# Recognition of Amides by New Rigid Calix[4]arene-Based Cavitands

Arturo Arduini, Andrea Secchi, and Andrea Pochini*

*Dipartimento di Chimica Organica e Industriale, Università di Parma, Parco Area delle Scienze 17/A, I-43100, Parma, Italy*

*pochini@unipr.it*

*Received August 2, 2000*

The synthesis of new hosts specifically designed for the recognition of amides, characterized by two binding regions: a rigid calix[4]arene cavity and a sidearm, inserted at its rim, able to form strong hydrogen bonds, is described. The binding abilities of the new receptors toward amides of general structure $R^1CONR^2R^3$ have been investigated in $CDCl_3$ solution by $^1H$ NMR spectroscopy. When the additional binding site is the *N*-phenylureido group spaced by a methylene unit from the apolar cavity, binding constants up to 756 $M^{-1}$ were measured. Neither the two separate potential binding sites, nor the model host, where the calix[4]arene skeleton is flexible show detectable binding ability toward the series of guests examined. The rigidity of the calix[4]arene apolar cavity is the key control element in determining the efficiency of these molecular recognition processes. The presence of NH groups in the guest controls the efficiency and selectivity of binding.

## Introduction

The calix[4]arenes in the cone conformation present an internal cavity which can potentially host neutral guest molecules of complementary size. In particular the inclusion of aromatic guest has been widely documented,[1] whereas any attempt to exploit their $\pi$-donor apolar cavity for the recognition in apolar solvents of these aromatic molecules gave very poor results. This was attributed to the high solvation phenomena and to the scarce preorganization of these hosts. However, the introduction of bulky substituents on the phenolic oxygens, which prevent the cone-to-cone ring inversion, afforded tetra-O-alkylated calix[4]arenes cone isomers which show no complexing ability.

Moving from recent findings which show that in solution a residual conformational mobility of these cone isomers still exist,[2] other approaches to reduce this conformational flexibility have been pursued. After the successful results using upper rim bridged calix[4]arenes,[3] with the aim to exploit the aromatic cavity of calix[4]arenes as the only binding site for neutral organic molecules, very rigid and undistorted calix[4]arene-bis(crown-3) cone derivatives were obtained by the linkage of two proximal phenol rings with short diethylene glycol bridges, and they were able to recognize nitromethane and malononitrile as guests in apolar organic solvents.[4]

Another interesting result, which confirms the importance of rigidity and, consequently, of the preorganization of the cone conformer of calix[4]arenes in determining their recognition ability, is obtained by the comparison between *p-tert*-butylcalix[4]arene tetraamide and its sodium picrate complex in the binding of nitromethane in $CDCl_3$. In fact, while the conformationally mobile tetramide derivative does not show any significant complexation, its sodium complex, which is rigid, significantly binds $CH_3NO_2$.[4]

The possibility to rigidify calix[4]arene-based hosts using different strategies based on noncovalent interactions was confirmed by other authors. Stibor and coworkers[5] saw evidence of the possibility to utilize calix[4]arene compounds partially alkylated at the lower rim, e.g. 1,3-dialkoxy derivative, as efficient hosts for guests bearing acidic C−H bonds. The explanation of these results can be found in the studies on the conformational distribution and interconversion of lower rim partially alkylated calix[4]arenes performed by Reinhoudt and coworkers[6] and experimentally confirmed by Böhmer and co-workers.[7] In particular, the conformations of partially methylated derivatives are far less mobile than either the tetrahydroxy- or the tetramethoxycalix[4]arenes; therefore, for these hosts the rigidity derives from a combination of hydrogen bonds interactions and steric repulsions.

Regardless the strategy followed to immobilize the cone structure, in all the binding studies, only guests bearing acid $CH_3$ or $CH_2$ groups were bound. These findings, together with the presence of electron rich phenolic nuclei

(1) (a) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713−745. (b) Pochini, A.; Ungaro, R. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., McNicol, D. D., Vögtle, F., Eds.; Pergamon: Oxford, 1996; Vol. 2, pp 103−142. (c) Gutsche, C. D. *Calixarenes Revisited - Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry, Cambridge, 1998; Vol. 6.

(2) (a) Ikeda, A.; Tsuzuki, H.; Shinkai, S. *J. Chem. Soc., Perkin Trans 2* **1994**, 2073−2080. (b) Arduini, A.; Fabbi, M.; Mantovani, M.; Mirone, L.; Pochini, A.; Secchi, A.; Ungaro, R. *J. Org. Chem.* **1995**, *60*, 1454−1457.

(3) (a) Arduini, A.; Cantoni, M.; Graviani, E.; Pochini, A.; Secchi, A.; Sicuri, A. R.; Ungaro, R.; Vincenti, M. *Tetrahedron* **1995**, *51*, 599−606. (b) Arduini, A.; McGregor, W. M.; Pochini, A.; Secchi, A.; Ugozzoli, F.; Ungaro, R. *J. Org. Chem.* **1996**, *61*, 6881−6887.

(4) Arduini, A.; McGregor, W. M.; Paganuzzi, D.; Pochini, A.; Secchi, A.; Ugozzoli, F.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1996**, 839−846.

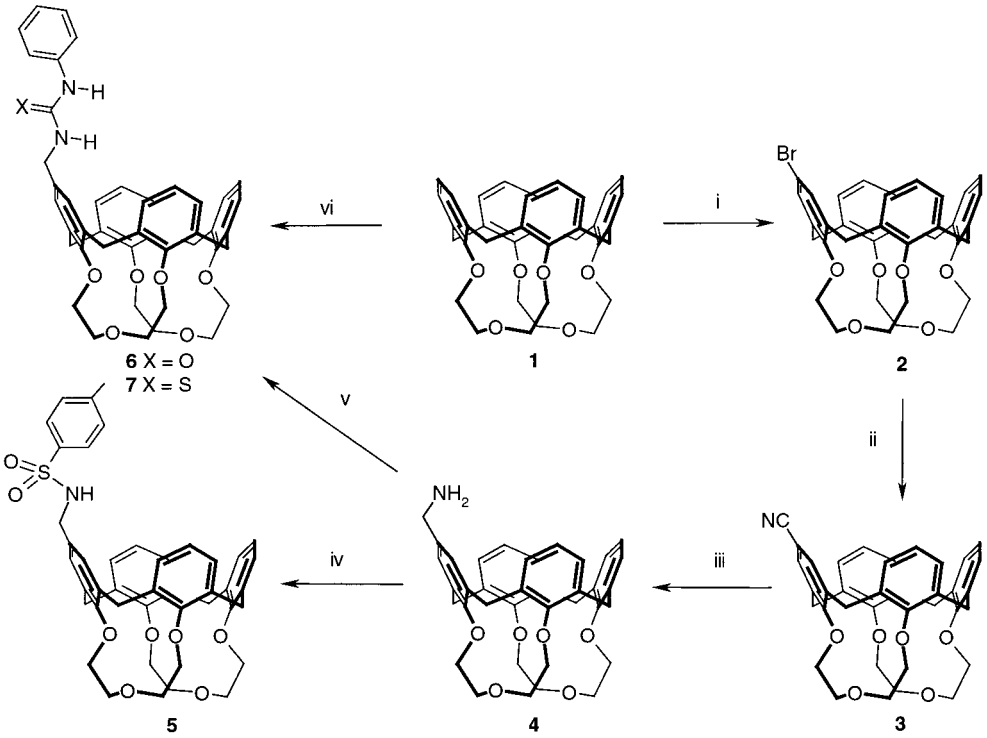
(5) Smirnov, S.; Sidorov, V.; Pinkhassik, E.; Havlicek, J.; Stibor, I. *Supramol. Chem.* **1997**, *8*, 187−196.

(6) Van Hoorn, W. P.; Morshuis, M. G. H.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *J. Phys. Chem. A* **1998**, *102*, 1130−1138.

(7) Kusano, T.; Tabatabai, M.; Okamoto, Y.; Böhmer, V. *J. Am. Chem. Soc.* **1999**, *121*, 3789−3790.

10.1021/jo005596n CCC: $19.00 
Published on Web 12/02/2000

**Scheme 1**[a]




[a] Reagents and conditions: (i) NBS, methyl ethyl ketone; (ii) CuCN, DMF, $T$ = 200 °C; (iii) $B_2H_6$, THF, reflux; (iv) TsCl, pyridine, $CH_2Cl_2$; (v) $C_6H_5NCX$, $CH_2Cl_2$; (vi) $C_6H_5NHCONHCH_2OH$, $CF_3COOH/CH_2Cl_2$.

in the host skeleton, suggest the importance of specific CH−$\pi$ aromatic interactions[8] to stabilize these complexes. A solid state study, based on the X-ray crystal structure of these complexes, complementary with those performed in solution, revealed that the guest molecule lies inside the cavity with the $CH_3$ or $CH_2$ groups facing the aromatic nuclei and afforded further insights in the role played by these weak interactions. In particular, an interesting dependence of the complexation mode on the nature of either the guest and host employed was evidenced.[9]

The previous reported studies can be seen as iterative processes which developed from the better understanding of the intermolecular interactions to allow design of new molecular receptors for specific guests useful for the preparation of a new generation of sensing devices where efficiency and selectivity are governed by molecular recognition processes.

In this context, however, the recognition of neutral species bearing specific functional groups by the calixarene cavity remains unexplored. This need should encourage the tailoring of an appropriate receptor able to bind the guest through more specific interactions. In such cases, the aid of one or more supplementary binding sites could be used to drive the complexation. This strategy, though well documented for calixarenes-based ionophores,[10] has found only few applications for the recognition of neutral molecules so far.[11]

In view of the current interest, particularly in biological field, in the recognition of the amide functional group, such as, for example, peptides and/or surface protein recognition,[12] we describe herein the synthesis of a series of calixarene derivatives specifically designed for the recognition of low molecular weight amides through the cooperative action of two distinct binding sites: the rigid calix[4]arene cavity and a hydrogen bond donor−acceptor sidearm inserted on its wider rim.

The binding ability of these new hosts was investigated by NMR techniques in $CDCl_3$ toward a series of amides, *N*-alkyl and *N*,*N*-dialkyl amides derived from formic, acetic, and benzoic acids.

## Results and Discussion

**Design and Synthesis of the Hosts.** The synthesis of new receptors **5**−**7** was based on the analysis of molecular models, obtained by preliminary molecular mechanics studies, which showed that the introduction of methyleneamido or sulfonamido moieties ($CH_2NHY$; Y = COR, $SO_2R$) on the upper rim of the rigidified calix[4]arene-bis(crown-3) **1** would result in receptors having the appropriate stereoelectronic matching to interact with the guest carbonyl group. The precursor of these new receptors was the methylenamino derivative **4** prepared

(8) (a) Nishio, M.; Umezawa, Y.; Hirota, M.; Takeuchi, Y. *Tetrahedron* **1995**, *51*, 8665−8701. (b) Umezawa, Y.; Tsuboyama, S.; Honda, K.; Uzawa, J.; Nishio, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1207−1213. (c) Braga, D.; Grepioni, F.; Tedesco, E. *Organometallics* **1998**, *17*, 2669−2672. (d) Further information about CH−$\pi$ interactions is available in the following web site: http://www.tim.hi-ho.ne.jp/dionisio/.

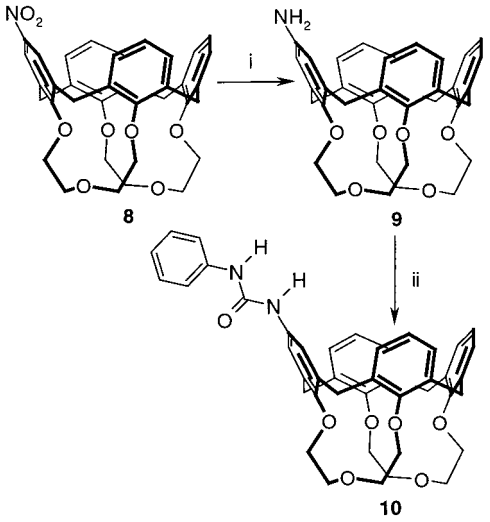
(9) Arduini, A.; Nachtigall, F. F.; Pochini, A.; Secchi, A.; Ugozzoli, F. *Supramol. Chem.* **2000**, in press.

(10) See,for example, (a) Casnati, A.; Fochi, C.; Minari, P.; Pochini, A.; Reggiani, M.; Ungaro, R.; Reinhoudt, D. N. *Gazz. Chim. Ital.* **1996**, *126*, 99−106. (b) Magrans, J. O.; Ortiz, A. R.; Molins, M. A.; Lebouille, P. H. P.; Sànchez-Quevada, J.; Prados, P.; Pons, M.; Gago, F.; de Mendoza, J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1712−1715. (c) Pelizzi, N.; Casnati, A.; Friggeri, A.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1307−1311.

(11) See e.g. Starnes, S. D.; Rudkevich, D. M.; Rebek, J., Jr. *Org. Lett.* **2000**, *2*, 1995−1198.

(12) See,for example, Peczuh, M. W.; Hamilton, A. D. *Chem. Rev.* **2000**, *100*, 2479−2494.

**Scheme 2**[a]




[a] Reagents and conditions: (i) $NH_2NH_2 \cdot H_2O$, Pd/C, $C_2H_5OH$, reflux; (ii) $C_6H_5NCO$, $CH_2Cl_2$.

according to Scheme 1, starting from the monobromo derivative **2** as intermediate. Careful choice of the reaction conditions and the ratio between reagents was chosen as the strategy for the monofunctionalization of **1**. Thus, reacting NBS with an excess of **1** gave **2** in reasonable yield (30%). This compound was then converted to the corresponding aminomethyl derivative **4** in high yield via the sequence Br/CN exchange, using CuCN, followed by reduction of the monocyano derivative **3** with $B_2H_6$. Subsequent reaction of **4** with tosyl chloride, phenyl isocyanate, or phenyl iso(thio)cyanate gave receptors **5**, **6**, and **7**. The $^1$H NMR spectra of derivatives **2**−**7** in $CDCl_3$ clearly show the typical fingerprint of monofunctionalized calix[4]arene-bis(crown-3) with the four equatorial and the four axial methylene protons resonating as eight separated AX systems.[13]

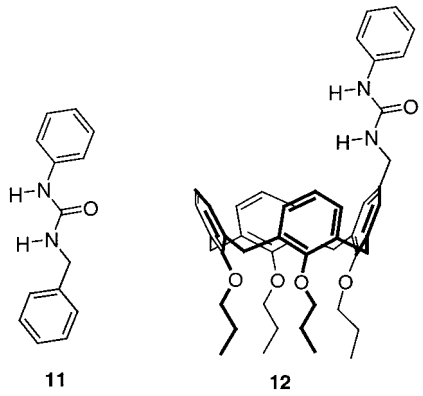
For comparison, the receptor **10** having the *N*-phenylureido additional binding site directly attached to the cavity, was prepared with an overall yield of 60%, starting from the previously reported mononitro calix[4]arene-bis(crown-3) **8**[13] as described in Scheme 2.

All the monosubstituted calix[4]arene-bis(crown-3) derivatives are chiral molecules, nevertheless this property was not exploited in the present study.

Having verified the good efficiency of the methylene-*N*-phenylureido derivative **6** (see ahead), a simpler synthetic approach to this host was studied. We found that by a Tscherniac−Einhorn amidomethylation reaction[14] using *N*-hydroxymethyl-*N*′-phenylurea[15] in a trifluoroacetic−dichloromethane mixture, this receptor was directly prepared in a 25% yield from derivative **1** in a one-step process (see Scheme 1).[16]

**Binding Studies.** Preliminary binding studies were carried out to compare the efficiency of the new hosts

**Chart 1. *N*-benzyl-*N*′-phenylurea 11 and Phenylureidomethyl-tetrapropoxy-calix[4]arene 12 as Models of the Supplementary Binding and of the Flexible Analogue of 6, Respectively**




(**5**−**7** and **10**) toward formamide and acetamide as guests, by $^1$H NMR spectroscopy in $CDCl_3$. The starting compound **1** and the model *N*-benzyl-*N*′-phenylurea **11** were also studied to verify the cooperative effect of the two binding sites. Finally the tetrapropoxycalix[4]arene bearing the methylene-*N*-phenylureido group on the upper rim (**12**)[10a] which is the flexible analogue of **6** was studied with the aim to verify the effect of the cavity rigidity on the recognition efficiency (Chart 1).

By adding increasing amounts of a $1 \times 10^{-1}$ M solution of the guest to a $1 \times 10^{-2}$ M solution of the host in $CDCl_3$, several signals of the receptors and of the guests were shifted upon complexation. In particular, with the 1:1 complex of **6** with acetamide, a downfield complexation induced shift (CIS)[17] of ca. 1.0 ppm was experienced by both the two NH protons of the host, as expected on the base of their involvement in hydrogen bonding with the oxygen of the guest carbonyl group. On the contrary, the $NH_2$ and $CH_3$ guest signals are upfield shifted up to 1.9 and 1.1 ppm, respectively, as a consequence of the anisotropy shielding effects exerted by the aromatic rings of the cavity, thus accounting for their inclusion into the host cavity. Similar results were also obtained with the other calixarene hosts **5**, **7**, and **10**.

In all titration experiments the $^1$H NMR spectra showed time-averaged signals for the free and complexed species. The binding constants ($K_{as}$), based on monitoring the NH signal of the host amidomethyl group (see Figure 1), were calculated using methods already described,[18] and the results are summarized in Table 1.

The analysis of the binding constants allowed us to make important considerations about the binding mode. The good complexation efficiency showed by hosts **5**, **6**, and **7** was the evidence that the recognition of the amide guests can occur only when the two distinct binding sites, the rigid calix[4]arene cavity and the additional group having hydrogen bond ability, are present in the same receptor. These results account for the cooperative action

(13) Arduini, A.; Pochini, A.; Secchi, A. *Eur. J. Org. Chem.* **2000**, 2325−2334.

(14) (a) Zaugg, H. E.; Martin, W. B. In *Organic Reactions*; Cope, A. C., Ed.; Wiley: New York, 1965; Vol. 14, pp 52−269. (b) Zaugg, H. E. *Synthesis* **1970**, 49−73. (c) Zaugg, H. E. *Synthesis* **1984**, 85−110.

(15) Zigeneur, G.; Voglar, K.; Pitter, R. *Montash. Chem.* **1954**, *85*, 1196−1207.

(16) For the synthesis of calix[4]arene derivatives using the Tscherniac−Einhorn amidomethylation reaction, see van Bommel, K. J. C.; Westerhof, F.; Verboom, W.; Reinhoudt, D. N.; Hulst, R. *J. Prakt. Chem.* **1999**, *341*, 284−290.

(17) (a) Hunter, C. A.; Packer, M. J. *Chem. Eur. J.* **1999**, *5*, 1891−1897. (b) Rüdiger, V.; Schneider, H.-J. *Magn. Reson. Chem.* **2000**, *38*, 85−89 and references therein.

(18) (a) Wilcox, C. S. In *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H.-J., Dürr, H., Eds.; VCH: Weinheim, 1991; pp 123−143. (b) Tsukube, H.; Furuta, H.; Odani, A.; Takeda, Y.; Kudo, Y.; Inoue, Y.; Liu, Y.; Sakamoto, H.; Kimura, K. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Eds.; Pergamon: Oxford, 1996; Vol. 8, pp 123−143.

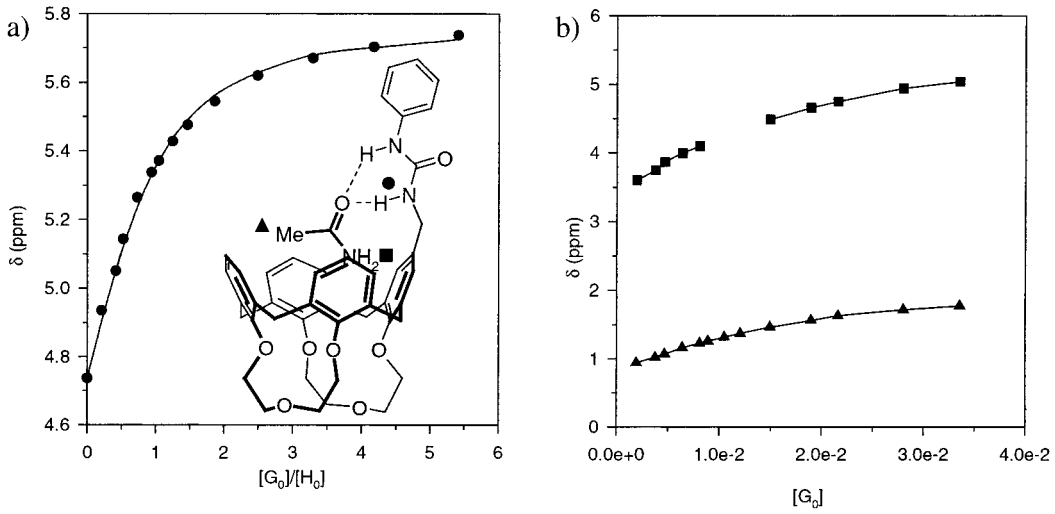



**Figure 1.** (a) Titration of host **6** with $CH_3CONH_2$ in $CDCl_3$ ($T$ = 300 K, initial concentrations [$\mathbf{6}_0$] = 9.4 × $10^{-3}$ M, [$G_0$] = 9.8 × $10^{-2}$ M), $K_{as}$ = 359 $M^{-1}$ determined monitoring the downfield shift of the host NH (●) signal; (b) chemical shifts of the guest signals recorded during the titration: $NH_2$ (■, few signals overlapped, $\delta$ free guest = 5.32 ppm) and $CH_3$ (▲, $\delta$ free guest = 2.02 ppm).

**Table 1. Association Constants ($K_{as}$, $M^{-1}$) for Hosts 1, 5−7, 10−12 with Formamide and Acetamide Guests[a]**

| guest | 1 | 5 | 6 | 7 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|
| $HCONH_2$ | *b* | 80(11) | 746(161) | 118(20) | 11(2) | *b* | *b* |
| $CH_3CONH_2$ | *b* | 12(2) | 342(25) | 37(4) | *b* | *b* | *b* |

[a] Determined by $^1$H NMR in $CDCl_3$ ($T$ = 300 K); all values result from at least duplicate experiments, standard deviations are in brackets. [b] Negligible complexation.

of the two binding sites in these molecular recognition processes which has been indirectly confirmed by the lack of complexation ability experienced by the calix[4]arene-bis(crown-3) **1**, and by *N*-benzyl-*N*′-phenylurea **11**.

The presence of two NH groups in the host increases its efficiency (**5** in comparison with **6** and **7**), whereas the results obtained with host **10** support the importance of the methylene group as spacer between the cavity and the hydrogen bond active binding site. The lower stability constants experienced by host **7** for both guests compared with those showed by **6** are not easy to rationalize. In fact it is well-known from the literature that calix[4]-arenes,[10a] or calix[6]arenes[19] bearing phenyl(thio)ureido groups, are in general better complexing agents, toward, for example, anion species, when compared with analogues receptors having the phenylureido groups. This behavior is usually justified, invoking the higher acidity[20] of the NH protons of the thioureido moiety as reported in a former work by Hamilton and co-worker,[21] although the effect of the O/S substitution on the NH acidity is far from fully understood. [22]

Finally, the comparison of the complexing ability of the rigid host **6** with those of the flexible analogue **12** further supports the importance of the cavity preorganization in determining the recognition of neutral molecules.

Considering that the phenylureido sidearm itself could, in principle, act as both hydrogen bond donor through its NH's or acceptor through its CO, it is quite remarkable to note that it is the rigid electron rich calix[4]arene cavity which governs the recognition process by pivoting also the receptor binding mode (see ahead).

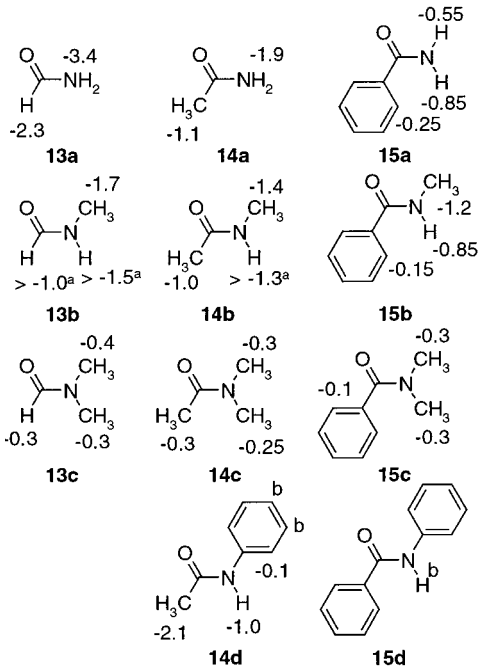



**Figure 2.** Chemical-induced shift (CIS) of proton amide guests **13**−**15** measured during the titration with host **6** in $CDCl_3$ ($T$ = 300 K). [a]Overlapped signals; [b]no significant variations of the signals.

The $^1$H NMR binding experiments were then extended to a series of amides, *N*-alkyl and *N*,*N*-dialkyl amides derived from formic (**13a**−**c**), acetic (**14a**−**d**), and benzoic acid (**15a**−**d**) (see Figure 2). This study was carried out using only host **6** because of its better binding efficiency. The association constants obtained are summarized in Table 2.

Host **6** is able to efficiently recognize amides bearing the $NH_2$ or NHR group (**13a**,**b**, **14a**,**b**, **14d**, and **15a**,**b**), whereas a substantial decrease of the $K_{as}$ was observed

(19) Scheerder, J.; Engbersen, J. F. J.; Casnati, A.; Ungaro, R.; Reinhoudt, D. N. *J. Org. Chem.* **1995**, *60*, 6448−6454.
(20) For the acidity of the thioamide group, see, for example, Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463.
(21) Fan, E.; Van Arman, S. A.; Kincaid, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1992**, *115*, 369−370.
(22) See, for example, Haushalter, K. A.; Lau, J.; Roberts, J. D. *J. Am. Chem. Soc.* **1996**, *118*, 8891−8896.

**Table 2. Association Constants ($K_{as}$, $M^{-1}$) for Host 6 with Amide Guests ($R^1CONR^2R^3$)[a]**

| $R^1$ | $R^2 = R^3 = H$ | $R^2 = CH_3$, $R^3 = H$ | $R^2 = R^3 = CH_3$ | $R^2 = C_6H_5$, $R^3 = H$ |
|---|---|---|---|---|
| H | **13a** 746(161) | **13b** 204(8) | **13c** 38(7) | *b* |
| $CH_3$ | **14a** 342(25) | **14b** 261(24) | **14c** 56(30) | **14d** 198(10) |
| $C_6H_5$ | **15a** 96(10) | **15b** 245(17) | **15c** < 10 | **15d**[c] |

[a] Determined by $^1H$ NMR in $CDCl_3$ ($T = 300$ K); all values result from at least duplicate experiments, standard deviations are in brackets. [b] Not determined. [c] Negligible complexation.

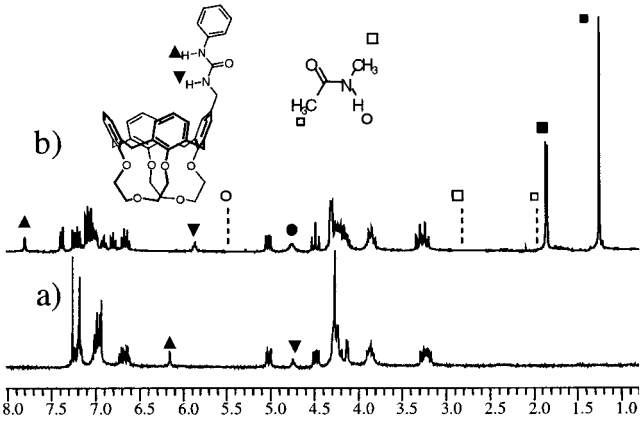



**Figure 3.** $^1H$ NMR spectra in $CDCl_3$ (300 MHz, 300 K): (a) free host **6**; (b) 1:1.5 complex **6** ⊃ **14b**. The host NH signals are designated as ▲ and ▼; free guest signals as ○, small open box, and □, whereas the complexed ones marked as ●, small solid box, and ■.

when the guest bears the *N*,*N*-dimethylamino groups (**13c**, **14c**, and **15c**). The comparison of the binding constants obtained with guests bearing phenyl groups (**14d**, **15a**, **15b**, and **15d**) gives useful information on the binding mode. Host **6** binds efficiently guests having only one bulky phenyl group either on the amino (acetanilide **14d**) or on the carbonyl group (benzamide **15a** and *N*-methylbenzamide **15b**), whereas the presence of two phenyl groups in the guest (**15d**) results in the complete lack of host−guest interaction. These results strongly support the inclusion of the $CH_3CONH$ and $CH_3NHCO$ groups into the aromatic cavity.

On the basis of these data and from the observation that, upon complexation, all the protons present in the guest are substantially upfield shifted (see Figures 2 and 3), we hypothesize the existence of two complementary binding modes. In particular $R^1CONH$ ($R^1$ = H or $CH_3$) or $CONHR^2$ ($R^2$ = H or $CH_3$) groups can interact with the aromatic cavity of **6** probably through NH−$\pi$ interactions[23,24] (see Figure 4).

The difference of the $K_{as}$ of host **6** with amide or *N*-methylamide derivatives of formic, acetic, and benzoic acid supports the hypothesis that the binding mode and consequently the intermolecular interactions are strongly

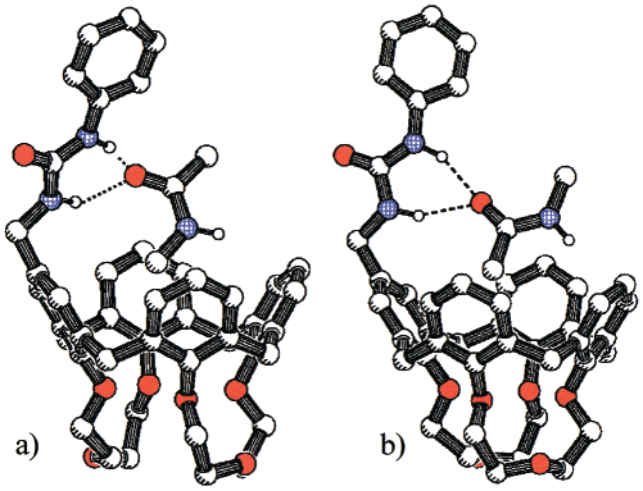



**Figure 4.** Energy-minimized structures (molecular mechanics, MM+ force field) of complex **6** ⊃ **14b**. Hydrogen atoms except those of the guest molecule and phenylureido group have been omitted for clarity: (a) *endo*-cavity $CONHCH_3$, (b) *endo*-cavity $NHCOCH_3$.

affected by the nature of $R^1$ group. In fact while formamide **13a** is better bound than *N*-methylformamide **13b**, the corresponding acetamide **14a** and *N*-methylacetamide **14b** are recognized with comparable efficiency. On the contrary, with benzoic acid derivatives **15a** and **15b**, a reversed efficiency was observed. Probably with formic derivatives the better matching of the geometrical requirements which favors the formation of two strong NH−$\pi$ aromatic interactions are fulfilled. On the contrary, the increase of steric requirements of the $R^1$ group results in a strong decrease of the specific interactions of the second NH so that the dispersion forces of the methyl group with the host cavity become relatively stronger.

In particular, the three amides formamide **13a**, acetamide **14a**, and benzamide **15a** showed CIS ($-\Delta\delta$) of their NH: 3.4, 1.9, and 0.6−0.9 ca. ppm, respectively (see Figure 2), and this is due to their different interactions with the calix[4]arene cavity. In the case of the *N*-methylamide derivatives **13b**, **14b**, and **15b** the *N*-methyl group experience upfield larger than that showed by the corresponding NH group, thus suggesting its deep engulfment into the cavity of the calix.

Finally some short considerations on the energy of the recognition process. Since it is known that amides bearing an NH group are associated in apolar organic solvents,[25,26] the energy balance for complex formation must overcome not only that required for the desolvation of the interacting species, but also that required by both host and guest self-dissociation. Thus, the energy gain in the host−guest complex formation could be due to the simultaneous interaction of the guest with the aromatic cavity and the additional binding site. The rigidified aromatic cavity interacts with the guest both by London dispersion forces and as well as hydrogen bond acceptor. These last intermolecular forces and in particular NH−$\pi$

(23) (a) Desiraju, G. R.; Steiner, T. *The Weak Hydrogen Bond*, *IUCr Monographs on Cristallography Vol. 9*; Oxford Science Pub.: Oxford, 1999. (b) Mitchell, J. B. O.; Nandi, C. L.; McDonald, I. K.; Thornton, J. M.; Price, S. L. *J. Mol. Biol.* **1994**, *239*, 315−331. (c) Malone, J. F.; Murrey, C. M.; Charlton, M. H.; Docherty, R.; Lavery, A. J. *J. Chem. Soc., Faraday Trans.* **1997**, *93*, 3429−3436. (d) Braga, D.; Grepioni, F.; Tedesco, E. *Organometallics* **1998**, *17*, 2669−2672. (e) Umezawa, Y.; Suboyama, S.; Takahashi, H.; Uzawa, J.; Nishio, M. *Tetrahedron* **1999**, *55*, 10047−10056.

(24) For an application of NH−$\pi$ aromatic interactions to molecular recognition see: Adams, H.; Carver, F. J.; Hunter, C. A.; Osborne, N. J. *Chem. Commun.* **1996**, 2529−2530.

(25) See, for eample, Fruwert, J.; Dombrowski, D.; Geiseler, G. *Z. Physik. Chem.* **1964**, *227*, 349.

(26) Dimerization constants for derivatives **6** and **7** ($K_d = 48 \pm 4$ and $15 \pm 3$, respectively) have been determined, assuming a dimeric structure, through $^1H$ NMR dilution experiments following the procedure reported by Horma, I.; Dreux, B. *Helv. Chim. Acta* **1984**, *67*, 754−764.

aromatic interactions seem to determine the efficiency and the selectivity in the recognition process of the amide.

**Conclusions.** This study demonstrates that the strategy to introduce an additional binding site properly designed onto the wider rim of the calix[4]arene cavity can yield receptors able to recognize neutral organic guests having specific functional groups in apolar media. The rigidity of the calix[4]arene cavity is an essential requisite to allow the additional sidearm to efficiently act as binding site.

Despite the stronger host−guest interactions with the phenylureido group, which can be predicted on the base of hydrogen bonding, it seems that the rigid calixarene cavity governs the whole recognition process. This binding site seems to operate not only by London dispersion forces but also by specific XH−$\pi$ aromatic interactions. These results could thus disclose the possibility to predict the interaction with new guests. In fact preliminary results show that dimethylurea is bound by host **6** with a binding constant $K_{as} = 745(90)$ $M^{-1}$ in $CDCl_3$. Studies are in progress to better understand whether specific interactions of amide NH of the guest with the aromatic cavity of calixarenes play a role in these recognition processes and to extend this approach to the design of new families of more complex receptors able to efficiently and selectively recognize guests bearing specific functional groups.

## Experimental Section

All reactions were carried out under nitrogen; all solvents were freshly distilled under nitrogen and stored over molecular sieves for at least 3 h prior to use. All other reagents were of reagent grade quality as obtained from commercial suppliers and were used without further purification. NMR spectra were recorded in $CDCl_3$ unless otherwise indicated. Mass spectra were determined in CI mode ($CH_4$). Melting point are uncorrected. As observed by other authors,[27] the elemental analysis of calixarenes are very often incorrect. Nevertheless, the spectral data were in full agreement with the proposed structure of these new compounds (see Supporting Information). Compound **1**,[4] **8**,[13] **11**,[28] and **12**[10a] were synthesized according to literature procedures.

**5-Bromo-25,26-27,28-bis(crown-3)-calix[4]arene (2).** To a solution of **1** (1.77 mmol, 1.0 g) in methyl ethyl ketone (100 mL) was added NBS (1.59 mmol, 0.28 g). The resulting mixture was stirred overnight and then diluted with ethyl acetate (100 mL) and treated with saturated aq $Na_2SO_3$ solution (100 mL). The organic layer was separated, washed with brine (2 × 100 mL), and dried ($Na_2SO_4$), and the solvent was completely evaporated in vacuo. Purification of the residue by chromatography (ethyl acetate/hexane, 60:40) gave 0.34 g (30%) of **2**: mp > 270 °C (dec). $^1$H NMR (300 MHz) $\delta$: 3.17, 3.23, 3.24, and 3.29 (4d, 4H, $J^1 = J^2 = J^3 = J^4 = 12.3$ Hz); 3.8−4.0 (m, 4H); 4.2−4.3 (m, 12H); 4.46, 4.50, 5.02, and 5.04 (4d, 4H); 6.77 (t, 3H, $J = 7.5$ Hz); 6.9−7.1 (m, 6H); 7.12 (bd, 2H). $^{13}$C (75 MHz) $\delta$: 29.5, 29.7, 30.5, 30.6, 74.4, 74.7, 76.2, 76.3, 76.4, 115.8, 123.7, 123.8, 127.9, 128.0, 128.3, 128.8, 128.9, 129.2, 130.7, 131.6, 134.4, 134.6, 135.2, 135.4, 135.5, 135.7, 137.6, 137.8, 154.7, 155.0, 155.1. CI(+) MS *m/e*: 644 [$MH^+$]. Anal. Calcd for $C_{36}H_{35}BrO_6 \cdot H_2O$: C, 65.36; H, 5.64. Found: C, 65.45; H, 5.66.

**5-Cyano-25,26-27,28-bis(crown-3)-calix[4]arene (3).** To a solution of **2** (1.56 mmol, 1.0 g) in DMF (30 mL) was added CuCN (3.12 mmol, 0.28 g). The resulting heterogeneous mixture was poured in a thick wall glass autoclave and then heated at 200 °C overnight. After cooling to rt, the solvent was completely evaporated in vacuo, and the sticky residue was extracted twice with hot ethyl acetate (2 × 50 mL). The combined organic phases were washed with brine (2 × 100 mL) and dried ($Na_2SO_4$), and the solvent was completely evaporated in vacuo (the separated water phase was carefully treated with aq sodium hypochlorite to destroy residual cyanide ions). Purification of the residue by chromatography (ethyl acetate/hexane, 50:50) gave 0.84 g (90%) of **3**: mp 278−280 °C. $^1$H NMR (400 MHz) $\delta$: 3.20, 3.21, 3.25, and 3.26 (4d, 4H, $J^1 = J^3 = 12.5$, $J^2 = J^4 = 12.2$ Hz); 3.8−4.0 (m, 4H); 4.1−4.4 (m, 12H); 4.47, 4.50, 5.03, and 5.10 (4d, 4H); 6.71 (t, 1H, $J = 7.5$ Hz); 6.80 (bt, 2H, $J = 7.6$ Hz); 6.9−7.0 (m, 4H); 7.06 (bt, 2H, $J = 7.2$ Hz); 7.23 and 7.25 (dd, 2H, $J = 2.0$ Hz). $^{13}$C (75 MHz) $\delta$: 29.4, 29.8, 30.5, 30.6, 73.6, 74.2, 74.7, 74.9, 76.0, 76.3, 76.4, 107.1, 119.3, 123.6, 123.8, 124.0, 128.0, 128.7, 128.9, 129.1, 129.5, 132.2, 133.2, 134.1, 134.5, 134.9, 135.8, 136.1, 136.9, 151.3, 155.0, 155.4, 158.9. CI(+) MS *m/e*: 590 [$MH^+$]. IR(KBr) $\nu$ ($cm^{-1}$): 2224 (w). Anal. Calcd for $C_{37}H_{35}NO_6 \cdot H_2O$: C, 73.13; H, 6.14; N, 2.30. Found: C, 73.52; H, 6.35; N, 2.28.

**5-Aminomethyl-25,26−27,28-bis(crown-3)-calix[4]-arene (4).** To a solution of **3** (0.93 mmol, 0.55 g) in dry THF (20 mL) was added $B_2H_6$ (1 M solution in THF, 10 mL). The resulting mixture was refluxed overnight under argon atmosphere, cooled, treated with methanol (20 mL, CAUTION!), and then refluxed for additional 30 min. The solvent was then completely evaporated in vacuo and the residue taken up with $CH_2Cl_2$ (50 mL) and saturated aq $Na_2CO_3$ solution (50 mL). The organic layer was separated, washed with brine (2 × 100 mL), and dried ($Na_2SO_4$), and the solvent was completely evaporated in vacuo. Purification of the residue by chromatography ($CH_2Cl_2/CH_3OH$, 50:50) gave 0.50 g (90%) of **4**: mp 211 °C (dec). $^1$H NMR (300 MHz) $\delta$: 2.46 (bs, 2H); 3.21 and 3.26 (2d, 4H, $J^1 = 12.0$, $J^2 = 12.3$ Hz); 3.39 (bs, 2H); 3.8−3.9 (m, 4H); 4.2−4.4 (m, 12H); 4.46, 4.50, 5.01, and 5.03 (4d, 4H, $J^1 = J^2 = J^3 = J^4 = 12.0$ Hz); 6.56 (bt, 1H); 6.77 (t, 2H, $J = 6.9$ Hz); 6.9−7.1 (m, 8H). $^{13}$C (25 MHz) $\delta$: 29.7, 29.8, 30.7, 45.2, 74.6, 74.7, 76.2, 123.6, 123.7, 127.1, 127.9, 128.0, 128.8, 128.9, 129.0, 135.3, 135.4, 135.6, 154.1, 155.1. CI(+) MS *m/e*: 595 [$MH + 1^+$]. Anal. Calcd for $C_{37}H_{39}NO_6 \cdot 3/2H_2O$: C, 71.59; H, 6.82, N, 2.26. Found: C, 71.52; H, 6.90; N 2.32.

**5-(4-Methylbenzenesulfonamido)methyl-25,26−27,28-bis(crown-3)-calix[4]arene (5).** To a solution of **4** (0.84 mmol, 0.5 g) in dry $CH_2Cl_2$ (25 mL) were added pyridine (4.2 mmol, 0.33 g) and TsCl (1.25 mmol, 0.24 g). The resulting mixture was stirred for 2 h, poured into water (50 mL), and diluted with $CH_2Cl_2$ (50 mL). The organic layer was separated, washed with water (2 × 100 mL), and dried ($Na_2SO_4$), and the solvent was completely evaporated in vacuo. Purification of the residue by chromatography (ethyl acetate/hexane, 40:60) gave 0.22 g (35%) of **5**: mp 170 °C (dec). $^1$H NMR (300 MHz) $\delta$: 2.43 (s, 3H), 3.10, 3.16, 3.20, and 3.26 (4d, 4H, $J^1 = 12.1$, $J^2 = 12.8$, $J^3 = 12.6$, $J^4 = 12.3$ Hz); 3.7−3.9 and 3.88 (m and d, 6H, $J = 5.9$ Hz); 4.1−4.3 (m, 12H); 4.36 (bt, 1H); 4.43, 4.47, 4.97, and 5.01 (4d, 4H); 6.7−6.8 (m, 5H); 6.8−7.0 (2m, 6H); 7.30 (d, 2H, $J = 8.1$ Hz); 7.73 (d, 2H). $^{13}$C (25 MHz) $\delta$: 21.7, 30.0, 31.0, 47.3, 75.0, 76.6, 123.8, 124.0, 127.2, 128.0, 128.2, 128.9, 129.2, 129.9, 131.3, 136.0, 155.3, 155.5. CI(+) MS *m/e*: 748 [$MH^+$]. IR(KBr) $\nu$ ($cm^{-1}$): 3435 (s); 1455 (s). Anal. Calcd for $C_{44}H_{45}NO_8S \cdot H_2O$: C, 69.00; H, 6.18, N, 1.83; S, 4.19. Found: C, 69.02; H, 6.21; N, 1.80; S 4.13.

**5-Amino-25,26−27,28-bis(crown-3)-calix[4]arene (9).** To a solution of **8** (1.64 mmol, 1.0 g) in absolute $C_2H_5OH$ (100 mL) were added a spatula tip of Pd/C catalyst (CAUTION!) and $NH_2NH_2 \cdot H_2O$ (16.4 mmol, 0.82 g, CAUTION!). The resulting heterogeneous mixture was refluxed overnight and cooled, and the palladium catalyst was filtered off on Celite under nitrogen atmosphere. The resulting solution was completely evaporated in vacuo, and the residue was partitioned between water (100 mL) and $CH_2Cl_2$ (100 mL). The organic layer was separated, the water phase was further extracted with $CH_2Cl_2$, the combined organic portions were washed twice with brine and dried with $CaCl_2$, and the solvent was completely evaporated to dryness. Purification of the residue by

(27) (a) Böhmer, V.; Jung, K.; Schon, M.; Wolff, A. *J. Org. Chem.* **1992**, *57*, 790−792. (b) Gutsche, C. D.; See, K. A. *J. Org. Chem.* **1992**, *57*, 4527−4539.

(28) Suto, M. J.; Gayo-Fung, L. M.; Palanki, M. S. S.; Sullivan, R. *Tetrahedron* **1998**, *58*, 4141−4150.

chromatography (ethyl acetate/hexane, 50:50) gave 0.85 g (90%) of **9**: mp 228−230 °C. $^1$H NMR (300 MHz) $\delta$: 3.09, 3.14, 3.22, and 3.27 (4d, 4H, $J^1 = J^2 = 12.0$, $J^3 = J^4 = 12.3$ Hz); 3.7−3.9 (m, 4H); 4.1−4.3 (m, 14H); 4.42, 4.50, 4.96, and 5.03 (4d, 4H); 6.31 and 6.33 (dd, 2H, $J = 2.7$ Hz); 6.74 (t, 3H, $J = 7.5$ Hz); 6.9−7.1 (m, 6H). $^{13}$C (75 MHz) $\delta$: 29.7, 29.8, 30.7, 74.5, 74.6, 74.7, 74.8, 76.1, 76.2, 76.4, 115.0, 116.1, 123.5, 123.6, 128.0, 128.8, 128.9, 135.3, 135.4, 135.6, 135.9, 141.4, 148.0, 155.0, 155.2. CI(+) MS *m/e*: 580 [MH$^+$]. IR(KBr) $\nu$ (cm$^{-1}$): 3457 (s); 3380 (s). Anal. Calcd for $C_{36}H_{37}NO_6 \cdot {}^1/_2H_2O$: C, 73.45; H, 6.51, N, 2.38. Found: C, 73.78; H, 6.62; N, 2.25.

**General Procedure for the Synthesis of Cavitands 6, 7, and 10.** A solution of the appropriate amino derivative (**4** or **9**, 1 mmol) in dry $CH_2Cl_2$ (25 mL) was reacted with the proper electrophile (tosyl chloride, phenyl isocyanate, or phenyl isothiocyanate, 1.1 mmol). The resulting mixture was stirred for 8 h, poured into water (50 mL), and diluted with $CH_2Cl_2$ (50 mL). The organic layer was separated, washed with water (2 × 100 mL), and dried ($Na_2SO_4$), and the solvent was completely evaporated in vacuo.

**5-(*N*-Phenylureido)methyl-25,26−27,28-bis(crown-3)-calix[4]arene (6):** eluent ethyl acetate/hexane, 40:60; 0.5 g (70%); mp 178−180 °C. $^1$H NMR (300 MHz) $\delta$: 3.19, 3.21, 3.24, and 3.27 (4d, 4H, $J^1 = J^4 = 12.0$, $J^2 = 11.9$, $J^3 = 12.3$ Hz); 3.8−3.9 (m, 4H); 4.13 (d, 2H, $J = 4.8$ Hz); 4.2−4.3 (m, 12H); 4.47 and 4.50 (2d, 2H); 4.75 (bt, 1H); 5.01 and 5.02 (2d, 2H); 6.16 (s, 1H); 6.6−6.7 (m, 3H); 6.9−7.1 (m, 9H); 7.1−7.2 (m, 4H). $^{13}$C (75 MHz) $\delta$: 29.6, 29.7, 30.6, 44.2, 74.6, 74.7, 74.8, 76.3, 76.4, 120.8, 123.4, 123.7, 123.8, 127.4, 127.9, 128.1, 128.3, 128.8, 129.1, 135.4, 135.5, 135.7, 135.8, 154.8, 155.1, 155.2. CI(+) MS *m/e*: 713 [MH$^+$]. Anal. Calcd for $C_{44}H_{44}N_2O_7 \cdot H_2O$: C, 72.31; H, 6.34, N, 3.83. Found: C, 72.41; H, 6.36; N, 3.75.

**5-(*N*-Phenyl(thio)ureido)methyl-25,26−27,28-bis(crown-3)-calix[4]arene (7)**: eluent ethyl acetate/hexane, 50:50; 0.58 g (80%); mp 149−151 °C. $^1$H NMR (300 MHz) $\delta$: 3.1−3.3 (m, 4H); 3.8−3.9 (m, 4H); 4.2−4.3 (m, 12H); 4.46 and 4.48 (2d, 2H, $J^1 = J^2 = 12.1$ Hz); 4.6−4.7 (m, 2H); 5.01 and 5.02 (2d, 2H, $J^1 = J^2 = 12.0$ Hz); 6.11 (bs, 1H); 6.6−6.7 (m, 3H); 6.88 (s, 2H); 6.9−7.0 (m, 9H); 7.11 (d, 2H, $J = 7.5$ Hz); 7.2−7.4 (m, 2H); 7.56 (bs, 1H). $^{13}$C (75 MHz) $\delta$: 29.7, 30.7, 49.3, 74.5, 74.6, 74.8, 76.3, 76.4, 123.6, 123.7, 125.1, 127.0, 127.2, 127.9, 128.0, 128.1, 128.8, 128.9, 129.0, 130.2, 131.8, 135.2, 135.4, 135.5, 135.7, 135.8, 136.0, 154.8, 155.1, 155.2, 180.8. CI(+) MS *m/e*: 729 [MH$^+$]. IR(KBr) $\nu$ (cm$^{-1}$): 3390 (s), 1450 (s). Anal. Calcd for $C_{44}H_{44}N_2O_6S \cdot {}^1/_2H_2O$: C, 71.62; H, 6.15, N, 3.80, S, 4.35. Found: C, 71.81; H, 6.15; N, 3.67; S, 3.89.

**5-(*N*-Phenylureido)-25,26:27,28-bis(crown-3)-calix[4]-arene (10):** eluent ethyl acetate/hexane, 50:50; 0.49 g (70%); mp 205−207 °C. $^1$H NMR (300 MHz) $\delta$: 3.1−3.3 (m, 4H); 3.7−4.0 (m, 4H); 4.1−4.4 (m, 12H); 4.49, 4.50, 5.05, and 5.06 (4d, 4H, $J^1 = J^2 = 12.2$ Hz, $J^3 = J^4 = 12.1$ Hz); 6.08 (s, 1H); 6.32 (s, 1H); 6.63 (t, 1H, $J = 7.5$ Hz); 6.7−6.8 (m, 2H); 6.87(bd, 2H); 6.9−7.0 and 7.1−7.2 (2m, 11H). $^{13}$C (75 MHz) $\delta$: 29.7, 30.7, 73.8, 74.0, 75.1, 75.2, 76.2, 76.3, 120.2, 123.3, 123.4, 123.5, 123.9, 124.4, 127.8, 128.0, 128.3, 128.7, 129.0, 132.2, 135.1, 135.6, 135.7, 136.0, 136.4, 138.1, 153.7, 154.7, 155.5. CI(+) MS *m/e*: 699 [MH$^+$]. IR (KBr) $\nu$ (cm$^{-1}$): 3386 (s), 1653−1598 (s). Anal. Calcd for $C_{43}H_{42}N_2O_7 \cdot {}^1/_2H_2O$: C, 72.97; H, 6.12, N, 3.96. Found: C, 73.41; H, 6.26; N, 3.75.

**Direct Synthesis of 5-(*N*′-Phenylureido)methyl-25,26−27,28-bis(crown-3)-calix[4]arene (6).** To a solution of **1** (3.3 mmol, 1.85 g) in $CH_2Cl_2$ (60 mL) and $CF_3COOH$ (20 mL) solvents mixture, maintained at 0 °C, was dropwise added (10 min) a solution of $C_6H_5NHCONHCH_2OH$ (1.98 mmol, 0.32 g) in $CH_2Cl_2$ (20 mL). The resulting purple mixture was allowed to stir at room temp for 1 h and then quenched with water (100 mL). The organic phase was separated and washed with saturated aq $Na_2CO_3$ up to neutrality and dried ($Na_2SO_4$), and the solvent was completely removed under reduced pressure. The solid residue was purified by chromatography (see above); 0.57 g (25%).

**Acknowledgment.** We thank the Ministero dell' Università e della Ricerca Scientifica e Tecnologica (MURST) "Supramolecular Devices" project, for financial support and C.I.M. (Centro Interdipartimentale di Misure "G. Casnati") of the University of Parma for NMR and mass measurements.

**Supporting Information Available:** Copies of $^1$H NMR spectra of new compounds **2**−**7**, **9**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO005596N