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Synthesis and anion binding properties of the smallest *meso-***expanded calix**[4]**pyrrole**

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Abstract. The smallest core expanded calix[4]pyrrole derivative (5) was synthesized *via* incorporation of an additional sp³ *meso*-carbon at the periphery of the macrocycle. Anion binding study of the macrocycle reveals clearly the effect of core size on its affinity towards various tested ions (F^- , Cl^- , Br^- , I^- , AcO^- , $H_2PO_4^-$, HSO_4^- , ClO_4^- , PF_6^- , NO_3^- , NO_2^- , N_3^- and CN^-). The macrocycle displays the highest affinity towards fluoride and acetate ions, albeit with reduced affinities compared to parent octamethylcalix[4]pyrrole.

Keywords. Calix[4]pyrrole; meso-expanded Calix[4]pyrrole; host-guest complex; hydrogen-bond; anion.

1. Introduction

The increased attention towards selective recognition of fluoride ion is driven by its applications in environmental and health sectors, especially in dental care and in the treatment of osteoporosis.¹ As a result, a large number of synthetic receptors containing H-bond donor motifs, Lewis acidic sites and electron deficient organic π -systems have been designed.² In this direction, calix[4]pyrrole 1 has emerged as an attractive neutral host for anions in the last two decades (Figure 1).³ Consequently, a large number of transformations have been effected on the periphery of this macrocycle, including modification of its binding core.⁴ As calix[4]pyrrole **1** mostly binds to smaller halide ions, it was anticipated that bigger core size would be more suitable to bind larger anions. The core expansion could be achieved by increasing the number of pyrrolic moieties (increases the number of binding sites for hydrogen bonding) or by incorporation of a spacer between the constituent pyrrolic units. Towards this, in 1997 the first expanded calixpyrrole was reported by Sessler and coworkers,⁵ subsequently, higher calix[n]pyrroles were synthesized.⁶ Further, a new type of expanded calix[4]pyrroles, containing bigger core size, were made by using spacer units viz., carbazole and benzene moieties.⁷ In this regard, recently we have reported calix[2]bispyrrolylethenes (2); among these receptors, **2a** displayed colorimetric sensing of fluoride ion in polar aprotic solvents (Figure 1).⁸ Similarly, we could also demonstrate fluorometric sensing of fluoride ion by calix[2]bispyrrolylarenes **3a–b** (Figure 1).⁹ However, the calix[2]bispyrrolylarenes, in spite of their close resemblance to calix[2]bispyrrolylethene, display significant affinity towards acetate ion.⁹ Further, recently we reported a new type of *meso*-expanded calix[4]pyrrole **4** *i.e.*, calix[2]bispyrrolylethane, which stabilizes infinite 1D chain of water molecules in solid state, whose anion binding studies will be reported separately (Figure 1).¹⁰

Herein, we report the synthesis of a novel *meso*expanded calix[4]pyrrole **5**, which belongs to a new class of macrocycle, namely, the smallest expanded calix[4]pyrrole. Further, we have also investigated the anion binding properties of this new macrocycle in both solution and solid states. The objective was to explore the relation between the core size and the anion affinity and selectivity *via* an incremental change in core size of the parent calix[4]pyrrole **1** and subsequently compare their anion binding behavior. In particular, we were interested to know whether the expansion of core size can lead to the specific selectivity of the macrocycle towards fluoride ion.

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Figure 1. Calix[4]pyrrole 1 and some of its *meso*-expanded calix[4]pyrrole analogues (2–4).

2. Experimental

2.1 Materials and physical measurements

Chemicals, reagents and solvents were purchased from commercially available sources. Solvents were purified with appropriate drying procedure.¹¹ All the tetrabutyl ammonium salts and analytical grade solvents for NMR and ITC titration experiments were purchased from Sigma-Aldrich and were directly used in the titration experiments.

Melting points were determined by slides with coverslips on MR-Vis⁺ visual melting point range apparatus from LABINDIA Instruments Private limited. IR spectra were recorded on a JASCO FTIR model 5300 and NICOLET 5700 FT-IR spectrometers. LCMS analyses were carried out by Shimadzu-LCMS-2010 mass spectrometer and HRMS data were obtained with Bruker Maxis spectrometer. NMR spectra were recorded on Bruker 400 MHz FT-NMR spectrometer operating at ambient temperature. TMS was used as internal standard for ¹H NMR spectra.

2.2 Synthesis of macrocycle 5

5,5'-Dimethyldipyrromethane 6^{12} (108 mg, 0.625 mmol) and bispyrrolylethane (BPE) 7^{10} (100 mg, 0.625 mmol) were dissolved in dry dichloromethane (20 mL), to this dry acetone (2.3 mL, 0.312 mmol) was added under nitrogen atmosphere. Then, boron trifluoride diethyl etherate (10 µL, 0.156 mmol) was added and stirred at room temperature. After 30 min, the starting material was finished and as anticipated, three new spots were observed in TLC. Then, the reaction was stopped by quenching with sat. sodium bicarbonate solution (5 mL), the organic layer was separated and concentrated in a rotary evaporator, and the crude product was purified by silica gel column chromatography by slow elution with 5–10% ethyl acetate in hexane. The three products were isolated as (5, 34 mg, 13%), (4, 30 mg, 23%) and (1, 17 mg, 13%).

Characterization data of compound **5**: Melting point: 162– 164 °C (dec.); FTIR Data (KBr): 3386.91, 2970.97, 1416.85, 1040.00, 688.23 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ in ppm 7.47 (s, 2H, NH), 7.08 (s, 2H, NH), 5.95–5.89 (m, 6H, pyrrole β -CH), 5.82–5.80 (brs, 2H, pyrrole β -CH), 2.81 (brs, 4H, –CH₂), 1.51 (s, 18H, CH₃). ¹³C NMR (100 MHz, CDCl₃): δ in ppm 137.91, 137.84, 137.75, 131.71, 104.92, 103.32, 102.82, 35.42, 35.12, 29.16, 28.98, 26.85. HRMS m/z calculated for (M + H⁺) C₂₇H₃₅N₄: 415.2862, found: 415.2856.

Starting materials 6^{12} and 7^{10} were synthesized, characterized according to the procedure available in literature, and the characterization data of compounds 4^{10} and 1^3 were matched with the available literature data.

2.3 Single crystal X-ray diffraction analysis

Crystallographic data for 5 was collected on a dual source Oxford Gemini A Ultra diffractometer and Mo-K_{α} (λ = 0.71073 Å) radiation was used to collect the X-ray reflections. Data reduction was performed using CrysAlis^{Pro} 171.33.55 software.¹³ The structure was solved by using Olex2-1.0 with anisotropic displacement parameters for non-H atoms and final refinement was done by SHELXL-2014/7.14 Empirical absorption correction was done using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm. Crystallographic data for 5. TBACl was collected on BRUKER SMART-APEX CCD diffractometer and Mo-K α ($\lambda = 0.71073$ Å) radiation was used to collect the reflections on the single crystal. Data reduction was performed using Bruker SAINT¹⁵ software. Intensities for absorption were corrected using SADABS¹⁶ and refined using SHELXL-2014/7¹⁴ with anisotropic displacement parameters for non-H atoms. Hydrogen atoms on O and N were experimentally located in difference electron density maps. All C-H atoms were fixed geometrically using HFIX command in SHELX-TL. A check of the final CIF file using PLATON¹⁷ did not show any missed symmetry (Table 1).

2.4 Anion binding study

¹H NMR titration studies were carried out in a 400 MHz NMR spectrometer in acetonitrile- d_3 (0.5% v/v D₂O in case of fluoride ion) solvent at 25 °C. All anions were used in the form of their tetrabutylammonium (TBA) salts (fluoride salt as its trihydrate). The receptor solutions were titrated by adding known quantities of a concentrated solution of the anions in question. The anion solution used to effect the titrations contained the receptor at the same concentration as the receptor solutions into which they were being titrated. The data

 Table 1.
 Crystallographic data and structure refinement information.

Compound	5.EtOAc	5·TBACl	
Formula	C ₃₁ H ₄₂ N ₄ O ₂	C ₄₃ H ₇₀ Cl N ₅	
Formula weight	502.69	692.49	
Color	Colorless	Colorless	
Temperature	293(2) K	298(2) K	
Wavelength	0.71073 Å	0.71073 Å	
Crystal system	Triclinic	Monoclinic	
Space group	P-1	Cc	
Unit cell dimensions	$a = 11.031(3) \text{ Å}, \alpha = 105.86(2)^{\circ}$	$a = 11.604(4) \text{ Å}, \alpha = 90^{\circ}$	
	b = 12.413(3) Å, $\beta = 107.21(2)^{\circ}$	$b = 19.303(6) \text{ Å}, \beta = 93.080(6)^{\circ}$	
	$c = 12.599(3) \text{ Å}, v = 106.45(2)^{\circ}$	$c = 19.312(6) \text{ Å}, v = 90^{\circ}$	
	Volume = $1455.4(6)$ Å ³	Volume = $4320(2)$ Å ³	
Z	2	4	
Density (calculated)	$1.147 \mathrm{g/cm^3}$	$1.065 {\rm g/cm^3}$	
Absorption coefficient	$0.072 \mathrm{mm}^{-1}$	$0.122 \mathrm{mm}^{-1}$	
F(000)	544	1520	
Crystal size	$0.21 \times 0.20 \times 0.16 \mathrm{mm}^3$	$0.28 \times 0.27 \times 0.25 \mathrm{mm^3}$	
Theta range for data collection	2.77 to 24.30°	2.05 to 26.63°	
Index ranges	$-12 \le h \le 12, -11 \le k \le 14,$	$-14 \le h \le 14, -24 \le k \le 24,$	
-	$-14 \le l \le 11$	$-24 \le 1 \le 24$	
Reflections collected	8599	22473	
Independent reflections	4735 [R(int) = 0.1958]	8835 [R(int) = 0.1252]	
Completeness to theta	99.9% (θ 24.30°)	98.7% (θ 25.242°)	
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents	
Max. and min. transmission	0.989 and 0.985	0.970 and 0.966	
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F ²	
Data/restraints/parameters	4735/13/344	8835/10/436	
Goodness-of-fit on F ²	0.917	0.944	
Final R indices [I > 2sigma(I)]	R1 = 0.1301, $wR2 = 0.3054$	R1 = 0.1079, wR2 = 0.2485	
R indices (all data)	R1 = 0.3476, wR2 = 0.4073	R1 = 0.3097, wR2 = 0.3520	
Largest diff. peak and hole	$0.35 \text{ and } -0.28 \text{ e.} \text{\AA}^{-3}$	$0.227 \text{ and } -0.201 \text{ e.}\text{\AA}^{-3}$	

were fitted to a 1:1 binding profile in *MATLAB 7.0* package according to the method of Wilcox¹⁸ using the changes in the pyrrolic NH resonances in the ¹H NMR spectra. Job's plot for host vs. anion was performed in acetonitrile- d_3 at 25 °C. Equal concentration of compound and anion solution were mixed in ratios from 1:10 to 10:1 and the chemical shift was monitored and noted vs the residual CD₃CN (1.94 ppm) resonance. In this experiment β -CH proton (in case of TBAF) and NH proton (in case of other ions) resonances of pyrrole are monitored.

Microcalorimetric titrations were performed using an isothermal titration calorimeter (ITC) purchased from Microcal Inc., MA. The Origin software provided by Microcal Inc. was used to calculate the binding constant (K_a) and the enthalpy change (Δ H). Host–guest solutions are prepared in 0.5% water in acetonitrile in case of fluoride as a guest and only in acetonitrile (HPLC grade with < 0.05% water) in case of other ions. The host solution is about 2–2.5 mL of required concentration prepared and taken in VPITC cell (volume ~1.44 mL), and the corresponding guest solution about 1–2 mL of required concentration is prepared and taken in VP-ITC syringe (whose volume

is $\sim 286 \,\mu$ L). Further, we have checked ITC profile of the basic octamethylcalix[4]pyrrole (1) in presence of TBAF, and TBACl to confirm the accuracy and reproducibility of performed methods.

2.5 Computational Calculations

All DFT structure optimization calculations were done in Gaussian09 software by using B3LYP method 6-31G*(d,p) basis set in the gas phase.¹⁹ In all these calculations, the host molecule was set in cone conformation and assumed 1:1 complex with respect to anions.

3. Results and Discussion

3.1 Synthesis and characterization of macrocycle 5

Mixed condensation of 5,5'-dimethyldipyrromethane 6^{12} and bispyrrolylethane (BPE) 7^{10} with acetone in presence of BF₃·OEt₂ or TFA as the acid catalyst



Scheme 1. Synthesis of macrocycle 5.



Figure 2. ORTEP-POVray diagram of **5**, top view (left) and two different side views (right). Solvent molecule (EtOAc), all hydrogens bound to carbon atom are excluded for clarity. Thermal ellipsoids are scaled upto 35% probability level. Color code: grey = Carbon, white = Hydrogen and blue = Nitrogen.

(Scheme 1) resulted in the formation of three macrocycles as expected (Scheme 1), where the formation of macrocycle **5** (2nd fraction, 13%) remain unaltered. However, in the presence of BF₃·OEt₂, the reaction completes rapidly (in 30 min) with higher yield of macrocycle **4** (3rd fraction, 23%) and lower yield of calix[4]pyrrole **1** (1st fraction, 13%); on the other hand, TFA catalysed reaction needed longer time to complete (~5 h) and yielded lesser amount of **4** (8%) and more of **1** (17%). The products formed were rigorously characterized by various spectroscopic tools (SI = Supplementary Information).

3.2 Crystal structure analysis of macrocycle 5

The semi-expanded macrocycle **5** was crystallized by slow evaporation of 5% ethyl acetate in hexane solution, which resulted in an ethyl acetate solvate (**5** EtOAc). The macrocycle **5** adopts 1,3-alternate conformation (Figure 2), similar to the basic octamethylcalix[4]pyrrole **1**,³ with slightly bigger cavity and smaller than *meso*-expanded calix[4]pyrrole **4**.¹² Further, the two of the opposite pyrrole units (N1 and N3) adopts almost orthogonal geometry with regard to the calixpyrrole core and the alternate NHs are directed in opposite direction with respect to each other [with dihedral angles between the two pyrrole units (N1 and N3) \sim 22°] while, the remaining two pyrroles [with dihedral angles (N2 and N4) is \sim 21 to 29°] are slightly tilted with their NHs disposed towards the core (because of the flexible ethylene bridge) (Figure 2).

Further, ethylacetate molecule resides as solvate in the crystal lattice with hydrogen bonding interactions, where the carbonyl oxygen of ethyl acetate molecule is H-bonded with one of the pyrrole-NH of the constituent BPE moiety, having N···O distance of 2.99(2) Å, with associated N–H···O angle of ~163° (Figure S5 in Supplementary Information).

3.3 Anion binding study of macrocycle 5

Preliminary solution phase anion binding studies were carried out for macrocycle 5 by using ¹H NMR studies in CD₃CN with various anions viz., F⁻, Cl⁻, Br⁻, I⁻, AcO^- , $H_2PO_4^-$, HSO_4^- , ClO_4^- , PF_6^- , NO_3^- , NO_2^- , N_3^- and CN⁻ as their tetrabutylammonium (TBA) salts and the spectral changes observed indicate moderate to weak binding for most of the ions (Figure S6 in Supplementary Information). On the other hand, perchlorate and hexafluorophosphate ions display no observable interaction with the host. Subsequent detailed analysis by ¹H NMR titration and evaluation of association constants were performed by using Wilcox 1:1 binding equation¹⁸ (Table 2, Figures S7–S15 in Supplementary Information), and stoichiometry confirmed via Job's plot analysis (Figures S16-S19 in Supplementary Information). The data reveal that 5 displays maximum affinity towards fluoride and acetate ions but with no

Table 2. Summary of association constants K_a (M⁻¹) of receptors **1** and **5** in the presence of different anions obtained from ¹H NMR in acetonitriled₃ at 22–25 °C.

	$TBAF^{a}$	TBACl	TBAOAc	TBAH ₂ PO ₄
1	$> 10^{4b}$	$> 5 \times 10^{3b}$ $9.5 \pm 1.4 \times 10^{3}$	N. D.	1.3×10^{3b}
5	6.33 ± 2.9 × 10 ³		> 10 ⁴	$6.46 \pm 2.2 \times 10^{3b}$

'a' = in acetonitrile- d_3 (0.5% v/v D₂O) at 22 °C; 'b' = from ref²⁰; 'N. D.' = not determined.

Table 3. Summary of thermodynamic parameters of different anions with receptors 1 and 5 obtained from ITC in acetonitrile at $30 \,^{\circ}$ C.

Host	Guest	Δ H (kcal/mol)	$T\Delta S$ (kcal/mol)	ΔG (kcal/mol)	$K_a (\mathrm{M}^{-1})$
1	TBAF (0.5% water in Acetonitrile)	-4.3 ± 0.03	2.99	-7.39	$1.82 \pm 0.13 \times 10^{5}$
5		-3.52 ± 0.11	1.85	-5.37	$7.61 \pm 0.54 \times 10^{3}$
1^a	TBACI	1.4×10^{5}			
5		-4.65 ± 0.13	0.92	-5.57	$1.04 \pm 0.07 \times 10^4$
1^b	$TBAH_2PO_4$	-11.60	-5.81	-5.79	$1.51 \pm \times 10^4$
5		-7.6 ± 0.21	-2.08	-5.50	$9.26 \pm 0.62 \times 10^{3}$
1^c	TBAOAc	-11.62 ± 0.08	-4.03	-7.60	2.90×10^{5}
7		-11.55 ± 0.17	-5.06	-6.48	$4.76 \pm 0.41 \times 10^4$

a, *b* and *c*: from refs.²², ^{21a} and ²³, respectively (recorded in acetonitrile); All the experiments were performed for minimum three times and the obtained values are reproducible within $\pm 15\%$ error.

clear selectivity towards any other anions like the parent calix[4]pyrrole **1** (Table 2). Interestingly, the distinct characteristic of the two pyrrolic NH signals of the **5** is retained even after complexation with anions except in the case of dihydrogenphosphate ion (only at very high anion concentration one peak was observed), indicating the differential strength of interaction of the two sets of NHs with the incoming anions (Figures S6 and S12 in Supplementary Information). Further, ¹H NMR competition experiment reveals calixpyrrole **5** has superior affinity towards fluoride ion over chloride and acetate ions (Figures S20–S21 in Supplementary Information) in identical conditions, similar to the one noticed in case of calixpyrrole **1**.

These complexation processes were further subjected to isothermal titration calorimetric (ITC) experiments, to evaluate the energetics of the overall binding event²¹ and the corresponding association constants are briefly summarized in Table 3 (Figures S22–S26 in Supplementary Information).

The above studies clearly reveal that receptor **5** displays a better preference towards fluoride and acetate ions, albeit with reduced affinity compared to **1**, and also shows a relatively weaker affinity towards chloride and dihydrogen phosphate ions.

Several attempts to obtain diffraction grade crystals of the host–guest complexes of the calix[4]pyrrole derivative **5** with anions were made. Slow evaporation of compound 5 from its acetonitrile solution, in presence of excess TBACl, resulted in the successful isolation of the diffraction grade crystals of chloride complex. The macrocycle 5 adopts an irregular cone conformation (owing to its inherent structure), with all the four pyrrolic NHs hydrogen bonded with the chloride ion (Figure 3). As a result of this irregular cone structure, one of the pyrrolic NH of the BPE constituent resides closest to the anion (N3-Cl distance 3.26(2) Å), whereas the other pyrrolic NH of the BPE moiety resides at the farthest (N4-Cl distance 3.42(2) Å) and the pyrrole unit opposite to it (N1-Cl distance 3.31(1) Å) and adjacent to it from the dipyrromethane constituent (N2-Cl distance 3.38(1) Å), residing at intermediate lengths. This also confirmed the slightly bigger and unsymmetrical nature of the binding domain of calix[4]pyrrole 5 than 1 (N-Cl distance 3.26–3.33 Å).^{3b}

To further understand the reason behind the preference in binding behavior of the semi-expanded calix[4] pyrrole **5** towards fluoride and acetate ions among tested ions, density functional theory (DFT) calculations for the structure optimization with respective anions were performed (Figures 4, S27–S29 in Supplementary Information), which reveal the favorable binding nature of different anions (Table S1 in Supplementary Information).¹⁹ For example, the hybrid macrocycle **5** displays good affinity towards acetate ion and the optimized structure of **5** with acetate ion supports well and reveals



Figure 3. ORTEP-POVray diagram of **5.TBACl** complex: top view (left) and side view (right). Tetrabutylammonium cation and all hydrogens bound to carbon atoms are excluded for clarity, and thermal ellipsoids are scaled up to 35% probability level. Color code: blue: Nitrogen, grey: Carbon, white: Hydrogen and green: Chloride; hydrogen bonds are shown as black dashed lines.



Figure 4. Space filled diagram of DFT optimized structure of **5**.**AcO**⁻ complex in two different views. Color code: grey: Carbon, white: Hydrogen, blue: Nitrogen and red: Oxygen.

its greater fit of binding of both oxygens of anion with pyrrolic NHs of the macrocycle, possibly indicating the reason behind the greater affinity (Figure 4).

4. Conclusions

We have designed and synthesized a new *meso*-expanded calix[4]pyrrole receptor, which belongs to the first example of a new class of smallest expanded calix[4] pyrrole. This macrocycle is endowed with a slightly bigger binding domain, which is also unsymmetric in nature compared to the parent calix[4]pyrrole moiety. This resulted in relatively reduced anion affinities of this macrocycle compared to the latter. However, exclusive selectivity towards fluoride ion could not be achieved and at present efforts are directed towards this. The new macrocycle displays highest affinity towards fluoride and acetate ions among the tested ions.

Supplementary Information (SI)

Crystallographic data (including the structure factor files) for structures **5** and **5**.**TBACI** in this paper have been deposited in the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 1017831 and 1017832, 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). Compound characterization, ¹H NMR titration, ITC and computational data are available as Supplementary Information at www.ias.ac.in/chemsci.

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