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FEATURE ARTICLE

Calixpyrroles

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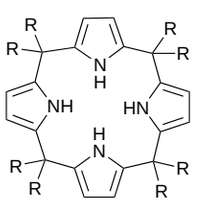
The calix[4]pyrroles are a class of old but new heterocalixarene analogues that show interesting anion and neutral substrate binding properties. Calix[4]pyrroles are easy to make and functionalize. As such, they have been employed in the production of separation media for anionic and neutral species. Calixpyrroles also provide useful precursors for the generation of novel calixpyridinopyrroles and calixpyridines.

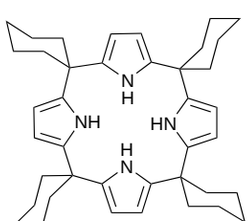
Introduction

This short review article covers the chemistry of systems that resemble calixarenes but are not calixarenes. Specifically, it discusses the synthesis and properties of calixpyrroles and other heterocyclic calixarene analogues. This story starts with Baeyer's publication of his paper on the condensation of pyrrole and acetone[1] which appeared in 1886, some fourteen years after he initiated his first studies of phenol–formaldehyde condensation chemistry.[2]

Although he did not appreciate it at the time, the white crystalline product Baeyer obtained by mixing pyrrole, acetone and hydrochloric acid was an octamethyl substituted form of porphyrinogen **1**. Porphyrinogens are naturally occurring



1 R = Me
3 R = Et



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colourless macrocycles consisting of four pyrrole rings linked through the α (*i.e.* pyrrolic 2 and 5) or *meso*-like positions by sp^3 hybridized carbon atoms. The chemistry of porphyrinogens containing hydrogen atoms in the *meso*-position is well known as these species readily oxidize to form aromatic porphyrins. However, fully *meso*-substituted porphyrinogens have attracted much less attention, precisely because they do not constitute useful porphyrin precursors. Nonetheless, for reasons outlined in a recent communication,[3] we felt that these materials might be interesting. Specifically, we felt this class of macrocycle was perhaps mis-named and might better be referred to as calix[4]pyrroles. This renaming, which is supported by structural studies (*vide infra*), helps establish an obvious analogy to the calixarenes. It also led us to consider that this class of cyclic tetrapyrroles might display interesting anion binding characteristics. Thus, this exercise in nomenclature provided us with an incentive to begin studying further this venerable set of macrocycles.

As implied above, the chemistry of calix[4]pyrroles goes way back. Indeed, subsequent to the work of Baeyer, Dennstedt and Zimmermann also studied this reaction, using 'chlorzink' as the acid catalyst.[4–6] Thirty years later, during the First World War, Chelintzev and Tronov repeated these reactions and proposed (correctly) a cyclic tetrameric structure for a calix[4]pyrrole.[7] These same authors carried out several other reactions. These included an acid catalysed condensation of pyrrole with methyl ethyl ketone, which yielded a small quantity of a single calix[4]pyrrole configurational isomer. Additionally, methyl ethyl ketone and acetone were co-condensed with pyrrole forming a mixed *meso*-hexamethyldiethylcalix[4]pyrrole of unknown structure.[8] In the 1950s, Rothemund and Gage used methanesulfonic acid as the acid catalyst and obtained improved yields.[9] In the early 1970s, Brown *et al.* reported a refined procedure that permitted them to obtain tetraspirocyclohexylcalix[4]pyrrole **2**,[10] a compound that had previously been reported by Chelintzev, Tronov and Karmanov in 1916,[11] in decent yield. Calixpyrroles with functionalizable groups in the *meso*-positions (chloroalkyl or cyano) were also reported recently by Lehn and co-workers in a book chapter.[12–14] In work that is of a very different character, the transition metal coordination chemistry of deprotonated *meso*-octaalkylcalix[4]pyrroles, particularly *meso*-octaethylcalixpyrrole **3**, has been extensively studied by Floriani and co-workers. This chemistry has recently been highlighted in a Feature Article appearing in this journal.[15] It is, therefore, omitted from this review.

Structural studies

Several crystal structures of calix[4]pyrrole macrocycles (Fig. 1) have been elucidated. Taken in concert, these reveal that the macrocycle adopts a 1,3-alternate conformation in the solid state (*i.e.* adjacent pyrrole moieties are oriented in opposite directions).[3,16] Interestingly, in contradistinction to what is true for calix[4]arenes, in calix[4]pyrroles there is no possibility for the formation of a hydrogen bonded array between the various pyrrolic NH groups. Thus, in the absence of an added substrate there is no propensity for the free macrocycles to adopt the cone conformation, a motif so prevalent in calix[4]arene chemistry.

Anion binding properties

On a track that is very different from that of Floriani (see above), our group in Austin has focused on studying the anion binding properties of the calix[4]pyrroles. Our interest in this line of study, abetted by our renaming process (*vide supra*), came about as the result of our previous work with sapphyrins. Sapphyrin, a pentapyrrolic expanded porphyrin first synthesized by Woodward,[17] is an excellent receptor for anions (particularly fluoride) when diprotonated.[18] Knowing this, we were keen to test whether *neutral* non-aromatic polypyrrolic macrocycles, such as the calix[4]pyrroles, could also serve as anion binding agents.

The solution binding properties of **1** and **2** were studied using ^{1}H NMR titration techniques. Stability constants were then determined using the EQNMR least-squares fitting procedure.[19] The findings, summarized in Table 1, revealed that compounds **1** and **2** are not only effective 1 : 1 anion binding agents in solution, they are also selective. Specifically, they show a marked preference for F^- over other putative anionic guests (*viz.* Cl^-, Br^-, I^-, $H_2PO_4^-$ and HSO_4^-).

X-Ray crystal analyses of the Bu_4NCl complex of calixpyrrole **1** and the Bu_4NF complex of **2** revealed that in both cases the calix[4]pyrrole ligand adopts a cone-like conformation in the solid state such that the four NH protons can hydrogen bond to the halide anion (Fig. 2). While these two structures are similar, in the case of the chloride complex [Fig. 2(*a*)] the nitrogen-to-anion distances are in the range of 3.264(7)–3.331(7) Å, while for the corresponding fluoride complex they are 2.790(2) Å [Fig. 2(*b*)] (the four pyrrole groups are equivalent by symmetry). As a result, in these two complexes the chloride and fluoride anions reside 2.319(3) and 1.499(3) Å above the N_4 root mean square planes of calixpyrroles **1** and **2**, respectively. Thus, the fluoride anion appears to be more tightly bound, at least in the solid state.

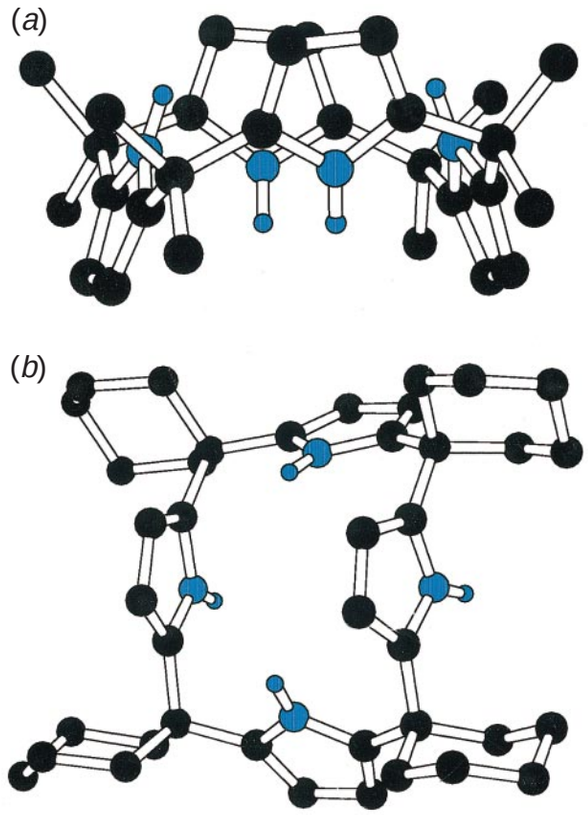


Fig. 1 X-Ray crystal structure of (*a*) **1** and (*b*) **2**·CH_2Cl_2. In (*b*) the solvent is omitted for clarity. Nitrogen and pyrrolic hydrogen atoms are blue. This figure was generated using data originally published in ref. 3.

Table 1 Stability constants for compounds **1** and **2** with anionic substrates[a] in CD_2Cl_2 at 298 K. For further details, see ref. 3

	Stability constant/M^{-1}	
Anion	**1**	**2**
Fluoride[b,c]	17 170 (± 900)	3600 (± 395))
Chloride	350 (± 5.5)	117 (± 4.0)
Bromide	10 (± 0.5)	[d]
Iodide	< 10	[d]
Dihydrogen phosphate[e]	97 (± 3.9)	< 10
Hydrogen sulfate	< 10	[d]

[a] Anions were added as 0.1 M CD_2Cl_2 solutions of their Bu_4N^+ salts to 10 mM solutions of the receptor in CD_2Cl_2, with concentration changes being accounted for by EQNMR. In determining the stability constants, the possible effects of ion pairing (if any) were ignored. [b] Bu_4NF was added as the trihydrate. [c] A repeat titration with compound **1** at 1.0 mM concentration gave concordant results. [d] Not determined. [e] A repeat titration with compound **1** at 100 mM concentration gave concordant results.

In an effort to study the conformational properties of the calix[4]pyrroles in solution, variable temperature ^{1}H NMR studies were carried out on a CD_2Cl_2 solution of **1** in the absence and presence of fluoride anions. In the presence of 3 equiv. of Bu_4NF, the *meso*-methyl resonance splits into two separate signals as the temperature is lowered. By contrast, in the absence of fluoride anions, there is no significant change in the ^{1}H NMR spectrum of compound **1**. The splitting seen in the presence of F^- may be due to the calixpyrrole adopting a cone conformation in solution when bound to this, and presumably other anions. Certainly, such a model is consistent with experiment. This is because it leads to the prediction that in the presence of F^- at low temperature the *meso*-methyl groups will be arranged in either axial or equatorial positions and thus resonating at different frequencies, as is indeed observed.

Surprisingly, the pyrrole NH resonance was also found to split into two peaks as the temperature was lowered in the presence of fluoride (Fig. 3). It was considered that a likely cause for this engendered splitting might be coupling between the NH protons and the ^{19}F nucleus of the bound fluoride anion. To test this supposition, a ^{19}F NMR spectrum of the fluoride complex was acquired at 193 K. The bound fluoride nucleus was found to resonate as a quintet (with a coupling constant of 39.5 Hz), confirming the proposed coupling effect (Fig. 3).

Binding of neutral substrates

In work that was designed to complement the above, it was found that the molecular recognition chemistry of the calix[4]pyrroles is not limited to anionic substrates. Indeed, the coordination of neutral species was explicitly achieved using *meso*-octamethylcalix[4]pyrrole **1**. In this instance, ^{1}H NMR titration experiments in C_6D_6 and subsequent analysis of the titration curves using the EQNMR computer program,[19] revealed that this calix[4]pyrrole forms complexes with neutral species, including short chain alcohols, amides and other oxygen-containing neutral species. Although the binding constants are modest, a clear trend is evident in both the alcohol and

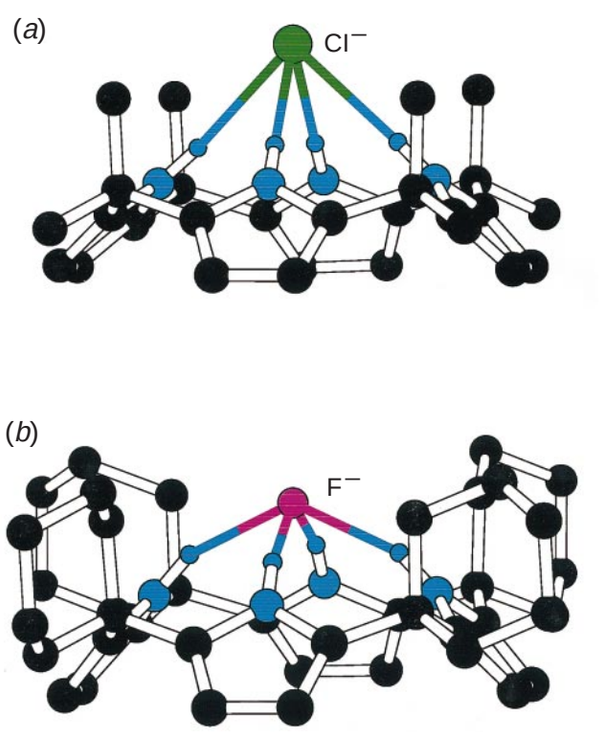


Fig. 2 X-Ray crystal structure of (*a*) the chloride complex of compound **1** and (*b*) the fluoride complex of compound **2**. Nitrogen and pyrrolic hydrogen atoms are blue, chloride is green and fluoride is magenta. This figure was generated using data originally published in ref. 3.

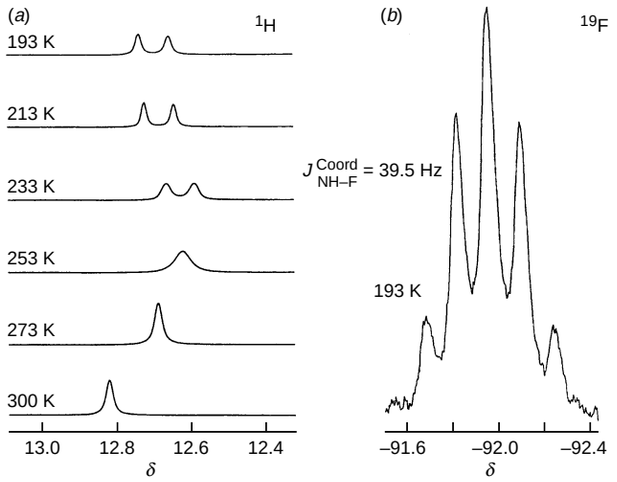


Fig. 3 (*a*) The NH resonance of **1**·F$^-$ splits as the temperature is lowered to 193 K (*b*), indicating coupling to the bound fluoride anion

amide series. Specifically, it was found that the relevant stability constants decrease as the steric bulk around the oxygen atom is increased (Table 2).[20]

The structure of **1** coordinated to two molecules of MeOH was determined by X-ray diffraction analysis. In contrast to the crystal structures of the anion-bound forms of **1** and **2** (discussed above), the calixpyrrole in this neutral substrate complex adopts a 1,3-alternate conformation in the solid state [Fig. 4(*a*)]. The two MeOH molecules are each coordinated to the calixpyrrole *via* two sets of hydrogen bonds involving the pyrrolic moieties [the $N_{pyrrole}$-O_{MeOH} distances are 3.155(4) Å].

The single crystal X-ray structure of the DMF complex of **1** was also solved. As in the bis(methanol) adduct, each of the two DMF molecules was found to be coordinated to a single calix[4]pyrrole macrocycle *via* two hydrogen bonds. However, in the case of the DMF complex the calix[4]pyrrole adopts a 1,2-alternate conformation, wherein each DMF molecule is coordinated to adjacent pyrrole moieties [$N_{pyrrole}$–O_{DMF} = 2.908(2) and 2.924(2) Å]. Each of the DMF molecules lies *ca.* 3.4 Å over the plane of one of the pyrrole rings to which it is not hydrogen bonded. This finding led us to suggest that π–π interactions help stabilize the 1,2-alternate conformation of this particular calix[4]pyrrole-neutral substrate complex [Fig. 4(*b*)].[20]

Table 2 Association constants for **1** with neutral substrates. [a] For further details, see ref. 20

Substrate added	K_a M^{-1}
MeOH	12.7 ± 1.0
EtOH	10.7 ± 0.7
BnOH	9.7 ± 0.7
Pr^{i}OH	7.0 ± 0.4
Bu^{s}OH	6.2 ± 0.4
N-Formylglycine ethyl ester	13.3 ± 1.0
DMF	11.3 ± 0.8
N,*N*-Dimethylacetamide	9.0 ± 0.9
1,1,3,3-Tetramethylurea	2.2 ± 0.1
DMSO	16.2 ± 1.1
1,2-Dimethylimidazole	5.4 ± 0.3
Acetone	2.2 ± 0.2
Nitromethane[b]	—

[a] In C_6D_6 at 298 K. For each titration, the concentration of **1** was held constant (at *ca.* 4 10^{-3} M) as aliquots of the substrate in C_6D_6 (*ca.* 1 M) were added. [b] In this instance, the induced shifts in the NH proton(s) of **1** were too small (< 0.15 ppm) to afford a reliable K_a value.

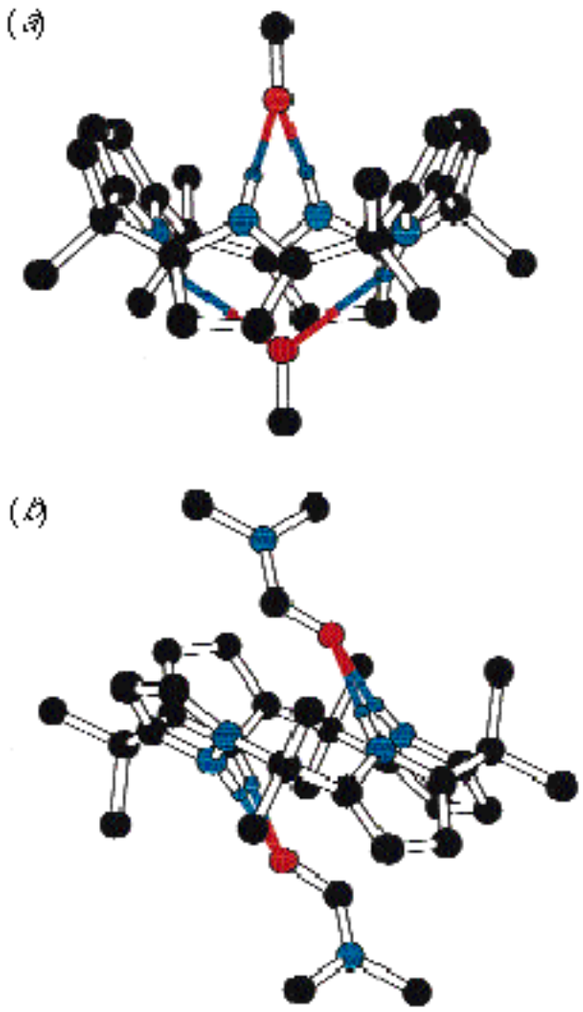
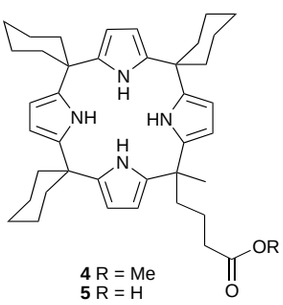


Fig. 4 X-Ray crystal structure of (*a*) **1**·2(MeOH) and (*b*) **1**·2(DMF). Nitrogen and pyrrolic hydrogen atoms are blue and oxygen is red. This figure was generated using data originally published in ref. 20.

Functionalized systems

The introduction of a 'tailed' butanoate group to a calix[4]pyrrole produces an anionic calixpyrrole with interesting self-assembly properties.[21] The requisite '*meso*-hook' calix[4]pyrrole monoester **4** was synthesized by co-condensing methyl 4-acetylbutyrate, cyclohexanone and pyrrole. After column chromatography, the monoester was isolated from a mixture of calixpyrroles containing different numbers of ester functional groups in 12% yield. Subsequent hydrolysis of **4** yielded the monoacid **5**.

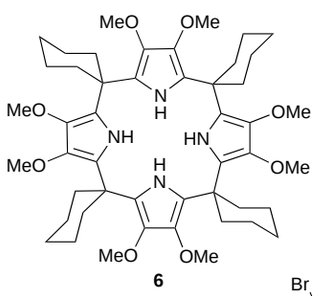


X-Ray quality crystals of the calixpyrrole carboxylate **5** were obtained by slow evaporation of a CH_2Cl_2 solution of **5** in the

presence of excess $Bu_4NF{\cdot}xH_2O$. Interestingly, the crystals did not contain any fluoride anions within the lattice. Rather, this latter was found to be comprised entirely of the tetrabutylammonium calix[4]pyrrole carboxylate salt. The structure of the salt revealed that the calixpyrrole carboxylate self-assembles in the solid state. Specifically, the carboxylate functionality of one calixpyrrole was found to be bound to the pyrrolic array of an adjacent calixpyrrole and *vice versa*. The net result of these interactions is a dimeric cyclic structure as indicated in Fig. 5. In this instance, the calix[4]pyrrole adopts a cone conformation with four hydrogen bonds from the calixpyrrole pyrrole groups serving, as implied above, to bind the carboxylate 'tail' of a second functionalized calixpyrrole unit.[21]

A ROESY NMR spectrum of the trimethylammonium salt of **5** in CD_2Cl_2 provided evidence for aggregation in solution. Two resonances were observed between δ 7.0 and 7.5 corresponding to non-complexed pyrrole NH protons. Another resonance was observed at approximately δ 11. This was assigned to bound pyrrole NH protons, in exchange with the unbound NH resonances. As such, this datum point provides evidence in favour of aggregate formation in solution. The dimer could also be observed using FAB MS techniques.[21] In any event, to the best of our knowledge, this self-assembling calix[4]pyrrole system (**5**) represents the first and only example wherein purely anionic sub-units are seen to self-assemble.

In addition to the above, we have recently described the synthesis of several novel calix[4]pyrrole molecules containing functional groups appended to the carbon- or *C*-rim of the calix[4]pyrrole 'bowl'. Two strategies were pursued in the synthesis of these materials. The first involved a direct condensation approach. Using such a strategy the β-octamethoxy-*meso*-tetraspirocyclohexylcalix[4]pyrrole **6** was prepared *via* the condensation of 3,4-dimethoxypyrrole and cyclohexanone in glacial acetic acid. The resulting calixpyrrole was then isolated in 8% yield after column chromatography.[22]



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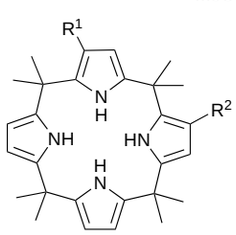
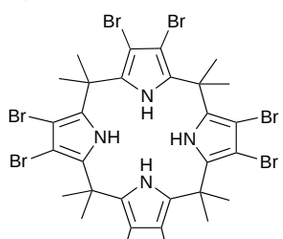


7 $R^1 = CH_2CO_2Et$, $R^2 = H$ (26%)
8 $R^1 = R^2 = CH_2CO_2Et$ (3%)



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The second strategy involved modifying the *C*-rim of a presynthesized calix[4]pyrrole. In this case, *meso*-octamethylcalix[4]pyrrole was dissolved in dry THF and cooled to −78 °C. A solution of *n*-butyllithium in hexanes (4.0 equiv.) was added dropwise to the calixpyrrole solution followed by 4.0 equiv. of ethyl bromoacetate. Purification by column chromatography afforded two isolatable products, a *C*-rim monoester **7** (formed in 26% yield) and a diester **8** (3% yield). Surprisingly ^1H and ^{13}C NMR experiments showed that the diester **8** present in the fraction collected was a single isomer, with the ester groups

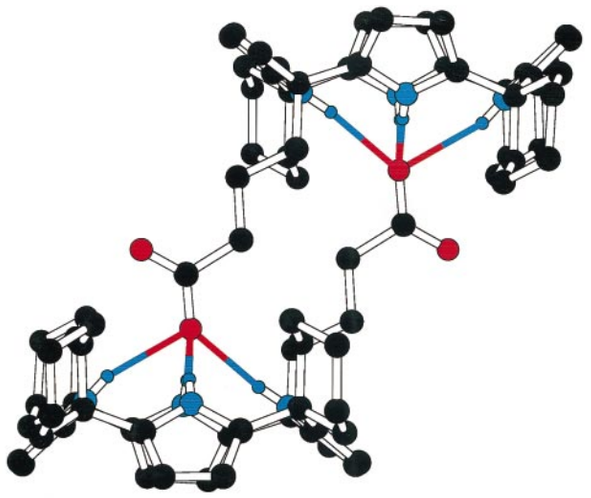


Fig. 5 X-Ray crystal structure of the calix[4]pyrrole carboxylate dimer (**5·5** − $2H^+$). Nitrogen and pyrrolic hydrogen atoms are blue and oxygen is red. This figure was generated using data originally published in ref. 21.

attached to the calixpyrrole in the 2 and 7 positions, as judged from single crystal X-ray diffraction and NMR analyses.[22]

In chemistry somewhat related to the above, β-octabromo-*meso*-octamethylcalix[4]pyrrole **9** was synthesized in 90% yield by reacting *meso*-octamethylcalix[4]pyrrole with *N*-bromosuccinimide in dry THF at reflux. In this instance, an X-ray structure (Fig. 6) revealed the calixpyrrole macrocycle **9** exists in a chair-like flattened 1,2-alternate conformation in the solid state (*i.e.*, the dihedral angles between pyrrole rings and plane through the calixpyrrole *meso*-carbon atoms are 66.8°, 5.8, −66.8 and −5.8°, respectively).[22]

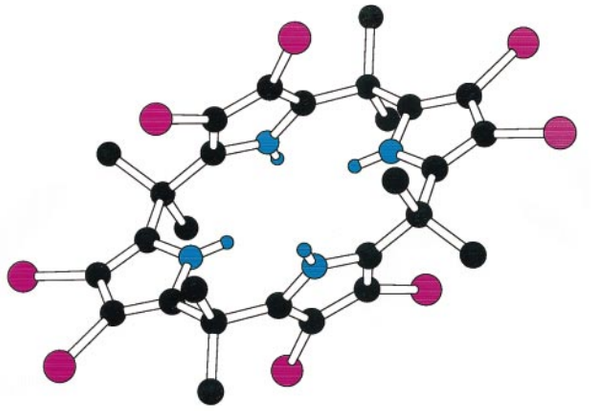


Fig. 6 X-Ray crystal structure of compound **9**. Nitrogen and pyrrolic hydrogen atoms are blue and bromine is magenta. This figure was generated using data originally published in ref. 22.

The solution anion binding properties of the β-octamethoxy derivative **6** and the β-octabromo derivative **9** have been studied in CD_2Cl_2 using ^1H NMR titration techniques (Table 3).[22] Compound **6** displays lower stability constants than the corresponding 'β-free' analogue **2**, presumably due to the electron-donating effects of the methoxy groups (this decreases the acidity of the pyrrole NH protons and therefore lowers the stabilty of the calixpyrrole–anion complex formed). By contrast, compound **9** displays higher stability constants with anions than its 'β-free' control (compound **1**) as a result, presumably, of the electron-withdrawing effect of the bromine substituents.[22]

Higher order systems

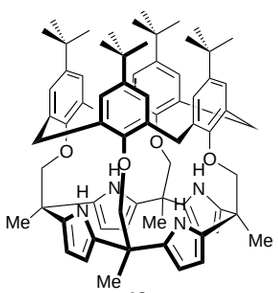
While currently the chemistry of calix[4]pyrroles is fairly well worked out, that of higher order systems (*i.e.* calix[*n*]pyrroles

Table 3 Stability constants for compounds **6** and **9** with anionic substrates[a] in CD_2Cl_2 at 298 K. For further details, see ref. 22

	Stability constants/M^{-1}	
Anion added	**6**	**9**
Fluoride	$1.7 (\pm 0.2) \times 10^2$	$2.7 (\pm 0.4) \times 10^4$[b]
Chloride	< 10	$4.3 (\pm 0.6) \times 10^3$
Dihydrogen phosphate	*c*	$6.5 (\pm 0.4) \times 10^2$

[a] Anions were added as 0.3 M CD_2Cl_2 solutions of their Bu_4N^+ salts to 3 mM solutions of the receptor in CD_2Cl_2 with concentration changes being accounted for by EQNMR. In determining the stability constants, the possible effects of ion pairing (if any) were ignored. [b] Estimated value. The NH proton resonance broadened considerably during the titration, forcing the frequency of the resonance to be noted manually. This value should therefore, be treated with caution. [c] Not determined.

with $n > 4$) is still essentially unexplored. While such species may be identified as by-products in condensations leading to the generation of calix[4]pyrroles, they have yet to be isolated cleanly.[3] Recently it occurred to us that a *p-tert*-butylcalix[*n*]arene could be used as a template around which a calix[*n*]pyrrole could form. Such a strategy could prove useful in the synthesis of higher order calix[*n*]pyrroles (*i.e.* those where $n > 4$). As a first step towards this approach, *p-tert*-butylcalix[4]arene tetramethyl ketone[23] was condensed with pyrrole in the presence of methanesulfonic acid. This afforded the cylindrical calix[4]arene-calix[4]pyrrole pseudo-dimer **10** in 32% yield.[24]



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The X-ray structure of **10** was solved. It revealed, as expected, that the calixarene adopts a cone conformation. Further, two of the pyrrole NH groups were seen to form hydrogen bonds to the phenolic oxygen atoms at the lower rim of the calixarene (Fig. 7).

The hydrogen bonding between the pyrrole NH groups and phenolic oxygen atoms is maintained in solution, as evidenced by ^{1}H NMR spectroscopic studies.[24] Here, it was found, for instance, that the pyrrole NH protons resonate at δ 11.22. This is consistent with the proposal that they are deshielded as a result of their participation in the suggested hydrogen bonding interactions. Addition of polar solvents such as CD_3OD or anions such as fluoride does not disrupt the hydrogen bonding array. This latter finding thus supports the notion that the molecule adopts a cylindrical conformation in solution.

When *p-tert*-butylcalix[5]arene pentamethyl ketone[25] was condensed with 5 equiv. of pyrrole in the presence of $BF_3{\cdot}OEt_2$, a calix[5]pyrrole-calix[5]arene pseudo-dimer **11** was formed in 10% yield.[26] Compound **11** is, to the best of our knowledge, the first example of an expanded calixpyrrole. The intramolecular hydrogen bonding array in compound **11** appears to be weaker than that of the tetramer. For example, the NH protons resonate at δ 9.88 in the pentamer, and addition of CD_3OD or chloride anions cause shifts in the NH protons.

The use of other templates, such as cyclodextrins, using the same strategy, may lead to the synthesis of new expanded calixpyrroles and porphyrins. This approach is currently being pursued in the authors' laboratory.

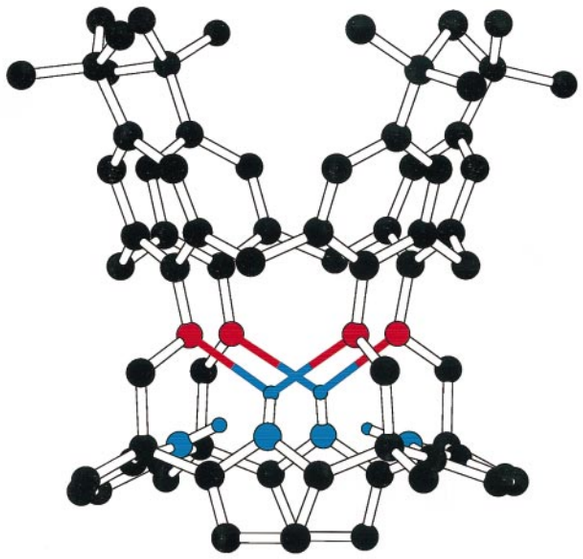
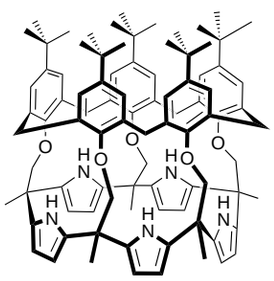


Fig. 7 X-Ray crystal structure of compound **10** showing intramolecular pyrrole NH–phenolic oxygen hydrogen bonding: N(2)···O(1) 2.701(6), N(2)···O(2) 2.739(6) Å. Nitrogen and pyrrolic hydrogen atoms are blue and oxygen is red. This figure was generated using data originally published in ref. 24.



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Towards possible commercial applications

The fact that calixpyrroles are easy to make has led us to consider that products based on the calixpyrrole technology could be commercially viable. With a view towards testing this hypothesis, we decided to investigate whether calixpyrrole-based solid supports could be used to separate oligonucleotides and other polyanionic substrates. Thus in work that is still ongoing, we have recently attached carboxylic acid functionalized calix[4]pyrroles to aminopropyl silica gel *via* both the *meso*- and β-positions. As determined from HPLC studies,[27] the resulting media allow for the ready separation of mixtures of (i) AMP, ADP, and ATP, (ii) aromatic carboxylates, and (iii) oligonucleotides of varying chain length (Fig. 8) under isochratic conditions. These same media also permit the HPLC-based separation of mixtures of neutral species such as polyfluorobiphenyls.

The synthesis of pyridine-containing macrocycles calixpyrroles as synthetic precursors

While pyridine-containing macrocycles are among the most versatile and important of all those known, in the heterocalixarene analogue area pyridine remains a minor player. Indeed, until the authors' recent contributions,[28] calix[4]pyridine was actually unknown. However a decade ago (1987), Newkome *et al.* did report the synthesis of several interesting calixpyridine analogues including compound **12**.[29]

In work that is of a very different nature, Floriani has succeeded in producing calix[1]pyridino[3]pyrroles and calix[2]pyridino[2]pyrroles. This was done by carrying out an

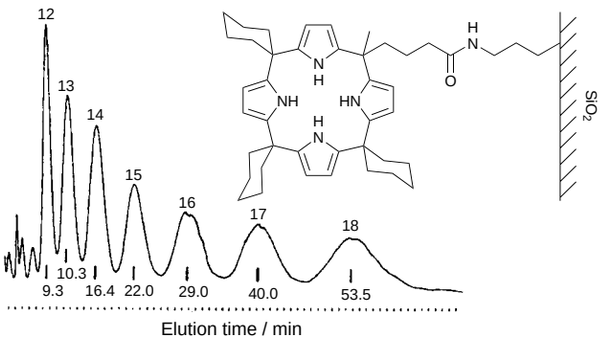
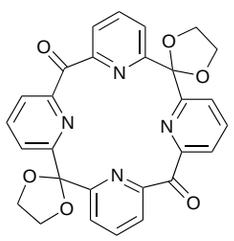


Fig. 8 Separation of $dT_{12–18}$ on calixpyrrole modified silica gel column. Flow rate 0.4 ml min^{-1}, mobile phase MeCN–[aq. NaCl (250 мм) + aq. Na_3PO_4 (50 мм)], 1 : 1 (v/v) (isochratic), pH = 7.0, column temperature 25 °C, UV detection at 265 nm.



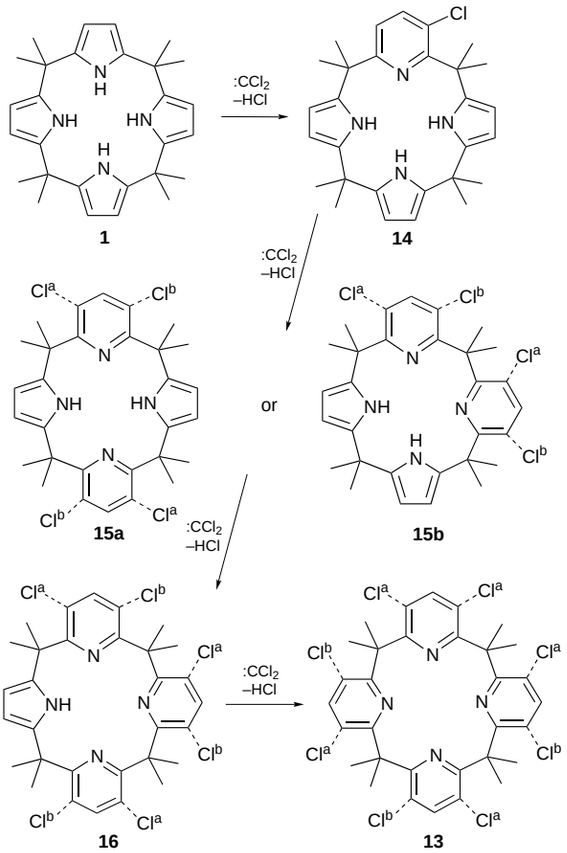
12

homologation of the pyrrole rings effected by reacting the zirconium complex of deprotonated *meso*-octaethylcalix[4]pyrrole with CO.[30]

Recently the present authors have discovered a very versatile and easy entry into the chemistry of calixpyridines. It is predicated on the use of calixpyrroles and dichlorocarbene and, as illustrated in Scheme 1, provides ready access to the previously unknown calix[3]pyridino[1]pyrrole and calix[4]pyridine families.

Our initial synthetic efforts were based on attempts to condense substituted pyridine *N*-oxides in a manner analogous to *p-tert*-butylphenol in calixarene synthesis.[31–33] However, using this approach none of the desired products could be isolated from the reaction mixtures. Our attention then turned on finding a way that would allow us to convert calix[4]pyrroles (*e.g.* **1**) into calix[4]pyridines. Here, we were inspired by the fact that the reaction of dichlorocarbene with pyrrole, imidazole or indole rings will lead to an insertion of the $:CCl_2$ unit (generated *inter alia* by heating sodium trichloroacetate under neutral conditions) into one of the double bonds.[34] In the case of pyrroles, subsequent elimination of HCl and rearrangement produces a 3-chloropyridine ring. We therefore decided to apply this methodology to calix[4]pyrrole and investigate whether a tetrachloro calix[4]pyridine derivative might not be obtainable in this way.

The conversion of *meso*-octamethylcalix[4]pyrrole **1** into tetrachloro-*meso*-octamethylcalix[4]pyridine **13** was attempted in several different solvents using a range of reaction times as well as different (excess) concentrations of sodium trichloroacetate. Using 1,4-dioxane as the solvent, and 15 equiv. of sodium trichloroacetate, a 2.4 : 1 mixture of the mono- and dipyridine macrocycles (**14** and **15**) was formed. Interestingly, when the same reaction conditions were employed using 1,2-dimethoxyethane as the solvent, a mixture of di- (**15**), tri- (**16**) and tetra-pyridine (**13**) species was obtained in a 1 : 1 : 1 ratio. The latter conditions, therefore, allowed us to obtain chlorinated derivatives of two previously unknown heterocalixarene analogues, namely, calix[3]pyridino[1]pyrrole (**16**) and calix[4]pyridine (**13**). Improved yields of the latter products could be obtained by adding separate batches of the dichlorocarbene precursor. In fact, using this approach the



Scheme 1

reaction process could be made to favour, as desired, the formation of either **15** and **16**, or just **13**. The calix[2]pyridino[2]pyrrole, calix[3]pyridino[1]pyrrole, and calix[4]pyridine products prepared in this way can be easily separated by column chromatography (silica gel, CH_2Cl_2–hexane eluent). Thus, it has proved possible, depending on the choice of conditions, to obtain **15**, **16** and **13** in optimized yields of 65, 42 and 26%, respectively. The NMR spectra of the crude products obtained from the above reactions are complicated due to the presence of isomers. This is reflected in Scheme 1 wherein each pyridine ring is bound to either Cl^a or Cl^b (not to both).

The X-ray crystal structure of **15** [Fig. 9(*a*)] reveals that there are two crystallographically distinct molecules in the unit cell. Both adopt the cone conformation in the solid state. The pyrrolic NH groups are oriented near the pyridine nitrogen atoms such that potential NH···N hydrogen bonds may be formed. These hydrogen bonds may influence the conformational properties of the macrocycle.

The X-ray crystal structure of **16** has also been elucidated [Fig. 9(*b*) and (*c*)]. As in the case of **15**, there are two molecules of **16** per asymmetric unit. However unlike **15**, where the two molecules were found to be conformationally equivalent, the two molecules of **16** assume strikingly different conformations. In Fig. 9(*b*), the molecular conformation is similar to that found in compound **13** (see below) wherein alternate rings are either parallel or nearly perpendicular. In this case, the pyrrole NH group is not hydrogen-bonded to any of the pyridine nitrogen atoms. The other molecule [Fig. 9(*c*)] in the asymmetric unit displays a dramatically different conformation.

Finally, in work that is still very recent,[28] the single crystal X-ray structure of the calix[4]pyridine **13** was solved. This structure revealed that the molecule adopts a flattened partial cone conformation in the solid state [Fig. 9(*d*)]. As importantly, by virtue of simply being solved, this structure served to confirm the existence of **13**. As such, it provides a critical proof

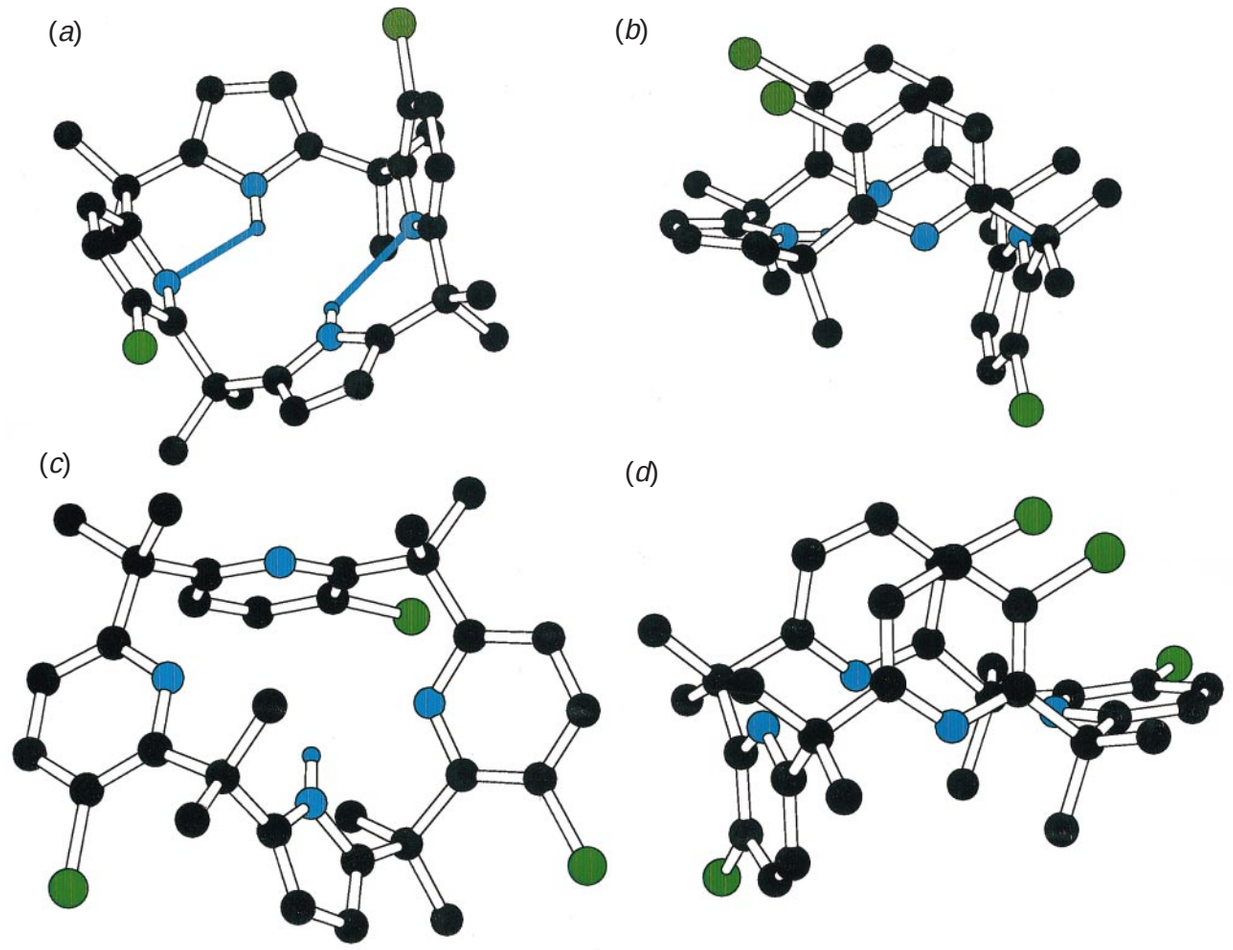


Fig. 9 X-Ray crystal structures of (*a*) bis(chloro)calix[2]pyridino[2]pyrrole **15**, (*b*) and (*c*) tri(chloro)calix[3]pyridino[1]pyrrole **16** in two conformations and (*d*) tetra(chloro)calix[4]pyridine **13**. Nitrogen and pyrrolic hydrogen atoms are blue and chlorine is green.

that calix[4]pyridines can be made and that they are potentially well-organized in the solid state.

Conclusion

The goal of this review has been to summarize the current state of calixpyrrole chemistry and, by implication, highlight the similarities and differences that exist with regard to normal calixarene chemistry. One feature that is particularly noteworthy is the fact that the calixpyrroles act as such effective receptors for neutral and anionic substrates. This finding leads us to suggest that related systems, such as the calixindoles,[35,36] might be worth studying in this regard. Indeed we think the chemistry of heterocalixarenes in general is one that is likely to be blessed with a rich supramolecular future.

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