Calix[4]arene-Based Receptors with Hydrogen-Bonding Groups Immersed into a Large Cavity

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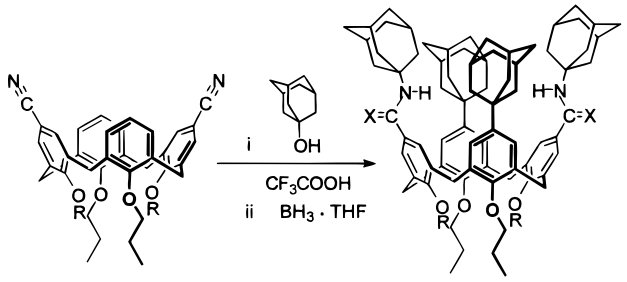
A one-pot procedure, which combines the Ritter and Friedel−Crafts reactions, produced the first members of a new type of calix[4]arene-based receptors. The cavity in these receptors is formed by a calix[4]arene framework fixed in the *cone* conformation and bulky adamantyl or (and) phenylacetylene moieties. Amido and amino groups were used as potential hygrogen bond donors. Preliminary studies revealed interesting complexation properties, in particular, the tetrahedral recognition of water molecules performed by one of the receptors.

Introduction

Hydrogen bonds are the most important of all noncovalent bond types in biochemistry.[1] They play an essential role in the formation of biological macromolecules such as the globular proteins and the DNA double helix and in the mechanism of enzyme−substrate recognition.[1] Formation of hydrogen bonds as a driving force of the molecular recognition has also been widely used in artificial receptors.[2] Complexation of calix[4]arene derivatives with neutral molecules has always been the subject of special attention.[3] Early works demonstrated the ability of calix[4]arenes to form inclusion complexes in the solid state, while more recent publications deal with complexation in aqueous and apolar media.[4] Several hydrogen bonding calix[4]arenes have been recently described.[5] In some cases, such receptors tend toward self-association.[5c] One may speculate that the immersion of H-bond active groups into a large cavity should disfavor the self-association in favor of the coordination of a substrate. In this paper, we report our results in the design and synthesis of a series of calix[4]arene-based receptors with hydrogen-bonding groups immersed into a large cavity as well as the preliminary complexation study.

Scheme 1



1 R = n-C_3H_7

2 R = H

3 R = n-C_3H_7, X = O 42 %

4 R = H, X = O 44 %

5 R = H, X = 2H 82 %

Results and Discussion

Design. According to the proposed concept, the receptor is made of a calix[4]arene framework, a hydrogen-bonding group, and a bulky moiety. Calix[4]arene fixed in the *cone* conformation predetermines the shape of the cavity and to a great extent the conformational mobility. By choosing the proper substitution at the lower rim, one may vary the conformational features of the calix[4]arene framework.[6] This task can be accomplished using both noncovalent fixation by means of intramolecular hydrogen bonds or covalent fixation by a properly chosen rigid bridge. Both approaches are used below. H-bond active groups are attached to the upper rim of calix[4]arene. Their role is supposed to be the hydrogen bond formation

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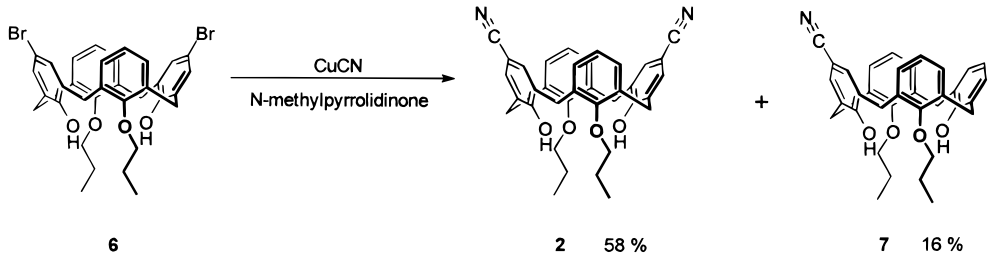
Scheme 2



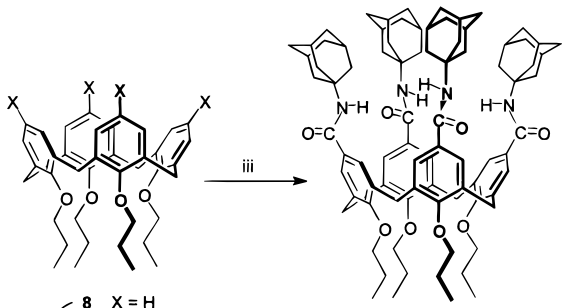
6 **2** 58 % **7** 16 %

with a substrate. The number, nature, and placement of hydrogen-bonding groups can be varied. The receptor design is completed by bulky moieties. They extend the cavity of the calix[4]arene skeleton and shield the substrate from the solvent molecules. Moreover, they can possibly be involved in the additional binding of a substrate. The preference has been given to the adamantyl unit for several reasons: this is a bulky and highly symmetric structure; a number of readily available and cheap adamantyl-containing intermediates makes the introduction of adamantyl moiety to the receptor relatively easy;[7] the adamantyl unit has several positions for the attachment of the additional substituents that opens the road to the further development of this type of receptors (possible fine-tuning of selectivity, formation of chiral cavity, etc.). Another possible candidate for the enlargement of the cavity is a rigid π-electron-containing unit that can be involved in $\pi-\pi$ interactions between the cleftlike receptor and a substrate.[8]

Synthesis. Among many suitable reactions leading to the formation of an amide function, the Ritter reaction[9] attracted our attention due to the possibility to combine it with the Friedel–Crafts alkylation that promises the shortest way to the proposed type of receptors. Indeed, the adamantylation[10] of the dicyanocalix[4]arene **1** in the presence of trifluoroacetic acid led to the desired product **3** in 42% yield (Scheme 1). This way, the construction of a large cavity and the introduction of H-bond active groups there occurred simultaneously in a one-pot procedure.

It was shown in the previous reports that the substitution pattern in the lower rim of calix[4]arene strongly affects its binding properties.[4c] Thus, for example, calix[4]arenes with two hydroxyl groups in the distal positions at the lower rim reveal stronger binding of simple organic molecules than tetrahydroxy or tetraalkoxy calix[4]arenes.[4c] It is interesting therefore to compare **3** with its analogue dialkylated in the lower rim. For this purpose, we need the corresponding intermediate—5,11-dicyano-25,27-dihydroxy-26,28-dipropoxycalix[4]arene. The exchange of bromine for a cyano function in the reaction of **6** with cuprous cyanide gave the desired calix[4]arene **2** in 58% yield together with an unexpected coproduct **7** (16%) (Scheme 2), apparently due to the reduction by monovalent copper. The adamantylation of **2** led to the target structure **4** in 44% yield (Scheme 1). As follows from the ^{1}H NMR spectrum, the calix[4]arene moiety in **4** is fixed in the flattened cone conformation by the array of intramolecular hydrogen bonds in the lower rim.

Scheme 3



i) N-bromosuccinimide / ethyl methyl ketone, ii) CuCN / N-methylpyrrolidinone, iii) 1-adamantanol / CF_3COOH

Obviously, **7** seems to be also attractive for the receptor synthesis. However, the adamantylation of **7** performed in several runs gave no desired product.

The reduction of **4** with BH_3·THF produced **5** with amino groups as potential hydrogen bond donors (Scheme 1).

Compound **11** bearing four amido groups has been synthesized according to Scheme 3. The reaction pathway consisted of exhaustive bromination of tetrapropoxycalix[4]arene **8** by *N*-bromosuccinimide, introduction of the cyano functions, and the subsequent adamantylation of tetracyanocalix[4]arene **10**.

The idea of using $\pi-\pi$ aromatic interactions in the receptors adopted from nature proved to be very fruitful.[11] We may apply it to our system by keeping two amido functions with bulky adamantyl units and modifying the two remaining positions with the substituents of aromatic nature. To form a stable cleftlike structure, these substituents should be coplanar with the phenolic units of calix[4]arene skeleton. One of the most promising candidates for this role is the phenylacetylene moiety. Its attachment to the calix[4]arene framework via the corresponding iodo derivative has been discussed elsewhere.[12] Adamantylation of diiododicyanocalix[4]arene **12** produced **13**, and the subsequent exchange of iodine to phenylacetylene led to **14** (Scheme 4). As a result of the bulk and polarizability of iodine, **13** may be of interest not only as an intermediate for the preparation of phenylacetylene derivatives but also as a potential receptor for the coordination of electron deficient substrates.

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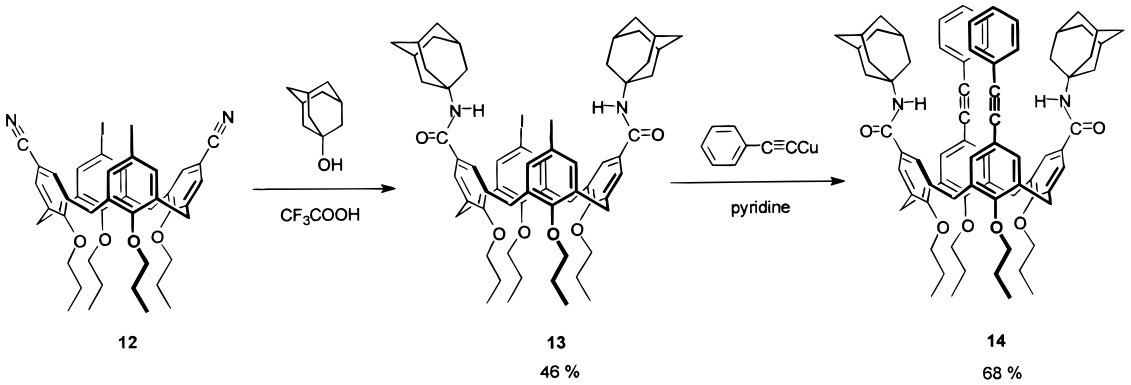
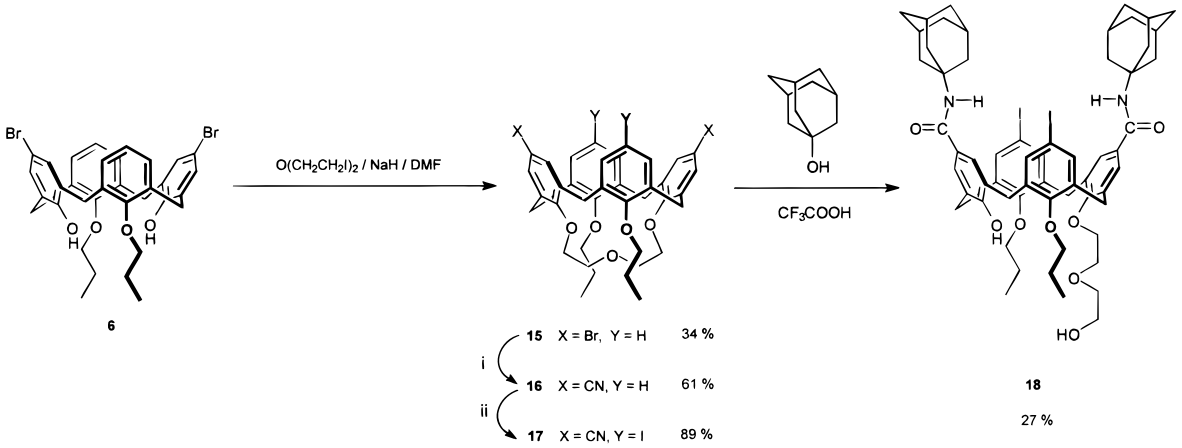
Scheme 4



Scheme 5



i) CuCN / N-methylpyrrolidinone, ii) I_2 / CF_3COOAg

Another option for the synthesis of such a type of receptors is the rigidification of the cavity by capping of calix[4]arene with the rigid bridge in the lower rim. In this case, calix[4]arene is fixed in the pinched *cone* conformation by the covalent linkage.[6d] Initially, the following retrosynthetic approach to the proposed compound has been chosen: coupling with cuprous phenylacetylide ⇒ adamantylation ⇒ iodination ⇒ exchange of bromine for cyano group ⇒ introduction of a bridge to dibromodipropoxycalix[4]arene (Scheme 5). The introduction of the short bridge to the calix[4]arene **6** was performed according to the recently published protocol using 2-iodoethyl ether as an alkylating agent and NaH as a base in DMF.[6d] Subsequent exchange of bromine for cyano functions in **15** was performed by the standard method (with CuCN in *N*-methylpyrrolidinone).[14] The iodination of **16** followed a recently published procedure using iodine with silver trifluoroacetate in chloroform.[15] However, the adamantylation of the bridged calix[4]arene **17** led together with the desired amide formation, to the undesired ring opening in the lower rim. No expected product was isolated from the reaction mixture. The possible reason for this can be the action of strong trifluoroacetic acid on the strained ethereal system. Therefore, we have changed the approach to the desired compound, with the bridge being introduced after adamantylation: exchange of iodine for phenylacetylene moiety ⇒ introduction of a bridge ⇒ adamantylation ⇒ iodination of dicyanodihydroxycalix[4]arene **2**. Iodination of **2** was performed in the same way as mentioned above for **16**; adamantylation of **19** has produced diamide **20**. The reaction of **20** with 2-iodoethyl ether/NaH in DMF introduced the ethereal bridge. The final step in the synthetic sequence was the coupling of **21** with cuprous phenylacetylide, which gave **22**. This strategy was successful, and the desired compound **22** was isolated in 6% overall yield from **2** (Scheme 6).

One more factor to change is the placement (and nature) of the amido function. To accomplish this, the cyano groups in **12** were reduced (BH_3·THF) to aminomethyl functions and the resulting compound **23** was coupled with adamantylcarbonyl chloride to give diamide **24** followed by exchange of iodine for the phenylacetylene moiety (Scheme 7). The product **25** possesses the reversed orientation of amido groups compared with those present in the previous series of receptors.

To reveal the role of amido groups in this type of receptors, we have synthesized two model compounds, the structural analogues of **3** and **4**. The syntheses of **27** and **28**, performed according to standard procedures, required exhaustive and selective alkylation of **26**, respectively (Scheme 8).[16]

Complexation Studies. The preliminary complexation studies were performed with guests traditionally

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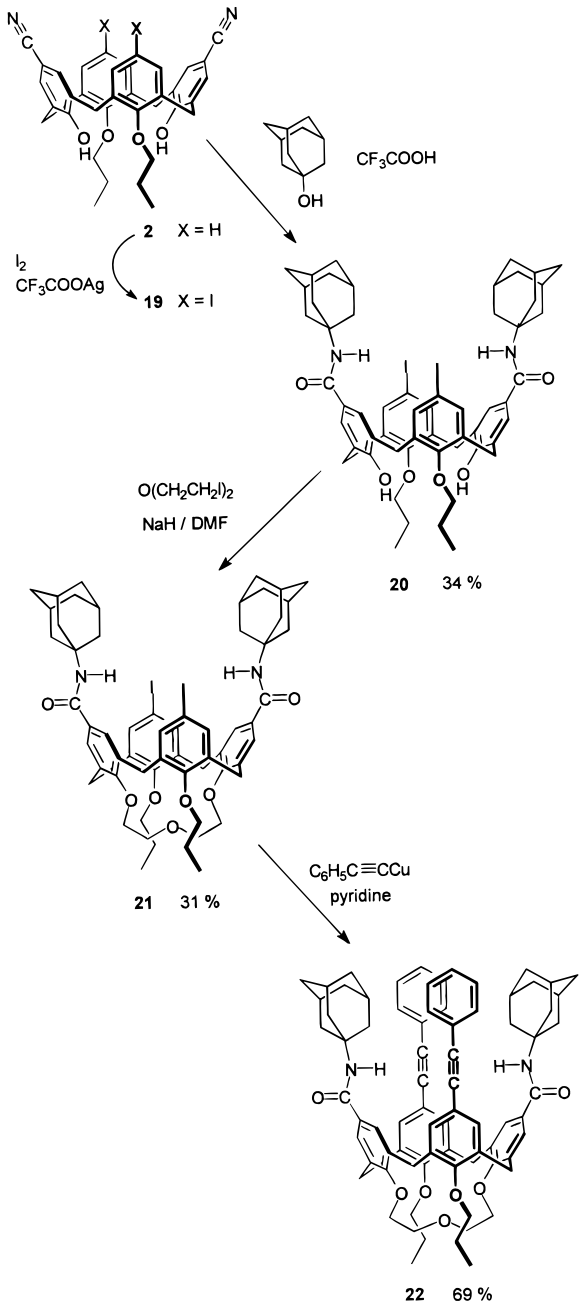
Scheme 6



capable of hydrogen bond formation like, for example, water and those known to form stable inclusion complexes with some calix[4]arene derivatives in apolar media. The results are summarized in Table 1.

Compound **3** forms strong complex with water, which is inevitably present in every solvent and complicates the correct description of the complexation.[17] The ^{1}H NMR spectrum of a CCl_4 solution of the linear analogue of **3**, *N*-(1-adamantyl)benzamide, did not exhibit any changes upon saturation with water; therefore, complexation of water by **3** could hardly be confined to simple water−amide interactions.

Taking this into account, we undertook a more detailed study of the complex of **3** with H_2O. The results of the direct and reversed ^{1}H NMR titrations (see experimental part) prove the 1:1 stoichiometry of the formed complex, **3**·H_2O, which indicates the binding of a single molecule of water and not the water associate. We performed the NOE difference experiment with a solution of this complex in CCl_4. Irradiating protons of water, we observed NOE peaks with the protons of aromatic units bearing directly attached adamantyl moieties (Figure 1). The downfield complexation-induced shift (CIS) of the amide proton (0.6 ppm) indicates that the amido groups act as hydrogen bond donors forming the bonds with the oxygen lone pairs. According to the NOE experiment, the water molecule is held inside the cavity. Usually the encapsulation of the guest into the aromatic cavity causes a large upfield shift of its protons.[18] However, the signal of water protons undergoes the moderate downfield CIS (0.3 ppm). We suppose that this is the result of the superposition of two factors: shielding by the aromatic cavity (large upfield CIS expected) and the presence of O−H···π interactions (large downfield CIS expected). On the basis of these data, the geometry of the complex is supposed to be as shown in Figure 1. The water molecule is bound by N−H···O hydrogen bonds and fixed inside the cavity by O−H···p interactions. Although we cannot allege the four-point caption of the water molecule, which can as well oscillate between the mentioned binding sites, its averaged position is clear and indicates the tetrahedral recognition of an H_2O molecule by **3**.[19]

Interestingly, a lower rim disubstituted analogue of **3** (compound **4**) reveals no affinity toward water. As the chemical nature of the cavity in both compounds seems to be the same, the different behavior is caused by the difference in their geometry. Lower rim 1,3-disubstituted calix[4]arenes are known to exist in a stable pinched *cone* conformation in solution, with the aromatic units bearing hydroxyl groups being perpendicular.[20] Tetraalkoxycalix[4]arens undergo fast interconversion between two pinched *cone* conformations.[6c] Evidently, **3** can adopt the geometry suitable for the accommodation of water, while in **4**, the amido groups are kept apart by the array of hydrogen bonds in the lower rim, and the change of geometry for this compound is inevitably accompanied by a loss of energy. Compound **27**, the analogue of **3** without amido groups, also does not show the binding of H_2O, which indicates that OH···π interactions alone are not sufficient for the capture of the water molecule within the cavity.

Thus, we see that all the structural elements of **3** are essential for binding of the water molecule: the presence of two amido groups in the upper rim, flexibility of calix[4]arene framework provided by the substitution pattern in the lower rim, and the shielding from the solvent molecules by bulky adamantyl moieties.

Considering guests unable to form strong hydrogen bonds, it is remarkable that **4** reveals the similar binding properties with **28**. Consequently, in the cases when amido groups do not form hydrogen bonds with the guest, the complexation is not altered by their presence. At the same time, **4** binds pyrazine and DMF contrary to **28** that evidences the positive role of amido groups.

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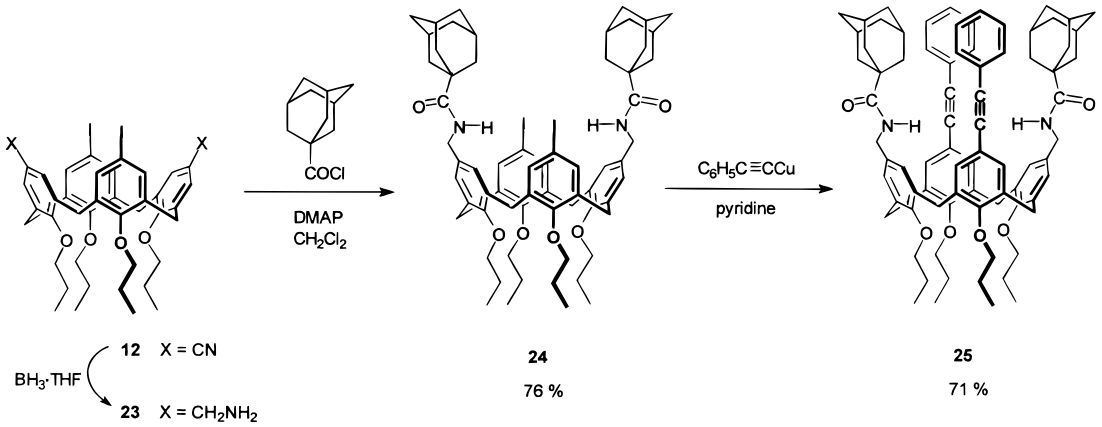
(18) Diederich, F. In *Cyclophanes, Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; RSC: Cambridge 1991; Vol. 3, p 82.

(19) For several other receptors capable of tetrahedral recognition of water, see: (a) Chand, D. K.; Ragunathan, K. G.; Mak, T. C. W.; Bharadwaj, P. K. *J. Org. Chem.* **1996**, *61*, 1169. (b) Dixon, D. A.; Dobbs, K. D. *J. Phys. Chem.* **1994**, *98*, 13435.

(20) Timmerman, P.; Boerrigter, H.; Verboom, W.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 103.

Scheme 7



Scheme 8

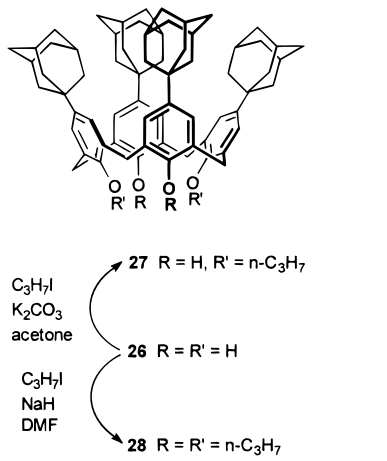


Table 1

	3	4	14	22	27	28
H_2O	270 ± 52	NC	138 ± 12	NC	NC	NC
DMSO	NC[a]	29 ± 2		NC	NC	NC
pyradazine	NC[a]	104 ± 9	34 ± 6	NC	NC	78 ± 20
pyrazine	NC[a]	13 ± 1	NC	NC	NC	NC
CH_3CN	NC[a]	108 ± 12	28 ± 6	NC	NC	134 ± 3
$ClCH_2CH_2CN$	NC[a]	68 ± 24			NC	84 ± 2

[a] Due to the presence of water in CCl_4, NC corresponds to K < 10 M^{-1}.

14 can be considered an analogue of **3** where two adamantyl groups are substituted by phenylacetylene moieties. Unlike **3**, it complexes acetonitrile and pyridazine, which indicates the presence of host−guest $\pi-\pi$ interactions. **22** seems to be too rigid to bind any of the guests studied so far.

The majority of complexes reported herein are of moderate stability. It is known that the systems with multipoint binding are very sensitive to the precise mutual correspondence between host and guest. Further development of this type of receptor and the search for appropriate host−guest pairs are the subjects of future work.

Conclusions

A new type of calix[4]arene-based receptors with hydrogen-bonding groups immersed into a large cavity has been proposed and synthesized. Syntheses of **3** and **4** were achieved by the combination of the Ritter and Friedel−Crafts reactions in a one-pot procedure. Compound **3** revealed the tetrahedral recognition of the water molecule. In several cases, the difference between the complexation by the amide-containing receptors (**3**, **4**) and their analogues (**27**, **28**) was attributed to the positive role of the amido groups.

Experimental Section

Melting points are uncorrected. Column chromatography was performed with silica gel (0.040−0.100 mm). Preparative

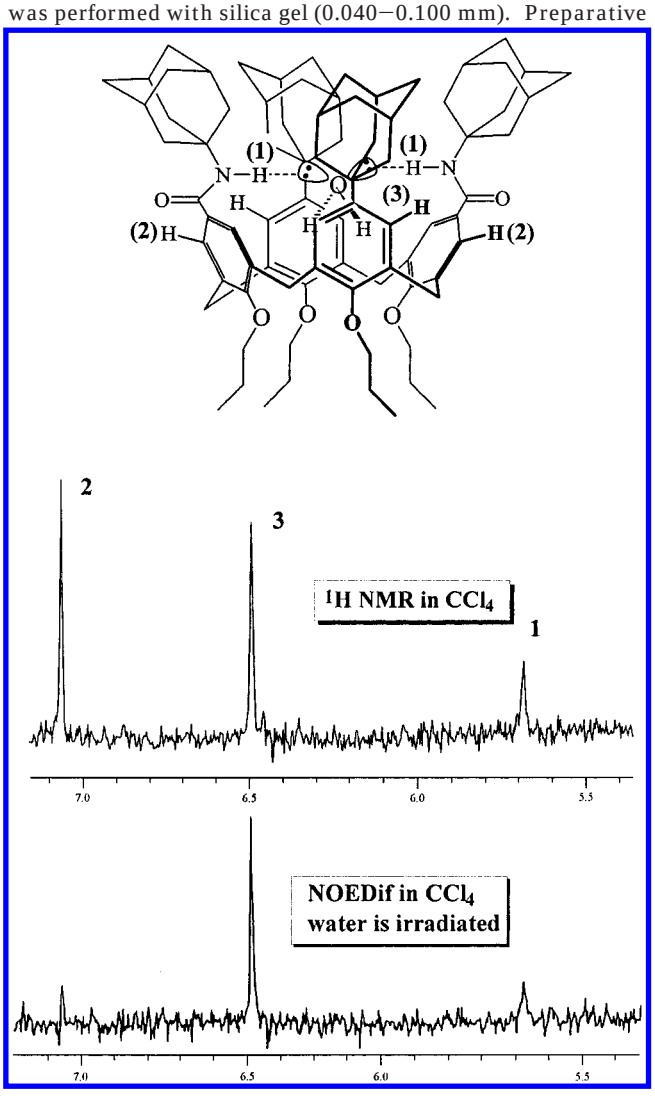


Figure 1.

Table 2. Concentration of Water in Saturated CCl_4 Solution ($M \times 10^{-5}$) at 298 K

	^{1}H NMR					gravimetry			
ref comp	$ClCH_2CN$	CH_3NO_2	CH_2Cl_2	$C_6H_5NO_2$	ClC_2H_4Cl	no.	1	2	3
$conc_{H_2O}$	376	365	357	383	371		330	412	353

thin-layer chromatography was performed with silica gel (Merck, 60 PF_{254}). Chemicals were of reagent grade purchased from Aldrich and were used without further purification. CH_2Cl_2 and DMF were distilled from CaH_2 and were stored over molecular sieves (4 Å). THF was distilled from K/benzophenone. CH_3CN was dried over molecular sieves (4 Å) prior to use. Petroleum ether refers to the fraction with bp 40−60 °C. Reactions with moisture- and air-sensitive reagents were performed in a dry nitrogen atmosphere.

NMR spectra were recorded on a Varian Gemini 300 HC spectrometer. The resonance frequency was 300.08 MHz for the ^{1}H measurements and 75.02 MHz for the ^{13}C measurements. Determination of stability constants was performed by ^{1}H NMR titration at 298 K in CCl_4 solutions. A capillary filled with D_2O was placed along the axis of the NMR tube and was used for system lock and shimming. Measurements were done with scan numbers varying from 16 through 2048 depending on the solution concentrations. Sensitivity-enhancing weighting was applied with LB = 0.2 Hz.

Concentrations of the components in the titration series were adjusted by sequential planning in order to cover the range from 40 to 90% of minor component saturation and to have equidistant positions of experimental points on the Scatchard plot that was used with the Fisher test for model consistence testing.[17] Binding constants and CIS values were computed with the original nonlinear regression curve-fitting program.[21] Typically, binding constants were estimated from data obtained for different protons and compared for self-consistency of the result. As a rule, calixarene protons were monitored in the presence of an excess of the guest. When possible, guest and host concentrations were reversed and guest protons were monitored and the results were compared.[16]

The evaluation of the stability constants of the water complexes was performed in the following way,

1. The concentration of water in the water-saturated CCl_4 was determined both gravimetrically and by comparison of the peak squares of different reference compounds of known concentration and water in ^{1}H NMR spectra. To determine the water solubility gravimetrically, three independent portions of saturated CCl_4 (at 25 °C) of known weight were refluxed for 48 h over P_2O_5 powder of known weight in the apparatus, isolated from the atmosphere by a silicon bulb playing the role of pressure buffer, and placed in the AtmosBag[22] filled with dry argon. To avoid the release of P_2O_5 dust, the top of the weighted flask was equipped with pore-glass membrane. Then the solvent was removed under reduced pressure on the oil pump until a constant weight was reached. The increase in the weights were ascribed to the capture of water from the solvent and averaged with the results of ^{1}H NMR measurements (Table 2) to give $(3.70 \pm 0.12) \times 10^{-3}$ M of water solubility in CCl_4 at 298 K.

2. The portion of CCl_4 was dried in two steps. (a) The solvent was refluxed over P_2O_5 powder for 24 h in the apparatus, isolated from the atmosphere by silicon bulb, and placed in the AtmosBag filled with dry argon. (b) Then the solvent was distilled into the flask containing the fresh phosphorus pentoxide and refluxed for 48 h more.

The distillation of solvent was always done directly before preparation of samples.

3. The titration series of **3**−water and **14**−water was prepared by the mixing of certain amounts of the solution of dry ligand in the dry solvent and water-saturated CCl_4. The final amount of water in the samples was controlled by the comparison of ^{1}H NMR peaks of water and reference compound (TMS) of known concentration.

All titration series with moisture-sensitive ligands were performed using freshly dried equipment and agents. Samples were prepared in the AtmosBag filled with dry argon. NMR tubes, vessels, and solid ligands were dried under vacuum and increased temperature (>200 °C) for 3−4 h. Syringes were dried by the attachment to the vacuum line in the flow of dry argon and washed several times with freshly distilled CCl_4 before use. NMR measurements were accomplished within 1 h after preparation of the samples.

The NOE difference experiments were performed with the number of transients accumulated from 640 to 2048, depending on the pulse width. Sensitivity-enhancing weighting with LB = 0.5 was applied. Samples were degassed by conventional methods.[23] To separate the Overhauser effect from the possible exchange of protons, the NOE difference experiments were performed with different pulse widths and acquisition and delay times. The similarity of the obtained spectra demonstrates the validity of ascribing the signals to NOE. The NOE difference experiment performed for the **4**−water mixture, where the water signal was irradiated, did not result in any reasonable response; this gives additional proof of the correctness of the above-discussed experiments.

Compounds **1**,[15] **6**,[15] **8**,[20] **12**,[12] **23**,[12] **26**,[4g] and **28**[10] were synthesized according to the literature procedures.

Compound 3. A mixture of **1** (322 mg, 0.5 mmol), 1-adamantanol (609 mg, 4 mmol), trifluoroacetic acid (1 mL), and chloroform (1 mL) was refluxed for 24 h. The reaction mixture was quenched with 10 mL of 2 N KOH and extracted with dichloromethane. The organic layer was separated, washed with water, and dried, and the solvent was evaporated. The residue was submitted to column chromatography (silica gel, CH_2Cl_2) to give 255 mg (42%) of white solid. mp 193−6 °C. ^{1}H NMR ($CDCl_3$): δ = 7.07 (s, 4H), 6.69 (s, 4H), 5.73 (s, 2H), 4.45 and 3.16 (2d, 8H, J = 13 Hz), 3.98 and 3.67 (2t, 8H, J = 7 Hz), 2.16−1.6 (m, 68H), 1.07 and 0.92 (2t, 12H, J = 7 Hz). ^{13}C NMR ($CDCl_3$): 168.22, 158.29, 155.44, 146.22, 135.75, 134.18, 131.13, 127.18, 125.94, 52.37, 46.04, 44.17, 42.21, 37.55, 37.13, 36.78, 36.41. MS (FAB) m/z 1215.6. Anal. Calcd for **3**·$2H_2O$: C, 78.68%; H, 8.86%. Found: C, 78.49%; H, 8.91%.

Reaction of 6 with CuCN. A mixture of **6** (1.00 g, 1.50 mmol) and CuCN (0.47 g, 5.25 mmol) in dry *N*-methylpyrrolidinone (20 mL) was refluxed with stirring for 5 h. The reaction mixture was cooled to 100 °C and poured into a solution of $FeCl_3 \cdot 6H_2O$ (2 g) and concd HCl (6 mL) in water (40 mL). It was stirred at 100−110 °C for 1 h. The precipitate was then filtered off, dried, and submitted to column chromatography (silica gel, CH_2Cl_2/petroleum ether, 1:1 v/v, then CH_2Cl_2) to give **2** (360 mg, 58%) and **7** (129 mg, 16%).

a. Calixarene 2. mp 232−4 °C. ^{1}H NMR ($CDCl_3$): δ = 9.16 (s, 2H), 7.39 (s, 4H), 6.98−6.81 (m, 6H), 4.26 and 3.42 (2d, 8H, J = 13 Hz), 4.00 (t, 4H, J = 6 Hz), 2.14−2.01 (m, 4H), 1.32 (t, 6H, J = 6 Hz). MS (CI) m/z 558.3 (M^+). Anal. Calcd: C, 77.40%; H, 6.13%. Found: C, 77.23%; H, 6.21%.

b. Calixarene 7. mp 195 °C. ^{1}H NMR ($CDCl_3$): δ = 9.24 (s, 1H), 8.24 (s, 1H), 7.38 (s, 2H), 7.07, 6.97, 6.89 (3d, 6H, J = 7.5 Hz), 6.80 (t, 2H, J = 7.5 Hz), 6.66 (t, 1H, J = 7.5 Hz), 4.30 and 4.29 (2d, 4H, J = 13 Hz), 4.07−3.91 (m, 4H), 3.40 (d, 4H, J = 13 Hz), 2.08 (m 4H), 1.32 (t, 6H, J = 7 Hz). MS (CI) m/z 533.5 (M^+). Anal. Calcd: C, 78.77%; H, 6.61%; N, 2.62%. Found: C, 78.54%; H, 6.72%; N, 2.43%.

Calixarene 4. A mixture of **2** (279 mg, 0.5 mmol), 1-adamantanol (609 mg, 4 mmol), trifluoroacetic acid (1 mL), and chloroform (1 mL) was stirred at the reflux for 24 h. The reaction mixture was cooled, quenched with 10 mL of 2 N KOH

(21) The detailed description of the titration method and supplementary software is available at our address upon request.

(22) Purchased from Aldrich Chemical Co.

(23) Derome, A. *Modern NMR Technique for Chemical Research*; Organic Chemistry Series, 6; Pergamon Press: New York, 1987.

and extracted with dichloromethane. The organic layer was separated, washed with water, and dried, and the solvent was evaporated. The residue was submitted to column chromatography (silica gel/CH_2Cl_2) to give 232 mg (41%) of white solid. mp 224 °C. ^{1}H NMR ($CDCl_3$): δ = 8.91 (s, 2H), 7.40 (s, 4H), 6.98 (s, 4H), 5.52 (s, 2H), 4.32 and 3.41 (2d, 8H, J = 13 Hz), 3.97 (t, 4H, J = 6.5 Hz), 2.21−1.48 (m, 64H), 1.28 (t, 6H, J = 6.5 Hz). MS (CI) m/z 1130.6 (M^+). Anal. Calcd for **4**·H_2O: C, 80.67%; H, 8.37%; N, 2.48%. Found: C, 80.34%; H, 8.54%; N, 2.23%.

Calixarene 5. To a solution of **4** (40 mg, 0.035 mmol) in dry THF (5 mL) was added dropwise BH_3 (1 M in THF, 1 mL, 1 mmol) under nitrogen. The reaction mixture was then heated at 70 °C for 7 h. After being cooled, the solution was carefully hydrolyzed by the addition of water, and the mixture was stirred for 30 min at room temperature. The solvent was then distilled off, and the solid residue was heated to reflux for 3 h in 6 N HCl (5 mL). After being cooled, the acidic solution was evaporated to dryness in vacuo, 2 N NaOH (5 mL) was added to the reaction flask, and the product was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layer was dried over $MgSO_4$, and the solvent was evaporated to dryness to give 32 mg (82%) of **5**. mp >170 °C (decomp). ^{1}H NMR ($CDCl_3$): δ = 8.24 (s, 2H), 7.27 and 6.91 (2s, 8H), 4.29 and 3.34 (2d, 8H, J = 12.5 Hz), 3.99−3.50 (m, 10H), 2.11−1.18 (m, 70H). MS (CI) m/z 1102.9 (M^+).

Calixarene 9. A solution of **8** (5.93 g, 10 mmol) and *N*-bromosuccinimide (17.8 g, 100 mmol) in ethylmethyl ketone (200 mL) was stirred at room temperature for 24 h. The mixture was then mixed with 150 mL of 10% $Na_2S_2O_5$ and stirred for 15 min. The organic layer was separated, washed with water, and dried, and the solvent was evaporated. The solid yellow residue was recrystallized from $CHCl_3$/CH_3OH to give 6.96 g (77%) of white crystals. mp 181−183 °C. ^{1}H NMR ($CDCl_3$): δ = 6.81 (s, 8H), 4.35 and 3.08 (2d, 8H, J = 13.5 Hz), 3.81 (t, 8H, J = 7.5 Hz), 1.82 (seq, 8H, J = 7.5 Hz), 0.97 (t, 12H, J = 7.5 Hz). MS (CI) m/z 908.4 (M^+). Anal. Calcd for $C_{40}H_{44}Br_4O_4$: C, 52.89%; H, 4.88%; Br, 35.18%. Found: C, 52.55%; H, 5.07%; Br, 34.92%.

Calixarene 10. A mixture of **9** (6.0 g, 6.6 mmol) and CuCN (3.6 g, 40 mmol) in *N*-methylpyrrolidinone (120 mL) was refluxed with stirring in a nitrogen atmosphere for 5 h. The reaction mixture was cooled to 100 °C and poured into a solution of $FeCl_3$·$6H_2O$ (15 g) and concd HCl (40 mL) in water (250 mL). It was stirred at 100−110 °C for 1 h. The precipitate was then filtered off, dried, and submitted to column chromatography (silica gel, CH_2Cl_2) to give 2.8 g (61%) of **10**. ^{1}H NMR ($CDCl_3$): δ = 7.00 (s, 8H), 4.45 and 3.26 (2d, 8H, J = 13.5 Hz), 3.91 (t, 8H, J = 7.5 Hz), 1.89 (seq, 8H, J = 7.5 Hz), 1.00 (t, 12H, J = 7.5 Hz). MS (CI) m/z 692.1 (M^+). Anal. Calcd for $C_{44}H_{44}N_4O_4$: C, 76.28%; H, 6.40%; N, 8.09%. Found: C, 75.79%; H, 6.78%; N, 7.82%.

Calixarene 11. A mixture of **10** (100 mg, 0.144 mmol), 1-adamantanol (200 mg, 4 mmol), trifluoroacetic acid (1 mL), and chloroform (1 mL) was stirred at the reflux for 24 h. The reaction mixture was cooled, quenched with 10 mL of 2 N KOH, and extracted with dichloromethane. The organic layer was separated, washed with water, and dried, and the solvent was evaporated. The residue was submitted to column chromatography (silica gel/CH_2Cl_2) to give 232 mg (41%) of white solid. mp 210−212 °C. ^{1}H NMR ($CDCl_3$): δ = 7.08 (s, 8H), 5.84 (s, 4H), 4.46 and 3.24 (2d, 8H, J = 13 Hz), 3.88 (t, 8H, J = 7.5 Hz), 2.14−1.42 (m, 68 H), 0.98 (t, 12H, J = 7.5 Hz). MS (CI) m/z 1302.4 (M^+ + 1). Anal. Calcd for **11**·$2H_2O$: C, 76.27%; H, 8.15%. Found: C, 76.51%; H, 8.19%.

Calixarene 13. A mixture of **12** (250 mg, 0.294 mmol), 1-adamantanol (255 mg, 1.68 mmol), trifluoroacetic acid (1 mL), and chloroform (1 mL) was stirred at the reflux for 24 h. The reaction mixture was cooled, quenched with 10 mL of 2 N KOH, and extracted with dichloromethane. The organic layer was separated, washed with water, and dried, and the solvent was evaporated. The solid residue was submitted to column chromatography (silica gel/CH_2Cl_2) to give 154 mg (46%) of white solid product. mp 198 °C. ^{1}H NMR ($CDCl_3$): δ = 7.43 (s, 4H), 6.64 (s, 4H), 5.79 (s, 2H), 4.38 and 3.18 (2d, 8H, J = 13 Hz), 4.04 and 3.68 (2t, 8H, J = 7 Hz), 2.26−1.68 (m, 38H), 1.07 and 0.87 (2t, 12H, J = 7 Hz). ^{13}C NMR ($CDCl_3$): 167.04, 160.62, 156.19, 137.40, 136.45, 136.22, 130.70, 128.29, 86.99, 42.45, 37.19, 31.59, 30.31, 24.04, 23.56, 11.31, 10.52. MS (FAB) m/z 1199.4 (M + 1). Anal. calcd for **13**·$1.5H_2O$: C, 60.73%; H, 6.49%. Found: C, 60.83%; H, 6.51%.

Calixarene 14. A mixture of **13** (100 mg, 0.083 mmol), cuprous phenylacetylide (41 mg, 0.250 mmol), and dry pyridine (1 mL) was stirred at the reflux in an inert atmosphere for 24 h. The reaction mixture was cooled, poured into 10 mL of 1 N HCl, and extracted with dichloromethane (2 × 10 mL). The organic layer was washed with 1 N HCl and water and dried, and the solvent was evaporated. The residue was submitted to preparative TLC to furnish 65 mg (68%) of **14**. mp 184−186 °C. ^{1}H NMR ($CDCl_3$): δ = 7.37 (s, 4H), 7.34−7.01 (m, 10H), 6.68 (s, 4H), 5.81 (s, 2H), 4.45 and 3.22 (2d, 8H, J = 13 Hz), 4.02 and 3.76 (2t, 8H, J = 7 Hz), 2.22−1.64 (m, 38H), 1.05 and 0.92 (2t, 12H, J = 7 Hz). ^{13}C NMR ($CDCl_3$): 167.46, 160.20, 156.53, 136.09, 134.05, 132.07, 132.00, 130.74, 128.43, 128.05, 127.89, 124.16, 117.96, 51.37, 42.21, 37.01, 31.60, 30.14, 23.85, 23.54, 11.07, 10.51. MS (FAB) m/z 1147.6 (M + 1). Anal. Calcd: C, 80.38%; H, 7.61%; N, 2.40%. Found: C, 80.09%; H, 7.83%; N, 2.26%.

Calixarene 15. To a suspension of **6** (1.50 g, 2.25 mmol) and NaH (60% in oil, 1 g, 25 mmol, washed twice with hexane) in dry DMF (100 mL) was added dropwise a solution of 2-iodoethyl ether (1.47 g, 4.5 mmol) in dry DMF (10 mL). The reaction mixture was heated at 80 °C for 24 h and then evaporated to dryness. The residue was dissolved in CH_2Cl_2 (50 mL), washed with 1 N HCl (2 × 50 mL) and water, and dried over $MgSO_4$, and the solvent was evaporated to dryness. The residue was purified by column chromatography (silica gel, CH_2Cl_2/petroleum ether 2:1 v/v) and gave 0.56 g (34%) of **15**. mp 240−242 °C. ^{1}H NMR ($CDCl_3$): δ = 7.30 (s, 4H), 6.27 (t, 2H, J = 7.5 Hz), 6.06 (d, 4H, J = 7.5 Hz), 4.33 and 3.14 (2d, 8H, J = 13.5 Hz), 4.18 and 3.98 (2t, 8H, J = 4 Hz), 3.44 (t, 4H, J = 7 Hz), 1.92−1.77 (m, 4H), 1.08 (t, 6H, J = 7 Hz). ^{13}C NMR ($CDCl_3$): 153.48, 155.52, 139.88, 133.07, 132.43, 128.15, 123.05, 115.46, 77.73, 73.89, 71.01, 31.28, 24.19, 11.60. MS (CI) m/z 734.4 (M^+). Anal. Calcd: C, 61.97%; H, 5.47%. Found: C, 61.62%; H, 5.56%.

Calixarene 16. A mixture of **15** (680 mg, 0.92 mmol), CuCN (330 mg, 3.69 mmol), and dry *N*-methylpyrrolidinone (10 mL) was refluxed with stirring in an inert atmosphere for 5 h. The reaction mixture was cooled to 100 °C and poured into a solution of $FeCl_3$ (2 g), concd HCl (5 mL), and water (25 mL). The mixture was stirred at 100 °C for 1 h, and the precipitate was filtered off, dried, and submitted to column chromatography (silica gel, CH_2Cl_2/petroleum ether 2:1 v/v) to give 354 mg (61%) of **16** as a white solid. mp 212−216 °C. ^{1}H NMR ($CDCl_3$): δ = 7.49 (s, 4H), 6.26 (t, 2H, J = 7.5 Hz), 5.98 (d, 4H, J = 7.5 Hz), 4.39 and 3.24 (2d, 8H, J = 13.5 Hz), 4.17 and 4.05 (2t, 8H, J = 4 Hz), 3.66 (t, 4H, J = 7 Hz), 1.92−1.78 (m, 4H), 1.10 (t, 6H, J = 7 Hz). ^{13}C NMR ($CDCl_3$): 163.16, 155.53, 139.14, 133.81, 132.55, 128.28, 123.28, 120.09, 106.46, 77.90, 73.89, 70.79, 31.23, 24.18, 11.58. MS (CI) m/z 628.6 (M^+). Anal. Calcd: C, 76.41%; H, 6.41%. Found: C, 76.14%; H, 6.71%.

Calixarene 17. To a suspension of CF_3COOAg (527 mg, 2.39 mmol) in $CHCl_3$ (30 mL) was added a solution of **16** (300 mg, 0.477 mmol) in $CHCl_3$ (20 mL), and the cloudy solution was refluxed for 25 min, and then I_2 (605 mg, 2.39 mmol) was added. After 1 h, the precipitated AgI was filtered off and the solution was treated with a 20% aqueous $Na_2S_2O_5$ solution (50 mL) until the violet color had disappeared. The organic layer was separated, washed twice with water, dried over Na_2SO_4, and evaporated to afford the diiodo calix[4]arene **17** as a yellow solid, which was purified by crystallization (CH_2Cl_2/CH_3OH), yield 374 mg (89%). mp 234−238 °C. ^{1}H NMR ($CDCl_3$): δ = 7.49 (s, 4H), 6.48 (s, 4H), 4.32 and 3.22 (2d, 8H, J = 13.5 Hz), 4.20 and 4.03 (2t, 8H, J = 4 Hz), 3.64 (t, 4H, J = 7 Hz), 1.93−1.78 (m, 4H), 1.08 (t, 6H, J = 7 Hz). ^{13}C NMR ($CDCl_3$): 162.7, 155.6, 138.3, 137.4, 134.9, 133.9, 107.4, 86.88, 78.4, 74.1, 71.3, 30.85, 24.08, 11.45. MS (CI) m/z 881.0 (M^+ + 1). Anal. Calcd: C, 54.56%; H, 4.35%. Found: C, 54.21%; H, 4.32%.

Adamantylation of 17. A mixture of **17** (150 mg, 0.215 mmol), 1-adamantanol (131 mg, 0.860 mmol), trifluoroacetic acid (1 mL), and chloroform (1 mL) was stirred at the reflux for 24 h. The reaction mixture was cooled, quenched with 10 mL of 2 N KOH, and extracted with dichloromethane. The organic layer was separated, washed with water, and dried, and the solvent was evaporated. The solid residue was submitted to preparative TLC (silica gel/CH_2Cl_2) to give 70 mg (27%) of white solid product **18**. ^{1}H NMR ($CDCl_3$): δ = 7.67, 7.53, 6.76, 6.39 (4s, 8H), 7.14 (s, 2H), 5.86 (s, 2H), 4.58−3.98 (m, 14H), 3.72 (t, 4H, J = 7 Hz), 3.38−3.16 (m, 4H), 2.23−1.68 (m, 34H), 1.09 (t, 6H, J = 7.5 Hz). MS (CI) m/z 1202.7 (M^+). Anal. Calcd for **18**·2H_2O: C, 58.16%; H, 6.18%. Found: C, 57.91%; H, 6.26%.

Calixarene 19. To a suspension of CF_3COOAg (5.53 g, 25.0 mmol) in $CHCl_3$ (100 mL) was added a solution of **2** (3.50 g, 6.26 mmol) in $CHCl_3$ (50 mL). The cloudy solution was refluxed for 25 min, and then I_2 (6.35 g, 25.0 mmol) was added. After 1 h, the precipitated AgI was filtered off and the solution was treated with a 20% aqueous $Na_2S_2O_5$ solution (50 mL) until the violet color had disappeared. The organic layer was separated, washed twice with water, dried over Na_2SO_4, and evaporated to afford calix[4]arene **19** as a yellow solid, which was purified by crystallization (CH_2Cl_2: CH_3OH), yield 4.27 g (84%). mp 192−194 °C. ^{1}H NMR ($CDCl_3$): δ = 9.02 (s, 2H), 7.39 (s, 4H), 7.28 (s, 4H), 4.17 and 3.39 (2d, 8H, J = 13 Hz), 3.97 (t, 4H, J = 7.5 Hz), 2.14−1.98 (m, 4H), 1.30 (t, 6H, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$): 158.22, 152.48, 139.19, 135.09, 133.61, 128.78, 120.10, 103.24, 90.44, 79.67, 31.49, 24.08, 11.51. MS (CI) m/z 810.8 (M^+). Anal. Calcd: C, 57.93%; H, 4.32%. Found: C, 57.61%; H, 4.39%.

Calixarene 20. A mixture of **19** (400 mg, 0.494 mmol), 1-adamantanol (304 mg, 2.0 mmol), trifluoroacetic acid (2 mL), and chloroform (2 mL) was stirred at reflux for 24 h. The reaction mixture was cooled, quenched with 10 mL of 2 N KOH, and extracted with dichloromethane. The organic layer was separated, washed with water, and dried, and the solvent was evaporated. The solid residue was submitted to column chromatography (silica gel/CH_2Cl_2) to give 187 mg (34%) of **20** as a white solid product. mp 172 °C. ^{1}H NMR ($CDCl_3$): δ = 8.53 (s, 2H), 7.46 (s, 4H), 7.26 (s, 4H), 5.73 (br s, 2H), 4.20 and 3.39 (2d, 8H, J = 13 Hz), 3.95 (t, 4H, J = 7 Hz), 2.24−1.58 (m, 34H), 1.28 (t, 6H, J = 7 Hz). MS (CI) m/z 1115.3 (M^+). Anal. Calcd for **20**·1.5H_2O: C, 58.90%; H, 5.91%. Found: C, 58.58%; H, 6.01%.

Calixarene 21. To a suspension of **20** (120 mg, 0.11 mmol) and NaH (60% in oil, 50 mg, 1.25 mmol) in dry DMF (15 mL) was added dropwise a solution of 2-iodoethyl ether (82 mg, 0.25 mmol) in dry DMF (5 mL). The reaction mixture was heated at 80 °C for 24 h and then evaporated to dryness. The residue was dissolved in CH_2Cl_2 (20 mL), washed with 1 N HCl (2 × 20 mL) and water, and dried over $MgSO_4$, and the solvent was evaporated to dryness. The residue was purified by preparative TLC (silica gel, CH_2Cl_2/petroleum ether 2:1 v/v) and gave 40 mg (31%) of **21**, all of which was used in the subsequent reaction with cuprous phenylacetylide. mp 212 °C. ^{1}H NMR ($CDCl_3$): δ = 7.54 (s, 4H), 6.52 (s, 4H), 5.86 (s, 2H), 4.32 and 3.22 (2d, 8H, J = 13.5 Hz), 4.19 and 3.97 (2 br s, 8H), 3.64 (t, 4H, J = 7 Hz), 2.26−1.58 (m, 34H), 1.08 (t, 6H, J = 7 Hz). MS (CI) m/z 1185.2 (M^+ + 1).

Calixarene 22. A mixture of **21** (40 mg, 0.034 mmol), cuprous phenylacetylide (22 mg, 0.136 mmol), and dry pyridine (1 mL) was stirred at the reflux in an inert atmosphere for 24 h. The reaction mixture was cooled, poured into 10 mL of 1 N HCl, and extracted with dichloromethane (2 × 10 mL). The organic layer was washed with 1 N HCl and water and dried, and the solvent was evaporated. The residue was submitted to preparative TLC (silica gel, CH_2Cl_2) to furnish 27 mg (69%) of **22**. ^{1}H NMR ($CDCl_3$): δ = 7.64−7.14 (m, 18H), 5.89 (s, 2H), 4.39 and 3.31 (2d, 8H, J = 13.5 Hz), 4.20 and 3.98 (2 br s, 8H), 3.67 (t, 4H, J = 7 Hz), 2.26−1.58 (m, 34H), 1.08 (br t, 6H, J = 7 Hz). MS (CI) m/z 1133.4 (M^+ + 1). Anal. Calcd: C, 79.27%; H, 7.18%. Found: C, 78.93%; H, 7.21%.

Calixarene 24. 1-Adamantanecarbonyl chloride (40 mg, 0.20 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise to a solution of **23** (90 mg, 0.10 mmol) and DMAP (27 mg, 0.22 mmol) in dry CH_2Cl_2 (5 mL) at room temperature in an inert atmosphere. The reaction mixture was stirred at room temperature overnight, washed with 1 N HCl (2 × 10 mL) and water (10 mL), dried over $MgSO_4$ and evaporated to dryness. The solid residue was submitted to preparative TLC (silica gel, CH_2Cl_2/petroleum ether, 2:1 v/v) to give 93 mg (76%) of **24**. mp 165−168 °C. ^{1}H NMR ($CDCl_3$): δ = 7.21 (s, 4H), 6.46 (br t, 2H), 6.18 (s, 4H), 4.34 and 3.05 (2d, 8H, J = 13 Hz), 4.04 (br d, 4H), 3.92 and 3.67 (2t, 8H, J = 7 Hz), 2.18−1.68 (m, 38H), 1.03 and 0.91 (2t, 12H, J = 7 Hz). ^{13}C NMR ($CDCl_3$): 178.44, 157.8, 155.1, 139.1, 137.7, 133.9, 132.9, 126.2, 86.03, 78.11, 77.61, 42.51, 41.45, 40.19, 37.41, 31.50, 29.10, 24.09, 23.75, 11.32, 10.75. MS (CI) m/z 1227.4 (M^+ + 1). Anal. Calcd for **24**·H_2O: C, 61.73%; H, 6.64%. Found: C, 62.04%; H, 6.61%.

Calixarene 25. A mixture of **24** (50 mg, 0.041 mmol), cuprous phenylacetylide (27 mg, 0.163 mmol), and dry pyridine (1 mL) was stirred at the reflux in an inert atmosphere for 24 h. The reaction mixture was cooled, poured into 10 mL of 1 N HCl, and extracted with dichloromethane (2 × 10 mL). The organic layer was washed with 1 N HCl and water and dried, and the solvent was evaporated. The residue was submitted to preparative TLC (silica gel, CH_2Cl_2) to furnish 33 mg (69%) of **25**. mp 180−182 °C. ^{1}H NMR ($CDCl_3$): δ = 7.66−7.08 (m, 18H), 6.51 (br t, 2H), 4.27 and 3.16 (2d, 8H, J = 13 Hz), 4.09 (br s, 4H), 3.94 and 3.75 (2t, 8H, J = 7 Hz), 2.20−1.68 (m, 38H), 1.09 and 0.95 (2t, 12H, J = 7 Hz). MS (CI) m/z 1175.4 (M^+ + 1). Anal. Calcd for **25**·1.5H_2O: C, 79.90%; H, 7.79%. Found: C, 80.12%; H, 7.74%.

Calixarene 27. To a suspension of **26** (300 mg, 0.312 mmol) and NaH (60% in oil, 100 mg, 2.50 mmol) in dry DMF (20 mL) was added dropwise propyl iodide (0.25 mL, 2.50 mmol). The reaction mixture was heated at 80 °C for 24 h and then evaporated to dryness. The residue was dissolved in CH_2Cl_2 (20 mL), washed with 1 N HCl (2 × 20 mL) and water, and dried over $MgSO_4$, and the solvent was evaporated to dryness. The residue was purified by crystallization (CH_2Cl_2/CH_3OH) to furnish 260 mg (74%) of **27**. ^{1}H NMR ($CDCl_3$): δ = 6.82 (s, 8H), 4.42 and 3.13 (2d, 8H, J = 12 Hz), 3.81 (t, 8H, J = 7.5 Hz), 2.16−1.52 (m, 68H), 1.00 (t, 12H, J = 7.5 Hz). MS (CI) m/z 1129.1 (M^+). Anal. Calcd: C, 85.06%; H, 9.28%. Found: C, 84.81%; H, 9.33%.

***N*-(1-adamantyl)benzamide.** A mixture of benzonitrile (1 mL, 9.79 mmol) and 1-adamantanol (3.73 g, 24.50 mmol, 2.5-fold excess) was dissolved in trifluoroacetic acid (10 mL) and stirred for 15 h at 55 °C. Then, the solvent was removed under reduced pressure and the solid residue was dissolved in dichloromethane and washed with 0.1 M K_2CO_3 and water. The organic layer was separated, dried over $MgSO_4$, and evaporated to give the crude solid consisted of mainly N-(1-adamantyl)benzamide and an excess of adamantanol. Submission to column chromatography (silica gel, CH_2Cl_2) afforded the pure product (2.18 g, 8.54 mmol, 87% yield). The analytical and spectral data of N-(1-adamantyl)benzamide obtained correspond to those available from the literature.[24]

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