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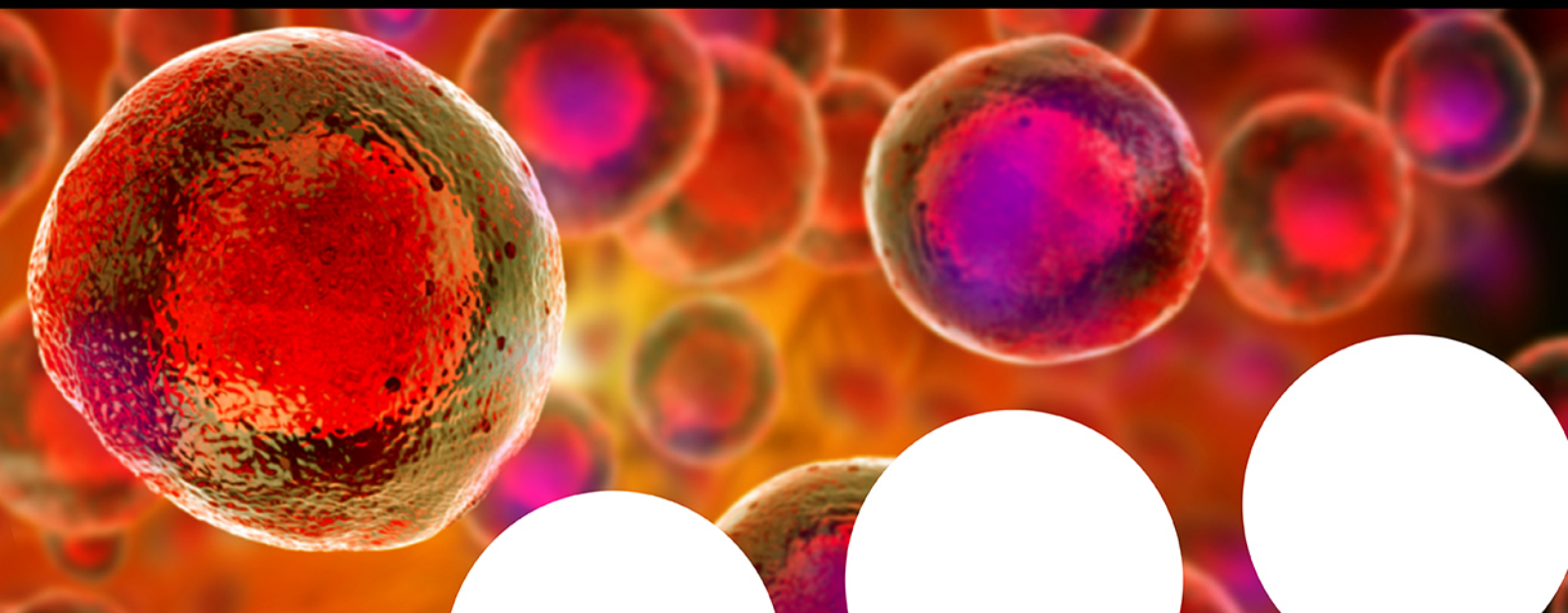
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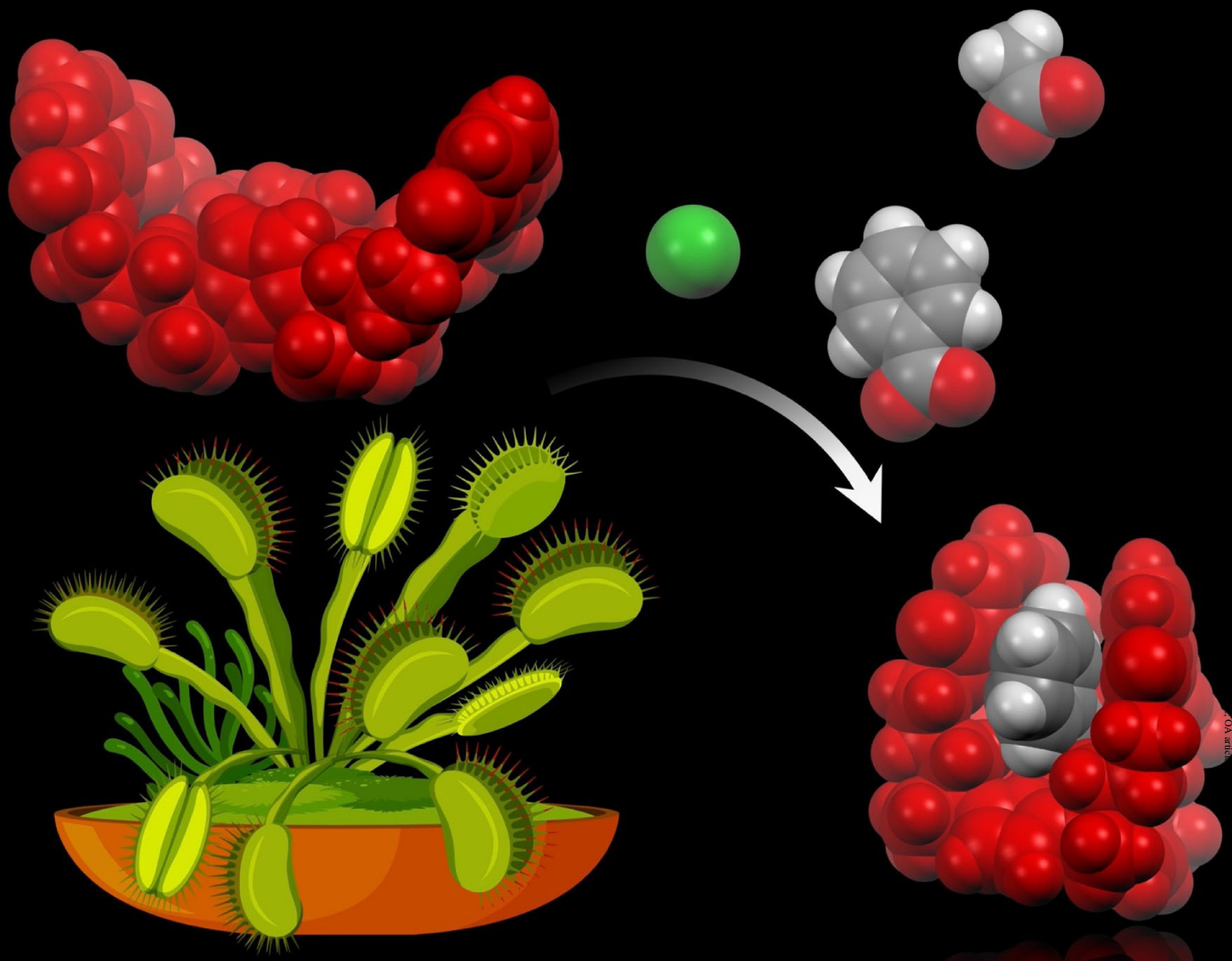


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Anion Responsive Molecular Switch Based on a Doubly Strapped Calix[4]pyrrole



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Anion Responsive Molecular Switch Based on a Doubly Strapped Calix[4]pyrrole

Kaisa Helttunen*^[a]

A calix[4]pyrrole receptor bearing two proximally *meso-meso* linking isophthaloyl straps displays open and closed states depending on the calix[4]pyrrole conformation. In the crystal structures and in non-polar solvent, the calix[4]pyrrole adopts open 1,3-alternate conformation with straps on the sides. Anion binding triggers a closed state of the receptor providing two types of interactions with an aromatic benzoate guest: hydro-

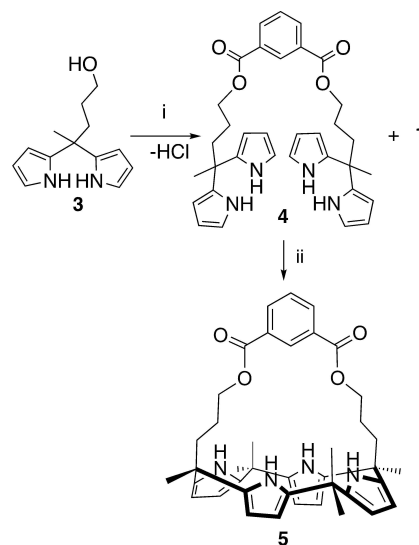
gen bonds from the pyrrolic NH groups and $\pi\cdots\pi$ interactions from the phenyl groups of the straps. Slow exchange dynamics was observed on the NMR timescale indicating that benzoate, acetate and chloride anions, which bind with relatively low affinity get kinetically trapped in the receptor as insects in a Venus flytrap.

Introduction

Molecular switches and tweezers experiencing conformational change upon chemical stimulus attract increasing attention due to the vast potential in functional materials, chemosensors, and pharmaceutical applications.^[1–3] Anion responsive molecular switches have been prepared from foldamers^[4] and macrocyclic amide receptors,^[5] and their applications cover two-photon absorption,^[6] pseudorotaxane disassembly^[7] and a chemosensor operating via polymer helix switching.^[8]

Calix[4]pyrroles,^[9] tetrapyrrolic neutral anion receptors, are capable of switching conformation from a more stable 1,3-alternate^[10,11] to a higher energy cone upon complexation of an anion.^[12] Tetrathiafulvalene annulated calix[4]pyrroles generate a particularly large conformational movement when binding halide anions and this has been applied for logic gates, sensing and self-assembly.^[13–15] Furthermore, switching between vase and kite conformations of calix[4]pyrrole-resorcin[4]arene hybrid cavitands was achieved albeit to a reduced extent using an electron-deficient aromatic guest.^[16]

Diametrically strapped calix[4]pyrroles bearing a single linking strap between *meso*-carbons (5, Scheme 1)^[17,18] contain a highly complementary binding pocket for halides, which induces two-three orders of magnitude increase in binding affinities for chloride to $K\sim 10^5\text{ M}^{-1}$ in dimethylsulfoxide and $K\sim 10^6\text{ M}^{-1}$ in acetonitrile in comparison to $K\sim 10^3\text{ M}^{-1}$ obtained with unsubstituted *meso*-octamethylcalix[4]pyrrole.^[19] In addition, diametrically strapped calix[4]pyrrole derivatives bearing



Scheme 1. Synthesis of doubly strapped calix[4]pyrrole 1 and calix[4]pyrrole 5 bearing a single strap,^[17,18] i) isophthaloyl chloride, pyridine, dichloromethane; ii) acetone, $\text{BF}_3\cdot\text{Et}_2\text{O}$. Scheme S1 shows a potential mechanism for the formation of 1 via acid-catalyzed cleavage of *meso*-carbon pyrrole bonds of 4.

triazole, oligoether and bisamide straps have shown anion transport activity in liposomes^[20,21] and in living cells inducing apoptosis.^[22] However, strapped calix[4]pyrroles do not usually show notable shape change between 1,3-alternate and cone conformations. Herein, a doubly strapped calix[4]pyrrole showing large conformational change accompanied with slow guest release dynamics is presented.

Results and Discussion

A reaction of dipyrromethane 3 with isophthaloyl dichloride according to a modified literature method^[17] produced a small amount (10%) of the expected bis-ester and a doubly strapped

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calix[4]pyrrole **1** (Figure 1), which precipitated as a white crystalline solid from the chromatographic fractions (1.5%).

The ^1H NMR spectrum of **1** recorded in CD_2Cl_2 displayed characteristic signals of a calix[4]pyrrole including two broad singlets for NH protons at 7.37 and 6.94 ppm, and two doublets for β -pyrrolic protons at 5.90 and 5.85 ppm. The methylene groups on the straps α to the oxygen (g) are diastereotopic and resonated as two multiplets at 4.56 and 4.09 ppm. The methylene group protons e and f were observed as four multiplets between 2.09–1.63 ppm. The isophthaloyl ring protons resonated as two triplets at 8.48 for the inner aryl proton (j) and 7.58 ppm for the outer aryl proton (i), and as a doublet of doublets at 8.22 ppm for h. The ratio of the isophthaloyl and β -pyrrolic protons indicated that one isophthaloyl strap per two pyrrole rings was present in the molecule.

Lee et al.^[23] have discovered a precedent for a doubly strapped calix[4]pyrrole with proximally *meso-meso* linking straps bearing flexible ether linkages (**2** in Figure 1) from an attempted synthesis of a diametrically doubly strapped calix[4]pyrrole. The reaction proceeded via acid-catalyzed cleavage of a pyrrole group from a bis-dipyrromethane analogous to **4** (Scheme 1), followed by an intramolecular

nucleophilic attack from an adjacent pyrrole, and subsequent condensation with a bis-ketone and the released pyrrole to yield **2**. In light of acid-lability of dipyrromethanes,^[24] which may induce reorganization of the starting materials known as ‘scrambling’, the synthesis of calix[4]pyrroles has previously produced isomers with different substitution patterns from a single precursor.^[25] Therefore, it is expected that reorganization of the starting materials under acid-catalyzed equilibrium conditions during formation of **4** produces small amount of **1**. A hypothetical reaction mechanism is shown in Scheme S1, even though other types of reaction mechanisms are possible.

The symmetry of the ^1H NMR spectrum in $[\text{D}_2]$ dichloromethane suggested that the structure of the new doubly strapped calix[4]pyrrole **1** contains proximally *meso-meso* linking straps on the same side (*cis*). An ^1H - ^1H COSY spectrum (Figure S4) allowed the assignment of the NH and β -pyrrolic protons residing in each pyrrole ring. In addition, diagnostic NOEs (Figure S7) from one NH (b) to β -pyrrolic c protons and to the strap protons (e), and from the other NH (a) only to the *meso*-methyl groups indicated that the calix[4]pyrrole **1** adopts a 1,3-alternate conformation in which adjacent pyrrole rings point up and down, respectively.

Crystals of **1** suitable for a single crystal X-ray diffraction grew directly from the chromatographic fractions without any solvent molecules in the lattice (structure **1a**, Figure 2). The conformation of the calix[4]pyrrole is 1,3-alternate as depicted from the NMR experiments. The isophthaloyl straps extend to the sides of the molecule generating an “open” state with a distance between the isophthaloyl ring centroids being 14.9 Å. It should be noted that the NH groups do not form any intermolecular hydrogen bonds in the crystal structure. In contrast, the β -pyrrolic protons of the down-pointing pyrrole rings have intermolecular short contacts with *meso*-methyl groups, and the β -pyrrolic protons of up-pointing pyrrole rings are close to the *meso*-methylene groups of the straps. These short contacts allow the molecules to pack regularly into pillars with a short interplanar distance (6.2 Å) between the mean planes defined by the four pyrrolic nitrogens. The previously investigated *cis*-**2**^[23] (NEHHUF) formed less regular twisted pillars and retained slightly longer distance between the adjacent calix[4]pyrroles (6.8 Å interplanar distance of pyrrolic nitrogens) while incorporating solvent molecules hydrogen bonded to the down-pointing pyrrole NH groups.

Interestingly, second crystal form of **1** was obtained when crystals grew from dichloromethane. In structure **1b**, the conformation of the host and the pillar packing motif was highly conserved. However, solvent filled channels containing dichloromethane formed along the c-axis shifting the pillars, which introduced new solvent-mediated and host-to-host C–H...O bonds (magenta lines in Figure 2c). In **1b**, a partially occupied water molecule was located under the cavity forming hydrogen bonds with a lower occupancy site of the down-pointing pyrrole rings. These interactions induced a convergent orientation of the down-pointing pyrrole rings resembling the conformation of *cis*-**2**, while the major occupancy site retained the divergent NH group geometry as in **1a** (Figure S25). This indicates that the torsion angles of the pyrrole rings of **1** may

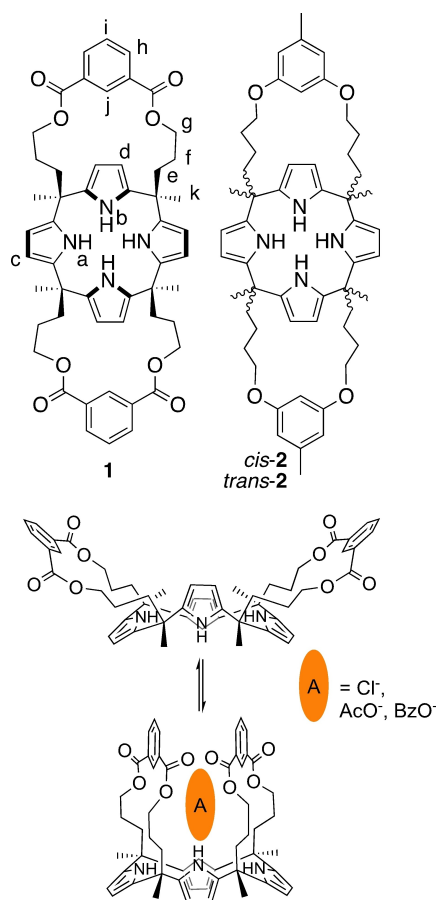


Figure 1. Structure of *cis*-doubly-strapped calix[4]pyrrole **1** featuring ester bridged straps, and the previously discovered doubly strapped calix[4]pyrrole **2**.^[23] Anion binding (orange ellipsoid) induces a change from an open 1,3-alternate to a closed cone conformation in host **1**. Letters indicate the NMR assignment.

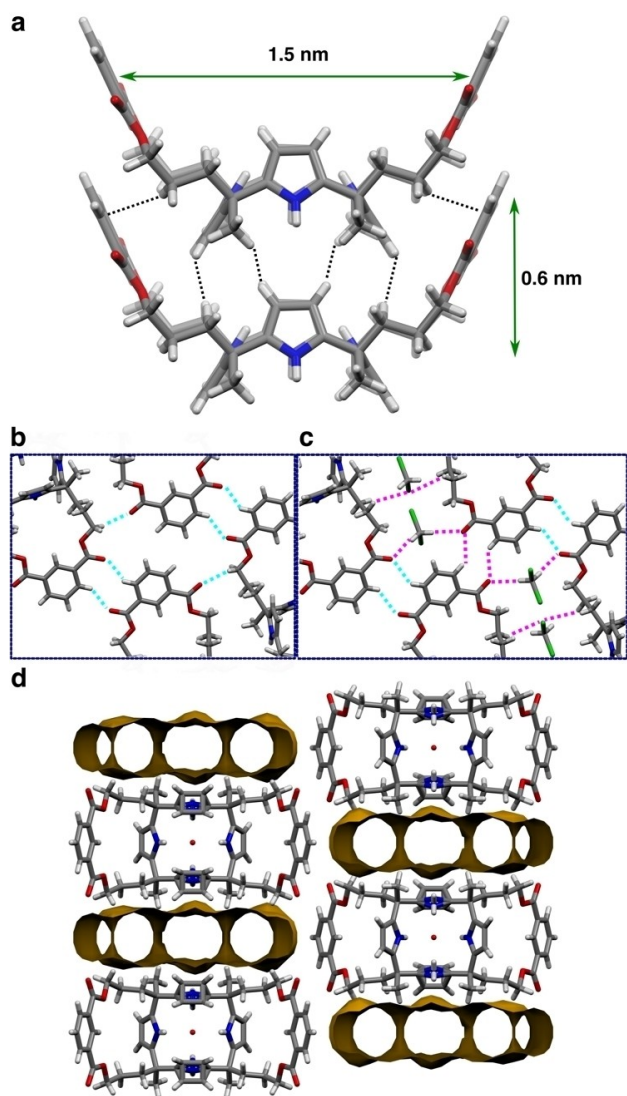


Figure 2. Crystal structure **1a** shows open conformation and short contacts between two molecules in pillar packing (a). Intermolecular C–H...O bonds in **1a** and **1b**; colour code: aqua – bonds present in both crystal forms, magenta – bonds unique to **1b**. d) Solvent filled channels in **1b** where the space occupied by dichloromethane is depicted in gold. Distances correspond to the centroid-centroid distance between the isophthaloyl rings and the interplanar distance of the four pyrrolic nitrogens. Atom colours: C = grey, Cl = green, H = white, N = blue, O = red.

rotate to several positions depending on whether the NH groups find a suitable hydrogen bonding partner.^[18]

The conformational properties of **1** were further investigated by computational methods. First, the initial coordinates from **1a** were optimized with OPLS4 force field. The conformation of the optimized structure resembles closely the X-ray coordinates, however, the torsion angles of the pyrrole rings changed few degrees closer to an average value of *meso*-octamethylcalix[4]pyrrole in 1,3-alternate conformation.^[10] Next, a conformational search was carried out, which gave 29 structures within 5 kcal/mol from the identified global minimum (Figure 3a, Figure S26). Notably, all structures maintained the calix[4]pyrrole in a 1,3-alternate conformation, and even

twisting of the straps and the calix[4]pyrrole core within the ensemble of conformations maintained the *meso*-CH₃...β-pyrrolic proton distance and the closest NH...β-pyrrolic proton distance in agreement with the NOE signals.

The conformation of **1** was adjusted to a cone by placing a chloride anion at a hydrogen bonding distance from all NH groups. The lowest energy conformation from a conformational search afforded all *meso*-methylene groups of the straps in an axial orientation and a short distance (3.9 Å) between the isophthaloyl rings measured from a centroid of the aromatic ring to the mean plane of the second ring. The cone conformation with a bound anion thus induces a “closed” state of the receptor. Also, acetate and benzoate complexes of **1** were optimized using the same method. In both cases, **1** remained in the cone conformation, however, the aromatic rings pointed to the sides in the acetate complex while the benzoate guest showed an excellent fit within the binding site forming π...π interactions with the isophthaloyl rings in the closed state of the receptor (Figure 3).

The anion binding properties of **1** were investigated using NMR titrations in CD₂Cl₂. Incremental addition of tetrabutylammonium chloride to a 1 mM solution of **1** induced broadening of the host signals, most notably the NH protons, which disappeared from the spectra. These changes were interpreted as low thermodynamic stability of the chloride complex with bound and free host experiencing intermediate exchange rate in the NMR timescale. In contrast, binding studies with acetate anion showed approximately 0.1 ppm shifts in the aromatic protons of strap, the inner *j* moving downfield, and *h* and *i* upfield. The signals of β-pyrrolic protons merged and shifted 0.14 ppm upfield upon addition of 11 equivalents of guest. A binding constant of $K=350\text{ M}^{-1}$ was extracted by fitting a theoretical 1:1 binding isotherm to the titration data (Table 1, Figure S11), which is of similar magnitude as previously obtained for octamethylcalix[4]pyrrole.^[26] It should be noted that a 0.1 ppm downfield shift for the protons α to the tetrabutylammonium nitrogen was observed during the titration, which suggests that the cation may be partially associated with the host-anion complex in a receptor-separated geometry, but the interaction is relatively weak. It has been shown that tetrabutylammonium halides form ion pairs in a non-polar solvent,^[27] and therefore, a more sophisticated binding model involving an ion-pair complex was fitted to the titration data. However, the second fit returned similar values for the K , and as a result, only the results of more simple binding model are shown (see SI).

Table 1. Binding constants (K , M^{-1}) for 1:1 complexes of **1** with anions.^[a] Guests were added as their tetrabutylammonium salts.

Solvent	Cl ⁻	AcO ⁻	BzO ⁻
DCM ^[b]	ND ^[d]	350	590
DMSO ^[c]	400	1400	800

[a] Errors < 20%. [b] Fast exchange in [D₂]dichloromethane at 25 °C. [c] Slow exchange in [D₆]DMSO at 30 °C. [d] Broadening of the host signals observed.

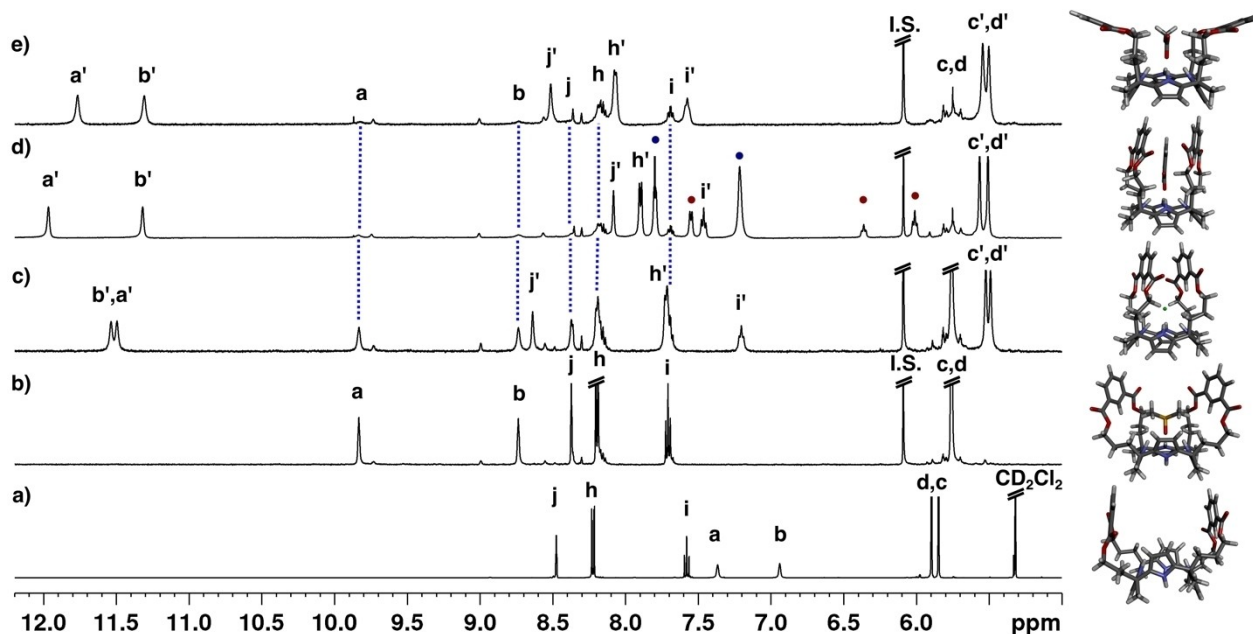


Figure 3. The NMR spectra of **1** in $[D_2]$ dichloromethane (a), in $[D_6]$ DMSO (b), with 3 equiv. of TBACl in $[D_6]$ DMSO (c), with 3 equiv. of TBAOBz (d; free and bound benzoate indicated with blue and red spheres, respectively), and with 3 equiv. of TBAOAc in $[D_6]$ DMSO (e). Primed letters correspond to signals of the bound host in the 1:1 complex; I.S. = 1,3,5-trimethoxybenzene. The lowest energy structures from conformational searches of **1** and its complexes with DMSO, chloride, benzoate, and acetate are shown on right.

An analogous titration experiment with benzoate induced upfield shifts of all the aromatic strap protons, including the inner aryl proton *j*. Also, guest protons experienced slight upfield shift in complex regarding to the free benzoate suggesting a shielding effect from the aromatic groups of the host. Fitting of the data yielded a binding constant of similar magnitude as with acetate (Figure S12).

Next, the effect of anions was investigated in dimethylsulfoxide, which was expected to preorganize the calix[4]pyrrole to a cone conformation. A conformational search of the host with a molecule of DMSO in the cavity yielded 49 conformations, in which the host adopted a partial cone, 1,3-alternate, or a cone conformation. The 1H spectrum of free **1** in $[D_6]$ DMSO showed the NH proton resonances significantly downfield shifted at 9.83 and 8.73 ppm indicating hydrogen bonding interactions with DMSO (Figure 3b). In addition, β -pyrrolic protons gave one signal at 5.76 ppm suggesting that the host adopts a symmetrical cone conformation or is in fast equilibrium between multiple low-energy conformations as depicted by computational results and the NOE difference experiment (Figure S16).

The addition of incremental amounts of chloride induced the emergence of a second set of signals that were assigned to a 1:1 host-guest complex experiencing slow exchange dynamics on the NMR timescale with the free host (Figure 3c). In this case, no chemical shift changes for the tetrabutylammonium protons were observed during the titration, which is in agreement with solvation of the cation in a medium with higher dielectric constant. Upon addition of chloride, both NH protons appeared near 11.5 ppm indicating symmetrical hydrogen

bonding to the spherical anion, and the slight downfield shift of the inner aryl proton suggested a weak C–H...Cl⁻ interaction.^[18] In contrast, the outer aryl protons *h* and *i* shifted significantly upfield by 0.5 ppm indicating magnetic shielding, which was induced by proximity of the isophthaloyl groups of the straps in the closed state. Interestingly, addition of one equivalent of the chloride induced complexation of only circa 25% of the host, and at three equivalents 55% of the host was bound, which corresponds to a binding constant of approximately $400 M^{-1}$. On the other hand, an NMR titration with acetate showed a slight increase in the binding constant to $1400 M^{-1}$ with 1 equivalent of added guest inducing complexation of approximately 50% of the host. In addition, the bound NH signals appeared separately at 11.77 and 11.31 ppm, respectively, probably due to an asymmetrical binding mode of the non-spherical anion. The aromatic strap protons experienced a downfield shift for inner aryl proton *j* and only slight upfield shifts for *h* and *i*.

Similar changes were observed upon addition of benzoate. Again, the bound NH signals appeared separately at 11.97 and 11.32 ppm, respectively, whereas all the aromatic signals of the straps and the bound guest shifted 0.2–1.2 ppm upfield, which indicates that they are magnetically shielded. These spectral features coincide well with the unsymmetrically bound benzoate in the closed state of the receptor (Figure 3d) experiencing π ... π interactions with the straps. The affinity to benzoate was intermediate ($K \sim 800 M^{-1}$) in comparison to chloride and acetate.

The energy barrier for the complexation **1** and benzoate was investigated with EXSY spectroscopy at 1:2 molar ratio of

host and guest. Integral values of the exchange cross peaks between free and bound receptor were used to determine the rate constants k_{12} and k_{21} for the magnetization exchange with EXSYCalc software (see SI for details). Eyring-Polanyi equation^[28] was used to calculate the energy barrier for the complex dissociation from the $k_{21}=k_{\text{off}}=5.4\text{ s}^{-1}$. The obtained value $\Delta G^{\ddagger}_{-1}=16.7\pm 0.1\text{ kcal}\cdot\text{mol}^{-1}$ indicates high kinetic stability of the anion complex. As a reference, the kinetic stability of chloride complex with **5**, which is known to be thermodynamically highly stable ($K\sim 10^5\text{ M}^{-1}$)^[17,18] was investigated with the same method. The analysis of the EXSY cross-peaks of the free and bound host at 1:0.5 (host:guest) molar ratio yielded $k_{21}=2.5\text{ s}^{-1}$ and $\Delta G^{\ddagger}_{-1}=17.2\pm 0.1\text{ kcal}\cdot\text{mol}^{-1}$, which is slightly higher energy barrier compared to the benzoate complex of **1**, as expected. Nevertheless, the relatively low thermodynamic but high kinetic stability of the anion complexes of **1** likely results from the high energy barrier of the conformational change of the host required from closed to open state for guest release.

Conclusion

Unexpected doubly strapped calix[4]pyrrole was isolated and characterized with NMR spectroscopy and single crystal X-ray diffraction. Free calix[4]pyrrole displays an open state adopting a 1,3-alternate conformation in non-polar solvent. Interactions with anions induce a large conformational movement to a closed state reminiscent of a shape change of a Venus flytrap that was kinetically stabilized in a polar non-protic solvent. Even though the double strapping does not enhance thermodynamic stability of the anion complexes as significantly as single strapping, slow guest release from the complexes was observed, accompanied with slightly smaller energy barrier for complex dissociation as with thermodynamically stable chloride complex of a calix[4]pyrrole bearing a single strap. This combination of relatively low affinity and high kinetic stability for chloride, acetate and benzoate has not been previously reported for diametrically and proximally strapped calix[4]pyrroles.

Experimental Section

Reagents and solvents, including dry dichloromethane and dry pyridine were purchased from Sigma-Aldrich and used as received. NMR spectra were measured with Bruker Avance 500 (500 MHz for ¹H NMR and 126 MHz for ¹³C NMR) and Bruker Avance 500 equipped with a Prodigy cryoprobe. The J values are given in Hz. High Resolution Mass Spectra (HRMS) were measured with a Bruker HPLC-QqTOF (MaXis Impact) using ESI ionization mode. Melting points were measured with Stuart SMP30 and are uncorrected.

Synthesis: Calixpyrrole **1**. A dry 250 ml two-necked flask was connected to a Schlenk line and charged with dipyrromethane **3**^[17] (2.41 g, 11.0 mmol) and isophthaloyl chloride (0.88 g, 4.3 mmol) under argon. Dry dichloromethane (144 ml) and dry pyridine (1.1 ml, 13.6 mmol) were added to the flask. The flask was wrapped in aluminum foil to protect it from light and the mixture was stirred at room temperature for 16 hours. The mixture was poured into 200 ml of deionized water. The solution was shaken and the

organic phase was collected. The water phase was extracted twice with 150 ml of DCM. The combined organic extracts were dried with Na₂SO₄ and evaporated yielding 3.2 g of yellow-brownish oil. The crude was purified by column chromatography (1 g of crude with 46 g of silica) using 95:5 DCM/EtOAc eluent until compounds **1** and **4** had eluted, and finally up to 100% EtOAc to elute dark brown oligomeric and polymeric pyrroles (major product). The fraction containing the bis-strapped calix[4]pyrrole was concentrated with a rotary evaporator and the product was crystallized as a white solid, which was filtrated with suction, washed with hexane and dried under vacuum, yield 56 mg (1.5%) m.p. >270 °C (decomp.), R_f 0.21 (DCM/acetone 99:1). ¹H NMR (500 MHz, [D₂]dichloromethane, 25 °C): δ =8.48 (t, J =1.7, 2H), 8.22 (dd, J =17.7 and 1.7, 4H), 7.58 (t, J =7.7, 2H), 7.37 (s, br, 2H, NH), 6.94 (s, br, 2H, NH), 5.90 (d, J =2.7, 4H, β -Py), 5.85 (d, J =2.7, 4H, β -Py), 4.56 (m, 4H, OCH₂), 4.09 (m, 4H, OCH₂), 2.09 (m, 4H, CCH₂), 1.96 (m, 4H, CCH₂), 1.88–1.78 (m, 4H, CH₂), 1.73–1.63 (m, 4H, CH₂), 1.52 (s, 12H, CH₃) ppm. ¹³C NMR (126 MHz, [D₂]dichloromethane, 25 °C): δ =165.98, 137.97, 136.84, 134.09, 131.22, 130.43, 129.27, 104.04, 103.96, 65.56, 38.81, 38.49, 23.83, 23.30 ppm. HR-MS (ESI-TOF): m/z calcd. for C₅₂H₅₆N₄O₈ + Na⁺: 887.3990 [M + Na]⁺; found: 887.4003.

X-ray crystallography: Single crystal X-ray data for structure **1a** were recorded on a Bruker Apex DUO diffractometer equipped with an APEX 2 4 K CCD area detector, and a Microfocus Source E025 luS using MoK α (λ =0.71073 Å) radiation monochromatized with Quazar MX Multilayer Optics. The data were processed with Bruker APEX2 v2014.9-0 and empirical absorption correction was made with SADABS-2014/4. The structure was solved with Sir2014 using direct methods and refined with ShelXle using ShelXL refinement package with least squares minimization. Single crystal X-ray data for structure **1b** were recorded on an Agilent SuperNova, Single source at offset, Eos diffractometer using an Agilent Atlas CCD detector with mirror monochromatized MoK α (λ =0.71073 Å). The data were processed, and empirical absorption correction was made with CrysAlisPro. The structure was solved with CrysAlisPro using AutoChem. The structure was refined with Olex2 using ShelXL refinement package with least squares minimization. The hydrogen atoms were calculated to their idealized positions with isotropic temperature factors (1.2 or 1.5 times the C temperature factor) and refined as riding atoms.

Deposition Numbers 2172497 (for **1a**) and 2172498 (for **1b**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Computational: Computational studies were carried out using Maestro package (Schrödinger Release 2021-4: Maestro and Macro-Model, Schrödinger, LLC, New York, NY, 2021) with OPLS4 force field^[29] in vacuum. Conformational search was performed in a mixed torsional low mode sampling mode with 10 000 steps using 2.0 Å as maximum atom deviation cutoff and 18.0 Å as maximum distance for low-mode move.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Anions · Calix[4]pyrroles · Molecular switch · NMR spectroscopy · Supramolecular chemistry

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