Combination of Calix[4]arenes and Resorcin[4]arenes for the Complexation of Steroids

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Receptor molecules with large cavities synthesized by the combination of building blocks that already possess a cavity, *viz.* calix[4]arenes and resorcin[4]arenes, are described. These receptor molecules are synthesized by reaction of one or two upper rim 1,2-difunctionalized calix[4]arene fragments oriented either *endo* or *exo* toward a cavitand unit. The *endo:exo* ratio depends on the substituents at the 3- and 4-positions of the calix[4]arenes. These novel receptor molecules complex steroids with association constants of (0.9−9.5) × 10^2 M^{-1} in $CDCl_3$.

Introduction

In the first 25 years of host−guest chemistry the work has been mainly focused on receptors for small guests like cations, anions, and small neutral molecules. Recently, there has been an increasing interest in the complexation of larger guest molecules such as steroids by synthetic receptor molecules. Most of these complexation studies have been performed in aqueous solutions, in which hydrophobic interactions govern the stability and selectivity of the complexation. Diederich *et al.*[1] described the synthesis of a double cyclophane that complexes cholesterol with an association constant of 1.5 × 10^5 M^{-1} in water. Cage-type cyclophanes were studied by Murakami *et al.*[2] for the binding of steroids in D_2O/CD_3OD (3:1 v/v); they reported association constants between 3.6 and 13.0 × 10^2 M^{-1}. Several groups used cyclodextrins for the complexation of steroids. Pitha *et al.*[3a,b] described that hydroxypropyl-derivatized β-cyclodextrins solubilize cholesterol in water. Hamada *et al.*[3c] have used a γ-cyclodextrin derivative as a fluorescent receptor molecule for a number of cholic acid derivatives. In their studies of β-cyclodextrin·steroid inclusion complexes Djedani *et al.*[3d] showed that the substitution pattern of the steroid determines the stoichiometry of inclusion.

Aoyama *et al.*[4] found that in apolar organic media CH−π interactions play an important role in the complexation of steroids by resorcin[4]arenes. They demonstrated that the formation of hydrogen-bonded complexes in chloroform involves an additional substantial contribution (up to ca. 1.4 kcal/mol) of attractive guest−host CH−π interaction. Whitcombe *et al.*[5] have used polymers obtained *via* molecular imprinting to bind cholesterol.[6]

Our new strategy for the synthesis of artificial receptor molecules comprises the combination of medium-sized building blocks. The building blocks should be easily accessible and have relatively rigid structures, and it should be possible to introduce selectively different functional groups. We have already synthesized different classes of large synthetic receptor molecules by the combination of calix[4]arenes with β-cyclodextrins[7] and porphyrins.[8]

The combination of calix[4]arenes[9] with resorcin[4]-arenes[10] or cavitands[11] can be achieved in different ways. Recently, we reported the synthesis of compound **1** by combination of 1,3-bis(chloroacetamido)calix[4]arene[12] and tetrahydroxycavitand **2** (see Chart 1).[10]

Combination of two calix[4]arenes and two resorcin-[4]arenes in a cyclic array leads to the extremely rigid holand **3**,[13] in which the calix[4]arene and cavitand moieties are connected via highly organized amido spacers. A systematic search for suitable guest molecules for holand **3** using the computer simulation program DOCK[14]

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(12) We have given each of the calix[4]arene aromatic rings a number (1−4); substituents are always at the *para* position relative to the phenolic oxygen.

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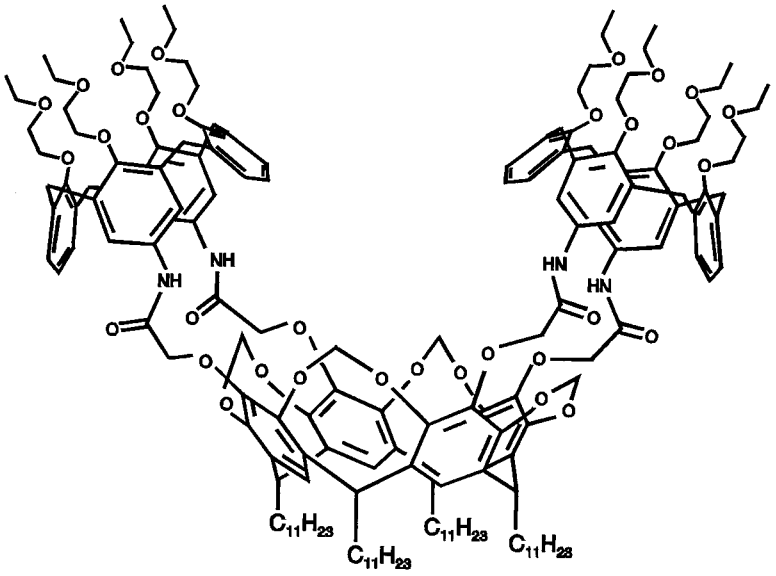
Chart 1



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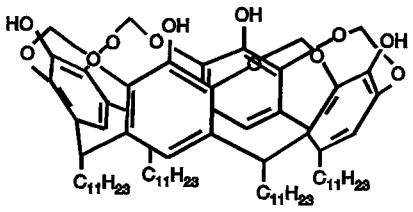

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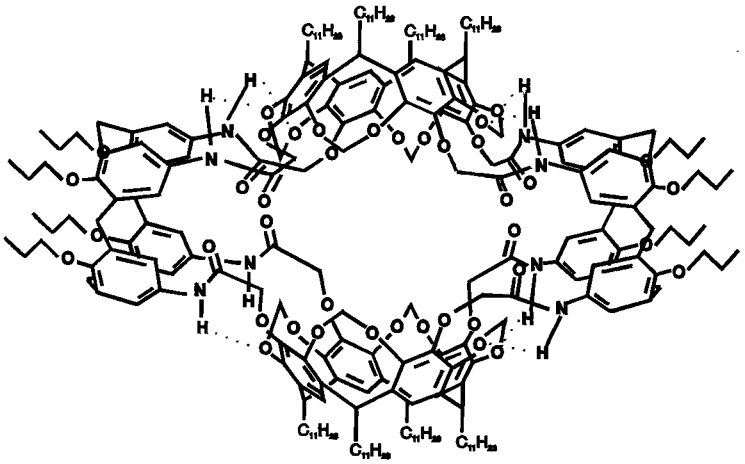

3

showed that steroids are a suitable class of guest compounds. However, so far we have found no complexation at all by holand **3**, probably because the extreme rigidity of holand **3** prevents the structural deformations that might be necessary for complexation. Receptor molecules **4**−**6**, composed of two calix[4]arenes and one resorcin[4]arene (see Chart 2), have a cavity very similar to that of holand **3** but are more flexible; this might allow them to accommodate the structural deformations necessary for complexation.

In this paper we describe the synthesis of a series of such potential receptor molecules by combination of calix[4]arenes (**7**, **8**, **12**, **16**, **19**, and **22**) with tetrahydroxycavitand **2**. We have systematically varied the substituents at the 3- and 4-positions and studied their influence on the stereochemistry of the products. The affinity of both the 1:1 and the 2:1 products[15] for prednisolone-21-acetate and derivatives was studied by ^{1}H NMR titration experiments.[16]

(15) Throughout this paper the 1:1 addition products are simplified to *endo*-**23** and *exo*-**24** and the 2:1 addition products to *endo,endo*-**4**, *endo,exo*-**5**, and *exo,exo*-**6**.

Results and Discussion

Synthesis of 1,2-Difunctionalized Calix[4]arenes. Previously, we described the synthesis of 1,2-bis(chloroacetamido)calix[4]arenes **7**[13] and **8**[17] that have either hydrogens or nitro groups at the remaining *p*-positions of the aromatic rings of the calix[4]arene moieties (Chart 3). For the synthesis of 1,2-bis(chloroacetamido)calix[4]-arenes with two phthalimido,[18] acetamido, or cyano groups at the remaining *p*-positions of the aromatic rings, we used the dinitrocalix[4]arenes **9** and **10**, carrying either two iodo or two phthalimido groups. These were also used as starting materials in the synthesis of calix[4]arene **8**.[17]

Reduction of 1,2-dinitro-3,4-diphthalimidocalix[4]arene **10** with $SnCl_2 \cdot 2H_2O$ in refluxing ethanol gave 1,2-diamino-3,4-diphthalimidocalix[4]arene **11** in 89% yield;

(16) A small part of this work was published as a preliminary communication: Timmerman, P.; Brinks, E. A.; Verboom, W.; Reinhoudt, D. N. *J. Chem. Soc., Chem. Commun.* **1995**, 417.

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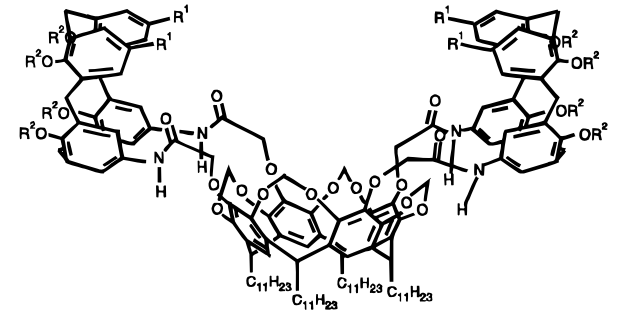
(18) Throughout this paper the abbreviation "pht" is used in the text and charts for a phthalimido group.

Chart 2



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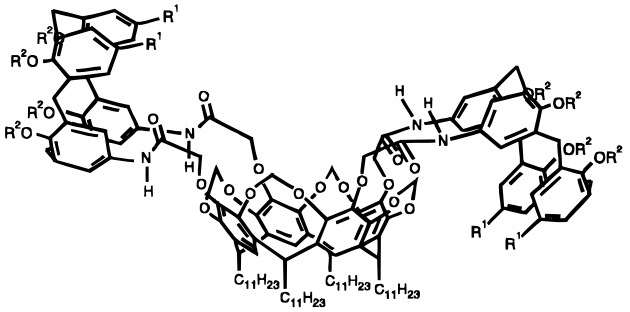

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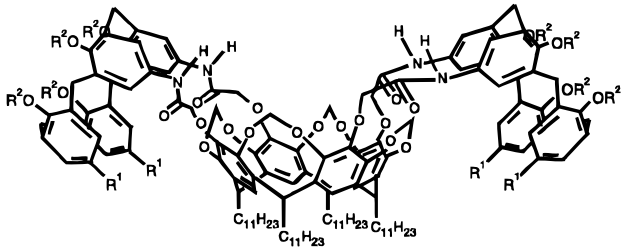

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a) R^1 = H, R^2 = $(CH_2)_2OCH_2CH_3$

b) R^1 = NO_2, R^2 = $(CH_2)_2CH_3$

c) R^1 = pht, R^2 = $(CH_2)_2CH_3$

d) R^1 = $NHC(O)CH_3$, R^2 = $(CH_2)_2CH_3$

e) R^1 = *t*-Butyl, R^2 = $(CH_2)_2CH_3$

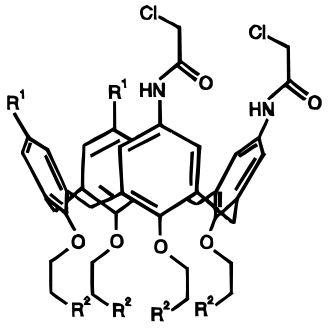
f) R^1 = CN, R^2 = $(CH_2)_2CH_3$

the absorption around 6.0 ppm in the ^{1}H NMR spectrum is characteristic for aromatic hydrogens *ortho* to an amino group. Subsequent reaction with α-chloroacetyl chloride afforded 1,2-bis(chloroacetamido)-3,4-diphthalimidodicalix[4]arene **12** in 89% yield. Deprotection of the masked amino groups in **10** gave 1,2-diamino-3,4-dinitrocalix[4]arene **13**,[17] which was converted to 1,2-bis(acetamido)-3,4-dinitrocalix[4]arene **14** by reaction with acetyl chloride in 67% yield. Reduction of the nitro groups with hydrazine led to 1,2-diacetamido-3,4-diaminocalix[4]arene **15**, and subsequent acylation with α-chloroacetyl chloride gave 1,2-diacetamido-3,4-bis(chloroacetamido)-calix[4]arene **16** in 80% overall yield.

Previously, we described the direct replacement of two adjacent *tert*-butyl groups via *ipso* aromatic nitration as a useful method for the preparation of 1,2-di-*tert*-butyl-3,4-dinitrocalix[4]arene **17**.[19] Reduction of **17** with hydrazine gave 1,2-diamino-3,4-di-*tert*-butylcalix[4]arene **18**

(19) Verboom, W.; Durie, A.; Egberink, R. J. M.; Asfari, Z.; Reinhoudt, D. N. *J. Org. Chem.* **1992**, *57*, 1313.

Chart 3



7 R^1 = H, R^2 = OCH_2CH_3

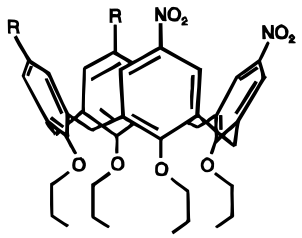
8 R^1 = NO_2, R^2 = CH_3

12 R^1 = pht, R^2 = CH_3

16 R^1 = $NHC(O)CH_3$, R^2 = CH_3

19 R^1 = *t*-Butyl, R^2 = CH_3

22 R^1 = CN, R^2 = CH_3



9 R = I

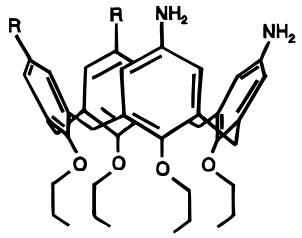
10 R = pht

13 R = NH_2

14 R = $NHC(O)CH_3$

17 R = *t*-Butyl

20 R = CN



11 R = pht

15 R = $NHC(O)CH_3$

18 R = *t*-Butyl

21 R = CN

in quantitative yield. The 1,2-di-*tert*-butyl-3,4-bis(chloroacetamido)calix[4]arene **19** was prepared in 83% yield by acylation of calix[4]arene **18**. 1,2-Diiodo-3,4-dinitrocalix[4]arene **9** was converted into 1,2-dicyano-3,4-dinitrocalix[4]arene **20** in quantitative yield by reaction with Cu(I)-CN followed by treatment with $FeCl_3$. Reduction of the nitro groups in calix[4]arene **20** with hydrazine does not affect the cyano groups and gave 1,2-diamino-3,4-dicyanocalix[4]arene **21** in 77% yield. Subsequent reaction of calix[4]arene **21** with α-chloroacetyl chloride afforded 1,2-bis(chloroacetamido)-3,4-dicyanocalix[4]arene **22** in 50% yield.

Reactions of 1,2-Bis(chloroacetamido)calix[4]-arenes (7, 8, 12, 16, 19, and 22) with Tetrahydroxy-cavitand 2: Synthesis of Receptor Molecules 4, 5, 6, 23, and 24. Previously, we have described the synthesis of receptor molecules via the reaction between 1,2-bis(chloroacetamido)calix[4]arenes and tetrahydroxy-cavitand **2**. Reaction of 1,2-bis(chloroacetamido)calix[4]-arene **7** and **2** afforded the 1:1 products *endo* **23a** and *exo* **24a** (entry 1 in Table 1, Chart 4), and the 2:1 isomers *endo,endo*-**4a**, *endo,exo*-**5a**, and *exo,exo*-**6a** (entry 2 in Table 1) in nearly statistical yields.[10]

For these compounds, we have shown that an amide hydrogen resonating at lower field (8.7−9.8 ppm) corresponds to an *endo*-coupled calix[4]arene moiety, whereas an *exo*-coupled amide gives rise to a signal at somewhat higher field (8.0−8.3 ppm).[20] Throughout this paper we have used this difference in chemical shift to assign the stereochemistry of all coupled products **4**−**6**, **23**, and **24**. The ^{1}H NMR spectra of 2:1 isomers **4e**, **5e**, and **6e** in $CDCl_3$ are given in Figure 1.

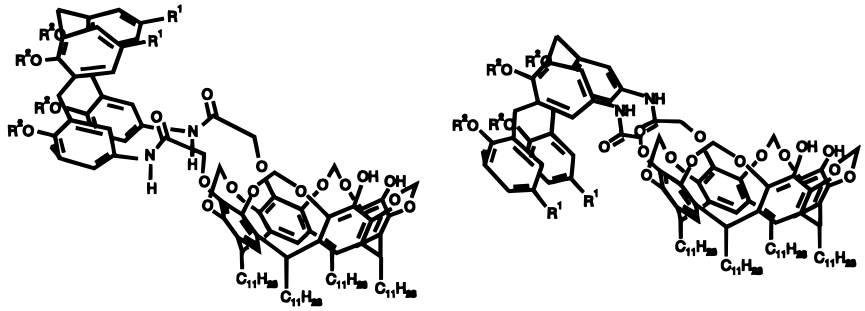
(20) The position of the amide hydrogen signal is influenced by the subsituents at the remaining 3- and 4-positions of the calix[4]arene moiety.

Table 1. Results of Coupling Reactions between 1,2-Bis(chloroacetamido)calix[4]arenes 7, 8, 12, 16, 19, and 22 and Tetrahydroxycavitand 2[a]

entry	calixarene	ratio calix:**2**	yield (%) *endo*-**23**	yield (%) *exo*-**24**	yield (%) *endo,endo*-**4**	yield (%) *endo,exo*-**5**	yield (%) *exo,exo*-**6**
1	**7**	1	19	32			
2	**7**	2			16	39	20
3	**8**	1	42				
4	**8**	2			20	21	
5	**12**	0.33	41		8	8	
6	**12**	1	26		14	18	
7	**16**	0.33	45				
8	**16**	2	17			27	
9	**19**	2			14	18	4
10	**22**	2			4	6	3

[a] Results described in entries 1−4 were published previously.[10]

Chart 4



23 24

a) R^1 = H, R^2 = $(CH_2)_2OCH_2CH_3$

b) R^1 = NO_2, R^2 = $(CH_2)_2CH_3$

c) R^1 = pht, R^2 = $(CH_2)_2CH_3$

d) R^1 = $NHC(O)CH_3$, R^2 = $(CH_2)_2CH_3$

e) R^1 = *t*-Butyl, R^2 = $(CH_2)_2CH_3$

f) R^1 = CN, R^2 = $(CH_2)_2CH_3$

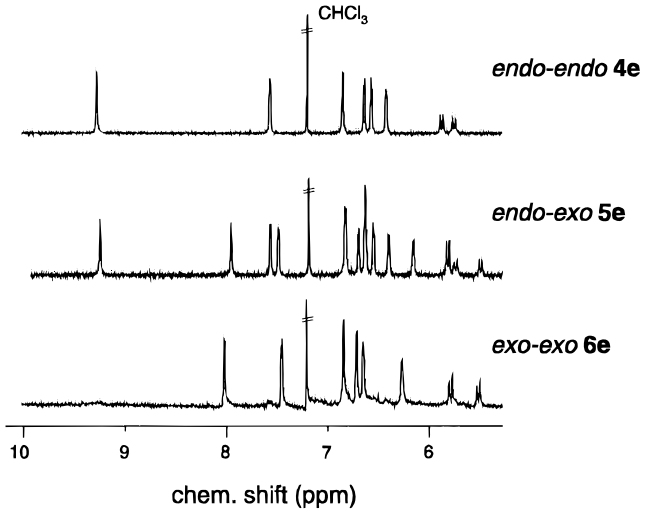


Figure 1. ^{1}H NMR spectra of *endo,endo*-**4e**, *endo,exo*-**5e**, and *exo,exo*-**6e** (R^1 = −*tert*-butyl) in $CDCl_3$ at room temperature.

Reaction between tetrahydroxycavitand **2** and 1,2-bis-(chloroacetamido)-3,4-dinitrocalix[4]arene **8** in a 1:1 ratio exclusively gave *endo*-**23b** (entry 3 in Table 1).[21] Reaction of this product with a second equivalent of **8** gave a statistical mixture of *endo,endo*-**4b** and *endo,exo* isomer **5b** (entry 4 in Table 1).[10] The absence of both the *exo* and the *exo,exo* products prompted us to conclude that the stereochemistry of the 1:1 products is determined during the formation of the *second bond* between the two building blocks; after formation of the *first bond* both isomers can still be formed (see Figure 2). In route a) the calix[4]arene moiety has to rotate *toward* the cavitand moiety, and this leads to the *endo* isomer. In route b) the calix[4]arene moiety has to rotate *away* from the cavitand moiety, which leads to the *exo* isomer. Therefore, the preference for an *endo* or *exo* orientation of the first calix[4]arene moiety will be determined by *intramolecular* interactions.

The stereochemistry of the 2:1 products, however, is already established with the formation of the *first bond* to the second calix[4]arene unit; after formation of the *first bond* only one isomer can be formed because only one chloroacetamido functionality and one hydroxyl group remain. Consequently, the orientation of the second calix[4]arene is exclusively determined before formation of the *first bond* and therefore by *intermolecular* interactions. In this paper, we address the question whether the stereochemistry of the products can be influenced by the functionality at the 3- and 4-positions of the 1,2-bis(chloroacetamido)calix[4]arene.

Reaction between 1,2-bis(chloroacetamido)-3,4-diphthalimidodicalix[4]arene **12** and tetrahydroxycavitand **2**, performed under different reaction conditions, gave only three of the five possible products. The results are summarized in Table 2. Reaction in CH_3CN (1:1 ratio) (entry 1 in Table 2) produced in addition to 26% of *endo*

(21) Because of its instability isomer *endo*-**23b** was isolated after silylation of the free hydroxyl groups with *tert*-butyldimethylsilyl chloride.

Table 2. Total Yield and Product Distribution of the Reaction between Calix[4]arene 12 and Tetrahydroxycavitand 2 under Different Reaction Conditions

entry	ratio **12**/**2**	solvent	[**12**], mM	reaction time[a] (h)	total yield (%)	yield (%) *endo*-**23c**	yield (%) *endo,endo*-**4c**	yield (%) *endo,exo*-**5c**
1	1.0	CH_3CN	2.0	7 + 8	72[b]	26	14	18
2	0.33	CH_3CN	1.8	6 + 10	71[c]	41	8	8
3	2.1	CH_3CN	4.3	8 + 32	10[d]		5	5
4	2.1	DMF[e]	4.3	8 + 9	6		3	3

[a] Time used for addition of **12** plus additional reaction time. [b] Includes an additional 14%, which was obtained as a mixture of isomers **24c**, **4c**, and **5c** (6%, 8%, and 8%, respectively, according to ^{1}H NMR). [c] Includes an additional 14%, which was obtained as a mixture of isomers **23c** and **24c** (both 7%, according to ^{1}H NMR). [d] Unreacted **12** was isolated in 46% yield. [e] Reaction was performed at 100 °C.

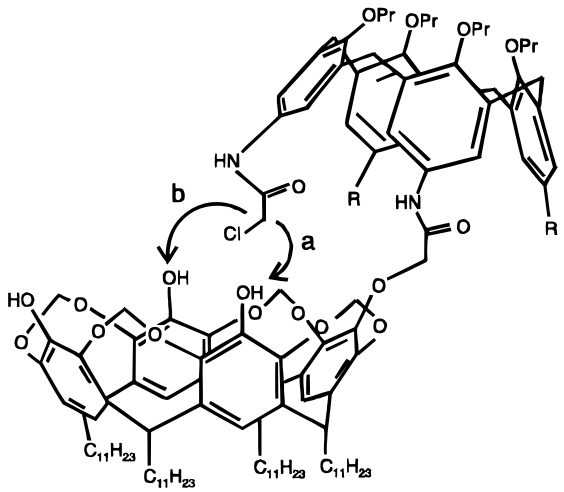


Figure 2. *Intramolecular* interaction leading to *endo*-**23** (route a), or *exo*-**24** (route b).

23c considerable amounts of *endo,endo*-**4c** and *endo,exo*-**5c** (14% and 18%, respectively). A small amount of *exo*-**24c** was observed (~4%) but could not be separated from unreacted tetrahydroxycavitand **2**. When the reaction was carried out with 3 equiv of tetrahydroxycavitand **2** (entry 2 in Table 2) the yield of *endo*-**23c** improved to 41% but the 2:1 isomers *endo,endo*-**4c** and *endo,exo*-**5c** were still formed in 8% yield each. Also in this case a small amount of *exo*-**24c** was found. Reaction in a 2:1 ratio in CH_3CN (entry 3 in Table 2) for 40 h at reflux temperature gave only small amounts (5%) of the 2:1 products *endo,endo*-**4c** and *endo,exo*-**5c** together with unreacted 1,2-bis(chloroacetamido)-3,4-bis(phthalimido)-calix[4]arene **12** (46%). Even in DMF (2:1 ratio) at elevated temperatures (100 °C, entry 4 in Table 2), only very small amounts of 2:1 isomers *endo,endo*-**4c** and *endo,exo*-**5c** (~3% each) were isolated. Because the *endo* isomer **23c** is stable under the conditions used, the most likely explanation for these results is polymerization of calix[4]arene and cavitand fragments.

Reaction between 1,2-bis(acetamido)-3,4-bis(chloroacetamido)calix[4]arene **16** and an excess of tetrahydroxycavitand **2** in CH_3CN (entry 7 in Table 1) gave *endo* isomer **23d** in 45% yield. Reaction in a 2:1 ratio (entry 8 in Table 1) afforded only the *endo,exo*-coupled product **5d** and the *endo*-coupled product **23d** in 27% and 17% yield, respectively. Traces of other products were present but could not be isolated.

In order to investigate whether bulky substituents at the 3- and 4-positions of the 1,2-bis(chloroacetamido)-calix[4]arene influence the isomer distribution, we studied the reaction between 1,2-di-*tert*-butyl-3,4-bis(chloroacetamido)calix[4]arene **19** and tetrahydroxycavitand **2** (entry 9 in Table 1). Reaction in DMF gave the three 2:1 isomers in moderate yields: 14% of *endo,endo*-**4e**, 18% of *endo,exo*-**5e**, and 4% of *exo,exo*-**6e**. Reaction between 1,2-bis(chloroacetamido)-3,4-dicyanocalix[4]arene **22** and tetrahydroxycavitand **2** in DMF (entry 10 in Table 1) gave the three 2:1 isomers **4**−**6f** in an almost statistical ratio in a total yield of 13%.

The fact that both the *exo*-**24** and the *exo,exo*-**6** isomers are virtually absent in the coupling reactions between tetrahydroxycavitand **2** and the 1,2-bis(chloroacetamido)-calix[4]arenes **8** (R^1 = $-NO_2$), **12** (R^1 = −pht), and **16** (R^1 = $-NHC(O)CH_3$) indicates that there is a strong preference for an *endo* orientation of the first calix[4]-arene moiety with respect to the cavitand moiety. This can be attributed to a favorable interaction of the polar functional groups at the 3- and 4-positions of the calix-[4]arene during formation of the second bond. In the reaction leading to the *exo* isomer the functional groups at the 3- and 4-positions are too remote to have an interaction with the cavitand moiety. The results of the coupling reaction with 1,2-bis(chloroacetamido)calix-[4]arenes **19** (R^1 = −*tert*-butyl) and **22** (R^1 = −CN) indicate that the directing effect of these substituents is much smaller or even negligible.

The statistical distribution of 2:1 products *endo,endo*-**4**, *endo,exo*-**5**, and *exo,exo*-**6** (R^1 = −H, $-NO_2$, −pht, or −*tert*-butyl)[22] indicates that there is no preference for an *endo* or *exo* orientation in the reaction of a 1:1 product with the second calix[4]arene. Apparently, there is no specific interaction during the reaction. An exception to this statistical distribution is the coupling with 1,2-bis-(acetamido)-3,4-bis(chloroacetamido)calix[4]arene **16**, where exclusively the *endo,exo* isomer **5d** was formed. There has to be an *intermolecular* interaction between previously formed *endo*-**23d** and a second equivalent of calix[4]arene, which favors the formation of the second calix[4]arene in an *exo*-fashion with respect to *endo*-**23d**. From the literature,[4] it is known that acetyl groups show strong interactions with a cavitand. In the case of calix-[4]arene **16**, acetamido groups could penetrate inside the cavity of *endo* isomer **23d** (see a in Figure 3). Assuming that the other acetamido functionality will interact with an amido bridge or an acetamido group of the *endo* isomer **23d** (b in Figure 3), formation of the *endo,exo* isomer **5d** is most likely because one of the chloroacetamido functionalities is in close proximity to one of the two remaining hydroxyl groups (c in Figure 3, the hydroxyl group at the aromatic ring in the back) while the other chloroacetamido group is not close to one of the hydroxyl groups. After formation of this bond the calix[4]arene moiety has to rotate *away* from the 1:1 *endo* cavity to make it possible to form the second bond between the remaining chloroacetamido and hydroxyl groups. Reac-

(22) The results of the coupling reactions in a 1:1 ratio are taken into consideration: if no *exo* isomer was found the statistical distribution of 2:1 products *endo,endo*-**4**, *endo,exo*-**5**, and *exo,exo*-**6** is 1:1:0, if the *exo* isomer was found this distribution is 1:2:1.

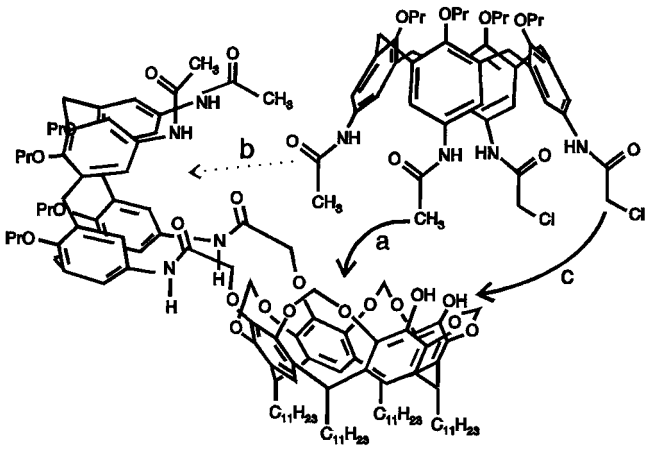


Figure 3. *Intermolecular* interaction between *endo*-**23d** ($R^1 = -NHC(O)CH_3$) and calix[4]arene **16** exclusively leading to the formation of *endo,exo*-**5d**.

tion following this pathway can only lead to an *exo* orientation of the second calix[4]arene moiety.

Conformational Properties of 2:1 Receptor Molecules 5a, d, and e. The ^{1}H NMR spectrum of *endo,exo* isomer **5d** ($R^1 = -NHC(O)CH_3$) at room temperature in $CDCl_3$ showed an additional four peaks in the amide region indicating the presence of minor conformers (see Figure 4a). ROESY NMR spectroscopy[23] showed cross peaks between the major *endo* amide hydrogen and a set of two signals and cross peaks between the major *exo* amide hydrogen and another set of two signals (see Figure 4b).

Although rotation of one amide bridge results in principle in four different amide hydrogens, it is reasonable to assume that the rotation of an amide bridge on one side of the 2:1 isomer does not influence the amide hydrogens on the other side to a large extent. This means that there are two minor conformers present, one in which one of the *endo* amide bridges is rotated and one in which one of the *exo* amide bridges is rotated.[24] $\Delta G°_{298}$ values of ~6 kJ mol^{-1} were calculated for both the *endo* and the *exo* amide bridge. By using ROESY NMR spectroscopy $\Delta G^{‡}_{303}$ values of 70 and 83 kJ mol^{-1} were determined for the rotation of *endo* and *exo* amide bridges, respectively. Because the minor conformers are only present in a small amount, the conformer in which two amide bridges are rotated (either two on one side or one on both sides) does not appear in the NMR spectra.

In contrast with the ^{1}H NMR spectrum of *endo,exo*-**5d** ($R^1 = -NHC(O)CH_3$), the ^{1}H NMR spectra of *endo,exo* isomers **5a** ($R^1 = -H$) and **5e** ($R^1 = -$*tert*-butyl) in $CDCl_3$ at room temperature do not exhibit the presence of a minor conformer. Cooling leads to a broadening of the signal for the *exo* amide proton at −60 °C in the case of product **5e**, indicating that the rotation of the *exo* amido bridge becomes slow on the NMR time scale. At −80 °C broadening of the signal for the *exo* amide hydrogen of product **5a** occurs. Therefore, we can conclude that the parent *endo,exo* isomer **5a** ($R^1 = -H$) shows the fastest rotation of the amide bridge (has the lowest $\Delta G^{‡}$ value), the *tert*-butyl groups in *endo,exo* isomer **5e** hinder this rotation, while the acetamido groups of *endo,exo* isomer

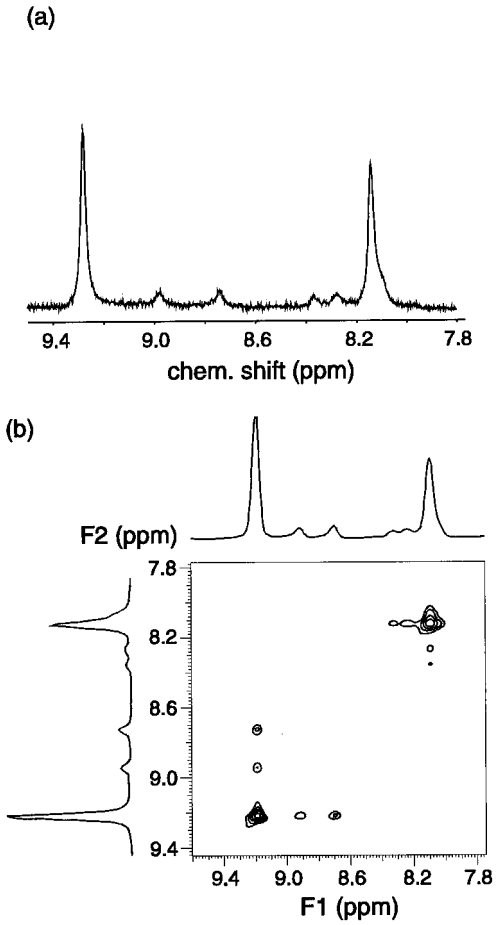


Figure 4. (a) ^{1}H NMR spectrum of *endo,exo*-**5d** ($R^1 = -NHC(O)CH_3$) in $CDCl_3$ at room temperature and (b) ROESY NMR spectrum of *endo,exo*-**5d** ($R^1 = -NHC(O)CH_3$) in $CDCl_3$ at 30 °C.

5d slow the rotation to such extent that two minor conformers are present at room temperature. This behavior can be explained by an intramolecular interaction between the amide bridge and the acetamido groups at the 3- and 4-positions of the calix[4]arenes.

Complexation Properties. Following the results of the DOCK study with holand **3**, which showed that steroids are potential guest compounds, we studied the affinity of 2:1 isomers **4**−**6**, having a cavity very similar to that of holand **3**, for steroids, in particular corticosteroids. Corticosteroids are hormonal steroids characterized by an oxygen function at C_{11}, which are widely used against rheumatoid arthritis, severe asthma, and other inflammatory diseases.[25]

First, the complexation behavior of the 2:1 isomers **4a**, **5a**, and **6a** ($R^1 = -H$) was studied. Upon addition of prednisolone 21-acetate (**25**, Chart 5) to a solution of one of these compounds in $CDCl_3$ at 25 °C, the amide hydrogen signals in the ^{1}H NMR spectrum split into two signals of equal intensity. This splitting is a result of the chirality of the guest, which makes the overall complex chiral. Due to fast exchange between the free host and the complex on the ^{1}H NMR chemical shift time scale, only two signals are observed for the four amide

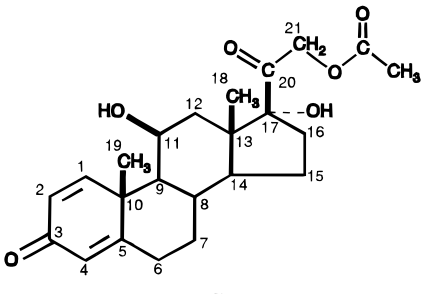
(23) Bothner-By, A. A.; Stephens, R. L.; Lee, J.; Warren, C. D.; Jeanloz, R. W. *J. Am. Chem. Soc.* **1984**, *106*, 811.

(24) It is not clear from the experiments whether this is an interconversion between the *trans* and the *cis* amide or a rotation of the bond between the aromatic carbon and the amide nitrogen.

(25) (a) Ganong, W. F. *Review of Medical Physiology*, 14th ed.; Prentice Hall: London, 1989; Chapter 4. (b) Siegel, S. C. *J. Allergy Clin. Immunol.* **1985**, *76*, 312.

(26) de Boer, J. A. A.; Reinhoudt, D. N.; Harkema, S.; van Hummel, G. J.; de Jong, F. *J. Am. Chem. Soc.* **1982**, *104*, 4073.

Chart 5



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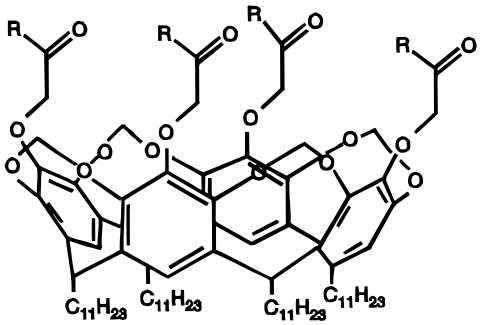


26

a) R = *p*-$NHC_6H_4OCH_3$

b) R = OCH_3

c) R = OH

Table 3. Results of Prednisolone 21-Acetate (25) Complexation by Receptor Molecules 4a, 5a−e, and 6a[a]

entry	receptor	K_{assoc} (M^{-1})	ΔG_{298} (kJ mol^{-1})
1	**4a**	4.3×10^2	−15.0
2	**5a**	8.3×10^2	−16.7
3	**5b**	$<0.5 \times 10^2$	<−10
4	**5c**	5.0×10^2	−15.4
5	**5d**	9.5×10^2	−17.0
6	**5e**	1.2×10^2	−11.9
7	**6a**	5.3×10^2	−15.5

[a] Determined at 25 °C in $CDCl_3$. The estimated error is 5%.

hydrogens. The K_{assoc} values of the complexes **4a·25**, **5a·25**, and **6a·25** in $CDCl_3$ at 25 °C were determined to be 4.3×10^2, 8.3×10^2, and 5.3×10^2 M^{-1}, respectively (see entries 1, 2, and 7 in Table 3). Job plots of the titration experiments proved the 1:1 stoichiometry of the complexes; an example is given in Figure 5.

Subsequently, the complexation properties of *endo,endo* host molecules **4b** ($R^1 = -NO_2$), **4c** ($R^1 = -$pht), and **4e** ($R^1 = -$*tert*-butyl) were determined, having substituents at the remaining aromatic *p*-positions of the calix[4]arene fragments, which might change the complexation properties compared to the *endo,endo* **4a**. Surprisingly, in the ^1H NMR spectra of **4b**, **4c**, and **4e** the amide proton signals do not split or shift upon the addition of prednisolone 21-acetate (**25**). The lack of complexation might be due to a shielding or even filling of the cavity by the substituents. *Endo,exo* host molecules **5c** ($R^1 = -$pht), **5d** ($R^1 = -NHC(O)CH_3$), and **5e** ($R^1 = -$*tert*-butyl) behave very similar to **5a** ($R^1 = -H$) and, indeed, show complexation of prednisolone 21-acetate (**25**). The association constants of complexes **5c·25**, **5d·25**, and **5e·25** are 5.0×10^2, 9.5×10^2, and 1.2×10^2 M^{-1}, respectively (see entries 4−6 in Table 3). For *endo,exo* isomer **5b** ($R^1 = -NO_2$), the association constant could not be determined due to the very small shifts of the amide proton signals upon addition of prednisolone 21-acetate (**25**) (see entry 3 in Table 3).

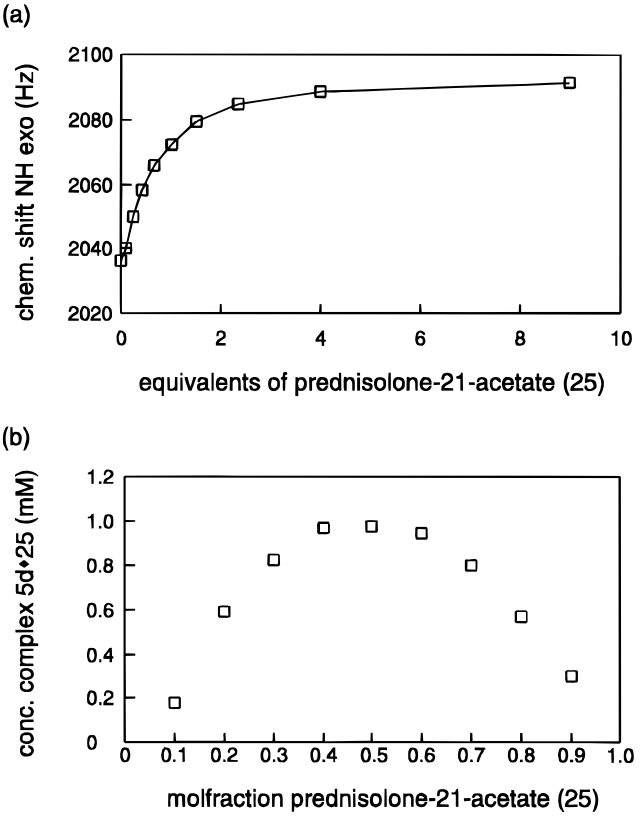
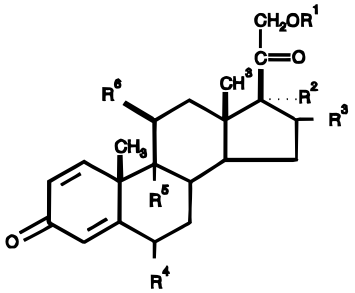


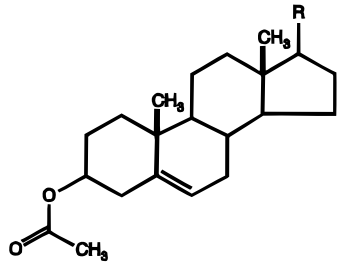
Figure 5. (a) Titration curve and (b) Job plot of the titration experiment between *endo,exo*-**5d** ($R^1 = -NHC(O)CH_3$) and prednisolone 21-acetate (**25**) in $CDCl_3$.

In order to examine the role of the calix[4]arene moieties, several control experiments were performed. Addition of up to 9 equiv of prednisolone 21−acetate (**25**) to a solution of *endo*-**23c** ($R^1 = -$pht) in $CDCl_3$ revealed no splitting or shifting of the amide proton signals of the host, indicating that both calix[4]arene units need to be present. In order to investigate the influence of the flexibility of the four amide bridges connecting the cavitand and the two calix[4]arenes, cavitand **26a**, carrying four flexible amido substituents, was synthesized. Direct alkylation of tetrahydroxycavitand **2** with 4-(2-chloroacetamido)anisole using K_2CO_3 as a base and KI as a catalyst is not possible either in CH_3CN or in DMF. Therefore, **26a** was synthesized starting from tetraester **26b**, which was obtained by reaction of tetrahydroxycavitand **2** with methyl bromoacetate in quantitative yield. Hydrolysis of **26b** with 2 N NaOH in THF gave tetracarboxylic acid **26c**, which was subsequently converted to tetraamide **26a** in 53% overall yield. Not a single signal of host or guest shifted upon addition of up to 10 equiv of prednisolone 21-acetate (**25**) to a solution of **26a** in $CDCl_3$. This proves the necessity of the two calix[4]arenes in the observed complexation of prednisolone 21-acetate (**25**). The relatively small differences in K_{assoc} values between receptor molecules **4a**, **5a**, **5c**, **5d**, **5e**, and **6a** suggest that neither the orientation nor the substituents of the two calix[4]arene fragments give a significant contribution to the complexation.

In order to determine what functionalities in prednisolone-21-acetate (**25**) are essential for the observed complexation, several related steroid molecules were studied.

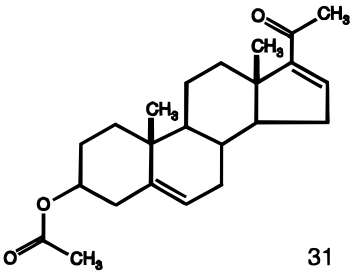
Chart 6



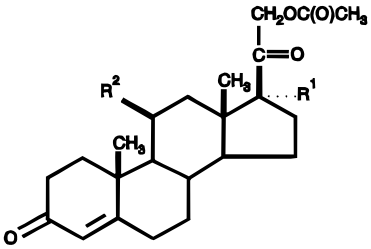


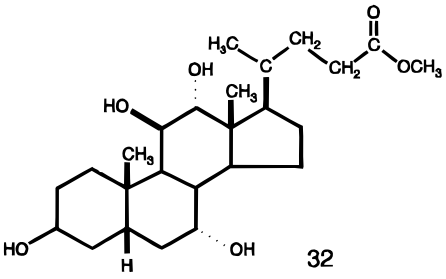
29 R = =O
30 R = $CH(CH_3)(CH_2)_3CH(CH_3)_2$

	R^1	R^2	R^3	R^4	R^5	R^6
27 Prednisolone	-H	-OH	-H	-H	-H	-OH
28 Prednisone	-H	-OH	-H	-H	-H	=O
36 Dexamethasone acetate	$-C(O)-CH_3$	-OH	$-CH_3$	-H	-F	-OH
37 Fluocinolone acetonide 21-acetate	$-C(O)-CH_3$	$-OC(CH_3)_2O-$		-F	-F	-OH



31





32

	R^1	R^2
33 Cortisone acetate	-OH	=O
34 Corticosterone acetate	-H	-OH
35 Cortisole acetate	-OH	-OH

For this purpose, a solution of *endo,exo* **5c** (R^1 = −pht) in $CDCl_3$ was used.

Addition of prednisolone (**27**, Chart 6), lacking the acetate group at C_{21}, and prednisone (**28**), without the acetate group but with a keto function at C_{11}, to a solution of receptor molecule **5c** in $CDCl_3$ did not give rise to any significant shift of guest or host signals. To investigate whether the position of the acetate group is important for complexation, steroids **29**, **30**, and **31** were studied. Neither the proton signals of the host nor those of the guest showed a significant change. Also, cholic acid methyl ester (**32**), with an ester function at C_{21}, did not cause any shifts upon addition to a solution of receptor molecule **5c**. Apparently, the acetate group at C_{21} is essential for complexation by this class of receptor molecules.

To determine the role of the two hydroxyl groups at C_{11} and C_{17} the steroids cortisone acetate (**33**), having a keto function instead of a hydroxyl group at C_{11}, and corticosterone acetate (**34**), lacking the hydroxyl group at C_{17}, were studied. Not a single signal shifted upon the addition of one of these steroids to a solution of **5c**, which also shows that both hydroxyl groups are essential for complexation.

Steroids with structures very similar to that of prednisolone 21-acetate (**25**) are cortisole acetate (or hydrocortisone acetate) (**35**) and dexamethasone acetate (**36**). Upon addition of one of these guests to a solution of receptor molecule **5c** the amide proton signals split up as expected. The K_{assoc} values are 4.9×10^2 and 3.5×10^2 M^{-1} for steroids **35** and **36**, respectively (entries 2 and 3, Table 4).

Table 4. Results of Complexation of Different Guest Molecules by Receptor 5c[a]

entry	guest	K_{assoc} (M^{-1})	ΔG_{298} (kJ mol^{-1})
1	**25**	5.0×10^2	−15.4
2	**35**	4.9×10^2	−15.3
3	**36**	3.5×10^2	−14.5
4	**37**	0.9×10^2	−11.1

[a] Determined at 25 °C in $CDCl_3$. The estimated error is 5%.

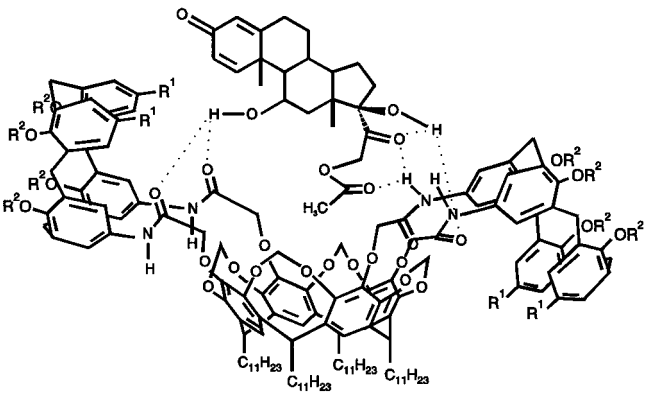


Figure 6. Proposed structure of complex **5·25** in $CDCl_3$.

Addition of fluocinolone acetonide acetate (**37**), containing a protected hydroxyl group at C_{17}, to a solution of host **5c** resulted in a shift of the *endo* amide proton signal, whereas the *exo* amide proton signal is split. The determined K_{assoc} value of 0.9×10^2 M^{-1} (entry 4, Table 4) is significantly lower compared to the other values, which can be explained by the presence of the protecting acetonide of the hydroxyl functionality at C_{17}.

The above-discussed complexation studies revealed that three structural features in the steroid skeleton are important for complexation by receptor molecule **5c** in $CDCl_3$: the hydroxyl group at C_{11}, the hydroxyl group at C_{17}, and the acetate group at C_{21}. Without one of these functionalities complexation was not observed. The control experiments with molecules other than the 2:1 isomers showed the necessity of both calix[4]arenes, although the substituents at the 3- and 4-positions do not influence this complexation to a large extent, unless they shield the cavity as in the case of **4b** ($R^1 = -NO_2$), **4c** ($R^1 = -$pht), and **4e** ($R^1 = -$*tert*-butyl).

The complexation between this new class of receptor molecules and prednisolone 21-acetate (**25**) is most likely based on a combination of hydrophobic CH−π interactions and formation of several hydrogen bonds. A hypothetical structure that explains most of the observed effects is shown in Figure 6. Because all three isomers show a comparable complexation with prednisolone 21-acetate (**25**), different hydrogen bonds might be formed in the complexes **4·25**, **5·25**, and **6·25**.

Conclusions

A new class of steroid receptor molecules (**4**−**6**, **23**, and **24**) was synthesized by reaction of 1,2-bis(chloroacetamido)calix[4]arenes (**7**, **8**, **12**, **16**, **19**, and **22**) with tetrahydroxycavitand **2**. To the best of our knowledge, they represent the first receptors for the selective complexation of steroids in *nonaqueous* media.

In this reaction the exclusive formation of the *endo* isomer **23** is promoted by polar substituents at the 3- and 4-positions of the calix[4]arenes, such as nitro, acetamido, and phthalimido groups. Reaction of *endo*-**23d** ($R^1 = -NHC(O)CH_3$) with a second equivalent of calix[4]arene **16** provided the first example of specific *intermolecular* interactions leading to *exo* positioning of the second calix[4]arene moiety with respect to the cavitand moiety.

2:1 isomers **4a**, **5a-e**, and **6a** selectively complex steroids **25** and **35**−**37** with association constants of (0.9−9.5) $\times 10^2$ M^{-1} in $CDCl_3$. Complexation studies with structural related corticosteroids revealed that the acetate group at C_{21} and the two hydroxyl groups at C_{11} and C_{17} are crucial functionalities for complexation of the steroids by this group of receptor molecules in $CDCl_3$.

Experimental Section

General Procedures. Melting points are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$. Fast atom bombardment (FAB) mass spectra were obtained with *m*-nitrobenzyl alcohol 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 an argon atmosphere. The presence of solvent in the analytical samples was confirmed by ^1H NMR spectroscopy. Tetrahydroxycavitand **2**,[10] calix[4]arenes **7**,[13] **8**−**10**, **13**,[17] and **17**,[19] 1:1 isomers **23a,b**, **24a**, and 2:1 isomers **4**−**6a**, **4b**, and **5b**[10] were obtained following published procedures.

5,11-Diamino-17,23-diphthalimido-25,26,27,28-tetrapropoxycalix[4]arene (11). A suspension of calix[4]arene **10** (1.35 g, 1.39 mmol) and $SnCl_2 \cdot 2H_2O$ (3.13 g, 13.9 mmol) in EtOH (100 mL) was refluxed overnight. The reaction mixture was allowed to cool to room temperature and poured into ice−water. The solution was adjusted to pH ≃ 9 with 1 N NaOH, filtered over Celite, and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with H_2O (2 × 25 mL) and brine (25 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* to give calix[4]arene **11**, which was used without further purification: yield 1.13 g (89%); ^1H NMR δ 7.8−7.6 (m, 8 H), 6.8−6.7, 6.0−5.9 (m, 8 H), 4.5−4.2 (m, 4 H), 3.9−3.7 (m, 8 H), 3.2−2.8 (m, 8 H), 1.9−1.8 (m, 8 H), 1.0−0.9 (m, 12 H).

5,11-Bis(2-chloroacetamido)-17,23-diphthalimido-25,26,27,28-tetrapropoxycalix[4]arene (12). To a solution of calix[4]arene **11** (2.55 g, 2.80 mmol) in CH_2Cl_2 (125 mL) were added NEt_3 (1.9 mL, 14 mmol) and $ClC(O)CH_2Cl$ (1.1 mL, 14 mmol), and the solution was stirred at room temperature for 15 min. The reaction mixture was washed with 1 N HCl (2 × 25 mL), with H_2O (25 mL), with 1 N NaOH (25 mL), with H_2O (25 mL), and with brine (25 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* to give the crude product, which was triturated with MeOH to give pure calix[4]arene **12**: yield 2.65 g (89%); mp 193−195 °C (MeOH); ^1H NMR δ 8.06 (s, 2 H), 7.9−7.8, 7.8−7.7 (m, 8 H), 6.9−6.8 (m, 8 H), 4.6−4.4, 3.3−3.2 (m, 8 H), 4.00 (s, 4 H), 4.0−3.8 (m, 8 H), 2.0−1.9 (m, 8 H), 1.1−0.9 (m, 12 H); ^{13}C NMR δ 167.4, 163.9; MS-FAB *m/e* 1065.4 ($[M + H]^+$, calcd 1065.4). Anal. Calcd for $C_{60}H_{58}Cl_2N_4O_{10} \cdot 0.5H_2O$: C, 67.03; H, 5.53; N, 5.21. Found: C, 67.04; H, 5.50; N, 5.15.

5,11-Diacetamido-17,23-dinitro-25,26,27,28-tetrapropoxycalix[4]arene (14) was prepared following the procedure described for **12** (with $ClC(O)CH_3$ instead of $ClC(O)CH_2Cl$), using **13** (2.19 g, 3.07 mmol), NEt_3 (2.1 mL, 15 mmol), and $ClC(O)CH_3$ (1.1 mL, 15 mmol) in CH_2Cl_2 (150 mL) to give the crude product, which was purified by column chromatography (SiO_2, EtOAc/PE, 40:60): yield 1.64 g (67%); mp 180−182 °C; ^1H NMR δ 7.5−7.4 (m, 6 H), 6.8−6.7 (m, 4 H), 4.51 and 3.31 (ABq, 2 H, J = 14.2 Hz), 4.41 and 3.23 (ABq, 4 H, J = 13.9 Hz), 4.31 and 3.01 (ABq, 2 H, J = 13.7 Hz), 4.0−3.6 (m, 8 H), 2.09 (s, 6 H), 1.9−1.7 (m, 8 H), 1.0−0.9 (m, 12 H); ^{13}C NMR δ 169.2; MS-FAB *m/e* 797.3 ($[M + H]^+$, calcd 797.4). Anal. Calcd for $C_{44}H_{52}N_4O_{10} \cdot 0.4H_2O$: C, 65.72; H, 6.62; N, 6.97. Found: C, 65.70; H, 6.75; N, 6.81.

5,11-Diacetamido-17,23-diamino-25,26,27,28-tetrapropoxycalix[4]arene (15). To a suspension of calix[4]arene **14** (1.25 g, 1.57 mmol) in MeOH (125 mL) was dropwise added $NH_2NH_2 \cdot H_2O$ (7.6 mL, 16 mmol) and a catalytic amount of Raney Ni, and the suspension was refluxed overnight. The reaction mixture was filtered over Celite and evaporated to dryness. The residue was dissolved in CH_2Cl_2 (125 mL), washed with H_2O (2 × 50 mL) and with brine (50 mL), and dried over Na_2SO_4. The solvent was removed *in vacuo* to give crude calix[4]arene **15**, which was used without further purification: yield 1.21 g (99%); ^{1}H NMR δ 8.40 (s, 2 H), 6.8−6.7, 6.3−6.2, 6.1−6.0 (m, 8 H), 4.35 and 3.02 (ABq, 2 H, J = 14.0 Hz), 4.32 and 3.00 (ABq, 4 H, J = 13.6 Hz), 4.30 and 2.89 (ABq, 2 H, J = 13.7 Hz), 3.8−3.7 (m, 8 H), 3.27 (br s, 4 H), 2.01 (s, 6 H), 1.9−1.7 (m, 8 H), 1.0−0.9 (m, 12 H).

5,11-Diacetamido-17,23-bis(2-chloroacetamido)-25,26,-27,28-tetrapropoxycalix[4]arene (16) was prepared following the procedure described for **12**, using **15** (1.15 g, 1.56 mmol), NEt_3 (1.1 mL, 7.8 mmol), and $ClC(O)CH_2Cl$ (0.62 mL, 7.8 mmol) in CH_2Cl_2 (70 mL) to give the crude product, which was purified by column chromatography (SiO_2, EtOAc/PE, 70:30): yield 1.11 g (80%); mp 273−275 °C; ^{1}H NMR (DMSO-d_6) δ 9.86, 9.47 (s, 4 H), 6.92 (d, 8 H, J = 1.9 Hz), 4.4−4.3, 3.1−3.0 (m, 8 H), 4.14 (s, 4 H), 3.8−3.7 (m, 8 H), 1.9−1.8 (m, 14 H), 0.96 (t, 12 H, J = 7.4 Hz); ^{13}C NMR (DMSO-d_6) δ 167.4, 163.7; MS-FAB m/e 889.2 ([M + H]$^+$, calcd 889.4). Anal. Calcd for $C_{48}H_{58}Cl_2N_4O_8 \cdot 0.8H_2O$: C, 63.75; H, 6.64; N, 6.20. Found: C, 63.91; H, 6.71; N, 6.12.

5,11-Diamino-17,23-bis(1,1-dimethylethyl)-25,26,27,28-tetrapropoxycalix[4]arene (18) was prepared following the procedure described for **15**, using **17** (1.90 g, 2.39 mmol) and $NH_2NH_2 \cdot H_2O$ (7.0 mL, 140 mmol) in MeOH (100 mL) to give calix[4]arene **18**, which was used without further purification: yield 1.70 g (97%); ^{1}H NMR δ 6.70, 6.67 (d, 4 H, J = 2.5 Hz), 6.08 (s, 4 H), 4.45 and 3.12 (ABq, 2 H, J = 13.0 Hz), 4.37 and 3.00 (ABq, 4 H, J = 12.9 Hz), 4.29 and 2.89 (ABq, 2 H, J = 12.8 Hz), 3.9−3.7 (m, 8 H), 3.07 (br s, 4 H), 2.0−1.9 (m, 8 H), 1.08 (s, 18 H), 1.0−0.9 (m, 12 H); MS-FAB m/e 734.6 (M$^+$ calcd for $C_{48}H_{66}N_2O_4$ 734.5).

5,11-Bis(2-chloroacetamido)-17,23-bis(1,1-dimethylethyl)-25,26,27,28-tetrapropoxycalix[4]arene (19) was prepared following the procedure described for **12**, using **18** (0.52 g, 0.75 mmol), NEt_3 (0.50 mL, 3.7 mmol), and $ClC(O)CH_2Cl$ (0.30 mL, 3.7 mmol) in CH_2Cl_2 (30 mL) to give the crude product, which was purified by recrystallization from CH_2Cl_2/hexane: yield 0.52 g (83%); mp 148−150 °C (CH_2Cl_2/hexane); ^{1}H NMR δ 7.83 (s, 2 H), 6.97, 6.80 (d, 4 H, J = 2.6 Hz), 6.68, 6.64 (d, 4 H, J = 2.3 Hz), 4.42 and 3.13 (ABq, 8 H, J = 13.0 Hz), 4.09 (s, 4 H), 3.9−3.8 (m, 8 H), 2.0−1.9 (m, 8 H), 1.05 (s, 18 H), 1.0−0.9 (m, 12 H); ^{13}C NMR δ 163.1; MS-FAB m/e 886.6 (M$^+$, calcd 886.4). Anal. Calcd for $C_{52}H_{68}Cl_2N_2O_6 \cdot 0.4H_2O$: C, 69.77; H, 7.75; N, 3.13. Found: C, 69.54; H, 7.73; N, 3.10.

5,11-Dicyano-17,23-dinitro-25,26,27,28-tetrapropoxycalix[4]arene (20). A mixture of calix[4]arene **9** (2.00 g, 2.14 mmol) and Cu(I)CN (0.67 g, 7.5 mmol) was refluxed in *N*-methylpyrrolidinone (NMP, 50 mL) for 4 h. The reaction mixture was allowed to cool to 100 °C, and a solution of $FeCl_3$ (1.58 g, 9.74 mmol) in HCl/H_2O (20/80 mL) was added. The reaction mixture was stirred for 1 h and filtered over Celite. The residue was extracted with CH_2Cl_2 (3 × 50 mL), washed with brine (2 × 50 mL), and dried over $MgSO_4$. The solvent was removed *in vacuo* to give crude **20**, which was recrystallized from CH_2Cl_2/hexane: yield 1.51 g (96%); mp > 300 °C; ^{1}H NMR δ 7.73, 7.59 (d, 4 H, J = 2.6 Hz), 6.98, 6.95 (d, 4 H, J = 2.5 Hz), 4.52, 4.48, 4.44, 3.40, 3.33, 3.25 (3 ABq, 8 H, J = 14.0 Hz), 4.0−3.9 (m, 8 H), 1.9−1.8 (m, 8 H), 1.0−0.9 (m, 12 H); ^{13}C NMR δ 106.6; MS-FAB m/e 733.3 ([M + H]$^+$, calcd 733.3). Anal. Calcd for $C_{42}H_{44}N_4O_8 \cdot 0.75H_2O$: C, 67.59; H, 6.14; N, 7.51. Found: C, 67.53; H, 6.00; N, 7.38.

5,11-Diamino-17,23-dicyano-25,26,27,28-tetrapropoxycalix[4]arene (21) was prepared following the procedure described for diamine **15**, using **20** (0.74 g, 1.0 mmol) and NH_2-$NH_2 \cdot H_2O$ (2.6 mL, 53 mmol) in MeOH (65 mL), and was used without further purification: yield 0.52 g (77%); ^{1}H NMR δ 7.01, 6.89 (d, 4 H, J = 2.0 Hz), 6.04, 5.91 (d, 4 H, J = 2.7 Hz), 4.46 and 3.17 (ABq, 2 H, J = 13.8 Hz), 4.35 and 3.05 (ABq, 4 H, J = 13.6 Hz), 4.25 and 2.93 (ABq, 2 H, J = 13.2 Hz), 4.0−3.6 (m, 8 H), 3.28 (br s, 4 H), 1.9−1.8 (m, 8 H), 1.0−0.9 (m, 12 H); ^{13}C NMR δ 105.3.

5,11-Bis(2-chloroacetamido)-17,23-dicyano-25,26,27,28-tetrapropoxycalix[4]arene (22) was prepared following the procedure described for **12**, starting from **21** (0.51 g, 0.74 mmol), NEt_3 (0.50 mL, 3.7 mmol), and $ClC(O)CH_2Cl$ (0.30 mL, 3.7 mmol) in CH_2Cl_2 (50 mL) to give the crude product, which was purified by column chromatography (SiO_2, EtOAc/PE, 30:70): yield 0.31 g (50%); mp 177−179 °C; ^{1}H NMR δ 7.98 (s, 2 H), 6.97, 6.88 (d, 4 H, J = 1.8 Hz), 6.84 (s, 4 H), 4.45 (part of ABq, 1 H, J = 14.0 Hz), 4.42 (part of ABq, 2 H, J = 13.7 Hz), 4.39 (part of ABq, 1 H, J = 15.2 Hz), 4.15 (s, 4 H), 4.0−3.7 (m, 8 H), 3.2−3.1 (m, 4 H), 1.9−1.8 (m, 8 H), 1.1−0.9 (m, 12 H); ^{13}C NMR δ 164.0, 105.7; MS-FAB m/e 825.3 (M$^+$, calcd 825.3). Anal. Calcd for $C_{46}H_{50}Cl_2N_4O_6 \cdot 0.5H_2O$: C, 66.18; H, 6.16; N, 6.71. Found: C, 66.07; H, 6.12; N, 6.53.

General Procedure for the Preparation of Isomers 4−6, 23, and 24. To a suspension of **2**, Cs_2CO_3, and KI in CH_3CN (reflux temperature) or DMF (100 °C) was added a solution of calix[4]arene **12**, **16**, **19**, or **22** in CH_3CN or DMF over 6−8 h, and the reaction mixture was subsequently stirred for 7−32 h at this 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 over Na_2SO_4.

17,23,51,57-Tetraphthalimido-12,28,46,62,93,94,98,99-octapropoxy-79,85,86,87-tetraundecyl-14*H*,20*H*,26*H*,32*H*,-48*H*,54*H*,60*H*,66*H*-4,70-(epoxymethanoxy)-1,81:3,71:11,29:45,63:73,77-pentamethano-9,13:15,19:21,25:27,31:43,47:49,53:55,59:61,65-octametheno-6*H*,40*H*,79*H*-dibenzo[*d*,*d*′]-[1,3]dioxocino[4,5-*l*$_1$:8,7-*l*′$_1$]bis[1,3,6,36,9,33]benzotetraoxadiazacyclooctatriacontine-7,33,41,67(8*H*,34*H*,42*H*,-68*H*)tetrone (2:1 *endo*,*endo*, R = phthalimido) (4c) was prepared starting from calix[4]arene **12** (0.49 g, 0.46 mmol), cavitand **2** (0.55 g, 0.47 mmol), Cs_2CO_3 (0.61 g, 1.9 mmol), and KI in CH_3CN (230 mL) and THF (20 mL). The calix[4]arene was added over 8 h, and subsequently, the reaction mixture was stirred at reflux temperature for 7 h to give the crude reaction mixture, which was purified by column chromatography (SiO_2, EtOAc/PE, 45:55): yield 0.10 g (14%); mp 263−265 °C; ^{1}H NMR δ 9.81 (s, 4 H), 7.8−7.5 (m, 16 H), 7.3−6.7 (m, 20 H), 6.58, 5.94 (d, 4 H, J = 7.0 Hz), 4.8−4.2 (m, 16 H), 4.65 and 4.25 (ABq, 8 H, J = 15.8 Hz), 4.0−3.8 (m, 16 H), 3.3−3.2 (m, 8 H), 2.3−2.2 (m, 8 H), 2.0−1.9 (m, 16 H), 1.4−1.2 (m, 72 H), 1.1−1.0 (m, 24 H), 1.0−0.8 (m, 12 H); ^{13}C NMR δ 167.2, 166.5; MS-FAB m/e 3203.5 (M$^+$, calcd 3203.6). Anal. Calcd for $C_{196}H_{224}N_8O_{32} \cdot 1.9H_2O$: C, 72.70; H, 7.09; N, 3.46. Found: C, 72.70; H, 7.41; N, 3.32.

2:1 *Endo*−*exo*, R = phthalimido (5c) was isolated from the same reaction mixture as **4c**: yield 0.13 g (18%); mp 268−271 °C; ^{1}H NMR δ 9.77, 8.05 (s, 4 H), 7.9−7.6 (m, 16 H), 7.3−6.4 (m, 20 H), 6.55, 6.08, 5.88 (d, 4 H, J = 7.0 Hz), 4.8−4.1 (m, 24 H), 4.0−3.8 (m, 16 H), 3.3−3.2 (m, 8 H), 2.3−2.2 (m, 8 H), 2.0−1.9 (m, 16 H), 1.4−1.2 (m, 72 H), 1.1−1.0 (m, 24 H), 0.9−0.8 (m, 12 H); ^{13}C NMR δ 167.3, 167.1, 166.3, 165.7; MS-FAB m/e 3202.9 (M$^+$, calcd 3203.6). Anal. Calcd for $C_{196}H_{224}N_8$-$O_{32} \cdot 2.3H_2O$: C, 72.54; H, 7.10; N, 3.45. Found: C, 72.54; H, 7.37; N, 3.32.

17,23,51,57-Tetraacetamido-12,28,46,62,93,94,98,99-octapropoxy-79,85,86,87-tetraundecyl-14*H*,20*H*,26*H*,32*H*,-48*H*,54*H*,60*H*,66*H*-4,70-(epoxymethanoxy)-1,81:3,71:11,29:45,63:73,77-pentamethano-9,13:15,19:21,25:27,31:43,47:49,53:55,59:61,65-octametheno-6*H*,40*H*,79*H*-dibenzo[*d*,*d*′]-[1,3]dioxocino[4,5-*l*$_1$:8,7-*l*′$_1$]bis[1,3,6,36,9,33]benzotetraoxadiazacyclooctatriacontine-7,33,41,67(8*H*,34*H*,42*H*,-68*H*)tetrone (2:1 *endo*−*exo*, R = acetamido) (5d) was prepared starting from calix[4]arene **16** (0.60 g, 0.67 mmol), cavitand **2** (0.41 g, 0.34 mmol), Cs_2CO_3 (0.89 g, 2.7 mmol), and KI in CH_3CN (200 mL) and THF (50 mL). The calix[4]arene was added over 8 h, and subsequently, the reaction mixture was stirred at reflux temperature for 32 h to give the crude reaction mixture, which was purified by column chromatography (SiO_2, EtOAc/PE, 90:10): yield 0.22 g (23%); mp 296−298 °C; ^{1}H NMR (acetone-d_6) δ 9.36, 8.74, 8.58, 8.44 (s, 8 H), 7.5−6.6 (m, 20 H), 6.25, 6.05, 5.82 (d, 4 H, J = 7.4 Hz), 4.8−4.1 (m, 24 H), 3.9−3.7 (m, 16 H), 3.2−2.9 (m, 8 H), 2.4−2.2

(m, 8 H), 2.0−1.8 (m, 28 H), 1.4−1.2 (m, 72 H), 1.1−1.0 (m, 24 H), 1.0−0.8 (m, 12 H); ^{13}C NMR δ 168.3, 166.9, 165.7; MS-FAB *m/e* 2874.6 ([M + Na]$^+$, calcd 2874.6). Anal. Calcd for $C_{172}H_{224}N_8O_{28}\cdot 3.5H_2O$: C, 70.88; H, 7.99; N, 3.84. Found: C, 70.81; H, 7.85; N, 3.83.

17,23,51,57-Tetrakis(1,1-dimethylethyl)-12,28,46,62,93,-94,98,99-octapropoxy-79,85,86,87-tetraundecyl-14*H*,20*H*,-26*H*,32*H*,48*H*,54*H*,60*H*,66*H*-4,70-(epoxymethanoxy)-1,81:3,71:11,29:45,63:73,77-pentamethano-9,13:15,19:21,25:27,31:43,47:49,53:55,59:61,65-octametheno-6*H*,40*H*,79*H*-dibenzo[*d*,*d*′][1,3]dioxocino[4,5-*l*$_1$:8,7-*l*′$_1$]bis[1,3,6,36,9,33]-benzotetraoxadiazacyclooctatriacontine-7,33,41,67(8*H*,-34*H*,42*H*,68*H*)tetrone (2:1 *endo*−*endo*, R = *tert*-butyl) (4e) was prepared starting from calix[4]arene **19** (0.50 g, 0.563 mmol), cavitand **2** (0.34 g, 0.28 mmol), Cs_2CO_3 (0.74 g, 2.3 mmol), and KI in DMF (150 mL). The calix[4]arene was added over 8 h, and subsequently, the reaction mixture was stirred at 100 °C for 38 h to give the crude reaction mixture, which was purified by column chromatography (SiO_2, EtOAc/PE, 12.5:87.5): yield 0.11 g (14%); mp 222−224 °C; ^{1}H NMR δ 9.27 (s, 4 H), 7.56, 6.63, 6.56, 6.41 (d, 16 H, J = 2.2 Hz), 6.84 (s, 4 H), 5.86, 5.74 (d, 4 H, J = 7.2 Hz), 4.7−4.3 (m, 16 H), 4.58 and 4.24 (ABq, 8 H, J = 15.6 Hz), 3.8−3.7 (m, 16 H), 3.1−3.0 (m, 8 H), 2.2−2.1 (m, 8 H), 2.0−1.8 (m, 16 H), 1.4−1.2 (m, 72 H), 1.0−0.9 (m, 60 H), 0.9−0.8 (m, 12 H); ^{13}C NMR δ 166.0; MS-FAB *m/e* 2847.1 (M$^+$, calcd 2847.8). Anal. Calcd for $C_{180}H_{244}N_4O_{24}\cdot 2.0H_2O$: C, 74.97; H, 8.67; N, 1.94. Found: C, 74.95; H, 8.86; N, 1.89.

2:1 *Endo*−*exo*, R = *tert*-butyl (5e) was isolated from the same reaction mixture as **4e**: yield 0.14 g (18%); mp 223−225 °C; ^{1}H NMR δ 9.32, 8.02 (s, 4 H), 7.63, 7.56, 6.90, 6.76, 6.70, 6.62, 6.47, 6.22 (d, 20 H, J ∼2.2 Hz), 5.88, 5.80, 5.55 (d, 4 H, J = 7.1 Hz), 4.8−4.0 (m, 24 H), 3.8−3.7 (m, 16 H), 3.2−2.9 (m, 8 H), 2.2−2.1 (m, 8 H), 2.0−1.9 (m, 16 H), 1.4−1.2 (m, 72 H), 1.1−0.9 (m, 60 H), 0.9−0.8 (m, 12 H); ^{13}C NMR δ 166.0, 165.2; MS-FAB *m/e* 2847.1 (M$^+$, calcd 2847.8). Anal. Calcd for $C_{180}H_{244}N_4O_{24}\cdot 2.0H_2O$: C, 74.97; H, 8.67; N, 1.94. Found: C, 74.95; H, 8.81; N, 1.86.

2:1 *Exo*−*exo*, R = *tert*-butyl (6e) was isolated from the same reaction mixture as **4e**: yield 0.03 g (4%); mp 219−221 °C; ^{1}H NMR δ 8.01 (s, 4 H), 7.44, 6.70, 6.64, 6.25 (d, 16 H, J ∼ 2.2 Hz), 6.83 (s, 4 H), 5.77 (d, 3 H, J = 7.1 Hz), 5.49 (d, 3 H, J = 6.6 Hz), 4.7−4.3 (m, 16 H), 4.56 and 4.04 (ABq, 8 H, J = 14.8 Hz), 3.7−3.6 (m, 16 H), 3.1−2.9 (m, 8 H), 2.2−2.1 (m, 8 H), 1.9−1.8 (m, 16 H), 1.3−1.1 (m, 72 H), 1.0−0.9 (m, 60 H), 0.9−0.8 (m, 12 H); ^{13}C NMR δ 165.3; MS-FAB *m/e* 2847.5 (M$^+$, calcd 2847.8). Anal. Calcd for $C_{180}H_{244}N_4O_{24}\cdot 2.0H_2O$: C, 74.97; H, 8.67; N, 1.94. Found: C, 74.98; H, 8.84; N, 1.92.

17,23,51,57-Tetracyano-12,28,46,62,93,94,98,99-octapropoxy-79,85,86,87-tetraundecyl-14*H*,20*H*,26*H*,32*H*,48*H*,-54*H*,60*H*,66*H*-4,70-(epoxymethanoxy)-1,81:3,71:11,29:45,-63:73,77-pentamethano-9,13:15,19:21,25:27,31:43,47:49,53:55,59:61,65-octametheno-6*H*,40*H*,79*H*-dibenzo[*d*,*d*′]-[1,3]dioxocino[4,5-*l*$_1$:8,7-*l*′$_1$]bis[1,3,6,36,9,33]benzotetraoxadiazacyclooctatriacontine-7,33,41,67(8*H*,34*H*,42*H*,-68*H*)tetrone (2:1 *endo*−*endo*, R = CN) (4f) was prepared starting from calix[4]arene **22** (0.65 g, 0.79 mmol), cavitand **2** (0.46 g, 0.38 mmol), Cs_2CO_3 (1.05 g, 3.15 mmol), and KI in DMF (190 mL). The calix[4]arene was added over 8 h, and subsequently, the reaction mixture was stirred at 100 °C for 10 h to give the crude reaction mixture, which was purified by column chromatography (SiO_2, EtOAc/PE, 30:70): yield 0.04 g (4%); mp 237−238 °C; ^{1}H NMR δ 8.65 (s, 4 H), 7.17, 6.93, 6.84, 6.50 (d, 16 H, J ∼ 2.1 Hz), 6.81 (s, 4 H), 5.82, 5.76 (d, 4 H, J = 7.3 Hz), 4.7−4.3 (m, 16 H), 4.66 and 4.20 (ABq, 8 H, J = 15.6 Hz), 3.9−3.7 (m, 16 H), 3.2−3.1 (m, 8 H), 2.2−2.1 (m, 8 H), 1.9−1.8 (m, 16 H), 1.3−1.1 (m, 72 H), 1.0−0.9 (m, 24 H), 0.8−0.7 (m, 12 H); ^{13}C NMR δ 166.7, 105.9; MS-FAB *m/e* 2723.5 (M$^+$, calcd 2723.5). Anal. Calcd for $C_{168}H_{208}N_8O_{24}\cdot 3H_2O$: C, 72.65; H, 7.77; N, 4.03. Found: C, 72.73; H, 7.85; N, 3.84.

2:1 *Endo*−*exo*, R = CN (5f) was isolated from the same reaction mixture as **4f**: yield 0.06 g (6%); mp 248−250 °C; ^{1}H NMR δ 8.70, 8.22 (s, 4 H), 7.24, 7.21, 7.00, 6.93, 6.48, 6.33 (d, 12 H, J = ∼ 2.0 Hz), 6.9−6.8 (m, 8 H), 5.8−5.7 (m, 3 H), 5.50 (d, 1 H, J = 6.7 Hz), 4.7−4.2 (m, 24 H), 3.9−3.7 (m, 16 H), 3.2−3.0 (m, 8 H), 2.2−2.1 (m, 8 H), 1.9−1.7 (m, 16 H), 1.3−1.1 (m, 72 H), 1.0−0.9 (m, 24 H), 0.8−0.7 (m, 12 H); ^{13}C NMR δ 166.7, 166.5, 106.2, 105.9; MS-FAB *m/e* 2723.4 (M$^+$, calcd 2723.5). Anal. Calcd for $C_{168}H_{208}N_8O_{24}\cdot 3H_2O$: C, 72.65; H, 7.77; N, 4.03. Found: C, 72.47; H, 7.81; N, 4.07.

2:1 *Exo*−*exo*, R = CN (6f) was isolated from the same reaction mixture as **4f**: yield 0.03 g (3%); mp 246−248 °C; ^{1}H NMR δ 8.24 (s, 4 H), 7.16, 6.99, 6.82, 6.80, 6.40 (d, 20 H, J = ∼ 2.0 Hz), 5.79, 5.50 (d, 4 H, J = 6.8 Hz), 4.7−4.3 (m, 24 H), 3.9−3.7 (m, 16 H), 3.2−3.0 (m, 8 H), 2.2−2.1 (m, 8 H), 1.9−1.7 (m, 16 H), 1.2−1.1 (m, 72 H), 1.0−0.9 (m, 24 H), 0.8−0.7 (m, 12 H); ^{13}C NMR δ 166.5, 106.2; MS-FAB *m/e* 2723.2 (M$^+$, calcd 2723.5). Anal. Calcd for $C_{168}H_{208}N_8O_{24}\cdot 4H_2O$: C, 72.18; H, 7.79; N, 4.01. Found: C, 72.02; H, 7.92; N, 4.11.

41,59-Dihydroxy-19,25-diphthalimido-14,30,62,63-tetrapropoxy-1,47,49,57-tetraundecyl-16*H*,22*H*,28*H*,34*H*-13,-31:51,55-dimethano-2,46:3,45:11,15:17,21:23,27:29,33-hexametheno-1*H*,8*H*,47*H*,49*H*-[1,3]benzodioxocino-[9′,8′:4,5][1,3]benzodioxocino[9,10-*d*][1,3]dioxocino[4,5-*l*$_1$]-bis[1,3,6,36,9,33]benzotetraoxadiazacyclooctatriacontine-9,35(10*H*,36*H*)dione (1:1 *endo*, R = phthalimido) (23c) was prepared starting from calix[4]arene **12** (0.50 g, 0.47 mmol), cavitand **2** (1.72 g, 1.41 mmol), Cs_2CO_3 (0.62 g, 1.9 mmol), and KI in CH_3CN (260 mL) and THF (20 mL). The calix[4]arene was added over 6 h, and subsequently, the reaction mixture was stirred at reflux temperature for 9.5 h to give the crude reaction mixture, which was purified by column chromatography (SiO_2, EtOAc/PE, 55:45): yield 0.43 g (41%); mp 210−212 °C; ^{1}H NMR δ 9.82 (s, 2 H), 7.8−7.6 (m, 8 H), 7.35, 6.73 (d, 4 H, J = 2.4 Hz), 6.94, 6.65 (s, 4 H), 6.9−6.8 (m, 4 H), 6.55 (d, 1 H, J = 7.0 Hz), 6.0−5.9 (m, 3 H), 4.8−4.5 (m, 12 H), 4.59 and 4.22 (ABq, 4 H, J = 15.8 Hz), 4.0−3.8 (m, 10 H), 3.3−3.2 (m, 4 H), 2.3−2.2 (m, 8 H), 2.0−1.9 (m, 8 H), 1.4−1.2 (m, 72 H), 1.1−1.0 (m, 12 H), 0.9−0.8 (m, 12 H); ^{13}C NMR δ 167.2, 166.5; MS-FAB *m/e* 2210.5 (M$^+$, calcd 2210.2). Anal. Calcd for $C_{136}H_{168}N_4O_{22}\cdot 2.2H_2O$: C, 72.58; H, 7.72; N, 2.49. Found: C, 72.61; H, 7.87; N, 2.35.

19,25-Diacetamido-41,59-dihydroxy-14,30,62,63-tetrapropoxy-1,47,49,57-tetraundecyl-16*H*,22*H*,28*H*,34*H*-13,31:51,55-dimethano-2,46:3,45:11,15:17,21:23,27:29,33-hexametheno-1*H*,8*H*,47*H*,49*H*-[1,3]benzodioxocino[9′,8′:4,5]-[1,3]benzodioxocino[9,10-*d*][1,3]dioxocino[4,5-*l*$_1$]bis[1,3,6,-36,9,33]benzotetraoxadiazacyclooctatriacontine-9,35-(10*H*,36*H*)dione (1:1 *endo*, R = acetamido) (23d) was prepared starting from calix[4]arene **16** (0.32 g, 0.34 mmol), cavitand **2** (1.24 g, 1.01 mmol), Cs_2CO_3 (0.44 g, 1.3 mmol), and KI in CH_3CN (150 mL) and THF (40 mL). The calix[4]arene was added over 8 h, and subsequently, the reaction mixture was stirred at reflux temperature for 32 h to give the crude reaction mixture, which was purified by column chromatography (SiO_2, EtOAc/PE, 90:10): yield 0.32 g (45%); mp 242−244 °C; ^{1}H NMR (acetone-d_6) δ 9.30, 8.67 (s, 4 H), 7.95, 6.62, 6.51 (s, 6 H), 7.6−6.8 (m, 6 H), 6.05, 5.82, 5.70 (d, 4 H, J = 7.0 Hz), 4.7−3.9 (m, 18 H), 3.8−3.7 (m, 8 H), 3.4−2.9 (m, 4 H), 2.3−2.2 (m, 8 H), 1.9−1.6 (m, 14 H), 1.4−1.2 (m, 72 H), 1.0−0.9 (m, 12 H), 0.9−0.7 (m, 12 H); ^{13}C NMR δ 168.2, 166.7; MS-FAB *m/e* 2034.4 (M$^+$, calcd 2034.2). Anal. Calcd for $C_{124}H_{168}N_4O_{20}\cdot 5H_2O$: C, 70.09; H, 8.44; N, 2.64. Found: C, 70.22; H, 8.31; N, 2.69.

7,11,15,28-Tetrakis[(methoxycarbonyl)methoxy]-1,21,-23,25-tetraundecyl-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 (26b). A solution of tetrahydroxycavitand **2** (0.35 g, 0.29 mmol), K_2CO_3 (0.40 g, 2.9 mmol), and methyl bromoacetate (0.12 mL, 1.3 mmol) in CH_3CN (35 mL) was refluxed for 20 h. The reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 mL), washed with 1 N HCl (10 mL), H_2O (3 × 10 mL), and brine (10 mL), and dried over $MgSO_4$. After filtration, the solution was evaporated to dryness to give pure **26b**: yield 0.34 g (99%); mp 188−190 °C (CH_2Cl_2/MeOH); ^{1}H NMR δ 6.79 (s, 4 H), 5.72 (d, 4 H, J = 7.4 Hz), 4.68 (t, 4 H, J = 7.9 Hz), 4.54 (s, 8 H), 4.42 (d, 4 H, J = 7.4 Hz), 3.75 (s, 12 H), 2.2−2.1 (m, 8 H), 1.5−1.2 (m, 72 H), 0.88 (t, 12 H, J = 6.5 Hz); ^{13}C NMR δ 169.7; MS-FAB *m/e*

1506.1 (M^+, calcd 1505.9). Anal. Calcd for $C_{88}H_{128}O_{20}$: C, 70.18; H, 8.57. Found: C, 70.21; H, 8.58.

7,11,15,28-Tetrakis[(hydroxycarbonyl)methoxy]-1,21,-23,25-tetraundecyl-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 (26c). To a solution of **26b** (0.34 g, 0.23 mmol) in THF (15 mL) was added 2 N NaOH (5 mL), and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was acidified with 1 N HCl (15 mL), and the THF was removed under reduced pressure. The precipitate formed was filtered over Celite and thoroughly washed with H_2O. After drying of the solid at 80 °C under vacuum for 3 h, it was suspended in THF and filtered. The solution was evaporated to dryness to give pure **26c**: yield 0.32 g (98%); mp 218−220 °C; ^{1}H NMR δ 6.83 (s, 4 H), 5.83 (d, 4 H, J = 7.1 Hz), 4.68 (t, 4 H, J = 7.9 Hz), 4.63 (s, 8 H), 4.44 (d, 4 H, J = 7.0 Hz), 2.3−2.1 (m, 8 H), 1.5−1.2 (m, 72 H), 0.88 (t, 12 H, J = 6.6 Hz); ^{13}C NMR δ 172.8; MS-FAB m/e 1450.1 (M^+, calcd 1449.8). Anal. Calcd for $C_{84}H_{120}O_{20}\cdot 2H_2O$: C, 67.90; H, 8.41. Found: C, 67.50; H, 8.26.

7,11,15,28-Tetrakis[[[(*p*-methoxyphenyl)amino]carbonyl]methoxy]-1,21,23,25-tetraundecyl-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 (26a). To a suspension of **26c** (0.19 g, 0.13 mmol) in dry CH_2Cl_2 (10 mL) was added freshly distilled oxalyl chloride (0.23 mL, 2.6 mmol), and the mixture was refluxed for 16 h. The solvent was removed in vacuo, and the product was dried under high vacuum for 30 min. Subsequently, it was dissolved in dry CH_2Cl_2 (10 mL) and added dropwise to a solution of *p*-anisidine (0.16 g, 1.3 mmol) and NEt_3 (0.18 mL, 1.3 mmol) in CH_2Cl_2 (10 mL) at room temperature. After being stirred for 3 h, the reaction mixture was diluted with CH_2Cl_2 (30 mL), successively washed with 1 N HCl (10 mL), H_2O (3 × 10 mL), and brine (10 mL), and dried over Na_2SO_4. After filtration, the solution was evaporated to dryness to give crude **26a**, which was further purified by flash column chromatography (SiO_2, EtOAc/CH_2Cl_2, 30:70) to afford pure **26a**: yield 0.13 g (53%); mp 200−202 °C; ^{1}H NMR δ 9.34 (s, 4 H), 7.56, 6.91 (d, 16 H, J = 9.0 and 8.9 Hz), 6.93 (s, 4 H), 6.07 (d, 4 H, J = 7.2 Hz), 4.76 (t, 4 H, J = 7.9 Hz), 4.72 (s, 8 H), 4.55 (d, 4 H, J = 7.2 Hz), 3.81 (s, 12 H), 2.3−2.1 (m, 8 H), 1.5−1.2 (m, 72 H), 0.87 (t, 12 H, J = 6.6 Hz); ^{13}C NMR δ 166.8; MS-FAB m/e 1869.7 ([M + H]$^+$, calcd 1869.3). Anal. Calcd for $C_{112}H_{148}N_4O_{20}\cdot 1.6H_2O$: C, 70.83; H, 8.03; N, 2.95. Found: C, 70.52; H, 8.13; N, 3.03.

Association Constants. The association constants were determined by mixing 5 mM solutions of host and guest in $CDCl_3$ in nine different ratios (1:9−9:1) and monitoring the chemical shift. Because all the guest proton signals are obscured by host proton signals if a large excess of the host is present, these could not be used as a probe. The host amide proton signals on the other hand, shift and even split upon the addition of steroid guests and could be used as a probe. The K_{assoc} values were obtained with a nonlinear two-parameter fit of the chemical shift of the complex and the association constant.[26]

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