Sulfoniumcalixpyrrole: the decoration of a calix[4]pyrrole host with positive charges boosts affinity and selectivity of anion binding in DMSO solvent†‡

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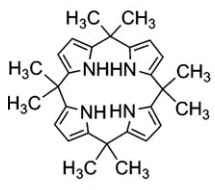
With the goal to improve host–guest binding affinity, while retaining guest selectivity, the parent calixpyrrole artificial receptor unit was decorated with four sulfonium moieties (*e.g.* **3b**) placed rigidly in symmetrical fashion remote from the core binding site. The determination of binding constants using isothermal titration calorimetry (ITC), in conjunction with trend analyses in a series of related anions, reveals the occurrence of several specific and unspecific binding steps. The former predominate in affinity by 20–1000 fold depending on guest charge and structure. The dissection of the free energy of association into its enthalpic and entropic parts, in combination with structural variation in the guest anion, offers insight into the nature and diversity of the guest binding modes. On these grounds, the supplementation of parent host scaffolds with rigidly positioned positive charge centers, holds promise as a general concept for anion binding in competitive media.

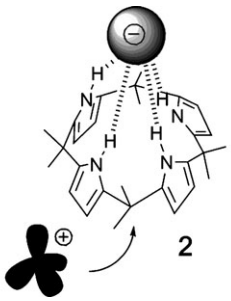
Introduction

Calixpyrroles are stable porphyrinogenes showing considerable potential in the host–guest binding of salt-like compounds.[1,2] Initially, the easy-to-make and long-known parent compound **1** was characterized as an artificial receptor for binding anions in particular for fluoride or hydrogenphosphate.[3] Meanwhile, following up on an earlier suspicion voiced before,[4] Sessler and Gale showed that large cations may readily bind to the concave surface of the macrocycle formed as a result of convergent hydrogen bonding of the pyrrole N–H-donor groups towards the complexed anion (*cf.* **2**).[5,6]

Hydrogen bonding appears to be the prime interaction type in this host as deduced from the sensitivity of complex affinity on the H-bond acceptor strength of the anion and its decrease with increasing polarity of the solvent. In fact, a recent study corroborated the dramatic drop in the affinity of chloride binding on going from the less competitive non-hydrogen-bonding solvent dichloromethane (DCM) to strongly competing dimethyl sulfoxide (DMSO).[7] Solvents of intermediate polarity (acetonitrile, nitromethane) fall in between although the results do not correlate with straightforward polarity scales.[7] As the affinity decreases, binding selectivity is lost, as well impairing any use of these host systems under more stringent solvation conditions. A number of efforts have been undertaken to save selectivity by restricting the accessibility of the binding site. Bulky groups have been introduced at the *meso*-positions to construct a deeper binding cleft[8] or straps have been connected to opposing *meso*-positions in the macrocycle creating a molecular cavity that limits the variety of energetically favorable host–guest configurations thus fostering selectivity.[9] Though these attempts have met with some success, they require quite laborious and low-yielding compound preparations.



1



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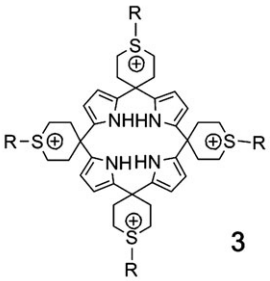

3

	R
a	CH_3
b	$CH_2COOC_2H_5$
c	CH_2COO

Instead, we reasoned that the patterned incorporation of cationic charges into the calixpyrrole might provide a viable and preparative simpler alternative. The introduction of

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† Dedicated to Professor George Gokel on the occasion of his 60th birthday.

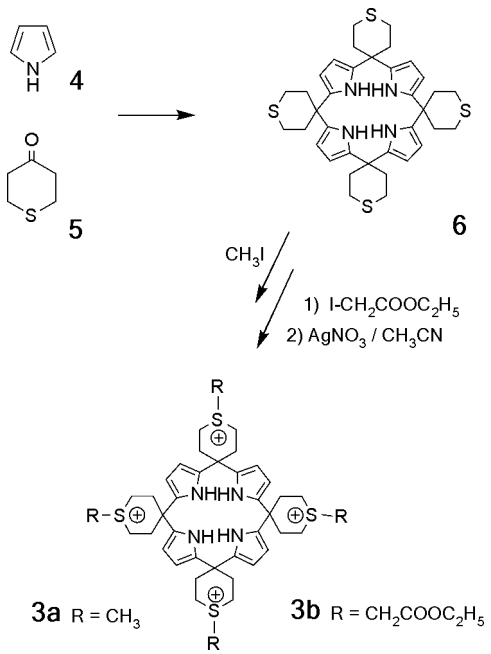
‡ Electronic supplementary information (ESI) available: Single-crystal X-ray data; NMR and ESI-MS spectra of the novel compounds, graphs of the ITC titration data (18 pp). See DOI: 10.1039/b617465e

positively charged non-hydrogen-bonding centers remote from the actual guest binding site should elevate the general affinity for the anionic guest *via* an ordinary electrostatic field effect, yet should be innocent in perturbing the fundamental binding mechanism of the guest species and, thus, should minimize interference with respect to selectivity. Of course, the overall pattern of binding site arrangement must not be affected, nor should the possibility for pyrrole ring flips from the 1,3-alternate conformation of the uncomplexed host to the cone structure required for guest binding be touched. Toward this end, the placing of onium charges in rigid moieties attached to the *meso*-positions of the calixpyrrole core, as in compounds **3** appeared optimal. The rigid anchoring of the onium centers of nitrogen- and sulfur-macrocycles to furnish artificial hosts capable to complex ordinary inorganic and organic anions even in water has been demonstrated early on.[10,11] Here we report on the combination of coulombic charge attraction with the subtle features of calixpyrrole hydrogen-bonding to generate artificial receptors capable of high affinity anion binding in DMSO.

Results and discussion

Synthesis

A straightforward way to incorporate four positive charges at the periphery of the calixpyrrole macrocycle, however, near the equator plane to avoid influencing the conformational equilibrium of the core structure made use of the thiopyrano derivative **6**. This thioether can be conveniently prepared from pyrrole **4** and commercial thiopyranone **5** under acid catalysis[12] as it forms an insoluble chloroform solvate-complex which precipitates from the solution in this solvent.



The $CHCl_3$ adduct is destroyed on dissolution in acetone or DMSO, but re-forms and precipitates again when the material obtained from evaporation of the former solvent is dissolved in $CHCl_3$. The single-crystal X-ray structure of the acetone solvate (Fig. 1) shows the expected antiparallel axial orientation of neighboring pyrrole ring dipoles similar to the 1,3-alternate conformation of the parent compound **1**. The sulfur atoms occupy mirror image positions with respect to both mirror planes dissecting the juxtaposed pyrrole rings. Thus, they are optimally exposed for subsequent alkylation and cannot interfere directly with any binding event happening at the central core. Methylation of **6** using methyl iodide in methanol proceeded smoothly to the tetrasulfonium stage furnishing the permethylated compound **3a** in excellent yield. The methylation is rendered reversible on addition of thioacetate. Attack of this nucleophile on **3a** exclusively demethylates this salt and does not yield products in which the six-membered thioether ring is opened up. Another attempt to open the sulfonium ring by Hofmann elimination failed as well.

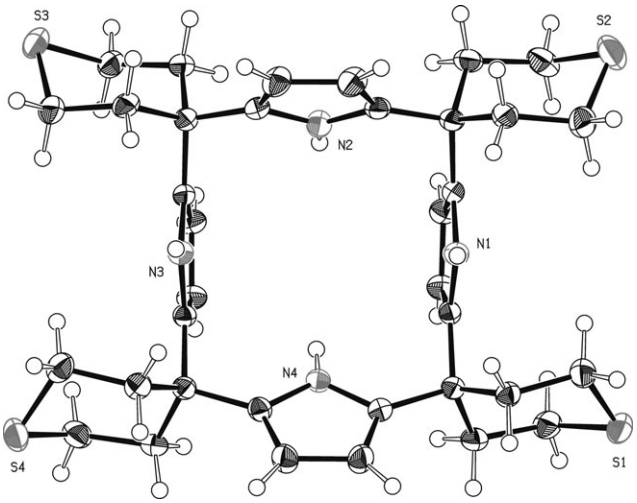


Fig. 1 Molecular structure of the thiopyrano calixpyrrole **6** in the solid state. The atomic thermal ellipsoids are shown at the 50% probability level.

With the vision to ultimately create zwitterionic calixpyrroles which are electroneutral, yet water-soluble, analogues of parent **1** and thus would enable binding studies of the electrostatically unperturbed calixpyrrole macrocycle, we alkylated thioether **6** with iodoacetic acid derivatives. Whilst iodoacetamide or iodoacetic acid proved unsuitable, because they yielded complicated product mixtures, ethyl iodoacetate furnished a clean stepwise alkylation. Using a 4-fold excess of alkylating agent over each thioether site, full alkylation could still not be achieved, since an equilibrium state containing 20% of trisalkylated sulfonium product was approached at ambient temperature. Raising the temperature or deliberate addition of more inorganic iodide salt increased this fraction attesting to the reversibility of the alkylation reaction. In order to drive the conversion to completion, and at the same time introduce a suitable counteranion for the subsequent host–guest binding studies, the equilibrium mixture was treated with a stoichiometric amount of silver nitrate in acetonitrile. Silver iodide precipitated and the tetraalkylated sulfonium compound **3b** remained as the only detectable product in solution. Feeding this solution into a large volume of hexane precipitated **3b** as the nitrate salt. This compound apparently populates quite a number of different and slowly (on the timescale of a 500 MHz

NMR instrument) interconverting conformations in water as judged from the rather complicated pattern of NMR signals, in particular for the pyrrole CH and NH resonances. Furthermore, **3b** underwent rapid hydrolysis or transesterification in water or alcoholic solutions accompanied by ring-opening Hofmann eliminations which were especially obvious in the ESI-MS spectra. Mild base hydrolysis of **3b** using an anion exchange resin in OH^- form finally furnished the extremely hydrophilic and deliquescent tetra-zwitterions **3c**. So far this compound could not be obtained in an analytically pure state due to its hygroscopic nature. Therefore the host–guest binding studies were focused on the well characterized and easier to handle tetrasulfonium compound **3b**.

Binding studies

Among the various methods well suited for determining the affinity of a molecular guest towards an artificial host compound, isothermal titration calorimetry (ITC) stands out with respect to sensitivity, universality and the capacity to elucidate the enthalpic and entropic components of the free energy, allowing an intimate view on the entire binding energetics. We chose to analyze the host–guest complexation of the tetrasulfonium calixpyrrole **3b** with a variety of salts in DMSO solution aiming at a meaningful comparison to the parent calixpyrrole **1** which had been studied under identical conditions recently.[7] In an initial attempt a titration of **3b** with tetramethylammonium fluoride in DMSO was carried out inspired by the putative selectivity of the parent calixpyrrole **1** for fluoride anion in DCM.[3] However, Fig. 2 reports a clean triphasic titration curve (exothermic to endothermic to exothermic response again) that is not finished at the end of the run at an 8-fold excess of fluoride over **3b**. Clearly, this result is incompatible with an exclusive supramolecular scenario, but rather suggests some covalent bond modification (*e.g.* transprotonation). Since we could not detect any product by gradient HPLC analysis of the reaction mixture after an acid quench, a reasonable cause for the titration result would be proton abstraction from the exocyclic sulfonium methylene group and/or the pyrrolic NH moieties, which was reversed in the quench process. In the light of a recent study of fluoride basicity[13] both groups should be acidic enough[14] to readily protonate unhydrated fluoride to the HF_2-stage.[15] Thus, supramolecular associations in this system can only be observed with less basic anions.

A first candidate in this respect was chloride anion that was probed as tetramethyl- (TMA), tetraethyl- (TEA) and tetrabutyl- (TBA) ammonium salts. Quite unlike the profound dependency found in the case of calixpyrrole **1**, complexing these salts in DCM (a factor of 100 in affinity between TEA and TBA chloride was noted[7]), no substantial difference in this series was observed with compound **3b** in DMSO (*cf.* Fig. 3 and Table 1). The minor differences seen are barely significant and may well derive from a variation in the ion-pairing behavior of the uncomplexed salts rather than from higher order complexation of the {$Cl^- \subset$ **3b**} complex with an additional countercation.[18] The titration curves, however (Fig. 3), are incompatible with an ordinary 1 : 1 stoichiometric binding scheme. Rather the pronounced maximum at a guest to host molar ratio of 1 (corresponding to the location of the inflection point at a molar ratio of 0.5) followed by a slow descent

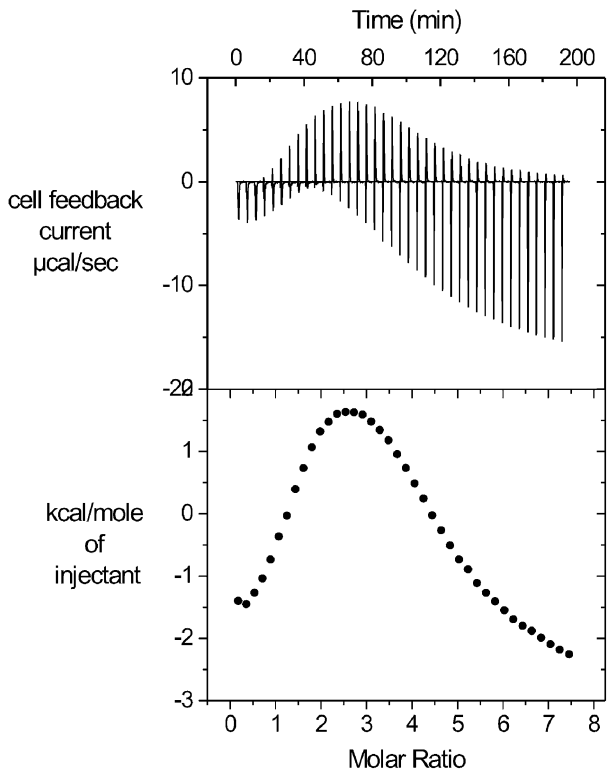


Fig. 2 ITC titration of sulfonium calixpyrrole **3b** (0.5 mM) with TMA fluoride (19.4 mM) in DMSO at 298 K. The upper panel shows the actual heat pulses in each titration step (6 µl) whilst the lower one depicts the time integral (*i.e.* the titration curve of the energies observed).

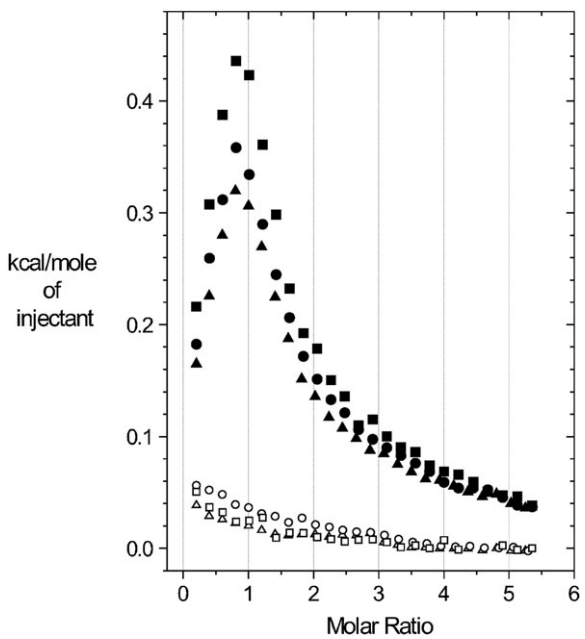


Fig. 3 Overlay of the titration curves of **3b** with tetraalkylammonium chloride in DMSO at 298 K. TMA: circles; TEA: triangles; TBA: squares. Open symbols represent the reference titrations without the host compound.

Table 1 Energetics of specific chloride complexation to **3b** in DMSO at 298 K. The 1 : 1 and 2 : 1 host–guest binding steps are found to possess identical affinity. The apparent association constant for unspecific chloride binding to **3b** amounts to 300–500 M^{-1}, but resisted deconvolution due to high statistical cross correlation of the parameters

Salt	n^a	K_a (1 : 1)/M^{-1}	ΔG°/kJ mol^{-1}	ΔH°/kJ mol^{-1}	$T\Delta S^\circ$/kJ mol^{-1}
TMA^+Cl^-	0.49	1.6×10^4	−23.9	+0.3	+24.2
TEA^+Cl^-	0.51	1.9×10^4	−24.4	+0.3	+24.7
TBA^+Cl^-	0.56	1.5×10^4	−23.8	+0.5	+24.3
TEA^+Cl^- + **1**[b]	1.0	1.2×10^3	−17.5	−8.1	+9.4

[a] Experimental stoichiometry factor. [b] From ref. 7.

towards higher molar ratios points to a molecular scenario in which a 2 : 1 host–guest complex is initially formed when the host compound is still present in major excess over the guest. Continued addition of guest transforms the 2 : 1 complex into the 1 : 1 species yielding the stoichiometry observed. These specific complexation steps, which apparently possess very similar affinities (*i.e.* free energies) are overlaid to an endothermic process that decreases much more slowly, indicative of unspecific low affinity ion-pairing. Based on this model, a good fit to the experimental data was achieved in each case, furnishing the energetic parameters contained in Table 1.

Compared to calixpyrrole **1**,[7] the tetracationic derivative **3b** exhibits a 10–15-fold improvement in affinity, however, at the cost of diminished structural definition of the complexes. The association enthalpy is raised to slightly endothermic (*i.e.* binding opposing) levels and the complexes owe their stability entirely to the much enhanced entropy of association. If one assumes that the solvation changes of chloride complexation by **1** or **3b** are similar, because the core binding sites are identical, the much increased entropy contribution seen with **3b** would indicate a massive loosening of the host structure brought about by chloride binding. Presumably the electrostatic repulsion of the charged corners stiffens the structure allowing some relaxation when this strain is weakened on binding the anionic guest.

Considerably higher affinities were found in a series of monocharged anions and the energetic results are collected in Table 2. Apart from hydrogensulfate which eluded the analysis as no significant heat effect was recorded in the titration, benzoate, acetate and dihydrogenphosphate all showed well behaved responses, that could be easily fitted to a binding model involving two independent binding sites. The success of such a model is most obvious in the titration of **3b** with the benzoate where an exothermic primary 1 : 1 association step is followed by an endothermic event of lower affinity (*cf.* Fig. 4). In the case of acetate (administered as the tetrahydrate) and dihydrogenphosphate the association enthalpies addressing the individual sites of interaction are of the same sign: endothermic in the former, exothermic in the latter case. In fact, dihydrogenphosphate shows the most intense enthalpic host–guest binding, that contrary to the energetic profile of the parent host compound **1**,[4] is even assisted by a positive entropy component to render this complex the most stable one among the monoanions. Throughout the series, we note a uniform gradation in affinity of the second *vs.* the first guest binding step by a factor of 20 to 50, representing a *ca.* 9 kJ mol^{-1} preference in free energy of specific over unspecific binding. This view is also supported by the general energetic signature. The specific complexation step features the more negative enthalpy and entropy whilst the lower affinity binding step shows the ordinary pattern of ion-pairing in polar solvents (highly positive entropies in connection with weak or substantially positive enthalpies).

One might expect that this trend is emphasized by guest charge enhancement. A study of organic dianions corroborated this presumption, but also proved subtle structural influences. The ITC-analysis produced the results depicted in Table 3. The common feature is again a strongly positive association entropy that testifies to extensive desolvation of host and guest on complex formation, probably in addition to a high configurational entropy component, arising from a broad diversity of host–guest binding modes. Among the dianions tested, phthalate represents a special case that is apparently also expressed in its congener benzene-1,2,4,5-tetracarboxylate. Both titration curves (see Fig. 5) display well reproducible patterns that, however, elude interpretation in terms of simple association models. Rather the very distinct calorimetric features observed at high stoichiometric ratios point to an assembly phenomenon that is not apparent in the associations with any other guest. Also the systematic fine structure of the heat pulses support the assumption that successive binding and rearrangement processes in the molecular complexes formed at the beginning must happen over seconds after guest addition.

Table 2 Thermodynamic state functions of the association of various monoanions with sulfonium calixpyrrole **3b** in DMSO at 298 K. The parameters were derived from a binding model based on two independent binding sites

Salt	$n_1{}^a$	K_{a1}/M^{-1}	ΔG°_1/ kJ mol^{-1}	ΔH°_1/ kJ mol^{-1}	$T\Delta S^\circ_1$/ kJ mol^{-1}	$n_2{}^a$	K_{a2}/M^{-1}	ΔG°_2/ kJ mol^{-1}	ΔH°_2/ kJ mol^{-1}	$T\Delta S^\circ_2$/ kJ mol^{-1}
TEA^+PhCOO^-	1.0	2.4×10^4	−24.9	−7.0	+17.9	1.2	1.1×10^3	−17.3	+42.2	+59.6
TEA^+MeCOO^-	1.5	1.8×10^5	−29.9	+6.9	+36.8	2.3	5.8×10^3	−21.5	+19.5	+40.9
$TBA^+H_2PO_4^-$	0.8	3.3×10^5	−31.5	−20.1	+11.5	1.3	6.5×10^3	−21.8	−12.9	+8.9
TBA^+HSO_4	No heat effect									

[a] Experimental stoichiometry factor.

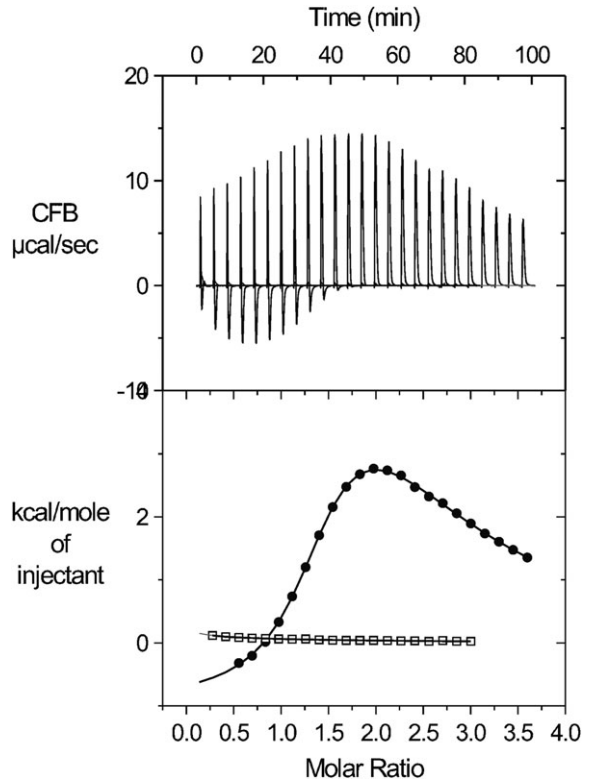


Fig. 4 ITC-titration of **3b** with TEA benzoate in DMSO at 298 K. The reference titration run (open squares) was fitted by an exponential function for correction of the original data (solid circles).

The other benzenedicarboxylate regioisomers exhibit a regular response comprising a specific 1 : 1 host–guest binding step superimposed on general ion-pairing, that in the case of these dianions, is 70 to 100 fold weaker in affinity than the specific process. Extending the mutual distance of the charged carboxylate groups by insertion of vinylene rigid spacers between the benzene ring and the anionic function in terephthalate does not influence the affinity very much (entries 4 and 5), but has a profound effect on the energetic profile. The exothermic specific binding step seen in the case of terephthalate is transformed into an endothermic one with a concomitant increase in entropy. The change in binding enthalpy likely reflects a switch in the dominant binding mode due to the misfit of the stick-like expanded dianion that may no longer bind at the central core as is most probably true for terephthalate, but may ion-pair in a tangential fashion connecting adjacent cationic sulfonium centers at the rim of the molecule. Quite possibly, stacking interaction of the aromatic moieties of host and guest may favor such a binding mode at the same time. If this binding motif is not possible, as in the case of *trans,trans*-muconate (entry 6), the enthalpy is even more endothermic (unfavorable) and, moreover, is counterbalanced to some extent by an appreciable entropy increase. Desolvation cannot account for this result[16] since the chemical nature of the interface in the supramolecular complexes of entries 5 and 6 should be quite similar. The desolvation costs in turn scale with total surface area buried on complexation leading to the anticipation that a more expanded interface must give the greater gain in entropy. The observation of the contrary suggests an enhanced contribution from configurational entropy[17] in the case of muconate, caused by less restricted and more fuzzy ion-pairing interactions with this guest, as it resides at the periphery of the disc-shaped host molecule **3b**. This molecular scenario is also supported by the distinct 1 : 2 host : guest stoichiometry found that prevents further ion-pairing interactions.

Structural reasoning remains vague on the basis of trend analysis alone comparing the energetics of compounds differing by subtle structural variation. Nevertheless, in the absence of more direct structural information *e.g.* from NMR which is, however, silent in this case, our arguments offer a rational and plausible explanation of the experimental facts.

Smaller guest anions possess higher affinities, and the enthalpies are rendered more exothermic while entropy production is lowered. Both trends indicate that fumarate, oxalate and squarate (entries 7, 8, 9) undergo specific complexation at the calixpyrrole core unit of **3b** supplemented by unspecific ion-pairing to a similar extent at the sulfonium peripheric moieties. The specific binding step profits from increasing the charge density (*e.g.* oxalate, entry 8, *vs.* fumarate, entry 7). Furthermore, the highly symmetrical distribution of charge in the guest species is likewise favorable, presumably due to the generation of degenerate binding modes. Association entropy benefits from this factor and emerges as the origin of a dramatic increase in affinity for squarate dianion. The magnitude of the association constant for squarate specific binding to **3b** exceeds the unspecific ion-pairing background interaction by a factor of 1000. In absolute terms this is one of the strongest specific complexes observed with artificial receptors in DMSO solvent. This feeds the expectation that the concept of charge supplementation on neutral anion hosts of proven utility is a viable approach to abiotic receptors functioning even under more demanding biological conditions.

Conclusions

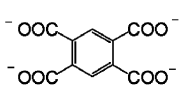
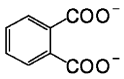
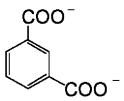
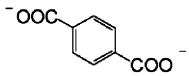
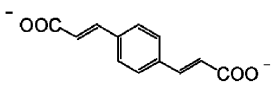
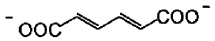
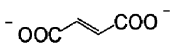
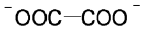
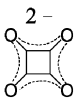
The decoration of the parent calixpyrrole nucleus with positive charges leads to a substantial increase in anion affinity even in a highly polar solvent such as DMSO. Though the introduction of charge triggers unspecific ion-pairing with the guest, the specific interaction outmatches this background binding by a factor of 20 up to 1000. Within this span, anions of elevated charge occupy the high end regime. Specific binding is also characterized by more negative association enthalpies and smaller, yet still positive entropies. Although accessibility of the binding site in these calixpyrroles is hardly restricted, they show structural preferences for the anionic guest species, that may translate into distinct assembly processes.

Experimental

Syntheses

Reagents and chemicals were purchased from Aldrich and used as received. All reactions were monitored by HPLC using standard RP-columns with a 10 to 90% methanol gradient over 20 min (flow 1.0 ml min^{-1}). NMR spectra were obtained

Table 3 Energetics of binding dianions (TEA-salts) to sulfonium calixpyrrole **3b** in DMSO at 298 K. The parameters were derived on the basis of a binding model comprising two independent binding sites

Nr.	Salt	n_1[a]	K_{a1}/M^{-1}	ΔG°_1/ kJ mol^{-1}	ΔH°_1/ kJ mol^{-1}	$T\Delta S^\circ_1$/ kJ mol^{-1}	n_2[a]	K_{a2}/M^{-1}	ΔG°_2/ kJ mol^{-1}	ΔH°_2/ kJ mol^{-1}	$T\Delta S^\circ_2$/ kJ mol^{-1}
1		No determination of thermodynamic parameters possible									
2		No determination of thermodynamic parameters possible									
3		1.2	1.3×10^6	−34.8	−4.9	+29.8	2.8	1.2×10^4	−23.8	+17.2	+40.5
4		1.1	1.9×10^5	−30.1	−3.6	+26.6	3.1	2.9×10^3	−19.7	+18.9	+38.6
5		0.8	1.5×10^5	−29.5	+4.4	+33.8	1.0	3.1×10^3	−19.9	+35.5	+54.9
6		2.3	2.7×10^3	−19.6	+20.2	+39.8					
7		1.0	3.4×10^5	−31.5	−9.7	+21.9	2.9	7.0×10^3	−21.9	+26.1	+48.0
8		1.0	5.6×10^5	−32.8	−18.2	+14.6	4.0	3.2×10^3	−20.0	+27.6	+47.6
9		1.3	1.4×10^7	−40.8	−17.2	+23.6	3.2	1.7×10^4	−24.1	+24.3	+48.4

[a] Experimental stoichiometry factor.

on Bruker AM-360 or AM-500 instruments and are referenced to the standard solvent resonance. ESI-MS spectra were measured either by loop injection or *via* HPLC on a Finnigan LCQ machine. Elemental analyses were conducted by the microanalytical laboratory of the TU Munich.

Calix[4]pyrrole tetrathioether derivative 6

A catalytic amount of trifluoroacetic acid (25 µl) was added to a solution of pyrrole (320 µl, 4.80 mmol) and tetrahydrothiopyran-4-one (540 mg, 4.65 mmol) in chloroform (10 ml). The reaction mixture was refluxed for 1 h and subsequently stirred for 3 h at room temperature. A white solid precipitate was collected which was washed with chloroform (2 × 20 ml) and dried *in vacuo* (935 mg, 90%, calculated for complex with two molecules of chloroform). The material can be recrystallized from a small volume of hot DMSO. ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 360 MHz): δ 2.31 (16 H, m, CH_2CCH_2), 2.53 (16 H, m, CH_2S), 5.80 (8 H, d, J = 2.3 Hz, β-pyrrole), 7.64 (3.5 H, s, $CHCl_3$), 8.18 (4 H, s, NH). ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 90.6 MHz): δ 24.91, 37.56, 39.36, 78.72 ($CDCl_3$), 104.57, 136.27. ^{1}H NMR (CD_2Cl_2, 360 MHz): δ 2.31 (16 H, m, CH_2), 2.64 (16 H, m, CH_2), 5.98 (8 H, d, J = 2.8 Hz), 7.08 (4 H, s, NH), 7.34 (2 H, s, $CHCl_3$) ^{13}C NMR (CD_2Cl_2, 90.6 MHz): δ 25.00, 37.99, 39.56, 78.00 ($CHCl_3$), 105.13, 136.08. MS-ESI ($C_{36}H_{44}N_4S_4$) 659 (100%, M^+).

Calix[4]pyrrole methylsulfonium iodide derivative 3a

Calixpyrrole thioether **6** (200 mg, 303 mmol) was suspended in 2 ml of methyl iodide and stirred at ambient temperature. After 20 h, 2 ml of methanol were added, and the reaction was allowed to continue for another 10 h. Then all volatiles were evaporated by a stream of air leaving a light yellow residue of the **3a** iodide salt (quantitative). ^{1}H NMR (D_2O, 360 MHz): δ 2.38–2.70 (16 H, m, CH_2C); 2.77 (12 H, s, CH_3S); 3.17 (8 H, m, CH_2S), 3.47 (8 H, m, CH_2S), 6.03 (8 H, m, β-pyrrole). MS-ESI ($C_{40}H_{56}N_4S_4I_4$) 1100 (3%, $(M - I)^+$), 959 (20%, $(M - CH_3I_2)^+$), 817 (15%, $(M - (CH_3)_2I_3)^+$), 675 (5%, $(M - (CH_3)_3I_4)^+$), 487 (15%, $(M - I_2)^{2+}$), 416 (100%, $(M - CH_3I_3)^{2+}$), 282 (10%, $(M - I_3)^{3+}$), 180 (5%, $(M - I_4)^{4+}$).

The iodide salt of **3a** was stirred with Serdolit AS-6 anion exchanger (quaternary ammonium acrylic amide) in the nitrate form (15 meq.) in water for 2 days. The suspension was then filtered through a short column of the same anion exchanger, followed by extensive washing with water (100 ml). The effluent was collected and lyophilized to leave 270 mg (96%) of a light brown powder of the nitrate salt. ^{1}H NMR (D_2O, 360 MHz): δ 2.57 (8 H, br m, CH_2), 2.69 (8 H, m, CH_2), 2.87 (12 H, m, CH_3), 3.26 (8 H, m, CH_2), 3.54 (8 H, m, CH_2), 6.13 (8 H, m, β-pyrrole), 8.54 (3 H, m, NH). ^{13}C NMR (D_2O, 90.6 MHz): δ 20.8–21.3, 29.2–29.6, 33.7–34.1, 37.5, 105.3–105.7, 135.0–135.8. MS-ESI ($C_{40}H_{56}N_8S_4O_{12}$) 906 (5%, $(M - NO_3)^+$), 829 (12%, $(M - CH_3 - (NO_3)_2)^+$), 766 (5%,

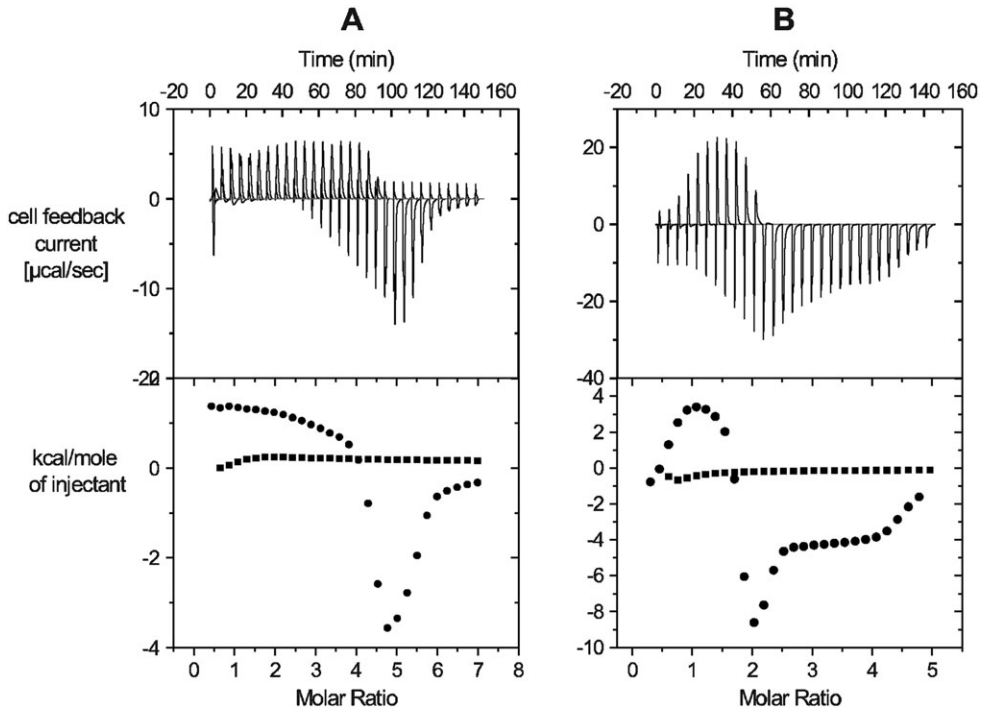


Fig. 5 ITC-titration of **3b** with (A) TEA phthalate and (B) TEA benzene-1,2,4,5-tetracarboxylate in DMSO at 298 K. The calorimetric profiles were reproducible, but resisted our attempts of interpretation.

(M − H − CH_3 −$(NO_3)_3)^+$), 752 (5%, (M − $(CH_3)_2$ − $(NO_3)_3)^+$), 675 (3%, (M − $(CH_3)_3$ − $(NO_3)_4)^+$), 422 (20%, (M − $(NO_3)_2)^{2+}$), 391 (40%, (M − H − $(NO_3)_3)^{2+}$), 359 (50%, (M − H_2 − $(NO_3)_4)^{2+}$), 352 (60%, (M − H − CH_3 − $(NO_3)_4)^{2+}$), 240 (100%, ((M − H − $(NO_3)_4)^{3+}$), 235 (27%, (M − CH_3 − $(NO_3)_4)^{3+}$), 180 (15%, (M − $(NO_3)_4)^{4+}$).

Calixpyrrole ethoxycarbonylmethylsulfonium iodide salt 3b

330 mg (500 μmol) of thiacyclohexanocalixpyrrole **6** were mixed with 1 ml of ethyl iodoacetate and 1 ml of dry nitromethane. On stirring at room temperature the compound slowly dissolved to give a dark yellow solution. The reaction was monitored by HPLC: 125 × 4 mm Nucleodur RP-8, linear gradient from 10 to 90% methanol–0.1% trifluoroacetic acid, flow 1 ml min^{-1}; R_t(tetra-alkylated product) = 11.0 min; R_t(tris-alkylated product) = 13.4 min. When equilibrium was reached 2.1 ml of a 1 M solution of $AgNO_3$ in acetonitrile was added. After 1 h stirring at room temperature the precipitate of silver iodide was removed by filtration through Celite and the filtrate was diluted into hexane (40 ml). The precipitated product (nitrate salt) was collected by centrifugation and the sedimented pellet was thoroughly washed with ether. Vacuum drying of the residue left 596 mg (95%) of a slightly yellow powder. Elemental analysis: $C_{52}H_{72}N_8O_{20}S_4 \cdot 2H_2O$ requires C 48.29; H 5.92; N 8.66. Found: C 48.58; H 5.87; N 8.49%. ^{1}H NMR (D_2O, 360 MHz): δ 2.53 (8 H, m, CH_2); 2.73 (8 H, m, CH_2); 3.33 (8 H, m, CH_2CH_2S); 3.53 (8 H, m, CH_2CH_2S); 4.70 (8 H + signal of H_2O, s, CH_2SCH_2CO), 6.05–6.20 (8 H, m, β-pyrrole). ^{13}C NMR (D_2O, 90.6 MHz): δ 30.1–30.5, 32.7–33.1, 37.7–37.8, 104.6, 106.3, 134.8, 135.8, 168.50. MS-ESI ($C_{44}H_{52}N_4O_8S_4$): 983 (7%, (M − H_3 + $Na_4)^+$), 961 (10%, (M − H_2 + $Na_3)^+$), 939 (15%, (M − H + $Na_2)^+$), 915 (5%, (M + Na)$^+$), 893 (15%, (M + H)$^+$), 871 (20%, (M + Na − $CO_2)^+$), 849 (20%, (M + H − $CO_2)^+$), 827 (45%, (M + Na − $(CO_2)_2)^+$), 805 (25%, (M + H − $(CO_2)_2)^+$), 783 (30%, (M + Na − $(CO_2)_3)^+$), 777 (15%, (M + H − $(C_2H_2O_2)_2)^+$), 761 (65%, (M + H − $(CO_2)_3)^+$), 739 (15%, (M + Na − $(CO_2)_4)^+$), 719 (65%, (M + H − $(C_2H_2O_2)_3)^+$), 717 (100%, (M + H − $(CO_2)_4)^+$), 703 (60%, (M + H − $(CO_2)_3C_2H_2O_2)^+$), 689 (65%, (M + H − $(CO_2)_2(C_2H_2O_2)_2)^+$), 674 (20%, (M + H − $CO_2(C_2H_2O_2)_3)^+$), 660 (7%, (M + H − $(C_2H_2O_2)_4)^+$), 469 (7%, (M + $Na_2)^{2+}$), 458 (15%, (M + H + Na)$^{2+}$), 447 (35%, (M + $H_2)^{2+}$), 403 (15%, (M + H − $(CO_2)_2)^{2+}$), 370 (15%, (M + Na + H − $(CO_2)_4)^{2+}$) 359 (30%, (M + H_2 − $(CO_2)_4)^{2+}$), 352 (20%, (M + H_2 − $(CO_2)_3C_2H_2O_2)^{2+}$).

Calorimetric titration studies

ITC titrations were conducted using a fully computer-operated Microcal MCS-ITC machine. Solutions were prepared in dry DMSO (<0.005% H_2O, stored over molecular sieves) using recrystallized and vacuum dried tetraalkylammonium salts and lyophilized samples of the host **3b**. In all cases the anion under study was titrated into the host solution. The original titration data were corrected by blind titrations of the same salt solution titrated into plain solvent. Data analysis used Microcal Origin 5.0 software provided with the instrument.

Single-crystal X-ray structure determination of compound 6[19]

Crystal data. $C_{36}H_{44}N_4S_4 \cdot 2C_3H_6O$, M_r = 777.19, orthorhombic, space group *Pbca* (no. 61), a = 16.0948(1), b = 26.2675(1), c = 19.2980(1) Å, U = 8158.62(7) Å^3, T = 173 K, Z = 8, D_c = 1.265 g cm^{-3}, μ(Mo-Kα) = 0.274 mm^{-1}.

Data collection. Suitable single crystals for the X-ray diffraction study were grown from acetone. A clear colorless fragment was stored under perfluorinated ether, transferred in a Lindemann capillary, fixed, and sealed. Preliminary examination and data collection were carried out on a κ-CCD device (Nonius Mach3) with an Oxford Cryosystems cooling device at the window of a rotating anode (Nonius FR591) with graphite monochromated Mo-Kα radiation (λ = 0.710 73 Å). Data collection was performed within a θ-range of $1.55 < \theta < 25.36^\circ$. The detector to crystal distance was set to 40 mm. Seven data sets in rotation scan mode with $\Delta\varphi/\Delta\omega = 1.0^\circ$ were measured and a total number of 152 651 intensities were integrated. Raw data were corrected for Lorentz, polarization, and, arising from the scaling procedure, for latent decay and absorption effects. After merging (R_{int} = 0.044) a sum of 7476 (all data) and 6473 [$I_o > 2\sigma(I_o)$], respectively, remained and all data were used.

Solution. The structure was solved by a combination of direct methods and difference-Fourier syntheses. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms of the target molecule **6** were found and were allowed to refine freely with individual isotropic displacement parameters, whereas all hydrogen atoms of the solvent molecules were calculated in ideal positions (riding model).

Refinement. Full-matrix least-squares refinements with 670 parameters were carried out by minimizing $\Sigma w(F_o^2 - F_c^2)^2$ with the Shelxl-97 weighting scheme and converged with $R1$ = 0.0354 [$I_o > 2\sigma(I_o)$], $wR2$ = 0.0908 (all data), GOF = 1.016, and a shift/error of <0.084. The final difference Fourier map shows no striking features ($\Delta e_{min/max}$ = +0.39/−0.45 e Å^{-3}). One solvent molecule appeared to be disordered over two positions [0.869(4)/0.131(4)].

CCDC reference number 632829.

For crystallographic data in CIF or other electronic format see DOI: 10.1039/b617465e

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