did not contain any bound solvent molecules. However, a similar folded tennis-ball seam-like conformation was still adopted (Figure 2). Here, the central cavity is essentially self-filling though there is a small cleft between the O(1) and O(5) furan rings, which are separated by approximately 5.4 Å. In the crystal, this cleft is partially filled by the edge of the O(1) furan ring of a centrosymmetrically related molecule. The conformation is to some extent stabilized by a pair of intramolecular N$-$H$\cdots$O hydrogen bonds between adjacent pyrrole and furan rings and a weak transannular C$-$H$\cdots\pi$ interaction between one of the isopropylidene methyl groups and the N(2) containing pyrrole ring.

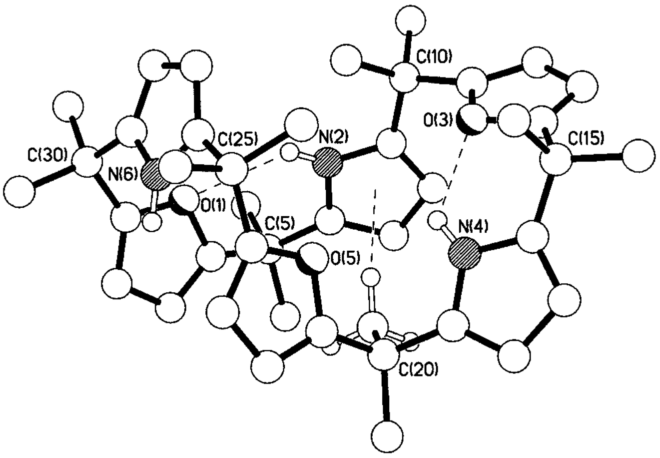


Figure 2. The tennis-ball seam-like geometry adopted by **12** in the solid state showing the intramolecular N$-$H$\cdots$O and C$-$H$\cdots\pi$ stabilizing interactions.

Crystals of **13** were obtained from EtOH. An X-ray analysis indicated that the crystals contained two independent C_i symmetric molecules in the unit cell. Both molecules have virtually identical conformations that differ substantially from those observed for both the complexed (vide infra) and uncomplexed calix[6]pyrrole **2** and from the calix[3]furan[3]-pyrrole **12** analyzed in this study. The molecule has an extended geometry (Figure 3), and a backbone (comprising the six quaternary isopropylidene carbon atoms) that has a pronounced zigzag pattern. In contrast, the six heteroatoms are coplanar to within 0.07 Å. Four of the rings (those containing O(1), N(2), O(1′), and N(2′)) are approximately equally inclined by around 35° to this plane and have their heteroatoms oriented inwards towards the macroring center, whilst the other two (those containing N(3) and N(3′)) are aligned orthogonally. The macrocycles are self-filling, and the central cavity is occupied by the inwardly directed C(15) methyl groups. The conformations are to some extent constrained by the presence of N$-$H$\cdots$O hydrogen bonds between the adjacent O(1) and N(2)—and by symmetry, O(1′) and N(2′)—containing furan and pyrrole rings. The crystals also contain molecules of ethanol in stoichiometric proportions that are linked by N$-$H$\cdots$O hydrogen bonds to the N(3)-containing pyrrole rings. Although the hydroxy hydrogen atoms of the ethanol molecules could not be located, if they are placed in ideal staggered geometries with respect to the carbon backbone, they point directly towards the N(2) pyrrole ring center at a distance of only approximately 2.3 Å. This distance would be consistent with an O$-$H$\cdots\pi$ interaction very similar to that observed between water and **2** (vide supra). There are no other dominant intermolecular interactions worthy of note.

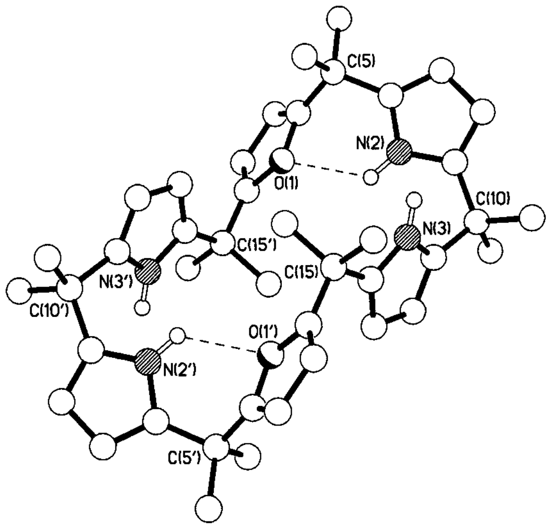


Figure 3. One of the pair of independent C_i symmetric molecules of **13** present in the solid state showing the intramolecular N$-$H$\cdots$O stabilizing interactions, and the filling of the central cavity by the inwardly directed isopropylidene methyl groups.

Unfortunately, all our attempts to grow single crystals of the calix[1]furan[5]pyrrole **14** from a range of different solvents have so far failed (vide infra).

Complexation studies; general remarks: On the bases of the previously reported data on the complexing ability of calix[4]pyrroles,[3c] we chose to screen the binding abilities of the new macrocycles towards halogen anions, dihydrogen phosphate, hydrogen sulfate, nitrate, and cyanide. Nitrate was included because of its symmetry relationship with calix[6]pyrrole **2** and calix[3]furan[3]pyrrole **12** (D_{3h} versus time-averaged D_{6h} and D_{3h}, respectively). Cyanide was included because of its linear shape and favorable length for potentially bridging between the pyrrole NH units in calix[2]furan[4]pyrrole **13**. The formation of complexes in solution was investigated by the analysis of changes in the ^{1}H NMR spectra of the macrocycles upon addition of the different anions[21] as their *n*-tetrabutylammonium salts in CD_2Cl_2 at 21 °C. The presence of trace quantities of water in CD_2Cl_2 was expected to have a substantial effect in lowering the host–guest binding constants (K_as) of the macrocycles under investigation towards the selected anions.[22] As was observed in the X-ray structure of **2**, water has the potential to compete with the anions for binding to the macrocycles. Similarly, it could also compete with the NH units by solvating the anions. However, strictly anhydrous conditions are not only experimentally difficult to achieve and maintain, but also unrealistic, since adventitious water is invariably present in any "real" medium. Thus, the ^{1}H NMR titration experiments described below fall into two categories: 1) those conducted in D_2O-saturated CD_2Cl_2 (0.18 %, v/v) indicated as "wet conditions" in the following discussion, and 2) those determined in CD_2Cl_2 in which the content of water was kept as low as possible, but without the use of special techniques to achieve strictly anhydrous conditions. The K_a values measured under these latter conditions should be regarded as minimum values that can be achieved in truly dry CD_2Cl_2. For the sake of convenience, experiments in "almost dry" CD_2Cl_2 are indicated as "dry conditions" in the following discussion. The K_a values were obtained from the titration data (δ_{obs} for the NH resonances versus anion concentration; for $[\mathbf{14}\cdot Br^-]$, the δ_{obs} used was that of the pyrrole CH resonances vide infra) using the WinEQNMR program.[23] In some cases K_a values were found to be too high to be determined by NMR methods,[21] but they were determined by the Cram extraction method[24, 25] using D_2O/CD_2Cl_2 at 16 °C. The K_a values obtained in this way should be compared only very carefully with those obtained by NMR titration, not only because of the different temperatures at which the two types of determinations were conducted, but also because of the approximations associated with the Cram method. Finally, in several cases (vide infra), the K_a value of the macrocycle under investigation towards a given anion could only be evaluated by competitive binding with another macrocycle with a known K_a for that anion.[26] We used calix[4]pyrrole **1** as the "reference macrocycle" and since the K_a values of **1** for fluoride and chloride in wet CD_2Cl_2 were not available in the literature, these were determined as part of the present study. A summary of the K_a values obtained in this study is given in Table 1.

Table 1. Association constants (K_a, M^{-1}) for the 1:1 complexes of the $n\text{Bu}_4\text{N}^+$ salts of the listed anions and macrocycles.[a]

	1	**2**	**14**	**13**	**12**
F^-	$2.7 \times 10^3 \pm 200$[b]	33 ± 3[e]	–[f]	–[f]	–[h]
		ca. 3.2×10^5[g]		$5.7 \times 10^4 \pm 9 \times 10^3$[g]	
Cl^-	46 ± 8[b]	$1.2 \times 10^4 \pm 10^3$[e]	$5.5 \times 10^3 \pm 600$[e]	65 ± 8[b]	–[h]
Br^-	10[d]	710 ± 25[c]	69 ± 8[c]		–[h]
		57 ± 2[b]		< 10[b]	
I^-	< 10[d]	–[h]	–[h]	–[h]	–[h]
$H_2PO_4^-$	97 ± 4[d]	–[i]	–[h]	–[h]	–[h]
HSO_4^-	< 10[d]	ca. 10[c]	–[h]	–[h]	–[h]
NO_3^-	< 10[d]	16 ± 0.4[c]	< 10[c]	–[h]	–[h]
CN^-	< 10[b]	ca. 10^2[b]	–[i]	< 10^2[b]	–[h]

[a] Where applicable, values obtained for each anion by the same method have been listed on the same line.[b] Measured by NMR titration in D_2O saturated CD_2Cl_2. [c] Measured by NMR titration in "dry" CD_2Cl_2. [d] From ref. [3c], measured by NMR titration in "dry" CD_2Cl_2.[e] Determined with the Cram extraction method. [f] K_a is too high to be determined by NMR titration methods, but the compound is also ineffective as a phase transfer agent between D_2O and CD_2Cl_2; thus, the Cram method cannot be used. [g] Measured by competition experiment using calix[4]pyrrole **1** as competitor. [h] No detectable binding observed in either dry or wet CD_2Cl_2. [i] An interaction is observed, but the NH resonances disappeared upon addition of the salt; thus, the K_a could not be measured.

Complexation studies with calix[6]pyrrole 2: The addition of fluoride or chloride to **2** revealed the formation of strong complexes, which were also kinetically slow on the NMR time-scale. The signals for the NH protons, which resonate at $\delta = 7.68$ ppm in the free host, appeared at $\delta = 10.92$ and 10.91 ppm in the fluoride and chloride complexes, respectively. Moreover, the intensity of the signals for the complexes corresponded (within experimental error) to the amount of salt added. When the CD_2Cl_2 was previously saturated with D_2O, a titration experiment with fluoride gave a qualitative indication of the formation of a kinetically fast complex. In fact, the free host and the complex no longer had distinct sets of resonances. However, the peak due to the NH protons disappeared when approximately 0.5 equivalents of salt had been added. In the case of chloride, the presence of water had only barely visible effects: the *meso*-methyl groups that appeared as two clearly distinct singlets in dry CD_2Cl_2, were now almost coalesced to a single resonance. As a result, the determination of the association constants K_a by the ^{1}H NMR titration method[21] was not possible and they were therefore determined by the Cram extraction method.[24] The K_a values found for fluoride and chloride were 33 ± 3 and $12800 \pm$

$1300\,\text{M}^{-1}$, respectively. This K_a value for fluoride is surprisingly low, but we believe this result to be of only marginal significance. Indeed this determination is likely to have been considerably more affected by the high hydration energy[27] of this anion compared to that of the others screened, and by the limitations of the extraction method. In fact, a competitive binding experiment[26] with a 1:1 mixture of **1** and **2** in wet CD_2Cl_2 indicates (^1H NMR data) that K_a $[\mathbf{2}\cdot F^-]$ is approximately 120 times greater than K_a $[\mathbf{1}\cdot F^-]$.

The addition of bromide to **2** in dry CD_2Cl_2 revealed complexation-induced shifts (CISs) consistent with a kinetically fast process, and the titration data gave a K_a value of $710 \pm 25\,\text{M}^{-1}$ using the WinEQNMR program.[23] The titration data in wet conditions gave a K_a value of $57 \pm 2\,\text{M}^{-1}$.

No significant interaction could be detected between **2** and iodide either by ^1H NMR, or by extraction experiments.

Upon addition of dihydrogen phosphate in either dry or wet CD_2Cl_2 or CD_3CN, the NH resonances "disappeared". This behavior prevented the collection of titration data. However, we rule out any significant interaction, because the modest CIS normally observed for the β-pyrrole protons upon formation of the complexes with the other anions are absent here. Moreover, **2** was ineffective as a phase-transfer agent for dihydrogen phosphate.

Hydrogen sulfate and nitrate were found to bind weakly in dry CD_2Cl_2 ($K_a < 10\,\text{M}^{-1}$ and $16 \pm 0.4\,\text{M}^{-1}$, respectively).

The addition of cyanide produced distinctive CIS for the NH resonances in both dry and wet CD_2Cl_2. However, upon addition of larger amounts of salt, one additional resonance for the NH protons became visible at $\delta = 10.91$. As more salt was added, one NH resonance moved further downfield and gradually decreasing in intensity, and that at $\delta = 10.91$ increased accordingly (Figure 4). We believe that this behavior is due to the presence of chloride and fluoride as contaminants in the (commercial) sample of n-tetrabutylammonium cyanide; this presence was also confirmed by chromatographic analyses. Thus, in the initial stages of the titration the behavior is characterized by the complexation of cyanide, but as the stoichiometric proportion of salt is increased (and consequently that of the contaminants), the higher binding ability of **2** towards chloride and fluoride is responsible for the displacement of cyanide from the $[\mathbf{2}\cdot CN^-]$ complex and for the predominant formation of more stable $[\mathbf{2}\cdot X^-]$ complexes. Unfortunately, we could not obtain a purer sample of the cyanide salt, nor establish with sufficient accuracy the exact amount of each of the contaminants. By a number of crude approximations ($K_a[\mathbf{2}\cdot X^-] \gg K_a[\mathbf{2}\cdot CN^-]$, approximately 10% X^- as contaminant) we estimate that **2** binds cyanide with a K_a of a few hundred M^{-1} in wet CD_2Cl_2 and approaches one thousand M^{-1} in "dry" conditions. We exclude the possibility of an equilibrium between two different complexes of cyanide with **2** because the spectral changes described above were reproduced and magnified using a cyanide solution to which an additional 10% of chloride salt had been added.

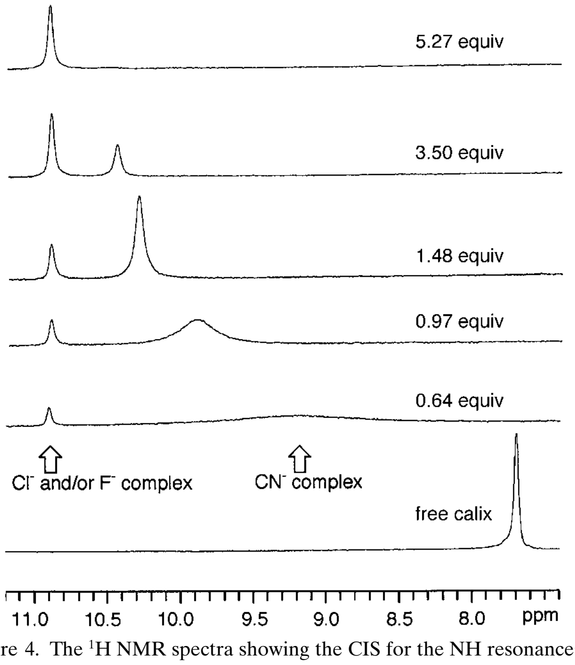


Figure 4. The ^1H NMR spectra showing the CIS for the NH resonances of calix[6]pyrrole **2** upon addition of the indicated amounts $nBuN_4CN$ containing also $nBuN_4Cl$ and $nBuN_4F$ (ca. 10% overall). The spectra are recorded in dry CD_2Cl_2 at concentrations of **2** in the range $3-5 \times 10^{-3}\,\text{M}$.

To date, crystalline inclusion complexes of calix[6]pyrrole **2** with the screened anions have only been obtained with chloride and bromide as their n-tetrabutylammonium salts. The X-ray analyses of the 1:1 complexes[11b] indicate that the two structures are isomorphous (Figure 5). The host macrocycle is seen to have undergone a substantial conformational change from that observed for the 1:1 complex with water.[11a] Here, the complex adopts approximate D_{3d} symmetry with all six NH groups directed inwards towards the centrally bound halide anion. The hydrogen bonding geometries for the chloride complex are very similar to those observed[3c] in the smaller tetrapyrrole analogue **1**. A noticeable and significant difference between the two complexes is the degree of displacement of the anion out of the plane of the six nitrogen atoms, and the associated departures from D_{3d} symmetry in the host. In $[\mathbf{2}\cdot Cl^-]$, the chloride ion lies approximately 0.37 Å out of the plane of the six heteroatoms, whereas for the

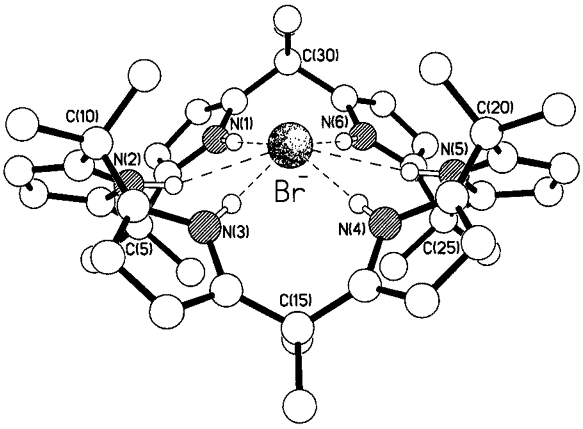


Figure 5. Ball-and-stick representation of the solid-state structure of $[\mathbf{2}\cdot Br^-]$ showing the N–H$\cdots$Br hydrogen bonding and the elevation of the bromide ion out of the plane of the six pyrrole nitrogen atoms.

bromide this displacement is 0.69 Å. These changes in the anion positions are accompanied by associated folding of "upper" and "lower" isopropylidene groups towards and away from the molecular C_3 axis, respectively. In [**2** $\cdot$ Cl$^-$], the mean C$\cdots$C separations between the inwardly directed methyl groups of the "upper" and "lower" set of isopropylidene groups are 5.25 and 4.40 Å, respectively, whilst in [**2** $\cdot$ Br$^-$] these distances are 5.62 and 4.31 Å, respectively. We conjecture that our failure to complex iodide may be due to the fact that to achieve analogous linear N–H$\cdots$I hydrogen bonding would place too great a strain on the ring conformation and cause steric overcrowding of the "lower" inwardly-directed isopropylidene methyl groups.[28] The differences in the two solid-state structures are consistent with the ability of **2** to discriminate between the two halogen anions (chloride and bromide) by size. The anions, cations, and solvent molecules are all well separated in both structures, and there are no significant intermolecular interactions.

Complexation studies with calix[3]furan[3]pyrrole 12: The addition of any of the selected anions did not cause any visible change in the ^{1}H NMR spectrum of this macrocycle in either dry or wet CD_2Cl_2. This compound was also found to be ineffective as a phase transfer agent between D_2O and CD_2Cl_2 for any of the selected anions.

Complexation studies with calix[2]furan[4]pyrrole 13: The ^{1}H NMR titration experiments of calix[2]furan[4]pyrrole **13** with fluoride in dry CD_2Cl_2 did not yield a K_a value because the complexation is both kinetically slow and too strong to be evaluated by this technique. Changes in the NMR spectrum included the presence of a novel doublet at $\delta = 12.87$ ppm for the NH protons of the complex which are coupled to the fluoride ($J_{F,H} = 29.2$ Hz) and which normally resonate as a singlet at $\delta = 7.70$ ppm in the free macrocycle.[29] The ABX systems due to the β-pyrrole protons in the complex undergo a small but significant upfield CISs (average $\Delta\delta = 0.22$ ppm); the furan protons appear unaffected. These spectral changes are consistent with the complexation of fluoride by inclusion and with a passive role being adopted by the furan rings, which appear to act just as spacers.

In a competitive binding experiment using a 1:1 mixture of **1** and **13** (10^{-2} M of each in wet CD_2Cl_2), the K_a for [**13** $\cdot$ F$^-$] was found to be 21.2 ± 1.8 times larger that for [**1** $\cdot$ F$^-$], that is, $5.7 \times 10^4 \pm 9 \times 10^3$ M^{-1}.

The addition of chloride to calix[2]furan[4]pyrrole **13** in dry CD_2Cl_2 caused the NH resonance to "disappear". In the course of the titration, the pyrrole β-protons undergo changes leading to overlapping signals and finally in the presence of one equivalent of chloride, the aromatic resonances appear similar to those described above for the fluoride complex. However, in wet conditions, the aromatic resonances appeared sufficiently resolved to allow the use of titration data to obtain a K_a of 65 ± 8 M^{-1}.

Attempts to determine the K_a values for the complexation of fluoride and chloride by the extraction method were fruitless because calix[2]furan[4]pyrrole was not effective as a phase transfer agent for these anions. Moreover, the ^{1}H NMR spectrum of **13** in wet CD_2Cl_2 had small but significant downfield shifts for the NH and the furan CH resonances ($\Delta\delta = 0.28$ and 0.06 ppm, respectively) compared to those under dry conditions. This observation suggests that water is effectively competing with the anions in the binding process, although no conclusive evidence was found for the water being bound by inclusion.

The ^{1}H NMR titration with bromide (dry CD_2Cl_2) shows modest CIS for the NH signal, from which a $K_a < 10$ M^{-1} was estimated.

No CISs were observed (dry CD_2Cl_2) after the addition of dihydrogen phosphate, hydrogen sulfate, and nitrate. Moreover, none of these salts were extracted from D_2O in CD_2Cl_2 by **13**.

The CISs produced by the addition of cyanide (wet CD_2Cl_2) indicate a substantial binding of this anion. The K_a could not be determined due to the same type of interferences described for calix[6]pyrrole **2**, and which are even greater here because the K_a of **13** for cyanide can be seen (qualitatively) to be lower than that of **2**.

Complexation studies with calix[1]furan[5]pyrrole 14: The addition of fluoride in dry CD_2Cl_2 caused dramatic changes in the ^{1}H NMR spectrum of **14**, which were consistent with strong binding (too high to be determined by ^{1}H NMR methods) and slow kinetic behavior. The changes can be best appreciated for the NH and aromatic protons (Figure 6), because the methyl resonances partly overlap with those of the *n*-butylammonium cation. The NH resonances are all shifted to low field in the complex, with a "crossover" of their δ values by which the "unique" NH proton appears at $\delta = 12.67$, a value that is lower than those ($\delta = 12.47$ and 10.86,

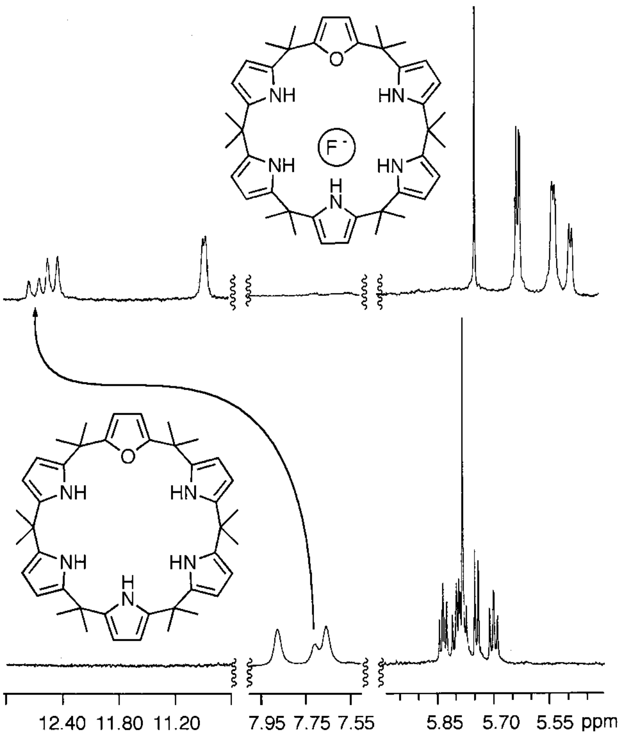


Figure 6. The ^{1}H NMR spectra of **14** and of its fluoride complex showing the significant CISs.

respectively) owing to the other pairs of NH protons. All of these resonances have a coupling with fluoride. The larger the $\Delta\delta$ experienced by the NH resonances, the larger the coupling ($J_{F,H} = 38$, 36, and 10 Hz for the "unique" and for the two pairs of NH protons, respectively). These observations are consistent with the fluoride occupying a time-averaged position which does not coincide with the center of the macrocycle but is displaced towards the "unique" pyrrole unit. The aromatic protons are all shifted upfield in the complex. These CISs were similarly observed in wet CD_2Cl_2.

Considering the rather meaningless figure obtained for the K_a value of [**2**$\cdot F^-$] by the Cram method, this measurement was not attempted for [**14**$\cdot F^-$]. Moreover, an evaluation of the K_a by competition experiments with either **1** or **2** was prevented by the overlapping and broadening of the NH resonances of **14** in the course of the titration.

The K_a value with chloride could not be measured by ^{1}H NMR titration because it was too large and the complexation was kinetically slow in both dry and wet CD_2Cl_2. The aromatic resonances appeared very similar to those observed for the fluoride complex, but the NH protons resonate within a considerably narrower range and partially overlap to give two signals (at $\delta = 11.52$ and 11.58 in dry/wet CD_2Cl_2). The Cram extraction method gave a K_a value of $5.5 \times 10^3 \pm 600\,\mathrm{M}^{-1}$.

Bromide was found to form a weak complex for which a K_a of $69 \pm 8\,\mathrm{M}^{-1}$ was measured by NMR titration in dry CD_2Cl_2.

We could obtain no evidence for the binding of iodide, dihydrogen phosphate, or hydrogen sulfate. However, a weak binding (below $10\,\mathrm{M}^{-1}$) with nitrate could be measured in dry CD_2Cl_2.

The addition of cyanide caused a broadening of the NH resonances preventing an estimate of the K_a value.

After a number of fruitless attempts to obtain single crystals of the chloride complex of **14** using the *n*-tetrabutylammonium salt, we decided to test the possibility of growing crystals using KCl and [18]crown-6. Thus, by using sonication we extracted a solid sample of KCl with an equimolar solution of the two macrocycles in CH_2Cl_2. After filtration, the solvent was removed and the residue was redissolved in CH_3CN. Slow evaporation of solvent gave single crystals of a "salt". The X-ray structure (Figure 7) shows that the crystals are the adduct formed between calix[1]furan[5]pyrrole, [18]crown-6 and potassium chloride. The chloride and potassium ions are positioned on independent inversion centers, the former sited centrally within the calix[1]furan[5]pyrrole macrocycle and the latter complexed within the [18]crown-6 moiety. The calix[1]furan[5]pyrrole adopts a conformation essentially identical to that of the 1:1 complex between calix[6]pyrrole and chloride (vide supra). The location of the furan ring within the macrocycle is not resolved, and is therefore randomized uniformly throughout the crystal about all six possible positions. The N/O$\cdots$Cl distances range between 3.225(2) and 3.291(2) Å; essentially the same values as those seen for the calix[6]pyrrole complex. However, here the chloride anion lies within the plane of the six heteroatoms (which are coplanar to within 0.009 Å), whereas with **2**, a pseudo perching geometry is observed with the chloride lying 0.37 Å "above" the heteroatom plane. Also here the mean separations of both the "upper" and "lower" isopropylidene carbon atoms are the same at about 4.80 Å. The potassium [18]crown-6 unit has conventional[30] D_{3d} symmetry with K$\cdots$O distances in the range 2.752(2)–2.802(2) Å with the potassium atom lying 0.17 Å out of the planes of the upper and lower triads of ether oxygen atoms. The potassium and chloride ions are remote from each other in the structure with a minimum inter-atomic separation of 7.80 Å. There are no significant interactions between the two complexes, although in this unusual[31] salt the KCl must clearly have acted as an initial template for the formation of this cocrystal containing the two different macrocyclic species. This result is of particular interest in light of the aforementioned failure to obtain suitable crystals of the calix[1]furan[5]pyrrole component by itself.

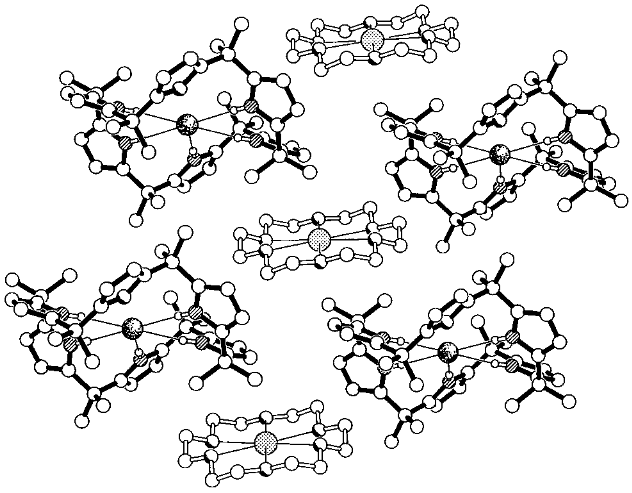


Figure 7. Crystal packing of the "supramolecular salt" [**14**$\cdot Cl^-$][[18]crown-6$\cdot K^+$]. Although the position of the furan ring within the macrocycle could not be determined, since they are randomly distributed among the six possible sites in **14**, it has been assigned a specific location for illustrative purposes. Acetonitrile solvent molecules are not shown for the sake of clarity.

Conclusion

A comparison of the data obtained for the binding of the macrocycles **2**, **14**, **13**, and **12** with the screened anions must take into account that not all of the K_a values were determined under identical conditions nor by the same method. However, some key features emerge.

All of these compounds exhibit a wide range of selectivities towards the screened anions as demonstrated by the different values of the K_as for a given macrocycle. For each halogen anion, the K_as increase with the number of NH units present in the macrocycle. In the case of **12**, it appears that just three widely spaced NH pyrrole units are not sufficient to provide interactions that are large enough to achieve a detectable complexation.[32]

The larger K_a value obtained for **13** with fluoride with respect to that of **1** is an indication of the favorable effect of a larger cavity size while the number of pyrrole units is kept constant. The corresponding data for chloride also appear to be similarly influenced, although less substantially. We also note that **13** exhibits considerably greater selectivity between fluoride and chloride than **1**.

However, the lack of binding observed for **13** towards iodide, dihydrogen phosphate, and hydrogen sulfate, compared to the complexations observed with **1**, indicates that cavity size and the number of NH units are not the only factors that come into play, especially in the case of nonspherical anions. This is also confirmed by the negligible differences in the K_a values of **1** and **2** for hydrogen sulfate and nitrate. It is also interesting to note that cyanide interacts very weakly (if at all) with **1** but significantly with **2** and **13** (with decreasing strengths respectively).

The data presented here provide clues for the use of pyrrole units as components of two- and three-dimensional scaffolds for the construction of anion receptors. The study of complexation processes of the calixpyrroles and "hybrid" calixfuranpyrrole reported here but involving other anionic and neutral species is in progress.

Experimental Section

General methods and instrumentation: All chemicals were standard reagent grade and were used without further purification. All air-sensitive and/or moisture sensitive reactions were conducted under a dry argon atmosphere. Thin layer chromatography (TLC) was conducted on Merck SiO_2 $60F_{254}$ plastic plates. Compounds were visualized with iodine, vanilin, or by examination under UV light. Column chromatography was conducted on Aldrich silica gel 230–400 mesh, 60 Å. ^1H and ^{13}C NMR spectra were recorded on Varian Gemini-300 at 300 and 75 MHz respectively using the residual proton resonances of the solvents ($CDCl_3$, CD_3CN, and CD_2Cl_2) as reference. Electron impact (EI) and positive fast atom bombardment (FAB, *m*-nitrobenzyl alcohol as matrix) mass spectra were measured on a Finnigan Mat 90 spectrometer operated by Dr. Marcello Saitta. ESI-MS and MALDI-TOF mass spectra were acquired on a ESI-Mariner (Applyed Biosistem) and a Voyager SRT equipped with reflectron from PerSeptive Biosystem, Framingham MA, fitted with a pulsed nitrogen laser (337 nm) with a 3 ns pulse duration using 2,4,6-trihydroxyacetophenone (THAP) matrix by Dr. Domenico Garozzo at Catania University. Melting points were determined on a Kofler hot stage apparatus, and are not corrected.

^{1}H NMR titrations: The *n*-tetrabutylammonium salts were dried in a vacuum oven for at least 24 h. For measurements in "dry" CD_2Cl_2 this was stored on dry alumina and care was taken to minimize exposure to the atmosphere during sample preparation and titrations. Wet CD_2Cl_2 was obtained by vigorous stirring with D_2O for 1 h at 20 °C, and the two phases were then carefully separated. The content of D_2O in CD_2Cl_2 was measured by saturating a sample with H_2O as described for D_2O, and measuring the H_2O content by ^1H NMR integration using 1,4-dioxane as an internal standard. The concentration of water in CD_2Cl_2 was found to be 0.18% (v/v). The anions were added (by syringe) as carefully measured volumes of solutions (ca. 0.1 M) in either dry or wet CD_2Cl_2 to solutions of the macrocycles under investigation (0.01 or 0.005 M) in the same solvent. After each addition, the stoichiometric ratios between the salt and macrocycle were also re-determined from the intensities of the resonances of the methyl and aromatic protons of the hosts versus those of the *n*-tetrabutylammonium cation. Quantitative ^1H NMR integration were obtained by the use of appropriate pulse delays in all cases.[33] Processing the data with the WinEQNMR[23] program, which accounts for the dilutions, produced the reported K_a values for the 1:1 complexation model. Relative values of K_a in competitive binding experiments were determined by treatment of 1:1 solutions of the two different macrocycles with variable quantities of salt (0.2–0.6 equivalents) and using the method described by Whitlock.[26]

Extraction experiments: Equal volumes of solutions containing the salt and the macrocycles in water and CD_2Cl_2 respectively were stirred vigorously at 16 °C for 1 h. After careful separation of the two phases, the amount of anion transferred in CD_2Cl_2 was determined by ^1H NMR from the relative intensities of the resonances of the macrocycle and those of the *n*-tetrabutylammonium cation, which has to follow the anion into the organic phase. The amount of anion subtracted from the D_2O phase was similarly indirectly evaluated against a known amount of dioxane added after the separation of the two phases. Potential interference by the hydroxo ions was ruled out by tests in which the pH was altered in the range 7–11 by the addition of NaOH to the water phase.

The syntheses and experimental data for compounds **4** and **5**,[18] **2**, **6**, **7**, **9**, **10**, **12**, **13**, and partial data for **8** have been reported.[11a]

Decaeneketone 8: ^{13}C NMR ($CDCl_3$): $\delta = 20.0$, 21.2, 22.8 (CH_3), 48.1, 60.5, 60.7 ($C(CH_3)_2$), 107.1 (furan CH), 133.1, 134.2, 135.0, 136.1, 137.3 (olefin), 156.7 (furan C*q*), 200.1, 201.2, 201.6, 201.7, 202.4 (CO); positive ESI-MS ($CHCl_3$/MeOH 2:1): *m/z*: 729 [M^++1].

Decaketone 11: Palladium on charcoal (10% Pd, 10 mg) was added to a solution of **8** (100 mg, 0.13 mmol) in ethyl acetate (20 mL). The mixture was stirred under a hydrogen atmosphere at room pressure and temperature for 4 h, then filtered and concentrated to give **11** (over 96%) of sufficient purity for use in the synthesis of **14**. Thus **11** was not subjected to further purification procedures: ^1H NMR ($CDCl_3$): $\delta = 1.35$, 1.41 (2 s, 12 H and 24 H; 2 CH_3), 2.44–2.80 (m, 20 H; CH_2), 6.15 (s, 2 H; furan); ^{13}C NMR ($CDCl_3$): $\delta = 21.4$, 21.5, 21.3 (CH_3), 31.7, 31.9, 32.1, 32.2, 32.3 (CH_2), 48.5 (next to furan $C(CH_3)_2$), 61.7, 61.8 ($C(CH_3)_2$), 106.5 (furan CH), 157.4 (furan C*q*), 207.9, 208.0, 208.3, 208.4, 209.9 (CO); positive ESI-MS ($CHCl_3$/MeOH 2:1): *m/z*: 739 [M^++1].

Calix[1]furan[5]pyrrole 14: The decaketone **11** (1.00 g, 1.35 mmol) and ammonium acetate (0.78 g, 10.15 mmol) were heated at reflux for 40 h in anhydrous EtOH. The mixture was concentrated and extracted with CH_2Cl_2/water. The organic phase was dried ($MgSO_4$), concentrated, and the brown oil was subjected to column chromatography over silica (hexanes/EtOAc 9:1) to give **14** (137 mg, 15.7% yield). M.p. 172 °C (light petroleum); ^1H NMR ($CDCl_3$): $\delta = 1.52$, 1.55, 1.56 (3 s, 3 × 12 H; CH_3), 5.77, 5.92 (2 t, 2 × 2 H; pairs of β-CH in one pair "equivalent" pyrrole units), 5.80 (d, 2 H; β-CH for the "unique" pyrrole ring), 5.83 (s, 2 H; furan), 5.85 (2 overlapping t, 4 H; β-CH in one pair "equivalent" pyrrole units), 7.79, 8.10 (2 s, 2 × 2 H; NH for the two pairs of "nonequivalent" pyrrole ring), 7.88 (s, 1 H; NH for the "unique" pyrrole ring); ^1H NMR (CD_2Cl_2): $\delta = 1.46$, 1.48, 1.53 (3 s, 3 × 12 H; CH_3), 5.70, 5.83 (2 t, 2 × 2 H; pairs of β-CH in one pair "equivalent" pyrrole units), 5.74 (d, 2 H; β-CH for the "unique" pyrrole ring), 5.78 (s, 2 H; furan), 5.80 (2 overlapping t, 4 H; β-CH in one pair "equivalent" pyrrole units), 7.65, 7.87 (2 s, 2 × 2 H; NH for the two pairs of "nonequivalent" pyrrole ring), 7.70 (s, 1 H, NH for the "unique" pyrrole ring); ^{13}C NMR ($CDCl_3$): $\delta = 27.8$, 29.2, 29.3 (CH_3), 35.3, 35.5, 36.2 ($C(CH_3)_2$), 102.8, 103.0, 103,1, 103.2, 103.4, 104.0 (CH), 137.4, 138, 138.2, 138.5, 138.6 (pyrrole C*q*), 159.8 (furan C*q*); MALDI-TOF (THAP): *m/z*: 666 [M+Na]$^+$.

Crystal data for calix[2]furan[4]pyrrole 13: $C_{42}H_{52}N_4O_2 \cdot 2\,EtOH$, $M_r = 737.0$, triclinic, $P\bar{1}$ (no. 2), $a = 9.087(1)$, $b = 10.476(1)$, $c = 25.715(2)$ Å, $\alpha = 88.11(1)$, $\beta = 89.13(1)$, $\gamma = 64.75(1)°$, $V = 2212.8(3)$ Å^3, $Z = 2$ (two crystallographically independent C_i symmetric molecules), $\rho_{calcd} = 1.106\ g\,cm^{-3}$, $\mu(Cu_{K\alpha}) = 5.50\ cm^{-1}$, $T = 293$ K, colorless plates, 6571 independent measured reflections (F^2 refinement, $R_1 = 0.079$, $wR_2 = 0.189$, 4744 independent observed reflections ($|F_o| > 4\sigma|F_o|$, $2\theta \leq 120°$), 531 parameters. CCDC-180963 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336033; or deposit@ccdc.cam.uk).

crystal data for [Calix[1]furan[5]pyrrole · Cl$^-$][18C6 · K$^+$]: $[C_{42}H_{53}N_5OCl]$-$[C_{12}H_{24}O_6K] \cdot 2\,MeCN$, $M_r = 1064.9$, triclinic, $P\bar{1}$ (no. 2), $a = 9.131(1)$, $b = 13.190(2)$, $c = 14.220(1)$ Å, $\alpha = 63.81(1)$, $\beta = 88.44(1)$, $\gamma = 76.05(1)°$, $V = 1485.4(3)$ Å^3, $Z = 1$ (C_i symmetry), $\rho_{calcd} = 1.190\ g\,cm^{-3}$, $\mu(Cu_{K\alpha}) = 16.3\ cm^{-1}$, $T = 183$ K, colorless platy needles, 4216 independent measured reflections, F^2 refinement, $R_1 = 0.049$, $wR_2 = 0.128$, 3639 independent observed absorption corrected reflections ($|F_o| > 4\sigma|F_o|$, $2\theta \leq 120°$), 351 parameters. The position of the furan ring within the calix[1]furan[5]-pyrrole macrocycle is indeterminate, and was established by occupancy refinement to be uniformly distributed amongst the six possible sites within the macrocycle throughout the crystal. CCDC-180964 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44)1223-336033; or deposit@ccdc.cam.uk).

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