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Anion binding by *meta* ureido-substituted thiacalix[4]arenes

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ABSTRACT

The regioselective nitration of 25,26,27,28-tetrapropoxythiacalix[4]arene (1,3-*alternate*) led to the formation of mono- and dinitro derivatives bearing NO_2 groups in the *meta* positions at the same side of the molecule. Their reduction and subsequent condensation with arylisocyanates gave the new types of anion receptors with a so far unknown *meta*-substitution pattern. In a highly HB-competitive solvent like DMSO, the novel ligands showed good complexation abilities. Moreover, as can be documented by higher complexation constants, achiral receptors **9a**, **9b** are better preorganized for anion binding than corresponding stereoisomers **10a**, **10b**. Our results indicate that anion receptors based on *meta*-substituted thiacalixarenes possess complexation abilities fully comparable with common *para*-substituted analogues.

1. Introduction

Calix[n]arenes[1] are used frequently as molecular scaffolds in the synthesis of various ligands and receptors. As macrocyclic compounds with well-established basic chemistry, they offer an almost unlimited degree of freedom in regioselective or stereoselective derivatisation with many applications in the design of novel functional molecules. One of them, anion complexation, has been recognised as an important part of supramolecular chemistry. The principal role of anions in biological systems, various chemical processes, or environmental pollution issues can be demonstrated by the vast literature focused on this topic published recently.[2]

Not surprisingly, calix[4]arene derivatives represent a very popular macrocyclic skeleton for the design of anion receptors.[3] The unique three-dimensional tuneable shape of the molecule makes this compound especially versatile for the preparation of neutral anion receptors, where successful binding of anions requires high degree of preorganisation, interaction directionality and complementarity. Thus, the introduction of amide or urea/thiourea moieties onto the calixarene skeleton enables the design of neutral anion receptors, which possess highly directional hydrogen bonds from suitably preorganised –NH– functions.

During our on-going research on anion recognition, we have reported[4] a series of new bis- to tetrakis-(ureido)calix[4]arenes immobilized in the *cone* or 1,3-*alternate*[5] conformations, which were proven as very efficient ligands for the complexation of anions possessing different geometries. The characteristic feature of all these receptors is the fact that they are based on *para*-substituted calixarene derivatives (which is a consequence of general calixarene reactivity). Very recently, we have described unusual regioselectivity of thiacalix[4]arene[6] derivatives enabling the introduction of various substituents into the *meta* positions of the thiacalixarene skeleton. Thus, regioselective formylation, chloromethylation or nitration[7] opens the door for completely novel substitution pattern, essentially inaccessible in classical calixarene chemistry so far.

Here we report on the synthesis and complexation ability of ureido-thiacalix[4]arenes having one or two arylurea units appended to the upper rim of the thiacalixarene skeleton. As the ureido functions are placed at the *meta* positions of thiacalixarenes, this kind of receptor is unprecedented in calixarene chemistry.

2. Results and discussion

Tetrapropoxy derivative **1**, immobilized in the 1,3-*alternate* conformation, was prepared by a known procedure[8] using alkylation of the starting thiacalix[4]arene with PrI/K_2CO_3 in acetone. The nitration of **1** was carried out in a $CHCl_3$–glacial acetic acid mixture using aqueous 65% HNO_3 as the nitration agent.[7a] Mononitro derivative **2** was prepared on a gram-scale in a 74% yield by reaction with 80 equiv of HNO_3. Similarly, using higher excess of HNO_3, dinitro derivatives **3** and **4** were obtained (both in 26% yields) after column chromatography of the crude reaction mixture

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on silica gel. Nitro derivatives **2**–**4** were then reduced with $SnCl_2 \cdot 2H_2O$ in refluxing ethanol to give amino derivatives **5**, **6** and **7** in 88, 95 and 95% yields, respectively. Target receptors **8**–**10** were obtained by the reaction of amines with appropriate isocyanates (*p*-tolyl or *p*-nitrophenyl) in dichloromethane at room temperature and they were isolated in 60–71% yields.

The structures of novel compounds were confirmed by the combination of ^{1}H NMR and MS analysis. Thus, the ESI MS of derivative **9a** showed a signal at *m*/*z* 983.34, corresponding to the diureido compound with a sodium cation $[M+Na]^+$. Similarly, compounds **8a** and **8b** exhibited molecular peaks $[M+H]^+$ at *m*/*z* 813.34 and 844.20, respectively, proving the presence of only one arylureido group in the molecule. The expected feature of the ^{1}H NMR spectra of all *meta*-substituted derivatives should be the occurrence of two doublets in aromatic region with a coupling constant of 8.4–8.5 Hz. These doublets correspond to characteristic signals from the *meta*-substituted thiacalixarene rings. Whereas this expected splitting pattern is well observable in amino derivatives **5**–**7** (Fig. 1), the ^{1}H NMR spectra of final receptors are frequently too complicated due to overlapping with the signals of *p*-tolyl or *p*-nitrophenyl moieties. Anyhow, compound **9a** possesses two typical doublets at 7.73 and 7.38 ppm, while nitrourea derivative **10b** shows doublets at 7.75 and 7.18 ppm ($CDCl_3$/CD_3OD=4:1).

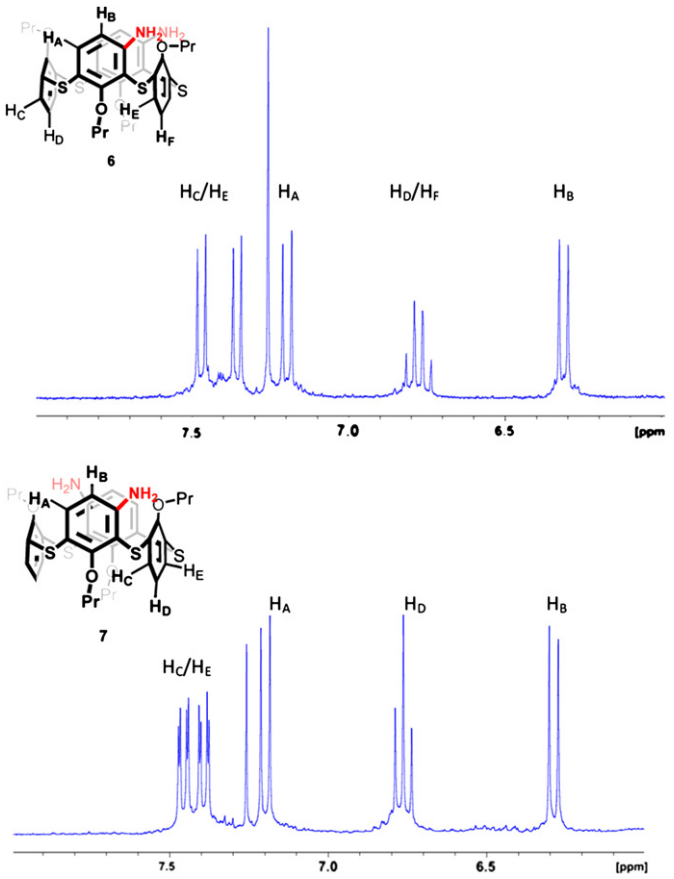


Fig. 1. Partial ^{1}H NMR spectra of **6** and **7** showing a typical splitting pattern of *meta*-substituted thiacalix[4]arenes (300 MHz, 298 K, $CDCl_3$).

The final unequivocal structural evidence was obtained using single crystal X-ray crystallography. Albeit we were unable to grow suitable monocrystals for diureido derivatives **9** and **10**, monoureido compound **8b** was obtained in a suitable quality after the crystallization from THF/EtzOH mixture. As shown in Fig. 2, compound **8b** crystallizes in *P*−1 space group with one molecule of THF. The solvent is held by two nonsymmetrical hydrogen bonds from ureido NH functions with O···H distances 2.20 and 2.72 Å, respectively (Fig. 2a). It indicates that the −NH− group connected directly to the *p*-nitrophenyl moiety is more acidic than the other, and consequently, creates stronger hydrogen bond towards the oxygen atom in THF. An unexpected intermolecular interaction was observed for *p*-nitrophenylureido moieties. These units are strictly coplanar to each other forming dimer with interplanar distance 3.33 Å where the carbonyl C atom is situated exactly above the C1 atom of *p*-nitrophenyl moiety.

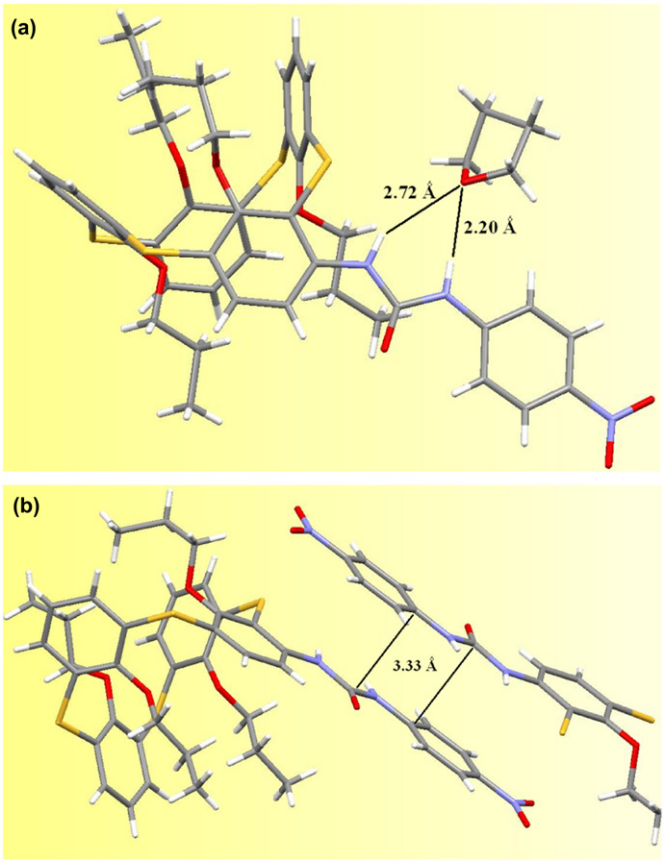


Fig. 2. Crystallographic structure of compound **8b**, (a) complex with THF; (b) packing motif with π–π interactions of *p*-nitrophenylureido moieties (THF and second thiacalix[4]arene molecule partly deleted for better clarity).

The ^{1}H NMR titration experiments towards selected anions were performed in DMSO-d_6. As the complexation phenomenon is based on the hydrogen bonding interactions of ureido −NH− groups with anions, the resulting complexation constants are rather small if compared with less competitive solvents (e.g., $CDCl_3$). On the other hand, using the HB-competitive solvent was necessary to avoid extensive oligomerization of compounds **8**–**10** due to the intermolecular hydrogen bonds. As shown in Fig. 3a, the ^{1}H NMR spectrum of compound **10b** in $CDCl_3$ exhibits very intricate and highly diffused peak patterns indicating nonspecific HB interactions of the molecules. These interactions can be smoothly destroyed by addition of CD_3OD (Fig. 3b). Unfortunately, this led simultaneously to the disappearance of ureido −NH− signals, which are usually used as the indicators of complexation phenomenon. Thus, the DMSO-d_6 solutions of our receptors (Fig. 3c) represent the best choice, as the corresponding ^{1}H NMR spectra of **8**–**10** are well resolved (only monomeric structures are present) and the signals of ureido functions are well observable in the low-field part of the spectra.

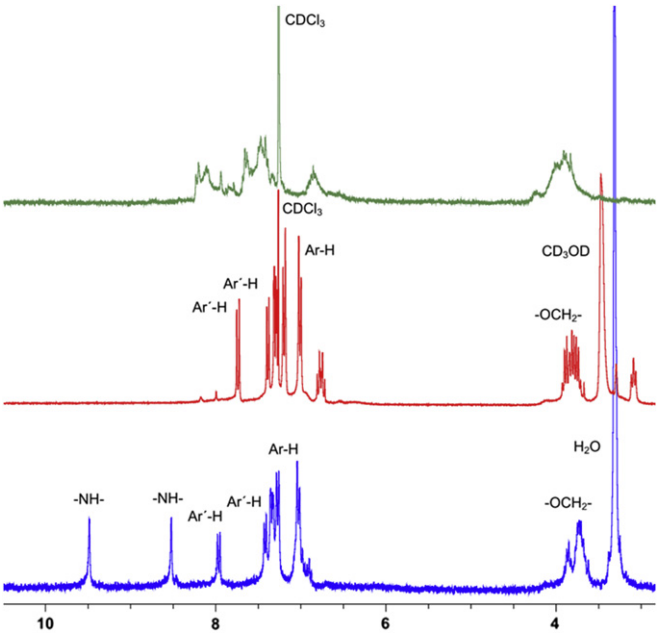


Fig. 3. ^{1}H NMR spectra of derivative **9a** in $CDCl_3$ (green), $CDCl_3/CD_3OD$ mixture (red), and DMSO-d_6 (blue); (300 MHZ, 298 K).

The ^{1}H NMR titrations were carried out using a constant calixarene host concentration (0.5–2.0 mM) and an increasing concentration of appropriate anion to obtain different host/anion ratios (1 to 20:1). All anions (BzO^-, AcO^-, Cl^-, Br^- and $H_2PO_4^-$) were added in the form of tetrabutylammonium (TBA) salts to minimise any possible interference of cation due to undesirable interactions with calixarene cavities. The results obtained are summarised in Table 1.In all cases, the large complexation-induced shifts (CIS >2 ppm) were observed for the NH protons of the urea moiety. It suggests that these groups are responsible for the binding of anions via cooperative hydrogen bonding interactions. The complexation constants for the anions were determined by analyzing the binding isotherms (obtained from NMR data) using the original nonlinear curve-fitting program (program OPIUM).[9] The titration curves (Fig. 4) suggest the formation of complexes with 1:1 stoichiometry. All titration experiments confirmed the expected fact that receptors possessing electron-withdrawing *p*-nitrophenylgroups (**8b**, **9b**, **10b**) form complexes with higher association constants than receptors having *p*-tolyl substituents (**8a**, **9a**, **10a**). Thus, compare $K_{\mathbf{10b}}$ (AcO^-)=650±160 for receptor **10b** with the same constant for *p*-tolyl derivative **10a**-$K_{\mathbf{10a}}$ (AcO^-)=200±10 mol^{-1} dm^3. Rather unexpected results were obtained in the case of diureido receptors **9** and **10**. It is known that receptors with two or even more ureido moieties on the upper rim of calixarene create stronger complexes with anions (1:1 stoichiometry) than corresponding monourea derivatives. This effect is based on the preorganisation of ureido moieties, which can bind an anion by cooperative hydrogen bonding. However, no significant differences in the complexation constants were observed for mono- or di-ureido receptors in the case of *meta*-substituted derivatives **8**–**10**. Thus, the highest association constant for acetate was found for compound **8b** having only one ureido group ($K_{\mathbf{8b}}$=2900±890 mol^{-1} dm^3), while achiral **9b** and chiral **10b** analogues possess much lower complexation constants: $K_{\mathbf{9b}}$=920±100 mol^{-1} dm^3 and $K_{\mathbf{10b}}$=660±150 mol^{-1} dm^3, respectively. This anomalous behaviour could be explained by the long distance and the wrong mutual geometry of both ureido functions in chiral derivatives (**10a** and **10b**). On the other hand, in the case of achiral receptors **9a** and **9b** the neighbouring propoxy group invokes a steric hindrance to the system, which effectively obstructs the cooperative binding from both ureido functions.

Table 1
Binding constants K [M^{-1}][a] of receptors **8**–**10** towards selected anions. ^{1}H NMR titrations (300 MHz, DMSO-d_6, 298 K)

Anion	8a	8b	9a	9b	10a	10b
$PhCOO^-$	170±40	820±170	230±40	1300±230	130±40	360±40
CH_3COO^-	180±50	2900±890	430±60	920±100	200±10	660±150
Cl^-	25±5	50±10	280±40	270±70	27±7	150±10
Br^-	6±1	18±5	12±1	14±3	9±1	22±6
$H_2PO_4^-$	230±50	1070±130	140±35	—[b]	180±50	106±36

[a] All anions were used as tetra-*n*-butylammonium (Bu_4N^+) salts.
[b] Unclear stoichiometry.

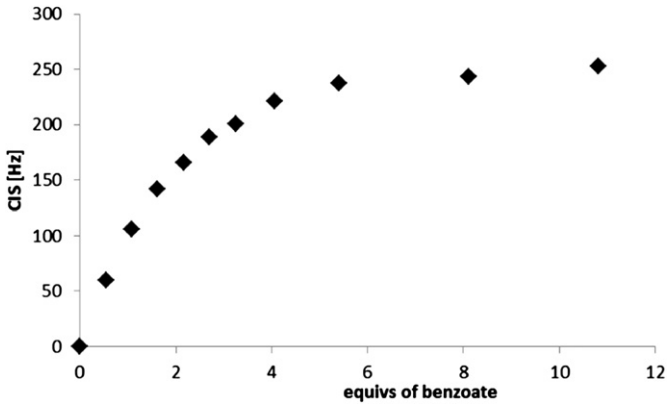


Fig. 4. ^{1}H NMR titration of receptor **9a** with Bu_4N^+ benzoate (DMSO-d_6, 300 MHz, 298 K).

3. Conclusions

In conclusion, the direct nitration of alkylated thiacalix[4]arene enabled the construction of novel class of calixarene-based receptors with so far inaccessible *meta*-substitution pattern. These compounds, possessing arylureido moieties, are capable of anion binding and showed very good complexation ability even in highly HB-competitive solvent, such as DMSO. As can be documented by respective complexation constants, achiral receptors **9a**, **9b** are better preorganized for the anion binding than the corresponding chiral regioisomers **10a**, **10b**.

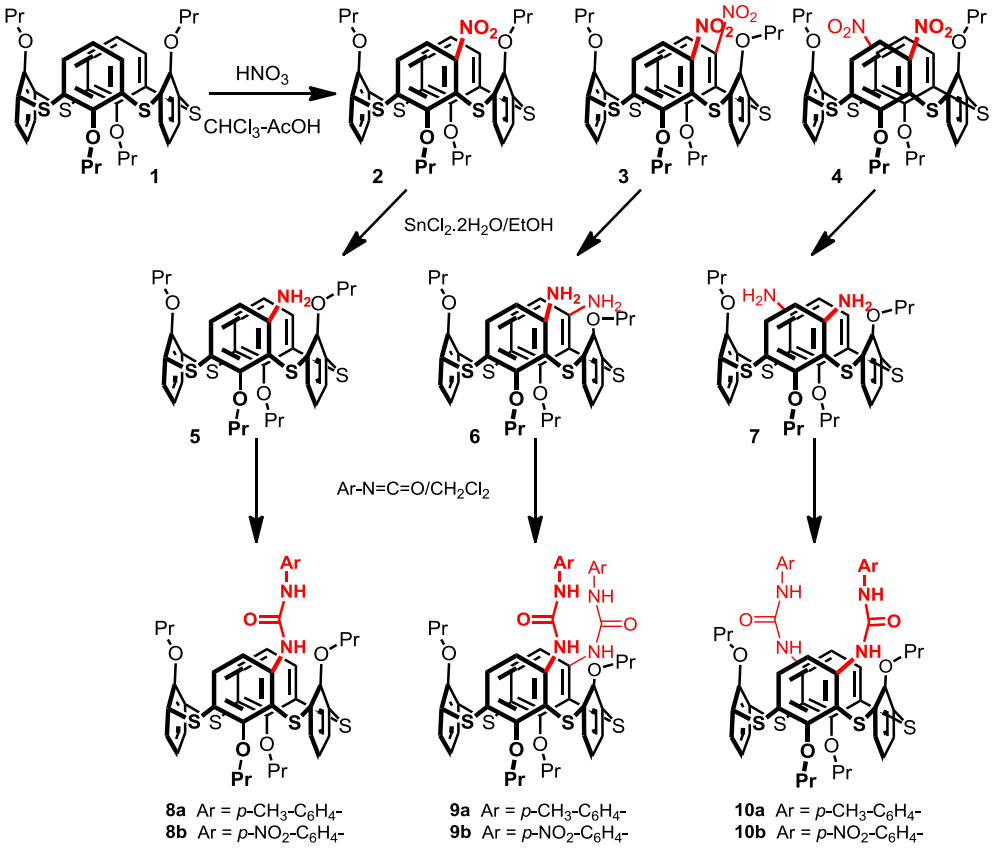
4. Experimental

4.1. General

Melting points are uncorrected and were determined using Heiztisch Mikroskop—Polytherm A (Wagner and Munz, Germany). The IR spectra were measured on an FT-IR spectrometer Nicolet 740 in KBr. Mass spectra were measured using ESI technique on Q–TOF (Micromass) spectrometer. Elemental analyses were measured on Perkin–Elmer 240, Elementar vario EL (Elementar, Germany) or Mitsubishi TOX–100 instruments.^{1}H NMR spectra were recorded on a Varian Gemini 300 spectrometer. Dichloromethane (DCM) used for the reactions was dried with CaH_2 and stored over molecular sieves. The courses of reactions were monitored by TLC using TLC aluminium sheets with Silica gel 60 F_{254} (Merck).

The synthesis of all three nitro derivatives **2**–**4** (Scheme 1) has been recently published by our group.[7a]

*4.1.1. 4-Amino-25,26,27,28-tetrapropoxythiacalix[4]arene (1,3-alternate) **5**.* Nitroderivative **2** (260 mg, 0.37 mmol) was dissolved in 50 ml of ethanol and refluxed with $SnCl_2\cdot 2H_2O$ (830 mg, 3.66 mmol) overnight. The course of reaction was checked by TLC (hexane/DCM=1:2 v/v). Then the solvent was evaporated under



Scheme 1. Preparation of ureido-substituted receptors **8**–**10**.

reduced pressure, the solid residue dissolved in DCM and washed with 1 M KOH and then with water (3×50 ml). The organic layer was dried over $MgSO_4$ and the solvent was evaporated under vacuum. The title compound was obtained (220 mg, 88%) as grey solid, which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K) δ (ppm): 7.44 (d, J=7.6 Hz, 1H, arH), 7.37 (m, 4H, arH), 7.22 (d, J=8.5 Hz, 1H, arH), 6.44 (d, J=8.2 Hz, 1H, arH), 3.85 (m, 8H, −O−*CH*$_2$−), 1.55–1.20 (m, 8H, −OCH$_2$−*CH*$_2$−), 0.75 (m, 9H, −CH_3), 0.68 (t, J=7.6 Hz, 3H, −CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K) δ (ppm): 161.94, 159.99, 159.07, 147.64, 134.01, 133.43, 133.11, 132.82, 132.49, 132.43, 132.16, 129.90, 129.35, 128.87, 128.77, 128.69, 122.75, 122.69, 122.54, 117. 86, 116.62, 114. 07, 71.86, 71.36, 71.14, 22.96, 22.62, 22.45, 22.36, 10.28, 10.09, 9.96, 9.81. IR (KBr) ν_{max} (cm^{-1}): 3375, 3053, 2959, 2873, 1600, 1561, 1473, 1457, 1431, 1380, 1315, 1235. MS-ESI$^+$ m/z: 680.17 $[M+H]^+$ (100%).

4.1.2. 4,18-Diamino-25,26,27,28-tetrapropoxythiacalix[4]arene (1,3-alternate) ***6***. Derivative **3** (338 mg, 0.448 mmol) was dissolved in ethanol (50 mL) and $SnCl_2\cdot 2H_2O$ (1.01 g, 4.48 mmol) was added. The reaction mixture was then heated to reflux overnight. After cooling, the solvent was evaporated and a solution of 1 M NaOH was added to bring pH to 10. A product was extracted with DCM, the organic phase was washed with water, dried over $MgSO_4$ and evaporated to dryness. Product **6** (296 mg) was obtained in a 95% yield and was used in the next step without further purification. Mp 120–123 °C. ^{1}H NMR ($CDCl_3$/CD_3OD, 300 MHz, 298 K) δ (ppm): 7.47 (d, J=8.1 Hz, 2H, arH), 7.36 (d, J=7.7 Hz, 2H, arH), 7.20 (d, J=8.4 Hz, 2H, arH), 6.78 (q, J=7.4 Hz, 2H, arH), 6.31 (d, J=8.4 Hz, 2H, arH), 4.02–3.78 (m, 4H, −O−CH_2−), 3.75–3.67 (m, 2H, −O−CH_2−), 3.61 (t, J=7.3 Hz, 2H, −O−CH_2−), 1.61–1.31 (m, 8H, −OCH$_2$−*CH*$_2$−), 0.96–0.68 (m, 12H, −CH_3). ^{13}C NMR ($CDCl_3$/CD_3OD, 75 MHz, 298 K) δ (ppm): 162.2, 160.5, 158.9, 148.5, 130.1, 129.1, 116.9, 114.1, 72.4, 72.2, 23.2, 23.1, 10.6, 10.0. IR (KBr) ν_{max} (cm^{-1}): 3444, 2961, 2919, 2874, 2851, 1603, 1457, 1433, 1378, 1231. EA for $C_{36}H_{42}N_2O_4S_4$ calcd: C, 62.21; H, 6.09; N, 4.03; S, 18.45%; found: C, 62.01; H, 5.88; N, 3.90; S, 18.01%. MS ESI$^+$ m/z 695.21$[M+H]^+$.

4.1.3. 4,16-Diamino-25,26,27,28-tetrapropoxythiacalix[4]arene (1,3-alternate) ***7***. Dinitroderivative **4** (368 mg, 0.487 mmol) was dissolved in ethanol (50 mL) and $SnCl_2\cdot 2H_2O$ (1.10 g, 4.87 mmol) was added. The reaction mixture was then heated to reflux overnight. After cooling, the solvent was evaporated and a solution of 1 M NaOH was added to bring pH to 10. The mixture was extracted with DCM, the organic phase was washed with water, dried over $MgSO_4$ and evaporated to dryness. Product **7** (322 mg) was obtained in a 95% yield. Mp 200–202 °C ^{1}H NMR ($CDCl_3$/CD_3OD, 300 MHz, 298 K) δ (ppm): 7.46 (d, J=7.7 Hz, 2H, arH), 7.40 (d, J=7.7 Hz, 2H, arH), 7.21 (d, J=8.3 Hz, 2H, arH), 6.76 (t, J=7.8 Hz, 2H, arH), 6.29 (d, J=8.3 Hz, 2H, arH), 4.02–3.67 (m, 8H, −O−CH_2−), 2.05–1.76 (m, 2H, −OCH$_2$−*CH*$_2$−), 1.70–1.37 (m, 6H, −OCH$_2$−*CH*$_2$−), 0.82 (t, J=7.4 Hz, 12H, −CH_3).^{13}C NMR ($CDCl_3$/CD_3OD, 75 MHz, 298 K) δ (ppm): 162.5, 159.6, 134.9, 134.7, 130.1, 129.2, 122.8, 122.7, 116.5, 114.7, 109.9, 109.7, 73.07, 72.8, 23.4, 23.1, 10.6, 10.2 ppm. IR (KBr) ν_{max} (cm^{-1}): 3471, 2962, 2934, 2874, 1601, 1457, 1433, 1378, 1316, 1232. EA for $C_{36}H_{42}N_2O_4S_4$ calcd: C, 62.21; H, 6.09; N, 4.03; S, 18.45%; found: C, 62.01; H, 5.88; N, 3.90; S, 18.01%. MS ESI$^+$ m/z 717.19 $[M+Na]^+$.

4.2. Synthesis of receptors 8a,b—general procedure

Aminothiacalixarene **5** (100 mg, 147 mmol) was dissolved in 20 ml of dry DCM and stirred under nitrogen with appropriate isocyanate (0.441 mmol) for 4 days at room temperature. To quench the reaction, methanol (30 ml) was added and the mixture was stirred for 15 min. Solvents were then removed under reduced

pressure and the resulting solid was triturated with 40 ml of MeOH/DCM=40:1 mixture. The product in the form of white precipitate was collected by filtration, washed with methanol and dried.

4.2.1. 4-N′-(4-methylphenyl)ureido-25,26,27,28-tetrapropoxythiacalix[4]arene (1,3-alternate) ***8a***. Mp >300 °C (decomp.), yield: 63%. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K) δ (ppm): 7.96 (s, 1H, −NH−), 7.84 (d, J=8.5 Hz, 1H, arH), 7.36 (m, 6H, arH), 7.29 (d, J=7.9 Hz, 1H, arH), 7.22 (d, J=8.5 Hz, 2H, arH), 7.12 (d, J=7.9 Hz, 2H, arH), 6.81 (t, J=7.6 Hz, 2H, arH), 6.80 (t, J=7.6 Hz, 1H, arH), 6.51 (s, 1H, −NH−), 4.05−3.68 (m, 7H, −O−CH_2−), 3.38 (q, 1H, −O−CH_2−), 2.29 (s, 3H, ar-CH_3), 1.41−1.10 (m, 8H, −OCH_2−CH_2−), 0.71 (q, J=7.6 Hz, 6H, −CH_3), 0.62 (q, J=7.3 Hz, 6H, −CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K) δ (ppm): 160.93, 160.00, 159.68, 158.72, 152.80, 139.41, 134.75, 134.65, 133.46, 132.98, 132.54, 132.27, 132.13, 131.56, 129.92, 129.24, 129.13, 128.76, 128.59, 128.05, 122.88, 122.71, 122.69, 122.34, 122.04, 118.27, 114.62, 71.69, 71.11, 70.78, 22.80, 22.46, 22.18, 20.86, 10.18, 10.04, 9.87, 9.63. IR (KBr) ν_{max} (cm^{-1}): 2962, 2875, 1663, 1609, 1574, 1544, 1506, 1465, 1430, 1382, 1366, 1311, 1290, 1250, 1232, 1200. MS-ESI$^+$ m/z: 813.34 $[M+H]^+$ (100%).

4.2.2. 4-N′-(4-nitrophenyl)ureido-25,26,27,28-tetrapropoxythiacalix[4]arene (1,3-alternate) ***8b***. Mp >300 °C (decomp.), yield: 64%. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K) δ (ppm): 8.17 (d, J=9.1 Hz, 2H, arH), 7.89 (s, 1H, −NH−), 7.65 (d, J=8.2 Hz, 1H, arH), 7.60 (d, J=9.1 Hz, 2H, arH), 7.56 (s, 1H, −NH−), 7.41 (m, 6H, arH), 7.31 (d, J=7.9 Hz, 1H, arH), 6.83 (t, J=7.6 Hz, 3H, arH), 4.08−3.77 (m, 6H, −O−CH_2−), 3.64 (q, 2H, −O−CH_2−), 1.52−1.17 (m, 8H, −OCH_2−CH_2−), 0.75 (m, 6H, −CH_3), 0.69 (t, J=7.6 Hz, 3H, −CH_3), 0.63 (t, J=7.6 Hz, 3H, −CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K) δ (ppm): 161.39, 160.03, 159.78, 159.25, 158.80, 151.70, 145.00, 142.57, 138.86, 134.80, 134.14, 134.01, 133.45, 133.43, 132.65, 132.14, 129.61, 129.05, 128.97, 128.91, 128.81, 127.86, 125.11, 124.14, 123.16, 122.99, 118.21, 116.25, 72.97, 72.12, 71.16, 22.89, 22.68, 22.37, 22.28, 10.17, 9.87, 9.70. IR (KBr) ν_{max} (cm^{-1}): 2963, 2876, 1721, 1616, 1598, 1559, 1508, 1498, 1465, 1430, 1381, 1366, 1331, 1300, 1257, 1231, 1176. MS-ESI$^+$ m/z: 844.20 $[M+H]^+$ (43%).

4.3. Synthesis of receptors 9 and 10—general procedure

Diamino derivatives **6** or **7** (70 mg, 0.100 mmol) were dissolved in dry DCM (10 ml) and stirred under nitrogen with 6 equiv of the corresponding isocyanate (0.600 mmol) at room temperature for 2 days. To quench the reaction, methanol (30 mL) was added and the mixture was stirred for 1 h. The solvents were then removed under reduced pressure and the resulting solid was triturated with methanol (40 mL) in an ice bath. The product was filtered off, washed with methanol and dried.

4.3.1. 4,18-Bis[N′-(4-tolyl)ureido]-25,26,27,28-tetrapropoxythiacalix[4]arene (1,3-alternate) ***9a***. Mp 182−185 °C, yield: 61%. ^{1}H NMR ($CDCl_3$/CD_3OD, 300 MHz, 298 K) δ (ppm): 7.74 (d, J=8.7 Hz, 2H, arH), 7.39 (d, J=7.8 Hz, 2H, arH), 7.30 (dd, J=8.7 and 2.3 Hz, 4H, arH), 7.19 (d, J=8.3 Hz, 4H, arH), 7.00 (d, J=8.3 Hz, 4H, arH), 6.80−6.71 (m, 2H, arH), 3.92−3.71 (m, 8H, −O−CH_2−), 2.20 (s, 6H, ar-CH_3), 1.34−1.24 (m, 6H, −OCH_2−CH_2−), 1.05−0.95 (m, 2H, −OCH_2−CH_2−), 0.71−0.62 (m, 9H, −CH_3), 0.44 (t, J=7.7 Hz, 3H, −CH_3). ^{13}C NMR ($CDCl_3$/CD_3OD, 300 MHz, 298 K) δ (ppm): 165.0, 164.2, 161.7, 157.5, 143.5, 140.1, 136.9, 133.5, 133.1, 132.6, 127.3, 126.9, 126.1, 121.9, 76.1, 75.3, 33.8, 26.7, 26.0, 14.2, 13.2. IR (KBr) ν_{max} (cm^{-1}): 3339, 2964, 2935, 2875, 1699, 1609, 1574, 1545, 1507, 1433, 1364, 1290, 1250, 1221. EA for $C_{52}H_{56}N_4O_6S_4$ calcd: C, 64.97; H, 5.87; N, 5.83; S, 13.34%; found: C, 64.54; H, 5.30; N, 5.67; S, 13.05%. MS ESI$^+$ m/z 983.30 $[M+Na]^+$.

4.3.2. 4,18-Bis[N′-(4-nitrophenyl)ureido]-25,26,27,28-tetrapropoxythiacalix[4]arene (1,3-alternate) ***9b***. Mp 205−207 °C, yield 71%. ^{1}H NMR ($CDCl_3$/CD_3OD, 300 MHz, 298 K) δ (ppm): 8.12 (d, J=9.0 Hz, 2H, arH), 8.05 (d, J=9.0 Hz, 4H, arH), 7.77 (d, J=8.7 Hz, 2H, arH), 7.52 (d, J=9.0 Hz, 4H, arH), 7.40 (d, J=7.8 Hz, 2H, arH), 7.33 (dd, J=8.2 and 2.1 Hz, 2H, arH), 6.83−6.74 (m, 2H, arH), 3.95−3.71 (m, 8H, −O−CH_2−), 1.34−1.24 (m, 6H, −OCH_2−CH_2−), 1.07−0.94 (m, 2H, −OCH_2−CH_2−), 0.72 (t, J=7.7 Hz, 3H, −CH_3), 0.65 (t, J=7.5 Hz, 6H, −CH_3), 0.42 (t, J=7.4 Hz, 3H, −CH_3). ^{13}C NMR ($CDCl_3$/CD_3OD, 300 MHz, 298 K) δ (ppm): 202.9, 175.8, 164.7, 149.9, 146.1, 142.7, 137.0, 132.9, 132.6, 129.3, 127.2, 122.4, 121.7, 76.7, 75.4, 27.6, 26.8, 26.1, 14.2. IR (KBr) ν_{max} (cm^{-1}): 3364, 2964, 2876, 1722, 1598, 1567, 1496, 1364, 1331, 1301, 1254. EA for $C_{50}H_{50}N_6O_{10}S_4$ calcd: C, 58.69; H, 4.93; N, 8.21; S, 12.53%; found: C, 58.31; H, 4.46; N, 7.94; S, 12.28%. MS ESI$^+$ m/z 1061.21 $[M+K]^+$.

4.3.3. 4,16-Bis[N′-(4-tolyl)ureido]-25,26,27,28-tetrapropoxythiacalix[4]arene (1,3-alternate) ***10a***. Mp 164−166 °C, yield: 68%. ^{1}H NMR ($CDCl_3$/CD_3OD, 300 MHz, 298 K) δ (ppm): 7.77 (d, J=8.7 Hz, 2H, arH), 7.28−7.25 (m, 4H, arH), 7.16 (dd, J=8.7 and 1.4 Hz, 4H, arH), 6.97 (d, J=8.2 Hz, 6H, arH), 6.72 (t, J=7.7 Hz, 2H, arH), 3.85−3.75 (m, 2H, −O−CH_2−), 3.72−3.64 (m, 4H, −O−CH_2−), 3.41−3.33 (m, 2H, −O−CH_2−), 2.17 (s, 6H, ar-CH_3), 1.25−1.18 (m, 4H, −OCH_2−CH_2−), 1.08−0.98 (m, 4H, −OCH_2−CH_2−), 0.60−0.50 (m, 12H, −CH_3). ^{13}C NMR ($CDCl_3$/CD_3OD, 300 MHz, 298 K) δ (ppm): 164.8, 162.7, 143.9, 140.0, 137.2, 133.6, 133.1, 132.4, 127.0, 125.4, 124.5, 122.2, 75.5, 75.4, 26.7, 26.2, 24.8, 14.1, 13.7. IR (KBr) ν_{max} (cm^{-1}): 3319, 2963, 2936, 2875, 1678, 1610, 1574, 1546, 1504, 1432, 1365, 1222. EA for $C_{52}H_{56}N_4O_6S_4$ calcd: C, 64.97; H, 5.87; N, 5.83; S, 13.34%; found: C, 64.40; H, 5.33; N, 5.49; S, 13.04%. MS ESI$^+$ m/z 978.34 $[(M+H_2O)]^+$.

4.3.4. 4,16-Bis[N′-(4-nitrophenyl)ureido]-25,26,27,28-tetrapropoxythiacalix[4]arene (1,3-alternate) ***10b***. Mp 236−239 °C, yield: 60%. ^{1}H NMR ($CDCl_3$/CD_3OD, 300 MHz, 298 K) δ (ppm): 8.00 (d, J=8.9 Hz, 4H, arH), 7.76 (d, J=8.5 Hz, 2H, arH), 7.50 (d, J=8.9 Hz, 4H, arH), 7.28 (d, resonance overlapped with solvent signal, 4H, arH), 7.19 (d, J=8.9 Hz, 2H, arH), 6.71 (t, J=7.6 Hz, 2H, arH), 3.86−3.78 (m, 2H, −O−CH_2−), 3.72−3.65 (m, 4H, −O−CH_2−), 3.49−3.41 (m, 2H, −O−CH_2−), 1.22−0.98 (m, 8H, −OCH_2−CH_2−), 0.57−0.46 (m, 12H, −CH_3). ^{13}C NMR ($CDCl_3$/CD_3OD, 300 MHz, 298 K) δ (ppm): 164.8, 162.7, 156.3, 150.2, 146.1, 143.3, 136.4, 133.0, 132.3, 129.3, 126.1, 121.9, 75.5, 75.4, 26.7, 26.2, 14.1, 13.5. IR (KBr) ν_{max} (cm^{-1}): 3354, 2964, 2936, 2876, 1717, 1598, 1559, 1455, 1433, 1365, 1330, 1302, 1257, 1222, 1192 cm^{-1}. EA for $C_{50}H_{50}N_6O_{10}S_4$ calcd: C, 58.69; H, 4.93; N, 8.21; S, 12.53%; found: C, 58.42; H, 4.60; N, 8.03 S, 12.22%. MS ESI$^+$ m/z 1040.28 $[M+H_2O]^+$.

4.4. NMR titration experiments

The ^{1}H NMR titration experiments were performed using a constant calixarene host concentration (0.5−2.0 mM) and increasing concentration of appropriate guest to obtain different host/guest ratios (1 to 20:1) in DMSO-d_6 as solvent using a Varian Gemini 300 spectrometer (300 MHz, 298 K). The corresponding binding constants (Table 1) were calculated using the original non-linear regression curve-fitting program.[8]

4.5. X-ray crystallography

4.5.1. Crystallographic data for $C_{43}H_{45}N_3O_7S_4 \cdot 0.5C_4H_8O \cdot 0.5C_2H_5OH$. M=903.20, triclinic system, space group P−1, a=11.0289(11) Å, b=11.1273(15) Å, c=20.7232(18) Å, α=89.396(9)°, β=81.766(8)°, γ=63.438(12)°, Z=2, V=2247.2(5) Å^3, D_c=1.335 g cm^{-3}, μ(Cu Kα)= 2.403 mm^{-1}, crystal dimensions of 0.15×0.21×0.36 mm. Data were collected at 170(2) K on a Xcalbur OnyxCCD diffractometer with graphite monochromated Cu Kα radiation. The structure was solved by direct methods[9,10] using the CRYSTALS suite of programs[10,11] and anisotropically refined by full matrix least squares on F squared

value to final R=0.0757 and R_w=0.238 using 9234 independent reflections (Θ_{max}=80.2°), 604 parameters and 51 restrains. The positions of mixed solvent were found from the electron density maps. Mixed solvents were then placed in appropriate positions, and all distances between neighbouring atoms and angles were fixed. Site occupancies were assigned resulting in similar thermal parameters for both solvent molecules. The hydrogen atoms were placed in calculated positions for carbon and solvent atoms. For nitrogen atoms hydrogen atoms were found from differential electron density maps and refined with soft restrains to regularize their geometry. The structure was deposited into Cambridge Structural Database under number CCDC 819648.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.08.062.

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