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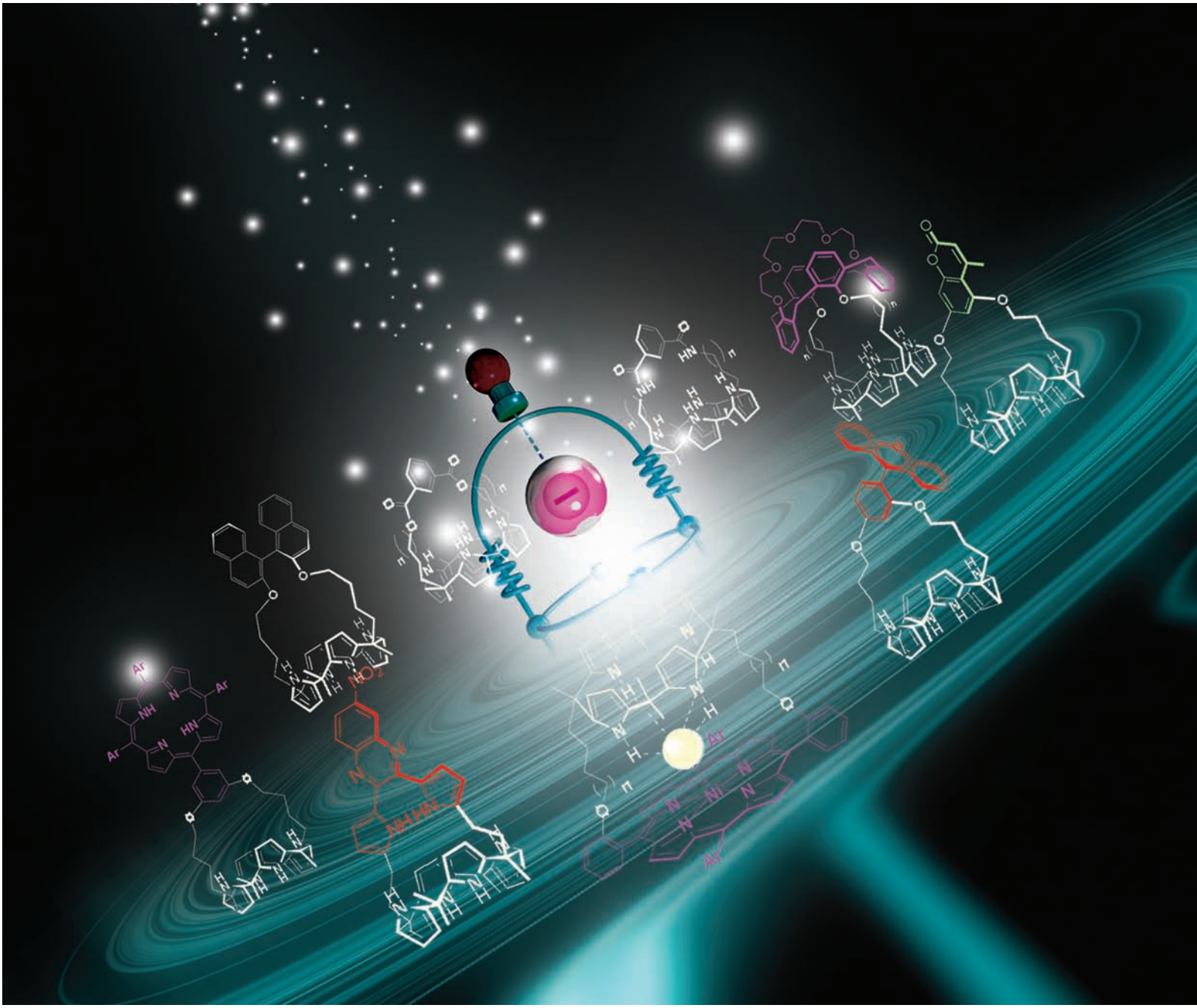

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Trichlorogallium and trialkylgalliums in organic synthesis

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# Strapped and other topographically nonplanar calixpyrrole analogues. Improved anion receptors

**Chang-Hee Lee,*[a] Hidekazu Miyaji,[a] Dae-Wi Yoon[a] and Jonathan L. Sessler*[b]**

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Calixpyrroles and related macrocycles are non-aromatic synthetic anion receptors that have attracted considerable attention in recent years. The unfunctionalized, parent calix[4]pyrrole system, also known as octamethylporphyrinogen, may be prepared in one step and in high yield from pyrrole and acetone, and is an effective anion receptor, showing a preference for fluoride, phosphate, carboxylate and chloride anions in organic media. Efforts to improve the anion binding affinity of calix[4]pyrrole and to modify its inherent selectivity have led to the synthesis of a variety of new, modified calixpyrroles. Among the most effective of these are derivatives that contain bridging ''straps''. In this *Feature Article*, the preparation and properties of these and other topographically nonplanar calixpyrrole analogues are reviewed from the perspective of the anion recognition chemist.

Synthetic receptors capable of effecting the selective binding and recognition of anionic substrates are of interest due to the importance of such species in areas as diverse as nuclear waste remediation, environmental chemistry and biology.[1–6] For instance, an appropriate concentration of fluoride in beverages is appreciated to have a benefit in the fight against dental caries, while high concentrations of this anion can engender teeth mottling, bone density loss, or other toxic effects. Likewise, a number of diseases, including cystic fibrosis,[7] Dent's Disease and Pendred's syndrome,[8–10] are associated with poorly expressed or malfunctioning anion transport systems. Various anions, ranging from simple species, such as inorganic phosphate, to ATP, cyclic GMP, RNA and DNA, play critical roles in a range of physiological processes, including metabolism, cell signalling, and the expression of genetic information. On the environmental level, the eutrophication of waterways caused by excess nitrate or phosphate anion is a problem that can threaten both food stocks and navigation. Cyanide from gold mining operations and fluoride from semiconductor manufacture represent further specific environmental threats.[11] Some radioactive nuclear waste products, particularly the pertechnetate anion ($TcO_4^-$), are also anionic and mobile in the environment, making their control and monitoring important.[12] The removal of sulfate from radioactive waste streams has also been proposed as a means of improving vitrification and long-term storage.[13] As a consequence, considerable effort has been devoted of late to the generation of new anion receptors, with a number of reviews and two books on the topic now being available.[3,14] In this Feature article, the focus will be on structurally modified

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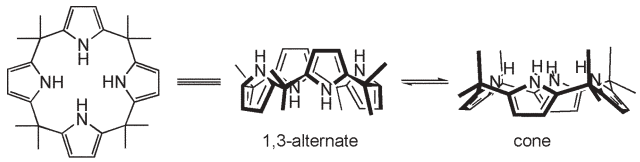
calixpyrroles, an emerging class of anion receptors that, to the best of the authors' knowledge, has not been treated extensively in any prior review.




**1**

Calix[4]pyrrole or octamethylporphyrinogen (**1**) has been known for more than 100 years. However, it was only a bit over a decade ago that it was discovered that this easy-to-prepare heterocalixarene analogue interacts strongly with several small anions, notably fluoride, chloride and phosphate in polar aprotic media.[15] In the course of these studies it was found that anion binding favours the so-called "cone" conformation, whereas the 1,3-alternate form is favoured in the absence of a strongly bound substrate (*cf.* structure **1**). Note, however, that for the sake of simplicity in complex structures, the calix[4]pyrrole core will often be shown in a stylized flat representation.

In the years following the initial 1996 discovery of its anion binding properties, considerable effort was devoted to developing calix[4]pyrrole and its derivatives as anion receptors, extractants and sensors. Included in the progress made to date is the demonstration of so-called naked-eye anion detection,[16] stationary phase-based separation of oligonucleotides,[17] and anti-Hofmeister behaviour in electrochemical sensing and extraction.[18] The ability of functionalized calixpyrroles to interact with neutral substrates, including nitroaromatics and $C_{60}$, has also been demonstrated.[19]

Until 2000, when ring-expanded calixpyrrole systems started to be developed systematically, most modifications of the calix[4]pyrrole skeleton focused on functionalization of the β-pyrrolic or *meso*-positions. Such peripheral modifications remain among the easiest changes to effect in calixpyrrole chemistry and some of the most versatile in terms of supporting calixpyrrole-based applications. However, they are subject to important limitations, particularly with regard to potential enhancements in selectivity and affinity; even the introduction of eight highly electron-withdrawing fluorine substituents in the β-pyrrolic positions serves only to improve the anion affinities in most cases by less than a factor of 5.[20] Thus, new methods are currently being sought to access calixpyrrole receptors with improved anion recognition properties. As detailed in this Feature article, one of the most effective ways of doing this is by producing strapped and other protected cavity systems, wherein the anion binding domain is both effectively defined and isolated more fully from solvent. Until recently, such systems were all but unknown in the context of calixpyrrole chemistry.

The isolation of the binding domain from the solvent matrix imparts a number of advantages in terms of substrate recognition. Firstly, such isolation can serve to enhance the affinity for a targeted guest or substrate by reducing guest–solvent and guest–counter cation interactions. Secondly, the modifications needed to effect such isolation usually produce binding domains of controlled size and shape that, in turn, generally give rise to greater inherent selectivity. Thirdly, in the specific case of calixpyrroles, these structural variations can be used to lock the conformation of the receptor into the so-called cone form, a conformation that is known to favour anion binding. Such a preorganized 'locking' would thus be expected to enhance further the anion affinities. These concepts, namely binding site isolation and preorganization, are not new. Indeed, they represent well established principles in the area of supramolecular chemistry whose origins can be traced back through the seminal contributions of current and early leaders in the field to the famous lock-and-key principle expressed so eloquently by Emil Fisher over a century ago.[21]

In spite of this generalized precedence, it was only in 2002 that the Chun-Cheon group recognized that such venerable approaches could be used to good effect in the area calixpyrrole chemistry. This led to the preparation of the so-called "strapped calixpyrroles", a series of compounds that have now been studied extensively, often in collaboration with the Austin group. In addition, several very elegant three-dimensional oligopyrrole systems have been reported by a number of groups in addition to those of the authors. The goal

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of this Feature article is to provide a generalized review of ongoing efforts to develop the chemistry of topographically nonplanar calixpyrrole anion receptors and related systems. Because it reflects the current state of the art, most of the emphasis will be on receptors containing a single calix[4]pyrrole core. However, larger oligopyrrole systems are known and will be discussed as appropriate. Excluded completely from the discussion are systems based on non-pyrrolic frameworks (*e.g.*, calixarenes), or ones containing mixed pyrrole–heterocycle skeletons (*e.g.*, calixpyridinepyrroles). Three-dimensional systems based solely on aromatic porphyrins are also considered to lie outside the scope of this Feature article.

The intellectual progression leading to the development of protected cavity calix[4]pyrroles is summarized in Fig. 1. This schematic shows a series of sequential modifications. The simplest involves generation of a functionalized calix[4]pyrrole (**2**) bearing one (or more) ''arms''. The second one, illustrated by generalized structure **3**, embodies so-called deep cavity models, calix[4]pyrrole derivates that contain bulky *meso*-substituents. The third modification entails strapped systems, which are represented by structure **4**, while the fourth level of complexity involves capped models, such as generic system **5**. Since the degree of preorganization is increasing along the progression from **2** to **5**, it might be expected that both the inherent anion selectivity and the thermodynamics of binding for appropriately sized anionic substrates would increase in a corresponding fashion. However, since (i) receptors of type **5** could prove to be *too* rigid, thus reducing affinity, and because (ii) their greater complexity was expected to complicate synthesis, the initial decision was to focus on strapped systems; in this case the prediction was that large enhancements in the affinity would be seen as a direct consequence of inhibiting solvent–guest interactions. In point of fact, this expectation was realized. However, prior to discussing the chemistry of strapped (and capped) calixpyrroles, it is useful to summarize what has been learned from various topographically planar models of type **2** and **3**.

A number of functionalized calixpyrroles, including many of type **2** above, have been reported over the last decade. These

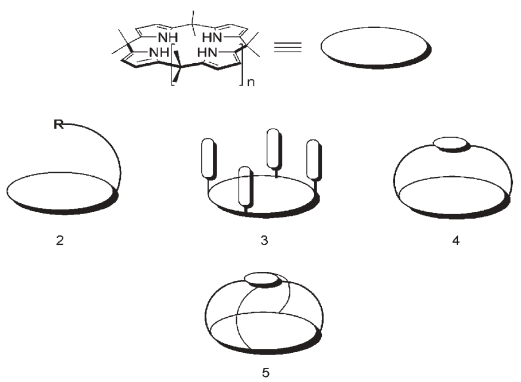
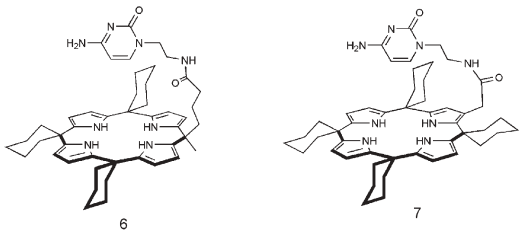



**Fig. 1** Schematic representation showing various possible modifications to the basic calix[4]pyrrole core. This diagram is meant to be illustrative, not all-inclusive. Note: The calix[4]pyrrole is shown in a flattened representation in this and other complex structures for simplicity; *cf*. structures **1** for more accurate three-dimensional representations.

systems have provided the basis for many of the applications-focused advances reported to date, including colorimetric sensing, separations *via* attachment to a solid support, and the creation of receptors displaying enhanced selectivity. While much of this work has been reviewed elsewhere,[22] a few examples are worth noting. For instance, in work from the Austin group, the pyrimidine-functionalized calix[4]pyrroles **6** and **7** were prepared and found to effect the targeted recognition and transport of complementary nucleotides.[23] Likewise, when a properly functionalized calix[4]pyrrole ''arm'' was attached to a solid support, such as silica gel, selective separation of anionic substrates could be effected, including both mixtures of ATP, ADP and AMP and, separately, oligonucleotides on the basis of size and overall charge.




6 7

On a more fundamental level, β-pyrrole functionalization was used early on to adjust the anion binding affinities of the calix[4]pyrrole core. For instance, under conditions where the simple unfunctionalized calix[4]pyrrole (**1**) was reported to bind the chloride anion (studied in the form of the tetrabutylammonium (TBA) salt) with an affinity, $K_a$, of $1.4 \times 10^5$ $M^{-1}$, as measured by ITC in dry $CH_3CN$, the corresponding $K_a$ value for the β-pyrrole functionalized octafluoro derivatives was $5.3 \times 10^5$ $M^{-1}$.[20] Such results provide clear support for the intuitively reasonable conclusion that the presence of the electron-withdrawing substituents increases the acidity of the pyrrole NH and, as a consequence, serves to enhance the anion binding affinities of the calix[4]pyrrole core. In general, however, the degree of enhancement achieved using this approach has been smaller than that attained *via* strapping (*vide infra*).

Examples of generalized system **3**, namely calix[4]pyrroles with deep cavities are fewer in number.[24] Typically, such systems have been prepared by ''appending'' substituted aryl groups onto the four *meso*-positions. This produces a sterically encumbered binding site that in favourable cases has been shown to display somewhat improved affinities and selectivities with regard to anion binding. However, this approach is plagued by the fact that the use of methyl ketones containing a second large substituent (*e.g.*, an aryl group) results in the formation of up to four separate configurational isomers for the final calix[4]pyrrole. Of these, only one has all four bulky *meso*-aryl groups on the same side of the calix[4]pyrrole mean plane. This often leads to problems in separation and characterization.

Strapped systems, such as generalized structure **4**, have an inherent advantage over deep cavity systems in that the pre-organization of the central binding domain may be better controlled. In particular, the use of a diametrically crossed strap is expected to create a well-defined binding domain,

while manipulation of the strap length is expected to allow the size of the resulting 'pocket' to be adjusted more completely. This should translate into enhanced selectivity.

Such systems, by virtue of having two free *meso*-positions, may also allow for follow-up functionalization; in principle, both the normal *meso* and β-pyrrolic "handles", as well as the straps themselves can be used as points for attachment to, *e.g.*, solid supports, chromophores, or ancillary binding moieties. Thus, there is an inherent versatility to this approach that makes it quite appealing. The same holds true for fully capped systems, such as **5**. These latter systems are also attractive because they might allow for more effective trapping or encapsulation of a targeted substrate. However, synthetic access to fully capped targets is far more challenging. Thus, to date most work on topographically nonplanar calixpyrroles has involved systems of general structure **4**.

In designing strapped calixpyrroles of type **4**, two synthetic approaches appeared attractive. These involve, respectively, either initial construction of the calixpyrrole core, followed by spanning with a strap (route A; Fig. 2) or creation of a linked precursor (incipient strap), followed by calixpyrrole ring formation (route B; Fig. 2). In point of fact, it was the second of these strategies that was first implemented successfully, with the first example of this kind of strapped calix[4]pyrrole (**10**) being reported by Lee and co-workers in 2002.[25]

The synthesis of host **10** was accomplished in three steps (Scheme 1). The condensation of 5-hydroxy-2-pentanone with pyrrole in the presence of an acid catalyst afforded the corresponding dipyrromethane **8**.

The reaction of isophthaloyl dichloride with two equivalents of **8** in the presence of pyridine gave **9**. Subjecting this latter acyclic precursor to acid-catalyzed condensation with acetone then afforded product **10** in 16% yield. A crystallographic analysis of **10** revealed that the calix[4]pyrrole core exists in a twisted, 1,3-alternate conformation in the solid state, as shown in Fig. 3.

A single-crystal X-ray structural analysis of the chloride complex of **10** was also carried out (*cf.* Fig. 4); it revealed that

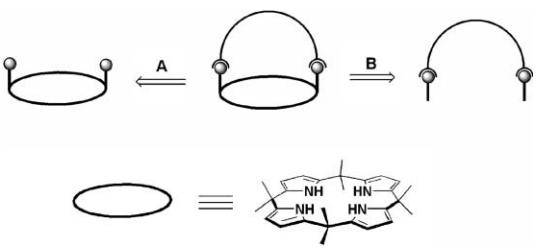
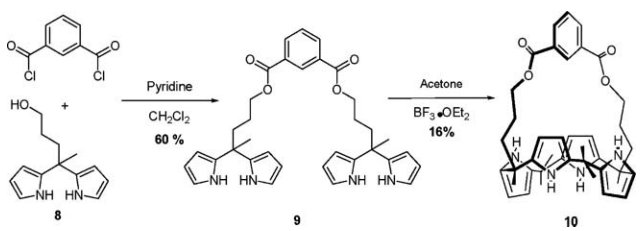



**Fig. 2** Retrosynthetic analysis of strapped system




**Scheme 1** Synthesis of the *cis* ester strapped calix[4]pyrrole (**10**).

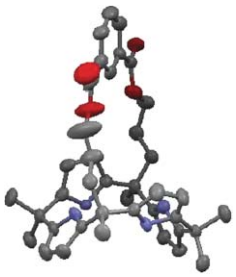


**Fig. 3** Single-crystal X-ray structure of receptor **10**. Hydrogen atoms are omitted for clarity.

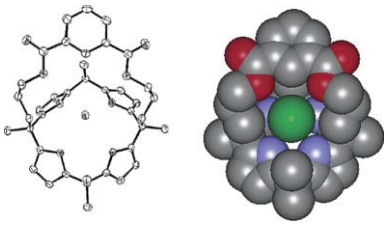
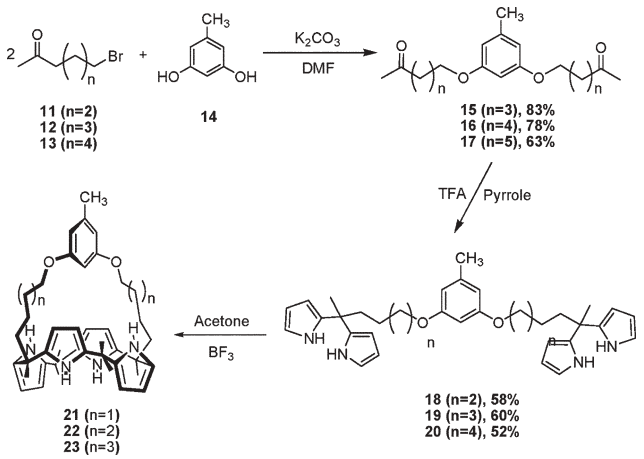


**Fig. 4** Single-crystal X-ray structure of the chloride anion complex of receptor **10**. Hydrogen atoms and the triethylammonium counter-cation are omitted for clarity.

the anion resides within the cavity and that the calix[4]pyrrole portion of the receptor exists in a cone-like conformation. This structure also provided support for the notion the central aryl-CH is involved in anion recognition through hydrogen bonding. Specifically, the distance between the arylic-C and the bound Cl atoms was found to be 2.92 Å, a value consistent with the formation of a CH···Cl hydrogen bond of moderate strength.

Initial evaluations of the anion binding properties of receptor **10** were carried out in DMSO solution using standard $^1$H NMR spectroscopic titrations and isothermal titration calorimetry (ITC) analyses. Taken in concert, these studies revealed that the chloride and fluoride anions (studied as the corresponding TBA salts) are bound essentially irreversibly under these solution phase conditions. The affinity constant, $K_a$, for chloride anion could be calculated directly based on these studies and was found to be $1.0 \times 10^5$ M$^{-1}$ for a 1 : 1 binding stoichiometry. Since an accurate determination of the binding constant for fluoride anion proved to be problematic by ITC, a fluoride-for-chloride competition experiment was used to estimate the affinity constant for fluoride anion; a $K_a$ value of $3.9 \times 10^6$ M$^{-1}$ was derived in this way.

Due to difficulties encountered when trying to vary the length of the ester containing strap, efforts were devoted to generating a series of strapped calix[4]pyrroles incorporating ether-based bridges of different length. This series of receptors was expected to provide insight into the effect, if any, that changes in the cavity size would have on the anion-binding selectivity of the elaborated receptor. As shown in Scheme 2, retro-Barbier type reaction of a cyclic tertiary alcohol produced the corresponding bromo-ketones in quantitative yield. *m*-Orcinol (**14**) was then reacted with the appropriate bromoketone (**11**, **12** and **13**) to afford the key dialkoxy toluene derivatives **15**, **16** and **17**, respectively. Acid-catalyzed




**Scheme 2** Synthesis of the *cis* ether strapped calix[4]pyrroles, **21–23**.

condensation of these latter ketones with pyrrole resulted in the formation of the corresponding bis-dipyrromethanes **18**, **19** and **20**, which afforded the desired receptors **21**, **22** and **23** upon condensation with acetone.[26]

The chloride and bromide anion binding affinities of the strapped systems **21–23** were determined by isothermal titration calorimetry (ITC) in dry acetonitrile using the corresponding TBA salts. Table 1 summarizes the results of these studies. This table also includes comparison data for the unsubstituted parent calix[4]pyrrole, (**1**), as well as the first generation ester strapped system, **10**. Considered in concert, these data provide support for the notion that strapping one face of the calix[4]pyrrole core does indeed lead to systems with substantially increased chloride and bromide anion affinities. For instance, the data in Table 1 reveal that the chloride anion affinity of **21** is 25 times larger than that of **1**.

On a more detailed level, the data presented in Table 1 serve to highlight the effects of relatively small modification in structure. For instance, within the congruent series provided by **21–23**, the largest chloride anion affinity was seen with receptor **21**, bearing the shortest strap ($n$ = 1). On the other hand, the largest affinity for bromide anion was recorded in the case of the receptor containing the longest strap (**23**; $n$ = 3). Since bromide is bound but poorly by calix[4]pyrrole (**1**), on the basis of these observations, it was concluded that not only the size of the cavity, but also its ability to stabilize aryl-C*H*$\cdots X^-$ (X = Cl, Br) hydrogen bond interactions play key roles in regulating the observed anion affinities. While no structural data for the anion-bound forms of **21**–**23** is currently available, the solid state structure of the chloride anion complex of the ester strapped system **10** alluded to above provides support for the proposed aryl-C*H*$\cdots X^-$ interactions in the solid state (*cf.* Fig. 4).

**Table 1** Halide anion association constants measured by ITC in acetonitrile at 30 °C. The anions were studied in the form of their tetrabutylammonium (TBA) salts

| | **1** | **10** | **21** | **22** | **23** |
|---|---|---|---|---|---|
| $Cl^-$ | $1.4 \times 10^5$ | $1.4 \times 10^6$ | $3.6 \times 10^6$ | $1.4 \times 10^6$ | $1.4 \times 10^6$ |
| $Br^-$ | $3.4 \times 10^3$ | $7.5 \times 10^3$ | $3.0 \times 10^4$ | $3.1 \times 10^4$ | $1.2 \times 10^5$ |

Evidence for these interactions was also inferred from the $^1$H NMR spectroscopic analyses. For instance, the central aromatic C*H* proton in **10**, a singlet resonating at 8.65 ppm, was shifted to lower field (9.52 ppm) upon binding with chloride anion. A representative illustration of these changes is shown in Fig. 5.

Fig. 5 also serves to show that the effect of adding $Cs^+$ to the chloride anion bound form of receptor **10** is minimal. The lack of spectroscopic changes produced as the result of this addition stands in contrast to what is seen in the case of calix[4]pyrrole (**1**), where evidence of $Cs^+X^-$ (X = F, Cl, Br) ion pairing has recently been forthcoming.[27] Apparently, in the case of the strapped system, binding of the chloride anion guest within the central cavity serves to ''protect'' the system from an appreciable interaction with a counter cation. Presumably, this protection extends to the solvent, with this effect accounting in part for the high relative affinities displayed by systems **10** and **21–23**.

Since the basic strapping approach embodied in systems **10** and **21–23** was found to enhance the halide anion binding affinity of calix[4]pyrrole significantly, it was thought that the incorporation of additional hydrogen-bonding donor sites within the strap would serve to increase the affinity even further. In accord with such thinking, efforts were made to synthesize several strapped systems bearing isophthalate-derived diamide spacers diametrically linked to the tetrapyrrolic core.[28]

As shown in Scheme 3, the appropriate aminoketones were reacted with isophthaloyl dichloride to give amides **26** and **27**, which were then condensed with pyrrole to afford **28** and **29**. Subsequent condensation with acetone was then found to give rise to two sets of products, **30**, **31** and **32**, **33** corresponding to ''*cis*'' and ''*trans*'' isomeric linkages at the point of transverse attachment of the diamide containing straps.

Unfortunately, analogues of **30** and **31**, bearing shorter straps (*i.e.*, $n < 2$), could not be obtained readily using the procedure shown in Scheme 3. However, such a target could be synthesized using an alternative method, as shown in Scheme 4.

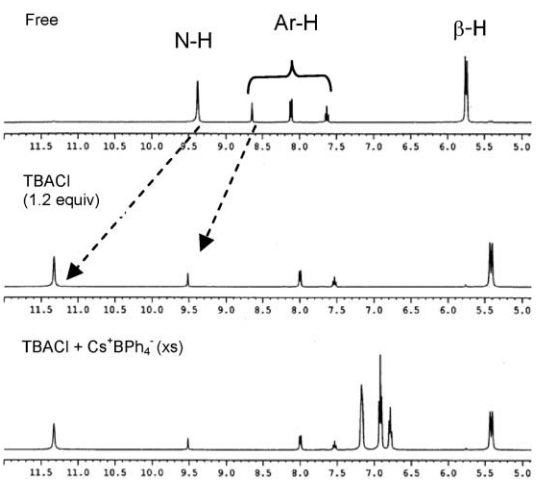
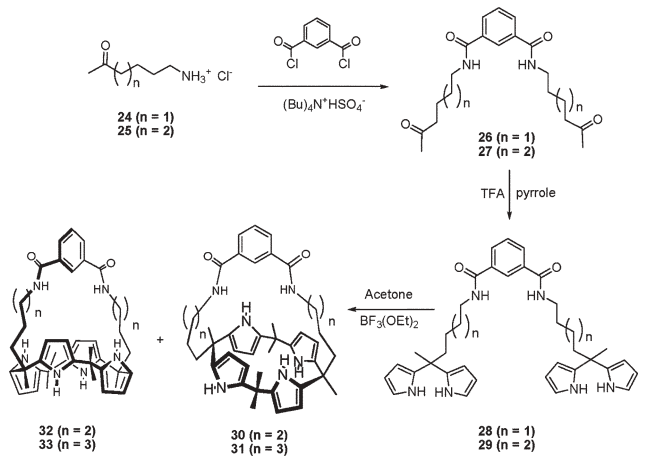



**Fig. 5** Changes in the chemical shift of key resonances for receptor **10** observed upon the addition of first tetrabutylammonium chloride (TBACl) and then excess caesium tetraphenylborate ($Cs^+BPh_4^-$) in DMSO-$d_6$ at 25 °C.

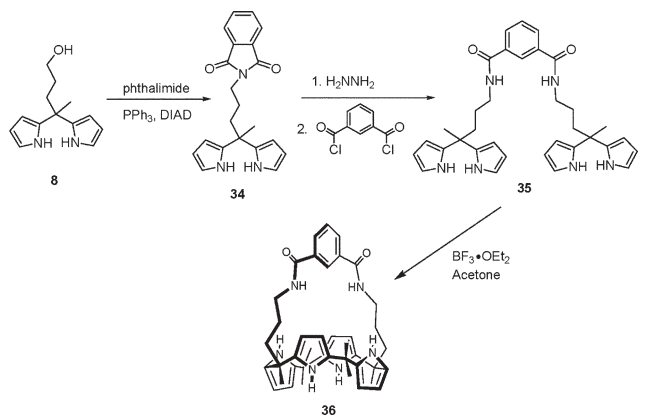



**Scheme 3** Synthesis of *cis* and *trans* amide strapped calix[4]pyrroles **30–33**.

In this approach, the dipyrromethane (**8**) was converted into its phthalimide derivative **34**. After conversion to the corresponding amine by treatment with hydrazine, immediate reaction with isophthaloyl dichloride afforded the bis-dipyrromethane **35**. Acid-catalyzed condensation of **35** with acetone provided the desired product **36**. In this case, no evidence for the formation of the isomeric *trans*-strapped system was seen. Presumably, this reflects the fact that the strap is too short to permit the formation of such an inherently strained species.

The anion-binding behaviour of these receptors was investigated using proton NMR spectroscopy and isothermal titration calorimetry (ITC), with selected results being given in Table 2. As gauged from both sets of analyses, these new strapped systems were found to display affinities for both the chloride and bromide anions that are enhanced compared to those of normal, unstrapped calix[4]pyrrole but similar to those of **10** and **21–23**.

However, contrary to expectations (and in marked contrast to what was seen in the case of **21–23**), no size-dependent selectivity for these anions was observed as the length of the bridging strap is varied. Such results were interpreted in terms of anion-binding processes that occur outside the central pocket defined by the strap, but that still favour strong associations as the result of the increased number of hydrogen-bonding donors provided by the amide groups.[28]




**Scheme 4** Synthesis of the *cis* amide strapped calix[4]pyrrole **36**.

**Table 2** Halide anion association constants measured by ITC in dry acetonitrile at 30 °C. The anions were studied in the form of their tetrabutylammonium (TBA) salts

| Anion | **36** $K_a/M^{-1}$ | **32** $K_a$ | **33** $K_a$ |
|---|---|---|---|
| $Cl^-$ | $3.89 \times 10^6$ | $3.35 \times 10^6\ M^{-1}$ | $3.24 \times 10^6\ M^{-1}$ |
| $Br^-$ | $1.41 \times 10^6$ | $1.25 \times 10^6\ M^{-2}$ | $7.0 \times 10^5\ M^{-2}$ |
| $I^-$ | ND | $2.30 \times 10^3\ M^{-2}$ | $3.0 \times 10^3\ M^{-2}$ |

$^1$H NMR spectroscopic titrations of **32** with halide anions (studied as their corresponding TBA salts) in $CD_3CN$ (1.0 mM), provided support for the above conclusion. While with fluoride anion, the saturation point in the binding curve was reached only after the addition of a full stoichiometric equivalent of the anion, in the case of chloride and bromide more complex behaviour was seen, In particular, saturation is seen after the addition of 0.5 molar equiv. of bromide anion and after the addition of $\sim$0.7 molar equivalents of chloride anion (Fig. 6).

In accord with the finding that greater than 0.5 molar equiv. but less than one full stoichiometric equivalent of TBACl was required to effect a considerable change in the overall spectral features, the maximum of the Job plot (Fig. 7), corresponding to the binding of chloride anion to **32**, was observed when the $Cl^-$ mole fraction was 0.4.

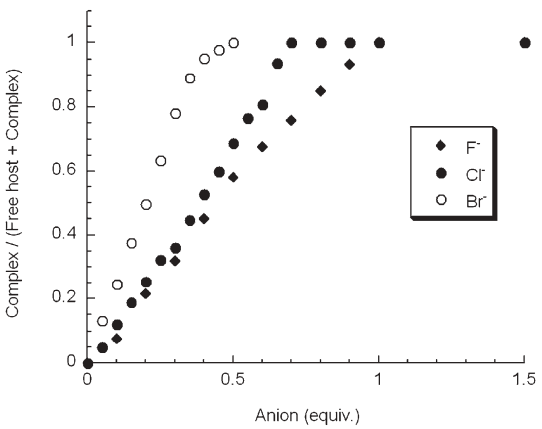



**Fig. 6** Titration of compound **32** with halide anions (studied in the form of their respective TBA salts) in $CD_3CN$ (1.0 mM).

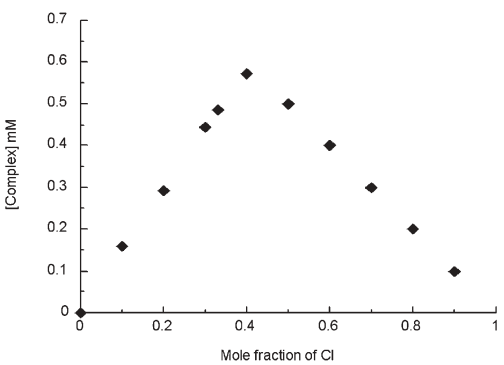


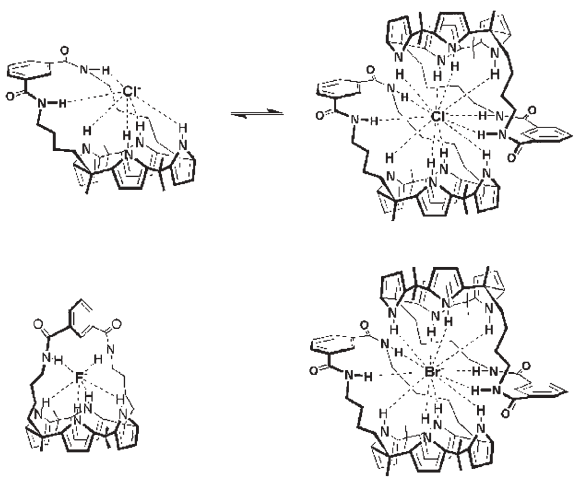

**Fig. 7** Job plot corresponding to the titration of compound **32** with chloride anion (as TBACl) in $CD_3CN$.

Such a mole fraction value, which was found to be entirely reproducible, is not consistent with the formation of a 2 : 1 (receptor : anion) binding stoichiometry Nor, is it consistent with the formation of a 1 : 1 complex. However, it may indicate the existence of equilibrium between a 1 : 1 and 2 : 1 (receptor : anion) complex as shown in Scheme 5. In particular, it is suggested that at high relative receptor concentrations (*i.e.*, after the addition of only a small amount of TBACl), a 2 : 1 (receptor : anion) complex forms with **32** that then dissociates to produce a 1 : 1 complex as the relative concentration of the anionic substrate increases. Thus, the measured stability constant for chloride anion must actually reflect the sum of two binding equilibria (represented by constants, $K_1$ and $K_2$), corresponding to the formation of the 1 : 1 and 2 : 1 complexes, which cannot be calculated separately under the experimental conditions. In the case of fluoride, a complex of 1 : 1 stoichiometry is formed, whereas in the case of bromide it is the 2 : 1 species (receptor : anion ratio) that predominates.

In spite of the complexities of the chloride anion binding stoichiometry, a possible application of these isophthalate-derived diamide strapped systems for the detection of anions was demonstrated. In the mixed solvent system 1% $H_2O$–$CD_3CN$ the chemical shifts of the pyrrolic N*H* protons observed in the $^1$H NMR spectrum of **32** were found to be correlated uniquely with the nature of the anions in question (*e.g.* F = 11.9, $Cl^-$= 10.3, $Br^-$ = 10.0 ppm). Moreover, by using the relative integral of the chloride-bound N*H* peak, which was in slow exchange with the N*H* signal seen in the absence of an added anion, it proved possible to determine semi-quantitatively the concentration of chloride anion in both sea water and drinking water (see Fig. 8).[29]

A new strapped calix[4]pyrrole, **38**, containing a fluorophore as a part of the strap, was also synthesized in 2005.[30] It was prepared from 5,7-dihydroxy-4-methylcoumarin *via* the dipyrromethane analogue **37** (Scheme 6) and follow-up condensation with acetone gave the coumarin-containing receptor **38**.

Association constants with various anions were determined using both fluorescence titration and isothermal titration calorimetry (ITC). Gratifyingly, the association constants



**Scheme 5** Proposed binding modes for the halide anion complexes of **32**.

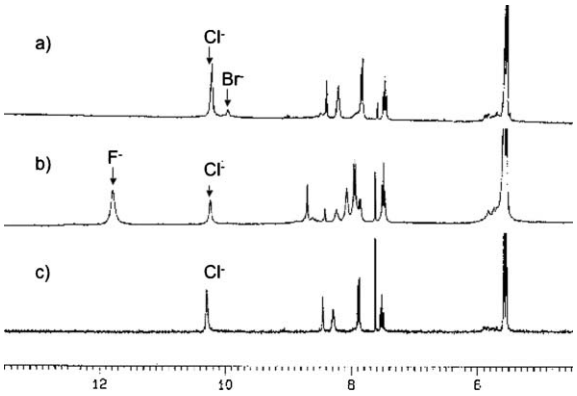
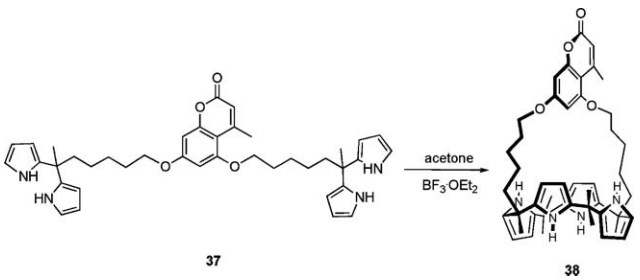



**Fig. 8** 300 MHz $^1$H NMR spectra of (a) diamide-strapped calix[4]-pyrrole (**32**) (1 mM) + TBABr (1 mM) + TBACl (1 mM); (b) **32** (1 mM) + TBABr (1 mM) + TBACl (1 mM) + TBAF (1 mM) in $CD_3CN$; (c) **32** (1 mM) in 495 μL of $CD_3CN$ + 5 μL of sea water (collected at Incheon, Korea).




**Scheme 6** Synthesis of coumarin strapped calix[4]pyrrole **38**.

obtained by these two different methods were found to be in good agreement with one another (Table 3).

An interesting feature of receptor **38** is that its fluorescence emission properties could be controlled *via* the addition of appropriate cations and anions (Fig. 9). In particular, it was found that the fluorescence intensity could be enhanced *via* the addition of sodium cations. Presumably, this reflects the fact that these latter species bind to the carbonyl moiety in coumarin, thereby turning off an inherent photoinduced electron transfer (PET) quenching process. In contrast, the fluorescence intensity of **38** could be reduced *via* the addition of anions that are known to bind within the calix[4]pyrrole core.[30] Such systematic, substrate-dependent changes in fluorescence emission intensity means that this receptor acts as a rudimentary supramolecular logic device.

Another fluorogenic model system, **41**, a strapped calix[4]-pyrrole bearing an acridine moiety, has been synthesized

**Table 3** Association constants ($K_a$) of **38** with various anions in 3% $H_2O$–$CH_3CN$, $NaPF_6$–$CH_3CN$ and $CH_3CN$ at 298 K

| | $10^{-4}K_a/M^{-1}$ | | |
|---|---|---|---|
| Anion source | 3% $H_2O$–$CH_3CN^a$ | $NaPF_6$–$CH_3CN^a$ | $CH_3CN^b$ |
| TBACl | 190 | 230 | 360 |
| TBABr | 3.7 | 10 | 11 |
| TBAOAc | 89 | 130 | 190 |

[a] Determined by fluoresence emission. [b] Determined by ITC; average of three determinations at two different concentrations.

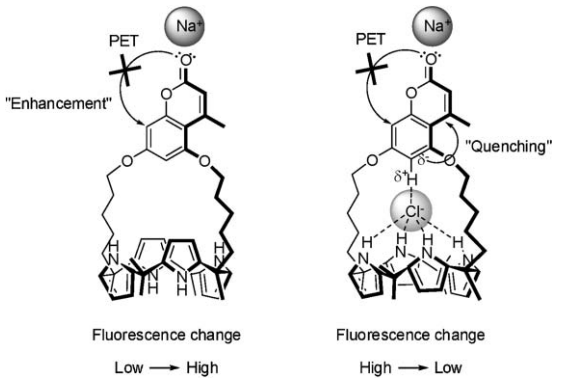


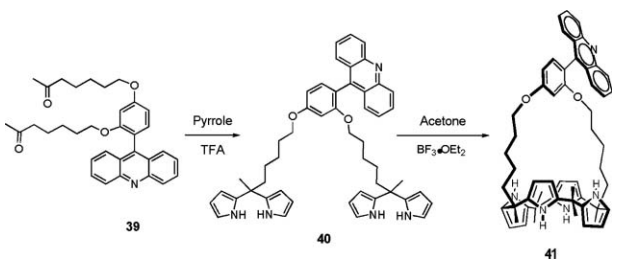

**Fig. 9** Schematic representation of the proposed interactions between **38** and sodium cation and chloride anion. (a) The $Na^+$ cation is thought to bind to the coumarin carbonyl oxygen atom, thereby inhibiting an inherent PET quenching process. (b) In contrast, the binding of chloride anion ($Cl^-$) activates a different PET mode and serves to quench the fluorescence.

recently.[31] The acridine moiety is of particular interest because it can act not only as a fluorophore, but also as a proton acceptor. The synthesis of **41** is shown in Scheme 7. Here, acid catalyzed condensation of **39** with pyrrole gave the bis-dipyrromethane derivative **40**, which was then condensed with acetone to afford the desired receptor **41**.

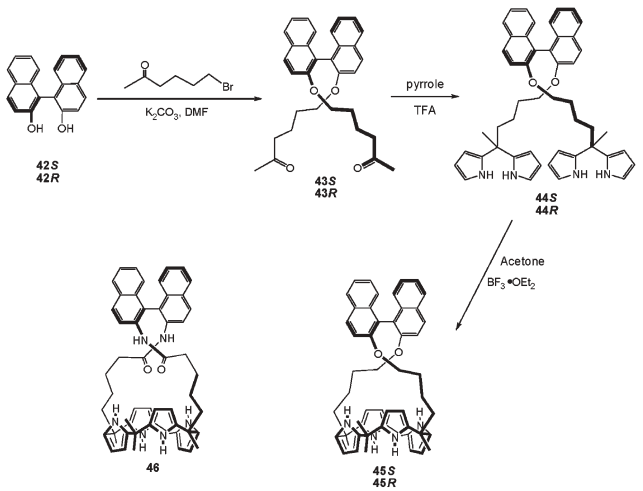
Quantitative analyses of the solution phase chloride and bromide anion binding properties of **41** were made using ITC. The resulting association constants, determined in reagent grade $CH_3CN$ at 30 °C, corresponding to the formation of the chloride and bromide complexes of **41**, were $2.41 \times 10^7$ $M^{-1}$ and $6.81 \times 10^4$ $M^{-1}$ for $Cl^-$ and $Br^-$, respectively. Receptor **41** thus shows a relatively high selectivity factor of ~350 for chloride anion over bromide anion.

In addition to generating sensing systems based on various built-in or appended chromophores, effort has been devoted to the preparation of chiral, nonracemic calix[4]pyrroles *via* the use of appropriately chosen straps. Such systems would be potentially useful in the recognition and, potentially, separation of various anion-containing enantiomeric species, including amino acids eventually.

With these considerations in mind, a pair of chiral calix[4]pyrroles, **45*R*** and **45*S***, bearing an (*R*) or (*S*)-Binol (1,1′-bi(2-naphthol)) derived diether strap on one side of the tetrapyrrolic core, was prepared.[32] The synthesis is summarized in Scheme 8. 6-Bromo-2-hexanone was reacted with (*R*)-(+)-1,1′-bi(2-naphthol) (**42*R***) or (*S*)-(−)-1,1′-bi(2-naphthol) (**42*S***) to afford the bisketones **43*R*** and **43*S***,




**Scheme 7** Synthesis of the acridine strapped calix[4]pyrrole **41**.




**Scheme 8** Synthesis of chiral, nonracemic Binol strapped calix[4]pyrroles **45*R*** and **45*S***.

respectively. Compounds **43*R*** and **43*S*** were then condensed with pyrrole in the presence of a catalytic amount of trifluoroacetic acid to give dipyrromethanes **44*R*** and **44*S***. Condensation of the resulting dipyrromethanes with neat acetone in the presence of a catalytic amount of $BF_3 \cdot OEt_2$ afforded the desired chiral receptors **45*R*** and **45*S***.

The CD spectra of the two enantiomeric Binol-strapped calix[4]pyrroles **45*R*** and **45*S*** were found to be nearly mirror images of one another (Fig. 10). The resulting system **45*S*** were found to bind the chiral carboxylate anions (*R*)-2-phenylbutyrate or (*S*)-2-phenylbutyrate (studied as the tetrabutylammonium salts) with high affinity in acetonitrile. In accord with design expectations, the association constants ($K_a$) were *ca.* 10 times larger for the (*S*)-guest–(*S*)-host pair than in the case of the corresponding (*R*)-guest–(*S*)-host combination.

Proposed binding modes for the complex formed between the Binol-strapped calix[4]pyrrole (**45*S***) and (*R*)-2-phenylbutyrate and (*S*)-2-phenylbutyrate, respectively, are shown in Fig. 11. These depictions serve to illustrate the intuitively appealing assumption that the lower association constant observed for the combination of **45*S*** and (*R*)-2-phenylbutyrate reflects unfavourable steric interactions between the chiral,

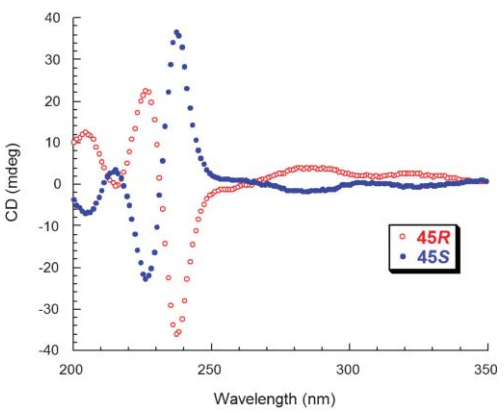



**Fig. 10** CD spectra of **45*R*** (*R*) and **45*S*** (*S*) in acetonitrile ($1 \times 10^{-5}$ M at 25 °C).

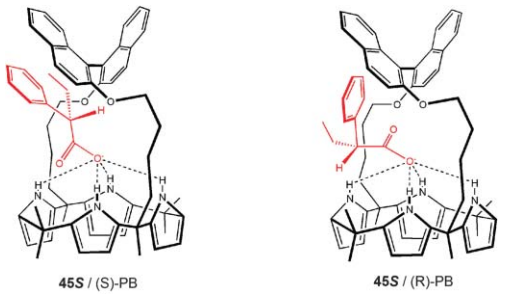
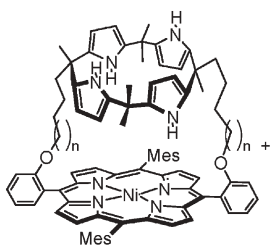



**Fig. 11** Proposed binding modes for the diastereomeric complexes formed between receptor **45*S*** and (*S*)-2-phenylbutyrate anion (left) and (*R*)-2-phenylbutyrate anion (right) (studied as the tetrabutylammonium salt) showing the relevant intermolecular interactions. Note the destabilizing steric interactions that are present in the latter structure.

nonracemic receptor and the phenyl group of the guest. By contrast, the larger association constant observed for **45*S*** and (*S*)-2-phenylbutyrate can be rationalized in terms of favourable edge-centered interactions between one of the receptor naphthyl groups and the phenyl group of the bound substrate.

With chiral Binol-derived strapped calix[4]pyrroles bearing additional hydrogen bonding donor sites on the strap, even higher selectivity would be expected. To test this hypothesis, the new (*R*) and (*S*)-BINAP (1,1′-bi(2-naphthyl-2,2′-diamine) derived diamide-strapped calix[4]pyrrole (**46**) were synthesized and studied.

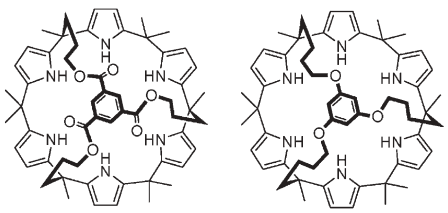
As expected, this new chiral host displayed enhanced selectivity in the binding of the enantiomeric carboxylate anions, (*S*)-phenylbutyrate and (*R*)-phenylbutyrate (studied as the tetrabutylammonium salts). In fact, the association constants ($K_a$) were found to be *ca.* 20 times larger in the case of the (*S*)-guest than in the case of the (*R*)-guest.[29] Construction of a pre-organized receptor containing both hydrogen bonding donor sites and a Lewis acidic metal ion centre is also something that can be conceived within the strapped calixpyrrole paradigm. Since the putative metal-centre could act as an electron-pair acceptor or as a redox active site, the ensuing combination of anion recognition and metal cation coordination could lead to enhancements in substrate binding or selectivity. These potential benefits provided the incentive to prepare the calix[4]pyrrole-metalloporphyrin conjugates **47–49**.[33]




**47 (n=1)**
**48 (n=2)**
**49 (n=3)**

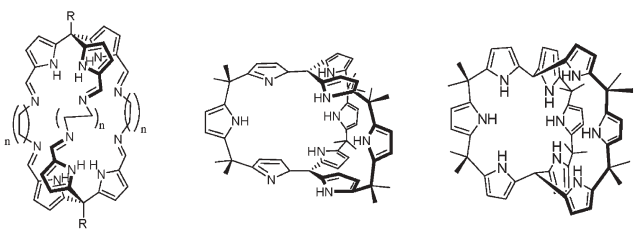
Anion binding studies revealed that receptors **47–49** bound fluoride anion strongly in organic solvents, with none of the compounds displaying any appreciable affinity for $Cl^-$, $Br^-$ or $I^-$. Presumably, this strong size selectivity is imposed by the combination of the Lewis acid and hydrogen bonding recognition functionality present within this preorganized receptor.[34] Consistent with this conclusion were the results of standard $^1H$ NMR spectroscopic titrations and associated Job plots, which provided support for the bound fluoride anion residing within the cavity.

While still at an early stage of development, some effort has been made to extend the principle of strapping and binding site isolation beyond the realm of simple calix[4]pyrroles; to date, this has been done *via* the synthesis of the capped calix[6]pyrroles **50** and **51**.[35] Interestingly, these larger systems, like their smaller congeners discussed above, were found to display appreciable selectivity for the fluoride anion, at least in organic media.



**50** **51**

A different approach to achieving non-planar topographies involves constructing cryptand-like systems. The first such system to be characterized structurally was the imine-linked tripyrromethane dimer **52·53** reported by P. Beer in 2001.[36] In this case, the neutral substrate, ethylenediamine, was found within the cavity, with the corresponding solution phase binding affinity being 1500 $M^{-1}$ in $CDCl_3$. Slightly thereafter, the Sessler group reported the synthesis and structure of a '3-D calixpyrrole' **54** and its oxidized analogue **55**.[37] Neither of these latter systems contains a cavity-like void space. As a result, only solvent molecules, such as water and dichloromethane, were found trapped inside. However, in the case of **54**, outside binding of anions was observed.



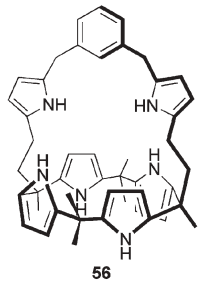
**52 (n=1)**
**53 (n=2)**

**54** **55**

A system that in some respects is closer to being a real cryptand-like calix[4]pyrrole was recently synthesized by the Lee group.[38] The product in question **56** was designed so as to incorporate additional pyrrolic NH donor functionality within a strapped calix[4]pyrrole framework.

Quantitative analyses of the solution phase fluoride anion binding properties of **56** were performed using isothermal titration calorimetry (ITC) in DMSO. It was found that for $K_a$ values measured were substantially larger than for other analogous strapped systems. The titration isotherms also revealed the presence of a second event after the initial heat



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evolving process (Fig. 12). This second event is ascribed to the binding of a second fluoride anion by the two pyrrole N*H* protons of the bridging strap. Evidence of such ancillary binding interactions was not found in the case of chloride or acetate anion. The calculated $K_{a1}$ value for fluoride anion binding was $1.28 \times 10^8$ $M^{-1}$, while the calculated $K_{a2}$, corresponding to the proposed second fluoride anion binding event, was $1.35 \times 10^5$ $M^{-1}$, both in DMSO at 25 °C. The 1 : 1 affinity constants for chloride and acetate anion binding in the same solvent were $3.27 \times 10^7$ $M^{-1}$ and $9.35 \times 10^6$ $M^{-1}$, respectively. These values are noteworthy for being substantially larger than those seen for any other neutral pyrrolic anion receptor, especially in light of the fact that the solvent (spectral grade DMSO) was not subject to any special drying. It thus appears as if the use of pyrrole-bearing straps provides a particularly effective means of enhancing the anion binding affinities of strapped calix[4]pyrrole anion receptors.

## Conclusions

While completely unknown until recently, the chemistry of strapped calix[4]pyrroles has blossomed in the past several years. Although less well developed, the important strides have been made to generate other classes of topographically non-planar oligopyrroles. Taken in concert, these systems demonstrate enhanced anion affinities and improved selectivities relative to analogous compounds with a lower level of preorganization. For instance, the affinity constants measured in the same solvent system (*e.g.*, acetonitrile) are seen to increase upon the introduction of straps, increasing the number of hydrogen bonding donors, or in the most general terms, upon going from 2D to 3D as far as the receptor topography is concerned. Such a global conclusion leads us to suggest that the chemistry of pre-organized calixpyrroles, which is still in its early days, is rife with possibilities and that ever more elaborate systems, containing different kinds of straps, caps, or oligopyrrolic cores, will allow for even greater diversity and selectivity in terms of substrate recognition.

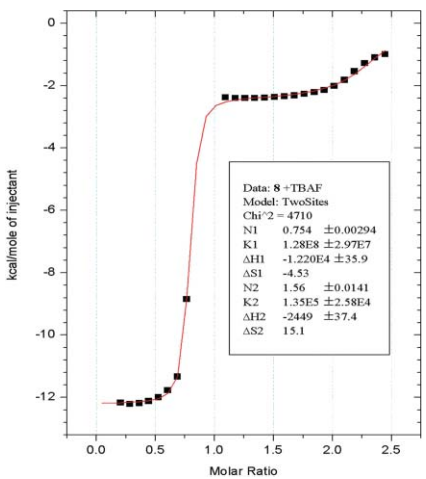


**Fig. 12** ITC titration curve for the interaction of receptor **56** with tetrabutylammonium fluoride in DMSO at 25 °C. The concentration of **56** is 0.754 mM.


## Acknowledgements

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