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Tuning the anion binding properties of calixpyrroles by means of *p*-nitrophenyl substituents at their *meso*-positions

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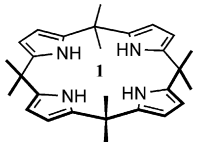
Abstract—Extended cavity calix[4]pyrroles and a calix[6]pyrrole were synthesized by cyclization of 5-methyl-5-(4-nitrophenyl)dipyrromethane with acetone in the presence of acid. The solid-state structures of the novel macrocycles were determined by X-ray crystallography. The host–guest chemistry of these receptors towards halide ions was investigated in solution by ^{1}H NMR titration techniques and compared with those of the *meso*-octamethylcalix[4]pyrrole and *meso*-dodecamethylcalix[6]pyrrole. The binding of chloride anions was observed to occur with different affinities on the two faces of the novel calix[6]pyrrole derivative described here.

1. Introduction

Calixpyrroles are a topic of considerable current interest in supramolecular chemistry because of their ability to act as receptors for anions.[1] These macrocycles bind anions by means of hydrogen-bonding interactions between the polar NH units and the electron-rich guests.[2] The simplest member of this family is calix[4]pyrrole **1**, which has been known since 1886,[3] but used as a receptor for anions only since 1996.[4] Over the last decade, studies on calixpyrroles as anion receptors have proliferated and a large number of derivatives have been reported. These include expanded calixpyrroles containing more than four pyrrole units,[5] 'hybrid' calixpyrroles[6] in which the macrocyclic structure also contains aromatic units other than pyrrole, calixpyrroles in which all or some of the pyrrole units have substituents other than hydrogen at their 3,4-positions,[7] *meso*-functionalized calixpyrroles (i.e., having substituents other than the methyl groups at the quaternary carbon atoms connecting the pyrrole units),[8] 'strapped calixpyrroles' in which an additional chain of atoms joins two *meso*-positions.[9] A number of calixpyrroles that have a combination of the above-mentioned features have also been reported.[10] These modifications of the basic calix[4]pyrrole structure produce a vast range of macrocycles having different and varied anion binding abilities.



meso-Substituted calixpyrroles are in principle especially easy to prepare because they can be assembled by the acid promoted condensation of pyrrole with the appropriate ketone. However, different ketones exhibit different reactivities towards condensation with pyrrole, and the initially formed '*meso*-substituted' dipyrromethanes also show different behaviours when subjected to macrocyclization with ketones under acidic conditions, depending on the nature of the *meso*-substituent(s).

Some elegant and well-exploited examples of this 'tuning' of the reactivity of the dipyrromethane moiety as a function of the *meso*-substituent(s) are the syntheses of expanded *meso*-substituted calix[6]pyrroles achieved by Eichen.[5d]

Previous studies have highlighted that the presence of electron-withdrawing substituents at the *meso*-positions of calixpyrroles enhances their ability to bind anions.[8e] Moreover, the use of the calixpyrrole structure as a means to 'hold' aryl units in a calixarene-like arrangement was explored by Floriani[8f] and Sessler,[8b,d,g] who also demonstrated the formation of various stereoisomers of tetra-*meso*-substituted calix[4]pyrrole from the condensation of unsymmetrical ketones (e.g., *p*-hydroxyacetophenone) and pyrrole.[8g]

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Inspired by these studies, we decided to synthesize the calixpyrroles that can be formed from 4-nitroacetophenone, pyrrole and acetone and to study their properties as receptors for anions. The *p*-nitrophenyl unit was selected for having electron-withdrawing character that would enhance the anion binding properties of the calixpyrroles to be synthesized,[8e] and for its potential to provide rather acidic CH units capable of forming additional hydrogen bonds[11] with anionic guests besides those provided by the pyrrole NH units. The *p*-nitrophenyl unit also has the potential to be involved in anion–π interactions with the selected (vide infra) substrates.[12]

2. Results and discussion

Treatment of a solution of 4-nitroacetophenone **2** in pyrrole (used as the solvent) with trifluoroacetic acid (TFA) gave the 5-methyl-5-(4-nitrophenyl)dipyrromethane (**3**), which was easily isolated (40%) by flash chromatography followed by crystallization from AcOEt (Scheme 1). Condensation of **3** with acetone (also used as the solvent) in the presence of TFA gave, after chromatographic separation, the α,α- and α,β-stereoisomeric calix[4]pyrroles **4a** and **4b** in comparable yields (18%) and the α,α,β-tris-4-nitrophenyl calix[6]-pyrrole **5b** in low yield (5%). We were unable to find evidence for the presence of the 'all α' stereoisomer **5a** in the reaction mixture.

The stereochemistries of **4a**, **4b** and **5b** were evident from their ^{1}H NMR spectra, which contained a number of resonances consistent with the symmetries of each macrocycle according to conformations averaged on the NMR timescale. Thus the methyl protons of **4a** (in $CDCl_3$) resonate as three signals of equal intensity, whilst those of **4b** appear as two resonances having 1:2 intensities. The ^{1}H NMR spectrum of **5b** shows three resonances for the NH protons and three ABX systems (partially overlapping) for the β-CH protons of the pyrrole units, and two different resonances (1:2 intensities) for the *meso*-methyl protons adjacent to the aryl units. These spectral features are consistent with an α,α,β-configuration of the *p*-nitrophenyl units at the *meso*-positions.

In the case of **4a** and **4b** their structures were also confirmed by X-ray crystallography, whilst to date we have been unable to obtain crystals of **5b** suitable for X-ray analysis.

The X-ray crystal structure of **4a** (Fig. 1) confirmed the α,α-configuration assigned by means of NMR spectroscopy. The calix[4]pyrrole adopts a 1,3-alternate conformation as observed for calix[4]pyrrole **1** when this is not binding a negatively charged guest.[13] The *meso*-carbon atoms have an rms deviation from their mean plane of only 0.08 Å. The two diametrically placed pyrrole units N3 and N6 rings are tilted with their NH units towards the macroring centre, their planes forming dihedral angles of 59° with the macroring mean plane defined by the four *meso*-carbon atoms. The other two pyrrole rings N2 and N5 have their planes almost perpendicular to the macroring plane (dihedral angles 94°, the NH units pointing away from the macroring centre). The molecule is helically twisted along the axis C1–C20, hence the aryl units are skewed by an angle of 51°. Unlike the α,β-isomer **4b** (vide infra), here the aryl groups have their planes almost facing the macroring centre (these planes, pivoting about the C1–C2 and C20–C21 *meso*-bonds, are tilted by 77° and 74°, respectively, with respect to the macroring

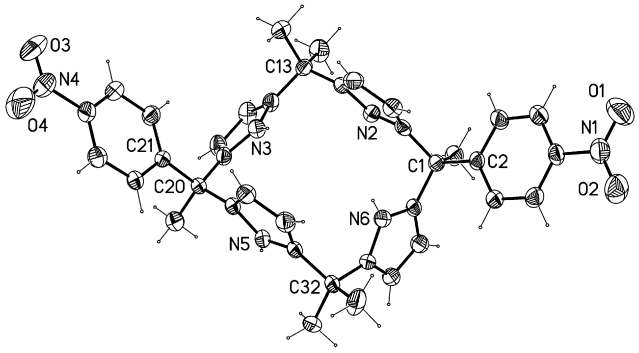
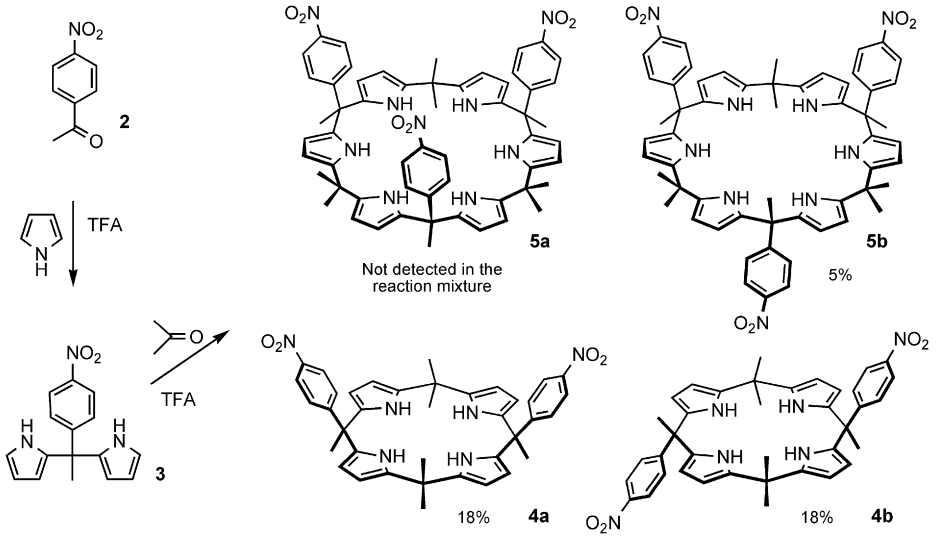


Figure 1. The X-ray crystal structure of macrocycle **4a** showing the labels of some key atoms. The two acetone solvent molecules are omitted for clarity. Thermal ellipsoids are drawn at 25% of probability level while H atom size is arbitrary.



Scheme 1.

centroid). The two benzo rings define a wedge-shaped cleft, which at its narrow end (i.e., the two diametrically placed *meso*-carbon atoms C1 and C20) is 7.1 Å wide, whilst the distance between the centroids of the two benzo rings is 11.26 Å. The latter distance can become considerably shorter by means of conformational changes of the calix[4]pyrrole moiety that can occur in solution and the aryl units can easily approach putative anionic substrates either with their π-systems or by means of their CH units.

The structure contains acetone solvent, two molecules for each macrocycle. Each acetone molecule is hydrogen bonded with its carbonyl oxygen atom to one of the NH units of either pyrrole N5 or N2. The acetone molecule hydrogen bonded to N5 [N5–H···O distances (Å) and angle (°) 3.01, 2.25, 171] also inserts one of its methyl groups into the cleft formed by the pyrrole rings N3 and N6: there are two CH–π interactions between this methyl group and the heterocyclic rings (C–H···pyrrole centroid distances of 3.5 Å). The molecular packing is dominated by the usual weak van der Waals interactions.

The X-ray crystal structure of **4b** (Fig. 2) confirmed the α,β-configuration of the two *p*-nitrophenyl units, which adopt an anti-parallel orientation with their C1–N1 or C1′–N1′ vectors forming angles of 136° with the C1–C1′ vector. These aryl rings have an edge-on orientation with respect to the macroring centre, and their planes form dihedral angles of 61° with the mean plane of the macrocycle defined by the four *meso*-carbon atoms. The pyrrole units adopt a 1,2-alternate conformation, their planes forming dihedral angles of 53° with the plane of the macrocycle. The molecule has a centrosymmetric conformation and lies on a crystallographic centre of inversion. This conformation differs from the 1,3-alternate conformation observed for the α,α-isomer **4a**. There is no solvent included in the crystal lattice. The supramolecular structure of the crystal is stabilized by a network of hydrogen bonds involving the pyrrole NH units and the oxygen atom of the nitro group of an adjacent molecule at the equivalent position: $-x+1/2, y+1/2, -z+1/2$: N2–H2···O2 and N3–H3···O2 bond lengths (Å) and angles (°): 3.30, 2.46, 166.8 and 3.21, 2.36, 170.8, respectively.

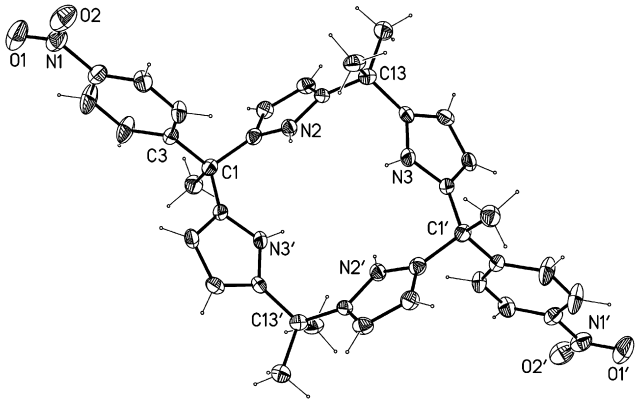
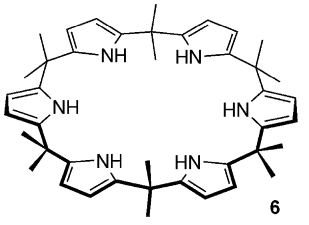


Figure 2. The X-ray crystal structure of **4b** showing the labels of some key atoms. The molecule is placed on a crystallographic centre of symmetry and only half the unit is independent while the other equivalent half is generated by the symmetry operation $-x, 1-y, -z$. Thermal ellipsoids are drawn at 25% of probability level while H atom size is arbitrary.

The novel receptors were tested for their ability to bind halide anions (as their n-Bu_4N^+ salts) by means of ^{1}H NMR titration experiments[14] based on the complexation induced shifts (CISs) of the NH resonances upon addition of the salts at 21 °C. Satisfactory fitting of the data was obtained for the 1:1 binding model. In several cases (vide infra) the K_a values of the macrocycles under investigation towards a given anion were determined by competitive binding with another receptor having a known K_a for that anion.[15] We selected CD_2Cl_2 as the solvent in order to obtain data that would be comparable with previous studies on calix[4]pyrrole **1**[4] and calix[6]-pyrrole **6**.[5b] Since water is known to have a dramatic effect on the K_a values for complexation involving hydrogen bonds,[16] titration experiments were conducted both in 'as dry as possible conditions' and in water-saturated CD_2Cl_2 (D_2O 0.18% v/v at 21 °C) hereafter referred to as 'dry' and 'wet', respectively. The 1:1 K_a values thus obtained are listed in



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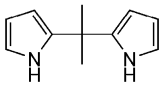

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Table 1. Association constants (K_a M^{-1}, 21 °C) for the formation of 1:1 complexes of the listed receptors with the indicated halide anions as *n*-butylammonium salts

	F^-		Cl^-		Br^-
	D[a]	W[a]	D[a]	W[a]	D[a]
4a	ca. 8.4×10^5 [b]	$1.1\times10^4\pm388$	2300±80	380±24	34±10
4b	ca. 1.2×10^5 [b]	$1.2\times10^4\pm1000$	163±25	30±3	Not tested
5b	ca. 8.4×10^5 [c]	NH disappears	ca. 2×10^5 [c]	NH disappears	Not tested
3	5600±1000	382±29	173±8	59±3	40±3
1	$1.7\times10^4\pm900$[d]	2700±201[e]	350±5[d]	46±8[e]	10±0.5[d]
7	1725±176	188±15	85±11	37±3	<10
6	ca. 1.7×10^6 [f]	ca. 3.2×10^5 [e]	ca. 10^7 [f]	$1.2\times10^4\pm10^3$ [e]	710±25

[a] D and W: dry and water-saturated CD_2Cl_2, respectively.
[b] K_a measured by competition using **1**.
[c] K_a estimated by competition using **4a**.
[d] Data from Ref. 4.
[e] Data from Ref. 5b.
[f] K_a measured by competition using **5b**.

Table 1 and include those of the dipyrromethanes **3** and **7** because these compounds represent structural subunits of the receptors **4** and **5**. The relevant K_a values for **1** and **6** published previously[1,5b] are also included. Data for the binding of bromide in wet solvent were not collected because the K_a values observed in dry solvent were very small and they appeared to be even smaller in the presence of water. Iodide did not interact appreciably with any of the new macrocycles.

2.1. Complexation studies

The addition of fluoride in 'dry' CD_2Cl_2 to **4a** revealed the formation of a highly stable complex. The K_a was too high for NMR titration and the value of ca. 8.4×10^5 M^{-1} was determined by competitive binding with **1**. The signals for the NH protons, which resonate as broad singlets at δ=7.32 ppm for the free host appear at δ=12.6 ppm after the addition of 1 equiv of salt and the complex appeared to be quantitatively formed. The NH signal in the complex also exhibited a coupling with fluoride (J_{H-F}=42 Hz). The aryl protons *meta* to the nitro group exhibited larger CISs than the *ortho* ones (from δ=7.14 to δ=6.80 ppm and from δ=8.06 to δ=7.94 ppm, respectively). These spectral changes suggest an interaction between the *meta*-aryl protons and the anion, and hence we believe that fluoride is bound by **4a** on the face that contains the two aryl residues.[17] In wet CD_2Cl_2 the complex **4a**·F^- had a K_a value of $1.1\times10^4\pm388$ M^{-1}.

Chloride was complexed by **4a** with K_a values of 2300±80 and 380±24 M^{-1} in dry and wet CD_2Cl_2, respectively. In **4a**·Cl^- the signals of the aryl protons were only marginally affected with respect to the free receptor. Therefore, we believe that, unlike fluoride, chloride interacts with this receptor on the face that *does not* contain the aryl units. This difference of the mode of interaction seems reasonable on the basis of steric considerations (chloride is larger than fluoride). However, the mechanism by which the *p*-nitrophenyl units in **4a** boost (compared to **1**) the affinity of the calix[4]-pyrrole moiety towards chloride although they are not conjugated with the pyrrole units and remote from the anion in the complex is rather puzzling and would require additional investigation.

Bromide was complexed by **4a** only weakly (K_a=34± 10 M^{-1} in dry CD_2Cl_2).

The K_a of **4b** with fluoride in dry CD_2Cl_2 could not be determined by direct titration because it was too high. Moreover the NH resonances disappeared in the initial stages of the experiment. In a competitive experiment **4b** was found to bind fluoride with a K_a value (1.2×10^5 M^{-1}) seven times larger than that of calix[4]pyrrole **1**. A competitive titration of **4a** and **4b** (1:1 in dry CD_2Cl_2, 0.005 M) showed that **4a** binds fluoride with a K_a value that is larger than that of **4b**. In fact, during this titration the NH resonances of **4b** show significant CISs only after the addition of over 0.5 equiv of salt. The broadening of the resonances and the fact that some of them disappeared during the titration prevented an accurate evaluation of the relative strengths of the two K_as, which appeared to differ by a factor of 5–8. However, the two receptors **4a** and **4b** had very similar affinities for fluoride in wet CD_2Cl_2 (K_a values 1.1×10^4 and 1.2×10^4 M^{-1}, respectively).

Macrocycle **4b** binds chloride weakly (K_a=163±25 and 30±3 M^{-1} in dry and wet CD_2Cl_2, respectively). With the exception of the NH resonances, the CISs for all of the aryl and β-pyrrole protons are marginal.

The addition of fluoride to **5b** in both dry and wet CD_2Cl_2 produced broadening of all of the signals and the disappearance of the NH resonances. In competitive titration **5b** and **4a** were found to bind fluoride with equal strength, competitive titration of **5b** and calix[6]pyrrole **6** (1:1, dry CD_2Cl_2, 0.005 M) showed that **6** binds fluoride 2.2 times more strongly than **5b**. By correlating the data described so far, we conclude that the K_a of **5b**·F^- is ca. 8.4×10^5 M^{-1} and the K_a of **6**·F^- is ca. 1.7×10^6 M^{-1}.

In the initial stages of the titration of **5b** with chloride in dry CD_2Cl_2 all of the resonances broadened considerably. The NH resonances that appeared in the free receptor as three different signals of equal intensity at δ=7.58, 7.69 and 7.60 ppm (Fig. 3a) disappeared and became visible as two different signals (1:1 intensities) at δ=10.25 and 10.49 ppm (Fig. 3b) after the addition of a slight excess (1.3 equiv) of salt. This behaviour prevented the determination of a K_a value by direct titration at room temperature (21 °C). A competitive titration of **5b** and **4a** (1:1, dry CD_2Cl_2, 0.005 M) showed that **4a** begins to bind chloride only after **5b** is fully complexed by the addition of just over 1 equiv of salt. This behaviour is consistent with **5b** binding fluoride ca. 100 times more strongly than **4a**, hence we entered the value of ca. 2×10^5 in Table 1. In a competitive binding of **5b** and **6**, the latter appeared fully complexed after the addition of 1 equiv of salt, while **5b** was still unaffected. This sets the minimum value of ca. 10^7 M^{-1} for the K_a of **6**·Cl^-.

Upon cooling to −50 °C the spectrum of the 1:1 mixture of **5b** with chloride became sharp (Fig. 3c) showing two discrete sets of signals for the NH, the aryl and the pyrrole protons. We ascribe these spectral features to the slow exchange of the bound chloride between the two different faces of the macroring (see diagrams in Fig. 3). At this temperature the two complexes are formed in a 1:2 proportion (each set of resonances is in a 1:2 intensity ratio with the other). Inspection of the CISs and intensities of the aryl protons indicates that the most favoured complex is that in which the chloride ion is bound to the face containing two aryl residues. The assignments indicated in Figure 3 for the aryl protons were confirmed by means of a COSY experiment at the same temperature.

This modest preference for the chloride to complex **5b** with the face having the two aryl substituents indicates that the *meta*-aryl and the pyrrole NH protons interact with the anion synergically. This mode of binding differs from that described above for **4a** and we believe that it is made possible by the larger size of receptor **5b** in which there is enough space for the chloride ion to approach in this way.

3. Conclusions

Comparing the K_a values of the receptors having *meso*-*p*-nitrophenyl groups with those having only *meso*-methyl

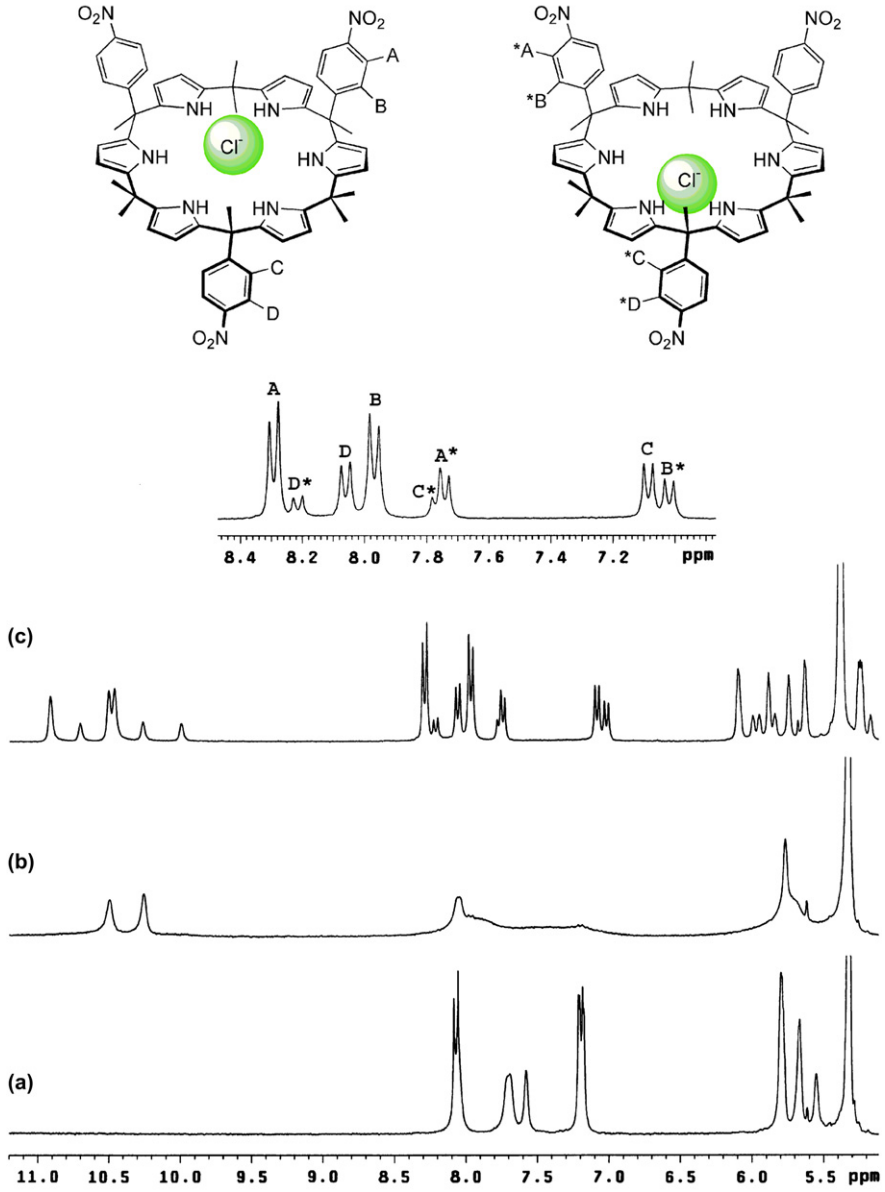

Figure 3. Partial ^{1}H NMR spectrum in CD_2Cl_2 of (a) **5b** at 21 °C; (b) a mixture of **5b** and TBACl (1:1) at 21 °C; (c) the same sample as in (b) at −50 °C; the expanded aromatic region shows the spectral assignments obtained by means of a COSY experiment at this temperature.

groups (Table 1) one can conclude that the presence of the electron-poor aromatic rings has a positive effect on the anion binding as previously reported for other calixpyrrole derivatives with electron-withdrawing groups at the *meso*-positions.[8e] This effect is clearly seen by comparing the K_a values of the dipyrromethane components **3** and **7**. However, when these become part of the macrocyclic structures the stereochemistry at the *meso*-centres plays a crucial role. Thus the anion binding behaviour of **4a** and **4b** differ substantially, this difference being more pronounced for the complexation of the larger chloride anion with respect to fluoride. Considering the K_a values of **4b**, **3** and **7** for chloride, one is led to conclude that **4b** is probably interacting with chloride by means of just one of its dipyrromethane moieties, i.e., using only two NH units.

Compared to calix[4]pyrrole **1**, which exhibits fluoride/chloride preference factors of ca. 50 and 7 in dry and wet CD_2Cl_2, respectively, **4a** and **4b** are considerably more selective, the corresponding factors being ca. 360 and 30 for **4a**, and ca. 730 and 400 for **4b**. It is also noteworthy that calix[6]pyrrole **6** is the strongest chloride ligand among those listed in Table 1. We speculate that compound **5a** could be an even better ligand for chloride than calix[6]pyrrole. Moreover, should it become available, it would provide a means to gain additional insight into the role of the *p*-nitrophenyl groups in the anion recognition process. Unfortunately in our laboratory **5a** still remains an elusive prey. We believe that the results outlined in this paper provide information that is relevant to evaluate the use of the *p*-nitrophenyl substituents at the *meso*-position of calixpyrroles as a means to tune their anion binding properties.

4. Experimental

4.1. General methods and instrumentation

Acetone was distilled from dry $CaCO_3$. Pyrrole was distilled before use. All other chemicals were of standard reagent grade and were used without further purification. All air-sensitive and/or moisture-sensitive reactions were conducted under a dry argon atmosphere. Thin layer chromatography (TLC) was conducted on Merck SiO_2 60 F_{254} plastic plates. Compounds were visualized with iodine, vanillin, or by examination under UV light. Column chromatography was conducted on Aldrich Silica gel 230–400 mesh, 60 Å. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini-300 at 300 and 75 MHz, respectively, using the residual proton resonances of the solvents ($CDCl_3$ and CD_2Cl_2) as δ reference. Melting points were determined on a Kofler hot stage apparatus, and are not corrected. Electron impact (EI) mass spectra were measured on a Finnigan Mat 90 spectrometer operated by Dr. Marcello Saitta.

Accurate mass measurements were recorded in reflector mode using an APPLIED BIOSYSTEMS 4800 MALDI TOF/TOF™ instrument. Samples were diluted in 500 μL acetonitrile. This solution (1 μL) was mixed with the same volume of the matrix (3 mg/mL α-cyano-4-hydroxycinnamic acid in TFA 0.1%/CH_3CN 2:1), directly spotted onto a 384-well MALDI plate (APPLIED BIOSYSTEMS) and allowed to dry at room temperature. Resolution was better than 16,000. Internal calibration was used so that mass accuracy was better than 20 ppm. Comparisons between measured and calculated isotopic patterns were also performed.

4.2. Crystal data

Crystal data for compound **4a** [**4b**]. Chemical formula=$C_{44}H_{50}N_6O_6$ [$C_{38}H_{38}N_6O_4$]; crystal system=triclinic [monoclinic]; space group=*P*-1 [$P2_1/n$]; cell parameters: a=10.530(2) [11.778(3)] Å, b=14.019(2) [10.390(2)] Å, c=15.092(2) [13.322(3)] Å, α=96.528(3) [90]°, β=105.524(3) [94.400(6)]°, γ=96.820(3) [90]°; V=2106.4(6) [1625.5(6)] Å^3; Z=2 [2]; collected refls=12,155 [10,894]; unique refls=5975 [2075]; refls with $I>2\sigma(I)=gt$=2024 [1194]; refined params=516 [220]; R (all)=0.1202 [0.1477]; $R(gt)$=0.0500 [0.1111]; wR (all)=0.1111 [0.3385]; $wR(gt)$=0.1018 [0.3231]; GOF=0.676 [1.178]; max residual=0.164 [0.625] eÅ^{-3}.

Diffraction data were collected at room temperature for both compounds on a Bruker single crystal diffractomer APEX 8 by using graphite monochromated Mo X-ray radiation. Both structures were solved by using standard direct methods[18] and refined by the combination of the Fourier difference maps and weighted least square technique with all the independent intensities and no constraints.[19] In both structural models all non-H atoms were refined anisotropically while the hydrogens were included by the SHELX 'reading model' method. Crystallographic data (excluding structure factors) for compounds **4a** and **4b** have been deposited with the Cambridge Crystallography Data Centre as supplementary publication numbers CCDC 639715 and 639716, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.3. ^1H NMR titrations

The *n*-tetrabutylammonium salts were dried in a vacuum oven for at least 24 h. For measurements in 'dry' CD_2Cl_2 this was stored on dry alumina and care was taken to minimize exposure to the atmosphere during sample preparation and titration. Wet CD_2Cl_2 was obtained by vigorous stirring with D_2O for 1 h at 21 °C (see Ref. 5b). The anions were added as measured volumes of solutions (ca. 0.035 M) in CD_2Cl_2 to the solution of the macrocycle under investigation (0.005 M) in the same solvent (0.7 mL). The sample volume was kept constant by evaporating the excess solvent with a flow of dry nitrogen. After each addition the stoichiometric ratios between the salt and macrocycle were also re-determined from the intensities of the resonance of the pyrrole protons of the host versus those of the *n*-tetrabutylammonium cation. Quantitative ^1H NMR integrations were obtained by the use of appropriate pulse delays in all cases. Processing the data with the WinEQNMR[14b] program produced the reported K_a values for the 1:1 complexation model.

4.4. Syntheses

4.4.1. 5-Methyl-5-(4-nitrophenyl)dipyrromethane 3. TFA (2.77 mL, 36 mmol) was added to a solution of *p*-nitroacetophenone (2.0 g, 12 mmol) in pyrrole (21 mL), at 0 °C. The mixture was stirred under argon atmosphere at room temperature for 3 h, then neutralized (NaOH 1 M) and extracted (2×25 mL CH_2Cl_2). The organic phase was dried ($MgSO_4$) and concentrated to fractionally remove CH_2Cl_2 and excess pyrrole under reduced pressure. The crude brown oil was subjected to column chromatography (SiO_2, hexane/EtOAc 3:1) and crystallized from EtOAc to give **3**: 1.27 g, 40%, mp 141–142 °C; ^1H NMR ($CDCl_3$): δ 2.07 (s, 3H, CH_3), 5.95 and 6.19 (2×m, 2×2H, pyrrole β-CH), 6.72 (m, 2H, pyrrole α-CH), 7.25 and 8.10 (2×2H, AA′BB′ system, Ar-H), 7.88 (br s, 2H, NH); ^1H NMR (CD_2Cl_2): δ 2.06 (s, 3H, CH_3), 5.92 and 6.16 (2×m, 2×2H, pyrrole β-CH), 6.72 (m, 2H, pyrrole α-CH), 7.27 and 8.10 (2×2H, AA′BB′ system, Ar-H), 7.94 (br s, 2H, NH); ^{13}C NMR ($CDCl_3$): δ 28.4 (CH_3), 45.0 (Cq), 106.9, 108.4, 117.7, 123.2, 128.4 (CH), 135.7, 146.5, 155.0 (Cq); EIMS, *m/z* (%): 281 (M^+ 31), 266 (100), 220 (23), 159 (13).

4.4.2. 5,10,15,20,22,24-Hexahydro-5,5,10,15,15,20-hexamethyl-10α,20α-bis(4-nitrophenyl)-calix[4]pyrrole 4a, 5,10,15,20,22,24-hexahydro-5,5,10,15,15,20-hexamethyl-10α,20β-bis(4-nitrophenyl)-calix[4]pyrrole 4b and 2,2,7,12,12,17,22,22,27-nonamethyl-7α,17α,27β-tris(4-nitrophenyl)-calix[6]pyrrole 5b. TFA (5.4 mL, 7.1 mmol) was added to a solution of **3** (2.0 g, 0.71 mmol) in dry acetone (50 mL), at 0 °C. The mixture was stirred under argon atmosphere at room temperature for 4 h, then neutralized (NaOH 1 M) and then concentrated to 15 mL and extracted (2×50 mL CH_2Cl_2). The organic phase was dried ($MgSO_4$), concentrated and the brown oil was subjected to column chromatography (SiO_2, $PhCH_3$/EtOAc, 92:8) to give in order of elution (R_f values 0.6, 0.5, 0.4, respectively).

Compound **4b**: 416 mg, orange solid, 18%, mp 250 °C dec from EtOH; ^{1}H NMR ($CDCl_3$): δ 1.56 (s, 12H, CH_3), 1.93 (s, 6H, CH_3), 5.76 and 5.96 (2×m, 2×4H, pyrrole CH), 7.24 (br s, 4H, NH), 7.30 and 8.12 (2×2H, AA′BB′ system, Ar-H); ^{1}H NMR (CD_2Cl_2): δ 1.54 (s, 12H, CH_3), 1.91 (s, 6H, CH_3), 5.75 and 5.95 (2×m, 2×4H, pyrrole CH), 7.22 (br s, 4H, NH), 7.28 and 8.10 (2×2H, AA′BB′ system, Ar-H); ^{13}C NMR (CD_2Cl_2): δ 29.0, 29.2 (CH_3), 35.3, 45.0 (Cq), 103.6, 106.3, 123.1, 128.3 (CH), 135.0, 139.0, 146.7, 154.2 (Cq); EIMS, *m/z* (%): 642 (M^+ 100), 627 (93), 612 (10), 597 (10), 520 (8), 453 (12), 321 (9), 306 (20).

Compound **4a**: 416 mg, yellow solid, 18%, mp 290 °C dec from acetone; ^{1}H NMR ($CDCl_3$): δ 1.55 (s, 6H, CH_3), 1.64 (s, 6H, CH_3), 1.93 (s, 6H, CH_3), 5.61 and 5.96 (2×m, 2×4H, pyrrole CH), 7.15 and 8.09 (2×4H, AA′BB′ system, Ar-H), 7.25 (br s, 4H, NH); ^{1}H NMR (CD_2Cl_2): δ 1.64 (s, 6H, CH_3), 1.92 (s, 6H, CH_3), 2.12 (s, 6H, CH_3), 5.64 and 5.96 (2×m, 2×4H, pyrrole CH), 7.14 and 8.07 (2×4H, AA′BB′ system, Ar-H), 7.33 (br s, 4H, NH); ^{13}C NMR ($CDCl_3$): δ 27.6, 27.8, 30.0 (CH_3), 35.1, 44.9 (Cq), 103.6, 106.4, 122.9, 128.3 (CH), 135.1, 138.8, 146.6, 155.3 (Cq); EIMS, *m/z* (%): 642 (M^+ 100), 627 (93), 612 (10), 597 (10), 520 (8), 453 (12), 321 (9), 306 (20).

Compound **5b**: 114 mg, orange solid, 5%, mp 167–168 °C from toluene; ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 12H, CH_3), 1.50 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 1.92 (s, 6H, CH_3), 5.55, 5.70 and 5.83 (3×m, 2H, 4H, 6H, pyrrole CH), 7.19 and 8.04 (2×6H, AA′BB′ system, Ar-H), 7.53, 7.66, 7.68 (3×br s, 3×2H, NH); ^{1}H NMR (CD_2Cl_2): δ 1.49 (br s, 18H, CH_3), 1.86 (s, 3H, CH_3), 1.92 (s, 6H, CH_3), 5.56, 5.64, 5.74 (3×m, 2H, 4H, 6H, pyrrole CH), 7.20 and 8.07 (2×m, 2×6H, Ar-H), 7.46 and 7.55 (2×br s, 2H, 4H, NH); ^{13}C NMR ($CDCl_3$): δ 29.1, 29.1, 29.2, 29.2, 29.3, 29.3 (CH_3), 35.5, 35.5, 44.9, 45.0 (Cq), 103.8, 103.9, 104.1, 106.7, 106.7, 106.8, 123.3, 123.3, 128.1, 128.1 (CH), 134.7, 135.0, 138.9, 139.0, 139.2, 146.6, 154.7, 155.0 (Cq); EIMS, *m/z* (%): 963 (M^+ 100), 948 (90), 933 (20), 918 (37), 453 (27), 322 (25), 306 (43).

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