STUDIA UNIVERSITATIS BABEŞ-BOLYAI, CHEMIA, XLIX, 1, 2004

APPLICATIONS OF CALIX[4]PYRROLES

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INTRODUCTION

The self-assembly of complementary fragments occurs throughout nature and plays an essential role in the construction of biological "superstructures" such as nucleic acids, multicomponent enzymes, cell membranes, etc.[1,2]. The structural information required for facile self-assembly is preprogrammed in the topography and functionality of the building block surfaces [3,4].

Calix[4]pyrroles are a class of old[5] but yet new compounds that show interesting anion and neutral substrate binding properties[6]. The anion binding properties of *meso*-octamethylcalix[4]pyrrole **1**, was first mentioned by Jonathan L. Sessler and coworkers[7], and subsequently developed by his group[8].

The discovery that calix[4]pyrroles such as **1** are effective anion binding agents in solution has led to the synthesis of a variety of new calixpyrrole macrocycles that have been used for anion binding, sensing and for new anion separation technologies. The general route for the synthesis of calix[4]pyrroles is the condensation of pyrrole with ketones in the acid catalysis[5,9]

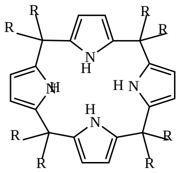
This review is dedicated to some applications of calix[4]pyrroles as anion and neutral binders, chromatic, fluorescent and electrochemical sensors.

THE BINDING AND SEPARARATION OF ANIONS

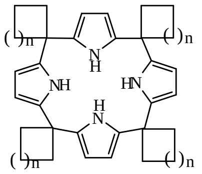
Anions play essential roles in biological processes; indeed, it is believed that they participate in 70% of all enzymatic reactions[7].

Different research groups, which work in the field of molecular recognition, synthesized receptors that bind anions by using hydrogen bonds alone, or in concert with electrostatic interactions.

The solution binding properties of calix[4]pyrroles **1-5**, were studied by using ^{1}H NMR titration techniques in CD_2Cl_2 and stability constants were determined using the EQNMR least-squares fitting procedure[10]. The data summarized in **Table 1**, revealed that all compounds are not only effective 1:1 anion binding agents in solution but they are also selective. Specifically, they show a marked preference for F^- over other anionic guests (Cl^-, Br^-, I^-,$H_2PO_4^-$ and HSO_4^-).



1 R = Me



2a n=3 **2b** n=2 **2c** n=1

The stability constants for *spiro*-calix[4]pyrroles **2b** and **2c** in CD_2Cl_2 are lower (fluoride: 3000 and 2300; chloride: 100 and <100, respectively) than for macrocycle **2a** (**Table 1**). All *spiro*-calix[4]pyrroles demonstrate the much lower stability constants than octamethyl **1** does; so the anion binding ability decreases in the order: octamethyl > *spiro*-cyclohexyl > *spiro*-cyclopentyl > *spiro*-cyclobutyl (i. e., **1** > **2a** > **2b** > **2c**)[11].

Table 1

*Stability constants for compounds **1-5** with anionic substrates in CD_2Cl_2 at 298K. " - " – not determined*

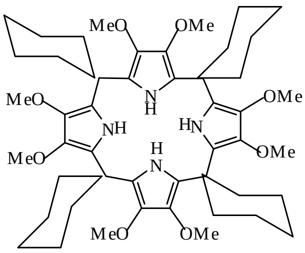
anion - "guest"	*Stability constant (M^{-1})*				
	1[7]	**2a**[7]	**3**[12]	**4**[12]	**5**[12]
F^-	17 170(± 900)	3600 (± 395)	170(±20)	1100(±200)	27000(±4000)
Cl^-	350(±5.5)	117(±4.0)	<10	47(±1)	4300(±600)
Br^-	10(±0.5)	-	-	-	-
I^-	<10	-	-	-	-
$H_2PO_4^-$	97(±3.9)	<10	-	-	-
HSO_4^-	<10	-	-	<10	650(±40)

The similar titrations of the monomeric 2,5-dimethylpyrrole using fluoride anion demonstrate that the binding properties of anions are not so pronounced.

The anion binding properties of calix[4]pyrroles are an obvious proof of the capacity of polypyrrolic macrocycles of similar sizes and shapes to form hydrogen bonds[13].

Compound **3** and **4** show lower stability constants with fluoride and chloride than calix[4]pyrroles **1** and **2a**. This is due to the electron-donating ability of eight *C*-rim methoxy groups causing a decrease in the acidity of the pyrrole NH protons in **3** and to unfavourable interactions between the bound anion and the lone pair electrons on the oxygen atoms of the *C*-rim ester group in **4**.

In contradiction to receptors **3** and **4**, compound **5** exhibits higher stability constants for the binding of fluoride, chloride and dihydrogen phosphate anions than does **1** under the same conditions as the substitution with electron–withdrawing bromine atoms increases the acidity of the pyrrole NH protons thus enhancing anion binding ability.



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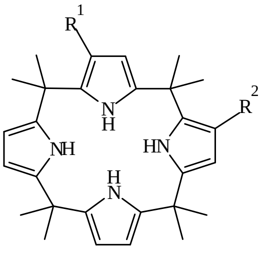
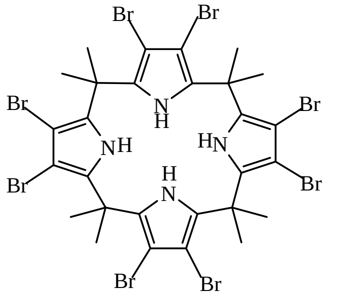


4 $R^1 = CH_2CO_2Et, R^2 = H$

These last three examples illustrate that the anion binding property of the calix[4]pyrroles can be tuned by appending different groups to the carbon in *C*-rim of the calixpyrrole. Receptors of increased anion binding ability such as **5** may have potential uses as anion sequestering agents (for example, in removal of phosphate pollutants from aqueous environments) while those with decreased anion binding ability (compound **3** and **4**) could prove useful in HPLC; in this latter application low affinity constants and fast complexation-decomplexation rates generally lead to efficient separation of substrates.

The introduction of the electron-withdrawing fluorine substituents to the *β*-pyrrolic positions of calix[4]pyrrole (**5a**) results in a dramatic increase of the affinity this receptor displays toward anionic substrates in solution[14].



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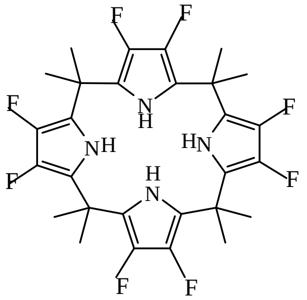


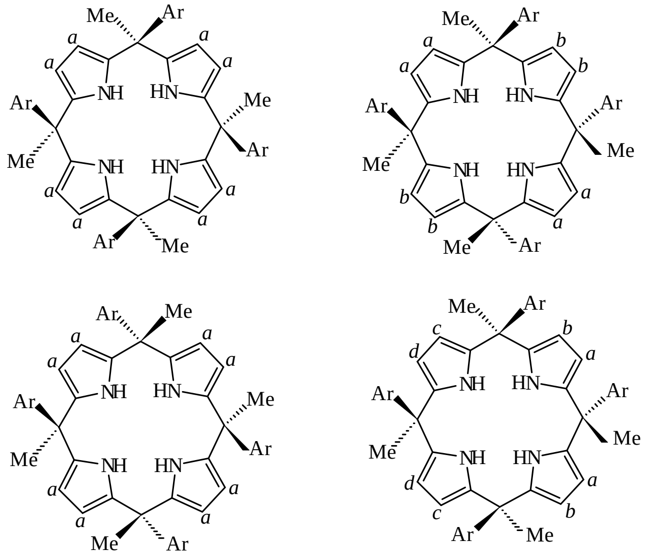
5a

Calix[4]pyrrole **5a** displays not only increased affinity for anions, specifically chloride and dihydrogen phosphate for which accurate K_a values for 1:1 complex formation could be obtained, but also increased selectivities for certain anions as compared to **1** (*Table 1).* Affinity constants for **5a** (mol^{-1}) for anionic substrates (in the form of their tetrabutylammonium salts) and DMSO-d_6 as neutral substrate recorded in acetonitrile-d_3 (0.5% v/v D_2O) at 22°C are the following: 17100 (F^-), 10700 (Cl^-), 9100 ($H_2PO_4^-$), 20 (DMSO-d_6). The ratio of the binding constants of **5a** and **1** ($R_{5a/1}$) are: for F^- - ≥1.71, for Cl^- - 2.14, for $H_2PO_4^-$ - 7.0 and for DMSO-d_6 - >4.0.

Studies of mono-halogen substituted calix[4]pyrroles reveal that replacement of a single *β*-pyrrolic hydrogen atom can increase the anion binding ability of calix[4]pyrroles for a variety of anions (*e.g.* Cl^-, Br^-, $H_2PO_4^-$, HSO_4^-) in comparison to normal non-halogen substituted calix[4]pyrrole. The chlorine substituted calix[4]pyrrole was found to display a slightly higher affinity in the case of each anion than the fluorine-bearing derivate[15].

The fact that the substituents of the calix[4]pyrroles (in the *C*-rim or in the *meso*-position) influence the anion binding capacity, led to the synthesis of new functionalized calix[4]pyrroles as illustrated in the examples **6** and **7**. By using NMR spectroscopy to probe the effect of anion binding in solution, it was found that under conditions of strong binding, such as those proved true for fluoride, phosphate, and chloride anions interacting with the αααα isomers of **6** and **7** and fluoride anions interacting with the ααββ isomer of **6**, addition of the substrate served to lock the system into the expected cone conformation[16].

In the case of the αααβ isomer of **6** and the ααββ isomer of **7**, high concentrations of fluoride anion served to lock the system into separate, well-defined conformations that, on the basis of symmetry considerations, were assigned as being the two conformationally accessible conelike forms and the cone and partial cone conformations, respectively. In other systems, where weaker anion binding occurred, the addition of anions did not serve to lock the fluxional calixpyrrole core into a single conformation. Quantitative assessments of anion binding affinity were made using the induced changes in the ^{1}H NMR spectra as a function of anion concentration. From these analyses (**Table 2**) it became clear that the affinities of **6** and **7** for chloride and dihydrogenphosphate anions are actually lower than those of **1**. This, presumably, is due to a combination of electronic effects and steric interactions between the *meso*-aryl groups and the anion.



6 Ar = 4-hydroxyphenyl; **7** Ar = 4-methoxyphenyl

Table 2

*Stability constants for compounds **1**, **6** and **7** (M^{-1}) with anionic substrats in acetonitrile-d_3 (0.5% v/v D_2O) at 22°C*

anion-"guest"	**1**[16]	**6**[16]			**7**[16]		
		ααββ	αααβ	αααα	ααββ	αααβ	αααα
F^-	>10 000	>10 000	5 000	>10 000	4 600	1 100	10 000
Cl^-	>5 000	1 400	260	320	<100	220	300
$H_2PO_4^-$	1 300	520	230	500	<100	<80	<100

It is important to appreciate that isomers in the **6** and **7** do serve to modulate the anion binding affinities. For example, the αααα isomer of **7** has the highest affinity for anions among the three isomers of **7**.

It was observed that the anion binding affinities of **6** are greater than those of **7.** The explanation offered by the analysis is the presence of hydroxy groups in **6** able to serve as secondary hydrogen-bonding recognition elements that stabilize the calix[4]pyrrole-anion complex. In the case of the αααα isomer of **6** this effect reverses the intrinsic fluoride>chloride>phosphate selectivity that has previously been observed for calix[4]pyrroles[8a].

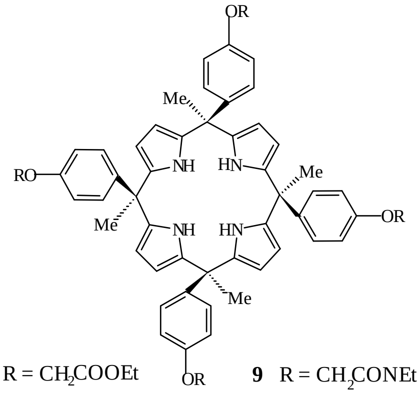
Not only *p*-hydroxyacetophenone, but also *m*-hydroxyacetophenone can be used as ketone in order to obtain calix[4]pyrroles in three isomeric forms, with the cone conformer displaying topologicaly variabile multi-site or multi-point surfaces for binding anionic or neutral substrates[17].

Tetra-ester (**8**) and tetra-amide (**9**) macrocycles with «super-extended cavities» were noticed to have higher selective anion coordination properties[18].

The adition of 20 equivalents of Cl^-, Br^-, I^-, $H_2PO_4^-$ or HSO_4^- anions (as tetrabutylammonium salts) to deuteriated DMSO solutions of **8** and **9** caused no changes in the NMR spectra of these calix[4]pyrroles. This means that compounds **8** and **9** do not interact with these anionic guests in DMSO solution.

On the other hand, the addition of fluoride anions in the same conditions causes changes in the ^1H NMR spectra of compounds **8** and **9**, corresponding to the formation of fluoride complexes with slow complexation/decomplexation kinetics.

The presence of an extended cavity in compound **6** and a super-extended cavity in compounds **8** and **9** serves to decrease (**6**) and switch off (**8** and **9**) the affinity of this class of receptors for anions other than fluoride in DMSO solution[18].



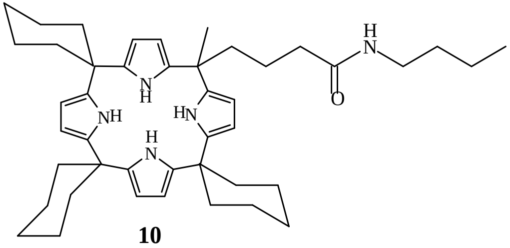
8 R = CH_2COOEt **9** R = CH_2CONEt_2

The binding behavior of the «super-extended cavity» tetraacetylcalix[4]pyrrole[19]. was investigated by NMR titration, and the complex was found to exclusively bind fluoride anions in DMSO-d_6 The binding behavior was investigated by Monte Carlo free energy perturbation simulations and Poisson calculations, and the ion specificity was seen to result from the favorabile electrostatic interactions that the fluoride gains by sitting lower in the phenolic cavity of the receptor[20].

Using different symmetrical or asymmetrical ketones were elaborated diverse calixpyrrole *meso*-substituted systems. It was observed that many of these systems demonstrate basic anion binding characteristics of the calix[4]pyrrole skeleton [21] and these properties are indeed affected by the number and type of substituents present on the *meso*-like bridges and/or β–pyrrolic sites.

An interesting application of functionalised calix[4]pyrroles is the separation of different mixtures using carboxylic acid functionalized calix[4]pyrroles attached to aminopropyl silica gel *via* both the *meso*-position (**10**) and *β*-positions (**11**). The stability constants (M^{-1}) of **10** and **11** in CD_2Cl_2 solution for different anions are respectively: chloride – 415(±45), 405(±10); dihydrogenphosphate - 62(±6), 80(±15); hydrogensulfate - <10, <10[22].

The calix[4]pyrrole-modified silica provide a new solid support for the HPLC separation of nucleotides, oligonucleotides, N-protected aminoacids and perfluorinated biphenyls. Using **Gel A** and **Gel B** (***Fig.1***) were separated: a) fluoride, chloride, bromide, hydrogensulfate, and dihydrogenphosphate anions; b) phenyl arsenate, phenyl phosphate, phenyl sulfonate; c) N-protected anionic aminoacids (serine, glutamine, alanine, phenylalanine, tryptophan, aspartate, and glutamate).



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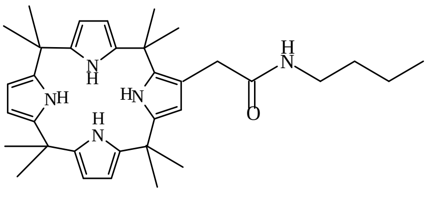

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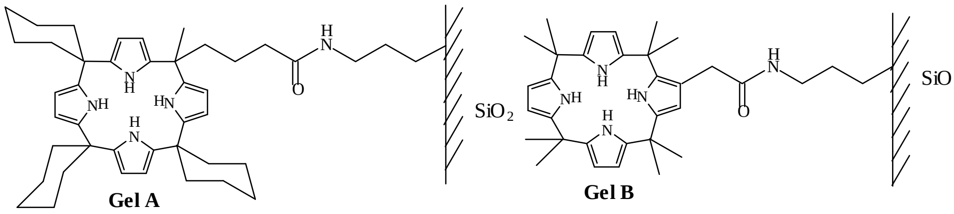
The **Gel A** was used for the HPLC separation of 5´-adenosine monophosphate (AMP), 5´-adenosine diphosphate (ADP), and 5´-adenosine triphosphate (ATP)[22].

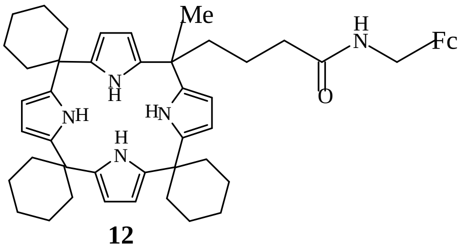


Gel A **Gel B**

Fig.1

These same media also permit the HPLC-based separation of mixtures of neutral species such as polyfluorobiphenyls[8a].

Calix[4]pyrroles containing the ferrocenyl (Fc) moiety attached to one of the *meso*-positions **12** and **13** bind anions in dichlorometane-d_2 solution[23].



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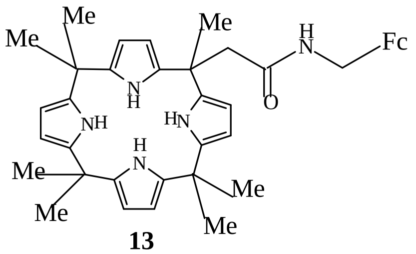
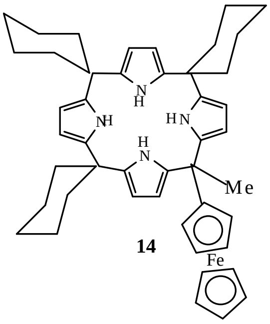


13

It was demonstrated by ^1H NMR titration studies in acetonitrile-d_3/ DMSO-d_6 (9:1, v/v) that calix[4]pyrrole **14** coordinates fluoride, chloride and dihydrogen phosphate in this solvent mixture with association constants (M^{-1}): 3375, 3190 and 304[24].

In the **Fig. 2** is designed the schematic representation of the ferrocene CH and calix[4]pyrrole NH hydrogen-bonding interactions, which permit to stabilise the bound anion.



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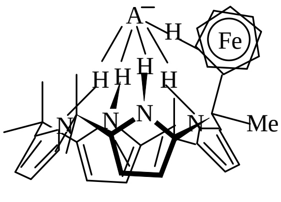
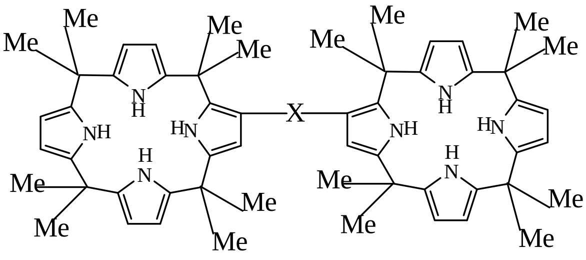


Fig. 2

Supramolecular interaction of calix[4]pyrroles with several inorganic anions was reported by addition of this macrocycle to the background electrolyte in capillary zone electrophoresis (CZE)[25]. It was observed that the retention time of all anions increases with increasing concentration of calix[4]pyrroles and the effect of F^- is most evident.

The analyses via FABMS of calix[4]pyrroles derived from steroidal ketones demonstrate that these macrocycles are reasonable in effecting the enantioselective recognition of appropriate organic anions. Results for antipodal R>S selectivity were obtained in the case of tartaric acid and mandelic acid[26].

Calix[4]pyrrole dimmers **15** [X=bond, p-C_6H_4, m-C_6H_4] synthesized by palladium (0) catalysed C-C bond formation show an interesting effect of cooperative binding[27]. In the case of **15** [X=bond] authors made a detailed study of carboxyl ate anion binding using ^1H NMR spectroscopy. For isophthalate anion it was observed a 1:1 binding stoichiometry and a much higher association constants was found than for the control monomer, octamethylcalix[4]pyrrole. For phthalate and benzoate anions, 1:2 (host:guest) binding stoichiometries and lower association constants were recorded than with isophthalate anion. The controle compound, octamethylcalix[4]pyrrole, showed a 1:1 binding stoichiometry and much lower association constants than **15** [X=bond], not just with isophthalate, but also phthalate and benzoate anions[27].



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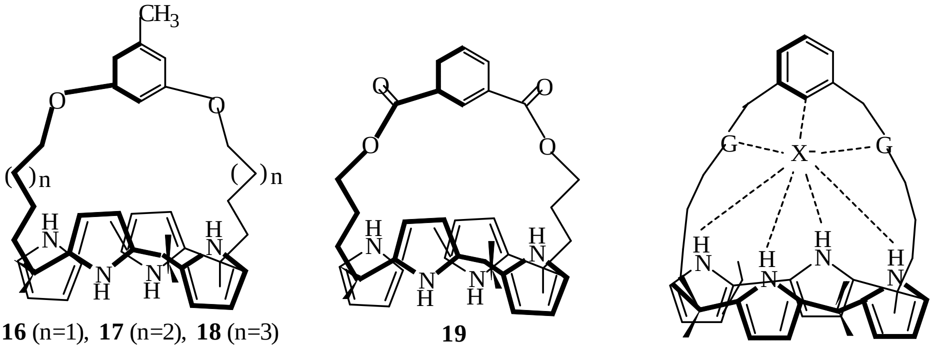
The calix[4]pyrroles bearing m-orcinol-derived diether straps of different lengths on one side of tetrapyrrolic core **16-18**[28] and the analogous diester **19**[29] display enhanced affinities for chloride and bromide anion.

Schematic representation of strapped calix[4]pyrroles show how the properties of the parent system can be modified (X^- represents an anion and G – an ancillary binding motif) [**Fig.3**].

It was found that the anion binding ability of these systems could be effectively tuned by modifying the length and nature of the bridging straps. In the specific case of the diether systems the largest chloride affinity in acetonitrile and DMSO was seen with the shortest strap, whereas the highest affinity for bromide anion was recorded in the case of the longest strap (**Table 3**).



16 (n=1), **17** (n=2), **18** (n=3) **19**

Fig. 3

Table 3

*Association constants for the binding of chloride and bromide by compound **16-19** measured by isothermal titration calorimetry (ITC) at 30°C using the corresponding alkylammonium and cryptand salts.*

TBA=tetrabutylammonium.

calix[4]pyrrole[28]	*TBA-Cl*[28]	*K-cryptand-Cl*[28]	*TBA-Br*[28]	*TBA-Cl*[28]
	CH_3CN			*DMSO*
16	3 630 000	4 270 000	30 000	340 000
17	1 370 000	1 810 000	31 000	11 000
18	1 370 000	1 810 000	120 000	7 400
19	1 380 000	1 620 000	~0	110 000

On the basis of these findings, as well as supporting ^1H NMR spectroscopic studies, it was postulated that not only cavity size, but also the ability of the aryl portion of the strap to serve as CH hydrogen bond site are important in tuning the observed anion affinities.

X-Ray crystal analyses of the Bu_4NCl complex of calixpyrrole **1** and the Bu_4NF complex of calixpyrrole **2** revealed that in both cases the calix[4]pyrrole ligand adopts a cone-like conformation in the solid state. In the case of the chloride complex (**Fig.4**) the nitrogen-anion distances are in the range of 3.3264(7)-3.331(7)Å, while for the corresponding fluoride complex they are 2.790(2)Å[8a]. The results demonstrate that in these two complexes the chloride and fluoride anions reside 2.319(3) and 1.499(3) Å above N_4 root mean square planes of calixpyrrole **1** and **2**, respectively. Thus, the fluoride anion appears to be more tightly bound, at least in the solid state.

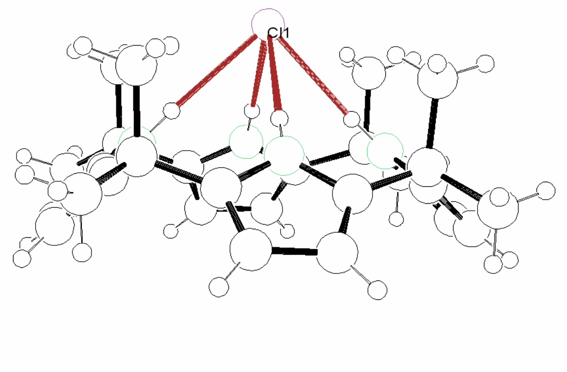


Fig. 4

In order to find the explanation of the conformation of calix[4]pyrroles in the absence of halide anion in comparison with its conformation in the presence of the same anion some theoretical studies were made. The complexation of anions by octamethylcalix[4]pyrrole **1** and 2,5-dimethylpyrrole were investigated by energy minimizations in the gas phase and by Monte Carlo (MC) simulations in dichloromethane using the OPLS force field[30]. It was found that, in agreement with experiment, the 1,3-alternate conformation of **1**, in which adjacent pyrrole rings are pointing in opposite directions, is the most stable conformation in the absence of a halide anion. The cone conformer of **1**, having all pyrrole units in a parallel orientation, is not stable in the absence of halide anion, but it is the most stable conformation upon anion binding due to the formation of four NH-halide hydrogen bonds. The relative free energies of binding of chloride, bromide and iodide with the cone of **1** in dichloromethane were calculated with free energy perturbation (FEP) simulations to be in the excellent agreement with experiment. The calculations predict a far greater affinity for fluoride ion than was measured. Authors explained this fact by the influence of the presence of trace amounts of water.

Later it was examined the influence of different factors on the anion binding properties of calix[4]pyrroles. The binding of different anions to calix[4]pyrrole was studied using molecular dynamics coupled to thermodynamic integration calculations. The effect of diverse apolar solvents, octafluoro substitution, and the change in binding free energy derived from the presence of cosolute and water traces were studied [31]. It was demonstrated that both calix[4]pyrrole **1** and octafluorocalix[4]pyrrole **5a** have preference for F^- in the gas phase and pure aprotic solvents, but the situation can change much in protic solvents or in the presence of the hydrated cation which is used as cosolute of the anion. These results provide interesting clues for a better understanding of the process detected experimentally as «binding».

CALIX[4]PYRROLES – SENSORS FOR ANIONS

The development of chemosensors for specific chemical species is emerging as a research area of considerable importance within the generalized field of supramolecular chemistry.

As shown before the calix[4]pyrroles are very good anion receptors[8a] so they show considerable promise in the area of anion sensing.

In general, such systems contain some combinations of substrate-recognition functionality (receptor) and optical-signaling capacity (cromophore), either directly linked or appropriately associated in a noncovalent manner, and are designed to permit the detection of substrates by binding-induced changes in absorption or emission properties[32]. The use of calix[4]pyrroles as chromatic sensors and fluorescent sensors is presented below.

Chromatic sensors

While the utility of these approaches are becoming increasingly appreciated in terms of both qualitative and quantitative analysis, the number of chromatic sensors available at present for anionic substrates remains quite limited. Only a few chemical systems are known that undergo colour changes of sufficient magnitude that they can be used for the direct «naked-eye» sensing of anions[6].

In the process of the formation of the complex from *meso*-octamethylcalix[4]pyrrole **1** and the 4-nitrophenolate anion (yellow) **20** in MeCN or CH_2Cl_2 the colour of the complex **1•20** disappears (*Scheme 1*)[6]. Complexation studies were made using ^1H NMR titration techniques. Significant downfield shift (from δ 7.0 to 10.6) of the pyrrole NH proton was observed upon the addition of 5 equiv. of tetrabutylammonium 4-nitrophenolate, consistent with the formation of calixpyrrole – phenolate hydrogen bonds. Analysis of titration data using the EQNMR computer program[10] revealed that *meso*-octamethylcalix[4]pyrrole forms a 1:1 complex with 4-nitrophenolate with a stability constant of 290 (±9.7) $dm^3\ mol^{-1}$.

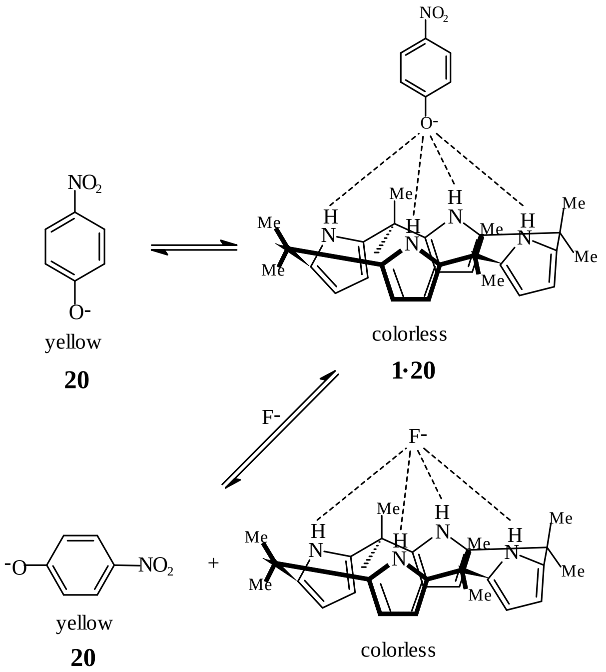
Because this value is much lower than that reported earlier for F^- (17 200 M^{-1}), the substitution of a *p*-nitrophenolate by F^- took place when a CD_2Cl_2 solution of the complex **1•20** was treated with aliquots of tetrabutylammonium fluoride. After an initial addition of 0.2 equiv. of fluoride, the NH proton resonance broadened and could not be located in the NMR spectrum. Only after addition of 1.0 equiv. of fluoride did the NH resonance reappear, further shifted downfield by over 3 ppm as compared to **1•20**, indicating the formation of a calixpyrrole-fluoride complex. As expected from the values of the stability constants, tetrabutylammonium chloride and dihydrogenophosphate produced smaller downfield shifts (0.78 for Cl^- and 0.37 ppm for $H_2PO_4^-$).

The strongest absorbance is observed upon addition of fluoride anions followed by chloride and dihydrogenphosphate anions. This trend reflects the absolute and relative affinities of *meso*-octamethylcalix[4]pyrrole for these anionic guests (**Table 4**)[6].

Table 4

Relative absorbance values for calixpyrrole – 4-nitrophenolate solutions containing equimolar concentrations of various anions.

Anions	**F^-**	**Cl^-**	**$H_2PO_4^-$**	**Br^-**	**HSO_4^-**
Δ Absorbance	0.282	0.193	0.162	0.092	0.015
Relative absorbance	1.0	0.68	0.57	0.33	0.05

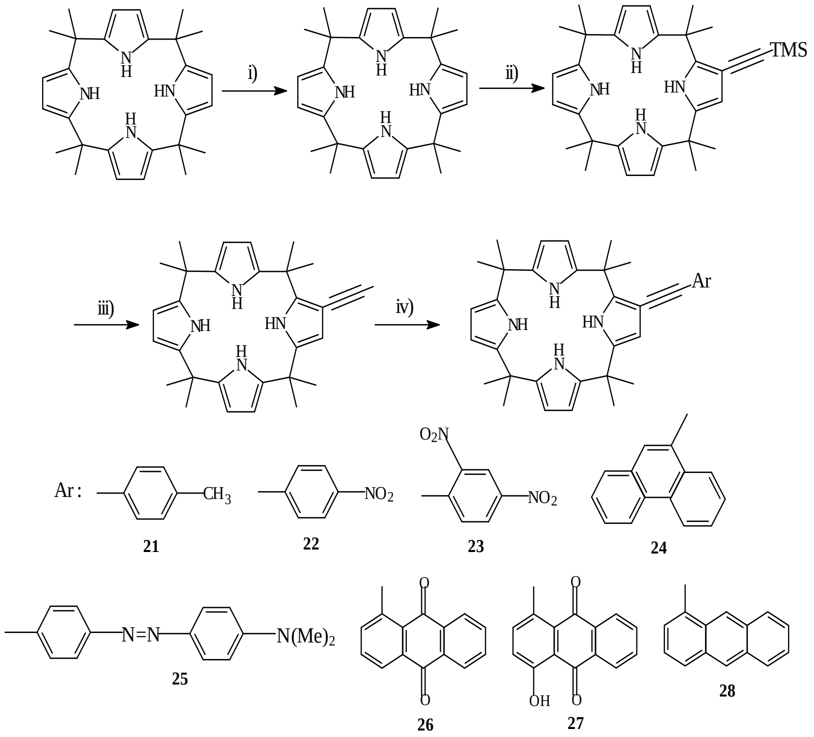


Scheme 1

The calix[4]pyrroles, such as **1**, may be used to produce anion sensors that can report the presence of anions (for example, fluoride anion) by means of a colour change.

Compounds **21-25** with arylalkynyl groups onto one of the *β*-pyrrolic positions of the calix[4]pyrrole skeleton (*Scheme 2)* were prepared by metal-mediated carbon-carbon bond cross coupling reactions, especially the Sonogashira reactions. Compound **21** contains an electron-donating substituent, whereas both calix[4]pyrroles **22** and **23** contain electron-withdrawing aryl subunits. Furthermore, compounds **24** and **25** contain a built-in fluorophore and a built-in chromophore, respectively[33].

It was found[33] that the mono- and dinitrophenyl-functionalized systems **22** and **23** undergo naked eye-detectable spectral changes upon exposure to the tetrabutylammonium salts of fluoride, chloride, and phosphate anions in a dichloromethane solution. The addition of fluoride anion to dichloromethane solutions of **23** (5×10^{-5}M) leads to a significant broadening of the UV – VIS absorption bands while engendering a noticeable red-shift in the position of the absorption maximum (λ_{max} shifts from 441 to 498 nm). As a consequence of these anion-induced spectral changes, the solution undergoes a naked-eye detectable colour change from yellow to red. Addition of 200 equiv. of tetrabutylammonium chloride caused the change of the color from yellow to orange (the absorption maximum, λ_{max}, shifts from 441 to 483 and 478 nm, respectively). Exposure to bromide, iodide and sulfate anions, even in vast excess did not lead to any noticeable changes in either colour or basic spectral properties.



Scheme 2. (i) I_2-$(CF_3CO_2)_2$PhI (20%); (ii) TMS acetylene, Pd$(PPh_3)_4$ (73%), CuI; (iii) tetrabutylammonium fluoride, then $NaHCO_3$ (89%); (iv) ArI, Pd$(PPh_3)_4$, CuI.

The treatment of the mononitrobenzene conjugated calix[4]pyrrole **22** with 20 equiv. of tetrabutylammonium fluoride changed the colour of the solution from pale yellow to intense yellow related to the shift of the absorption peak from 391 to 433 nm[6]. The presence of chloride and phosphate anions could also be detected from the intense final yellow colour after their exposure to **22**. No discernable change could be noticed when dichloromethane solution of **22** was exposed to 200 equiv. of bromide, iodide and sulfate anions.

No important changes were observed for compound **21** when it was treated with anions. It is thus clear that "attachment" of nitro groups produces a bathochromic shift in the absorption peak (this effect is especially pronounced in the case of dinitrobenzene compound **23**).

The functionalized calix[4]pyrroles of the type described above could emerge as useful anion sensors and the ***Fig. 5*** represents the schematic mechanism of the changes in colour observed when calix[4]pyrrole **23** is exposed to certain anions.

Calix[4]pyrrol-anthraquinones systems **26**, **27** and **28**[32] act as an optically sensitive indicator of anion binding.

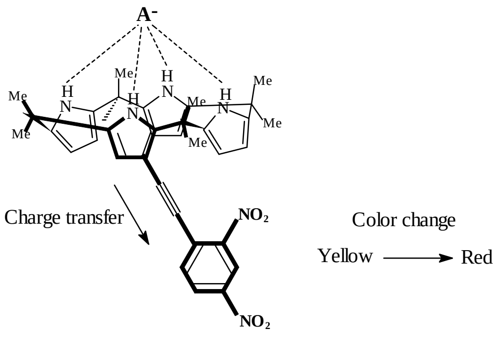


Fig.5

System **26** represents a good sensor for F^-, Cl^- and $H_2SO_4^-$ in dichloromethane and the effect can be detected with "naked-eye". In the absence of anions, the absorption spectrum of receptor **26** is characterized by the presence of two peaks at λ_{max}=357 and 467 nm, (in comparison with anthraquinone itself which has λ_{max}=327 nm). Upon the addition of fluoride anion, the peak at 467 nm decreases while a new peak appears at 518nm, the color of the solution modifies from yellow to red. These changes are complete after the addition of only six equivalents of F^- ions. The addition of either chloride or phosphate ions induced a less impressive colour change (from yellow to reddish-orange) and required greater amounts of anion to effect a commensurate change (the absorption peak shifts to 501 and 497 nm upon the addition of 100 equivalents of tetrabutylammonium chloride and phosphate, respectively).

Exposure to bromide, iodide, and sulfate anions, species that do not bind to calix[4]pyrroles appreciably[32], did not lead to any noticeable change in colour. This combination of anion-specific response/nonresponse makes this system an effective naked-eye-detectable anion sensor.

The addition of 100 equivalents of various anions to dilute (5.0×10^{5}M) solutions of **27** in dichloromethane is accompanied by the colour change of the system from red to blue or purple, again with the most pronounced effect for fluoride ions.

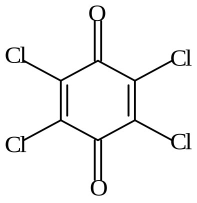
The above qualitative changes are reflected in more quantifiable terms in the corresponding absorption spectra. Whereas 4-hydroxyanthraquinone itself is pale yellow and displays an absorption maximum at 405 nm in dichloromethane, conjugation to calix[4]pyrrole through an alkyne spacer shifts the absorption maximum to the red region of the spectrum and produces a species with lowest energy absorption maximum at 526 nm. Upon the addition of fluoride ions, the absorption maximum is shifted even further (to 613 nm) and the solution turns blue. Similar, but less pronounced bathochromic shifts are seen upon the addition of excess chloride and dihydrogen phosphate ions, with the lowest energy maxims being observed at 567 and 549 nm, respectively. In these cases the colour of the solution change from red to purple and to dark purple, respectively.

No significant colour changes were observed upon the addition of bromide, iodide, and sulfate ions. These spectral results, as well as the corresponding visual changes, are thus completely consistent with the association constants for **27** with different anions, namely $F^->Cl^->H_2PO_4^->>Br^-\sim I^-\sim HSO_4^-$.

The origins of the dramatic colour changes observed with chemosensors **26** and **27**, was ascribed to charge-transfer interactions between the electron-rich, calix[4]pyrrole-bound anions and the electron-deficient anthraquinone moieties. The anthracene-containing control compound **28**, a calix[4]pyrrole system bearing a more electron-rich appendage, does not act as a naked-eye-detectable anion sensor, while the addition of 100 equivalents of tetrabutylammonium fluoride to a 5.0×10^5M solution in CH_2Cl_2 induced only a slight bathochromic shift in the absorption maximum (λ_{max} shifts from 408 to 416 nm) along with a modest reduction in absorption intensity. Detailed ^1H NMR spectroscopic and fluorescence analyses revealed, however, that **28** nonetheless acts as an efficient receptor for F^- Cl^-, and $H_2PO_4^-$ ions under these conditions[11].

The non-covalent calix[4]pyrrole-chloranil aggregation has been used as anion sensor for the facile identification of F^- and $H_2PO_4^-$ ions in chloroform and it can be used as a chromatic sensor for effective and selective detection of F^- and $H_2PO_4^-$ anions. The specific phosphate/chloride selectivity is potentially advantageous in biological sensing applications[34].

These systems were investigated using UV-VIS spectroscopic techniques. Chloranil **29** itself displays an absorption maximum at 370 nm in chloroform. In the presence of calix[4]pyrrole **30**, the peak at 370 nm undergoes an obvious increase, while a new absorption peak appears at 622 nm. The colour of mixed system changed from pale yellow to blue, as a result of the formation of 1:1 molecular complex (with the binding constant 5800 M^{-1}), which was confirmed by Job plot analysis.



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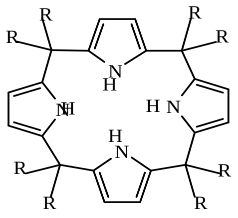


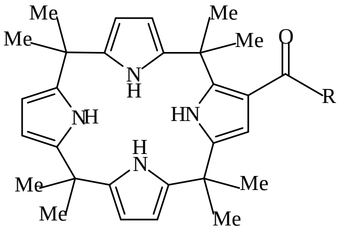
30 R = Et

Similarly, the addition of *meso*-cyclopentylcalix[4]pyrrole **2b** to the solution of chloranil changes the colour from pale yellow to purple (at 550 nm). However, under the same conditions, less impressive changes were observed upon addition of *meso*-octamethylcalix[4]pyrrole **1**, or *meso*-tetracyclohexylcalix[4]pyrrole **2** to the solution of **29**[34].

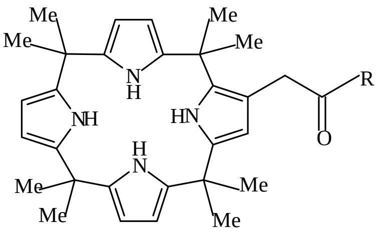
Fluorescent sensors

Fluorescent anthracene-calix[4]pyrrole conjugates **31-33** are the receptors which can detect the presence of anions by a significant quenching of their fluorescence[35].

Quenching was observed in varying degrees upon addition of other anions to receptors **31-33**; the addition of fluoride anion to **31** causes the highest fluorescence quenching, followed by dihydrogenphosphate and chloride anions.



31 R = NH-1-anthryl



32 R = NH-1-anthryl
33 R = $NHCH_2$-9-anthryl

The same anion can quench the fluorescence of different calix[4]pyrrolic systems with distinct efficiency, as it is shown in **Table 5**.

Table 5

*Stability constants for compounds **31**, **32** and **33** with various anions (as tetrabutylammonium salts) in CH_2Cl_2 and CH_3CN as determined from fluorescence quenching analyses at 25°C.*
"-" - quenching insufficient to provide an accurate stability constant value.

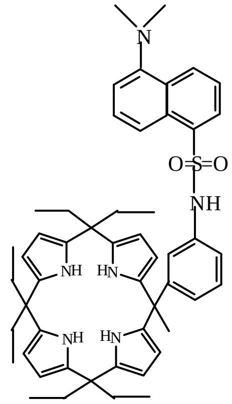
Anions	*Log K (in CH_2Cl_2)*			*Log K (in CH_3CN)*		
	31[35]	**32**[35]	**33**[35]	**31**[35]	**32**[35]	**33**[35]
F^-	4.94	4.52	4.49	5.17	4.69	4.69
Cl^-	3.69	2.96	2.79	4.87	3.81	3.71
Br^-	3.01	-	-	3.98	2.86	-
$H_2PO_4^-$	4.20	3.56	-	4.96	3.90	-

The highest stability constants found for compounds **31** can be explained by the conjugated bond pathway linking the fluorophore and anion-binding site of the calixpyrrole providing an electronic communication pathway between them. Compounds **31-33** represent prototypical calix[4]pyrrole based-fluorescent anion sensing agents.

Calix[4]pyrroles **34-36** represent the second generation of calixpyrrole-based fluorescent anion sensors[36]. These systems bind anions with greater affinity than previous systems while displaying a more efficient fluorescent response. In the design of sensors **34-36**, a rigid aromatic spacer was used so as to fix the distance between the quencher (anion) and the signalling moiety. This spacer element contained either a sulphonamide (compounds **34** and **35**) or thiourea (sensor **36**) group.

These linker moieties were introduced with the expectation that they might provide additional hydrogen bond donor sites that would act in concert with the calixpyrrole NH protons to enhance the overall anion binding affinities. The affinity constants for all three sensors and four anions are listed in **Table 6**[36].

Sensors **34-36** display the highest anion binding affinities so far recorded for calixpyrrole-type receptors. They are also the first to show high phosphate/chloride selectivity (2 orders of magnitude) and, in the case of sensor **36**, the first such systems to operate successfully in the presence of water at physiological pH.



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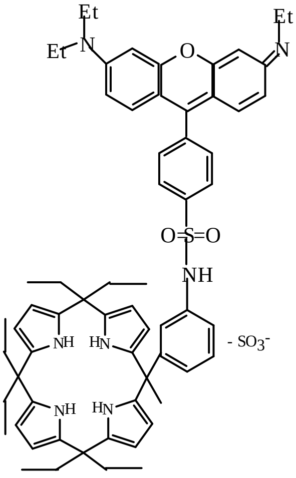

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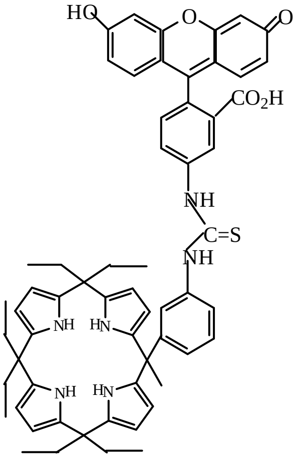


36

Table 6

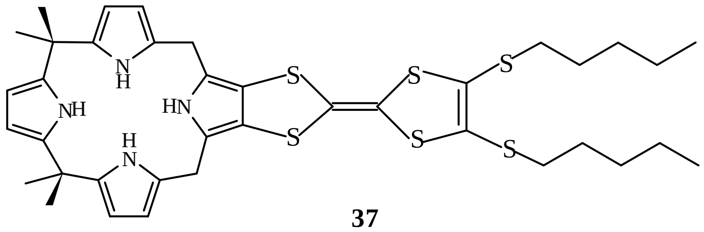
*Affinity constants for sensors **34-36** and anionic substrates as determined in acetonitrile (0.01% v/v water) for sensors **34** and **35** and acetonitrile-water (96 :4, pH=7.0±0.1) for sensor **36**.*

Anions	*Association constants (mol^{-1}) determined by emission quenching*		
	34 (5×10^{-6}M) [36]	**35** (5×10^{-6}M) [36]	**36** (5×10^{-6}M) [36]
F^-	222 500	>1 000 000	>0 200 000
Cl^-	10 500	18 200	<10 000
$H_2PO_4^-$	168 300	446 000	682 000
$HP_2O_7^{3-}$	131 000	170 000	>2 000 000

Electrochemical sensors

Only a few electrochemically active sensors based on calix[4]pyrroles have been reported[37,38]**.** Electrochemically active sensors, designed to permit the detection of substrates by binding-induced changes in the redox properties, are generally composed of a receptor unit, which works by the covalent association of a substrate-recognition functionality, and an electrochemical-signaling capacity (redox-active unit).

The redox-active tetrathiafulvalene (TTF) unit can exist in three stabile redox states (TTF^0, TTF^+, and TTF^{2+}). This unit was used in the synthesis of the first calix[4]pyrrole incorporating a TTF redox moiety **37** which is an efficient chemosensor and allows the detection of anions by electrochemical means[38].



37

This system displays the strongest anion binding affinities yet recorded for calix[4]pyrrole receptors, and the binding constants between **37** and Br^-, Cl^-, and F^- ions are two orders of magnitude higher than those reported for *meso*-octamethylcalix[4]pyrrole **1** under the same conditions[8a] (**Table 7**).

Table 7[38]

Binding constants between ***37*** *and the* Br^-*,* Cl^-*, and* F^- *ions determined by* ^1H *NMR spectroscopy at 300 K, and first redox potentials* $E^1_{1/2}$ *of the complexes* ***37***$\cdot X^-$ *(where X is a halide) determined by CV at 298K.*

X^-	K_a $[M^{-1}]$ $(CD_3CN/0.5\%\ v/v\ D_2O)$	$E^1_{1/2}$ [mV](MeCN)[a]	ΔE[mV](MeCN)[b]
Br^-	7 600[c]	+467	-34
Cl^-	120 000[d]	+462	-43
F^-	2 100 000[e]	-	-

[a] – values obtained from 1:1 mixtures of **37** and nBu_4NX; [b] – maximum (ΔE_{max}) were obtained from 1:2 mixtures of **37** and nBu_4NX; [c] – a CD_3CN (0.5% v/v D_2O) solution of nBu_4NBr which also contained receptor **37** at the initial concentration to account for dilution effects; [d] – determined from competitive binding experiments. An average K_{rel} of 16.8 for the ions Cl^-/Br^- was obtained by analyzing a CD_3CN (0.5% v/v D_2O) solution of **37** (3.9 mM) containing Br^- (3.9 equiv.) and Cl^- (either 1.6 or 2.1 equiv.), estimated error was <15%; [e] – determined from competitive binding experiments. An average K_{rel} of 16.9 for F^-/Cl^- was obtained by analyzing a CD_3CN (0.5% v/v D_2O) solution of **37** (3.9 mM) containing Cl^- (7.4 equiv.) and F^- (either 2.0 or 2.2 equiv.), estimated error was <15%.

The stronger affinity of **37** towards anions is presumably a direct consequence of the pyrrolo-TTF-NH proton being more acidic than the other NH protons of **37**. This fact implies that the pyrrolo-TTF-NH proton is able to form a stronger hydrogen bond with anions upon complexation, as compared to NH protons in the parent calix[4]pyrrole.

Calix[4]pyrroles were used as anion binding agents in liquid polymeric membrane ion-selective electrodes. Poly(vinyl chloride)-derived ion-selective electrodes prepared from *meso*-octamethylcalix[4]pyrrole **1** display at lower pH values (*i.e.*, 3.5 and 5.5) strong anionic responses toward Br^-, Cl^-, and $H_2PO_4^-$ and, to a much lesser extent in the case of F^-. By contrast, at high pH (*i.e.*, 9.0) ion-selective electrodes not only display cationic responses toward chloride and bromide anions but also selectivities (*i.e.*, $Br^- < Cl^- < OH^- \approx F^- < H_2PO_4^-$)[39]. This fact was considered consistent with the poly(vinyl chloride)-supported receptor behaving as a direct anion binding agent at low pH but acting as a hydroxide-complexing receptor at higher pH.

Using cyclic voltammetry were studied the electrochemical properties of ferrocenyl including calix[4]pyrroles **12** and **13** and it was demonstrated that these systems bind anions in dichloromethane-d_2 solution[23]. Electrochemical studies using cyclic voltammetric and square-wave voltammetric techniques of calix[4]pyrroles **14** containing a ferrocene moiety attached to one of the *meso*-position show cathodic shifts of up to 100 mV with dihydrogenphosphate anions[24].

BINDING OF NEUTRAL SUBSTRATES

Molecular recognition of neutral compounds presents a challenge in the area of supramolecular chemistry. Binding of substrates such as short-chain alcohols and simple monoamides is particulary difficult because these molecules have few functionalized sites available for hydrogen bonding, and they lack the large hydrocarbon surface necessary to participate in efficient hydrophobic or π - π stacking interactions. Association constants for neutral substrate/synthetic receptor complexes are thus generally modest, even though the architectural complexity of the receptors is often high[1].

It was found that the molecular recognition chemistry of the calix[4]pyrroles is not limited to anionic substrates. The coordination of neutral species was achieved using *meso*-octamethylcalix[4]pyrrole **1**. The ^{1}H NMR titration experiments in C_6D_6, revealed that this calix[4]pyrrole forms complexes with neutral species, including short chain alcohols, amides and other oxygen-containing neutral species[10]. Although the binding constants are modest, a clear trend is evident within the alcohol and amide series. Specifically, it was found that the relevant stability constants decrease as the steric bulk around the oxygen atom is increased (**Table8**)[8a].

The structure of **1** coordinated to two molecules of MeOH was determined by X-ray diffraction analysis. The calixpyrrole in this neutral substrate adopts a 1,3-alternate conformation in the solid state. In the case of DMF molecules, each of the two DMF molecules was found to be coordinated to a single calix[4]pyrrole macrocycle *via* two hydrogen bonds and this complex adopts a 1,2-alternate conformation [8a].

Similarly, using X-ray analysis it was found that calix[4]pyrrole **2a** also acts as a receptor by H-bond interactions to an EtOH solvent. The pyrrole groups are arranged in a 1,3-alternate conformation that gives rise to disorder in the EtOH guest, due to its ability to coordinate both above and below the plane of the macrocycle[40].

Table 8

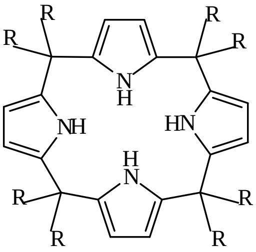
*Association constants for **1** with neutral substrates*

Neutral substrate	*$K_a(M^{-1})$*	*Neutral substrate*	*$K_a(M^{-1})$*
MeOH	12.7±1.0	*N,N*-dimethylacetamide	9.0±0.9
EtOH	10.7±0.7	1,1,3,3-tetramethylurea	2.2±0.1
BnOH	9.7±0.7	DMSO	16.2±1.1
Pr^iOH	7.0±0.4	1,2-dimethylimidazole	5.4±0.3
Bu^sOH	6.2±0.4	acetone	2.2±0.2
N-formylglycine ethyl ester	13.3±1.0	nitromethane	-
DMF	11.3±0.8		

Meso-octaethylcalix[4]pyrrole **30** inclusion crystals with lower alcohols undergo reversible guest-responsive structural changes, for much a long-range cooperative effect with a Hill coefficient of 40 was observed[41].

According to the X-ray analysis, the conformation of octabenzylcalix[4]pyrrole **38** in **38**$\cdot$2(acetone)$\cdot$acetone$_{lattice}$ is 1,3-alternate (as in **1**$\cdot$2(MeOH)), but the two acetone guests are both located on the *same* face of the ligand, held in place by single H-bonds.

The molecular structure of **38**$\cdot$2(acetone)$\cdot$acetone$_{lattice}$ demonstrates that the NH groups of bulky calixpyrrole 38 can access the carbonyl portion of acetone**,** thus, the weak solution binding of acetone by unhindered **1** (K_a = 2.2±0.2 M^{-1}) cannot be explained on steric grounds. In this case, water could not be completely removed from the solution used in the titrations, and the presence of this competing H-bonding material could account for the low apparent K_a.



38 R = CH_2Ph

These results confirm that the calixpyrroles can be used to bind neutral species both in solution and in the solid state.

Calix[4]pyrroles **6** and **7** containing deep cavities and fixed walls show binding properties not only for anions, but also for neutral species. For example, in the specific case of the αααα isomer of **6**, a deep cavity structure was observed in the solid state, wherein the calixpyrrole core is in a so-called cone conformation (***Fig.6***). Structures of lower symmetry are seen in the case of the other isomers, with conformations other than pure cone (*e.g.*, 1,3-alternate, partial cone) being observed in certain instances (*e.g.*, the αααβ isomer of **7**; **Fig.6**)[16].

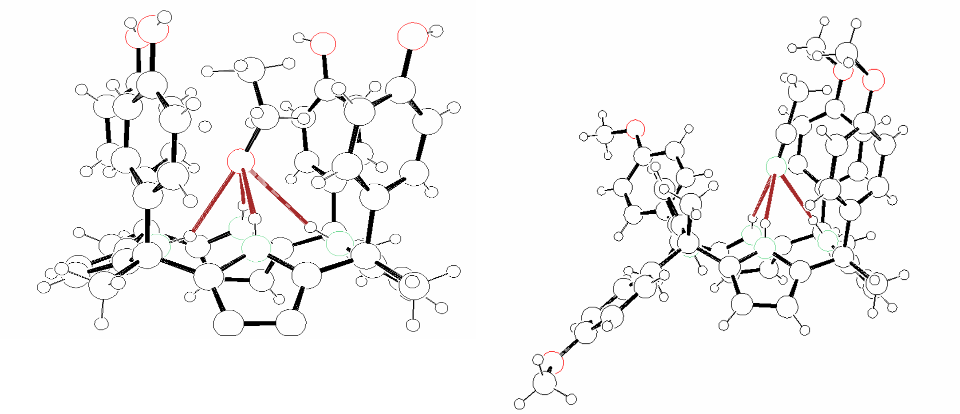


Fig. 6. *View of the molecular structures of the ethanol adducts of the αααα isomer of **6** in the cone conformation (left) and the acetonitrile adduct of the αααβ isomer of **7** in the partial cone conformation (right). Dashed lines are indicative of a hydrogen-bonding interaction.*

Some calix[4]pyrroles with extended or superextended cavities play an important role in multi-point or multi-site host-guest interactions. For instance, compound **6** in its cone conformation **a** is associated into dimmers or trimmers, the molecular complexity being determined by the guest molecule. In the presence of hydrogen-binding substrates such as DMF or acetic acid, the isomer **6a** is assembled into closed two-basket cavity dimmers, **6a**·DMF, or into cyclic turmeric units **6a**·AcOH[3].

The trimeric cavity hosts nine molecules of AcOH, three of them being associated to the calix[4]pyrrole moieties while the other six establish an intermolecular hydrogen bonding network with other trimmers.

It was observed that not only the attached moiety, but also its position influences the selectivity of the calix[4]pyrroles. Systems containing cytosine-substituted calix[4]pyrrole conjugates, bearing the appended cytosine attached at either a β- or *meso*-pyrrolic position, were tested as nucleotide-selective carriers and as active components of nucleotide-sensing ion-selective electrodes at pH 6.6[42]. Studies of carrier selectivity were made using a Pressman-type model membrane system consisting of an initial pH 6.0 aqueous phase, an intervening dichloromethane barrier containing the calix[4]pyrrole conjugate, and a receiving basic aqueous phase. Good selectivity was found for the Watson-Crick complementary nucleotide, 5'-guanosine monophosphate (5'-GMP), in the case of the *meso*-linked conjugate with the relative rates of through-membrane transport being 7.7:4.1:1 for 5'-GMP, 5'-AMP, and 5'-CMP, respectively. By contrast, the β-substituted conjugate, while showing a selectivity for 5'-GMP that was enhanced relative to unsubstituted calix[4]pyrrole, was found to transport 5'-CMP roughly 4.5 times more quickly than 5'-GMP. Higher selectivities were also determined for 5'-CMP when both the β-and *meso*-substituted conjugates were incorporated into polyvinyl chloride membranes and tested as ion selective electrodes at pH 6.6, whereas near-equal selectivities were observed for 5'-CMP and 5'-GMP in the case of unsubstituted calix[4]pyrroles. These seemingly disparate results are consistent with a picture wherein the *meso*-substituted cytosine calix[4]pyrrole conjugate, but not its β- linked congener, is capable of acting as a ditopic receptor, binding concurrently both the phosphate anion and nucleobase portions of 5'-GMP to the calixpyrrole core and cytosine "tails" of the molecule, respectively, with the effect of this binding being most apparent under the conditions of the transport experiments[42].

Another use of calix[4]pyrroles is the investigation of thin films of *meso*-tetra(methyloctyl) calix[4]pyrrole, which were transferred onto hydrophobized quartz and silicon oxide sheets by using the Langmuir-Schaefer (LS) method (horizontal lifting). Scanning force microscopy investigation show that the LS films are almost homogeneous and are consistent with the X-type configuration with the hydrophobic tails of the calix[4]pyrrole disposed almost perpendicularly with respect to the substrate. Induced circular dichroism (ICD) measurements were performed in the presence of chiral alcohol vapors, such as (-)-(R)-2-butanol, (-)-(R)-2-pentanol, and (-)-(R)-2-hexanol. The results show that although not chiral by themselves this kind of calix[4]pyrrole molecules within the film exhibit chirality induced by binding with the chiral guests. The reversibility of the binding event, coupled with the differentiated response observed towards the investigated alcohols, makes the LS films promising active layers for the chemical recognition of short-chain polar neutral molecules[43].

Silver surfaces covered with Langmuir-Blodgett (LB) films of *meso*-octaethyl-calix[4]pyrrole **30** were investigated as sensing material for alcohol vapors recognition by Surface Plasmon Resonance (SPR) transduction methodology[44,45,46] In particular, SPR tests were performed by exposure of calix[4]pyrrole **30** films at fast sequential alcohol insets in the optical cell. The results demonstrate that this calix[4]pyrrole provides a clear recognition of alcohol species used in the inset sequences.

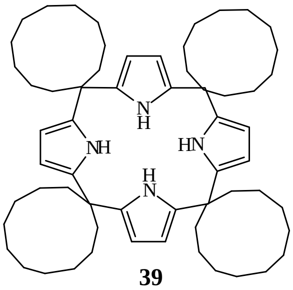
The same calix[4]pyrrole films were inspected by Atomic Force Microscopy (AFM). The films deposited onto silver were also tested for recognition of alcohol vapors by the SPR technique. The results reveal an increased sensitivity in the series isopropanol > ethanol > methanol[47].

CALIX[4]PYRROLES – POTENTIOMETRIC SENSORS FOR NEUTRAL SPECIES

Calix[4]pyrroles were applied as a new class of ligands of potentiometric sensors for neutral nitrophenol isomers. Lipophilic macrocyclic and acyclic derivatives of pyrrole were applied as sensory elements of liquid membrane potentiometric sensors destined for the recognition of neutral form of nitrophenol isomers. It was determined that the potential of liquid membranes containing pyrrole derivatives strongly depend on the pH of the solution. Their potentiometric responses generated in the presence of nitrophenol derivatives were studied at three different pH: 4.0, 6.0 and 8.0. It was found that all studied membranes respond towards the neutral form of nitrophenol isomers and do not respond to their anionic forms. It was determined that the symmetry of the macrocyclic cavity of calix[4]pyrroles has a very mild effect on the molecular recognition of nitrophenol guests and the membrane incorporating macrocycle pyrrole derivatives generate a higher potentiometric signal in the presence of neutral nitrophenol in comparison to membranes containing acyclic pyrrole derivatives. It was noticed that these sensors display higher selectivity for *para*-nitrophenol[48].

Using the same manner and calix[4]pyrrole **2a** and **39** as ligands authors[49] show a very high affinity of calix[4]pyrrole-containing liquid membrane electrodes to uptake of protons and very high selectivity toward *para*-nitrophenol, in his neutral form in the presence of other nitrophenols and dihydroxybenzene isomers.

They also demonstrate the mechanism of the potentiometric signal generation of these sensors, generally, consisting on the reversible interaction of protonated calix[4]pyrrole membrane surface with the neutral nitrophenol guest, and subsequent proton transfer from the interface to the aqueous solution.



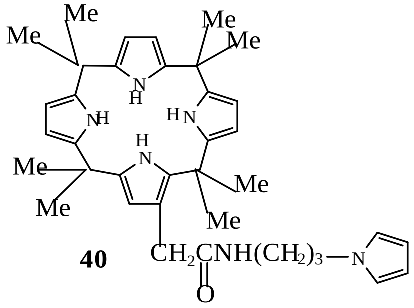
39

Potentiometric discrimination of fluoro- and chlorophenols isomers based on the host functionality of calix[4]pyrolle at liquid membrane interfaces was also reported by the same group of authors[50].

OTHER APPLICATIONS OF CALIX[4]PYRROLES

Tl(I) selective electrodes based on *meso*-octamethylcalix[4]pyrrole **1**, *meso*-octaethylcalix[4]pyrrole **30** and *meso*-tetraspirocyclohexylcalix[4]pyrrole **2** as sensor molecules were tested. This electrode exhibit a fast response time of 30 s and high selectivity over Na^+, K^+ and other metal ions with only Ag^+ interfering. It was demonstrated that this electrode works well in the pH range 2.0-11.0 and can be successfully employed for the determination of Tl^{+}. The presented electrode was also used as an indicator electrode in potentiometric titration of Tl^{+}[51].

The electropolymerization properties of calix[4]pyrroles containing pendant N-substituted pyrrole moieties **40** and **41** were studied and it was found that electrochemical copolymerisation with pyrrole was successful. By contrast, attempts to polymerise the calix[4]pyrroles alone failed[52].



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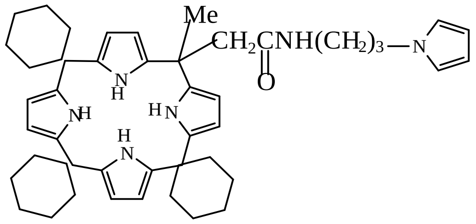

41

The examples presented in this review suggest that there could be a rich molecular recognition chemistry associated with calix[4]pyrroles. Not only the introduction of *meso*-, but also the β- substituents allow the anion and neutral binding and selectivity of the calix[4]pyrrole skeleton. Facile fictionalisation of calix[4]pyrrole systems opens the possibility of producing calixpyrroles with an endless variety of secondary binding sites that may allow for the optimised recognition of cationic, anionic, and neutral guests[16]. On the other hand, calix[4]pyrroles exhibit very interesting chromatic, fluorescent and electrochemical sensing properties, which can be used in different area.

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