# An Efficient Synthesis of Bis(calix[4]arenes), Bis(crown ether)-Substituted Calix[4]arenes, Aza-Crown Calix[4]arenes, and Thiaza-Crown Calix[4]arenes

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The easy transformation of 5,11,17,23-tetra-*tert*-butyl-25,27-bis(aminoethoxy)-26,28-dihydroxycalix[4]arene (**2**) into 5,11,17,23-tetra-*tert*-butyl-26,28-dihydroxy-25,27-bis(2-isothiocyanoethoxy)calix[4]arene (**3**) and 5,11,17,23-tetra-*tert*-butyl-25,27-bis(chloroacetamidoethoxy)-26,28-dihydroxycalix[4]arene (**4**) has been exploited for the development of an efficient and expeditious synthesis of a variety of calix[4]arene derivatives [bis(calix[4]arenes), bis(crown ether) calix[4]arenes, aza-crown calix[4]arenes, and thiaza-crown calix[4]arenes]. The functionality of compounds **2** and **3** allowed the formation of intramolecular bridges, leading to capped calix[4]arenes (compounds **5**, **10**, and **14**) as well as to the construction of double calix[4]arene units by means of spacers containing thiourea or amide-sulfur groups (compounds **6** and **15**, respectively). In addition, the bis(isothiocyanate) derivative **3** gave access to a high-yield preparation of heteroditopic bis(crown ether) calix[4]arenes (**7**–**9**) from commercial amino crown ethers.

## Introduction

The development of supramolecular chemistry has led to a growing interest in the design and synthesis of macrocyclic molecules incorporating intramolecular cavities.[1] Calixarenes[2−17] have been used as building blocks for the synthesis of large host molecules with different supramolecular functions. Like crown ethers and cyclodextrins, calixarenes are oligomeric macrocyclic molecules made up of phenol units and incorporating a cavity. They offer the advantage of their easy synthesis on a large scale in a simple one-pot procedure from inexpensive starting material[14−17] and, in addition, are readily amenable to chemical modification on both smaller (lower) and larger (upper) rims, by attachment of a wide range of potential ligating groups.

The versatility of calix[4]arenes as host molecules suggested that they might serve as potential building blocks for designing more elaborate structures, consisting of double calix[4]arenes.[18,19] Depending on the connecting site, there are three possible modes of assembly for these double calix[4]arenes: *head-to-head*, *tail-to-tail*, or *head-to-tail*. Or, put another way, by both larger (upper) rims, by both smaller (lower) rims, or by the larger (upper) rim of one and the smaller (lower) rim of another, respectively. Shinkai et al.[20−22] have reported the synthesis of a series of bis(calix[4]arenes) possessing two metal binding sites, each containing four ester or four ether groups. Double and triple calix[4]arenes connected through the oxygen atoms have been described,[23] produced by reactions between calix[4]arenes 1,3-difunctionalized at the smaller (lower) rim and difunctional reagents such as diacid dichlorides or diamines.[23,24] Double calixarenes linked through one bridge at the smaller (lower) rim and bearing urea groups on the larger (upper) rims have also been reported.[25,26] Recently, Rebek et al. have described[27] the synthesis and the encapsulation behaviour of bis(calix[4]arenes) linked by one bridge at the larger (upper) rims and bearing urea groups in the same rims. Bis(calix[*n*]arenes) singly and doubly bridged at the larger (upper) rims by 2-butenyl or 2-methylenepropyl moieties have been prepared by tandem Claisen rearrangement of bis(calix[*n*]arenes) singly and doubly bridged by ether linkages at the smaller (lower) rims with the same spacers. The complexation behaviour of these bis(calixarenes) toward fullerenes C60 and C70 has been studied.[28] A series of bis(calix[4]arene) derivatives linked through their phenolic oxygens with the aid of a single aliphatic or aromatic chain (*tail-to-tail*) have been obtained by alkylation of 28-hydroxy-25,26,27-tripropoxycalix[4]arenes with α,ω-dibromoalkanes in the presence of NaH,[29] and by condensation of *p-tert*-butylcalix[4]arene with methyl 2,6-bis(bromomethyl)benzoate,[30] 2,6-bis(bromomethyl)-4-methylanisole,[31] or with 5,5’-bis(bromomethyl)-2,2’-bipyridine *N*,*N*′-dioxide.[32] Bis- and oligocalix[4]arenes have been obtained by intermolecular metathesis of dialkenylcalix[4]arene derivatives.[33]

The term “calixcrowns” refers to the family of macropolycyclic molecules in which a monocyclic calixarene structure is linked through its phenolic oxygens to a cyclic polyether moiety, hence combining calixarene and polyether elements in their structures[8,10,11,19]. Since first reported by Ungaro,[34] these compounds have emerged as a new, exciting class of ionophores, thanks to their tendency − strongly dependent on their conformation − to bind alkali and alkaline earth metal cations selectively.[35−43] In the past dec-

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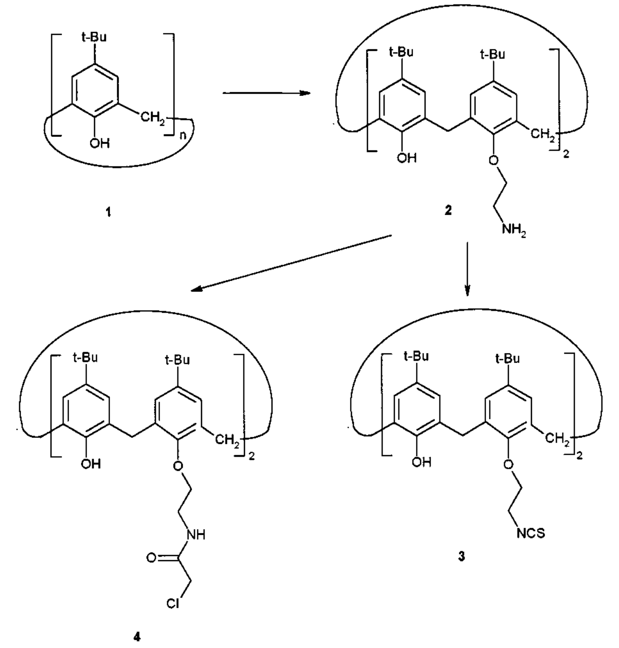
ade, the design of new ditopic receptors for the simultaneous complexation of anionic and cationic guest species has become an active new area of coordination chemistry, of interest for the selective extraction and/or transportation across lipophobic membranes, of metal salts. In this area, Beer et al.[44] reported the synthesis and coordination chemistry of new heteroditopic calix[4]arene compounds containing benzo-15-crown-5 units linked through amides at the smaller (lower) rim. As well as this, it should be also mentioned that hydrogen-bonding donor thiourea functions have been used for the design of anion receptors.[45−62]

In this paper, we report the synthesis from the easily accessible 25,27-bis(aminoethoxy)calix[4]arene (**2**) of a series of *tail-to-tail* bis(calix[4]arenes), bis(crown ether) calix[4]arenes, aza-crown calix[4]arenes and thiaza-crown calix[4]arenes.

## Results and Discussion

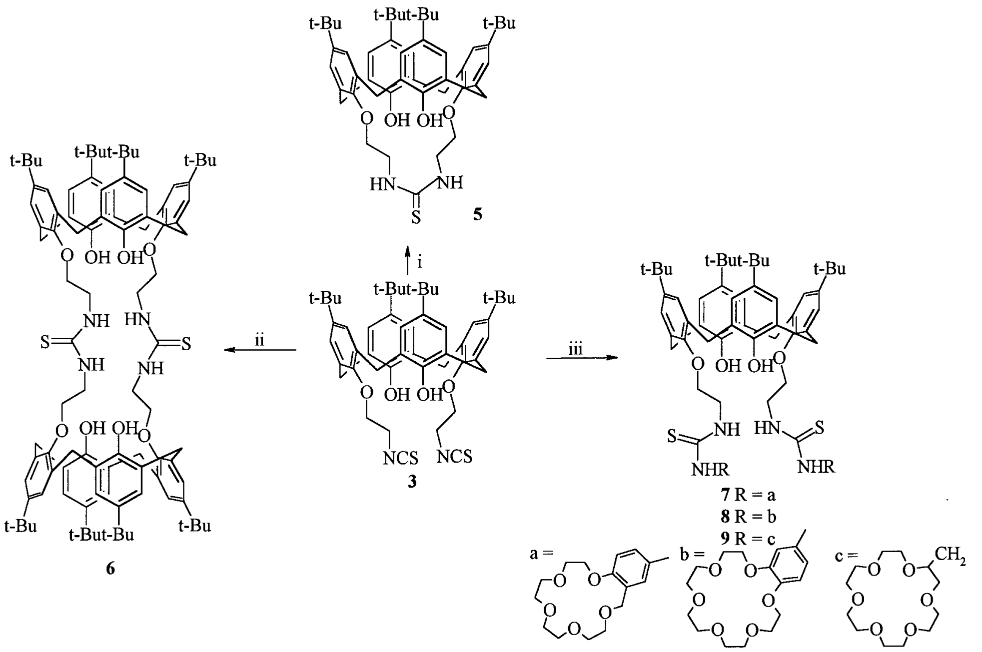
In a project directed towards synthetic applications of the isothiocyanate function,[63,64] it was proposed that isothiocyanate derivatives of calixarenes could be suitable precursors for the easy construction of calixarene-based heterotopic receptors. As the starting material, 25,27-bis(aminoethoxy)calix[4]arene (**2**) was chosen. This is readily obtained in two steps from *p-tert*-butylcalix[4]arene (**1**), by reaction with bromoacetonitrile and reduction of the cyano function with $LiAlH_4$.[65] We performed the transformation of **2** into the corresponding diisothiocyanate derivative **3** in excellent yields, using thiophosgene as reported by García-Fernández et al.[66] (see Scheme 1). Previous observations, from our group and others, have demonstrated[64] that isocyanates and isothiocyanates are readily transformed into the corresponding symmetric *N,N′*-disubstituted ureas and thioureas by a simple treatment with pyridine−water. Application of those conditions to compound **3** resulted in the isolation of the capped calix[4]arene **5**, in 52% yield (see Scheme 2). The formation of this compound is explained by the intermolecular reaction of the isothiocyanate functions, competing with the intramolecular process.

Assembly of double calixarene units linked by thiourea bridges could be effected by direct reaction of the diamino derivative **2** with the diisothiocyanate derivative **3**. The reaction was performed in pyridine under high dilution conditions. In this way, the bis(calix[4]arene) **6** was the only reaction product formed, isolated in good yields (60%) (see Scheme 2). The reactivity of isothiocyanates with amines also found application in the construction of heteroditopic structures base on compound **3**. The synthesis of bis(crown ether)-substituted calix[4]arenes was accomplished by treatment of that compound with commercial amino crown-ether derivatives (4′-aminobenzo-15-crown-5, 4′-aminobenzo-18-crown-6, and 2-(aminomethyl)-18-crown-6). We carried out these reactions in ethyl acetate in the presence of triethylamine, allowing easy coupling (94−98% yield) of the two different subunits, followed by the isolation of compounds **7−9** (see Scheme 2).

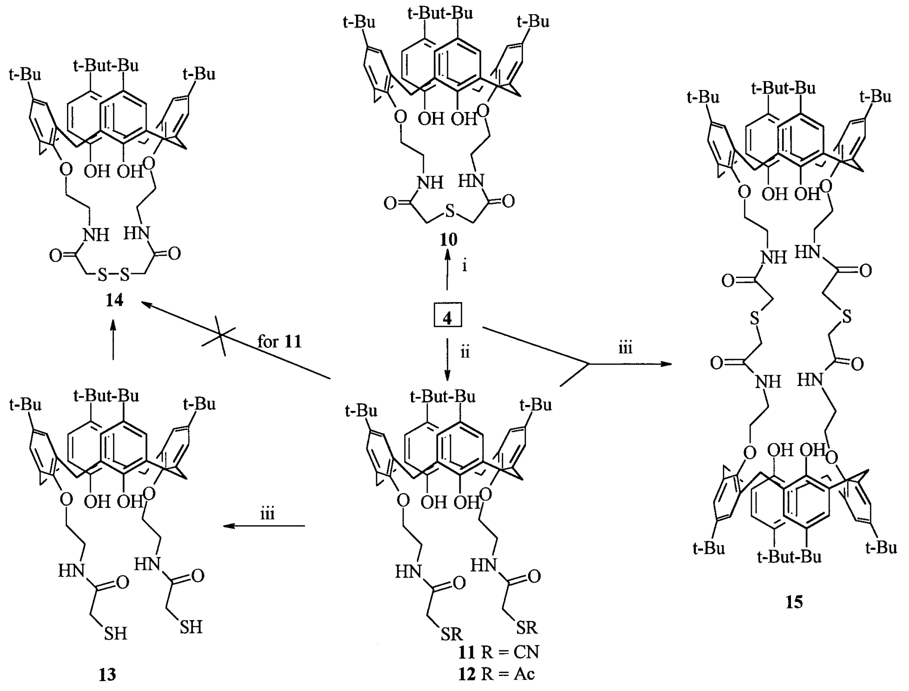


Scheme 1. Reagents and conditions: (i) see ref.[67]; (ii) $Cl_2CS$, $BaCO_3$, $CH_2Cl_2$, room temp.; (iii) $(ClCH_2CO)_2O$, AcOEt, room temp.

Because of the faculty of those groups to suffer nucleophilic displacement reactions, the transformation of the amino functions of compound **2** into the corresponding chloroacetamido groups was then investigated, as a potential gateway to the preparation of different calix[4]arene derivatives. Treatment of **2** with chloroacetic anhydride, using ethyl acetate as solvent, led to the dichloroacetamido derivative **4** in high yield (84%) (see Scheme 1). The two arms of that compound were linked by treatment with $Na_2S$ in refluxing methanol at high dilution, yielding the capped calixarene derivative **10** in moderate yield (47%) (see Scheme 3). The next goal was the construction of an analogous compound, but with a disulfide bridge. Bis(crown ether)s containing disulfide bridges have attracted attention as redox-switchable systems, for their utility in ion extraction and ion transport across liquid membranes.[67,68] Cyclic disulfides are typically prepared by oxidative dimerisation of α,ω-dithiols,[69−75] or α,ω-bisthiocyanates.[76−79] For this reason, we first carried out the synthesis of the bisthiocyanate derivative **11** (85%), by treatment of **4** with KSCN in refluxing acetone (see Scheme 3). Our attempts to obtain the disulfide bridge using the conditions previously described[79] were unsuccessful, however, in spite of the good yields reported by Field et al. for this reaction. Therefore, we considered a new strategy, entailing the synthesis of the bisdithiol derivative **13** via the corresponding bis(acetylthio) derivative **12**. That compound was easily obtained by reaction of **4** with KSAc in refluxing acetone (73%) and was then *S*-deacetylated, using NaOMe in MeOH (95%). Complete spontaneous transformation of compound **13** into the desired disulfide **14** was then observed during the purification process of **13** by standard column chromatography. Compound **14** was isolated in 60% overall yield from **12** (see Scheme 3).



Scheme 2. Reagents and conditions: (i) Py, $H_2O$, $Et_3N$, 60 °C; (ii) **2**, Py, room temp.; (iii) amino crown-ether, AcOEt, room temp.



Scheme 3. Reagents and conditions: (i) $Na_2S \cdot 9\ H_2O$, MeOH, reflux; (ii) KSCN or KSAc, acetone, reflux; (iii) NaOMe/MeOH, room. temp.

The in situ generation of the dithiol **13** from the bis(acetylthio) derivative **12** in the presence of the dichloroacetamide derivative **4** gave rise to bis(calix[4]arene) **15**. The reaction was performed using NaOMe/MeOH at room temp., yielding **15** in 52% yield (see Scheme 3).

In all cases the structures of the new calix[4]arene derivatives **3–15** were established by elemental analysis and/or high resolution FAB spectroscopy and from spectroscopic data (IR and NMR) (see Experimental Section).

## Conclusions

In summary, the construction of a variety of "tailor-made" calix[4]arene derivatives (biscalix[4]arenes, bis(crown ether) calix[4]arenes, aza-crown calix[4]arenes, and thiaza-crown calix[4]arenes) has been achieved easily from 25,27-bis(aminoethoxy)calix[4]arene **2**. The key step in these synthesis was the direct transformation of compound **2** into the corresponding bis(isothiocyanate) and bis(chloroacetamido) derivatives **3** and **4**. The functionality of these compounds permitted the formation of intramolecular bridges, leading to capped calix[4]arenes (compounds **5**, **10**, and **14**) as well as to the assembly of double calix[4]arene units by means of spacers containing thiourea or amide-sulfur groups (compounds **6** and **15**, respectively). In addition, the bis(isothiocyanate) derivative **3** gave access to a high-yielding preparation of heteroditopic bis(crown ether) calix[4]arenes (**7−9**) from commercial amino crown ethers.

## Experimental Section

**General Experimental Details:** TLC was performed on Merck silica gel 60F$_{245}$ aluminium sheets, with detection by Mostain reagent [ceric sulfate (1% w/v and ammonium molybdate (2.5% w/v) in 10% (v/v) aqueous sulfuric acid] and by UV light when applicable. Flash column chromatography on Merck or Scharlau silica gel (230−400 mesh. ASTM). − All evaporations were carried out under reduced pressure at 40 °C. − Melting points were determined with a Gallenkamp apparatus and are uncorrected. − NMR spectra were recorded at room temperature on a Bruker AM-300 spectrometer. $^1$H chemical shifts are given in ppm and referenced to internal $CHCl_3$ ($\delta$ = 7.26) for $CDCl_3$ solutions. $^{13}$C chemical shifts are given in ppm and referenced to $CDCl_3$ ($\delta$ = 77.0). *J* values are given in Hz. − FAB mass spectra were obtained on a Fisons VG Autospec-Q spectrometer, using *m*-nitrobenzyl alcohol or thioglycerol as matrix. − Anhydrous solvents were prepared according to standard procedures and were freshly distilled prior to use. For reasons of clarity and to reduce space, the names calix[4]arene (pentacyclo-[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene), benzo-15-crown-5 (2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxacyclopentadecine), and benzo-18-crown-6 (2,3,5,6,8,9,11,12,14,15-decahydro-1,4,7,10,13,16-benzohexaoxacyclooctadecine) have been used instead of the original IUPAC names.

**5,11,17,23-Tetra-*tert*-butyl-26,28-dihydroxy-25,27-bis(2-isothiocyanoethoxy)calix[4]arene (3):** To a solution of **2** (0.5 g, 0.68 mmol) in $CH_2Cl_2$ (10 mL) was added thiophosgene (0.15 mL, 2.04 mmol), $BaCO_3$ (0.8 g, 4.1 mmol), and $H_2O$ (3 mL). The reaction was stirred for 24 h at room temp. After filtration, $CH_2Cl_2$ (10 mL) was added and the system was extracted with $H_2O$ (10 mL). The organic phase was dried and evaporated, yielding **3** (0.535 g, 96%) as a solid: M.p. 267−270 °C (dec). − IR (KBr): $\tilde{\nu}$ = 3393, 2193, 2097, 1485, 1346, 1302, 1202, 1126, 1045, 874 cm$^{-1}$. − $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.07 (s, 4 H; ArH), 6.92 (s, 2 H; OH), 6.82 (s, 4 H; ArH), 4.25 (d, *J* = 13.0 Hz, 4 H; $ArCH_2Ar$), 4.20−4.14 (m, 8 H; 2 $OCH_2CH_2NCS$), 3.36 (d, *J* = 13.0 Hz, 4 H; $ArCH_2Ar$), 1.26, 0.97 (2 s, 36 H; 4 $Me_3C$). − $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 150.6, 149.3, 147.5, 141.8, 132.3, 127.7, 125.9, 125.3 (Ar, NCS), 73.4 ($OCH_2$), 45.1 ($CH_2NCS$), 33.9 ($CMe_3$), 31.8, 31.1 ($ArCH_2Ar$, $Me_3C$). − HR-MS (FAB+) $C_{50}H_{62}N_2O_4NaS_2$: calcd for [M + Na]$^+$ 841.4048; found. 841.4051. − $C_{50}H_{62}N_2O_4S_2$ (819.2): calcd. C 73.31, H 7.63, N 3.42, S 7.83; found C 73.30, H 8.10, N 3.53, S 8.10.

**5,11,17,23-Tetra-*tert*-butyl-25,27-bis{[(chloromethyl)carbonylamino]ethoxy}-26,28-dihydroxycalix[4]arene (4):** To a solution of **2** (0.7 g, 0.95 mmol) in AcOEt (50 mL) was added chloroacetic anhydride (0.36 g, 2.09 mmol). The reaction was kept at room temp. and monitored by TLC (AcOEt) until complete disappearance of **2** (1 h). The reaction mixture was washed with aqueous saturated $NaHCO_3$ solution (2 × 15 mL). The organic phase was dried and evaporated, giving a crude product that was purified by short column chromatography ($CH_2Cl_2$/hexane 2:1), yielding **4** (0.71 g, 84%) as a solid: M.p. 246−247 °C. − IR (KBr): $\tilde{\nu}$ = 3422, 1665, 1541, 1485, 1362, 1202 cm$^{-1}$. − $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.37 (br s, 2 H; 2 NH), 8.11 (s, 2 H, 2 OH), 7.05, 6.95 (2 s, 8 H; Ar), 4.20 (d, *J* = 13.0 Hz, 4 H; $ArCH_2Ar$), 4.12 (t, *J* = 4.7 Hz, 4 H; 2 $OCH_2$), 4.11 (s, 4 H; 2 $CH_2Cl$), 3.97 (m, 4 H; 2 $CH_2NH$), 3.39 (d, *J* = 13.0 Hz, 4 H; $ArCH_2Ar$) 1.26, 1.07 (2 s, 36 H; 4 $Me_3C$). − $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 166.9 (CO), 149.8, 148.6, 148.1, 142.6, 132.9, 127.6, 126.1, 125.6 (Ar), 75.1 ($OCH_2$), 42.7 ($NHCH_2$), 40.0 ($CH_2Cl$), 34.2, 33.9 ($Me_3C$), 32.1 ($ArCH_2Ar$), 31.7, 31.1 ($Me_3C$). − HR-MS (FAB+) $C_{52}H_{68}Cl_2N_2O_6Na$: calcd. for [M + Na]$^+$ 909.4352; found 909.4357. − $C_{52}H_{68}Cl_2N_2O_6$ (888.0): calcd. C 70.33, H 7.72, N 3.15; found C 70.15, H 7.99, N 2.87.

**1,7-(5,11,17,23-Tetra-*tert*-butyl-26,28-dihydroxy-25,27-dioxy-calix[4]arene)-3,5-diaza-4-heptanethione (5):** To a solution of **3** (0.164 g, 0.2 mmol) in Py/$H_2O$ (18:2 mL) was added triethylamine (0.1 mL). The reaction mixture was heated at 60 °C for 24 h. Evaporation and coevaporation with toluene gave a crude product that was triturated with ether/hexane (1:1), giving **5** (0.08 g, 52.5%) as a solid after filtration: M.p. 140−142 °C. − IR (KBr): $\tilde{\nu}$ = 3388, 3239, 3180, 1554, 1485, 1295, 1252, 1199, 1034 cm$^{-1}$. − $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.90 (s, 2 H; 2 OH), 7.30 (br s, 2 H; 2 NH), 7.07, 7.01 (2 s, 8 H; Ar), 4.40 (br s, 4 H; 2 $OCH_2$), 4.30 (d, *J* = 12.9 Hz, 4 H; $ArCH_2Ar$), 4.15 (br s, 4 H; 2 $CH_2NH$), 3.41 (d, *J* = 12.9 Hz, 4 H; $ArCH_2Ar$), 1.21, 1.19 (2 s, 36 H; 4 $Me_3C$). − $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 188.5 (CS), 150.0, 149.5, 148.0, 142.5, 133.5, 127.8, 126.6, 125.5 (Ar), 73.5 ($CH_2O$), 45.4 ($CH_2NH$), 34.3, 34.0 ($Me_3C$), 33.2 ($ArCH_2Ar$) 31.6, 31.3 ($Me_3C$). − HR-MS (FAB+): $C_{49}H_{64}N_2O_4NaS$: calcd. for [M + Na]$^+$ 799.4484; found. 799.4487. − $C_{49}H_{64}N_2O_4S$ (777.1): calcd. C 75.13, H 8.30, N 3.6; found C 75.3, H 8.41, N 3.44.

**25,25′,27,27′-Bis[*N*,*N*′-bis(oxyethyl)thioureido]-bis(5,11,17,23-tetra-*tert*-butyl-26,28-dihydroxycalix[4]arene) (6):** To a solution of **3** (0.082, 1 mmol) in Py (25 mL) was added **2** (0.073, 0.1 mmol). The reaction mixture was kept at room temp. for 30 h and monitored by TLC (chloroform/ether 3:1). Evaporation of the solvents gave a crude product that was triturated with MeOH to give **6** (0.093 g, 60%) as a solid: M.p. 165−167 °C. − IR (KBr): $\tilde{\nu}$ = 3385, 1637, 1545, 1475, 1298, 1201, 1037 cm$^{-1}$. − $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.65 (br s, 8 H, 4 OH; 4 NH), 7.04, 6.81 (2 s, 16 H, ArH), 4.40−4.00 (m, 24 H; 4 $OCH_2CH_2NH$, $ArCH_2Ar$), 3.26 (d, *J* = 13.0 Hz, 8 H; $ArCH_2Ar$), 1.29, 1.05 (2 s, 72 H, 8 $Me_3C$).− $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 149.5, 148.9, 147.8, 142.8, 132.5, 127.9, 125.9, 125.3(Ar), 77.3 ($CH_2O$), 45.3 ($CH_2NH$), 34.1, 34.0 ($Me_3C$), 31.7, 31.1 ($ArCH_2Ar$, $Me_3C$). − HR-MS (FAB+) $C_{98}H_{128}N_4O_8S_2Na$: calcd. for [M + Na]$^+$ 1554.928 found 1554.933. − $C_{98}H_{128}N_4O_8S_2$ (1554.23): calcd. C 75.73, H 8.31, N 3.61, S 4.12; found C 75.30, H 8.58, N 3.66, S 4.08.

**General Procedure for the Synthesis of Bis(crown ether)-Substituted Calix[4]arenes 7−9:** To a solution of **3** (0.146 g, 0.178 mmol) in AcOEt (5 mL) was added the corresponding amino crown ether (0.39 mmol) and triethylamine (0.05 mL). The reaction was monitored by TLC ($CH_2Cl_2$/MeOH 10:1) until complete disappearance of the starting materials (24 h for **7** and **8**, and 3 h for **9**). AcOEt (50 mL) was then added and the system was washed with 5% HCl (25 mL) and $H_2O$ (25 mL). The organic phase was dried and evaporated, giving a crude product.

**5,11,17,23-Tetra-*tert*-butyl-25,27-bis{[*N*′-(4′-benzo-15-crown-5)-thioureido]ethoxy}-26,28-dihydroxycalix[4]arene (7):** Column chromatography of the crude product ($CH_2Cl_2$/hexane 7:1) gave **7** (0.231 g, 94%) as a solid: M.p. 134−137 °C. − IR (KBr): $\tilde{\nu}$ = 3383, 1560, 1540, 1508, 1240, 1132 $cm^{-1}$. − $^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.89 (s, 2 H; 2 OH), 7.80 (br s, 2 H; 2 × NH), 7.73 (s, 2 H; 2 × NH), 6.93 (s, 4 H; ArH), 6.90 (s, 4 H; ArH), 6.75 (d, $J$ = 2.2 Hz, 2 H; $HNC_6H_3$), 6.64 (dd, $J$ = 8.4, 2.2 Hz, 2 H; $HNC_6H_3$), 6.27 (d, $J$ = 8.4 Hz, 2 H; $HNC_6H_3$), 4.14−3.71 [m, 44 H; 2 × $OCH_2CH_2N$, 2 × $-O(CH_2CH_2O)_4-$, $ArCH_2Ar$], 3.28 (d, $J$ = 13.1 Hz, 4 H; $ArCH_2Ar$, 1.21, 1.08 (2 s, 36 H; 4 × $Me_3C$). − $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 182.3 (CS), 149.6, 149.4, 148.5, 148.2, 147.9, 142.3, 133.1, 128.3, 127.8, 125.9, 125.5, 119.3, 113.4, 112.4 (Ar, $C_6H_3$), 75.2, 71.3, 71.2, 70.7, 69.6, 69.5, 69.0, 68.5 [$OCH_2CH_2N$, $-O(CH_2CH_2O)_4-$], 46.3 ($CH_2N$), 34.2, 33.8 ($Me_3C$), 32.1, 31.5 ($ArCH_2Ar$), 31.7 and 31.1 ($Me_3C$). − HR-MS (FAB+) $C_{78}H_{104}N_4O_{10}NaS_2$: calcd. for [M + Na]$^+$ 1407.689; found 1407.686. − $C_{78}H_{104}N_4O_{14}S_2$ (1385.81): calcd. C 67.6, H 7.56, N 4.04; found C 67.12, H 7.81, N 3.91.

**5,11,17,23-Tetra-*tert*-butyl-25,27-bis{[*N*′-(4′-benzo-18-crown-6)-thioureido]ethoxy}-26,28-dihydroxycalix[4]arene (8):** Column chromatography of the crude product ($CH_2Cl_2$:hexane 7:1) gave **8** (0.257 g, 94%) as a solid (98%): M.p. 142−144 °C. − IR (KBr): $\tilde{\nu}$ = 3300, 1558, 1541, 1516, 1508, 1238, 1126 $cm^{-1}$. − $^1H$ NMR (300 MHz, $CDCl_3$): δ = 8.07 (s, 2 H; 2 OH), 7.90 (bt, $J$ = 5.5 Hz, 2 H; 2 $HNCH_2$), 7.71 (s, 2 H; 2 $NHC_6H_3$), 6.93 (s, 4 H; ArH), 6.92 (s, 4 H; ArH), 6.77 (d, $J$ = 2.2 Hz, 2 H; 2 $C_6H_3$), 6.61 (dd, $J$ = 8.5, 2.2 Hz, 2 H;2 $C_6H_3$), 6.20 (d, $J$ = 8.5 Hz, 2 H; 2 $C_6H_3$), 4.17 (m, 4 H; 2 $HNCH_2$), 4.08 (m, 4 H; 2 $OCH_2CH_2N$), 4.00-3-97, 3.87−3.83, 3.79−3.71, 3.66−3.56 [4 m, 44 H; 2 $-O(CH_2CH_2O)_5-$, $ArCH_2Ar$], 3.30 (d, $J$ = 13.0 Hz, 4 H; $ArCH_2Ar$), 1.21, 1.10 (2 s, 36 H; 4 $Me_3C$). − $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 182.4 (CS), 149.6, 148.6, 148.0, 142.3, 133.3, 127.9, 126.0, 125.6, 119.3, 112.9, 112.2 (Ar, $C_6H_3$), 75.4, 71.0, 70.9, 70.8, 70.7, 69.6, 69.0, 68.4 [$OCH_2CH_2N$, $-O(CH_2CH_2O)_5-$], 46.6 ($CH_2N$), 34.2, 33.3 ($Me_3C$), 32.1 ($ArCH_2Ar$), 31.7, 31.2 ($Me_3C$). − HR-MS (FAB+) $C_{82}H_{112}N_4O_{16}NaS_2$: calcd. for [M + Na]$^+$ 1495.7406; found 1495.7412. − $C_{82}H_{112}N_4O_{16}S_2$ (1473.92): calcd. C 66.82, H 7.66, N 3.80, S 4.35; found C 66.63, H 7.89, N 3.71, S 3.75.

**5,11,17,23-Tetra-*tert*-butyl-26,28-dihydroxy-25,27-bis{[*N*′-(2-methyl-18-crown-6)thioureido]ethoxy}calix[4]arene (9):** Treatment of the crude product with ether:hexane yielded **9** (0.242 g, 97%) as an amorphous solid: M.p. 70−72 °C. − $^1H$ NMR (300 MHz, $CDCl_3$): δ 8.15 (br s, 2 H, 2 NH) 7.05 (br s, 2 H, 2 NH), 7.03 (s, 6 H, 2 OH, ArH), 6.89 (s, 4 H, ArH), 4.23 (d, $J$ = 13.0 Hz, 4 H; $ArCH_2Ar$), 4.18 (m, 4 H; 2 $CH_2O$), 3.77−3.44 [m, 54 H; 2 $CH_2NHC(S)NHCH_2$, 2 × $(CH_2CH_2O)_5CH_2CHO$], 3.36 (d, 4 H, $J$ = 12.8 Hz, 2 H; $ArCH_2Ar$), and 1.24, 1.04 (2 s, 36 H; 4 $Me_3C$). − $^{13}C$ NMR (300 MHz, $CDCl_3$): δ 183.0 (CS), 149.5, 149.0, 147.7, 142.7, 132.8, 128.0, 125.9, 125.5 (Ar), 77.0, 75.5, 71.7, 70.7, 70.4, 70.2, 68.9 [$(CH_2CH_2O)_5CH_2CHO$, $OCH_2CH_2N$], 45.4, 44.5 ($OCH_2CH_2N$, $CH_2N$), 34.1, 33.9 ($Me_3C$), 32.0, 29.7 ($ArCH_2Ar$), 31.7, 31.0 ($Me_3C$). − HR-MS (FAB+) $C_{76}H_{116}N_4O_{16}NaS_2$: calcd. for [M + Na] $^+$ 1427.8; found 1427.9.

**1,11-(5,11,17,23-Tetra-*tert*-butyl-26,28-dihydroxy-25,27-dioxycalix-[4]arene)-6-thia-3,9-diaza-4,8-undecanedione (10):** A solution of **4** (0.1 g, 0.113 mmol) and $Na_2S \cdot 9\,H_2O$ (0.02 g, 0.250 mmol) in MeOH (60 mL) was refluxed for 24 h. Evaporation of the solvent gave a crude product that was dissolved in AcOEt (50 mL) and washed with $H_2O$ (2 × 10 mL). The organic phase was dried and evaporated, giving a crude product that was purified by column chromatography (AcOEt) to yield **10** (0.045 g, 47%) as a solid: M.p. 297−230° C (dec) (from ether/hexane). − IR (KBr): $\tilde{\nu}$ = 3424, 3298, 1672, 1650, 1560, 1485, 1461, 1362, 1202, 1103 $cm^{-1}$. − $^1H$ NMR (300 MHz): δ = 8.25 (br s, 2 H; 2 NH), 7.81 (s, 2 H; 2 OH), 7.08, 6.94 (2 s, 8 H; Ar), 4.23 (d, $J$ = 13.0 Hz, 4 H; $ArCH_2Ar$), 4.15 (t, $J$ =4.4 Hz, 4 H; 2 $OCH_2$), 3.97 (m, 4 H; 2 $CH_2N$), 3.45 [s, 4 H; $(CH_2)_2S$], 3.40 (d, $J$ = 13.0 Hz, 4 H; $ArCH_2Ar$), 1.28, 1.06 (2 s, 36 H; 4 $Me_3C$). − $^{13}C$ NMR ($CDCl_3$, 75 MHz): δ = 168.6 (CO), 149.9, 148.8, 147.9, 142.6, 132.7, 127.8, 126.0, 125.5, (Ar), 75.1 ($OCH_2$), 40.2, 37.5 ($CH_2NHCOCH_2$), 34.2, 34.0 ($Me_3C$), 32.1, 32.0 ($ArCH_2Ar$), 31.7, 31.1 ($Me_3C$). − HR-MS $C_{52}H_{68}N_2O_6NaS$: calcd. for [M + Na]$^+$ 871.4696; found. 871.4674. − $C_{52}H_{68}N_2O_6S$ (849.18): calcd. C 73.55, H 8.07, N 3.30; found C 73.14, H 8.30, N 3.22.

**5,11,17,23-Tetra-*tert*-butyl-26,28-dihydroxy-25,27-bis{[(thiocyanomethyl)carbonylamino]ethoxy}calix[4]arene (11):** A solution of **4** (0.420 g, 0.474 mmol) and KSCN (0.230 g) in dry acetone (25 mL) was refluxed for 18 h. After cooling, the solvent was evaporated, yielding a crude product that was dissolved in AcOEt (75 mL) and washed with $H_2O$ (10 mL). The organic phase was dried and evaporated, giving a crude product that was purified by column chromatography (AcOEt/hexane 1:1) to give **11** (0.378 g, 85.5%) as a solid: M.p. 240−242 °C. − $^1H$ NMR (300 MHz, $CDCl_3$): δ = 8.91 (br s, 2 H; 2 NH), 8.68 (s, 2 H; 2 OH), 7.07, 7.02 (2 s, 8 H; Ar), 4.23 (d, $J$ = 13.1 Hz, 4 H; $ArCH_2Ar$), 4.18−4.10, 4.01−3.93 (2 m, 8 H; 2 $NHCH_2CH_2O$), 3.78 (s, 4 H; 2 $CH_2S$), 3.44 (d, $J$ = 13.1 Hz, 4 H; $ArCH_2Ar$), 1.24, 1.12 (2 s, 36 H;4 $Me_3C$). − $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 165.6 (CO), 148.6, 143.8, 133.2, 127.9, 126.4, 126.1 (Ar), 112.0 (SCN), 75.7 ($OCH_2$), 40.3, 37.3 ($CH_2NHCOCH_2S$), 34.3, 34.0 ($Me_3C$), 32.3 ($ArCH_2Ar$), 31.6, 31.1 ($Me_3C$). − HR-MS (FAB+) $C_{54}H_{68}N_4O_6NaS_2$: calcd. for [M + Na]$^+$ 955.4478; found 955.4476.

**5,11,17,23-Tetra-*tert*-butyl-25,27-bis{[(acetylthiomethyl)-carbonylamino]ethoxy}-26,28-dihydroxycalix[4]arene (12):** A solution of **4** (0.1 g, 0.113 mmol) and KSAc (0.150 g) in dry acetone (10 mL) was refluxed for 1 h. After cooling, the solvent was evaporated, yielding a crude product that was dissolved in AcOEt (50 mL) and washed with $H_2O$ (10 mL). The organic phase was dried and evaporated, giving a crude product that was purified by column chromatography (AcOEt/hexane 3:1) to produce **12** (0.08 g, 73%) as a solid: M.p. 220−222 °C (from ether/hexane). − IR (KBr): $\tilde{\nu}$ = 3410, 3335, 1707, 1651, 1532, 1485, 1362 $cm^{-1}$. − $^1H$ NMR (300 MHz, $Cl_3CD$): δ = 8.69 (s, 2 H; 2 OH), 8.51 (t, $J$ = 5.4 Hz, 2 H; 2 NH), 7.07, 7.02 ( 2 s, 8 H; ArH), 4.27 (d, $J$ = 13.0 Hz, 4 H; $ArCH_2Ar$), 4.14 (t, $J$ = 4.5 Hz, 4 H; 2 $OCH_2$), 3.93 (m, 4 H; 2 $CH_2N$), 3.72 (s, 4 H; 2 $CH_2S$), 3.40 (d, $J$ = 13.0 Hz, 4 H; $ArCH_2Ar$), 2.09 (s, 6 H; AcS), 1.23, 1.13 (2 s, 36 H; $Me_3C$). − $^{13}C$ NMR (75 MHz, $Cl_3CD$): δ = 194.5 [C(O)S], 168.3 [C(O)N], 149.5, 148.7, 148.3, 143.1, 133.2, 127.8, 126.2, 125.8 (Ar), 75.8 ($OCH_2$), 39.9 ($CH_2N$), 34.3, 33.9 ($Me_3C$), 33.2, 32.3 ($CH_2S$, $ArCH_2Ar$), 31.6, 31.2 ($Me_3C$), 29.8 (MeC(O)S). − HR-MS (FAB+) $C_{56}H_{74}N_2O_8NaS_2$: calcd. for [M + Na]$^+$ 989.4784; found 989.4773. − $C_{56}H_{74}N_2O_8S_2$ (967.33): calcd. C 69.53, H 7.71, N 2.89, S 6.63; found C 69.15, H 7.35, N 2.98, S 6.54.

**5,11,17,23-Tetra-*tert*-butyl-26,28-dihydroxy-25,27-bis{[(thiomethyl)carbonylamino]ethoxy}calix[4]arene (13):** To a solution of **12** (0.110 g, 0.114 mmol) in MeOH (25 mL) was added a 1 N NaOMe solution in MeOH until pH 9−10 was reached. The reaction mixture was kept at room temp. for 1 h. Addition of AcOH (0.25 mL) was followed by evaporation of the solvent, yielding a crude product that was dissolved in $CH_2Cl_2$ (50 mL) and washed with $H_2O$ (5 mL). The organic phase was dried and evaporated, giving **13** (0.095 g, 95%) as a solid foam: $^1H$ NMR (300 MHz, $Cl_3CD$): δ = 8.43 (t, $J$ = 5.5 Hz, 2 H; 2 NH), 8.29 (s, 2 H; 2 OH), 7.01, 6.66 (2 s, 8 H; ArH), 4.17 (d, $J$ = 13.0 Hz, 4 H; $ArCH_2Ar$), 4.07 (t, $J$ =

4.6 Hz, 4 H; 2 OCH$_2$), 3.91 (m, 4 H; 2 CH$_2$N), 3.62 (d, $J$ = 13.0 Hz, 4 H; ArC$H_2$Ar), 3.24 (d, $J$ = 8.4 Hz, 4 H; 2 C$H_2$SH), 2.09 (t, $J$ = 8.4 Hz, 2 H; 2 SH), 1.21, 1.04 (2 s, 36 H; 4 Me$_3$C). − $^{13}$C NMR (75 MHz, Cl$_3$CD): δ = 170.2 (CO), 149.3, 148.5, 1498.1, 149.9, 132.8, 127.7, 126.0, 125.8 (Ar), 75.4 (CH$_2$O), 39.8 (CH$_2$N, CH$_2$S), 34.1, 33.8 (Me$_3$C), 32.1 (ArCH$_2$Ar), 31.6, 31.1 ($Me_3$C).

**1,12-(5,11,17,23-Tetra-*tert*-butyl-26,28-dihydroxy-25,27-dioxycalix[4]arene)-3,10-diaza-6,7-dithia-4,9-dodecanedione (14):** Preparation of **13** as described above, followed by column chromatography (AcOEt), yielded **14** (60% from **12**) as a solid: M.p. 260−262 °C. − IR (KBr): $\tilde{\nu}$ = 3426, 1655, 1551, 1485, 1204 cm$^{-1}$. − $^1$H NMR (300 MHz, Cl$_3$CD): δ = 7.82 (t, $J$ = 5.4 Hz, 2 H; 2 NH), 7.50 (s, 2 H; 2 OH), 7.07, 6.86 (2 s, 8 H; ArH), 4.22 (d, $J$ = 13.0 Hz, 4 H; ArC$H_2$Ar), 4.13 (t, $J$ = 3.7 Hz, 4 H; 2 OCH$_2$), 4.03 (m, 4 H; 2 CH$_2$N), 3.50 (s, 4 H; 2 CH$_2$S), 3.38 (d, $J$ =13.0 Hz, 4 H; ArC$H_2$Ar), 1.29, 0.99 (2 s, 36 H; 4 Me$_3$C). − $^{13}$C NMR (75 MHz, Cl$_3$CD): δ = 169.1 (CON), 149.9, 149.2, 147.6, 132.6, 132.5, 127.7, 125.9, 125.5 (Ar), 75.7 (OCH$_2$), 42.5, 40.3 (CH$_2$N, CH$_2$S), 33.9 (Me$_3$$C$), 31.8 (ArCH$_2$Ar), 31.7, 31.0 ($Me_3$C),. − HR-MS (FAB+) $C_{52}H_{68}N_2O_6NaS_2$: calcd. for [M + Na]$^+$ 903.4416; found 903.4412. − $C_{52}H_{68}N_2O_6S_2$ (881.24): calcd. C 70.87, H 7.78, N 3.18; found C 70.98, H 7.41, N 3.41.

**Bis(5,11,17,23-tetra-*tert*-butyl-26,28-dihydroxycalix[4]arene)-25,25′,27,27′-bis{[(oxyethylamino)carbonylmethyl]sulfide} (15):** To a solution of **4** (0.050 g, 0.056 mmol) and **12** (0.055 g, 0.057 mmol) in dry MeOH (75 mL) was added 1 N NaOMe solution in MeOH (2 mL). The reaction mixture was kept at room temp. for 24 h. AcOH (1 mL) was added and then the solvent was evaporated, giving a crude product that was dissolved in CH$_2$Cl$_2$ (50 mL) and washed with H$_2$O (5 mL). The organic phase was dried and evaporated. The crude product obtained was purified by column chromatography (AcOEt/hexane 5:1), yielding **15** (0.050 g, 52%) as a solid: M.p. 285−288 °C. − IR (KBr): $\tilde{\nu}$ = 3474, 3350, 3277, 1736, 1650, 1529, 1485, 1465, 1286, 1203 cm$^{-1}$. − $^1$H NMR (300 MHz, CDCl$_3$): δ = 8.75 (t, $J$ = 5.4 Hz, 4 H; 4 NH), 7.17, 6.85 (2s, 16 H; ArH), 7.14 (s, 4 H; 4 OH), 4.29 (d, $J$ = 13.0 Hz, 8 H; ArC$H_2$Ar), 4.10 (m, 8 H; 4 CH$_2$O), 3.98 (m, 8 H; 4 CH$_2$N), 3.64 (s, 8 H; 4 CH$_2$S), 3.41 (d, $J$ = 13.0 Hz, 8 H; ArC$H_2$Ar), 1.41, 1.01 (2s, 72 H; 8 Me$_3$C). − $^{13}$C NMR 170.0, 150.4, 148.9, 147.3, 141.8, 132.3, 127.9, 125.5, 125.2, 75.0, 39.3, 37.4, 34.0, 33.9, 31.8, 31.2, 31.0. − HR-MS (FAB+) $C_{104}H_{136}N_4O_{12}NaS_2$: calcd. for [M + Na]$^+$ 1719.9493. − Found 1719.95.

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