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(Thio)ureido Anion Receptors Based on a 1,3-Alternate Oxacalix[2]arene[2]pyrimidine Scaffold

Wim Van Rossom,[†] Jef Caers,[†] Koen Robeyns,[‡,§] Luc Van Meervelt,[‡] Wouter Maes,*[,†,⊥] and Wim Dehaen*[,†]

[†]Molecular Design and Synthesis, Department of Chemistry, Katholieke Universiteit Leuven (KU Leuven), Celestijnenlaan 200F, 3001 Leuven, Belgium

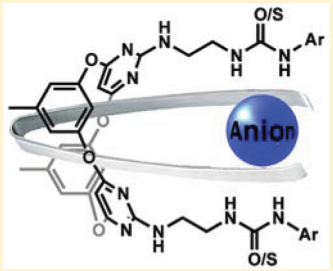
[‡]Biomolecular Architecture, Department of Chemistry, Katholieke Universiteit Leuven (KU Leuven), Celestijnenlaan 200F, 3001 Leuven, Belgium

[§]Institute of Condensed Matter and Nanosciences (IMCN), Université Catholique de Louvain (UCL), Bâtiment Lavoisier, place Louis Pasteur 1, bte 3, 1348 Louvain-la-Neuve, Belgium

[⊥]Design & Synthesis of Organic Semiconductors (DSOS), Institute for Materials Research (IMO-IMOMEC), Hasselt University, Agoralaan 1 − Building D, 3590 Diepenbeek, Belgium

Supporting Information

ABSTRACT: In pursuit of highly preorganized macrocyclic host molecules for the complexation of anions, a series of oxacalix[2]arene[2]pyrimidine-based bis(thio)ureido receptors were synthesized and fully characterized. The pincer-like 1,3-alternate conformation of the oxacalix[4]arene scaffold, essential for an efficient host−guest interaction, was visualized by single-crystal X-ray analysis and supported by variable-temperature NMR studies. The anion binding properties of the receptors were evaluated via ^{1}H NMR titration experiments, showing intermolecular interactions with $H_2PO_4^-$, AcO^-, BzO^-, and Cl^- ions. The host molecule bearing 4-nitrophenyl substituents on the bisurea binding pocket showed association constants in the range of 200−400 M^{-1} in the strongly competitive solvent mixture of DMSO/0.5% H_2O.



INTRODUCTION

Neutral organic host molecules containing polarized N−H moieties are known to act as hydrogen-bond donors toward anions and are widely used for anion recognition and sensing purposes, which renders these receptors of great significance in biology, medicine, catalysis, and environmental chemistry.[1,2] Calixarenes are well-established as one of the most versatile molecular platforms for supramolecular applications, due to their highly preorganized cavity and straightforward functionalization at both the upper and the lower rim.[3,4] Several studies have focused on either *intra*- or *extra*-annular introduction of (thio)ureido moieties to optimize the calixarene's binding properties. In general, a 1,3-alternate calixarene conformation is preferred, as this preorganization has resulted in the best association constants for a 1:1 host−guest stoichiometry.[5]

Heteracalixarenes,[6,7] in which heteroatoms replace the methylene linkages of traditional calixarenes, are particularly attractive for applications in supramolecular chemistry since the bridging heteroatoms enable tuning the ring size, the electron density on the arene constituents, and the host conformation and may provide additional binding sites, resulting in an improved (induced) fit of a desirable guest. Among the heteracalixarenes, the thia analogues have been studied most intensively, and they are nowadays widely recognized as effective receptors for small organic compounds and heavy/transition metals.[6b,c] During the past decade, reports on the chemistry of oxacalixarenes have steadily increased.[6e−g,8] Most efforts have been directed to the development of novel synthetic procedures and postmacrocyclization modifications of the calixarenoid framework, although the enlarged scope of O-bridged calix(hetero)aromatics has already triggered a few initiatives toward supramolecular applications.[8] In general, a (distorted) 1,3-alternate solid-state conformation has been observed for the smallest and most rigid homologues of the series, the oxacalix[4]arenes, and this conformation has also been proposed as the most likely one in solution (although a very fast conformational interconversion at the NMR time scale cannot really be excluded). The 1,3-alternate conformation makes these systems excellent candidates as highly preorganized scaffolds toward selective tweezer-type receptors.[6e−g,8] Introduction of porphyrinoid moieties onto the oxacalixarene periphery has previously provided access to a bis(porphyrin) tweezer showing a selective interaction with fullerene C_{70} over C_{60}.[8s] Fullerene complexation was also established with triptycene-derived oxacalixarenes with an expanded cavity.[8o] Heteroaromatic guest molecules, such as 1,10-phenanthroline, 2,2′-pyridine, and 4,4′-bipyridine, could be complexed by functionalized oxacalix[2]arene[2]triazines,[8l] whereas oxacalix[2]arene[2]naphthyridines

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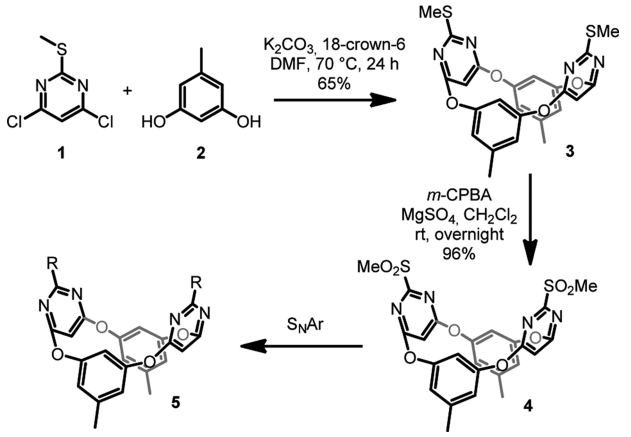
have shown interactions with *o*-salicylic acid and Hg^{2+} metal ions.[8e,v]

Although oxacalixarene macrocycles provide excellent platforms for the construction of effective recognition sites, only one group has reported on oxacalixarene-based receptors for anions so far. Wang and co-workers observed anion complexation—F^- and Cl^-, in combination with H_2O—with a dichlorooxacalix[2]arene[2]triazine derivative via anion−π interactions, and very recently also extended this approach to ion-pair receptors.[8g,w,9] Therefore, we envisaged synthesizing a series of bis(thio)ureido receptors starting from a versatile oxacalix[2]arene[2]pyrimidine scaffold and analyzing their affinity for anionic guests by ^{1}H NMR titration studies.

RESULTS AND DISCUSSION

In previous work, a convenient one-pot nucleophilic aromatic substitution (S_NAr) procedure toward oxacalix[2]arene[2]-pyrimidines has been developed (Scheme 1).[8d] The use of

Scheme 1. Three-Step Procedure from Pyrimidine Precursor 1 to Functionalized Oxacalix[4]arenes 5



4,6-dichloro-2-methylsulfanylpyrimidine (**1**) as the electrophilic building block, resulting in oxacalix[2]arene[2]pyrimidine **3** upon [2 + 2] cyclocondensation with orcinol (5-methyl-1,3-dihydroxybenzene), was shown to be a highly valuable tool for further decoration of the outer perimeter via Liebeskind−Srögl or S_NAr postmacrocyclization reactions (after conversion to the methylsulfonyl analogue), providing access to a substantial library of variously functionalized macrocycles (Scheme 1).[8h]

As for most heteracalix[4]arenes, oxacalix[4]arenes have shown a high preference to adopt (solid-state) 1,3-alternate conformations,[6e−g,8] which has been ascribed to dipole−dipole interactions among the aromatic rings and the absence of *intra*-annular hydroxyl groups favoring cone-type conformations.[8,10] Previous results have shown that oxacalix[2]arene[2]-pyrimidines also afford single-crystal structures with the oxacalix[4]arene macrocycle in a 1,3-alternate conformation.[8d,h] To analyze the conformation of parent scaffold **3** in the solid state, suitable crystals were grown by vapor diffusion of pentane into a $CHCl_3$ solution of **3**. The single-crystal X-ray structure showed once more a 1,3-alternate solid-state conformation (Figure 1).

In an analogous way, the sulfur analogue, bis(methylsulfanyl)thiacalix[2]arene[2]pyrimidine **6**, was obtained in 80% yield via the combination of 4,6-dichloro-2-methylsulfanylpyrimidine (**1**) and benzene-1,3-dithiol under the same

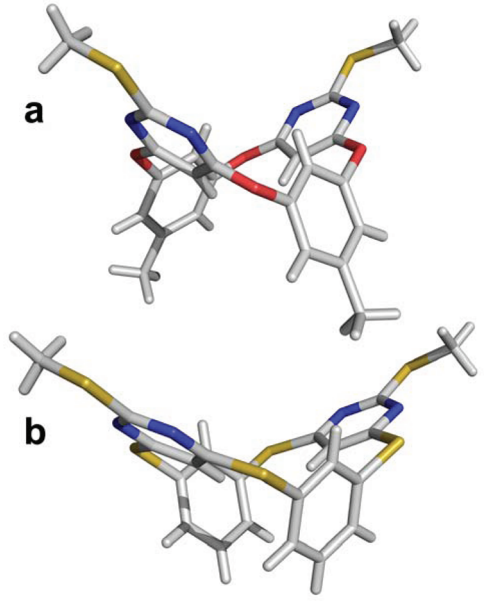


Figure 1. Single-crystal X-ray structures for (a) bis(methylsulfanyl)-oxacalix[4]arene **3** and (b) bis(methylsulfanyl)thiacalix[4]arene **6**.

S_NAr-based reaction conditions as previously optimized for oxacalix[4]arenes.[8d] Similar to the oxacalix[4]arene's structure, a 1,3-alternate solid-state conformation was observed by X-ray analysis (Figure 1). Fitting the centroids of the aromatic rings onto each other revealed a large resemblance between the two heteracalixarene structures (see Figure S3, Supporting Information). One expects a larger enclosed cavity (assessed by the distances between the centroids of the opposite benzene and pyrimidine rings) for the S-bridged macrocycle, because of the longer C−S bonds with respect to the C−O bonds (1.771 vs 1.375 Å, respectively), and indeed, for the longer pyrimidine−pyrimidine distance, this hypothesis holds true. The effect of the longer bond length is, however, evened out by the smaller C−S−C angle (<102.7°> vs <118.8°>) and the absence of the methyl group for the thiacalix[4]arene, which seems to direct the opposing benzene rings outward. The resulting (estimated) cavity size is 5.713 Å × 6.487 Å for thiacalix[4]arene **6** and 4.612 Å × 7.749 Å for oxacalix[4]arene **3**.

Because of the unusual high-field chemical shifts observed for the interior protons of the electrophilic pyrimidine components (e.g., H_{pyrim} **3** at δ = 5.04 ppm vs 6.30 ppm for 4,6-dimethoxy-2-methylsulfanylpyrimidine), attributed to the proximity of the anisotropic shielding cone of the adjacent aromatic rings, it has been suggested that oxacalix[2]arene[2]pyrimidines adopt a 1,3-alternate conformation in solution as well.[8d,h,j] A basic investigation of the most likely conformation in solution was performed by variable-temperature NMR (VT-NMR) analysis of parent macrocycle **3** (in $CDCl_3$) from 223 to 323 K (see Figure S4, Supporting Information). The proton resonances remained sharp and consistent over the whole temperature range, indicating the existence of either a certain conformation at high percentage or very fast conformational interconversion on the NMR time scale, even at low temperature.

Inspired by the high current interest in selective anion receptors, and stimulated by the likeliness of a highly preorganized 1,3-alternate conformation and the ease by which postmacrocyclization S_NAr functionalization reactions can be applied on the outer rim, it was envisaged to introduce a

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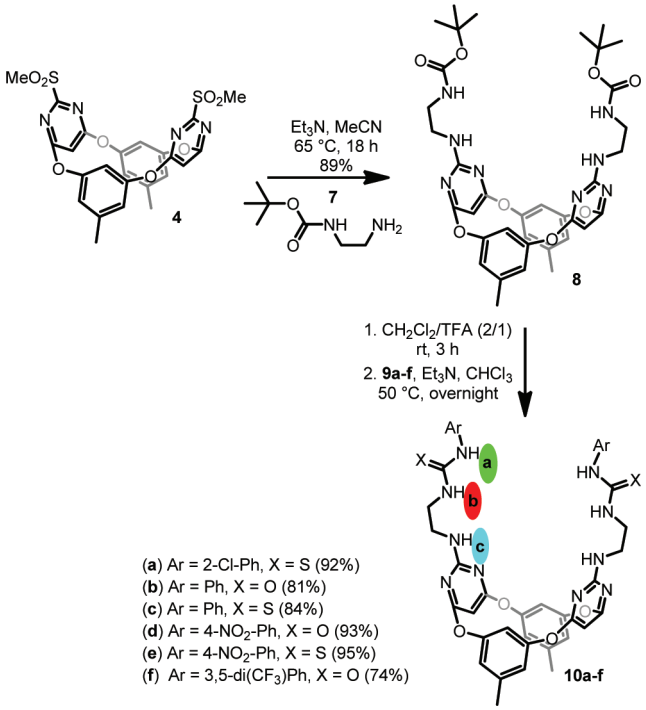
number of (thio)ureido anion receptor motifs on the oxacalix[2]arene[2]pyrimidine skeleton.[11] (Thio)ureido functions have previously been shown to be particularly valuable as neutral hydrogen-donor groups,[12] due to their effective and directional hydrogen bonds. For this reason, bis(thio)ureido tweezer-type molecules were developed, attaching the (thio)urea groups to the oxacalixarene platform via a short ethylenediamine linker (Scheme 2).

Scheme 2. Synthesis of Oxacalix[2]arene[2]pyrimidine-Based Bis(thio)ureido Receptors 10a−10f



The synthesis of precursor macrocycle **3**, as previously reported,[8d] could be scaled up to gram scale after slight adjustments to the reaction conditions. An elevated reaction temperature (100 °C) and an extended reaction time (4 days), together with simplified purification via recrystallization from dichloromethane (avoiding the need for column chromatographic purification), resulted in the isolation of 70% of pure cyclotetramer **3** (Scheme 1). The oxidation of **3** with *m*-CPBA to obtain bis(methysulfonyl)oxacalix[4]arene **4**, as described earlier,[8d,h] could be performed on a gram scale as well (in 95% yield) without further adjustments.

In initial endeavors to functionalize the outer calixarene periphery with urea moieties directly connected to the scaffold, a few problems were encountered. Oxacalix[4]arene **4** was successfully converted to the 5,15-diamine derivative (**5**; R = NH_2, Scheme 1) according to previously described reaction conditions.[8h] However, various attempts to react the 2-aminopyrimidine moieties with either *N*,*N*′-carboxydiimidazole (CDI) or phenylchloroformate failed to afford the targeted *N*-carboxyimidazole or carbamate derivatives, respectively. In addition, condensation of the diaminooxacalix[4]arene with phenyliso(thio)cyanate did not result in the envisaged di(thio)urea compound(s). The difficulty to insert urea groups directly on the oxacalixarene skeleton directed us to the introduction of a short linker between the urea moieties and the heteracalixarene macrocycle. Initial attempts to decorate platform **4** directly with priorly prepared (thio)ureido-type linkers resulted in a mixture of mono- and disubstituted products, which unfortunately could not be separated efficiently. Therefore, an amended procedure was applied, attaching the linker unit to the upper rim before the conversion to (thio)ureido groups. An additional advantage of the latter method is that the differentiation between the various receptors is only made in the final step, which is also beneficial from a practical point of view. Oxacalix[4]arene **4** and *tert*-butyl-2-aminoethylcarbamate (**7**) ("monoprotected ethylenediamine") were combined in an S_NAr reaction (MeCN, Et_3N as a base, 65 °C, 18 h) to produce 1,3-disubstituted oxacalixarene **8** as a white precipitate in 89% yield (Scheme 2). Prereceptor **8** was then converted into anion receptors **10a−10f** (74−95% yield) by a quantitative deprotection with trifluoroacetic acid (TFA) in dichloromethane and subsequent condensation with various iso(thio)cyanates **9a−9f** (Scheme 2). In many cases, the final receptors precipitated from the reaction mixture and were obtained in pure form without requiring chromatographic purification.

Addition of electron-withdrawing groups increases the acidity of the urea protons, which is known to be beneficial to form stronger complexes.[13] The introduction of thiourea moieties is also recognized to enhance anion binding due to the increased acidity of the NH protons (pK_a: urea 26.9, thiourea 21.1 in DMSO).[14,15] Therefore, in our search for a strong and selective host, a series of both urea and thiourea receptors with and without additional electron-deficient groups were prepared. All receptors **10a−10f** showed the same upfield chemical shift for the 5-pyrimidinyl proton (at $\delta \sim 4.50$ ppm), suggesting that the 1,3-alternate conformation is preserved throughout the complete synthetic protocol.

The obtained receptors were analyzed for their anion affinity features by ^1H NMR titrations (in DMSO-d_6/0.5% H_2O at 400 MHz, 5 mM host solution). Initially, host molecule **10a** was titrated with various tetra-*n*-butylammonium salts, showing proton resonance shifts for the NH protons (as visualized in Scheme 2) with anionic guests $H_2PO_4^-$, AcO^-, BzO^-, and Cl^-, whereas no noticeable changes in the NMR spectra were observed upon addition of NO_3^-, HSO_4^-, or Br^-. The lack of interaction of the host with the latter anionic species might be attributed to the lesser basic character and/or lower charge density of the guests. Since no interaction was observed with these species, they were not included in further studies with the other receptors (Table 1).

The host−guest stoichiometries of the complexes formed between receptor **10a** and the different oxyanions were determined via Job plot analyses, indicating a 1:1 ratio in all cases (Figure 2 and the Supporting Information). Despite the lack of (thio)urea moieties, prereceptor **8** was also subjected to ^1H NMR titration studies with the selected anions. As anticipated, no significant binding was observed, indicating that the precursor itself is not an efficient anion receptor.

Titration of Cl^- to the different host solutions resulted in a clear downfield shift of the (thio)urea protons (NH_a and NH_b) in all cases. However, a large amount of anion was required to saturate the binding site(s), resulting in low association constants (Table 1). For both AcO^- and BzO^-, fewer equivalents were needed to give complete deshielding, pointing to stronger interaction with the guest ions (K_a between 50 and 740 M^{-1}; Table 1). Next to the NH protons, no other resonances of the oxacalix[4]arene framework showed a significant shift, which implies that the anions are bound by hydrogen bridges to the

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Table 1. K_a Values (M^{-1}) for the Complexation of Oxacalixarene-Based Receptors 8 and 10a–10f with Anionic Guests (in DMSO-d_6/0.5% water, 5×10^{-3} M Host Solution at 298 K)[e]

receptor	AcO^-	BzO^-	$H_2PO_4^-$	Cl^-
8	[a]	[a]	[a]	[a]
10a	152	94	131[b]	<10
10b	133	87	125	<10
10c	63	50	50[b]	<10
10d	362	232	349	19
10e	534[c]	145	740[d]	17
10f	81	95	331[b]	<10

[a]No shift observed. [b]NH_a deprotonated, K_a calculated for NH_b and NH_c. [c]NH_a deprotonated, K_a determined for NH_b only. [d]NH_a and NH_b deprotonated, K_a determined for NH_c only. When simultaneous deprotonation was observed, the K_a values have to be approached with caution.[17] [e]Determined by HypNMR with errors estimated < 15%.[16] The stability constants were calculated based on the shifts of the (thio)urea NH protons (NH_a and NH_b). The proton assignment is indicated in Scheme 2.

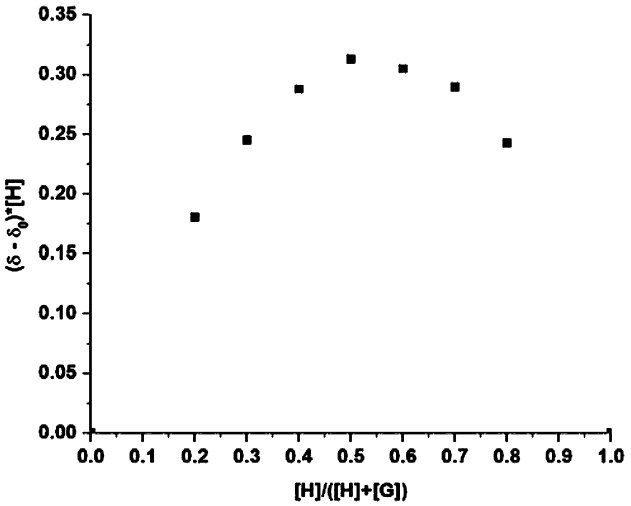

Figure 2. Job plot for the complexation of receptor **10a** (5×10^{-5} M) with tetra-*n*-butylammonium acetate in DMSO-d_6/0.5% H_2O.

NH groups rather than by the electron-deficient pyrimidine rings in the cavity and that the preorganized 1,3-alternate conformation of the calixarene platform is likely to be maintained throughout the titration experiment. After addition of a first aliquot of $H_2PO_4^-$ to the thiourea compounds **10a** and **10c** and urea derivative **10f**, the most acidic proton NH_a disappeared due to deprotonation. On the other hand, a clear shift was seen for protons NH_b and NH_c. Receptor **10e** showed complete deprotonation of both NH_a and NH_b, while a downfield shift for NH_c suggests further association with the anion. Besides, for $H_2PO_4^-$, the most basic anion in the series, no deprotonation was observed, except for the combination **10e**-AcO^-, where the NH_a proton resonance also disappeared after addition of about 1 equivalent of anion to the host solution. In contrast to the combination **10e**-$H_2PO_4^-$, no shift and hence no increased contribution of NH_c was observed after deprotonation of NH_a by AcO^-.[17]

Addition of AcO^- or $H_2PO_4^-$ to receptor **10e** resulted in a concomitant color change from yellow to orange (Figure 3). This suggests that a negatively charged *p*-nitroanilide ion was formed, which causes a significant increase in charge density on

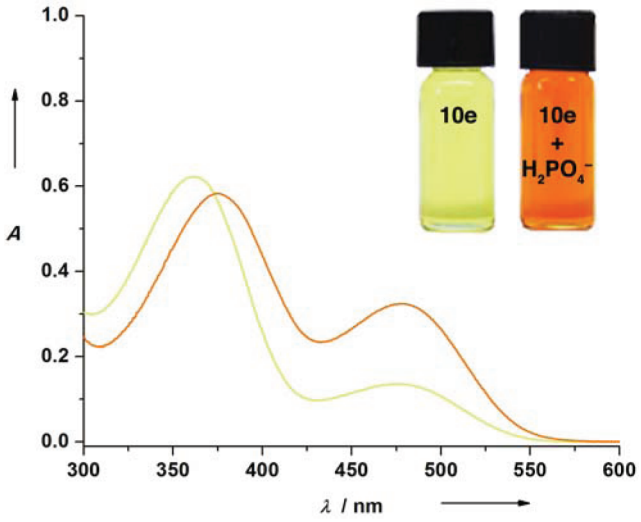

Figure 3. UV–vis spectra for **10e** (yellow) and **10e**-$H_2PO_4^-$ (orange) in DMSO (at 293 K, $c = 1 \times 10^{-5}$ M). Inset: visual color change upon addition of $H_2PO_4^-$ (10 equiv).

the thioureido nitrogen atom, resulting in a clear red shift for the low-wavelength band from 362 to 374 nm and a hyperchromic shift for the high-wavelength band at ~475 nm (Figure 3).

Among the urea-based receptors, host molecule **10d**, bearing electron-withdrawing nitro groups on the phenyl entities, did not undergo deprotonation and showed relatively strong complexation with AcO^-, BzO^-, and $H_2PO_4^-$ (362, 232, and 349 M^{-1}, respectively) and rather weak binding with Cl^- (19 M^{-1}) (Figure 4). Compared to this, receptor **10b**, lacking

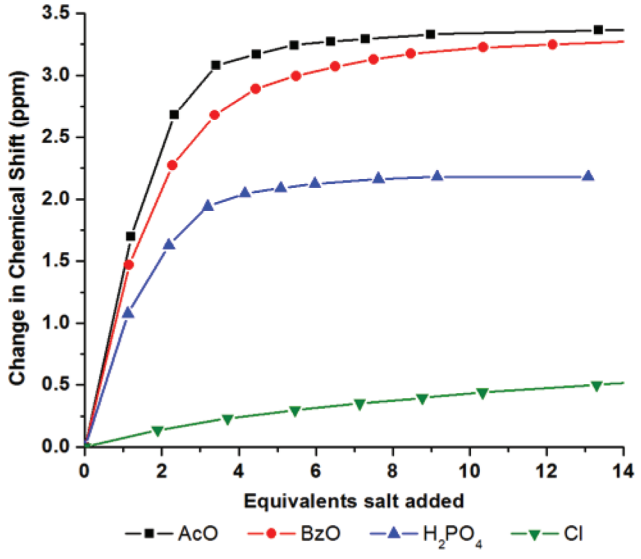

Figure 4. Variation of the chemical shift of NH_b vs the number of equivalents of tetra-*n*-butylammonium salt added for host molecule **10d** (5×10^{-3} M in DMSO-d_6/0.5% H_2O, 293 K).

the electron-withdrawing functionality, showed a 3 times weaker association with the anions (Table 1). For receptor **10f**, an interesting selectivity toward $H_2PO_4^-$ (331 M^{-1}) over AcO^-, BzO^-, and Cl^- (81, 95, and <10 M^{-1}, respectively) was observed, notwithstanding the deprotonation of NH_a.

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CONCLUSIONS

A series of oxacalix[2]arene[2]pyrimidine-based bis(thio)-ureido anion receptors were synthesized via a straightforward postmacrocyclization functionalization method. In most cases, the need for column chromatographic purification could be completely avoided throughout the whole synthetic sequence. The scaffold's 1,3-alternate preorganization, affording an appropriate arrangement of the receptor motifs, was confirmed by single-crystal X-ray (solid-state) and VT NMR (solution) analysis. ^{1}H NMR titration studies indicated reasonably strong molecular interactions with oxyanionic guests $H_2PO_4^-$, AcO^-, and BzO^-, and weak associations with Cl^-, whereas no noteworthy affinity was observed for NO_3^-, Br^-, or HSO_4^-. The introduction of thiourea groups in combination with electron-withdrawing moieties resulted in deprotonation of the most acidic protons and visible formation of a *p*-nitroanilide ion. For the bisurea receptor with nitrophenyl end groups, for which no complication due to deprotonation occurred, reasonable association constants (200−400 M^{-1} in the highly competitive solvent mixture DMSO/0.5% H_2O) were observed, showing the potential of this class of receptor molecules to act as neutral hydrogen-bonding anion hosts in polar media.[18]

EXPERIMENTAL SECTION

General Experimental Methods. NMR spectra were acquired on commercial instruments, and chemical shifts (δ) are reported in parts per million (ppm) referenced to tetramethylsilane (^{1}H) or the internal (NMR) solvent signals (^{13}C).[19] NMR peak assignments were performed based on standard 2D NMR methods (COSY, HMQC, and HMBC) and the knowledge previously gained from analogous oxacalix[2]arene[2]pyrimidine macrocycles.[8d,h,j] Exact mass measurements were acquired in the EI (at a resolution of 10 000) or ESI (at a resolution of 60 000) mode. IR spectra were recorded on an FT-IR spectrometer with a universal sampling module. UV−vis spectra were measured with a quartz cuvette (path length of 1 cm) at 293 K in DMSO. Melting points were determined by using a Reichert Thermovar apparatus and were not corrected. For column chromatography, 70−230 mesh silica 60 was used as the stationary phase. MPLC flash chromatography was performed using a Büchi Sepacore Flash apparatus. Chemicals received from commercial sources were used without further purification. Reaction solvents (DMF, $CHCl_3$, THF; 99.5+ %) were dried on molecular sieves (4 Å) or distilled prior to use (CH_2Cl_2). Tetra-*n*-butylammonium salts were dried overnight under vacuum at 40 °C prior to use. All ^{1}H NMR titrations to study anion complexation were performed using 500 μL of the host solution with an initial concentration of 5×10^{-3} M in DMSO-d_6/0.5 v% H_2O, to which guest solutions with concentrations of 5×10^{-1} M (prepared with host solution) were added gradually, and the chemical shifts of the relevant N−H protons were recorded following each addition.

*4,6,16,18-Tetraaza-11,23-dimethyl-5,17-bis(methylsulfanyl)-2,8,14,20-tetraoxacalix[4]arene (**3**).* This compound has been prepared before.[8d] The synthesis could be scaled up to (multi)gram scale after slight adjustments to the reaction conditions. A mixture of 4,6-dichloro-2-methylsulfanylpyrimidine (5.00 g, 25.6 mmol, 1 equiv), orcinol (3.18 g, 25.6 mmol, 1 equiv), K_2CO_3 (9.05 g, 65.5 mmol, 2.5 equiv), and 18-crown-6 (660 mg, 2.5 mmol, 10 mol %) in DMF (250 mL) was stirred at 100 °C under an Ar atmosphere during 4 days. DMF was removed under vacuum, and the residue was redissolved in ethyl acetate and washed with water. The organic fraction was dried over $MgSO_4$ and filtered, and the solvent was removed under vacuum. After recrystallization from CH_2Cl_2, the desired oxacalix[4]arene (8.84 g, 70%) was obtained in pure form as a white solid. Material identity and purity were confirmed by mp, MS, and ^{1}H and ^{13}C NMR.[8d]

*4,6,16,18-Tetraaza-11,23-dimethyl-5,17-bis(methylsulfonyl)-2,8,14,20-tetraoxacalix[4]arene (**4**).* This compound has been prepared before.[8h] The procedure could be scaled up to (multi)gram scale without particular adjustments. Material identity and purity were confirmed by mp, MS, and ^{1}H and ^{13}C NMR.

*4,6,16,18-Tetraaza-5,17-bis(methylsulfanyl)-2,8,14,20-tetrathiacalix[4]arene (**6**).* A mixture of 4,6-dichloro-2-methylsulfanylpyrimidine (100 mg, 0.51 mmol, 1 equiv), benzene-1,3-dithiol (59 μL, 0.51 mmol, 1 equiv), K_2CO_3 (183 mg, 1.32 mmol, 2.6 equiv), and 18-crown-6 (24 mg, 0.09 mmol, 5.6 mol %) in DMF (5 mL) was stirred at 70 °C under an Ar atmosphere during 48 h. DMF was removed under vacuum, and the residue was redissolved in dichloromethane (100 mL) and washed with water (3 × 50 mL). The organic fraction was dried over $MgSO_4$ and filtered, and the solvent was removed under vacuum. After column chromatographic purification (silica, MPLC: eluent heptane−ethyl acetate, 8:2), the desired thiacalix[4]arene **6** (109 mg, 80%) was isolated in pure form as a white solid. mp 286.4−287.3 °C; MS (ESI+) *m*/*z* 528.8 $[M + H]^+$; HRMS (EI) calcd for $C_{22}H_{16}N_4S_6$: *m*/*z* 527.9699 $[M]^+$; found: *m*/*z* 527.9701; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 2H; 2-Ph), 7.54 (d, ^3J = 7.9 Hz, 4H; 4,6-Ph), 7.42 (t, ^3J = 7.7 Hz, 2H; 5-Ph), 5.33 (s, 2H; 5-pyrim), 2.56 (s, 6H; SCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8 (C; 4,6-pyrim), 171.7 (C; 2-pyrim), 143.7 (CH; 2-Ph), 138.4 (CH; 4,6-Ph), 131.2 (CH; 5-Ph), 130.1 (C; 1,3-Ph), 106.2 (CH; 5-pyrim), 14.4 (CH_3); IR (ATR) ν_{max} (cm^{-1}) 2920, 2851, 1491, 1394, 1359, 1249, 1106, 1073, 812, 687.

*tert-Butyl-2-aminoethylcarbamate (**7**).* This compound has been prepared before.[20] Material identity and purity were confirmed by mp, MS, and ^{1}H and ^{13}C NMR.

*4,6,16,18-Tetraaza-11,23-dimethyl-5,17-bis[tert-butyl-(2-aminoethyl)carbamoyl]-2,8,14,20-tetraoxacalix[4]arene (**8**).* A mixture of bis(methylsulfonyl)oxacalix[2]arene[2]pyrimidine **4** (1.016 g, 1.82 mmol, 1 equiv), *tert*-butyl-(2-aminoethyl)carbamate (**7**) (731 mg, 4.56 mmol, 2.5 equiv), and triethylamine (1.3 mL, 9.34 mmol, 5.1 equiv) in dry MeCN (20 mL) was stirred at 65 °C under an Ar atmosphere during 18 h. The white precipitate was filtered off, washed with MeCN, and dried under vacuum at 40 °C. Yield 89% (1.161 g); mp 235.3−236.3 °C; MS (ESI+) *m*/*z* 717.4 $[M + H]^+$; HRMS (ESI+) calcd for $C_{36}H_{45}N_8O_8$: *m*/*z* 717.3360 $[M + H]^+$; found: *m*/*z* 717.3369; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.40 (s_{br}, 2H; NH), 6.91 (s, 4H; 4,6-orc), 6.87−6.84 (m, 4H; 2-orc, NH); 4.51 (s, 2H; 5-pyrim), 3.35−3.25 (m, 4H; CH_2), 3.15−3.05 (m, 4H; CH_2), 2.27 (s, 6H; CH_3), 1.38 (s, 18H; *t*-Bu); ^{13}C NMR (150 MHz, DMSO-d_6) δ 172.7/172.1 (C; 4,6-pyrim), 162.6 (C; 2-pyrim), 155.8 (C; C═O), 152.7 (C; 1,3-orc), 142.7 (C; 5-orc), 119.8 (CH; 4,6-orc), 112.4 (CH; 2-orc), 77.8 (CH; 5-pyrim), 76.6 (C), 40.7 (CH_2), 40.0 (CH_2), 28.3 (CH_3; *t*-Bu), 20.7 (CH_3; Me); IR (ATR) ν_{max} (cm^{-1}) 3276 (NH), 3147 (NH), 2975, 1709 (C═O), 1584, 1543, 1458, 1339, 1304, 1162, 789.

*4,6,16,18-Tetraaza-11,23-dimethyl-5,17-bis[(2-(N′-(2-chlorophenyl)thioureido)ethyl)amino]-2,8,14,20-tetraoxacalix[4]-arene (**10a**) (General Procedure 1).* A solution of oxacalix[4]arene **8** (200 mg, 0.28 mmol, 1 equiv) in CH_2Cl_2/TFA (4/2 mL) was stirred at rt under an Ar atmosphere during 3 h, after which the volatiles were removed under reduced pressure. The residue was redissolved in chloroform (5 mL), stirred with triethylamine (1.2 mL, 8.6 mmol, 30 equiv), and 2-chlorophenylisothiocyanate (**9a**) (110 μL, 0.84 mmol, 3 equiv) was added. The reaction was then continued at 50 °C under an Ar atmosphere during 18 h. The precipitate was filtered off, washed with chloroform, and dried under vacuum at 40 °C to obtain the desired oxacalix[4]arene **10a** (222 mg, 92%) as a pure white solid. mp 159.9−160.9 °C; MS (ESI+) *m*/*z* 856.1 $[M + H]^+$; HRMS (ESI+) calcd for $C_{40}H_{37}N_{10}O_4S_2Cl_2$ $[M + H]^+$: *m*/*z* 855.1818; found: *m*/*z* 855.1826; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.29 (s, 2H; NH_a), 8.04 (s_{br}, 2H; NH_b), 7.65 (s_{br}, 2H; NH_c), 7.58−7.45 (dd, ^3J = 7.5 Hz, 4H; 3,6-Ph), 7.31 (t, ^3J = 7.7 Hz, 2H; 4/5-Ph), 7.18 (t, ^3J = 6.6 Hz, 2H; 4/5-Ph), 6.93 (s, 4H; 4,6-orc), 6.84 (s, 2H; 2-orc), 4.53 (s, 2H; 5-pyrim), 3.69 (s_{br}, 4H; CH_2), 3.49 (s_{br}, 4H; CH_2), 2.28 (s, 6H; CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 181.5 (C; C═S), 172.7/172.1 (C; 4,6-pyrim), 162.7 (C; 2-pyrim), 152.6 (C; 1,3-orc), 142.8 (C; 5-orc), 136.0 (C; Ph), 129.5 (CH; Ph), 129.1 (CH; Ph), 127.3 (CH; Ph), 119.8 (CH; 4,6-orc), 112.3 (CH; 2-orc), 76.7 (CH; 5-pyrim), 43.4 (CH_2), 40.0 (CH_2), 20.7 (CH_3); IR (ATR) ν_{max} (cm^{-1}) 3251 (NH), 3133 (NH), 2930, 1610 (C═S), 1585, 1545, 1472, 1347, 1297, 1163, 792, 748, 682.

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*4,6,16,18-Tetraaza-11,23-dimethyl-5,17-bis[(2-(N′-phenylureido)-ethyl)amino]-2,8,14,20-tetraoxacalix[4]arene (**10b**).* Synthesis according to general procedure 1: phenylisocyanate (**9b**) (91 μL, 0.84 mmol, 3 equiv). After the reaction, the solvent was evaporated and the crude residue was purified by column chromatography (silica, MPLC: eluent ethyl acetate−methanol, 95:5) to obtain the desired oxacalix[4]arene **10b** (170 mg, 81%) as a pure white solid. mp 184.7−185.7 °C; MS (ESI+) m/z 755.7 $[M + H]^+$; HRMS (ESI+) calcd for $C_{40}H_{39}N_{10}O_6$ $[M + H]^+$: m/z 755.3054; found: m/z 755.3060; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.52 (s, 2H; NH_a), 7.50 (t, ^3J = 4.9 Hz, 2H; NH_b), 7.39 (d, ^3J = 7.9 Hz, 4H; *o*-Ph), 7.20 (t, ^3J = 7.7 Hz, 4H; *m*-Ph), 6.91 (s, 4H; 4,6-orc), 6.88 (t, ^3J = 7.4 Hz, 2H; *p*-Ph), 6.81 (s, 2H; 2-orc), 6.24 (t, ^3J = 5.3 Hz, 2H; NH_c), 4.50 (s, 2H; 5-pyrim), 3.40−3.31 (s_{br}, 4H; CH_2), 3.30 (t, ^3J = 5.3 Hz, 4H; CH_2), 2.27 (s, 6H; CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.7/172.0 (C; 4,6-pyrim), 162.7 (C; 2-pyrim), 155.4 (C; C═O), 152.5 (C; 1,3-orc), 142.7 (C; 5-orc), 140.4 (C; *ipso*-Ph), 128.6 (CH; Ph), 121.0 (CH; *p*-Ph), 119.7 (CH; 4,6-orc), 117.6 (CH; Ph), 112.3 (CH; 2-orc), 76.4 (CH; 5-pyrim), 41.2 (CH_2), 38.6 (CH_2), 20.6 (CH_3); IR (ATR) ν_{max} (cm^{-1}) 3374 (NH), 3344 (NH), 2957, 1662 (C═O), 1613, 1574, 1541, 1359, 1341, 1309, 1162, 1038, 755, 687.

*4,6,16,18-Tetraaza-11,23-dimethyl-5,17-bis[(2-(N′-phenylthioureido)ethyl)amino]-2,8,14,20-tetraoxacalix[4]arene (**10c**).* Synthesis according to general procedure 1: phenylisothiocyanate (**9c**) (100 μL, 0.837 mmol, 3 equiv); reaction time 2 h. The precipitate formed during the reaction was filtered off, washed with dichloromethane, and dried under vacuum at 40 °C to obtain the desired oxacalixarene **10c** (185 mg, 84%) as a pure white solid. mp 171.3−172.3 °C; MS (ESI+) m/z 787.6 $[M + H]^+$; HRMS (ESI+) calcd for $C_{40}H_{39}N_{10}O_4S_2$ $[M + H]^+$: m/z 787.2597; found: m/z 787.2613; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.61 (s, 2H; NH_a), 7.82 (s_{br}, 2H; NH_b), 7.53 (t, ^3J = 4.9 Hz, 2H; NH_c), 7.39 (d, ^3J = 7.5 Hz, 4H; *o*-Ph), 7.31 (t, ^3J = 7.5 Hz, 4H; *m*-Ph), 7.10 (t, ^3J = 7.2 Hz, 2H; *p*-Ph), 6.92 (s, 4H; 4,6-orc), 6.81 (s, 2H; 2-orc), 4.52 (s, 2H; 5-pyrim), 3.70 (s_{br}, 4H; CH_2), 3.47−3.44 (s_{br}, 4H; CH_2), 2.28 (s, 6H; CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 180.6 (C═S), 172.7/172.2 (C; 4,6-pyrim), 162.7 (C; 2-pyrim), 152.6 (C; 1,3-orc), 142.9 (C; 5-orc), 139.1 (C; *ipso*-Ph), 128.8 (CH; Ph), 124.4 (CH; Ph), 123.3 (CH; *p*-Ph), 119.9 (CH; 4,6-orc), 112.4 (CH; 2-orc), 76.7 (CH; 5-pyrim), 43.4 (CH_2), 40.2 (CH_2), 20.8 (CH_3); IR (ATR) ν_{max} (cm^{-1}) 3252 (NH), 3142 (NH), 2980, 1667, 1608, 1586, 1539, 1463, 1343, 1299, 1161, 1125, 791, 682.

*4,6,16,18-Tetraaza-11,23-dimethyl-5,17-bis[(2-(N′-(4-nitrophenyl)ureido)ethyl)amino]-2,8,14,20-tetraoxacalix[4]arene (**10d**).* Synthesis according to general procedure 1: 4-nitrophenylisocyanate (**9d**) (138 mg, 0.84 mmol, 3 equiv). After the reaction, the solvent was evaporated and the crude residue was purified by column chromatography (silica, MPLC: eluent ethyl acetate−methanol, gradient 10:0 to 9:1) to obtain the desired oxacalix[4]arene **10d** (217 mg, 93%) as a pale yellow solid. mp 176.7−177.7 °C; MS (ESI+) m/z 845.8 $[M + H]^+$; HRMS (ESI+) calcd for $C_{40}H_{37}N_{12}O_{10}$ $[M + H]^+$: m/z 845.2756; found: m/z 845.2750; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.37 (s, 2H; NH_a), 8.14 (d, ^3J = 9.0 Hz, 4H; Ph), 7.63 (d, ^3J = 9.2 Hz, 4H; Ph), 7.54 (t, ^3J = 5.1 Hz, 2H; NH_c), 6.90 (d, ^3J = 4.1 Hz, 4H; 4,6-orc), 6.83 (s, 2H; 2-orc), 6.56 (t, ^3J = 4.9 Hz, 2H; NH_b), 4.50 (s, 2H; 5-pyrim), 3.41−3.38 (m, 4H; CH_2), 3.37−3.34 (m, 2H; CH_2), 2.27 (s, 6H; CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.6/172.0 (C; 4,6-pyrim), 162.7 (C; 2-pyrim), 154.6 (C═O), 152.5 (C; 1,3-orc), 147.2 (C; *ipso*-NO_2-Ph), 142.6 (C; 5-orc), 140.3 (C; *ipso*-Ph), 125.1 (CH; Ph), 119.7 (CH; 4,6-orc), 116.8 (CH; Ph), 112.3 (CH; 2-orc), 76.5 (CH; 5-pyrim), 40.8 (CH_2), 38.8 (CH_2), 20.6 (CH_3); IR (ATR) ν_{max} (cm^{-1}) 3270 (NH), 2954, 2922, 2853, 1684 (C═O), 1541, 1500, 1459, 1326, 1298, 1221, 1160, 1106, 849, 789, 750, 680.

*4,6,16,18-Tetraaza-11,23-dimethyl-5,17-bis[(2-(N′-(4-nitrophenyl)thioureido)ethyl)amino]-2,8,14,20-tetraoxacalix[4]-arene (**10e**).* Synthesis according to general procedure 1: 4-nitrophenylisothiocyanate (**9e**) (151 mg, 0.84 mmol, 3 equiv). After the reaction, the solvent was evaporated and the crude residue was purified by column chromatography (silica, MPLC: eluent heptane−ethyl acetate, gradient 8:2 to 0:10) to obtain the desired oxacalix[4]-arene **10e** (232 mg, 95%) as a yellow solid. mp 162.1−163.1 °C; MS (ESI+) m/z 877.7 $[M + H]^+$; HRMS (ESI+) calcd for $C_{40}H_{37}N_{12}O_8S_2$ $[M + H]^+$: m/z 877.2299; found: m/z 877.2321; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.23 (s, 2H; NH_a), 8.39 (s, 2H; NH_b), 8.17 (d, ^3J = 8.8 Hz, 4H; Ph), 7.81 (d, ^3J = 8.8 Hz, 4H; Ph), 7.58 (s_{br}, 2H; NH_c), 6.91 (s, 4H; 4,6-orc), 6.83 (s, 2H; 2-orc), 4.54 (s, 2H; 5-pyrim), 3.80−3.65 (m, 4H; CH_2-urea), 3.60−3.45 (m, 4H; CH_2-pyrim), 2.27 (s, 6H; CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 180.3 (C═S), 172.6/172.0 (C; 4,6-pyrim), 162.6 (C; 2-pyrim), 152.5 (C; 1,3-orc), 146.2 (C; *ipso*-NO_2-Ph), 142.7 (C; 5-orc), 141.8 (C; *ipso*-Ph), 124.5 (CH; Ph), 120.4 (CH; Ph), 119.7 (CH; 4,6-orc), 112.3 (CH; 2-orc), 76.7 (CH; 5-pyrim), 43.5 (CH_2), 39.6 (CH_2), 20.7 (CH_3); IR (ATR) ν_{max} (cm^{-1}) 3249 (NH), 2971, 2923, 2853, 1580, 1536, 1505, 1459, 1325, 1297, 1250, 1160, 1109, 1033, 849, 788, 680; UV−vis (DMSO) λ_{max} (log ε) 362 (4.79), 477 (4.13).

*4,6,16,18-Tetraaza-11,23-dimethyl-5,17-bis[(2-(N′-(3,5-di(trifluoromethyl)phenyl)ureido)-ethyl)amino]-2,8,14,20-tetraoxacalix[4]arene (**10f**).* Synthesis according to general procedure 1: 3,5-di(trifluoromethyl)phenylisocyanate (**9f**) (121 μL, 0.84 mmol, 3 equiv); The white precipitate formed during the reaction was filtered off, washed with chloroform, and dried under vacuum at 40 °C to obtain the desired oxacalix[4]arene **10f** (213 mg, 74%). mp 294.6−295.6 °C; MS (ESI+) m/z 1027.2 $[M + H]^+$; HRMS (ESI+) calcd for $C_{44}H_{35}N_{10}O_6F_{12}$ $[M + H]^+$: m/z 1027.2549; found: m/z 1027.2573; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.33 (s, 2H; NH_a), 8.09 (s, 4H; *o*-Ph), 7.53 (s, 2H; *p*-Ph), 7.51 (t, ^3J = 5.4 Hz, 2H; NH_b), 6.88 (d, ^3J = 7.3 Hz, 4H; 4,6-orc), 6.81 (s, 2H; 2-orc), 6.59 (t, ^3J = 5.3 Hz, 2H; NH_c), 4.50 (s, 2H; 5-pyrim), 3.45−3.40 (m, 4H; CH_2), 3.40−3.30 (m, 4H; CH_2), 2.27 (s, 6H; CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.7/172.1 (C; 4,6-pyrim), 162.8 (C; 2-pyrim), 155.0 (C═O), 152.6 (C; 1,3-orc), 142.6 (C; 5-orc), 131.3/130.9/130.4/130.0 (q; C_i-CF_3, $^2J_{CF}$ = 43 Hz), 128.8/125.2/121.6/118.0 (q; CF_3, $^1J_{CF}$ = 361 Hz), 119.8 (CH; 4,6-orc), 117.3 (CH; *o*-Ph), 113.5 (CH; *p*-Ph), 112.4 (CH; 2-orc), 76.5 (CH; 5-pyrim), 40.8 (CH_2), 39.0 (CH_2), 20.7 (CH_3); IR (ATR) ν_{max} (cm^{-1}) 3365 (NH), 3104 (NH), 2971, 1678 (C═O), 1613, 1576, 1543, 1474, 1387, 1341, 1273, 1162, 1038, 887, 790, 680.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra, X-ray crystallographic data and figures for heteracalixarenes **3** and **6**, VT-NMR data for **3**, and additional details on the anion titration experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wim.dehaen@chem.kuleuven.be (W.D.), wouter.maes@uhasselt.be (W.M.).

Notes

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