Urea-Derivatized *p-tert*-Butylcalix[4]arenes: Neutral Ligands for Selective Anion Complexation

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Functionalization of the lower rim of *p-tert*-butylcalix[4]arene with four (thio)urea groups, results in a class of receptors selective for spherical *anions* that are bound *exclusively through hydrogen bonding*. ^{1}H NMR spectroscopy in $CDCl_3$ reveals a selectivity for Cl^- over Br^- and I^-. The stoichiometry is 1:1 in all cases as was confirmed by Job plots. The association constants are strongly dependent on the nature of the substituent at the urea moiety. The bidentate phenylurea derivative **9** shows the strongest complexation ($K_{ass.}$ $Cl^- = 7.1 \times 10^3$ M^{-1}) and the largest selectivity for Cl^-.

Introduction

Selective binding of ions is an important aspect of ion detection and ion transport. In the framework of our research program on membrane transport[1] and sensors based on chemically modified field effect transistors (CHEMFETS)[2] we have developed various receptors with selectivity for cations based on modified calix[4]arenes.[2] Selective complexation of anions is more demanding than that of cations in view of the higher free energies of solvation of anions and the frequently occuring pH dependency of anion complexation. Generally, the ligands that have been developed for anion complexation in organic solvents can be divided into two classes. The first class consists of positively charged ligands, e.g. with ammonium[3] or guanidinium moieties.[4] The anion binding is achieved by electrostatic interactions as is the case for binding of ATP by polyammonium receptors developed by Lehn et al.[3c,5] and binding of carboxylates using guanidinium-based receptors developed by Schmidtchen and co-workers.[4c,d] Hydrogen bonding can provide additional binding energy as was shown for the binding of Cl^-, F^-, Br^-, and N_3^-,[3a,d], zwitterionic ω-amino carboxylates,[3b] bisphenylphosphate and phosphoric acid,[3d] and for guanidinium-based receptors in the binding of carboxylates[4b,5] and cAMP.[4a,5] Recently, receptor molecules in which ferrocene or cobalticium moieties are combined with amide moieties have been used by de Beer et al.[6] for complexation of Cl^-, Br^-, NO_3^-, and HSO_4^-. These systems also are based on mutual electrostatic interactions and hydrogen bonding.

The second class of anion receptors are the neutral ligands, of which most have Lewis acid centers, like Si,[7,8] B,[8,9] Sn,[10] or Hg,[11] covalently incorporated. In these systems the complexation is based on the interaction between the Lewis acid centers and the anion. Also in these systems additional hydrogen bonding can provide further recognition sites, as was shown for uranyl–salophens complexes functionalized with pendant amide groups developed earlier in our group.[12] These anion receptors exhibit high selectivities for $H_2PO_4^-$.

From crystal structures of sulfate[13] and phosphate[14] binding proteins it is known that nature can bind anions with high selectivity, exclusively by the formation of hydrogen bonds. Prokaryotic, periplasmic phosphate and sulfate binding proteins, exhibit selectivities of more than 10^5 for binding of phosphate over sulfate and of sulfate over phosphate, respectively.[15] Previously, we have reported that selective complexation of $H_2PO_4^-$ over Cl^- and HSO_4^- can be achieved by synthetic neutral tridentate sulfonamide receptors derived from tris(aminoethyl)-

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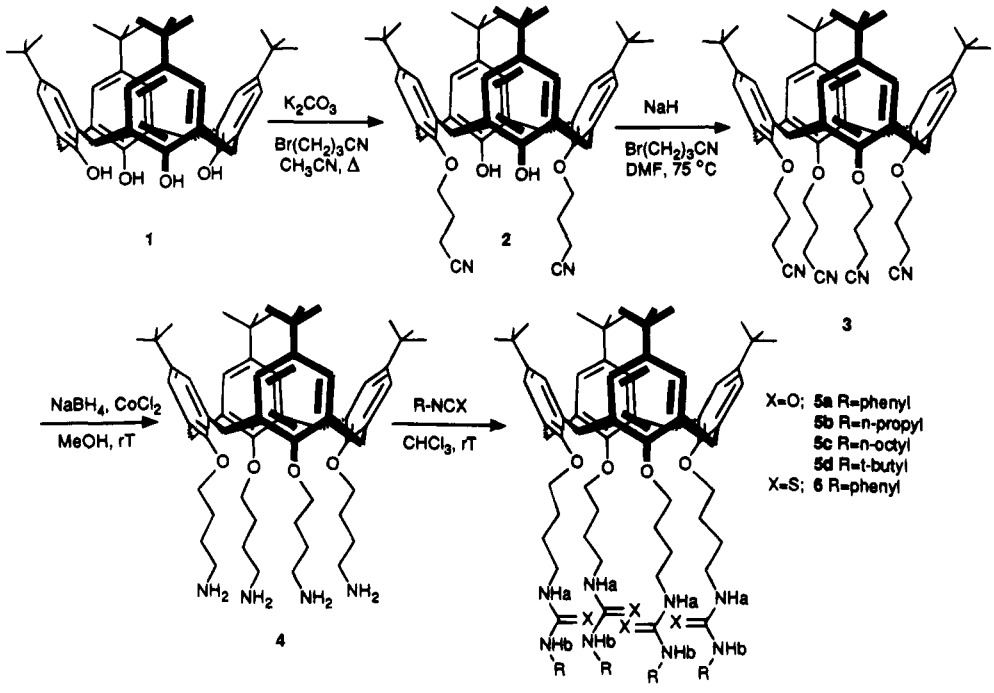
Scheme 1



amine (TREN)[16] and that four sulfonamide groups positioned at the upper rim of calix[4]arene are well suited for complexation of HSO_4^-.[17] Both systems *complex anions exclusively through hydrogen bonding*. As an extension of this work the anion binding and recognition properties of preorganized urea moieties have been explored. The urea moiety is a powerful hydrogen bond donor as was recently shown by Hamilton et al.[18,19a] and Rebek et al.[19b] in the complexation of (di)carboxylate anions.

Here, we report the synthesis and complexation behavior of various *p-tert*-butylcalix[4]arenes **5a–d**, **6**, and **9** modified with substituted (thio)urea groups at the lower rim via an alkyl spacer. These novel neutral anion receptors also bind anions exclusively through hydrogen bonding. The stoichiometry of binding is 1:1 and the selectivity is strongly dependent on the number of urea units and the nature of the substituents at the urea moiety.

Results and Discussion

Due to its preorganized structure *p-tert*-butylcalix[4]arene[20] is well suited as a molecular building block for the positioning of ligating groups.[21] Modification of the lower rim of *p-tert*-butylcalix[4]arene with four urea moieties via a spacer would lead to a ligand possessing eight hydrogen-bond donor sites directed to one face. According to molecular modeling, a butylene spacer is able to orient the four urea moieties properly to create a cavity suitable for the complexation of anions.

The key intermediate for the synthesis of the urea calix[4]arenes is the tetrakis[(aminobutyl)oxy]calix[4]arene **4**, which was obtained by the borohydride reduction of the tetrakis[(cyanopropyl)oxy]calix[4]arene **3**. The tetrakis[(cyanopropyl)oxy]calix[4]arene **3** was prepared in two steps from *p-tert*-butylcalix[4]arene **1** (Scheme 1).

Reaction of *p-tert*-butylcalix[4]arene with 10 equiv of Na_2CO_3 and 4-bromobutyronitrile in refluxing CH_3CN gave only the disubstituted 25,27-bis[(cyanopropyl)oxy]-26,28-dihydroxy-*p-tert*-butylcalix[4]arene **2** in 68% yield after trituration with MeOH. When the reaction was performed with 8 equiv of NaH and 4-bromobutyronitrile in DMF at 75 °C for prolonged time a mixture of the starting material **1**, the disubstituted calix[4]arene **2**, and the desired tetrakis[(cyanopropyl)oxy]calix[4]arene **3** was obtained. However, compound **2** could be alkylated completely using 10 equiv of NaH and 4-bromobutyronitrile in DMF at 75 °C, yielding calix[4]arene **3** in 52% yield. The ^1H NMR of **3** shows a pair of doublets at 4.27 and 3.22 ppm for the bridging methylene protons, and the ^{13}C NMR spectrum showed a triplet at 31.0 ppm for the corresponding carbon atoms, indicating that the cone conformation was retained.[22,23] Reduction of the cyano groups with $NaBH_4/CoCl_2$[24] in MeOH yielded the tetrakis[(aminobutyl)oxy]calix[4]arene **4** in 84% yield. Addition of 4 equiv of alkyl- or aryl(thio)isocyanate in $CHCl_3$ to tetrakis[(aminobutyl)oxy]calix[4]arene **4** at room temperature[25] gave the corresponding aryl- or alkyl(thio)urea derivatives in 40–76% yield.

The bidentate phenylurea derivative **9** was synthesized as depicted in Scheme 2. The hydroxyl groups of com-

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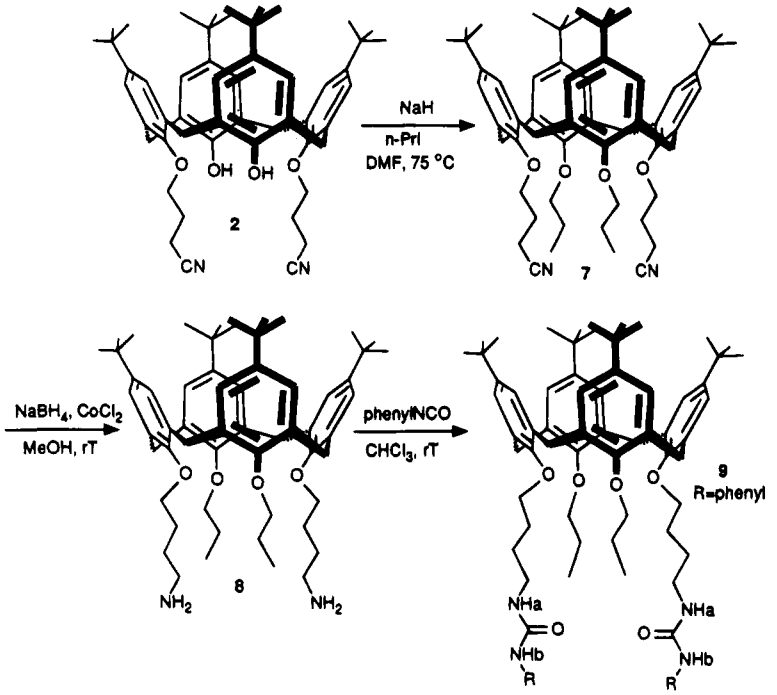
Scheme 2



pound **2** were propylated using NaH/*n*-propyl iodide in DMF. Under these conditions the cone conformation of the tetrasubstituted calix[4]arene is obtained.[26] Reduction of the cyano groups and reaction with phenyl isocyanate were performed as described above, yielding the phenylurea derivative **9** in 35% yield.

It is well known that intermolecular association in N,N′-diarylated urea derivatives[27] and N,N′-dialkylated urea derivatives[28] occurs by the formation of two-centered hydrogen bonds. However, according to molecular modeling, the NH^b protons in the urea calix[4]arene derivatives are well positioned for intramolecular hydrogen bonding to the neighboring carbonyl groups, which points the NH^a protons toward the neighboring R group. In the case of R = phenyl (**5a**) the NH^a protons then have an edge-to-face interaction with the phenyl rings, explaining the upfield shift of the NH^a protons (0.45 ppm) which is observed for this compound as compared with the n-propylurea derivative **5b**.

Since it is known that Cl^- and Br^- anions are good hydrogen bond acceptors[29] and the hydrogen bond donor sites of the urea moiety act as hard Lewis acids[30] it was expected that the addition of the hard Lewis bases Cl^- and Br^- would lead to complexation. In the negative FAB mass spectrum of 1:1 mixtures of **5a** with Cl^-, Br^-, and I^- (prepared by evaporating a 1:1 mixture of host and the corresponding tetrabutylammonium salts in $CHCl_3$) a peak corresponding to $[\mathbf{5a} + Cl^-]^-$, $[\mathbf{5a} + Br^-]^-$, and $[\mathbf{5a} + I^-]^-$ was observed in addition to the peak of the free ligand. In ^1H NMR experiments a downfield shift of all NH protons was observed upon addition of tetrabutylammonium salts of Cl^-, Br^-, I^-, CN^-, and SCN^- to hosts **5a–d**, **6**, and **9**. The ^1H NMR titration curve of the titrations of Cl^-, Br^-, and I^- to host **5a** is depicted in Figure 1. In all cases the stoichiometry is 1:1 as was confirmed by Job plots[31] (see for an example Figure 2). The association constants of the various anion receptors were determined by a nonlinear regression program[32] and are summarized in Table 1.

The data in Table 1 show that the association constant for anion binding of the various calix[4]arene derivatives is strongly dependent on the nature of the substituent at the urea moiety. Generally, the host compounds show a preference for the anions in the order of $Cl^- > Br^- > CN^-$ and only limited binding affinity for I^- and SCN^-. None of the urea derivatives show complexation with F^- and $H_2PO_4^-$ ions.

Especially in the case of phenylurea derivative **5a** and bidentate phenylurea derivative **9** the change in chemical shift upon the addition of anions is large. Addition of 1 equiv of Bu_4NCl causes a downfield shift of 0.68 ppm for NH^a and 0.91 ppm for NH^b for compound **5a** and a downfield shift of 1.09 ppm for NH^a and 1.38 ppm for NH^b for compound **9**. Also, a small downfield shift for the ortho protons of the phenyl rings and small upfield shifts of the meta and para protons of the phenyl groups are observed, which may be attributed to an increased electron density in the phenyl rings due to the presence of the anion.

Phenylurea derivative **5a** shows a relatively strong association with Cl^- and only very weak complexation with I^- and SCN^-. The latter may be attributed to the soft nature of these anions. The selectivity of Cl^- over Br^- and CN^- may be attributed to the stronger hydrogen bond accepting properties of Cl^- and the higher complementarity of the cavity of **5a** for Cl^-, respectively. Although F^- is a very strong hydrogen bond acceptor, no complexation is observed. Molecular modeling shows

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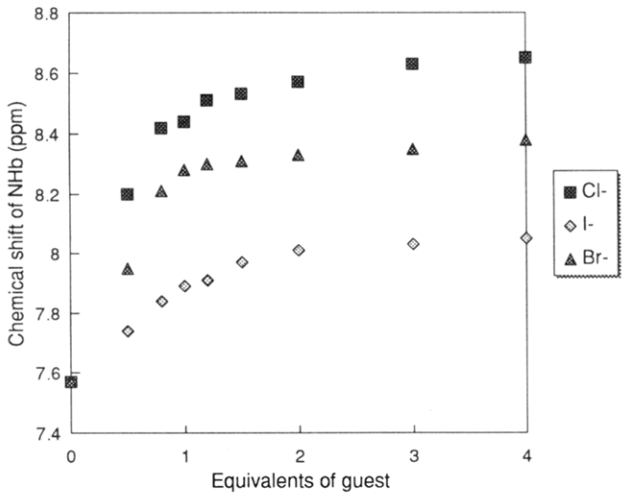

Figure 1. Titration curve of tetraphenylurea calix[4]arene **5a** with Bu_4NCl, Bu_4NBr, and Bu_4NI in $CDCl_3$. Concentration host is 5 mM.

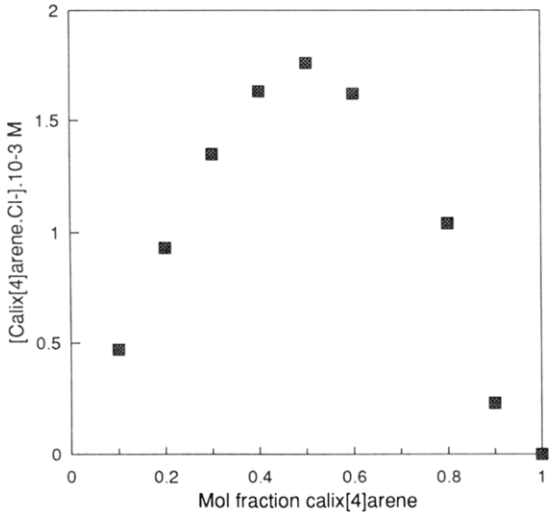

Figure 2. Job plot of the titration of 5 mM Bu_4NCl in $CDCl_3$ with 5 mM tetraphenylurea calix[4]arene **5a** in $CDCl_3$.

Table 1. $K_{ass.}$ Values (M^{-1}) of Urea-Derivatized *p-tert*-Butylcalix[4]arenes

compd	Cl^- [a]	Br^-	I^-	CN^-	SCN^-
5a	2660	1735	<25	855	<25
5b	<25	<25	<25	<25	<25
5c	285	450	–	550	–
5d	2015	1225	–	80	–
6	335	575	<25	855	<25
9	7105	2555	605	1115	<25

[a] Tetrabutylammonium salts. Concentration host is 5 mM in $CDCl_3$. Concentration guest is 5 mM in $CDCl_3$. Estimated error <5%.

that the tetrahedral $H_2PO_4^-$ is too large to fit into the cavity. Moreover, the hydrogen bond donor and acceptor sites of this anion are not complementary with the hydrogen bond donor sites in the cavity.

For the n-propylurea derivative **5b** only weak binding of anions is observed. The NH protons of the free host **5b** show almost no change in chemical shift when 0.5 equiv of Bu_4NCl are added, and addition of 1 equiv of Bu_4NCl causes only a downfield shift of 0.11 and 0.12 ppm for NH^b and NH^a, respectively. The weak anion binding ability of **5b** is most likely due to the fact that this compound, having relatively small propyl substituents at the urea moieties, forms intra- and intermolecular hydrogen bonds to a high degree, which must be disrupted upon anion complexation.[33,34]

For the purpose of membrane transport studies[35] the more lipophilic tetrakis(n-octylurea)calixarene **5c** and tetrakis(*tert*-butylurea) calixarene **5d** were synthesized. Both compounds show no complexation of I^- and SCN^- anions. Compound **5c** shows only weak complexation and some selectivity for $CN^- > Br^- > Cl^-$. However, the *tert*-butylurea compound **5d** shows strong complexation of Cl^- and Br^- and weak complexation of CN^-. Molecular models show that the bulky *tert*-butyl groups hinder the formation of intra- and intermolecular hydrogen bonding, thus creating a cavity more apt to bind a guest anion. The selectivity is more governed by geometry than by size, since large differences in binding constants were observed for Cl^- and CN^-, having approximately the same size (Cl^-: 1.81 Å; CN^-: 1.82 Å) but different geometry.

In an attempt to further increase the strength of the anion complexation the phenyl*thio*urea derivative **6** was synthesized. Due to the increased acidity of the NH protons of thiourea compared to urea (thiourea pK_a = 21.0; urea pK_a = 26.9),[36] the anion complexation was expected to be stronger. The increased acidity is evident from the ^1H NMR spectrum of **6** where the NH^b protons are shifted 0.19 ppm and the NH^a proton 0.63 ppm to lower field compared to the urea analogue **5a**. However, only weak complexation and selectivity is observed for **6**. A modest selectivity for CN^- over Cl^- and Br^- is present and no complexation of I^- and SCN^- is observed. The reason for the weaker anion binding properties of **6** may be that the enhanced hydrogen donating ability of the thiourea groups more strongly promotes the competing intra- and intermolecular hydrogen bonding, resulting in decreased anion binding affinity.

The binding properties of bidentate phenylurea **9** were studied in order to evaluate the influence of the number of hydrogen bond donor sites of the receptors. Two counteracting effects may play a role. First derivative **9** is less preorganized than tetrakis(phenylurea) compound **5a**, which may cause a decrease in association constant. Second, for bidentate phenylurea derivative **9** the self-association of the urea moieties[27,28] will be reduced which may give rise to a higher association constant with guest species. The changes in chemical shifts upon addition of anions are larger for the bidentate phenylurea **9** than for tetrakis(phenylurea) **5a**. Addition of 1 equiv of Bu_4NCl shifts the NH^b proton of **5a** 0.91 ppm and that of **9** 1.31 ppm downfield. Although compound **9** has four hydrogen bond donor sites less, the association constants are significantly higher and the selectivity for Cl^- over Br^- and CN^- is increased. Since less self-complementary urea moieties are present, the extent of intra- and intermolecular hydrogen bond association is much lower in the bidentate phenylurea derivative **9** than in the tetrakis(phenylurea) derivative **5a**. As a consequence, the disruption of self-associative hydrogen bonds is less pronounced for **9**, making anion complexation energeti-

(33) An example of self-association of calix[4]arenes at the upper rim functionalized with pyridone moieties has been described: Van Loon, J.-D.; Janssen, R. G.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron Lett.* **1992**, *34*, 5125.

(34) The self-association of compounds **5a**–**e**, **6**, and **9** is currently under investigation.

(35) The work on membrane transport studies will be reported later.

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cally more favorable. The lower degree of hydrogen bonding of **9** is also reflected in the large difference in chemical shift of the NH^b protons of the anion-free and anion-complexed form of **9** compared to the difference noted with **5a**. In the presence of 9 equiv of Bu_4NCl (almost complete complexation of the host) the change in chemical shift is 0.93 ppm for **5a** and 1.62 ppm for **9**.

Conclusions

We have synthesized a new class of neutral ligands which are able to bind anions in a 1:1 stoichiometry exclusively through hydrogen bonding. A good selectivity for spherical anions is obtained, in the order $Cl^- > Br^- > I^-$. Only moderate complexation of CN^-, weak complexation of SCN^-, and no binding with F^- and $H_2PO_4^-$ is observed. The use of these ligands as carriers for anion transport of spherical anions in membranes and as anion receptors in ion-selective membranes for ion sensing are currently under investigation.

Experimental Section

Melting points were determined with a Reichert melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded with a Bruker AC250F (250 MHz) spectrometer in $CDCl_3$, unless stated otherwise, with Me_4Si as an internal standard. FAB mass spectra were obtained with a Finnigan MAT90 mass spectrometer using *m*-nitrobenzyl alcohol (NBA) as a matrix. FTIR spectra were recorded on a Biorad 3200 spectrometer. *p-tert*-Butylcalix[4]arenes were prepared according a modified literature procedure.[37] NaH was used as an 80% dispersion in oil and washed twice with n-hexane before use. CH_2Cl_2 was distilled from $CaCl_2$ and stored over molecular sieves (4 Å). DMF was stored over molecular sieves (4 Å), CH_3CN was stored over molecular sieves (3 Å). MeOH was distilled over Mg and stored over molecular sieves (4 Å). All other solvents and chemicals were of reagent grade and were used without purification. Silica gel (particle size 0.040–0.063 mm, 230–240 mesh) was obtained from Merck. All reactions were carried out under an argon atmosphere. For reasons of clarity and in order to reduce space, the name calix[4]arene was used instead of the original IUPAC name: 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-dodecane. The presence of solvent in the analytical samples was confirmed by ^1H NMR spectroscopy.

5,11,17,23-Tetra-*p-tert*-butyl-25,27-bis[(cyanopropyl)-oxy]-26-28-dihydroxycalix[4]arene (2). *p-tert*-Butylcalix-[4]arene (5.0 g, 7.72 mmol) **1**, K_2CO_3 (1.28 g, 9.26 mmol), and 4-bromobutyronitrile (2.40 g, 16.20 mmol) was refluxed in CH_3CN (80 mL) for 5 days. The reaction was monitored by TLC (SiO_2; CH_2Cl_2:MeOH = 99:1). The solvent was evaporated and the residue was taken up in CH_2Cl_2 (300 mL), washed with 1 N HCl (100 mL), H_2O (50 mL), and brine (50 mL), and dried with $MgSO_4$. CH_2Cl_2 was evaporated and the residue was recrystallized from $CHCl_3$/MeOH yielding a white solid: yield 70%; mp ≥300 °C; IR (KBr) 2247 cm^{-1} (CN); ^1H NMR δ 7.39 (s, 2 H), 7.06 (s, 4 H), 6.88 (s, 4 H), 4.17 and 3.39 (ABq, 4 H, J = 12.5 Hz), 4.09 (t, 4 H), 3.03 (t, 4 H), 2.32 (m, 4 H), 1.28 (s, 18 H), 1.00 (s, 18 H); ^{13}C NMR δ 150.3 (s), 148.8 (s), 147.6 (d), 142.1 (s), 132.5 (s), 127.5 (s), 125.8 (d), 125.3 (s), 119.4 (s), 73.3 (t), 34.0 (s), 33.9 (s), 31.8 (t), 31.7 (t), 31.0 (q), 26.6 (t), 14.2 (t); FAB mass spectrum, +*m/e* 783.2 ([M + H]$^+$, calcd 783.5). Anal. Calcd for $C_{52}H_{66}N_2O_4$·0.1CH_2Cl_2: C, 78.95; H, 8.41; N, 3.53. Found: C, 79.29; H, 8.77; N, 3.60.

5,11,17,23-Tetra-*p-tert*-butyl-25,26,27,28-tetrakis[(cyanopropyl)oxy]calix[4]arene (3). NaH (1.00 g, 33.20 mmol) and *p-tert*-butylcalix[4]arene (2.60 g, 3.30 mmol) **2** was stirred 1 h at room temperature in DMF (125 mL). 4-Bromobutyronitrile (3.95 g, 330 mmol) was added and the mixture was stirred at 75 °C for 20 h. DMF was evaporated and the residue was taken up in CH_2Cl_2 (200 mL) and washed with 1 N HCl (100 mL, 2×), saturated NH_4Cl (100 mL, 3×), and brine (100 mL), and dried with $MgSO_4$. After filtration CH_2Cl_2 was evaporated and the residue was triturated with MeOH yielding a pure white solid: yield 70%; mp 277–278 °C; IR (KBr) 2246 cm^{-1} (CN); ^1H NMR δ 6.80 (s, 8 H), 4.27 and 3.22 (ABq, 8 H, J = 12.6 Hz), 4.02 (t, 8 H), 2.30 (t, 8 H), 2.28 (m, 8 H), 1.08 (s, 36 H); ^{13}C NMR δ 152.4 (s), 145.4 (s), 133.2 (d), 125.4 (s), 119.4 (s, CN), 72.9 (t), 31.4 (q), 31.0 (t, $ArCH_2Ar$), 25.8 (t), 14.2 (t); FAB mass spectrum, +*m/e* 916.4 ([M], calcd 916.6). Anal. Calcd for $C_{60}H_{76}N_4O_4$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.51; H, 8.26; N, 6.05.

5,11,17,23-Tetra-*p-tert*-butyl-25,26,27,28-tetrakis-[(aminobutyl)oxy]calix[4]arene (4). To a suspension of calix[4]arene **3** (1.00 g, 1.08 mmol) and $CoCl_2$·2H_2O (2.04 g, 8.57 mmol) in MeOH (20 mL) was added $NaBH_4$ (1.60 g, 42.29 mmol) batchwise. The black suspension was stirred at room temperature for 26 h. CH_2Cl_2 (50 mL) was added, 3 N HCl added until the black precipitate was dissolved and 25% ammonia solution added until basic pH. The solution was extracted with CH_2Cl_2 (50 mL, 3×). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL) and dried with Na_2SO_4. Evaporation of the solvent yielded a yellowish foam which was immediately used for further reactions: yield 84%; IR (KBr) 3357 and 3284 cm^{-1} (NH_2); ^1H NMR δ 6.76 (s, 8 H), 4.37 and 3.12 (ABq, 4 H, J = 12.4 Hz), 3.86 (t, 8 H), 2.78 (t, 8 H), 2.04 (m, 8 H), 1.72 (br m, 8 H), 1.55 (m, 8 H), 1.07 (s, 36 H); ^{13}C NMR δ 153.5 (s), 144.4 (s), 133.7 (d), 124.9 (s), 75.0 (t), 42.4 (t), 33.8 (s), 31.4 (q), 31.1 (t), 30.5 (t), 27.7 (t); FAB mass spectrum, +*m/e* 933.5 ([M], calcd 933.3).

General Procedure for the Preparation of 5,11,17,23-Tetra-*p-tert*-butyl-25,26,27,28-tetrakis[[(*N'*-R-(thio)ureido)-butyl]oxy]calix[4]arene (5a–d and 6). To *p-tert*-butylcalix-[4]arene **4** (0.50 g, 0.54 mmol), dissolved in $CHCl_3$ (20 mL), was added 2.16 mmol of the appropriate isocyanate (for **5a–d**) or phenylisothiocyanate (for **6**). The mixture was stirred at room temperature for 3 h. H_2O (20 mL) was added and the organic layer was separated, washed with brine (20 mL), and dried with $MgSO_4$. Evaporation of the solvent yielded the crude products which were purified as described below.

5a: R = phenyl; recrystallized twice from CH_2Cl_2/n-hexane; yield 40% of a white solid; mp 231–232 °C; IR (KBr) 3327 cm^{-1} (NH), 1649 cm^{-1} (C=O); ^1H NMR δ 7.67 (s, 4 H), 7.31 (d, 8 H), 7.21–7.08 (m, 12 H), 6.77 (s, 8 H), 6.05 (t, 4 H), 4.33 and 3.10 (ABq, 4 H, J = 12.4 Hz), 3.79 (t, 8 H), 3.29 (q, 8 H), 2.02 (br q, 8 H), 1.60 (br q, 8 H), 1.07 (s, 36 H); ^{13}C NMR 157.1 (s), 153.3 (s), 144.6 (s), 139.0 (s), 133.7 (s), 129.0 (d), 125.0 (d), 122.8 (d), 119.7 (d), 74.6 (t), 40.7 (t), 33.9 (s), 31.6 (t), 31.5 (q), 31.0 (t), 28.1 (t), 27.0 (t); FAB mass spectrum: +*m/e* 1432.0 ([M + Na^+]$^+$, calcd 1432.8); −*m/e* 1408.0 ([M − H]$^-$, calcd 1408.8), 1443.8 ([M + Cl^-]$^-$, calcd 1445.3), 1488.9 ([M + Br^-]$^-$, calcd 1489.7), 1534.9 ([M + I^-]$^-$, calcd 1536.7). Anal. Calcd for $C_{88}H_{112}N_8O_8$·0.8H_2O: C, 74.23; H, 8.03; N, 7.87. Found: C, 73.90; H, 7.99; N, 7.64. Karl Fisher for 0.8H_2O calcd 1.02%. Found: 1.00%.

5b: R = n-propyl; recrystallized from CH_2Cl_2/n-hexane; yield 46% of a white solid; mp 232–233 °C; IR (KBr) 3343 cm^{-1} (NH), 1628 cm^{-1} (C=O); ^1H NMR δ 6.76 (s, 8 H), 5.84 (t, 4 H), 5.60 (t, 4 H), 4.32 (ABq, 4 H, J = 12.4 Hz), 3.89 (t, 8 H), 3.25 (t, 8 H), 3.10 (m, 12 H), 2.93 (q, 8 H), 1.54 (m, 8 H), 1.50 (m, 8 H), 1.06 (s, 36 H), 0.93 (t, 12 H); ^{13}C NMR δ 159.6 (s), 153.4 (s), 144.5 (s), 133.7 (d), 125.0 (s), 75.1 (t), 42.3 (t), 40.3 (t), 33.8 (s), 31.4 (t), 30.9 (t), 28.1 (t), 27.3 (t), 23.4 (t), 11.4 (q); FAB mass spectrum, +*m/e* 1296.7 ([M + Na^+]$^+$, calcd 1296.6). Anal. Calcd for $C_{76}H_{112}N_8O_8$·1.2H_2O·0.1$CHCl_3$: C, 70.10; H, 9.47; N, 8.59. Found: C, 69.75; H, 9.32; N, 8.36. Karl Fisher for 1.2H_2O calcd: 1.66%. Found: 1.74%.

5c: R = n-octyl; purified by column chromatography (SiO_2: CH_2Cl_2:MeOH = 97:3) followed by recrystallization from MeOH; yield 42%; mp 163–164 °C; IR (KBr) 3344 cm^{-1} (NH), 1623 cm^{-1} (C=O); ^1H NMR δ 7.12 (s, 8 H), 5.76 (t, 4 H), 5.46 (t, 4 H), 4.41 and 3.06 (ABq, 4 H, J = 12.4 Hz), 3.80 (t, 8 H), 3.25 (q, 8 H), 3.15 (q, 8 H), 2.05 (m, 8 H), 1.60 (m, 8 H), 1.47 (m, 8 H), 1.26 (m, 40 H), 1.06 (s, 36 H), 0.87 (t, 12 H); ^{13}C

(37) Gutsche, C. D.; Iqbal, M.; Stewart, D. *J. Org. Chem.* **1986**, *51*, 742.

NMR δ 159.7 (s), 153.4 (s), 144.4 (s), 133.7 (d), 125.0 (s), 75.1 (t), 40.7 (t), 40.4 (t), 33.8 (s), 31.9 (t), 31.4 (t), 30.9 (q), 30.5 (t), 29.5 (t), 29.4 (t), 28.1 (t), 27.3 (t), 27.1 (t), 22.7 (t), 14.1 (q); FAB mass spectrum, +*m/e* 1554.1 ([M], calcd 1554.1), −*m/e* 1552.7 ([M − H]⁻, calcd 1553.2). Anal. Calcd for $C_{96}H_{160}N_8O_8$·MeOH: C, 73.45; H, 10.41; N, 7.06. Found: C, 73.51; H, 10.22; N, 6.74.

5d: R = *tert*-butyl; purified by column chromatography (SiO_2: CH_2Cl_2:MeOH = 96:4) followed by recrystallization from 1-propanol/Et_2O; yield 59%; mp ≥300 °C; IR (KBr) 3357 cm⁻¹ (NH), 1628 cm⁻¹ (C=O); ¹H NMR δ 6.76 (s, 8 H), 5.81 (br s, 4 H), 5.35 (br s, 4 H), 4.32 and 3.09 (ABq, 4 H, *J* = 12.4 Hz), 3.79 (t, 8 H), 3.21 (q, 8 H), 2.03 (m, 8 H), 1.60 (m, 8 H), 1.31 (s, 36 H), 1.06 (s, 36 H); ¹³C NMR δ 159.0 (s), 153.4 (s), 144.4 (s), 133.7 (d), 125.0 (s), 75.2 (t), 50.0 (t), 40.4 (t), 33.8 (s), 31.5 (q), 30.9 (t), 29.7 (q), 28.1 (s), 27.3 (t); FAB mass spectrum, +*m/e* 1330.2 ([M + H]⁺, calcd 1330.0). Anal. Calcd for $C_{80}H_{128}N_8O_8$·1.5H_2O: C, 70.74; H, 9.87; N, 8.30. Found: C, 70.81; H, 9.72; N, 8.26. Karl Fisher for 1.5 H_2O calcd: 2.03%. Found: 1.96%.

6: R = phenyl, purified by trituration with diisopropyl ether followed by column chromatography (SiO_2: CH_2Cl_2:MeOH = 97:3) of the precipitate; yield 41%; mp 143−144 °C; IR (KBr) 3235 cm⁻¹ (NH); ¹H NMR δ 7.86 (s, 4 H), 7.28 (m, 8 H), 7.19 (m, 12 H), 6.69 (s, 8 H), 6.68 (s, 4 H), 4.32 and 3.12 (ABq, 4 H, *J* = 12.4 Hz), 3.85 (t, 8 H), 3.72 (q, 8 H), 2.05 (m, 8 H), 1.73 (m, 8 H), 1.08 (s, 36 H); ¹³C NMR δ 180.4 (s), 153.3 (s), 144.6 (s), 135.6 (s), 133.7 (s), 129.7 (d), 126.7 (d), 125.0 (d), 122.4 (d), 74.6 (t), 45.6 (t), 33.8 (s), 31.5 (q), 31.1 (t), 27.9 (t), 26.0 (t); FAB mass spectrum, +*m/e* 1496.7 ([M + Na^+]⁺, calcd 1497.0), −*m/e* 1470.6 ([M − H]⁻, calcd 147.8). Anal. Calcd for $C_{88}H_{112}N_8O_4S_4$: C, 71.70; H, 7.66; N, 7.60; S, 8.70. Found: C, 71.51; H, 8.01; N, 7.46; S, 8.37.

5,11,17,23-Tetra-*p-tert*-butyl-25,27-bis[(cyanopropyl)oxy]-26,28-dipropoxycalix[4]arene (7). NaH (0.31 g, 7.66 mmol) and calix[4]arene **2** (1.0 g, 1.28 mmol) in DMF (50 mL) were stirred for 1 h at room temperature. n-Propyl iodide (0.76 mL, 7.80 mmol) was added and the mixture was stirred for 24 h at 75 °C. DMF was evaporated and the residue was taken up in CH_2Cl_2 (100 mL) and washed with 1 N HCl (50 mL, 2×), saturated NH_4Cl (30 mL, 3×), and brine (50 mL) and dried with $MgSO_4$. After evaporation of the solvent the crude product was triturated with MeOH. An analytically pure sample was obtained by recrystallization from $CHCl_3$/MeOH: yield 61%; mp 217−219 °C; IR (KBr) 2245 cm⁻¹ (CN); ¹H NMR δ 7.07 (s, 4 H), 6.49 (s, 4 H), 4.31 and 3.16 (ABq, 4 H, *J* = 12.4 Hz), 4.07 (t, 4 H), 3.72 (t, 4 H), 2.68 (t, 4 H), 2.41 (m, 4 H), 1.93 (m, 4 H), 1.30 (s, 18 H), 1.04 (t, 6 H), 0.86 (s, 18 H); ¹³C NMR δ 153.4 (s), 152.3 (s), 145.5 (s), 144.2 (s), 135.1 (d), 132.1 (d), 125.6 (s), 124.7 (s), 119.0 (s), 72.7 (t), 34.1 (s), 33.7 (s), 31.7 (q), 31.2 (q), 31.0 (t), 25.9 (t), 23.6 (t), 14.1 (t), 10.6 (q); FAB mass spectrum, +*m/e* 866.9 ([M], calcd 866.6). Anal. Calcd for $C_{58}H_{78}N_2O_4$: C, 80.33; H, 9.07; N, 3.23. Found: C, 80.15; H, 9.19; N, 3.01.

5,11,17,23-Tetra-*p-tert*-butyl-25,27-bis[(aminobutyl)oxy]-26,28-dipropoxycalix[4]arene (8). The same procedure as for the preparation of compound **4** was followed. The yellowish foam was immediately used for further reactions: yield 87%; IR (KBr) 3380 cm⁻¹ (NH_2); ¹H NMR δ 6.74 (s, 4 H), 6.66 (s, 4 H), 4.37 and 3.03 (ABq, 4 H, *J* = 12.5 Hz), 3.82 (t, 4 H), 3.73 (t, 4 H), 2.72 (t, 4 H), 2.02−1.82 (m, 8 H), 1.54−1.42 (m, 8 H), 1.03 (s, 18 H), 0.97 (s, 18 H), 0.93 (t, 6 H); ¹³C NMR δ 153.7 (s), 153.5 (s), 144.4 (s), 144.2 (s), 134.0 (d), 133.5 (d), 125.0 (s), 124.9 (s), 74.9 (t), 42.5 (t), 33.9 (s), 33.8 (s), 31.8 (t), 31.5 (q), 31.4 (q), 31.1 (t), 30.7 (t), 27.6 (t), 23.4 (t), 10.5 (q); FAB mass spectrum, +*m/e* 875.7 ([M], calcd 875.2).

5,11,17,23-Tetra-*p-tert*-butyl-25,27-bis[[(*N'*-phenylureido)butyl]oxy]-26,28-dipropoxycalix[4]arene (9). The same procedure as for the preparation of compounds **5a−d** was followed. Purified by column chromatography (SiO_2: CH_2Cl_2:MeOH = 98:2) followed by recrystallization from MeOH: yield 35%; mp 251−252 °C; IR (KBr) 3350 cm⁻¹ (NH), 1655 cm⁻¹ (C=O); ¹H NMR δ 7.71 (br s, 2 H), 7.24 (d, 4 H), 7.16 (t, 4 H), 7.10 (s, 4 H), 6.93 (t, 2 H), 6.45 (s, 4 H), 6.12 (br t, 2 H), 4.36 and 3.11 (ABq, 4 H, *J* = 12.4 Hz), 3.97 (t, 4 H), 3.62 (t, 4 H), 3.35 (q, 4 H), 2.20 (m, 4 H), 1.86 (m, 4 H), 1.50 (m, 4 H), 1.33 (s, 18 H), 0.95 (t, 6 H), 0.83 (s, 18 H); ¹³C NMR δ 156.8 (s), 154.7 (s), 152.5 (s), 144.8 (s), 143.9 (s), 139.1 (s), 135.6 (d), 131.9 (d), 129.0 (d), 125.5 (s), 124.4 (s), 122.9 (d), 120.1 (d), 74.7 (t), 40.7 (t), 34.1 (s), 33.6 (s), 31.8 (q), 31.2 (q), 31.1 (t), 27.7 (t), 26.8 (t), 23.6 (t), 10.9 (q); FAB mass spectrum, +*m/e* 1113.9 ([M], calcd 1113.5), −*m/e* 1112.1 ([M − H]⁻, calcd 1112.5). Anal. Calcd for $C_{72}H_{90}N_4O_6$·2H_2O: C, 75.23; H, 8.76; N, 4.87. Found: C, 74.96; H, 8.54; N, 4.87. Karl Fisher for 2H_2O calcd: 3.13%. Found: 3.12%.

¹H NMR Titrations. A 5 mM solution of the host in $CDCl_3$ was prepared. To 1 mL of this solution 0−4 equiv of the tetrabutylammonium salts were added in the ¹H NMR tube and the spectra were recorded. The chemical shifts of the NH proton were followed and plotted against the equivalents of guest added. The association constants were determined using a nonlinear regression procedure.[32]

Job Plot.[31] Stock solution for the host (5 mM) and for the tetrabutylammonium salts (5 mM) in $CDCl_3$ were prepared. Ten ¹H NMR tubes were filled with 500 μL solutions of the host and guest in the following volume ratios: 50:450, 100:400, 150:350, 200:300, 250:250, 300:200, 350:150, 400:100, 450:50, 500:0. ¹H NMR spectra were recorded and the concentration of the complex was calculated as follows: [complex] = $([calix]_{tot}) \times (\delta_{obs} - \delta_{calix})/(\delta_{complex} - \delta_{calix})$, where $[calix]_{tot}$ is the total concentration of the host in solution, δ_{obs} is the observed chemical shift, δ_{calix} is the chemical shift of the NH protons of the host, and $\delta_{complex}$ is the chemical shift of the NH protons in the complex.

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