A Modular Approach to Potential Synthetic Receptors with Large Surfaces Based on Crown[*n*]cavitands

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Crown[*n*]cavitands were synthesized by alkylation of tetrahydroxycavitands with polyethyleneglycol ditosylates. The bridging of two hydroxy groups at adjacent aromatic rings by a pentaethyleneglycol unit is favored over the bridging of two hydroxy groups at opposite aromatic rings. The presence of a sodium base enhances the formation of the 1,2-crown[*n*]cavitand and improves the yield. The combination of 1,2-crown[6]cavitands with calix[4]arenes or resorcin[4]arenes resulted in potential receptor molecules with large hydrophobic surfaces.

Our modular approach towards synthetic receptors with large well-defined cavities is based on the proper combination of medium-sized building blocks[1]. Building blocks that are widely used in the field of supramolecular chemistry are cyclodextrins, porphyrins, steroids, calix[4]arenes, and resorcin[4]arenes. Previously, we have described the synthesis of several classes of synthetic receptor molecules by combination of calix[4]arenes with β-cyclodextrins[2] and porphyrins[3].

The combination of calix[4]arenes and resorcin[4]arenes can be achieved in different ways. In a 1:1 ratio a calix[4]arene and a resorcin[4]arene can form a carcerand that encapsulates amides, sulphoxides, or ketones[4]. The combination of two calix[4]arenes and two resorcin[4]arenes yields a molecule that has a much larger, rigid cavity of nanosize dimensions[5]. Combinations of either two calix[4]arenes and one resorcin[4]arene[6] or of one calix[4]arene and two resorcin[4]arenes[7] afford more flexible receptor molecules with large preorganized cavities or surfaces that complex steroids, sugar derivatives, and alkaloids in non-aqueous media.

Several groups have combined calix[4]arenes also with crown ethers. The advantage of these *calix[4]crowns*, a very useful class of compounds, is the proximity of a hydrophobic cavity of the calix[4]arene and the binding sites of the crown ether. The efficiency and selectivity in ion binding of these calix[4]arene ionophores depends on the ring size and on the nature of the additional binding sites, and on the conformation of the calix[4]arene (cone, partial cone, 1,3-alternate, or 1,2-alternate)[8]. For example, while 1,3-calix[4]arene-crown[6] ionophores in the 1,3-alternate conformation, incorporated in supported liquid membranes, transport cesium cations with a high preference over sodium cations[8a], 1,3-calix[4]arene-crown[5] ionophores in the 1,3-alternate conformation show high selectivities for potassium[8b].

The more rigid cavitands provide a higher degree of preorganization of functional groups attached to this building block. Until now, tetrafunctionalized cavitands have been used primarily for the synthesis of (hemi)carcerands[9] and only a limited number of selectively functionalized resorcin[4]arenes has been described in the literature[10].

In this paper we describe our work on crown[*n*]cavitands[11] **1**–**3** and biscrown[6]cavitand **5** as a further example of our "building block approach". The remaining two hydroxy groups at adjacent aromatic rings of crown[*n*]cavitands **1**–**3** offer the possibility to combine these molecules with other building blocks. Combinations of crown[6]cavitands with other resorcin[4]arenes and with 1,2-difunctionalized calix[4]arenes will also be discussed. These are starting materials for receptor molecules with a large hydrophobic surface and a crown ether fragment as an additional binding site. These are comparable with the calix-resorcinarene combinations as described previously by our group[5][6][7].

Results and Discussion

Synthesis of Crown[*n*]cavitands[12]

Calix[4]crowns have been synthesized by alkylation of the lower rim of a calix[4]arene with a polyethyleneglycol ditos-

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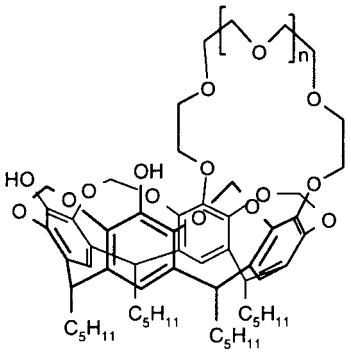
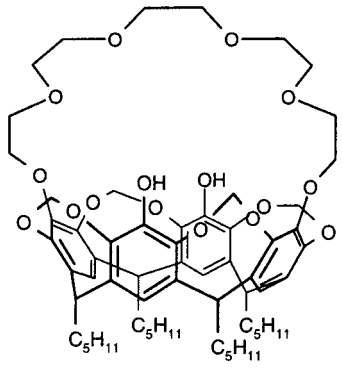
ylate, the base used determines in which conformation the calix[4]arene is fixed[8][13]. Alkylation of tetrahydroxycavitand **6** (Scheme 2) with polyethyleneglycol ditosylates can afford different products: a 1,2-crown[*n*]cavitand (**1**−**3** in Scheme 1) in which two hydroxy groups at adjacent rings are connected, a 1,3-crown[*n*]cavitand (**4** in Scheme 1) in which two hydroxy groups at opposite rings are connected, or a biscrown[*n*]cavitand (**5** in Scheme 1) in which two crown units each link two hydroxy groups at adjacent rings.

Scheme 1



1 n = 1
2 n = 2
3 n = 3



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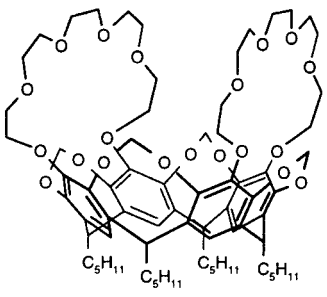

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To study the influence of the reaction conditions on the product distribution of the reaction between tetrahydroxycavitand **6** and a polyethyleneglycol ditosylate, the reaction with pentaethyleneglycol ditosylate was performed with different bases and in two different solvents. The results are summarized in Table 1.

Scheme 2

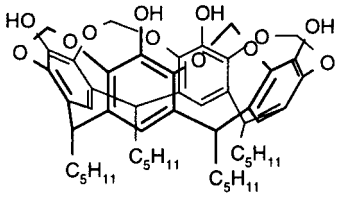

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Table 1. Results of the synthesis of crown[*n*]cavitands by reaction between tetrahydroxycavitand **6** and polyethyleneglycol ditosylates

Entry	Glycol ditosylate[a]	Solvent	Base	Yield (%) tetrol[b]	1,2-crown	1,3-crown	bis-crown
1	$n = 5$	DMF	NaH	21	33	–	–
2	$n = 5$	DMF	Na_2CO_3	22	18	–	–
3	$n = 5$	DMF	K_2CO_3	22	2	2	8
4	$n = 5$	DMF	Cs_2CO_3	40	2	2	10
5	$n = 5$	CH_3CN	Na_2CO_3	3	13	3	–
6	$n = 4$	DMF	NaH	6	8	–	–
7	$n = 6$	DMF	NaH	27	20	–	–

[a] Three different polyethyleneglycol ditosylates were used: tetra-, penta-, and hexaethyleneglycol ditosylate indicated by $n = 4$, 5, and 6, respectively. – [b] Unreacted **6** which was isolated.

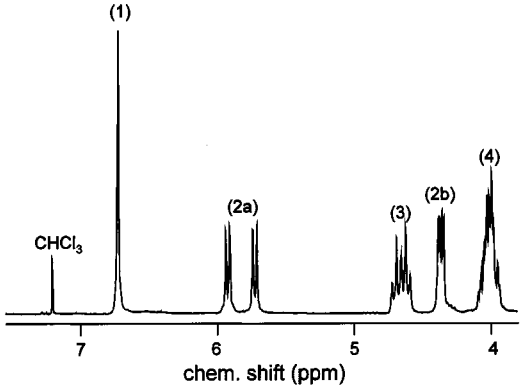
Alkylation of tetrahydroxycavitand **6** with 1.2 equivalents of pentaethyleneglycol ditosylate with NaH as a base in DMF (entry 1 in Table 1)
gave 1,2-crown[6]cavitand **2** in 33% yield, while 21% of unreacted tetrahydroxycavitand **6** was isolated. Under the same reaction conditions, except with Na_2CO_3 as a base instead of NaH (entry 2 in Table 1), a lower yield of 1,2-crown[6]cavitand **2** (18%) and a comparable amount of unreacted starting material was obtained.

When the reaction was carried out with K_2CO_3 (entry 3 in Table 1), besides unreacted tetrahydroxycavitand **6** (22%), 8% of biscrown[6]cavitand **5** was isolated, together with small amounts of 1,2-crown[6]cavitand **2** and 1,3-crown[6]cavitand **4** (both 2%). With Cs_2CO_3 as a base (entry 4 in Table 1) a similar product distribution was obtained with the biscrown[6]cavitand as the major product, although in a very modest yield (10%).

The different products can be easily distinguished by the ^{1}H-NMR spectra. For the 1,2-crown[6]cavitand **2** and 1,3-crown[6]cavitand **4** two aromatic signals of equal intensity are present while biscrown[6]cavitand **5** gives rise to only one aromatic signal (for the ^{1}H-NMR spectrum of **5** see Figure 1). The 1,2- and the 1,3-crown[6]cavitand can be distinguished by the doublets for the methylene hydrogen atoms of the cavitands at $\delta \approx 6$. While in the case of 1,3-crown[6]cavitand **4** only one doublet is present, 1,2-crown-[6]cavitand **2** gives rise to a combination of doublets in the ratio 1:2:1.

Besides DMF, also CH_3CN was used as a solvent in a reaction with Na_2CO_3 as a base. Under these conditions 1,2-crown[6]cavitand **2** was obtained as the major product in 13% yield (entry 5 in Table 1).

Figure 1. ^{1}H-NMR spectrum of biscrown[6]cavitand **5** in $CDCl_3$ at room temperature; (1) signal for aromatic hydrogen atom, (2a) and (2b) doublets for the methylene hydrogen atoms of the cavitands (OCH_2O), (3) triplets for the methylene hydrogen atoms of the cavitands (ArCHRAr), and (4) multiplet for a part of the crown moiety



Reaction of tetrahydroxycavitand **6** with the shorter tetraethyleneglycol ditosylate was performed with NaH as a base in DMF (entry 6 in Table 1). Only a small amount (8%) of 1,2-crown[5]cavitand **1** was obtained. Reaction with the longer hexaethyleneglycol ditosylate was performed under the same conditions and afforded 1,2-crown[7]cavitand **3** in a reasonable yield of 20%.

The results of the alkylations of tetrahydroxycavitand **6** with polyethyleneglycol ditosylates indicate that the bridging of two hydroxy groups at adjacent aromatic rings leading to 1,2-crown[*n*]cavitands **1**−**3** is favored over the formation of 1,3-crown[*n*]cavitands **4**. In the case of the reaction of tetrahydroxycavitand **6** with pentaethyleneglycol ditosylate, 1,2-crown[6]cavitand **2** is obtained in the highest yields with a sodium base (either NaH or Na_2CO_3). This might indicate that there is a template effect of the cation used. Folding of the polyethyleneglycol unit around the cation after formation of the first bond, brings the second tosyl group closer to a hydroxy group of an adjacent aromatic ring and consequently, enhances the formation of 1,2-crown[*n*]cavitands. The results indicate that the size of sodium is the most appropriate for bridging two hydroxy groups at adjacent aromatic rings by a pentaethyleneglycol unit.

If the reaction is performed in CH_3CN instead of DMF the yields decline.

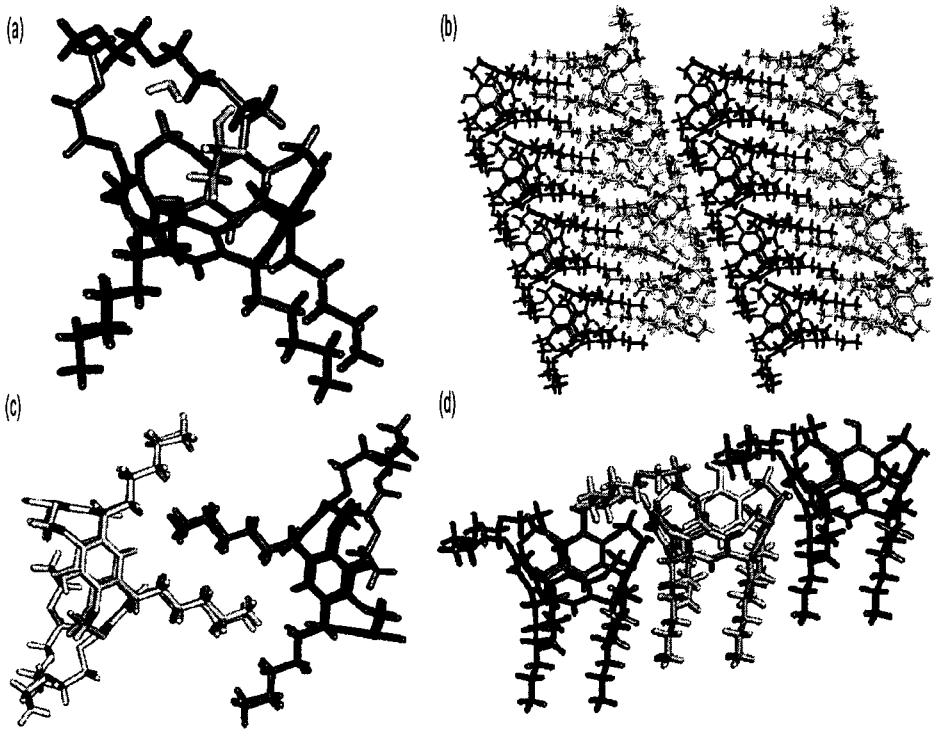
Reactions with the shorter tetra-, and with the longer hexaethyleneglycol ditosylate seem to indicate that in case of the 1,2-crown[5]cavitand **1** the crown is too much strained (this can also be seen from CPK molecular models) which lowers the yield while the larger crown is suitable for bridging adjacent hydroxy groups; 1,2-crown[7]cavitand **3** was obtained in a reasonable yield.

Crystal Structure of 1,2-Crown[6]cavitand 2

Recrystallization of 1,2-crown[6]cavitand **2** from a mixture of CH_2Cl_2 and ethanol gave suitable single crystals for X-ray analysis (see Figure 2).

The X-ray crystal structure clearly shows the local C_{4v} symmetry of the resorcin[4]arene moiety[14]. Although the crown ether linkage is positioned partly above the two aromatic rings to which it is connected, it adopts more an oval than a ring conformation. The methyl group of an included ethanol molecule is inside the resorcin[4]arene cavity. A

Figure 2. X-ray structure liquorice representations of 1,2-crown[6]cavitand **2**[27], (a) monomer structure with ethanol and water molecule, (b) packing of the molecule with bilayer formation, (c) tail-tail folding, and (d) side view of folding crown moieties



water molecule donates hydrogen bonds to an oxygen atom of the crown moiety and with the oxygen atom of the ethanol molecule [Figure 2a, the donor···acceptor distances are 2.857(6) and 2.806(6) A, respectively]. A second water molecule donates hydrogen bonds to the first water molecule and the crown moiety [O···O distances of 2.831(5) and 2.916(5) A, respectively].

Furthermore, the X-ray crystal structure shows a very interesting packing of the molecules (Figure 2b). The cavitands align in one plane and form some sort of bilayer; the last carbon atoms of the pentyl chains at the bottom stick in between the alkyl chains of the next layer (Figure 2c). The crown moiety bends over the hydroxyl groups of the neighboring cavitand (Figure 2d), forming aligning planes of molecules. Hydrogen bonds involving the free hydroxy groups form links between the bilayers.

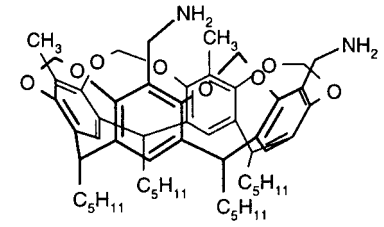
Combination of 1,2-Crown[6]cavitand 2 with 1,2-Bis(chloroacetamidomethyl)cavitand 8; Synthesis of Methylcavitand-Cavitand-crowns 9 and 10

Previously, we have described flexible "hemicarcerands" in which the two cavitands are linked via two linkages; partly bridged cavitands were selectively debrominated and the remaining two bromo atoms were substituted by hydroxy groups to give a 1,2-diol cavitand. Two of these cavitands were coupled with bromochloromethane to give a hemicarcerand[15].

Chloroacetamidomethyl functionalities at the cavitand platform starting from aminomethyl-functionalized cavitands offers the possibility to react these with hydroxy-functionalized cavitands.

As a starting compound for combinations with hydroxy-functionalized cavitands, 1,2-bis(chloroacetamidomethyl)-cavitand **8** was synthesized in 95% yield by reaction of 1,2-bis(aminomethyl)cavitand **7** with chloroacetyl chloride.

Scheme 3



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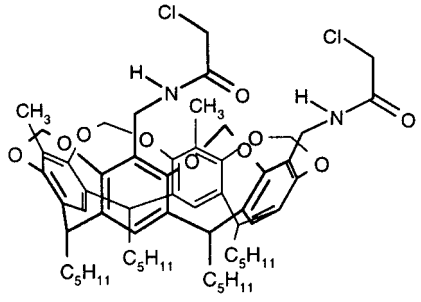

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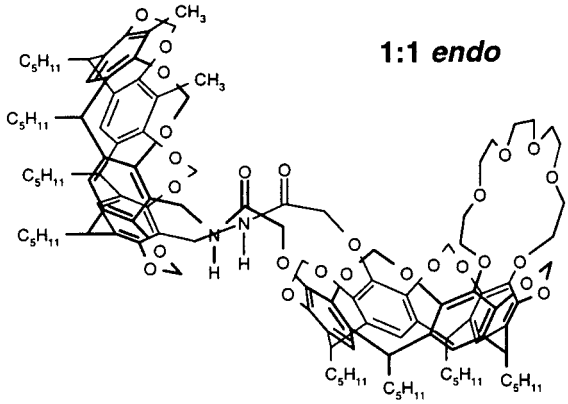
Scheme 4



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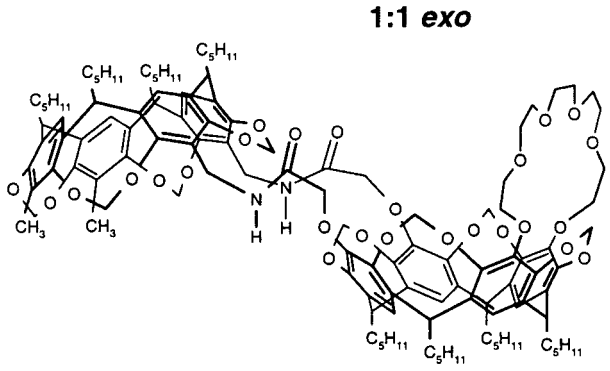

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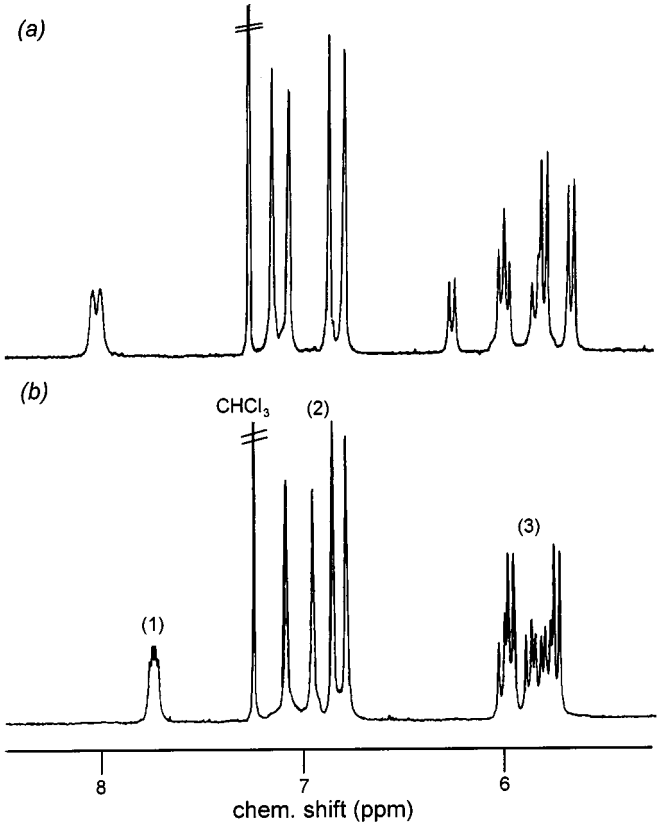
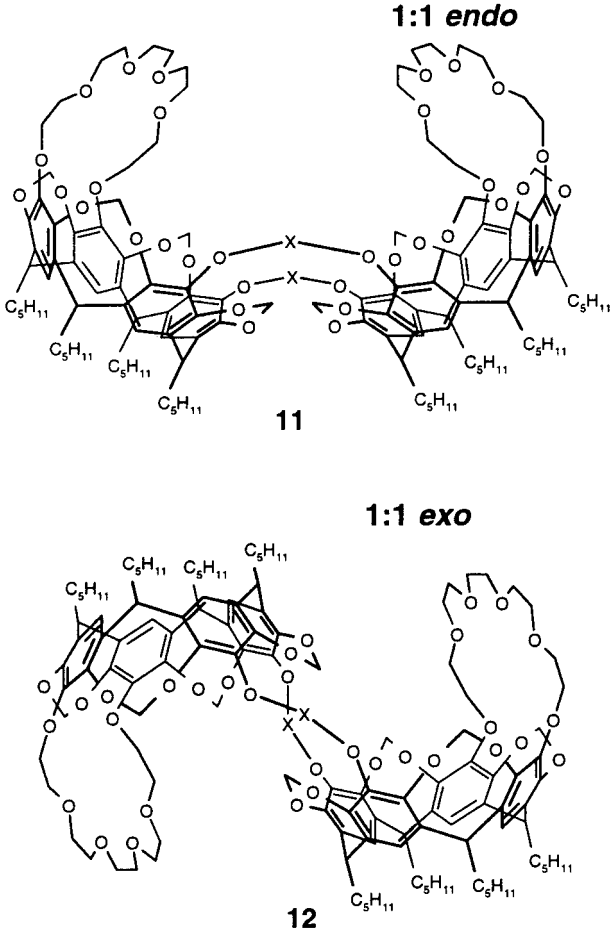
Reaction between 1,2-crown[6]cavitand **2** and 1,2-bis(chloroacetamidomethyl)cavitand **8** was performed in CH_3CN in a 1:1 ratio with Cs_2CO_3 as a base. After separation by column chromatography, two products (isomer **A1** and isomer **B1**) were isolated both in approximately 35% yield. The FAB MS data of both products are almost identical and clearly show a signal for 1:1 coupled resorcin[4]arenes, in addition to signals for $[M + Na]^+$ and $[M + K]^+$. Comparable with all the combinations of two building blocks via two linkages[6], reaction of 1,2-crown[6]cavitand **2** with 1,2-bis(chloroacetamidomethyl)cavitand **8** can in principle lead to two different diastereoisomers, namely 1:1 *endo* isomer **9** and 1:1 *exo* isomer **10** (Scheme 4). The ^{1}H-NMR spectra of the two products are to a large extent similar (Figure 3). In both ^{1}H-NMR spectra four singlets are present for the aromatic hydrogen atoms, and the signals for the outer methylene hydrogen atoms clearly show two combinations both in a 1:2:1 ratio, as expected. The spectra show that the desired 1:1 crown[6]cavitand-cavitand combinations **9** and **10** are formed, although it is not possible to determine which product is the *endo* isomer and which is the *exo* isomer.

Figure 3. ^{1}H-NMR spectra of 1:1 crown[6]cavitand-cavitand combinations (a) isomer **A1** and (b) isomer **B1** in $CDCl_3$ at room temperature; (1) signal for amide hydrogen atom, (2) signal for aromatic hydrogen atoms, and (3) doublets for the methylene hydrogen atoms of the cavitands (OCH_2O)



Scheme 5



Combination of Two 1,2-Crown[6]cavitands 2; Synthesis of Bis(crown[6]cavitands) 11 and 12

Connection of two 1,2-crown[6]cavitands **2** via symmetrical spacers will lead to more symmetrical biscrown 1:1 products, namely 1:1 *endo* **11** and 1:1 *exo* **12** (Scheme 5).

To combine two 1,2-crown[6]cavitands, spacers were used which were also applied in the synthesis of carcerands[16]. First the rigid *meta*-xylene was introduced as a spacer.

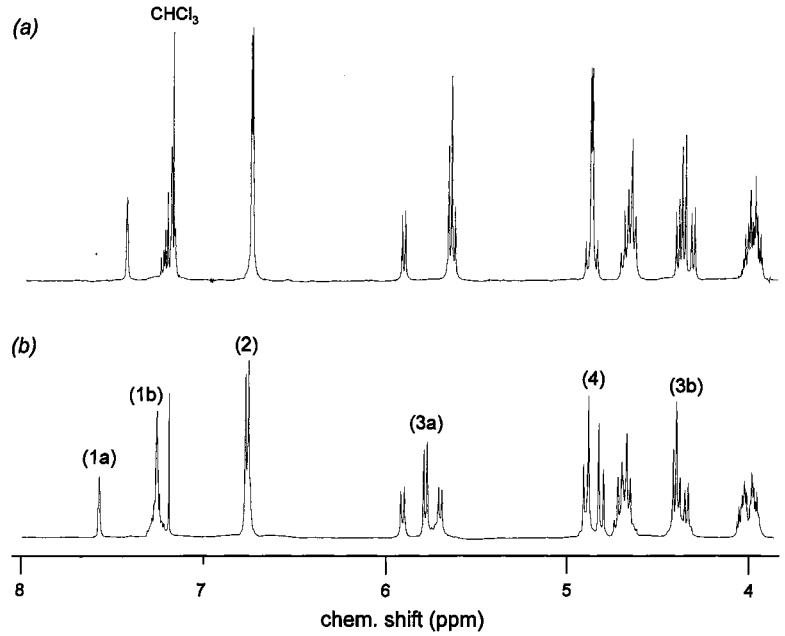
Reaction between 1,2-crown[6]cavitand **2** and α,α-dibromo-*meta*-xylene was performed in a 1:1 ratio to prevent the formation of only dialkylated crown[*n*]cavitands and to enhance reactions in which two cavitands are connected, and under the same conditions as described above. After separation by column chromatography, two products (1:1 *endo* **11a** and 1:1 *exo* **12a**) were obtained, both in approximately 40% yield.

The FAB MS and the ^{1}H-NMR (Figure 4) data clearly showed that 1:1 bis(crown[6]cavitands) are formed. In the ^{1}H-NMR spectra, both compounds display two singlets for the aromatic cavitand hydrogen atoms (signals 2 in Figure 4), and the signals for the outer (signals 3a in Figure 4) and for the inner (signals 3b in Figure 4) methylene hydrogen atoms show combinations of signals in a 1:2:1 ratio, indicating that both remaining hydroxy groups of 1,2-crown[6]cavitand **2** have reacted to the same functional group. Furthermore, in the ^{1}H-NMR spectra a singlet and a multiplet are present for the aromatic xylene hydrogen atoms (signals 1a and 1b in Figure 4), and the xylene methylene hydrogen atoms give doublets at $\delta \approx 4.9$ (signals 4 in Figure 4) showing that there is a restricted rotation of the xylene units and that they are symmetrically substituted.

To determine which isomer is 1:1 *endo* **11a** and which is 1:1 *exo* **12a**, 2D-NMR experiments were performed. NOE contacts between aromatic hydrogen atoms of the xylene bridge and methylene hydrogen atoms of the cavitands show that the bridging xylene units "wiggle" in both isomers.

With the NOE spectra it was possible to assign the stereochemistry of the isomers 1:1 *endo* **11a** and 1:1 *exo* **12a**. For one of the two isomers there is an increase in NOE activity between the *outer* and the *inner* hydrogen atom of one pair of the methylene hydrogen atoms (the one in between the two xylene bridges) in comparison with the other isomer. Inspection of the CPK molecular models showed that in case of the *exo* isomer these hydrogen atoms point towards their mirror-image hydrogen atoms (and will there-

Figure 4. ^{1}H-NMR spectra of (a) 1:1 *endo* **11b** and (b) 1:1 *exo* **12b** in $CDCl_3$ at 30°C; (1a) and (1b) signals for aromatic hydrogen atoms of xylene bridge, (2) signals for aromatic hydrogen atoms of cavitand, (3a) and (3b) doublets for the methylene hydrogen atoms of the cavitands (OCH_2O), and (4) doublets for the xylene methylene hydrogen atoms



fore not give an NOE signal) while in case of the *endo* isomer the *inner* hydrogen atoms point towards the *outer* hydrogen atoms and vice versa. Although in both isomers there will be NOE contacts between an *inner* and an *outer* hydrogen atom connected to the same carbon atom, only the *endo* isomer will give rise to an additional NOE contact.

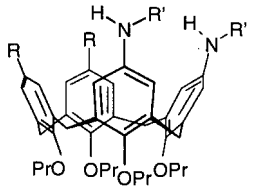
Reaction between 1,2-crown[6]cavitand **2** and the more flexible spacer 1,4-butanediyl ditosylate, was performed under the same conditions as for the xylyl spacer. After purification of the isomers by column chromatography, two products (isomer **A2** and isomer **B2**) were obtained in approximately 40% yield each. Both the FAB MS and ^{1}H-NMR data of the individual isomers **A2** and **B2** clearly prove the formation of 1:1 bis(crown[6]cavitands)[17].

Combination of 1,2-Crown[6]cavitand 2 with 1,2-Bis(chloroacetamido)calix[4]arenes 13 and 14; Synthesis of Crown[6]cavitand-Calix[4]arenes 15 and 16

Previously, we have described that calix[4]arenes can be combined with resorcin[4]arenes by reaction of 1,2-bis(chloroacetamido)calix[4]arenes **13** and **14** (see Scheme 6) with tetrahydroxycavitands[6]. The remaining two hydroxy groups of 1,2-crown[6]cavitand **2** can also be used for this purpose. In this case the crown ether at the cavitand moiety might serve as an additional binding site.

Reaction of 1,2-crown[6]cavitand **2** with 1,2-bis(chloroacetamido)calix[4]arenes can lead to 1:1 *endo* **15** and 1:1 *exo* **16** (Scheme 7). To maintain the possibility of further functionalizations, calix[4]arenes were used with phthalimido or nitro groups at the remaining 3- and 4-positions (calix[4]arenes **13** and **14**, respectively).

Scheme 6



13 R = -pht, R' = $-C(O)CH_2Cl$
14 R = $-NO_2$, R' = $-C(O)CH_2Cl$

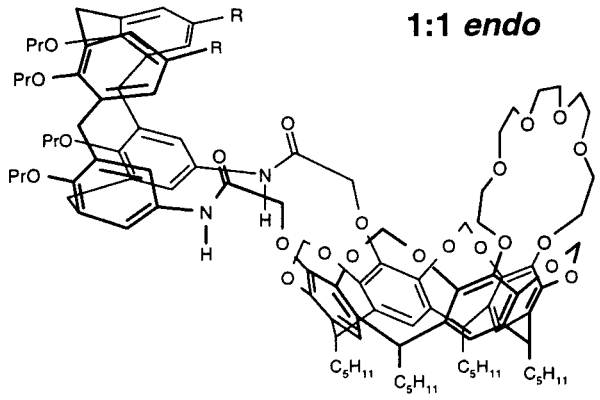
Reaction of 1,2-crown[6]cavitand **2** with 3,4-diphthalimidocalix[4]arene **13** was performed in a 1:1 ratio with Cs_2CO_3 as a base in refluxing CH_3CN. A mixture of 1:1 *endo* **15a** and 1:1 *exo* **16a** was obtained in nearly quantitative yield. It was not possible to separate the two isomers by column chromatography.

Reaction of 1,2-crown[6]cavitand **2** with 3,4-dinitrocalix[4]arene **14** was performed under the same reaction conditions and also in this case a mixture of approximately equal amounts of 1:1 *endo* **15b** and 1:1 *exo* **16b** was obtained.

In both cases the two isomers can be detected in the ^{1}H-NMR spectra by the position of the amido hydrogen signal, an *endo* amido hydrogen atom gives a signal at $\delta \approx 9$ while an *exo* amido hydrogen atom gives a signal at higher field[6] (for the ^{1}H-NMR spectrum of the mixture of 1:1 *endo* **15a** and 1:1 *exo* **16a**, R = -pht, see Figure 5).

From the relative intensities it could be determined that approximately 55% of the mixture is 1:1 *endo* **15a** and 45%

Scheme 7



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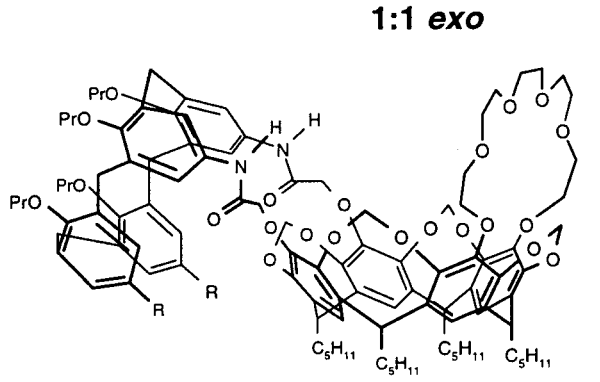

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a) R = -pht
b) R = -NO_2
c) R = -NH_2
d) R = -NHC(O)CH_2Cl
e) R = -NHC(S)NH-*p*-C_6H_4F

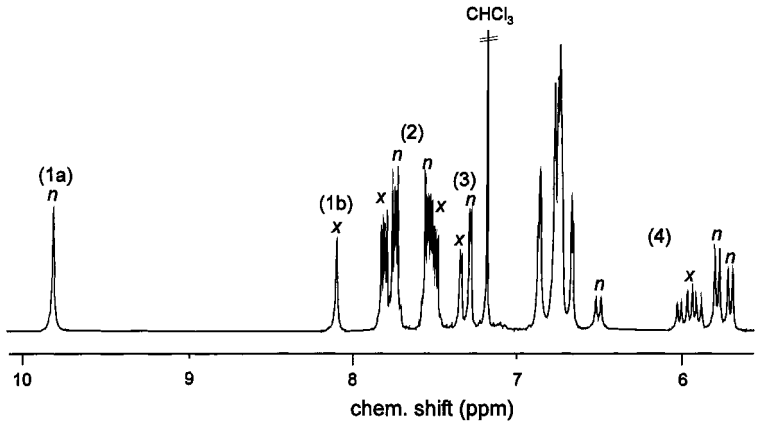
is 1:1 *exo* **16a**, and consequently the signals of the phthalimido, aromatic, and methylene hydrogen atoms could be assigned to either the 1:1 *endo* or the 1:1 *exo* isomer (signals 2, 3, and 4 in Figure 5).

The stereochemistry of these 1:1 calix[4]arene-resorcin[4]arene coupled products is determined in the formation of the first bond, and consequently the orientation is exclusively determined by intermolecular interactions (comparable with the formation of 2:1 calix[4]arene-resorcin[4]arene combinations)[6a]. Since both isomers are present in the reaction mixtures in almost equal amounts, it can be concluded that there are no specific interactions during the reaction.

To make it possible to separate the two isomers and to introduce additional functional groups at the calix[4]arene moiety, the masked amino groups in the mixture of **15a** and **16a** (R = -pht) were deprotected with hydrazine in EtOH/THF to give a mixture of **15c** and **16c** (R = -NH_2) which was proven by FAB MS and ^{1}H-NMR spectroscopy. Subsequently, the amino groups were acylated by reaction with α-chloroacetyl chloride to give 1:1 *endo* **15d** and 1:1 *exo* **16d** which were both obtained in approximately 35% yield after separation by column chromatography (calculated starting from 1,2-crown[6]cavitand **2** and 3,4-diphthalimidocalix[4]arene **13**). Instead of using the chloroacetamido functionalities in **15d** and **16d** to introduce another resorcin[4]arene molecule, for simplicity reasons the amino groups of **15c** and **16c** were used directly to introduce additional possible binding sites.

It is possible to introduce two *para*-fluorophenylthiourea fragments at adjacent positions of calix[4]arenes as potential additional binding sites. Reaction of diamino 1:1 mixture **15c** and **16c** with *para*-fluorophenyl isothiocyanate in CH_2Cl_2 gave after separation by column chromatography 1:1 *endo* **15e** and 1:1 *exo* **16e** both in approximately 25% yield (starting from diphthalimidocalix[4]arene **13** and 1,2-crown[6]cavitand **2**).

Figure 5. ^{1}H-NMR spectrum of mixture of 1:1 *endo* **15a** (indicated with *n*) and 1:1 *exo* **16a** (indicated with *x*) in $CDCl_3$ at room temperature; (1a) and (1b) signals for amide hydrogen atoms, (2) signals for the phthalimido hydrogen atoms, (3) signal for the aromatic hydrogen atom *ortho* to the amido group, and (4) doublets for the methylene hydrogen atoms of the cavitands (OCH_2O)



Preliminary Complexation Studies

Based on cation complexation by calix[4]crowns[8], the affinity of 1,2-crown[6]cavitand **2** for alkali cations was studied. Unfortunately, extraction experiments[18] (from water to chloroform) with picrate salts (sodium, potassium, rubidium, and cesium) showed that 1,2-crown[6]cavitand **2** is inappropriate for the complexation of alkali cations[19][20].

Conclusions

In conclusion, we have further demonstrated that the proper combination of easily accessible building blocks, gives rise to potential synthetic receptor molecules with large hydrophobic surfaces. Crown[*n*]cavitands were synthesized by alkylation of tetrahydroxycavitand **6** with polyethyleneglycol ditosylates and this building block was combined with either 1,2-bis(chloroacetamidomethyl)cavitand **8**, with itself via xylyl or butyl spacers, or with 1,2-bis(chloroacetamido)calix[4]arenes **13** and **14** to obtain potential receptor molecules.

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Experimental Section

Melting points were determined with a Reichert melting point apparatus and are uncorrected. − NMR: Bruker AC250 (^{1}H NMR: 250 MHz) or Varian Unity 400 (^{1}H NMR: 400 MHz) spectrometer in $CDCl_3$. Residual solvent protons were used as internal standard and chemical shifts are given in ppm relative to tetramethylsilane (TMS). − FAB MS: Finnigan MAT 90 spectrometer using *meta*-nitrobenzyl alcohol (NBA) as a matrix. − All solvents were purified by standard procedures. Petroleum ether (PE) refers to the fraction with bp 60−80°C. All other chemicals were analytically pure and were used without further purification. All reactions were carried out under argon. The presence of solvent in the analytical samples was confirmed by ^{1}H-NMR spectroscopy. − Flash chromatography was performed on silica gel (E. Merck, SiO_2, 0.040−0.063 mm, 230−400 mesh). − Preparative thin-layer chromatography (TLC) was performed using precoated silica plates (E. Merck, Kieselgel 60 F_{254}, 2 mm). For dropwise additions a perfuser was used. Tetrahydroxycavitand **6**[22], 1,2-bis(aminomethyl)cavitand **7**[10a], 1,2-bis(chloroacetamido)-3,4-diphthalimidocalix[4]arene **13**[6a], and 1,2-bis(chloroacetamido)-3,4-dinitrocalix[4]arene **14**[23] were obtained following published procedures.

General Procedure for the Preparation of Cavitands **1−5**: A suspension of tetrahydroxycavitand **6**, base, and a polyethyleneglycol ditosylate in DMF was stirred at 70°C. The solvent was removed in vacuo and the residue was dissolved in CH_2Cl_2, washed with 1 N HCl, with H_2O, and dried with $MgSO_4$.

7,11-Crown[5]-15,18-dihydroxy-1,21,23,25-tetrapentylcavitand (**1**) was prepared starting from tetrahydroxycavitand **6** (0.50 g, 0.568 mmol), tetraethyleneglycol ditosylate (0.34 g, 0.681 mmol), and NaH (0.45 g, 11.35 mmol) in DMF (60 ml). The reaction mixture was stirred at 70°C for 4 d to give the crude reaction mixture which was purified by column chromatography (SiO_2, EtOAc/CH_2Cl_2, 90:10). Besides 0.03 g (6%) of tetrahydroxycavitand **6**, 7,11-crown[5]cavitand **1** was obtained. Yield 0.05 g (8%), m.p. 154−156°C. − ^{1}H NMR: δ = 6.81 [s, 2 H, *para*-(OCH$_2$)*ArH*], 6.59 [s, 2 H, *para*-(OH)*ArH*], 6.27, 5.95, 5.84 (d, 4 H, *J* = 7.2 Hz, OCH_2O), 5.5 (br. s, 2 H, OH), 4.79, 4.67 (t, 4 H, *J* = 7.9 Hz, ArCHRAr), 4.53, 4.44, 4.33 (d, 4 H, *J* = 7.2 Hz, OCH_2O), 4.2−4.1, 3.9−3.8 (m, 4 H, ArO*CH*$_2$CH$_2$O), 3.8−3.6 (m, 12 H, crown), 2.2−2.0 [m, 8 H, *CH*$_2$(CH$_2$)$_3$CH$_3$], 1.4−1.2 [m, 24 H, CH$_2$(*CH*$_2$)$_3$CH$_3$], 0.9−0.8 [m, 12 H, CH$_2$(CH$_2$)$_3$*CH*$_3$]. − ^{13}C NMR: δ = 148.9, 148.1, 144.0, 142.1, 142.0, 140.9, 139.4, 138.5, 138.2 (s, Ar), 114.4, 109.9 (d, Ar). − FAB MS; *m/z*: 1038.6 [M$^+$]. − $C_{60}H_{78}O_{15}\cdot 1.5\ H_2O$ (1066.3): calcd. C 67.59, H 7.66; found C 67.61, H 7.65.

7,11-Crown[6]-15,18-dihydroxy-1,21,23,25-tetrapentylcavitand (**2**) was prepared starting from tetrahydroxycavitand **6** (0.75 g, 0.851 mmol), pentaethyleneglycol ditosylate (0.56 g, 1.022 mmol), and NaH (0.68 g, 17.03 mmol) in DMF (85 ml). The reaction mixture was stirred at 70°C for 7 d to give the crude reaction mixture which was purified by column chromatography (SiO_2, EtOAc/CH_2Cl_2, 90:10). Besides 0.16 g (21%) of tetrahydroxycavitand **6**, 7,11-crown[6]cavitand **2** was obtained. Yield 0.30 g (33%), m.p. 159−162°C. − ^{1}H NMR: δ = 6.75 [s, 2 H, *para*-(OCH$_2$)*ArH*], 6.49 [s, 2 H, *para*-(OH)*ArH*], 6.17, 6.06, 5.87 (d, 4 H, *J* = 7.2 Hz, OCH_2O), 6.16 (s, 2 H, OH), 4.7−4.6 (m, 4 H, ArCHRAr), 4.26, 4.23, 4.20 (d, 4 H, *J* = 7.2 Hz, OCH_2O), 4.1−3.8 (m, 4 H, ArO*CH*$_2$CH$_2$O), 3.8−3.5 (m, 16 H, crown), 2.2−2.0 [m, 8 H, *CH*$_2$(CH$_2$)$_3$CH$_3$], 1.4−1.1 [m, 24 H, CH$_2$(*CH*$_2$)$_3$CH$_3$], 0.9−0.8 [m, 12 H, CH$_2$(CH$_2$)$_3$*CH*$_3$]. − ^{13}C NMR: δ = 148.6, 148.2, 143.6, 142.2, 142.0, 141.3, 139.1, 138.5, 138.0 (s, Ar), 115.1, 109.4 (d, Ar). − FAB MS; *m/z*: 1105.9 [M$^+$ + Na]. − $C_{62}H_{82}O_{16}\cdot 1.5H_2O$ (1110.4): calcd. C 67.07, H 7.72; found C 67.04, H 7.75.

7,11-Crown[7]-15,18-dihydroxy-1,21,23,25-tetrapentylcavitand (**3**) was prepared starting from tetrahydroxycavitand **6** (0.15 g, 0.170 mmol), hexaethyleneglycol ditosylate (0.12 g, 0.204 mmol), and NaH (0.14 g, 3.41 mmol) in DMF (20 ml). The reaction mixture was stirred at 70°C for 8 d to give the crude reaction mixture which was purified by column chromatography (SiO_2, EtOAc/CH_2Cl_2, 90:10). Besides 0.04 g (27%) of tetrahydroxycavitand **6**, 7,11-crown[7]cavitand **3** was obtained. Yield 0.04 g (20%), m.p. 207−208°C. − ^{1}H NMR: δ = 6.80 [s, 2 H, *para*-(OCH$_2$)*ArH*], 6.54 [s, 2 H, *para*-(OH)*ArH*], 6.4 (br. s, 2 H, OH), 6.20, 5.97, 5.93 (d, 4 H, *J* = 7.2 Hz, OCH_2O), 4.7−4.6 (m, 4 H, ArCHRAr), 4.3−4.2 (m, 4 H, OCH_2O), 4.1−4.0 (m, 4 H, ArO*CH*$_2$CH$_2$O), 3.9−3.6 (m, 20 H, crown), 2.2−2.0 [m, 8 H, *CH*$_2$(CH$_2$)$_3$CH$_3$], 1.4−1.2 [m, 24 H, CH$_2$(*CH*$_2$)$_3$CH$_3$], 0.9−0.8 [m, 12 H, CH$_2$(CH$_2$)$_3$*CH*$_3$]. − ^{13}C NMR: δ = 148.3, 148.1, 144.0, 142.2, 141.9, 141.3, 139.2, 139.0, 138.5 (s, Ar), 114.9, 109.4 (d, Ar). − FAB MS; *m/z*: 1149.5 [M$^+$]. − $C_{64}H_{86}O_{17}$ (1127.4): calcd. C 68.19, H 7.69; found C 67.99, H 7.77.

7,11-15,18-Biscrown[6]-1,21,23,25-tetrapentylcavitand (**5**) was obtained according to the method described for 7,11-crown[6]cavitand **2**, with tetrahydroxycavitand **6** (0.50 g, 0.568 mmol), pentaethyleneglycol ditosylate (0.37 g, 0.681 mmol), and Cs_2CO_3 (3.70 g, 11.36 mmol) in DMF (60 ml). Besides 0.20 g (40%) of tetrahydroxycavitand **6**, biscrown[6]cavitand **5** was obtained. Yield 0.07 g (10%), m.p. 243−245°C. − ^{1}H NMR: δ = 6.72 (s, 4 H, ArH), 5.92, 5.72 (d, 4 H, *J* = 7.3 Hz, OCH_2O), 4.68, 4.61 (t, 4 H, *J* = 7.9 Hz, ArCHRAr), 4.4−4.3 (m, 4 H, OCH_2O), 4.1−3.9 (m, 8 H, ArO*CH*$_2$CH$_2$O), 3.7−3.5 (m, 32 H, crown), 2.2−2.0 [m, 8 H, *CH*$_2$(CH$_2$)$_3$CH$_3$], 1.4−1.2 [m, 24 H, CH$_2$(*CH*$_2$)$_3$CH$_3$], 0.9−0.8 [m, 12 H, CH$_2$(CH$_2$)$_3$*CH*$_3$]. − ^{13}C NMR: δ = 148.5, 148.3, 144.2, 139.1, 138.7 (s, Ar), 114.2 (d, Ar). − FAB MS; *m/z*: 1285.5 [M$^+$]. − $C_{72}H_{100}O_{20}\cdot H_2O$ (1145.4): calcd. C 66.34, H 7.89; found C 66.32, H 7.80.

7,11-Bis(chloroacetamidomethyl)cavitand-1,21,23,25-tetrapentylcavitand (**8**). A solution of 7,11-bis(aminomethyl)-15,18-di-

methylcavitand (0.16 g, 0.18 mmol), $ClC(O)CH_2Cl$ (0.1 ml, 1.1 mmol), and NEt_3 (0.2 ml, 1.4 mmol) in CH_2Cl_2 (10 ml) was refluxed for 2 h. The solution was extensively washed with 2 N HCl (4 × 10 ml) and 2 N NaOH (6 × 10 ml) and dried with Na_2SO_4. The solvent was removed in vacuo to give **8**. Yield 0.18 g (95%), m.p. 166−168°C. − ^{1}H NMR: δ = 7.11, 6.96 (s, 4 H, ArH), 5.99, 5.93, 5.87 (d, 4 H, *J* = 6.9 Hz, OCH_2O), 4.8−4.7 (m, 4 H, ArCHR), 4.4−4.3 (m, 4 H, OCH_2O), 4.02 (s, 4 H, Ar*CH*$_2$NH), 2.3−2.1 [m, 8 H, *CH*$_2$(CH$_2$)$_3$CH$_3$], 1.97 (s, 6 H, $ArCH_3$), 1.5−1.3 [m, 24 H, CH_2(*CH*$_2$)$_3$CH$_3$], 0.92 [t, 12 H, *J* = 6.8 Hz, $CH_2(CH_2)_3CH_3$]. − ^{13}C NMR: δ = 165.7 (s, C=O). − FAB MS; *m*/*z*: 1077.6 [M$^+$ + Na]. − $C_{60}H_{76}Cl_2N_2O_{10}\cdot H_2O$ (1074.2): calcd. C 67.65, H 7.29, N 2.63; found C 67.69, H 7.27, N 2.57.

General Procedure for the Preparation of Isomers **9−12**, **15a** *and* **b**, *and* **16a** *and* **b**: A solution of the building blocks, Cs_2CO_3, and KI in CH_3CN was stirred at reflux temperature. The solvent was removed in vacuo and the residue was dissolved in CH_2Cl_2, washed with 1 N HCl, with H_2O, and with brine, and dried with Na_2SO_4.

Methylcavitand-Cavitandcrown[6], 1:1 Isomer **A1** (**9** or **10**) was prepared starting from 7,11-crown[6]cavitand **2** (0.075 g, 0.069 mmol), 7,11-bis(chloroacetamidomethyl)cavitand **8** (0.073 g, 0.069 mmol), Cs_2CO_3 (0.23 g, 0.69 mmol), and KI in CH_3CN (35 ml). The reaction mixture was stirred at reflux temperature for 4 d to give the crude reaction mixture which was purified by column chromatography (SiO_2, EtOAc/PE, 45:55) to afford isomer **A1**. Yield 0.05 g (35%). − ^{1}H NMR: δ = 8.1−8.0 (m, 2 H, NH), 7.14, 7.06, 6.86, 6.78 (s, 8 H, ArH), 6.24, 5.65 (d, 3 H, *J* = 7.0 Hz, OCH_2O), 6.0−5.9, 5.8−5.7 (m, 5 H, OCH_2O), 5.0−3.9 [m, 28 H, $OCH_2C(O)$, Ar*CH*$_2$NH, ArCHRAr, OCH_2O, ArO*CH*$_2$CH$_2$O], 3.7−3.5 (m, 16 H, crown), 2.2−2.0 [m, 16 H, *CH*$_2$(CH$_2$)$_3$CH$_3$], 1.95 (s, 6 H, $ArCH_3$), 1.4−1.2 [m, 48 H, CH_2(*CH*$_2$)$_3$CH$_3$], 1.0−0.9 [m, 24 H, $CH_2(CH_2)_3CH_3$]. − FAB MS; *m*/*z*: 2088.6 [M$^+$ + Na, $C_{122}H_{156}N_2NaO_{26}$ (2088.1)].

1:1 Isomer **B1** (**9** or **10**) was isolated from the same reaction mixture as isomer **A1** (**9** or **10**). Yield 0.05 g (35%). − ^{1}H NMR: δ = 7.8−7.7 (m, 2 H, NH), 7.09, 6.96, 6.86, 6.80 (s, 8 H, ArH), 6.0−5.7 (m, 8 H, OCH_2O), 5.0−3.9 [m, 28 H, $OCH_2C(O)$, Ar*CH*$_2$NH, ArCHRAr, OCH_2O, ArO*CH*$_2$CH$_2$O], 3.8−3.6 (m, 16 H, crown), 2.2−2.0 [m, 16 H, *CH*$_2$(CH$_2$)$_3$CH$_3$], 1.97 (s, 6 H, $ArCH_3$), 1.4−1.1 [m, 48 H, CH_2(*CH*$_2$)$_3$CH$_3$], 1.0−0.9 [m, 24 H, $CH_2(CH_2)_3CH_3$]. − FAB MS; *m*/*z*: 2088.5 [M$^+$ + Na, $C_{122}H_{156}N_2NaO_{26}$ (2088.1)].

Bis(7,11-crown[6]cavitand)-meta-xylyl, 1:1 endo (**11a**) was prepared starting from 7,11-crown[6]cavitand **2** (0.050 g, 0.046 mmol), α,α-dibromo-*meta*-xylene (0.013 g, 0.051 mmol), and Cs_2CO_3 (0.15 g, 0.46 mmol) in CH_3CN (50 ml). The reaction mixture was stirred at reflux temperature for 4 d to give the crude reaction mixture which was purified by column chromatography (SiO_2, EtOAc/PE, 90:10). Yield 0.02 g (36%); m.p. 292−293°C. − ^{1}H NMR: δ = 7.49 (s, 2 H, xyl-ArH), 7.4−7.2 (m, 6 H, xyl-ArH), 6.81 (s, 8 H, cav-ArH), 5.98 (d, 2 H, *J* = 7.3 Hz, OCH_2O), 5.8−5.6 (m, 6 H, OCH_2O), 4.90, 4.86 (d, 8 H, *J* = 11.2 Hz, OCH_2xyl), 4.8−4.6 (m, 8 H, ArCHRAr), 4.46, 4.43, 4.37 (d, 8 H, *J* = 7.5 Hz, OCH_2O), 4.1−4.0 (m, 8 H, OArO*CH*$_2$CH$_2$O), 3.7−3.5 (m, 32 H, crown), 2.2−2.0 [m, 16 H, *CH*$_2$(CH$_2$)$_3$CH$_3$], 1.4−1.2 [m, 48 H, CH_2(*CH*$_2$)$_3$CH$_3$], 0.9−0.8 [m, 24 H, $CH_2(CH_2)_3CH_3$]. − ^{13}C NMR: δ = 148.4, 148.3, 148.2, 144.1, 139.0, 138.9, 138.8, 138.7, 138.1, 127.9, 126.6, 125.9, 114.1 (Ar). − FAB MS; *m*/*z*: 2393.1 [M$^+$ + Na]. − $C_{140}H_{176}O_{32}\cdot 0.5\ H_2O$(2379.9): calcd. C 70.66, H 7.50; found C 70.58, H 7.56.

1:1 exo (**12a**) was isolated from the same reaction mixture as **11a**. Yield 0.02 g (36%); m.p. 128−129°C. − ^{1}H NMR: δ = 7.63 (s, 2 H, xyl-ArH), 7.4−7.3 (m, 6 H, xyl-ArH), 6.83, 6.82 (s, 8 H, cav-ArH), 5.97, 5.85, 5.76 (d, 8 H, *J* = 7.2 Hz, OCH_2O), 4.96, 4.86 (d, 8 H, *J* = 10.7 Hz, OCH_2xyl), 4.8−4.7 (m, 8 H, ArCHRAr), 4.5−4.4 (m, 8 H, OCH_2O), 4.1−4.0 (m, 8 H, OArO*CH*$_2$CH$_2$O), 3.8−3.6 (m, 32 H, crown), 2.2−2.0 [m, 16 H, *CH*$_2$(CH$_2$)$_3$CH$_3$], 1.4−1.2 [m, 48 H, CH_2(*CH*$_2$)$_3$CH$_3$], 0.9−0.8 [m, 24 H, $CH_2(CH_2)_3CH_3$]. − ^{13}C NMR δ 148.5, 148.3, 144.6, 144.2, 139.1, 139.0, 138.9, 138.7, 137.9, 128.3, 128.1, 127.7, 114.2 (Ar). − FAB MS; *m*/*z*: 2393.0 [M$^+$ + Na]. − $C_{140}H_{176}O_{32}\cdot 3H_2O$ (2425.0): calcd. C 69.34, H 7.56; found C 69.29, H 7.74.

Bis(7,11-crown[6]cavitand)butyl, 1:1 Isomer **A2** (**11b** or **12b**) was prepared starting from 7,11-crown[6]cavitand **2** (0.050 g, 0.046 mmol), 1,4-butanediyl ditosylate (0.020 g, 0.051 mmol), and Cs_2CO_3 (0.15 g, 0.46 mmol) in CH_3CN (50 ml). The reaction mixture was stirred at reflux temperature for 4 d to give the crude reaction mixture which was purified by column chromatography (SiO_2, EtOAc/petroleum ether, 80:20). Yield 0.02 g (38%). − ^{1}H NMR: δ = 6.78, 6.76 (s, 8 H, ArH), 5.98, 5.79, 5.77 (d, 8 H, *J* ≈ 7.0 Hz, OCH_2O), 4.8−4.6 (m, 8 H, ArCHRAr), 4.50, 4.42 (d, 8 H, *J* = 7.0 Hz, OCH_2O), 4.1−3.9 [m, 16 H, ArO*CH*$_2$CH$_2$O, ArO*CH*$_2$(CH$_2$)$_2$], 3.8−3.6 (m, 32 H, crown), 2.2−2.0 [m, 16 H, *CH*$_2$(CH$_2$)$_3$CH$_3$], 1.9−1.8 [m, 8 H, $ArOCH_2$(*CH*$_2$)$_2$], 1.4−1.2 [m, 48 H, CH_2(*CH*$_2$)$_3$CH$_3$], 0.9−0.8 [m, 24 H, $CH_2(CH_2)_3CH_3$]. − FAB MS; *m*/*z*: 2297.3 [M$^+$ + Na, $C_{132}H_{176}NaO_{32}$ (2296.2)].

1:1 Isomer **B2** (**11b** or **12b**) was isolated from the same reaction mixture as isomer **A2** (**11b** or **12b**). Yield 0.02 g (38%). − ^{1}H NMR: δ = 6.78, 6.77 (s, 8 H, ArH), 5.97 (d, 2 H, *J* ≈ 7.0 Hz, OCH_2O), 5.9−5.8 (m, 6 H, OCH_2O), 4.8−4.6 (m, 8 H, ArCHRAr), 4.5−4.4 (m, 8 H, OCH_2O), 4.1−4.0 (m, 8 H, ArO*CH*$_2$CH$_2$O), 4.0−3.9 [m, 8 H, ArO*CH*$_2$(CH$_2$)$_2$], 3.7−3.6 (m, 32 H, crown), 2.2−2.0 [m, 16 H, *CH*$_2$(CH$_2$)$_3$CH$_3$], 1.9−1.8 [m, 8 H, $ArOCH_2$(*CH*$_2$)$_2$], 1.4−1.2 [m, 48 H, CH_2(*CH*$_2$)$_3$CH$_3$], 0.9−0.8 [m, 24 H, $CH_2(CH_2)_3CH_3$]. − FAB MS; *m*/*z*: 2296.6 [M$^+$ + Na, $C_{132}H_{176}NaO_{32}$ (2296.2)].

Crown[6]cavitand-Calix[4]arenes, 1:1 Isomers, R = -pht (*endo* **15a** and *exo* **16a**) were prepared starting from 7,11-crown[6]cavitand **2** (0.50 g, 0.46 mmol), 5,11-bis(chloroacetamido)-17,23-diphthalimidocalix[4]arene **13** (0.49 g, 0.46 mmol), Cs_2CO_3 (1.50 g, 4.62 mmol), and KI in CH_3CN (100 ml). The reaction mixture was stirred at reflux temperature for 2 d to give the crude reaction mixture which was used without further purification. Yield 0.97 g. − ^{1}H NMR[21] (for ^{n} and ^{x} see Figure 5): δ = 9.82^n, 8.11^x (s, 2 H, NH), 7.9−7.8^x, 7.8−7.7^n, 7.6−7.5^n, 7.5−7.4^x (m, 8 H, phtArH), 7.35^x, 7.29^n, (d, 2 H, *J* = 2.4 Hz, ArH), 6.9−6.6, 6.4−6.3 (m, 10 H, ArH), 6.51^n, 6.02^x, 5.96^x, 5.90^x, 5.79^n, 5.71^n (d, 4 H, *J* ca. 7.0 Hz, OCH_2O), 4.8−3.5 [m, 44 H, $ArCH_2Ar$, OCH_2O, ArCHRAr, $OCH_2C(O)$, O*CH*$_2$CH$_2$CH$_3$, crown], 3.3−3.1 (m, 4 H, $ArCH_2Ar$), 2.3−1.7 [m, 16 H, *CH*$_2$(CH$_2$)$_3$CH$_3$, $OCH_2CH_2CH_3$], 1.4−1.2 [m, 24 H, CH_2(*CH*$_2$)$_3$CH$_3$], 1.1−0.8 [m, 24 H, $OCH_2CH_2CH_3$, $CH_2(CH_2)_3CH_3$]. − FAB MS; *m*/*z*: 2075.8 [M$^+$ $C_{122}H_{138}N_4O_{26}$ (2076.0)].

Crown[6]cavitand-Calix[4]arenes, 1:1 Isomers, R = -NO$_2$ (*endo* **15b** and *exo* **16b**) were prepared starting from 7,11-crown[6]cavitand **2** (0.050 g, 0.046 mmol), 5,11-bis(chloroacetamido)-17,23-dinitrocalix[4]arene **14** (0.040 g, 0.046 mmol), Cs_2CO_3 (0.15 g, 0.46 mmol), and KI in CH_3CN (10 ml). The reaction mixture was stirred at reflux temperature for 2 d to give the crude reaction mixture which was used without further purification. Yield 0.10 g. − ^{1}H NMR[21]: δ = 8.96^n, 7.96^x (s, 2 H, NH), 7.6−7.3, 6.9−6.7, 6.5−6.4, 6.1−6.0 (m, 12 H, ArH), 6.0−5.6 (m, 4 H, OCH_2O), 4.8−3.5 [m, 44 H, $ArCH_2Ar$, OCH_2O, ArCHRAr, $OCH_2C(O)$, O*CH*$_2$CH$_2$CH$_3$, crown], 3.3−3.1 (m, 4 H, $ArCH_2Ar$), 2.3−2.1 [m, 8 H, *CH*$_2$(CH$_2$)$_3$CH$_3$], 1.9−1.7 (m, 8 H, $OCH_2CH_2CH_3$), 1.4−1.2

[m, 24 H, $CH_2(CH_2)_3CH_3$], 1.1−0.8 [m, 24 H, $OCH_2CH_2CH_3$, $CH_2(CH_2)_3CH_3$].

Crown[6]cavitand-Calix[4]arenes, 1:1 Isomers, R = -NH$_2$ (*endo* **15c** and *exo* **16c**): A solution of 1:1 *endo* and *exo* (R = -pht) **15a** and **16a** (0.66 g) and $NH_2NH_2 \cdot H_2O$ (1.5 ml, 31 mmol) in EtOH/THF (15/10 ml) was stirred at reflux temperature for 3 h. The solvent was removed in vacuo and the residue was dissolved in CH_2Cl_2 (50 ml), washed with 1 N HCl (25 ml), with 1 N NaOH (25 ml), H_2O (2 × 25 ml), and with brine (25 ml), and dried with Na_2SO_4. The crude reaction mixture was used without further purification. Yield 0.40 g. − ^{1}H NMR[21]: δ = 8.99^n, 8.50^x (s, 2 H, NH), 7.33, 6.97, 6.60, 6.53 (d, 4 H, *J* ca. 2 Hz, ArH), 7.8−7.7, 6.1−5.9 (m, 8 H, ArH), 5.8−5.7 (m, 3 H, OCH_2O), 5.57 (d, 1 H, *J* ca. 7 Hz, OCH_2O), 4.7−3.5 [m, 48 H, $ArCH_2Ar$, OCH_2O, ArCHRAr, $OCH_2C(O)$, $OCH_2CH_2CH_3$, NH_2, crown], 3.2−2.8 (m, 4 H, $ArCH_2Ar$), 2.2−2.0 [m, 8 H, $CH_2(CH_2)_3CH_3$], 1.9−1.7 (m, 8 H, $OCH_2CH_2CH_3$), 1.4−1.1 [m, 24 H, $CH_2(CH_2)_3CH_3$], 1.0−0.7 [m, 24 H, $OCH_2CH_2CH_3$, $CH_2(CH_2)_3CH_3$]. − FAB MS; *m/z*: 1817.0 [M$^+$ + H $C_{106}H_{135}N_4O_{22}$ (1817.0)].

Crown[6]cavitand-Calix[4]arene, 1:1 endo, R = -NHC(O)CH$_2$Cl (**15d**). To a solution of 1:1 *endo* and *exo* (R = -NH_2) **15c** and **16c** (0.05 g, 0.03 mmol) in CH_2Cl_2 (15 ml) were added NEt_3 (0.1 ml, 0.7 mmol) and $ClC(O)CH_2Cl$ (0.05 ml, 0.6 mmol) and the solution was stirred at room temperature for 30 min. The reaction mixture was washed with 1 N HCl (2 × 5 ml), with H_2O (5 ml), with 1 N NaOH (5 ml), with H_2O (5 ml), and with brine (5 ml), and dried with Na_2SO_4. The solvent was removed in vacuo to give the crude product which was purified by column chromatography (SiO_2, EtOAc/petroleum ether, 70:30). Yield 0.03 g (95%). − ^{1}H NMR: δ = 9.41 [s, 2 H, *NH*C(O)CH_2O], 7.82 [s, 2 H, *NH*C(O)CH_2Cl], 7.37, 6.96, 6.53, 6.49 (d, 8 H, *J* ca. 2 Hz, ArH), 6.82, 6.77 (s, 4 H, ArH), 6.10, 5.97, 5.80 (d, 4 H, *J* ≈ 7 Hz, OCH_2O), 4.8−3.5 [m, 48 H, $ArCH_2Ar$, OCH_2O, ArCHRAr, $OCH_2C(O)$, $OCH_2CH_2CH_3$, $C(O)CH_2Cl$, crown], 3.2−2.9 (m, 4 H, $ArCH_2Ar$), 2.2−2.0 [m, 8 H, $CH_2(CH_2)_3CH_3$], 1.9−1.7 (m, 8 H, $OCH_2CH_2CH_3$), 1.4−1.1 [m, 24 H, $CH_2(CH_2)_3CH_3$], 1.0−0.7 [m, 24 H, $OCH_2CH_2CH_3$, $CH_2(CH_2)_3CH_3$]. − FAB MS; *m/z*: 1991.5 [M$^+$ + Na; $C_{110}H_{136}Cl_2N_4NaO_{24}$ (1991.9)].

1:1 exo, R = -NHC(O)CH$_2$Cl (**16d**) was isolated from the same reaction mixture as **15d**. Yield 0.03 g (95%). − ^{1}H NMR: δ = 8.10 [s, 2 H, *NH*C(O)CH_2O], 7.81 [s, 2 H, *NH*C(O)CH_2Cl], 7.28, 6.97, 6.62, 6.28, (d, 8 H, *J* ca. 2 Hz, ArH), 6.77, 6.62 (s, 4 H, ArH), 5.92 (d, 1 H, *J* ca. 7 Hz, OCH_2O), 5.8−5.7 (m, 3 H, OCH_2O), 4.7−3.5 [m, 48 H, $ArCH_2Ar$, OCH_2O, ArCHRAr, $OCH_2C(O)$, $OCH_2CH_2CH_3$, $C(O)CH_2Cl$, crown], 3.1−2.9 (m, 4 H, $ArCH_2Ar$), 2.2−2.0 [m, 8 H, $CH_2(CH_2)_3CH_3$], 1.9−1.7 (m, 8 H, $OCH_2CH_2CH_3$), 1.4−1.1 [m, 24 H, $CH_2(CH_2)_3CH_3$], 1.0−0.7 [m, 24 H, $OCH_2CH_2CH_3$, $CH_2(CH_2)_3CH_3$]. − FAB MS; *m/z*: 1991.2 [M$^+$ + Na; $C_{110}H_{136}Cl_2N_4NaO_{24}$ (1991.9)].

Crown[6]cavitand-Calix[4]arene, 1:1 endo, R = -NHC(S)NH-para-C$_6$H$_4$F (**15e**): A solution of 1:1 *endo* and *exo* (R = -NH_2) **15c** and **16c** (0.05 g, 0.03 mmol) in CH_2Cl_2 (10 ml) was added *para*-fluorophenyl isothiocyanate (0.08 g, 0.55 mmol) and the solution was stirred at room temperature for 1 d. The reaction mixture was washed with 1 N HCl (2 × 5 ml), with H_2O (5 ml), and with brine (5 ml), and dried with Na_2SO_4. The solvent was removed in vacuo to give the crude product which was purified by column chromatography (SiO_2, EtOAc/petroleum ether, 70:30). Yield ca. 25% starting from calix[4]arene **13** and resorcin[4]arene **2**, m.p. > 300°C. − ^{1}H NMR: δ = 9.14 [s, 2 H, *NH*C(O)CH_2O], 7.58, 6.35 [br. s, 4 H, NHC(S)NH], 7.5−6.3 (m, 20 H, ArH), 5.98, 5.87, 5.80 (d, 4 H, *J* = 7.2 Hz, OCH_2O), 4.7−3.9 [m, 24 H, $ArCH_2Ar$, OCH_2O, ArCHRAr, $OCH_2C(O)$, $OCH_2CH_2CH_3$], 3.9−3.6 (m, 20 H, crown), 3.2−3.0 (m, 4 H, $ArCH_2Ar$), 2.2−2.0 [m, 8 H, $CH_2(CH_2)_3CH_3$], 1.9−1.7 (m, 8 H, $OCH_2CH_2CH_3$), 1.3−1.0 [m, 24 H, $CH_2(CH_2)_3CH_3$], 0.9−0.7 [m, 24 H, $OCH_2CH_2CH_3$, $CH_2(CH_2)_3CH_3$]. − ^{13}C NMR: δ = 180.0 (s, C=S), 167.0 (s, C=O). − FAB MS; *m/z*: 2121.3 [M$^+$]. − $C_{120}H_{142}F_2N_6O_{22}S_2$ (2122.6): calcd. C 67.90, H 6.74, N 3.96; found C 67.89, H 6.78, N 4.08.

1:1 exo, R = -NHC(S)NH-para-C$_6$H$_4$F (**16e**) was isolated from the same reaction mixture as **15e**. Yield ca. 25% starting from calix[4]arene **13** and resorcin[4]arene **2**, m.p. > 300°C. − ^{1}H NMR: δ = 8.19 [s, 2 H, *NH*C(O)CH_2O], 7.05, 6.36 [br. s, 4 H, NHC(S)NH], 7.6−7.5, 7.3−7.2, 7.0−6.6 (m, 20 H, ArH), 5.91, 5.73, 5.43 (d, 4 H, *J* = 7.1 Hz, OCH_2O), 4.7−3.9 [m, 24 H, $ArCH_2Ar$, OCH_2O, ArCHRAr, $OCH_2C(O)$, $OCH_2CH_2CH_3$], 3.8−3.5 (m, 20 H, crown), 3.1−3.0 (m, 4 H, $ArCH_2Ar$), 2.2−2.0 [m, 8 H, $CH_2(CH_2)_3CH_3$], 1.9−1.8 (m, 8 H, $OCH_2CH_2CH_3$), 1.4−1.2 [m, 24 H, $CH_2(CH_2)_3CH_3$], 1.0−0.8 [m, 24 H, $OCH_2CH_2CH_3$, $CH_2(CH_2)_3CH_3$]. − ^{13}C NMR: δ = 180.7 (s, C=S), 166.6 (s, C=O). − FAB MS; *m/z*: 2121.8 [M$^+$ (2121.0)]. − $C_{120}H_{142}F_2N_6O_{22}S_2$ (2122.6)]: calcd. C 67.90, H 6.74, N 3.96; found C 68.29, H 6.77, N 4.06.

Crystal-Structrure Determination of **2**: $C_{62}H_{82}O_{16} \cdot C_2H_6O \cdot 2\,H_2O$, M_r = 1165.42, colorless, plate-shaped crystal (0.1 × 0.3 × 0.4 mm), monoclinic, space group $P2_1/c$, *a* = 25.384(5), *b* = 13.910(3), *c* = 18.654(5) A, β = 108.425(13)°, *V* = 6249(3) A^3, *Z* = 4, D_x = 1.2388(6) g/cm^3, *F*(000) = 2512, μ(Mo-K_α) = 0.9 cm^{-1}. 11392 Reflections measured, 11007 independent, R_{int} = 0.0489, (0.85° < θ <25.0°, −30 < *h* < 28, −16 < *k* < 0, 0 < *l* < 22, ω scan, Δω = 0.76 + 0.35tanθ°, *T* =◦ 150 K, Mo-K_α radiation, graphite monochromator, λ = 0.71073 A) with an Enraf-Nonius CAD4 diffractometer on rotating anode. Data were corrected for Lp effects and for linear instability of 2% of the reference reflections, but not for absorption. The structure was solved by automated direct methods (SHELXS86[24]). Refinement on F^2 was carried out by full-matrix least-squares techniques (SHELXL97[25]); no observance criterion was applied during refinement. The pentyl group containing C34 displayed disorder in the two terminal carbon atoms, for which a two-site disorder model was introduced; the site occupation factor of the major component refined to 0.710(10). Hydrogen atoms were included in the refinement on calculated positions riding on their carrier atoms. Hydroxy and methyl hydrogen atoms were allowed to rotate around the O−C and C−C bonds, respectively. The hydrogen atoms of the water molecules were included in a rigid group with the oxygen atom as pivot atom. All ordered non-hydrogen atoms were refined with anisotropic displacement parameters; hydrogen atoms were refined with a fixed isotropic atomic displacement parameter related to the value of the equivalent isotropic displacement parameter of their carrier atoms. Refinement converged at a final w*R2* value of 0.1754, $w = 1/[\sigma^2(F^2) + (0.035P)^2 + 2.0P]$, where $P = [\mathrm{Max}(F_o^2,0) + 2F_c^2)/3$, *R*1 = 0.0814 [for 5582 reflections with $I > 2\sigma(I)$], *S* = 1.369, 760 parameters. A final difference Fourier map showed no residual outside −0.48 and 0.44 e A^{-3}. Scattering factors were taken from the International Tables for Crystallography[26]. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Centre as supplementary publication no. CCDC-101145. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk].

Picrate Extraction Experiments with 1,2-Crown[n]cavitand **2**: Before the extraction experiments, 1,2-crown[6]cavitand **2** was thor-

oughly washed with doubly distilled water until conductivity and pH measurements of the washing layers showed that a compound free of salts and traces of acid was obtained. Equal volumes (2 × 0.5 ml) of stock solutions (7.5 mM) of metal picrates in deionized and doubly distilled water, and of 1,2-crown[6]cavitand **2** in $CDCl_3$ were stirred vigorously overnight in a stoppered vial. The two layers were centrifugated, and ^{1}H-NMR spectra were recorded from the organic layers.

Solid-Liquid Extraction Experiments with 1:1 Crown[n]cavitand-Calix[4]arenes **15e**: To a vial containing 2.5 mmol of guest molecule was added 0.5 ml of a 5 mM stock solution of host molecule **15e** in $CDCl_3$. The mixtures were sonicated for at least 1 h and heated at reflux for 5 min in the closed vials. After allowing to cool to room temperature the ^{1}H-NMR spectra of the mixtures were recorded.

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[11] Although the combination of calix[4]arenes and crown ether elements are referred to as calix[4]crowns, the combinations of resorcin[4]arenes and crown ether elements will be referred to as crown[*n*]cavitands to make it possible to distinguish between 1,2-crown[*n*]cavitands **1**−**3** and 1,3-crown[*n*]cavitands.

[12] The official name for the unsubstituted methylene-bridged cavitand with R groups at the *para* positions and with four alkyl chains at the bottom is 7,11,15,28-tetra"R"-1,21,23,25-tetra-"alkyl"-2,20:3,19-dimetheno-1*H*,21*H*,23*H*,25*H*-bis[1,3]dioxocino[5,4-*i*:5′,4′-*i*′]benzo[1,2-*d*:5,4-*d*′]bis[1,3]benzodioxocin. For simplicity reasons we have given each of the resorcin[4]arene aromatic rings a number (1−4); therefore, we call a 7,11-difunctionalized cavitand a 1,2-difunctionalized cavitand.

[13] In most calix[*n*]crowns, the crown ether unit is introduced after dialkylation of the calix[4]arene at opposite rings. In those cases, the crown ether unit will connect two hydroxy groups at opposite rings.

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[20] Addition of prednisolone-21-acetate, quinidine, or β-D-ribofuranose tetraacetate to a solution of **15e** in chloroform did not give any significant shift of host or guest signals. Extraction experiments with dipeptides glycyl-leucine and glycyl-tyrosine, tripeptide glycyl-glycyl-leucine, and tetrapeptide glycyl-glycyl-glycyl-glycine showed that 1:1 *endo* **15e** does not complex these peptides. Also solid-liquid (chloroform) and liquid-liquid (water and chloroform) extraction experiments with 5-amino-*n*-valeric acid, 4-aminophenyl acetic acid, and 4-(aminomethyl)benzoic acid did not give any indications for complexation by 1:1 *endo* **15e**.

[21] For mixtures of isomers, in the assignment of signals of the ^{1}H-NMR spectra with a superscript "*n*" or "*x*" is shown (as far as known) indicating whether the signal belongs to the *endo* or the *exo* isomer, respectively. The number of hydrogen atoms is assigned as if only one isomer is present.

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[98070]